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Synthesis of *N*-Fused Polycyclic Indole Derivatives via Ru(II)-Catalyzed C−H Bond Activation and Intramolecular Hydroarylation

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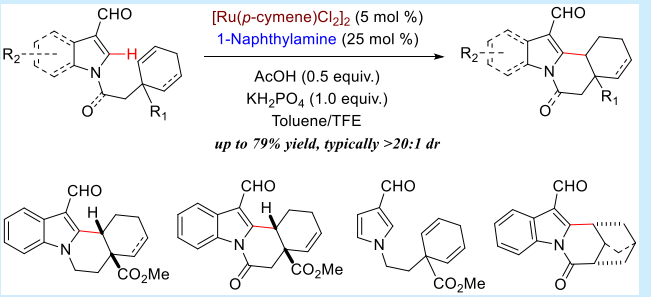
ABSTRACT: A new synthesis of *N*-fused tetracyclic indole derivatives and their related polycyclic analogues has been developed based on ruthenium(II)-catalyzed C−H activation and intramolecular hydroarylation. A series of polycyclic indoles with a 3-formyl group have been prepared in good to high yields. Various aliphatic and aromatic amines have been studied to form a transient directing group with the aldehyde for the catalytic process. A significant impact of the structures of the aromatic amines was identified, and 1-naphthylamine was shown to enable the catalytic process. DFT computations were performed to gain further insight into the role of the transient directing groups.



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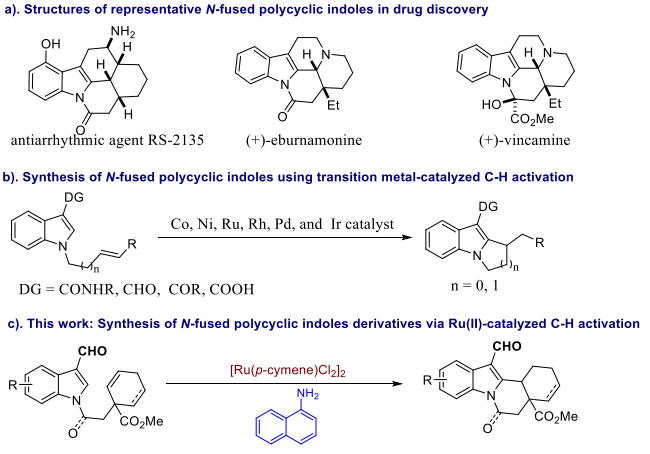
Polycyclic indole derivatives are essential scaffolds in many drug molecules and natural products.[1] Among different types of core structures, *N*-fused polycyclic indoles represent a major class that has been attractive, especially in drug discovery (Scheme 1a).[2] Consequently, the development of efficient and selective reactions that construct these fused cyclic systems has attracted more attention in recent years. Syntheses of *N*-fused tetracyclic indole derivatives have so far been achieved by the development of a variety of methods. For instance, Diels−Alder reactions have been known as a general way to access *N*-fused tetracyclic scaffolds.[2a,3] Photocatalytic intramolecular coupling reactions[4] and radical-based cascade approaches[5] have also been well developed to synthesize polycyclic indole derivatives. Transition metal-catalyzed cyclization,[6] intramolecular annulation/amination,[7] oxidative coupling,[8] and C−H functionalization[9] are recently developed strategies to synthesize *N*-fused polycyclic indoles. During the past few decades, transition metal-catalyzed C−H functionalization has been explored as an increasingly major effective tool for building organic molecules with synthetic efficiency.[10] The catalytic activation of the C−H bonds in indole rings, together with intramolecular annulation reactions with π-bonded systems, has provided a general synthetic route for accessing *N*-fused polycyclic indole derivatives.[7d,8a,9,11] Pioneering works of Bergman and Ellman have provided a new synthetic approach to the synthesis of *N*-fused polycyclic indoles by incorporating rhodium catalyst and phosphoramidite ligands via imine-directed C−H functionalization.[11d,e,12] Later, major developments were carried out by various groups. For instance, the Yoshikai group developed a cobalt-*N*-heterocyclic carbene-catalyzed intramolecular hydroarylation reaction with aldimine as a directing group to synthesize polycyclic indole derivatives.[9b] The Takano group reported an iridium-catalyzed intramolecular alkylation using an aroyl-directing group,[11b] while the Lopez group reported a carboxamide-assisted olefinic C−H bond activation by iridium-catalysis.[13] Recently, the Liu

