JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Rhodium-Catalyzed NH-Indole-Directed C−H Carbonylation with Carbon Monoxide: Synthesis of 6*H*-Isoindolo[2,1-*a*]indol-6-ones

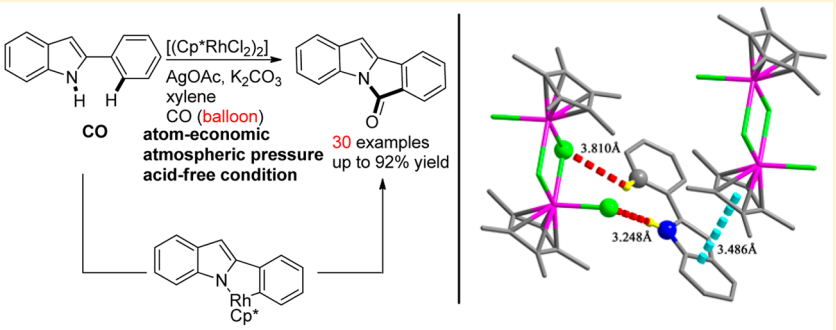
Qiufeng Huang,*[†,‡] Qingshuai Han,[†,‡] Shurong Fu,[†,‡] Zizhu Yao,[§] Lv Su,[†,‡] Xiaofeng Zhang,[†,‡] Shen Lin,*[§] and Shengchang Xiang[§]

[†]College of Chemistry & Chemical Engineering, Fujian Normal University, Fuzhou 350007, People's Republic of China

[‡]Key Laboratory of Coal to Ethylene Glycol and Its Related Technology, Chinese Academy of Sciences, Fuzhou 350002, People's Republic of China

[§]Fujian Key Laboratory of Polymer Materials, Fuzhou 350007, People's Republic of China

Supporting Information



ABSTRACT: An efficient synthesis of 6*H*-isoindolo[2,1-*a*]indol-6-ones through rhodium-catalyzed NH-indole-directed C−H carbonylation of 2-arylindoles with carbon monoxide has been developed. Preliminary mechanistic studies revealed that this reaction proceeds via N−H bond cleavage and subsequent C−H bond cleavage. Reaction monitoring via ESI-MS was used to support the formation of five-membered rhodacycle species in the catalytic cycle.

INTRODUCTION

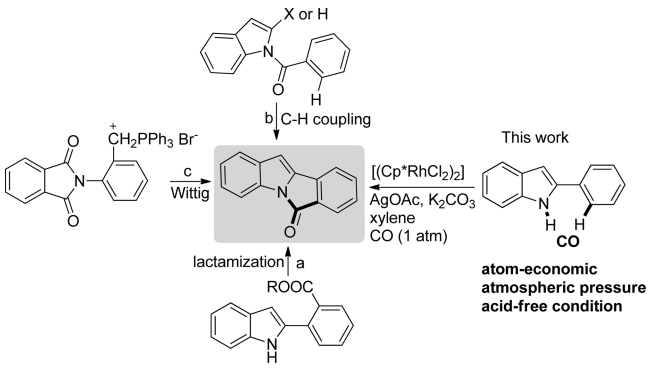
The transition-metal-catalyzed carbonylation of organic compounds with carbon monoxide (CO) is a versatile synthetic tool for the preparation of carbonyl compounds.[1] Since the seminal work of Heck in 1974,[2] a number of carbonylations of C−X (X = halides or pseudohalides) bonds with various nucleophiles, such as amines, alcohols, alkynes, and water, in the presence of CO have been well developed.[3] However, from an economic and environmental point of view, a much more appealing approach would be the transition-metal-catalyzed direct carbonylation through C−H bond functionalization.[4,5] Among the many C−H carbonylation reactions reported to date, the most effective strategy to achieve site selectivity is to install a directing group on the substrates. Various functional groups, such as heterocycle,[6] amide,[7] amines,[8] urea derivative,[9] aniline,[10] phenol derivative,[11] sulfonamide,[12] and carboxylic acid,[13] have been employed as directing groups. However, most these methods required additional steps to install and remove the undesired directing groups. In contrast, intrinsic directing groups, which can often act as nucleophiles as well in C−H carbonylation, would be attractive alternatives to more traditional approaches.[14,15] Indole scaffolds are highly important structural motifs frequently found in a large number of biologically or pharmaceutically active natural and unnatural compounds.[16] Therefore, NH-indole would be an ideal intrinsic directing group in transition-metal-catalyzed C−H functionalization. Recently, independent reports by Miura and Ackermann's research groups have demonstrated the rhodium- and ruthenium-catalyzed synthesis of indolo[2,1-*a*]-isoquinolines from 2-arylindoles with alkynes via oxidative coupling/cyclization.[17] Very recently, Lan and You displayed a palladium-catalyzed tandem N−H/C−H arylation of 2-arylindoles with 1,2-dihaloarenes for the synthesis of indolo-[1,2-*f*]phenanthridine.[18] However, no example has been reported on the transition-metal-catalyzed NH-indole-directed C−H carbonylation. Herein, we report the first rhodium-catalyzed intramolecular C−H carbonylation of 2-arylindoles for the synthesis of 6*H*-isoindolo[2,1-*a*]indol-6-ones.

6*H*-Isoindolo[2,1-*a*]indol-6-ones not only are applied as versatile intermediates in diverse organic synthesis[19] but also exhibit various important biological activities.[20] Consequently, finding an efficient route for the synthesis of 6*H*-isoindolo[2,1-*a*]indol-6-ones with different substituent groups would be highly desirable. Among the known synthetic routes, the intramolecular lactamization of 2-carboxylphenyl indole (Scheme 1, route a),[19c,20b,21] intramolecular C−H coupling of *N*-benzoylindole (route b),[19b,22] and intramolecular Wittig

Received: May 20, 2016
Published: November 14, 2016

DOI: 10.1021/acs.joc.6b01200
J. Org. Chem. 2016, 81, 12135−12142

Scheme 1. Synthetic Methods of 6*H*-Isoindolo[2,1-*a*]indol-6-ones

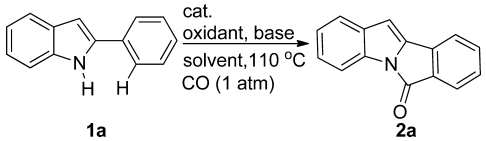


reaction of *N*-phenylphthalimide derivatives (route c)[23] are the most popular methods. However, most of these methods usually require multistep procedures under harsh reaction conditions and lead to a limited range of substrates. In contrast, a strategy based on the intramolecular carbonylation of C−H bonds could provide a straightforward approach to 6*H*-isoindolo[2,1-*a*]indol-6-ones from readily available 2-aryl-1*H*-indole precursors.[24]

RESULTS AND DISCUSSION

The intramolecular carbonylation of 2-phenyl-1*H*-indole (**1a**) was initially chosen as a model reaction to screen the optimal reaction conditions as summarized in Table 1. When a mixture of **1a** (0.2 mmol), $[(Cp^*RhCl_2)_2]$ (0.005 mmol), and AgOAc (0.4 mmol) in xylene (2.0 mL) under atmospheric pressure of CO was heated at 110 °C for 24 h, 6*H*-isoindolo[2,1-*a*]indol-6-one (**2a**) was obtained in 39% yield (Tabel 1, entry 1). $[Rh(cod)Cl]_2$ and $RhCl_3{\cdot}3H_2O$ were found to be ineffective (entries 2 and 3). Oxidant screening showed that using AgOAc can give the best yield, followed by $Cu(OAc)_2$ (entry 4); other oxidants such as $K_2S_2O_8$, benzoquinone (BQ), or O_2 did not give the desired product (entries 5−8). External bases, which are believed to act as proton abstractors in C−H cleavage, have been intensively investigated (entries 9−15). Among various inorganic and organic bases, K_2CO_3 was found to be the most effective, thus affording **2a** in 60% yield (entry 11). The choice of solvent is crucial for the reaction. Acid solvent, which was frequently used in many C−H aminocarbonylations,[7,8,14c−e,25,26] is not suitable for this transformation (entry 19). Other solvents screening revealed that xylene was still the most effective solvent (entries 16−19). Interestingly, variations in the amount of oxidizing agent influenced the reaction outcomes. Increasing the loading of AgOAc from 2 to 3 equiv resulted in a considerable increase of **2a** yield (entry 20, 87% yield). The yield decreased with decreasing the amount of $[Cp^*RhCl_2]_2$ (entry 21, 75% yield). The optimum reaction conditions thus far developed employ 1 atm of carbon monoxide, 1 equiv of **1a** (0.2 mmol), 2.5 mol % of $[Cp^*RhCl_2]_2$, 3 equiv of AgOAc, and 2 equiv of anhydrous potassium carbonate in xylene (2.0 mL) at 110 °C for 24 h; this

