Letter

RhCl3•3H2O-Catalyzed Regioselective C(sp2)-H Alkoxycarbonylation: Efficient Synthesis of Indole- and Pyrrole-2-carboxylic Acid Esters

Kang Zhao, Rongrong Du, Bingyang Wang, Jianhua Liu, Chun-gu Xia, and Lei Yang

ACS Catal., **Just Accepted Manuscript** • DOI: 10.1021/acscatal.9b01193 • Publication Date (Web): 13 May 2019

$RhCl_3 \cdot 3H_2O$-Catalyzed Regioselective C(sp²)–H Alkoxycarbonylation: Efficient Synthesis of Indole- and Pyrrole-2-carboxylic Acid Esters

Kang Zhao,[†,§] Rongrong Du,[†,§] Bingyang Wang,[†] Jianhua Liu,[†] Chungu Xia,[†] and Lei Yang*[,†,‡]

[†]State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, University of Chinese Academy of Sciences, Chinese Academy of Sciences, Lanzhou 730000, P. R. China

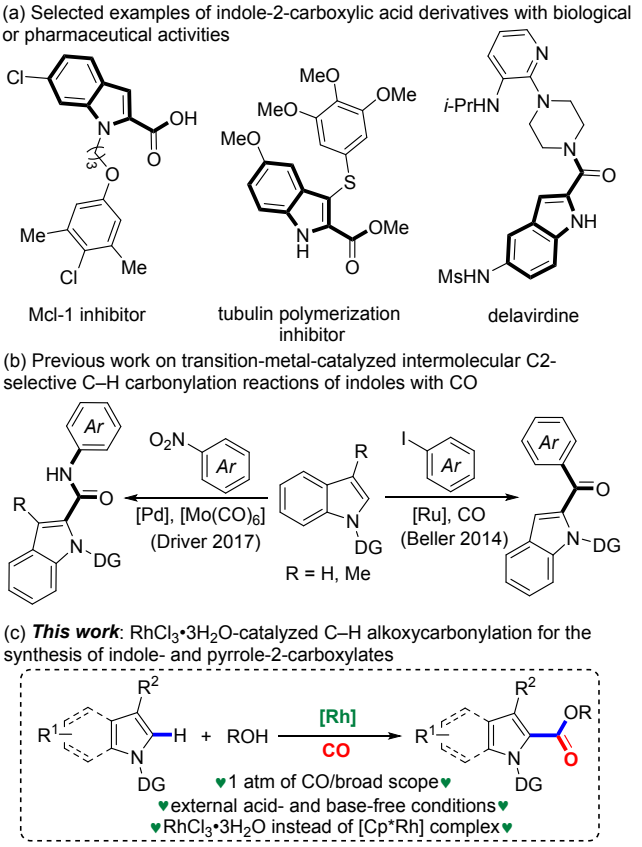
[‡]Key Laboratory of Organosilicon Chemistry and Material Technology of Ministry of Education, Hangzhou Normal University, Hangzhou 311121, P. R. China

ABSTRACT: The C2-selective C–H alkoxycarbonylation of indoles with alcohols and CO catalyzed by $RhCl_3 \cdot 3H_2O$ is disclosed that offers convenient access to diverse indole-2-carboxylic esters. The rhodium-based catalysts outperformed all other precious-metal catalysts investigated. In addition, this protocal was found applicable to the synthesis of pyrrole-2-carboxylic esters, and allowed the C–H alkoxycarbonylation in an intramolecular fashion. Preliminary mechanistic studies indicate that C–H cleavage is not likely involved in the rate-determining step, and a five-membered rhodacycle might be an intermediate involved in the reaction.

KEYWORDS: indole-2-carboxylic esters, pyrrole-2-carboxylic esters, C–H activation, alkoxycarbonylation, rhodium

The indole skeleton has been recognized as a privileged structural motif in natural products, pharmaceuticals, agrochemicals, and other functional molecules.[1] In particular, indole-2-carboxylic esters and derivatives thereof are ubiquitous structural features in many biologically active natural alkaloids and pharmaceutical agents (Scheme 1a).[2] Consequently, considerable efforts have been directed toward the synthesis of indole-2-carboxylic esters and their derivatives.[3] Traditionally, these indole scaffolds are constructed by the well-known cyclization reactions, such as Hemetsberger indole synthesis,[4] Cadogan-Sundberg indole synthesis,[5] intramolecular Ullmann[6] or Heck coupling reactions[7]. Though elegant, these cyclization reactions usually demand the preparation of specific substrates through multi-step reactions, which dramatically limit its application. Therefore, the development of a more efficient and straightforward route to achieve indole-2-carboxylic esters is still highly desired.

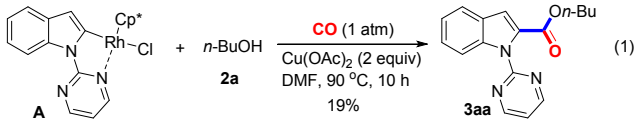
Recently, transition-metal-catalyzed direct C–H carbonylation of indole framework itself has emerged as a new avenue to access carbonyl-functionalized indole derivatives on account of its atom economy and simplified procedure.[8] In this context, because of its low price and ready availability, the use of carbon monoxide (CO) in transition-metal-catalyzed intermolecular C–H carbonylation reactions of indoles with different nucleophiles is of great interest.[9,10] Compared to the well-established C3 selective C–H carbonylation of indoles with CO, direct regioselective C2 carbonylation is less explored.[10] To the best of our knowledge, only two examples towards the synthesis of ketones or amides have been reported so far (Scheme 1b). In 2014, Beller and co-workers[11] first reported the ruthenium-catalyzed C2-selective carbonylative arylation of iodoarene with CO



Scheme 1. State-of-the-art on C2-Selective Carbonylation of Indoles with CO

(30 bar) and indoles containing pyridyl or pyrimidyl directing group (DG) in the presence of base at 120 °C. Notably, using pivalic acid as the additive and $[Mo(CO)_6]$ as the origin of CO and the reductant, the Driver group[12] developed an elegant three-component palladium-catalyzed aminocarbonylation of 2-aryl- or 2-heteroaryl-pyridines and nitroarenes. In this case, two 2-pyridyl indoles were reported to deliver the desired amides. In view of the potential easy transformation of esters, and the fact that the C2-selective alkoxycarbonylation of indoles with CO still remains a formidable challenge,[3] it would be particularly attractive to realize the synthesis of indole-2-carboxylic esters via alkoxycarbonylation of indoles with CO.[13] Herein, we report for the first time the C2-selective alkoxycarbonylation of indoles with CO catalyzed by $RhCl_3·3H_2O$ (Scheme 1c),[14] which is seldom used as the catalyst in C–H activation reactions compared to the typically used expensive $[Cp^*RhCl_2]_2$ catalyst.[15]

