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Carboxylic Acid Promoted Single-step Indole Construction from Simple Anilines and Ketones via Aerobic Cross-Dehydrogenative Coupling.

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KEYWORDS: indole synthesis, Pd-catalysis, CDC, aniline, aerobic, dioxygen, single-step

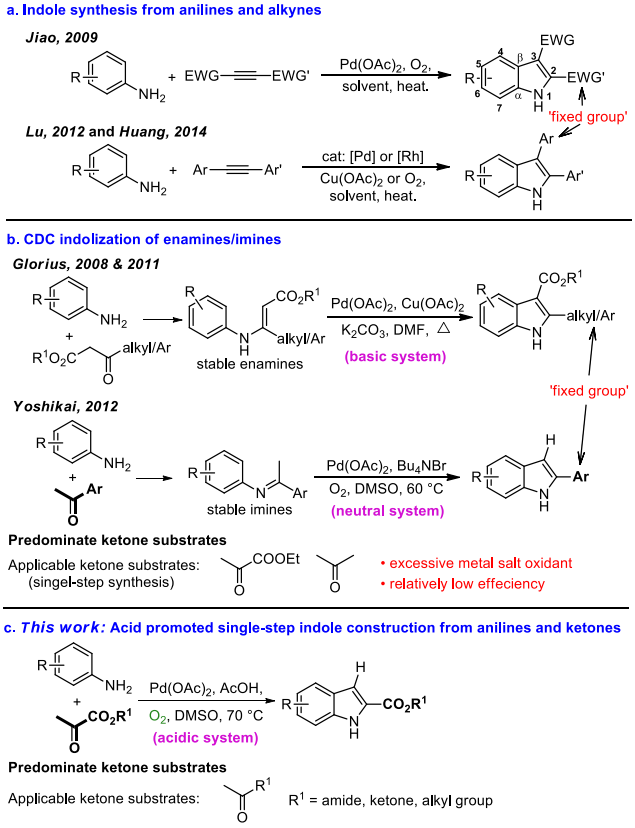
ABSTRACT: The cross dehydrogenative coupling (CDC) reaction is an efficient strategy for indole synthesis. However, most CDC methods require special substrates, and the presence of inherent groups limits the versatility for further transformation. A carboxylic acid promoted aerobic catalytic system is developed herein for a single-step synthesis of indoles from simple anilines and ketones. This versatile system is featured by the broad substrate scope and the use of ambient oxygen as oxidant, and is convenient and economical for both laboratory and industry application. The existence of the labile hydrogen at C-3 and the highly transformable carbonyl at C-2 makes the indoles versatile building blocks for organic synthesis in different contexts. Computational studies based on the density functional theory (DFT) suggests that the rate-determining step is carboxylic acid-assisted condensation of the substrates, rather than the functionalization of aryl C-H. Accordingly, a pathway via imine intermediates is deemed to be the preferred mechanism. In contrast to the general deduction, the *in situ* formed imine, instead of its enamine isomer, is believed to be involved in the first ligand exchange and later carbopalladation of the α-Me, which shed new lights on this indolization mechanism.

1. INTRODUCTION

Indole is a ubiquitous scaffold occurring in nature products[1-3] and also a commonly used heterocycle building block for a large variety of functional molecules in different fields.[4-7] Owing to the well-documented diverse biological properties associated with indole derivatives, indole has long been regarded as a 'privileged structure' in pharmaceutical science.[1,8] Accordingly, the research zeal on indole synthesis and functionalization has never ceased over a century.[9] A large collection of methods have been developed, and many of them have been listed as name reactions, such as Bartoli reaction, Larock reaction and the most widely used Fischer reaction.[10-12] These classic methods unexceptionally have their own limitations and usually demand the preparation of special substrates through multistep chemical operations.[13-14]

Along with the formidable boom of metal-catalysis chemistry, indole synthesis has experienced a profound revolution in recent decades, which aims for more accessible substrates and more efficient protocols.[15-16] Metal-catalyzed cross-dehydrogenative coupling (CDC) has so far been one of the most fascinating strategies for indole synthesis, and it enables the indole C_3-C_β bond to be formed directly from unactivated aryl C-H bond.[17-18] In general, the CDC indole syntheses could start from simple anilines and alkynes in a cascade reaction or by forming various *N*-aryl enamines/imines. The transformation of simple anilines with alkynes substituted by EWGs (electron-withdrawing groups) was first achieved by Jiao in 2009, using the readily available O_2 as oxidant (**Scheme 1a**).[19] While Lu, in 2012, reported the transformation of simple anilines with di-aryl alkynes which required stoichiometric $Cu(OAc)_2$ as oxidant.[20]

Scheme 1. Indole Syntheses from Simple Anilines



According to Huang's work, this transformation could also be accomplished by [Rh]/O_2 catalytic system (**Scheme 1a**).[21] The indole synthesis from *N*-aryl enamines disclosed by Glorius in 2008 and 2011 utilized a basic Pd-catalytic system (**Scheme 1b**).[22,23] While in 2012, Yoshikai *et al*. reported an indole synthesis from stable *N*-aryl imines, which is featured by a neutral Pd-catalytic system and the oxidant of O_2 (**Scheme 1b**).[24] In spite of these improvements, the following two issues still hinder the realization of desired versatility and applicability of CDC method.

Firstly, EWGs or aryl (Ar) substituents are generally required for either the alkyne substrates or the *N*-aryl enmanies/imine substrates (**Scheme 1a** and **1b**).[19-28] Consequently, the indoles produced tend to be permanently substituted with 'fixed groups' (e.g. difficult to be removed or reluctant for further transformation), which makes the methodologies exclusive but also limits their versatility. This limitation could be part of the reason that in spite of its shortcomings, the traditional Fischer method remains the first resort for indolization under many circumstances.

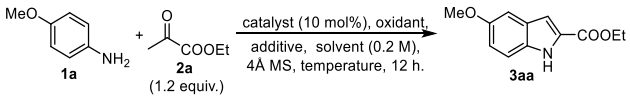
Secondly, although ketones are more accessible than alkynes, indole synthesis by single-step reaction from simple anilines and ketones was scarcely reported. To the best of our knowledge, only two such examples have been reported so far (**Scheme 1b**).[24] In Yoshikai's efforts to prepare indoles directly from anilines and ketones, indole products were successfully obtained in moderate yields via a condensation-CDC cascade. Instead of the standard Pd/O_2 condition applied to *N*-aryl imines, excessive copper salt was used as oxidant for single-step indole construction, which limits the applicability of the approach. Such situation summons for new methods to achieve the direct transformation more efficiently and adaptably, which needs no preparation of *N*-aryl imines and therefore are applicable for substrates generally unable to produce stable imines.

As an endeavor to cope with the two issues raised above, we report herein a carboxylic acid promoted Pd-catalytic system that affords indoles efficiently from simple anilines and ketones in a single step using O_2 (1 atm) as the oxidant (**Scheme 1c**). The presence of a hydrogen at C-3 and a carbonyl at C-2 distinguishes the indoles constructed herein from those previously prepared via CDC strategy. Instead of other intractable groups, such as aryl, alkyl, or cyano, a sole carbonyl is installed at C-2, which is readily transformable to a variety of functional groups as illustrated by previous cases.[29-42] The existence of a labile hydrogen at C-3 further extends the structural flexibility. Such features make the current method adaptable to a range of diverse indoles.

2. RESULTS AND DISCUSSION

2.1. Development of single-step CDC Indolization of simple aniline with ketone. Our initial efforts attempted to synthesize indole-2-carboxylate from 4-methoxyaniline (**1a**) and ethyl pyruvate (**2a**) using metal-catalyzed CDC strategy under 1 atm of O_2 (**Table 1**, for details see the Supporting Information (SI)). Under the catalysis of $Pd(OAc)_2$, various solvents were first screened and the reaction worked when DMSO was used (entries 1-3). Changing O_2 to air or argon rendered significant decrease in the yield (entries 4-5), which suggested a role of oxidant for O_2. The reaction went worse as other palladium species (entry 6) or other mental catalysts were loaded (data not shown). To improve the yield, a series of phosphorus and nitrogen-based ligands were screened. However, these efforts failed to offer better results (entry 7). Notably, some carboxylic acids were shown to be favorable for this transformation (cf. entries 8-10). Bases and hyamines (phase-transfer catalysts) were generally unfavorable. With the addition of 4 equiv. of AcOH, the yield increased to 75% (entry 11). Subsequent optimization of temperature and reaction time further increased the yield to 81% (entry 12). Finally, when 2 equiv. of **2a** was loaded, better yield was observed (entry 13), which was applied as a standard condition for later investigation.

Table 1. Optimization of Reaction Conditions for CDC Indolization of Aniline (1a) with Ketone (2a)[a]



entry	catalyst	lig. / add. (equiv.)	solvent	temp. (°C)	yield[b]
1	$Pd(OAc)_2$	none	MeCN	90	0
2	$Pd(OAc)_2$	none	Toluene	90	0
3	$Pd(OAc)_2$	none	DMSO	90	30%
4[c]	$Pd(OAc)_2$	none	DMSO	90	11%
5[d]	$Pd(OAc)_2$	none	DMSO	90	< 5%
6	$PdCl_2$	none	DMSO	90	< 5%
7	$Pd(OAc)_2$	X-Phos (0.1)	DMSO	90	10%
8	$Pd(OAc)_2$	AcOH (2)	DMSO	90	41%
9	Pd(OAc)2	PivOH (2)	DMSO	90	39%
10	$Pd(OAc)_2$	TFAOH (2)	DMSO	90	< 5%
11	$Pd(OAc)_2$	AcOH (4)	DMSO	90	75%
12[e]	$Pd(OAc)_2$	AcOH (4)	DMSO	70	81%
13[e,f]	**$Pd(OAc)_2$**	**AcOH (4)**	**DMSO**	**70**	**86%**

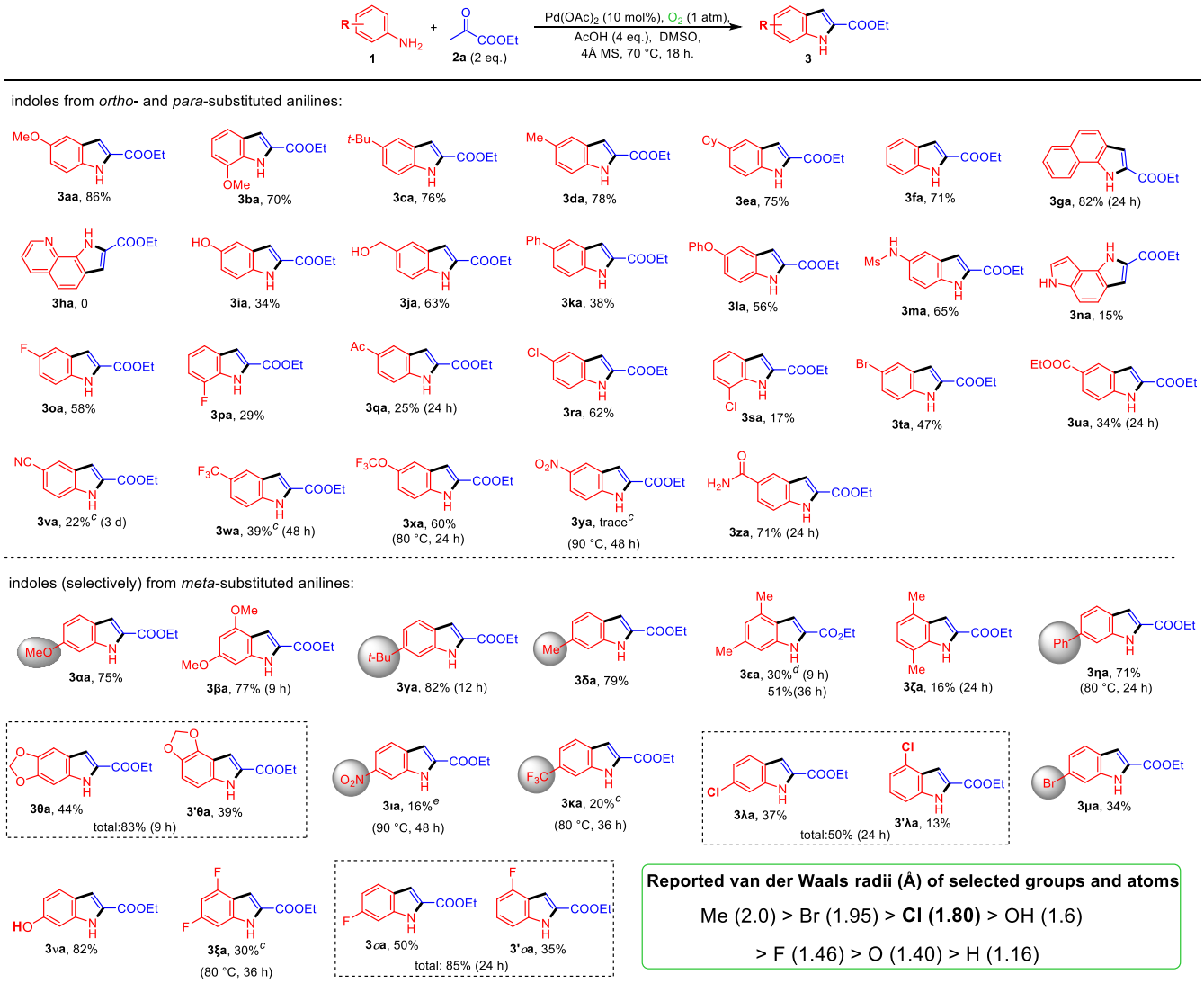
[a]Reaction conditions: **1a** (0.4 mmol), **2a** (0.48 mmol), catalyst (0.04 mmol), O_2 (1 atm), ligand or additive, solvent (2 mL), 4Å MS (80 mg), 90 °C, 12 h. [b]Isolated yield (%). [c]Air (1 atm) was used instead of O_2 (1 atm). [d]Ar (1 atm) was used instead of O_2 (1 atm). [e]Stirred for 18 h. [f]0.8 mmol of **2a** (2 equiv.) was added.

2.2. Investigation on Substrate Scope. We first examined the tolerance to various substitutions on aniline. The reaction of unsubstituted aniline delivered the simplest indole-2-carboxylate in a yield of 71% (**Table 2**, **3fa**). Generally, anilines with EDGs (electron-donating groups) would lead to comparable or higher yields (**3aa**-**3ea**, **3αa**-**3δa**), while those with EWGs result in similar or lower yields (**3oa**-**3za**, **3ιa**-**3μa**). For the same functional group, substitution at the *ortho*-position would also end with a lower yield than those at other positions (**3ba**, **3pa**, **3sa**, also cf. **3ζa & 3εa**), which is probably due to the presence of only one activatable C-H bond in the *ortho*-congener. To explore the effect of fused rings on reactivity, naphthalen-1-amine was used and the desired indole-type product (**3ga**) was obtained in high yield, while no quinoline product from C-H bond activation (CHA) at C-8 position was detected. It could be deduced from this result that seven-membered cyclic Pd-intermediate could not be formed under this system. Such a hypothesis was further confirmed by the reaction of 2-methylated naphthalen-1-amine, in which no desired product was found (**Eqn S1** in SI). Heterocyclic aromatic amines were also tested. Some gave indole products in low yields (**3na**, also see **Eqn S2** and **S3** in SI), while others showed no transformation, possibly because of chelation with the catalyst (**3ha**). To our delight, phenolic

hydroxyl (**3ia**), benzyl hydroxyl (**3ja**), primary benzamide (**3za**), methanesulfonyl (e.g. **3ma**), cyano (**3va**), nitryl (**3ya**), chloride (e.g. **3ra**) and even bromide (e.g. **3ta**) were all well compatible with this system.

