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$RhCl_3·3H_2O$-Catalyzed C7-Selective C−H Carbonylation of Indolines with CO and Alcohols

Rongrong Du,[†,‡] Kang Zhao,[†] Jianhua Liu,[*,†] Feng Han,[§] Chungu Xia,[†] and Lei Yang[*,†,‡,∥]

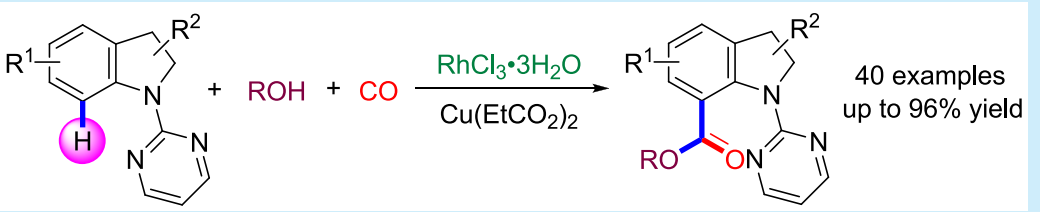
[†]State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, University of Chinese Academy of Sciences, Chinese Academy of Sciences, Lanzhou 730000, China

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

[§]College of Chemistry and Material Science, Shandong Agricultural University, Taian 271018, China

[∥]Engineering Research Center of High Performance Polymer and Molding Technology, Ministry of Education, College of Chemistry and Molecular Engineering, Qindao University of Science and Technology, Qingdao 266042, China

Supporting Information



ABSTRACT: An attractive method for the synthesis of indoline-7-carboxylates through $RhCl_3$-catalyzed C−H carbonylation of indolines with CO and alcohols was developed. The copper-based oxidant and removable pyrimidyl directing group played important roles in achieving high-level yields of the title products. Based on control experiments, a possible catalytic cycle was proposed.

Recently, transition-metal-catalyzed chelation-assisted site-selective C−H carbonylation with carbon monoxide (CO) has appeared as one of the most straightforward tools for the formation of carbonyl compounds due to its excellent regioselectivity and reactivity.[1] Within this reaction class, spectacular advances have been achieved mainly using palladium catalysts. In contrast, although the utilization of rhodium catalysts could offer unique synthetic methods to achieve structural diversity and molecular versatility of C−H carbonylation reactions, which are inaccessible under palladium catalysis,[2] rhodium-catalyzed chelation-assisted site-selective C−H carbonylation with CO has been less developed.[3]

Furthermore, to access high catalytic turnover, an olefin-coordinated Rh^{I} or Rh^{III} complex, which is generally prepared from the coordination reaction of $RhCl_3·3H_2O$ with an olefin, was usually required in this type of rhodium-catalyzed chelation-assisted C−H carbonylation with CO. Thus, development of efficient synthetic methodologies via simple $RhCl_3·3H_2O$-catalyzed C−H carbonylation with CO is highly appealing.[4]

C7-substituted indoline scaffolds are ubiquitous structural motifs found in many natural products and pharmaceutically important compounds.[5] In particular, C7-carboxylated indolines or their derivatives usually display particular biological activities (Figure 1).[6] For this reason, development of effective methods for the access of C7-carboxylated indolines and derivatives thereof has been disclosed, and a host of reactions have been reported.[7,8] Conventional procedures for preparing C7-carboxylated indolines and their derivatives mainly involve commonly used organometallic reagents by direct functionalization of indoline cores[7a] or cyclization reactions to form the indoline cycles.[7b−d] In recent years, transition-metal-catalyzed site-selective C−H carbonylation with CO and different nucleophiles has emerged as an attractive method enabling the straightforward synthesis of C7-carbonylated indolines or their derivatives (Scheme 1).[8] In 2012, a study on Ru^0-catalyzd direct C7 carbonylation of *N*-pyridylindolines with CO and olefins appeared for accessing C7-aliphatic acyl-derived compounds (Scheme 1a).[8a] However, high reaction temperature was required, and the substrate scope was narrow with respect to

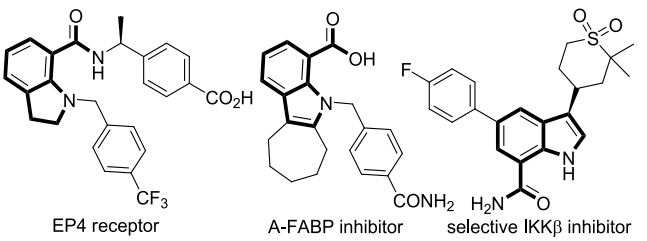


Figure 1. Selected bioactive molecules based on indoline-7-carboxylic acid and their derivatives.

