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Rh(III)-Catalyzed C−H Cyclization of Arylnitrones with Diazo Compounds: Access to 3-Carboxylate Substituted *N*-Hydroxyindoles

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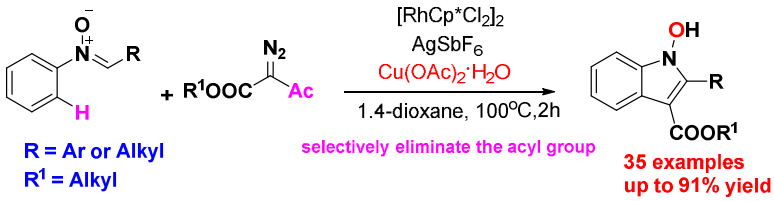
Graphic Abstract



Abstract

Recently, *N*-hydroxyindole derivatives have received much interest because of their unique structural motif and various biological activities. In this study, we report the first example of a Rh (III)-catalyzed reaction of arylnitrones with α-diazoketoesters or α-diazodiketones to produce *N*-hydroxyindole derivatives. Intriguingly, we could build the *N*-hydroxyindole scaffold by blocking the cleavage of the N-O bond selectively while eliminating the acyl group of α-diazoketoesters or α-diazodiketones preferentially.

Introduction

Indoles represent an important structural motif that is found ubiquitously in a diverse array of bioactive natural products, pharmaceuticals, and agrochemicals.[1] In particular, *N*-hydroxyindole derivatives have received much interest recently[2] because of their unique structural motif and various biological activities, such as antibiotic, antiproliferative, and platelet aggregation inhibitory activities (Figure 1).[3] Despite their pharmacological significance, only a few methods for the synthesis of these *N*-hydroxyindole derivatives have been reported.[4] Therefore, it is desired to develop highly efficient methods to directly access various *N*-hydroxyindole derivatives.

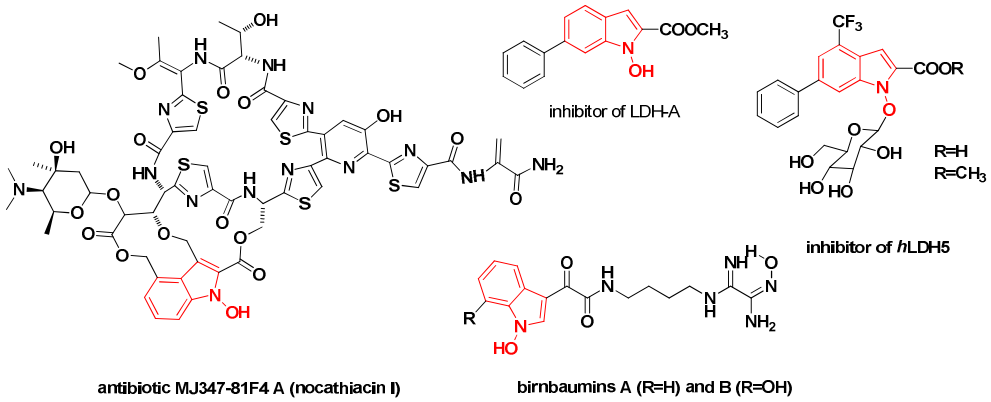
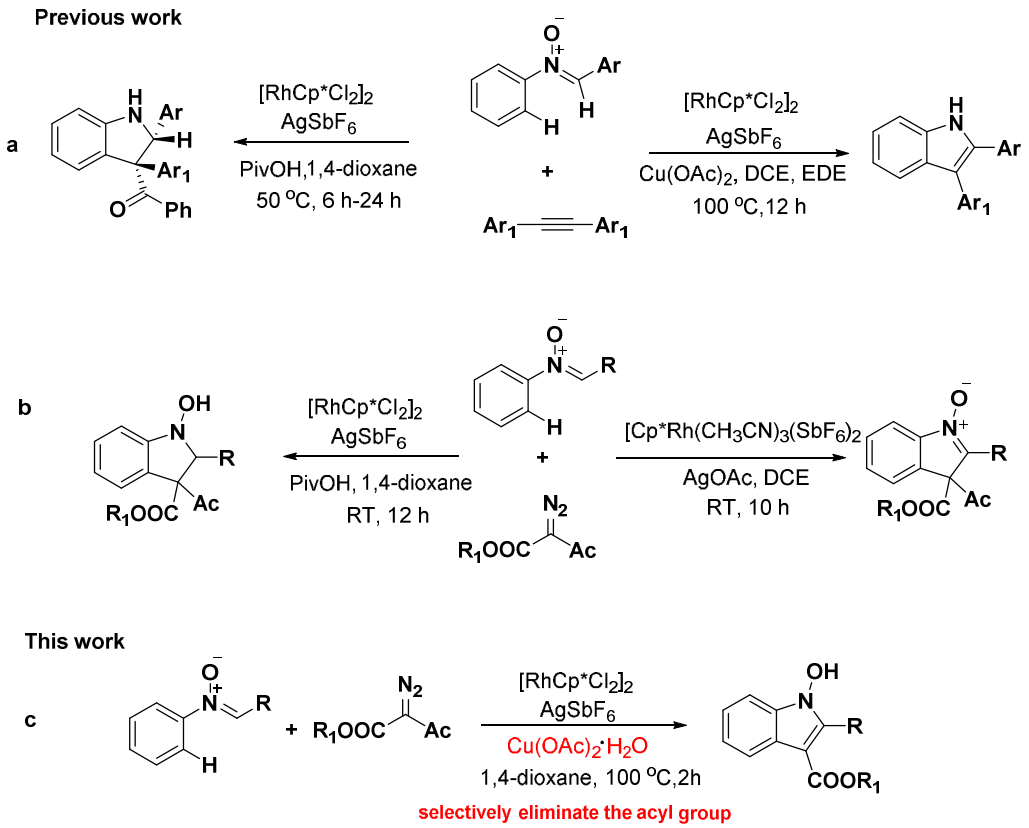


Figure 1. Selected examples of functional and bioactive *N*-hydroxyindoles

In the past decades, Rh(III)-catalysts have played many important roles in the activation of smart C-H bonds.[5] Notably Rh(III)-catalyzed C−H functionalization has been explored for the synthesis of a broad range of heterocycles,[6] in which the nitrone group[7] has been applied widely in the synthesis of indoles and indolines because of the polar nature of the N-O bond. For example, Chang's group and Wan's group both reported an intriguing Rh(III)-catalyzed C−H functionalization of nitrones with diaryl alkynes to give 2,3-diarylindole derivatives, in which the additive played an important role in deciding which indole scaffolds could be established (Scheme 1a).[8a,8b] Although it is a significant strategy to construct indole scaffolds, the production of the pharmaceutically important *N*-hydroxyindoles using this strategy has been reported rarely, presumably because of the preferential cleavage of the N-O bond.[9, 10] Recently, Zhou et al. reported an interesting [4+1] cyclative capture approach to prepare 3*H*-indole-N-oxides (Scheme 1b), in which the diazo compounds undergo migratory insertion, and followed by intramolecular addition to the polarized C=N bond and in situ oxidation.[11] Similarly, Chang reported an interesting transformation to produce



Scheme1. Rhodium(III)-catalyzed C-H functionalization.

N-hydroxyindolines (Scheme 1b).[12] However, the synthesis of *N*-hydroxyindoles is still a problematic by Rh (III)-catalyzed C−H direct cyclization of nitrones in reaction with diazo compounds, because it is very difficult to control the cleavage of $C(N_2)$-C(acyl) bond.

During our studies to develop direct C−H functionalization reactions,[13] we found that treatment of arylnitrones and α-diazoketoesters with the Rh(III)/$AgSbF_6$/$Cu(OAc)_2 \cdot H_2O$ catalyst system could build 3-carboxylate substituted *N*-hydroxyindole scaffolds by eliminating the acyl group (Scheme 1c).

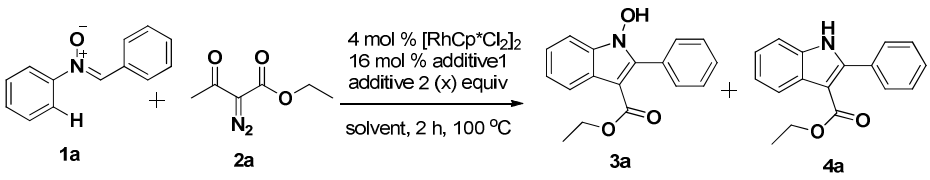
Results and discussion

Therefore, our investigations commenced with the treatment of a nitrone species **1a**

and diazoacetylacetate ester **2a** under the complex catalytic system of Rh(III)/$AgSbF_6$/PivOH at 100 ^oC in 1,4-dioxane. The results demonstrated that an intriguing 3-carboxylate *N*-hydroxyindole **3a** could be obtained with 35% yield, meanwhile a dehydroxylation byproduct **4a** was also isolated in 14% yield (Table 1, entry 1). Encouraged by these results, we further explored the reaction conditions to prepare the desired product **3a** selectively. First, different additives were screened; however, replacement of the PivOH with AcONa or AcOH gave the desired product **3a** in only trace amounts (Table 1, entries 2-3). However, introducing $Cu(OAc)_2$ as an additive resulted in a significant improvement in the yield of product **3a** (Table 1, entry 4). The yield was improved to 81% by replacement of $Cu(OAc)_2$ with $Cu(OAc)_2{\cdot}H_2O$ (Table 1, entry 5). Subsequently, screening other silver salts demonstrated that $AgSbF_6$ remained the best choice for this transformation (Table 1, entries 6-8). An exploration of solvents revealed that no reaction took place in CH_3CN, and using THF gave a low yield of the target product. Additionally, performing the reaction in MeOH and DCE only provided product **3a** with moderate yields (Table 1, entries 9−12). With these results in hand, we sought to further improve the yield of desired product **3a**. Our studies displayed that a lower loading of the $Cu(OAc)_2{\cdot}H_2O$ (1 equiv) increased the yield of **3a** to 88% (Table 1, entry 13) and only a trace amount of byproduct **4a** was detected. Lowering the reaction temperature to 25°C or 40 °C showed that the rection no occur (Table 1, entry 14). In addition, the requirement for two additives was also evaluated, and the results revealed that the reaction did not proceed in the absence of $AgSbF_6$ or $Cu(OAc)_2{\cdot}H_2O$ (Table 1, entries