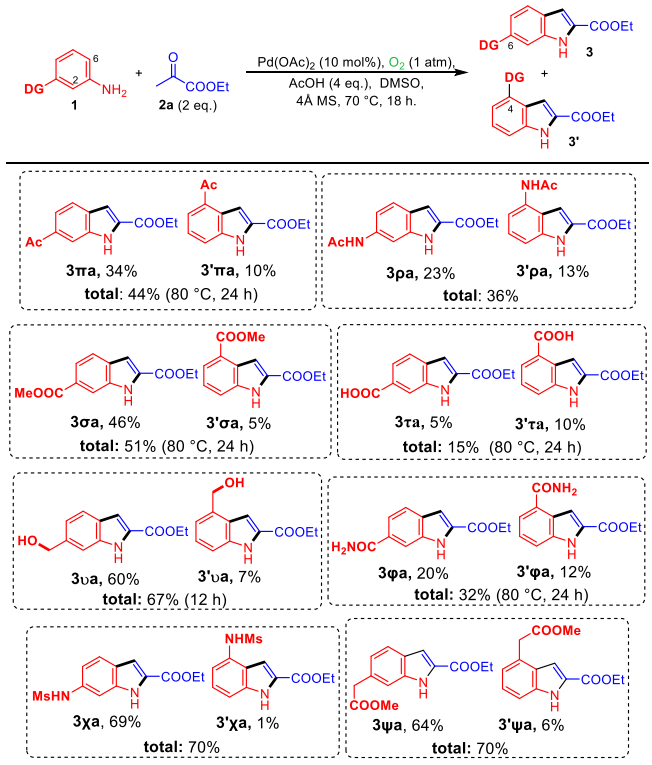
A pronounced *meta*-steric effect presented in the anilines with methyl (**1δ**), methoxyl (**1α**), *tert*-butyl (**1γ**) and phenyl (**1η**) substituted at C-3 (**Table 2**). The high yields showed an obvious preference of CHA at C-6 over that at C-2 and the regioisomers from C-2 CHA were hardly detected. Similar regioselectivity was also observed in reactions of anilines with relatively bulky EWG at *meta*-position, yet in lower yields (**3ιa**, **3κa**). However, when *m*-chloroaniline was examined, the regioselectivity profile differed. Products resulted from C-2 and C-6 CHA were obtained in the ratio of 1: 3 (**3λa & 3'λa**). It was surmised that the difference in regioselectivity profiles might be attributed to steric effects of substituents at *meta*-position. Therefore, various substituents differing by virtue of their van der Waals radii (Å)[29-33] were then examined for their regioselectivity profiles. When fluorine (1.46 Å) was introduced to the *meta*-position of aniline, the two products were obtained in higher total yield with a greater ratio of C-2 CHA isomer (**3*o*a & 3'*o*a**). To exclude the possibility of a special nature related to halides, bromide (1.95 Å) with a similar size as methyl group (2.0 Å) was investigated for its influence on regioselectivity. As expected, the reaction with *m*-Br aniline was similar to *meta*-methyl aniline and only the sole regioisomer from CHA at C-6 rather than C-2 was afforded (**3μa**). The significantly lower yield of **3εa** as compared with that of **3δa** could also be attributed to the *meta*-steric effect. However, the 3,5-dimethoxylaniline produced the desired product in a yield comparable to that of *m*-methoxyaniline with much shorter reaction time (9 h) (cf. **3αa** and **3βa**). It seems that the *meta*-steric effect was undetected for methoxyl group. The particular steric effect of methoxyl group (-OMe) could come from the rotatability of the C-O bond. When the methyl of -OMe rotates away from C-2, the steric effect at C-2 was merely derived from the oxygen atom (1.40 Å), which was less significant than *m*-methyl. To validate this supposition, methylenedioxyaniline was chosen as the substrate. In alignment with our expectation, two regioisomers were isolated in comparable yields (**3θa & 3'θa**).

Table 2. Carboxylic Acid Promoted Pd-catalyzed CDC Indolization of Anilines (1) with Ketone (2a)[a,b]



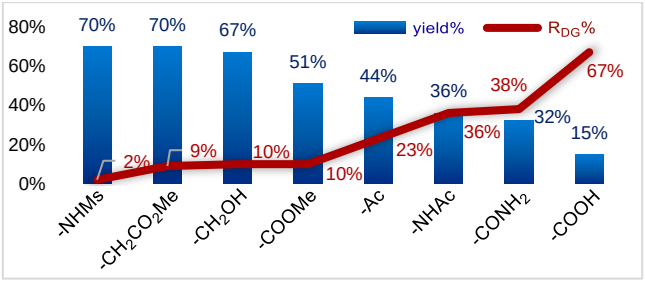
[a]Standard conditions: **1** (0.4 mmol), **2a** (0.8 mmol), $Pd(OAc)_2$ (0.04 mmol), O_2 (1 atm), AcOH (1.6 mmol), DMSO (2 mL), 4Å MS (80 mg), 70 °C (unless noted otherwise), 18 h (unless noted otherwise). [b]Isolated yields. [c]**2a** (1.2 mmol). [d]AcOH (0.4 mmol), DMSO (3 mL). [e]**2a** (2.0 mmol).

Table 3. DG Directed Pd-Catalyzed CDC Indolization of Anilines (1) with Ketone (2a)[a,b]



[a]Standard conditions: **1** (0.4 mmol), **2a** (0.8 mmol), $Pd(OAc)_2$ (0.04 mmol), O_2 (1 atm), AcOH (1.6 mmol), DMSO (2 mL), 4Å MS (80 mg), 70 °C (unless noted otherwise), 18 h (unless noted otherwise). [b]Isolated yields.

Chart 1. Total Yields (Yield%) and the Percentage of 3' in Total Yields (R_{DG}%) in the Reactions of Anilines with Different *meta*-DGs.



Based on the van der Waals radii of selected groups (**Table 2**)[29-33] and the discussion above, the steric effects of the *meta*-substituents on aniline could be deduced. For a *meta*-substituent with a van der Waals radius equivalent to or less than that of chlorine (1.80 Å), two indole regioisomers could be produced under this catalytic system. Otherwise, high regioselectivity could be perceived. However, phenolic hydroxyl at the *meta*-position seemed to be an exception. Despite the van der Waals volume of hydroxyl is smaller than that of chlorine, 3-hydroxyaniline afforded the C-6 CHA product in a high yield (**3υa**). It was thereby reasoned that the acidity of phenolic hydroxyl might competitively disturb the dehydrogenation process of CHA at C-2, which suggests a possible concerted metalation-deprotonation (CMD) mechanism rather than a simple electrophilic aromatic substitution (S_EAr) mechanism for the aromatic palladation. A closer examination of the results above further supported such a hypothesis. Generally, EDGs tended to facilitate the formation of indole products and led to higher yield and shorter reaction duration than substrates with EWGs. Furthermore, for EDG substituents, 4-substitution was generally favored over 3-substitution (cf. **3aa** and **3αa**). In contrast, for EWG substituents, 3-substitution was preferred over 4-substitution (cf. **3ya** and **3ιa**, **3oa** and **3*o*a & 3'*o*a**). Notably, the low yields were generally owing to low transformation rates of substrates (e.g. **3ad**, also see **Eqn S5** in SI). These observations were again conflict with the simple S_EAr mechanism. However, a more convincing explanation for the tendency that stronger EDGs led to higher yields could be that the *N*-aryl imine/enamine intermediates from electron-rich anilines might be more readily formed than those from electron-poor anilines, and subsequently favored the whole transformation.

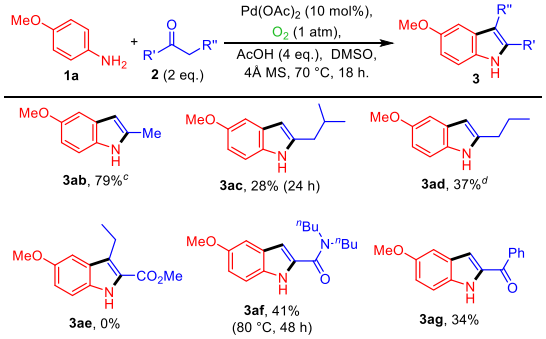
To extend the synthetic method to indole skeletons with bulky 4-substituents, the strategy of introducing directing group (DG) in the aniline substrate was attempted.[34] In this study, some potential DGs were incorporated to the C-3 of anilines (**Table 3**). These DGs were assumed to coordinate with [Pd] by forming a five- or six-membered metallacycle, thereby direct the catalytic center to the *ortho*-site of the DGs to produce 4-substituted indoles. The effects of DGs on regioselectivity to C-2 CHA of aniline were demonstrated by the generally increased percentage of 4-substituted product in the total indole yield (R_{DG}%). Various functional groups with carbonyl oxygen were first examined for their effects as directing groups. The total yield and R_{DG}% for acetamido group were both comparable to those of carbamyl group (products of **1ρ** and **1φ**), while acetyl group achieved a lower R_{DG}% with a higher total yield (products of **1π**). Although different coordinating metallacycles might be involved, the R_{DG}% generated by formic ester and acetic ester was similarly poor (products of **1σ** and **1ψ**). Aliphatic hydroxyl group was also capable of directing CHA at C-2 and affording 4-substituted indole in a similar level as corresponding esters (products of **1υ** and **1σ**). However, the mesyl group showed a poor directing effect, yet resulted in the highest yield (**3χa & 3'χa**), which was probably attributed to the higher catalytic rate of CHA at C-6 of aniline and the relatively weak coordination of the mesyl with the catalyst. Conversely, due to its relatively strong electron-withdrawing and metal coordinating effects, the carboxy group led to the highest R_{DG}%, whereas, the lowest total yield (**3τa & 3'τa**). As shown in **Chart 1**, there seemed to be a clear inverse relationship between the total yield and the R_{DG}%. In general, the lower the total yield is, the higher the R_{DG}% appears, and *vice versa*. Such a trend might be attributed to multiple factors, including yet not limited to the electronic nature and the chelating effect of the DGs.

The scope of ketones (**2**) was further investigated. The simplest aliphatic ketone, acetone, was then tested under the standard conditions and a satisfying yield was achieved (**Table 4**, **3ab**). When 4-methyl pentan-2-one and pentan-2-one were tested, only a single isomer was identified for each ketone substrate and only α-CH_3 (**3ac** and **3ad**) rather than α'-CH_2 (**Eqn S4** and **S5** in SI) of the ketone could be incorporated into the indole skeleton as C-3. Given these results, methyl 2-oxopentanoate (**2e**), a ketone without methyl group at its α-positions, was chosen for further examination. As expected, the reaction failed to give any indole product. Thus, the presence of an α-methyl group in the ketone might be a prerequisite for successful indolization. In addition, indoles substituted with amido (**3af**) and ketone (**3ag**) at C-2 could also be directly afforded under this

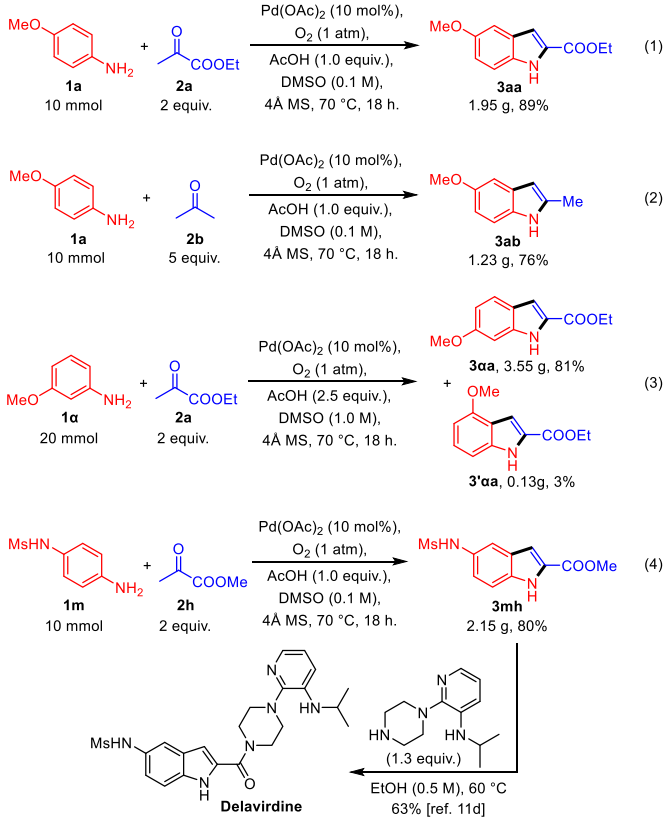
catalytic system. However, the current method seemed to be inapplicable to aromatic ketone substrates, such as acetophenone.

As compared to the previous report,[24] products **3aa** and **3ab** were obtained in higher yield yet without the requirement for excessive metal salt, which makes the current method more efficient and convenient. This method is also applicable to a variety of aniline and ketone substrates, and the broad substrate scope expands the molecular diversity of accessible indole derivatives.

Table 4. Pd-Catalyzed CDC Indolization of Aniline (1a) with Ketones (2)[a,b]

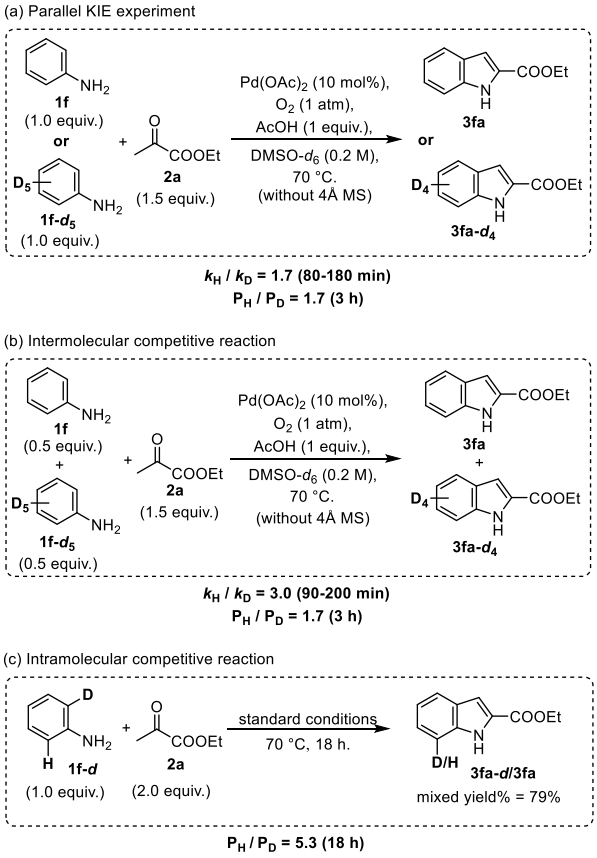


[a]Standard conditions: **1** (0.4 mmol), **2a** (0.8 mmol), $Pd(OAc)_2$ (0.04 mmol), O_2 (1 atm), AcOH (1.6 mmol), DMSO (2 mL), 4Å MS (80 mg), 70 °C (unless noted otherwise), 18 h (unless noted otherwise). [b]Isolated yields. [c]**2** (2.0 mmol). [d]AcOH (0.4 mmol), **2** (2.0 mmol), DMSO (8 mL).



2.3 Applicability in large-scale synthesis. We further applied the synthetic method to large-scale synthesis. To maintain the original yields, minor adjustments were made to the reaction conditions during scaling up (**Table S5** in SI). For anilines with *para*-substituted EDG, a low reaction concentration was generally favored, since it reduces the by-product from nucleophilic reactions. When the model substrate **1a** was reacted with **2a** under the concentration of 0.1 M, approximate 2 grams of product **3aa** was afforded in a yield of 89% (**Eqn 1**). Under the same conditions, **1a** reacted with the aliphatic ketone **2b** in gram-scale, and the yield reached 76% (**Eqn 2**). For anilines with *meta*-substituted EDG, a high concentration would be preferred. For instance, under the concentration of 1.0 M, 20 mmol of *m*-methoxyaniline **1α** reacted smoothly with **2a** and provided 6-methoxyl product **3αa** in a yield of 81% (**Eqn 3**). Meanwhile, the regioisomer **3'αa** was also isolated in the yield of 3%, which further supported the unique steric effect of methoxyl group. Methyl 5-(methylsulfonamido)-1*H*-indole-2-carboxylate (**3mh**), the key intermediate for the synthesis of the clinically used anti-HIV drug Delavirdine,[49-51] was also synthesized as another application example, and 2.2 grams of **3mh** was provided in a yield of 80% (**Eqn 4**). As compared with the multiple-step synthesis of **3mh** applied in industry,[51] the current method is more convenient and efficient.

Scheme 2. H/D Kinetic Isotope Effect Experiments



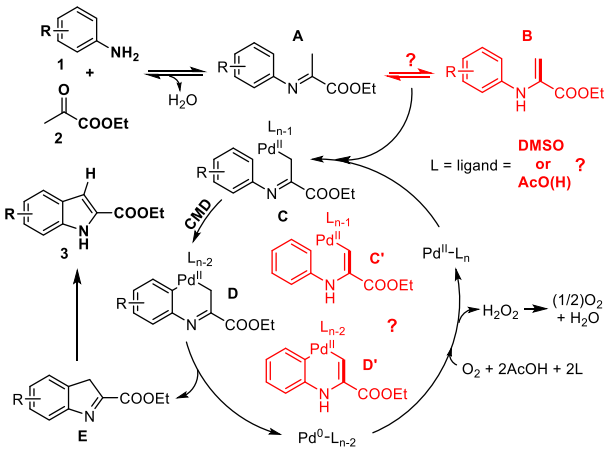
2.4 Mechanistic Studies.

