JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

Ruthenium-Catalyzed Addition of Aromatic Amides to Internal Alkynes and Subsequent Intramolecular Cyclization for the Atom-Economical Synthesis of Isoindolinones

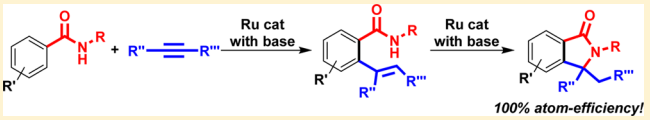
Hiroki Miura,*[,†,‡,§] Sachie Terajima,[†] Kentaro Tsutsui,[†] and Tetsuya Shishido*[,†,‡,§]

[†]Department of Applied Chemistry, Graduate School of Urban Environmental Sciences and [‡]Research Center for Hydrogen Energy-based Society, Tokyo Metropolitan University, 1-1 minami-Osawa, Hachioji, Tokyo 192-0397, Japan

[§]Elements Strategy Initiative for Catalysts and Batteries, Kyoto University, Katsura, Nishikyo-ku, Kyoto 615-8520, Japan

Supporting Information

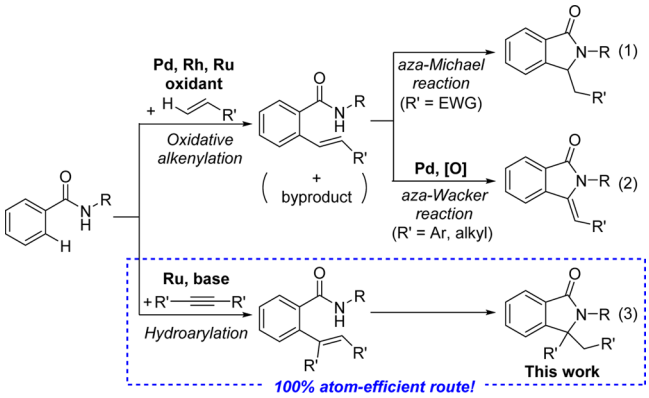
ABSTRACT: A selective and atom-economical synthesis of isoindolinones is described. This novel synthetic strategy involves two catalytic reactions: the ruthenium-catalyzed regioselective alkenylation of aromatic C−H bond of aromatic amides with internal alkynes, and subsequent intramolecular cyclization of the resulting alkene with amide functionalities. The addition of only a catalytic amount of bases is required for efficient construction of the desired isoindolinones, and no byproducts are formed in the tandem catalytic reactions. Various kinds of aromatic amides and internal alkynes can be used in the present reactions, and the corresponding isoindolinones bearing a quaternary carbon at the C3 position are obtained in good to high yields.



INTRODUCTION

Benzo-fused nitrogen-containing heterocycles are ubiquitous in natural products that show a wide range of important bioactivities, and the development of novel synthetic strategies for their rapid and step-economical construction is an important issue for synthetic chemists.[1] Isoindolinones exhibit various important pharmaceutical and biological activities, such as anxiolytic, anti-inflammatory, antifungal, and antibacterial properties.[2] Hence, considerable effort has been devoted to achieve the facile synthesis of isoindolinone moieties.[3] In this regard, the transition-metal-catalyzed oxidative coupling of aromatic amides with alkenes is one of the most practical methods for the preparation of isoindolinones thanks to both the ready availability of the starting substrates and the step-economy of the reaction (Scheme 1). This synthetic strategy using Pd,[4] Rh,[5] Ru,[6] and Co[7] catalysts involves two reactions: the oxidative *ortho*-alkenylation of a C−H bond of aromatic amides with alkenes, and the intramolecular cyclization of an amide with the resulting alkene functionality [aza-Michael or aza-Wacker reaction; eqs 1 and 2 in Scheme 1]. Although these tandem catalytic systems offer many advantages, the addition of stoichiometric or catalytic amount of oxidants, such as $Cu(OAc)_2$ or benzoquinone, or the use of an acidic solvent is required to achieve the catalytic alkenylation of aromatic C−H bonds. Thus, a novel method that can reduce the formation of unwanted byproducts is highly desired. In the course of our studies on C−H bond functionalization,[8] we have demonstrated the Ru-catalyzed coupling reaction of aromatic carboxylic acids with internal alkynes to give isobenzofuranone derivatives with 100% atom-efficiency.[8e] These reactions consist of the hydroarylation of internal alkynes and subsequent intramolecular cyclization, in which the carboxylic functionality serves as both a directing group for C−H bond activation and a nucleophilic reagent for the resulting trisubstituted alkenes.

Scheme 1. Isoindolinone Synthesis *via* Transition-Metal-Catalyzed C−H Alkenylation



Herein, we report a novel method for the synthesis of isoindolinones through the coupling of aromatic amides with internal alkynes in the presence of Ru catalysts together with a catalytic amount of base [eq 3 in Scheme 1]. This reaction provides various isoindolinones bearing a quaternary carbon with 100% atom-efficiency.

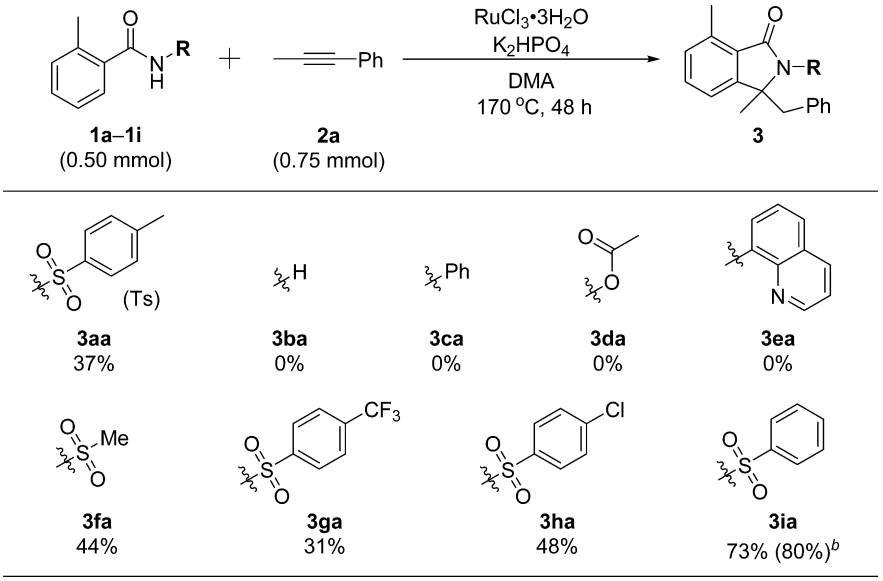
RESULTS AND DISCUSSION

The reaction of *N*-tosyl aromatic amide (**1a**) with an internal alkyne (**2a**) in the presence of $RuCl_3 \cdot 3H_2O$ together with a

Received: October 20, 2016
Published: December 21, 2016

DOI: 10.1021/acs.joc.6b02552
J. Org. Chem. 2017, 82, 1231−1239

Scheme 2. Effect of Substituents at N-Atom of Aromatic Amides

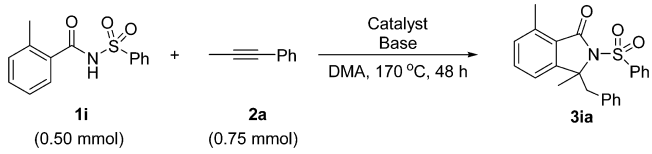


[a]Reaction conditions: **1** (0.50 mmol), **2a** (0.75 mmol), $RuCl_3 \cdot 3H_2O$ (0.050 mmol as Ru), K_2HPO_4 (0.15 mmol), DMA (1.0 mL), at 170 °C, 48 h, under Ar. [b]Reaction for 72 h.

catalytic amount of K_2HPO_4 in DMA at 170 °C for 48 h gave the isoindolinone **3aa** in an isolated yield of 37% (Scheme 2). The reaction proceeded selectively to afford the isoindolinone with a methyl and benzyl group-substituted quaternary carbon at the C3 position. The sulfonyl substituent on the N-atom of the amide plays a crucial role for the smooth conversion of **1a**, and the reaction of aromatic amides bearing H, Ph, or an acetoxy group on the N-atom resulted in no conversion of the substrates. The conversion of *N*-8-quinolyl aromatic amide was observed by GC analysis, and the corresponding isoindolinone was not obtained at all. Next, we sought to identify the optimal sulfonyl substituent group for the present catalytic reactions. Neither (4-(trifluoromethyl)phenyl)sulfonyl-, (4-chlorophenyl)sulfonyl, nor methylsulfonyl groups remarkably increased the product yield. In contrast, the reaction of *N*-benzenesulfonyl aromatic amide gave the corresponding isoindolinone **3ia** in the highest isolated yield of 73%. Furthermore, the yield of **3ia** further increased to 80% when the reaction was allowed to proceed for 72 h.