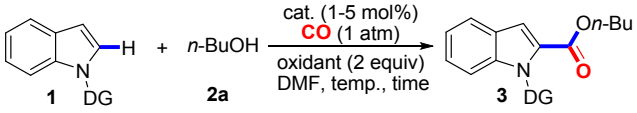
We recently reported an efficient Rh/O_2 catalytic system for selective oxidative C2-alkenylation of indoles.[16] During this work, we identified that a five-membered cyclometalated Rh(III) complex, which could undergo migrative insertion of an alkene and then followed by reductive elimination to produce the final product, was a key intermediate involved in the catalytic cycle. We were curious whether this class of five-membered cyclometalated Rh(III) complex could enable the migrative insertion of CO and then accept the nucleophilic attack of an appropriate nucleophile, thus giving rise to access molecules with increased complexity. To this end, we initially synthesized cyclometalated Rh(III) complex **A** by treatment of 1-(pyrimidin-2-yl)-1*H*-indole (**1a**) with $[RhCp^*Cl_2]_2$.[17] The stoichiometric reaction of complex **A** with 1 atm of CO and *n*-BuOH (**2a**, 5 equiv) in the presence of $Cu(OAc)_2$ was then conducted (eq 1). To our delight, the expected ester **3aa** could be formed, albeit in relatively low yield (19%), supporting that the alkoxycarbonylation of **1a** with CO would be indeed possible. This promising result led us to focus on developing this C–H alkoxycarbonylation reaction into a catalytic process.



(1)

Guided by the preliminary investigation above, we initially focused on the catalytic C–H alkoxycarbonylation of **1a** with **2a** (5-11 equiv) employing readily available rhodium catalysts. As shown in Table 1,[18] we were surprised to find that the desired product **3aa** was formed in quantitative yield under the conditions of $[Cp^*RhCl_2]_2$ (2.5 mol%), $Cu(OAc)_2$ (2 equiv), CO (1 atm), DMF, 110 °C, 14 h (entry 1). Interestingly, switching of the catalyst from $[Cp^*RhCl_2]_2$ to $[Rh(OAc)_2]_2$ or $[Rh(cod)Cl]_2$ led to excellent NMR yield of **3aa** (entries 2 and 3), too. Notably, we were delighted to find that full conversion of **1a** to **3aa** was observed when simple inorgnic salt, $RhCl_3·3H_2O$ or

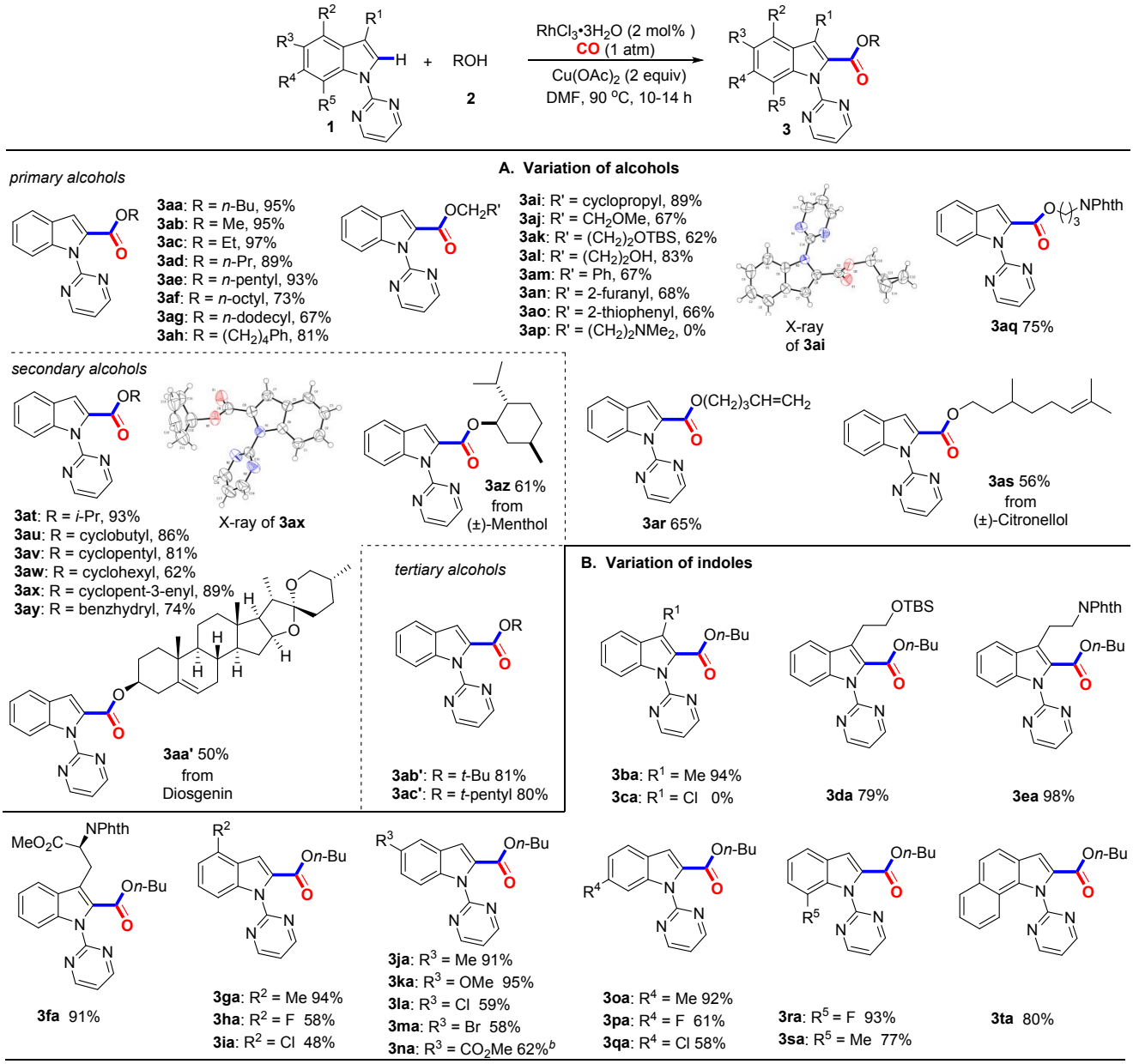
Table 1. Optimization of the C2-Selective C–H Alkoxycarbonylation[a]



