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Pd-Catalyzed Direct C−H Activation for the C5-Olefination of Methyleneindolinones

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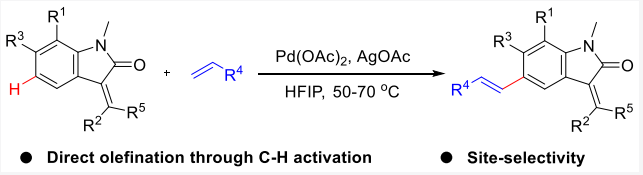
ABSTRACT: The direct C−H activation without directing groups can realize the *para*-selectivity, which is a powerful and concise approach for functionalization of arenes. Utilizing the strategy, a C5-olefination of methyleneindolinones has been successfully developed by palladium-catalyzed direct C−H activation, which provides an expeditious access to 5-vinylindolin-2-ones with high regioselectivity. The protocol is distinguished by a mild reaction system avoiding ligand and high temperature. The kinetic isotope experiments indicate that the C−H bond cleavage is the rate-limiting step.



Methyleneindolinones, as an important family of indolin-2-ones, are common structural motifs applied in a wide range of biologically active pharmaceuticals.[1,2] Different substituents in the benzene core of methyleneindolinones have a significant effect on their biological activity (Figure 1).[2]

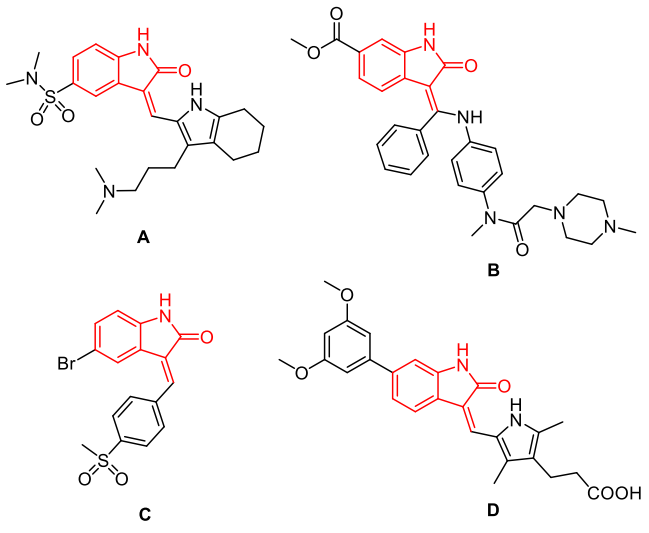


Figure 1. Representative bioactive methyleneindolinones.

For instance, compound **A** with a tertiary sulfonamide substitution at the C5-position has been reported as a potent inhibitor of non-receptor tyrosine kinases.[2a] Compound **B** with a similar methyleneindolinone motif was discovered as a triple angiokinase inhibitor, which enhanced the cytotoxic therapy response in pancreatic cancer.[2b] The simple methyleneindolinone **C** with a Br group at the same C5-position exhibited anti-inflammatory and analgesic activities and enhanced gastric tolerability in vivo.[2c] The compound **D** with a Br group at the same position was evaluated over the SPC-A1 lung cancer cell line and displayed better antiproliferative activity than Sunitinib.[2d] Therefore, several methods have been developed to functionalize the benzene core of methyleneindolinones and their analogues.[2−4] For example, Friedel−Crafts acylations have been used with an acyl chloride and an excess of $AlCl_3$ to afford methyleneindolinones incorporating an acyl substituted benzene core.[3] Furthermore, well-developed cross-coupling methods, such as Suzuki,[4a] Heck,[4d] and Stille[4g] coupling reactions, have been utilized to achieve the substitution of the benzene core in methyleneindolinones at various positions.[4] However, such protocols generally require organometallic reagents or organic halides and generate stoichiometric amounts of toxic byproducts. Therefore, further development of more direct strategies addressing atom economy issues is crucial for the efficient functionalization of the benzene core of methyleneindolinones.

In the past decades, transition-metal-catalyzed C−H bond activation reactions have been developed as eco-friendly methods for the efficient construction of C−C bonds, which can significantly reduce the number of synthetic steps and harmful byproducts.[5] However, achieving selectivity is very difficult in C−H functionalization reactions when several inequivalent C−H bonds are present. For the C(sp^2)−H functionalization of benzene, the usual strategy leading to *ortho*-selectivity is the introduction of *σ*-chelating directing

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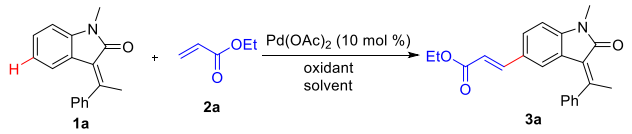
groups, which can form conformationally rigid five- or six-membered metallacycle intermediates to ensure site-selectivity.[6] The σ-chelation strategy was also employed in remote C−H activation. Furthermore, U-[7] and D-shaped[8] template-directed remote C−H activations, both generating metallacycles larger than a seven-membered ring, were proven to be applicable in *meta*- and *para*-selective functionalization, respectively. However, the pre-installation and removal procedures of these directing groups or complex templates significantly limit their synthetic applications. Despite the potential of the σ-chelating directing strategy, wherein different site-selectivity can be controlled, direct C−H functionalization without directing groups can reach sites that are not currently accessible by a directing group approach.[9] Recently, Yu discovered a powerful palladium catalyst with an electron-deficient 2-pyridone ligand, thereby enabling direct C−H olefination, cyanation, and carboxylation of unfunctionalized arenes, although these reactions required high temperatures.[10]

Inspired by Yu's protocol of direct C−H activation, in this study, we developed a new reaction utilizing the direct C−H functionalization strategy with palladium acetate as the catalyst, thereby achieving C5-olefination of the benzene core of methyleneindolinones. The reaction did not require the addition of an exogenous ligand and was applicable to the coupling of a variety of olefins.

Initially, methyleneindolinone **1a** and ethyl acrylate **2a** were selected as model substrates to screen the reaction conditions (Table 1). When 10 mol % $Pd(OAc)_2$ was used as the catalyst and AgOAc (2 equiv) was used as the oxidant at 90 °C, HFIP was found to be the optimal solvent for the reaction, providing the desired product **3a** in 51% yield (Table 1, entries 1−5). The structure of product **3a** was confirmed by single-crystal X-ray diffraction analysis (see Figure S4 in the Supporting Information),[11] nuclear magnetic resonance, and high-resolution mass spectrometry. According to the control experiments (see Table S1 in the Supporting Information), oxidant played a crucial role in the reaction. Therefore, by testing silver salts, we found that acetate was the best counterion compared to sulfate, carbonate, and nitrite (Table 1, entries 6−9). Other common oxidants such as air, $K_2S_2O_8$, $Cu(OAc)_2$, or $Mn(OAc)_3{\cdot}2H_2O$ were also screened, but none of them achieved the same effect as silver acetate (Table 1, entries 10−14). Subsequently, the influence of reaction temperature was examined. The high temperature was unfavorable for the transformation (Table 1, entry 15), and when the temperature was gradually lowered to 50 °C, product **3a** was afforded in a high yield of 86% (Table 1, entries 16 and 17), whereas a lower temperature resulted in a poor yield (Table 1, entry 18). For the reaction on a gram scale, 1.12 g of product **3a** was isolated in 67% yield from 1.25 g of **1a** at 50 °C. Moreover, in the presence of air, decreasing the amount of AgOAc to 50 or 10 mol % led to the decreased yields of **3a** (entries 19 and 20). In addition, lowering the loading of $Pd(OAc)_2$ led to the decreased yields of **3a** (entries 21 and 22).