Table 1. Optimization of Reaction Conditions[a]



entry	cat.	oxidant	base	solvent	yield (%)[b]
1	$[(Cp^*RhCl_2)_2]$	AgOAc		xylene	39
2	$[Rh(cod)Cl]_2$	AgOAc		xylene	trace
3	$RhCl_3{\cdot}3H_2O$	AgOAc		xylene	trace
4	$[(Cp^*RhCl_2)_2]$	$Cu(OAc)_2$		xylene	31
5	$[(Cp^*RhCl_2)_2]$	$K_2S_2O_8$		xylene	0
6	$[(Cp^*RhCl_2)_2]$	Ag_2O		xylene	0
7	$[(Cp^*RhCl_2)_2]$	BQ		xylene	0
8	$[(Cp^*RhCl_2)_2]$	O_2		xylene	0
9	$[(Cp^*RhCl_2)_2]$	AgOAc	Li_2CO_3	xylene	40
10	$[(Cp^*RhCl_2)_2]$	AgOAc	Na_2CO_3	xylene	51
11	$[(Cp^*RhCl_2)_2]$	AgOAc	K_2CO_3	xylene	60
12	$[(Cp^*RhCl_2)_2]$	AgOAc	Cs_2CO_3	xylene	35
13	$[(Cp^*RhCl_2)_2]$	AgOAc	Et_3N	xylene	45
14	$[(Cp^*RhCl_2)_2]$	AgOAc	DBU	xylene	0
15	$[(Cp^*RhCl_2)_2]$	AgOAc	DABCO	xylene	30
16	$[(Cp^*RhCl_2)_2]$	AgOAc	K_2CO_3	1,4-dioxane	39
17	$[(Cp^*RhCl_2)_2]$	AgOAc	K_2CO_3	DMF	trace
18	$[(Cp^*RhCl_2)_2]$	AgOAc	K_2CO_3	DMSO	0
19	$[(Cp^*RhCl_2)_2]$	AgOAc	K_2CO_3	AcOH	0
20[c]	$\mathbf{[(Cp^*RhCl_2)_2]}$	**AgOAc**	$\mathbf{K_2CO_3}$	**xylene**	**87(80)**
21[d]	$[(Cp^*RhCl_2)_2]$	AgOAc	K_2CO_3	xylene	75
22[e]	$[(Cp^*RhCl_2)_2]$	AgOAc	K_2CO_3	xylene	(73)

[a]Conditions: **1a** (0.2 mmol), Rh catalyst (5 mol %), oxidant (2 equiv), base (2 equiv), solvent (2 mL), CO (1 atm), 24 h. [b]Yield according to GC analysis on the basis of the amount of **1a** used. Number in parentheses is isolated yield. [c]AgOAc (3 equiv). [d]AgOAc (3 equiv), $[(Cp^*RhCl_2)_2]$ (1.5 mol %) [e]AgOAc (3 equiv), 1 mmol of **1a**.

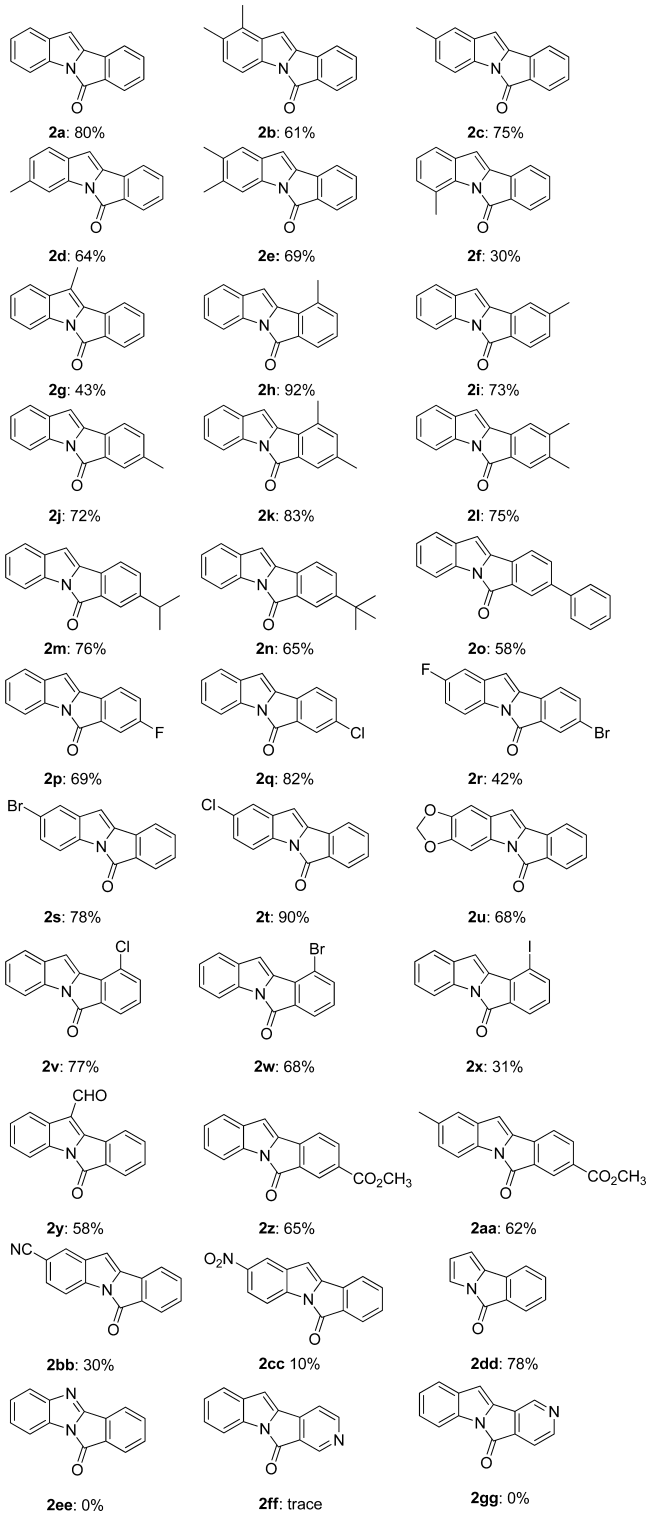
DOI: 10.1021/acs.joc.6b01200
J. Org. Chem. 2016, 81, 12135−12142

procedure provided an isolated yield of 80%. Notably, the reaction was successfully performed on a 1.0 mmol scale to afford **2a** in 73% isolated yield (entry 22).

With the optimized reaction conditions established, we set out to examine the generality of the reaction (Table 2). The methyl group on 4-,5-,6-positions of the indole ring or the ortho-, meta-, para-positions of the benzene ring favored the reaction, providing corresponding methyl-substituted 6*H*-isoindolo[2,1-*a*]indol-6-ones in good to excellent yields (see **2b−e** and **2h−l**). However, when a methyl group was present in the C3- or C7-position of the indole, only a moderate yield of the desired product was obtained presumably due to steric hindrance (see **2f** and **2g**). For 2-(*m*-tolyl)-1*H*-indole and 2-(3,4-dimethylphenyl)-1*H*-indole, the reaction selectively occurred at less hindered C−H sites to generate single carbonylation product 9-methyl-6*H*-isoindolo[2,1-*a*]indol-6-one (see **2i**, 73%) and 8,9-dimethyl-6*H*-isoindolo[2,1-*a*]indol-6-one (see **2l**, 75%), respectively. These results suggest that steric effects play a major role in the carbonylation reaction. It is found that the electronic nature of the substituents on the indole ring also has influence on the reaction efficiency. 2-Phenyl-1*H*-indoles substituted with electron-donating or weak electron-withdrawing groups, such as methyl, dimethyl, [1,3]-dioxole, Br, and Cl, reacted smoothly and resulted in the desired products **2b−e** and **2s−u** in 61−92% yields, while a strong electron-withdrawing group (F) was relatively sluggish and provided a moderate yield (see **2r**, 42%). Substrates bearing electron-rich and electron-deficient substituents on the benzene ring underwent carbonylation smoothly to give 6*H*-isoindolo[2,1-*a*]indol-6-one derivatives **2h−q** in good yields. Notably, a substrate with halogens afforded the corresponding products in good yields, which could provide opportunities for further derivatization via functional group transformation or cross-coupling reactions (see **2p−t**, **2v−2x**). Further, blockage of one of the ortho positions on the benzene ring was tolerable, as demonstrated by the formation of 10-methyl-6*H*-isoindolo-[2,1-*a*]indol-6-one (see **2h**), 10-chloro-6*H*-isoindolo[2,1-*a*]-indol-6-one (see **2v**), and 10-bromo-6*H*-isoindolo[2,1-*a*]-indol-6-one (see **2w**) in good yields. 2-(2-Iodophenyl)-1*H*-indole carbonylated with CO produced the desired C−H carbonylation product **2x** in 31% yield together with the intramolecular C−I carbonylation product **2a** in 57% yield. Substrates bearing an aldehyde or ester group could transfer to the desired product in good yields (see **2y−2aa**). Nitrile and nitro groups are also compatible with the process, albeit affording the products in low yields (see **2bb−2cc**), and the starting materials were recovered in 65% and 80% yield, respectively. 2-Phenyl-1*H*-pyrrole produced the desired 5*H*-pyrrolo[2,1-*a*]isoindol-5-one in 78% yield (see **2dd**). However, when 2-phenyl-1*H*-benzo[*d*]imidazole was employed, all of the starting materials decompose and none of the desired product was observed (see **2ee**). Unfortunately, no reaction occurred when 2-pyridine-substituent indole was employed as the substrate, which supposedly resulted from the chelating ability of the pyridine group (see **2ff−2gg**).