Scheme 1. Catalytic C−H Functionalization for the Synthesis of *N*-Fused Polycyclic Indole Derivatives



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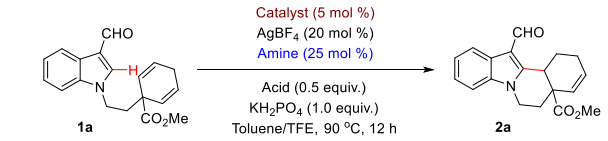
group disclosed a ruthenium-catalyzed decarboxylative and oxidative coupling reaction for the synthesis of tetrahydropyridoindoles.[11a] Moreover, nickel-catalyzed directing-group-free C−H hydroarylation was reported by Cramer and co-workers for the synthesis of tetrahydropyridoindoles and tetrahydroindolizines (Scheme 1b).[14]

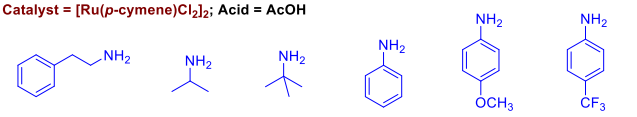
Among practical catalysts, $[Ru(p\text{-cymene})Cl_2]_2$ has been proven to be a readily available and relatively inexpensive catalyst that effectively catalyzes C−H activation and intramolecular hydroarylation reactions of alkenes.[15] While different directing groups have been utilized for these reactions, aldehydes represent one of the most readily transformable groups and thus feature high synthetic practicality. A suitable amine, either aromatic or aliphatic, is used to transiently form an imine as a more effective directing group in the catalytic system.[16] Without prior installation or removal of the directing group and the ability to be used at a catalytic amount, the transient directing group (TDG) strategy significantly increased the cost and step economy for the C−H activation process. Herein, we report the development of $[Ru(p\text{-cymene})Cl_2]_2$-catalyzed C−H activation of indole-3-carbaldehydes and its subsequent intramolecular hydroarylation to cyclic alkenes (Scheme 1c). The catalytic reaction is effectively promoted by the use of a catalytic amount of 1-naphthylamine. The process produces a class of *N*-fused tetracyclic indole derivatives and their polycyclic analogues.

The initial experimental attempts began with the synthesis of 3-formylindole derivative **1a** as a model substrate from readily available starting materials (see SI). Commercially available $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol %) was used as the catalyst and phenethylamine (**A1**) was explored as the first cocatalyst in an amount of 25 mol %. Meanwhile, $AgBF_4$, acetic acid, and KH_2PO_4 were used as additives with a mixture of toluene and 2,2,2-trifluoroethanol (TFE) in a 1:1 ratio as the solvent. This initial system resulted in no desired product observed in the reaction mixture (Table 1, entry 1). Beyond this linear amine, more α-branched amines (**A2** and **A3**) were used, however, without positive results (entries 2 and 3). Alternatively, aniline and its derivatives (**A4**−**A6**) with electron-donating and -withdrawing groups were tested to be ineffective in producing the desired product (entries 4−6), and significant amounts of starting material were recovered from all reactions. Increased steric activity on the aniline (**A7**−**A9**) did not give rise to the production of the desired polycyclic **2a** at first. Interestingly, **2a** was identified in 43% yield when 2-aminobiphenyl (**A10**) was used under the same other conditions (entry 10). This observation encouraged us to examine other aniline derivatives that have relatively larger substituents in their ortho-position. Subsequent studies showed that 1-naphthylamine (**A11**) promoted the reaction in a significantly higher yield of **2a** (entry 11), while 2,6-dimethylaniline (**A12**) resulted in almost no reaction, presumably due to excessive steric hindrance (entry 12). With **A11** as the optimal amine, the effects of several organic acids were screened and did not lead to any further improvement (entries 13 and 14). Additionally, less hindered $[Ru(benzene)Cl_2]_2$ was found to decrease the reaction yield (entry 15), and the phosphine-ruthenium complex $RuCl_2(PPh_3)_3$ was shown to be inactive for this catalytic process (entry 16). Moreover, Ru species with counterions other than halides were tested (entries 17 and 18), and $[Ru(OAc)_2(p\text{-cymene})]$ was able to produce 69% of product **2a**. Between the two most effective ruthenium catalysts, $[Ru(p\text{-cymene})Cl_2]_2$ was chosen as the catalyst for this system due to its commercial availability. We assessed the significance of KH_2PO_4 through a series of catalytic experiments (entries 19−21). In the absence of KH_2PO_4, 19% product **2a** was obtained. Substituting KH_2PO_4 with K_2HPO_4 resulted in a yield of 28%, while using K_3PO_4 yielded 10% of product **2a**. Notably, all productive reaction conditions afforded product **2a** in high diastereoselectivity with >20:1 diastereomeric ratio (for further detailed condition optimization, see Tables S1−S4 in the Supporting Information).