With the optimized reaction conditions, we explored the scope of methyleneindolinones (Scheme 1). The reaction of methyleneindolinones containing electron-donating groups, such as Me and MeO, at the C7 site with **2a** under the optimized conditions resulted in the formation of alkenylated products **3b** and **3c** in good yields; however, at the same position (**3d** and **3e**), electron-withdrawing substituted groups, such as Cl or F, resulted in an obvious decrease in yield even

Table 1. Optimization of Reaction Conditions[a]



entry	oxidant	temp (°C)	solvent	yield[b] (**3a**, %)
1	AgOAc	90	THF	ND
2	AgOAc	90	toluene	5
3	AgOAc	90	DCM	7
4	AgOAc	90	MeCN	17
5	AgOAc	90	HFIP	51
6	Ag_2SO_4	90	HFIP	trace
7	Ag_2CO_3	90	HFIP	trace
8	$AgNO_2$	90	HFIP	43
9	AgOTf	90	HFIP	trace
10	air	90	HFIP	ND
11	$K_2S_2O_8$	90	HFIP	ND
12	$Cu(OAc)_2$	90	HFIP	ND
13	$Mn(OAc)_3{\cdot}2H_2O$	90	HFIP	trace
14	$PhI(OAc)_2$	90	HFIP	21
15	AgOAc	110	HFIP	32
16	AgOAc	70	HFIP	77
17	AgOAc	50	HFIP	86[c] (67)[d]
18	AgOAc	30	HFIP	26
19[e]	AgOAc	50	HFIP	39
20[f]	AgOAc	50	HFIP	7
21[g]	AgOAc	50	HFIP	72
22[h]	AgOAc	50	HFIP	31

[a]Reaction conditions: **1a** (0.2 mmol), oxidant (0.4 mmol), $Pd(OAc)_2$ (0.02 mmol), HFIP (2 mL), then **2a** (0.4 mmol), under Ar, 18 h. [b]Isolated yield of **3a**. ND: not detected. [c]The isomer byproducts were hard to be determined in the reaction. [d]Isolated yield of a gram scale reaction. [e]AgOAc (0.1 mmol) was used under the air. [f]AgOAc (0.02 mmol) was used under the air. [g]$Pd(OAc)_2$ (0.01 mmol) was used. [h]$Pd(OAc)_2$ (0.004 mmol) was used.

when the reactions were performed at 70 °C for 24 h. These results demonstrate that the electronic properties of the substituents on the benzene core of methyleneindolinones had a significant effect on the reaction. Notably, methyleneindolinone with a Me group at C6 site gave **3f** in 61% yield. Methyleneindolinone with a smaller conjugation system could perform the reaction to produce the desired product **3g**, but the yield was only 38%. However, product **3h** with a larger conjugation system was obtained in 34% yield, showing no obvious conjugation effect in the reaction. Unfortunately, *N*-H methyleneindolinone failed the olefination with **2a** to form the desired product, while *N*-Boc substituted methyleneindolinone performed the olefination to afford complex products. In addition, simple 1-methyl-2-indolione was tested in this reaction, but no desired product was detected. When (*E*)-1,5-dimethyl-3-(1-phenylethylidene)indolin-2-one, whose C5-position is blocked, reacted with **2a** under the optimized conditions, only trace C7-olefination product was detected.

Then, we investigated the scope of olefins in the C5-olefination of methyleneindolinones (Scheme 1). The transformation proceeded well for a wide range of acrylates, such as methyl acrylate, *n*-butyl acrylate, 1,1,1-trifluoroethyl acrylate, benzyl acrylate, and phenyl acrylate, providing good to high yields (63−86%) of the desired products **3i**−**3m**. Moreover, ethyl methacrylate underwent the reaction with **1a** to generate the corresponding product **3n** in 50% yield, whereas ethyl

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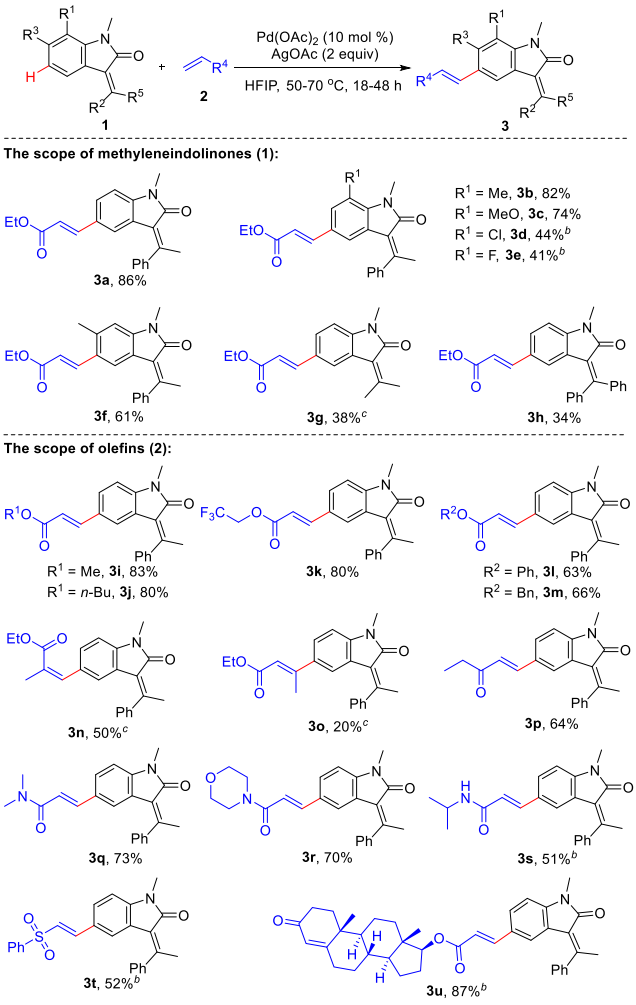
Scheme 1. Substrate Scope[a]



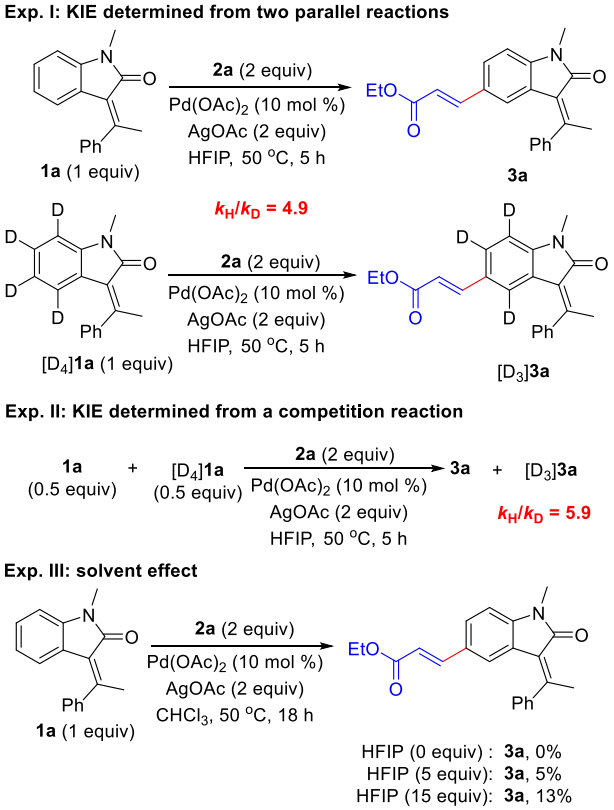
[a]Reaction conditions: **1a** (0.2 mmol), oxidant (0.4 mmol), $Pd(OAc)_2$ (0.02 mmol), HFIP (2 mL), then **2a** (0.4 mmol), under Ar, 18 h. Isolated yields are indicated. [b]The reaction was performed at 70 °C, 24 h. [c]The reaction was performed at 70 °C, 48 h.

crotonate gave the desired product **3o** in only 20% yield. These results suggest that steric hindrance at the olefins inhibits olefination. Ethyl vinyl ketone can also perform well in the reaction, giving the desired product **3p** in 64% yield. Subsequently, acrylamides were evaluated. *N*-disubstituted acrylamides, such as *N*,*N*-dimethylacrylamide and 4-acryloylmorpholine, participated in the reaction under the optimized conditions to afford the corresponding products **3q** and **3r** in 73% and 70% yields, respectively. Furthermore, *N*-isopropylacrylamide successfully participated in the reaction to form the desired product **3s** in 51% yield. Interestingly, phenyl vinyl sulfone exhibited a normal reactivity in the reaction, delivering product **3t** in 52% yield. Notably, the unactivated olefins such as 1-decene and styrene failed in the olefination with **1a** to form the desired products.

To verify the versatility of the reaction, ethyl acrylate derived from testosterone was synthesized and subjected to a reaction with **1a** under the optimized conditions. Desired product **3u** was isolated in 87% yield, indicating that the proposed method is a powerful tool for the combination of methyleneindolinone skeletons into natural products.

