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Isoindolinones via Copper-Catalyzed Intramolecular Benzylic C–H Sulfamidation

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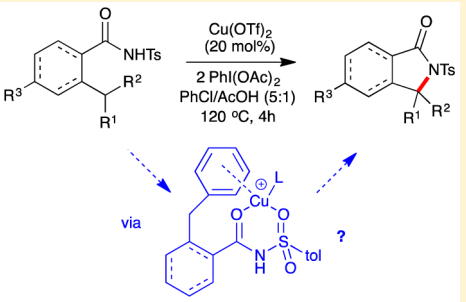
Supporting Information

ABSTRACT: 2-Benzyl-*N*-tosylbenzamides and related substrates undergo copper-catalyzed intramolecular sulfamidation at the benzylic methylene to give *N*-arylsuflonyl-1-arylisoindolinones, which can be N-deprotected using samarium iodide to generate the free 1-arylisoindolinones. Preliminary mechanistic studies indicate that the rate-determining step is not C–H bond cleavage but are instead consistent with slow oxidation of a copper π-arene intermediate.



INTRODUCTION

The isoindolinone core is a privileged structure with examples showing a range of biological functions and medicinal applications.[1] For instance, pazinaclone (Figure 1) has demonstrated anxiolytic properties,[2] **1** is a dopamine receptor antagonist,[3] **2** shows antiretroviral activity,[4] lenalidomide is used in the treatment of multiple myeloma,[5] while pestalachloride A, isolated from the fungus *Pestalotiopsis adusta*, is reported to have significant antimicrobial activity.[6]

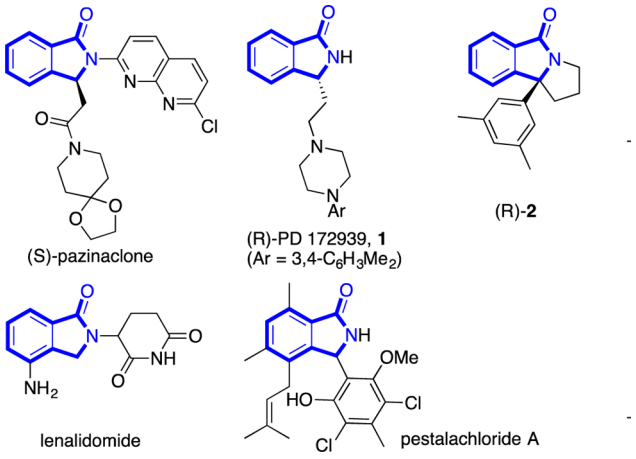


Figure 1. Examples of biologically active isoindolinones.

Catalytic intramolecular sp^3–C-H amidation represents an excellent approach to the synthesis of *N*-heterocycles,[7] and inspired by recent reports of catalytic benzylic C–H amination,[8,9] we wondered whether such an approach could be applied to the synthesis of *N*-sufonyl isoindolinones via C–H sulfamidation. Such sulfamidation routes would be preferable to recently reported catalyzed or catalyst-free amidation reactions with *N*-aryl substrates,[10,11] as the products should undergo comparatively facile N-deprotection to yield the free isoindolinones.

RESULTS AND DISCUSSION

In the first instance, we undertook an optimization study, examining the copper-catalyzed[12] cyclization of substrate **3a**, which could be easily prepared in one step from benzylbenzoic acid and *p*-toluenesulfonyl isocyanate, to the isoindolinone **4a**, and the results from this study are summarized in Table 1.

In the absence of catalyst, no conversion to the desired product was observed under air, using four equivalents of phenyliodonium diacetate as the oxidant and 1,2-dichloroethane (DCE) as the solvent (entry 1). Adding a high loading of copper(II) triflate (50 mol %, entry 2) led to a reasonable amount of the desired product; however, the reaction was clearly not catalytic. Repeating the reaction under inert conditions or under O_2 proved deleterious (entries 3 and 4). Replacing $PhI(OAc)_2$ with either hydroxy(tosyloxy)-iodobenzene (HTIB) or $PhI(O_2CCF_3)_2$ (PIFA) shut down the reaction (entries 5 and 6). While the use of neat acetic acid as solvent was deleterious (entry 7), the use of acetic acid in chlorinated solvents proved beneficial (entries 8–10), with the best activity obtained using chlorobenzene. With this solvent system, both the amount of oxidant (2 equiv) and the catalyst loading (20 mol %) could be reduced, to give the optimum conditions indicated in entry 12. Reducing the catalyst loading further proved to be detrimental, as did either replacing acetic acid with trifluoroacetic acid (entry 14) or changing the temperature (entries 15 and 16).

With optimized conditions in hand, we next briefly explored the range of substrates that undergo the intramolecular

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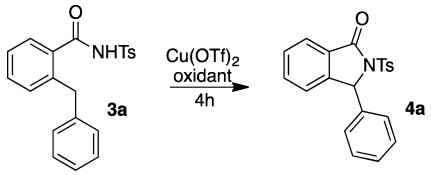
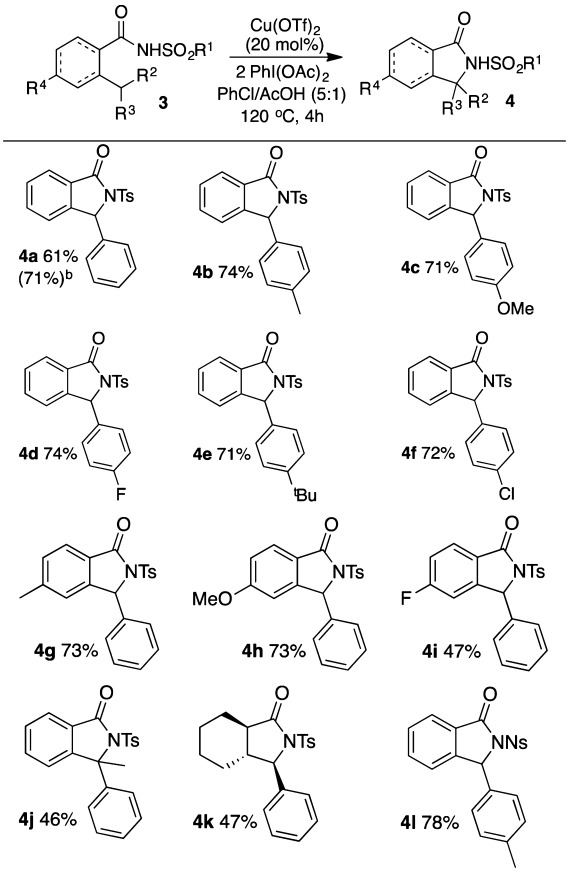
Table 1. Optimization of the Reaction Conditions



