JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

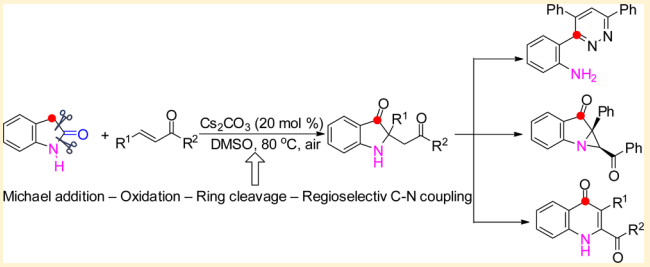
# The $Cs_2CO_3$–Catalyzed Reaction of 2-Oxindoles with Enones for the Preparation of Indolin-3-Ones and Their Further Transformation

Ying Shao,[†] Yu-Mei Zeng,[†] Jie-Ying Ji, Xiao-Qiang Sun, Hai-Tao Yang, and Chun-Bao Miao*

Jiangsu Key Laboratory of Advanced Catalytic Materials and Technology, Advanced Catalysis and Green Manufacturing Collaborative Innovation Center, School of Petrochemical Engineering, Changzhou University, Changzhou 213164, China

Supporting Information

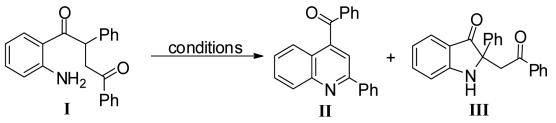
**ABSTRACT:** The $Cs_2CO_3$-catalyzed reaction of 2-oxindoles with enones affords 2,2-disubstituted indolin-3-ones through domino "Michael addition–oxidation–ring-cleavage–C–N coupling" process. $O_2$ acts as the sole oxidant to accomplish the oxidative process. The indolin-3-ones can be further transformed to pyridazine, azirdine-fused 3-oxindoles, 4-quinolone derivatives easily.




2,2-Disubstituted indolin-3-one scaffolds exist in a lot of natural products, such as isatisine A,[1] austamide,[2] aristotelone,[3] fluorocarpamine,[4] brevianimide,[5] diketopiperazine alkaloid,[6] rauniticine pseudoindoxyl,[7] ervaoffines A/B, and iboluteine,[8] and can be used in the total synthesis of biologically active alkaloids.[9] Therefore, considerable synthetic effort has been devoted to the synthesis of this valuable scaffold and various preparative methods have been developed. The protocol of oxidation of 2,3-disubstituted indoles followed by rearrangement[2,10] or reaction with *C*-nucleophiles[1a,9a,11] represents one of the most versatile routes to 2,2-disubstituted indolin-3-one scaffolds. However, the methodology suffered from some limitations, such as stepwise operation, requirement of stoichiometric amount of oxidants, or using a transition-metal catalyst. Other methods for the construction of 2,2-disubstituted indolin-3-one skeletons possess limited scope and utility. For instance, the reaction of arynes with amino acid esters,[12] the reaction of ortho-bromophenyl ketones with sodium azide via sequential $S_NAr$–Smalley cyclization,[13] the Au-catalyzed reaction of 2-alkynyl arylazides with allylic alcohols or propargylic alcohols,[14] the Au-catalyzed nitroalkyne cycloisomerization followed with an intermolecular/intramolecular [3+2]-cycloaddition with alkenes,[15] the Au-catalyzed *C*-2 annulation of 3-phenoxy alkynyl indoles or an acid-catalyzed cascade oxidative dearomatization/semipinacol rearrangement reaction of indol-2-yl cyclobutanol with *N*-sulfonyloxaziridine as oxidant,[16] the Rh(III)-catalyzed [4+1] annulation reaction of 2-aminobenzaldehydes with allenes,[17] and the Pd-catalyzed reaction of *N*-benzyl-2-iodoanilines with CO and diazocompounds[18] have been documented. Generally, the substrates in these transition metal catalyzed reaction needed to be prepared by multistep procedures. In continuation of our interest in using molecular oxygen as an ideal green oxidant in organic transformation,[19] herein, we wish to report the synthesis of 2,2-disubstituted indolin-3-ones from the easily available 2-oxinoles and enones catalyzed by a base through domino process.

Most recently, we have reported a $K_2CO_3$-catalyzed reaction of 2-oxindoles with enones for the synthesis of 1,4-diketone compounds bearing amino group via a cascade "Michael addition–oxidation–ring-cleavage" process.[19c] The product **I** could be transformed to the interesting cyclization product indolin-3-one **III** in 30% yield accompanying with the formation of 46% yield of quinoline **II** upon treating with catalytic amount of hydrochloric acid (Scheme 1). The selectivity was very poor and we attempted to realize the selective conversion to single product. To our delight, upon changing the acid condition to a basic medium, selective

**Scheme 1**




| | II | III |
|---|---|---|
| **acidic condition:** (ref. 17c) | | |
| HCl (0.15 equiv), DMSO/$H_2O$, air, 90 °C, 22 h | 46% | 30% |
| **basic condition:** | | |
| $K_2CO_3$, DMSO, air, 80 °C, 5 h | 0% | 85% |
| $Cs_2CO_3$, DMSO, air, 80 °C, 1 h | 0% | 94% |
| NaOH, DMSO, air, 80 °C, 5 h | 0% | 52% |
| DBU, DMSO, air, 80 °C, 5 h | 0% | 50% |
| DMSO, air, 80 °C, 12 h | 0% | 0% |
| $Cs_2CO_3$, DMSO, $N_2$, 80 °C, 4 h | 0% | 0% |
| $Cs_2CO_3$, DMF, air, 80 °C, 2 h | 0% | 94% |
| $Cs_2CO_3$, $CH_3CN$, air, 80 °C, 24 h | 0% | 38% |
| $Cs_2CO_3$, 1,4-dioxane, air, 80 °C, 8 h | 0% | 0% |
| $Cs_2CO_3$, toluene, air, 80 °C, 8 h | 0% | 0% |
| $Cs_2CO_3$, $ClCH_2CH_2Cl$, air, 80 °C, 8 h | 0% | 0% |
| $Cs_2CO_3$, EtOH, air, 80 °C, 6 h | 0% | 10% |

**Received:** August 14, 2016
**Published:** November 15, 2016





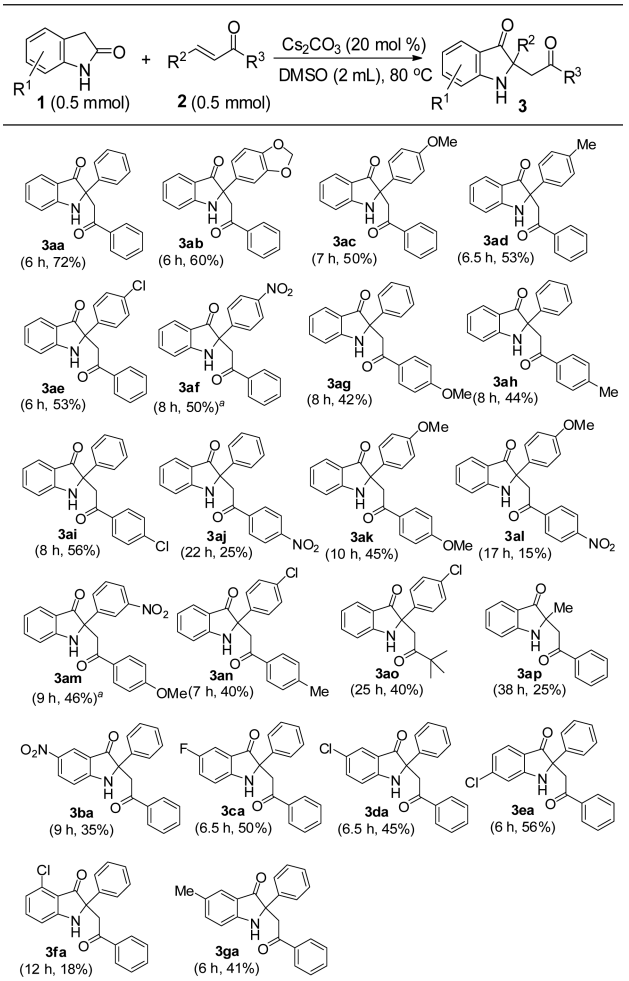
DOI: 10.1021/acs.joc.6b01993
J. Org. Chem. 2016, 81, 12443–12450

transformation to **III** was achieved. When **I** was treated with 20 mol% of $Cs_2CO_3$ in DMSO at 80 °C in air for 1 h, **III** was obtained nearly quantitatively (94%). Among the two types of $\alpha$-C of carbonyl, the C−N coupling occurred selectively at the position benefiting to the formation of five-membered ring. Although the $K_2CO_3$ was also effective, longer reaction time (5 h vs 1 h) was needed and the yield was slightly lower (85%) (Scheme 1). At room temperature, the reaction proceeded very slowly and only trace of product could be observed on TLC after 24 h. Using NaOH or DBU as the base only gave moderate yield of product. A certain amount of byproducts with very high polarity was generated under NaOH conditions probably due to its strong basicity, while many starting material remained uncovered under DBU conditions. Aerobic oxygen and base were crucial to the transformation, and no reaction occurred in the absence of base or under nitrogen atmosphere. The solvent screening showed that only DMSO and DMF were the optimal solvent. The reaction in $CH_3CN$ delivered 38% of the product after 24 h, while using 1,4-dioxane, toluene, DCE, or EtOH as the solvent led to failure of the reaction or very low yield.

Direct intramolecular oxidative C($sp^3$)−N bond formation through C($sp^3$)−H amination is an efficient protocol to construct nitrogen-containing heterocycles.[20] Particularly noteworthy, the nitrogen sources are mostly limited to amide, sulfonamides carbamate, and sulfamate esters, and transition-metal catalysts are always needed. The C($sp^3$)−H activation always need a directing group on nitrogen atom.[21] Developing other nitrogen sources especially the unprotected anilines to realize the intramolecular C($sp^3$)−N coupling reaction is more challenging and attractive.