Experimental Studies. To shed light on the underlying mechanism, three types of hydrogen/deuterium kinetic isotope effect (H/D KIE) experiments were performed (**Scheme 2**).[52,53] The KIE between aniline (**1f**) and its penta-deuterated analogue (**1f-*d*$_5$**) was first measured in two independent parallel reactions by real-time NMR analysis (see SI). A modest KIE of 1.7 was

given by comparing either the reaction rates during their fast converting stage (k_H/k_D, 80-180 min) or the reaction yields arrested at selected time (P_H/P_D, 3 h) before rate degradation (**Scheme 2a**). The same NMR measurement was then adopted to examine the KIE of intermolecular competition between **1f** and **1f-*d*$_5$** in the same reaction. A greater KIE of 3.0 was monitored by kinetic comparison of the two reactions. Nevertheless, the KIE measured by yields at the time point of 3h was similar to that in parallel experiments, which was further confirmed by the isolated yields at the endpoint of 3 h (**Scheme 2b** and also see **Figure S6** in SI). The modest KIE observed in both parallel experiment and intermolecular competition suggested that aromatic C-H bond activation might be a turnover-limiting step.[23,24,53] Finally, mono-deuterated imine **1f-*d*** was employed for the intramolecular competitive reaction. The KIE was reflected by the ratio of final yields under standard conditions and reached a greater value of 5.3 (**Scheme 2c**). This magnitude of KIE indicates that a concerted metalation-deprotonation (CMD) process is preferred during the aromatic C-H bond activation, [22,24,54] which is also supported by evidences accumulated in the scope investigation.

To explore the valence variation of palladium during indolization, a reaction with stoichiometric amount of $Pd(OAc)_2$ was next performed under argon (**Eqn S6** in SI). The resultant yield of 68% as well as the appearance of palladium black suggested the involvement of a Pd(II)/Pd(0) redox process. Along with the discussion above, a plausible mechanism is proposed in **Scheme 3**. Firstly, aryl imine (**A**) or enamine (**B**) is formed by the condensation of the two substrates (**1** and **2**). Then an *α*-palladated imine **C** is generated *in situ* from **A** or **B**, which is the first dehydrogenative carbopalladation. The intramolecular *ortho*-CHA of imine **C** via CMD provides six-membered palladacycle **D**. The reductive elimination of **D** happens next to give 3*H*-indole **E** and Pd(0). The aromatization of **E** affords the final indole **3**, while the Pd(0) is oxidized by molecular dioxygen to regenerate Pd(II) catalyst.[55,56]

Scheme 3. The possible mechanism for aerobic Pd-catalyzed indolization of anilines (1) with ketones (2)



Although the proposed mechanism is consistent with the available experimental evidences, there are still several issues to be unraveled: 1) Is it imine **A** or enamine **B** that is metallized during the first carbopalladation? 2) Why DMSO and AcOH are critical for this single-step transformation and does any of them serve as a ligand in the reaction? 3) Which pathway, the enamine or the imine pathway, is actually involved in the α-carbopalladation and the CMD process? To provide a clearer view and refine the mechanism, we resorted to computational studies next.

Computational studies. Based on the mechanism outlined in **Scheme 3**, computational studies were performed by applying the density functional theory (DFT) to the model reaction.[57] The condensation of **1a** and **2a** was first studied. Among possible approaches to access imine **A** (**Figure S13** in SI), the AcOH-assisted pathway was shown to be favored, which offered an explanation for the important role of AcOH in the reaction. According to **Figure 1,** however, an energy barrier up to 31.7 kcal/mol is required for the completion of the transformation, which makes the condensation a kinetically difficult process. Moreover, the reverse process of the condensation (negative equilibrium shift) is thermodynamically advantaged over the forward process (positive equilibrium shift), since the free energy of starting materials is 4.2 kcal/mol lower than that of the produced imine (**A**). Taking together, the imine product is neither easy to form nor stable with AcOH in the given solvent.

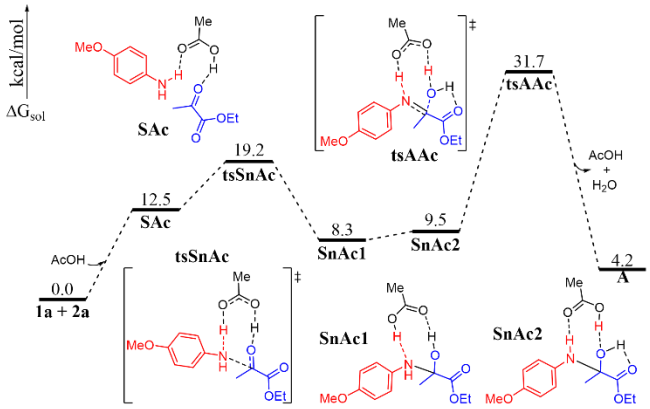


Figure 1. The energy profile of the AcOH-assisted condensation of **1a** and **2a** to afford imine **A**.

Next, we investigated the tautomerization between imine **A** and enamine **B**, as well as the first ligand exchange of $Pd(OAc)_2$ with **A** or **B**. As presented in **Figure 2**, the ligand exchange of $Pd(OAc)_2$ with **A** decreases the free energy of the system by 3.0 kcal/mol, and is also an exothermic process (ΔH = −15.5 kcal/mol), which contributes to the positive shift of the condensation equilibrium. In the resulted complex **APd**, palladium is coordinated to **A** through the lone pair electrons of the nitrogen atom and stabilized probably by the conjugative effect of π-electrons from the imine double bond. In contrast, the ligand exchange of $Pd(OAc)_2$ with **B** demands a free energy cost of 3.6 kcal/mol. Forming the enamine-Pd species **BPd** from **A** via the intramolecular tautomerization of **APd** requires an activation energy of 18.9 kcal/mol, while the AcOH-aided tautomerization of **A** to **B** needs to overcome a much higher free energy barrier of 27.0 kcal/mol. Therefore, the formation of an enamine species **B** through tautomerization is not necessary for the generation of **BPd**. The first ligand exchange is likely to happen directly with the *in situ* formed imine **A** and then offer **BPd** through intramolecular tautomerization. It is worth noting that although in the tautomerization of **APd** to **BPd** the α-methyl-H is extracted by an oxygen atom of acetate ligand (AcO^-), the proton is bonded more tightly to amino nitrogen atom (1.05 Å)

than to the oxygen atom of AcO^- (1.68 Å, more like a hydrogen bond) in the resting state of the produced **BPd**.

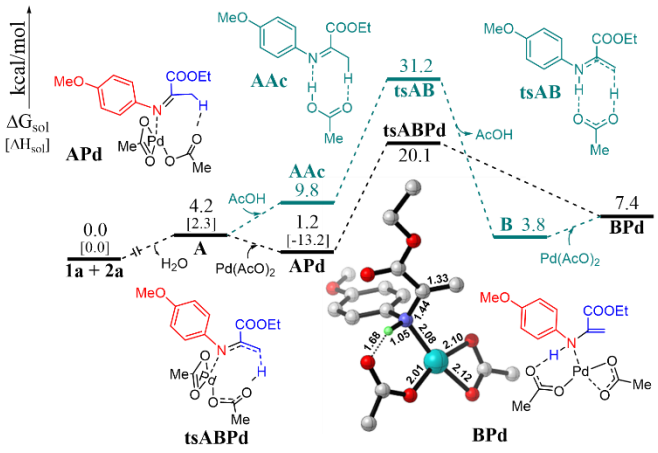


Figure 2. Comparison of the energy profiles of the pathway from **A** to the enamine-Pd species **BPd** by tautomerization before ligand exchange (dark green) or after ligand exchange (black). Hydrogens besides the extracted α-methyl-H (green) are omitted for clarity in the 3D structure of **BPd** with key distances (Å) presented.

For the first carbopalladation (**Figure 3**), a η^3-$NCCH_2$-coordinated Pd species **B2C** has been located in the route of transformation from the enamine-Pd species **BPd** to the α-methyl carbopalladation product **Ca**, which suggested a [1,3]-im-migration approach for the carbopalladation of the ketone α-Me. The formation of **B2C** crosses a barrier of 12.3 kcal/mol (**tsBPd**), while the conversion from the η^3-mode **B2C** to the sp3 C-bonded Pd species **Ca** is a facile and exergonic process (ΔH = −3.2 kcal/mol). There is a relatively week vinyl-Pd coordination in the transition state **tsBPd**, which leads to the η^3-mode coordination in **B2C** (the lengths of two newly formed Pd-C bonds are 2.20 Å and 2.10 Å). The single coordination of the oxygen atom in AcOH to Pd is nearly disappeared in **B2C** (the distance of Pd···O is 2.92 Å), and the oxygen atom is stabilized by an α-methyl-H through a newly formed hydrogen bond (2.42 Å). Nonetheless, along with the formation of **Ca**, such a single coordination is recovered (the distance of Pd···O is 2.13 Å). Meanwhile, the N atom and carbonyl C atom disengage from the coordination to Pd to reform the imine double bond (1.29 Å, shortened from 1.44 Å in **BPd**).

Notably, the hydrogen bond between AcOH and N atom seems rather essential for the stability of **Ca**, as its absence leads to the formation of a U-shaped stationary conformation (**C1**) with a significant increase in free energy (8.1 kcal/mol). Intriguingly, if AcOH is replaced by DMSO to coordinate with Pd via the intermediate **Cad** (ΔG = 10.4 kcal/mol), another much more stable U-shaped stationary point **Cd1** will be located ($\Delta\Delta G$ = −5.7 kcal/mol). This result evidently provides an explanation for the overwhelming superiority of DMSO in the solvent screening experiments (*vide ante*). By forming intermediate **Cad**, another possibility has also been considered. It goes through AcOH-assisted imine-enamine tautomerization ($\Delta G^{\ddagger}$ = 17.1 kcal/mol) to yield an enamine-type sp2 C-Pd species **C$_e$d1** (pathway b). The U-shaped conformation of **C$_e$d1** possesses a stationary energy comparable to its imine isomer **Cd1**. Given the free energy cost of this process is extremely close to that of the early condensation (31.6 kcal/mol *vs* 31.7 kcal/mol relative to **1a** + **2a**), pathway b could not be locally ruled out.

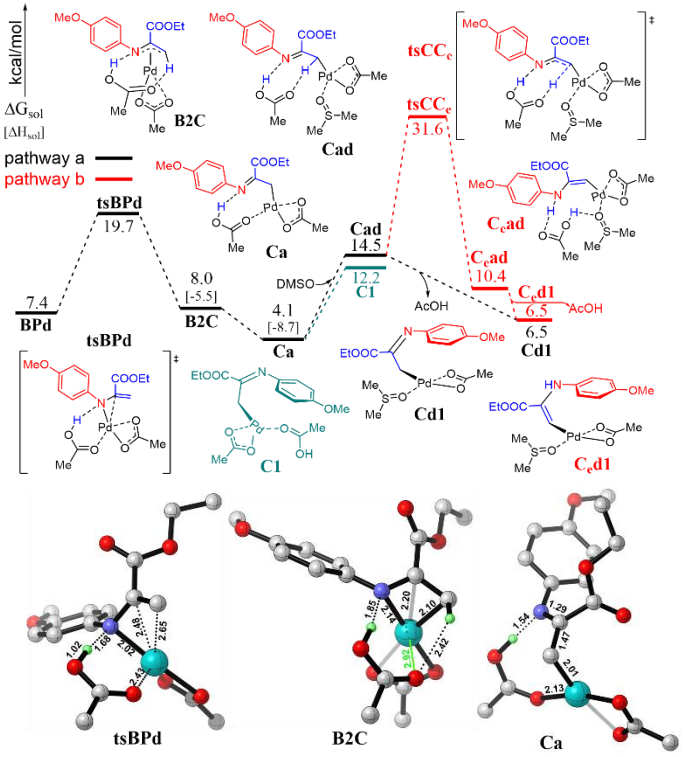


Figure 3. Energy profile of the immigration transformation of enamine-Pd species **BPd**, and the two possible pathways lead to the final α-methyl carbopalladation products, **Cd1** (dark) and **C$_e$d1** (red). Except for those involved in hydrogen bonds, hydrogens are omitted for clarity in the 3D structures with key distances (Å) presented.

According to the experimental studies above, the calculation of CMD process was then conducted for both imine (pathway a) and enamine pathway (pathway b) (**Figure 4**).[58] A key intermediate with an agostic interaction (**Cdn** or **C$_e$dn**) prior to the formation of new aryl C-Pd bond has been located during the CMD process.[59,60] Interestingly, the agostic intermediates in the two pathways not only originate from two individual C-Pd species sharing the same level of free energy (**Cd1** and **C$_e$d1**), but also take the same level of activation energy ($\Delta G^{\ddagger}$ = 7.0 kcal/mol). In their geometries, a new coordinative interaction between the *ortho*-carbon and Pd emerges (2.37 Å in **Cdn**, 2.34 Å in **C$_e$dn**) and displaces one arm of the η^2-AcO^-. For the imine **Cdn**, the distanced oxygen atom of AcO^- is immobilized by the *ortho*-H through hydrogen bonding (2.26 Å), setting up ideally a favorable six-membered cycle for the H-extraction followed. Whereas, in enamine **C$_e$dn**, it is the *meta*-H that is donated to the distanced oxygen atom of the AcO^- (2.32 Å), while the *ortho*-H keeps apart from the oxygen (3.17 Å). This more stretched conformation may contribute in part to its lower free energy (2.0 kcal/mol lower than its imine isomer), but will also leave a higher energy barrier to conquer for the completion of the *ortho*-H-transfer (4.0 kcal/mol higher than its imine isomer). The formation of the agostic intermediates gives a strong mechanistic support for the *meta*-steric effect manifested in the scope investigation (*vide ante*), as the presence of *meta*-substituents will impede effective agostic interaction or at least decrease

their stability. Moreover, for the double *meta*-substituted substrates (e.g. **1β** in **Table 2**), only pathway a that forms *ortho*-sited hydrogen bond in its agostic intermediate seems to be acceptable.

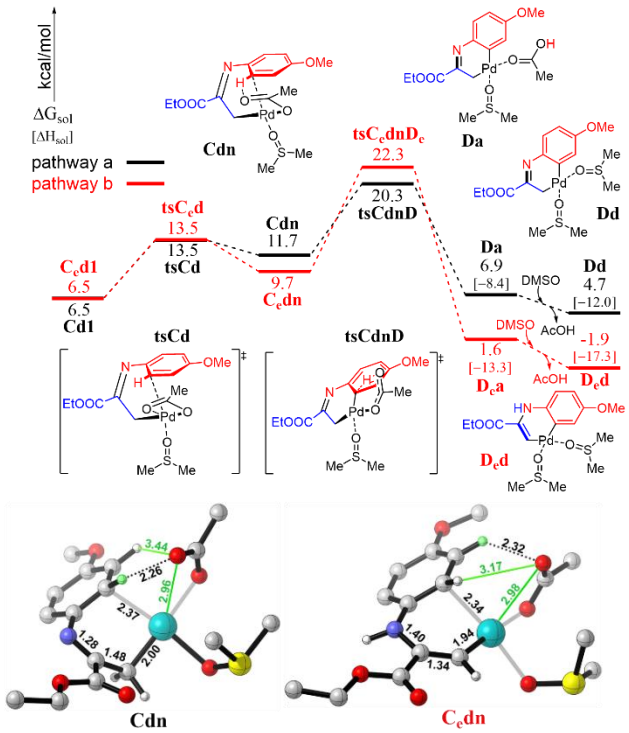


Figure 4. Comparison of the energy profiles of the pathway a (dark, for imines) and pathway b (red, for enamines) for CMD process. Nonparticipating hydrogens are partly omitted for clarity in the 3D structures with key distances (Å) presented.