Entry	Cat. (mol%)	Oxidant	Yield (%)[b]
1	$[Cp^*RhCl_2]_2$ (2.5)	$Cu(OAc)_2$	>99
2	$[Rh(OAc)_2]_2$ (2.5)	$Cu(OAc)_2$	93
3	$[Rh(cod)Cl]_2$ (2.5)	$Cu(OAc)_2$	95
4	$RhCl_3·3H_2O$ (5)	$Cu(OAc)_2$	>99
5	$RhCl_3$ (5)	$Cu(OAc)_2$	>99
6	$Pd(OAc)_2$ (5)	$Cu(OAc)_2$	0
7	$RuCl_3·3H_2O$ (5)	$Cu(OAc)_2$	0
8	$IrCl_3·3H_2O$ (5)	$Cu(OAc)_2$	0
9[c]	$RhCl_3·3H_2O$ (5)	$Cu(OAc)_2$	98(94)[e]
10	$RhCl_3·3H_2O$ (5)	$Cu(OAc)_2$	>99
11	$RhCl_3·3H_2O$ (5)	$Cu(TFA)_2$	0
12	$RhCl_3·3H_2O$ (5)	$Cu(OTf)_2$	trace
13	$RhCl_3·3H_2O$ (5)	$Cu(EtCO_2)_2$	97
14	$RhCl_3·3H_2O$ (5)	$Cu(i\text{-}PrCO_2)_2$	94
15	$RhCl_3·3H_2O$ (5)	$Cu(OPiv)_2$	50
16	$RhCl_3·3H_2O$ (5)	$Cu(1\text{-}AdCO_2)_2$	0
17	$RhCl_3·3H_2O$ (5)	AgOAc	trace
18[d]	$RhCl_3·3H_2O$ (5)	$Cu(OAc)_2$	>99
19[d]	$RhCl_3·3H_2O$ (2)	$Cu(OAc)_2$	>99(95)[e]
20[d]	$RhCl_3·3H_2O$ (1)	$Cu(OAc)_2$	78
21[d,f]	$RhCl_3·3H_2O$ (2)	$Cu(OAc)_2$	75

[a]Reaction conditions: **1a** (0.2 mmol, 1 equiv), **2a** (11 equiv), cat. (1-5 mol%), oxidant (2 equiv), and DMF (2 mL) under 1 atm of CO in sealed tube at 110 °C for 14 h (entries 1-9) or at 90 °C for 10 h (entries 10-20). [b]Yield determined by ^1H NMR using 1,3,5-trimethoxybenzene as internal standard. [c]1-(pyridin-2-yl)-1*H*-indole was used as the substrate. [d]**2a** (5 equiv). [e]Isolated yield. [f]Performed at 85 °C for 10 h.

$RhCl_3$, was introduced to the reaction (entries 4 and 5). Other simple and readily available palladium, rhuthenium and iridium catalysts were also screened. These efforts, however, did not produce the desired product (entries 6-8). Various directing groups were then tested.[18] In addition to 2-pyimidinyl group, 2-pyridyl group was also an effective directing group for this reaction (entry 9). Investigation on solvents showed that toluene or NMP also gave a good yield of **3aa**.[18] The reaction temperature could be lowered to 90 °C without loss of any reactivity (entry 10). Among the oxidants tested, only copper-based oxidants were workable and $Cu(OAc)_2$ gave the best results (entries 10-17). Moreover, we observed that the anion size of the copper carboxylate salts affected the efficiency of the alkoxycarbonylation reaction (entries 10, 13-16). Of note, the same yield was maintained while



[a]**1** (0.2-1 mmol, 1 equiv), **2a** (5 equiv), $RhCl_3{\cdot}3H_2O$ (2 mol%), $Cu(OAc)_2$ (2 equiv), DMF (2 mL/0.2 mmol **1**), CO (1 atm), 90 °C, 10-14 h. [b]**1n** (0.2 mmol), **2a** (11 equiv), $RhCl_3{\cdot}3H_2O$ (5 mol%), $Cu(OAc)_2$ (2 equiv), DMF (2 mL), CO (1 atm), 110 °C, 14 h. Phth=phthaloyl, TBS=*tert*-butyldimethylsilyl.

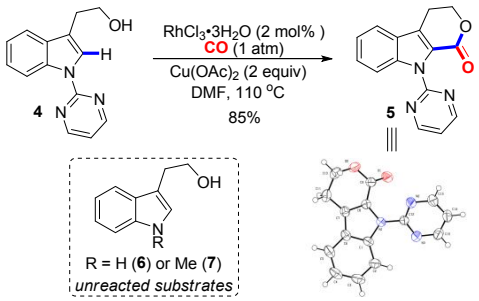
Scheme 2. Scope and Limitations of Alkoxycarbonylation of Indoles and Alcohols[a]

lowering both the catalyt loading (to 2 mol%, entry 19) and the amount of **2a** (to 5 equiv, entry 18). Further lowering the catalyst loading and reaction temperature resulted in decreased yield of **3aa** (entries 20 and 21). Control experiments indicated that no reaction was detected in the absence of CO or rhodium catalyst.[18]

Having etablished optimal reaction conditions, we next investigate the scope and limitations of the reaction. Initially, we checked the generality of the alcohol coupling partner. As shown in Scheme 2, the carbonylative functionalization occurred smoothly at the C-2 position of *N*-pyrimidine indole **1a** with a variety of alcohols, giving rise to the corresponding indole-2-carboxylates in good to excellent yields. Numerous primary alcohols bearing various functional groups were reacted. Simple aliphatic alcohols with different chain lengths were all suitable nucleophiles and these reactions gave the desired products (**3aa**-**3ag**) in high yields. Different functional groups such as aryl (**3ah**), cyclopropyl (**3ai**, with crystal structure)[19], methoxy (**3aj**), and *tert*-butyldimethylsilyl ether (**3ak**) were well-tolerated. Interestingly, the direct conversion of 1,3-propanediol (**2l**) into its corresponding monoester with a free hydroxy group (**3al**) was observed.[18,20] Benzylic (**3am**) or heterobenzylic (**3an** and **3ao**) alcohols also proved to be efficient coupling partners. Not surprisingly, although 3-(dimethylamino)propan-1-ol (**2p**) was completely unreactive, *N*-protected amino alcohol **2q** was

successfully converted to **3aq** in 75% yield. In addition, we found that alkenyl functional group (**3ar** and **3as**) was also tolerated and in particular, citronellol (**2s**) was successfully acylated to furnish **3as** in decent yield. To explore the applicability of alcohols, various secondary alcohols were then examined. Reactions of simple both linear and cyclic alcohols, such as isopropanol, cyclobutanol, cyclopentanol, and cyclohexanol, proceeded well to afford the corresponding esters in excellent yields (**3at**-**3aw**). Again, we were pleased to find that the cyclic alcohol **2x** bearing one alkenyl double bond could undergo direct carbonylation to give **3ax** (with crystal structure[19]). Gratifyingly, diphenylmethanol **2y** was found to be compatible. Importantly, some structurally complex secondary alcohols such as diosgenin and (±)-menthol reacted smoothly with **1a** to provide **3aa**' and a racemic product **3az**[18], respectively, hence indicating a proof of concept of our methodology for further late-stage functionalization. It is especially noteworthy that tertiary alcohols, such as *tert*-pentyl alcohol and *tert*-amyl alcohol, could be used as the nucleophile in this reaction (**3ab**' and **3ac**'), thus indicating the unique feature of this $RhCl_3$-based system in C–H carbonylation in contrast with previously reported results.[21]