In the above cyclizative reaction, the amine source is unsubstituted arylamine and this kind of intramolecular C($sp^3$)−H amination has never been reported to the best of our knowledge. With the primary results in hand, we decided to investigate this kind of reaction in-depth. Taking into account of the similar basic condition with that of our previously reported $K_2CO_3$-catalyzed reaction of 2-oxindoles with enones in DMSO at room temperature for the preparation of 1,4-diketones bearing amino group,[19c] the possibility of $Cs_2CO_3$-promoted one-step synthesis of indolin-3-one **3aa** directly from 2-oxindoles with enones was examined by increasing the reaction temperature to 80 °C. Fortunately, the 2,2-disubstituted indolin-3-one **3aa** was obtained in 72% yield via a cascade "Michael addition−oxidation−ring-cleavage−C−N coupling" process. Various substrates were examined under the conditions to evaluate the scope and generality of the methodology (Table 1). Either electron-withdrawing or electron-donating groups on phenyl ring of $R^2$ generated the desired products **3** in moderate yields (**3aa**−**3af**). For the substrate **2f** and **2m**, which linked with an $NO_2$ group, the reaction must be carried out at lower temperature (40 °C). Otherwise a very low yield was obtained. In terms of $R^3$, a striking electron effect was observed. A strong electron-withdrawing group, such as $NO_2$, on the phenyl ring resulted in very low yield of products (**3aj** and **3al**). Either $R^2$ or $R^3$ was replaced by an alkyl group, the reactions proceeded very slowly and the yields were unsatisfactory (**3ao** and **3ap**). Other 2-oxindoles are also effective in this conversion (**3ba**−**3ga**). Strong electron-withdrawing group gave much lower yield (**3ba**). 4-Chloro-2-oxindole gave very low yield of product **3fa** partially because of the steric hindrance (**3fa**).

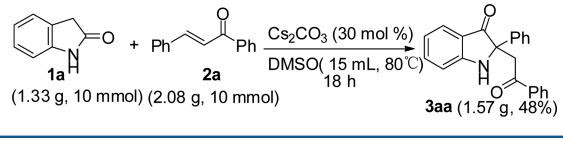
**Table 1. Synthesis of Indolin-3-ones 3 from 2-Oxindoles and Enones**




[a]Reacted at rt for 1.5 h and then at 40 °C for given time.

To show the practicality of this protocol, a large-scale experiment was carried out by performing the reaction of **1a** (1.33 g, 10 mmol) with **2a** (2.08 g, 10 mmol) in 15 mL of DMSO in the presence of 3 mmol of $Cs_2CO_3$ (Scheme 2). This transformation proceeded smoothly to afford **3aa** in 48% yield within 18 h. In order to increase the concentration of oxygen in the reaction mixture, air was concurrently bubbled into the reaction mixture through a glass dropper.

**Scheme 2. Large Scale Synthesis of 3aa**

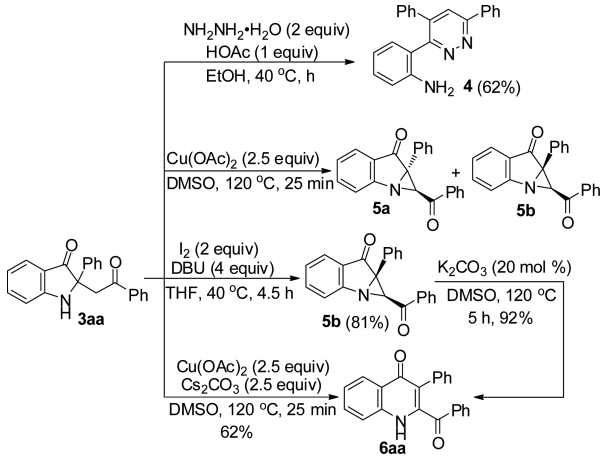



Due to the concurrent existence of amino and carbonyl group, the synthetic potential of the indolin-3-one **3aa** through the intramolecular reaction was investigated (Scheme 3). The reaction of **3aa** with hydrazine hydrate in the presence of acetic acid gave 2-(4,6-diphenylpyridazin-3-yl) aniline **4** in 62% yield accompanied by the cleavage of C−N bond. Treatment of **3aa** with 2.5 equiv of $Cu(OAc)_2$ in DMSO at 120 °C for 25 min furnished the two stereoisomers of azirdine-fused 3-oxindoles **5a** and **5b** in 26% and 56% yield, respectively. It was



DOI: 10.1021/acs.joc.6b01993
J. Org. Chem. 2016, 81, 12443−12450

**Scheme 3. Further Transformations of 3aa**



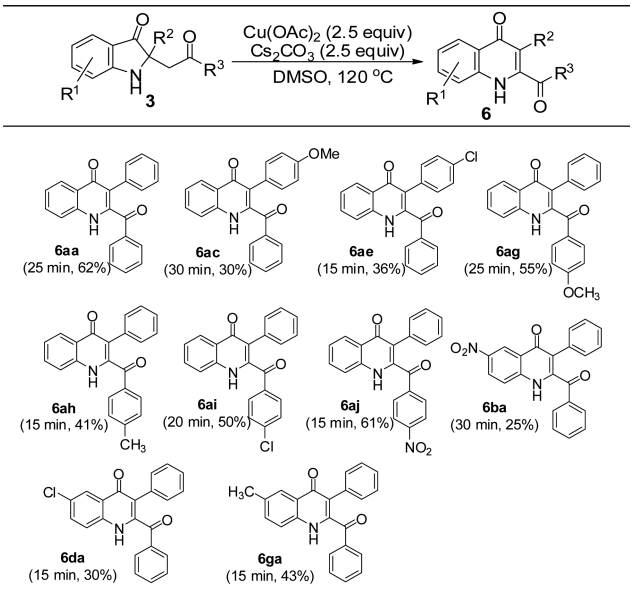

noteworthy that the reaction proceeded very quickly and further prolonging the reaction time led to complex mixture. In the presence of 2 equiv of $I_2$ and 4 equiv of DBU, **3aa** afforded the main isomer **5b** in 81% yield through intramolecular nucleophilic substitution. When **5b** was treated with catalytic amount of $K_2CO_3$ in DMSO, the ring opening of azirdine ring occurred to generate 4-quinolone derivative **6aa** in nearly quantitative yield. In consideration of the generation of **5a**/**5b** under $Cu(OAc)_2$ condition, the combination of $Cu(OAc)_2$ with a base to realize the one-step conversion to **6aa** was tried. The reaction of **3aa** with 2.5 equiv of $Cu(OAc)_2$ and 2.5 equiv of $Cs_2CO_3$ in DMSO for 25 min indeed provided **6aa** in a moderate yield of 62%. However, in the presence of $I_2$, changing the base from DBU to $Cs_2CO_3$ and increasing the temperature from 40 to 120 °C could not provide the **6aa**.

4-Quinolone scaffolds are commonly used in the pharmaceutical chemistry, constituting a large class of marketed antibiotic drug.[22] As a result, the synthesis of 4-quinolones has attracted considerable interest. Herein, a new access to quinolin-4(1H)-ones was explored starting from indolin-3-ones **3**. Under $Cu(OAc)_2$ and $Cs_2CO_3$ conditions, various quinolin-4(1H)-ones **6** could be prepared, however, the yield was unsatisfactory (Table 2).

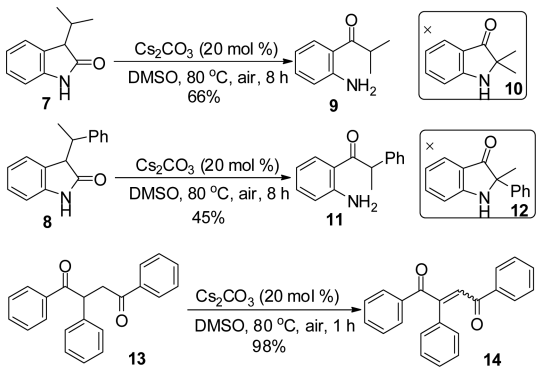
All the new compounds were fully characterized by $^1$H NMR, $^{13}$C NMR, and HRMS. The structure of **3aa** and **6ai** was further established unambiguously by their single crystals (see SI). The steric configuration of **5a** was confirmed by the NOESY spectrum analysis. The methine proton $H_a$ has correlation with both $H_b$ and $H_c$ on the two different phenyl rings, which indicates that the phenyl group and the benzoyl group derived from enone are in the *trans*- position (see SI).

To gain insight into the regioselective intramolecular C−H amination, some control experiments were carried out (Scheme 4). First, **7** and **8** were prepared and introduced to the $Cs_2CO_3$ catalyzed reaction. No intramolecular cyclization product **10** or **12** was detected. Instead, the ring-cleavage products **9** and **11** were isolated in 66% and 45% yield, respectively, which indicated that an acyl group (in compound **I**) deriving from the enones played an essential role to the success of C−N coupling reaction. When the 1,2,4-triphenyl-1,4-butanedione **13**, which lacked an amino group compared with compound **I**, was treated with catalytic amount of $Cs_2CO_3$ in DMSO at 80 °C for 1 h, the oxidative dehydrogenation product **14** was afforded almost quantitatively.

**Table 2. Synthesis of Various Quinolin-4(1H)-ones 6**

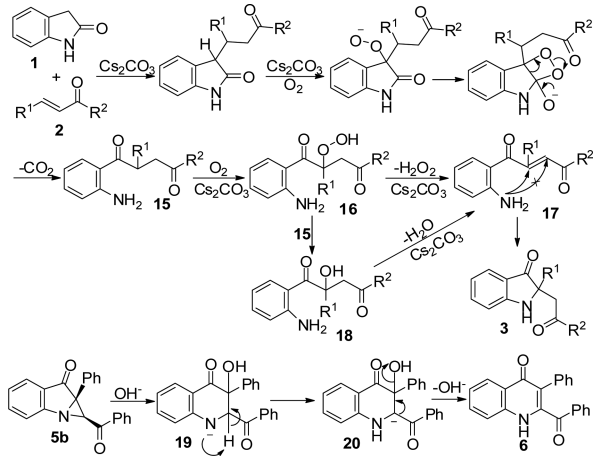



**Scheme 4. Control Experiments**




Based on these results and our previous work, a possible reaction pathway is described in Scheme 5. Intermediate **15** is generated under $Cs_2CO_3$ conditions through a consecutive "Michael addition−oxidation−ring-cleavage" process.[19c] Next, under $Cs_2CO_3$ conditions **15** reacts with molecular oxygen to generate the peroxide **16**.[23] An alternative pathway for the

**Scheme 5. Proposed Mechanisms**






DOI: 10.1021/acs.joc.6b01993
J. Org. Chem. 2016, 81, 12443−12450

formation of peroxide involving a single electron transfer from carbonion to oxygen followed by the trap of *C*-centered radical with oxygen was also possible.[19b,24] Under basic condition, release of hydrogen peroxide from **16** gives the key intermediate **17** followed by a regioselective intramolecular Michael addition to afford the indolin-3-one **3**. An alternative pathway to **17** also cannot be excluded, that is, peroxide **16** reacts with **15** to generate the hydroxylated product **18** followed by extrusion of $H_2O$. At present, the reason for the excellent regioselectivity in the C−N bond formation is not clear. Under basic conditions, nucleophilic attack of hydroxyl anion on azirdine ring leads to ring-opening intermediate **19**, which abstract proton from the $\alpha$-C of carbonyl followed by extrusion of hydroxyl anion to afford the quinolin-4(1H)-one **6**.