The single-coordinate AcOH in the newly formed six-membered cyclopalladation product is subsequently replaced by the solvent molecule DMSO. This ligand exchange is a facile exergonic process that decreases the free energy (2.2 kcal/mol for pathway a, 3.5 kcal/mol for pathway b) of the system. Again, it suggests a significant role of DMSO in stabilizing intermediates during the reaction. For this reaction stage, pathway a is kinetically more advantaged than pathway b ($\Delta\Delta G^{\ddagger}$ = 2.0 kcal/mol). On the other hand, regarding to the final 2DMSO-coordinate palladacycle intermediates, the vinyl-Pd species **D$_e$d** in pathway b appears much more thermodynamically stable than its counterpart **Dd** in pathway a ($\Delta\Delta G$ = 6.6 kcal/mol).

For the reductive elimination, a transition state demanding the highest activation energy (**tsDdEm**, $\Delta G^{\ddagger}$ = 24.1 kcal/mol) has been located in pathway a (**Figure 5**). The product of reductive elimination is observed to be a metal coordinate (**Em** or **Pm**). In the imine **Em**, Pd(0) is tethered by the benzene ring in η^2-mode, coordinating to the functionalized *ortho*-carbon (2.26 Å) and the adjacent *meta*-carbon (2.15 Å). In the amine **Pm**, contrastively, Pd(0) is arrested by the newly formed pyrrole ring in η^2-mode, coordinating to the two vinyl carbons (2.23 Å and 2.22 Å respectively). One of the two DMSO molecules is then detached from the Pd center (the distance of O⋯Pd is 4.42 Å), which is also different from the situation in **Em**. The energy barrier of reductive elimination for the enamine isomer is 7.5 kcal/mol lower than that for the imine isomer. In addition, the decrease in free energy and enthalpy for the enamine process is 8.7 kcal/mol and 8.6 kcal/mol greater than those for the imine process. Therefore, the enamine pathway is both kinetically and thermodynamically favored. After the release of a zero-valent [Pd(DMSO)$_2$], pathway b directly gives the final indole product (**3aa**). However, pathway a still needs to go through an AcOH-assisted proton transfer of 3*H*-indole **E**, which requires 23.1 kcal/mol more free energy to complete (**Figure S14** in SI). Pathway b is thereby absolutely preferred for the stage of reductive elimination. In addition, the regeneration of Pd(OAc)$_2$ catalyst by molecular dioxygen might involve the formation of multinuclear Pd-O intermediate and the disproportionation of hydrogen peroxide.[61] The presence of AcOH in the catalytic system may also benefit the regeneration of Pd(OAc)$_2$, given that the basic effect of acetate in the amphiphilic catalyst is essential for the dehydrogenation in CMD process.

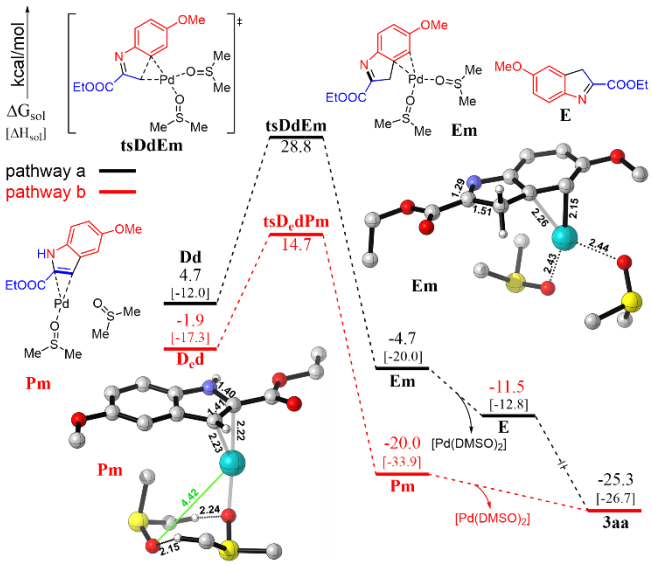


Figure 5. Comparison of the energy profiles of the pathway a (dark, for imines) and pathway b (red, for enamines) for reductive elimination process. Hydrogens are partly omitted for clarity in the 3D structures with key distances (Å) presented.

In respect to the whole energy profile of the two pathways (**Figure S15** in SI), the rate-determining step is the starting step of condensation, which provides the imine intermediate **A** and requires the largest free energy increase of 31.7 kcal/mol. The later steps decrease the free energy of the system by 29.5 kcal/mol (from **A** to **3aa**), and thereby drive the rate-determining equilibrium shift forward constantly. These later steps of the two pathways were compared, and the utmost free energy increases for pathway a and pathway b are 28.8 kcal/mol (**Figure 5**) and 31.6 kcal/mol (**Figure 3**), respectively. Therefore, the imine pathway is energetically favored and is expected to be the predominant mechanism for this reaction. Nonetheless, given that the largest free energy increase in the later steps of pathway b is 0.1 kcal/mol smaller than that in the rate-determining step, those enamine intermediates, though energetically unfavored, may still be a minor mechanistic pathway for the reaction.

3. Conclusion

A carboxylic acid promoted Pd-catalytic system for indole synthesis directly from anilines and ketones has been developed.

For the first time, a large scope of indoles was prepared from simple anilines by a single-step aerobic reaction. Unlike previous CDC methods, the current system does not require aryl imines/enamine substrates stable enough for isolation, which further enriches the diversity of indoles constructed by the CDC strategy. Such a transformation is featured by fine atom-economy, broad substrate applicability and high compatibility with various functional groups. The presence of the labile hydrogen at C3 and the highly transformable carbonyl group at C2 makes the produced indoles versatile building blocks for organic synthesis. Meanwhile, the relatively cheap reagents and the ambient pressure of gas oxygen make the protocol convenient and economical for both laboratory and industry application.[62]

Mechanistic studies have offered plenteous interesting insights into the reaction. The condensation of the substrates is estimated to be the rate-determining step of the reaction and the addition of carboxylic acid (AcOH) favors the formation of imine kinetically, which promotes the single-step construction of indoles. Different from the initially proposed mechanism based on literature, the first ligand exchange of the catalyst is believed to involve the *in situ* formed imine, and the carbopalladation of the α-Me proceeds via a [1,3]-sigmatropic rearrangement, rather than an electronic approach with its enamine isomer. In addition to its role as solvent, DMSO serves as a ligand to replace η^1-AcOH and decreases free energy of the system. The pathway via imine-type sp3 C-Pd intermediates is observed to be the preferred mechanism. The *ortho*-C-H bond activation has been illustrated to be a CMD process both experimentally and computationally. However, this step actually proceeds much more facilely than the reductive elimination. Furthermore, the located agostic intermediate in CMD process is deemed to be responsible for the *meta*-steric effect.

In summary, the CDC single-step synthesis of indoles developed herein provides versatile prototype indole cores and significantly expands the molecular diversity of indole derivatives accessible by currently available methods. Computational clues highlight a preferred mechanistic pathway via imine intermediates. The results obtained so far broaden both the applicability of and mechanistic insights on indole synthesis via CDC strategy.

EXPERIMENTAL SECTION

1. General Information.

Flash Column Chromatography (FCC) was applied to obtain all reaction yields (unless otherwise noted) and was performed on silica gel 300-400 mesh. NMR spectra were recorded on a JEOL ECZ-400S (400 MHz) or a Bruker AVANCEIII-400 (400 MHz) spectrometer. ^{1}H-NMR Chemical shifts (δ) were reported in units parts per million (ppm) referring to TMS (trimethyl silane) signal by assigning its resonance as 0.00 ppm in chloroform-*d* or referring to resonance of DMSO as 2.50 ppm in DMSO-d_6. All ^{13}C{^{1}H}-NMR Chemical shifts were reported in units ppm by assigning resonance of $CHCl_3$ as 77.16 ppm in chloroform-*d* or that of DMSO as 39.52 ppm in DMSO-d_6. Multiplicities were indicated as s (singlet), d (doublet), t (triplet), q (quartet), p (quintet/pentet), m (multiplet), and br (broad). All coupling constants (*J*) were reported in Hertz (Hz). Molecular mass were measured on a Thermo-Exactive Plus liquid chromatograph-mass spectrometer (LCMS) in positive ion mode (ESI) and high-resolution mass spectra (HRMS) were recorded for new compounds. Thin Layer Chromatograms (TLC) was visualized under UV and via potassium permanganate or iodine steam staining.

All catalysts were purchased in high quality and all commercially obtained reactants and reagents were used as received. Anhydrous solvents were distilled in small scale with CaH_2 and stored under Argon or purchased from J&K Chemical without further purification. 4Å MS is received as a white powder and used after activated under 400 °C for 4h. Reactions were carried in Schlenk tube under given conditions with a magnetic stirrer. Unless otherwise stated, yields were calculated based on the quantity of anilines (starting material).

2. Experimental Procedures and Characterization Data of Products.

a. Indole Syntheses for Scope Investigation

*Ethyl 5-methoxy-1H-indole-2-carboxylate (**3aa**)*.[63] Typical procedure: **1a** (49.2 mg, 0.4 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol) and 4Å MS (80 mg) were added to a 25 mL schlenk tube equipped with a magnetic stirrer bar. After air-evacuation and refilled with O_2 for three times or more, **2a** (92.8 mg, 0.8 mmol), AcOH (96.0 mg, 1.6 mmol) and DMSO (2.0 mL) were added via syringe. The mixture was stirred at 70 °C for 18 h. Upon cooling to room temperature, the reaction mixture was diluted with 10 mL of ethyl acetate and filtered through a pad of celite using 5 mL of ethyl acetate as additional eluent. The filtrate was washed with NaCl aqueous solution (3 x 10 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified through Flash Column Chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 30:1) to afford **3aa** (75.3 mg, 86% yield). **3aa**: White solid; ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 9.05 (brs, 1H), 7.31 (d, *J* = 8.9, 1H), 7.16 – 7.13 (m, 1H), 7.07 (d, *J* = 2.4, 1H), 6.99 (dd, *J* = 8.9, 2.4, 1H), 4.41 (q, *J* = 7.1, 2H), 3.85 (s, 3H), 1.41 (t, *J* = 7.1, 3H); ^{13}C{1H} NMR (101 MHz, Chloroform-*d*) δ: 162.2, 154.8, 132.4, 128.0, 128.0, 117.1, 112.9, 108.3, 102.7, 61.1, 55.8, 14.5; LCMS (ESI, positive): 220.1 $[M+H]^+$.

*Ethyl 7-methoxy-1H-indole-2-carboxylate (**3ba**)*.[64] The reaction of **1b** (49.2 mg, 0.4 mmol), **2a** (92.8 mg, 0.8 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 70 °C, under O_2 (1 atm), 18 h, afforded product **3ba** (74.0 mg, 85% yield, eluent: petroleum ether/ethyl acetate = 30:1). **3ba**: light brown solid; ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 9.17 (brs, 1H), 7.26 (d, *J* = 8.1, 1H), 7.19 (d, *J* = 2.2, 1H), 7.04 (t, *J* = 7.9, 1H), 6.69 (d, *J* = 7.6, 1H), 4.39 (q, *J* = 7.1, 2H), 3.93 (s, 3H), 1.39 (t, *J* = 7.1, 3H); ^{13}C{1H} NMR (101 MHz, Chloroform-*d*) δ: 161.9, 146.6, 128.7, 128.2, 127.3, 121.2, 114.9, 108.9, 104.2, 61.0, 55.5, 14.5; LCMS (ESI, positive): 220.1 $[M+H]^+$.

*Ethyl 5-(tert-butyl)-1H-indole-2-carboxylate (**3ca**)*.[65] The reaction of **1c** (59.7 mg, 0.4 mmol), **2a** (92.8 mg, 0.8 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 70 °C, under O_2 (1 atm), 18 h, afforded product **3ca** (74.2 mg, 76% yield, eluent: petroleum ether/ethyl acetate = 50:1). **3ca**: white solid; ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 9.22 (brs, 1H), 7.67 – 7.63 (m, 1H), 7.41 (dd, *J* = 8.8, 1.8, 1H), 7.35 (dt, *J* = 8.8, 0.8, 1H), 7.19 (dd, *J* = 2.1, 0.9, 1H), 4.41 (q, *J* = 7.1, 2H), 1.41 (t, *J* = 7.1, 3H), 1.37 (s, 9H); ^{13}C{1H} NMR (101 MHz, Chloroform-*d*) δ: 162.4, 143.7, 135.4, 127.6, 127.5, 124.2, 118.0, 111.6, 108.9, 61.1, 34.7, 31.8, 14.5; LCMS (ESI, positive): 246.2 $[M+H]^+$.

*Ethyl 5-methyl-1H-indole-2-carboxylate (**3da**)*.[66] The reaction of **1d** (42.8 mg, 0.4 mmol), **2a** (92.8 mg, 0.8 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 70 °C, under O_2 (1 atm), 18 h, afforded product **3da** (63.3 mg, 78% yield, eluent: petroleum ether/ethyl acetate

= 40:1). **3da**: white solid; ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 9.05 (brs, 1H), 7.47 – 7.43 (m, 1H), 7.31 (d, *J* = 8.4, 1H), 7.17 – 7.11 (m, 2H), 4.41 (q, *J* = 7.1, 2H), 2.43 (s, 3H), 1.41 (t, *J* = 7.1, 3H); ^{13}C{1H} NMR (101 MHz, Chloroform-*d*) δ: 162.3, 135.5, 130.2, 127.9, 127.6, 127.4, 121.9, 111.7, 108.3, 61.1, 21.5, 14.5; LCMS (ESI, positive): 204.1 $[M+H]^+$.

*Ethyl 5-cyclohexyl-1H-indole-2-carboxylate (**3ea**).* The reaction of **1e** (70.1 mg, 0.4 mmol), **2a** (92.8 mg, 0.8 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 70 ºC, under O_2 (1 atm), 18 h, afforded product **3ea** (81.4 mg, 75% yield, eluent: petroleum ether/ethyl acetate = 50:1). **3ea**: white solid; mp 143-144 ºC; ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 9.00 (brs, 1H), 7.50 – 7.47 (m, 1H), 7.33 (d, *J* = 8.5, 1H), 7.20 (dd, *J* = 8.6, 1.6, 1H), 7.17 (dd, *J* = 2.1, 0.9, 1H), 4.41 (q, *J* = 7.1, 2H), 2.57 (td, *J* = 11.5, 3.3, 1H), 1.89 (dd, *J* = 26.8, 11.9, 4H), 1.76 (d, *J* = 13.8, 1H), 1.52 – 1.36 (m, 7H), 1.33 – 1.21 (m, 1H); ^{13}C{1H} NMR (101 MHz, Chloroform-*d*) δ: 162.3, 140.9, 135.7, 127.8, 127.6, 125.6, 119.6, 111.7, 108.6, 61.1, 44.7, 35.1, 27.2, 26.4, 14.5; HRMS (ESI, positive): m/z calculated for $C_{17}H_{22}NO_2$ ($[M+H]^+$) 272.1645, found: 272.1646.

*Ethyl 1H-indole-2-carboxylate (**3fa**).*[67] The reaction of **1f** (37.2 mg, 0.4 mmol), **2a** (92.8 mg, 0.8 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 70 ºC, under O_2 (1 atm), 18 h, afforded product **3fa** (53.7 mg, 71% yield, eluent: petroleum ether/ethyl acetate = 30:1). **3fa**: white solid; ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 8.92 (brs, 1H), 7.69 (d, *J* = 8.2, 1H), 7.42 (d, *J* = 8.2, 1H), 7.32 (t, *J* = 7.7, 1H), 7.25 – 7.21 (m, 1H), 7.15 (t, *J* = 7.6, 1H), 4.42 (q, *J* = 7.1, 2H), 1.42 (t, *J* = 7.1, 3H); ^{13}C{1H} NMR (101 MHz, Chloroform-*d*) δ: 162.4, 137.1, 127.6, 125.4, 122.7, 120.9, 112.1, 112.0, 108.8, 61.2, 14.5; LCMS (ESI, positive): 190.1 $[M+H]^+$.

*Ethyl 1H-benzo[g]indole-2-carboxylate (**3ga**).*[68] The reaction of **1g** (57.3 mg, 0.4 mmol), **2a** (92.8 mg, 0.8 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 70 ºC, under O_2 (1 atm), 24 h, afforded product **3ga** (78.6 mg, 82% yield, eluent: petroleum ether/ethyl acetate = 30:1). **3ga**: off-white solid; ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 10.33 (brs, 1H), 8.29 (d, *J* = 7.5, 1H), 7.90 (d, *J* = 7.5, 1H), 7.66 (d, *J* = 8.7, 1H), 7.56 – 7.46 (m, 3H), 7.34 (d, *J* = 2.1, 1H), 4.50 (q, *J* = 7.1, 2H), 1.46 (t, *J* = 7.1, 3H); ^{13}C{1H} NMR (101 MHz, Chloroform-*d*) δ: 162.5, 133.2, 132.1, 129.0, 126.0, 125.9, 125.7, 123.9, 122.2, 122.1, 121.4, 120.9, 110.4, 61.3, 14.6; LCMS (ESI, positive): 240.1 $[M+H]^+$.