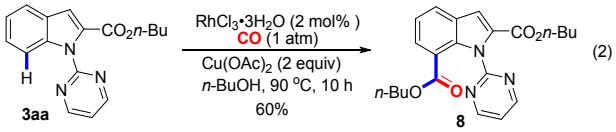
Afterward, we explored the scope of the reaction with respect to different indole derivatives. A series of indole derivatives with various substituents were subjected to the alkoxycarbonylation of *n*-BuOH and CO (Scheme 2). Generally, the use of electron-rich indoles possessing methyl (**1b**, **1g**, **1j**, **1o** and **1s**) and methoxy (**1k**) substituents at various positions delivered corresponding products (**3ba**, **3ga**, **3ja**, **3oa**, **3sa** and **3ka**) in good to excellent yields, while indoles with electron-withdrawing groups, such as fluoro, chloro, and bromo, provided the corresponding products in moderate to good yields (**3ha**, **3ia**, **3la**, **3ma**, **3pa**, **3qa**, and **3ra**). For 3-substituted indoles, the reaction was sensitive to the electronic nature of the substituents (**3ba** *vs* **3ca**). It is worth noting that substituents at the 7-position caused an interesting electronic/steric synergistic effect (**3ra** *vs* **3sa**). Interestingly, electron deficient indole **1n** with an ester group reacted well to give **3na** in good yield. More importantly, pharmaceutically useful compounds, such as tryptophol, tryptamine and tryptophan derivatives, also reacted smoothly to provide **3da**, **3ea** and **3fa** in 79-98% yields. In addition, the C–H carbonylation proceeded without racemization of the stereogenic center in **2f**.[18] Finally, reacting 1-(pyrimidin-2-yl)-1*H*-benzo[*g*] indole **1t** and **2a** under standard conditions led to **3ta** in 80% yield.



Scheme 3. Intramolecular C–H Alkoxycarbonylation

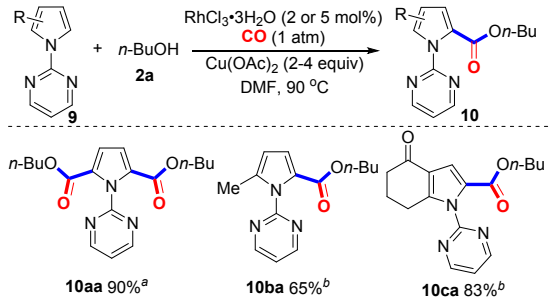
We next sought to apply this protocal to intramolecular C–H carbonylation (Scheme 3). To our delight, the reaction of **4** with CO gave the desired product **5** (with crystal structure[19]) in 72% yield under standard conditions. A high isolated yield (85%) of **5** was obtained just by increasing the temperature from 90 °C to 110 °C. Interestingly, when we exposed **6** and **7** to the standard conditions, we didn't observe any carbonylative product, thereby highlighting the directing role of pyrimidyl group in **4**.[22] The present method offers a new complementary route to synthesize indole δ-lactone motif.[23]

Of note, the C7-selective C–H carbonylation of **3aa** proceeded smoothly in the presence of $RhCl_3/Cu(OAc)_2$ in *n*-BuOH, giving rise to **8** in 60% yield, which marks the first example of rhodium-catalyzed C–H carbonylation of indole with CO at the C7-position (eq 2).[24] The structure of **8** was confirmed by single-crystal X-ray diffraction.[19]



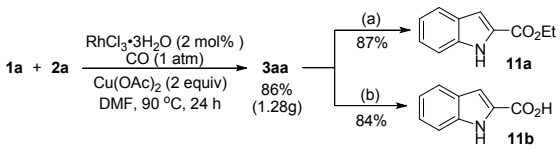
(2)

Moreover, this methodology could be used to prepare ester-functionalized pyrrole derivatives. As shown in Scheme 4, not unexpectedly, double alkoxycarbonylation product **10aa** was produced in 90% yield when 2-(1*H*-pyrrol-1-yl)pyrimidine **9a** was used as the substrate. In contrast, under the optimal reaction conditions, C2-substituted pyrrole derivatives **9b** and **9c** afforded the corresponding pyrrole-2-carboxylate products **10ba** and **10ca** in 65% and 83% yield, respectively.



[a]**9a** (0.2 mmol, 1 equiv), **2a** (20 equiv), $RhCl_3{\cdot}3H_2O$ (5 mol%), $Cu(OAc)_2$ (4 equiv), DMF (2 mL), 90 °C, 24 h. [b]**9** (0.2 mmol, 1 equiv), **2a** (5 equiv), $RhCl_3{\cdot}3H_2O$ (2 mol%), $Cu(OAc)_2$ (2 equiv), DMF (2 mL), CO (1 atm), 90 °C, 10 h.

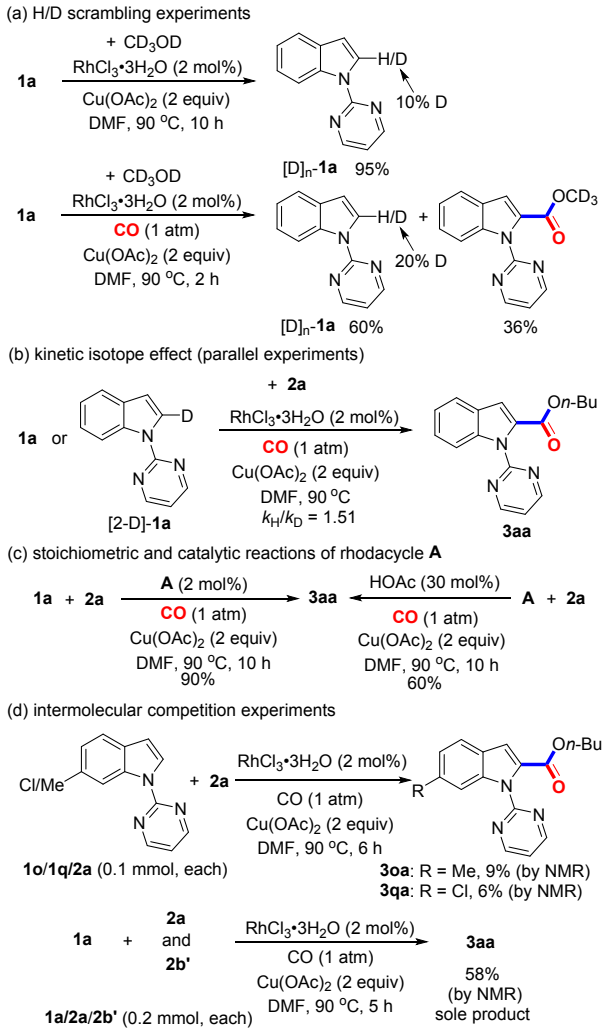
Scheme 4. Alkoxycarbonylation of Pyrroles with CO



Reaction conditions: (a) LiOEt (3 equiv, 1 M in EtOH), DMSO, 90 °C, 3 h. (b) NaOEt (3 equiv, 8% in EtOH), DMSO, 100 °C, 11 h.