15-16). Briefly, the optimum results were obtained when nitrone species (0.1 mmol, **1a**) and diethyl 2-diazomalonate (0.12 mmol, **2a**) in 1, 4-dioxane were treated with the catalytic system of $[RhCp^*Cl_2]_2$, $AgSbF_6$, $Cu(OAc)_2 \cdot H_2O$ at 100 °C for 2 h. The structure of the product **3a** was confirmed by X-ray crystallographic analysis.[14]

Table 1. Optimization of reaction conditions.[a]



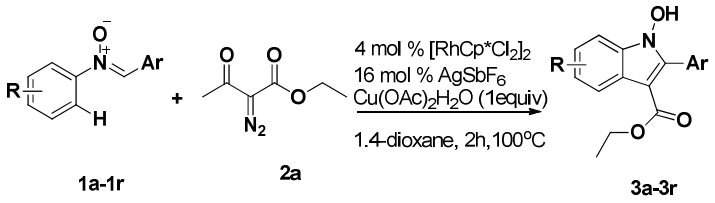
entry	additive 1	additive 2 (x equiv)	solvent	yield (%) **3a** (**4a**)
1	$AgSbF_6$	PivOH (2)	1,4-dioxane	35 (10)
2	$AgSbF_6$	AcONa (2)	1,4-dioxane	Trace
3	$AgSbF_6$	AcOH (2)	1,4-dioxane	Trace
4	$AgSbF_6$	$Cu(OAc)_2$ (2)	1,4-dioxane	57 (4)
5	$AgSbF_6$	$Cu(OAc)_2 \cdot H_2O$ (2)	1,4-dioxane	81 (8)
6	AgOTf	$Cu(OAc)_2 \cdot H_2O$ (2)	1,4-dioxane	46 (20)
7	AgOTs	$Cu(OAc)_2 \cdot H_2O$ (2)	1,4-dioxane	0
8	$AgNTf_2$	$Cu(OAc)_2 \cdot H_2O$ (2)	1,4-dioxane	61 (18)
9	$AgSbF_6$	$Cu(OAc)_2 \cdot H_2O$ (2)	CH_3CN	0
10	$AgSbF_6$	$Cu(OAc)_2 \cdot H_2O$ (2)	THF	27 (4)
11	$AgSbF_6$	$Cu(OAc)_2 \cdot H_2O$ (2)	MeOH	52 (6)
12	$AgSbF_6$	$Cu(OAc)_2 \cdot H_2O$ (2)	DCE	53 (20)

13	$AgSbF_6$	$Cu(OAc)_2 \cdot H_2O$ (1)	1,4-dioxane	88 (trace)
14	$AgSbF_6$	$Cu(OAc)_2 \cdot H_2O$ (1)	1,4-dioxane	0[b]
15	-	$Cu(OAc)_2 \cdot H_2O$ (1)	1,4-dioxane	0
16	$AgSbF_6$	-	1,4-dioxane	0

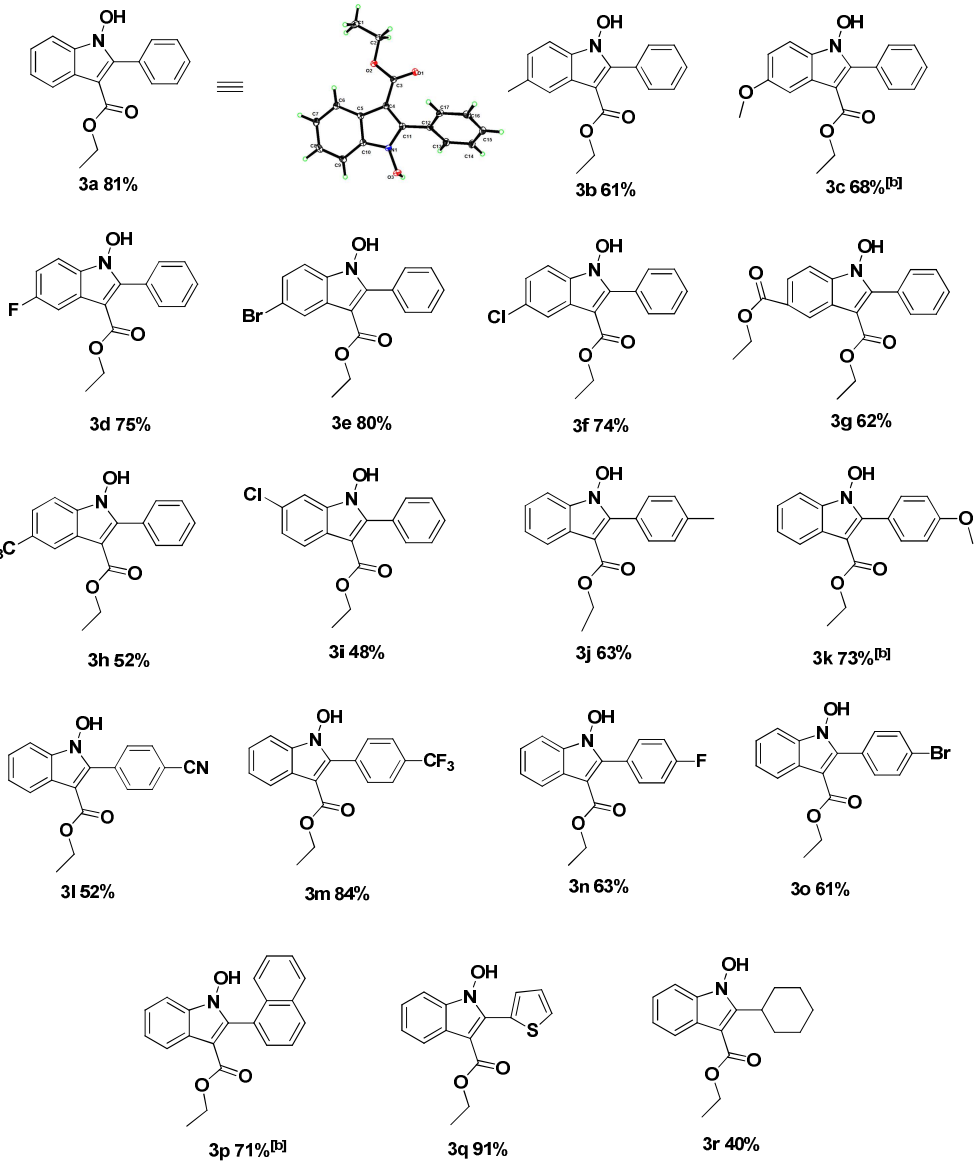
[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), $[RhCp^*Cl_2]_2$ (4 mol %), additive 1 (16 mol %), additive 2 (X equiv) in Solvent (3 mL) at 100 °C, 2 h. [b]At 25 °C or 40 °C. THF = tetrahydrofuran, DCE = 1, 2-dichloroethane.

With the optimized reaction conditions established, we next investigated the scope of different substituted arylnitrones in this [4+1] annulation reaction with diethyl 2-diazomalonate **2a** (Table 2). In general, nitrones bearing various electron-donating, electron-withdrawing, and halide substituents at the *N*-aryl moiety all underwent smooth coupling with diethyl 2-diazomalonate **2a**, and the desired 3-carboxylate *N*-hydroxyindoles were obtained with moderate to excellent yields (**3a-3r**, 48−80%). Introduction of electron-donating groups (-Me, and -OMe) to the benzene ring gave good yields (**3b** and **3c**). The reaction efficiency was maintained at a high level when halogens were introduced into the *para* position of the *N*-aryl moiety of the nitrones (**3d-3f**). Similarly, introducing ethyl carboxylate into the *para* position of the benzene ring also gave a good yield (**3g**). However, the substrates substituted by a chlorine or trifluoromethyl moiety at the

Table 2. Substrate Scope of Arylnitrones [a]



