Advanced Synthesis & Catalysis

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Authors: shenghai guo, Fang Wang, Lincong Sun, Xinying Zhang, and Xuesen Fan

To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201800347

Link to VoR: http://dx.doi.org/10.1002/adsc.201800347

10.1002/adsc.201800347

FULL PAPER

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Palladium-Catalyzed Oxidative Cyclocarbonylation of Isoquinolones with CO via C-H/N-H Bond Cleavage: Easy Access to Isoindolo[2,1-*b*]isoquinoline-5,7-dione Derivatives

Shenghai Guo,[a,*] Fang Wang,[a] Lincong Sun,[a] Xinying Zhang,[a] and Xuesen Fan[a,*]

[a] Henan Key Laboratory of Organic Functional Molecule and Drug Innovation, Collaborative Innovation Center of Henan Province for Green Manufacturing of Fine Chemicals, Key Laboratory of Green Chemical Media and Reactions, Ministry of Education, School of Chemistry and Chemical Engineering, Henan Normal University, Xinxiang, Henan 453007, P. R. China
Fax: (+86)-373-332-6336; e-mail: shguo@htu.cn, xuesen.fan@htu.cn
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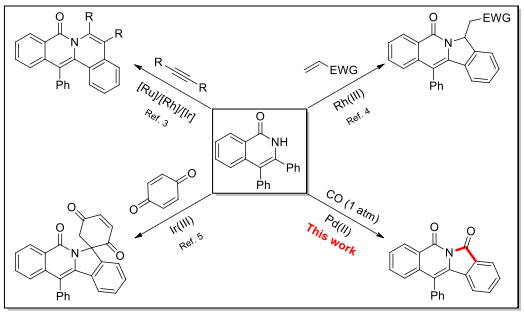
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.

Abstract: An efficient and practical synthesis of isoindolo[2,1-*b*]isoquinoline-5,7-diones through Pd-catalyzed C-H activation/carbonylative annulation of isoquinolones with CO (1 atm) is presented. Deuterium-labeling experiments revealed that the aryl C(sp^2)-H bond activation might be the rate-determining step. More interestingly, the title compounds could also be prepared directly from the cascade reaction of *N*-methoxy benzamides and internal alkynes, as the precursors of isoquinolones, under an atmospheric pressure of carbon monoxide through a Rh/Pd relay catalysis in a user-friendly manner.

Keywords: C-H activation; Cyclocarbonylation; Carbon monoxide; Isoquinolone; Isoindolo[2,1-*b*]isoquinoline-5,7-dione

Introduction

Transition metal-catalyzed unreactive C-H bond activation/functionalization has emerged as one of the most powerful tools for the construction of various C-C and C-heteroatom bonds and for the rapid synthesis of bioactive compounds in modern organic synthesis as it obviates the need for pre-functionalized substrates in comparison with the traditional cross-coupling reactions.[1] To achieve highly site-selective C-H cleavage and functionalization, the most frequently used strategy is to install a directing group, such as amide, ketone, alcohol, carboxylic acid, ester, nitrogen heterocycle, and others.[2] Recently, NH isoquinolone unit has emerged as an effective directing group to enable several oxidative annulation reactions through transition metal-catalyzed C-H and N-H bond cleavage, thus leading to the formation of several isoquinolone-containing heterocycles (Scheme 1). For example, the oxidative annulation of NH isoquinolones with alkynes has been successfully applied for the preparation of dibenzo[*a*,*g*]quinolizin-8-one derivatives under the catalysis of Ru, Rh, or Ir complex.[3] In addition, isoindolo[2,1-*b*]isoquinolin-5(7*H*)-ones could also be obtained through Rh-catalyzed oxidative coupling of 3-arylisoquinolones with activated olefins.[4] Recently, Wang et al. reported an Ir-catalyzed oxidative spirocyclization reaction of 3-phenylisoquinolones with benzoquinone to give novel spiro isoquinolone derivatives.[5] Therefore, the development of more isoquinolone-directed ortho C-H activation/annulation reactions for the synthesis of polycyclic isoquinolone derivatives is highly desirable.



Scheme 1. Transition-metal-catalyzed oxidative annulations of NH isoquinolones.

Directing group-assisted oxidative C-H carbonylation followed by an intramolecular annulation reaction with CO as a C1 feedstock proved to be one of the most promising methods for the fast construction of a large number of carbonyl-containing carbocyclic and heterocyclic skeletons.[6] For example, *N*-containing functional group-directed oxidative C-H/N-H carbonylation reactions have been extensively employed for the preparation of different five- and six-membered lactam compounds with a wide range of biological activities.[7] However, as far as we know, an oxidative C-H carbonylative cyclization reaction with the use of a NH

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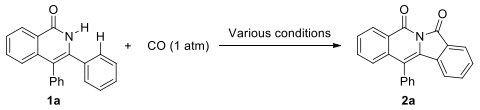
isoquinolone group as a directing group and carbon monoxide as a carbonyl source to give lactams has not been reported yet. As a continuation of our recent study on palladium-catalyzed cyclocarbonylation reactions,[8] we disclose herein a palladium-catalyzed NH isoquinolone-directed oxidative cyclocarbonylation reaction of 3-arylisoquinolin-1(2*H*)-ones with CO (1 atm), thus offering a practical and straightforward access to isoindolo[2,1-*b*]isoquinoline-5,7-diones, which exhibit potential fluorescent properties and are usually hard-to-prepare via the known methods.[9]

Results and Discussion

Initially, we chose 3,4-diphenylisoquinolin-1(2*H*)-one (**1a**) as a model substrate to optimize the reaction parameters for the formation of **2a**, including catalysts, oxidants, bases, and solvents (Table 1). When **1a** was treated with $PdCl_2$ (10 mol %), AgOTFA (2.0 equiv.), and Na_2CO_3 (0.5 equiv.) in chlorobenzene (2 mL) at 120 °C for 15 h under an atmospheric pressure of CO, the oxidative cyclocarbonylation reaction proceeded smoothly and afforded the desired 12-phenylisoindolo[2,1-*b*]isoquinoline-5,7-dione (**2a**) in 49% yield (entry 1). The structure of **2a** was unambiguously confirmed by X-ray analysis (see the Supporting Information). To improve the efficiency, different catalysts such as $Pd(OAc)_2$, $Pd(OTFA)_2$, $Pd(PPh_3)_2Cl_2$, and $[Cp^*RhCl_2]_2$ were screened (entries 2-5). Among them, $Pd(OAc)_2$ exhibited the highest catalytic activity (81%). With $Pd(OAc)_2$ as the catalyst, we also examined the effect of other oxidants including $Cu(OAc)_2$, $Cu(OTf)_2$, $K_2S_2O_8$, AgOAc, $Cu(OTFA)_2$, O_2, and BQ on this oxidative cyclocarbonylation reaction (entries 6-12), and AgOTFA was proved to be the best oxidant (entries 2 vs. 6-12). Next, five other inorganic and organic bases were also tested (entries 13-17), however, all of them were less effective than Na_2CO_3 (entries 13-17 vs. 2). In addition, with the use of toluene, *o*-xylene, DMSO, and DMF as the reaction solvents, decreased yields of **2a** were observed (entries 18-21). Changing the amount of $Pd(OAc)_2$, AgOTFA, or Na_2CO_3 failed to improve the yield of **2a** (entries 22-26). In following studies, it was also found that, without $Pd(OAc)_2$, this reaction failed to afford **2a** (entry 27). Besides, in the absence of AgOTFA or Na_2CO_3, the formation of **2a** was suppressed obviously (entries 28-29). Finally, when the reaction was carried out at 100 or 140 °C, **2a** was obtained in 52% or 80% yield.