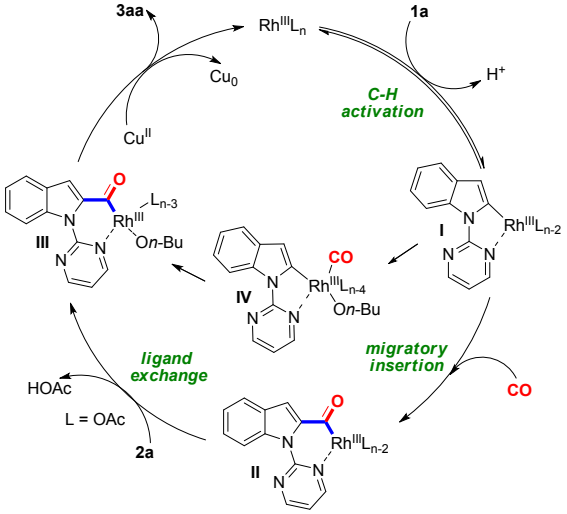
Scheme 5. Gram-scale Synthesis and Synthetic Utility

Considering the synthetic potential of this C–H alkoxycarbonylation method, the gram-scale experiment was then performed by utilizing **1a** and **2a** (10 equiv) on a 25-fold (5 mmol) scale (Scheme 5). Still, very high efficiency was observed, with an excellent yield of **3aa** obtained. Furthermore, we have tried the removal of pyrimidyl group from **3aa**, as the free N–H estered indole could bring more synthetic values. The choice of the base is crucial for the success of this reaction. After several trials,[18] we were happy to find that the pyrimidinyl group could be removed efficiently under different conditions to afford the unprotected transesterification indole **11a** or indole-2-carboxylic acid **11b** in 87% and 84% yield, respectively.



Scheme 6. Preliminary Mechanistic Studies

Several experiments were next conducted in order to gain some insights into the mechanism of this process (Scheme 6). First, deuterium labeling experiments were conducted with **1a**. H/D scrambling experiments in the absence and in the presence of CO were suggestive of a reversible C–H rhodation and highlighted an organometallic C–H activation mechanism, albeit this process is low (Scheme 6a). Second, an intermolecular kinetic isotope effect (KIE) study from two parallel kinetic experiments on **1a** or [2-D]-**1a** (94% D) with *n*-BuOH revealed a low k_H/k_D value of 1.51 (average of two runs),[18] which indicated that the C–H cleavage is not likely to be the rate-limiting step (Scheme 6b). In addition, when complex **A** was used as the catalyst, a high yield of **3aa** (90%) was obtained (Scheme 6c, left). In contrast to the stoichiometric reaction in the absence of acidic additive (eq. 1), the reaction of **A** and **2a** in the presence of HOAc gave **3aa** in 60% yield (Scheme 6c, right). These results support that a rhodacycle species might be most likely as a reaction intermediate involved in this reaction and the proton released from the C–H metalation was essential for catalytic turnover. Moreover, intermolecular competition experiments between differently substituted indoles with **2a** indicated that while a more electron-rich indole (**10**) reacts to a greater extent than an electron-deficient one (**1q**), the difference is not substantial, which is consistent with the proposal of indole C–H activation not being turnover-limiting. Reactions of **1a** with **2a** and **2b'** were suggestive of less sterically hindered alcohols are more reactive in this transformation (Scheme 6d).



Scheme 7. Possible Catalytic Cycle for $RhCl_3$-Catalyzed Alkoxycarbonylation

Given the results obtained above and previous reports,[13,21a,25] a plausible mechanistic pathway is postulated (Scheme 7). Initially, coordination of the nitrogen directing group in **1a** to Rh(III) catalyst precedes the C–H activation event, which gives five-membered rhodacycle species **I**. Next, one molecule of CO binds to the putative rhodacycle, followed by 1,1-migratory insertion of CO into the Rh–C bond to generate intermediate **II**[26]. Subsequently, alcohol **2a** coordinates to **II** via ligand exchange with a loss of one molecule of HOAc, leading to intermediate **III**. At this point, reductive elimination can occur to afford the desired product **3aa** and a rhodium(I) species, which requires an oxidation to re-enter the catalytic cycle. However, a mechanism involving coordination of CO and **2a** to rhodium via ligand exchange to form intermediate **IV** and sequential migratory insertion of CO to afford **III** could not be ruled out at this stage.

In summary, we have developed a $RhCl_3 \cdot 3H_2O$-catalyzed C–H carbonylation of indoles with alcohols and CO. The reaction generates a diverse range of indole-2-carboxylic esters. It is noteworthy that the same rhodium-based catalytic system could be applied to synthesize pyrrole-2-carboxylic esters and indole *δ*-lactone moity, and the latter was produced via intramolecular C–H alkoxycarbonylation. This process represents the first example of transition-metal-catalyzed C2-selective C–H alkoxycarbonylation of indoles with CO and the first successful example of $RhCl_3 \cdot 3H_2O$-catalyzed direct carbonylation of aromatic C–H bonds with CO.[27] We believe that this $RhCl_3 \cdot 3H_2O$-based system might show broad applicability to different types of including but not limited to C–H carbonylation reactions. Efforts towards this direction are currently underway in our laboratory.

AUTHOR INFORMATION

Corresponding Author

*E-mail: lyang@licp.cas.cn

Author Contributions

§(K.Z., R.D.) These authors contributed equally to this work.

Notes

The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website at http://pubs.acs.org.