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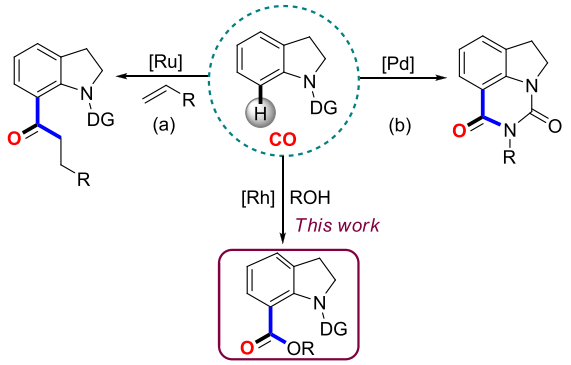
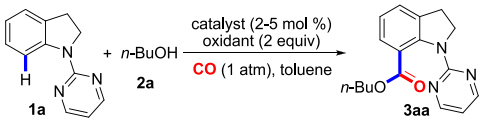
Scheme 1. Transition-Metal-Catalyzed C7-Selective C−H Carbonylation of Indolines with CO



both olefins and indolines. Recently, an expedient synthesis of pyrroloquinazolinediones was achieved via Pd^{II}-catalyzed intermolecular C7-selective C−H carbonylation of indolines with CO in AcOH (Scheme 1b).[8b] Despite these advances, access to C7-carbonylated indolines of structural diversity via this strategy is still limited; in particular, there is no catalytic method for the synthesis of indoline-7-carboxylic esters despite the synthetic attractiveness of esters. Inspired by the well-developed transition-metal-catalyzed direct C7 C−H functionalization of indolines[8,9a] and as part of our continuing interests in simple rhodium-catalyzed C−H activation,[10b] herein, we successfully demonstrate the first $RhCl_3·3H_2O$-catalyzed chelation-assisted C7-selective C−H carbonylation of indolines with CO and alcohols.

To test the feasibility of C7-selective carbonylation, we started our investigations by exploring the use of a rhodium catalyst in the presence of an oxidant. Initially, the pyrimidine group directed indoline **1a** and *n*-BuOH **2a** were used as model substrates for the carbonylation. Gratifyingly, a promising yield of 34% was observed when common $[Cp^*RhCl_2]_2$ was employed as the Rh catalyst, and $Cu(OAc)_2$ served as the oxidant in toluene (Table 1, entry 1). Encouraged by this initial result, we evaluated the effect of other common rhodium catalysts (Table 1, entries 2−6). Interestingly, it turned out that $RhCl_3·3H_2O$ is the best choice in our case, affording **3aa** in 56% yield (Table 1, entry 3). Comparable yields were also obtained for $RhCl_3$ and $[Rh(cod)Cl]_2$, whereas $[Rh(OAc)_2]_2$ was completely inert for this transformation. In contrast, a set of widely used Pd, Ru, and Ir catalysts was also examined.[11] However, the reaction did not occur in most cases, or only a trace amount of product was detected, thus showing the unique features of rhodium catalysts in the current transformation. In addition, after an extensive screening of solvents, it was found that performing the reactions in aromatic solvents led to the improved yield of **3aa**, in which toluene is the best choice. Notably, among the oxidants tested, only copper-based oxidants were workable and $Cu(EtCO_2)_2$ gave the best result (Table 1, entries 7−16). Interestingly, alkoxycarbonylation could occur in the presence of catalytic amounts of $Cu(EtCO_2)_2$ under mixed CO/O_2 gas (Table 1, entry 16). Finally, further refinement of the reaction parameters was conducted using $Cu(EtCO_2)_2$, including reaction temperature, catalyst loading, and reaction time. These studies allowed an 85% isolated yield of **3aa** to be achieved when using 5 mol % of $RhCl_3·3H_2O$ in combination with 2 equiv of $Cu(EtCO_2)_2$, in toluene at 110 °C after 24 h (Table 1, entry 23). The structure of the desired product **3aa** was confirmed unambiguously by single-crystal X-ray diffraction analysis.