entry	$Cu(OTf)_2$ loading (mol %)	oxidant (equiv)	solvent (v/v)	temp (°C)	yield 4a[a] (%)
1	0	$PhI(OAc)_2$ (4)	DCE	120	0
2	50	"	"	"	41
3[b]	"	"	"	"	12
4[c]	"	"	"	"	21
5	"	HTIB (4)	"	"	0
6	"	PIFA (4)	"	"	0
7	"	$PhI(OAc)_2$ (4)	AcOH	"	9
8	"	"	DCE/AcOH (5:1)	"	51
9	"	"	$CHCl_3$/AcOH (5:1)	"	43
10	"	"	PhCl/AcOH (5:1)	"	60
11	"	$PhI(OAc)_2$ (2)	"	"	58
12	***20***	"	"	"	***71***
13	10	"	"	"	20
14	20	"	PhCl/TFA (5:1)	"	0
15	"	"	PhCl/AcOH (5:1)	140	48
16	"	"	"	100	15

[a]Spectroscopic yield determined by ^1H NMR (1,3,5-$C_6H_3(OMe)_3$ internal standard). [b]Under N_2. [c]Under O_2

Table 2. Successful C−H Sulfamidation Reactions[a]



[a]Isolated yields. [b]Spectroscopic yield determined by ^1H NMR (1,3,5-$C_6H_3(OMe)_3$ internal standard).

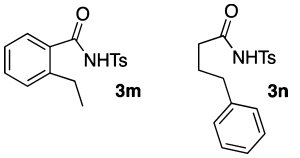
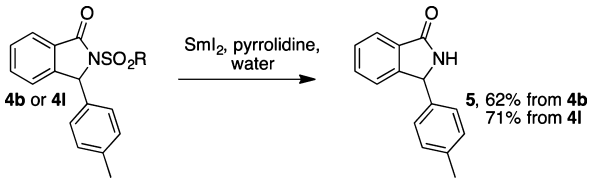


Figure 2. Substrates that failed to cyclize.

Scheme 1. Deprotection of *N*-Sulfonyl Isoindolinones



sulfamidation reaction. The successful results are summarized in Table 2, while the substrates that failed to cyclize are shown in Figure 2.

Diarylmethane-based substrates with electron-withdrawing and -donating groups on either of the aryl rings underwent the desired reaction to generate the isoindolinones **4a−4i**. Interestingly, C−H functionalization at a tertiary carbon center was also achieved, yielding the product **4j** in moderate yield. In contrast with Kondo's related amidation reactions with *N*-aryl precursors,[10] the sulfamidation reaction fails for the substrate **3m**. While it is tempting to conclude from this that two aryl groups are required at the benzylic center for electronic reasons, this is clearly not the case in the formation of the **4k**. Instead, it appears that a "pro-exocyclic" arene substituent is required for activity. In addition to the requirement for a pro-exocyclic arene, it appears that the benzylic site of C−H functionalization must be incorporated into a structurally rigid framework. Thus, while **4k** is formed, no cyclization is observed with the conformationally flexible substrate **4n**, suggesting that the transition state for C−H activation requires a sulfonamide-coordinated copper complex to be held in close proximity to the reactive center.

The formation of **4l** demonstrates that the reaction can be extended to sulfamidation with the *p*-nosyl function. Importantly, both **4l** and the related tosyl-containing **4b** undergo "instantaneous" samarium-mediated deprotection[13] to yield the free NH-isoindolinone, **5** (Scheme 1).

In order to gain further mechanistic insight, we followed the formation of the products **4a−f** against time from their precursors **3a−f**, and the results of this study are summarized in Figure 3. It is immediately apparent that the reaction is favored by electron-donating groups on the pro-exocyclic arene, with the *p*-anisyl-based substrate **3c** giving by far the highest rate, with maximum conversion obtained prior to the first sampling point. Furthermore, the reactions with all the other substrates examined show pronounced induction periods of around 5−10 min before the onset of catalytic activity. Whatever the catalyst activation process is, it is clear that it is substrate-dependent.

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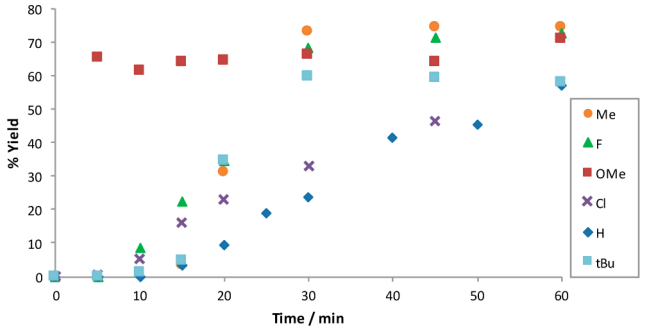


Figure 3. Formation of **4a–f** over time. Spectroscopic yields determined by ^{1}H NMR (1,3,5-$C_6H_3(OMe)_3$ internal standard).