Experiment details, spectra data, copies of ^1H and ^{13}C NMR spectra for all new compounds (PDF)
X-ray data for **3ai** (CCDC 1879313) (CIF)
X-ray data for **3ax** (CCDC 1879312) (CIF)
X-ray data for **5** (CCDC 1879311) (CIF)
X-ray data for **8** (CCDC 1879310) (CIF)

ACKNOWLEDGMENT

This work was financially supported by the National Natural Science Foundation of China (Grant Nos. 21372231, 21173241 and 21673260). L.Y. acknowledges the financial support from the Hangzhou Normal University. We thank Mr. Zhiqiang Shen, Mr. Xudong Gao and Ms. Xiaoning Wei for assistance with NMR experiments, Ms. Xiaoxue Hu for HRMS analyses, and Ms. Peiju Yang for X-ray diffraction analyses. We also thank Prof. Wei Sun and Dr. Qiangsheng Sun for their help with HPLC separation.

REFERENCES

(1) (a) Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: New York, 1970. (b) Brown, R. K. Synthesis of the Indole Nucleus. In *Indoles, Part I, Chemistry of Heterocyclic Compounds*; Houlihan, W. J., Ed.; Wiley-Interscience: New York, 1972; Vol. 25, pp 227–558. (c) Humphrey, G. R.; Kuethe, J. T. Practical Methodologies for the Synthesis of Indoles. *Chem. Rev.* **2006**, *106*, 2875–2911. (d) Bandini, M.; Eichholzer, A. Catalytic Functionalization of Indoles in a New Dimension. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608–9644. (e) Kochanowska-Karamyan, A. J.; Hamann, M. T. Marine Indole Alkaloids: Potential New Drug Leads for the Control of Depression and Anxiety. *Chem. Rev.* **2010**, *110*, 4489–4497. (f) Welsch, M. E.; Snyder, S. A.; Stockwell, B. R. Privileged Scaffolds for Library Design and Drug Discovery. *Curr. Opin. Chem. Biol.* **2010**, *14*, 347–361. (g) Bartoli, G.; Dalpozzo, R.; Nardi, M. Applications of Bartoli Indole Synthesis. *Chem. Soc. Rev.* **2014**, *43*, 4728–4750.

(2) (a) Saxton, J. E. Recent Progress in the Chemistry of Indole Alkaloids and Mould Metabolites. *Nat. Prod. Rep.* **1990**, *7*, 191–243. (b) Ishikura, M.; Abe, T.; Choshi, T.; Hibino, S. Simple Indole Alkaloids and Those with a Non-rearranged Monoterpenoid Unit. *Nat. Prod. Rep.* **2013**, *30*, 694–752. (c) Romero, D. L.; Busso, M.; Tan, C.-K.; Reusser, F.; Palmer, J. R.; Poppe, S. M.; Aristoff, P. A.; Downey, K. M.; So, A. G.; Resnick, L.; Tarpley, W. G. Nonnucleoside Reverse Transcriptase Inhibitors that Potently and Specifically Block Human Immunodeficiency Virus Type 1 Replication. *Proc. Natl. Acad. Sci. USA.* **1991**, *88*, 8806–8810. (d) Martino, G. D.; Regina, G. L.; Coluccia, A.; Edler, M. C.; Barbera, M. C.; Brancale, A.; Wilcox, E.; Hamel, E.; Artico, M.; Silvestri, R. Arylthioindoles, Potent Inhibitors of Tubulin Polymerization. *J. Med. Chem.* **2004**, *47*, 6120–6123. (e) Okano, K.; Tokuyama, H.; Fukuyama, T. Total Synthesis of (+)-Yatakemycin. *J. Am. Chem. Soc.* **2006**, *128*, 7136–7317. (f) Friberg, A.; Vigil, D.; Zhao, B.; Daniels, R. N.; Burke, J. P.; Garcia-Barrantes, P. M.; Camper, D.; Chauder, B. A.; Lee, T.; Olejniczak, E. T.; Fesik, S. W. Discovery of Potent Myeloid Cell Leukemia 1 (Mcl-1) Inhibitors Using Fragment-Based Methods and Structure-Based Design. *J. Med. Chem.* **2013**, *56*, 15–30.

(3) Gribble, G. W. *Indole ring synthesis: From natural products to drug discovery*; John Wiley & Sons: West Sussex, U.K., 2016.

(4) For recent examples, see: (a) Stokes, B. J.; Dong, H.; Leslie, B. E.; Pumphrey, A. L.; Driver, T. G. Intramolecular C–H Amination Reactions: Exploitation of the Rh_2(II)-Catalyzed Decomposition of Azidoacrylates. *J. Am. Chem. Soc.* **2007**, *129*, 7500–7501. (b) Bonnamour, J.; Bolm, C. Iron(II) Triflate as a Catalyst for the Synthesis of Indoles by Intramolecular C–H Amination. *Org. Lett.* **2011**, *13*, 2012–2014. (c) Farney, E. P.; Yoon, T. P. Visible-Light Sensitization of Vinyl Azides by Transition-Metal Photocatalysis. *Angew. Chem., Int. Ed.* **2014**, 53, 793–797.

(5) For selected examples, see: (a) Sundberg, R. J.; Yamazaki, T. Rearrangements and Ring Expansions during the Deoxygenation of *β, β*-Disubstituted *o*-Nitrostyrenes. *J. Org. Chem.* **1967**, *32*, 290–294. *(*b) Cadogan, J. I. G. A New Series of Nitrene-Induced Aromatic Rearrangements. *Acc. Chem. Res.* **1972**, *5*, 303–310. (c) Creencia, E. C.; Kosaka, M.; Muramatsu, T. Kobayashi, M.; Iizuka, T.; Horaguchi, T. Microwave-Assisted Cadogan Reaction for the Synthesis of 2-Aryl-2*H*-indazoles, 2-Aryl-1*H*-benzimidazoles, 2-Carbonylindoles, Carbazole, and Phenazine. *J. Heterocycl. Chem.* **2009**, *46*, 1309–1317.

(6) For recent reports, see: (a) Cai, Q.; Li, Z.; Wei, J.; Ha, C.; Pei, D.; Ding, K. Assembly of Indole-2-carboxylic Acid Esters through a Ligand-free Copper-catalysed Cascade Process. *Chem. Commun.* **2009**, 7581–7583. (b) Koenig, S. G.; Dankwardt, J. W.; Liu, Y.; Zhao, H.; Singh, S. P. Copper-Catalyzed Synthesis of Indoles and Related Heterocycles in Renewable Solvents. *ACS Sustainable Chem. Eng.* **2014**, 2, 1359–1363.

(7) For selected reports, see: (a) Yamazaki, K.; Nakamura, Y.; Kondo, Y. Solid-Phase Synthesis of Indolecarboxylates Using Palladium-Catalyzed Reactions. *J. Org. Chem.* **2003**, *68*, 6011–6019. (b) Ji, X.; Huang, H.; Wu, W.; Li, X.; Jiang, H. Palladium Catalyzed Oxidative Coupling of Aromatic Primary Amines and Alkenes under Molecular Oxygen: Stereoselective Assembly of *(Z)*-Enamines. *J. Org. Chem.* **2013**, *78*, 11155–11162.

