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Note

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Synthesis of Sulfonylated Lactams by Copper-Mediated Aminosulfonylation of 2-Vinylbenzamides with Sodium Sulfinates

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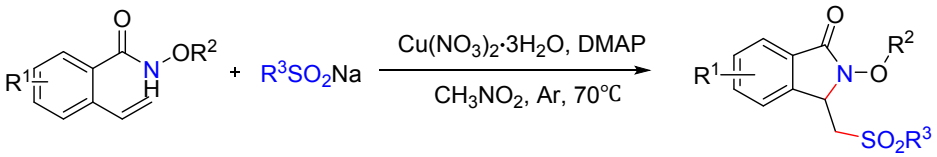
ABSTRACT

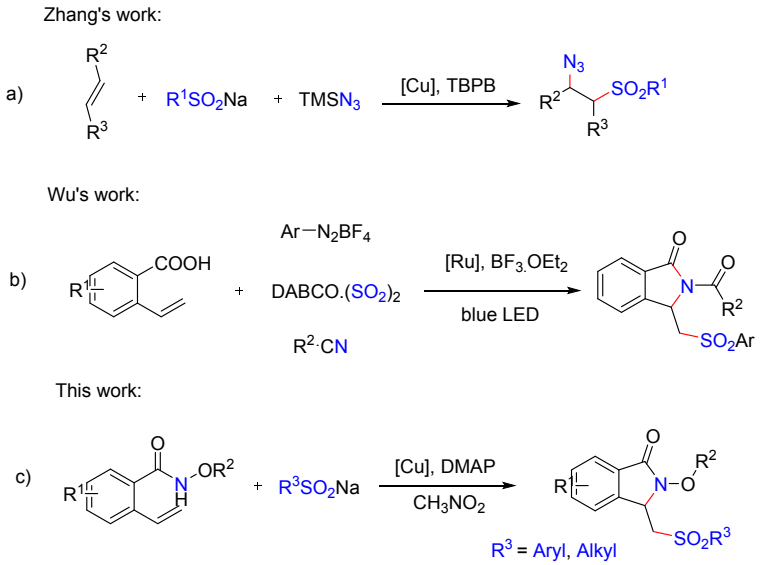


Treatment of 2-vinylbenzamide derivatives with sulfinate sodiums in the presence of $Cu(NO_3)_2 \cdot 3H_2O$ led to an intra-/intermolecular aminosulfonylation reaction to produce sulfonylated lactams in moderate to good yields. The developed method features the easily available and stable sulfone reagents, the ease of operation, and a broad functional group tolerance.

Sulfonylated compounds play a significant role in organic chemistry. Because they are found to be a key structural motif in a diversity of drug molecules, bioactive natural products, and organic materials.[1] More importantly, sulfones are also versatile synthons in organic transformations.[2-3] As a consequence, the efficient synthesis of sulfonylated compounds is of significant interest to the chemists and pharmacologists. In recent years, the sulfonyl cascade/difunctionalization of unsaturated compounds has been widely developed in the synthesis of organic sulfones.[4] To date, two general methodologies have been established, including intermolecular multi-component difunctionalization of simple alkenes and alkynes,[5] and intra-/intermolecular tandem cyclization of unsaturated compounds.[6] However, among them the direct aminosulfonylations are limited, despite the fact that the frequent appearances of amino and sulfone groups in pharmaceuticals and natural products.[7] Furthermore, the majority of the known aminosulfonylation literatures have focused on cascade aminosulfonylation of alkynes.[8] While the related aminosulfonylation of alkenes has been less explored. Very recently, the Zhang group realized a copper-catalyzed azido sulfonylation reactions of alkenes with sodium sulfinates, producing *β*-azidosulfonate derivatives (Scheme 1a).[9] Besides, the Wu group reported a four-component reaction of 2-vinylbenzoic acids, aryldiazonium tetrafluoroborates, sulfur dioxide surrogate of DABCO·$(SO_2)_2$, and nitriles, which was promoted by photocatalysis in the presence of visible light, leading to sulfonated 1-isoindolinones (Scheme 1b).[10] As part of our continuing interest in sulfonylation reactions[11] and nitrogen-containing heterocycles synthesis,[12] herein, we report an efficient and general method for the rapid synthesis

of numerous sulfonylated lactams by using 2-vinylbenzamides and sulfinate sodiums as the starting material and $Cu(NO_3)_2{\cdot}3H_2O$ as the promoter in a one-pot manner (Scheme 1c). This reaction provides a complementary strategy to the aminosulfonylation of alkenes.

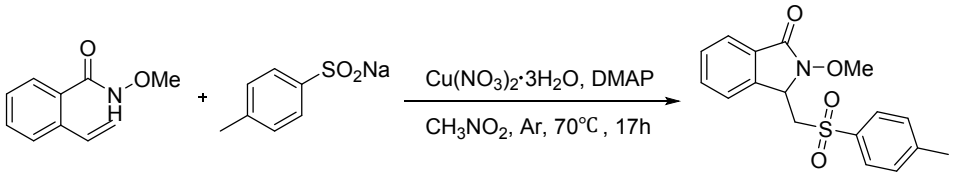
Scheme 1. Aminosulfonylation of alkenes.



Our study began with the intra-/intermolecular aminosulfonylation reaction of *N*-methoxy-2-vinylbenzamide **1a** with readily available sodium *p*-toluenesulfinate **2a** in the company of a Cu^{II} salt. It was found that the sulfonated 1-isoindolinone **3a** was obtained in 30% yield when the reaction was performed in the presence of $Cu(OAc)_2$ in 3 mL of DCE at 50 °C (Table 1, entry 1). And the structure of **3a** was unambiguously confirmed by X-ray crystallographic analysis (see Supporting Information). Subsequent survey on a range of copper salts indicated that $Cu(NO_3)_2{\cdot}3H_2O$ gave the best result (entries 2-4). Different solvents were also investigated, and CH_3NO_2 was found to be the most efficient one (45%) among CH_3CN and THF (entries 5-7). We then turned to additives for a trial: DMAP, Et_3N,

DBU, 2,2'-Bipyridine, NaOAc, K_2CO_3, and KF were all effective for this reaction, and the yield could be improved to 56% by using 2.0 equiv of DMAP (entries 8-14). Encouraged by the above result, we continued to examine the effect of temperature, pleasingly, the yield of **3a** was improved to 64% at 70 °C (entries 15-17). Additionally, we studied the loading of $Cu(NO_3)_2{\cdot}3H_2O$ on the reaction, but there were no better yields (entries 18 and 19). Furthermore, the loading of DMAP was evaluated as well (entries 20-22). To our delight, the yield could be further increased to 74% when using 3.0 equiv. of DMAP (entry 21). Then, the screening of the loading of **2a** indicated that 2.0 equiv. of **2a** is still the best choice for this transformation (entries 23 and 24). Control experiments with air were investigated as well (entries 25-26). The yield was reduced to 55% when the reaction was carried out under an air atmosphere (entry 25). And the reaction didn't work when we reduced $Cu(NO_3)_2{\cdot}3H_2O$ to 0.2 equiv under the above conditions (entry 26). Furthermore, in order to avoid the high loading of copper salts, we want to test whether we can realize this aminosulfonylation reaction efficiently in a catalytic way by introducing oxidizing agents such as $K_2S_2O_8$, SelectFluour and $PhI(OAc)_2$, but regretfully they were not suitable in this transformation (entries 27-29).

