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Synthesis of 2,3-Disubstituted *NH* Indoles *via* Rhodium(III)-Catalyzed C–H Activation of Arylnitrones and Coupling with Diazo Compounds

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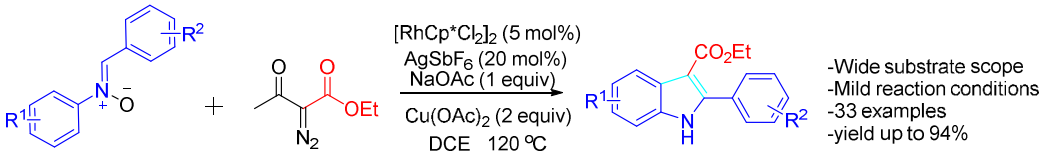


Abstract: A rhodium-catalyzed intermolecular coupling between arylnitrones and diazo compounds by C-H activation/[4+1] annulation with a C(N_2)-C(acyl) bond cleavage is reported, and 2,3-disubstituted *NH* indoles are directly synthesized in up to a 94% yield. A variety of functional groups are applicable to this reaction to give the corresponding products with high selectivity. Compared to other previously reported Rh(III)-catalyzed synthesis of homologous series, this method is simpler, more general, and more efficient.

Introduction

As one of the most abundant and relevant heterocycles, the indole unit has been found in many natural products, agrochemicals, pharmaceuticals, and organic functional materials.[1] In the last few decades, many efforts

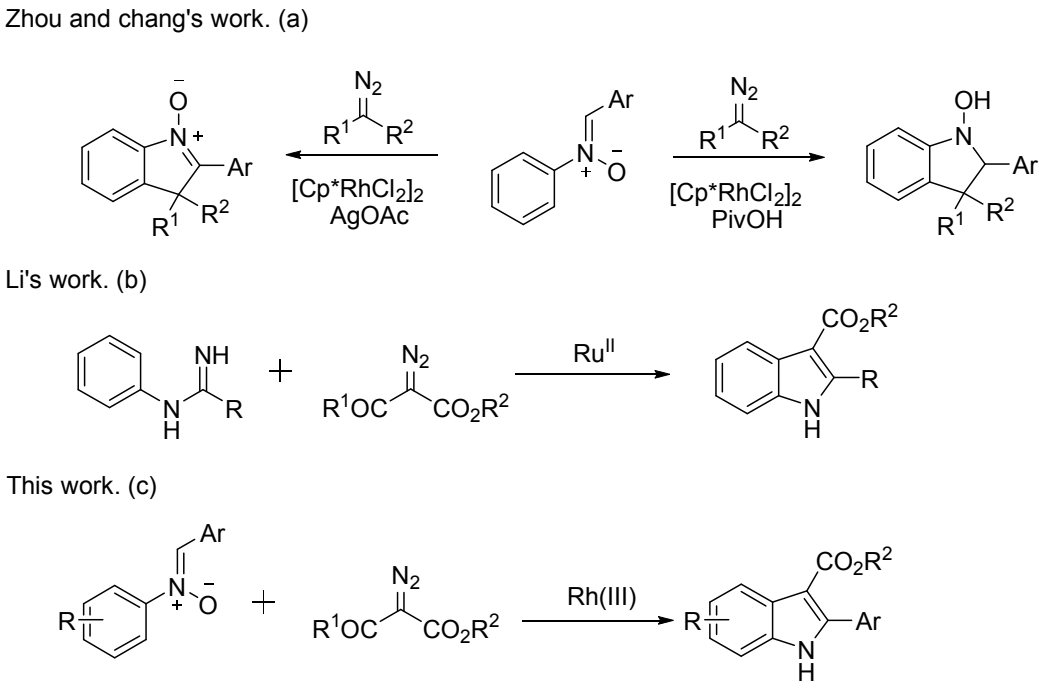
have been made to develop new synthetic methods for the generation of indole models and a number of strategies have been reported.[2-4] However, *via* these methods, harsh reaction conditions, low atom economy and low functional-group tolerance often limit the versatility of indole synthesis. Finding new synthetic methods to synthesis indoles is still in great demand.