To gain some preliminary understanding of the reaction mechanism, several stoichiometric reactions were carried out. First, **1a** was reacted with a stoichiometric amount of $[(Cp^*RhCl_2)_2]$ in xylene for 1 h. The dichloro(pentamethylcyclopentadienyl)rhodium(III) dimer-2-phenylindole adduct **A** was isolated in 90% yield [Scheme 2, eq 1], and its structure was confirmed by X-ray crystallography (Figure 1). In the crystal structure of **A**, there are π-stacking interactions between the indole ring and Cp* ring (d = 3.486 Å). In addition to π-stacking, N1 and C24 of 2-phenyl-1*H*-indole have hydrogen-bonding interaction with Cl1 (d[Cl1···N1] = 3.328 Å) and Cl2 (d[Cl2···C24] = 3.810 Å),[27] respectively. The bond length of Cl···H···N is much less than that of Cl···H···C, suggesting that

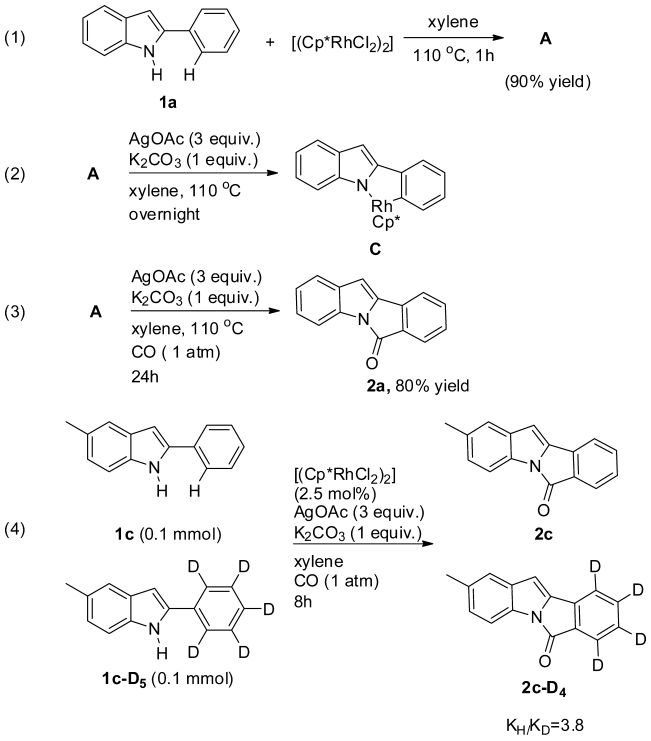
Table 2. Substrate Scope of Rh-Catalyzed C−H Carbonylation[a]



[a]Conditions: **1** (0.2 mmol), $[(Cp^*RhCl_2)_2]$ (2.5 mol %), AgOAc (3 equiv), K_2CO_3 (2 equiv), xylene (2 mL), CO (1 atm), 24 h. Isolated yields reported.

DOI: 10.1021/acs.joc.6b01200
J. Org. Chem. 2016, 81, 12135−12142

Scheme 2. Preliminary Mechanistic Studies



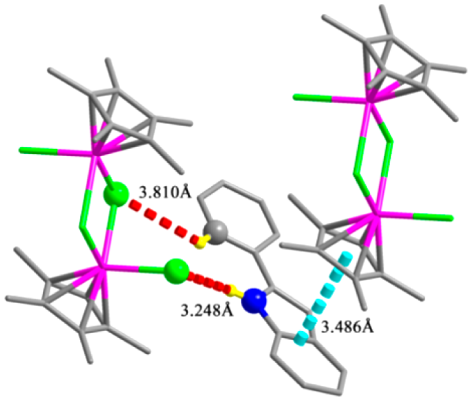
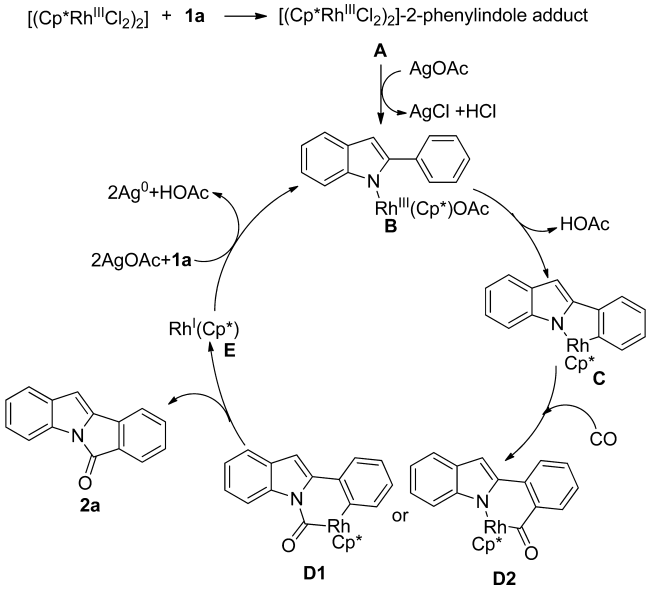


Figure 1. π-Stacking interactions and H-bonding interactions in the X-ray structure of **A**.

N−H bond cleavage is more favorable than C−H bond cleavage in the next stage. Next, the treatment of **A** with AgOAc and K_2CO_3 in the absence of CO was analyzed by the ESI-MS technique as shown in Figure 2 [Scheme 2, eq 2]. A prominent peak at m/z = 431.1060 was observed, which supported the formation of five-membered rhodacycle **C**. Finally, treating **A** with AgOAc and K_2CO_3 in the presence of CO gave **2a** in 80% yield [Scheme 2, eq 3]. These results suggest that rhodium species **A** and **C** should be intermediates in the carbonylation reaction. An intermolecular competition reaction between 5-methyl-2-phenyl-1*H*-indole **1c** and its deuterated derivative **1c-D5** gave a significant KIE of 3.8, indicating that the C−H bond cleavage might be the rate-determining step [Scheme 2, eq 4].

On the basis of the above experiment results, a plausible mechanism is proposed as shown in Scheme 3 using substrate

Scheme 3. Plausible Reaction Mechanism



1a as an example. Initially, the 1:1 adduct of $[(Cp^*RhCl_2)_2]$ with 2-phenylindole **1a** was formed in xylene. Then **A** undergoes N−H bond cleavage and subsequent C−H bond cleavage to give five-membered rhodacycle **C**. Migratory insertion of CO into the Rh−N or Rh−C bond of **C** gives six-membered rhodacycle **D1** or **D2**, respectively. At this point, reductive elimination occurs with **D1** or **D2** to afford the desired product **2a** and a rhodium(I) species **E**. The Cp*Rh(I) species **E** can undergo two single electron oxidation via AgOAc to regenerate the catalytically active rhodium complex **B**.

CONCLUSIONS

In conclusion, we have established an efficient rhodium-catalyzed cyclocarbonylation of 2-arylindoles with carbon monoxide via N−H bond cleavage and subsequent C−H bond cleavage to prepare 6*H*-isoindolo[2,1-*a*]indol-6-ones in moderate to excellent yields for 30 examples. Notable features are the atom economy, atmospheric pressure, and acid-free condition. A key five-membered rhodacycle complex involving the NH-indole-directed C−H activation was detected by ESI-

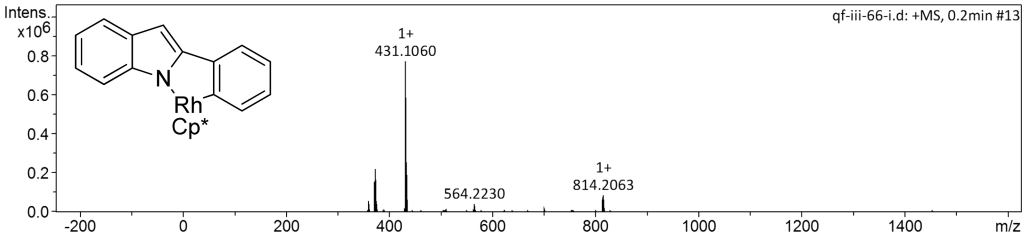


Figure 2. ESI-MS analysis of the treatment of **A** with AgOAc and K_2CO_3 in the absence of CO.

DOI: 10.1021/acs.joc.6b01200
J. Org. Chem. 2016, 81, 12135−12142

MS. Computational mechanistic studies and further applications of this transformation are in progress.

EXPERIMENTAL SECTION

General Method. 2-Phenyl-1*H*-indole (**1a**), 2-(4-fluorophenyl)-1*H*-indole (**1p**), 2-(4-bromophenyl)-5-fluoro-1*H*-indole (**1r**), 6-phenyl-5*H*-[1,3]dioxolo[4,5-*f*]indole (**1u**), and 2-phenyl-1*H*-indole-3-carbaldehyde (**1y**) are commercially available. Other 2-arylindoles were synthesized from phenylhydrazine hydrochlorides via Fisher indole synthesis,[28] or from 2-iodoanilines via palladium-catalyzed Sonogashira reaction and base-assisted cycloaddition.[29] 2-Phenyl-1*H*-pyrrole was synthesized from pyrrole via direct arylation with aryliodonium salts.[30] Research grade carbon monoxide (99.99%) was used as received. ^{1}H NMR spectra were recorded at 400 MHz, and ^{13}C NMR spectra, at 101 MHz, respectively. ^{1}H chemical shifts (δ) were referenced to TMS, and ^{13}C NMR chemical shifts (δ) were referenced to internal solvent resonance. GC analyses of organic compounds were performed on GC (with a 25 m capillary column) instrument. ESI-HRMS spectra were recorded by using a Q-TOF mass spectrometer. Element analyses (C, H, and N) were performed on an elemental analyzer. The Fourier transform infrared spectra were recorded by using KBr pellets. Data collection and structural analysis of the crystal were performed on a Single Crystal Diffractometer equipped with graphite monochromatic Cu Kα radiation (λ = 1.541 84 Å).