Table 1. Screening of the reaction conditions.[a]



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

Entry	Solvent	[Cu] (2.0 equiv)	Additives (equiv)	T(℃)	**3a** Yield (%)
1	DCE	$Cu(OAc)_2$	-	50	30

2	DCE	$Cu(ClO_4)_2·6H_2O$	-	50	23
3	DCE	Cu(2-ethylhexanoate)$_2$	-	50	32
4	DCE	$Cu(NO_3)_2·3H_2O$	-	50	37
5	CH_3NO_2	$Cu(NO_3)_2·3H_2O$	-	50	45
6	CH_3CN	$Cu(NO_3)_2·3H_2O$	-	50	26
7	THF	$Cu(NO_3)_2·3H_2O$	-	50	38
8	CH_3NO_2	$Cu(NO_3)_2·3H_2O$	DMAP (2.0)	50	56
9	CH_3NO_2	$Cu(NO_3)_2·3H_2O$	Et_3N (2.0)	50	49
10	CH_3NO_2	$Cu(NO_3)_2·3H_2O$	DBU (2.0)	50	54
11	CH_3NO_2	$Cu(NO_3)_2·3H_2O$	2,2'-Bipyridine (2.0)	50	50
12	CH_3NO_2	$Cu(NO_3)_2·3H_2O$	NaOAc (2.0)	50	46
13	CH_3NO_2	$Cu(NO_3)_2·3H_2O$	K_2CO_3 (2.0)	50	43
14	CH_3NO_2	$Cu(NO_3)_2·3H_2O$	KF (2.0)	50	53
15	CH_3NO_2	$Cu(NO_3)_2·3H_2O$	DMAP (2.0)	60	62
16	CH_3NO_2	$Cu(NO_3)_2·3H_2O$	DMAP (2.0)	70	64
17	CH_3NO_2	$Cu(NO_3)_2·3H_2O$	DMAP (2.0)	80	60
18[b]	CH_3NO_2	$Cu(NO_3)_2·3H_2O$	DMAP (2.0)	70	62
19[c]	CH_3NO_2	$Cu(NO_3)_2·3H_2O$	DMAP (2.0)	70	64
20	CH_3NO_2	$Cu(NO_3)_2·3H_2O$	DMAP (1.0)	70	52
21	**CH_3NO_2**	**$Cu(NO_3)_2·3H_2O$**	**DMAP (3.0)**	**70**	**74**
22	CH_3NO_2	$Cu(NO_3)_2·3H_2O$	DMAP (3.5)	70	70
23[d]	CH_3NO_2	$Cu(NO_3)_2·3H_2O$	DMAP (3.0)	70	64
24[e]	CH_3NO_2	$Cu(NO_3)_2·3H_2O$	DMAP (3.0)	70	72
25[f]	CH_3NO_2	$Cu(NO_3)_2·3H_2O$	DMAP (3.0)	70	55
26[f,g]	CH_3NO_2	$Cu(NO_3)_2·3H_2O$	DMAP (3.0)	70	-
27[g]	CH_3NO_2	$Cu(NO_3)_2·3H_2O$	DMAP (3.0), $K_2S_2O_8$ (2.0)	70	18
28[g]	CH_3NO_2	$Cu(NO_3)_2·3H_2O$	DMAP (3.0), SelectFluour (2.0)	70	42
29[g]	CH_3NO_2	$Cu(NO_3)_2·3H_2O$	DMAP (3.0), $PhI(OAc)_2$ (2.0)	70	-

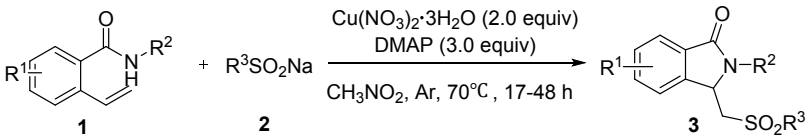
[a] Reaction conditions: a mixture of **1a** (0.2 mmol), **2a** (2.0 equiv), copper salts (2.0 equiv), DMAP (3.0 equiv) and CH_3NO_2 (3 mL) was stirred at 70 °C in schlenk tube under argon. [b] 1.5 equiv of $Cu(NO_3)_2·3H_2O$ was used. [c] 3.0 equiv of $Cu(NO_3)_2·3H_2O$ was used. [d] 1.5 equiv of **2a** was used.[e] 3.0 equiv of **2a** was used. [f] Reaction was performed under air atmosphere. [g] 0.2 equiv of $Cu(NO_3)_2·3H_2O$ was used.

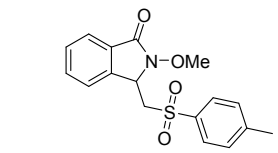
After establishing the above optimized condition, we explored the scope of this aminosulfonylation, and the results are summarized in Scheme 2. First, compatibility of the substitutions on the aryl group (**1a-g**) was explored. Substrates, including those that were electron-donating (**1c-d**), electron-withdrawing (**1e-g**), or located at a

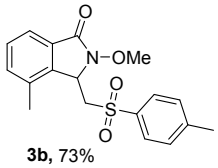
sterically obstructing *ortho* position (**1b**), participated well in the reaction, affording the aminosulfonylation products **3b-g** in good yields. In addition, the intra-/intermolecular cyclization could be smoothly carried out on a 1 mmol scale without difficulty, as showed in the case of **3a**. Then, unsaturated amide **1h** was used as the substrate, however, the reaction did not yield the expected 6-membered lactam product **3h**, and **1h** was recovered in 23%. While unsaturated amide **1i** was decomposed and gave a messy result. We think that the carbon-carbon double bond directly tethered to an aromatic ring is critical for the reactivity of the substrates. But the details of the reason is still unclear. We continued to survey the structural effect of the *N*-R^2 moiety. Fortunately, **1j-l** containing *N*-OR moiety all could afford the desired products in good yields. But, the simple amides **1m** was failed to produce the desired product. Next, we shifted our attention to various sodium sulfinates to test the synthetic potential of this method. As expected, sodium substituted benzenesulfinates with a series of electronic properties operated well under the standard conditions and produced compounds **3n-w** in moderate to good yields. Moreover, sodium 2,4,6-trimethylbenzenesulfinate **2x** and sodium naphthalene-2-sulfinate **2y** could be transformed into the corresponding products in 20% and 24% yields, respectively. Notably, sodium alkanesulfinates were also suitable for this transformation. We can get the aminosulfonylation compounds **3z-ac** in good yields with them. Furthermore, to expand the scope of this reaction, we also investigated substrate **1ad**, but it was not suitable for this transformation.

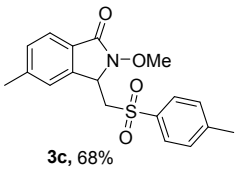
Scheme 2. Scope of copper-mediated aminosulfonylation of 2-vinylbenzamides with

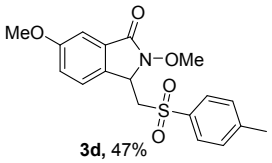
sulfinate sodiums.[a]

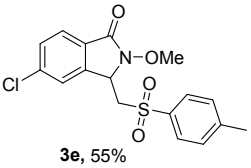


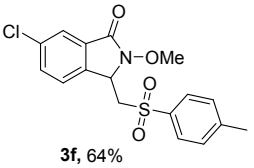

3a, 74% (58%)[b]

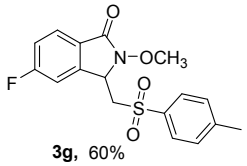

3b, 73%

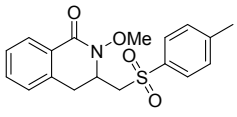

3c, 68%

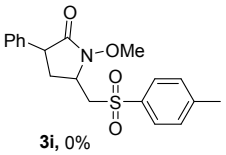

3d, 47%

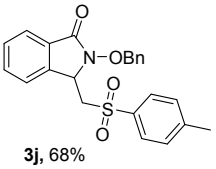

3e, 55%

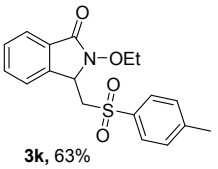

3f, 64%

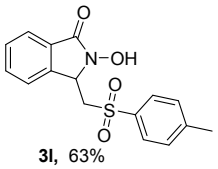

3g, 60%

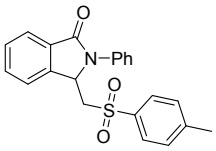

3h, 0%

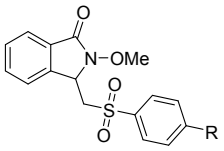

3i, 0%

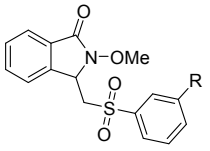

3j, 68%

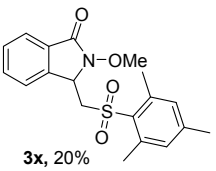

3k, 63%

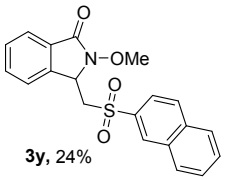

3l, 63%

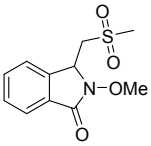

3m, 0%

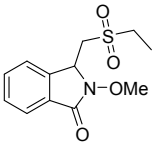

3n (R = H, 64%)
3o (R = OMe, 58%)
3p (R = ^{t}Bu, 50%)
3q (R = Cl, 61%)
3r (R = Br, 51%)
3s (R = F, 42%)
3t (R = Ph, 33%)

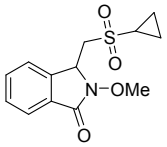

3u (R = CH_3, 61%)
3v (R = Br, 34%)
3w (R = F, 47%)

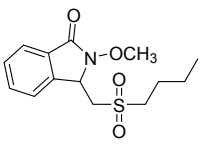

3x, 20%

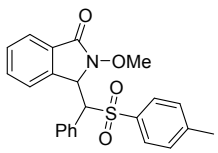

3y, 24%


3z, 67%


3aa, 52%


3ab, 57%

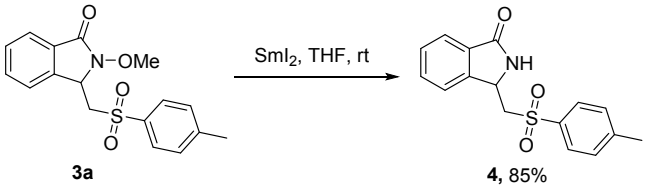

3ac, 38%


3ad, 0%

[a] Reaction conditions: a mixture of **1** (0.2 mmol), **2** (2.0 equiv), $Cu(NO_3)_2 \cdot 3H_2O$ (2.0 equiv),

DMAP (3.0 equiv) and CH_3NO_2 (3 mL) was stirred at 70 °C in schlenk tube under argon. [b] 1.0 mmol of **1a** was used.