1a-1r 2a 3a-3r

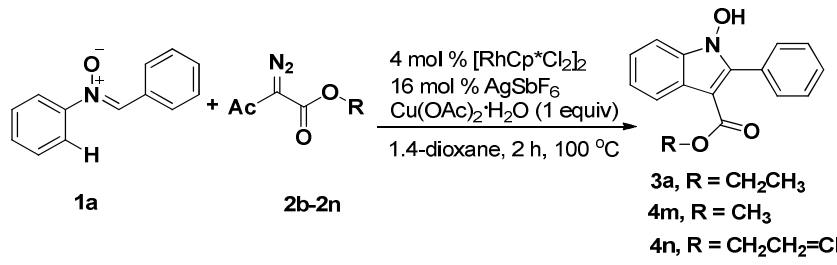


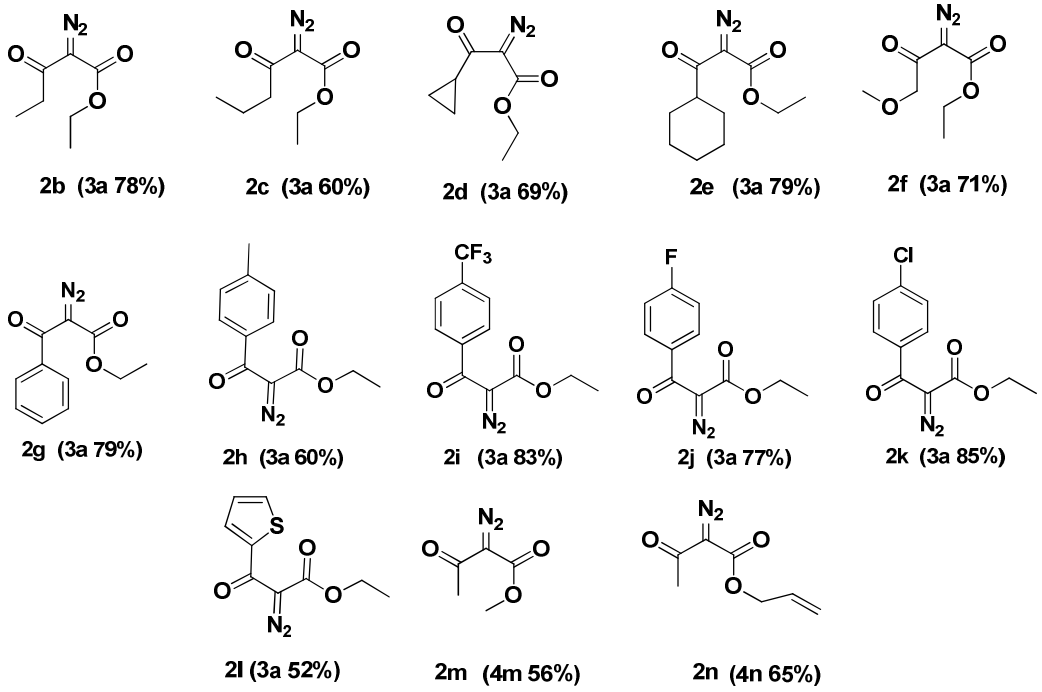
[a]Reaction conditions: 1a (0.2 mmol), 2a (0.24 mmol), $[RhCp^*Cl_2]_2$ (4 mol %), $AgSbF_6$ (16 mol %), $Cu(OAc)_2 \cdot H_2O$ (1 equiv) in 1,4-dioxane (4 mL) at 100 °C, 2 h. [b] At 80 °C, 30 min.

meta or *para* position of the *N*-aryl moiety resulted in slightly decreased yields (**3h** and **3i**). In addition, the cyclization reaction could be expanded to nitrones bearing substituents on the phenylimino moiety. For example, diversified phenylnitrones bearing methyl and methoxy groups at the *para* position of the phenylimino moiety could undergo cyclization to give the corresponding products (**3j** and **3k**) in good yields under the standard reaction conditions. Notably, various functionalized benzamides bearing cyano, trifluoromethyl, and halide moieties were compatible with the standard reaction conditions (**3l-3o**), which guaranteed further transformations. Additionally, the nitrones substituted with naphthyl or thiophene groups were also subjected to the standard reaction conditions, and the corresponding indole products (**3p** and **3q**) were obtained in good to excellent yields. Particularly remarkable was the participation of nitrones bearing an alkyl group in this reaction. Despite the instability of *C*-alkyl nitrones,[8, 15] we could still prepare the corresponding 2-alkyl-substituted *N*-hydroxyindole **3r** effectively at 40% yield.

We next explored the scope of the diazo reactants (Table 3). The coupling of nitrone **1a** and various α-diazoketoesters **2b-2n** gave the desired products in moderate to excellent yields (**3a-4n**). Dissymmetrical diazo compounds **2b-2f**, bearing various alkyl, cycloalkyl, and ether-alkyl ketone groups, could react

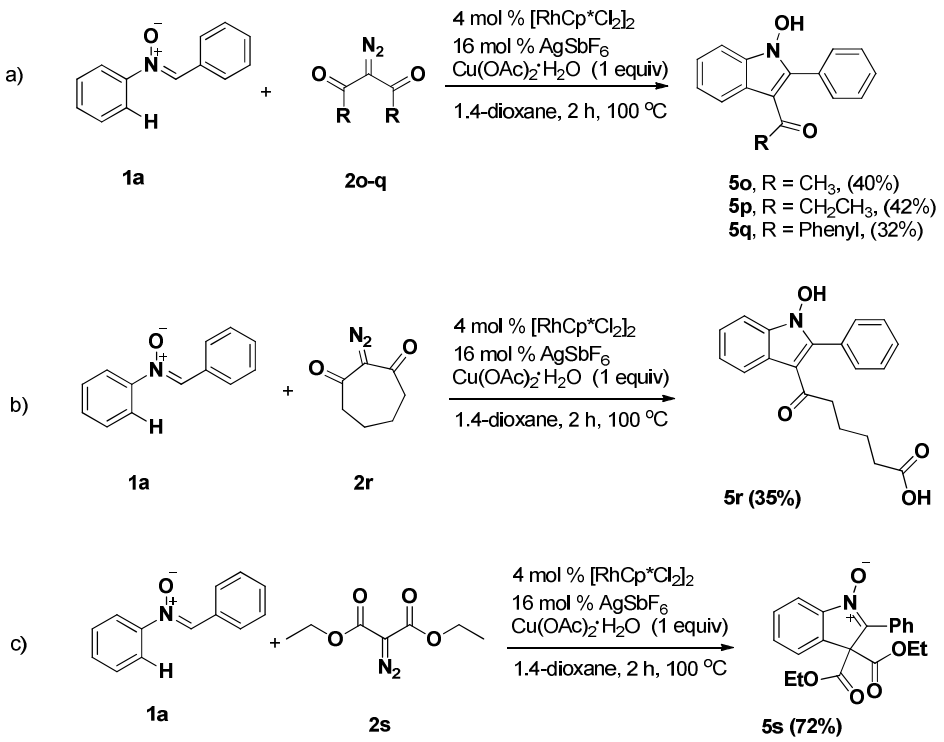
Table 3. Scope of Diazo Compounds[a]





[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), $[RhCp^*Cl_2]_2$ (4 mol %), $AgSbF_6$ (16 mol %), $Cu(OAc)_2{\cdot}H_2O$ (1 equiv) in 1,4-dioxane (4 mL) at 100 °C, 2 h.

with nitrone **1a** to give the desired product **3a** with satisfactory efficiency (60% -79% yields). Interestingly, the α-diazobenzoylacetate **2g** was also tolerated in the present cyclization reaction. In addition, when introducing electron-donating, electron-withdrawing, and halide groups into the *para*

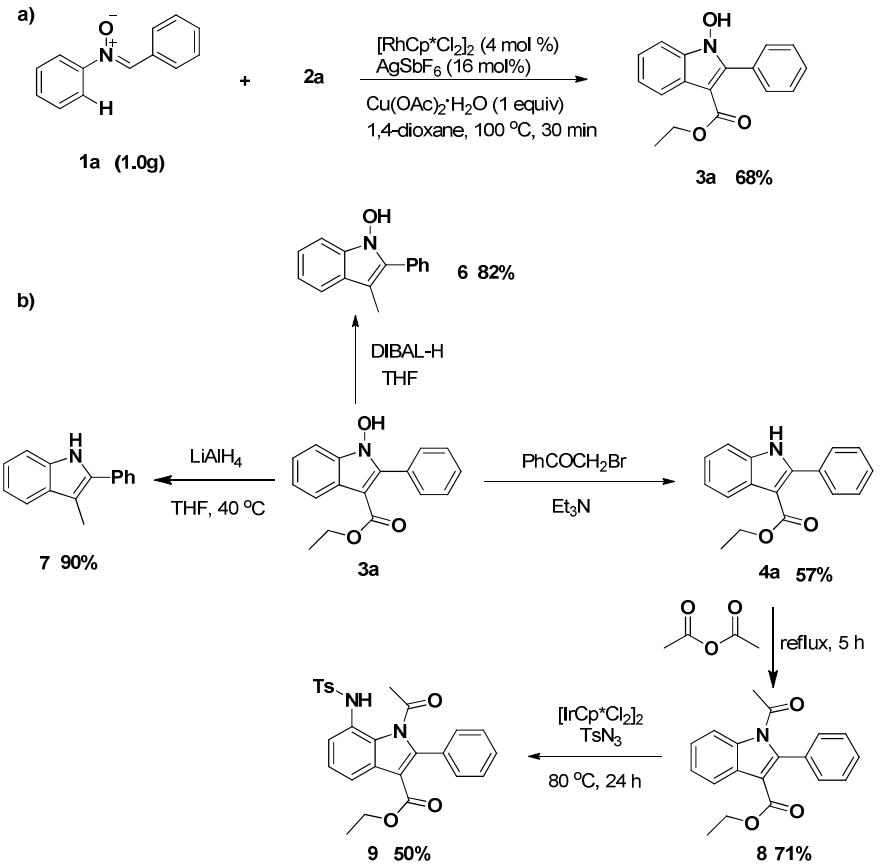


Scheme 2. Scope of Symmetry Diazo Compounds

position of the benzene ring (**2h-2k**), the desired product **3a** was also obtained in good yields. Additionally, the use of a thiophene ring instead of a benzene ring produced **3a** in moderate yield (**2l**). The scope of esters was further examined: they were all converted into the desired products in reasonable yields (**4m** and **4n**). Additionally, some symmetrical diazo compounds, such as symmetrical α-diazodiketones **2o-2q**, were also subjected to the standard reactions, and the corresponding *N*-hydroxyindoles **5o-5q** were obtained at moderate yields (Scheme 2a). Notably, a cyclic diketone diazo compound 2-diazocycloheptane-1,3-dione (**2r**) was also tolerated in the present cyclization reaction, and gave an interesting 3-ketonic acid substituted *N*-hydroxyindole (**5r**) at 35% yield (Scheme 2b). Besides, the nitrone **1a** could also react with the