With the benzenesulfonyl group as an optimal substituent in hand, we next investigated the effects of the catalysts and bases (Table 1). The reactions with $Ru(acac)_3$, $[RuCl_2(p\text{-cymene})]_2$, and $[Cp^*RuCl_2]_2$ also gave the desired product (entries 2–4), albeit the yields of **3ia** were lower than with $RuCl_3 \cdot 3H_2O$ (entry 1). Although we preliminarily reported that ZrO_2-supported Ru (Ru/ZrO_2) catalysts were effective for the coupling of aromatic carboxylic acids with internal alkynes to give isobenzofuranones, the reaction with the Ru/ZrO_2 catalyst resulted in a low yield of **3ia** (entry 5). Other transition-metal chlorides, including $RhCl_3 \cdot 3H_2O$, $PdCl_2$, $PtCl_4 \cdot nH_2O$, $CoCl_2 \cdot 6H_2O$, and $CuCl_2 \cdot 3H_2O$, were totally ineffective for the present catalytic reaction (entries 6–10). The base additives also remarkably affected the reaction efficiency. As shown in entries 11–22 in Table 2, the highest yield of **3ia** was achieved when K_2HPO_4 was used as a base additive, and both stronger inorganic bases, such as K_2CO_3, K_3PO_4, and KO^{t}Bu, and weaker bases, such as K_2HPO_4, KOAc, and $NaHCO_3$, reduced the yield of the product. Although the product yield was

Table 1. Effect of Catalysts and Bases

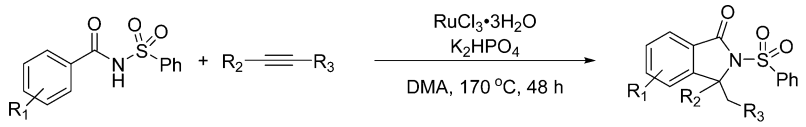


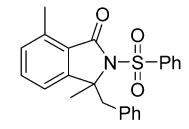
entry	catalyst	additive	yield of **3ia** (%)[b]
1	$RuCl_3 \cdot 3H_2O$	K_2HPO_4	73
2	$Ru(acac)_3$	K_2HPO_4	51
3	$[RuCl_2(p\text{-cymene})]_2$	K_2HPO_4	36
4	$[Cp^*RuCl_2]_2$	K_2HPO_4	9
5	Ru/ZrO_2	K_2HPO_4	29
6	$RhCl_3 \cdot 3H_2O$	K_2HPO_4	0
7	$PdCl_2$	K_2HPO_4	0
8	$PtCl_4 \cdot nH_2O$	K_2HPO_4	0
9	$CoCl_2 \cdot 6H_2O$	K_2HPO_4	0
10	$CuCl_2 \cdot 2H_2O$	K_2HPO_4	0
11	$RuCl_3 \cdot 3H_2O$	NaH_2PO_4	14
12	$RuCl_3 \cdot 3H_2O$	KH_2PO_4	16
13	$RuCl_3 \cdot 3H_2O$	NaOAc	23
14	$RuCl_3 \cdot 3H_2O$	KOAc	44
15	$RuCl_3 \cdot 3H_2O$	$NaHCO_3$	43
16	$RuCl_3 \cdot 3H_2O$	Na_2HPO_4	62
17	$RuCl_3 \cdot 3H_2O$	K_2CO_3	47
18	$RuCl_3 \cdot 3H_2O$	K_3PO_4	46
19	$RuCl_3 \cdot 3H_2O$	KOH	0
20	$RuCl_3 \cdot 3H_2O$	^{t}BuONa	25
21	$RuCl_3 \cdot 3H_2O$	^{t}BuOK	45
22	$RuCl_3 \cdot 3H_2O$	DBU	41
23	$RuCl_3 \cdot 3H_2O$	none	0
24	none	K_2HPO_4	0
25	$RuCl_3 \cdot 3H_2O$	K_2HPO_4	60[c]

[a]Reaction conditions: **1i** (0.50 mmol), **2a** (0.75 mmol), catalyst (0.050 mmol as metal), additive (0.15 mmol), DMA (1.0 mL), at 170 °C, 48 h, under Ar. [b]Yields were determined by GLC. [c]Reaction at 150 °C.

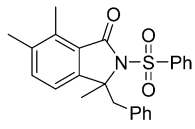
DOI: 10.1021/acs.joc.6b02552
J. Org. Chem. 2017, 82, 1231−1239

Table 2. Scope of Substrates[a]

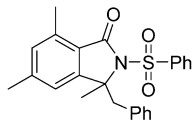




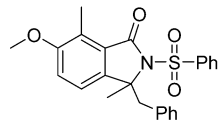
3ia: 73%[b], 80%[b,c]



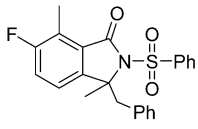
3ja: 46%



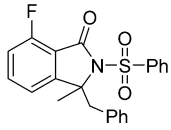
3ka: 62%



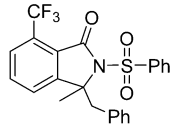
3la: 61%



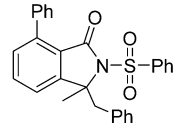
3ma: 67%



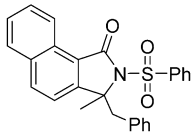
3na: 30%



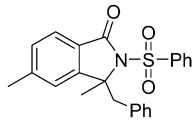
3oa: 49%



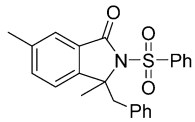
3pa: 58%



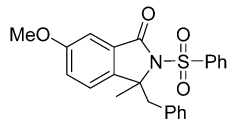
3qa: 59%



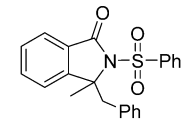
3ra: 27%



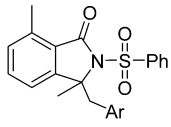
3sa: 71%



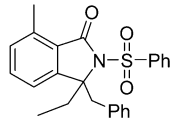
3ta: 45%



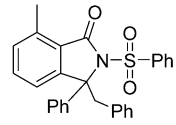
3ua: 57%



3ib: 47%
(Ar = *p*-tolyl)



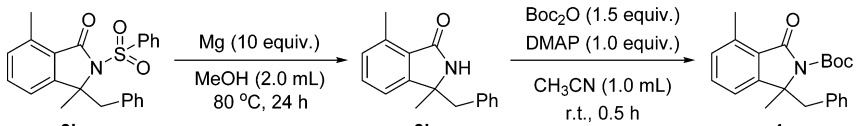
3ic: 63%



3id: 30%

[a]Reaction conditions: **1** (0.50 mmol), **2a** (0.75 mmol), $RuCl_3 \cdot 3H_2O$ (0.050 mmol as Ru), K_2HPO_4 (0.15 mmol), DMA (1.0 mL), at 170 °C, 48 h, under Ar. Isolated yeids. [b]GC yieid [c]Yieid after the reaction for 72 h.

Scheme 3. Desulfonylation and Boc-Protection of Amide



moderate, DBU could also be used as an organic base in the reaction. In contrast, no reaction took place in the absence of bases or Ru catalysts (entries 23 and 24). A high temperature at around 170 °C was required to proceed the reaction efficiently, and the reaction at 150 °C decreased the product yield (entry 25). The reactions of aromatic amides with internal alkynes in the presence of Ru, Rh or Pd catalysts together with metallic oxidants, such as $Cu(OAc)_2$, have been reported to selectively give six-membered isoquinolones.[9] In contrast, such isoquinolones were not formed in our Ru and base catalytic systems.

The scope of the substrates in the present Ru-catalyzed reactions was investigated under the optimized reaction conditions. The reaction of **2a** with *ortho* methyl-substituted aromatic amides proceeded smoothly to give the corresponding isoindolinones (**3ja**−**3ma**) in good yields. Isoindolinones with fluoro, trifluoromethyl, and phenyl substituents at the *ortho* position (**3na**, **3oa** and **3pa**) were also obtained in moderate to good yields. *1H*-Benzo[*e*]isoindolinone derivative **3qa** could be synthesized from *N*-sulfonyl naphthylamide. The reactions of *meta*- and *para*-substituted aromatic amides gave the corresponding products (**3ra**−**3ua**) in moderate to good yields. The reactions of **1i** with unsymmetrical internal alkynes other than **2a** were also examined with the present Ru catalytic system. The reactions of 1-*p*-tolyl-1-propyne (**2b**), 1-phenyl-1-butyne (**2c**), and diphenylacetylene (**2d**) gave the corresponding isoindolinones (**3ib**−**3id**) in moderate to good yields. Notably, the reaction of the unsymmetrical internal alkynes proceeded regioselectively, and other regioisomers were not obtained either immediately after the reaction or after subsequent purification by column chromatography. In the case of the reaction of terminal alkyne, phenylacetylene, no desired product was obtained. The sulfonyl group that plays an important role in the catalytic reactions can be readily removed by treatment with Mg powder in methanol to give the N-protonated isoindolinone **3ba**.[10] The formed N−H bond could

DOI: 10.1021/acs.joc.6b02552
J. Org. Chem. 2017, 82, 1231−1239

also be protected by Boc_2O to provide *N*-Boc isoindolinone **4** (Scheme 3).