*Ethyl 5-hydroxy-1H-indole-2-carboxylate (**3ia**).*[69] The reaction of **1i** (43.6 mg, 0.4 mmol), **2a** (92.8 mg, 0.8 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 70 ºC, under O_2 (1 atm), 18 h, afforded product **3ia** (28.1 mg, 34% yield, eluent: petroleum ether/ethyl acetate = 10:1). **3ia**: light brown solid; ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 8.86 (brs, 1H), 7.29 (d, *J* = 8.8, 1H), 7.13 – 7.08 (m, 1H), 7.06 (d, *J* = 2.2, 1H), 6.93 (dd, *J* = 8.8, 2.4, 1H), 4.82 (brs, 1H), 4.40 (q, *J* = 7.1, 2H), 1.41 (t, *J* = 7.1, 3H); ^{13}C{1H} NMR (101 MHz, Chloroform-*d*) δ: 162.2, 150.3, 132.5, 128.4, 128.3, 116.3, 112.9, 108.0, 106.1, 61.2, 14.5; LCMS (ESI, positive): 206.1 $[M+H]^+$.

*Ethyl 5-(hydroxymethyl)-1H-indole-2-carboxylate (**3ja**).*[70] The reaction of **1j** (49.2 mg, 0.4 mmol), **2a** (92.8 mg, 0.8 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 70 ºC, under O_2 (1 atm), 18 h, afforded product **3ja** (55.4 mg, 63% yield, eluent: petroleum ether/ethyl acetate = 4:1). **3ja**: light yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.81 (brs, 1H), 7.58 (s, 1H), 7.41 (d, *J* = 8.5, 1H), 7.24 (d, *J* = 8.4, 1H), 7.12 (s, 1H), 5.10 (t, *J* = 5.6, 1H), 4.55 (d, *J* = 5.5, 2H), 4.34 (q, *J* = 7.0, 2H), 1.34 (t, *J* = 7.0, 3H); ^{13}C{1H} NMR (101 MHz, DMSO-d_6) δ: 161.4, 136.7, 134.4, 127.5, 126.6, 124.5, 119.7, 112.3, 107.7, 63.5, 60.4, 14.4; LCMS (ESI, positive): 220.1 $[M+H]^+$.

*Ethyl 5-phenyl-1H-indole-2-carboxylate (**3ka**).*[66] The reaction of **1k** (67.7 mg, 0.4 mmol), **2a** (92.8 mg, 0.8 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 70 ºC, under O_2 (1 atm), 18 h, afforded product **3ka** (40.3 mg, 38% yield, eluent: petroleum ether/ethyl acetate = 40:1). **3ka**: yellow solid; ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 9.05 (brs, 1H), 7.90 – 7.87 (m, 1H), 7.66 – 7.61 (m, 2H), 7.58 (dd, *J* = 8.6, 1.7, 1H), 7.50 – 7.42 (m, 3H), 7.35 – 7.30 (m, 1H), 7.27 (dd, *J* = 2.1, 0.9, 1H), 4.43 (q, *J* = 7.1, 2H), 1.43 (t, *J* = 7.1, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ: 162.1, 142.0, 136.4, 134.5, 128.9, 128.3, 128.2, 127.5, 126.8, 125.5, 121.0, 112.3, 109.1, 61.3, 14.6; LCMS (ESI, positive): 266.1 $[M+H]^+$.

*Ethyl 5-phenoxy-1H-indole-2-carboxylate (**3la**).* The reaction of **1l** (74.1 mg, 0.4 mmol), **2a** (92.8 mg, 0.8 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 70 ºC, under O_2 (1 atm), 18 h, afforded product **3la** (63.0 mg, 56% yield, eluent: petroleum ether/ethyl acetate = 40:1). **3la**: light yellow solid; mp 137-139 ºC; ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 9.24 (brs, 1H), 7.40 (d, *J* = 8.9, 1H), 7.34 – 7.26 (m, 3H), 7.16 (dd, *J* = 2.1, 0.9, 1H), 7.09 (dd, *J* = 8.9, 2.3, 1H), 7.07 – 7.02 (m, 1H), 7.00 – 6.95 (m, 2H), 4.42 (q, *J* = 7.1, 2H), 1.42 (t, *J* = 7.1, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ: 162.2, 158.9, 151.0, 134.0, 129.7, 128.7, 128.2, 122.5, 119.6, 117.8, 113.1, 112.1, 108.6, 61.3, 14.5; HRMS (ESI, positive): *m/z* calculated for $C_{17}H_{16}NO_3$ ($[M+H]^+$) 282.1125, found: 282.1116.

*Ethyl 5-(methylsulfonamido)-1H-indole-2-carboxylate (**3ma**).* The reaction of **1m** (74.5 mg, 0.4 mmol), **2a** (92.8 mg, 0.8 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 70 ºC, under O_2 (1 atm), 18 h, afforded product **3ma** (73.3 mg, 65% yield, eluent: petroleum ether/ethyl acetate = 3:1). **3ma**: light yellow solid; mp 171-172 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.93 (s, 1H), 9.44 (s, 1H), 7.52 (d, *J* = 1.8, 1H), 7.42 (d, *J* = 8.8, 1H), 7.18 (dd, *J* = 8.8, 2.0, 1H), 7.14 (d, *J* = 1.4, 1H), 4.33 (q, *J* = 7.1, 2H), 2.89 (s, 3H), 1.33 (t, *J* = 7.1, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ: 161.2, 135.2, 131.0, 128.3, 127.0, 121.1, 114.7, 113.3, 107.7, 60.6, 38.5, 14.4; HRMS (ESI, positive): *m/z* calculated for $C_{12}H_{15}N_2O_4S$ ($[M+H]^+$) 283.0747, found: 283.0741.

*Ethyl 1,6-dihydropyrrolo[2,3-e]indole-2-carboxylate (**3na**).* The reaction of **1n** (52.8 mg, 0.4 mmol), **2a** (92.8 mg, 0.8 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 70 ºC, under O_2 (1 atm), 18 h, afforded product **3na** (13.7 mg, 15% yield, eluent: petroleum ether/ethyl acetate = 5:1). **3na**: brown solid; mp 173-174 ºC; ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 9.29 (brs, 1H), 8.46 (brs, 1H), 7.44 (d, *J* = 8.7, 1H), 7.33 (d, *J* = 2.1, 1H), 7.23 (d, *J* = 8.7, 1H), 7.21 – 7.18 (m, 1H), 6.77 – 6.73 (m, 1H), 4.43 (q, *J* = 7.1, 2H), 1.43 (t, *J* = 7.1, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ: 162.4, 134.4, 131.1, 124.5, 122.3, 121.1, 117.1, 113.0, 110.6, 107.4, 99.8, 60.8, 14.7; HRMS (ESI, positive): *m/z* calculated for $C_{13}H_{13}N_2O_2$ ($[M+H]^+$) 229.0972, found: 229.0971.

*Ethyl 5-fluoro-1H-indole-2-carboxylate (**3oa**).*[64] The reaction of **1o** (44.4 mg, 0.4 mmol), **2a** (92.8 mg, 0.8 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 70 ºC, under O_2 (1 atm), 18 h, afforded product **3oa** (48.0 mg, 58% yield, eluent: petroleum ether/ethyl acetate = 40:1). **3oa**: white solid; ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 9.24 (brs, 1H), 7.36 (dd, *J* = 8.9, 4.4, 1H), 7.31 (dd, *J* = 9.2, 2.5, 1H), 7.18 (dd, *J* = 2.1, 0.7, 1H), 7.08 (td, *J* = 9.1, 2.5, 1H), 4.43 (q, *J* = 7.1, 2H), 1.42 (t, *J* = 7.1, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ: 162.1, 158.3 (d, *J* = 236.6), 133.7, 129.1, 127.8 (d, *J* = 10.4), 114.6 (d, *J* = 27.0), 113.0 (d, *J* = 9.5), 108.6 (d, *J* = 5.4),

106.9 (d, *J* = 23.3), 61.4, 14.5; LCMS (ESI, positive): 208.1 $[M+H]^+$.

*Ethyl 7-fluoro-1H-indole-2-carboxylate (**3pa**).* The reaction of **1p** (44.4 mg, 0.4 mmol), **2a** (92.8 mg, 0.8 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 70 ºC, under O_2 (1 atm), 18 h, afforded product **3pa** (24.0 mg, 29% yield, eluent: petroleum ether/ethyl acetate = 50:1). **3pa**: white solid; mp 136-137 ºC; ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 9.34 (brs, 1H), 7.44 (d, *J* = 8.0, 1H), 7.27 – 7.22 (m, 1H), 7.09 – 6.97 (m, 2H), 4.44 (q, *J* = 7.1, 2H), 1.43 (t, *J* = 7.1, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ: 161.8, 149.8 (d, *J* = 245.9), 131.0 (d, *J* = 4.8), 128.6 (d, *J* = 1.3), 125.9 (d, *J* = 13.8), 121.0 (d, *J* = 5.8), 118.4 (d, *J* = 4.0), 109.7 (d, *J* = 15.7), 109.1 (d, *J* = 2.6), 61.5, 14.5; HRMS (ESI, positive): *m/z* calculated for $C_{11}H_{11}NO_2F$ ($[M+H]^+$) 208.0768, found: 208.0759.

*Ethyl 5-acetyl-1H-indole-2-carboxylate (**3qa**).*[71] The reaction of **1q** (54.0 mg, 0.4 mmol), **2a** (92.8 mg, 0.8 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 70 ºC, under O_2 (1 atm), 24 h, afforded product **3qa** (23.1 mg, 25% yield, eluent: petroleum ether/ethyl acetate = 10:1). **3qa**: light yellow solid; ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 9.48 (brs, 1H), 8.38 – 8.35 (m, 1H), 7.99 (dd, *J* = 8.8, 1.7, 1H), 7.47 (d, *J* = 8.8, 1H), 7.33 (dd, *J* = 2.0, 0.9, 1H), 4.45 (q, *J* = 7.1, 2H), 2.67 (s, 3H), 1.44 (t, *J* = 7.1, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ: 198.0, 161.8, 139.3, 131.0, 129.3, 127.1, 125.2, 125.1, 112.1, 110.2, 61.5, 26.7, 14.5; LCMS (ESI, positive): 232.1 $[M+H]^+$.

*Ethyl 5-chloro-1H-indole-2-carboxylate (**3ra**).*[72] The reaction of **1r** (51.0 mg, 0.4 mmol), **2a** (92.8 mg, 0.8 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 70 ºC, under O_2 (1 atm), 18 h, afforded product **3ra** (55.4 mg, 62% yield, eluent: petroleum ether/ethyl acetate = 40:1). **3ra**: white solid; ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 9.19 (brs, 1H), 7.66 (s, 1H), 7.35 (d, *J* = 8.8, 1H), 7.26 (dd, *J* = 8.6, 2.2, 1H), 7.15 (dd, *J* = 2.1, 0.9, 1H), 4.43 (q, *J* = 7.1, 2H), 1.42 (t, *J* = 7.1, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ: 162.0, 135.2, 128.9, 128.5, 126.6, 126.0, 121.9, 113.1, 108.1, 61.4, 14.5; LCMS (ESI, positive): 224.0 $[M+H]^+$.

*Ethyl 7-chloro-1H-indole-2-carboxylate (**3sa**).*[67] The reaction of **1s** (51.0 mg, 0.4 mmol), **2a** (92.8 mg, 0.8 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 70 ºC, under O_2 (1 atm), 18 h, afforded product **3sa** (15.2 mg, 17% yield, eluent: petroleum ether/ethyl acetate = 50:1). **3sa**: light yellow solid; ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 9.04 (brs, 1H), 7.59 (d, *J* = 8.1, 1H), 7.32 (dd, *J* = 7.6, 0.8, 1H), 7.25 (d, *J* = 2.2, 1H), 7.11 – 7.06 (m, 1H), 4.43 (q, *J* = 7.1, 2H), 1.43 (t, *J* = 7.1, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ: 161.6, 134.3, 128.9, 128.4, 124.6, 121.6, 121.3, 117.4, 109.4, 61.4, 14.5; LCMS (ESI, positive): 224.0 $[M+H]^+$.

*Ethyl 5-bromo-1H-indole-2-carboxylate (**3ta**).*[73] The reaction of **1t** (68.8 mg, 0.4 mmol), **2a** (92.8 mg, 0.8 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 70 ºC, under O_2 (1 atm), 18 h, afforded product **3ta** (49.8 mg, 47% yield, eluent: petroleum ether/ethyl acetate = 25:1). **3ta**: white solid; ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 9.14 (brs, 1H), 7.84 – 7.81 (m, 1H), 7.39 (dd, *J* = 8.8, 1.9, 1H), 7.30 (d, *J* = 8.8, 1H), 7.15 (dd, *J* = 2.1, 0.9, 1H), 4.42 (q, *J* = 7.1, 2H), 1.42 (t, *J* = 7.1, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ: 161.9, 135.5, 129.2, 128.7, 128.4, 125.1, 114.1, 113.5, 108.0, 61.5, 14.5; LCMS (ESI, positive): 268.0 $[M+H]^+$.

*Ethyl 1H-indole-2,5-dicarboxylate (**3ua**).* The reaction of **1u** (66.1 mg, 0.4 mmol), **2a** (92.8 mg, 0.8 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 70 ºC, under O_2 (1 atm), 24 h, afforded product **3ua** (35.4 mg, 34% yield, eluent: petroleum ether/ethyl acetate = 20:1). **3ua**: light yellow solid; mp 140-142 ºC; ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 9.44 (brs, 1H), 8.49 – 8.46 (m, 1H), 8.02 (dd, *J* = 8.7, 1.6, 1H), 7.45 (dt, *J* = 8.7, 0.8, 1H), 7.31 (dd, *J* = 2.1, 0.9, 1H), 4.44 (q, *J* = 7.1, 2H), 4.41 (q, *J* = 7.1, 2H), 1.43 (t, *J* = 7.1, 3H), 1.42 (t, *J* = 7.1, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ: 167.3, 161.9, 139.3, 129.1, 127.1, 126.4, 125.8, 123.5, 111.8, 109.9, 61.5, 60.9, 14.6, 14.5; HRMS (ESI, positive): *m/z* calculated for $C_{14}H_{16}NO_4$ ($[M+H]^+$) 262.1074, found: 262.1072.

*Ethyl 5-cyano-1H-indole-2-carboxylate (**3va**).*[74] The reaction of **1v** (47.2 mg, 0.4 mmol), **2a** (139.2 mg, 1.2 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 70 ºC, under O_2 (1 atm), 3 d, afforded product **3va** (18.8 mg, 22% yield, eluent: petroleum ether/ethyl acetate = 10:1). **3va**: light yellow solid; ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 9.27 (brs, 1H), 8.10 – 8.05 (m, 1H), 7.56 – 7.49 (m, 2H), 7.28 (d, *J* = 2.0, 1H), 4.45 (q, *J* = 7.1, 2H), 1.44 (t, *J* = 7.1, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ: 161.5, 138.1, 129.9, 128.7, 127.7, 127.3, 120.1, 113.1, 109.0, 104.5, 61.8, 14.5; LCMS (ESI, positive): 215.1 $[M+H]^+$.

*Ethyl 5-(trifluoromethyl)-1H-indole-2-carboxylate (**3wa**).*[63] The reaction of **1w** (64.4 mg, 0.4 mmol), **2a** (139.2 mg, 1.2 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 70 ºC, under O_2 (1 atm), 2 d, afforded product **3wa** (40.1 mg, 39% yield, eluent: petroleum ether/ethyl acetate = 40:1). **3wa**: white solid; ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 9.47 (brs, 1H), 8.03 – 7.98 (m, 1H), 7.56 – 7.49 (m, 2H), 7.30 (dd, *J* = 2.0, 0.6, 1H), 4.46 (q, *J* = 7.1, 2H), 1.44 (t, *J* = 7.1, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ: 161.9, 138.1, 129.3, 126.8, 125.0 (q, *J* = 282.0), δ: 123.5 (q, *J* = 42.5), 121.9 (q, *J* = 3.2), 120.6 (q, *J* = 4.4), 112.6, 109.4, 61.6, 14.5; LCMS (ESI, positive): 258.1 $[M+H]^+$.