The role of the electronics of the pro-exocyclic ring on the rate-determining step of the reaction was probed by a Hammett analysis of the reactions (Figure 4) based on the observed

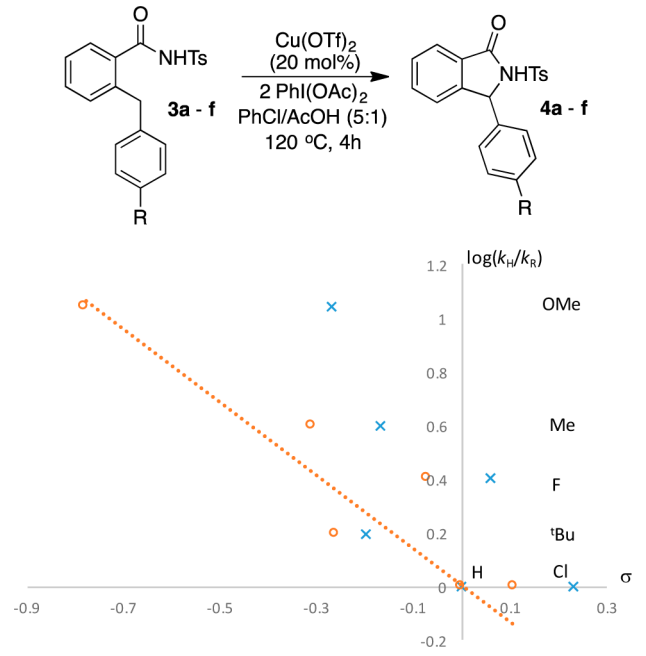
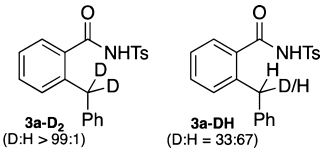


Figure 4. Hammett correlation of maximum rate against both σ (blue ×) and σ^+ (red circle) values.

maximum rates. The plot against σ gave a poor correlation, while that against σ^+ gave a moderate R^2 of 0.79 and $\rho \approx -1.4$.[14] This suggests that the rate-determining step involves loss of electron density.[15]

In order to determine whether C–H bond-cleavage features in the rate-limiting step in the catalytic cycle, we undertook a variety of kinetic isotope effect studies. Subjecting **3a** and its dideuterated analogue **3a-D$_2$** to cyclization under identical conditions gave the same rate of formation of the products **4a** and **4a-D** (k_H = 0.062 mM/min; k_D = 0.063 mM/min).[16] Similarly, a competition reaction, containing equal amounts of **3a** and **3a-D$_2$**, quenched at approximately 30% conversion, gave a product mixture containing equal amounts of **4a** and **4a-D**. The lack of a kinetic isotope effect in both cases indicates that C–H bond-cleavage is not involved in the rate-determining step.[17] By contrast, subjecting the 2:1 mixture of the deuterium-enriched substrate **3a-HD** and **3a** to the standard reaction gave a 3:2 ratio of **4a** and **4a-D**, which corresponds to a KIE of 1.5. These KIE data are consistent with the rate-determining step involving substrate interaction with the copper and occurring prior to the C–H functionalization step.[17] Consistent with this suggestion is the observation that the relative rate data above shows a strong influence of the electronics of the exocyclic arene on the rate of catalysis.



Any mechanistic proposal must address the following observations: (i) A pro-exocyclic aryl group is essential for activity; (ii) the sulfonamide and benzyl functions must be held proximate within a stereochemically rigid framework; (iii) the rate-determining step is accelerated by increasing electron-density on the pro-exocyclic aryl ring but does not involve C–H cleavage and likely occurs before C–H activation; and (iv) the high sensitivity of the reaction to the precise nature of the oxidant.

One possible explanation that can satisfy all of these criteria is the involvement of an η^n-arene-coordinated copper intermediate of the type **I** (Figure 5), which undergoes slow

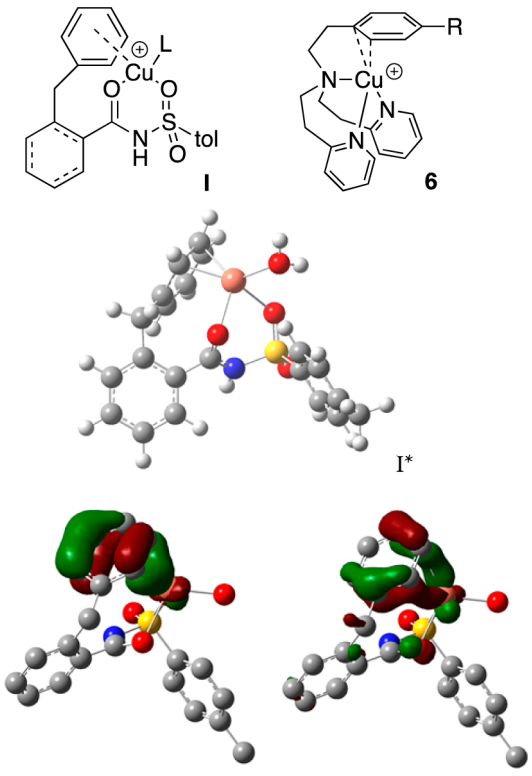


Figure 5. Top: Putative generalized Cu-arene intermediates, **I**, and the previously reported Cu(I) η^2-arene complex, **6**.[19e] Middle: DFT computational model, **I*** (B3LYP-D3BJ/6-311+G(p,d). Bottom: HOMO–10 (left) and HOMO–9 (right); hydrogens are omitted for clarity; isovalue = 0.05 (electron/bohr^3)$^{1/2}$.

oxidation, facilitated by increasing electron-density on the aryl ring. It has been suggested that a copper(I)/(III) manifold is active in many C–H functionalization processes,[18] in which case **I** would contain Cu(I). While we do not have direct evidence for such a species at present, stable Cu(I) arene π-complexes with η^1-, η^2- and even η^6-arene interactions are known.[19] Meanwhile, a DFT examination of a model of **I**, **I*** (L

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= H_2O; phenylene backbone)[16] returned a plausible ground-state structure with an η^2-arene interaction (Figure 5).

The calculated Cu−C distances of 2.15 and 2.25 Å are comparable with the bond metrics associated with previously reported, structurally characterized Cu(I) arene complexes, **6**.[19e] The DFT analysis suggests that the bonding interaction between the η^2-arene function and the copper center has both σ and π-symmetry components. Interestingly, Fukuzumi and Itoh showed that both the redox potential and the rate of oxidation of the complexes **6** are strongly dependent on the electronic properties of the substituted arene, with more facile oxidation occurring with inductive substituents.[19e] In the reaction of **6** with oxygen, the oxidation rate increases with decreasing Cu-arene stability, which is in turn associated with a less electron-rich arene, suggesting that formation of the bridging peroxo LCu-O_2−CuL occurs after arene dissociation.[19e] In contrast, our data indicate an increased rate of reaction with more electron-rich arenes suggesting that the oxidation of the copper occurs prior to arene decoordination, consistent with Fukuzumi and Itoh's electrochemical oxidations.[19e] With regard to the subsequent C−H activation step, this may well occur by a radical pathway as evidenced by the suppression of cyclization of **3a** in the presence of two equivalents of TEMPO and the recovery of >95% of the starting material.