In summary, an efficient $Cs_2CO_3$-catalyzed reaction of 2-oxindoles with enones for the preparation of 2,2-disubstituted indolin-3-ones has been explored through domino "Michael addition−oxidation−ring-cleavage−C−N coupling" process. A mechanism was proposed according to the controlling experiments. The final C−N coupling reaction displays excellent regioselectivity. The further transformations of indolin-3-ones **3** give an easy access to pyridazine, azirdine-fused 3-oxindoles, quinolin-4(1H)-one derivatives.

## EXPERIMENTAL SECTION

**General Information.** $^1$H, $^{13}$C NMR, NOESY spectra were recorded on 300 or 400 MHz (75 or 100 MHz for $^{13}$C NMR) spectrometer. Melting points were determined on a micromelting point apparatus without corrections. Flash column chromatography was performed over silica gel (200−300 mesh).

**Preparation of Starting Materials.** Compounds **7** and **8** were prepared according to the reported procedure: Condensation of 2-oxindole with ketonic compounds followed by reduction with $NaBH_4$.[25] Compound **13** was prepared according to the reported procedure.[26]

*General Procedure for the $Cs_2CO_3$−Catalyzed Reaction of 2-Oxindoles (**1**) with Enones (**2**) in DMSO for the Preparation of **3**.* A mixture of 2-oxindoles **1** (0.5 mmol), enones **2** (0.5 mmol), and $Cs_2CO_3$ (0.1 mmol) in 2 mL of DMSO was stirred in a tube (Φ18 × 150 mm) under open air at 80 °C for a given time. Upon completion of the reaction as determined by TLC, 20 mL of water was added and the mixture was extracted with dichloromethane (15 mL × 3). The combined organic phases were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate/petroleum ether: 1/10−1/6) to provide the corresponding products **3**. (It was noteworthy that some of the C−N coupling products **3** have same polarity with the uncoupling products in TLC analysis. In this case, the mixture of isopropyl ether and hexane should be used as the eluent in TLC detection.)

2-(2-Oxo-2-phenylethyl)-2-phenylindolin-3-one **3aa** (yellow solid, 117.8 mg, 72%, mp 149−150 °C): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.92 (d, $J$ = 7.2 Hz, 2H), 7.53−7.61 (m, 4H), 7.40−7.52 (m, 3H), 7.24−7.32 (m, 2H), 7.21 (tt, $J$ = 7.2, 1.3 Hz, 1H), 6.96 (d, $J$ = 8.3 Hz, 1H), 6.81 (ddd, $J$ = 7.8, 7.2, 0.7 Hz, 1H), 6.31 (s, br, 1H), 4.45 (d, $J$ = 18.0 Hz, 1H), 3.18 (d, $J$ = 17.9 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 200.8 (*C*═O), 197.9 (*C*═O), 160.4, 138.1, 137.9, 136.7, 133.9, 128.9, 128.8, 128.2, 127.7, 125.8, 125.4, 119.0, 118.2, 111.9, 69.4 (NHC−CO), 44.8 ($COCH_2$); HRMS (ESI-Q-TOF) $m/z$ $[M+H]^+$ calcd for $C_{22}H_{18}NO_2$ 328.1338, found 328.1326.

2-(Benzo[d][1,3]dioxol-5-yl)-2-(2-oxo-2-phenylethyl)indolin-3-one **3ab** (yellow solid, 110.4 mg, 60%, mp 186−188 °C): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.93 (d, $J$ = 7.2 Hz, 2H), 7.54−7.61 (m, 2H), 7.41−7.53 (m, 3H), 7.05 (d, $J$ = 1.7 Hz, 1H), 7.02 (dd, $J$ = 8.1, 1.8 Hz, 1H), 6.95 (d, $J$ = 8.2 Hz, 1H), 6.81 (t, $J$ = 7.4 Hz, 1H), 6.71 (d, $J$ = 8.1 Hz, 1H), 6.27 (s, br, 1H), 5.84−5.93 (m, 2H), 4.37 (d, $J$ = 18.0 Hz, 1H), 3.11 (d, $J$ = 18.0 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 200.8 (*C*═O), 198.0 (*C*═O), 160.2, 148.1, 147.2, 137.9, 136.6, 133.9, 132.0, 128.9, 128.2, 125.7, 119.0, 118.8, 118.1, 111.9, 108.4, 106.3, 101.2, 69.1 (NHC−CO), 44.7 ($COCH_2$); HRMS (ESI-Q-TOF) $m/z$ $[M+H]^+$ Calcd for $C_{23}H_{18}NO_4$ 372.1236; Found 372.1229.

2-(4-Methoxyphenyl)-2-(2-oxo-2-phenylethyl)indolin-3-one **3ac** (yellow solid, 89.0 mg, 50%, mp 120−122 °C): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.91 (d, $J$ = 7.2 Hz, 2H), 7.57 (t, $J$ = 7.4 Hz, 2H), 7.40−7.51 (m, 5H), 6.94 (d, $J$ = 8.3 Hz, 1H), 6.76−6.84 (m, 3H), 6.30 (s, br, 1H), 4.39 (d, $J$ = 17.9 Hz, 1H), 3.72 (s, 3H), 3.14 (d, $J$ = 17.9 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 201.1 (*C*═O), 197.9 (*C*═O), 160.3, 159.0, 137.7, 136.6, 133.7, 130.1, 128.7, 128.1, 126.6, 125.6, 118.7, 118.2, 114.1, 111.9, 68.9 (NHC−CO), 55.2 ($OCH_3$), 44.6 ($COCH_2$); HRMS (ESI-Q-TOF) $m/z$ $[M+H]^+$ Calcd for $C_{23}H_{20}NO_3$ 358.1443; Found 358.1440.

2-(4-Methyphenyl)-2-(2-oxo-2-phenylethyl)indolin-3-one **3ad** (yellow solid, 90.3 mg, 53%, mp 206−207 °C): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.93 (d, $J$ = 7.1 Hz, 2H), 7.54−7.61 (m, 2H), 7.38−7.52 (m, 5H), 7.09 (d, $J$ = 8.0 Hz, 2H), 6.95 (d, $J$ = 8.3 Hz, 1H), 6.80 (ddd, $J$ = 7.8, 7.2, 0.7 Hz, 1H), 6.26 (s, br, 1H), 4.42 (d, $J$ = 18.0 Hz, 1H), 3.16 (d, $J$ = 18.0 Hz, 1H), 2.26 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 200.9 (*C*═O), 197.9 (*C*═O), 160.4, 137.8, 137.4, 136.7, 135.1, 133.8, 129.6, 128.8, 128.2, 125.7, 125.3, 118.9, 118.3, 111.8, 69.3 (NHC−CO), 44.7 ($COCH_2$), 21.1 ($CH_3$); HRMS (ESI-Q-TOF) $m/z$ $[M+H]^+$ Calcd for $C_{23}H_{20}NO_2$ 342.1494; Found 342.1490.

2-(4-Chlorophenyl)-2-(2-oxo-2-phenylethyl)indolin-3-one **3ae** (yellow solid, 96.1 mg, 53%, mp 151−153 °C): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.91 (d, $J$ = 7.2 Hz, 2H), 7.55−7.63 (m, 2H), 7.42−7.55 (m, 5H), 7.25 (d, $J$ = 8.5 Hz, 2H), 6.97 (d, $J$ = 8.3 Hz, 1H), 6.83 (t, $J$ = 7.4 Hz, 1H), 6.30 (s, br, 1H), 4.39 (d, $J$ = 18.0 Hz, 1H), 3.15 (d, $J$ = 18.0 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 200.4 (*C*═O), 197.8 (*C*═O), 160.2, 138.1, 136.8, 136.4, 134.0, 133.7, 128.91, 128.89, 128.2, 127.0, 125.8, 119.2, 118.0, 112.0, 68.9 (NHC−CO), 44.9 ($COCH_2$); HRMS (ESI-Q-TOF) $m/z$ $[M+H]^+$ Calcd for $C_{22}H_{17}ClNO_2$ 362.0948; Found 362.0942.

2-(4-Nitrophenyl)-2-(2-oxo-2-phenylethyl)indolin-3-one **3af** (yellow solid, 93.7 mg, 50%, mp 195−197 °C): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.15 (d, $J$ = 9.0 Hz, 2H), 7.90 (d, $J$ = 7.1 Hz, 2H), 7.79 (d, $J$ = 9.0 Hz, 2H), 7.51−7.65 (m, 3H), 7.47 (t, $J$ = 7.6 Hz, 2H), 7.01 (d, $J$ = 8.3 Hz, 1H), 6.87 (t, $J$ = 7.4 Hz, 1H), 6.35 (s, br, 1H), 4.45 (d, $J$ = 18.2 Hz, 1H), 3.24 (d, $J$ = 18.2 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 199.2 (*C*═O), 197.6 (*C*═O), 160.2, 147.5, 145.9, 138.5, 136.2, 134.4, 129.1, 128.2, 126.8, 125.9, 123.9, 119.7, 117.8, 112.3, 69.3 (NHC−CO), 45.5 ($COCH_2$); HRMS (ESI-Q-TOF) $m/z$ $[M+H]^+$ Calcd for $C_{22}H_{17}N_2O_4$ 373.1188; Found 373.1182.