With the optimized reaction conditions (Table 1, entry 2) in hand, we next studied the scope and limitation of this Pd-catalyzed NH isoquinolone-directed oxidative cyclocarbonylation reaction forming isoindolo[2,1-*b*]isoquinoline-5,7-diones (**2**). As demonstrated in Table 2, both electron-donating and electron-withdrawing R^1 attached on 6-, 7-, and 8-positions of isoquinolones (**1**) were well compatible with the optimized reaction conditions to give the corresponding isoindolo[2,1-*b*]isoquinoline-5,7-diones **2b**-**2i** in 65-82 yields, and no obvious electronic and steric effects was observed. Besides isoquinolones (**1a**-**1i**), other fused pyridones (**1j**-**1n**) were also proved to be good substrates and underwent this carbonylative annulation reaction smoothly to give the corresponding products in reasonable to good yields. For example, with two naphtho-fused pyridones as reactants, the Pd-catalyzed cyclocarbonylation reactions could afford the desired pentacyclic lactam products **2j** and **2k** in 74% and 52% yields, respectively. When furo- and thieno-fused pyridones were employed, the reactions could also yield the expected carbonylated products **2l-2n** in 68%-81% yields. In addition, we also investigated the Pd-catalyzed reaction of alkyl substituted pyridone with CO (1 atm), and it turned out that the reaction proceeded smoothly to afford **2o**

Table 1. Optimization of reaction conditions for the synthesis of **2a**.[a]



1a **2a**

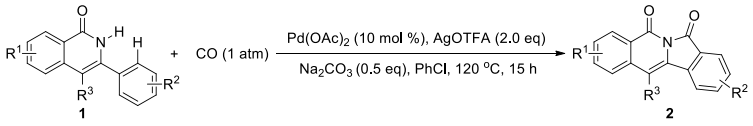
Entry	Catalyst	Oxidant	Base	Solvent	Yield (%)[b]
1	$PdCl_2$	AgOTFA	Na_2CO_3	PhCl	49
2	$Pd(OAc)_2$	AgOTFA	Na_2CO_3	PhCl	81
3	$Pd(OTFA)_2$	AgOTFA	Na_2CO_3	PhCl	66
4	$Pd(PPh_3)_2Cl_2$	AgOTFA	Na_2CO_3	PhCl	47
5	$[Cp^*RhCl_2]_2$	AgOTFA	Na_2CO_3	PhCl	0
6	$Pd(OAc)_2$	$Cu(OAc)_2$	Na_2CO_3	PhCl	47
7	$Pd(OAc)_2$	$Cu(OTf)_2$	Na_2CO_3	PhCl	15
8	$Pd(OAc)_2$	$K_2S_2O_8$	Na_2CO_3	PhCl	61
9	$Pd(OAc)_2$	AgOAc	Na_2CO_3	PhCl	59
10	$Pd(OAc)_2$	$Cu(OTFA)_2$	Na_2CO_3	PhCl	21
11[c]	$Pd(OAc)_2$	O_2	Na_2CO_3	PhCl	6
12	$Pd(OAc)_2$	BQ	Na_2CO_3	PhCl	39
13	$Pd(OAc)_2$	AgOTFA	K_2CO_3	PhCl	54
14	$Pd(OAc)_2$	AgOTFA	K_3PO_4	PhCl	51
15	$Pd(OAc)_2$	AgOTFA	DBU	PhCl	72
16	$Pd(OAc)_2$	AgOTFA	DABCO	PhCl	32
17	$Pd(OAc)_2$	AgOTFA	TEA	PhCl	59
18	$Pd(OAc)_2$	AgOTFA	Na_2CO_3	toluene	50
19	$Pd(OAc)_2$	AgOTFA	Na_2CO_3	xylene	25
20	$Pd(OAc)_2$	AgOTFA	Na_2CO_3	DMSO	0
21	$Pd(OAc)_2$	AgOTFA	Na_2CO_3	DMF	0
22[d]	$Pd(OAc)_2$	AgOTFA	Na_2CO_3	PhCl	60
23[e]	$Pd(OAc)_2$	AgOTFA	Na_2CO_3	PhCl	38
24[f]	$Pd(OAc)_2$	AgOTFA	Na_2CO_3	PhCl	80
25[g]	$Pd(OAc)_2$	AgOTFA	Na_2CO_3	PhCl	68
26[h]	$Pd(OAc)_2$	AgOTFA	Na_2CO_3	PhCl	79
27		AgOTFA	Na_2CO_3	PhCl	0
28	$Pd(OAc)_2$		Na_2CO_3	PhCl	4
29	$Pd(OAc)_2$	AgOTFA		PhCl	55

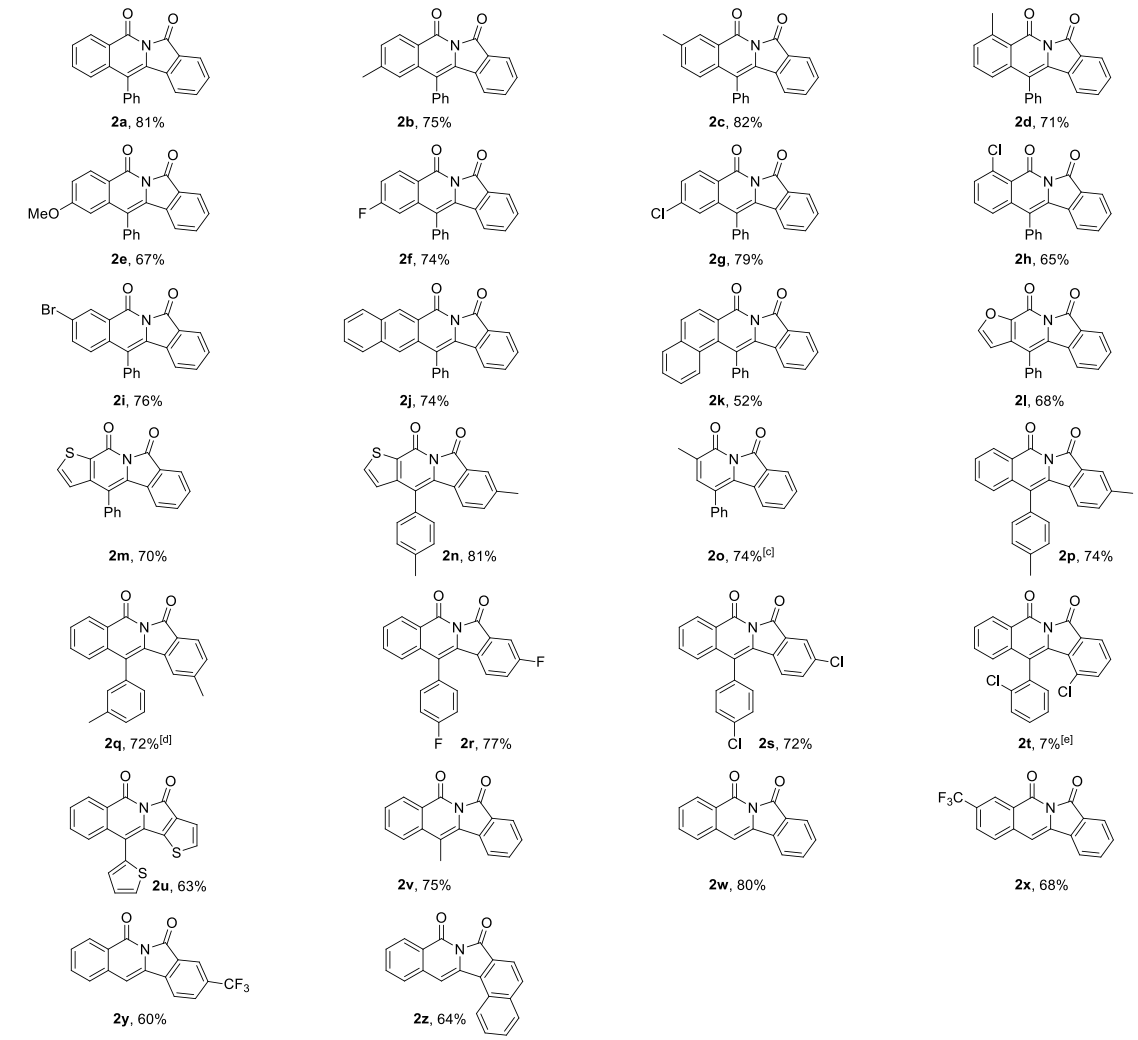
[a]The reactions were run with **1a** (0.4 mmol), CO (1 atm), catalyst (0.04 mmol), oxidant (0.8 mmol), base (0.2 mmol), solvent (2 mL), 120 °C, 15 h. [b]Isolated yield. [c]$CO:O_2$=2:1. [d]With $Pd(OAc)_2$ (0.02 mmol). [e]With AgOTFA (0.4 mmol). [f]With AgOTFA (1.2 mmol). [g]With Na_2CO_3 (0.08 mmol). [h]With Na_2CO_3 (0.4 mmol).