*A Representative Procedure for the Cyclocarbonylation of 2-Phenylindole (**1a**) with Carbon Monoxide.* Formation of 6*H*-isoindolo[2,1-*a*]indol-6-one **2a**: 2-Phenylindole **1a** (38.6 mg, 0.2 mmol), $[RhCp^*Cl_2]_2$ (3.09 mg, 0.005 mmol), AgOAc (100.2 mg, 0.6 mmol), K_2CO_3 (55.2 mg, 0.4 mmol), and xylene (2 mL) were placed in a 50 mL Schlenk tube (a balloon was connected to the Schlenk). The reaction solution was degassed three times and refilled with CO (1.0 atm). The mixture was heated in an oil bath at 110 °C with stirring for 24 h. After the reaction vessel was cooled to room temperature, the gas in the balloon was released carefully. Then the crude reaction mixture was diluted with CH_2Cl_2 to 5 mL, and $C_{18}H_{38}$ (0.2 mmol) was added as an internal standard for GC analysis. After GC and GCMS analyses of the reaction mixture, volatiles were removed under reduced pressure, and the residue was subjected to silica gel column chromatography [eluting with petroleum ether/ethyl acetate = 20:1] to afford **2a** in 80% yield. The GC analyses of the reaction mixture disclosed the formation of **2a** in 87% yield.

*6H-Isoindolo[2,1-a]indol-6-one (**2a**).*[22d] 35.0 mg (80%); yellow solid, mp 134−136 °C (recrystallization with *n*-hexane and CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 7.5 Hz, 1H), 7.53−7.48 (m, 2H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.37−7.30 (m, 1H), 7.30−7.25 (t, *J* = 7.6 Hz, 1H), 7.14 (t, J = 7.6 Hz, 1H), 6.60 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7, 138.9, 134.8, 134.6, 134.0, 133.8, 133.7, 128.9, 126.4, 125.4, 124.0, 122.4, 121.3, 113.4, 103.6. Anal. Calcd for $C_{15}H_9NO$: C, 82.18; H, 4.14; N, 6.39. Found: C, 82.13; H, 4.17; N, 6.28. IR (KBr): 1731 cm^{-1} (ν_{CO}).

*1,2-Dimethyl-6H-isoindolo[2,1-a]indol-6-one (**2b**).* 30.1 mg (80%); yellow solid, mp 158−160 °C (recrystallization with *n*-hexane and CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.5 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 4.1 Hz, 2H), 7.30 (td, *J* = 8.0, 4.1 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 6.63 (s, 1H), 2.36 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7, 138.4, 134.9, 134.7, 134.1, 133.6, 132.0, 131.8, 130.1, 128.6, 128.4, 125.3, 121.1, 110.6, 102.8, 19.5, 15.6. Anal. Calcd for $C_{17}H_{13}NO$: C, 82.57; H, 5.30; N, 5.66. Found: C, 82.54; H, 5.35; N, 5.59. IR (KBr): 1726 cm^{-1} (ν_{CO}).

*2-Methyl-6H-isoindolo[2,1-a]indol-6-one (**2c**).*[31] 35.0 mg (75%); yellow solid, mp 125−127 °C (recrystallization with *n*-hexane and CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (t, *J* = 7.3 Hz, 2H), 7.50−7.44 (m, 2H), 7.33−7.27 (m, 1H), 7.21 (s, 1H), 7.07 (d, *J* = 8.1 Hz, 1H), 6.51 (s, 1H), 2.38 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7, 139.1, 134.9, 134.9, 134.1, 133.7, 133.6, 131.9, 128.8, 127.6, 125.3, 122.5, 121.2, 113.1, 103.5, 21.6. Anal. Calcd for $C_{16}H_{11}NO$: C, 82.38; H, 4.75; N, 6.00. Found: C, 82.20; H, 4.78; N, 5.93. IR (KBr): 1726 cm^{-1} (ν_{CO}).

*3-Methyl-6H-isoindolo[2,1-a]indol-6-one (**2d**).* 29.8 mg (64%); yellow solid, mp 132−134 °C (recrystallization with *n*-hexane and CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77−7.69 (m, 2H), 7.49 (d, *J* = 3.9 Hz, 2H), 7.35−7.28 (m, 2H), 6.96 (d, *J* = 7.9 Hz, 1H), 6.55 (s, 1H), 2.44 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.9, 138.4, 137.0, 135.0, 134.1, 134.0, 133.7, 132.3, 128.7, 125.4, 125.33, 122.0, 121.2, 113.9, 103.7, 21.88. Anal. Calcd for $C_{16}H_{11}NO$: C, 82.38; H, 4.75; N, 6.00. Found: C, 82.08; H, 4.77; N, 5.91. IR (KBr): 1736 cm^{-1} (ν_{CO}).

*2,3-Dimethyl-6H-isoindolo[2,1-a]indol-6-one (**2e**).* 34.1 mg (69%); yellow solid, mp 183−184 °C (recrystallization with *n*-hexane and CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 7.5, 0.8 Hz, 1H), 7.66 (s, 1H), 7.49−7.43 (m, 2H), 7.32−7.26 (m, 1H), 7.17 (s, 1H), 6.49 (s, 1H), 2.33 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7, 138.2, 135.8, 135.0, 134.0, 133.6, 132.7, 132.6, 132.5, 128.5, 125.2, 122.8, 121.0, 114.2, 103.6, 20.5, 20.2. Anal. Calcd for $C_{17}H_{13}NO$: C, 82.57; H, 5.30; N, 5.66. Found: C, 82.60; H, 5.32; N, 5.50. IR (KBr): 1732 cm^{-1} (ν_{CO}).

*4-Methyl-6H-isoindolo[2,1-a]indol-6-one (**2f**).*[31] 13.4 mg (80%); yellow solid, mp 110−112 °C (recrystallization with *n*-hexane and CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 11.2, 7.8 Hz, 2H), 7.54−7.49 (m, 2H), 7.36−7.30 (m, 1H), 7.18 (t, *J* = 7.7 Hz, 1H), 6.96 (d, *J* = 7.4 Hz, 1H), 6.67 (s, 1H), 2.48 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.9, 138.4, 134.9, 134.2, 133.9, 133.8, 133.5, 132.1, 128.8, 126.5, 125.4, 124.7, 121.2, 111.0, 102.3, 18.63. Anal. Calcd for $C_{16}H_{11}NO$: C, 82.38; H, 4.75; N, 6.00. Found: C, 82.29; H, 4.65; N, 5.83. IR (KBr): 1722 cm^{-1} (ν_{CO}).

*11-Methyl-6H-isoindolo[2,1-a]indol-6-one (**2g**).*[22b] 20.0 mg (43%); yellow solid, mp 159−160 °C (recrystallization with *n*-hexane and CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.9 Hz, 1H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.31−7.24 (m, 2H), 7.15 (t, *J* = 7.2 Hz, 1H), 2.40 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.4, 135.9, 135.1, 134.7, 134.1, 133.7, 133.5, 128.1, 126.6, 125.4, 123.7, 121.2, 120.3, 115.5, 113.4, 9.56. Anal. Calcd for $C_{16}H_{11}NO$: C, 82.38; H, 4.75; N, 6.00. Found: C, 82.54; H, 4.81; N, 5.85. IR (KBr): 1710 cm^{-1} (ν_{CO}).

*10-Methyl-6H-isoindolo[2,1-a]indol-6-one (**2h**).* 42.9 mg (92%); yellow solid, mp 136−137 °C (recrystallization with *n*-hexane and CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.0 Hz, 1H), 7.60 (d, *J* = 7.4 Hz, 1H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.30 (t, *J* = 6.6 Hz, 2H), 7.23 (d, *J* = 7.5 Hz, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 6.57 (s, 1H), 2.51 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1, 139.1, 135.3, 134.9, 133.9, 133.5, 133.6, 133.0, 129.0, 126.4, 123.9, 123.0, 122.3, 113.4, 105.2, 18.93. Anal. Calcd for $C_{16}H_{11}NO$: C, 82.38; H, 4.75; N, 6.00. Found: C, 82.64; H, 4.66; N, 5.91. IR (KBr): 1724 cm^{-1} (ν_{CO}).

*9-Methyl-6H-isoindolo[2,1-a]indol-6-one (**2i**).*[22b] 34.0 mg (73%); yellow solid, mp 165−167 °C (recrystallization with *n*-hexane and CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.0 Hz, 1H), 7.60 (d, *J* = 7.7 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.31−7.23 (m, 2H), 7.16−7.08 (m, 2H), 6.54 (s, 1H), 2.41 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.9, 144.8, 139.0, 135.1, 134.6, 133.7, 131.4, 129.7, 126.3, 125.2, 123.8, 122.3, 122.0, 113.3, 103.2, 22.1. Anal. Calcd for $C_{16}H_{11}NO$: C, 82.38; H, 4.75; N, 6.00. Found: C, 82.17; H, 4.64; N, 5.93. IR (KBr):1729 cm^{-1} (ν_{CO}).

*8-Methyl-6H-isoindolo[2,1-a]indol-6-one (**2j**).*[31] 33.5 mg (72%); yellow solid, mp 133−134 °C (recrystallization with *n*-hexane and CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.8 Hz, 1H), 7.54 (s, 1H), 7.45−7.34 (m, 2H), 7.31−7.22 (m, 2H), 7.12 (t, *J* = 7.4 Hz, 1H), 6.52 (s, 1H), 2.39 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.0, 139.4, 139.2, 134.7, 134.5, 134.2, 133.7, 132.2, 126.2, 125.9, 123.9, 122.2, 121.2, 113.3, 102.9, 21.6. Anal. Calcd for $C_{16}H_{11}NO$: C, 82.38; H, 4.75; N, 6.00. Found: C, 82.69; H, 4.82; N, 5.90. IR (KBr): 1731 cm^{-1} (ν_{CO}).