Figure 1 shows the time course of the reaction of **1i** with **2a** under the reaction conditions described in Scheme 1. The yield

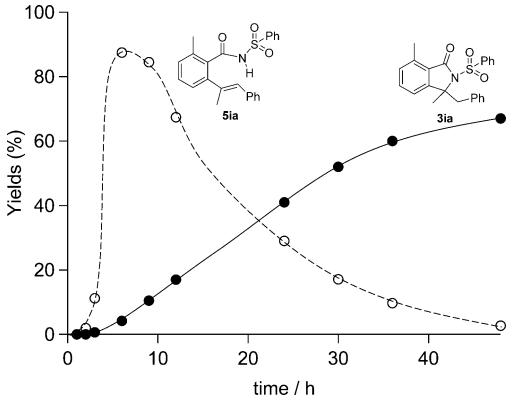
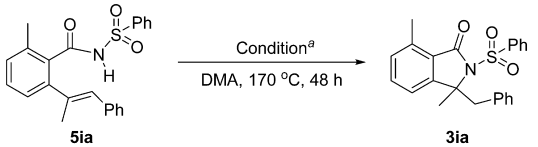


Figure 1. Time course of the reaction of **1i** with **2a**; yield of **3ia** (●) and **5ia** (○).

of **3ia** gradually increased over 48 h. On the other hand, the rapid formation of *ortho*-alkenylated aromatic amide **5ia** was observed at the initial stage of the reaction, and the yield of **5ia** gradually decreased after 6 h. These results clearly indicate that the synthesis of isoindolinones involves two reactions: (a) regioselective alkenylation of an aromatic C−H bond of an amide with an internal alkyne, and (b) intramolecular cyclization of the amide with the resulting alkene functionality. The time course also suggests that the intramolecular cyclization is much slower than the alkenylation of aromatic C−H bonds, and the high temperature at around 170 °C is mainly required to proceed the cyclization step.

To understand the effects of Ru catalysts and bases on the present catalytic reactions, we examined the cyclization of **5ia** under several different conditions (Scheme 4). The reaction of

Scheme 4. Intramolecular Cyclization of 5ia



Entry	catalyst (0.025 mmol)	base (0.075 mmol)	Yield of **3ia**[b]
1	$RuCl_3{\cdot}H_2O$	K_2HPO_4	55%
2	$RuCl_3{\cdot}H_2O$	none	32%
3	none	K_2HPO_4	58%
4	none	K_2HPO_4[c]	69%
5	none	DBU	62%
6	none	none	14%

[a]Reaction conditions: **5ia**(0.25 mmol), catalyst (0.025 mmol as Ru), additive (0.075 mmol), DMA (0.50 mL), at 170 °C, 48 h, under Ar. [b]GC yields. [c]0.050 mmol of K_2HPO_4 was used.

5ia in the presence of $RuCl_3{\cdot}3H_2O$ together with K_2HPO_4 at 170 °C for 48 h gave **3ia** in 50% yield (entry 1). On the other hand, the reaction in the absence of K_2HPO_4 resulted in lower yield of **3ia** (entry 2). In contrast, cyclization took place in the absence of Ru catalyst, and the treatment of **5ia** with K_2HPO_4 or DBU afforded **3ia** in respective yields of 58% and 62%. Furthermore, the increased yield of **3ia** was obtained by the reaction with reduced amount of K_2HPO_4. On the other hand, the noncatalytic treatment of **5ia** in DMA resulted in a very low yield of **3ia**. These results suggest that the intramolecular cyclization of **5ia** to **3ia** mainly proceeded *via* base catalysis.

A plausible reaction mechanism is shown in Scheme 5. The catalytic reaction begins with the ligand exchange of *in situ*-generated Ru^{II} species with **1** to form ruthenium amide **A**. In this step, the coordination of the oxygen atom of the sulfonyl group to the ruthenium center may promote dissociation of the N−H bond of the amide group. The acidity of N−H bond and basicity of sulfonyl oxygen atom may be controlled by the substituent of N-atom at amide, which concertedly functions to promote the generation of the ruthenium amide. In this regard, benzenesulfonyl group may be the most electronically balanced substituent for the present catalytic alkenylation. Subsequently, *ortho*-ruthenation of **A** affords ruthenacycle intermediate **B** accompanied by the formation of potassium dihydrogen phosphate. Regioselective insertion of alkyne into the Ru−C bond of **B** gives seven-membered ruthenacycle **C**.[11] Successive protonation of the Ru−C and Ru−N bonds of **C** provides *ortho*-alkenylated aromatic amide **5**. In our previous study on the Ru-catalyzed coupling of aromatic acids with internal alkynes, we proposed that the reaction included Brønsted acid-promoted protonation steps based on the results of a detailed D-labeling experiment.[8,12] Finally, intramolecular cyclization of **5** by base catalysis gives isoindolinone **3** as a final product. As described in Table 1, potassium hydrogen phosphate was shown to be the most suitable base for the present catalytic reaction. The conjugate base of an oxo acid, such as acetate, carbonate or phosphate, can promote the formation of metallacycles *via* a concerted metalation deprotonation mechanism.[13] On the other hand, the acidic protons of potassium dihydrogen phosphate that are produced during the dissociation of N−H and C−H bonds may efficiently promote the protonation of intermediate **C** to give **5**.

■ CONCLUSION

In summary, we have developed an atom-efficient synthesis of isoindolinones through the Ru-catalyzed addition of aromatic amides to internal alkynes and subsequent intramolecular cyclization. The sulfonyl substituents on the N-atom of amides play a crucial role in the realization of these tandem catalytic reactions. Various isoindolinones bearing quaternary carbons could be synthesized with 100% atom efficiency. Further investigations on the underlying mechanism and the development of novel catalytic reactions using this strategy are underway in our laboratory.

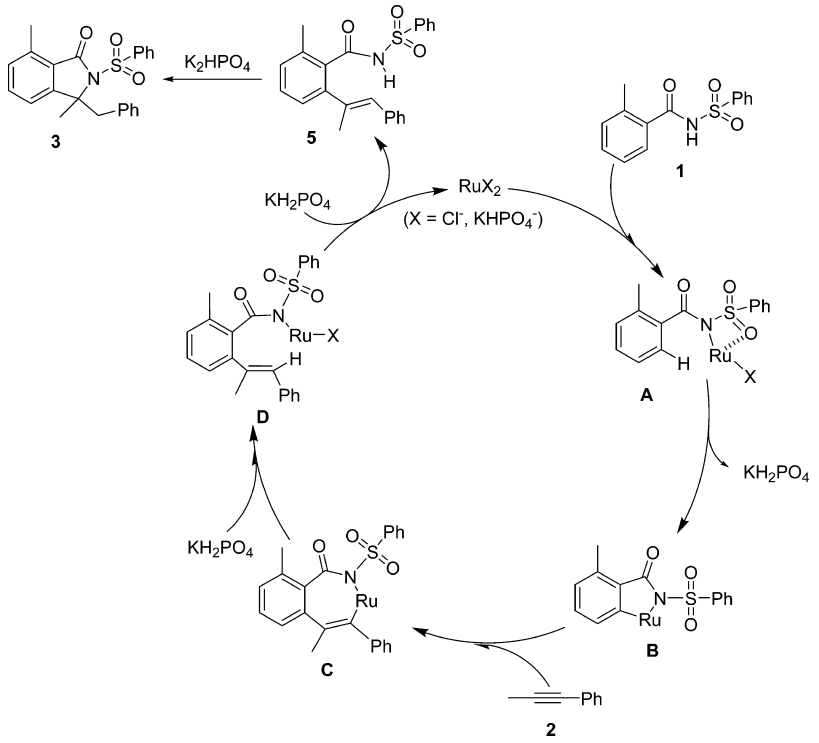
■ EXPERIMENTAL SECTION

General Method and Materials. All manipulations were performed under an argon atmosphere using standard Schlenk techniques. $[RuCl_2(p\text{-cymene})]_2$, all of the aromatic carboxylic acids, aromatic amides (**1b** and **1c**), all of the internal alkynes, inorganic bases, and DMA were obtained commercially and used without further purification. Aromatic amides (**1d** and **1e**) were synthesized as reported in the literature.[14] The products of the catalytic runs were analyzed by GC-MS and gas chromatography. NMR spectra were recorded on a 400 MHz (^1H), 100 MHz (^{13}C)) instrument. Chemical shifts (δ) of ^1H and $^{13}C\{^1H\}$ NMR spectra are referenced to $SiMe_4$. High-resolution mass spectra (fast atom bombardment (FAB)-magnetic sector analyzer) were recorded with *m*-nitrobenzyl alcohol (*m*-NBA) as a matrix.

General Procedure for the Synthesis of *N*-Sulfonyl Aromatic Amides (1). A round-bottom flask under an argon atmosphere was

DOI: 10.1021/acs.joc.6b02552
J. Org. Chem. 2017, 82, 1231−1239

Scheme 5. A Plausible Reaction Mechanism



filled with sulfonamide (1 equiv), ethyl acetate (2 M), triethylamine (2.5 equiv), and DMAP (0.005 equiv). A solution of acid chloride (1.1 equiv) in toluene (0.8 M) was added *via* a syringe over 15 min. The mixture was stirred under an argon atmosphere for 2 h at 55 °C, cooled to room temperature, and quenched with a solution of hydrochloric acid (0.5 mL, 3 M). The resulting mixture was then extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated. The products were isolated by silica-gel column chromatography (hexane/EtOAc).

*2-Methyl-N-tosylbenzamide (**1a**).* White solid; yield 72%, 2.95 g (10 mmol scale); mp 112−114 °C; hexane/EtOAc = 1/1; IR (Zn/Se-ATR, neat) 1683 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.81 (br, 1H), 8.00 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 7.6 Hz, 1H), 7.32−7.35 (m, 3H), 7.16−7.20 (m, 2H), 2.45 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.2, 145.1, 137.9, 135.5, 132.0, 131.7, 131.7, 129.6, 128.5, 127.2, 125.9, 21.7, 20.1; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{15}H_{16}NO_3S$ 290.0851, found 290.0862.

*2-Methyl-N-(methylsulfonyl)benzamide (**1f**).* White solid; yield 61%, 0.66 g (5.0 mmol scale); mp 109−112 °C; hexane/EtOAc = 2/1; IR (Zn/Se-ATR, neat) 1673 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.68 (br, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.41 (t, J = 7.6 Hz, 1H), 7.23−7.28 (m, 2H), 3.39 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 167.4, 138.3, 132.1, 131.9, 131.6, 127.4, 126.0, 41.6, 20.3; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_9H_{12}NO_3S$ 214.0538, found 214.0528.