Table 1. Reaction Development[a]



entry	catalyst	oxidant	temp (°C)	yield (%)[b]
1	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2$	120	34
2	$[Cp^*Rh(OAc)_2(H_2O)]_2$	$Cu(OAc)_2$	120	49
3	$RhCl_3·3H_2O$	$Cu(OAc)_2$	120	56
4	$RhCl_3$	$Cu(OAc)_2$	120	54
5	$[Rh(OAc)_2]_2$	$Cu(OAc)_2$	120	trace
6	$[Rh(cod)Cl]_2$	$Cu(OAc)_2$	120	54
7	$RhCl_3·3H_2O$	AgOAc	120	0
8	$RhCl_3·3H_2O$	$AgSbF_6$	120	0
9	$RhCl_3·3H_2O$	$K_2S_2O_8$	120	0
10	$RhCl_3·3H_2O$	$PhI(OAc)_2$	120	0
11	$RhCl_3·3H_2O$	$Cu(EtCO_2)_2$	120	76
12	$RhCl_3·3H_2O$	$Cu(i\text{-}PrCO_2)_2$	120	57
13	$RhCl_3·3H_2O$	$Cu(n\text{-}PrCO_2)_2$	120	63
14	$RhCl_3·3H_2O$	$Cu(OPiv)_2$	120	32
15	$RhCl_3·3H_2O$	$Cu(1\text{-}AdCO_2)_2$	120	0
16[c]	$RhCl_3·3H_2O$	$Cu(EtCO_2)_2$/O_2	120	30
17	$RhCl_3·3H_2O$	$Cu(EtCO_2)_2$	130	62
18	$RhCl_3·3H_2O$	$Cu(EtCO_2)_2$	140	30
19	$RhCl_3·3H_2O$	$Cu(EtCO_2)_2$	110	77
20	$RhCl_3·3H_2O$	$Cu(EtCO_2)_2$	100	70
21	$RhCl_3·3H_2O$	$Cu(EtCO_2)_2$	80	62
22[d]	$RhCl_3·3H_2O$	$Cu(EtCO_2)_2$	110	83
23[d,e]	$RhCl_3·3H_2O$	$Cu(EtCO_2)_2$	110	86(85)[f]

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (1 mmol), catalyst (2 mol %), oxidant (2 equiv), toluene (2.0 mL), CO (1 atm), 12 h. [b]Yield determined by ^1H NMR using 1,3,5-trimethoxybenzene as internal standard. [c]CO/O_2 = 1:1 (1 atm). [d]$RhCl_3·3H_2O$ (5 mol %). [e]24 h. [f]Isolated yield.

With the optimized reaction conditions in hand, we then began scoping studies with respect to the alcohol coupling partner (Scheme 2). We were pleased to find that the simple linear alkyl alcohols including low-carbon aliphatic alcohols, such as methanol and ethanol, were all suitable for this transformation (**3aa**−**3ag**). Notably, the reaction could be performed on a gram scale. Treatment of 5 mmol of **1a** and 25 mmol **2a** under standard reaction conditions furnished 1.33 g of **3aa** (90% yield). Introduction of functionalities such as alkoxy, cyclopropyl, aryl, alkenyl, phthalamidyl, and methoxy into the scaffolds of aliphatic alcohols did not greatly influence the transformation in most cases (**3ah**−**3an**), hence demonstrating the high compatibility of the catalytic system. Moreover, benzylic alcohols also proved to be ideal alcohol coupling partners under the standard reaction conditions (**3ao** and **3ap**). When secondary alcohols were used, desired products were smoothly delivered as well in good to excellent yields (**3aq**−**3at**). Unfortunately, only moderate yields of the desired products (**3au** and **3av**) were obtained when tertiary alcohols such as *tert*-pentyl alcohol and *tert*-amyl alcohol were employed as the coupling partner, even prolonging the reaction time and increasing the concentration of the catalyst, probably due to steric hindrance of the alcohol coupling partner.