To gain insight into the reaction mechanism, a kinetic isotope effect (KIE) was performed (Scheme 2). Two parallel

Scheme 2. Mechanistic Investigations



reactions determined a KIE value of 4.9 (Exp. I), whereas a competition reaction gave a KIE value of 5.9 (Exp. II). These results suggest that C−H bond cleavage is the rate-determining step in this reaction, demonstrating that the reaction process involves a Pd-mediated C−H cleavage step rather than a Lewis acid-mediated Friedel−Crafts reaction.[12]

In addition, when $[D_4]$**1a** was carried out in the absence of **2a** under the optimized conditions, the recovery of $[D_4]$**1a** was 88% and the deuterium rate of recycled $[D_4]$**1a** had almost no change, suggesting that C−H activation is an irreversible process. Moreover, the olefination was performed in $CHCl_3$ without HFIP, which failed to afford **3a**. In the same reaction condition, adding HFIP could promote the formation of **3a** (Exp. III). These results suggest that HFIP may provide a suitable acid condition to accelerate the C−H activation.

On the basis of the preliminary mechanistic observations and previous reports,[13] we proposed a possible reaction mechanism in Scheme 3. First, an electrophilic attack of Pd(II) to C5 of methyleneindolinone **1a** forms a six-membered transition state **A**, which undergoes deprotonation to generate palladated intermediate **B**. Then, **B** undergoes alkene insertion with **2a** to afford intermediate **C**. Finally, *β*-H elimination delivers the product **3a**, and the resulting Pd(0) species may be oxidized by a Ag(I) salt to regenerate active Pd(II), which is supported by the silver mirror phenomenon.

In summary, we have developed an efficient synthetic method for the direct C5-olefination of methyleneindolinones through palladium-catalyzed C−H activation without an external ligand, which resulted in a higher step economy compared to the traditional cross-coupling reactions. Several

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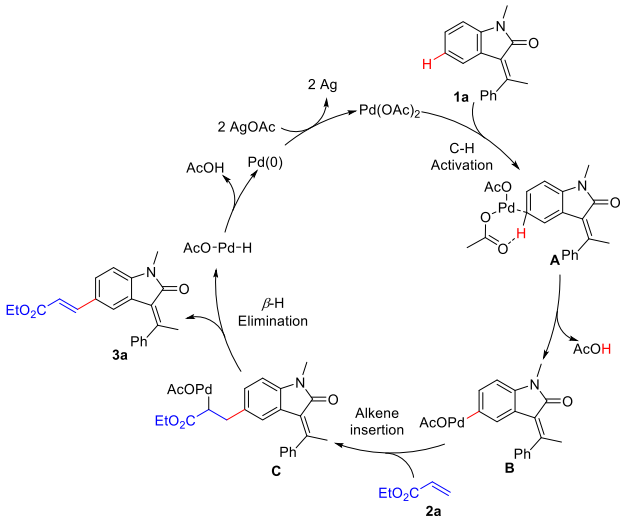
Scheme 3. Plausible Mechanism



olefins were well tolerated in this transformation. Mechanistic studies show that C−H bond cleavage is the rate-limiting step. Our protocol provides a successful example of direct C−H functionalization, which would inspire and stimulate more approaches for the efficient functionalization of arenes in valuable compounds such as fine chemicals and drugs.

EXPERIMENTAL SECTION

General Information. All manipulations were carried out under an argon atmosphere using standard Schlenk techniques, unless otherwise stated. Solvents and other chemicals were obtained from commercial sources and were used without further purification. Reactions were monitored using silica gel thin-layer chromatography (TLC). TLC plates were visualized with UV light (254 nm). Chemical shifts (δ, ppm) in the ^{1}H NMR and ^{13}C{^{1}H} NMR spectra were recorded on a Bruker AVANCE 400 (400 MHz) or Ascend 600 (600 MHz) spectrometer using using TMS as internal standard or internally referenced to $CHCl_3$ (δ = 7.26 ppm), DMSO (δ = 2.50 ppm), and coupling constants (J) are given in hertz (Hz). High-resolution mass spectra (HRMS) of all new compounds were recorded on a Waters GCT Premier mass spectrometer using EI-TOF (electron ionization time-of-flight), with accurate mass reported for the molecular ion [M]$^+$. Single crystals of **3a** were recrystallized from *n*-hexane/acetone at rt. A suitable crystal was selected and mounted on an APEX II diffractometer. Melting points (mp) were determined in opened capillary tubes and are uncorrected. The substrates **1a**−**1f**,[14] **1h**,[14] **1g**,[15] and **2u**[16] were prepared according to the reported literature procedure.

General Procedure for C5-Olefination of Methyleneindolinones. Methyleneindolinone **1** (0.2 mmol, 49.8 mg), $Pd(OAc)_2$ (0.02 mmol, 4.5 mg), and AgOAc (0.4 mmol, 66.8 mg) were added to 2 mL of HFIP; then **2** (0.4 mmol) was added under an argon atmosphere. The mixture was stirred at 50 °C (heated by heating mantle) for 18 h. The reaction mixture was cooled to room temperature and then filtered to a round-bottom flask by a short pad of silica gel (EtOAc eluent). Volatiles were evaporated under reduced pressure. The purification was performed by flash column chromatography on silica gel to afford the desired products **3**, which are easy to deteriorate when exposed to air in the solvents.

Detailed Procedure for the Gram Scale C5-Olefination of 1a with 2a. Methyleneindolinone **1a** (5.0 mmol, 1.25 g), $Pd(OAc)_2$ (0.5 mmol, 112 mg), and AgOAc (10 mmol, 1.65 g) were added to 44 mL of HFIP; then **2a** (10 mmol) was added under an argon atmosphere. The mixture was stirred at 50 °C (heated by oil bath) for 24 h. The reaction mixture was cooled to room temperature and then filtered to a round-bottom flask by a short pad of silica gel (EtOAc eluent). Volatiles were evaporated under reduced pressure. The purification was performed by flash column chromatography (EtOAc/petroleum = 1:10) on silica gel to afford the desired product **3a** (67%, 1.12 g).

*Ethyl (E)-3-((E)-1,7-Dimethyl-2-oxo-3-(1-phenylethylidene)-indolin-5-yl)acrylate (**3a**).* The compound was prepared from **1a** (0.2 mmol, 49.8 mg) and ethyl acrylate (0.4 mmol, 40 mg) following the general procedure. Purification by column chromatography (silica, 10:1 petroleum ether:EtOAc) afforded 60 mg (86%) of the title compound **3a**. Yellow solid, mp 126−128 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.55 (m, 3H), 7.26−7.34 (m, 4H), 6.75 (d, J = 8.12 Hz, 1H), 6.25 (d, J = 1.16 Hz, 1H), 5.79 (d, J = 15.92 Hz, 1H), 4.20 (q, J = 7.16 Hz, 2H), 3.29 (s, 3H), 2.83 (s, 3H), 1.30 (t, J = 7.12 Hz, 3 H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.2, 167.3, 156.6, 144.8, 143.9, 142.6, 129.4, 129.1, 128.7, 127.7, 126.3, 123.2, 122.8, 122.1, 115.4, 107.6, 60.3, 25.9, 22.9, 22.8, 14.4 ppm; HRMS (EI-TOF) ([M]$^+$) calcd for $C_{22}H_{21}NO_3$ 347.1521, Found 347.1522.

*Ethyl (E)-3-((E)-1,7-Dimethyl-2-oxo-3-(1-phenylethylidene)-indolin-5-yl)acrylate (**3b**).* The compound was prepared from **1b** (0.2 mmol, 50.3 mg) and ethyl acrylate (0.4 mmol, 40 mg) following the general procedure. Purification by column chromatography (silica, 10:1 petroleum: EtOAc) afforded 59 mg (82%) of the title compound **3b**. Yellow solid, mp 141−142 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.56 (m, 3H), 7.29 (s, 1H), 7.25−7.27 (m, 2H), 7.04 (s, 1H), 6.14 (d, J = 1.20 Hz, 1H), 5.78 (d, J = 15.88 Hz, 1H), 4.22 (q, J = 7.12, 2H), 3.60 (s, 3H), 2.85 (s, 3H), 2.58 (s, 3H), 1.32 (t, J = 14.28 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.8, 167.3, 156.2, 144.5, 142.8, 142.0, 132.6, 129.4, 128.6, 127.4, 126.2, 123.7, 122.6, 120.3, 119.2, 115.4, 60.3, 29.7, 29.1, 23.2, 19.4, 14.3 ppm; HRMS (EI-TOF) ([M]$^+$) calcd for $C_{23}H_{23}NO_3$ 361.1687, Found 361.1682.