in 74% yield by increasing the loading of Pd catalyst and the reaction time. Next, the effect of different R^2 was examined. The results suggested that isoquinolone substrates (**1**) with a methyl, fluoro, or chloro group on the para-, meta-, or ortho-position of the 3-phenyl moiety took part in this reaction to afford **2p**-**2t**, and it was observed that *p*- and *m*-substituted substrates provided much higher yields than *o*-substituted one (**2p**-**2s** vs. **2t**), suggesting that the steric hindance of R^2 affected the efficiency of this C-H activation/carbonylation reaction significantly. It is also noteworthy that, with *m*-methyl substituted isoquinolone (**1q**), this reaction provided two regioisomers **2q** and **2q'** in 72% and 4% yields, respectively. In addition, when 3,4-di(thiophen-2-yl)isoquinolin-1(2*H*)-one (**1u**) was subjected to the optimized conditions, the corresponding tetracyclic lactam (**2u**) was obtained in 63% yield. To further expand the substrate scope, the cyclocarbonylation reactions of 4-methyl substituted and 4-unsubstituted isoquinolones (**1v**-**1z**) were also tried, to our delight, these reactions proceeded smoothly to furnish the desried products **2v**-**2z** in 60-80% yields.

Thus far, we have established an efficient access to isoindolo[2,1-*b*]isoquinoline-5,7-diones (**2**) through Pd-catalyzed oxidative cyclocarbonylation of isoquinolones (**1**). As most of **1** were prepared through Rh-catalyzed oxidative annulation of readily obtainable *N*-methoxy benzamides with internal alkynes,[10] we were then interested in whether **2** could be synthesized directly from the cascade reaction of *N*-methoxy benzamides with internal alkynes and CO (1 atm) through a Rh/Pd relay catalysis. To check this hypothesis, *N*-methoxybenzamide (**3a**) was firstly treated with

Table 2. Scope for the synthesis of isoindolo[2,1-*b*]isoquinoline-5,7-dione derivatives (**2**)[a],[b]





[a]Reaction conditions: **1** (0.4 mmol), CO (1 atm), $Pd(OAc)_2$ (0.04 mmol), AgOTFA (0.8 mmol), Na_2CO_3 (0.2 mmol), PhCl (2 mL), 120 °C. [b]Isolated yields. [c]$Pd(OAc)_2$ (0.08 mmol), 30 h. [d]Another regioisomer **2q'** (4%). [e]**1t** (88%) was recovered.

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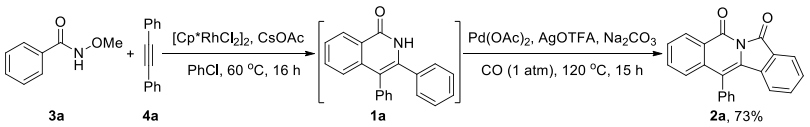
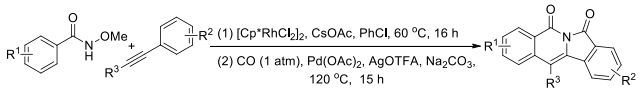


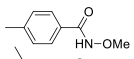
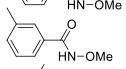
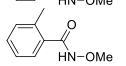
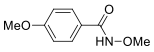
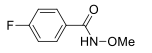
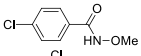
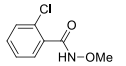
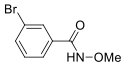
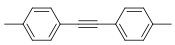
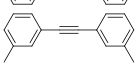
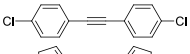
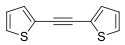
Scheme 2. One-pot two-step synthesis of **2a** through a Rh/Pd relay catalysis.

diphenylacetylene (**4a**, 1.1 equiv.) in the presence of $[Cp^*RhCl_2]_2$ (2.5 mol %) and CsOAc (0.3 equiv.) at 60 °C for 16 h in PhCl, which is the best solvent for the subsequent cyclocarbonylation reaction. Then, $Pd(OAc)_2$ (10 mol %), AgOTFA (2.0 equiv.), and Na_2CO_3 (0.5 equiv.) were added to the reaction mixture, and the resulting mixture was stirred at 120 °C for 15 h under CO (1 atm). To our delight, the envisioned one-pot two-step reaction proceeded smoothly under a Rh/Pd relay catalysis to afford **2a** in a total yield of 73% (Scheme 2).