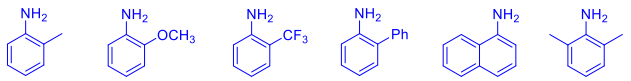
Table 1. Synthesis of *N*-Fused Polycyclic Indole Derivatives with Different Reaction Conditions[a]



Catalyst = $[Ru(p\text{-cymene})Cl_2]_2$; Acid = AcOH



entry 1: **A1** nd[b] | entry 2: **A2** nd | entry 3: **A3** nd | entry 4: **A4** nd | entry 5: **A5** nd | entry 6: **A6** nd



entry 7: **A7** nd | entry 8: **A8** nd | entry 9: **A9** nd | entry 10: **A10** 43 %, dr > 20:1 | entry 11: **A11** 67 % dr > 20:1 | entry 12: **A12** nd

entry 13:	Catalyst = $[Ru(p\text{-cymene})Cl_2]_2$;	Amine = **A11**; Acid = PivOH	39 %, dr > 20:1
entry 14:	Catalyst = $[Ru(p\text{-cymene})Cl_2]_2$;	Amine = **A11**; Acid = $PhCO_2H$	46 %, dr > 20:1
entry 15:	Catalyst = $[Ru(benzene)Cl_2]_2$;	Amine = **A11**; Acid = AcOH	23 %, dr > 20:1
entry 16:	Catalyst = $RuCl_2(PPh_3)_3$;	Amine = **A11**; Acid = AcOH	nd
entry 17[c]:	Catalyst = $[Ru(MeCN)_3(p\text{-cymene})](SbF_6)_2$;	Amine = **A11**; Acid = AcOH	18 %,dr>20:1
entry 18[c]:	Catalyst = $[Ru(OAc)_2(p\text{-cymene})]$;	Amine = **A11**; Acid = AcOH	69 %, dr > 20:1
entry 19[d]:	Additive = no KH_2PO_4;	Amine = **A11**; Acid = AcOH	19 %, dr > 20:1
entry 20[d]:	Additive = K_2HPO_4;	Amine = **A11**; Acid = AcOH	28 %, dr > 20:1
entry 21[d]:	Additive = K_3PO_4;	Amine = **A11**; Acid = AcOH	10 %, dr > 20:1

[a]Reactions were carried out with **1a** (0.1 mmol), Ru catalyst (5 mol %), $AgBF_4$ (20 mol %), KH2PO4 (1.0 equiv), Acid (0.5 equiv), Amine (25 mol %), Toluene (0.5 mL), TFE (0.5 mL), at 90 °C for 12 h. [b]nd: not detected. [c]Without $AgBF_4$. [d]$[Ru(p\text{-cymene})Cl_2]_2$ was used.

With the optimized conditions for this intramolecular catalytic process, substrates with various substituents on their indole rings as well as different cyclic alkene units were studied (Table 2). Several 4-substituted and 5-substituted indole derivatives **1b**−**1e** showed productive catalytic reactions in moderate to good yields, resulting in the isolation of **2b**−**2e** with exclusive diastereomeric control. The relative stereochemistry of product **2e** was determined to have cis-hydrogen and ester groups by X-ray crystallography in its single crystals. Continued substrate synthesis based on readily available materials indicated that 6-substituted and 7-substituted indole derivatives were also suitable for the catalytic process, producing **2f**−**2i** in up to 79% yield. In sharp contrast, substrate **1j**, with a tethered cyclohexene instead of the cyclohexadiene unit in the aforesaid substrates, produced more saturated product **2j** in almost no diastereomeric selection, albeit in a yield comparable to that of **2a**. However, the