*8,10-Dimethyl-6H-isoindolo[2,1-a]indol-6-one (**2k**).* 41.0 mg (83%); yellow solid, mp 180−181 °C (recrystallization with *n*-hexane and CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.38 (s, 1H), 7.25 (td, *J* = 7.7, 1.2 Hz, 1H), 7.12 (td, *J* = 7.7, 1.2 Hz, 1H), 7.10−7.08 (m, 1H), 6.49−6.46 (s, 1H), 2.44 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.2,

DOI: 10.1021/acs.joc.6b01200
J. Org. Chem. 2016, 81, 12135−12142

139.4, 139.3, 136.0, 135.0, 134.1, 133.5, 132.7, 130.9, 126.1, 123.8, 123.5, 122.1, 113.3, 104.35, 21.5, 18.8. Anal. Calcd for $C_{17}H_{13}NO$: C, 82.57; H, 5.30; N, 5.66. Found: C, 82.51; H, 5.33; N, 5.63. IR (KBr): 1719 cm^{-1} (ν_{CO}).

*8,9-Dimethyl-6H-isoindolo[2,1-a]indol-6-one (**2l**).* 37.1 mg (75%); yellow solid, mp 194−196 °C (recrystallization with *n*-hexane and CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, J = 7.8 Hz, 1H), 7.50 (s, 1H), 7.41 (d, J = 7.8 Hz, 1H), 7.28 (s, 1H), 7.25 (td, J = 7.6, 1.0 Hz, 1H), 7.12 (td, J = 7.6, 1.0 Hz, 1H), 6.51 (s, 1H), 2.32 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.2, 143.4, 139.3, 138.0, 134.7, 133.7, 132.8, 131.9, 126.3, 126.1, 123.7, 122.6, 122.2, 113.3, 102.6, 20.7, 20.2. Anal. Calcd for $C_{17}H_{13}NO$: C, 82.57; H, 5.30; N, 5.66. Found: C, 82.51; H, 5.27; N, 5.61. IR (KBr): 1728 cm^{-1} (ν_{CO}).

*8-Isopropyl-6H-isoindolo[2,1-a]indol-6-one (**2m**).* 39.7 mg (76%); yellow solid, mp 104−105 °C (recrystallization with *n*-hexane and CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.0 Hz, 1H), 7.64 (s, 1H), 7.42 (d, J = 8.0 Hz, 2H), 7.36 (dd, J = 7.8, 1.5 Hz, 1H), 7.26 (td, J = 7.7, 1.0 Hz, 1H), 7.13 (td, J = 7.7, 1.0 Hz, 1H), 6.54 (s, 1H), 2.96 (hept, J = 6.9 Hz, 1H), 1.29 (d, J = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1, 150.5, 139.2, 134.7, 134.3, 133.7, 132.5, 132.3, 126.2, 123.9, 123.3, 122.2, 121.3, 113.4, 102.9, 34.3, 23.9. Anal. Calcd for $C_{18}H_{15}NO$: C, 82.73; H, 5.79; N, 5.36. Found: C, 82.50; H, 5.63; N, 5.31. IR (KBr): 1732 cm^{-1} (ν_{CO}).

*8-(tert-Butyl)-6H-isoindolo[2,1-a]indol-6-one (**2n**).* 35.8 mg (65%); yellow solid, mp 128−130 °C (recrystallization with *n*-hexane and CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, J = 8.0, 0.8 Hz, 1H), 7.80 (dd, J = 1.8, 0.5 Hz, 1H), 7.54 (dd, J = 8.0, 1.8 Hz, 1H), 7.46−7.40 (m, 2H), 7.26 (td, J = 7.6, 1.0 Hz, 1H), 7.14 (td, J = 7.6, 1.0 Hz, 1H), 6.55 (s, 1H), 1.36 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.2, 152.9, 139.1, 134.7, 134.0, 133.7, 132.1, 131.0, 126.2, 123.9, 122.5, 122.2, 121.1, 113.4, 103.0, 35.3, 31.3. Anal. Calcd for $C_{19}H_{17}NO$: C, 82.88; H, 6.22; N, 5.09. Found: C, 82.74; H, 6.32; N, 5.01. IR (KBr): 1727 cm^{-1} (ν_{CO}).

*8-Phenyl-6H-isoindolo[2,1-a]indol-6-one (**2o**).* 34.2 mg (58%); yellow solid, mp 117−118 °C (recrystallization with *n*-hexane and CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.76−7.72 (m, 1H), 7.65−7.61 (m, 2H), 7.58 (d, J = 7.9 Hz, 1H), 7.51−7.44 (m, 3H), 7.43−7.37 (m, 1H), 7.29 (td, J = 7.8, 1.0 Hz, 1H), 7.16 (td, J = 7.8, 1.0 Hz, 1H), 6.63 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7, 142.3, 139.7, 138.8, 134.8, 134.7, 133.8, 133.5, 132.5, 129.2, 128.2, 127.0, 126.5, 124.1, 124.0, 122.4, 121.7, 113.5, 103.8. Anal. Calcd for $C_{21}H_{13}NO$: C, 85.40; H, 4.44; N, 4.74. Found: C, 85.61; H, 4.46; N, 4.65. IR (KBr): 1727 cm^{-1} (ν_{CO}).

*8-Fluoro-6H-isoindolo[2,1-a]indol-6-one (**2p**).* 32.7 mg (69%); yellow solid, mp 175−177 °C (recrystallization with *n*-hexane and CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, J = 8.0, 0.4 Hz, 1H), 7.50−7.41 (m, 3H), 7.28 (td, J = 7.6, 1.0 Hz, 1H), 7.20 (td, J = 8.6, 2.4 Hz, 1H), 7.15 (td, J = 7.6, 1.0 Hz, 1H), 6.56 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163.3 (d, $^1J_{C-F}$ = 250.5 Hz), 161.5, 138.1, 136.1 (d, $^3J_{C-F}$ = 8.3 Hz), 134.6, 133.9, 130.8, 126.6, 124.3, 122.8 (d, $^3J_{C-F}$ = 8.3 Hz), 122.5, 120.8 (d, $^2J_{C-F}$ = 23.8 Hz), 113.7, 112.9 (d, $^2J_{C-F}$ = 24.5 Hz), 103.7. Anal. Calcd for $C_{15}H_8FNO$: C, 75.94; H, 3.40; N, 5.90. Found: C, 75.98; H, 3.46; N, 5.87. IR (KBr): 1723 cm^{-1} (ν_{CO}).

*8-Chloro-6H-isoindolo[2,1-a]indol-6-one (**2q**).* 41.5 mg (82%); yellow solid, mp 179−180 °C (recrystallization with *n*-hexane and CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 8.0 Hz, 1H), 7.72−7.69 (m, 1H), 7.49−7.40 (m, 3H), 7.31−7.26 (m, 1H), 7.19−7.13 (m, 1H), 6.60 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.4, 138.0, 135.6, 135.1, 134.6, 133.8 (2C), 133.0, 126.8, 125.7, 124.4, 122.6, 122.3, 113.6, 104.4. Anal. Calcd for $C_{15}H_8ClNO$: C, 71.02; H, 3.18; N, 5.52. Found: C, 70.92; H, 3.16; N, 5.43. IR (KBr): 1726 cm^{-1} (ν_{CO}).

*8-Bromo-2-fluoro-6H-isoindolo[2,1-a]indol-6-one (**2r**).* 26.5 mg (42%); yellow solid, mp 194−195 °C (recrystallization with *n*-hexane and CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 1.8 Hz, 1H), 7.78 (dd, J = 8.7, 4.5 Hz, 1H), 7.63 (dd, J = 8.0, 1.8 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.11 (dd, J = 8.8, 2.4 Hz, 1H), 7.01 (td, J = 9.0, 2.5 Hz, 1H), 6.57 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 160.2 (d, $^1J_{C-F}$ = 242.4 Hz), 161.0, 139.6, 136.8, 135.6 (d, $^3J_{C-F}$ = 9.9 Hz), 135.5, 133.2, 130.1, 128.7, 123.2, 122.7, 114.3 (d, $^2J_{C-F}$ = 25.4 Hz), 114.1 (d, $^3J_{C-F}$ = 9.4 Hz), 108.6 (d, $^2J_{C-F}$ = 24.7 Hz), 103.9 (d, $^4J_{C-F}$ = 4.0 Hz). Anal. Calcd for $C_{15}H_7BrFNO$: C, 56.99; H, 2.23; N, 4.43. Found: C, 57.02; H, 2.10; N, 4.30. IR (KBr): 1728 cm^{-1} (ν_{CO}).

*2-Bromo-6H-isoindolo[2,1-a]indol-6-one (**2s**).*[22b] 46.3 mg (78%); yellow solid, mp 155−157 °C (recrystallization with *n*-hexane and CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.73−7.66 (m, 2H), 7.51 (d, J = 1.7 Hz, 1H), 7.50−7.44 (m, 2H), 7.36−7.29 (m, 2H), 6.47 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.5, 140.0, 136.2, 134.4, 134.1, 133.7, 132.3, 129.3, 129.1, 125.5, 125.0, 121.6, 117.0, 114.5, 102.5. Anal. Calcd for $C_{15}H_8BrNO$: C, 60.43; H, 2.70; N, 4.70. Found: C, 60.44; H, 2.76; N, 4.69. IR (KBr): 1727 cm^{-1} (ν_{CO}).