Over the past few decades, transition-metal-catalyzed direct C-H bond activation has been extensively investigated as a powerful strategy for direct synthesis of complexed structures.[5] Therefore, a wide variety of directing groups have been successfully explored.[6] As a relatively weaker ligating group, nitrones have been functioned as a directing group in rhodium-catalyzed C-H activation reactions because of its easy accessbility since 2013.[7] Then, many heterocyclic compounds have been synthesized by this building block.[8] Yu and co-workers demonstrated the first rhodium-catalyzed intermolecular coupling of arenes with diazomalonates *via* C-H activation.[9] Subsequently, many groups have made great progress in different heterocycle-species by such method.[10] For example, Zhou and Chang's groups developed a rhodium-(III)-catalyzed regioselective synthesis of 3*H*-indole-*N*-oxides from nitrones and diazo compounds (Scheme 1a).[11] More recently, Li's group reported ruthenium(II)-catalyzed of synthesis 2,3-disubstituted *NH*

indoles and 3*H*-indoles with imidamides and diazo compounds in 2016 (Scheme 1b).[12]

However, transformations on more challenging nitrones with diazo compounds to access *NH* indoles are thus far unprecedented. Encouraged by strategies above, we herein report the Rh(III)-catalyzed C-H functionalization of nitrones with diazo compounds to deliver the corresponding 2,3-disubstituted *NH* indoles under mild reaction conditions (Scheme 1c).

Scheme 1. Intermolecular Coupling with Diazo Com-pounds.

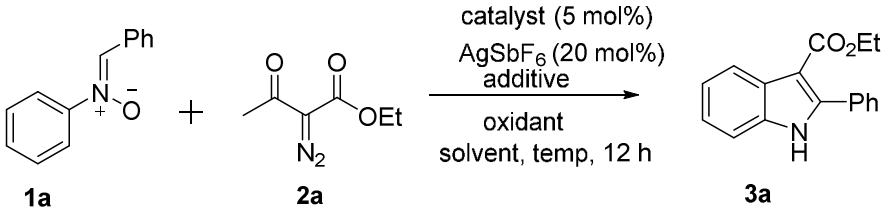


Results and Discussion Sections

We started our studies by testing different reaction conditions for the desired product of 2,3-disubstituted *NH* indole **3a** (Table 1). As we know,

Pd(II), Ru(II), and Rh(III) catalysts can easily react with diazo compounds to generate metal carbene intermediate.[13] Our first investigation began with nitrone (**1a**) and α-acyldiazoacetate (**2a**) in the

Table 1. Optimization of the Reaction Conditions[a]