Scheme 3. Deprotection of *N*-methoxyamide **3a**



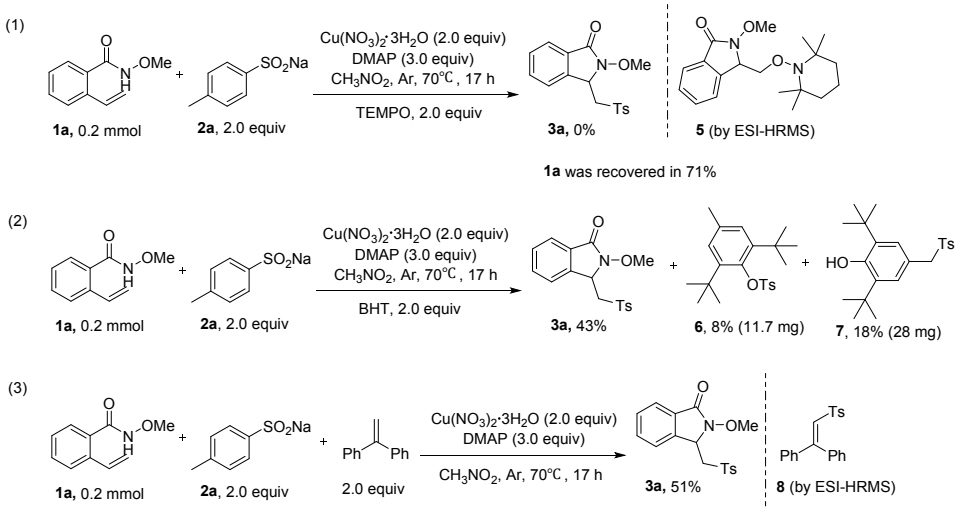
To demonstrate synthetic utility of the products derived from this reaction, the sulfonated 1-isoindolinone **3a** was treated with SmI_2, readily providing free lactam **4** in 85% yield (Scheme 3).

In order to shed some light on the mechanism of this transformation, several control experiments were performed (Scheme 4). First, this transformation was terminated and substrate **1a** was recovered in 71% yield, when 2.0 equiv of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) was added to the standard reaction. In addition, the TEMPO trapped compound **5** was detected by ESI-HRMS measurements of the crude reaction mixture (reaction 1 in Scheme 4). Next, when the reaction was carried out in the presence of BHT (butylated hydroxytoluene, 2.0 equiv), the yield of **3a** was decreased to 43% and the BHT trapped product **6** and **7** were obtained in 8% and 18% yields, respectively (reaction 2 in Scheme 4). Furthermore, when we tried to use 1,1-diphenylethylene (2.0 equiv) to trap the radical under the standard reaction conditions, **3a** was obtained in 51% yield and compound **8** could be detected by ESI-HRMS measurements of the crude reaction mixture (reaction 3 in Scheme 4). Together, these results clearly indicated that a radical pathway with C-centered radical intermediate and sulfonyl radical intermediate may be involved in the above

experiments.

Based on the above-mentioned experimental observations and literature reports,[12, 13] a plausible mechanism, containing two possible pathways, was proposed as in Scheme 5. Initially, copper(II) salts coordinate with alkene **1a** to form intermediate **A**, which followed by the intramolecular aminocupration to afford alkyl-copper intermediate **B**. The resulting complex **B** may undergo a reversible homocleavage to generate C-centered radical intermediate **C**. Meanwhile, sodium sulfinate **2a** is oxidized by Cu^{II} to give sulfonyl radical **D**. In path a, intermediate **B** couples with sulfonyl radical **D** to form intermediate **E**, which was followed by a reductive elimination process to afford the corresponding product **3a** and Cu^{I}. In path b, the obtained radical intermediate **C** directly couples with sulfonyl radical **D** to produce **3a**.

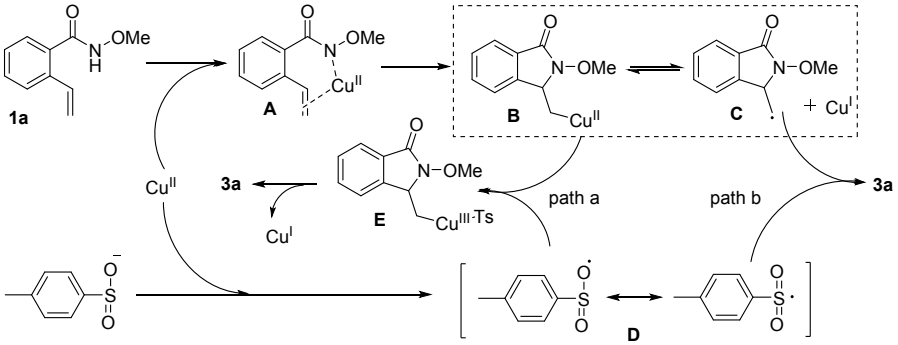
Scheme 4. Mechanistic studies



In summary, we have developed a new and practical copper-mediated alkene aminosulfonylation reaction that is effective to access a variety of sulfonated lactams in moderate to good yields. This reaction used easily available and stable sodium

sulfinates as the ideal sulfone sources. Notably, this strategy represents an appealing and complementary means to achieve alkene aminosulfonylation under mild reaction conditions. Further studies of this strategy are currently underway in our laboratory.

Scheme 5. Plausible mechanism.



Experimental Section

General Information. Reaction progress was monitored via thin layer chromatography (TLC) performed on GF254 silica gel plates. Column chromatography was carried out with silica gel (200-300 mesh). Unless stated otherwise, all reactions were performed in schlenk tube and carried out under an argon atmosphere. ^{1}H NMR spectra were recorded on 600 or 400 MHz in $CDCl_3$ or DMSO-d_6, $^{13}C\{H\}$ NMR spectra were recorded on 150 or 100 MHz in $CDCl_3$ or DMSO-d_6. ^{19}F NMR spectra were recorded on 564 MHz in $CDCl_3$. Chemical shifts (ppm) were recorded with tetramethylsilane (TMS) as the internal reference standard. Multiplicities are given as: s (singlet), d (doublet), t (triplet), dd (doublet of doublets), dt (doublet of triplets) or m (multiplet). IR spectra were recorded on a FT-IR spectrometer and only major peaks are reported in cm^{-1}. Melting points were determined on a microscopic apparatus and were uncorrected. Products **3**, were further characterized by high resolution MS (TLQ, Q-TOF or FTICR) (ESI ionization

sources); copies of their ^{1}H NMR，^{13}C NMR and ^{19}F NMR spectra are provided in the Supporting Information. Commercial grade solvents and reagents were used without further purification.

Starting Materials. Substrates **1**[13a, 14] and **2**[11] was prepared according to the literature.

Typical procedure for the preparation of product 3a. 3 mL CH_3NO_2 was added to **1a** (0.2 mmol, 35.4 mg), Tol-SO_2Na **2a** (0.4 mmol, 73.5mg), $Cu(NO_3)_2 \cdot 3H_2O$ (0.4 mmol, 97.6 mg) and 3.0 equiv DMAP (0.6 mmol, 74.0 mg) under Argon. The mixture was stirred for 17 h at 70 ℃. After the reaction finished as indicated by TLC, the reaction mixture was concentrated in *vacuo* and purified by chromatography on silica gel (elute: EtOAc/Petroleum ether 1/3, v/v) to give the desired product **3a** (49.0 mg, 74%).

10 mL CH_3NO_2 was added to 1.0 mmol (177.0 mg) **1a**, Tol-SO_2Na **2a** (2 mmol, 367.5 mg)**,** $Cu(NO_3)_2 \cdot 3H_2O$ (2 mmol, 488.0 mg) and 3.0 equiv DMAP (3 mmol, 370.0 mg) under Argon. The mixture was stirred for 36 h at 70 ℃. The **3a** was obtained in a yield of 58% (192.2 mg).