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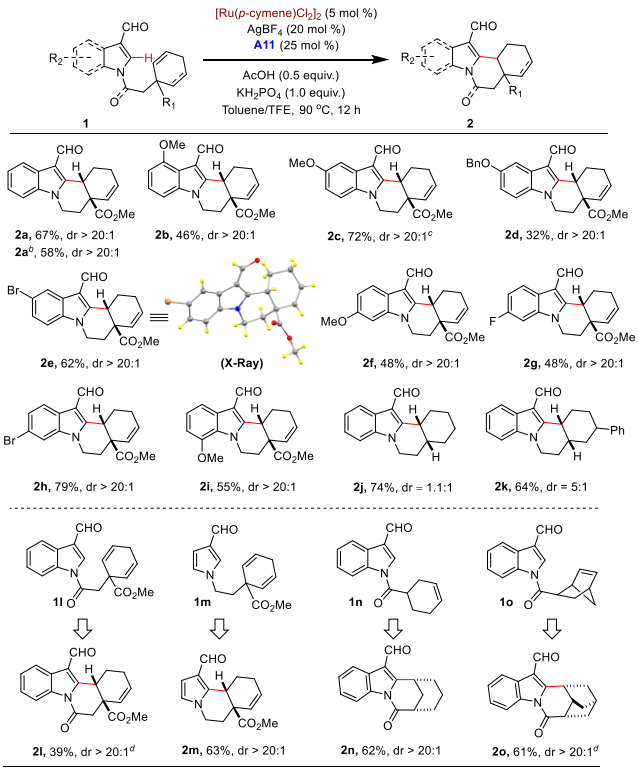
Table 2. Synthesis of Different *N*-Fused Polycyclic Indole Derivatives via Ru(II)-Catalyzed C−H Bond Functionalization[a]



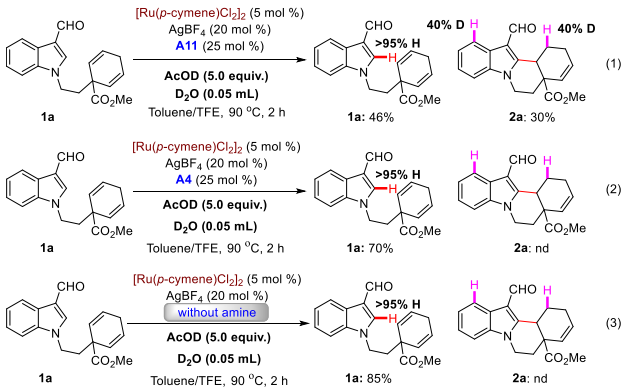
[a]Reaction conditions: **1a** (0.1 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol %), $AgBF_4$ (20 mol %), KH_2PO_4 (1.0 equiv), AcOH (0.5 equiv), A11 (25 mol %), toluene (0.5 mL), TFE (0.5 mL), at 90 °C for 12 h. [b]1.0 mmol scale reaction. [c]Reaction time is 24 h. [d]DCE (1.0 mL) was used as solvent.

substrate featuring a phenyl group on the cyclohexene ring **1k** displayed a higher yield of 64% (**2k**) with good diastereoselectivity (5:1). Besides *N*-alkyl indoles, *N*-acyl indole derivative **1l** was synthesized and afforded tetracyclic **2l** in 39% yield with excellent diastereoselectivity. It is worth noting that cleavage of the acyl linker was observed in the toluene/TFE solvent. The problem was solved by using 1,2-dichloroethane as solvent, although a decreased conversion was shown. It is demonstrated that the catalytic system also activates the corresponding C−H bond in pyrrole and produced tricyclic **2m** in 63% yield and in a single diastereomer.

Additionally, the catalytic system has been used to produce molecules bearing bridged polycyclic moieties. As an example, **1n** was demonstrated to be an effective substrate to form bridged tetracyclic **2n** in 62% yield and with >20:1 diastereomeric ratio. Moreover, norbornene-bearing substrate **1o** gave bridged polycyclic **2o** in good yield with excellent diastereocontrol under slightly modified conditions.