*2-Chloro-6H-isoindolo[2,1-a]indol-6-one (**2t**).*[31] 45.5 mg (90%); yellow solid, mp 163−164 °C (recrystallization with *n*-hexane and CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (m, 2H), 7.55−7.45 (m, 2H), 7.41−7.30 (m, 2H), 7.21 (d, J = 8.4 Hz, 1H), 6.51 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.5, 140.1, 135.8, 134.4, 134.0, 133.7, 131.9, 129.4, 129.3, 126.4, 125.5, 122.0, 121.6, 114.1, 102.6. Anal. Calcd for $C_{15}H_8ClNO$: C, 71.02; H, 3.18; N, 5.52. Found: C, 70.94; H, 3.17; N, 5.45. IR (KBr): 1730 cm^{-1} (ν_{CO}).

*6H-[1,3]Dioxolo[4,5-f]isoindolo[2,1-a]indol-6-one (**2u**).*[32] 35.8 mg (68%); yellow solid, mp 189−190 °C (recrystallization with *n*-hexane and CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (dt, J = 7.5, 0.8 Hz, 1H), 7.45 (td, J = 7.5, 1.1 Hz, 1H), 7.41−7.39 (m, 1H), 7.38 (s, 1H), 7.26 (td, J = 7.5, 1.1 Hz, 1H), 6.82 (s, 1H), 6.44 (s, 1H), 5.97 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.8, 147.5, 145.2, 137.9, 135.3, 133.9, 133.5, 128.9, 128.4, 128.2, 125.4, 120.6, 104.0, 101.6, 101.5, 95.5. Anal. Calcd for $C_{16}H_9NO_3$: C, 73.00; H, 3.45; N, 5.32. Found: C, 72.62; H, 3.46; N, 5.26 IR (KBr): 1727 cm^{-1} (ν_{CO}).

*10-Chloro-6H-isoindolo[2,1-a]indol-6-one (**2v**).* 39.0 mg (77%); yellow solid, mp 153−155 °C (recrystallization with *n*-hexane and CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 8.0 Hz, 1H), 7.64 (d, J = 7.4 Hz, 1H), 7.47−7.42 (m, 2H), 7.32−7.22 (m, 2H), 7.15 (td, J = 7.6, 1.0 Hz, 1H), 6.84 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.4, 136.6, 135.7, 134.7, 134.2, 133.7, 132.9, 129.9, 128.5, 127.98, 124.3, 123.7, 122.8, 113.5, 107.3. Anal. Calcd for $C_{15}H_8ClNO$: C, 71.02; H, 3.18; N, 5.52. Found: C, 70.63; H, 3.18; N, 5.45. IR (KBr): 1736 cm^{-1} (ν_{CO}).

*10-Bromo-6H-isoindolo[2,1-a]indol-6-one (**2w**).* 40.4 mg (68%); yellow solid, mp 146−147 °C (recrystallization with *n*-hexane and CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 7.4 Hz, 1H), 7.62 (d, J = 8.1 Hz, 1H), 7.48 (d, J = 7.8 Hz, 1H), 7.31 (t, J = 7.7 Hz, 1H), 7.22−7.14 (m, 2H), 6.97 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.4, 137.6, 137.2, 135.9, 135.1, 134.5, 133.7, 129.9, 127.0, 124.4, 124.3, 122.9, 116.59, 113.69, 107.2. Anal. Calcd for $C_{15}H_8BrNO$: C, 60.43; H, 2.70; N, 4.70. Found: C, 60.30; H, 2.79; N, 4.61. IR (KBr): 1737 cm^{-1} (ν_{CO}).

*10-Iodo-6H-isoindolo[2,1-a]indol-6-one (**2x**).* 21.4 mg (31%); yellow solid, mp 147−149 °C (recrystallization with *n*-hexane and CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (t, J = 7.4 Hz, 2H), 7.75 (d, J = 7.4 Hz, 1H), 7.50 (d, J = 7.8 Hz, 1H), 7.31 (t, J = 7.8 Hz, 1H), 7.21−7.15 (m, 2H), 7.05 (t, J = 7.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.3, 143.5, 139.3, 139.2, 135.7, 134.1, 133.8, 129.8, 127.1, 125.0, 124.4, 122.9, 113.6, 106.2, 87.8. Anal. Calcd for $C_{15}H_8INO$: C, 52.20; H, 2.34; N, 4.06. Found: C, 52.33; H, 2.12; N, 3.99. IR (KBr): 1732 cm^{-1} (ν_{CO}).

*6-Oxo-6H-isoindolo[2,1-a]indole-11-carbaldehyde (**2y**).*[33] 28.6 mg (58%); yellow solid, mp 219−220 °C (recrystallization with *n*-hexane and CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 10.47 (s, 1H), 8.04 (d, J = 7.6 Hz, 1H), 8.01 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.80 (d, J = 7.5 Hz, 1H), 7.62 (t, J = 7.6 Hz, 1H), 7.48 (t, J = 7.5 Hz, 1H), 7.37 (t, J = 7.7 Hz, 1H), 7.28 (t, J = 7.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.3, 162.9, 144.7, 134.9, 133.5, 133.3, 133.1, 131.2, 131.0, 127.5, 126.0, 125.4, 124.7, 122.1, 116.6, 113.5. Anal. Calcd for $C_{16}H_9NO_2$: C, 77.72; H, 3.67; N, 5.67. Found: C, 77.76; H, 3.65; N, 5.70. IR (KBr): 1738, 1670 cm^{-1} (ν_{CO}).

*Methyl 6-Oxo-6H-isoindolo[2,1-a]indole-8-carboxylate (**2z**).* 36.0 mg (65%); yellow solid, mp 239−240 °C (recrystallization with *n*-hexane and CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 8.39 (dd, J = 1.5, 0.8 Hz, 1H), 8.20 (dd, J = 8.0, 1.5 Hz, 1H), 7.90 (dd, J = 8.0, 0.8 Hz,

DOI: 10.1021/acs.joc.6b01200
J. Org. Chem. 2016, 81, 12135−12142

1H), 7.58 (d, J = 7.8, 1H), 7.48 (d, J = 7.8 Hz, 1H), 7.32 (td, J = 7.8, 1.0 Hz, 1H), 7.17 (td, J = 7.8, 1.0 Hz, 1H), 6.73 (s, 1H), 3.95 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.9, 161.8, 138.4, 137.9, 135.4, 134.46, 134.2, 134.0, 130.8, 127.2, 126.6, 124.4, 122.8, 121.2, 113.7, 105.6, 52.63. Anal. Calcd for $C_{17}H_{11}NO_3$: C, 73.64; H, 4.00; N, 5.05. Found: C, 73.60; H, 3.96; N, 5.10. IR (KBr): 1725 cm^{-1} (ν_{CO}).

*Methyl 2-Methyl-6-oxo-6H-isoindolo[2,1-a]indole-8-carboxylate (**2aa**).* 36.1 mg (62%); yellow solid, mp 252−253 °C (recrystallization with *n*-hexane and CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, J = 1.0 Hz, 1H), 8.19 (dd, J = 7.9, 1.5 Hz, 1H), 7.77 (d, J = 8.2 Hz, 1H), 7.54 (d, J = 7.9 Hz, 1H), 7.26 (s, 1H), 7.13 (dd, J = 8.2, 1.0 Hz, 1H), 6.65 (s, 1H), 3.95 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 161.7, 138.5, 138.0, 135.2, 134.7, 134.3, 134.1, 132.2, 130.6, 128.4, 126.5, 122.9, 121.0, 113.3, 105.5, 52.6, 21.6. Anal. Calcd for $C_{18}H_{13}NO_3$: C, 74.22; H, 4.50; N, 4.81. Found: C, 74.18; H, 4.50; N, 4.90. IR (KBr): 1723 cm^{-1} (ν_{CO}).

*6-Oxo-6H-isoindolo[2,1-a]indole-2-carbonitrile (**2bb**).* 14.6 mg (30%); yellow solid, mp 216−217 °C (recrystallization with *n*-hexane and CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.3 Hz, 1H), 7.81 (d, J = 7.5 Hz, 1H), 7.78 (d, J = 0.8 Hz, 1H), 7.61−7.57 (m, 2H), 7.55 (dd, J = 8.3, 1.5 Hz, 1H), 7.46−7.38 (m, 1H), 6.67 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.5, 140.8, 135.4, 134.7, 134.6, 134.3, 133.4, 129.9, 129.8, 126.7, 126.0, 122.1, 119.5, 114.0, 107.4, 102.5. Anal. Calcd for $C_{16}H_8N_2O$: C, 78.68; H, 3.30; N, 11.47. Found: C, 78.66; H, 3.24; N, 11.50. IR (KBr): 1735 cm^{-1} (ν_{CO}).

*2-Nitro-6H-isoindolo[2,1-a]indol-6-one (**2cc**).*[20a] 5.28 mg (10%); yellow solid, mp 236−237 °C (recrystallization with *n*-hexane and CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, J = 2.2 Hz, 1H), 8.22 (dd, J = 8.8, 2.2 Hz, 1H), 7.99 (d, J = 8.8 Hz, 1H), 7.84 (d, J = 7.6 Hz, 1H), 7.64−7.57 (m, 2H), 7.48−7.42 (m, 1H), 6.76 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.5, 144.7, 141.5, 136.7, 134.7, 134.7, 134.4, 133.3, 130.1, 126.1, 122.2, 122.1, 118.5, 113.1, 103.3. Anal. Calcd for $C_{15}H_8N_2O_3$: C, 68.18; H, 3.05; N, 10.60. Found: C, 68.15; H, 3.04; N, 10.51. IR (KBr): 1732 cm^{-1} (ν_{CO}).