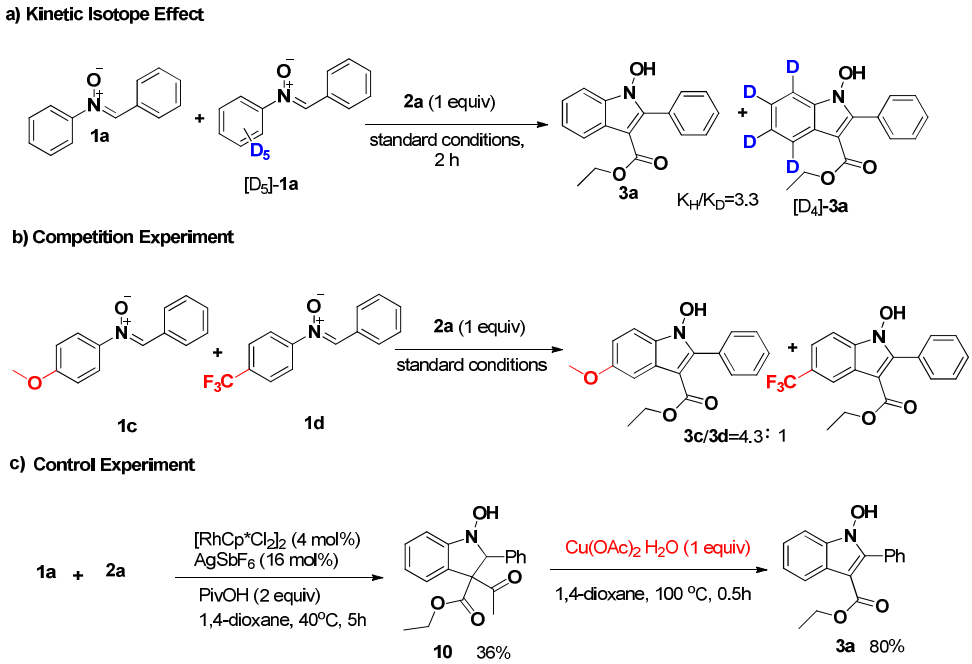
simple ethyl diazoacetate **2s** under the standard reaction conditions, but only 3,3-di-carboxylate subsituted *3H*-indole-*N*-oxides **5s** could detected in 72% yield (Scheme 2c).

To further evaluate the synthetic utility of *N*-hydroxyindole, a gram-scale preparation of product **3a** was carried out with 68% yield (Scheme 3a), and the product **3a** can also be transformed into diversified derivatives, such as 3-methyl substituted *N*-hydroxyindole (**6**) and indole (**7**) via different hydrogenation reduction by DIBAL-H and $LiAlH_4$, respectively. In addition, Compound **3a** could conveniently be transformed into 3-carboxylate indole **4a**



Scheme 3. Gram-scale preparation of **3a** and Synthetic Utilities of Indole Products

with dehydroxylation in a good yield (Scheme 3b). The resulting indole scaffold **4a** is an intriguing pharmacophore that can be transformed easily into diverse bioactive molecules. Recently, a large number of studies reported that C-7 substituted indoles exhibit interesting biological activities, such as antibacterial, antiviral, and antidiabetic properties.[16] Therefore, we attempted to derivatize these 3-carboxylate indole **4a** further. First, direct treatment of compound **4a** with acetic anhydride produced *N*-acetylindole (**8**) in 71% yield, which was further converted into 7-sulfamide substituted *N*-acetylindole (**9**), using an iridium(III)-catalyzed amidation, in 50% yield (Scheme 3b).



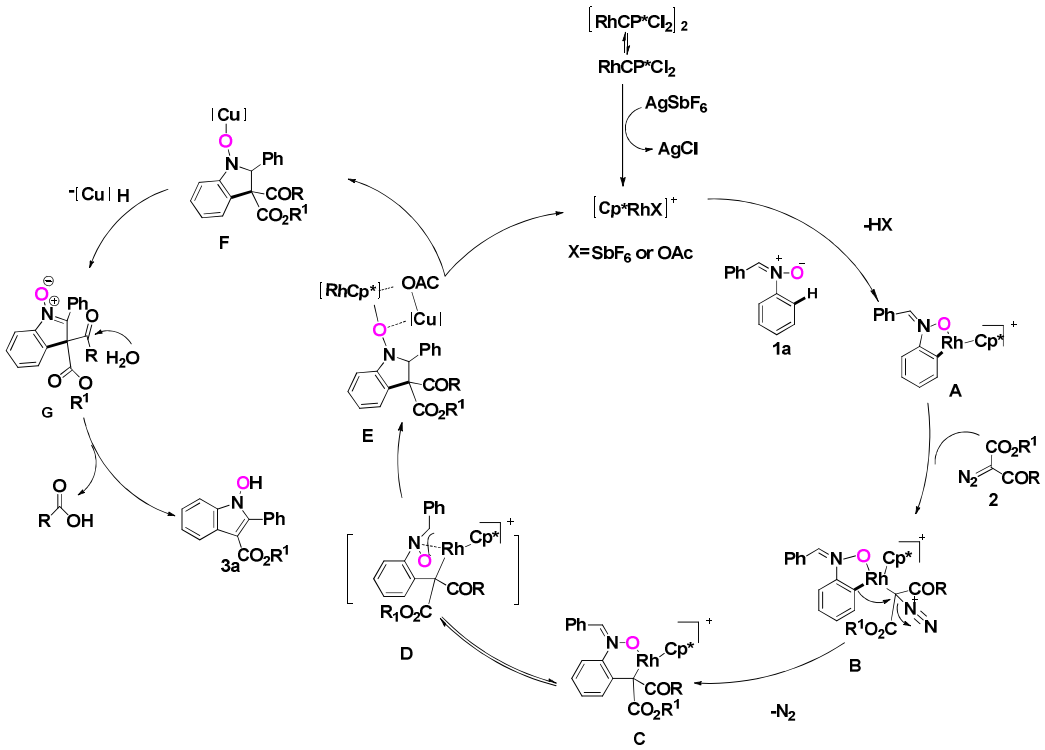
Scheme 4. Preliminary Mechanistic Studies

To gain further insight into the mechanism of this cyclization process, preliminary experiments were performed (Scheme 4). To probe the C-H activation process further, the kinetic isotope effect was determined by intermolecular competition

experiments using an equimolar mixture of **1a** and [D_5]-**1a**. A notable kinetic isotopic effect was detected (k_H/k_D = 3.3), suggesting that C−H bond cleavage might be involved in the turnover-limiting step (Scheme 4a).[17] In addition, we performed an illustrative competition reaction with an equimolar amount of **1c** and **1d** to determine the electronic preference of the reaction. The results showed that **3c** and **3d** were produced in a ratio of 4.3 : 1, which indicated that the reaction favored the electron-rich arene (Scheme 4b).[18] A control experiment involving *N*-hydroxyindolin **10** synthesized by Chang's reaction[12] condition from **1a** and **2a** was treated with $Cu(OAc)_2$•H_2O in dioxane at 100 °C indicates that the desired product **3a** could be obtained in 80% yield, suggesting that Cu slat play an important role to elimimate the acyl group (Scheme 4c).

On the basis of the preliminary mechanistic experiments and the published literature,[8b,12] a possible mechanism was proposed (Scheme 5**)**. The five-membered rhodacycle intermediate **A** is first generated by the Rh(III)-mediated *ortho* C-H bond activation of nitrone **1a**, followed by a diazo compound **2** coordination to give intermediate **B**. As reported by Yu,[19] Lee,[20] and Chang[12] et al., the subsequent diazo insertion produced the rhodacycle **C**. Intramolecular electrophilic attack of the imino moiety delivers intermediate **E** presumably via **D**,[12] in which transmetalation of the Rh catalyst with the copper salt,[21] and subsequent *γ*-hydrogen elimination,[8b] provided *3H*-indole-*N*-oxides **G**. Finally, a nucleophilic attack of H_2O toward COR results an elimination of the carboxylic group, further preparing the desired product **3a**. To explore the

eliminated carboxylic group, we employed the cyclic diketon diazo compound 2-diazocycloheptane-1, 3 - dione **2r** as the substrate. As expected, the 3-ketonic acid substituted *N*-hydroxyindole **5r** was produced 35% yield.