*Ethyl 5-(trifluoromethoxy)-1H-indole-2-carboxylate (**3xa**).* The reaction of **1x** (70.8 mg, 0.4 mmol), **2a** (92.8 mg, 0.8 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 80 ºC, under O_2 (1 atm), 24 h, afforded product **3xa** (65.4 mg, 60% yield, eluent: petroleum ether/ethyl acetate = 30:1). **3xa**: white solid; mp 138-140 ºC; ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 9.21 (brs, 1H), 7.56 – 7.52 (m, 1H), 7.42 (dt, *J* = 8.9, 0.7, 1H), 7.22 (dd, *J* = 2.1, 0.9, 1H), 7.20 (ddd, *J* = 8.9, 2.3, 0.8, 1H), 4.44 (q, *J* = 7.1, 2H), 1.43 (t, *J* = 7.1, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ: 161.9, 143.7, 135.2, 129.4, 127.6, 120.9 (q, *J* = 256.0), 119.7, 114.8, 112.9, 108.9, 61.5, 14.5; HRMS (ESI, positive): *m/z* calculated for $C_{12}H_{11}NO_3F_3$ ($[M+H]^+$) 274.0686, found: 274.0690.

*Ethyl 5-carbamoyl-1H-indole-2-carboxylate (**3za**).* The reaction of **1z** (54.4 mg, 0.4 mmol), **2a** (92.8 mg, 0.8 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 70 ºC, under O_2 (1 atm), 24 h, afforded product **3za** (65.9 mg, 71% yield, eluent: petroleum ether/ethyl acetate = 1:1). **3za**: white solid; mp 208-210 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.10 (s, 1H), 8.31 – 8.25 (m, 1H), 7.91 (s, 1H), 7.81 (dd, *J* = 8.7, 1.7, 1H), 7.46 (d, *J* = 8.7, 1H), 7.23 (dd, *J* = 2.1, 0.8, 1H), 7.19 (brs, 1H), 4.35 (q, *J* = 7.1, 2H), 1.34 (t, *J* = 7.1, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ: 168.5, 161.1, 138.7, 128.6, 126.7, 126.1, 124.2, 122.4, 112.0, 108.7, 60.6, 14.3; HRMS (ESI, positive): *m/z* calculated for $C_{12}H_{13}N_2O_3$ ($[M+H]^+$) 233.0921, found: 233.0914.

*Ethyl 6-methoxy-1H-indole-2-carboxylate (**3αa**).*[72] The reaction of **1α** (49.2 mg, 0.4 mmol), **2a** (92.8 mg, 0.8 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 70 ºC, under O_2 (1 atm), 18 h, afforded product **3αa** (65.7 mg, 75% yield, eluent: petroleum ether/ethyl acetate

= 30:1). **3αa**: white solid; ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 9.18 (brs, 1H), 7.53 (d, *J* = 8.5, 1H), 7.17 (s, 1H), 6.84 – 6.79 (overlap, 2H), 4.40 (q, *J* = 7.1, 2H), 3.83 (s, 3H), 1.40 (t, *J* = 7.1, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ: 162.3, 158.9, 138.2, 126.5, 123.5, 122.0, 112.4, 109.1, 93.9, 60.9, 55.6, 14.6; LCMS (ESI, positive): 220.1 $[M+H]^+$.

*Ethyl 4,6-dimethoxy-1H-indole-2-carboxylate (**3βa**).*[66] The reaction of **1β** (61.2 mg, 0.4 mmol), **2a** (92.8 mg, 0.8 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 70 ºC, under O_2 (1 atm), 9 h, afforded product **3βa** (76.7 mg, 77% yield, eluent: petroleum ether/ethyl acetate = 15:1). **3βa**: light yellow solid; ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 9.06 (brs, 1H), 7.26 (dd, *J* = 2.2, 0.8, 1H), 6.43 (dd, *J* = 1.8, 0.8, 1H), 6.18 (d, *J* = 1.8, 1H), 4.38 (q, *J* = 7.1, 2H), 3.90 (s, 3H), 3.82 (s, 3H), 1.39 (t, *J* = 7.1, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ: 162.2, 160.3, 155.2, 138.8, 125.0, 114.0, 106.9, 92.8, 86.3, 60.8, 55.7, 55.5, 14.5; LCMS (ESI, positive): 250.1 $[M+H]^+$.

*Ethyl 6-(tert-butyl)-1H-indole-2-carboxylate (**3γa**).*[68] The reaction of **1γ** (59.7 mg, 0.4 mmol), **2a** (92.8 mg, 0.8 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 70 ºC, under O_2 (1 atm), 12 h, afforded product **3γa** (80.4 mg, 82% yield, eluent: petroleum ether/ethyl acetate = 60:1). **3γa**: white solid; ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 9.29 (brs, 1H), 7.60 (d, *J* = 8.5, 1H), 7.41 (s, 1H), 7.23 (d, *J* = 8.6, 1H), 7.18 (s, 1H), 4.43 (q, *J* = 7.1, 2H), 1.42 (t, *J* = 7.1, 3H), 1.37 (s, 9H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ: 162.5, 149.1, 137.5, 127.3, 125.3, 122.1, 119.6, 108.5, 108.0, 61.1, 35.1, 31.6, 14.5; LCMS (ESI, positive): 246.2 $[M+H]^+$.

*Ethyl 6-methyl-1H-indole-2-carboxylate (**3δa**).*[75] The reaction of **1δ** (42.8 mg, 0.4 mmol), **2a** (92.8 mg, 0.8 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 70 ºC, under O_2 (1 atm), 18 h, afforded product **3δa** (64.1 mg, 79% yield, eluent: petroleum ether/ethyl acetate = 40:1). **3δa**: light yellow solid; ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 9.10 (brs, 1H), 7.56 (dd, *J* = 8.2, 2.7, 1H), 7.22 – 7.17 (m, 2H), 6.98 (d, *J* = 8.2, 1H), 4.40 (q, *J* = 7.2, 2H), 2.46 (s, 3H), 1.41 (t, *J* = 7.1, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ: 162.4, 137.5, 135.7, 127.0, 125.5, 123.0, 122.3, 111.7, 108.8, 61.1, 22.1, 14.6; LCMS (ESI, positive): 204.1 $[M+H]^+$.

*Ethyl 4,6-dimethyl-1H-indole-2-carboxylate (**3εa**).*[62] The reaction of **1ε** (48.4 mg, 0.4 mmol), **2a** (92.8 mg, 0.8 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 70 ºC, under O_2 (1 atm), 9 h, afforded product **3εa** (26.0 mg, 30% yield, eluent: petroleum ether/ethyl acetate = 50:1). The reaction of **1ε** (48.4 mg, 0.4 mmol), **2a** (92.8 mg, 0.8 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (24.0 mg, 0.4 mmol) and 4Å MS (80 mg) in DMSO (3.0 mL), at 70 ºC, under O_2 (1 atm), 36 h, afforded product **3εa** (44.3 mg, 51% yield, eluent: petroleum ether/ethyl acetate = 50:1). **3εa**: white solid; ^{1}H NMR (400 MHz, Chloroform-*d*) δ = 9.00 (brs, 1H), 7.22 (s, 1H), 7.02 (s, 1H), 6.78 (s, 1H), 4.41 (q, *J* = 7.1, 2H), 2.51 (s, 3H), 2.42 (s, 3H), 1.41 (t, *J* = 7.1, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ = 162.4, 137.4, 135.9, 131.9, 126.4, 125.8, 123.0, 109.2, 107.5, 61.0, 22.1, 18.7, 14.6; LCMS (ESI, positive): 218.1 $[M+H]^+$.

*Ethyl 4,7-dimethyl-1H-indole-2-carboxylate (**3ζa**).* The reaction of **1ζ** (48.4 mg, 0.4 mmol), **2a** (92.8 mg, 0.8 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 70 ºC, under O_2 (1 atm), 24 h, afforded product **3ζa** (13.9 mg, 16% yield, eluent: petroleum ether/ethyl acetate = 100:1). **3ζa**: light yellow solid; mp 114-116 ºC; ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 8.80 (brs, 1H), 7.27 (d, *J* = 2.2, 1H), 7.01 (d, *J* = 7.1, 1H), 6.86 (d, *J* = 7.1, 1H), 4.42 (q, *J* = 7.1, 2H), 2.53 (s, 3H), 2.48 (s, 3H), 1.43 (t, *J* = 7.1, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ: 162.3, 136.6, 129.9, 127.4, 126.8, 125.8, 121.0, 118.6, 107.9, 61.1, 18.5, 16.6, 14.6; LCMS (ESI, positive): 218.1 $[M+H]^+$.

*Ethyl 6-phenyl-1H-indole-2-carboxylate (**3ηa**).*[63] The reaction of **1η** (67.7 mg, 0.4 mmol), **2a** (92.8 mg, 0.8 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 80 ºC, under O_2 (1 atm), 24 h, afforded product **3ηa** (75.3 mg, 71% yield, eluent: petroleum ether/ethyl acetate = 30:1). **3ηa**: off-white solid; ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 9.22 (brs, 1H), 7.73 (d, *J* = 8.4, 1H), 7.62 (t, *J* = 8.6, 3H), 7.43 (q, *J* = 8.3, 7.9, 3H), 7.34 (t, *J* = 7.3, 1H), 7.23 (d, *J* = 7.9, 1H), 4.43 (q, *J* = 7.1, 2H), 1.42 (t, *J* = 7.1, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ: 162.2, 141.8, 138.9, 137.6, 128.9, 128.1, 127.5, 127.3, 126.9, 122.9, 121.0, 110.3, 108.7, 61.3, 14.5; LCMS (ESI, positive): 266.1 $[M+H]^+$.

*Ethyl 5H-[1,3]dioxolo[4,5-f]indole-6-carboxylate (**3θa**);*[75] *ethyl 6H-[1,3]dioxolo[4,5-e]indole-7-carboxylate (**3′θa**).* The reaction of **1θ** (54.8 mg, 0.4 mmol), **2a** (92.8 mg, 0.8 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 70 ºC, under O_2 (1 atm), 9 h, afforded product **3θa** (41.0 mg, 44% yield) and product **3′θa** (36.3 mg, 39% yield) (eluent: petroleum ether/ethyl acetate = 60:1). **3θa**: white solid; ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 9.17 (brs, 1H), 7.10 (s, 1H), 6.98 (s, 1H), 6.83 (s, 1H), 5.96 (s, 2H), 4.39 (q, *J* = 7.1, 2H), 1.40 (t, *J* = 7.1, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ: 162.1, 148.0, 144.3, 133.0, 126.3, 121.8, 109.2, 101.1, 99.9, 92.0, 60.9, 14.6; HRMS (ESI, positive): *m/z* calculated for $C_{12}H_{12}NO_4$ ($[M+H]^+$) 234.0761, found: 234.0752. **3′θa**: light yellow solid; ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 9.07 (brs, 1H), 7.13 (s, 1H), 6.97 (d, *J* = 8.6, 1H), 6.90 (d, *J* = 8.6, 1H), 6.04 (s, 2H), 4.42 (q, *J* = 7.1, 2H), 1.41 (t, *J* = 7.1, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ: 162.0, 140.5, 139.5, 135.1, 128.9, 113.9, 108.6, 103.8, 103.6, 101.3, 61.3, 14.5; HRMS (ESI, positive): *m/z* calculated for $C_{12}H_{12}NO_4$ ($[M+H]^+$) 234.0761, found: 234.0758.

*Ethyl 6-nitro-1H-indole-2-carboxylate (**3ιa**).*[68] The reaction of **1ι** (55.2 mg, 0.4 mmol), **2a** (232.0 mg, 2.0 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 90 ºC, under O_2 (1 atm), 48 h, afforded product **3ιa** (15.0 mg, 16% yield, eluent: petroleum ether/ethyl acetate = 10:1). **3ιa**: yellow solid; ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 9.43 (brs, 1H), 8.42 (s, 1H), 8.05 (dd, *J* = 8.9, 2.0, 1H), 7.78 (d, *J* = 8.9, 1H), 7.29 (dd, *J* = 2.0, 1.0, 1H), 4.48 (q, *J* = 7.1, 2H), 1.45 (t, *J* = 7.1, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ: 161.3, 145.7, 135.2, 132.6, 132.0, 123.1, 116.1, 108.9, 108.5, 62.0, 14.5; LCMS (ESI, positive): 235.1 $[M+H]^+$.

*Ethyl 6-(trifluoromethyl)-1H-indole-2-carboxylate (**3κa**).*[77] The reaction of **1κ** (64.4 mg, 0.4 mmol), **2a** (139.2 mg, 1.2 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 80 ºC, under O_2 (1 atm), 36 h, afforded product **3κa** (20.6 mg, 20% yield, eluent: petroleum ether/ethyl acetate = 60:1). **3κa**: white solid; ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 9.30 (brs, 1H), 7.79 (d, *J* = 8.4, 1H), 7.74 (s, 1H), 7.38 (dd, *J* = 8.4, 1.0, 1H), 7.28 – 7.26 (m, 1H), 4.45 (q, *J* = 7.1, 2H), 1.44 (t, *J* = 7.1, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ: 161.7, 135.6, 130.1, 129.7, 127.4 (q, *J* = 32.2), 124.8 (q, *J* = 272.5), 123.4, 117.5 (q, *J* = 3.4), 109.7 (q, *J* = 4.6), 108.4, 61.6, 14.5; LCMS (ESI, positive): 258.1 $[M+H]^+$.

*Ethyl 6-chloro-1H-indole-2-carboxylate (**3λa**);*[72] *ethyl 4-chloro-1H-indole-2-carboxylate (**3′λa**).*[58] The reaction of **1λ** (51.0 mg, 0.4 mmol), **2a** (92.8 mg, 0.8 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 70 ºC, under O_2 (1 atm), 24 h, afforded product **3λa** (33.1 mg, 37% yield) and **3′λa** (11.6 mg, 13% yield) (eluent: petroleum ether/ethyl acetate = 50:1). **3λa**: white solid; ^{1}H NMR (400 MHz,

Chloroform-*d*) δ: 9.17 (brs, 1H), 7.59 (d, *J* = 8.6, 1H), 7.42 (s, 1H), 7.19 (dd, *J* = 2.1, 0.9, 1H), 7.12 (dd, *J* = 8.6, 1.8, 1H), 4.43 (q, *J* = 7.1, 2H), 1.42 (t, *J* = 7.1, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*) δ: 162.0, 137.2, 131.4, 128.4, 126.2, 123.7, 122.0, 111.9, 108.8, 61.4, 14.5; LCMS (ESI, positive): 245.0 $[M+H]^+$. **3′λa**: white solid; ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 9.15 (brs, 1H), 7.35 – 7.30 (m, 2H), 7.23 (t, *J* = 7.9, 1H), 7.16 (dd, *J* = 7.5, 0.8, 1H), 4.43 (q, *J* = 7.1, 2H), 1.43 (t, *J* = 7.1, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*) δ: 161.9, 137.4, 128.1, 128.0, 126.8, 125.9, 120.6, 110.64, 107.14, 61.47, 14.52; LCMS (ESI, positive): 245.1 $[M+H]^+$.

*Ethyl 6-bromo-1H-indole-2-carboxylate (**3μa**).*[68] The reaction of **1μ** (68.8 mg, 0.4 mmol), **2a** (92.8 mg, 0.8 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 70 ºC, under O_2 (1 atm), 18 h, afforded product **3μa** (36.4 mg, 34% yield, eluent: petroleum ether/ethyl acetate = 40:1). **3μa**: white solid; ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 9.07 (brs, 1H), 7.59 (s, 1H), 7.54 (d, *J* = 8.6, 1H), 7.25 (dd, *J* = 8.2, 1.8, 1H), 7.22 – 7.16 (m, 1H), 4.42 (q, *J* = 7.1, 2H), 1.42 (t, *J* = 7.1, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*) δ: 162.0, 137.5, 128.2, 126.4, 124.5, 123.9, 119.2, 114.9, 108.8, 61.4, 14.5; LCMS (ESI, positive): 268.0 $[M+H]^+$.