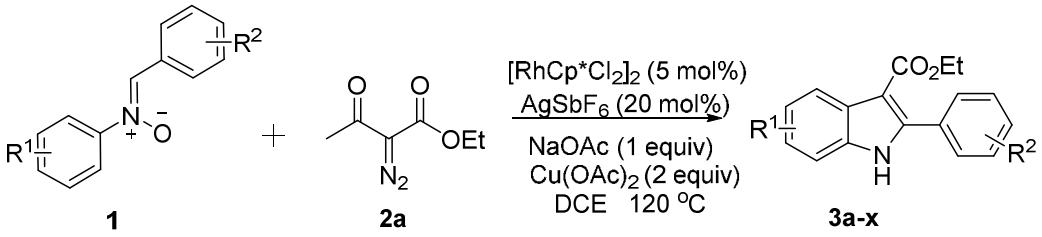
1a **2a** **3a**

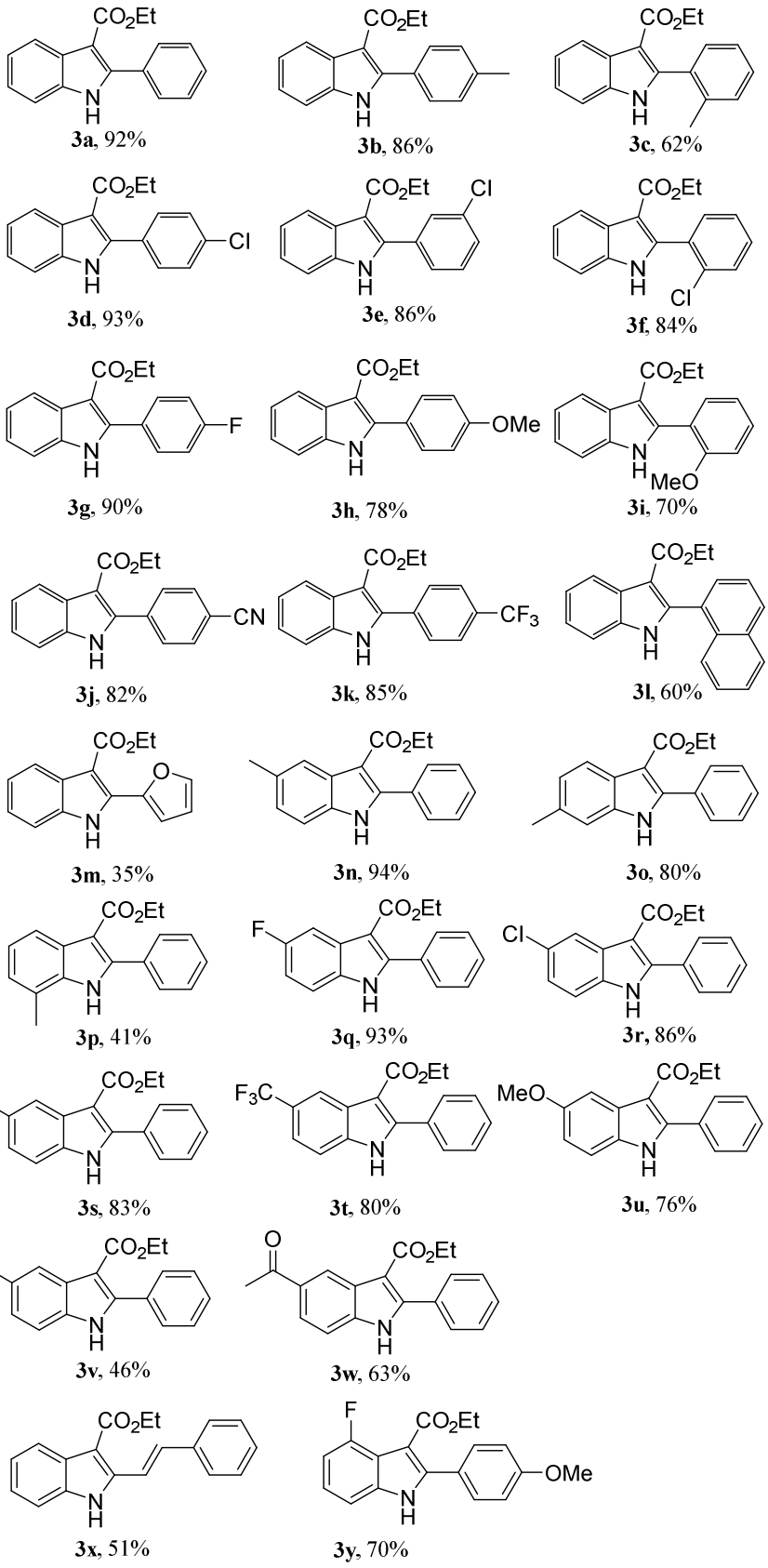
entry	catalyst	additive (equiv.)	oxidant (equiv.)	yield (%)[b]
1	$Pd(OAc)_2$	NaOAc (0.2)	-	0
2	$[Ru(p\text{-}cymene)Cl_2]_2$	NaOAc (0.2)	-	0
3	$[RhCp^*Cl_2]_2$	NaOAc (0.2)	-	15
4	$[RhCp^*Cl_2]_2$	NaOAc (0.2)	$Cu(OAc)_2$ (2.0)	52
5	$[RhCp^*Cl_2]_2$	NaOAc (1.0)	$Cu(OAc)_2$ (2.0)	67
6	$[RhCp^*Cl_2]_2$	AcOH (1.0)	$Cu(OAc)_2$ (2.0)	21
7	$[RhCp^*Cl_2]_2$	PivOH (1.0)	$Cu(OAc)_2$ (2.0)	43
8[c]	$[RhCp^*Cl_2]_2$	NaOAc (1.0)	$Cu(OAc)_2$ (2.0)	Trace
9	$[RhCp^*Cl_2]_2$	NaOAc (1.0)	AgOAc (2.0)	36
10	$[RhCp^*Cl_2]_2$	NaOAc (1.0)	CuO (2.0)	56
11[d]	$[RhCp^*Cl_2]_2$	NaOAc (1.0)	$Cu(OAc)_2$ (2.0)	trace
12[e]	$[RhCp^*Cl_2]_2$	NaOAc (1.0)	$Cu(OAc)_2$ (2.0)	32
13[f]	$[RhCp^*Cl_2]_2$	NaOAc (1.0)	$Cu(OAc)_2$ (2.0)	24
14[g]	$[RhCp^*Cl_2]_2$	NaOAc (1.0)	$Cu(OAc)_2$ (2.0)	trace
15[h]	$[RhCp^*Cl_2]_2$	NaOAc (1.0)	$Cu(OAc)_2$ (2.0)	19
16[i]	**$[RhCp^*Cl_2]_2$**	**NaOAc (1.0)**	**$Cu(OAc)_2$ (2.0)**	**92**
17[j]	$[RhCp^*Cl_2]_2$	NaOAc (1.0)	$Cu(OAc)_2$ (2.0)	67