*Ethyl (E)-3-((E)-7-Methoxy-1-methyl-2-oxo-3-(1-phenylethyl-idene)indolin-5-yl)acrylate (**3c**).* The compound was prepared from **1c** (0.2 mmol, 58.0 mg) and ethyl acrylate (0.4 mmol, 40 mg) following the general procedure. Purification by column chromatography (silica, 10:1 petroleum:EtOAc) afforded 56 mg (74%) of the title compound **3c**. Yellow solid, mp 159−160 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.54 (m, 3H), 7.25−7.28 (m, 3H), 6.87 (s, 1H), 5.92 (s, 1H), 5.86 (d, J = 15.88 Hz, 1H), 4.22 (q, J = 7.12 Hz, 2H), 3.86 (s, 3H), 3.58 (s, 3H), 2.84 (s, 3H), 1.32 (t, 7.12 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 186.3, 167.2, 156.8, 144.9, 144.8, 142.7, 132.5, 129.3, 128.7, 127.9, 126.3, 124.2, 123.0, 116.4, 115.5, 111.4, 60.3, 56.0, 29.1, 23.1, 14.3 ppm; HRMS (EI-TOF) ([M]$^+$) calcd for $C_{23}H_{23}NO_4$ 377.1627, Found 377.1628.

*Ethyl (E)-3-((E)-7-Chloro-1-methyl-2-oxo-3-(1-phenylethylidene)-indolin-5-yl)acrylate (**3d**).* **1d** (0.2 mmol, 58.6 mg), $Pd(OAc)_2$ (0.02 mmol, 4.5 mg), and AgOAc (0.4 mmol, 66.8 mg) were added to a neat sealed tube under argon; then 2 mL of HFIP and ethyl acrylate (0.4 mmol, 40 mg) were added, respectively, under an argon atmosphere. The mixture was stirred at 70 °C (heated by heating mantle) for 24 h. The reaction mixture was cooled to room temperature and then filtered to a round-bottom flask by a short pad of silica gel (EtOAc eluent). Volatiles were evaporated under reduced pressure. Purification by column chromatography (silica, 10:1 petroleum ether:EtOAc) afforded 33 mg (44%) of the title compound **3d**. Yellow solid, mp 116−117 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54−7.56 (m, 3H), 7.20−7.28 (m, 4H), 6.15 (d, J = 1.4 Hz, 1H), 6.78 (d, J = 15.95 Hz, 1H), 4.22 (q, J = 7.12 Hz, 2H), 3.69 (s, 3H), 2.86 (s, 3H), 1.32 (t, J = 7.12 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.2, 166.8, 158.2, 143.0, 142.3, 139.4, 130.4, 129.5, 128.9, 128.4, 126.1, 125.6, 122.0, 120.4, 116.9, 115.2, 60.4, 29.1, 23.4, 14.3 ppm; HRMS (EI-TOF) ([M]$^+$) calcd for $C_{22}H_{20}ClNO_3$ 381.1132, Found 381.1136.

*Ethyl (E)-3-((E)-7-Fluoro-1-methyl-2-oxo-3-(1-phenylethylidene)-indolin-5-yl)acrylate (**3e**).* **1e** (0.2 mmol, 53.4 mg), $Pd(OAc)_2$ (0.02 mmol, 4.5 mg), and AgOAc (0.4 mmol, 66.8 mg) were added to a neat sealed tube under argon; then 2 mL of HFIP and ethyl acrylate (0.4 mmol, 40 mg) were added, respectively, under an argon atmosphere. The mixture was stirred at 70 °C (heated by heating mantle) for 24 h. The reaction mixture was cooled to room temperature and then filtered to a round-bottom flask by a short pad

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of silica gel (EtOAc eluent). Volatiles were evaporated under reduced pressure. Purification by column chromatography (silica, 10:1 petroleum ether:EtOAc) afforded 30 mg (41%) of the title compound **3e**. Yellow solid, mp 102−104 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51−7.55 (m, 3H), 7.24−7.27 (m, 2H), 7.22 (d, J = 19.52 Hz, 1H), 7.03 (dd, J_1 = 19.2 Hz, J_2 = 1.12 Hz, 1H), 6.03 (d, J = 1.12 Hz, 1H), 5.82 (d, J = 15.92 Hz, 1H), 4.20 (q, J = 7.12 Hz, 2H), 3.50 (d, J = 2.84 Hz, 3H), 2.84 (s, 3H), 1.30 (t, J = 7.12 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.8, 166.9, 158.2, 147.3 (d, J = 242.22 Hz), 143.5 (d, J = 2.11 Hz), 142.3, 130.6 (d, J = 9.14 Hz), 129.5, 128.9, 128.3 (d, J = 6.40 Hz), 126.2, 125.7 (d, J = 4.46 Hz), 122.5 (d, J = 2.91 Hz), 118.6 (d, J = 24.04 Hz), 116.8, 115.4 (d, J = 19.86 Hz), 60.5, 28.3 (d, J = 6.14 Hz), 23.0, 14.3 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −137.2 ppm; HRMS (EI-TOF) ([M]$^+$) calcd for $C_{22}H_{20}FNO_3$ 365.1427, Found 365.1429.

*Ethyl (E)-3-((E)-1,6-Dimethyl-2-oxo-3-(1-phenylethylidene)-indolin-5-yl)acrylate (**3f**).* The compound was prepared from **1f** (0.2 mmol, 50.3 mg) and ethyl acrylate (0.4 mmol, 40 mg) following the general procedure. Purification by column chromatography (silica, 10:1 petroleum ether:EtOAc) afforded 43 mg (61%) of the title compound **3f**. Yellow solid, mp 129−130 °C. ^{1}H NMR (600) MHz, $CDCl_3$) δ 7.73 (d, J = 15.78 Hz, 1H), 7.50−7.56 (m, 3H), 7.27−7.29 (m, 2H), 6.57 (s, 1H), 6.25 (s, 1H), 5.49 (d, J = 15.78 Hz, 1H), 4.21 (q, J = 7.14 Hz, 2H), 3.26 (s, 3H), 2.82 (s, 3H), 2.39 (s, 3H), 1.32 (t, J = 7.14 Hz, 3 H) ppm; ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 168.4, 167.3, 155.0, 143.7, 142.8, 141.6, 138.8, 129.4, 128.5, 126.4, 126.1, 122.8, 121.1, 120.7, 116.2, 109.5, 60.2, 25.8, 22.4, 20.2, 14.4 ppm; HRMS (EI-TOF) ([M]$^+$) calcd for $C_{23}H_{23}NO_3$ 361.1678, Found 361.1682.

*Ethyl (E)-3-(1-Methyl-2-oxo-3-(propan-2-ylidene)indolin-5-yl)-acrylate (**3g**).* **1g** (0.2 mmol, 37.4 mg), $Pd(OAc)_2$ (0.02 mmol, 4.5 mg), and AgOAc (0.4 mmol, 66.8 mg) were added to a neat sealed tube under argon; then 2 mL of HFIP and ethyl acrylate (0.4 mmol, 40 mg) were added, respectively, under an argon atmosphere. The mixture was stirred at 70 °C (heated by heating mantle) for 48 h. The reaction mixture was cooled to room temperature and then filtered to a round-bottom flask by a short pad of silica gel (EtOAc eluent). Volatiles were evaporated under reduced pressure. Purification by column chromatography (silica, 10:1 petroleum ether:EtOAc) afforded 22 mg (38%) of the title compound **3g**. Yellow solid, mp 90−91 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (t, J_1 = 7.2 Hz, J_2 = 8.64 Hz, 2H), 7.46 (d, J = 7.98 Hz, 1H), 6.84 (d, J = 8.04 Hz, 1H), 6.37 (d, J = 15.9 Hz, 1H), 4.29 (q, J = 7.14 Hz, 2H), 3.27 (s, 3H), 2.66 (s, 3H), 2.44 (s, 3H), 1.37 (t, J = 7.14 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 167.9, 167.3, 156.9, 145.1, 143.8, 128.5, 128.1, 124.2, 122.7, 122.0, 115.5, 107.7, 60.4, 25.8, 25.4, 23.4, 14.4 ppm; HRMS (EI-TOF) ([M]$^+$) calcd for $C_{17}H_{19}NO_3$ 285.1365, Found 285.1367.