*5H-Pyrrolo[2,1-a]isoindol-5-one (**2dd**).* 26.37 mg (78%); yellow solid, mp 78−80 °C (recrystallization with *n*-hexane and CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 7.6 Hz, 1H), 7.35 (td, J = 7.6, 1.0 Hz, 1H), 7.20 (d, J = 7.6 Hz, 1H), 7.10 (td, J = 7.6, 0.6 Hz, 1H), 6.93 (dd, J = 3.1, 0.6 Hz, 1H), 6.14−6.11 (m, 1H), 6.09 (t, J = 3.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.2, 136.5, 135.8, 134.6, 132.1, 127.3, 125.9, 119.6, 117.3, 116.8, 107.5. Anal. Calcd for $C_{11}H_7NO$: C, 78.09; H, 4.17; N, 8.28. Found: C, 78.13; H, 4.15; N, 8.22. IR (KBr): 1753 cm^{-1} (ν_{CO}).

*Synthesis of Intermediate **A**.* 2-Phenyl-1*H*-indole **1a** (19.3 mg, 0.1 mmol) and $[RhCp^*Cl_2]_2$ (30.9 mg, 0.05 mmol) were added to a Schlenk flask. The flask was evacuated and backfilled with N_2 three times. The xylene (1 mL) was added to the flask. The mixture was stirred at 110 °C for 1 h. After cooling to room temperature, the brown solid was collected and washed with xylene (1 mL × 3). Then the solid was dissolved in CH_2Cl_2 and filtered to remove an insoluble solid. The filtrate was evaporated to give a solid of **A** (45.2 mg, 90% yield). A single crystal of **A** was obtained by slow evaporation from CH_2Cl_2/xylene solution.

Crystal data for **A**: $C_{24}H_{26}Cl_2NRh$, M = 502.27, orthorhombic, space group = *Pbca*, a = 8.7872(5) Å, b = 18.8893(11) Å, c = 26.3974(15) Å, α = 90°, β = 90°, γ = 90°, V = 4381.5(4) Å^3, Z = 8, density (calcd) = 1.523, total reflections collected = 15431, Independent reflections = 5333 (Rint = 0.1066), GOF = 1.011. The final R1 factor was 0.0656 ($I > 2\sigma(I)$) (wR2 = 0.1129, all data). The CCDC number is 1474565.

*Synthesis of Intermediate **C**.* Rhodium complex **A** (20 mg, 0.04 mmol), AgOAc (20 mg, 0.12 mmol), and K_2CO_3 (5.5 mg, 0.04 mmol) were added to a Schlenk flask. The flask was evacuated and backfilled with N_2 three times. The xylene (1 mL) was added to the flask. The mixture was stirred at 110 °C overnight. After cooling to room temperature, the reaction mixture was diluted with CH_2Cl_2 (1 mL) and filtered to remove insoluble solid. The filtrate was directly characterized by ESI-HRMS. HRMS: Calculated for $C_{24}H_{25}NRh$: 430.1042; Found: 431.1060 (M + H).

*Synthesis of **2a** from Possible Intermediate **A**.* Rhodium complex **A** (20 mg, 0.04 mmol), AgOAc (20 mg, 0.12 mmol), and K_2CO_3 (5.5 mg, 0.04 mmol) were placed in a 50 mL Schlenk tube (a balloon was connected to the Schlenk). The reaction solution was degassed three times and refilled with CO (1.0 atm). The mixture was heated in oil bath at 110 °C with stirring for 24 h. After the reaction vessel was cooled to room temperature, the gas in the balloon was released carefully. Then the crude reaction mixture was subjected to silica gel column chromatography [eluting with petroleum ether/ethyl acetate = 20:1] to afford **2a** in 80% yield.

Experiments for Intermolecular Kinetic Isotope Effects. The reaction of 5-methyl-2-phenyl-1*H*-indole **1c** (20.7 mg, 0.1 mmol) and D5-5-methyl-2-phenyl-1*H*-indole **1c-D5** (21.2 mg, 0.1 mmol) was run for 8 h following the general procedure. After the reaction the crude reaction mixture was subjected to silica gel column chromatography [eluting with petroleum ether/ethyl acetate = 20:1] to provide the product including **2c** and **2c-D4**. This mixture was analyzed by ^{1}H NMR to give the relative ratio of two isomers.

2c-D4. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.75 (d, J = 8.1 Hz, 1H), 7.25−7.20 (m, 1H), 7.12−7.06 (m, 1H), 6.53 (s, 1H), 2.39 (s, 3H).

■ ASSOCIATED CONTENT

Supporting Information

(PDF) and (CIF). The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01200.

Single crystal X-ray diffraction data for rhodium complex **A**, ^{1}H and ^{13}CNMR spectra of all compounds, ESI-MS spectra of **C** (PDF)

Crystallographic data for rhodium complex **A** (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: qiufenghuang@fjnu.edu.cn.

*E-mail: Shenlin@fjnu.edu.cn.

ORCID

Qiufeng Huang: 0000-0002-0166-2140

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the NSFC (Grant No. 21103022 and 61520106015) and Foundation of Fujian Educational Committee (Grant No. JK2014010) is gratefully acknowledged.

■ REFERENCES

(1) For reviews of transition-metal-catalyzed carbonylation with carbon monoxide, see: (a) Quintero-Duque, S.; Dyballa, K. M.; Fleischer, I. *Tetrahedron Lett.* **2015**, *56*, 2634. (b) Wu, X.-F.; Fang, X.; Wu, L.; Jackstell, R.; Neumann, H.; Beller, M. *Acc. Chem. Res.* **2014**, *47*, 1041. (c) Gadge, S. T.; Bhanage, B. M. *RSC Adv.* **2014**, *4*, 10367. (d) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Rev.* **2013**, *113*, 1. (e) Wu, X.-F.; Neumann, H. *ChemCatChem* **2012**, *4*, 447. (f) Omae, I. *Coord. Chem. Rev.* **2011**, *255*, 139. (g) Zhang, Z.; Zhang, Y.; Wang, J. *ACS Catal.* **2011**, *1*, 1621. (h) Barnard, C. F. J. *Organometallics* **2008**, *27*, 5402.

(2) (a) Schoenberg, A.; Heck, R. F. *J. Am. Chem. Soc.* **1974**, *96*, 7761. (b) Schoenberg, A.; Bartoletti, I.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3318. (c) Schoenberg, A.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3327.

(3) For reviews of transition-metal-catalyzed carbonylation of C−X bonds, see: (a) Wu, L.; Fang, X.; Liu, Q.; Jackstell, R.; Beller, M.; Wu, X.-F. *ACS Catal.* **2014**, *4*, 2977. (b) Sumino, S.; Fusano, A.; Fukuyama, T.; Ryu, I. *Acc. Chem. Res.* **2014**, *47*, 1563−1574. (c) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Soc. Rev.* **2011**, *40*, 4986.