Next, the substrate scope for this one-pot two-step synthesis of **2** was studied in detail, and the results are listed in Table 3. It turned out that various *N*-methoxy benzamides (**3**) with either electron-donating groups (CH_3- and CH_3O-) or electron-withdrawing groups (F-, Cl-, and Br-) on the para-, meta-, or ortho-position of the phenyl ring reacted

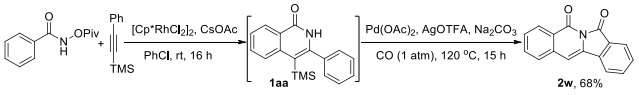
Table 3. Scope for the one-pot two-step synthesis of **2**[a]



Entry	Amide (**3**)	Alkyne (**4**)	Product (**2**)	Yield (%)[b]
1	**3a**	**4a**	**2a**	73
2		**4a**	**2b**	62
3		**4a**	**2c**	72
4		**4a**	**2d**	54
5		**4a**	**2e**	58
6		**4a**	**2f**	65
7		**4a**	**2g**	71
8		**4a**	**2h**	57
9		**4a**	**2i**	66
10	**3a**		**2p**	65
11	**3a**		**2q**	62
12	**3a**		**2r**	61
13	**3a**		**2s**	62
14	**3a**		**2u**	50
15	**3a**		**2v**	45

[a]Reaction conditions: (1) **3** (0.4 mmol), **4** (0.44 mmol), CsOAc (0.12 mmol), $[Cp^*RhCl_2]_2$ (0.01 mmol), PhCl (2 mL), 60 °C, 16 h; (2) CO (1 atm), $Pd(OAc)_2$ (0.04 mmol), AgOTFA (0.8 mmol), Na_2CO_3 (0.2 mmol), 120 °C, 15 h. [b]Isolated yields.

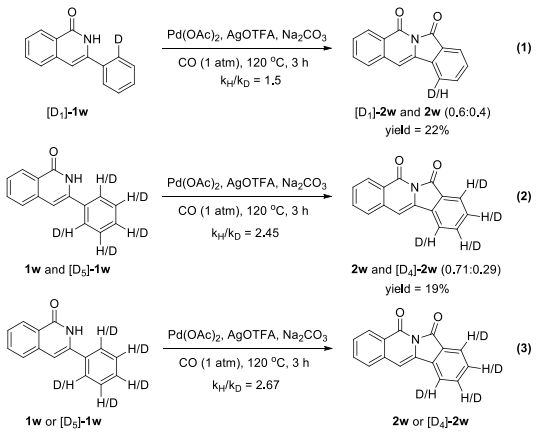
with **4a** and CO (1 atm) very well to provide the corresponding isoindolo[2,1-*b*]isoquinoline-5,7-diones **2a-2i** in moderate to good yields. In addition, we also investigated the reactions of different alkynes (**4**) with **3a** and CO (1 atm), and it was found that a series of Me-, F-, and Cl-substituted diarylacetylenes (**4**) proved to be good substrates and underwent this cascade reaction smoothly to give the expected products **2p-2s**. With 1,2-di(thiophen-2-yl)ethyne and asymmetric 1-phenylpropyne, this cascade reactions could also give rise to the corresponding products **2u** and **2v** in 50% and 45 yields, respectively. Finally, we also attempted to synthesize 12-unsubstituted isoindolo[2,1-*b*]isoquinoline-5,7-dione (**2w**) by changing internal alkynes to phenylacetylene. After several trials, it turned out that phenylacetylene could not react with either *N*-OMe- or *N*-OPiv-benzamide under the catalysis of Rh-complex to give the key intermediate 4-unsubstituted isoquinolone (**1w**). Accordingly, **2w** could not be obtained. In following studies, it was found that, when trimethyl(phenylethynyl)silane was employed as a surrogate of phenylacetylene, this one-pot two-step cascade reaction worked well. As shown in Scheme 3, treatment of *N*-OPiv-benzamide with trimethyl(phenylethynyl)silane in the presence of $[Cp^*RhCl_2]_2$ (0.5 mol %) and CsOAc (2.0 equiv.) in PhCl at room temperature for 16 h could afford the isoquinolone intermediate (**1aa**),[11] which then underwent a detrimethylsilylation and oxidative cyclocarbonylation cascade under the optimized reaction conditions for the synthesis of **2a** (Table 1, entry 2) to provide the target product (**2w**) in a total yield of 68%.



Scheme 3. One-pot synthesis of isoindolo[2,1-*b*]isoquinoline-5,7-dione (**2w**).

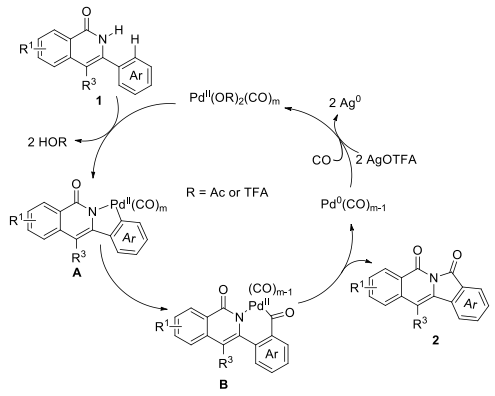
To gain some insight into the reaction mechanism for the Pd-catalyzed oxidative cyclocarbonylation of isoquinolones (**1**) with CO (1 atm), we carried out three deuterium-labeling experiments as shown in Scheme 4. First, treatment of the monodeuterated isoquinolone [D_1]-**1w** with CO (1 atm) under the optimized conditions for 3 h afforded [D_1]-**2w** and **2w** (0.6:0.4) as an inseparable mixture in a total yield of 22% (Scheme 4, Eq. 1). Second, an intermolecular competitive experiment by using an equimolar mixture of **1w** and [D_5]-**1w** was also performed under the standard conditions, and it was observed that a

mixture of **2w** and [D_4]-**2w** (0.71:0.29) was obtained in a total yield of 19% (Scheme 4, Eq. 2). Third, parallel reactions of **1w** and [D_5]-**1w** were also performed under the standard conditions for 3 h, and **2w** and [D_4]-**2w** were obtained in 16% and 6% yields, respectively (Scheme 4, Eq. 3)**.** Based on the above results, the intra-, intermolecular, and parallel KIE (kinetic isotopic effect) values are 1.5, 2.45, and 2.67, suggesting that the aromatic C(sp^2)-H bond activation might be the rate-determining step.



Scheme 4. Deuterium-labeling experiments.

On the basis of the above facts, a plausible mechanism for the formation of **2** is suggested as shown in Scheme 5. Initially, the chelation of the amide group of **1** with CO-ligated Pd^{II} species followed by double N-H/C-H bond cleavages gives rise to a five-membered palladacycle **A**. Subsequent migratory insertion of carbon monoxide into the aryl C(sp^2)-Pd bond of **A** affords a six-membered Pd^{II}-complex **B**. And then, intermediate **B** undergoes a reductive elimination to provide product **2** and a Pd^0-complex which is then reoxidized to the active Pd^{II}-species by AgOTFA.



Scheme 5. Proposed mechanism for the formation of **2**.

Conclusion

In summary, we have successfully established a novel and efficient synthetic route to isoindolo[2,1-*b*]isoquinoline-5,7-diones via the Pd-catalyzed oxidative double C-H/N-H bond cleavages of NH isoquinolone derivatives followed by the cyclocarbonylation with the use of CO (1 atm) as a carbonyl source. Based on the preliminary mechanistic studies, significant kinetic isotopic effects (KIE) were observed, suggesting that the aromatic C(sp^2)-H bond activation might be involved in the rate-determining step of this cyclocarbonylation reaction. In addition, we also disclosed a more practical procedure for the preparation of isoindolo[2,1-*b*]isoquinoline-5,7-diones starting from the NH isoquinolone's precursors, *N*-methoxy benzamides and internal alkynes, and carbon monoxide (1 atm) via a Rh/Pd relay catalysis. Further development of more transition-metal-catalyzed oxidative annulations of NH isoquinolones with other reagents is currently underway in our laboratory.