*Ethyl (E)-3-(3-(Diphenylmethylene)-1-methyl-2-oxoindolin-5-yl)-acrylate (**3h**).* The compound was prepared from **1h** (0.2 mmol, 62 mg) and ethyl acrylate (0.4 mmol, 40 mg) following the general procedure. Purification by column chromatography (silica, 5:1 petroleum ether:EtOAc) afforded 28 mg (34%) of the title compound **3h**. Yellow solid, mp 163−165 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48−7.54 (m, 3H), 7.32−7.40 (m, 9H), 6.77 (d, J = 8.10 Hz, 1H), 6.52 (s, 1H), 5.86 (d, J = 15.90 Hz, 1H), 4.21 (q, J = 7.14 Hz, 2H), 3.22 (s, 3H), 1.31 (t, J = 7.08 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 167.2, 166.8, 156.1, 144.8, 144.6, 140.9, 139.4, 130.1, 129.6, 129.5, 129.2, 129.2, 127.8, 123.9, 123.4, 122.5, 115.5, 107.9, 60.3, 26.0, 14.3 ppm; HRMS (EI-TOF) ([M]$^+$) calcd for $C_{27}H_{23}NO_3$ 409.1678, Found 409.1682.

*Methyl (E)-3-((E)-1-Methyl-2-oxo-3-(1-phenylethylidene)indolin-5-yl)acrylate (**3i**).* The compound was prepared from **1a** (0.2 mmol, 49.8 mg) and methyl acrylate (0.4 mmol, 34 mg) following the general procedure. Purification by column chromatography (silica, 10:1 petroleum ether:EtOAc) afforded 56 mg (83%) of the title compound **3i**. Yellow solid, mp 135−136 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (t, J_1 = 3.32 Hz, J_2 = 2.92 Hz, 3H), 7.26−7.36 (m, 4H), 6.74 (d, J = 8.08 Hz, 1H), 6.26 (s, 1H), 5.77 (d, J = 15.92 Hz, 1H), 3.74 (s, 3H), 3.28 (s, 3H), 2.83 (s, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.1, 167.7, 156.6, 145.0, 144.0, 142.5, 129.4, 129.3, 128.7, 127.6, 126.3, 123.2, 122.7, 121.9, 114.8, 107.6, 51.6, 25.9, 22.8 ppm; HRMS (EI-TOF) ([M]$^+$) calcd for $C_{21}H_{19}NO_3$ 333.1365, Found 333.1367.

*Butyl (E)-3-((E)-1-Methyl-2-oxo-3-(1-phenylethylidene)indolin-5-yl)acrylate (**3j**).* The compound was prepared from **1a** (0.2 mmol, 49.8 mg) and butyl acrylate (0.4 mmol, 51 mg) following the general procedure. Purification by column chromatography (silica, 10:1 petroleum ether:EtOAc) afforded 60 mg (80%) of the title compound **3j**. Yellow solid, mp 155−157 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.51−7.55 (m, 3H), 7.27−7.33 (m, 3H), 6.75 (d, J = 8.04 Hz, 1H), 6.24 (s, 1H), 5.79 (d, J = 15.9 Hz, 1H), 4.15 (q, J = 6.66 Hz, 2H), 3.28 (s, 3H), 2.83 (s, 3H), 1.66 (m, 2H), 1.42 (m, 2H), 0.97 (t, J = 7.44 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 168.2, 167.3, 156.6, 144.7, 143.9, 142.6, 129.4, 129.1, 128.7, 127.8, 126.3, 123.2, 122.8, 122.1, 115.4, 107.6, 64.2, 30.8, 25.9, 22.8, 19.2, 13.8 ppm; HRMS (EI-TOF) ([M]$^+$) calcd for $C_{24}H_{25}NO_3$ 375.1834; Found 375.1837.

*2,2,2-Trifluoroethyl (E)-3-((E)-1-Methyl-2-oxo-3-(1-phenylethylidene)indolin-5-yl)acrylate (**3k**).* The compound was prepared from **1a** (0.2 mmol, 49.8 mg) and 2,2,2-trifluoroethyl acrylate (0.4 mmol, 62 mg) following the general procedure. Purification by column chromatography (silica, 10:1 petroleum ether:EtOAc) afforded 64 mg (80%) of the title compound **3k**. Yellow solid, mp 120−122 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52−7.56 (m, 3H), 7.42 (d, J = 15.92 Hz, 1H), 7.27−7.32 (m, 3H), 6.77 (d, J = 8.08 Hz, 1H), 6.24 (d, J = 1.32 Hz, 1H), 5.80 (d, J = 15.92 Hz, 1H), 4.53 (q, J = 8.52 Hz, 2H), 3.29 (s, 3H), 2.84 (s, 3H) ppm; ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 168.2, 167.3, 156.6, 144.7, 143.9, 142.6, 129.4, 129.1, 128.7, 127.8, 126.3, 123.2, 122.8, 122.1, 115.4, 107.6, 64.2, 30.8, 25.9, 22.8, 19.2, 13.8 ppm; ^{19}F NMR (565 MHz, $CDCl_3$) δ −73.8 ppm; HRMS (EI-TOF) ([M]$^+$) calcd for $C_{22}H_{18}F_3NO_3$ 401.1239; Found 401.1237.

*Phenyl (E)-3-((E)-1-Methyl-2-oxo-3-(1-phenylethylidene)indolin-5-yl)acrylate (**3l**).* The compound was prepared from **1a** (0.2 mmol, 49.8 mg) and phenyl acetate (0.4 mmol, 54.4 mg) following the general procedure. Purification by column chromatography (silica, 10:1 petroleum ether:EtOAc) afforded 50 mg (63%) of the title compound **3l**. Yellow solid, mp 186−187 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.57 (m, 4H), 7.34−7.41 (m, 3H), 7.22−7.31 (m, 3H), 7.12 (d, J = 7.64 Hz, 2H), 6.79 (d, J = 8.08 Hz, 1H), 6.32 (s, 1H), 5.96 (d, J = 15.88 Hz, 1H), 3.30 (s, 3H), 2.85 (s, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.2, 165.7, 156.9, 150.9, 146.8, 144.3, 142.5, 129.7, 129.5, 129.4, 128.8, 127.5, 126.3, 125.7, 123.3, 122.7, 122.1, 121.7, 114.2, 107.7, 25.9, 22.9 ppm; HRMS (EI-TOF) ([M]$^+$) calcd for $C_{26}H_{21}NO_3$ 395.1521; Found 395.1518.

*(E)-5-((E)-4-(Benzyloxy)-3-oxobut-1-en-1-yl)-1-methyl-3-(1-phenylethylidene)indolin-2-one (**3m**).* The compound was prepared from **1a** (0.2 mmol, 49.8 mg) and 1-(benzyloxy)but-3-en-2-one (0.4 mmol, 70.4 mg) following the general procedure. Purification by column chromatography (silica, 10:1 petroleum ether:EtOAc) afforded 54 mg (66%) of the title compound **3m**. Yellow solid, mp 209−210 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.53 (m, 3H), 7.38 (d, J = 4.28 Hz, 4H), 7.25−7.36 (m, 5H), 6.74 (d, J = 8.08 Hz, 1H), 6.24 (d, J = 1.04 Hz, 1H), 5.84 (d, J = 15.92 Hz, 1H), 5.19 (s, 2H), 3.27 (s, 3H), 2.82 (s, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.1, 167.0, 156.6, 145.4, 144.0, 142.6, 136.3, 129.4, 129.2, 128.7, 128.6, 128.2, 128.1, 127.6, 126.3, 123.2, 122.7, 122.2, 114.9, 107.7, 66.1, 25.9, 22.8 ppm; HRMS (EI-TOF) ([M]$^+$) calcd for $C_{27}H_{23}NO_3$ 409.1678; Found 409.1679.

*Ethyl (E)-2-Methyl-3-((E)-1-methyl-2-oxo-3-(1-phenylethylidene)indolin-5-yl)acrylate (**3n**).* **1a** (0.2 mmol, 49.8 mg), $Pd(OAc)_2$ (0.02 mmol, 4.5 mg), and AgOAc (0.4 mmol, 66.8 mg) were added to a neat sealed tube under argon; then 2 mL of HFIP and ethyl methacrylate (0.4 mmol, 45.6 mg) were added, respectively, under an argon atmosphere. The mixture was stirred at 70 °C (heated by heating mantle) for 24 h. Purification by column chromatography (silica, 10:1 petroleum ether:EtOAc) afforded 36 mg (50%) of the title compound **3n**. Yellow solid, mp 83−84 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.51 (m, 3H), 7.39 (s, 1H), 7.28 (d, J = 6.72 Hz, 2H), 7.18 (d, J = 7.72 Hz, 1H), 6.79 (d, J = 8.08 Hz, 1H), 6.43 (s,

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1H), 4.20 (q, J = 7.12 Hz, 2H), 3.30 (s, 3H), 2.82 (s, 3H), 1.63 (d, J = 0.8 Hz, 3H), 1.31 (t, J = 7.12 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.6, 168.3, 155.9, 142.8, 142.3, 138.6, 131.3, 129.4, 129.2, 128.5, 126.3, 126.1, 123.7, 122.9, 122.6, 107.4, 60.7, 29.7, 25.9, 23.2, 14.3, 14.1 ppm; HRMS (EI-TOF) ($[M]^+$) calcd for $C_{23}H_{23}NO_3$ 361.1678; Found 361.1680.