CONCLUSION

In summary, we have developed the copper-catalyzed synthesis of isoindolinones via a tolylsulfonamide- or nosylsulfonamide-directed C−H functionalization, a process in which the sulfonamide acts as both the directing group and the functionalizing reagent. Subsequent samarium-mediated removal of the sulfonyl function leads to the free isoindolinone. The substrate scope of the reaction and the results from preliminary mechanistic and computational studies point to the possible involvement of arene π-coordination in the rate-determining step of the reaction, which may well be oxidation of the copper center. We are currently probing this putative mechanism more deeply with a view to exploiting it in novel catalytic processes, and the results of these studies will be presented in due course.

EXPERIMENTAL SECTION

General Experimental Information. Reagents were used as supplied from commercial sources. Anhydrous THF was obtained from a purification column composed of activated alumina and subsequently stored under nitrogen. All other anhydrous solvents were prepared by drying the corresponding reagent grade solvent over molecular sieves. Mass spectrometry was carried out with a MicrOTOF II spectrometer (Electrospray (ESI), with a time-of-flight (TOF) analyzer type.

General Procedure for the Preparation of Substrates, 3. Following a reported procedure,[20] *p*-toluenesulfonyl isocyanate (592 mg, 3 mmol) was added to a solution of the appropriate 2-benzylbenzoic acid (1 equiv) in THF (0.5 M solution) and stirred at room temperature for 10 min. Triethylamine (306 mg, 3 mmol) was added dropwise to the solution with evolution of gas, and the reaction progress was monitored using an oil bubbler. Upon completion of the reaction (typically 3 h), ethyl acetate and aqueous HCl (2M) were added to the mixture. The organic phase was washed with brine and dried over $MgSO_4$. The volatiles were removed under reduced pressure, and the resulting solid was purified by recrystallization from ethyl acetate/petroleum ether (60/80) (1:4) to give the pure product.

*2-Benzyl-N-tosylbenzamide (**3a**).* White solid (0.90 g, 82%). The spectroscopic data are in agreement with the literature,[21] mp 156−157 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 4.05 (s, 2H), 6.90−6.99 (m, 2H), 7.08−7.27 (m, 5H), 7.27−7.46 (m, 4H), 7.93 (d, J = 8.0 Hz, 2H), 8.44 (s, 1H, NH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.8, 38.4, 126.2, 126.6, 127.7, 128.5, 128.6, 128.8, 129.6, 131.6, 131.9, 132.5, 135.5, 140.1, 140.6, 145.1, 166.3. IR: 3066, 2862, 1672, 1575, 1594, 1493, 1440, 1351, 1255. IR (neat, cm^{-1}): 3065, 2861, 1672, 1594, 1574, 1493, 1439, 1351, 1255, 1167; 1075.72. HRMS (ESI): calcd for $C_{21}H_{20}NO_3S$ [(M + H)$^+$], 366.1158; found, 366.1164.

*2-(4-Methylbenzyl)-N-tosylbenzamide (**3b**).* White solid (0.95 g, 83%), mp 116−117 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 3H), 2.46 (s, 3H), 4.02 (s, 2H), 6.85 (d, J = 7.8 Hz, 2H), 6.96 (d, J = 7.7 Hz, 2H), 7.18−7.25 (m, 2H), 7.30−7.46 (m, 4H), 7.96 (d, J = 8.2 Hz, 2H), 8.51 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.0, 21.7, 37.9, 126.4, 127.7, 128.5, 128.6, 129.2, 129.5, 131.4, 131.8, 132.4, 135.4, 135.6, 136.9, 140.7, 145.0, 166.3. IR (neat, cm^{-1}): 3350, 3258, 1669, 1597, 1488, 1305, 1153, 1093, 900. HRMS (ESI): calcd for $C_{22}H_{22}NO_3S$ [(M + H)$^+$], 380.1315; found, 380.1316.

*2-(4-Methoxybenzyl)-N-tosylbenzamide (**3c**).* White solid (1.07 g, 91%), mp 136−137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47 (s, 3H), 3.76 (s, 3H), 4.01 (s, 2H), 6.66−6.72 (m, 2H), 6.85−6.91 (m, 2H), 7.20−7.24 (m, 1H), 7.26 (s, 1H), 7.29−7.45 (m, 4H), 7.95−8.00 (m, 2H), 8.11 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.8, 37.6, 55.3, 114.0, 126.6, 127.8, 128.6, 129.6, 129.8, 131.5, 131.9, 132.2, 132.5, 135.6, 141.1, 145.2, 158.0, 166.4. IR (neat, cm^{-1}): 3354, 3259, 3067, 2836, 1665, 1597, 1573, 1508, 1443, 1355, 1242, 1170. HRMS (ESI): calcd for $C_{22}H_{22}NO_4S$ [(M + H)$^+$], 396.1264; found, 396.1257.

*2-(4-Fluorobenzyl)-N-tosylbenzamide (**3d**).* White solid (0.96 g, 84%), mp 119−120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47 (s, 3H), 4.05 (s, 2H), 6.72−6.81 (m, 2H), 6.85−6.92 (m, 2H), 7.16−7.25 (m, 2H), 7.33 (m, 2H), 7.38 (m, 1H), 7.46 (m, 1H), 7.87−7.96 (m, 2H), 8.75 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.8, 37.8, 115.2 (d, J = 21.3 Hz, CHCF), 126.8, 127.9, 128.6, 129.7, 130.2 (d, J = 7.8 Hz, CHCHCF), 131.6, 132.1, 135.5, 135.9 (d, J = 3.1 Hz, CF), 140.8, 145.31, 160.2, 162.6, 166.3. ^{19}F NMR (377 MHz, $CDCl_3$) δ −116.8. IR (neat, cm^{-1}): 3248, 3102, 2856, 1677, 1597, 1575, 1506, 1412, 1345, 1220, 1188, 1165, 1062. HRMS (ESI): calcd for $C_{21}H_{19}FNO_3S$ [(M + H)$^+$], 384.1064; found, 384.1068.