Characterization data of 1c,1f, 1i and 1j:

***N*-methoxy-4-methyl-2-vinylbenzamide 1c**. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.94 (s, 1H), 7.34 (s, 1H), 7.25 (t, J = 7.2Hz, 1H), 7.04 (m, 1H), 6.97 (m, 1H), 5.68 (dd, J = 18Hz, J = 3.6Hz, 1H), 5.30 (dd, J = 10.8Hz, J = 4.8Hz, 1H), 3.81 (s, 1H), 2.35 (d, J = 2.4Hz, 1H). $^{13}C\{H\}$ NMR ($CDCl_3$, 150 MHz) δ 167.2, 140.6, 136.3, 133.9, 128.7, 128.1, 127.7, 126.5, 116.3, 64.1, 21.2.

5-chloro-*N*-methoxy-2-vinylbenzamide 1f. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.87 (s, 1H), 7.49 (d, *J* = 9Hz, 1H), 7.37 (d, *J* = 6.6Hz, 2H), 6.92 (dd, *J* = 16.8Hz, *J* = 10.8Hz, 1H), 5.71 (d, *J* = 17.4Hz, 1H), 5.38 (d, *J* = 10.8Hz , 1H), 3.86 (s, 3H). ^{13}C{H} NMR ($CDCl_3$, 150 MHz) δ 165.7, 134.9, 133.4, 132.8, 132.7, 130.8, 127.7, 127.6, 117.8, 64.6.

***N*-(benzyloxy)-2-vinylbenzamide 1j**. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.63 (s, 1H), 7.51 (d, *J* = 7.8Hz, 1H), 7.41 (s, 2H), 7.37-7.34 (m, 4H), 7.28 (d, *J* = 7.2, 1H), 7.20 (t, *J* = 7.8Hz, 1H), 6.89 (dd, *J* = 17.4Hz, *J* = 11.4Hz, 1H), 5.65 (d, *J* = 17.6Hz, 1H), 5.26 (d, *J* = 10.8Hz, 1H), 4.99 (s, 2H). ^{13}C{H} NMR ($CDCl_3$, 150 MHz) δ 167.0, 136.4, 135.1, 133.8, 131.6, 130.6, 129.2, 128.7, 128.5, 127.7, 127.5, 126.1, 117.0, 78.2.

***N*-ethoxy-2-vinylbenzamide 1k**. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.87 (s, 1H), 7.55 (d, *J* = 7.8Hz 1H), 7.39 (t, *J* = 7.8Hz 1H), 7.35 (d, *J* = 7.8Hz, 1H), 7.23 (t, *J* = 7.8Hz, 1H), 6.98 (dd, *J* = 16.8Hz, *J* = 11.4Hz, 1H), 5.70 (d, *J* = 17.4Hz, 1H), 5.33 (d, *J* = 10.8Hz, 1H), 4.04 (d, *J* = 6.0Hz, 2H), 1.29 (s, 3H). ^{13}C{H} NMR ($CDCl_3$, 150 MHz) δ 167.1, 136.2, 133.7, 131.7, 130.4, 127.6, 127.3, 125.8, 116.6, 72.0, 13.3.

Characterization data of 3a-3g, 3j-l, 3n-3ac:

2-methoxy-3-(tosylmethyl)isoindolin-1-one 3a. Light yellow solid (49.0 mg, 74%). mp 125-127 ℃. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.78 (d, *J* = 8.6Hz 2H), 7.73 (d, *J* = 7.8Hz, 1H), 7.70 (d, *J* = 7.2Hz, 1H), 7.54 (dt, *J* = 7.2Hz, *J* = 1.2Hz, 1H), 7.43 (t, *J* = 7.8Hz 1H), 7.32 (d, *J* = 7.8Hz 2H), 5.15 (dd, *J* = 7.8Hz, *J* = 3.0Hz, 1H), 3.78 (dd, *J* = 14.4Hz, *J* = 2.4Hz, 1H), 3.74 (s, 3H), 3.28 (dd, *J* = 14.4Hz, *J* = 7.8Hz, 1H), 2.39 (s, 3H). ^{13}C{H} NMR ($CDCl_3$, 150 MHz) δ 164.2, 145.4, 140.6, 136.2, 132.8, 130.1,

129.2, 129.1, 128.0, 124.1, 123.8, 63.6, 57.0, 53.5, 21.6. IR (neat, cm^{-1}): 2935, 1719, 1317, 1151, 1087, 998, 906, 815, 747, 687, 650, 562, 511. HRMS (ESI-TLQ) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{17}NO_4S$ 332.0944, Found: 332.0951.

2-methoxy-4-methyl-3-(tosylmethyl)isoindolin-1-one 3b. Light yellow solid (50.4 mg, 73%), mp 157-159 ℃. ^1H NMR ($CDCl_3$, 600 MHz) δ 7.63 (d, *J* = 8.4Hz, 2H), 7.57 (d, *J* = 8.4Hz, 1H), 7.32 (t, *J* = 7.8Hz, 1H), 7.26-7.24 (m, 3H), 5.23 (dd, *J* = 4.8Hz, *J* = 2.4Hz, 1H), 3.71 (s, 3H), 3.67 (dd, *J* = 15.6Hz, *J* = 2.4Hz, 1H), 3.59 (dd, *J* = 15.6Hz, *J* = 5.4Hz, 1H), 2.37 (s, 3H), 2.31 (s, 3H). $^{13}C\{H\}$ NMR ($CDCl_3$, 150 MHz) δ 164.9, 145.1, 137.9, 136.5, 134.3, 133.2, 129.9, 129.6, 129.4, 128.0, 121.5, 63.7, 56.2, 53.7, 21.6, 17.7. IR (neat, cm^{-1}): 2937, 2246, 1716, 1597, 1316, 1150, 1131, 1086, 1036, 900, 815, 748, 528, 514. HRMS (ESI-TLQ) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{19}NO_4S$ 346.1102, Found: 346.1108.

2-methoxy-5-methyl-3-(tosylmethyl)isoindolin-1-one 3c. Light yellow solid (47.0 mg, 68%). mp 125-127 ℃. ^1H NMR ($CDCl_3$, 600 MHz) δ 7.78 (d, *J* = 8.4Hz, 2H), 7.61 (d, *J* = 7.8Hz, 1H), 7.39 (s, 1H), 7.33 (d, *J* = 8.4Hz, 2H), 7.22 (d, *J* = 7.8Hz, 1H), 5.09 (dd, *J* = 7.2Hz, *J* = 2.4Hz, 1H), 3.77 (dd, *J* = 15.0Hz, *J* = 2.4Hz, 1H), 3.72 (s, 3H), 3.29 (dd, *J* = 14.4Hz, *J* = 7.2Hz, 1H), 2.40 (s, 3H), 2.37 (s, 3H). $^{13}C\{H\}$ NMR ($CDCl_3$, 150 MHz) δ 164.6, 145.4, 143.8, 140.9, 136.2, 130.1, 130.1, 128.1, 126.4, 124.3, 123.6, 63.5, 57.0, 53.5, 22.0, 21.6. IR (neat, cm^{-1}): 2931, 2359, 2248, 1716, 1620, 1456, 1316, 1152, 1086, 760, 727, 553, 515. HRMS (ESI-TLQ) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{20}NO_4S$ 346.1102, Found: 346.1108.

2,6-dimethoxy-3-(tosylmethyl)isoindolin-1-one 3d. white solid (33.97 mg, 47%).

mp 153-155℃. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.78 (d, *J* = 7.8Hz, 2H), 7.60 (d, *J* = 8.4Hz, 1H), 7.33 (d, *J* = 7.8Hz, 2H), 7.22 (d, *J* = 2.4Hz, 1H), 7.07 (dd, *J* = 8.4Hz, *J* = 2.4Hz, 1H), 5.11 (dd, *J* = 7.8Hz, *J* = 2.4Hz, 1H), 3.78 (s, 3H), 3.76 (d, *J* = 2.4Hz, 1H), 3.74 (s, 3H), 3.23 (dd, *J* = 14.4Hz, *J* = 7.8Hz, 1H), 2.40 (s, 3H). ^{13}C{H} NMR ($CDCl_3$, 150 MHz) δ 164.3, 160.6, 145.4, 136.3, 132.6, 130.5, 130.1, 128.0, 125.3, 120.6, 106.9, 63.6, 57.1, 55.7, 53.3, 21.6. IR (neat, cm^{-1}): 2939, 2838, 2359, 1717, 1595, 1493, 1316, 1286, 1147, 1087, 1017, 765 555, 517. HRMS (ESI-TLQ) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{19}NO_5S$ 362.1051, Found: 362.1057.