Scheme 5. Proposed Mechanism

Conclusion

In summary, we have developed the first synthetic route for *N*-hydroxyindole derivatives via the rhodium (III)-catalyzed C−H annulation of arylnitrones with α-diazoketoesters or α-diazodiketones. The intermolecular coupling between nitrones and diazo compounds produced *N*-hydroxyindoles by the selective cleavage of the C(N_2)-C(acyl) bond. This study will provide new opportunities

to enrich indole chemistry and will have applications in the synthesis of pharmaceutically important *N*-hydroxyindole derivatives.

Experimental Section

General Information. The reagents (chemicals) were purchased from commercial sources (J&K, TCI, Sigma-Aldrich, Adamas-beta, etc.), and used without further purification. Analytical thin layer chromatography (TLC) was HSGF 254 (0.15-0.2 mm thickness). All products were characterized by their NMR and MS spectra. ^{1}H and ^{13}C $\{^{1}H\}$ NMR spectra were recorded on a 400 MHz, 500 MHz or 600MHz instrument. Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Proton coupling patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), doublet of doublets (dd) and broad (br). High-resolution mass spectra (HRMS) were measured on Micromass Ultra Q-TOF spectrometer.

Representative procedures for the synthesis of product 3

A mixture of Arylnitrones **1** (0.2 mmol; 1 equiv), diazo compounds **2** (0.24 mmol; 1.2 equiv), $[RhCp^*Cl_2]_2$ (4.9 mg, 0.008 mol, 0.04 equiv), $AgSbF_6$ (11 mg, 0.032 mol, 0.16 equiv), and $Cu(OAc)_2 \cdot H_2O$ (33 mg, 0.2 mmol, 1 equiv) in 1,4-dioxane (4.0 mL) was stirred at 100°C for 2 h. The reaction mixture was filtered through a pad of celite washing with CH_2Cl_2 (5 mL x 3). The combined organic layers were dried with Na_2SO_4, filtered, concentrated and purified by column chromatography on silica gel (PE/EA = 10/1, v/v) to give desired product.

Analytical Characterization Data of Products.

Ethyl 1-hydroxy-2-phenyl-1H-indole-3-carboxylate (3a)

Following general procedure, Compound **3a**: 46 mg, 81% yield; white solid , mp 137 – 139 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.54 (s, 1H), 8.11 (d, J = 7.9 Hz, 1H), 7.59 (dd, J = 6.5, 3.0 Hz, 2H), 7.56 – 7.44 (m, 4H), 7.28 (dt, J = 22.9, 7.1 Hz, 2H), 4.13 (q, J = 7.1 Hz, 2H), 1.15 (t, J = 7.1 Hz, 3H) ppm. ^{13}C {^{1}H} NMR (126 MHz, DMSO-d_6) δ 163.9, 142.1, 133.3, 131.0, 128.9, 128.7, 127.4, 122.8, 122.3, 121.9, 120.9, 109.2, 98.9, 58.9, 14.0 ppm. HRMS (ESI) m/z: $[M - H]^-$ calcd for $C_{17}H_{14}NO_3$ 280.0979; Found 280.0972.

Ethyl 1-hydroxy-5-methyl-2-phenyl-1H-indole-3-carboxylate (3b)

Following general procedure, Compound **3b**: 36 mg, 61% yield; brown solid, mp 140 – 141 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.48 (s, 1H), 7.90 (s, 1H), 7.57 (dd, J = 6.5, 3.2 Hz, 2H), 7.52 – 7.45 (m, 3H), 7.41 (d, J = 8.3 Hz, 1H), 7.13 (dd, J = 8.3, 1.2 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 2.45 (s, 3H), 1.13 (t, J = 7.1 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 164.1, 142.0, 131.9, 131.1, 130.9, 129.2, 128.7, 127.4, 124.4, 122.7, 120.6, 109.0, 98.5, 58.9, 21.5, 14.1 ppm. HRMS (ESI) m/z: $[M - H]^-$ calcd for $C_{18}H_{16}NO_3$ 294.1136; Found 294.1130.

Ethyl 1-hydroxy-5-methoxy-2-phenyl-1H-indole-3-carboxylate (3c)

Following general procedure, at 80 °C, 30 min. Compound **3c**: 42 mg, 68% yield; brown solid, mp 150– 151 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.51 (s, 1H), 7.60 (d, J = 2.4 Hz, 1H), 7.57 (dd, J = 6.5, 3.2 Hz, 2H), 7.50 – 7.45 (m, 3H), 7.43 (d, J = 8.8 Hz, 1H), 6.95 (dd, J = 8.8, 2.4 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.82 (s, 3H),

1.14 (t, J = 7.1 Hz, 3H) ppm. ^{13}C {^{1}H} NMR (151 MHz, DMSO-d_6) δ 164.1, 155.5, 141.9, 131.1, 129.1, 128.7, 128.6, 127.4, 123.3, 112.9, 110.3, 102.6, 98.5, 58.9, 55.3, 14.0 ppm. HRMS (ESI) m/z: $[M - H]^-$ calcd for $C_{18}H_{16}NO_4$ 310.1085; Found 310.1077.

Ethyl 5-fluoro-1-hydroxy-2-phenyl-1H-indole-3-carboxylate (3d)

Following general procedure, Compound **3d**: 45 mg, 75% yield; brown solid, mp 138 – 140 ^{o}C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.71 (s, 1H), 7.77 (dd, J = 10.1, 2.3 Hz, 1H), 7.59 (dd, J = 6.5, 2.9 Hz, 2H), 7.55 (dd, J = 8.8, 4.5 Hz, 1H), 7.52 – 7.46 (m, 3H), 7.18 (td, J = 9.2 Hz, 2.4 Hz, 1H), 4.13 (q, J = 7.1 Hz, 2H), 1.14 (t, J = 7.1 Hz, 3H) ppm. ^{13}C {^{1}H} NMR (151 MHz, DMSO-d_6) δ 163.7, 158.7 (d, J = 234.6 Hz), 143.4, 131.0, 130.2, 129.1, 128.7, 127.5, 122.9 (d, J = 11.1 Hz), 111.3 (d, J = 26.3 Hz), 110.8 (d, J = 9.9 Hz), 105.9 (d, J = 25.3 Hz), 99.1(d, J = 4.3 Hz), 59.1, 14.1 ppm. HRMS (ESI) m/z: $[M - H]^-$ calcd for $C_{17}H_{13}FNO_3$ 298.0885; Found 298.0884.

Ethyl 5-bromo-1-hydroxy-2-phenyl-1H-indole-3-carboxylate (3e)

Following general procedure, Compound **3e**: 54 mg, 80 % yield; brown solid, mp 149 – 152 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.75 (s, 1H), 8.23 (d, J = 1.3 Hz, 1H), 7.59 (dd, J = 6.2, 2.8 Hz, 2H), 7.52-7.49 (m, 4H), 7.44 (dd, J = 8.6, 1.5 Hz, 1H), 4.14 (q, J = 7.1 Hz, 2H), 1.13 (t, J = 7.1 Hz, 3H) ppm. ^{13}C {^{1}H} NMR (151 MHz, DMSO-d_6) δ 163.6, 143.2, 132.2, 131.0, 129.1, 128.5, 127.6, 125.6, 123.9, 123.1, 114.7, 111.5, 98.7, 59.2, 14.0 ppm. HRMS (ESI) m/z: $[M - H]^-$, $[M + H]^+$ calcd for $C_{17}H_{13}BrNO_3$, $C_{17}H_{15}BrNO_3$ 358.0084, 360.0063; Found 358.0080, 360.0060.

Ethyl 5-chloro-1-hydroxy-2-phenyl-1H-indole-3-carboxylate (3f)

Following general procedure, Compound **3f**: 47 mg, 74% yield; brown solid, mp 159 – 161°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.75 (s, 1H), 8.08 (d, J = 1.8 Hz, 1H), 7.62 – 7.54 (m, 3H), 7.51 (dd, J = 6.6, 3.4 Hz, 3H), 7.33 (dd, J = 8.7, 2.0 Hz, 1H), 4.14 (q, J = 7.1 Hz, 2H), 1.14 (t, J = 7.1 Hz, 3H) ppm. ^{13}C {^{1}H} NMR (126 MHz, DMSO-d_6) δ 164.0, 143.8, 132.4, 131.5, 129.6, 128.9, 128.0, 127.1, 123.8, 123.5, 120.5, 111.5, 99.2, 59.7, 14.5 ppm. HRMS (ESI) m/z: $[M - H]^-$ calcd for $C_{17}H_{13}ClNO_3$ 314.0589; Found 314.0587.