*2-(4-(tert-Butyl)benzyl)-N-tosylbenzamide (**3e**).* White solid (1.12 g, 89%), mp 150−151 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (s, 9H), 2.47 (s, 3H), 4.03 (s, 2H), 6.91 (d, J = 8.1 Hz, 2H), 7.15−7.25 (m, 4H), 7.32−7.46 (m, 4H), 7.99 (d, J = 8.2 Hz, 2H), 8.45 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.8, 31.5, 34.4, 37.9, 125.6, 126.6, 127.8, 128.5, 128.7, 129.7, 131.5, 131.9, 132.6, 135.7, 137.1, 140.9, 145.2, 149.2, 166.5. IR (neat, cm^{-1}): 3258, 2960, 1702, 1594, 1513, 1409, 1345, 1162, 1042, 660. HRMS (ESI): calcd for $C_{25}H_{28}NO_3S$ [(M + H)$^+$], 422.1784; found, 422.1792.

*2-(4-Chlorobenzyl)-N-tosylbenzamide (**3f**).* White solid (0.63 g, 52%), mp 111−112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47 (s, 3H), 4.04 (s, 2H), 6.80−6.86 (m, 2H), 6.99−7.05 (m, 2H), 7.19 (d, J = 7.7 Hz, 1H), 7.22−7.29 (m, 1H), 7.33 (d, J = 8.1 Hz, 2H), 7.36−7.43 (m, 1H), 7.45 (dd, J = 7.6, 1.4 Hz, 1H), 7.87−7.93 (m, 2H), 8.44−8.54 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.9, 37.9, 127.0, 127.9, 128.5, 128.6, 129.7, 130.2, 131.8, 132.0, 132.2, 132.4, 135.5, 138.7, 140.6, 145.3, 166.2. IR (neat, cm^{-1}): 3068, 2868, 1672, 1597, 1573, 1436, 1357, 1254, 1169, 1088, 1069. HRMS (ESI): calcd for $C_{21}H_{19}ClNO_3S$ [(M + H)$^+$], 400.0769; found, 400.0779.

*2-Benzyl-4-methyl-N-tosylbenzamide (**3g**).* White solid (0.83 g, 73%), mp 126−127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 3H), 2.45 (s, 3H), 4.04 (s, 2H), 6.93−7.01 (m, 2H), 7.07 (d, J = 7.8 Hz, 1H), 7.16 (m, 4H), 7.28−7.35 (m, 3H), 7.95 (m, 2H), 8.97 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 20.7, 21.7, 37.9, 126.0, 128.4, 128.4, 128.47, 128.7, 129.6, 131.4, 132.1, 132.6, 135.5, 136.3, 137.6, 140.4, 145.0, 166.7. IR (neat, cm^{-1}): 3188, 2920, 1695, 1672, 1595, 1490, 1429, 1341, 1294, 1167, 1062. HRMS (ESI): calcd for $C_{22}H_{22}NO_3S$ [(M + H)$^+$], 380.1315; found, 380.1312.

*2-Benzyl-4-methoxy-N-tosylbenzamide (**3h**).* White solid (0.78 g, 66%), mp 147−148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45 (s, 3H), 3.74 (s, 3H), 4.10 (s, 2H), 6.66−6.73 (m, 2H), 6.93−7.00 (m, 2H), 7.09−7.18 (m, 3H), 7.31 (d, J = 8.1 Hz, 2H), 7.47 (d, J = 8.3 Hz, 1H), 7.94 (d, J = 8.4 Hz, 2H), 8.71 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.8, 38.7, 55.4, 111.1, 117.6, 124.2, 126.2, 128.5, 128.53, 128.9, 129.6,

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130.3, 135.7, 140.1, 143.9, 144.9, 162.3, 166.0. IR (neat, cm^{-1}): 3208, 3028, 2927, 2857, 1692, 1594, 1492, 1449, 1422, 1345, 1235, 1171. HRMS (ESI): calcd for $C_{22}H_{22}NO_4S$ $[(M + H)^+]$, 396.1264; found, 396.1263.

*2-Benzyl-4-fluoro-N-tosylbenzamide (**3i**).* White solid (0.85 g, 74%), mp 137−138 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.45 (s, 3H), 4.05 (s, 2H), 6.81−6.93 (m, 2H), 6.93−7.01 (m, 2H), 7.12−7.21 (m, 3H), 7.32 (d, J = 8.1 Hz, 2H), 7.44−7.51 (m, 1H), 7.89−7.97 (m, 2H), 8.80 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.7, 38.3, 113.5 (d, J = 21.8 Hz), 118.3 (d, J = 22.0 Hz), 126.5, 128.4 (d, J = 3.2 Hz), 128.5, 128.6, 128.8, 129.6, 130.2 (d, J = 9.3 Hz), 135.3, 139.2, 144.5 (d, J = 8.1 Hz), 145.2, 163.1, 165.6; ^{19}F NMR (283 MHz, $CDCl_3$) δ −106.2. IR (neat, cm^{-1}): 3105, 1674, 1597, 1581, 1454, 1439, 1358, 1237, 1175. HRMS (ESI): calcd for $C_{21}H_{19}FNO_3S$ $[(M + H)^+]$, 384.1064; found, 384.1058.

*2-(1-Phenylethyl)-N-tosylbenzamide (**3j**).* White solid (0.69 g, 61%), mp 132−133 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.51 (d, J = 7.2 Hz, 3H), 2.46 (s, 3H), 4.56 (q, J = 7.2 Hz, 1H), 6.97−7.05 (m, 2H), 7.08−7.23 (m, 4H), 7.28−7.44 (m, 5H), 7.92−8.00 (m, 2H), 8.33 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.9, 22.0, 39.8, 126.3, 126.3, 127.3, 127.7, 128.4, 128.5, 128.7, 129.7, 131.8, 132.9, 135.6, 145.3, 145.3, 145.5, 166.8. IR (neat, cm^{-1}): 3223, 3020, 2981, 1710, 1596, 1574, 1403, 1341, 1230, 1164. HRMS (ESI): calcd for $C_{22}H_{22}NO_3S$ $[(M + H)^+]$, 380.1315; found, 380.1295.