Experimental Section

General Information

Isoquinolones (**1**) were prepared through Rh-catalyzed oxidative annulation reaction of *N*-OMe or *N*-OPiv-benzamides with internal alkynes.[10-11] [D_1]-**1w** and [D_5]-**1w** were synthesized through copper-catalyzed cross-coupling reactions of 2-bromobenzamide with [D_1]-acetophenone and [D_5]-acetophenone.[12] Unless noted, other commercial reagents and solvents were used without further purification. Melting points were recorded with a micro melting point apparatus and uncorrected. The ^1H NMR spectra were recorded at 400 or 600 MHz. The ^{13}C NMR spectra were recorded at 100 or 150 MHz. High-resolution mass spectra (HRMS) were collected in ESI mode by using a MicrOTOF mass spectrometer. All reactions were monitored by thin-layer chromatography (TLC) using silica gel plates (silica gel 60 F254 0.25 mm), and components were visualized by observation under UV light (254 and 365 nm).

General Procedure for the Synthesis of Isoindolo[2,1-*b*]isoquinoline-5,7-diones (2) via Pd-Catalyzed Oxidative Cyclocarbonylation.

To a schlenk tube (15 mL) containing a mixture of NH isoquinolone **1** (0.4 mmol) in chlorobenzene (2 mL) were added $Pd(OAc)_2$ (0.04 mmol), AgOTFA (0.8 mmol), and Na_2CO_3 (0.2 mmol) under CO (1 atm) atmosphere. Next, the resulting mixture was stirred at 120 °C for 15 h until isoquinolone **1** was consumed completely. And then, the reaction was quenched with NH_4Cl and extracted with dichloromethane. The extract was washed with H_2O and brine and then dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on silica gel (dichloromethane/ethyl acetate = 10:1) to afford the corresponding isoindolo[2,1-*b*]isoquinoline-5,7-dione **2**.

12-Phenylisoindolo[2,1-*b*]isoquinoline-5,7-dione (2a): Yellow solid (105 mg, 81%), mp >300 °C. ^1H NMR ($CDCl_3$, 600 MHz) δ 6.26 (d, *J* = 7.8 Hz, 1H), 7.05 (d, *J* = 7.8 Hz, 1H), 7.26 (t, *J* = 7.8 Hz, 1H), 7.35-7.37 (m, 3H), 7.44-7.47 (m, 1H), 7.50-7.53 (m, 1H), 7.56-7.58 (m, 3H), 7.91 (d, *J* = 7.2 Hz, 1H), 8.51 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 119.8, 123.7, 125.4, 126.5, 127.9, 128.2, 128.5, 129.2, 129.3, 129.8, 129.9, 130.3, 131.5, 133.8, 133.9, 134.3, 135.2, 137.4, 159.8, 165.4. HRMS (ESI) calcd for $C_{22}H_{13}NNaO_2$ $[M + Na]^+$ 346.0838, found 346.0862. CCDC-1838542 contains the

supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

2-Methyl-12-phenylisoindolo[2,1-*b*]isoquinoline-5,7-dione (2b): Yellow solid (101 mg, 75%), mp 283-284 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.35 (s, 3H), 6.28 (d, *J* = 8.0 Hz, 1H), 6.87 (s, 1H), 7.30-7.34 (m, 2H), 7.40-7.43 (m, 3H), 7.63-7.65 (m, 3H), 7.97 (d, *J* = 7.6 Hz, 1H), 8.45 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 22.0, 119.9, 123.7, 125.3, 125.5, 126.6, 128.2, 129.2, 129.3, 129.8, 130.4, 131.6, 134.0, 134.3, 135.2, 137.4, 144.8, 159.7, 165.4 (two ^{13}C signals were not observed). HRMS (ESI) calcd for $C_{23}H_{15}NNaO_2$ $[M + Na]^+$ 360.0995, found 360.1011.

3-Methyl-12-phenylisoindolo[2,1-*b*]isoquinoline-5,7-dione (2c): Yellow solid (111 mg, 82%), mp >300 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.48 (s, 3H), 6.32 (d, *J* = 7.6 Hz, 1H), 7.01 (d, *J* = 8.0 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.38-7.43 (m, 4H), 7.62-7.63 (m, 3H), 7.97 (d, *J* = 7.6 Hz, 1H), 8.38 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 21.3, 120.0, 123.5, 125.3, 126.5, 127.7, 128.1, 129.1, 129.2, 129.6, 129.7, 130.3, 130.6, 134.0, 134.3, 135.0, 135.3, 139.0, 159.8, 165.4 (one ^{13}C signal was not observed). HRMS (ESI) calcd for $C_{23}H_{16}NO_2$ $[M + H]^+$ 338.1176, found 338.1176.

4-Methyl-12-phenylisoindolo[2,1-*b*]isoquinoline-5,7-dione (2d): Yellow solid (96 mg, 71%), mp >300 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.97 (s, 3H), 6.26 (d, *J* = 7.8 Hz, 1H), 6.97 (d, *J* = 7.8 Hz, 1H), 7.27 (d, *J* = 7.2 Hz, 1H), 7.30-7.33 (m, 1H), 7.39-7.42 (m, 4H), 7.62-7.63 (m, 3H), 7.94 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 24.1, 120.0, 123.6, 125.16, 125.21, 125.7, 128.4, 129.1, 129.7, 130.4, 131.3, 132.3, 132.8, 134.1, 134.5, 134.7, 138.9, 144.2, 160.7, 165.5 (one ^{13}C signal was not observed). HRMS (ESI) calcd for $C_{23}H_{15}$ $NNaO_2$ $[M + Na]^+$ 360.0995, found 360.0996.

2-Methoxy-12-phenylisoindolo[2,1-*b*]isoquinoline-5,7-dione (2e): Yellow solid (95 mg, 67%), mp 267-268 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.76 (s, 3H), 6.31 (d, *J* = 7.6 Hz, 1H), 6.50 (d, *J* = 2.0 Hz, 1H), 7.05 (dd, *J* = 2.0, 8.8 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.40-7.43 (m, 3H), 7.62-7.63 (m, 3H), 7.97 (d, *J* = 7.6 Hz, 1H), 8.51 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 55.5, 110.2, 115.2, 119.6, 121.1, 123.7, 125.3, 128.4, 129.2, 129.8, 129.9, 130.3, 131.5, 132.2, 133.8, 134.2, 135.1, 139.6, 159.4, 164.0, 165.3. HRMS (ESI) calcd for $C_{23}H_{16}NO_3$ $[M + H]^+$ 354.1125, found 354.1135.

2-Fluoro-12-phenylisoindolo[2,1-*b*]isoquinoline-5,7-dione (2f): Yellow solid (101 mg, 74%), mp >300 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 6.35 (d, *J* = 8.4 Hz, 1H), 6.75 (d, *J* = 9.6 Hz, 1H), 7.20 (t, *J* = 8.4 Hz, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.42-7.47 (m, 3H), 7.65 (m, 3H), 7.98 (d, *J* = 7.2 Hz, 1H), 8.57 (t, *J* = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 112.5 (d, *J* = 23.1 Hz, 1C), 116.4 (d, *J* = 23.0 Hz, 1C), 118.9 (d, *J* = 3.3 Hz, 1C), 123.9, 124.2, 125.4, 128.2, 129.5, 130.0, 130.2, 130.3, 132.3 (d, *J* = 11.0 Hz, 1C), 132.8, 133.2, 134.5, 134.9, 140.2 (d, *J* = 9.8 Hz, 1C), 158.8, 165.1, 166.3 (d, *J* = 253.8 Hz, 1C). HRMS (ESI) calcd for $C_{22}H_{13}FNO_2$ $[M + H]^+$ 342.0925, found 342.0922.