Diethyl 1-hydroxy-2-phenyl-1H-indole-3,5-dicarboxylate (3g)

Following general procedure, Compound **3g**: 44 mg, 62% yield; brown solid, mp 153 – 154 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.83 (s, 1H), 8.84 (s, 1H), 7.93 (dd, J = 8.6, 1.3 Hz, 1H), 7.62 (dd, J = 10.1, 5.8 Hz, 3H), 7.57 – 7.40 (m, 3H), 4.35 (q, J = 7.1 Hz, 2H), 4.15 (q, J = 7.1 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H), 1.15 (t, J = 7.1 Hz, 3H) ppm. ^{13}C {^{1}H} NMR (126 MHz, DMSO-d_6) δ 166.8, 164.0, 144.3, 136.0, 131.5, 129.6, 128.9, 128.0, 124.2, 124.1, 123.9, 122.2, 109.8, 100.8, 60.9, 59.7, 14.7, 14.3 ppm. HRMS (ESI) m/z: $[M - H]^-$ calcd for $C_{20}H_{18}NO_5$ 352.1190; Found 352.1198.

Ethyl 1-hydroxy-2-phenyl-5-(trifluoromethyl)-1H-indole-3-carboxylate (3h)

Following general procedure, Compound **3h**: 36 mg, 52% yield; brown solid, mp 151– 152 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.90 (s, 1H), 8.44 (s, 1H), 7.75 (d, J = 8.6 Hz, 1H), 7.63-7.60 (m, 3H), 7.58 – 7.46 (m, 3H), 4.16 (q, J = 7.1 Hz, 2H), 1.14 (t, J = 7.1 Hz, 3H) ppm. ^{13}C {^{1}H} NMR (151 MHz, DMSO-d_6) δ 163.5, 144.2, 134.8, 131.1, 129.3, 128.3, 127.6, 126.1, 122.7 (d, J = 31.5 Hz), 121.6, 119.4 (d, J = 3.0 Hz),

118.4 (d, J = 4.5 Hz), 110.4, 100.0, 59.4, 13.9 ppm. HRMS (ESI) m/z: $[M - H]^-$ calcd for $C_{18}H_{13}F_3NO_3$ 348.0853; Found 348.0843.

Ethyl 6-chloro-1-hydroxy-2-phenyl-1H-indole-3-carboxylate(3i)

Following general procedure, Compound **3i**: 30 mg, 48% yield; brown solid, mp 158 – 161 ^oC; ^1H NMR (400 MHz, DMSO-d_6) δ 11.72 (s, 1H), 7.59 (dd, J = 8.0, 1.6 Hz, 2H), 7.56 – 7.48 (m, 4H), 7.31 – 7.21 (m, 2H), 4.13 (q, J = 7.1 Hz, 2H), 1.09 (t, J = 7.1 Hz, 3H) ppm. ^{13}C {^1H} NMR (151 MHz, DMSO-d_6) δ 164.7, 139.0, 134.6, 130.0, 129.1, 128.4, 128.2, 124.5, 123.6, 122.1, 118.1, 108.5, 101.9, 60.4, 13.8 ppm. HRMS (ESI) m/z: $[M - H]^-$ calcd for $C_{17}H_{13}ClNO_3$ 314.0589; Found 314.0586.

Ethyl 1-hydroxy-2-(p-tolyl)-1H-indole-3-carboxylate (3j)

Following general procedure, Compound **3j**: 37 mg, 63% yield; brown solid, mp 138 – 140 ^oC; ^1H NMR (500 MHz, Acetone-d_6) δ 10.39 (s, 1H), 8.22 (d, J = 8.0 Hz, 1H), 7.68 – 7.42 (m, 3H), 7.36 – 7.28 (m, 3H), 7.25 (t, J = 7.5 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 2.43 (s, 3H), 1.20 (t, J = 7.1 Hz, 3H) ppm. ^{13}C {^1H} NMR (126 MHz, DMSO-d_6) δ 164.5, 142.8, 138.8, 133.9, 131.4, 128.5, 126.5, 123.2, 122.8, 122.4, 121.5, 109.7, 99.3, 59.4, 21.5, 14.6 ppm. HRMS (ESI) m/z: $[M - H]^-$ calcd for $C_{18}H_{16}NO_3$ 294.1136; Found 294.1135.

Ethyl 1-hydroxy-2-(4-methoxyphenyl)-1H-indole-3-carboxylate(3k)

Following general procedure, at 80 °C, 30 min. Compound **3k**: 45 mg, 73% yield; brown solid, mp 147– 150^oC; The two isomers were inseparable under previous purification conditions. ^1H NMR (400 MHz, DMSO-d_6) δ 11.49 (s, 1H), 8.09 (d, J = 7.9 Hz, 1H), 7.52 (dd, J = 14.5, 8.3 Hz, 3H), 7.26 (dt, J = 21.7, 7.1 Hz, 2H), 7.05 (d, J

= 8.7 Hz, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.84 (s, 3H), 1.19 (t, *J* = 7.1 Hz, 3H) ppm. $^{13}C\{^{1}H\}$ NMR (126MHz, DMSO-d_6) δ 164.5, 160.2, 142.7, 133.9, 133.0, 123.2, 122.9, 122.4, 121.4, 121.4, 113.4, 109.6, 99.1, 59.3, 55.7, 14.7 ppm. HRMS (ESI) m/z: $[M - H]^-$ calcd for $C_{18}H_{16}NO_4$ $[M - H]^-$: 310.1085; Found 310.1091.

Ethyl 2-(4-cyanophenyl)-1-hydroxy-1H-indole-3-carboxylate (3l)

Following general procedure, Compound **3l**: 32 mg, 52% yield; brown solid, mp 163 – 167 ^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.75 (s, 1H), 8.13 (d, *J* = 7.8 Hz, 1H), 7.99 (d, *J* = 7.9 Hz,2H), 7.81 (d, *J* = 7.9 Hz, 2H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.33 (dt, *J* = 31.9, 7.2 Hz,2H), 4.16 (q, *J* = 6.9 Hz, 2H), 1.17 (t, *J* = 6.9 Hz, 3H) ppm. $^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO-d_6) δ 164.2, 140.4, 134.4, 134.0, 132.6, 131.9, 123.9, 122.8, 122.6, 121.7, 119.2, 111.9, 109.9, 100.3, 59.7, 14.5 ppm. HRMS (ESI) m/z: $[M - H]^-$ calcd for $C_{18}H_{13}N_2O_3$ 305.0932; Found 305.0931.

Ethyl 1-hydroxy-2-(4-(trifluoromethyl)phenyl)-1H-indole-3-carboxylate (3m)

Following general procedure, Compound **3m**: 59 mg, 84% yield; brown solid, mp 146 – 150 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.70 (s, 1H), 8.12 (d, *J* = 7.9 Hz, 1H), 7.88-7.81 (m, 4H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.31 (dt, *J* = 25.3, 7.1 Hz, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 1.15 (t, *J* = 7.1 Hz, 3H) ppm. $^{13}C\{^{1}H\}$ NMR (125 MHz, DMSO-d_6) δ 164.2, 140.8, 133.9 (d, *J* = 24.2 Hz), 132.4, 129.6 (d, *J* = 32.1 Hz), 125.8, 124.8, 123.8, 123.6, 122.8, 122.6, 121.6, 109.9, 100.1, 59.6, 14.5 ppm. HRMS (ESI) m/z: $[M - H]^-$ calcd for $C_{18}H_{13}F_3NO_3$348.0853; Found 348.0853.

Ethyl 2-(4-fluorophenyl)-1-hydroxy-1H-indole-3-carboxylate (3n)

Following general procedure, Compound **3n**: 38 mg, 63% yield; brown solid, mp 160– 162 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.59 (s, 1H), 8.11 (d, J = 7.9 Hz, 1H), 7.65 (dd, J = 8.6, 5.6 Hz, 2H), 7.53 (d, J = 8.0 Hz, 1H), 7.43 – 7.16 (m, 4H), 4.14 (q, J = 7.1 Hz, 2H), 1.17 (t, J = 7.1 Hz, 3H) ppm. ^{13}C {^{1}H} NMR (126 MHz, DMSO-d_6) δ 164.4, 162.9 (d, J = 246.2 Hz), 141.5, 133.8 (d, J = 3.3 Hz), 133.8, 125.8 (d, J = 3.1 Hz), 123.5, 122.7, 122.6, 121.5, 115.0 (d, J = 21.7 Hz), 109.7, 99.6, 59.5, 14.6 ppm. HRMS (ESI) m/z: [M - H]$^{-}$ calcd for $C_{17}H_{13}FNO_3$ 298.0885; Found; 298.0883.

Ethyl 2-(4-bromophenyl)-1-hydroxy-1H-indole-3-carboxylate (3o)

Following general procedure, Compound **3o**: 44 mg, 61% yield; brown solid, mp 148 – 150 ^{o}C; ^{1}H NMR (400 MHz, DMSO) δ 11.64 (s, 1H), 8.10 (d, J = 7.8 Hz, 1H), 7.77 – 7.64 (m, 2H), 7.54 (dt, J = 4.5, 2.5 Hz, 3H), 7.36 – 7.29 (m, 1H), 7.28 – 7.23 (m, 1H), 4.15 (q, J = 7.1 Hz, 2H), 1.18 (t, J = 7.1 Hz, 3H) ppm. ^{13}C {^{1}H} NMR (101 MHz, DMSO) δ 164.3, 141.3, 133.9, 133.6, 131.0, 128.7, 123.6, 123.0, 122.7, 122.6, 121.6, 109.8, 99.7, 59.5, 14.6. ppm. HRMS (ESI) m/z: [M - H]$^{-}$, [M + H]$^{+}$ calcd for $C_{17}H_{13}BrNO_3$, $C_{17}H_{15}BrNO_3$ 358.0084, 360.0063; Found 358.0090, 360.0072.