*Ethyl (E)-3-((E)-1-Methyl-2-oxo-3-(1-phenylethylidene)indolin-5-yl)but-2-enoate (**3o**).* **1a** (0.2 mmol, 49.8 mg), $Pd(OAc)_2$ (0.02 mmol, 4.5 mg), and AgOAc (0.4 mmol, 66.8 mg) were added to a neat sealed tube under argon; then 2 mL of HFIP and (*E*)-but-2-enoate (0.4 mmol, 45.6 mg) were added, respectively, under an argon atmosphere. The mixture was stirred at 70 °C (heated by heating mantle) for 48 h. The reaction mixture was cooled to room temperature and then filtered to a round-bottom flask by a short pad of silica gel (EtOAc eluent). Purification by column chromatography (silica, 15:1 petroleum ether:EtOAc) afforded 14 mg (20%) of the title compound **3o**. Yellow solid, mp 132−133 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.46−7.56 (m, 3H), 7.29−7.34 (m, 3H), 6.76, (d, J = 8.2 Hz, 1H), 6.22 (d, J = 1.76 Hz, 1H), 5.77 (d, J = 1.2 Hz, 1H), 4.18 (q, J = 7.12 Hz, 2H), 3.31 (s, 3H), 2.86 (s, 3H), 2.22 (d, J = 1.16 Hz, 3H), 1.30 (t, J = 7.12 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 168.2, 167.0, 155.9, 154.9, 143.0, 142.8, 135.0, 129.3, 128.5, 126.4, 126.2, 123.2, 122.7, 121.2, 115.2, 107.2, 59.7, 53.4, 25.9, 22.7, 17.2, 14.4 ppm; HRMS (EI-TOF) ($[M]^+$) calcd for $C_{23}H_{23}NO_3$ 361.1678; Found 361.1681.

*Ethyl (E)-2-Methyl-3-((E)-1-methyl-2-oxo-3-(1-phenylethylidene)indolin-5-yl)acrylate (**3p**).* The compound was prepared from **1a** (0.2 mmol, 49.8 mg) and pent-1-en-3-one (0.4 mmol, 37 mg) following the general procedure. Purification by column chromatography (silica, 10:1 petroleum ether:EtOAc) afforded 42 mg (64%) of the title compound **3p**. Yellow solid, mp 97−98 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.54−7.57 (m, 3H), 7.28−7.31 (m, 3H), 7.24 (d, J = 16 Hz, 1H), 6.77 (d, J = 8.08 Hz, 1H), 6.29 (d, J = 0.76 Hz, 1H), 6.11 (d, J = 16 Hz, 1H), 3.29 (s, 3H), 2.84 (s, 3H), 2.56 (q, J = 7.36 Hz, 2H), 1.13 (t, J = 7.36, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.2, 167.0, 155.9, 154.9, 143.0, 142.8, 135.0, 129.3, 128.5, 126.4, 126.2, 123.2, 122.7, 121.2, 115.2, 107.2, 59.7, 53.4, 25.9, 22.7, 17.2, 14.4 ppm; HRMS (EI-TOF) ($[M]^+$) calcd for $C_{22}H_{21}NO_2$ 331.1572; Found 331.1575.

*(E)-N,N-Dimethyl-3-((E)-1-methyl-2-oxo-3-(1-phenylethylidene)-indolin-5-yl)acrylamide (**3q**).* The compound was prepared from **1a** (0.2 mmol, 49.8 mg) and *N*,*N*-dimethylacrylamide (0.4 mmol, 40 mg) following the general procedure. Purification by column chromatography (silica, 3:1 petroleum ether:EtOAc) afforded 50 mg (73%) of the title compound **3q**. Yellow solid, mp 179−181 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (t, J_1 = 7.12 Hz, J_2 = 7.64 Hz, 3H), 7.44 (t, J_1 = 7.48 Hz, J_2 = 7.36 Hz, 1H), 7.36 (d, J = 15.36 Hz, 1H), 7.31 (d, J = 1.36 Hz, 1H), 7.29 (s, 1H), 7.24 (d, J = 1.32, 1H), 6.74 (d, J = 16.04 Hz, 1H),6.31 (s, 1H), 6.18 (d, J = 15.32 Hz, 1H), 3.29 (s, 3H), 3.04 (d, J = 12.72 Hz, 6H), 2.83 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 168.2, 166.8, 155.9, 143.4, 143.0, 142.4, 129.7, 129.2, 128.6, 128.2, 126.5, 123.1, 123.0, 120.8, 114.4, 107.5, 27.3, 35.9, 29.7, 25.9, 22.7 ppm; HRMS (EI-TOF) ($[M]^+$) calcd for $C_{22}H_{22}N_2O_2$ 346.1681; Found 346.1683.

*(E)-1-Methyl-5-((E)-3-morpholino-3-oxoprop-1-en-1-yl)-3-(1-phenylethylidene)indolin-2-one (**3r**).* The compound was prepared from **1a** (0.2 mmol, 49.8 mg) and 1-morpholinoprop-2-en-1-one (0.4 mmol, 56 mg) following the general procedure. Purification by column chromatography (silica, 1:1 petroleum ether:EtOAc) afforded 54 mg (70%) of the title compound **3r**. Yellow solid, mp 167−168 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (t, J_1 = 7.28 Hz, J_2 = 7.68 Hz, 2H), 7.37−7.43 (m, 2H), 7.30 (t, J_1 = 7.64 Hz, J_2 = 1.36 Hz, 2H), 7.24−7.27 (m, 1H), 6.74 (d, J = 8.04 Hz, 1H), 6.29 (s, 1H), 6.14 (d, J = 15.28 Hz, 1H), 3.71 (s, 6H), 3.51 (br, 2H), 3.28 (s, 3H), 2.83 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.1. 165.6, 156.0, 143.6, 143.2, 143.1, 129.5, 129.3, 128.4, 128.0, 126.6, 123.1, 123.0, 121.0, 113.5, 107.5, 66.9, 46.1, 42.4, 25.9, 22.8 ppm; HRMS (EI-TOF) ($[M]^+$) calcd for $C_{24}H_{24}N_2O_3$ 388.1787; Found 388.1789.

*(E)-N-Isopropyl-3-((E)-1-methyl-2-oxo-3-(1-phenylethylidene)-indolin-5-yl)acrylamide (**3s**).* **1a** (0.2 mmol, 49.8 mg), $Pd(OAc)_2$ (0.02 mmol, 4.5 mg), and AgOAc (0.4 mmol, 66.8 mg) were added to a neat sealed tube under argon; then 2 mL of HFIP and *N*-isopropylacrylamide (0.4 mmol, 45 mg) were added, respectively, under an argon atmosphere. The mixture was stirred at 70 °C (heated by heating mantle) for 24 h. The reaction mixture was cooled to room temperature and then filtered to a round-bottom flask by a short pad of silica gel (EtOAc eluent). Purification by column chromatography (silica, 1:1 petroleum ether:EtOAc) afforded 37 mg (51%) of the title compound **3s**. Yellow solid, mp 223−224 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.46−7.53 (m, 3H), 7.20−7.28 (m, 4H), 6.69 (d, J = 8.12 Hz, 1H), 6.22 (s, 1H), 5.86 (d, J = 15.52 Hz, 1H), 5.51 (d, J = 7.44 Hz, NH), 4.16 (m, 1H), 3.26 (s, 3H), 2.81 (s, 3H), 1.19 (d, J = 6.56 Hz, 6H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.1, 165.3, 156.2, 143.3, 142.6, 140.8, 129.3, 128.6, 128.2, 127.8, 126.4, 123.0, 122.9, 122.6, 118.4 (d, J = 3.23 Hz), 107.6 (d, J = 3.17 Hz), 41.5, 25.9, 22.8 (t, J_1 = 4.86 Hz, J_2 = 3.45 Hz) ppm; HRMS (EI-TOF) ($[M]^+$) calcd for $C_{23}H_{24}N_2O_2$ 360.1838; Found 360.1841.