2-Chloro-12-phenylisoindolo[2,1-*b*]isoquinoline-5,7-dione (2g): Yellow solid (113 mg, 79%), mp >300 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.32 (d, *J* = 8.0 Hz, 1H), 7.06 (d, *J* = 1.2 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.41-7.43 (m, 2H), 7.45 (s, 1H), 7.48 (m, 1H), 7.65-7.67 (m, 3H), 7.98 (d, *J* = 7.2 Hz, 1H), 8.50 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 118.6, 123.9, 125.4, 126.0, 126.1, 128.1, 128.7, 129.5, 130.0, 130.27, 130.28, 130.8, 132.8, 133.1, 134.5, 134.9, 138.9, 140.7, 158.9, 165.1. HRMS (ESI) calcd for $C_{22}H_{13}ClNO_2$ $[M + H]^+$ 358.0629, found 358.0630.

4-Chloro-12-phenylisoindolo[2,1-*b*]isoquinoline-5,7-dione (2h): Yellow solid (93 mg, 65%), mp >300 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.26 (d, *J* = 8.0 Hz, 1H), 7.02 (d, *J* = 7.6 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.39-7.46 (m, 4H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.63-7.65 (m, 3H), 7.98 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 118.8, 123.9, 124.1, 125.3, 125.8, 128.3, 129.4, 129.9, 130.2, 130.4, 132.0, 132.2, 133.2, 133.8, 134.4, 134.5, 137.7, 140.4, 157.8, 165.0. HRMS (ESI) calcd for $C_{22}H_{12}ClNNaO_2$ $[M + Na]^+$ 380.0449, found 380.0446.

3-Bromo-12-phenylisoindolo[2,1-*b*]isoquinoline-5,7-dione (2i): Yellow solid (122 mg, 76%), mp >300 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.33 (d, *J* = 7.6 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.39-7.42 (m, 2H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.63-7.68 (m, 4H), 7.98 (d, *J* = 7.6 Hz, 1H), 8.68 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 119.1, 123.0, 123.8, 125.5, 128.0, 128.1, 129.2, 129.4, 129.9, 130.1, 130.3, 131.8, 133.3, 134.6, 135.1, 136.2, 136.9, 158.5, 165.1 (one ^{13}C signal was not observed). HRMS (ESI) calcd for $C_{22}H_{12}BrNNaO_2$ $[M + Na]^+$ 423.9944, found 423.9943.

14-Phenylbenzo[*g*]isoindolo[2,1-*b*]isoquinoline-5,7-dione (2j): Yellow solid (111 mg, 74%), mp >300 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.33 (d, *J* = 7.6 Hz, 1H), 7.34 (dt, *J* = 0.8, 7.6 Hz, 1H), 7.43 (dt, *J* = 0.8, 7.6 Hz, 1H), 7.49-7.51 (m, 3H), 7.53-7.57 (m, 2H), 7.67-7.70 (m, 3H), 7.74-7.76 (m, 1H), 7.98 (d, *J* = 7.6 Hz, 1H), 8.03-8.06 (m, 1H), 9.13 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 120.3, 123.8, 125.1, 125.3, 126.4, 127.5, 128.3, 128.4, 129.1, 129.2, 129.7, 129.78, 129.83, 130.4, 130.6, 131.5, 132.2, 133.3, 134.17, 134.19, 135.3, 135.7, 160.2, 165.3. HRMS (ESI) calcd for $C_{26}H_{15}NNaO_2$ $[M + Na]^+$ 396.0995, found 396.1008.

14-Phenylbenzo[*f*]isoindolo[2,1-*b*]isoquinoline-7,9-dione (2k): Yellow solid (78 mg, 52%), mp 266-267 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.84 (d, *J* = 8.0 Hz, 1H), 6.99-7.03 (m, 1H), 7.18-7.22 (m, 1H), 7.31 (dt, *J* = 0.8, 7.6 Hz, 1H), 7.38-7.41 (m, 2H), 7.45-7.47 (m, 2H), 7.57-7.64 (m, 3H), 7.76-7.78 (m, 1H), 7.83 (d, *J* = 8.8 Hz, 1H), 7.88 (d, *J* = 7.6 Hz, 1H), 8.54 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 120.8, 124.39, 124.40, 125.4, 126.3, 127.4, 127.6, 128.0, 129.3, 129.5, 129.9, 130.1, 130.37, 130.45, 133.1, 134.3, 134.5, 135.9, 137.2, 138.1, 159.6, 165.2 (two ^{13}C signals were not observed). HRMS (ESI) calcd for $C_{26}H_{16}NO_2$ $[M + H]^+$ 374.1176, found 374.1178.

4-Phenylfuro[3',2':4,5]pyrido[2,1-*a*]isoindole-9,11-dione (2l): Yellow solid (85 mg, 68%), mp >300 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 6.38 (s, 1H), 6.74 (d, *J* = 7.8 Hz, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.41 (t, *J* = 7.2 Hz, 1H), 7.49-7.50 (m, 2H), 7.59-7.61 (m, 3H), 7.74 (s, 1H), 7.96 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 108.0, 116.0, 123.0, 125.7, 128.3, 129.4, 129.5, 129.6, 129.8, 133.0, 133.3, 134.6, 135.0, 135.3, 143.6, 149.8, 151.0, 165.2. HRMS (ESI) calcd for $C_{20}H_{12}NO_3$ $[M + H]^+$ 314.0812, found 314.0828.

4-Phenylthieno[3',2':4,5]pyrido[2,1-*a*]isoindole-9,11-dione (2m): Yellow solid (92 mg, 70%), mp >300 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.56 (d, *J* = 8.0 Hz, 1H), 6.82 (d, *J* = 5.6 Hz, 1H), 7.34 (dt, *J* = 0.8, 7.6 Hz, 1H), 7.42 (dt, *J* = 0.8, 7.2 Hz, 1H), 7.46-7.48 (m, 2H), 7.60-7.61 (m, 3H), 7.69 (d, *J* = 4.8 Hz, 1H), 7.96 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 117.9, 123.2, 125.2, 125.6, 128.0, 129.3, 129.6, 129.7, 129.9, 132.4, 133.5, 134.1, 134.5, 135.1, 135.2, 146.7, 155.7, 165.5. HRMS (ESI) calcd for $C_{20}H_{12}NO_2S$ $[M + H]^+$ 330.0583, found 330.0592.