2-(2-(4-Methoxyphenyl)-2-oxoethyl)-2-phenylindolin-3-one **3ag** (yellow solid, 74.8 mg, 42%, mp 202−203 °C): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.91 (d, $J$ = 9.0 Hz, 2H), 7.52−7.66 (m, 3H), 7.49 (ddd, $J$ = 8.3, 7.2, 1.3 Hz, 1H), 7.28 (t, $J$ = 7.2 Hz, 2H), 7.20 (t, $J$ = 6.6 Hz, 2H), 6.96 (d, $J$ = 8.2 Hz, 1H), 6.91 (d, $J$ = 9.0 Hz, 2H), 6.80 (t, $J$ = 7.4 Hz, 1H), 6.37 (s, br, 1H), 4.39 (d, $J$ = 17.7 Hz, 1H), 3.86 (s, 3H), 3.10 (d, $J$ = 17.7 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 201.0 (*C*═O), 196.4 (*C*═O), 164.1, 160.4, 138.2, 137.9, 130.6, 129.8, 128.8, 127.6, 125.7, 125.5, 118.9, 118.2, 114.0, 111.9, 69.5 (NHC−CO), 55.7 ($OCH_3$), 44.3 ($COCH_2$); HRMS (ESI-Q-TOF) $m/z$ $[M+H]^+$ Calcd for $C_{23}H_{20}NO_3$ 358.1443; Found 358.1440.

2-(2-(4-Methylphenyl)-2-oxoethyl)-2-phenylindolin-3-one **3ah** (yellow solid, 75.2 mg, 44%, mp 180−181 °C): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.82 (d, $J$ = 8.3 Hz, 2H), 7.52−7.60 (m, 3H), 7.48 (ddd, $J$ = 8.3, 7.1, 1.3 Hz, 1H), 7.17−7.31 (m, 5H), 6.95 (d, $J$ = 8.3 Hz, 1H), 6.80 (ddd, $J$ = 7.8, 7.1, 0.8 Hz, 1H), 6.35 (s, br, 1H), 4.42 (d, $J$ = 17.9 Hz, 1H), 3.13 (d, $J$ = 17.9 Hz, 1H), 2.39 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 200.9 (*C*═O), 197.5 (*C*═O), 160.4, 144.8, 138.2, 137.9, 134.3, 129.5, 128.8, 128.4, 127.6, 125.7, 125.5, 118.9, 118.2, 111.9, 69.5 (NHC−CO), 44.6 ($COCH_2$), 21.8 ($CH_3$); HRMS (ESI-Q-TOF) $m/z$ $[M+H]^+$ Calcd for $C_{23}H_{20}NO_2$ 342.1494; Found 342.1489.

2-(2-(4-Chlorophenyl)-2-oxoethyl)-2-phenylindolin-3-one **3ai** (yellow solid, 101.8 mg, 56%, mp 172−174 °C): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.86 (d, $J$ = 8.7 Hz, 2H), 7.58 (d, $J$ = 7.8 Hz, 1H), 7.46−7.56 (m, 3H), 7.42 (d, $J$ = 8.7 Hz, 2H), 7.29 (t, $J$ = 7.3 Hz, 2H), 7.22 (t, $J$ = 7.3 Hz, 2H), 6.97 (d, $J$ = 8.3 Hz, 1H), 6.82 (ddd, $J$ = 7.8, 7.2, 0.7 Hz,



DOI: 10.1021/acs.joc.6b01993
J. Org. Chem. 2016, 81, 12443−12450

1H), 6.23 (s, br, 1H), 4.38 (d, $J$ = 17.9 Hz, 1H), 3.16 (d, $J$ = 17.9 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 200.6 (*C*=O), 196.7 (*C*=O), 160.3, 140.4, 138.03, 137.95, 135.0, 129.6, 129.2, 128.9, 127.8, 125.8, 125.4, 119.1, 118.3, 111.9, 69.3 (NHC−CO), 44.9 ($COCH_2$); HRMS (ESI-Q-TOF) $m/z$ $[M+H]^+$ Calcd for $C_{22}H_{17}ClNO_2$ 362.0948; Found 362.0945.

2-(2-(4-Nitrophenyl)-2-oxoethyl)-2-phenylindolin-3-one **3aj** (yellow solid, 47.1 mg, 25%, mp 166−167 °C): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.28 (d, $J$ = 8.9 Hz, 2H), 8.05 (d, $J$ = 8.9 Hz, 2H), 7.58 (d, $J$ = 7.8 Hz, 1H), 7.48−7.56 (m, 3H), 7.20−7.34 (m, 3H), 6.99 (d, $J$ = 8.3 Hz, 1H), 6.84 (t, $J$ = 7.4 Hz, 1H), 6.14 (s, br, 1H), 4.42 (d, $J$ = 18.0 Hz, 1H), 3.29 (d, J = 18.0 Hz, 1H); $^{13}$C NMR (75 MHz, CDCl3) $\delta$ 200.2 (*C*=O), 196.5 (*C*=O), 160.3, 150.7, 140.8, 138.1, 137.8, 129.3, 129.0, 128.0, 125.8, 125.3, 124.1, 119.4, 118.3, 112.0, 69.1 (NHC−CO), 45.7 ($COCH_2$); HRMS (ESI-Q-TOF) $m/z$ $[M+H]^+$ Calcd for $C_{22}H_{17}N_2O_4$ 373.1188; Found 373.1180.

2-(4-Methoxyphenyl)-2-(2-(4-methoxyphenyl)-2-oxoethyl)indolin-3-one **3ak** (yellow solid, 87.1 mg, 45%, mp 61−63 °C): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.90 (d, $J$ = 9.0 Hz, 2H), 7.56 (d, $J$ = 7.8 Hz, 1H), 7.43−7.51 (m, 3H), 6.94 (d, $J$ = 8.2 Hz, 1H), 6.91 (d, $J$ = 9.0 Hz, 2H), 6.75−6.84 (m, 3H), 6.36 (s, br, 1H), 4.34 (d, $J$ = 17.7 Hz, 1H), 3.86 (s, 3H), 3.72(s, 3H), 3.06 (d, $J$ = 17.7 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 201.3 (*C*=O), 196.5 (*C*=O), 164.1, 160.3, 159.1, 137.8, 130.6, 130.2, 129.8, 126.7, 125.7, 118.8, 118.3, 114.2, 114.0, 111.9, 69.1 (NHC−CO), 55.6 ($OCH_3$), 55.3 ($OCH_3$), 44.2 ($COCH_2$); HRMS (ESI-Q-TOF) $m/z$ $[M+H]^+$ Calcd for $C_{24}H_{22}NO_4$ 388.1549; Found 388.1544.

2-(4-Methoxyphenyl)-2-(2-(4-nitrophenyl)-2-oxoethyl)indolin-3-one **3al** (yellow solid, 30.3 mg, 15%, mp 89−90 °C): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.28 (d, $J$ = 9.0 Hz, 2H), 8.05 (d, $J$ = 9.0 Hz, 2H), 7.58 (d, $J$ = 7.8 Hz, 1H), 7.50 (ddd, $J$ = 8.4, 7.1, 1.3 Hz, 1H), 7.45 (d, $J$ = 8.9 Hz, 2H), 6.97 (d, $J$ = 8.3 Hz, 1H), 6.78−6.86 (m, 3H), 6.11 (s, br, 1H), 4.36 (d, $J$ = 17.9 Hz, 1H), 3.73 (s, 3H), 3.25 (d, $J$ = 17.9 Hz, 1H); $^{13}$C NM R (75 MHz, $CDCl_3$) $\delta$ 200.6 (*C*=O), 196.6 (*C*=O), 160.2, 159.3, 150.7, 140.9, 138.0, 129.6, 129.3, 126.5, 125.8, 124.1, 119.3, 118.4, 114.4, 112.0, 68.7 (NHC−CO), 55.3 ($OCH_3$), 45.6 ($COCH_2$); HRMS (ESI-Q-TOF) $m/z$ $[M+H]^+$ Calcd for $C_{23}H_{19}N_2O_5$ 403.1294; Found 403.1290.

2-(2-(4-Methoxyphenyl)-2-oxoethyl)-2-(3-nitrophenyl)indolin-3-one **3am** (yellow solid, 88.2 mg, 46%, mp 118−120 °C): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.51 (t, $J$ = 2.0 Hz, 1H), 8.07 (ddd, $J$ = 8.2, 2.2, 0.9 Hz, 1H), 7.97 (ddd, $J$ = 7.9, 1.7, 1.0 Hz, 1H), 7.87 (d, $J$ = 9.0 Hz, 2H), 7.59 (d, $J$ = 7.8 Hz, 1H), 7.53 (ddd, $J$ = 8.4, 7.1, 1.3 Hz, 1H), 7.46 (t, $J$ = 8.0 Hz, 1H), 7.01 (d, $J$ = 8.3 Hz, 1H), 6.90 (d, $J$ = 9.0 Hz, 2H), 6.85 (t, $J$ = 7.5 Hz, 1H), 6.48 (s, br, 1H), 4.37 (d, $J$ = 17.9 Hz, 1H), 3.85 (s, 3H), 3.17 (d, $J$ = 17.9 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 199.8 (*C*=O), 195.9 (*C*=O), 164.4, 160.3, 148.5, 141.0, 138.4, 132.0, 130.6, 129.6, 129.3, 125.7, 122.6, 121.1, 119.6, 117.8, 114.1, 112.5, 68.9 (NHC−CO), 55.7 ($OCH_3$), 44.9 ($COCH_2$); HRMS (ESI-Q-TOF) $m/z$ $[M+H]^+$ Calcd for $C_{23}H_{19}N_2O_5$ 403.1294; Found 403.1298.