*(1R,2S)-2-Benzyl-N-tosylcyclohexanecarboxamide (**3k**).* White solid (0.89 g, 80%), mp 107−108 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 0.82 (q, J = 11.5, 10.9 Hz, 1H), 0.94−1.23 (m, 2H), 1.31−1.45 (m, 1H), 1.50−1.65 (m, 2H), 1.64−1.90 (m, 3H), 1.90−2.14 (m, 2H), 2.39 (s, 3H), 2.50 (dd, J = 13.1, 2.6 Hz, 1H), 6.88−7.00 (m, 2H), 7.11−7.23 (m, 3H), 7.28−7.35 (m, 2H), 8.00 (d, J = 8.3 Hz, 2H), 8.98 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.8, 25.3, 25.4, 30.1, 30.2, 40.8 (2C), 51.7, 126.0, 128.2, 128.5, 129.4, 129.8, 135.7, 139.7, 145.3, 174.1. IR (neat, cm^{-1}): 3185, 2933, 2857, 1677, 1597, 1493, 1448, 1353, 1173, 1133, 1086. HRMS (ESI): calcd for $C_{21}H_{26}NO_3S$ $[(M + H)^+]$, 372.1628; found, 372.1624.

Procedure for the Synthesis of 2-(4-Methylbenzyl)-*N*-nosylbenzamide (3l). Following a reported procedure,[22] to a suspension of EDCI·HCl (0.11 g, 0.52 mmol) in CH_2Cl_2 (5 mL) was added DMAP (0.12 g, 1.05 mmol), and the mixture was stirred at room temperature for 15 min or until the solids dissolved. Then, the reaction was cooled to 0 °C and was added to 2-(4-methylbenzyl)-benzoic acid (0.1 g, 0.44 mmol) followed by *p*-nitrobenzenesulfonamide (0.12 g, 0.59 mmol), and the mixture was stirred for 24 h at room temperature. Diethyl ether was added, and the organic mixture was washed with aqueous HCl (2M). The aqueous layer was extracted with EtOAc, and the organic layers were combined, washed with brine, and dried over Na_2SO_4. The volatiles were removed under reduced pressure, and the resulting solid was purified by column chromatography using an EtOAc/hexane (5:5) mix as eluent to yield the pure product. White solid (0.14 g, 79%), mp 167−168 °C; ^1H NMR (500 MHz, $(CD_3)_2CO$) δ 2.20 (s, 3H), 4.04 (s, 2H), 6.77 (d, J = 7.9 Hz, 2H), 6.87 (d, J = 7.9 Hz, 2H), 7.32−7.27 (m, 2H), 7.46 (t, J = 7.8 Hz, 1H), 7.63 (d, J = 7.6 Hz, 1H), 8.26 (d, J = 9.3 Hz, 2H), 8.40 (d, J = 7.9 Hz, 2H); ^{13}C NMR (500 MHz, $(CD_3)_2CO$) δ 19.9, 37.3, 124.0, 126.1, 127.1, 128.3, 128.5, 128.7, 128.7, 128.9, 129.5, 130.4, 131.2, 131.4, 135.0, 137.5, 140.7. IR (neat, cm^{-1}): 3106, 2924, 1684, 1526, 1426, 1351, 1243, 1181, 1059. HRMS (ESI): calcd for $C_{21}H_{18}N_2O_5S$ $[(M + Na)^+]$, 433.0828; found, 433.0832.

Sulfamidation Optimization Study (Table 1). The optimization study was performed according to the general procedure given below, varied according to the entries in Table 1. The product, **4a**, was not isolated, rather the spectroscopic yield of **4a** was determined by ^1H NMR spectroscopy, using an internal standard (1,3,5-trimethoxybenzene).

General Procedure for the Synthesis of Isoindolinones, 4 (Table 1). The appropriate substrate **3** (0.3 mmol), $Cu(OTf)_2$ (22 mg, 0.06 mmol), and $PhI(OAc)_2$ (193 mg, 0.6 mmol) were added to a Young's tube under atmospheric conditions. Chlorobenzene (5 mL) and acetic acid (1 mL) were added sequentially, and the tube was sealed with a PTFE tap. The reaction vessel was heated to 120 °C and stirred at this temperature for 16 h. After cooling to room temperature, the volatiles were removed under reduced pressure, and the crude product was subjected to column chromatography using an EtOAc/petroleum ether (40−60 °C) 1:3 mix as eluent to yield the pure product.

*3-Phenyl-2-tosylisoindolin-1-one (**4a**).* White solid (66 mg, 61%). The spectroscopic data are in agreement with the literature,[23] mp 173−174 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 3H), 6.22 (s, 1H), 7.05−7.10 (m, 2H), 7.10−7.18 (m, 3H), 7.22−7.35 (m, 3H), 7.43−7.59 (m, 4H), 7.86 (d, J = 7.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.8, 65.8, 123.9, 124.9, 128.2, 128.3, 128.8, 128.9, 129.0, 129.1, 129.3, 134.5, 136.1, 137.1, 144.8, 146.6, 166.6. IR (neat, cm^{-1}): 3066, 1722, 1597, 1493, 1458, 1365, 1285, 1168. HRMS (ESI): calcd for $C_{21}H_{18}NO_3S$ $[(M + H)^+]$, 364.1002; found, 364.1002.

*3-(p-Tolyl)-2-tosylisoindolin-1-one (**4b**).* White solid (86 mg, 74%), mp 185−186 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 3H), 2.36 (s, 3H), 6.19 (s, 1H), 6.94−7.00 (m, 2H), 7.04−7.09 (m, 2H), 7.11−7.18 (m, 4H), 7.42−7.48 (m, 1H), 7.51−7.57 (m, 3H), 7.84 (dd, J = 7.6, 0.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.1, 21.6, 65.4, 123.6, 124.6, 127.9, 128.1, 128.8, 128.8, 129.1, 129.3, 133.9, 134.2, 135.9, 138.5, 144.6, 146.5, 166.4. IR (neat, cm^{-1}): 1730, 1610, 1595, 1468, 1351, 1286, 1168, 1099, 1019. HRMS (ESI): calcd for $C_{22}H_{20}NO_3S$ $[(M + H)^+]$, 378.1158; found, 378.1159.