Ethyl 1-hydroxy-2-(naphthalen-1-yl)-1H-indole-3-carboxylate (3p)

Following general procedure, at 80 °C, 30 min. Compound **3p**: 47 mg, 71% yield; brown solid, mp 138 – 140 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.54 (s, 1H), 8.18 (d, J = 7.7 Hz, 1H), 8.09 (d, J = 8.0 Hz, 1H), 8.03 (d, J = 8.1 Hz, 1H), 7.69 – 7.54 (m, 4H), 7.50 -7.44 (m, 2H), 7.34 (dt, J = 19.4, 7.4 Hz, 2H), 3.90 (q, J = 7.1 Hz, 2H), 0.76 (t, J = 7.1 Hz, 3H) ppm. ^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ 164.2, 140.9, 133.9,

133.3, 132.6, 129.6, 129.4, 128.6, 128.2, 126.9, 126.4, 125.9, 125.4, 123.4, 122.8, 122.5, 121.3, 109.8, 101.3, 59.1, 14.0 ppm. HRMS (ESI) m/z: $[M - H]^-$ calcd for $C_{21}H_{16}NO_3$ 330.1136; Found 330.1143.

Ethyl 1-hydroxy-2-(thiophen-2-yl)-1H-indole-3-carboxylate (3q)

Following general procedure, Compound **3q**: 52 mg, 91% yield; brown solid, mp 156– 157 ^oC; ^1H NMR (400 MHz, DMSO-d_6) δ 11.83 (s, 1H), 8.08 (d, J = 7.9 Hz, 1H), 7.84 (dd, J = 5.1, 1.1 Hz, 1H), 7.73 (dd, J = 3.7, 1.1 Hz, 1H), 7.51 (d, J = 8.1 Hz, 1H), 7.37 – 7.28 (m, 1H), 7.25-7.22 (m, 2H), 4.24 (q, J = 7.1 Hz, 2H), 1.27 (t, J = 7.1 Hz, 3H) ppm. ^{13}C {^1H} NMR (126 MHz, DMSO-d_6) δ 164.4, 135.4, 134.0, 132.4, 129.8, 128.4, 127.1, 123.7, 122.7, 122.8, 121.7, 109.6, 100.0, 59.7, 14.7 ppm. HRMS (ESI) m/z: $[M - H]^-$ calcd for $C_{15}H_{12}NO_3S$ 286.0543; Found 286.0541.

Ethyl 2-cyclohexyl-1-hydroxy-1H-indole-3-carboxylate (3r)

Following general procedure, Compound **3r**: 23 mg, 40% yield; brown oil; ^1H NMR (500 MHz, DMSO-d_6) δ 11.56 (s, 1H), 7.95 (d, J = 7.7 Hz, 1H), 7.39 (d, J = 7.9 Hz, 1H), 7.29 – 6.99 (m, 2H), 4.27 (q, J = 7.1 Hz, 2H), 3.924-3.869 (m, 1H), 2.178-2.103 (m, 2H), 1.82 (d, J = 12.7 Hz, 2H), 1.731-1.654 (m, 3H), 1.35 (t, J = 7.1 Hz, 3H), 1.33 – 1.20 (m, 3H) ppm. ^{13}C {^1H} NMR (151 MHz, DMSO-d_6) δ 164.8, 148.5, 133.2, 122.1, 122.0, 121.6, 120.9, 108.7, 97.0, 59.0, 35.1, 29.1, 26.5, 25.5, 14.5 ppm. HRMS (ESI) m/z: $[M - H]^-$ calcd for $C_{17}H_{20}NO_3$ 286.1449; Found 286.1442.

Methyl 1-hydroxy-2-phenyl-1H-indole-3-carboxylate (4m)

Following general procedure, Compound **4m**: 30 mg, 56% yield; brown solid, ^1H NMR (500 MHz, DMSO-d_6) δ 11.57 (s, 1H), 8.10 (d, J = 7.9 Hz, 1H), 7.71 – 7.56 (m,

2H), 7.56 – 7.42 (m, 4H), 7.37 – 7.30 (m, 1H), 7.30 – 7.23 (m, 1H), 3.68 (s, 3H) ppm. ^{13}C {^{1}H} NMR (126 MHz, DMSO-d_6) δ 164.9, 142.7, 133.9, 131.5, 129.3, 128.0, 123.4, 122.7, 122.5, 121.5, 109.7, 99.3, 51.0 ppm. HRMS (ESI) m/z: [M - H]$^-$ calcd for $C_{16}H_{12}NO_3$ 266.0823; Found 266.0821.

Allyl 1-hydroxy-2-phenyl-1H-indole-3-carboxylate (4n)

Following general procedure, Compound **4n**: 38 mg, 65% yield; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.57 (s, 1H), 8.11 (d, J = 7.6 Hz, 1H), 7.64 – 7.57 (m, 2H), 7.54 (d, J = 8.1 Hz, 1H), 7.53 – 7.46 (m, 3H), 7.36 – 7.23 (m, 2H), 5.90 (ddt, J = 18.1, 10.4, 5.3 Hz, 1H), 5.14 (d, J = 1.3 Hz, 1H), 5.13 – 5.08 (m, 1H), 4.64 (dd, J = 5.3, 1.3 Hz, 2H) ppm. ^{13}C {^{1}H} NMR (126 MHz, DMSO-d_6) δ 164.1, 142.9, 133.9, 133.5, 131.5, 129.4, 129.3, 128.0, 123.4, 122.8, 122.6, 121.5, 117.5, 109.8, 99.2, 64.1 ppm. HRMS (ESI) m/z: [M - H]$^-$ calcd for $C_{18}H_{14}NO_3$ 292.0979; Found 292.0987.

1-(1-Hydroxy-2-phenyl-1H-indol-3-yl)ethanone (5o)

Following general procedure, Compound **5o**: 20 mg, 40% yield; brown solid, mp 153– 157 ^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.56 (s, 1H), 8.30 (d, J = 7.9 Hz, 1H), 7.59 (br, 5H), 7.52 (d, J = 8.0 Hz, 1H), 7.33 (t, J = 7.4 Hz, 1H), 7.27 (t, J = 7.4 Hz, 1H), 1.95 (s, 3H) ppm. ^{13}C {^{1}H} NMR (126 MHz, DMSO-d_6) δ 193.3, 143.0, 133.8, 131.4, 130.3, 130.0, 128.8, 123.7, 123.0, 122.7, 122.0, 110.5, 109.5, 26.9 ppm. HRMS (ESI) m/z: [M - H]$^-$ calcd for $C_{16}H_{12}NO_2$ 250.0874; Found 250.0881.

1-(1-Hydroxy-2-phenyl-1H-indol-3-yl)propan-1-one (5p)

Following general procedure, Compound **5p**: 22 mg, 42% yield; brown solid, mp 152– 155 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.49 (s, 1H), 8.28 (d, J = 7.8 Hz, 1H),

7.63-7.53 (m, 5H), 7.50 (d, J = 8.0 Hz, 1H), 7.28 (dt, J = 25.5, 7.1 Hz, 2H), 2.27 (q, J = 7.3 Hz, 2H), 0.86 (t, J = 7.3 Hz, 3H) ppm. ^{13}C {^{1}H} NMR (126 MHz, DMSO-d_6) δ 196.6, 142.4, 133.8, 131.2, 130.5, 129.9, 128.8, 123.6, 122.9, 122.7, 122.0, 110.0, 109.5, 34.5, 9.2 ppm. HRMS (ESI) m/z: [M - H]$^-$ calcd for $C_{17}H_{14}NO_2$ 264.1030; Found 264.1025.

(1-Hydroxy-2-phenyl-1H-indol-3-yl)(phenyl)methanone (5q)

Following general procedure, Compound **5q**: 20 mg, 32% yield; brown solid, mp 153– 155 ^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.67 (s, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 8.1 Hz, 1H), 7.47 – 7.39 (m, 2H), 7.37 – 7.30 (m, 3H), 7.31 – 7.25 (m, 1H), 7.25 – 7.18 (m, 4H), 7.13 (t, J = 7.7 Hz, 2H) ppm. ^{13}C {^{1}H} NMR (126 MHz, DMSO-d_6) δ 191.7, 142.7, 140.3, 134.3, 131.6, 131.4, 129.3, 129.2, 129.0, 128.1, 123.8, 123.6, 122.7, 121.2, 109.8, 108.9 ppm. HRMS (ESI) m/z: [M - H]$^-$ calcd for $C_{21}H_{14}NO_2$ 312.103; Found: 312.1025.

6-(1-Hydroxy-2-phenyl-1H-indol-3-yl)-6-oxohexanoic acid (5r)

Following general procedure, Compound **5r**: 24 mg, 35% yield; brown solid, mp 156 – 160^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.07 (s, 1H), 11.92 (s, 1H), 8.17 (d, J = 7.4 Hz, 1H), 7.76 – 7.49 (m,5H), 7.42 (d, J = 7.3 Hz, 1H), 7.32 – 7.04 (m, 2H), 2.39 (t, J = 7.4 Hz, 2H), 2.05 (t, J = 7.4 Hz, 2H), 1.47 (br, 2H), 1.27 (br, 2H) ppm. ^{13}C {^{1}H} NMR (126 MHz, DMSO-d_6) δ 196.9, 174.7, 144.8, 135.9, 133.3, 130.3, 129.8, 128.9, 127.5, 123.3, 122.2, 122.0, 114.4, 112.1, 41.3, 33.9, 24.7, 24.5 ppm. HRMS (ESI) m/z: [M - H]$^-$ calcd for $C_{20}H_{18}NO_4$ 336.1241; Found 336.1247.