While ruthenium-catalyzed C−H bond activation with transient directing groups has been mechanistically investigated,[15a,17] the effect of the amines on the reactivity and selectivity has been a key factor for further studies. It is interesting to note in this catalytic system that aromatic amines 1-naphthylamine (**A11**) and aniline (**A4**) showed significantly different reactivity (Table 1). To gain further mechanistic insights, we carried out H/D exchange experiments with these two amines (Scheme 2). In the presence of AcOD and D_2O,

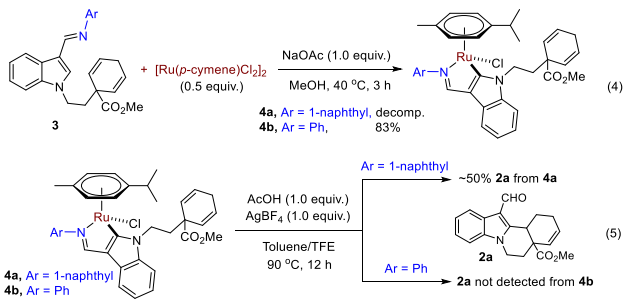
Scheme 2. H/D Exchange Experiments



A11 was able to afford product **2a** in moderate yield in 2 h. While no significant H/D exchange was observed in recovered **1a**, a 40% of H/D change of **2a** at the C-4 position was observed, as well as 40% deuteration on the saturated ring (eq 1). These results likely suggest that **1a** could not be reversibly formed after the C−H activation step. Notably, when **A4** was used under the same reaction conditions, neither H/D exchange on any C−H bond nor any conversion to product **2a** was observed (eq 2). A similar result was observed when the reaction was carried out in the absence of any amine, further indicating the ineffectiveness of aniline in this catalytic process (eq 3).

Continuing with the focus on the two amines, syntheses of ruthenacycles **4a** and **4b**, which are presumably related to the reaction intermediates after the C−H bond activation step, were attempted with the prepared imines **3** (Scheme 3).

Scheme 3. Synthesis of Ruthenacycles and Their Reactivity



Although complex **4a**, which bears a 1-naphthyl unit, was characterized by ^1H NMR and HRMS (see SI), **4a** showed instability, and a pure sample could not be obtained (eq 4). Interestingly, complex **4b** bearing a phenyl unit was isolated as a stable complex in 83% yield. While it is anticipated that amine **A11** was able to promote C−H bond activation, the formation of complex **4b** suggested that amine **A4** was also effective in enabling the C−H activation step. Subsequently, complexes **4a** and **4b** were treated by the optimized conditions of the catalytic process, including acetic acid and $AgBF_4$ (eq 5). In sharp contrast, while **4a** produced product **2a** in around 50% yield, **4b** failed to give any desired product, resulting in recovery of the starting aldehyde **1a**. While it is anticipated that amine **A11** was able to promote both C−H bond activation and the following hydroarylation reactions, the formation of complex **4b** suggested that amine **A4** was also effective in enabling the C−H activation step. However, the fact that **2a**

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did not result from **4b** suggests that aniline is not capable of this hydroarylation process under the conditions.

The computational results in Figure 1 reveal that the reaction occurs following three main steps: C−H bond

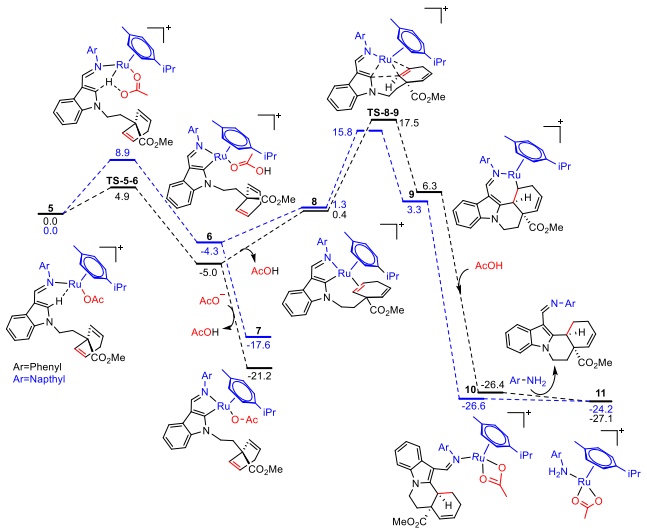

Figure 1. Gibbs free energy diagram (kcal/mol) for catalytic pathways with aniline (**A4**) and 1-naphthylamine (**A11**).