2-(4-Chlorophenyl)-2-(2-oxo-2-(p-tolyl)ethyl)indolin-3-one **3an** (yellow solid, 75.0 mg, 40%, mp 151−152 °C): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.79 (d, $J$ = 8.3 Hz, 2H), 7.57 (d, $J$ = 7.8 Hz, 1H), 7.44−7.54 (m, 3H), 7.20−7.26 (m, 4H), 6.95 (d, $J$ = 8.3 Hz, 1H), 6.81 (t, $J$ = 7.4 Hz, 1H), 6.37 (s, br, 1H), 4.36 (d, $J$ = 17.9 Hz, 1H), 3.10 (d, $J$ = 18.0 Hz, 1H), 2.39 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 200.5 (*C*=O), 197.4 (*C*=O), 160.3, 145.0, 138.1, 136.9, 134.0, 133.6, 129.6, 128.8, 128.3, 127.0, 125.7, 119.1, 118.0, 112.0, 69.0 (NHC−CO), 44.7 ($COCH_2$), 21.8 ($CH_3$); HRMS (ESI-Q-TOF) $m/z$ $[M+H]^+$ Calcd for $C_{23}H_{19}ClNO_2$ 376.1104; Found 376.1100.

2-(4-Chlorophenyl)-2-(3,3-dimethyl-2-oxobutyl)indolin-3-one **3ao** (yellow solid, 68.2 mg, 40%, mp 130−132 °C): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$7.55 (d, $J$ = 7.7 Hz, 1H), 7.51 (d, $J$ = 8.8 Hz, 2H), 7.49 (ddd, $J$ = 8.4, 7.0, 1.3 Hz, 1H), 7.26 (d, $J$ = 8.8 Hz, 2H), 6.94 (d, $J$ = 8.3 Hz, 1H), 6.80 (ddd, $J$ = 7.8, 7.1, 0.7 Hz, 1H), 6.32 (s, br, 1H), 3.88 (d, $J$ = 18.1 Hz, 1H), 2.62 (d, $J$ = 18.1 Hz, 1H), 1.05 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 214.2 (*C*=O), 200.5 (*C*=O), 160.0, 138.0, 136.8, 133.6, 128.7, 127.0, 125.7, 119.1, 118.1, 112.0, 68.7 (NHC−CO), 44.6, 43.9, 26.1 ($CMe_3$); HRMS (ESI-Q-TOF) $m/z$ $[M+H]^+$ Calcd for $C_{20}H_{21}ClNO_2$ 342.1261; Found 342.1258.

2-Methyl-2-(2-oxo-2-phenylethyl)indolin-3-one **3ap** (yellow solid, 32.9 mg, 25%, mp 114−115 °C): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.95 (d, $J$ = 7.2 Hz, 2H), 7.65 (d, $J$ = 7.8 Hz, 1H), 7.59 (tt, $J$ = 7.4, 1.2 Hz, 1H), 7.42−7.50 (m, 3H), 6.84 (d, $J$ = 8.3 Hz, 1H), 6.80 (t, $J$ = 7.4 Hz, 1H), 5.73 (s, br, 1H), 3.64 (d, $J$ = 17.7 Hz, 1H), 2.92 (d, $J$ = 17.7 Hz, 1H), 1.45 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 204.2 (*C*=O), 198.5 (*C*=O), 159.9, 137.6, 136.9, 133.8, 128.8, 128.2, 125.2, 119.0, 118.6, 112.4, 64.6 (NHC−CO), 43.9 ($COCH_2$), 22.0 ($CH_3$); HRMS (ESI-Q-TOF) $m/z$ $[M+H]^+$ Calcd for $C_{17}H_{16}NO_2$ 266.1181; Found 266.1179.

5-Nitro-2-(2-oxo-2-phenylethyl)-2-phenylindolin-3-one **3ba** (yellow solid, 65.0 mg, 35%, mp 207−208 °C): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.50 (d, $J$ = 2.3 Hz, 1H), 8.38 (dd, $J$ = 9.1 Hz, 2.3 Hz, 1H), 7.91 (d, $J$ = 7.1 Hz, 2H), 7.60 (tt, $J$ = 7.4, 1.3 Hz, 1H), 7.41−7.55 (m, 4H), 7.23−7.36 (m, 3H), 7.10 (s, br, 1H), 6.98 (d, $J$ = 9.1 Hz, 1H), 4.48 (d, $J$ = 18.1 Hz, 1H), 3.28 (d, $J$ = 18.1 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 198.8 (*C*=O), 197.3 (*C*=O), 162.3, 139.9, 136.5, 136.1, 134.2, 133.0, 129.1, 129.0, 128.3, 128.2, 125.2, 123.1, 117.7, 111.1, 70.9 (NHC−CO), 44.7 ($COCH_2$); HRMS (ESI-Q-TOF) $m/z$ $[M+H]^+$ Calcd for $C_{22}H_{17}N_2O_4$ 373.1188; Found 373.1186.

5-Fluoro-2-(2-oxo-2-phenylethyl)-2-phenylindolin-3-one **3ca** (yellow solid, 86.6 mg, 50%, mp 149−150 °C): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.91 (d, $J$ = 7.1 Hz, 2H), 7.51−7.62 (m, 3H), 7.45 (t, $J$ = 7.6 Hz, 2H), 7.18−7.33 (m, 5H), 6.94 (dd, $J$ = 8.6, 3.6 Hz, 1H), 6.17 (s, br, 1H), 4.41 (d, $J$ = 17.9 Hz, 1H), 3.21 (d, $J$ = 17.9 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 200.6 (d, $J_{4,C-F}$ = 3.3 Hz, *C*=O), 197.6 (*C*=O), 157.1, 156.4 (d, $J_{1,C-F}$ = 239.5 Hz), 154.8, 137.9, 136.5, 133.8, 128.84, 128.80, 128.2, 127.8, 125.9 (d, $J_{2,C-F}$ = 25.7 Hz), 125.4, 118.6 (d, $J_{3,C-F}$ = 7.3 Hz), 113.0 (d, $J_{3,C-F}$ = 7.4 Hz), 110.2 (d, $J_{2,C-F}$ = 22.5 Hz), 70.4 (NHC−CO), 45.0 ($COCH_2$); HRMS (ESI-Q-TOF) $m/z$: $[M+H]^+$ Calcd for $C_{22}H_{17}FNO_2$ 346.1243; Found 346.1240.

5-Chloro-2-(2-oxo-2-phenylethyl)-2-phenylindolin-3-one **3da** (yellow solid, 81.3 mg, 45%, mp 148−149 °C): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.91 (d, $J$ = 7.1 Hz, 2H), 7.58 (tt, $J$ = 7.4 Hz, 1.3 Hz, 1H), 7.40−7.55 (m, 6H), 7.29 (t, $J$ = 7.2 Hz, 2H), 7.23 (t, $J$ = 7.1 Hz, 1H), 6.92 (d, $J$ = 8.7 Hz, 1H), 6.31 (s, br, 1H), 4.42 (d, $J$ = 18.0 Hz, 1H), 3.20 (d, $J$ = 18.0 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 199.7 (*C*=O), 197.5 (*C*=O), 158.6, 137.7, 136.4, 133.9, 128.9, 128.8, 128.2, 127.8, 125.3, 124.8, 123.9, 119.2, 113.1, 70.1 (NHC−CO), 44.8 ($COCH_2$); HRMS (ESI-Q-TOF) $m/z$ $[M+H]^+$ Calcd for $C_{22}H_{17}ClNO_2$ 362.0948; Found 362.0943.

6-Chloro-2-(2-oxo-2-phenylethyl)-2-phenylindolin-3-one **3ea** (yellow solid, 101.6 mg, 56%, mp 174−175 °C): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.92 (d, $J$ = 7.1 Hz, 2H), 7.59 (tt, $J$ = 7.4 Hz, 1.3 Hz, 1H), 7.42−7.55 (m, 5H), 7.30 (t, $J$ = 7.2 Hz, 2H), 7.23 (t, $J$ = 7.1 Hz, 1H), 6.97 (d, $J$ = 1.4 Hz, 1H), 6.77 (dd, $J$ = 8.3 Hz, 1.7 Hz, 1H), 6.38 (s, br, 1H), 4.43 (d, $J$ = 18.0 Hz, 1H), 3.19 (d, $J$ = 18.0 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 199.4 (*C*=O), 197.7 (*C*=O), 160.5, 144.3, 137.7, 136.4, 133.9, 128.89, 128.85, 128.2, 127.8, 126.7, 125.3, 119.7, 116.7, 111.7, 69.9 (NHC−CO), 44.8 ($COCH_2$); HRMS (ESI-Q-TOF) $m/z$: $[M+H]^+$ Calcd for $C_{22}H_{17}ClNO_2$ 362.0948; Found 362.0953.

4-Chloro-2-(2-oxo-2-phenylethyl)-2-phenylindolin-3-one **3fa** (yellow solid, 33.3 mg, 18%, mp 108−110 °C): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.91 (d, $J$ = 7.2 Hz, 2H), 7.52−7.62 (m, 3H), 7.45 (t, $J$ = 7.6 Hz, 2H), 7.30 (t, $J$ = 8.0 Hz, 1H), 7.29 (t, $J$ = 7.2 Hz, 2H), 7.22 (t, $J$ = 7.1 Hz, 1H), 6.92 (d, $J$ = 8.7 Hz, 1H), 6.85 (d, $J$ = 8.2 Hz, 1H), 6.73 (d, $J$ = 7.7 Hz, 1H), 6.44 (s, br, 1H), 4.45 (d, $J$ = 18.0 Hz, 1H), 3.20 (d, $J$ = 18.0 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 198.0 (*C*=O), 197.8 (*C*=O), 161.4, 138.0, 137.7, 136.5, 134.0, 133.4, 128.89, 128.87, 128.2, 127.9, 125.4, 119.9, 114.9, 110.1, 69.7 (NHC−CO), 45.1 ($COCH_2$); HRMS (ESI-Q-TOF) $m/z$ $[M+H]^+$ Calcd for $C_{22}H_{17}ClNO_2$ 362.0948; Found 362.0945.