*2-Methyl-N-((4-(trifluoromethyl)phenyl)sulfonyl)benzamide (**1g**).* White solid; yield 71%, 1.27 g (4.4 mmol scale); mp 111−113 °C; hexane/EtOAc = 1/1; IR (Zn/Se-ATR, neat) 1699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.84 (br, 1H), 8.26 (d, J = 8.4 Hz, 2H), 7.83 (d, J = 8.4 Hz, 2H), 7.36−7.43 (m, 2H), 7.18−7.22 (m, 2H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.1, 141.9, 138.3, 135.6 (d, J_{C-F} = 33 Hz), 132.2, 131.9, 131.4, 129.1, 127.3, 126.1 (q, J_{C-F} = 3.7 Hz), 126.0, 123.0 (d, J_{C-F} = 270 Hz), 20.1; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{15}H_{13}F_3NO_3S$ 344.0568, found 344.0575.

*N-((4-Chlorophenyl)sulfonyl)-2-methylbenzamide (**1h**).* White solid; yield 82%, 2.54 g (10 mmol scale); mp 124−126 °C; hexane/EtOAc = 2/1; IR (Zn/Se-ATR, neat) 1712 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.89 (br, 1H), 8.06 (d, J = 8.8 Hz, 2H), 7.52 (d, J = 8.8 Hz, 2H), 7.34−7.42 (m, 2H), 7.17−7.21 (m, 2H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.2, 140.7, 138.1, 136.8, 132.0, 131.8, 131.7, 130.0, 129.3, 127.3, 126.0, 20.1; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{14}H_{13}ClNO_3S$ 310.0305, found 310.0310.

*2-Methyl-N-(phenylsulfonyl)benzamide (**1i**).* White solid; yield 87%, 2.38 g (10 mmol scale); mp 90−92 °C; hexane/EtOAc = 3/1; IR (Zn/Se-ATR, neat) 1676 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 9.01 (br, 1H), 8.10−8.12 (m, 2H), 7.65 (t, J = 7.6 Hz, 1H), 7.55 (t, J = 7.6 Hz, 2H), 7.40 (d, J = 7.6 Hz, 1H), 7.33 (t, J = 7.6 Hz, 1H), 7.14−7.18 (m, 2H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.3, 138.4, 137.9, 134.0, 131.9,131.7, 131.6, 128.9, 128.4, 127.3, 125.9, 20.0; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{14}H_{14}NO_3S$ 276.0694, found 276.0695.

*2,3-Dimethyl-N-(phenylsulfonyl)benzamide (**1j**).* Yellow solid; yield 69%, 2.44 g (10 mmol scale); mp 104−106 °C; hexane/EtOAc = 3/1; IR (Zn/Se-ATR, neat) 1683 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.80 (br, 1H), 8.09−8.12 (m, 2H), 7.66 (t, J = 7.4 Hz, 1H), 7.54−7.58 (m, 2H), 7.21 (d, J = 7.6 Hz, 1H), 7.16 (d, J = 7.6 Hz, 1H), 7.06 (t, J = 7.4 Hz, 1H), 2.23 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 167.2, 144.9, 138.4, 135.4, 134.0, 133.1, 132.9, 128.9, 128.4, 125.6, 124.6, 20.2, 16.1; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{15}H_{16}NO_3S$ 290.0851, found 290.0839.

*2,4-Dimethyl-N-(phenylsulfonyl)benzamide (**1k**).* White solid; yield 80%, 2.09 g (10 mmol scale); mp 105−106 °C; hexane/EtOAc = 3/1; IR (Zn/Se-ATR, neat) 1676 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.68 (br, 1H), 8.12−8.14 (m, 2H), 7.66 (t, J = 7.4 Hz,1H), 7.54−7.58 (m, 2H), 7.33 (d, J = 8.0 Hz, 1H), 6.98−7.01 (m, 2H), 2.32 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.0, 142.5, 138.5, 138.4, 133.9, 132.6, 129.0, 128.8, 128.4, 127.4, 126.6, 21.4, 20.2; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{15}H_{16}NO_3S$ 290.0851, found 290.0865.

*3-Methoxy-2-methyl-N-(phenylsulfonyl)benzamide (**1l**).* White solid; yield 74%, 2.28 g (10 mmol scale); mp 141−143 °C; hexane/EtOAc = 3/1; IR (Zn/Se-ATR, neat) 1697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.74 (br, 1H), 8.10−8.12 (m, 2H), 7.66 (t, J = 7.6 Hz, 1H), 7.54−7.58 (m, 2H), 7.14 (t, J = 8.0 Hz, 1H), 6.89−6.94 (m, 2H), 3.80 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.4, 158.1, 138.4, 134.0, 133.8, 128.9, 128.4, 126.7, 126.1, 118.7, 113.0, 55.7, 12.4; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{15}H_{16}NO_4S$ 306.0800, found 306.0786.

DOI: 10.1021/acs.joc.6b02552
J. Org. Chem. 2017, 82, 1231−1239

*3-Fluoro-2-methyl-N-(phenylsulfonyl)benzamide (**1m**).* White solid; yield 87%, 1.01 g (4.0 mmol scale); mp 91−93 °C; hexane/EtOAc = 1/1; IR (Zn/Se-ATR, neat) 1708 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 9.06 (br, 1H), 8.10−8.12 (m, 2H), 7.68 (t, J = 7.6 Hz, 1H), 7.55−7.59 (m, 2H), 7.08−7.21 (m, 3H), 2.18 (d, J_{H-F}= 2.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 165.3, 161.3 (d, J_{C-F} = 245 Hz), 138.2, 134.2, 129.0, 128.4, 127.2 (d, J_{C-F} = 9.0 Hz), 126.3, 125.1 (d, J_{C-F} = 18 Hz), 122.8 (d, J_{C-F} = 3.0 Hz), 118.5 (d, J_{C-F} = 23 Hz), 11.2 (d, J_{C-F} = 6.0 Hz); HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{14}H_{13}FNO_3S$ 294.0600, found 294.0614.

*2-Fluoro-N-(phenylsulfonyl)benzamide (**1n**).* White solid; yield 82%, 2.29 g (10 mmol scale); mp 125−127 °C; hexane/EtOAc = 1/1; IR (Zn/Se-ATR, neat) 1697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 9.07 (br, 1H), 8.16−8.18 (m, 2H), 7.95−8.00 (m, 1H), 7.64−7.68 (m, 1H), 7.51−7.59 (m, 3H), 7.24−7.28 (m, 1H), 7.13−7.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 160.3, 160.2 (d, J_{C-F} = 248 Hz), 138.3, 135.6 (d, J_{C-F} = 9 Hz), 134.1, 132.3, 128.9, 128.7, 126.3, 125.3 (d, J_{C-F} = 3 Hz), 118.4 (d, J_{C-F} = 10 Hz), 116.4 (d, J_{C-F} = 24 Hz); HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{13}H_{11}FNO_3S$ 280.0444, found 280.0458.

*N-(Phenylsulfonyl)-2-(trifluoromethyl)benzamide (**1o**).* White solid; yield 86%, 2.82 g (10 mmol scale); mp 112−114 °C; hexane/EtOAc = 1/1; IR (Zn/Se-ATR, neat) 1715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.97 (br, 1H), 8.06−8.08 (m, 2H), 7.63−7.70 (m, 2H), 7.52−7.58 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 164.5, 137.6, 134.3, 132.3, 132.1, 131.2, 128.9, 128.5, 128.3, 127.7 (q, J_{C-F} = 30 Hz), 126.6 (q, J_{C-F} = 4.8 Hz), 122.9 (q, J_{C-F} = 270 Hz); HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{14}H_{11}F_3NO_3S$ 330.0412, found 330.0411.

*N-(Phenylsulfonyl)-[1,1′-biphenyl]-2-carboxamide (**1p**).* White solid; yield 50%, 1.69 g (10 mmol scale); mp 154−157 °C; hexane/EtOAc = 1/1; IR (Zn/Se-ATR, neat) 1713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.86−7.89 (m, 2H), 7.64−7.70 (m, 2H), 7.50−7.54 (m, 3H), 7.37−7.43 (m, 2H), 7.33−7.35 (m, 1H), 7.26−7.30 (m, 2H), 7.17−7.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.2, 140.0, 138.7, 138.0, 133.9, 132.2, 131.8, 130.5, 129.5,, 129.1, 128.7, 128.6, 128.6, 128.4, 127.8; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{19}H_{16}NO_3S$ 338.0851, found 338.0852.

*N-(Phenylsulfonyl)-1-naphthamide (**1q**).* White solid; yield 75%, 2.33 g (10 mmol scale); mp 144−146 °C; hexane/EtOAc = 1/1; IR (Zn/Se-ATR, neat) 1699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 9.13 (br, 1H), 8.13−8.16 (m, 2H), 7.90 (d, J = 8.0 Hz, 1H), 7.78−7.80 (m, 1H), 7.63−7.67 (m, 2H), 7.52−7.56 (m, 2H), 7.45−7.49 (m, 2H), 7.34−7.38 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 165.9, 138.4, 134.1, 133.6, 132.9, 129.9, 129.8, 129.0, 128.5, 128.4, 127.9, 126.8, 126.6, 124.7, 124.3; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{17}H_{14}NO_3S$ 312.0694, found 312.0682.