5-chloro-2-methoxy-3-(tosylmethyl)isoindolin-1-one 3e. Light yellow solid (40.2mg, 55%). mp 168-170 ℃. ^{1}H NMR (DMSO-d_6, 600 MHz) δ 7.67 (d, *J* = 7.8Hz, 1H), 7.56 (d, *J* = 7.8Hz, 2H), 7.51 (dd, *J* = 7.8Hz, *J* = 1.2Hz, 1H), 7.44 (s, 1H), 7.34 (d, *J* = 8.4Hz, 2H), 5.27 (t, *J* = 4.8Hz, 1H), 4.20 (dd, *J* = 15.6Hz, *J* = 3.6Hz, 1H), 4.04 (dd, *J* = 15.6Hz, *J* = 5.4Hz, 1H), 3.78 (s, 3H), 2.40 (s, 3H). ^{13}C{H} NMR (DMSO-d_6, 150 MHz) δ 162.4, 144.5, 141.3, 136.9, 136.6, 129.7, 129.0, 128.3, 127.5, 124.5, 124.2, 63.0, 54.0, 53.7, 21.0. IR (neat, cm^{-1}): 2927, 2360, 2341, 1719, 1613, 1316, 1152, 1135, 1086, 761, 669, 515. HRMS (ESI-TLQ) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{16}ClNO_4S$ 366.0560, Found: 366.0561.

6-chloro-2-methoxy-3-(tosylmethyl)isoindolin-1-one 3f. Light yellow solid (46.8 mg, 64%). mp 114-115 ℃. ^{1}H NMR (DMSO-d_6, 600 MHz) δ 7.68 (d, *J* = 1.2Hz, 1H), 7.64 (d, *J* = 8.4Hz, 2H), 7.57-7.56 (m, 2H), 7.38 (d, *J* = 7.8Hz, 2H), 5.28 (dd, *J* = 5.4Hz, *J* = 4.2Hz, 1H), 4.14 (dd, *J* = 15.0Hz, *J* = 3.6Hz, 1H), 4.00 (dd, *J* = 15.6Hz, *J* = 5.4Hz, 1H), 13.74 (s, 3H), 2.40 (s, 3H). ^{13}C{H} NMR (DMSO-d_6, 150 MHz) δ

161.9, 144.5, 138.5, 136.6, 133.7, 132.0, 131.4, 129.7, 127.6, 125.9, 122.4, 63.0, 54.3, 53.9, 21.0. IR (neat, cm^{-1}): 2926, 2360, 2342, 1718, 1596, 1316, 1151, 1087, 816, 762, 668, 515. HRMS (ESI-TLQ) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{16}ClNO_4S$ 366.0560, Found: 366.0561.

5-fluoro-2-methoxy-3-(tosylmethyl)isoindolin-1-one 3g. Light yellow solid (42.0mg, 60%). mp 173-175 ℃.^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.86 (d, *J* = 8.4Hz, 2H), 7.81 (dd, *J* = 8.4Hz, *J* = 5.2Hz, 1H), 7.52 (dd, *J* = 8.4Hz, *J* = 2.0Hz, 1H), 7.42 (d, *J* = 8.0Hz, 2H), 7.21 (td, *J* = 8.8Hz, *J* = 2.4Hz, 1H), 5.21 (dd, *J* = 8.0Hz, *J* = 2.0Hz, 1H), 3.87 (dd, *J* = 14.4Hz, *J* = 2.4Hz, 1H), 3.83 (s, 3H), 3.33 (dd, *J* = 14.4Hz, *J* = 8.4Hz, 1H), 2.48 (s, 3H). ^{13}C{H} NMR ($CDCl_3$, 100 MHz) δ 166.9, 164.4, 163.4, 145.7, 143.0, 142.9, 135.9, 130.2, 128.0, 126.1, 126.0, 125.1, 125.1, 117.2, 117.0, 112.2, 111.9, 63.7, 56.5, 53.4, 53.3, 21.6. ^{19}F NMR ($CDCl_3$, 564 MHz) δ -103.8. IR (neat, cm^{-1}): 2935, 1720, 1599, 1481, 1317, 1243, 1151, 1087, 763, 556. HRMS (ESI-FTICR) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{17}FNO_4S$ 350.0854 Found: 350.0857.

2-(benzyloxy)-3-(tosylmethyl)isoindolin-1-one 3j. Light yellow solid (55.4 mg, 68%). mp 121-123 ℃. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.74 (d, *J* = 7.8Hz, 1H), 7.70-7.68 (m, 3H), 7.50 (t, *J* = 7.2Hz, 1H), 7.41 (t, *J* = 7.2Hz, 1H), 7.30-7.28 (m, 4H), 7.25 (t, *J* = 3.6Hz, 3H), 5.03 (d, *J* = 10.8Hz, 1H), 4.94 (d, *J* = 10.2Hz, 1H), 4.86 (dd, *J* = 8.4Hz, *J* = 1.8Hz, 1H), 3.57 (dd, *J* = 13.8Hz, *J* = 1.8Hz, 1H), 3.06 (dd, *J* = 14.4Hz, *J* = 8.4Hz, 1H), 2.38 (s, 3H). ^{13}C{H} NMR ($CDCl_3$, 150 MHz) δ 164.9, 145.3, 140.9, 136.3, 134.6, 132.7, 130.1, 129.7, 1291, 129.1, 129.0, 128.6, 127.9, 124.2, 123.7, 78.0, 56.5, 54.9,21.6. IR (neat, cm^{-1}): 3032, 1926, 2359, 1718, 1470, 1318, 1151, 1087, 748,

700, 561, 511. HRMS (ESI-TLQ) *m/z*: $[M+H]^+$ Calcd for $C_{23}H_{22}NO_4S$ 408.1258, Found: 408.1264.

2-ethoxy-3-(tosylmethyl)isoindolin-1-one 3k. Light yellow solid (43.5 mg, 63%), mp 91-93 ℃. ^1H NMR ($CDCl_3$, 600 MHz) δ 7..79 (d, *J* = 7.8Hz, 2H), 7.72 (dd, *J* = 12.0Hz t, *J* = 7.8Hz, 2H), 7.53 (t, *J* = 7.8Hz, 1H), 7.43 (t, *J* = 7.8Hz, 1H), 7.33 (d, *J* = 7.8Hz, 2H), 5.11 (dd, *J* = 7.8Hz t, *J* = 1.2Hz, 1H), 4.02-3.99 (m, 1H), 3.94-3.90 (m, 1H), 3.83 (dd, *J* = 14.4Hz t, *J* = 1.8Hz, 1H), 3.23 (dd, *J* = 14.4Hz t, *J* = 7.8Hz, 1H), 2.40 (s, 3H), 1.18 (t, *J* = 7.2Hz, 3H). $^{13}C\{H\}$ NMR ($CDCl_3$, 150 MHz) δ 164.2, 145.4, 140.8, 136.2, 132.7, 130.1, 129.2, 129.1, 128.0, 124.1, 123.7, 71.9, 56.7, 54.1, 21.6, 13.5. IR (neat, cm^{-1}): 2981, 2930, 2359, 1718, 1470, 1318, 1151, 1087, 1019, 748, 566, 511. HRMS (ESI-TLQ) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{19}NO_4S$ 346.1103, Found: 346.1108.

2-hydroxy-3-(tosylmethyl)isoindolin-1-one 3l. Light yellow solid (40.6mg, 63%). mp 148-150. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.87 (dd, *J* = 8.4Hz, *J* = 2.0Hz, 3H), 7.75-7.71 (m, 1H), 7.67 (dd, *J* = 3.6Hz, *J* = 0.4Hz, 1H), 7.57 (t, *J* = 7.6Hz, 1H), 7.40 (d, *J* = 8.0Hz, 2H), 5.95 (dd, *J* = 7.2Hz, *J* = 4.4Hz, 1H), 3.69 (dd, *J* = 15.2Hz, *J* = 4.4Hz, 1H), 3.59 (dd, *J* = 15.2Hz, *J* = 7.6Hz, 1H), 2.47 (s, 3H). $^{13}C\{H\}$ NMR ($CDCl_3$, 100 MHz) δ 169.0, 147.0, 145.5, 136.0, 134.6, 130.1, 130.0, 128.3, 125.9, 125.4, 122.5, 60.5, 21.7. IR (neat, cm^{-1}): 2926, 1770, 1598, 1467, 1316, 1304, 1289, 1142, 1061, 988, 743, 552. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{16}NO_4S$ 318.0970 Found: 318.0975.