(8) Sandtorv, A. H. Transition Metal-Catalyzed C–H Activation of Indoles. *Adv. Synth. Catal.* **2015**, *357*, 2403–2435.

(9) For the seminal work on intramolecular aminocarbonylation of tryptophan derivative under Pd/BQ/O_2/HOAc/NaOAc system, see: (a) Haffemayer, B.; Gulias, M.; Gaunt, M. J. Amine Directed Pd(II)-Catalyzed C–H Bond Functionalization under Ambient Conditions. *Chem. Sci.* **2011**, *2*, 312–315. A detailed study on

intramolecular aminocarbonylation of tryptophan and tryptamine derivatives under Pd/Cu/O_2 system appeared just prior to submission of this manuscript, see: (b) Han, H.; Yang, S.-D.; Xia, J.-B. Pd/Cu Cocatalyzed Oxidative Tandem C–H Amino- carbonylation and Dehydrogenation of Tryptamines: Synthesis of Carbolinones. *J. Org. Chem.* **2019**, *84*, 3357–3369.

(10) For selected reviews on direct C–H carbonylation involving CO, see: (a) Liu, Q.; Zhang, H.; Lei, A. Oxidative Carbonylation Reactions: Organometallic Compounds (R–M) or Hydrocarbons (R–H) as Nucleophiles. *Angew. Chem., Int. Ed.* **2011**, *50*, 10788–10799. (b) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. Weak Coordination as a Powerful Means for Developing Broadly Useful C–H Functionalization Reactions. *Acc. Chem. Res.* **2012**, *45*, 788–802. (c) Wu, X.-F.; Neumann, H.; Beller, M. Palladium-Catalyzed Oxidative Carbonylation Reactions. *ChemSusChem* **2013**, *6*, 229–241. (d) Wu, L.; Fang, X.; Liu, Q.; Jackstell, R.; Beller, M.; Wu, X.-F. Palladium-Catalyzed Carbonylative Transformation of C(sp^3)–X Bonds. *ACS Catal.* **2014**, *4*, 2977–2989. (e) Lang, R.; Xia, C.; Li, F. Carbonylative Diversification of Unactivated Heteroaromatic Compounds. *New J. Chem.* **2014**, *38*, 2732–2738. (f) Gadge, S. T.; Gautam, P.; Bhanage, B. M. Transition Metal-Catalyzed Carbonylative C–H Bond Functionalization of Arenes and C(sp^3)–H Bond of Alkanes. *Chem. Rec.* **2016**, *16*, 835–856. (g) Rajesh, N.; Barsu, N.; Sundararaju, B. Recent Advances in C(sp^3)–H Bond Carbonylation by First Row Transition Metals. *Tetrahedron. Lett.* **2018**, *59*, 862–868.

(11) Pospech, J.; Tlili, A.; Spannenberg, A.; Neumann, H.; Beller, M. Regioselective Ruthenium-Catalyzed Carbonylative Direct Arylation of Five-Membered and Condensed Heterocycles. *Chem. Eur. J.* **2014**, *20*, 3135–3141.

(12) Zhou, F.; Wang, D.-S.; Guan, X.; Driver, T. G. Nitroarenes as the Nitrogen Source in Intermolecular Palladium-Catalyzed Aryl C–H Bond Aminocarbonylation Reactions. *Angew. Chem., Int. Ed.* **2017**, *56*, 4530–4534.

(13) Liu, B.; Hu, F.; Shi, B.-F. Recent Advances on Ester Synthesis via Transition-Metal Catalyzed C–H Functionalization. *ACS Catal.* **2015**, *5*, 1863–1881.

(14) For examples on $RhCl_3{\cdot}3H_2O$-catalyzed C–H activation, see: (a) Witulski, B.; Schweikert, T. Synthesis of Indolo[2,3-*a*]pyrrolo [3,4-*c*]carbazoles by Oxidative Cyclization of Bisindolylmaleimides with a Rhodium(III)–Copper(II) Catalytic System. *Synthesis* **2005**, 1959–1966. (b) Wang, P.; Rao, H.; Hua, R.; Li, C.-J. Rhodium-Catalyzed Xanthone Formation from 2-Aryloxybenzaldehydes via Cross-Dehydrogenative Coupling (CDC). *Org. Lett.* **2012**, *14*, 902–905. (c) Ran, Y.; Yang, Y.; You, H.; You, J. $RhCl_3$-Catalyzed Oxidative C−H/C−H Cross-Coupling of (Hetero)aromatic Sulfonamides with (Hetero)arenes. *ACS Catal.* **2018**, *8*, 1796–1801. (d) Shi, Y.; Zhang, L.; Lan, J.; Zhang, M.; Zhou, F.; Wei, W.; You, J. Oxidative C–H/C–H Cross-Coupling Reactions between *N*-Acylanilines and Benzamides Enabled by a Cp*-Free $RhCl_3$/TFA Catalytic System. *Angew. Chem., Int. Ed.* **2018**, *57*, 9108–9012. (e) She, Z.; Wang, Y.; Wang, D.; Zhao, Y.; Wang, T.; Zheng, X.; Yu, Z.-X.; Gao, G.; You, J. Two-Fold C–H/C–H Cross-Coupling Using $RhCl_3{\cdot}3H_2O$ as the Catalyst: Direct Fusion of *N*-(Hetero)arylimidazolium Salts and (Hetero)arenes. *J. Am. Chem. Soc.* **2018**, *140*, 12566–12573.

(15) For selected reviews on Rh(III)-catalyzed C–H activation, see: (a) Satoh, T.; Miura, M. Oxidative Coupling of Aromatic Substrates with Alkynes and Alkenes under Rhodium Catalysis. *Chem. Eur. J.* **2010**, *16*, 11212–11222. (b) Song, G.; Wang, F.; Li, X. C–C, C–O and C–N Bond Formation via Rhodium(III)-Catalyzed Oxidative C–H Activation. *Chem. Soc. Rev.* **2012**, *41*, 3651–3678. (c) Kuhl, N.; Schröder, N.; Glorius, F. Formal S_N-Type Reactions in Rhodium(III)-Catalyzed C–H Bond Activation. *Adv. Synth. Catal.* **2014**, *356*, 1443–1460. (d) Hummel, J. R.; Boerth, J. A.; Ellman, J. A. Transition-Metal-Catalyzed C–H Bond Addition to Carbonyls, Imines, and Related Polarized π Bonds. *Chem. Rev.* **2017**, *117*, 9163–9227. (e) Park, Y.; Kim, Y.; Chang, S. Transition Metal-Catalyzed C–H Amination: Scope, Mechanism, and Applications. *Chem. Rev.* **2017**, *117*, 9247–9301. (f) Piou, T.; Rovis, T. Electronic and Steric Tuning of a Prototypical Piano Stool Complex: Rh(III) Catalysis for C–H Functionalization. *Acc. Chem. Res.* **2018**, *51*, 170–180. (g) Rej, S.; Chatani, N. Rh-Catalyzed Removable Directing Group Assisted sp^2 or sp^3-C–H Bond Functionalization. *Angew. Chem., Int. Ed.* in press.