5-Methyl-2-(2-oxo-2-phenylethyl)-2-phenylindolin-3-one **3ga** (yellow solid, 70.2 mg, 41%, mp 180−181 °C): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.92 (d, $J$ = 7.1 Hz, 2H), 7.50−7.60 (m, 3H), 7.45 (t, $J$ = 7.6 Hz, 2H), 7.37 (s, 1H), 7.33 (dd, $J$ = 8.3, 1.5 Hz, 1H), 7.23−7.31 (m, 2H), 7.20 (tt, $J$ = 7.4, 1.3 Hz, 1H), 6.89 (d, $J$ = 8.3 Hz, 1H), 6.13 (s, br, 1H), 4.42 (d, $J$ = 17.9 Hz, 1H), 3.18 (d, $J$ = 17.9 Hz, 1H), 2.28 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 200.9 (*C*=O), 197.9 (*C*=O),



DOI: 10.1021/acs.joc.6b01993
J. Org. Chem. 2016, 81, 12443−12450

158.9, 139.4, 138.4, 136.7, 133.8, 128.9, 128.8, 128.5, 128.2, 127.6, 125.4, 125.0, 118.4, 111.9, 69.7 (NHC−CO), 44.9 ($COCH_2$), 20.6 ($CH_3$); HRMS (ESI-Q-TOF) $m/z$ $[M+H]^+$ Calcd for $C_{23}H_{20}NO_2$ 342.1494; Found 342.1492.

*Conversion of **3aa** to **4** with $NH_2NH_2{\cdot}H_2O$ and HOAc in EtOH.* 85% concentration of $NH_2NH_2{\cdot}H_2O$ (11 μL, 0.193 mmol) and HOAc (5.5 μL, 0.095 mmol) were added to a solution of **3aa** (31 mg, 0.095 mmol) in EtOH (0.6 mL). The mixture was stirred at 40 °C for 4.5 h until the disappearance of **3aa** as determined by TLC. Twenty milliliters of aqueous solution of $Na_2CO_3$ was added and the mixture was extracted with dichloromethane (15 mL × 3). The combined organic phases were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate/petroleum ether: 1/8−1:4) to provide the corresponding products **4** (19.1 mg, 62%).

2-(4,6-Diphenylpyridazin-3-yl)aniline **4** (yellow solid, mp 190−191 °C): $^1$H NMR (300 MHz, $CDCl_3$) δ 8.13−8.20 (m, 2H), 7.93 (s, 1H), 7.48−7.60 (m, 3H), 7.27−7.37 (m, 5H), 7.10 (ddd, $J$ = 8.1, 7.4, 1.5 Hz, 1H), 6.81 (dd, $J$ = 8.1, 0.9 Hz, 1H), 6.72 (dd, $J$ = 7.7, 1.5 Hz, 1H), 6.50 (td, $J$ = 7.5, 1.0 Hz, 1H), 4.72 (s, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 158.7, 157.9, 146.0, 140.6, 137.2, 136.3, 132.1, 130.2, 130.0, 129.2, 129.0, 128.9, 128.8, 127.2, 125.5, 121.3, 118.0, 117.1; HRMS (ESI-Q-TOF) $m/z$ [M+H]+ Calcd for $C_{22}H_{18}N_3$ 324.1501; Found 324.1500.

*Reaction of **3aa** with $Cu(OAc)_2$ for the Synthesis of **5a** and **5b**.* A mixture of **3aa** (65.4 mg, 0.2 mmol) and $Cu(OAc)_2$ (91 mg, 0.5 mmol) in 2 mL of DMSO was stirred at 120 °C for 25 min until the disappearance of **3aa** as determined by TLC. After cooling to room temperature 20 mL of water was added and the mixture was extracted with dichloromethane (15 mL × 3). The combined organic phases were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate/petroleum ether: 1:15−1/6) to provide the corresponding products **5a** (lower polarity, 16.6 mg, 26%) and **5b** (higher polarity, 36.6 mg, 56%).

*cis*-1-Benzoyl-7a-phenyl-1H-azirino[1,2-*a*]indol-7(7aH)-one **5a** (yellow solid, mp 132−134 °C): $^1$H NMR (300 MHz, $CDCl_3$) δ 7.88−7.93 (m, 2H), 7.82−7.88 (m, 2H), 7.66 (ddd, $J$ = 7.6, 1.2, 0.7 Hz, 1H), 7.58 (tt, $J$ = 7.4, 1.4 Hz, 1H), 7.36−7.51 (m, 7H), 7.23 (ddd, $J$ = 8.2, 6.8, 1.4 Hz, 1H) 4.33 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 195.7 (C═O), 190.4 (C═O), 160.5, 135.7, 135.4, 134.5, 133.4, 131.4, 129.0, 128.9, 128.8, 128.7, 127.6, 126.9, 124.9, 122.9, 72.3, 58.2; HRMS (ESI-Q-TOF) $m/z$ [M+H]+ Calcd for $C_{22}H_{16}NO_2$ 326.1181; Found 326.1174.

*trans*-1-Benzoyl-7a-phenyl-1H-azirino[1,2-*a*]indol-7(7aH)-one **5b** (yellow solid, mp 161−162 °C): $^1$H NMR (300 MHz, $CDCl_3$) δ 7.80−7.88 (m, 3H), 7.75 (d, $J$ = 7.8 Hz, 1H), 7.70 (dd, $J$ = 7.0, 1.3 Hz, 1H), 7.62−7.68 (m, 2H), 7.55 (tt, $J$ = 7.4, 1.3 Hz, 1H), 7.36−7.45 (m, 3H), 7.21−7.32 (m, 3H), 3.92 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 196.7 (C═O), 188.2 (C═O), 165.9, 136.3, 135.5, 134.1, 128.9, 128.7, 128.55, 128.49, 128.45, 128.38, 127.2, 126.3, 122.0, 73.1, 59.4; HRMS (ESI-Q-TOF) $m/z$ [M+H]+ Calcd for $C_{22}H_{16}NO_2$ 326.1181; Found 326.1177.

*Reaction of **3aa** with $I_2$ for the Synthesis of **5b**.* A mixture of **3aa** (31.0 mg, 0.095 mmol), $I_2$ (49 mg, 0.191 mmol), and DBU (58 mg, 0.38 mmol) was stirred in 0.8 mL of THF at 40 °C for 4.5 h until the disappearance of **3aa** as determined by TLC. The reaction mixture was quenched with aqueous $Na_2S_2O_3$ and extracted with dichloromethane (15 mL × 3). The organic extracts were dried over sodium sulfate, filtered, and concentrated to give a residue, which was purified by column chromatography on silica gel (ethyl acetate/petroleum ether: 1/6) to afford the product **5b** (25.0 mg, 81%).

*$K_2CO_3$ Catalyzed Isomerization of **5b** to **6aa**.* A mixture of **5b** (13.0 mg, 0.040 mmol) and $K_2CO_3$ (1.1 mg, 0.008 mmol) was stirred in 0.4 mL of DMSO at 120 °C for about 5 h until the disappearance of **5b** as determined by TLC. The reaction mixture was extracted with dichloromethane (10 mL × 3). Then the organic extracts were dried over sodium sulfate, filtered, and concentrated to give a residue, which was purified by column chromatography on silica gel (ethyl acetate/petroleum ether: 1/6−1:3) to afford the product **6aa** (12.0 mg, 92%).

**General Procedure for $Cu(OAc)_2$ and $Cs_2CO_3$ Mediated Transformation of 3 to 6 in DMSO.** A mixture of **3** (0.1 mmol), $Cu(OAc)_2$ (0.25 mmol), and $Cs_2CO_3$ (0.25 mmol) in DMSO (0.8 mL) was stirred at 120 °C for less than 0.5 h until the disappearance of **3** as determined by TLC. Fifteen milliliters of water was added and the mixture was extracted with dichloromethane (15 mL × 3). The combined organic phases were dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate/petroleum ether: 1/6−1:3) to afford the corresponding products **6**.

2-Benzoyl-3-phenylquinolin-4(1H)-one **6aa** (white solid, 20.3 mg, 62%, mp 270−273 °C): $^1$H NMR (300 MHz, $d_6$-DMSO) δ 9.50 (s, br, 1H), 8.33 (d, $J$ = 7.8 Hz, 1H), 7.52−7.65 (m, 3H), 7.29−7.40 (m, 3H), 7.24 (d, $J$ = 7.0 Hz, 2H), 7.17 (t, $J$ = 7.7 Hz, 2H), 7.07 (t, $J$ = 7.2 Hz, 2H), 7.00 (t, $J$ = 7.1 Hz, 1H); $^{13}$C NMR (75 MHz, DMSO) δ 191.5 (C═O), 175.3 (C═O), 144.7, 139.4, 134.64, 134.59, 133.8, 132.4, 130.9, 129.6, 129.0, 127.6, 127.1, 125.5, 125.3, 123.9, 119.4, 118.6; HRMS (ESI-Q-TOF) $m/z$ [M+H]+ Calcd for $C_{22}H_{16}NO_2$ 326.1181; Found 326.1177.

2-Benzoyl-3-(4-methoxyphenyl)quinolin-4(1H)-one **6ac** (yellow solid, 10.8 mg, 30%, mp >300 °C): $^1$H NMR (300 MHz, $d_6$-DMSO) δ 12.28 (s, br, 1H), 8.21 (dd, $J$ = 8.2, 1.2 Hz, 1H), 7.69−7.79 (m, 3H), 7.60 (t, $J$ = 8.2 Hz, 2H), 7.37−7.47 (m, 3H), 7.08 (d, $J$ = 8.8 Hz, 2H), 6.73 (d, $J$ = 8.8 Hz, 2H), 3.64 (s, 3H); $^{13}$C NMR (75 MHz, $d_6$-DMSO) δ 191.7 (C═O), 175.5 (C═O), 158.2, 144.4, 139.4, 134.6, 132.3, 132.1, 129.6, 129.0, 125.8, 125.5, 125.2, 123.7, 119.0, 118.6, 113.8, 113.1, 54.9; HRMS (ESI-Q-TOF) $m/z$ $[M+H]^+$ Calcd for $C_{23}H_{18}NO_3$ 356.1287; Found 356.1284.

2-Benzoyl-3-(4-chlorophenyl)quinolin-4(1H)-one **6ae** (white solid, 13.0 mg, 36%, mp 292−293 °C): $^1$H NMR (300 MHz, $d_6$-DMSO) δ 12.42 (s, br, 1H), 8.22 (dd, $J$ = 8.1, 1.1 Hz, 1H), 7.72−7.81 (m, 3H), 7.60 (t, $J$ = 7.9 Hz, 2H), 7.40−7.49 (m, 3H), 7.24 (d, $J$ = 8.6 Hz, 2H), 7.18 (d, $J$ = 8.6 Hz, 2H); $^{13}$C NMR (75 MHz, $d_6$-DMSO) δ 191.4 (C═O), 175.1 (C═O), 144.8, 139.3, 134.8, 134.5, 132.8, 132.6, 132.6, 131.8, 129.7, 129.1, 127.7, 125.5, 125.3, 124.0, 118.7, 118.1; HRMS (ESI-Q-TOF) $m/z$ $[M+H]^+$ Calcd for $C_{22}H_{15}ClNO_2$ 360.0791; Found 360.0786.