2-methoxy-3-((phenylsulfonyl)methyl)isoindolin-1-one 3n. White solid (40.6 mg,

64%), mp 130-132 ℃. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.99 (d, *J* = 7.8Hz, 2H), 7.82 (d, *J* = 7.2Hz, 1H), 7.77 (d, *J* = 7.8Hz, 1H), 7.72 (t, *J* = 7.8Hz, 1H), 7.64-7.61 (m, 3H), 7.51 (t, *J* = 7.8Hz,1H), 5.25 (dd, *J* = 7.2Hz, *J* = 3.0Hz, 1H), 3.89 (dd, *J* = 14.4Hz, *J* = 3.0Hz, 1H), 3.81 (s, 3H), 3.39 (dd, *J* = 15.0Hz, *J* = 7.8Hz, 1H). ^{13}C{H} NMR ($CDCl_3$, 150 MHz) δ 164.1, 140.5, 139.1, 134.3, 132.8, 129.6, 129.3, 129.2, 128.0, 124.0, 123.8, 63.6, 56.9, 53.4. IR (neat, cm^{-1}): 3064, 2935, 2360, 1717, 1447, 1309, 1151, 1086, 998, 744, 687, 564, 523. HRMS (ESI-TLQ) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{15}NO_4S$ 318.0788, Found: 318.0795.

2-methoxy-3-(((4-methoxyphenyl)sulfonyl)methyl)isoindolin-1-one 3o. Light yellow solid (40.3 mg, 58%). mp 135-137 ℃. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.82 (d, *J* = 9.0Hz, 2H), 7.72 (dd, *J* = 15.6Hz, *J* = 7.2Hz, 2H), 7.54 (t, *J* = 7.8Hz, 1H), 7.43 (t, *J* = 7.8Hz, 1H), 6.98 (d, *J* = 9.0Hz, 2H), 5.15 (dd, *J* = 7.8Hz, *J* = 2.4Hz, 1H), 3.82 (s, 3H), 3.77 (dd, *J* = 15.0Hz, *J* = 3.0Hz, 1H), 3.75 (s, 3H), 3.28 (dd, *J* = 14.4Hz, *J* = 7.8Hz, 1H). ^{13}C{H} NMR ($CDCl_3$, 150 MHz) δ 164.2, 164.1, 140.6, 132.8, 130.5, 130.2, 129.2, 129.1, 124.1, 123.8, 114.7, 63.6, 57.1, 55.7, 53.6. IR (neat, cm^{-1}): 2938, 2842, 2360, 1718, 1594, 1498, 1319, 1262, 1147, 1089, 748,565. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{17}NO_5S$ 348.0901, Found: 348.0900.

3-(((4-(tert-butyl)phenyl)sulfonyl)methyl)-2-methoxyisoindolin-1-one 3p. Light yellow solid (37.3 mg, 50%). mp 142-143 ℃. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.90 (d, *J* = 8.4Hz, 2H), 7.82 (d, *J* = 7.8Hz, 1H), 7.75 (d, *J* = 7.8Hz, 1H), 7.63-7.59 (m, 3H), 7.51 (t, *J* = 7.8Hz, 1H), 5.24 (dd, *J* = 7.2Hz, d, *J* = 2.4Hz, 1H), 3.88 (dd, *J* = 15.0Hz, d, *J* = 2.4Hz, 1H), 3.80 (s, 3H), 3.36 (dd, *J* = 15.0Hz, d, *J* = 7.8Hz, 1H), 1.36 (s, 9H).

$^{13}C\{H\}$ NMR ($CDCl_3$, 150 MHz) δ 164.2, 158.4, 140.6, 136.0, 132.8, 129.2, 129.1, 127.9, 126.6, 124.0, 123.8, 63.5, 56.9, 53.5, 35.3, 31.0. IR (neat, cm^{-1}): 2963, 2360, 1718, 1471, 1318, 1293, 1155, 1108, 1085, 759, 574, 501. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{23}NO_4S$ 374.1423, Found: 374.1421.

3-(((4-chlorophenyl)sulfonyl)methyl)-2-methoxyisoindolin-1-one 3q. Light yellow solid (42.9 mg, 61%). mp 161-162 ℃. ^1H NMR ($CDCl_3$, 600 MHz) δ 7.82 (d, *J* = 9.0Hz, 2H), 7.74 (d, *J* = 7.2Hz, 1H), 7.68 (d, *J* = 7.8Hz, 1H), 7.56-7.53 (m, 1H), 7.50 (d, *J* = 8.4Hz, 2H), 7.44 (t, *J* = 7.8Hz, 1H), 5.17(dd, *J* = 7.2Hz, *J* = 3.0Hz, 1H), 3.80 (d, *J* = 3.0Hz, 1H), 3.78 (s, 3H), 3.34(dd, *J* = 15.0Hz, *J* = 7.8Hz, 1H). $^{13}C\{H\}$ NMR ($CDCl_3$, 150 MHz) δ 164.2, 141.1, 140.2, 137.6, 132.8, 129.8, 129.5, 129.3, 129.2, 124.0, 123.9, 63.7, 57.0, 53.5. IR (neat, cm^{-1}): 3088, 2926, 2854, 2360, 1717, 1472, 1319, 1154, 1088, 759, 737, 555, 524. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{14}ClNO_4S$ 352.0406, Found: 352.0405.

3-(((4-bromophenyl)sulfonyl)methyl)-2-methoxyisoindolin-1-one 3r. Light yellow solid (40.4mg, 51%). mp 158-160 ℃. ^1H NMR ($CDCl_3$, 600 MHz) δ 7.82 (d, *J* = 8.4Hz, 3H), 7.76-7.74 (m, 3H), 7.62 (t, *J* = 7.8Hz, 1H), 7.52 (t, *J* = 7.8Hz, 1H), 5.25 (dd, *J* = 7.2Hz, *J* = 2.4Hz, 1H), 3.87 (d, *J* = 3.0Hz, 1H), 3.85 (s, 3H), 3.41 (dd, *J* = 9.0Hz, *J* = 7.2Hz, 1H). $^{13}C\{H\}$ NMR ($CDCl_3$, 150 MHz) δ 164.2, 140.2, 138.2, 132.9, 129.7, 129.5, 129.4, 129.2, 123.9, 123.9, 63.7, 57.0, 53.5. IR (neat, cm^{-1}): 3087, 2934, 2360, 1717, 1574, 1471, 1319, 1154, 1084, 1067, 1009, 753, 551. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{14}BrNO_4S$ 395.9901, Found: 395.9900.

3-(((4-fluorophenyl)sulfonyl)methyl)-2-methoxyisoindolin-1-one 3s. Light yellow

solid (28.2 mg, 42%). mp 135-137 ℃. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.01-7.98 (m, 2H), 7.83 (d, *J* = 7.2Hz, 1H), 7.78 (d, *J* = 7.8Hz, 1H), 7.63 (dt, *J* = 7.8Hz, *J* = 1.2Hz, 1H), 7.53 (t, *J* = 7.2Hz, 1H), 7.29 (t, *J* = 8.4Hz, 2H), 5.26 (dd, *J* = 7.2Hz, *J* = 2.4Hz,, 1H), 3.88(d, *J* = 2.4Hz, 1H), 3.86 (s, 3H), 3.41 (dd, *J* = 14.4Hz, *J* = 7.2Hz, 1H). ^{13}C{H} NMR ($CDCl_3$, 150 MHz) δ 167.0, 165.3, 164.2, 140.3, 135.3, 132.9, 131.0, 131.0, 129.4, 129.2, 124.0, 123.9, 117.0, 116.9, 63.7, 57.1, 53.5. ^{19}F NMR ($CDCl_3$, 564 MHz) δ -102.0. IR (neat, cm^{-1}): 2936, 2360, 2342, 1717, 1590, 1494, 1319, 1149, 1086, 748, 562, 511. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{14}FNO_4S$ 336.0703, Found: 336.0700.

3-(([1,1'-biphenyl]-4-ylsulfonyl)methyl)-2-methoxyisoindolin-1-one 3t. Light yellow liquid (26.0 mg, 33%). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.97 (d, *J* = 8.4Hz, 2H), 7.76 (d, *J* = 7.8Hz, 1H), 7.74-7.73 (m, 3H), 7.57-7.54 (m, 3H), 7.46-7.42 (m, 3H), 7.38 (t, *J* = 7.82Hz, 1H), 5.22 (dd, *J* = 7.2Hz, *J* = 2.4Hz, 1H), 3.85 (dd, *J* = 15.0Hz, *J* = 3.0Hz, 1H), 3.77 (s, 3H), 3.35 (dd, *J* = 14.4Hz, d, *J* = 7.8Hz, 1H). ^{13}C{H} NMR ($CDCl_3$, 150 MHz) δ 164.2, 147.4, 140.6, 138.8, 137.6, 132.9, 129.3, 129.2, 129.2, 128.9, 128.6, 128.2, 127.4, 124.1, 123.9, 63.7, 57.1, 53.5. IR (neat, cm^{-1}): 3056, 2928, 2360, 1717, 1471, 1314, 1150, 1124, 1072, 907, 750, 557. HRMS (ESI-FTICR) *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{20}NO_4S$ 394.1113, Found: 394.1108.