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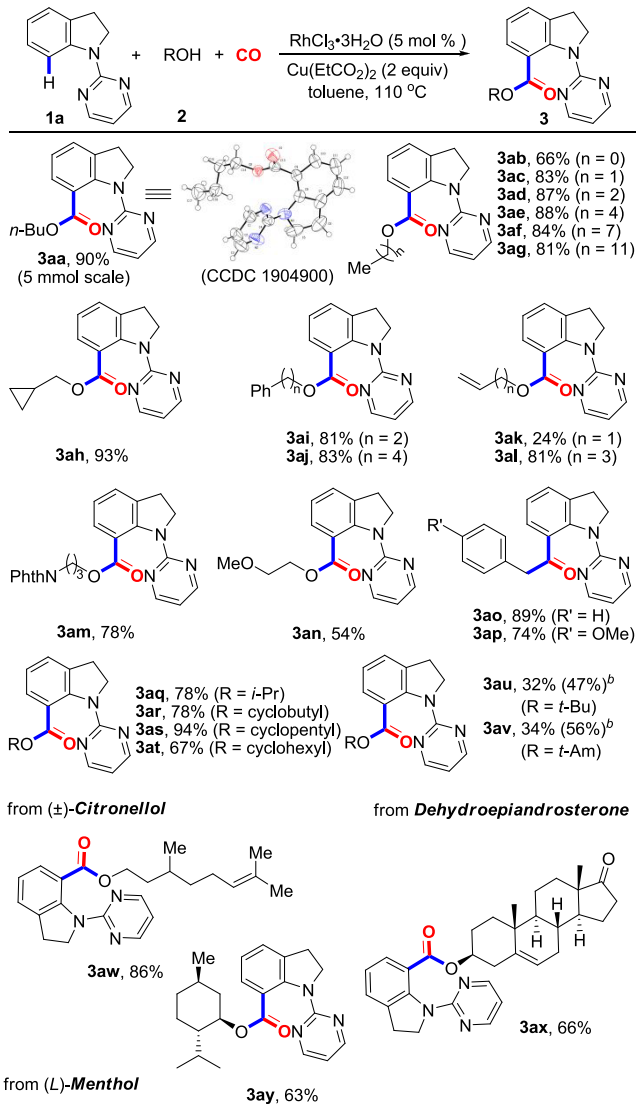
Scheme 2. Scope of Alcohols[a]

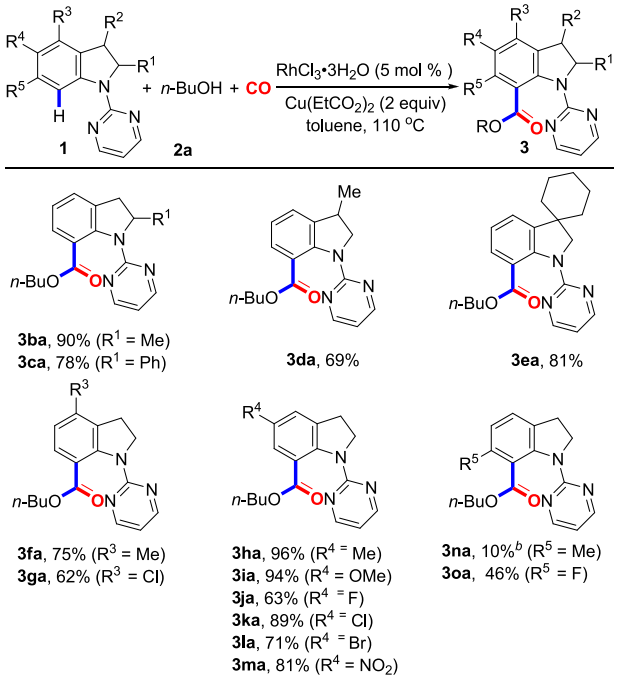


[a]Reaction conditions: **1a** (0.2 mmol), **2** (1 mmol), $RhCl_3·3H_2O$ (5 mol %), $Cu(EtCO_2)_2$ (2 equiv), toluene (2.0 mL) CO (1 atm), 110 °C, 24 h. [b]**1a** (0.2 mmol), **2u** or **2v** (1 mmol), $RhCl_3·3H_2O$ (5 mol %), $Cu(EtCO_2)_2$ (2 equiv), toluene (1.0 mL) CO (1 atm), 110 °C, 48 h. Isolated yields of **3** are given.

We next applied the developed reaction protocol to naturally occurring or bioactive alcohols. For instance, citronellol was successfully acylated to deliver **3aw** in 86% yield under the optimal conditions. In addition, secondary alcohols, such as dehydroepiandrosterone and L-menthol, could also be used to afford the corresponding products **3ax** and **3ay**[12] in 66 and 63% yield, respectively.