2-(4-Methoxybenzoyl)-3-phenylquinolin-4(1H)-one **6ag** (white solid, 19.4 mg, 55%, mp 299−300 °C): $^1$H NMR (300 MHz, $d_6$-DMSO) δ 12.30 (s, br, 1H), 8.20 (dd, $J$ = 8.2, 1.1 Hz, 1H), 7.68−7.77 (m, 3H), 7.61 (d, $J$ = 8.0 Hz, 1H), 7.40 (ddd, $J$ = 8.0, 6.9, 1.0 Hz, 1H), 7.07−7.22 (m, 5H), 6.94 (d, $J$ = 9.0 Hz, 2H), 3.79 (s, 3H); $^{13}$C NMR (75 MHz, $d_6$-DMSO) δ 189.6 (C═O), 175.2 (C═O), 164.2, 145.3, 139.4, 134.0, 132.33, 132.29, 130.8, 127.6, 127.5, 127.0, 125.5, 125.3, 123.8, 119.0, 118.6, 114.4, 55.8; HRMS (ESI-Q-TOF) $m/z$ $[M+H]^+$ Calcd for $C_{23}H_{18}NO_3$ 356.1287; Found 356.1283.

2-(4-Methylbenzoyl)-3-phenylquinolin-4(1H)-one **6ah** (white solid, 13.8 mg, 41%, mp >300 °C): $^1$H NMR (300 MHz, $d_6$-DMSO) δ 12.32 (s, br, 1H), 8.21 (dd, $J$ = 8.1, 1.1 Hz, 1H), 7.73 (ddd, $J$ = 8.4, 7.0, 1.5 Hz, 1H), 7.66 (d, $J$ = 8.2 Hz, 2H), 7.62 (d, $J$ = 8.1 Hz, 1H), 7.41 (ddd, $J$ = 8.0, 6.9, 0.9 Hz, 1H), 7.23 (d, $J$ = 8.1 Hz, 2H), 7.07−7.19 (m, 5H), 2.31 (s, 3H); $^{13}$C NMR (75 MHz, $d_6$-DMSO) δ 190.9 (C═O), 175.3 (C═O), 145.5, 145.0, 139.3, 133.9, 132.4, 132.1, 130.9, 129.8, 129.6, 127.6, 127.0, 125.5, 125.3, 123.8, 119.1, 118.6, 21.3; HRMS (ESI-Q-TOF) $m/z$ $[M+H]^+$ Calcd for $C_{23}H_{18}NO_2$ 340.1338; Found 340.1335.

2-(4-Chlorobenzoyl)-3-phenylquinolin-4(1H)-one **6ai** (yellow solid, 18.0 mg, 50%, mp 280−281 °C): $^1$H NMR (300 MHz, $d_6$-DMSO) δ 12.12 (s, br, 1H), 8.22 (d, $J$ = 7.3 Hz, 1H), 7.60−7.81 (m, 4H), 7.36−7.53 (m, 3H), 7.06−7.25 (m, 5H); $^{13}$C NMR (75 MHz, $d_6$-DMSO) δ 190.7 (C═O), 175.1 (C═O), 144.4, 139.6, 139.4, 133.8, 133.4, 132.4, 131.4, 130.9, 129.1, 127.6, 127.1, 125.5, 125.4, 123.9, 119.5, 118.9; HRMS (ESI-Q-TOF) $m/z$ $[M+H]^+$ Calcd for $C_{22}H_{15}ClNO_2$ 360.0791; Found 360.0789.

2-(4-Nitrobenzoyl)-3-phenylquinolin-4(1H)-one **6aj** (yellow solid, 22.5 mg, 61%, mp 295−297 °C): $^1$H NMR (300 MHz, $d_6$-DMSO) δ 12.42 (s, br, 1H), 8.23 (dd, $J$ = 8.1, 1.0 Hz, 1H), 8.16 (d, $J$ = 8.9 Hz, 2H), 7.97 (d, $J$ = 9.0 Hz, 2H), 7.53 (ddd, $J$ = 8.4, 6.9, 1.5 Hz, 1H), 7.68 (d, $J$ = 8.1 Hz, 1H), 7.44 (ddd, $J$ = 7.9, 6.6, 0.8 Hz, 1H), 7.05−7.20 (m, 5H); $^{13}$C NMR (75 MHz, $d_6$-DMSO) δ 190.9, 175.4 (C═O), 150.2 (C═O), 143.4, 139.5, 139.4, 133.5, 132.6, 131.1, 130.8, 127.7, 127.4,



DOI: 10.1021/acs.joc.6b01993
J. Org. Chem. 2016, 81, 12443−12450

125.54, 125.45, 124.1, 123.9, 120.0, 118.8; HRMS (ESI-Q-TOF) $m/z$ $[M+H]^+$ Calcd for $C_{22}H_{15}N_2O_4$ 371.1032; Found 371.1030.

2-Benzoyl-6-nitro-3-phenylquinolin-4(1H)-one **6ba** (white solid, 9.3 mg, 25%, mp >300 °C): $^1$H NMR (300 MHz, $d_6$-DMSO) $\delta$ 12.88 (s, br, 1H), 8.96 (d, $J$ = 2.6 Hz, 1H), 8.51 (dd, $J$ = 9.1, 2.7 Hz, 1H), 7.77−7.84 (m, 3H), 7.60 (tt, $J$ = 7.4, 1.3 Hz, 1H), 7.42 (t, $J$ = 7.7 Hz, 2H), 7.09−7.23 (m, 5H); $^{13}$C NMR (75 MHz, $d_6$-DMSO) $\delta$ 191.0 (C═O), 175.3 (C═O), 145.5, 143.2, 143.1, 134.9, 134.3, 132.7, 130.7, 129.7, 129.1, 127.8, 127.6, 126.5, 124.4, 122.2, 121.0, 120.6; HRMS (ESI-Q-TOF) $m/z$ $[M+H]^+$ Calcd for $C_{22}H_{15}N_2O_4$ 371.1032; Found 371.1028.

2-Benzoyl-6-chloro-3-phenylquinolin-4(1H)-one **6da** (yellow solid, 10.7 mg, 30%, mp 257−259 °C): $^1$H NMR (300 MHz, $d_6$-DMSO) $\delta$ 12.54 (s, br, 1H), 8.15 (d, $J$ = 2.3 Hz, 1H), 7.73−7.79 (m, 3H), 7.67 (d, $J$ = 8.8 Hz, 1H), 7.59 (tt, $J$ = 7.4, 1.3 Hz, 1H), 7.41 (t, $J$ = 7.7 Hz, 2H), 7.06−7.19 (m, 5H); $^{13}$C NMR (75 MHz, $d_6$-DMSO) $\delta$ 191.4 (C═O), 174.2 (C═O), 145.0, 138.1, 134.7, 134.5, 133.4, 132.6, 130.8, 129.6, 129.0, 128.5, 127.6, 127.2, 126.3, 124.4, 121.2, 119.7; HRMS (ESI-Q-TOF) $m/z$ $[M+H]^+$ Calcd for $C_{22}H_{15}ClNO_2$ 360.0791; Found 360.0794.

2-Benzoyl-6-methyl-3-phenylquinolin-4(1H)-one **6ga** (yellow solid, 14.7 mg, 43%, mp >300 °C): $^1$H NMR (300 MHz, $d_6$-DMSO) $\delta$ 12.27 (s, br, 1H), 8.01(s, 1H), 7.73 (d, $J$ = 7.2 Hz, 2H), 7.51−7.61 (m, 3H), 7.41 (t, $J$ = 7.7 Hz, 2H), 7.05−7.18 (m, 5H), 2.46 (s, 3H); $^{13}$C NMR (75 MHz, $d_6$-DMSO) $\delta$ 191.6 (C═O), 175.0 (C═O), 144.3, 137.4, 134.6, 134.5, 134.0, 133.8, 133.2, 130.9, 129.5, 128.9, 127.5, 126.9, 125.3, 124.6, 119.1, 118.5, 20.9; HRMS (ESI-Q-TOF) $m/z$ $[M+H]^+$ Calcd for $C_{23}H_{18}NO_2$ 340.1338; Found 340.1335.

*$Cs_2CO_3$−Catalyzed Transformation of **7/8** to **9/11**.* A mixture of **7** or **8** (0.30 mmol) and $Cs_2CO_3$ (0.06 mmol) in 1.3 mL of DMSO was stirred at 80 °C until the disappearance of **7** or **8** as determined by TLC. After cooling to room temperature, 15 mL of water was added and the mixture was extracted with dichloromethane (15 mL × 3). The combined organic phases were dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate/petroleum ether: 1:20−1:10) to provide the corresponding products **9** (32.1 mg, 66%)[27] or **11** (30.4 mg, 45%).[28]

1-(2-Aminophenyl)-2-methylpropan-1-one **9**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.77 (dd, $J$ = 8.3, 1.5 Hz, 1H), 7.25 (ddd, $J$ = 8.2, 7.1, 1.5 Hz, 1H), 7.60−7.70 (m, 2H), 6.30 (s, br, 2H), 3.59 (heptet, $J$ = 6.8 Hz, 1H), 1.20 (d, $J$ = 6.8 Hz, 6H).

1-(2-Aminophenyl)-2-phenylpropan-1-one **11**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.78 (dd, $J$ = 8.2, 1.2 Hz, 1H), 7.30(d, $J$ = 4.4, 4H), 7.14−7.25 (m, 2H), 6.50−6.64 (m, 2H), 6.32(s, 2H), 4.72 (dd, $J$ = 13.7, 6.9 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 202.8 (C═O), 151.2, 142.5, 134.2, 131.6, 129.0, 127.7, 126.8, 117.5, 117.3, 115.8, 47.7, 19.9.