*4-Methyl-N-(phenylsulfonyl)benzamide (**1r**).* White solid; yield 75%, 1.96 g (9.5 mmol scale); mp 139−141 °C; hexane/EtOAc = 2/1; IR (Zn/Se-ATR, neat) 1693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 9.41 (br, 1H), 8.15−8.18 (m, 2H), 7.71−7.73 (m, 2H), 7.63−7.66 (m, 1H), 7.53−7.57 (m, 2H), 7.53−7.60 (m, 2H), 7.21 (d, J = 8.0 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 164.3, 144.5, 138.5, 134.0, 129.5, 129.0, 128.5, 128.2, 127.9, 21.6; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{14}H_{14}NO_3S$ 276.0694, found 276.0685.

*3-Methyl-N-(phenylsulfonyl)benzamide (**1s**).* White solid; yield 83%, 2.17 g (9.5 mmol scale); mp 115−117 °C; hexane/EtOAc = 2/1; IR (Zn/Se-ATR, neat) 1668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 9.43 (br, 1H), 8.16−8.18 (m, 2H), 7.60−7.67 (m, 3H), 7.53−7.57 (m, 2H), 7.35 (d, J = 7.6 Hz, 1H), 7.29 (t, J = 7.6 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 164.5, 138.9, 138.4, 134.3, 134.0, 130.9, 129.0, 128.7, 128.5, 128.5, 124.9, 21.2; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{14}H_{14}NO_3S$ 276.0694, found 276.0681.

*3-Methoxy-N-(phenylsulfonyl)benzamide (**1t**).* Yellow solid; yield 53%, 0.94 g (5.0 mmol scale); mp 138−140 °C; hexane/EtOAc = 2/1; IR (Zn/Se-ATR, neat) 1683 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 9.55 (br, 1H), 8.15−8.17 (m, 2H), 7.65 (t, J = 7.8 Hz, 1H), 7.56 (t, J = 7.8 Hz, 2H), 7.34−7.40 (m, 2H), 7.30 (t, J = 8.0 Hz, 1H), 7.06−7.08 (m, 1H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 164.3, 159.9, 138.3, 134.1, 132.3, 129.9, 129.0, 128.5, 120.4, 119.9, 112.3, 55.5; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{14}H_{14}NO_4S$ 292.0644, found 292.0656.

*N-(Phenylsulfonyl)benzamide (**1u**).* White solid; yield 55%, 1.28 g (9.0 mmol scale); mp 149−152 °C; hexane/EtOAc = 1/1; IR (Zn/Se-ATR, neat) 1695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 9.53 (br, 1H), 8.16−8.18 (m, 2H), 7.82−7.84 (m, 2H), 7.65 (t, J = 7.4 Hz, 1H), 7.52−7.57 (m, 3H), 7.39−7.43 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 164.4, 138.4, 134.1, 133.5, 131.0, 129.0, 128.9, 128.5, 127.9; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{13}H_{12}NO_3S$ 262.0538, found 262.0532.

General Procedure for the Synthesis of Isoindolinones (3). A 20 mL Schlenk tube was charged with aromatic amide **1** (0.50 mmol), alkyne **2** (0.75 mmol), $RuCl_3{\cdot}3H_2O$ (0.050 mmol), dipotassium hydrogen phosphate (0.15 mmol), and DMA (1.0 mL) under an argon atmosphere. The reaction mixture was stirred at 170 °C for 48 h on a hot stirrer with a cooling block. After the reaction, the reaction solution was concentrated under reduced pressure. The products were isolated by silica-gel column chromatography (hexane/EtOAc).

*3-Benzyl-3,7-dimethyl-2-tosylisoindolin-1-one (**3aa**).* Yellow solid; yield 37%, 76.6 mg (0.50 mmol scale); mp 135−137 °C; hexane/EtOAc = 5/1; IR (Zn/Se-ATR, neat) 1719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.95 (d, J = 8.4 Hz, 2H), 7.33 (t, J = 7.8 Hz, 1H), 7.20 (d, J = 8.0 Hz, 2H), 6.98−7.02 (m, 4H), 6.93 (d, J = 7.6 Hz, 1H), 6.84−6.87 (m, 2H), 3.67 (d, J = 13.6 Hz, 1H), 3.41 (d, J = 13.6 Hz, 1H), 2.37 (s, 3H), 2.31 (s, 3H), 1.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.9, 150.6, 144.5, 139.0, 137.0, 134.9, 132.8, 130.5, 130.4, 129.3, 128.5, 127.7, 126.8, 125.3, 119.6, 70.9, 46.0, 26.2, 21.6, 17.6; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{24}H_{24}NO_3S$ 406.1477, found 406.1476.

*3-Benzyl-3,7-dimethyl-2-(methylsulfonyl)isoindolin-1-one (**3fa**).* Yellow solid; yield 44%, 56.9 mg (0.50 mmol scale); mp 136−138 °C; hexane/EtOAc = 5/1; IR (Zn/Se-ATR, neat) 1715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.48 (t, J = 7.6 Hz, 1H), 7.14−7.18 (m, 2H), 6.97−7.03 (m, 3H), 6.71 (d, J = 6.4 Hz, 2H), 3.63 (d, J = 14.0 Hz, 1H), 3.36 (d, J = 14.0 Hz, 1H), 3.12 (s, 3H), 2.51 (s, 3H), 1.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) 168.1, 151.4, 139.4, 135.3, 133.5, 130.7, 129.8, 127.9, 127.0, 125.2, 119.3, 70.9, 44.7, 42.6, 27.4, 17.6; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{18}H_{20}NO_3S$ 330.1164, found 330.1151.

*3-Benzyl-3,7-dimethyl-2-((4-(trifluoromethyl)phenyl)sulfonyl)-isoindolin-1-one (**3ga**).* Yellow solid; yield 31%, 69.8 mg (0.50 mmol scale); mp 182−185 °C; hexane/EtOAc = 5/1; IR (Zn/Se-ATR, neat) 1723 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.27 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 8.4 Hz, 2H), 7.46 (t, J = 7.6 Hz, 1H), 7.11−7.14 (m, 4H), 7.06 (d, J = 7.6 Hz, 1H), 6.91−6.92 (m, 2H), 3.75 (d, J = 13.6 Hz, 1H), 3.53 (d, J = 14.0 Hz, 1H), 2.47 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.9, 150.7, 143.1, 139.4, 134.9, 134.7, 133.3, 130.7, 130.4, 129.1, 127.9, 127.1, 125.7 (q, J_{C-F} = 3.8 Hz), 124.9, 123.1 (q, J_{C-F} = 270 Hz), 119.7, 71.3, 46.0, 26.4, 17.6; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{24}H_{21}F_3NO_3S$ 460.1194, found 460.1195.

*3-Benzyl-2-((4-chlorophenyl)sulfonyl)-3,7-dimethylisoindolin-1-one (**3ha**).* Yellow solid; yield 48%, 104 mg (0.50 mmol scale); mp 164−166 °C; hexane/EtOAc = 5/1; IR (Zn/Se-ATR, neat) 1715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.07−8.09 (m, 2H), 7.43−7.48 (m, 3H), 7.10−7.12 (m, 4H), 7.04 (d, J = 7.6 Hz, 1H), 6.91−6.93 (m, 2H), 3.73 (d, J = 13.6 Hz, 1H), 3.51 (d, J = 13.6 Hz, 1H), 2.47 (s, 3H), 2.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.9, 150.7, 140.2, 139.2, 138.3, 134.7, 133.1, 130.6, 130.4, 130.0, 129.0, 127.8, 126.9, 125.0, 119.6, 71.1, 46.0, 26.3, 17.6; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{23}H_{21}ClNO_3S$ 426.0931, found 426.0928.

*3-Benzyl-3,7-dimethyl-2-(phenylsulfonyl)isoindolin-1-one (**3ia**).* Yellow solid; yield 73%, 141 mg (0.50 mmol scale); mp 142−144 °C; hexane/EtOAc = 5/1; IR (Zn/Se-ATR, neat) 1725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.15−8.17 (m, 2H), 7.60 (t, J = 7.6 Hz, 1H), 7.51 (t, J = 7.6 Hz, 2H), 7.43 (t, J = 7.6 Hz, 1H), 7.09−7.12 (m, 4H), 7.02 (d, J = 8.0 Hz, 1H), 6.93−6.95 (m, 2H), 3.76 (d, J = 13.6 Hz, 1H), 3.51 (d, J = 14.0 Hz, 1H), 2.47 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.9, 150.7, 139.9, 139.2, 134.9, 133.6, 132.9, 130.5, 128.7, 128.5, 127.8, 126.9, 125.2, 119.6,

DOI: 10.1021/acs.joc.6b02552
J. Org. Chem. 2017, 82, 1231−1239

71.0, 46.1, 26.2, 17.6; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{23}H_{22}NO_3S$ 392.1320, found 392.1301.

*(E)-2-methyl-6-(1-phenylprop-1-en-2-yl)-N-(phenylsulfonyl)-benzamide (**5ia**).* Yellow solid; yield 62%, 122 mg (0.50 mmol scale); mp 63−65 °C; hexane/EtOAc = 3/1; IR (Zn/Se-ATR, neat) 1712 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.94−7.96 (m, 2H), 7.48 (t, J = 7.4 Hz, 1H), 7.34 (t, J = 7.4 Hz, 2H), 7.25−7.30 (m, 4H), 7.17 (d, J = 7.2 Hz, 2H), 7.09−7.12 (m, 2H), 6.41 (s, 1H), 2.28 (s, 3H), 1.89 (d, J = 1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.8, 143.2, 138.0, 137.0, 136.9, 135.7, 133.9, 132.2, 130.9, 130.2, 129.3, 129.0, 128.7, 128.3, 128.2, 126.8, 126.0, 19.7, 19.3; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{23}H_{22}NO_3S$ 392.1320, found 392.1328.