(16) Yang, L.; Zhang, G.; Huang, H. An Efficient Rhodium/ Oxygen Catalytic System for Oxidative Heck Reaction of Indoles and Alkenes via C–H Functionalization. *Adv. Synth. Catal.* **2014**, *356*, 1509–1515.

(17) Qin, X.; Liu, H.; Qin, D.; Wu, Q.; You, J.; Zhao, D.; Guo, Q.; Huang, X.; Lan, J. Chelation-assisted Rh(III)-Catalyzed C2-Selective Oxidative C–H/C–H Cross-coupling of Indoles/Pyrroles with Heteroarenes. *Chem. Sci.* **2013**, *4*, 1964–1969.

(18) See the Supporting Information for details.

(19) Crystallographic data for the compounds (CCDC 1879313 for **3ai**, 1879312 for **3ax**, 1879311 for **5**, and 1879310 for **8**) in this paper have been deposited with the Cambridge Crystallographic Data Centre as Supporting Information. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

(20) When **2l** and an excess of **1a** (5 equiv) were subjected to the reaction, a mixture of **3al** (47%) and a diester product (20%) via two-fold alkoxycarbonylation was observed.

(21) (a) Guan, Z.-H.; Ren, Z.-H.; Spinella, S. M.; Yu, S.; Liang, Y.-M.; Zhang, X. Rhodium-Catalyzed Direct Oxidative Carbonylation of Aromatic C–H Bond with CO and Alcohols. *J. Am. Chem. Soc.* **2009**, *131,* 729–733. (b) Chen, M.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. Palladium-Catalyzed Oxidative Carbonylation of Aromatic C–H Bonds of *N*-Alkylanilines with CO and Alcohols for the Synthesis of *o*-Aminobenzoates. *J. Org. Chem.* **2015**, *80*, 1258–1263. (c) Li, W.; Duan, Z.; Jiang, R.; Lei, A. Palladium/ Copper-Catalyzed Aerobic Oxidative C–H Carbonylation for the Synthesis of *o*-Aminobenzoates. *Org. Lett.* **2015**, *17*, 1397–1400.

(22) For an example of Pd(II)-catalyzed hydroxyl-directed C–H carbonylation, see: Lu, Y.; Leow, D.; Wang, X.; Engle, K. M.; Yu, J.-Q. Hydroxyl-directed C–H Carbonylation Enabled by Mono-*N*-protected Amino Acid ligands: An Expedient Route to 1-Isochromanones. *Chem. Sci.* **2011**, *2*, 967–2971.

(23) (a) Lehmann, J.; Ghoneim, K. M.; EI-Fattah, B. A.; El-Gendy, A. A. Lactones, Part 11. Syntheses of 4,9-Dihydropyrano[3,4-*b*]indol-1(3*H*)-ones from α-Ethoxalyl-γ-lactones. *Arch. Pharm.* **1987**, *320*, 22–29. (b) Lehmann, J.; Pohl, U. Lactones, Part 16. Syntheses of 4,9-Dihydropyranol[3,4-*b*]lindol-l(3*H*)-ones from *a*-Ethoxalyl-δ-valerolactones. *Arch. Pharm.* **1987**, *320*, 1202–1209. (c) Lehmann, J.; Heineke, D. Indole, Part 12. β-Carboline from Lactones–Synthesis of Ligands of the Norharmane Receptor. *Arch. Pharm.* **1994**, *327*, 715–720.

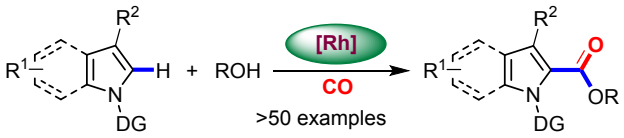
(24) For reports on C7-selective C–H activation of indoles, see: (a) Robbins, D. W.; Boebel, T. A.; Hartwig, J. F. Iridium-Catalyzed, Silyl-Directed Borylation of Nitrogen-Containing Heterocycles. *J. Am. Chem. Soc.* **2010**, *132*, 4068–4069. (b) Xu, L.; Zhang, C.; He, Y.; Tan, L.; Ma, D. Rhodium-Catalyzed Regioselective C7-Functionalization of *N*-Pivaloylindoles. *Angew. Chem., Int. Ed.* **2016**, *55*, 321–325. (c) Yang, Y.; Qiu, X.; Zhao, Y.; Mu, Y.; Shi, Z. Palladium-Catalyzed C–H Arylation of Indoles at the C7 Position. *J. Am. Chem. Soc.* **2016**, *138*, 495–498. (d) Borah, A. J.; Shi, Z. Rhodium-Catalyzed, Remote Terminal Hydroarylation of Activated Olefins through a Long-Range Deconjugative Isomerization. *J. Am. Chem. Soc.* **2018**, *140*, 6062–6066.

(25) (a) Du, Y.; Hyster, T. K.; Rovis, T. Rhodium(III)-Catalyzed Oxidative Carbonylation of Benzamides with Carbon Monoxide. *Chem. Commun*. **2011**, *47*, 12074–12076. (b) Lang, R.; Wu, J.; Shi, L.; Xia, C.; Li, F. Regioselective Rh-Catalyzed Direct Carbonylation of Indoles to Synthesize Indole-3-carboxylates.

Chem. Commun. **2011**, *47*, 12553–12555. (c) Iturmendi, A.; Sanz Miguel, P. J.; Popoola, S. A.; Al-Saadi, A. A.; Iglesias, M.; Oro, L. A. Dimethylphosphinate Bridged Binuclear Rh(I) Catalysts for the Alkoxycarbonylation of Aromatic C–H Bonds. *Dalton Trans*. **2016**, *45*, 16955–16965.

(26) Although we could not isolate the proposed rhodacycle species (**II**) at current stage, ESI-MS studies showed that rhodacycle (**II**) might be involved in the catalytic cycle. For more details, see the Supporting Information.

(27) For an elegant work on $RhCl_3$-catalyzed carbonylation of methane to acetic acid, see: Lin, M.; Sen, A. Direct Catalytic Conversion of Methane to Acetic Acid in an Aqueous Medium *Nature* **1994**, *368*, 613–615.



- 1 atm of CO
- external acid- and base-free conditions
- $RhCl_3$ instead of [Cp*Rh] complex

up to 98% yield