*(E)-1-Methyl-3-(1-phenylethylidene)-5-((E)-2-(phenylsulfonyl)-vinyl)indolin-2-one (**3t**).* **1a** (0.2 mmol, 49.8 mg), $Pd(OAc)_2$ (0.02 mmol, 4.5 mg), and AgOAc (0.4 mmol, 66.8 mg) were added to a neat sealed tube under argon; then 2 mL of HFIP and phenyl vinyl sulfone (0.4 mmol, 168 mg) were added, respectively, under an argon atmosphere. The mixture was stirred at 70 °C (heated by heating mantle) for 24 h. The reaction mixture was cooled to room temperature and then filtered to a round-bottom flask by a short pad of silica gel (EtOAc eluent). Purification by column chromatography (silica, 3:1 petroleum ether:EtOAc) afforded 43 mg (52%) of the title compound **3t**. Yellow solid, mp 152−153 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.87−7.88 (m, 2H), 7.61−7.64 (m, 1H), 7.53−7.57 (m, 2H), 7.44−7.48 (m, 3H), 7.31 (d, J = 15.32 Hz, 1H), 7.23−7.26 (m, 3H), 6.75 (d, J = 8.12 Hz, 1H), 6.14 (m, 2H), 3.28 (s, 3H), 2.82 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.0, 157.1, 144.6, 142.6, 142.5, 141.1, 133.2, 129.9, 129.7, 129.4, 129.2, 128.8, 128.1, 127.4, 126.3, 125.5, 124.1, 123.3, 122.5, 122.2, 107.7, 29.7, 26.0, 22.8 ppm; HRMS (EI-TOF) ($[M]^+$) calcd for $C_{25}H_{21}NO_3S$ 415.1242; Found 415.1244.

*(8R,9S,10R,13S,14S,17S)-10,13-Dimethyl-3-oxo-2,3,6,7,8,9,-10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]-phenanthren-17-yl (E)-3-((E)-1-Methyl-2-oxo-3-(1-phenylethylidene)indolin-5-yl)acrylate (**3u**).* **1a** (0.2 mmol, 49.8 mg), $Pd(OAc)_2$ (0.02 mmol, 4.5 mg), and AgOAc (0.4 mmol, 66.8 mg) were added to a neat sealed tube under argon; then 2 mL of HFIP and **2u** (0.4 mmol, 137 mg) were added, respectively, under an argon atmosphere. The mixture was stirred at 70 °C (heated by heating mantle) for 24 h. The reaction mixture was cooled to room temperature and then filtered to a round-bottom flask by a short pad of silica gel (EtOAc eluent). Purification by column chromatography (silica, 15:1 petroleum ether:EtOAc) afforded 103 mg (87%) of the title compound **3u**. Yellow solid, mp 207−211 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 7.12 Hz, 3H), 7.30 (d, J = 15.36 Hz, 4H), 6.75 (d, J = 7.72 Hz, 1H), 6.22 (s, 1H), 5.80 (d, J = 15.92 Hz, 1H), 5.74 (s, 1H), 4.67 (t, J = 8.32 Hz, 1H), 3.28 (s, 3H), 2.83 (s, 3H), 2.20−2.42 (m, 5H), 2.05 (d, J = 1.88 Hz, 1H), 1.37−1.89 (m, 9H), 1.21 (s, 3H), 0.88−1.14 (m, 7H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 199.5, 171.0, 168.1, 167.2, 156.5, 144.5, 143.9, 142.6, 129.4, 129.0, 128.6, 127.7, 126.3, 123.9, 123.1, 122.8, 122.1, 115.6, 107.6, 82.3, 53.7, 50.3, 42.7, 38.6, 36.7, 35.7, 35.4, 33.9, 32.8, 31.5, 27.7, 25.9, 23.6, 22.8, 20.6, 17.4, 12.1 ppm; HRMS (EI-TOF) ($[M]^+$) calcd for $C_{39}H_{43}NO_4$ 589.3192; Found 589.3195.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00637.

X-ray crystallographic data (ORTEP diagrams) of product **3a** along with its important crystal data, table of control experiments, details of mechanistic studies, copies of ^1H and ^{13}C spectra for all isolated compounds, and ^{19}F spectra of products **3e** and **3k** (PDF)

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Accession Codes

CCDC 2056775 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Singh, G. S.; Desta, Z. Y. Isatins As Privileged Molecules in Design and Synthesis of Spiro-Fused Cyclic Frameworks. *Chem. Rev.* **2012**, *112*, 6104−6155.

(2) (a) Guan, H.; Laird, A. D.; Blake, R. A.; Tang, C.; Liang, C. Design and synthesis of aminopropyl tetrahydroindole-based indolin-2-ones as selective and potent inhibitors of Src and Yes tyrosine kinase. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 187−190. (b) Awasthi, N.; Hinz, S.; Brekken, R. A.; Schwarz, M. A.; Schwarz, R. E. Nintedanib, a triple angiokinase inhibitor, enhances cytotoxic therapy response in pancreatic cancer. *Cancer Lett.* **2015**, *358*, 59−66. (c) Lai, Y.; Ma, L.; Huang, W.; Yu, X.; Zhang, Y.; Ji, H.; Tian, J. Synthesis and biological evaluation of 3-[4-(amino/methylsulfonyl)phenyl]methylene-indolin-2-one derivatives as novel COX-1/2 and 5-LOX inhibitors. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7349−7353. (d) Thakur, A.; Singh, A.; Kaur, N.; Ojha, R.; Nepali, K. Steering the antitumor drug discovery campaign towards structurally diverse indolines. *Bioorg. Chem.* **2020**, *94*, 103436. (e) Kammasud, N.; Boonyarat, C.; Tsunoda, S.; Sakurai, H.; Saiki, I.; Grierson, D. S.; Vajragupta, O. Novel inhibitor for fibroblast growth factor receptor tyrosine kinase. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4812−4818. (f) Collins, M. A.; Hudak, V.; Bender, R.; Fensome, A.; Zhang, P.; Miller, L.; Winneker, R. C.; Zhang, Z.; Zhu, Y.; Cohen, J.; Unwalla, R. J.; Wrobel, J. Novel pyrrole-containing progesterone receptor modulators. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2185−2189.

(3) (a) Sassatelli, M.; Bouchikhi, F.; Messaoudi, S.; Anizon, F.; Debiton, E.; Barthomeuf, C.; Prudhomme, M.; Moreau, P. Synthesis and antiproliferative activities of diversely substituted glycosyl-isoindigo derivatives. *Eur. J. Med. Chem.* **2006**, *41*, 88−100. (b) Bouchikhi, F.; Anizon, F.; Moreau, P. Synthesis and antiproliferative activities of isoindigo and azaisoindigo derivatives. *Eur. J. Med. Chem.* **2008**, *43*, 755−762. (c) Naidu, K. M.; Gajanan, R. N.; Chandra Sekhar, K. V. G. Design, synthesis and biological evaluation of 5-(2-(4-(substituted benzo[d]isoxazol-3-yl)piperazin-1-yl)acetyl)indolin-2-one and 5-(2-(4-substitutedpiperazin-1-yl)acetyl)-indolin-2-one analogues as novel anti-tubercular agents. *Arabian J. Chem.* **2019**, *12*, 2418−2429.

(4) (a) Liu, Y.-C.; Ye, C.-J.; Chen, Q.; Yang, G.-F. Efficient synthesis of bulky 4-substituted-isatins via microwave-promoted Suzuki cross-coupling reaction. *Tetrahedron Lett.* **2013**, *54*, 949−955. (b) Gianella-Borradori, M.; Christou, I.; Bataille, C. J. R.; Cross, R. L.; Wynne, G. M.; Greaves, D. R.; Russell, A. J. Ligand-based virtual screening identifies a family of selective cannabinoid receptor 2 agonists. *Bioorg. Med. Chem.* **2015**, *23*, 241−263. (c) Teng, Y.-O.; Zhao, H.-Y.; Wang, J.; Liu, H.; Gao, M.-L.; Zhou, Y.; Han, K.-L.; Fan, Z.-C.; Zhang, Y.-M.; Sun, H.; Yu, P. Synthesis and anti-cancer activity evaluation of 5-(2-carboxyethenyl)-isatin derivatives. *Eur. J. Med. Chem.* **2016**, *112*, 145−156. (d) Ke, M.; Song, Q. Copper/B_2pin_2-catalyzed C−H difluoroacetylation−cycloamidation of anilines leading to the formation of 3,3-difluoro-2-oxindoles. *Chem. Commun.* **2017**, *53*, 2222−2225. (e) Estrada, L. A.; Stalder, R.; Abboud, K. A.; Risko, C.; Brédas, J.-L.; Reynolds, J. R. Understanding the Electronic Structure of Isoindigo in Conjugated Systems: A Combined Theoretical and Experimental Approach. *Macromolecules* **2013**, *46*, 8832−8844. (f) Sanzone, A.; Mattiello, S.; Garavaglia, G. M.; Calascibetta, A. M.; Ceriani, C.; Sassi, M.; Beverina, L. Efficient synthesis of organic semiconductors by Suzuki−Miyaura coupling in an aromatic micellar medium. *Green Chem.* **2019**, *21*, 4400−4405. (g) Bessinger, D.; Ascherl, L.; Auras, F.; Bein, T. Spectrally Switchable Photodetection with Near-Infrared-Absorbing Covalent Organic Frameworks. *J. Am. Chem. Soc.* **2017**, *139*, 12035−12042. (h) Carrera, E. I.; McCormick, T. M.; Kapp, M. J.; Lough, A. J.; Seferos, D. S. Thermal and Photoreductive Elimination from the Tellurium Center of π-Conjugated Tellurophenes. *Inorg. Chem.* **2013**, *52*, 13779−13790.