2-methoxy-3-((m-tolylsulfonyl)methyl)isoindolin-1-one 3u. Light yellow solid (40.4 mg, 61%), mp 119-121 ℃. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.76 (d, *J* = 7.8Hz, 1H), 7.72 (d, *J* = 8.4Hz, 3H), 7.55 (dt, *J* = 7.2Hz, d, *J* = 1.2Hz, 1H), 7.46-7.41 (m, 3H), 5.18 (dd, *J* = 7.8Hz, *J* = 3.0Hz, 1H), 3.81 (dd, *J* = 14.4Hz, *J* = 2.4Hz, 1H), 3.75

(s, 3H), 3.29 (dd, J = 15.0Hz, J = 7.8Hz, 1H), 2.40 (s, 3H). $^{13}C\{H\}$ NMR ($CDCl_3$, 150 MHz) δ 164.2, 140.6, 140.0, 139.0, 135.1, 132.9, 129.5, 129.3, 129.2, 128.3, 125.2, 124.1, 123.9, 63.6, 56.9, 53.5, 21.3. IR (neat, cm^{-1}): 2926, 2360, 2342, 1717, 1742, 1457, 1318, 1302, 1145, 747, 685, 518. HRMS (ESI-TLQ) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{17}NO_4S$ 332.0944, Found: 332.0951.

3-(((3-bromophenyl)sulfonyl)methyl)-2-methoxyisoindolin-1-one 3v. Light yellow solid (26.9 mg, 34%). mp 138-139 ℃. ^1H NMR ($CDCl_3$, 600 MHz) δ 8.01 (s, 1H), 7.83 (d, J = 8.4Hz, 1H), 7.76 (d, J = 7.2Hz, 2H), 7.68 (d, J = 7.8Hz, 1H), 7.56 (t, J = 7.8Hz, 1H), 7.47-7.41 (m, 2H), 5.19 (dd, J = 7.2Hz, J = 3.0Hz, 1H), 3.82 (d, J = 3.0Hz, 1H), 3.79 (s, 3H), 3.36 (dd, J = 15.0Hz, J = 7.8Hz, 1H). $^{13}C\{H\}$ NMR ($CDCl_3$, 150 MHz) δ 164.2, 141.0, 140.2, 137.4, 132.9, 131.1, 131.0, 129.5, 129.2, 126.5, 124.0, 123.6, 63.7, 57.0, 53.4. IR (neat, cm^{-1}): 2925, 2854, 2360, 1717, 1471, 1458, 1319, 1295, 1153, 736, 678, 525. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{14}BrNO_4S$ 395.9901, Found: 395.9900.

3-(((3-fluorophenyl)sulfonyl)methyl)-2-methoxyisoindolin-1-one 3w. Light yellow solid (31.5 mg, 47%). mp 123-125 ℃. ^1H NMR ($CDCl_3$, 600 MHz) δ 7.75 (d, J = 7.8Hz, 1H), 7.69 (t, J = 7.8Hz, 2H), 7.60-7.59 (m, 1H), 7.56-7.52 (m, 2H), 7.45 (t, J = 7.8Hz, 1H), 7.34 (dt, J = 7.8Hz, J = 2.4Hz, 1H), 5.19 (dd, J = 7.2Hz, J = 3.0Hz, 1H), 3.81 (dd, J = 15.0Hz, J = 3.0Hz, 1H), 3.78 (s, 3H), 3.35 (dd, J = 14.4Hz, J = 7.2Hz, 1H). $^{13}C\{H\}$ NMR ($CDCl_3$, 150 MHz) δ 164.2, 163.4, 161.7, 141.2, 141.2, 140.2, 132.9, 131.5, 131.5,129.4, 129.2, 124.0, 123.9, 123.8, 123.8, 121.7, 121.5, 115.5, 115.3, 63.7, 56.9, 53.4. ^{19}F NMR ($CDCl_3$, 564 MHz) δ -108.2. IR (neat, cm^{-1}): 3074,

2926, 2360, 1717, 1472, 1436, 1322, 1305, 1225, 1131, 747, 678, 529. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{14}FNO_4S$ 336.0703, Found: 336.0700.

3-((mesitylsulfonyl)methyl)-2-methoxyisoindolin-1-one 3x. Light yellow solid (14.4 mg, 20%). mp 116-118 ℃. ^1H NMR ($CDCl_3$, 600 MHz) δ 7.86 (dd, *J* = 18.0Hz, *J* = 7.8Hz, 2H), 7.64 (dt, *J* = 7.8Hz, *J* = 0.6Hz 1H), 7.53-7.51 (m, 1H), 7.01 (s, 2H), 5.33 (dd, *J* = 7.8Hz, *J* = 2.4Hz, 1H), 3.93 (t, *J* = 3.0Hz, 1H), 3.86 (s, 3H), 3.31 (dd, *J* = 14.4Hz, *J* = 7.8Hz, 1H), 2.71 (s, 6H), 2.33 (s, 3H). $^{13}C\{H\}$ NMR ($CDCl_3$, 150 MHz) δ 164.1, 144.1, 141.1, 140.0, 132.9, 132.9, 132.5, 129.2, 129.1, 124.1, 123.9, 63.6, 56.5, 52.9, 22.9, 21.0. IR (neat, cm^{-1}): 2925, 2854, 2360, 1717, 1558, 1457, 1313, 1148, 748, 646, 578, 517. HRMS (ESI-TLQ) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{21}NO_4S$ 360.1256, Found: 360.1264.

2-methoxy-3-((naphthalen-2-ylsulfonyl)methyl)isoindolin-1-one 3y. Light yellow solid (17.6 mg, 24%). mp 127-128 ℃.^1H NMR ($CDCl_3$, 600 MHz) δ 8.6 (s, 1H), 8.06 (d, *J* = 9.0Hz, 1H), 8.01 (d, *J* = 8.4Hz, 1H), 7.96 (d, *J* = 8.4Hz, 1H), 7.93 (dd, *J* = 8.4Hz, *J* = 1.8Hz, 1H), 7.82 (d, *J* = 7.8Hz, 2H), 7.72 (t, *J* = 7.8Hz, 1H), 7.67 (t, *J* = 7.8Hz, 1H), 7.61 (t, *J* = 7.8Hz, 1H), 7.50 (t, *J* = 7.8Hz, 1H), 5.30 (dd, *J* = 7.2Hz, *J* = 2.4Hz, 1H), 3.97 (dd, *J* = 14.4Hz, *J* = 2.4Hz, 1H), 3.76 (s, 3H), 3.46 (d, *J* = 15.0Hz, *J* = 7.8Hz, 1H). $^{13}C\{H\}$ NMR ($CDCl_3$, 150 MHz) δ 164.2, 140.6, 135.9, 135.5, 132.9, 132.1, 130.1, 130.0, 129.7 129.5, 129.3, 129.2, 18.1, 124.1, 123.9, 122.3, 63.2, 56.9, 53.6. IR (neat, cm^{-1}): 2925, 2360, 2342, 1717, 1558, 1507, 1315, 1150, 1089, 744, 669, 517. HRMS (ESI-TLQ) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{17}NO_4S$ 368.0948, Found: 368.0951.

2-methoxy-3-((methylsulfonyl)methyl)isoindolin-1-one 3z. Light yellow solid (34.2 mg, 67%). mp 121-122 ℃. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.77 (d, *J* = 7.8Hz, 1H), 7.63 (d, *J* = 7.8Hz, 1H), 7.58-755 (m, 1H), 7.46 (t, *J* = 7.8Hz, 1H), 5.27 (d, *J* = 6.0Hz, 1H), 3.92 (s, 3H), 3.67 (dd, *J* = 14.4Hz, *J* = 6.8Hz, 1H), 3.34 (dd, *J* = 13.2Hz, *J* = 6.6Hz, 1H), 3.04 (s, 3H). ^{13}C{H} NMR ($CDCl_3$, 150 MHz) δ 164.1, 140.0, 132.9, 129.4, 129.2, 124.0, 123.7, 63.5, 56.6, 53.4, 42.7. IR (neat, cm^{-1}): 2931, 2360, 2342, 1716, 1471, 1308, 1127, 996, 746, 686, 541, 504. HRMS (ESI-TLQ) *m/z*: $[M+H]^+$ Calcd for $C_{11}H_{13}NO_4S$ 256.0634, Found: 256.0638.