Subsequently, to further expand the scope of our protocol, we applied the present catalytic system to a variety of N-substituted indolines. As shown in Scheme 3, a variety of *N*-pyrimidylindolines and alcohol **2a** were efficiently transformed into the desired indoline-7-ester derivatives **3** with good yields and excellent positional control. Notably, other carbonyl or carbamoyl directing groups were found to be ineffective in the C7 carbonylation of indolines.[11] The carbonylation reactions of C2- or C3-substituted indolines **1b**−**1e** provided the desired C7-carbonylated products **3ba**−**3ea** in good yields ranging from 69

Scheme 3. Scope of Indolines[a]



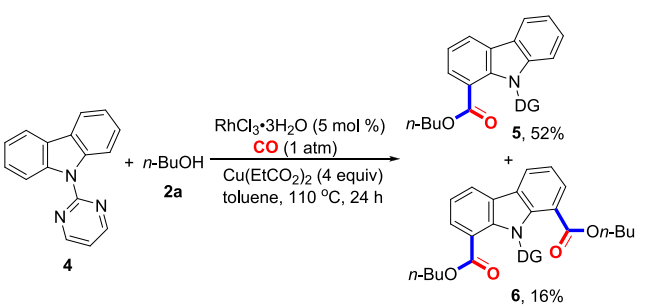
[a]Reaction conditions: **1** (0.2 mmol), **2a** (1 mmol), $RhCl_3·3H_2O$ (5 mol %), $Cu(EtCO_2)_2$ (2 equiv), toluene (2.0 mL), CO (1 atm), 110 °C, 24 h. Isolated yields of **3** are given. [b]**1n** (0.4 mmol), **2a** (2 mmol), $RhCl_3·3H_2O$ (5 mol %), $Cu(EtCO_2)_2$ (2 equiv), toluene (2.0 mL), CO (1 atm), 110 °C, 36 h. Isolated yield of **3na** is given.

to 90%. Indolines bearing an electron-donating group (methyl or methoxyl group) on the benzene ring showed better reactivity compared to those bearing an electron-withdrawing group, such as fluoro, chloro, bromo, and nitro, at the same position (**3fa** vs **3ga**, **3ha** and **3ia** vs **3ja**−**3ma**). However, the carbonylation of C6-substituted indolines **1n** and **1o** was found to be relatively less efficient, suggesting that this method was sensitive to steric factors.

The present $RhCl_3·3H_2O$-based catalytic system was not limited to C−H functionalization of indolines. For example, the C−H carbonylation of carbazole **4** with CO and *n*-BuOH catalyzed by $RhCl_3·3H_2O$ in the presence of $Cu(EtCO_2)_2$ gave a ∼3:1 mixture of mono- and double alkoxycarbonylation products (Scheme 4).

Apart from the gram-scale reaction, the synthetic utility of this $RhCl_3·3H_2O$-catalyzed C−H carbonylation strategy was further illustrated by facile diversification of **3ac** to prepare indole-7-carboxylic acid derivatives (Scheme 5). For instance, indole-7-

Scheme 4. C−H Carbonylation of Carbazole



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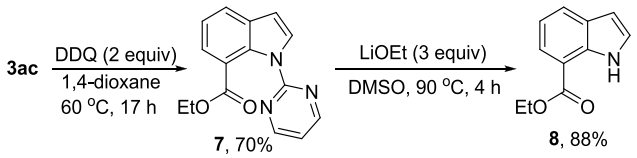
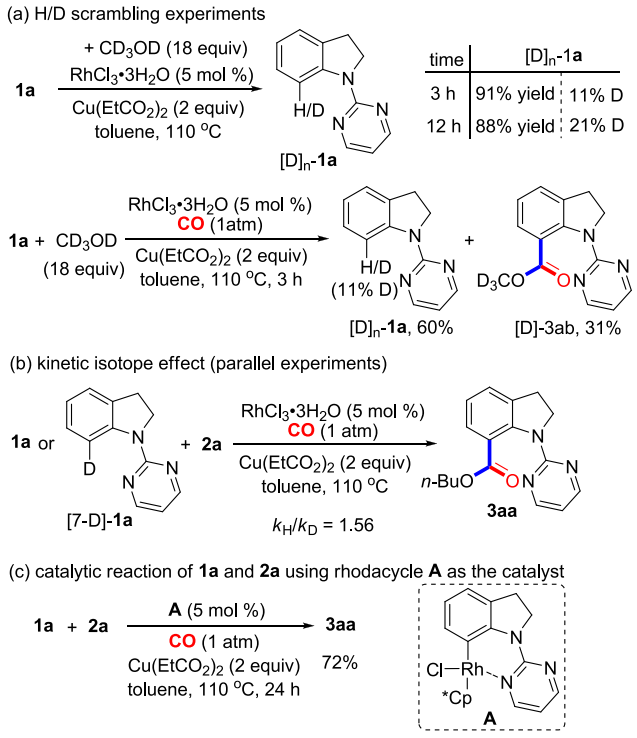
Scheme 5. Synthetic Derivatization of Indoline-7-carboxylates



ester **8** could be obtained via an oxidation/removal of the pyrimidyl group sequence.[13] Thus, this methodology would be of interest for facile synthesis of those bioactive inhibitors from readily available starting materials.[6]