*Ethyl 6-hydroxy-1H-indole-2-carboxylate (**3va**).* The reaction of **1v** (43.6 mg, 0.4 mmol), **2a** (92.8 mg, 0.8 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 70 ºC, under O_2 (1 atm), 18 h, afforded product **3va** (67.2 mg, 82% yield, eluent: petroleum ether/ethyl acetate = 6:1). **3va**: light yellow solid; mp 176-177 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.42 (s, 1H), 9.36 (s, 1H), 7.42 (d, *J* = 8.6, 1H), 7.02 (d, *J* = 1.3, 1H), 6.78 (d, *J* = 1.9, 1H), 6.61 (dd, *J* = 8.7, 2.1, 1H), 4.29 (q, *J* = 7.1, 2H), 1.31 (t, *J* = 7.1, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) δ: 161.3, 155.8, 138.9, 125.6, 122.7, 120.3, 112.1, 108.3, 96.3, 60.0, 14.4; HRMS (ESI, positive): *m/z* calculated for $C_{11}H_{12}NO_3$ ($[M+H]^+$) 206.0812, found: 206.0807.

*Ethyl 4,6-difluoro-1H-indole-2-carboxylate (**3ξa**).*[64] The reaction of **1ξ** (51.6 mg, 0.4 mmol), **2a** (139.2 mg, 1.2 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 80 ºC, under O_2 (1 atm), 36 h, afforded product **3ξa** (27.0 mg, 30% yield, eluent: petroleum ether/ethyl acetate = 50:1). **3ξa**: white solid; ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 9.38 (brs, 1H), 7.27 (overlap, 1H), 6.93 (d, *J* = 8.8, 1H), 6.65 (td, *J* = 10.0, 1.9, 1H), 4.44 (q, *J* = 7.1, 2H), 1.43 (t, *J* = 7.1, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*) δ: 161.7, 161.4 (dd, *J* = 243.4, 11.7), 157.1 (dd, *J* = 253.2, 15.2), 138.1 (dd, *J* = 14.9, 12.4), 128.1, 114.2 (d, *J* = 22.3), 105.0, 96.7 (dd, *J* = 29.3, 22.8), 94.3 (dd, *J* = 26.4, 4.8), 61.5, 14.5; LCMS (ESI, positive): 226.1 $[M+H]^+$.

*Ethyl 6-fluoro-1H-indole-2-carboxylate (**3oa**);*[68] *ethyl 4-fluoro-1H-indole-2-carboxylate (**3′oa**).* The reaction of **1o** (44.4 mg, 0.4 mmol), **2a** (92.8 mg, 0.8 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 70 ºC, under O_2 (1 atm), 24 h, afforded product **3oa** (41.4 mg, 50% yield) and **3′oa** (29.0 mg, 35% yield) (eluent: petroleum ether/ethyl acetate = 60:1). **3oa**: white solid; ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 9.35 (brs, 1H), 7.30 (d, *J* = 1.8, 1H), 7.26 – 7.19 (m, 2H), 6.80 (ddd, *J* = 10.2, 6.8, 1.6, 1H), 4.44 (q, *J* = 7.1, 2H), 1.43 (t, *J* = 7.1, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*) δ: 162.1, 157.3 (d, *J* = 250.4), 139.2 (d, *J* = 10.0), 127.7, 126.0 (d, *J* = 7.9), 117.5 (d, *J* = 22.4), 108.1 (d, *J* = 4.1), 105.2 (d, *J* = 18.5), 104.7 (d, *J* = 0.7), 61.5, 14.5; LCMS (ESI, positive): 208.1 $[M+H]^+$. **3′oa**: white solid; mp 137-139ºC; ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 9.34 (brs, 1H), 7.61 (dd, *J* = 8.8, 5.4, 1H), 7.21 (dd, *J* = 2.0, 0.8, 1H), 7.10 (dd, *J* = 9.4, 2.0, 1H), 6.93 (td, *J* = 9.4, 2.3, 1H), 4.43 (q, *J* = 7.1, 2H), 1.43 (t, *J* = 7.1, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*) δ: 162.1, 161.8 (d, *J* = 242.1), 137.1 (d, *J* = 12.9), 128.2 (d, *J* = 3.6), 124.2, 123.9 (d, *J* = 10.4), 110.5 (d, *J* = 25.3), 108.9, 98.0 (d, *J* = 26.1), 61.3, 14.5; HRMS (ESI, positive): *m/z* calculated for $C_{11}H_{11}NO_2F$ ($[M+H]^+$) 208.0768, found: 208.0767.

*Ethyl 6-acetyl-1H-indole-2-carboxylate (**3πa**); ethyl 4-acetyl-1H-indole-2-carboxylate (**3′πa**).* The reaction of **1π** (54.0 mg, 0.4 mmol), **2a** (92.8 mg, 0.8 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 80 ºC, under O_2 (1 atm), 24 h, afforded product **3πa** (31.4 mg, 34% yield, eluent: petroleum ether/ethyl acetate = 15:1) and **3′πa** (9.2 mg, 10% yield, eluent: petroleum ether/ethyl acetate = 20:1). **3πa**: light yellow solid; mp 142-143 ºC; ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 9.47 br(s, 1H), 8.14 – 8.11 (m, 1H), 7.77 (dd, *J* = 8.5, 1.4, 1H), 7.73 (d, *J* = 8.5, 1H), 7.24 (dd, *J* = 2.1, 0.9, 1H), 4.46 (q, *J* = 7.1, 2H), 2.68 (s, 3H), 1.44 (t, *J* = 7.1, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*) δ: 198.3, 161.8, 136.3, 134.2, 130.8, 122.6, 120.7, 113.3, 108.4, 61.6, 27.0, 14.5; HRMS (ESI, positive): *m/z* calculated for $C_{13}H_{14}NO_3$ ($[M+H]^+$) 232.0968, found: 232.0974. **3′πa**: white solid; mp 148-149 ºC; ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 9.21 (brs, 1H), 8.00 (dd, *J* = 2.2, 1.0, 1H), 7.79 (dd, *J* = 7.4, 0.8, 1H), 7.65 (dt, *J* = 8.3, 0.9, 1H), 7.39 (dd, *J* = 8.2, 7.4, 1H), 4.44 (q, *J* = 7.1, 2H), 2.72 (s, 3H), 1.43 (t, *J* = 7.1, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*) δ: 199.2, 162.2, 137.6, 131.0, 129.9, 125.6, 124.5, 117.3, 110.2, 61.5, 27.8, 14.5; HRMS (ESI, positive): *m/z* calculated for $C_{13}H_{14}NO_3$ ($[M+H]^+$) 232.0968, found: 232.0975.

*Ethyl 6-acetamido-1H-indole-2-carboxylate (**3ρa**); ethyl 4-acetamido-1H-indole-2-carboxylate (**3′ρa**).* The reaction of **1ρ** (60.0 mg, 0.4 mmol), **2a** (92.8 mg, 0.8 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 70 ºC, under O_2 (1 atm), 18 h, afforded product **3ρa** (22.6 mg, 23% yield, eluent: petroleum ether/ethyl acetate = 2:1) and **3′ρa** (12.8 mg, 13% yield, eluent: petroleum ether/ethyl acetate = 3:1). **3ρa**: light yellow solid; mp 220-221 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.73 (s, 1H), 9.97 (s, 1H), 8.04 (s, 1H), 7.53 (d, *J* = 8.7, 1H), 7.11 (dd, *J* = 8.7, 1.8, 1H), 7.07 (dd, *J* = 2.1, 0.9, 1H), 4.31 (q, *J* = 7.1, 2H), 2.06 (s, 3H), 1.32 (t, *J* = 7.1, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) δ: 168.2, 161.2, 137.8, 136.6, 126.9, 122.8, 122.0, 113.9, 107.9, 101.9, 60.2, 24.1, 14.3; HRMS (ESI, positive): *m/z* calculated for $C_{13}H_{15}N_2O_3$ ($[M+H]^+$) 247.1077, found: 247.1072. **3′ρa**: light yellow solid; mp 245-246 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.89 (s, 1H), 9.74 (s, 1H), 7.78 – 7.71 (m, 1H), 7.59 (d, *J* = 1.7, 1H), 7.20 – 7.13(m, 2H), 4.35 (q, *J* = 7.1, 2H), 2.15 (s, 3H), 1.35 (t, *J* = 7.1, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) δ: 168.6, 161.2, 138.0, 132.4, 126.0, 125.1, 119.0, 110.1, 107.9, 106.1, 60.4, 23.9, 14.3; HRMS (ESI, positive): *m/z* calculated for $C_{13}H_{15}N_2O_3$ ($[M+H]^+$) 247.1077, found: 247.1074.

*2-Ethyl 6-methyl 1H-indole-2,6-dicarboxylate (**3σa**); 2-ethyl 4-methyl 1H-indole-2,4-dicarboxylate (**3′σa**).* The reaction of **1σ** (60.4 mg, 0.4 mmol), **2a** (92.8 mg, 0.8 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 80 ºC, under O_2 (1 atm), 24 h, afforded product **3σa** (45.4 mg, 46% yield) and **3′σa** (5.2 mg, 5% yield) (eluent: petroleum ether/ethyl acetate = 15:1). **3σa**: light yellow solid; mp 160-161 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.30 (s, 1H), 8.12 (dt, *J* = 1.6, 0.8, 1H), 7.77 (d, *J* = 8.5, 1H), 7.66 (dd, *J* = 8.5, 1.5, 1H), 7.22 (dd, *J* = 2.2, 0.9, 1H), 4.37 (q, *J* = 7.1, 2H), 3.87 (s, 3H), 1.35 (t, *J* = 7.1, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) δ: 166.8, 161.0, 136.5, 130.5, 130.1, 125.4, 122.1, 120.3, 114.6, 107.5, 60.9, 52.0, 14.2; HRMS (ESI, positive): *m/z* calculated for $C_{13}H_{14}NO_4$ ($[M+H]^+$) 248.0917, found: 248.0912. **3′σa**: light yellow solid; ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 9.16 (brs, 1H), 7.96 (d, *J* = 7.4, 1H), 7.87 – 7.79 (m, 1H), 7.64 (d, *J* = 8.2, 1H), 7.38 (t, *J* = 8.0,

1H), 4.44 (q, *J* = 7.1, 2H), 4.01 (s, 3H), 1.44 (t, *J* = 7.1, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ: 167.6, 162.1, 137.4, 129.2, 126.7, 124.7, 124.6, 123.7, 117.0, 109.7, 61.5, 52.1 14.5; HRMS (ESI, positive): *m/z* calculated for $C_{13}H_{14}NO_4$ ($[M+H]^+$) 248.0917, found: 248.0915.

*2-(Ethoxycarbonyl)-1H-indole-6-carboxylic acid (**3τa**); 2-(ethoxycarbonyl)-1H-indole-4-carboxylic acid (**3′τa**).* The reaction of **1τ** (54.8 mg, 0.4 mmol), **2a** (92.8 mg, 0.8 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 80 ºC, under O_2 (1 atm), 24 h, afforded product **3τa** (4.7 mg, 5% yield) and **3′τa** (9.3 mg, 10% yield) (eluent: petroleum ether/ethyl acetate = 3:1). **3τa**: white solid; mp 258-260 ºC; ^1H NMR (400 MHz, DMSO-d_6) δ: 12.24 (s, 1H), 8.12 – 8.10 (m, 1H), 7.74 (d, *J* = 8.4, 1H), 7.65 (dd, *J* = 8.4, 1.4, 1H), 7.21 (dd, *J* = 2.1, 0.9, 1H), 4.37 (q, *J* = 7.1, 2H), 1.35 (t, *J* = 7.1, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ: 167.9, 161.0, 136.5, 130.2, 129.8, 126.6, 121.9, 120.6, 114.7, 107.4, 60.8, 14.3; HRMS (ESI, positive): *m/z* calculated for $C_{12}H_{12}NO_4$ ($[M+H]^+$) 234.0761, found: 234.0760. **3′τa**: white solid; mp 298-299 ºC; ^1H NMR (400 MHz, DMSO-d_6) δ: 12.21 (s, 1H), 7.79 (dd, *J* = 7.3, 1.0, 1H), 7.71 (dt, *J* = 8.3, 0.9, 1H), 7.60 (dd, *J* = 2.3, 0.9, 1H), 7.37 (dd, *J* = 8.2, 7.4, 1H), 4.36 (q, *J* = 7.1, 2H), 1.36 (t, *J* = 7.1, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ: 167.9, 161.2, 138.0, 128.9, 125.8, 123.9, 123.8, 123.4, 117.6, 108.4, 60.7, 14.3; HRMS (ESI, positive): *m/z* calculated for $C_{12}H_{12}NO_4$ ($[M+H]^+$) 234.0761, found: 234.0769.

*Ethyl 6-(hydroxymethyl)-1H-indole-2-carboxylate (**3υa**); ethyl 4-(hydroxymethyl)-1H-indole-2-carboxylate (**3′υa**).* The reaction of **1υ** (49.2 mg, 0.4 mmol), **2a** (92.8 mg, 0.8 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 70 ºC, under O_2 (1 atm), 12 h, afforded product **3υa** (52.6 mg, 60% yield) and **3′υa** (6.1 mg, 7% yield) (eluent: petroleum ether/ethyl acetate = 5:1). **3υa**: light brown solid; mp 103-104 ºC; ^1H NMR (400 MHz, DMSO-d_6) δ: 11.81 (s, 1H), 7.58 (d, *J* = 8.3, 1H), 7.43 – 7.41 (m, 2H), 7.10 (dd, *J* = 2.1, 0.9, 1H), 7.01 (dd, *J* = 8.3, 1.4, 1H), 4.58 (s, 2H), 4.33 (q, *J* = 7.1, 2H), 3.69 (brs, 1H), 1.34 (t, *J* = 7.1, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ: 161.4, 139.5, 137.6, 127.2, 125.6, 121.6, 119.6, 110.0, 107.7, 63.4, 60.3, 14.3; HRMS (ESI, positive): *m/z* calculated for $C_{12}H_{14}NO_3$ ($[M+H]^+$) 220.0968, found: 220.0972, 202.0867($[M-H_2O+H]^+$). **3′υa**: light yellow solid; ^1H NMR (400 MHz, DMSO-d_6) δ: 11.86 (s, 1H), 7.34 (d, *J* = 8.3, 1H), 7.27 – 7.18 (m, 2H), 7.05 (d, *J* = 7.2, 1H), 5.19 (t, *J* = 5.7, 1H), 4.77 (d, *J* = 5.7, 2H), 4.34 (q, *J* = 7.1, 2H), 1.34 (t, *J* = 7.1, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ: 161.4, 137.4, 135.9, 126.8, 124.9, 124.5, 117.5, 111.3, 106.4, 61.4, 60.4, 14.3; HRMS (ESI, positive): *m/z* calculated for $C_{12}H_{14}NO_3$ ($[M+H]^+$) 220.0968, found: 220.0969, 202.0860($[M-H_2O+H]^+$).

*Ethyl 6-carbamoyl-1H-indole-2-carboxylate (**3φa**); ethyl 4-carbamoyl-1H-indole-2-carboxylate (**3′φa**).* The reaction of **1φ** (54.4 mg, 0.4 mmol), **2a** (92.8 mg, 0.8 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 80 ºC, under O_2 (1 atm), 24 h, afforded product **3φa** (18.6 mg, 20% yield) and **3′φa** (11.1 mg, 12% yield) (eluent: petroleum ether/ethyl acetate = 2:1). **3φa**: light yellow solid; ^1H NMR (400 MHz, DMSO-d_6) δ: 12.21 (s, 1H), 8.07 – 7.95 (m, 2H), 7.68 (d, *J* = 8.5, 1H), 7.59 (dd, *J* = 8.5, 1.5, 1H), 7.31 (brs, 1H), 7.18 (dd, *J* = 2.1, 0.8, 1H), 4.36 (q, *J* = 7.1, 2H), 1.35 (t, *J* = 7.1, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ: 168.5, 161.1, 136.8, 130.7, 129.5, 128.6, 121.5, 119.3, 112.7, 107.4, 60.7, 14.3; HRMS (ESI, positive): *m/z* calculated for $C_{12}H_{13}N_2O_3$ ($[M+H]^+$) 233.0921, found: 233.0931. **3′φa**: light yellow solid; ^1H NMR (400 MHz, DMSO-d_6) δ: 12.05 (s, 1H), 7.88 (brs, 1H), 7.63 – 7.57 (m, 2H), 7.55 (d, *J* = 6.9, 1H), 7.37 – 7.25 (m, 2H), 4.35 (q, *J* = 7.1, 2H), 1.35 (t, *J* = 7.1, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ: 169.0, 161.3, 137.9, 128.2, 128.0, 125.0, 123.8, 120.1, 115.5, 108.6, 60.6, 14.3; HRMS (ESI, positive): *m/z* calculated for $C_{12}H_{13}N_2O_3$ ($[M+H]^+$) 233.0921, found: 233.0921.