*3-Benzyl-3,6,7-trimethyl-2-(phenylsulfonyl)isoindolin-1-one (**3ja**).* Yellow solid; yield 46%, 62.7 mg (0.50 mmol scale); mp 147−150 °C; hexane/EtOAc = 5/1; IR (Zn/Se-ATR, neat) 1717 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.14−8.16 (m, 2H), 7.58 (t, J = 7.4 Hz, 1H), 7.49 (t, J = 7.6 Hz, 2H), 7.32 (d, J = 8.0 Hz, 1H), 7.10−7.12 (m, 3H), 6.94−6.97 (m, 2H), 6.91 (d, J = 7.6 Hz, 1H), 3.71 (d, J = 13.6 Hz, 1H), 3.52 (d, J = 14.0 Hz, 1H), 2.42 (s, 3H), 2.24 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 167.2, 148.4, 139.9, 137.8, 137.6, 135.0, 134.6, 133.5, 130.5, 128.6, 128.4, 127.7, 126.8, 124.9, 119.1, 70.2, 46.0, 26.4, 19.2, 13.2; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{24}H_{24}NO_3S$ 406.1477, found 406.1459.

*3-Benzyl-3,5,7-trimethyl-2-(phenylsulfonyl)isoindolin-1-one (**3ka**).* Yellow solid; yield 62%, 125 mg (0.50 mmol scale); mp 140−143 °C; hexane/EtOAc = 5/1; IR (Zn/Se-ATR, neat) 1719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.14 (d, J = 7.6 Hz, 2H), 7.57 (t, J = 8.4 Hz, 1H), 7.48 (t, J = 7.8 Hz, 2H), 7.09−7.12 (m, 3H), 6.91−6.95 (m, 3H), 6.79 (s, 1H), 3.72 (d, J = 13.6 Hz, 1H), 3.50 (d, J = 13.6 Hz, 1H), 2.42 (s, 3H), 2.36 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.8, 151.0, 143.9, 140.0, 138.7, 135.0, 133.4, 131.5, 130.4, 128.6, 128.3, 127.7, 126.8, 122.7, 120.0, 70.8, 46.0, 26.2, 21.9, 17.4; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{24}H_{24}NO_3S$ 406.1477, found 406.1489.

*3-Benzyl-6-methoxy-3,7-dimethyl-2-(phenylsulfonyl)isoindolin-1-one (**3la**).* Yellow solid; yield 61%, 127 mg (0.50 mmol scale); mp 167−169 °C; hexane/EtOAc = 5/1; IR (Zn/Se-ATR, neat) 1712 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.14−8.16 (m, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.50 (t, J = 7.6 Hz, 2H), 7.12−7.14 (m, 3H), 7.02 (d, J = 8.0 Hz, 1H), 6.91−6.97 (m, 3H), 3.82 (s, 3H), 3.68 (d, J = 13.6 Hz, 1H), 3.53 (d, J = 13.6 Hz, 1H), 2.36 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 167.0, 157.7, 142.1, 140.0, 135.2, 133.5, 130.6, 128.7, 128.5, 127.8, 127.5, 126.8, 126.0, 120.0, 115.1, 70.3, 56.1, 46.2, 26.5, 9.7; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{24}H_{24}NO_4S$ 422.1426, found 422.1406.

*3-Benzyl-6-fluoro-3,7-dimethyl-2-(phenylsulfonyl)isoindolin-1-one (**3ma**).* Yellow solid; yield 67%, 127 mg (0.50 mmol scale); mp 189−191 °C; hexane/EtOAc = 5/1; IR (Zn/Se-ATR, neat) 1721 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.16−8.18 (m, 2H), 7.62 (t, J = 7.6 Hz, 1H), 7.53 (t, J = 7.6 Hz, 2H), 7.20 (t, J = 8.8 Hz, 1H), 7.13−7.15 (m, 3H), 6.93−6.96 (m, 3H), 3.73 (d, J = 13.6 Hz, 1H), 3.51 (d, J = 13.6 Hz, 1H), 2.39 (d, J = 2.0 Hz, 3H), 2.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.1 (d, J_{C-F} = 4.2 Hz), 160.7 (d, J_{C-F} = 248 Hz), 145.9, 139.7, 134.7, 133.7, 130.5, 128.6 (d, J_{C-F} = 24.8 Hz), 127.9, 127.1, 126.9 (d, J_{C-F} = 7.0 Hz), 125.5 (d, J_{C-F} = 19.3 Hz), 120.6 (d, J_{C-F} = 8.5 Hz), 120.2 (d, J_{C-F} = 25 Hz), 70.6, 46.0, 26.2, 8.9 (d, J_{C-F} = 3.8 Hz); HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{23}H_{21}FNO_3S$ 410.1226, found 410.1208.

*3-Benzyl-7-fluoro-3-methyl-2-(phenylsulfonyl)isoindolin-1-one (**3na**).* Yellow solid; yield 30%, 59.3 mg (0.50 mmol scale); mp 216−218 °C; hexane/EtOAc = 5/1; IR (Zn/Se-ATR, neat) 1736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.16−8.19 (m, 2H), 7.61 (t, J = 7.4 Hz, 1H), 7.50−7.58 (m, 3H), 7.13−7.14 (m, 3H), 6.95−7.03 (m, 4H), 3.81 (d, J = 13.6 Hz, 1H), 3.50 (d, J = 14 Hz, 1H), 2.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 161.7 (d, J_{C-F} = 253 Hz), 157.8, 152.4, 139.4, 135.5 (d, J_{C-F} = 7.6 Hz), 134.4, 133.9, 130.4, 128.8, 128.6, 128.0, 127.2, 118.2 (d, J_{C-F} = 4.1 Hz), 115.8, 115.6, 71.8, 45.9, 26.1; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{22}H_{19}FNO_3S$ 396.1070, found 396.1076.

*3-Benzyl-3-methyl-2-(phenylsulfonyl)-7-(trifluoromethyl)-isoindolin-1-one (**3oa**).* Yellow solid; yield 49%, 108 mg (0.50 mmol scale); mp 191−193 °C; hexane/EtOAc = 3/1; IR (Zn/Se-ATR, neat) 1736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.19−8.21 (m, 2H), 7.60−7.66 (m, 3H), 7.53 (t, J = 7.6 Hz, 2H), 7.36 (t, J = 4.4 Hz, 1H), 7.12−7.13 (m, 3H), 6.91−6.93 (m, 2H), 3.76 (d, J = 13.6 Hz, 1H), 3.58 (d, J = 14.0 Hz, 1H), 2.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 162.7, 152.2, 139.3, 134.3, 133.9, 133.0, 130.4, 128.9, 128.7, 128.0, 127.7 (q, J_{C-F} = 35 Hz), 127.2, 126.4 (q, J_{C-F} = 5.7 Hz), 126.2, 125.3, 122.0 (q, J_{C-F} = 272 Hz), 71.0, 46.0, 25.6; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{23}H_{19}F_3NO_3S$ 446.1038, found 446.1030.

*3-Benzyl-3-methyl-7-phenyl-2-(phenylsulfonyl)isoindolin-1-one (**3pa**).* Yellow solid; yield 58%, 85.6 mg (0.50 mmol scale); mp 192−194 °C; hexane/EtOAc = 3/1; IR (Zn/Se-ATR, neat) 1723 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.09−8.11 (m, 2H), 7.60 (t, J = 7.6 Hz, 1H), 7.52 (t, J = 7.6 Hz, 1H), 7.42 (t, J = 7.8 Hz, 2H), 7.24−7.33 (m, 5H), 7.12−7.17 (m, 5H), 6.95−6.97 (m, 2H), 3.95 (d, J = 13.6 Hz, 1H), 3.41 (d, J = 13.6 Hz, 1H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 165.3, 151.3, 141.9, 140.0, 136.6, 134.7, 133.5, 133.0, 130.8, 130.5, 129.3, 128.7, 128.3, 128.0, 127.8, 127.8, 126.9, 124.2, 120.8, 70.4, 46.6, 25.6; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{28}H_{24}NO_3S$ 454.1477, found 454.1496.

*3-Benzyl-3-methyl-2-(phenylsulfonyl)-2,3-dihydro-1H-benzo[e]-isoindol-1-one (**3qa**).* Yellow solid; yield 59%, 128 mg (0.50 mmol scale); mp 192−195 °C; hexane/EtOAc = 5/1; IR (Zn/Se-ATR, neat) 1706 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.87 (d, J = 8.4 Hz, 1H), 8.20−8.22 (m, 2H), 8.04 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 7.6 Hz, 1H), 7.50−7.59 (m, 5H), 7.29 (d, J = 8.0 Hz, 1H), 7.05−7.06 (m, 3H), 6.95−6.98 (m, 2H), 3.87 (d, J = 14.0 Hz, 1H), 3.62 (d, J = 14.0 Hz, 1H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 170.0, 151.3, 139.9, 134.8, 134.7, 133.6, 132.9, 130.4, 128.8, 128.7, 128.5, 128.3, 127.9, 127.1, 127.0, 123.7, 121.8, 119.0, 71.2, 45.5, 25.8; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{26}H_{22}NO_3S$ 428.1320, found 428.1326.