activation (**5** to **6**), C−C bond formation (**6** to **9**), and regeneration of catalyst (**9** to **11**). In both scenarios involving **A11** and **A4** amines, the C−H bond cleavage **TS-5−6** takes place rapidly, and it is not the rate- determining step (RDS), with Gibbs free activation energy values of Δ‡G° being 8.9 and 4.9 kcal/mol, respectively. Intermediate **6** can undergo either the ligand exchange process with an acetate anion or the intramolecular alkene to produce complexes **7** and **8**, respectively. Only complex **8** can produce intermediate **9**, which leads to the desired product. Complex **7** having relatively low energy is not directly involved in the reaction and is considered the resting state, residing outside of the catalytic cycle. The insertion step **TS-8−9** exhibits the highest energy barrier, regardless of whether **A11** or **A4** amine are the RDS. **TS-8−9** has Δ‡G° = 15.8 and Δ‡G° = 17.5 kcal/mol for **A11** and **A4** amine, respectively. Finally, the protonation process is followed by sequences of ligand exchange for regenerating the active catalyst and finishing the cycle (**9** to **11**). In terms of diastereoselectivity, there are four possible isomers of **TS-8−9** that can result in different products, as shown in SI (Figure S3). The predominant product aligns with the lowest energy isomers of **TS-8−9**, as illustrated in Figure 1. Other transition states are less favorable, mostly due to steric repulsion.

The disparity in reactivity between the reactions involving **A4** and **A11** can be elucidated through the concept of apparent energy activation from the DFT calculation. This value is deprived by the energy gap between resting state **7** and RDS **TS-8−9** (see Figure S2 for graphic representation). The energy activation for the **A4** amine is calculated to be 38.7 kcal/mol, while for the **A11** amine, the analogous calculation yields 33.4 kcal/mol. Importantly, it is worth noting that although resting state **7** is stable, it is present at very low concentrations due to the extremely limited amount of acetate [AcO^-]. Consequently, the computed values under standard conditions (where the concentration of each species is 1.0 M) might not accurately reflect the kinetic reality. This consideration accounts for the equilibrium between complexes **6** and **7** significantly shifting to **6** in a highly acidic environment. When adjusted to experimental concentrations, the apparent activation energy for **A4** becomes 29.8 kcal/mol, and for **A11**, it becomes 24.6 kcal/mol (see the details calculation in section 8.3 of Supporting Information). The results align with the observation that **A11** is a more effective amine in C−H functionalization. Such findings suggest that the bulkier steric nature in **A11** allows the reaction to avoid the thermodynamic sink of complex **7** and therefore decreases the kinetic energy demand. This hypothesis gains further validation through control experiments, one without added acid and the other by adding NaOAc (SI, Figure S1). We expected that the lack of acid component or excessive carboxylate anion would significantly shift the catalytic system to the undesired pathway, thus deactivating the catalyst. The yield in the trial with NaOAc (10%) or without AcOH (28%) is significantly lower than the yield in optimized conditions (67%).

In conclusion, an operationally simple and effective synthesis of *N*-fused tetracyclic and related polycyclic indole derivatives has been developed based on ruthenium(II)-catalyzed C−H activation with indole-3-aldehyde derivatives. 1-Naphthylamine was found to be an effective cocatalyst to form transient imines for the catalytic process. Experimental studies and results of DFT computations suggest that 1-naphthylamine was able to promote the hydroarylation step effectively, while simple aniline is not likely to be capable. Using 1-naphthylamine and commercially available $[Ru(p\text{-cymene})Cl_2]_2$, this catalytic system provides a practical method to access a series of polycyclic indole derivatives with a 3-formyl group, which may serve as building blocks for the syntheses of complex molecules.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c03757.

Experimental procedures, characterization data, crystal data, and NMR spectra (PDF)

Accession Codes

CCDC 2286869 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.

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Notes

The authors declare no competing financial interest.

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