*Ethyl 6-(methylsulfonamido)-1H-indole-2-carboxylate (**3χa**); ethyl 4-(methylsulfonamido)-1H-indole-2-carboxylate (**3′χa**).* The reaction of **1χ** (74.4 mg, 0.4 mmol), **2a** (92.8 mg, 0.8 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 70 ºC, under O_2 (1 atm), 18 h, afforded product **3χa** (77.8 mg, 69% yield) and **3′χa** (1.1 mg, 1% yield) (eluent: petroleum ether/ethyl acetate = 3:1). **3χa**: light yellow solid; mp 221-222 ºC; ^1H NMR (400 MHz, DMSO-d_6) δ: 11.81 (s, 1H), 9.68 (s, 1H), 7.60 (d, *J* = 8.6, 1H), 7.40 – 7.37 (m, 1H), 7.10 (dd, *J* = 2.2, 0.9, 1H), 6.99 (dd, *J* = 8.6, 2.0, 1H), 4.32 (q, *J* = 7.1, 2H), 2.95 (s, 3H), 1.33 (t, *J* = 7.1, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ: 161.1, 137.7, 135.5, 127.4, 123.7, 122.8, 115.0, 107.8, 103.2, 60.3, 38.8, 14.3; HRMS (ESI, positive): *m/z* calculated for $C_{12}H_{15}N_2O_4S$ ($[M+H]^+$) 283.0747, found: 283.0744. **3′χa**: light yellow solid; ^1H NMR (400 MHz, DMSO-d_6) δ: 11.97 (s, 1H), 9.69 (s, 1H), 7.52 (d, *J* = 1.7, 1H), 7.26 – 7.26 (m, 2H), 7.04 (dd, *J* = 6.6, 1.7, 1H), 4.34 (q, *J* = 7.1, 2H), 2.97 (s, 3H), 1.34 (t, *J* = 7.1, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ: 161.2, 138.4, 131.5, 126.8, 125.2, 121.1, 111.6, 109.2, 106.3, 60.5, 38.8, 14.3; HRMS (ESI, positive): *m/z* calculated for $C_{12}H_{15}N_2O_4S$ ($[M+H]^+$) 283.0747, found: 283.0743.

*Ethyl 6-(2-methoxy-2-oxoethyl)-1H-indole-2-carboxylate (**3ψa**); ethyl 4-(2-methoxy-2-oxoethyl)-1H-indole-2-carboxylate (**3′ψa**).* The reaction of **1ψ** (66.0 mg, 0.4 mmol), **2a** (92.8 mg, 0.8 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 70 ºC, under O_2 (1 atm), 18 h, afforded mixture of product **3ψa** and **3′ψa** (73.3 mg, 70% yield, 32 : 3 by NMR) (eluent: petroleum ether/ethyl acetate = 4:1). **3ψa**: off-white solid; ^1H NMR (400 MHz, Chloroform-*d*) δ: 9.06 (brs, 1H), 7.62 (d, *J* = 8.3, 1H), 7.34 (s, 1H), 7.19 (d, *J* = 1.8, 1H), 7.07 (d, *J* = 8.2, 1H), 4.41 (q, *J* = 7.1, 2H), 3.73 (s, 2H), 3.70 (s, 3H), 1.41 (t, *J* = 7.1, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ: 172.5, 162.2, 137.3, 131.5, 128.0, 126.8, 122.9, 122.7, 112.6, 108.7, 61.3, 52.3, 41.8, 14.6. **3′ψa**: off-white solid; ^1H NMR (400 MHz, Chloroform-*d*) δ: 9.18 (brs, 1H), 7.35 (overlap, 1H), 7.29 (d, *J* = 1.9, 1H), 7.26 (t, *J* = 7.5, 1H), 7.04 (overlap, 1H), 4.42 (q, *J* = 7.1, 2H), 3.91 (s, 2H), 3.69 (s, 3H), 1.42 (t, *J* = 7.1, 3H); HRMS (ESI, positive): *m/z* calculated for $C_{14}H_{16}NO_4$ ($[M+H]^+$) 262.1074, found: 262.1068.

*5-Methoxy-2-methyl-1H-indole (**3ab**).*[79] The reaction of **1a** (49.2 mg, 0.4 mmol), **2b** (116.0 mg, 2.0 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 70 ºC, under O_2 (1 atm), 18 h, afforded product **3ab** (50.9 mg, 79% yield, eluent: petroleum ether/ethyl acetate = 100:1). **3ab**: light yellow solid; ^1H NMR (400 MHz, Chloroform-*d*) δ: 7.73 (brs, 1H), 7.17 (d, *J* = 8.8, 1H), 6.99 (d, *J* = 2.4, 1H), 6.76 (dd, *J* = 8.7, 2.4, 1H), 6.14 (brs, 1H), 3.83 (s, 3H), 2.43 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ: 154.2, 136.1, 131.3, 129.6, 111.0, 110.8, 102.0, 100.4, 56.0, 13.9; LCMS (ESI, positive): 162.1 $[M+H]^+$.

*2-Isobutyl-5-methoxy-1H-indole (**3ac**).*[79] The reaction of **1a** (49.2 mg, 0.4 mmol), **2c** (80.0 mg, 0.8 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 70 ºC, under O_2 (1 atm), 24 h, afforded product **3ac** (22.7 mg, 28% yield, eluent: petroleum ether/ethyl acetate = 100:1). **3ac**: light yellow solid; ^1H NMR (400 MHz, Chloroform-*d*) δ: 7.73 (brs, 1H), 7.17 (d, *J* = 8.7, 1H), 7.01 (d, *J* = 2.4, 1H), 6.77 (dd, *J* = 8.7, 2.4, 1H), 6.15 (brs, 1H), 3.83 (s, 3H), 2.59 (d, *J* = 7.1, 2H), 2.03 – 1.89 (m, 1H), 0.97 (d, *J* = 6.6, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ: 154.2, 139.9, 131.1, 129.5, 111.1, 110.9,

102.1, 100.5, 56.0, 38.0, 29.1, 22.7; LCMS (ESI, positive): 204.1 $[M+H]^+$.

*5-Methoxy-2-propyl-1H-indole (**3ad**).*[80] The reaction of **1a** (49.2 mg, 0.4 mmol), **2d** (172.2 mg, 2.0 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (24.0 mg, 0.4 mmol) and 4Å MS (80 mg) in DMSO (8.0 mL), at 70 ºC, under O_2 (1 atm), 18 h, afforded product **3ad** (28.0 mg, 37% yield, the recovery% of **1a** is 42%, eluent: petroleum ether/ethyl acetate = 50:1). **3ad**: white solid; ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 7.74 (brs, 1H), 7.16 (d, *J* = 8.7, 1H), 7.01 (d, *J* = 2.4, 1H), 6.76 (dd, *J* = 8.7, 2.4, 1H), 6.16 (brs, 1H), 3.83 (s, 3H), 2.69 (t, *J* = 7.6, 2H), 1.73 (h, *J* = 7.4, 2H), 0.99 (t, *J* = 7.3, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ:= 154.2, 140.8, 131.1, 129.5, 111.0, 110.9, 102.1, 99.6, 56.1, 30.5, 22.7, 14.0; LCMS (ESI, positive): 290.1 $[M+H]^+$.

N,*N*-dibutyl-5-methoxy-1H-indole-2-carboxamide (**3af**).[81] The reaction of **1a** (49.2 mg, 0.4 mmol), **2f** (119.6 mg, 0.6 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 80 ºC, under O_2 (1 atm), 48 h, afforded product **3af** (49.6 mg, 41% yield, eluent: petroleum ether/ethyl acetate = 15:1). **3af**: light yellow solid; ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 9.88 (brs, 1H), 7.34 (d, *J* = 8.9, 1H), 7.07 (d, *J* = 2.3, 1H), 6.94 (dd, *J* = 8.9, 2.3, 1H), 6.68 (d, *J* = 1.6, 1H), 3.85 (s, 3H), 3.62 (brs, 4H), 1.72 (brs, 4H), 1.42 (h, *J* = 7.3, 4H), 0.99 (t, *J* = 7.2, 6H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ: 162.7, 154.5, 131.0, 130.5, 128.3, 115.6, 112.8, 104.0, 102.3, 55.8, 48.2 (d, *J* = 101.7), 30.56 (d, *J* = 109.6), 20.37, 14.05; LCMS (ESI, positive): 303.2 $[M+H]^+$.

*(5-Methoxy-1H-indol-2-yl)(phenyl)methanone (**3ag**).* The reaction of **1a** (49.2 mg, 0.4 mmol), **2g** (118.5 mg, 0.8 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), AcOH (96.0 mg, 1.6 mmol) and 4Å MS (80 mg) in DMSO (2.0 mL), at 70 ºC, under O_2 (1 atm), 18 h, afforded product **3ag** (34.0 mg, 34% yield, eluent: petroleum ether/ethyl acetate = 30:1). **3ag**: yellow solid; ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 9.29 (brs, 1H), 8.04 – 7.94 (m, 2H), 7.65 – 7.59 (m, 1H), 7.57 – 7.50 (m, 2H), 7.38 (d, *J* = 9.0, 1H), 7.13 – 7.03 (m, 3H), 3.86 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ: 187.1, 138.2, 134.9, 133.2, 132.4, 129.4, 128.6, 128.2, 118.6, 113.3, 112.4, 102.9, 55.8; HRMS (ESI, positive): *m/z* calculated for $C_{16}H_{14}NO_2$ ($[M+H]^+$) 252.1019, found: 252.1019.

b. Large-Scale Indole Syntheses

*Ethyl 5-methoxy-1H-indole-2-carboxylate (**3aa**).* Procedure: **1a** (1.23 g, 10 mmol), $Pd(OAc)_2$ (0.22 g, 1 mmol) and 4Å MS (1.0 g) were added to a 250 mL round-bottom flask equipped with a magnetic stirrer bar. After air-evacuation and refilled with O_2 for three times, **2a** (2.32 g, 20 mmol), AcOH (0.60 g, 10 mmol) and DMSO (100 mL) were added via syringe. The mixture was stirred at 70 °C for 18 h. The solution was then cooled to room temperature followed by the addition of ethyl acetate (200 mL) and saline (100 mL). After shaken, the mixture was filtered through a pad of celite using 30 mL of ethyl acetate as additional eluent and separated. The aqueous portion was extracted with ethyl acetate (50 mL). The organic portion was combined and washed with NaCl aqueous solution (2 x 100 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified through Flash Column Chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 30:1)) to afford the title compound (1.95 g, 89% yield).

*5-Methoxy-2-methyl-1H-indole (**3ab**).* Procedure: **1a** (1.23 g, 10 mmol), $Pd(OAc)_2$ (0.22 g, 1 mmol) and 4Å MS (1.0 g) were added to a 250 mL round-bottom flask equipped with a magnetic stirrer bar. After air-evacuation and refilled with O_2 for three times, **2b** (2.90 g, 50 mmol), AcOH (0.60 g, 10 mmol) and DMSO (100 mL) were added via syringe. The mixture was stirred at 70 °C for 18 h. The solution was then cooled to room temperature followed by the addition of ethyl acetate (200 mL) and saline (100 mL). After shaken, the mixture was filtered through a pad of celite using 30 mL of ethyl acetate as additional eluent and separated. The aqueous portion was extracted with ethyl acetate (50 mL). The organic portion was combined and washed with NaCl aqueous solution (2 x 100 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified through Flash Column Chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 30:1) to afford the title compound (1.23 g, 76% yield).

*Ethyl 6-methoxy-1H-indole-2-carboxylate (**3αa**); ethyl 4-methoxy-1H-indole-2-carboxylate (**3′αa**).* Procedure: 4Å MS (2.0 g) and $Pd(OAc)_2$ (0.44 g, 2 mmol) were added to a 100 mL round-bottom flask equipped with a magnetic stirrer bar. After air-evacuation and refilled with O_2 for three times, **1α** (2.46 g, 20 mmol), **2a** (4.64 g, 40 mmol), AcOH (1.20 g, 20 mmol) and DMSO (20 mL) were added via syringe. The mixture was stirred at 70 °C for 18 h. The solution was then cooled to room temperature followed by the addition of ethyl acetate (60 mL) and saline (30 mL). After shaken, the mixture was filtered through a pad of celite using 10 mL of ethyl acetate as additional eluent and separated. The aqueous portion was extracted with ethyl acetate (10 mL). The organic portion was combined and washed with NaCl aqueous solution (2 x 40 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified through Flash Column Chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 30:1) to afford **3′αa** (0.15 g, 3% yield) and **3αa** (3.55 g, 81% yield). **3′αa**: white solid; ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 9.26 (brs, 1H), 7.35 (s, 1H), 7.22 (t, *J* = 8.2, 1H), 7.01 (d, *J* = 8.3, 1H), 6.49 (d, *J* = 7.8, 1H), 4.41 (q, *J* = 7.1, 1H), 3.94 (s, 3H), 1.40 (t, *J* = 7.1, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ: 162.2, 154.7, 138.4, 126.5, 126.3, 119.1, 106.5, 105.0, 99.8, 61.1, 55.5, 14.5; HRMS (ESI, positive): *m/z* calculated for $C_{12}H_{14}NO_3$ ($[M+H]^+$) 220.0968, found: 220.0967.

*Methyl 5-(methylsulfonamido)-1H-indole-2-carboxylate (**3mh**).*[82] Procedure: **1m** (1.86 g, 10 mmol), $Pd(OAc)_2$ (0.22 g, 1 mmol) and 4Å MS (1.0 g) were added to a 250 mL round-bottom flask equipped with a magnetic stirrer bar. After air-evacuation and refilled with O_2 for three times, **2h** (2.04 g, 20 mmol), AcOH (0.60 g, 10 mmol) and DMSO (100 mL) were added via syringe. The mixture was stirred at 70 °C for 18 h. The solution was then cooled to room temperature followed by the addition of ethyl acetate (200 mL) and saline (100 mL). After shaken, the mixture was filtered through a pad of celite using 30 mL of ethyl acetate as additional eluent and separated. The aqueous portion was extracted with ethyl acetate (50 mL). The organic portion was combined and washed with NaCl aqueous solution (2 x 100 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified through Flash Column Chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 3:1) to afford the title compound (2.15 g, 80% yield). **3mh**: light yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.95 (s, 1H), 9.41 (s, 1H), 7.51 (d, *J* = 1.6, 1H), 7.41 (d, *J* = 8.8, 1H), 7.17 (dd, *J* = 8.8, 2.1, 1H), 7.15 (d, *J* = 1.7, 1H), 3.87 (s, 3H), 2.89 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ: 161.6, 135.1, 130.9, 127.9, 126.9, 121.0, 114.6, 113.2, 107.7, 51.8, 38.5; LCMS (ESI, positive): 269.1 $[M+H]^+$.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS publications website.

All details of reaction development, supportive experiments, details and results of DFT calculation, and copies of NMR spectra are available within the Supplementary Information.

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Notes

The authors declare no competing financial interest.

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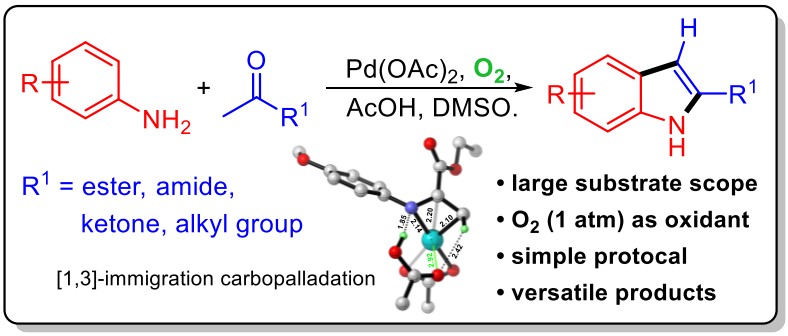
R
NH2
+
O
R1
Pd(OAc)2, O2,
AcOH, DMSO.
H
N
H
R
R1
R1 = ester, amide,
ketone, alkyl group
[1,3]-immigration carbopalladation
• large substrate scope
• O2 (1 atm) as oxidant
• simple protocal
• versatile products