*3-Benzyl-3,5-dimethyl-2-(phenylsulfonyl)isoindolin-1-one (**3ra**).* Yellow solid; yield 27%, 52.2 mg (0.50 mmol scale); mp 208−210 °C; hexane/EtOAc = 5/1; IR (Zn/Se-ATR, neat) 1717 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.15−8.17 (m, 2H), 7.59 (t, J = 7.6 Hz, 1H), 7.50 (t, J = 7.6 Hz, 2H), 7.38−7.39 (m, 2H), 7.08−7.13 (m, 4H), 6.94−6.96 (m, 2H), 3.75 (d, J = 13.6 Hz, 1H), 3.52 (d, J = 14.0 Hz, 1H), 2.35 (s, 3H), 2.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.4, 147.3, 139.8, 138.9, 134.8, 134.7, 133.6, 130.5, 128.7, 128.4, 128.1, 127.8, 126.9, 124.5, 122.0, 72.1, 45.9, 26.1, 21.2; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{23}H_{22}NO_3S$ 392.1320, found 392.1328.

*3-Benzyl-3,6-dimethyl-2-(phenylsulfonyl)isoindolin-1-one (**3sa**).* Yellow solid; yield 71%, 136 mg (0.50 mmol scale); mp 204−206 °C; hexane/EtOAc = 5/1; IR (Zn/Se-ATR, neat) 1724 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.14−8.16 (m, 2H), 7.58 (t, J = 7.4 Hz, 1H), 7.46−7.51 (m, 3H), 7,17 (d, J = 8.4 Hz, 1H), 7.10−7.12 (m, 3H), 6.98 (s, 1H), 6.92−6.94 (m, 2H), 3.75 (d, J = 14.0 Hz, 1H), 3.52 (d, J = 13.6 Hz, 1H), 2.43 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.2, 150.3, 144.7, 139.9, 134.8, 133.6, 130.5, 129.8, 128.7, 128.4, 127.8, 126.9, 125.5, 124.4, 122.6, 72.0, 46.0, 26.0, 22.2; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{23}H_{22}NO_3S$ 392.1320, found 392.1328.

*3-Benzyl-6-methoxy-3-methyl-2-(phenylsulfonyl)isoindolin-1-one (**3ta**).* Yellow solid; yield 45%, 94.9 mg (0.50 mmol scale); mp 165−168 °C; hexane/EtOAc = 5/1; IR (Zn/Se-ATR, neat) 1713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.16−8.18 (m, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.50 (t, J = 7.8 Hz, 2H), 7.12−7.15 (m, 4H), 7.08 (d, J = 8.4 Hz, 1H), 7.02 (d, J = 2.4 Hz, 1H), 6.94−6.97 (m, 2H), 3.75 (s, 3H), 3.73 (d, J = 13.6 Hz, 1H), 3.51 (d, J = 13.6 Hz, 1H), 2.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.3, 160.1, 142.4, 139.8, 134.8, 133.7, 130.5, 129.2, 128.7, 128.4, 127.8, 126.9, 123.2, 122.5, 106.2, 72.0, 55.6, 46.0, 26.0; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{23}H_{22}NO_4S$ 408.1270, found 408.1277.

*3-Benzyl-3-methyl-2-(phenylsulfonyl)isoindolin-1-one (**3ua**).* Yellow solid; yield 57%, 106 mg (0.50 mmol scale); mp 158−161 °C; hexane/EtOAc = 5/1; IR (Zn/Se-ATR, neat) 1731 cm^{-1}; ^1H NMR

DOI: 10.1021/acs.joc.6b02552
J. Org. Chem. 2017, 82, 1231−1239

(400 MHz, $CDCl_3$, ppm) δ 8.16−8.19 (m, 2H), 7.57−7.60 (m, 3H), 7.51 (t, J = 7.8 Hz, 2H), 7.36 (t, J = 7.8 Hz, 1H), 7.24 (t, J = 6.0 Hz, 1H), 7.09−7.11 (m, 3H), 6.93−6.95 (m, 2H), 3.79 (d, J = 13.6 Hz, 1H), 3.52 (d, J = 13.6 Hz, 1H), 2.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.2, 149.9, 139.8, 134.7, 1337, 133.6, 130.5, 128.7, 128.4, 128.0, 127.8, 126.9, 124.5, 122.2, 72.2, 45.9, 25.9; HRMS (FAB) m/z [M + H]$^+$ calcd for $C_{22}H_{20}NO_3S$ 378.1164, found 378.1174.

*3,7-Dimethyl-3-(4-methylbenzyl)-2-(phenylsulfonyl)isoindolin-1-one (**3ib**).* Yellow solid; yield 47%, 94.7 mg (0.50 mmol scale); mp 121−123 °C; hexane/EtOAc = 5/1; IR (Zn/Se-ATR, neat) 1725 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.08−8.10 (m, 2H), 7.52 (t, J = 7.6 Hz, 1H), 7.43 (t, J = 7.6 Hz, 2H), 7.36 (t, J = 7.6 Hz, 1H), 7.03 (d, J = 7.6 Hz, 1H), 6.96 (d, J = 7.6 Hz, 1H), 6.84 (d, J = 8.0 Hz, 2H), 6.74 (d, J = 8.0 Hz, 2H), 3.62 (d, J = 13.6 Hz, 1H), 3.41 (d, J = 13.6 Hz, 1H), 2.40 (s, 3H), 2.16 (s, 3H), 1.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.9, 150.8, 140.0, 139.1, 136.4, 133.5, 132.9, 131.7, 130.5, 130.4, 128.7, 128.5, 128.5, 125.3, 120.0, 71.2, 45.7, 26.2, 21.0, 17.6; HRMS (FAB) m/z [M + H]$^+$ calcd for $C_{24}H_{24}NO_3S$ 406.1477, found 406.1489.

*3-Benzyl-3-ethyl-7-methyl-2-(phenylsulfonyl)isoindolin-1-one (**3ic**).* Yellow solid; yield 63%, 128 mg (0.50 mmol scale); mp 153−156 °C; hexane/EtOAc = 5/1; IR (Zn/Se-ATR, neat) 1720 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.17−8.19 (m, 2H), 7.60 (t, J = 7.4 Hz, 1H), 7.51 (t, J = 7.6 Hz, 2H), 7.40 (t, J = 7.6 Hz, 1H), 7.09−7.15 (m, 4H), 6.91−6.94 (m, 2H), 6.84 (d, J = 7.6 Hz, 1H), 3.61−3.69 (m, 2H), 2.91−2.99 (m, 1H), 2.53 (s, 3H), 2.09−2.18 (m, 1H), 0.36 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 167.6, 148.7, 139.7, 139.1, 135.0, 133.6, 132.9, 130.7, 130.5, 128.7, 128.6, 127.8, 126.9, 126.2, 119.7, 75.7, 45.7, 30.6, 17.7, 8.1; HRMS (FAB) m/z [M + H]$^+$ calcd for $C_{24}H_{24}NO_3S$ 406.1477, found 406.1476.

*3-Benzyl-7-methyl-3-phenyl-2-(phenylsulfonyl)isoindolin-1-one (**3id**).* Yellow solid; yield 30%, 68.4 mg (0.50 mmol scale); mp 221−223 °C; hexane/EtOAc = 5/1; IR (Zn/Se-ATR, neat) 1713 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.38−7.45 (m, 2H), 7.31−7.33 (m, 3H), 7.20−7.25 (m, 5H), 7.12−7.14 (m, 1H), 7.05−7.09 (m, 4H), 7.00−7.03 (m, 2H), 6.96−6.98 (m, 1H), 4.78 (d, J = 13.2 Hz, 1H), 3.66 (d, J = 13.2 Hz, 1H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 167.3, 151.2, 139.2, 138.7, 134.0, 133.4, 133.2, 130.7, 130.4, 129.1, 128.7, 128.5, 128.4, 128.2, 128.1, 127.7, 126.8, 125.9, 120.6, 74.0, 52.1, 42.1, 17.5; HRMS (FAB) m/z [M + H]$^+$ calcd for $C_{28}H_{24}NO_3S$ 454.1477, found 454.1499.

Desulfonylation of 3ia. A 20 mL Schlenk tube was charged with **3ia** (0.30 mmol), Mg (3.0 mmol), and MeOH (2.0 mL) under an argon atmosphere. The reaction mixture was stirred at 80 °C for 24 h on a hot stirrer with a cooling block. After the reaction mixture was allowed to cool, the reaction solvent was removed under reduced pressure. The product **3ba** was isolated by silica-gel column chromatography (hexane/EtOAc = 3/1).

*3-Benzyl-3,7-dimethylisoindolin-1-one (**3ba**).* Yellow solid; yield 64%, 48.8 mg (0.30 mmol scale); mp 53−55 °C; IR (Zn/Se-ATR, neat) 1681 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.34 (t, J = 7.6 Hz, 1H), 7.12−7.18 (m, 4H), 7.08 (d, J = 7.6 Hz, 1H), 7.03−7.05 (m, 2H), 6.38 (s, 1H), 3.01 (d, J = 13.2 Hz, 1H), 2.82 (d, J = 13.2 Hz, 1H), 2.59 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ170.2, 152.6, 138.0, 136.1, 131.4, 130.3, 130.0, 128.2, 128.0, 126.9, 118.7, 60.6, 46.9, 25.5, 17.3; HRMS (FAB) m/z [M + H]$^+$ calcd for $C_{17}H_{18}NO$ 252.1388, found 252.1394.