7-Methyl-4-(*p*-tolyl)thieno[3',2':4,5]pyrido[2,1-*a*]isoindole-9,11-dione (2n): Yellow solid (116 mg, 81%), mp 282-283 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.31 (s, 3H), 2.44 (s, 3H), 6.44 (d, *J* = 8.4 Hz, 1H), 6.75 (d, *J* = 4.8 Hz, 1H), 7.08 (dd, *J* = 0.6, 8.4 Hz, 1H), 7.26 (d, *J* = 7.8 Hz, 2H), 7.31 (d, *J* = 7.8 Hz, 2H), 7.58 (d, *J* = 4.8 Hz, 1H), 7.67 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 21.4, 21.5,

117.2, 123.0, 125.3, 125.6, 128.1, 129.6, 130.2, 131.1, 131.9, 132.8, 133.7, 134.9, 135.5, 139.1, 140.5, 147.0, 155.8, 165.7. HRMS (ESI) calcd for $C_{22}H_{15}NNaO_2S$ [M + Na]$^+$ 380.0716, found 380.0716.

3-Methyl-1-phenylpyrido[2,1-*a*]isoindole-4,6-dione (2o): Yellow solid (85 mg, 74%), mp 144-145 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.15 (d, *J* = 1.2 Hz, 3H), 6.77 (d, *J* = 7.8 Hz, 1H), 7.02 (q, *J* = 1.2 Hz, 1H), 7.29 (dt, *J* = 1.2, 7.8 Hz, 1H), 7.33-7.37 (m, 3H), 7.44-7.47 (m, 3H), 7.87 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 16.5, 120.2, 122.9, 125.6, 127.3, 128.99, 129.04, 129.3, 130.0, 134.1, 134.5, 134.6, 134.8, 136.0, 140.0, 160.3, 165.6. HRMS (ESI) calcd for $C_{19}H_{14}NO_2$ [M + H]$^+$ 288.1019, found 288.1021.

9-Methyl-12-(*p*-tolyl)isoindolo[2,1-*b*]isoquinoline-5,7-dione (2p): Yellow solid (104 mg, 74%), mp >300 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.39 (s, 3H), 2.54 (s, 3H), 6.29 (d, *J* = 8.4 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.77 (s, 1H), 8.55 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.4, 21.5, 119.0, 123.6, 125.3, 126.4, 127.7, 128.1, 128.3, 129.1, 130.2, 130.4, 130.8, 131.7, 132.9, 133.6, 135.5, 137.7, 139.0, 140.5, 159.8, 165.5. HRMS (ESI) calcd for $C_{24}H_{17}NNaO_2$ [M + Na]$^+$ 374.1151, found 374.1163.

10-Methyl-12-(*m*-tolyl)isoindolo[2,1-*b*]isoquinoline-5,7-dione (2q): Yellow solid (101 mg, 72%), mp 236-237 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.19 (s, 3H), 2.48 (s, 3H), 6.13 (s, 1H), 7.15 (d, *J* = 7.6 Hz, 1H), 7.21-7.23 (m, 3H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.49-7.54 (m, 2H), 7.57 (d, *J* = 7.2 Hz, 1H), 7.83 (d, *J* = 7.6 Hz, 1H), 8.54 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 21.5, 22.3, 119.7, 124.3, 125.1, 125.7, 126.5, 127.3, 127.9, 128.3, 129.1, 129.5, 129.8, 130.8, 130.9, 131.5, 133.7, 133.8, 135.7, 137.5, 139.5, 145.4, 159.8, 165.4. HRMS (ESI) calcd for $C_{24}H_{17}NNaO_2$ [M + Na]$^+$ 374.1151, found 374.1150.

9-Fluoro-12-(4-fluorophenyl)isoindolo[2,1-*b*]isoquinoline-5,7-dione (2r): Yellow solid (111 mg, 77%), mp >300 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.34-6.37 (m, 1H), 7.07-7.11 (m, 2H), 7.35 (t, *J* = 8.4 Hz, 2H), 7.40-7.43 (m, 2H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.59-7.65 (m, 2H), 8.56 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 111.8 (d, *J* = 24.0 Hz, 1C), 117.1 (d, *J* = 21.9 Hz, 2C), 118.7, 122.2 (d, *J* = 23.0 Hz, 1C), 125.6 (d, *J* = 7.7 Hz, 1C), 126.4, 127.3, 128.6, 129.1, 129.4 (d, *J* = 3.3 Hz, 1C), 130.2 (d, *J* = 8.7 Hz, 1C), 131.0 (d, *J* = 2.3 Hz, 1C), 132.3 (d, *J* = 8.7 Hz, 2C), 134.0, 137.1, 159.3, 163.3 (d, *J* = 248.3 Hz, 1C), 163.5 (d, *J* = 252.8 Hz, 1C), 163.9 (d, *J* = 3.3 Hz, 1C) (one ^{13}C signal was not observed). HRMS (ESI) calcd for $C_{22}H_{11}F_2NNaO_2$ [M + Na]$^+$ 382.0650, found 382.0656.

9-Chloro-12-(4-chlorophenyl)isoindolo[2,1-*b*]isoquinoline-5,7-dione (2s): Yellow solid (113 mg, 72%), mp 261-262 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.34-6.37 (m, 1H), 7.07-7.10 (m, 2H), 7.36 (t, *J* = 8.0 Hz, 2H), 7.43-7.46 (m, 2H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.58-7.62 (m, 2H), 8.50 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 119.0, 124.7, 125.4, 126.3, 127.7, 128.9, 129.5, 129.7, 130.2, 131.0, 131.8, 132.0, 133.1, 134.1, 134.7, 135.7, 136.6, 136.8, 159.4, 163.9. HRMS (ESI) calcd for $C_{22}H_{11}Cl_2NNaO_2$ [M + Na]$^+$ 414.0059, found 414.0061.

11-Chloro-12-(2-chlorophenyl)isoindolo[2,1-*b*]isoquinoline-5,7-dione (2t): Yellow solid (11 mg, 7%), mp 246-247 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.01 (d, *J* = 7.8 Hz, 1H), 7.37-7.41 (m, 2H), 7.44 (t, *J* = 7.2 Hz, 1H), 7.47-7.51 (m, 2H), 7.55-7.60 (m, 3H), 8.00 (d, *J* = 7.2 Hz, 1H), 8.57 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 119.9, 124.2, 126.9, 127.38, 127.43, 129.0, 129.2, 129.9, 130.1, 130.7, 131.2, 131.9, 132.0, 132.5, 133.7, 134.1, 135.4, 136.2, 136.6, 138.1, 159.8, 164.0. HRMS (ESI) calcd for $C_{22}H_{11}Cl_2NNaO_2$ [M + Na]$^+$ 414.0059, found 414.0052.

11-(Thiophen-2-yl)thieno[2',3':3,4]pyrrolo[1,2-*b*]isoquinoline-4,6-dione (2u): Yellow solid (84 mg, 63%), mp >300 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.22-7.23 (m, 1H), 7.29-7.39 (m, 4H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.63 (t, *J* = 7.6 Hz, 1H), 6.67 (d, *J* = 5.2 Hz, 1H), 8.54 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 111.3, 121.5, 126.4, 128.2, 128.7, 128.9, 129.5, 129.8, 131.8, 132.7, 133.91, 133.93, 136.7, 137.0, 146.1, 159.0, 160.2 (one ^{13}C signal was not observed). HRMS (ESI) calcd for $C_{18}H_9NNaO_2S_2$ [M + Na]$^+$ 357.9967, found 357.9968.