3,3-Bis(ethoxycarbonyl)-2-phenyl-3H-indole -1-oxide (5s)

Following general procedure, Compound **5s**: 51 mg, 72% yield; white solid, ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42 (dd, J = 8.0, 1.8 Hz, 2H), 7.81 (d, J = 7.6 Hz, 1H), 7.76 (d, J = 7.6 Hz, 1H), 7.72 (dd, J = 7.7, 1.2 Hz, 1H), 7.66 (td, J = 7.4, 1.1 Hz, 1H), 7.59 – 7.49 (m, 3H), 4.22 – 4.09 (m, 4H), 1.01 (t, J = 7.1 Hz, 6H) ppm. ^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ 165.6, 147.5, 140.1, 131.4, 131.1, 130.9, 129.4, 128.8, 128.1, 127.8, 124.4, 115.5, 66.7, 63.5, 14.0 ppm. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{20}H_{20}NO_5$ 353.1263; Found 353.1261.

3-Methyl-2-phenyl-1H-indol-1-ol (6)

Diisobutylaluminium hydride 1M/toluene (1.1 mL, 1.1 mmol) is added dropwise to a stirred solution of **3a** (100 mg, 0.36 mmol) in THF (10 mL) at 0ºC. The reaction is stirred at room temperature for 0.5 hours. Methanol (1 mL) is added over the mixture at 0ºC and stirred for 10min. Then, water (3 mL) and EtOAc (15 mL) is added. The precipitate formed is filtered through celite and all the solvents are removed in vacuum to obtain a crude product. The crude product was purified by a silica gel column chromatography (PE/EA = 8/1, v/v) to obtain **6** (64 mg, 81%). ^{1}H NMR (400 MHz, DMSO) δ 10.80 (s, 1H), 7.61 (d, J = 7.2 Hz, 2H), 7.55 - 7.49 (m, 3H), 7.44 - 7.37 (m, 2H), 7.19 (t, J = 7.5 Hz, 1H), 7.05 (t, J = 7.4 Hz, 1H), 2.31 (s, 3H) ppm. ^{13}C {^{1}H} NMR (101 MHz, DMSO) δ 135.1, 134.9, 130.9, 130.3, 128.7, 127.9, 124.3, 122.4, 119.5, 119.0, 109.1, 104.3, 9.9 ppm. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{15}H_{14}NO$ 224.107; Found 224.1066

3-Methyl-2-phenyl-1H-indole (7)

Lithium aluminum hydride (27 mg, 0.72 mmol) was added to a tetrahydrofuran solution (10 ml) of **3a** (100 mg, 0.36 mmol) under ice-cooling. The resulting mixture was warmed up to 40 ^{o}C and then stirred 2 h. After completion of the reaction, water and a 15 percent aqueous sodium hydroxide solution were added thereto and stirred. The solid formed was removed by filtration, and the solvent was distilled off under reduced pressure to obtain a crude product. The crude product was purified by a silica gel column chromatography (PE/EA = 10/1, v/v) to obtain **7** (67 mg, 90%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.15 (s, 1H), 7.67 (d, J = 8.2 Hz, 2H), 7.54 - 7.49 (m, 3H), 7.43 - 7.31 (m, 2H), 7.10 (t, J = 7.5 Hz, 1H), 7.01 (t, J = 7.4 Hz, 1H), 2.41 (s, 3H) ppm. ^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ 136.4, 134.2, 133.6, 129.9, 129.2, 128.0, 127.4, 122.0, 119.0, 111.5, 107.2, 118.9, 10.3 ppm. HRMS (ESI) m/z: [M + H]$^{+}$ calcd for $C_{15}H_{14}N$ 207.1043; Found 207.1036.

A Gram-Scale Synthesis of ethyl-2-phenyl-1H-indole-3-carboxylate(4a)

The dry 50 mL round bottom flask were added **1a** (1.0 g, 5.07 mmol, 1 equiv), **2a** (0.950 g, 6.08 mmol, 1.2 equiv), $[RhCp^*Cl_2]_2$ (125 mg, 0.203 mmol, 0.04 equiv), $AgSbF_6$ (279 mg, 0.812 mmol, 0.16 equiv), $CuOAc{\cdot}H_2O$ (1.01g, 5.07 mmol, 1 equiv) and 20 mL 1, 4-dioxane. The mixture was stirred at 100 °C for 15 min with a condenser pipe. After that, the mixture was added 2-Bromoacetophenone (1.01 g, 5.07 mol, 1 equiv), Triethylamine (1.18 g, 11.6 mol, 2.3 equiv) and 10 ml MeOH and was stirred at r.t. for 12 h. After that, the reaction mixture was filtered through a pad of celite washing with CH_2Cl_2 (15 mL x 3). The combined organic layers were dried with Na_2SO_4, filtered, concentrated and purified by column chromatography on silica

gel (PE/EA = 10/1, v/v) to give desired product **4a** (0.97 g, 57% yield). White solid; mp 118 – 120 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.11 (s, 1H), 8.05 (dd, J = 6.5, 2.1 Hz, 1H), 7.78 – 7.58 (m, 2H), 7.57 – 7.40 (m, 4H), 7.30 – 7.11 (m, 2H), 4.19 (q, J = 7.1 Hz, 2H), 1.22 (t, J = 7.1 Hz, 3H) ppm. ^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 197.5, 144.6, 135.9, 133.4, 130.3, 129.7, 128.9, 127.5, 123.2, 122.1, 121.9, 114.2, 112.0, 34.8, 9.2 ppm. HRMS (ESI) m/z: $[M + H]^-$ calcd for $C_{17}H_{16}NO_2$ 266.1176; Found 266.1171.

Synthesis of ethyl 1-acetyl-2-phenyl-1H-indole-3-carboxylate (8)

4a (100 mg, 0.377 mmol, 1equiv), triethylamine (57.21 mg, 1.5 equiv) and *N*, *N*-dimethyl-4-aminopyridine (1 mg, 0.02 equiv) were dissolved in acetic anhydride (10 mL). The reaction mixture was reflux at 140 °C for 5 h. After the reaction, the reaction mixture was concentrated under reduced pressure and purified by column chromatography on silica gel (PE/EA = 8/1, v/v) to give desired product **8**. (82.2 mg, 71% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 – 8.29 (m, 1H), 8.24 – 8.18 (m, 1H), 7.54 – 7.45 (m, 5H), 7.45 – 7.35 (m, 2H), 4.20 (q, J = 7.1 Hz, 2H), 1.91 (s, 3H), 1.16 (t, J = 7.1 Hz,3H) ppm.^{13}C {^{1}H} NMR (150 MHz, DMSO-d_6) δ 172.1, 163.8, 144.4, 136.0, 132.6, 130.9, 129.8, 128.5, 126.9, 125.8, 124.7, 121.5, 115.9, 111.5, 60.1, 27.9, 14.1 ppm. HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{19}H_{17}NO_3Na$ 330.1101; Found 330.1099.

Synthesis of Compound 9

The dry sealed tube was charged with indole **8** (30.7 mg, 0.1 mmol), tosyl azide (29.6 mg, 0.15 mmol, 1.5 equiv), $[IrCp^*Cl_2]_2$ (4.0 mg, 5 mol %), $AgSbF_6$ (6.9 mg, 20

mol %), AgOAc (33.4 mg, 2 equiv), HOAc (12 mg, 2 equiv) and 1, 2-dichloroethane (1 mL). The mixture was stirred at 80 °C for 24 h, and organic solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (PE/EA = 4/1, v/v) to give the product **9** (23.8 mg, 50%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.87 (s, 1H), 7.90 (dd, J = 6.9, 2.5 Hz, 1H), 7.59 – 7.49 (m, 5H), 7.44 (dd, J = 5.1, 3.3 Hz, 2H), 7.43 – 7.32 (m, 2H), 7.29 (d, J = 8.0 Hz, 2H), 3.99 (q, J = 7.1 Hz, 2H), 2.32 (s, 3H), 1.87 (s, 3H), 0.74 (t, J = 7.1 Hz, 3H) ppm. ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ 172.2, 167.2, 145.2, 144.1, 137. 0, 136.6, 132.5, 130.7, 130.63, 130.2, 130.0, 128.6, 127.2, 126.5, 118.3, 116.4, 112.0, 110.4, 61.8, 28.1, 21.4, 13.4 ppm. HRMS (ESI) m/z: [M - H]$^-$ calcd for $C_{26}H_{23}N_2O_5S$ 475.1333; Found 475.1339.

ASSOCIATED CONTENT

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Notes

The authors declare no competing financial interests.

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Supporting Information.

The Supporting Information is available free of charge on the

ACS Publications website at DOI: xxxxx.

X-ray crystal structure of compound **3a** (CIF)

^{1}H and ^{13}C NMR spectra (PDF)

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