*$Cs_2CO_3$−Catalyzed Transformation of **13** to **14**.* A mixture of **13** (18.0 mg, 0.06 mmol) and $Cs_2CO_3$ (4 mg, 0.01 mmol) in DMSO (0.5 mL) was stirred at 80 °C for 1 h until the disappearance of **13** as determined by TLC. Ten milliliters of water was added and the mixture was extracted with dichloromethane (10 mL × 3). The combined organic phases were dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate/petroleum ether: 1:20−1:10) to afford the product **14** (17.5 mg, 98%).[29]

1,2,4-Triphenylbut-2-ene-1,4-dione **14**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.95−8.03 (m, 4H), 7.39−7.67 (m, 12H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 197.7 (C═O), 188.3 (C═O), 156.5, 137.4, 136.1, 134.9, 133.5, 133.5, 130.9, 129.3, 128.9, 128.9, 128.8, 128.7, 127.4, 121.0, 116.9.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01993.

$^1$H and $^{13}$C NMR spectra of the products, H−H COSY and NOESY spectra of **5a** (PDF)

X-ray crystallographic data of **3aa** (CIF)

X-ray crystallographic data of **6ai** (CIF)

## ■ AUTHOR INFORMATION


### Corresponding Author

*E-mail: estally@yahoo.com

### ORCID

Hai-Tao Yang: 0000-0001-9803-5452

Chun-Bao Miao: 0000-0003-4666-2619


### Author Contributions

†Y.S. and Y.-M.Z. contributed equally to this work.

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We are grateful for the financial support from the National Natural Science Foundation of China (Nos. 21202011), Natural Science Foundation of Jiangsu Province (BK20141171), the Jiangsu Key Laboratory of Advanced Catalytic Materials and Technology (BM2012110), and Jiangsu Province Key Laboratory of Fine Petrochemical Engineering (KF1303)

## ■ REFERENCES


(1) (a) Karadeolian, A.; Kerr, M. A. *J. Org. Chem.* **2010**, *75*, 6830. (b) Karadeolian, A.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2010**, *49*, 1133.

(2) Baran, P. S.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 7904.

(3) Bhakuni, D. S.; Silva, M.; Matlin, S. A.; Sammes, P. G. *Phytochemistry* **1976**, *15*, 574.

(4) Akhgari, A.; Laakso, I.; Seppänen-Laakso, T.; Yrjönen, T.; Vuorela, H.; Oksman-Caldentey, K.-M.; Rischer, H. *Phytochem. Anal.* **2015**, *26*, 331.

(5) (a) Williams, R. M.; Glinka, T.; Kwast, E.; Coffman, H.; Stille, J. K. *J. Am. Chem. Soc.* **1990**, *112*, 808. (b) Birch, A. J.; Wright, J. J. *Tetrahedron* **1970**, *26*, 2329.

(6) Wang, F.; Fang, Y.; Zhu, T.; Zhang, M.; Lin, A.; Gu, Q.; Zhu, W. *Tetrahedron* **2008**, *64*, 7986.

(7) Phillipson, J. D.; Supavita, N. *Phytochemistry* **1983**, *22*, 1809.

(8) Tang, B.-Q.; Wang, W.-J.; Huang, X.-J.; Li, G.-Q.; Wang, L.; Jiang, R.-W.; Yang, T.-T.; Shi, L.; Zhang, X.-Q.; Ye, W.-C. *J. Nat. Prod.* **2014**, *77*, 1839.

(9) For selected examples, see: (a) Higuchi, K.; Sato, Y.; Tsuchimochi, M.; Sugiura, K.; Hatori, M.; Kawasaki, T. *Org. Lett.* **2009**, *11*, 197. (b) Liu, Y.; McWhorter, W. W., Jr *J. Am. Chem. Soc.* **2003**, *125*, 4240.

(10) (a) Lerch, S.; Unkel, L.-N.; Brasholz, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 6558. (b) Han, S.; Morrison, K. C.; Hergenrother, P. J.; Movassaghi, M. *J. Org. Chem.* **2014**, *79*, 473. (c) Ding, W.; Zhou, Q.-Q.; Xuan, J.; Li, T.-R.; Lu, L.-Q.; Xiao, W.-J. *Tetrahedron Lett.* **2014**, *55*, 4648. (d) Mateo, C. A.; Urrutia, A.; Rodríguez, J. G.; Fonseca, I.; Cano, F. H. *J. Org. Chem.* **1996**, *61*, 810. (e) Zhao, G.; Xie, X.; Sun, H.; Yuan, Z.; Zhong, Z.; Tang, S.; She, X. *Org. Lett.* **2016**, *18*, 2447.

(11) (a) Guchhait, S. K.; Chaudhary, V.; Rana, V. A.; Priyadarshani, G.; Kandekar, S.; Kashyap, M. *Org. Lett.* **2016**, *18*, 1534. (b) Kobayashi, Y.; Buller, M. J.; Cook, T. G. *Heterocycles* **2007**, *72*, 163. (c) Ke-Qing, L. *Synth. Commun.* **1996**, *26*, 149. (d) Higuchi, K.; Sato, Y.; Kojima, S.; Tsuchimochi, M.; Sugiura, K.; Hatori, M.; Kawasaki, T. *Tetrahedron* **2010**, *66*, 1236.

(12) Okuma, K.; Matsunaga, N.; Nagahora, N.; Shioji, K.; Yokomori, Y. *Chem. Commun.* **2011**, *47*, 5822.

(13) Goriya, Y.; Ramana, C. V. *Chem. Commun.* **2013**, *49*, 6376.

(14) (a) Wetzel, A.; Gagosz, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 7354. (b) Li, N.; Wang, T.-Y.; Gong, L.-Z.; Zhang, L. *Chem. - Eur. J.* **2015**, *21*, 3585.




DOI: 10.1021/acs.joc.6b01993
J. Org. Chem. 2016, 81, 12443−12450

(15) (a) Suneel Kumar, C. V.; Ramana, C. V. *Org. Lett.* **2014**, *16*, 4766. (b) Suneel Kumar, C. V.; Ramana, C. V. *Org. Lett.* **2015**, *17*, 2870.
(16) (a) Zhang, Y.-Q.; Zhu, D.-Y.; Jiao, Z.-W.; Li, B.-S.; Zhang, F.-M.; Tu, Y.-Q.; Bi, Z. *Org. Lett.* **2011**, *13*, 3458. (b) Peng, J.-B.; Qi, Y.; Ma, A.-J.; Tu, Y.-Q.; Zhang, F.-M.; Wang, S.-H.; Zhang, S.-Y. *Chem. - Asian J.* **2013**, *8*, 883.
(17) Kuppusamy, R.; Gandeepan, P.; Cheng, C.-H. *Org. Lett.* **2015**, *17*, 3846.
(18) Zhou, P.-X.; Zhou, Z.-Z.; Chen, Z.-S.; Ye, Y.-Y.; Zhao, L.-B.; Yang, Y.-F.; Xia, X.-F.; Luo, J.-Y.; Liang, Y.-M. *Chem. Commun.* **2013**, *49*, 561.
(19) (a) Miao, C.-B.; Zhang, M.; Tian, Z.-Y.; Xi, H.-T.; Sun, X.-Q.; Yang, H.-T. *J. Org. Chem.* **2011**, *76*, 9809. (b) Miao, C.-B.; Wang, Y.-H.; Xing, M.-L.; Lu, X.-W.; Sun, X.-Q.; Yang, H.-T. *J. Org. Chem.* **2013**, *78*, 11584. (c) Miao, C.-B.; Zeng, Y.-M.; Shi, T.; Liu, R.; Wei, P.-F.; Sun, X.-Q.; Yang, H.-T. *J. Org. Chem.* **2016**, *81*, 43.
(20) For reviews, see: (a) Ramirez, T. A.; Zhao, B.; Shi, Y. *Chem. Soc. Rev.* **2012**, *41*, 931. (b) Collet, F.; Dodd, R. H.; Dauban, P. *Chem. Commun.* **2009**, 5061. (c) Gephart, R. T., III; Warren, T. H. *Organometallics* **2012**, *31*, 7728. (d) Du Bois, J. *Org. Process Res. Dev.* **2011**, *15*, 758.
(21) For selected examples: (a) He, G.; Zhao, Y.; Zhang, S.; Lu, C.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 3. (b) Wang, C.; Chen, C.; Zhang, J.; Han, J.; Wang, Q.; Guo, K.; Liu, P.; Guan, M.; Yao, Y.; Zhao, Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 9884 and references cited therein..
(22) Wiles, J. A.; Bradbury, B. J.; Pucci, M. J. *Expert Opin. Ther. Pat.* **2010**, *20*, 1295.
(23) Liang, Y.-F.; Jiao, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 548.
(24) Lubin, H.; Tessier, A.; Chaume, G.; Pytkowicz, J.; Brigaud, T. *Org. Lett.* **2010**, *12*, 1496.
(25) (a) Lee, H. J.; Lim, J. W.; Yu, J.; Kim, J. N. *Tetrahedron Lett.* **2014**, *55*, 1183. (b) Bartberger, M. D.; Gonzalez Buenrostro, A.; Beck, H. P.; Chen, X.; Connors, R. V.; et al. PCT Int. Appl. Piperidinone derivatives as mdm2 inhibitors for the treatment of cancer.-WO2011153509A1, December 8, 2011.
(26) Reddy, P. L.; Kumar, K. P.; Satyanarayana, S.; Narender, R.; Reddy, B. V. S. *Tetrahedron Lett.* **2012**, *53*, 1546.
(27) McDonald, I. M.; Austin, C.; Buck, I. M.; Dunstone, D. J.; Gaffen, J.; et al. *J. Med. Chem.* **2007**, *50*, 4789.
(28) Azadi-Ardakani, M.; Alkhader, M. A.; Lippiatt, J. H.; Patel, D. I.; Smalley, R. K.; Higson, S. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1107.
(29) Lin, C.-L.; Wu, Y.-L.; Chen, C.-L.; Chou, C.-M.; Luh, T.-Y. *J. Org. Chem.* **2007**, *72*, 8531.



DOI: 10.1021/acs.joc.6b01993
*J. Org. Chem.* 2016, 81, 12443−12450