*3-(4-Methoxyphenyl)-2-tosylisoindolin-1-one (**4c**).* White solid (84 mg, 71%), mp 161−162 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3H), 3.80 (s, 3H), 6.19 (s, 1H), 6.74−6.80 (m, 2H), 6.95−7.02 (m, 2H), 7.11−7.19 (m, 3H), 7.42−7.49 (m, 1H), 7.49−7.59 (m, 3H), 7.84 (dd, J = 7.6, 1.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.7, 55.5, 65.4, 114.1, 123.8, 124.7, 128.2, 128.9, 129.0, 129.0, 129.3, 129.6, 134.4, 136.2, 144.7, 146.8, 160.0, 166.5. IR (neat, cm^{-1}): 2928, 2836, 1728, 1608, 1597, 1510, 1466, 1348, 1248, 1167, 1084. HRMS (ESI): calcd for $C_{22}H_{19}NO_4S$ $[(M + H)^+]$, 394.1108; found, 394.1118.

*3-(4-Fluorophenyl)-2-tosylisoindolin-1-one (**4d**).* White solid (84 mg, 74%), mp 141−142 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.37 (s, 3H), 6.21 (s, 1H), 6.91−6.99 (m, 2H), 7.04−7.10 (m, 2H), 7.12−7.19 (m, 3H), 7.44−7.60 (m, 4H), 7.82−7.91 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.8, 65.0, 115.8 (d, J = 22.4 Hz), 123.8, 125.0, 128.2, 129.0, 129.3, 129.4, 130.0 (d, J = 8.8 Hz), 133.0, 134.6, 136.1, 145.0, 146.3, 162.9 (d, J = 248 Hz), 166.4; ^{19}F NMR (377 MHz, $CDCl_3$) δ −112.5. IR (neat, cm^{-1}): 2922, 2853, 1760, 1719, 1679, 1508, 1287, 1226, 1185, 1168. HRMS (ESI): calcd for $C_{21}H_{16}FNO_3S$ $[(M + H)^+]$, 382.0908; found, 382.0910.

*3-(4-(tert-Butyl)phenyl)-2-tosylisoindolin-1-one, (**4e**).* White solid (89 mg, 71%), mp 230−231 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (s, 9H), 2.34 (s, 3H), 6.20 (s, 1H), 6.93−6.98 (m, 2H), 7.05−7.10 (m, 2H), 7.16−7.21 (m, 1H), 7.21−7.25 (m, 2H), 7.41−7.49 (m, 3H), 7.53−7.58 (m, 1H), 7.87 (d, J = 7.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.7, 31.4, 34.7, 65.5, 123.9, 124.7, 125.6, 128.0, 128.1, 129.0, 129.1, 129.2, 133.7, 134.4, 136.2, 144.6, 146.6, 151.9, 166.5. IR (neat, cm^{-1}): 3668, 2965, 2928, 2863, 1736, 1718, 1594, 1493, 1554, 1358, 1168, 1106, 1085. HRMS (ESI): calcd for $C_{25}H_{26}NO_3S$ $[(M + H)^+]$, 420.1628; found, 420.1625.

*3-(4-Chlorophenyl)-2-tosylisoindolin-1-one (**4f**).* White solid (86 mg, 72%), mp 83−84 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H), 6.18 (s, 1H), 7.00−7.06 (m, 2H), 7.11−7.20 (m, 3H), 7.21−7.26 (m, 2H), 7.45−7.51 (m, 1H), 7.54−7.60 (m, 3H), 7.83−7.88 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.8, 64.9, 123.8, 125.0, 128.2, 128.9, 129.1, 129.4, 129.4, 129.5, 134.6, 134.8, 135.7, 136.0, 145.1, 146.0, 166.4. IR (neat, cm^{-1}): 3092, 2922, 2853, 1734, 1610, 1594, 1491, 1468, 1359, 1288, 1169, 1087. HRMS (ESI): calcd for $C_{21}H_{17}ClNO_3S$ $[(M + H)^+]$, 398.0612; found, 398.0622.

*5-Methyl-3-phenyl-2-tosylisoindolin-1-one (**4g**).* White solid (83 mg, 73%), mp 184−185 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 3H), 2.41 (s, 3H), 6.17 (s, 1H), 7.01−7.10 (m, 3H), 7.13 (d, J = 8.3 Hz, 2H), 7.22−7.26 (m, 2H), 7.28−7.39 (m, 2H), 7.51 (d, J = 8.3 Hz, 2H), 7.65 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.4, 21.7, 65.6, 123.6, 124.8, 128.2, 128.2, 128.7, 128.8, 129.1, 129.3, 135.6, 136.2, 137.3, 139.4, 144.0, 144.8, 166.7. IR (neat, cm^{-1}): 2917, 1720, 1594, 1493, 1362, 1185, 1079. HRMS (ESI): calcd for $C_{22}H_{20}NO_3S$ $[(M + H)^+]$, 378.1158; found, 378.1162.

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*5-Methoxy-3-phenyl-2-tosylisoindolin-1-one (**4h**).* White solid (83 mg, 73%), mp 208−209 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3H), 3.76 (s, 3H), 6.14 (s, 1H), 6.56 (d, J = 2.2 Hz, 1H), 6.97 (dd, J = 8.5, 2.1 Hz, 1H), 7.05−7.16 (m, 4H), 7.22−7.36 (m, 3H), 7.47−7.52 (m, 2H), 7.76 (d, J = 8.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.7, 55.9, 65.4, 107.7, 116.6, 121.4, 126.5, 128.2, 128.2, 128.8, 128.9, 129.3, 136.3, 137.3, 144.7, 149.1, 165.0, 166.2. IR (neat, cm^{-1}): 2942, 1727, 1605, 1490, 1359, 1295, 1244, 1169, 1094, 1080. HRMS (ESI): calcd for $C_{22}H_{20}NO_4S$ [(M + H)$^+$], 394.1108; found, 394.1120.