3-((ethylsulfonyl)methyl)-2-methoxyisoindolin-1-one 3aa. Light yellow liquid (28.0 mg, 52%). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.84 (d, *J* = 7.2Hz, 1H), 7.76 (d, *J* = 7.8Hz, 1H), 7.65-7.63 (m, 1H), 7.53 (t, *J* = 7.8Hz, 1H), 5.36 (dd, *J* = 6.6Hz, *J* = 4.2Hz, 1H), 3.99 (s, 3H), 3.72 (dd, *J* = 15.0Hz, *J* = 4.2Hz, 1H), 3.26 (dd, *J* = 15.0Hz, *J* = 7.2Hz, 1H), 3.20 (dd, *J* = 15.0Hz, *J* = 7.8Hz, 2H), 1.46 (t, *J* = 7.8Hz, 3H). ^{13}C{H} NMR ($CDCl_3$, 150 MHz) δ 164.2, 140.4, 132.9, 129.4, 129.2, 124.0, 123.9, 63.6, 53.5, 53.1, 49.2, 6.7. IR (neat, cm^{-1}): 2982, 2940, 2360, 1717, 1471, 1312, 1123, 997, 796, 752, 688, 501. HRMS (ESI-TLQ) *m/z*: $[M+H]^+$ Calcd for $C_{12}H_{15}NO_4S$ 270.0789, Found: 270.0795.

3-((cyclopropylsulfonyl)methyl)-2-methoxyisoindolin-1-one 3ab. Light yellow liquid (31.9mg, 57%). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.85 (d, *J* = 7.8Hz, 1H), 7.77 (d, *J* = 7.8Hz, 1H), 7.63 (td, *J* = 7.8Hz, *J* = 0.6Hz 1H), 7.53 (t, *J* = 7.2Hz, 1H), 5.35 (dd, *J* = 7.2Hz, *J* = 4.2Hz, 1H), 4.01 (s, 3H), 3.83 (dd, *J* = 14.4Hz, *J* = 4.2Hz, 1H), 3.37 (dd, *J* = 14.4Hz, *J* = 7.2Hz, 1H), 2.64-2.60 (m, 1H), 1.41-1.37 (m, 1H), 1.27-1.22 (m,

1H), 1.17-1.08 (m, 2H). $^{13}C\{H\}$ NMR ($CDCl_3$, 150 MHz) δ 164.2, 140.4, 132.8, 129.3, 129.2, 123.9, 123.9, 63.6, 55.1, 53.3, 31.0, 5.30, 5.10. IR (neat, cm^{-1}): 2921, 2850, 2360, 1716, 1653, 1558, 1471, 1318, 1291, 1123, 886, 748, 688. HRMS (ESI-FTICR) *m/z*: $[M+Na]^+$ Calcd for $C_{13}H_{15}NNaO_4S$ 304.0622 Found: 304.0614.

3-((butylsulfonyl)methyl)-2-methoxyisoindolin-1-one 3ac. Light yellow liquid (22.7 mg, 38%). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.85 (d, *J* = 7.6Hz, 1H), 7.76 (dd, *J* = 7.6Hz, *J* = 0.4Hz, 1H), 7.64 (td, *J* = 7.6Hz, *J* = 1.2Hz, 1H), 7.53 (t, *J* = 7.6Hz, 1H), 5.36 (dd, *J* = 6.8Hz, *J* = 4.0Hz, 1H), 3.99 (s, 3H), 3.72 (dd, *J* = 14.4Hz, *J* = 4.4Hz, 1H), 3.27 (dd, *J* = 14.4Hz, *J* = 6.8Hz, 1H), 3.19-3.14 (m, 2H), 1.92-1.83 (m, 2H), 1.56-1.46 (m, 2H), 0.98 (t, *J* = 7.6Hz, 3H). $^{13}C\{H\}$ NMR ($CDCl_3$, 100 MHz) δ 164.1, 140.4, 132.9, 129.4, 129.2, 123.9, 63.6, 54.5, 54.3, 53.0, 23.9, 21.6, 13.5. IR (neat, cm^{-1}): 2961, 2874, 1720, 1469, 1313, 1124, 998, 905, 749, 687, 497. HRMS (ESI-FTICR) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{20}NO_4S$ 298.1104 Found: 298.1108.

Product 4[13a] was prepared according to the literature.

3-(tosylmethyl)isoindolin-1-one 4. white solid (51.2mg, 85%). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.87-7.86 (m, 3H), 7.57 (t, *J* = 5.2Hz, 1H), 7.50 (t, *J* = 7.2Hz, 1H), 7.40 (dd, *J* = 12.8Hz, *J* = 5.2Hz, 3H), 7.09 (s, 1H), 5.08 (d, *J* = 7.2Hz, 1H), 3.68 (dd, *J* = 9.2Hz, *J* = 1.2Hz, 1H), 3.13 (dd, *J* = 9.2Hz, *J* = 7.2Hz, 1H), 2.47 (s, 3H). $^{13}C\{H\}$ NMR ($CDCl_3$, 100 MHz) δ 169.4, 145.7, 144.0, 135.7, 132.2, 131.7, 130.3, 129.1, 128.0, 124.3, 122.3, 60.8, 50.7, 21.6.

The mechanistic study

1. (see reaction 1 in Scheme 3):

The reaction was carried out according to the **Typical procedure for the preparation of product 3a**, except TEMPO (0.4 mmol) was used. The mixture was stirred for 17 h at 70℃. And then diluted with water and extracted with ethyl acetate for 3 times. The combined organic layers were washed with water, saturated brine, dried over Na_2SO_4, concentrated in *vacuo*. **1a** was recovered in 70% yield. Meanwhile, the product **4** was detected by ESI-HRMS measurement of the crude reaction mixture (HRMS (ESI-TLQ) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{28}N_2O_3$ 333.2163, Found: 333.2173).

2. (see reaction 2 in Scheme 3):

The reaction was carried out according to the **Typical procedure for the preparation of product 3a**, except butylated hydroxytoluene (0.4 mmol) was used. The mixture was stirred for 17 h at 70℃. And then diluted with water and extracted with ethyl acetate for 3 times. The combined organic layers were washed with water, saturated brine, dried over Na_2SO_4, concentrated in vacuo and purified by chromatography on silica gel (elute: EtOAc/Petroleum ether 1/5 - 1/3, v/v) to give the desired product **3a** (43%, 28.5 mg). Meanwhile, **5** was obtained in 8% yield (11.7 mg) and **6** was obtained in 18% yield (28 mg). **5**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.52 (d, *J* = 8.4Hz, 2H), 7.19 (d, *J* = 7.8Hz, 2H), 6.64 (s, 2H), 5.23 (s, 1H), 2.37 (s, 3H), 1.81 (s, 3H), 1.10 (s, 18H). **6**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.44 (d, *J* = 8.4Hz, 2H), 7.21 (d, *J* = 8.4Hz, 2H), 6.73 (s, 2H), 5.23 (s, 1H), 4.19 (s, 2H), 2.40 (s, 3H), 1.32 (s, 18H). ^{13}C{H} NMR ($CDCl_3$, 150 MHz) δ 154.2, 144.3, 136.0, 134.9, 129.3, 128.9, 127.6, 118.9, 63.2, 34.1, 30.0, 21.5.

3. (see reaction 3 in Scheme 3):

The reaction was carried out according to the **Typical procedure for the preparation of product 3a**, except 1,1-diphenylethylene (2.0 equiv) was used. The mixture was stirred for 17 h at 70℃. And then diluted with water and extracted with ethyl acetate for 3 times. The combined organic layers were washed with water, saturated brine, dried over Na_2SO_4, concentrated in *vacuo* and purified by chromatography on silica gel (elute: EtOAc/Petroleum ether 1/5 - 1/3, v/v) to give the desired product **3a** (51%, 33.8 mg). And when we detected the crude reaction mixture by ESI-HRMS measurement, we could find the radical coupling product **7** (HRMS (ESI-TLQ) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{18}O_2S$ 335.1094, Found: 335.1100.

SUPPORTING INFORMATION. Copies of the ^1H NMR and ^{13}C NMR spectra for **1c, 1f, 1j, 1k** and all products. Copies of the ^{19}F NMR spectra of **3g**, **3s** and **3w**. This material is available free of charge via the Internet at http://pubs.acs.org

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