12-Methylisoindolo[2,1-*b*]isoquinoline-5,7-dione (2v): Yellow solid (78 mg, 75%), mp 279-280 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.71 (s, 3H), 7.51-7.56 (m, 2H), 7.72-7.78 (m, 3H), 8.02-8.05 (m, 2H), 8.53 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 13.0, 114.6, 124.1, 124.2, 125.6, 127.8, 128.3, 129.3, 129.5, 131.0, 133.8, 134.7, 135.5, 136.9, 159.6, 165.1 (one ^{13}C signal was not observed). HRMS (ESI) calcd for $C_{17}H_{11}NNaO_2$ [M + Na]$^+$ 284.0682, found 284.0697.

Isoindolo[2,1-*b*]isoquinoline-5,7-dione (2w):[9a] Yellow solid (79 mg, 80%), mp 245-246 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.92 (s, 1H), 7.46 (t, *J* = 8.0 Hz, 1H), 7.50-7.53 (m, 2H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.70 (t, *J* = 7.2 Hz, 1H), 7.77 (d, *J* = 7.6 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 8.42 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 103.6, 120.6, 125.5, 127.5, 127.7, 128.2, 128.5, 129.4, 130.5, 133.9, 134.8, 135.0, 135.6, 159.7, 165.1 (one ^{13}C signal was not observed). HRMS (ESI) calcd for $C_{16}H_9NNaO_2$ [M + Na]$^+$ 270.0525, found 270.0532.

3-(Trifluoromethyl)isoindolo[2,1-*b*]isoquinoline-5,7-dione (2x): Yellow solid (86 mg, 68%), mp > 300 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.04 (s, 1H), 7.66 (t, *J* = 6.8 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.80 (t, *J* = 6.8 Hz, 1H), 7.87 (d, *J* = 7.6 Hz, 1H), 7.93 (dd, *J* = 1.6, 8.0 Hz, 1H), 8.07 (d, *J* = 7.6 Hz, 1H), 8.78 (s, 1H); ^{13}C NMR (CF_3COOD, 150 MHz) δ 108.1, 124.4, 126.5 (q, *J* = 270.2 Hz, 1C), 129.3, 129.6, 129.7, 129.9, 132.1, 135.0, 135.1, 135.3 (q, *J* = 33.9 Hz, 1C), 138.5, 139.8, 140.1, 142.5, 165.8, 171.8. HRMS (ESI) calcd for $C_{17}H_8F_3NNaO_2$ [M + Na]$^+$ 338.0399, found 338.0401.

9-(Trifluoromethyl)isoindolo[2,1-*b*]isoquinoline-5,7-dione (2y): Yellow solid (76 mg, 60%), mp 297-298 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.03 (s, 1H), 7.50-7.55 (m, 2H), 7.66 (dt, *J* = 0.8, 8.0 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 8.23 (s, 1H), 8.46 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 105.7, 121.2, 123.1 (q, *J* = 3.3 Hz, 1C), 123.3 (q, *J* = 271.2 Hz, 1C), 127.9, 128.3, 128.5, 129.4, 129.7, 131.5 (q, *J* = 3.3 Hz, 1C), 132.8 (q, *J* = 32.9 Hz, 1C), 133.9, 134.3, 135.1, 137.7, 159.5, 163.8. HRMS (ESI) calcd for $C_{17}H_8F_3NNaO_2$ [M + Na]$^+$ 338.0399, found 338.0394.

Benzo[6,7]isoindolo[2,1-*b*]isoquinoline-7,9-dione (2z): Yellow solid (76 mg, 64%), mp >300 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (s, 1H), 7.47 (dt, *J* = 1.2, 8.0 Hz, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.62-7.67 (m, 2H), 7.70 (dt, *J* = 1.2, 7.2 Hz, 1H), 7.90-7.94 (m, 3H), 8.42-8.46 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 108.6, 120.4, 124.1, 127.0, 127.4, 128.0, 128.2, 128.8, 128.9, 129.0, 129.3, 130.2, 132.0, 132.1, 134.0, 135.8, 136.1, 137.3, 159.7, 165.5. HRMS (ESI) calcd for $C_{20}H_{11}NNaO_2$ [M + Na]$^+$ 320.0682, found 320.0679.

General Procedure for the One-Pot Two-Step Synthesis of Isoindolo[2,1-*b*]isoquinoline-5,7-diones (2) via a Rh/Pd Relay Catalysis.

To a schlenk tube (15 mL) containing a mixture of *N*-methoxy benzamide **3** (0.4 mmol) and internal alkyne **4** (0.44 mmol) in chlorobenzene (2 mL) were added $[Cp^*RhCl_2]_2$ (0.01 mmol) and CsOAc (0.12 mmol). Then, the reaction mixture was stirred at 60 °C for 16 h until *N*-methoxy benzamide **3** was consumed completely. Next, $Pd(OAc)_2$ (0.04 mmol), AgOTFA (0.8 mmol), and Na_2CO_3

(0.2 mmol) were added into the above reaction system under CO (1 atm) atmosphere. After being stirred at 120 °C for 15 h, the resulting mixture was quenched with NH_4Cl and extracted with dichloromethane. The extract was washed with H_2O and brine and then dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on silica gel (dichloromethane/ethyl acetate = 10:1) to afford the corresponding isoindolo[2,1-*b*]isoquinoline-5,7-dione **2**.

Deuterium-Labeling Experiments.

(1) Intramolecular competitive experiment: The reaction of [D_1]-**1w** (88.8 mg, 0.4 mmol) was run for 3 h under the optimized conditions. After isolation and purification, the products [D_1]-**2w** and **2w** were obtained in 21.5 mg (22%), and the starting material [D_1]-**1w** was recovered in 55.8 mg (63%). The deuteration rate of the product was determined by ^{1}H NMR ([D_1]-**2w**:**2w** = 0.6:0.4).

(2) Intermolecular competitive experiment: A mixture of **1w** (44.2 mg, 0.2 mmol) and [D_5]-**1w** (45.2 mg, 0.2 mmol) was subjected to the optimized conditions for 3 h. After isolation and purification, the products **2w** and [D_4]-**2w** were obtained in 19.2 mg (19%). The deuteration rate of the product was determined by ^{1}H NMR (**2w**:[D_4]-**2w** = 0.71:0.29).

(3) Parallel experiment: Individual reactions of **1w** (44.2 mg, 0.2 mmol) and [D_5]-**1w** (45.2 mg, 0.2 mmol) were performed under the optimized conditions for 3 h. After isolation and purification, the products **2w** and [D_4]-**2w** were obtained in 16% and 6% yields, respectively.

Acknowledgements

We thank the National Natural Science Foundation of China (Grants 21202040 and 21572047), Project Funded by China Postdoctoral Science Foundation (2014M552007 and 2015T80771), the Program for Innovative Research Team in Science and Technology in University of Henan Province (15IRTSTHN003), Program for Science and Technology Innovation Talents in Universities of Henan Province (15HASTIT005), and the Plan for Scientific Innovation Talents of Henan Province (184200510012) for financial support.

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10.1002/adsc.201800347

FULL PAPER

Palladium-Catalyzed Oxidative Cyclocarbonylation of Isoquinolones with CO via C-H/N-H Bond Cleavage: Easy Access to Isoindolo[2,1-*b*]isoquinoline-5,7-dione Derivatives

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Shenghai Guo,* Fang Wang, Lincong Sun, Xinying Zhang, and Xuesen Fan*