DOI: 10.1021/acs.joc.6b01200
J. Org. Chem. 2016, 81, 12135−12142

(d) Brennführer, A.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 4114.
(4) For reviews of transition-metal-catalyzed carbonylation of the C−H bond, see: (a) Lang, R.; Xia, C.; Li, F. *New J. Chem.* **2014**, *38*, 2732. (b) Wu, X.-F.; Neumann, H.; Beller, M. *ChemSusChem* **2013**, *6*, 229. (c) Liu, Q.; Zhang, H.; Lei, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 10788.
(5) Recently, the Rh(III)-catalyzed coupling of the C(sp^2)−H bond and unsaturated C−N or C−O multiple bonds has already been well studied. For coupling of aldehyde: (a) Park, J.; Park, E.; Kim, A.; Lee, Y.; Chi, K.-W.; Kwak, J. H.; Jung, Y. H.; Kim, I. S. *Org. Lett.* **2011**, *13*, 4390. (b) Yang, Y.; Zhou, B.; Li, Y. *Adv. Synth. Catal.* **2012**, *354*, 2916. For coupling of imine: (c) Tsai, A. S.; Tauchert, M. E.; Bergman, R. G.; Ellman, J. *J. Am. Chem. Soc.* **2011**, *133*, 1248. (d) Li, Y.; Li, B.-J.; Wang, W.-H.; Huang, W.-P.; Zhang, X.-S.; Chen, K.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2011**, *50*, 2115. For coupling of isocyanate: (e) Hesp, K. D.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2011**, *133*, 11430. (f) Zhou, B.; Hou, W.; Yang, Y.; Li, Y. *Chem. - Eur. J.* **2013**, *19*, 4701. For coupling of diazo compounds: (g) Chan, W.-W.; Lo, S.-F.; Zhou, Z.; Yu, W.-Y. *J. Am. Chem. Soc.* **2012**, *134*, 13565. (h) Shi, Z.; Koester, D. C.; Boultadakis-Arapinis, M.; Glorius, F. *J. Am. Chem. Soc.* **2013**, *135*, 12204. (i) Zhou, B.; Chen, Z.; Yang, X.; Li, W.; Tang, H.; Wu, Y.; Zhu, W.; Li, Y. *Angew. Chem., Int. Ed.* **2015**, *54*, 12121. (j) Yang, Y.; Wang, X.; Li, Y.; Zhou, B. *Angew. Chem., Int. Ed.* **2015**, *54*, 15400.
(6) (a) Guan, Z.-H.; Ren, Z.-H.; Spinella, S. M.; Yu, S.; Liang, Y.-M.; Zhang, X. *J. Am. Chem. Soc.* **2009**, *131*, 729. (b) Ie, Y.; Chatani, N.; Ogo, T.; Marshall, D. R.; Fukuyama, T.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **2000**, *65*, 1475.
(7) Giri, R.; Lam, J. K.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 686.
(8) Li, H.; Cai, G.-X.; Shi, Z.-J. *Dalton Trans.* **2010**, *39*, 10442.
(9) Houlden, C. E.; Hutchby, M.; Bailey, C. D.; Ford, J. G.; Tyler, S. N. G.; Gagné, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *Angew. Chem., Int. Ed.* **2009**, *48*, 1830.
(10) (a) Li, W.; Duan, Z.; Jiang, R.; Lei, A. *Org. Lett.* **2015**, *17*, 1397. (b) Chen, M.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. *J. Org. Chem.* **2015**, *80*, 1258.
(11) Liu, B.; Jiang, H.-Z.; Shi, B.-F. *Org. Biomol. Chem.* **2014**, *12*, 2538.
(12) Dai, H.-X.; Stepan, A. F.; Plummer, M. S.; Zhang, Y.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 7222.
(13) Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14082.
(14) For selected examples of carbonylation of C−H bonds using amine as an intrinsic directing group, see: (a) Rajeshkumar, V.; Lee, T.-H.; Chuang, S.-C. *Org. Lett.* **2013**, *15*, 1468 and references cited therein. (b) Inoue, S.; Shiota, H.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2009**, *131*, 6898 and references cited therein. (c) Li, W.; Liu, C.; Zhang, H.; Ye, K.; Zhang, G.; Zhang, W.; Duan, Z.; You, S.; Lei, A. *Angew. Chem., Int. Ed.* **2014**, *53*, 2443. (d) Haffemayer, G.; Gulias, M.; Gaunt, M. J. *Chem. Sci.* **2011**, *2*, 312. (e) Ma, B.; Wang, Y.; Peng, J.; Zhu, Q. *J. Org. Chem.* **2011**, *76*, 6362. (f) Guan, Z.-H.; Chen, M.; Ren, Z.-H. *J. Am. Chem. Soc.* **2012**, *134*, 17490. (g) McNally, A.; Haffemayer, B.; Collins, B. S. L.; Gaunt, M. J. *Nature* **2014**, *510*, 129. (h) Ferguson, J.; Zeng, F.; Alwis, N.; Alper, H. *Org. Lett.* **2013**, *15*, 1998.
(15) For selected examples of carbonylation of C−H bonds using −OH as an intrinsic directing group, see: (a) Luo, S.; Luo, F.-X.; Zhang, X.-S.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2013**, *52*, 10598. (b) Chen, M.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. *Angew. Chem., Int. Ed.* **2013**, *52*, 14196. (c) Lu, Y.; Leow, D.; Wang, X.; Engle, K. M.; Yu, J.-Q. *Chem. Sci.* **2011**, *2*, 967. (d) Ji, F.; Li, X.; Wu, W.; Jiang, H. *J. Org. Chem.* **2014**, *79*, 11246. (e) Inamoto, K.; Kadokawa, J.; Kondo, Y. *Org. Lett.* **2013**, *15*, 3962. (f) Shin, S.; Jeong, Y.; Jeon, W. H.; Lee, P. H. *Org. Lett.* **2014**, *16*, 2930.
(16) (a) Zhang, M.-Z.; Chen, Q.; Yang, G.-F. *Eur. J. Med. Chem.* **2015**, *89*, 421. (b) Zi, W.; Zuo, Z.; Ma, D. *Acc. Chem. Res.* **2015**, *48*, 702. (c) Dalpozzo, R. *Chem. Soc. Rev.* **2015**, *44*, 742. (d) Lancianesi, S.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2014**, *114*, 7108. (e) Kochanowska-Karamyan, A. J.; Hamann, M. T. *Chem. Rev.* **2010**, *110*, 4489.
(17) (a) Ackermann, L.; Wang, L.; Lygin, A. V. *Chem. Sci.* **2012**, *3*, 177. (b) Morimoto, K.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 2068.
(18) Yan, L.; Zhao, D.; Lan, J.; Cheng, Y.; Guo, Q.; Li, X.; Wu, N.; You, J. *Org. Biomol. Chem.* **2013**, *11*, 7966.
(19) (a) Samosorn, S.; Bremner, J. B.; Ball, A.; Lewis, K. *Bioorg. Med. Chem.* **2006**, *14*, 857. (b) Laha, J. K.; Dayal, N.; Jethava, K. P.; Prajapati, D. V. *Org. Lett.* **2015**, *17*, 1296. (c) Crawford, L. A.; Clemence, N. C.; McNab, H.; Tyas, R. G. *Org. Biomol. Chem.* **2008**, *6*, 2334. (d) Scopton, A.; Kelly, T. R. *J. Org. Chem.* **2005**, *70*, 10004.
(20) (a) Guillaumel, J.; Léonce, S.; Pierré, A.; Renard, P.; Pfeiffer, B.; Arimondo, P. B.; Monneret, C. *Eur. J. Med. Chem.* **2006**, *41*, 379. (b) Boussard, M.-F.; Truche, S.; Rousseau-Rojas, A.; Briss, S.; Descamps, S.; Droual, M.; Wierzbicki, M.; Ferry, G.; Audinot, V.; Delagrange, P.; Boutin, J. A. *Eur. J. Med. Chem.* **2006**, *41*, 306. (c) Komoda, T.; Shinoda, Y.; Nakatsuka, S.-I. *Biosci., Biotechnol., Biochem.* **2003**, *67*, 659. (d) Pegan, S. D.; Sturdy, M.; Ferry, G.; Delagrange, P.; Boutin, J. A.; Mesecar, A. D. *Protein Sci.* **2011**, *20*, 1182. (e) Alarma-Estrany, P.; Crooke, A.; Mediero, A.; Peláez, T.; Pintor, J. *J. Pineal Res.* **2008**, *45*, 468.
(21) Hayashi, K.; Choshi, T.; Chikaraishi, K.; Oda, A.; Yoshinaga, R.; Hatae, N.; Ishikura, M.; Hibino, S. *Tetrahedron* **2012**, *68*, 4274.
(22) (a) Ambrus, J. I.; Kelso, M. J.; Bremner, J. B.; Ball, A. R.; Casadei, G.; Lewis, K. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4294. (b) He, H.-F.; Dong, S.; Chen, Y.; Yang, Y.; Le, Y.; Bao, W. *Tetrahedron* **2012**, *68*, 3112. (c) Kandukuri, S. R.; Oestreich, M. *J. Org. Chem.* **2012**, *77*, 8750. (d) Liégault, B.; Lee, D.; Huestis, M. P.; Stuart, D. R.; Fagnou, K. *J. Org. Chem.* **2008**, *73*, 5022.
(23) Duncanson, P.; Cheong, Y.-K.; Motevalli, M.; Griffiths, D. V. *Org. Biomol. Chem.* **2012**, *10*, 4266.
(24) For palladium-catalyzed carbonylative cyclization of 2-(2-halophenyl)-1*H*-indoles leading to 6*H*-isoindolo[2,1-*a*]indol-6-ones, see: (a) Yoo, J. M.; Ho, S. L.; Cho, C. S. *Synlett* **2016**, *27*, 1383. (b) Han, Q.; Fu, S.; Zhang, X.; Lin, S.; Huang, Q. *Tetrahedron Lett.* **2016**, *57*, 4165.
(25) Liang, D.; Hu, Z.; Peng, J.; Huang, J.; Zhu, Q. *Chem. Commun.* **2013**, *49*, 173.
(26) Liang, D.; He, Y.; Zhu, Q. *Org. Lett.* **2014**, *16*, 2748.
(27) Mokuolu, Q. F.; Duckmanton, P. A.; Hitchcock, P. B.; Wilson, C.; Blake, A. J.; Shukla, L.; Love, J. B. *Dalton Trans.* **2004**, *33*, 1960.
(28) Zhao, L.; Li, Z.; Chang, L.; Xu, J.; Yao, H.; Wu, X. *Org. Lett.* **2012**, *14*, 2066.
(29) Yu, X.; Park, E.-J.; Kondratyuk, T. P.; Pezzuto, J. M.; Sun, D. *Org. Biomol. Chem.* **2012**, *10*, 8835.
(30) Wen, J.; Zhang, R.-Y.; Chen, S.-Y.; Zhang, J.; Yu, X.-Q. *J. Org. Chem.* **2012**, *77*, 766.
(31) Tang, T.; Jiang, X.; Wang, J.-M.; Sun, Y.-X.; Zhu, Y.-M. *Tetrahedron* **2014**, *70*, 2999.
(32) Kadam, H. K.; Tilve, S. G. *Eur. J. Org. Chem.* **2013**, *2013*, 4280.
(33) Laha, J. K.; Dayal, N.; Singh, S.; Bhimpuria, R. *Eur. J. Org. Chem.* **2014**, *2014*, 5469.

DOI: 10.1021/acs.joc.6b01200
J. Org. Chem. 2016, 81, 12135−12142