*5-Fluoro-3-phenyl-2-tosylisoindolin-1-one (**4i**).* White solid (55 mg, 47%), mp 170−171 °C; ^{1}H NMR (400 MHz, $Cdcl_3$) δ 2.36 (s, 3H), 6.18 (s, 1H), 6.80−6.87 (m, 1H), 7.04−7.09 (m, 2H), 7.10−7.19 (m, 3H), 7.24−7.31 (m, 2H), 7.31−7.37 (m, 1H), 7.47−7.52 (m, 2H), 7.82−7.90 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.7, 65.2, 111.1 (d, J = 24.6 Hz), 117.4 (d, J = 24.0 Hz), 125.1, 127.2 (d, J = 10.0 Hz), 128.1, 128.2, 129.0, 129.0, 129.3, 135.9, 136.4, 144.9, 149.0 (d, J = 10.2 Hz), 165.3 (d, J = 255.5 Hz), 168.0; ^{19}F NMR (377 MHz, $CDCl_3$) δ −101.7. IR (neat, cm^{-1}): 3069, 2920, 1718, 1618, 1600, 1483, 1367, 1304, 1261, 1239, 1169. HRMS (ESI): calcd for $C_{21}H_{17}FNO_3S$ [(M + H)$^+$], 382.0908; found, 382.0903.

*3-Methyl-3-phenyl-2-tosylisoindolin-1-one (**4j**).* White solid (52 mg, 46%), mp 71−72 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (s, 3H), 2.40 (s, 3H), 7.05−7.10 (m, 1H), 7.13−7.22 (m, 4H), 7.22−7.34 (m, 3H), 7.39−7.47 (m, 1H), 7.50−7.59 (m, 3H), 7.83 (d, J = 7.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.7, 25.4, 71.7, 122.4, 124.7, 127.1, 127.5, 128.2, 128.6, 128.8, 128.8, 129.1, 134.7, 136.4, 139.7, 144.8, 153.2, 166.8. IR (neat, cm^{-1}): 2921, 2851, 1725, 1611, 1597, 1494, 1466, 1448, 1357, 1289, 1260, 1167. HRMS (ESI): calcd for $C_{22}H_{20}NO_3S$ [(M + H)$^+$], 378.1158; found, 378.1157.

*(3aR,7aR)-3-Phenyl-2-tosyloctahydro-1H-isoindol-1-one (**4k**).* White solid (52 mg, 47%), mp 173−174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15−1.28 (m, 4H), 1.53−1.86 (m, 4H), 1.96−2.19 (m, 2H), 2.41 (s, 3H), 4.72 (d, J = 9.9 Hz, 1H), 7.15 (d, J = 2.3 Hz, 2H), 7.21 (d, J = 8.6 Hz, 2H), 7.27−7.33 (m, 3H), 7.57−7.63 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.8, 25.2, 25.3, 25.4, 27.5, 48.5, 49.6, 69.8, 127.3, 128.3, 128.6, 129.2, 129.3, 136.6, 138.7, 144.6, 175.0. IR (neat, cm^{-1}):2928, 2857, 1736, 1594, 1493, 1454, 1357, 1159, 1106. HRMS (ESI): calcd for $C_{21}H_{24}NO_3S$ [(M + H)$^+$], 370.1471; found, 370.1467.

*3-(p-Tolyl)-2-nosylisoindolin-1-one (**4l**).* White solid (96 mg, 78%), mp 201−202 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ; 2.36 (s, 3H), 6.23 (s, 1H), 6.91 (d, J = 8.3 Hz, 2H), 7.06 (d, J = 7.6 Hz, 2H), 7.19 (dd, J = 7.6, 0.7 Hz, 1H), 7.52 (t, J = 7.5 Hz, 1H), 7.62 (t, J = 8.2 Hz, 1H), 7.77 (d, J = 9.1 Hz, 2H), 7.90 (d, J = 7.9 Hz, 1H), 8.14 (d, J = 9.1 Hz, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 21.1, 65.6, 123.6, 123.8, 124.8, 128.2, 128.3, 129.2, 129.2, 129.4, 133.1, 134.8, 139.2, 144.3, 146.3, 150.3, 166.2. IR (neat, cm^{-1}): 2928, 2857, 1722, 1528, 1384, 1348, 1285, 1176, 1102, 855. HRMS (ESI): calcd for $C_{21}H_{16}N_2O_5S$ [(M + Na)$^+$], 431.067213; found, 431.066711.

Procedure for the Deprotection of *N*-Sulfonyl Isoindolinones. Following a reported procedure,[13] to a solution of SmI_2 (26.4 mL, 0.1 M, 2.64 mmol) in THF was added the protected isoindolinone (**4b** or **4l**) (0.264 mmol), water (142 μL, 7.92 mmol), and pyrrolidine (0.44 mL, 5.28 mmol) under nitrogen atmosphere. The mixture of the reaction was diluted with diethyl ether (20 mL), and a solution of potassium sodium tartrate and potassium carbonate (10% w/v each) was added. The aqueous phase was extracted with diethyl ether, and the organic extract was dried over Na_2SO_4. The volatiles were removed under reduced pressure, and the resulting crude product was dissolved in DCM and purified by ion exchange column (propylsulfonic acid functionalized silica) to yield the pure product. White solid (36 mg, 62%, from **4b**) (42 mg, 71%, from **4l**). The spectroscopic data are in agreement with the literature,[24] mp 179−181 °C; ^{1}H NMR (400 MHz, DMSO) δ 2.29 (s, 3H), 5.69 (s, 1H), 7.18 (s, 4H), 7.29 (dd, J = 0.9, 7.3 Hz, 1H), 7.50 (t, J = 7.8 Hz, 1H), 7.56 (td, J = 1.3, 7.3 Hz, 1H), 7.72 (d, J = 7.1 Hz, 1H), 9.02 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 21.2, 60.7, 123.4, 123.9, 126.8, 128.4, 129.8, 131.7, 132.4, 135.4, 138.5, 148.2, 171.0. IR (neat, cm^{-1}): 3183, 3063, 2859, 1681, 1607, 1510, 1465, 1357, 1299, 1264, 1139, 1022, 951, 849. HRMS (ESI): calcd for $C_{15}H_{13}NO$[(M + Na)$^+$], 246.0889; found, 246.0900.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02970.

Details of deuterium-labeling experiments, copies of NMR spectra, computation methods and data (PDF)

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Notes

The authors declare no competing financial interest.

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in the reaction of the substrates with electron-withdrawing groups. Ignoring these two substrates leads to an improved correlation with σ^+ and σ with R^2 values of 0.91 and 0.64, respectively.
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