To perceive the reaction mechanism, the following reactions were conducted as described in Scheme 6. First, H/D

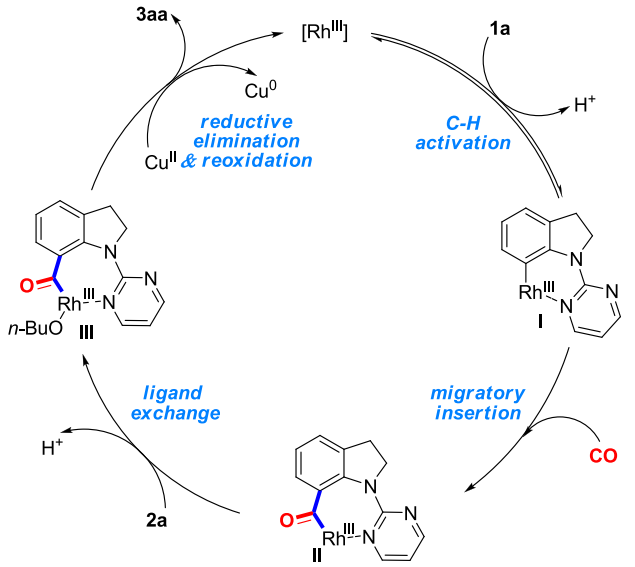
Scheme 6. Mechanistic Experiments



scrambling experiments using CD_3OD as the alcohol coupling partner in the presence and in the absence of CO were suggestive of a reversible C−H rhodation. Moreover, an intermolecular kinetic isotope effect study from two parallel kinetic experiments on **1a** or [7-D]-**1a** (93% D) with **2a** revealed a low k_H/k_D value of 1.56.[11] These results indicated that the C−H cleavage is not likely to be the rate-limiting step. In addition, a catalytic reaction of **1a** and **2a** using cyclometalated Rh(III) complex **A**[10b] as the catalyst was conducted. As a result, desired product **3aa** was obtained in 72% yield, together with the H/D scrambling experiments, indicating the plausible intermediacy of an active six-membered rhodacycle species in this transformation.

Based on our mechanistic studies and literature precedent,[3,10b,14] we have proposed a tentative catalytic cycle for this carbonylation process. As depicted in Scheme 7, the chelation-assisted reversible C−H cleavage produces a cyclometalated Rh(III) intermediate **I**. Coordination and insertion of one molecule of CO to the C−Rh bond of the putative

Scheme 7. Plausible Reaction Mechanism



rhodacycle **I** forms a seven-membered species **II**,[15] which undergoes ligand exchange to generate the rhodacycle **III**. Subsequent reductive elimination of rhodacycle **III** affords carbonylation product **3aa** and Rh(I), which is oxidized to Rh(III) by Cu(II) to regenerate the catalyst and complete the catalytic cycle.

In summary, we have developed an efficient rhodium(III)-catalyzed C7-selective oxidative C−H carbonylation of indolines with alcohols to afford indoline-7-carboxylic acid esters under 1 atm of CO using simple inorganic salt $RhCl_3{\cdot}3H_2O$ as the catalyst. The protocol features good functional group tolerance, broad substrate scope, and efficient scale-up. The present results demonstrate a new route for the synthesis of indoline- and indole-7-carboxylic acid esters and their derivatives. Further detailed studies to understand the reaction mechanism and potential application of this transformation are ongoing in our lab.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02321.

Experimental details and spectral data for all new compounds (PDF)

Accession Codes

CCDC 1904900 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

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

*E-mail: lyang@hznu.edu.cn or lyang@licp.cas.cn.

ORCID

Feng Han: 0000-0003-0707-8575

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Lei Yang: 0000-0001-9172-0879

Notes

The authors declare no competing financial interest.

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