Boc-protection of 3ba. A 20 mL Schlenk tube was charged with **3ba** (0.30 mmol), DMAP (0.020 mmol), and CH_3CN (1.0 mL) under an argon atmosphere. The reaction mixture was stirred at room temperature. After the reaction was allowed to proceed for 0.5 h, the reaction solvent was removed under reduced pressure. The product **4** was isolated by silica-gel column chromatography (hexane/EtOAc = 3/1).

*tert-Butyl 1-Benzyl-1,4-dimethyl-3-oxoisoindoline-2-carboxylate (**4**).* Colorless oil; yield 87%, 55.5 mg (0.30 mmol scale); IR (Zn/Se-ATR, neat) 1705 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.50 (t, J = 7.8 Hz, 1H), 7.29 (d, J = 7.6 Hz, 1H), 7.13 (d, J = 7.6 Hz, 1H), 6.99−7.04 (m, 3H), 6.61−6.63 (m, 2H), 3.81 (d, J = 13.6 Hz, 1H), 3.17 (d, J = 13.2 Hz, 1H), 2.53 (s, 3H), 1.86 (s, 3H), 1.66 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 167.0, 150.9, 150.5, 139.0, 135.4, 132.7, 130.3, 129.5, 127.7, 126.9, 126.7, 119.0, 82.7, 66.5, 44.0, 28.3, 25.9, 17.8; HRMS (FAB) m/z [M + H]$^+$ calcd for $C_{22}H_{26}NO_3$ 352.1913, found 352.1912.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02552.

^{1}H and ^{13}C NMR spectra for the *N*-sulfonyl aromatic amides, and the products **3**, **4**, and **5** (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: miura-hiroki@tmu.ac.jp.

*E-mail: shishido-tetsuya@tmu.ac.jp.

ORCID

Hiroki Miura: 0000-0002-2488-4432

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This study was supported in part by the Program for Element Strategy Initiative for Catalysts and Batteries (ESICB), Platform for Technology and Industry, a Grant-in-Aid for Young Scientists (B) (no. 26820353) and a Grant-in-Aid for Scientific Research (B) (no. 26289305), commissioned by the Ministry of Education, Culture, Sports, Science, and Technology (MEXT) of Japan.

■ REFERENCES

(1) (a) Wu, X.-F. *Transition Metal-Catalyzed Heterocycle Synthesis via C-H Activation*; John Wiley & Sons: Weinheim, 2015. (b) Mei, T. S.; Kou, L.; Ma, S.; Engle, K. M.; Yu, J. Q. *Synthesis* **2012**, *44*, 1778. (c) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960.

(2) (a) Belliotti, T. R.; Brink, W. A.; Kesten, S. R.; Rubin, J. R.; Wustrow, D. J.; Zoski, K. T.; Whetzel, S. Z.; Corbin, A. E.; Pugsley, T. A.; Heffner, T. G.; Wise, L. D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1499. (b) Honma, T.; Hayashi, K.; Aoyama, T.; Hashimoto, N.; Machida, T.; Fukasawa, K.; Iwama, T.; Ikeura, C.; Ikuta, M.; Suzuki-Takahashi, I.; Iwasawa, Y.; Hayama, T.; Nishimura, S.; Morishima, H. *J. Med. Chem.* **2001**, *44*, 4615. (c) Hardcastle, I. R.; Ahmed, S. U.; Atkins, H.; Calvert, A. H.; Curtin, N. J.; Farnie, G.; Golding, B. T.; Griffin, R. J.; Guyenne, S.; Hutton, C.; Kallblad, P.; Kemp, S. J.; Kitching, M. S.; Newell, D. R.; Norbedo, S.; Northen, J. S.; Reid, R. J.; Saravanan, K.; Willems, H. M. G.; Lunec, J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1515. (d) Zhao, Y.; Bernard, D.; Wang, S. *BioDiscovery* **2013**, *8*, 4. (e) Speck, K.; Magauer, T. *Beilstein J. Org. Chem.* **2013**, *9*, 2048.

(3) Mancuso, R.; Ziccarelli, I.; Armentano, D.; Marino, N.; Giofré, S. V.; Gabriele, B. *J. Org. Chem.* **2014**, *79*, 3506 and references cited therein..

(4) (a) Zhu, C.; Falck, J. R. *Org. Lett.* **2011**, *13*, 1214. (b) Wrigglesworth, J. W.; Cox, B.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *Org. Lett.* **2011**, *13*, 5326. (c) Li, D. D.; Yuan, T. T.; Wang, G. W. *Chem. Commun.* **2011**, *47*, 12789. (d) Xia, C.; White, A. J. P.; Hii, K. K. M. *J. Org. Chem.* **2016**, *81*, 7931.

(5) (a) Zhu, C.; Falck, J. R. *Chem. Commun.* **2012**, *48*, 1674. (b) Zhu, C.; Falck, J. R. *Tetrahedron* **2012**, *68*, 9192.

(6) (a) Ackermann, L.; Wang, L.; Wolfram, R.; Lygin, A. *Org. Lett.* **2012**, *14*, 728. (b) Manoharan, R.; Jeganmohan, M. *Chem. Commun.* **2015**, *51*, 2929. (c) Bechtoldt, A.; Tirler, C.; Raghuvanshi, K.; Warratz, S.; Kornhaaβ, C.; Ackermann, L. *Angew. Chem., Int. Ed.* **2016**, *55*, 264.

DOI: 10.1021/acs.joc.6b02552
J. Org. Chem. 2017, 82, 1231−1239

(7) (a) Ma, W.; Ackermann, L. *ACS Catal.* **2015**, *5*, 2822. (b) Hao, X. Q.; Du, C.; Zhu, X.; Li, P. X.; Zhang, J. H.; Niu, J. L.; Song, M. P. *Org. Lett.* **2016**, *18*, 3610.
(8) (a) Wada, K.; Miura, H.; Hosokawa, S.; Inoue, M. *J. Jpn. Pet. Inst.* **2013**, *56*, 69. (b) Miura, H.; Wada, K.; Hosokawa, S.; Inoue, M. *Chem. - Eur. J.* **2010**, *16*, 4186. (c) Miura, H.; Wada, K.; Hosokawa, S.; Inoue, M. *ChemCatChem* **2010**, *2*, 1223. (d) Miura, H.; Wada, K.; Hosokawa, S.; Inoue, M. *Chem. - Eur. J.* **2013**, *19*, 861. (e) Miura, H.; Tsutsui, K.; Wada, K.; Shishido, T. *Chem. Commun.* **2015**, *51*, 1654. (f) Miura, H.; Takeuchi, K.; Shishido, T. *Angew. Chem., Int. Ed.* **2016**, *55*, 278.
(9) (a) Guimond, N.; Gouliaras, C.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 6908. (b) Hyster, T. K.; Rovis, T. *J. Am. Chem. Soc.* **2010**, *132*, 10565. (c) Mochida, S.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Lett.* **2010**, *39*, 744. (d) Song, G.; Chen, D.; Pan, C. L.; Crabtree, R. H.; Li, X. *J. Org. Chem.* **2010**, *75*, 7487. (e) Ackermann, L.; Lygin, A. V.; Hofmann, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 6379. (f) Li, B.; Feng, H.; Xu, S.; Wang, B. *Chem. - Eur. J.* **2011**, *17*, 12573. (g) Zhong, H.; Yang, D.; Wang, S.; Huang, J. *Chem. Commun.* **2012**, *48*, 3236.
(10) (a) Yokoyama, Y.; Matsumoto, T.; Murakami, Y. *J. Org. Chem.* **1995**, *60*, 1486. (b) Nyasse, B.; Grehn, L.; Ragnarsson, U. *Chem. Commun.* **1997**, 1017.
(11) Ruthenium-catalyzed regioselective addition of aromatic C−H bonds to internal alkynes: (a) Hashimoto, Y.; Hirano, K.; Satoh, T.; Kakiuchi, F.; Miura, M. *Org. Lett.* **2012**, *14*, 2058. (b) Zhao, P.; Niu, R.; Wang, F.; Han, K.; Li, X. *Org. Lett.* **2012**, *14*, 4166. (c) Itoh, M.; Hashimoto, Y.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2013**, *78*, 8098. (d) Manikandan, R.; Jeganmohan, M. *Org. Lett.* **2014**, *16*, 912. (e) Padala, K.; Jeganmohan, M. *Chem. Commun.* **2014**, *50*, 14573.
(12) Unfortunately, the addition of D_2O or CH_3COOD completely inhibited the conversion of the starting substrates.
(13) (a) Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, *39*, 1118. (b) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (c) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879. (d) Gorelsky, S. I. *Coord. Chem. Rev.* **2013**, *257*, 153. (e) Musaev, D. G.; Figg, T. M.; Kaledin, A. L. *Chem. Soc. Rev.* **2014**, *43*, 5009. (f) Ackermann, L. *Acc. Chem. Res.* **2014**, *47*, 281. (g) De Sarkar, S.; Liu, W.; Kozhushkov, S. I.; Ackermann, L. *Adv. Synth. Catal.* **2014**, *356*, 1461.
(14) (a) Guimond, N.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2011**, *133*, 6449. (b) Roane, J.; Daugulis, O. *J. Am. Chem. Soc.* **2016**, *138*, 4601.

DOI: 10.1021/acs.joc.6b02552
J. Org. Chem. 2017, 82, 1231−1239