(5) (a) Qiu, X.; Deng, H.; Zhao, Y.; Shi, Z. Rhodium-catalyzed, P-directed selective C7 arylation of indoles. *Sci. Adv.* **2018**, *4*, No. eaau6468. (b) Yang, Y.; Li, R.; Zhao, Y.; Zhao, D.; Shi, Z. Cu-Catalyzed Direct C6-Arylation of Indoles. *J. Am. Chem. Soc.* **2016**, *138*, 8734−8737. (c) Rej, S.; Ano, Y.; Chatani, N. Bidentate Directing Groups: An Efficient Tool in C−H Bond Functionalization Chemistry for the Expedient Construction of C−C Bonds. *Chem. Rev.* **2020**, *120*, 1788−1887.

(6) (a) Guimond, N.; Gouliaras, C.; Fagnou, K. Rhodium(III)-Catalyzed Isoquinolone Synthesis: The *N*-O Bond as a Handle for C-*N* Bond Formation and Catalyst Turnover. *J. Am. Chem. Soc.* **2010**, *132*, 6908−6909. (b) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. Weak Coordination as a Powerful Means for Developing Broadly Useful C−H Functionalization Reactions. *Acc. Chem. Res.* **2012**, *45*, 788−802. (c) Ma, C.; Fang, P.; Mei, T.-S. Recent Advances in C−H Functionalization Using Electrochemical Transition Metal Catalysis. *ACS Catal.* **2018**, *8*, 7179−7189. (d) Rej, S.; Ano, Y.; Chatani, N. Bidentate Directing Groups: An Efficient Tool in C−H Bond Functionalization Chemistry for the Expedient Construction of C−C Bonds. *Chem. Rev.* **2020**, *120*, 1788−1887.

(7) (a) Leow, D.; Li, G.; Mei, T.-S.; Yu, J.-Q. Activation of remote *meta*-C−H bonds assisted by an end-on template. *Nature* **2012**, *486*, 518−522. (b) Bag, S.; Jayarajan, R.; Dutta, U.; Chowdhury, R.; Mondal, R.; Maiti, D. Remote *meta*-C−H Cyanation of Arenes Enabled by a Pyrimidine-Based Auxiliary. *Angew. Chem., Int. Ed.* **2017**, *56*, 12538−12542. (c) Xu, H.-J.; Kang, Y.-S.; Shi, H.; Zhang, P.; Chen, Y.-K.; Zhang, B.; Liu, Z.-Q.; Zhao, J.; Sun, W.-Y.; Yu, J.-Q.; Lu, Y. Rh(III)-Catalyzed *meta*-C−H Alkenylation with Alkynes. *J. Am. Chem. Soc.* **2019**, *141*, 76−79.

(8) (a) Bag, S.; Patra, T.; Modak, A.; Deb, A.; Maity, S.; Dutta, U.; Dey, A.; Kancherla, R.; Maji, A.; Hazra, A.; Bera, M.; Maiti, D. Remote *para*-C−H Functionalization of Arenes by a D-Shaped Biphenyl Template-Based Assembly. *J. Am. Chem. Soc.* **2015**, *137*, 11888−11891. (b) Patra, T.; Bag, S.; Kancherla, R.; Mondal, A.; Dey, A.; Pimparkar, S.; Agasti, S.; Modak, A.; Maiti, D. Palladium-Catalyzed Directed *para* C-H Functionalization of Phenols. *Angew. Chem., Int. Ed.* **2016**, *55*, 7751−7755. (c) Maji, A.; Guin, S.; Feng, S.; Dahiya, A.; Singh, V. K.; Liu, P.; Maiti, D. Experimental and Computational Exploration of *para*-Selective Silylation with a Hydrogen-Bonded Template. *Angew. Chem., Int. Ed.* **2017**, *56*, 14903−14907.

(9) (a) Cho, J.-Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E.; Smith, M. R. Remarkably Selective Iridium Catalysts for the Elaboration of Aromatic C-H Bonds. *Science* **2002**, *295*, 305. (b) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. C-H Activation for the Construction of C-B Bonds. *Chem. Rev.* **2010**, *110*, 890−931.

(10) (a) Wang, P.; Verma, P.; Xia, G.; Shi, J.; Qiao, J. X.; Tao, S.; Cheng, P. T. W.; Poss, M. A.; Farmer, M. E.; Yeung, K.-S.; Yu, J.-Q. Ligand-accelerated non-directed C−H functionalization of arenes. *Nature* **2017**, *551*, 489−493. (b) Liu, L.-Y.; Yeung, K.-S.; Yu, J.-Q. Ligand-Promoted Non-Directed C-H Cyanation of Arenes. *Chem. - Eur. J.* **2019**, *25*, 2199−2202.

(11) CCDC 2056775 contains the supplementary crystallographic data for compound **3a** in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(12) Ye, M.; Gao, G.-L.; Yu, J.-Q. Ligand-Promoted C-3 Selective C−H Olefination of Pyridines with Pd Catalysts. *J. Am. Chem. Soc.* **2011**, *133*, 6964−6967.

(13) (a) Yokota, T.; Tani, M.; Sakaguchi, S.; Ishii, Y. Direct Coupling of Benzene with Olefin Catalyzed by $Pd(OAc)_2$ Combined with Heteropolyoxometalate under Dioxygen. *J. Am. Chem. Soc.* **2003**, *125*, 1476−1477. (b) Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. Pd(II)-Catalyzed Olefination of Electron-Deficient Arenes Using 2,6-Dialkylpyridine Ligands. *J. Am. Chem. Soc.* **2009**, *131*, 5072−5074. (c) Wang, X.; Leow, D.; Yu, J.-Q. Pd(II)-Catalyzed *para*-Selective C−H Arylation of Monosubstituted Arenes. *J. Am. Chem. Soc.* **2011**, *133*, 13864−13867. (d) Nishikata, T.; Lipshutz, B. H. Cationic Pd(II)-Catalyzed Fujiwara-Moritani Reactions at Room Temperature in Water. *Org. Lett.* **2010**, *12*, 1972−1975. (e) Le Bras, J.; Muzart, J. Intermolecular Dehydrogenative Heck Reactions. *Chem. Rev.* **2011**, *111*, 1170−1214. (f) Zhang, Y.; Li, Z.; Liu, Z.-Q. Pd-Catalyzed Olefination of Furans and Thiophenes with Allyl Esters. *Org. Lett.* **2012**, *14*, 226−229. (g) Ali, W.; Prakash, G.; Maiti, D. Recent development in transition metal-catalyzed C−H olefination. *Chem. Sci.* **2021**, *12*, 2735−2759.

(14) Tang, S.; Peng, P.; Zhong, P.; Li, J.-H. Palladium-Catalyzed C-H Functionalization of *N*-Arylpropiolamides with Aryliodonium Salts: Selective Synthesis of 3-(1-Arylmethylene)oxindoles. *J. Org. Chem.* **2008**, *73*, 5476−5480.

(15) Kise, N.; Sasaki, K.; Sakurai, T. Reductive coupling of isatins with ketones and aldehydes by low-valent titanium. *Tetrahedron* **2014**, *70*, 9668−9675.

(16) Batz, H. G.; Ringsdorf, H.; Ritter, H. Pharmacologically active polymers, 7. Cyclophosphamide- and steroidhormone containing polymers as potential anticancer compounds. *Makromol. Chem.* **1974**, *175*, 2229−2239.

https://doi.org/10.1021/acs.joc.1c00637
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