[a]Unless otherwise noted, all the reactions were carried out using nitrone (**1a**) (0.20 mmol) and diazo compound (**2a**) (0.40 mmol) with metal catalysts (5 mol%) in the presence of additives in DCE (2.0 mL) at 100 °C for 12 h under air in a sealed reaction tube. [b]Isolated yield. [c]Without $AgSbF_6$. [d]In DMF. [e]In t-AmOH. [f]In toluene. [g]In CH_3CN. [h]The reaction temperature is 80 °C.[i]The reaction temperature is 120 °C. [j]2.5 mol % of $[Cp^*RhCl_2]_2$ were used as catalyst, the reaction temperature is 120 °C .

presence of various catalytic transition-metal salts with $AgSbF_6$ (20 mol%) and NaOAc (20 mol%) in 1,2-dichloroethane (DCE) at 100 °C under an air atmosphere for 12 h (entries 1-3). We soon found that only $[RhCp^*Cl_2]_2$ could afford the desired product in a 15% yield. Intriguingly, when 2 equivalent of $Cu(OAc)_2$ was used, the yield of **3a** was excellently improved to 52% (entry 4). Subsequently, with 1 equivalent of NaOAc as an additive, the yield was increased to 67% whereas other additives (AcOH and PivOH) were ineffective in this reaction (entries 5-7). A further explored reaction was not occurred in the absence of AgSbF6. When AgOAc and CuO were used as the oxidant, the yield was not improved (entries 9-10). Screening of the solvents revealed that DCE was optimal (entries 11-14). Under these conditions, by changing the reaction temperature, we found that the yield could be enhanced to 92% at 120 °C. Finally, decreasing the catalyst loading to 2.5 mol% resulted in a reduced yield to 67%.

Table 2. Synthesis of 2,3-Disubstituted *NH* Indoles.[a]





3a, 92% **3b**, 86% **3c**, 62%

3d, 93% **3e**, 86% **3f**, 84%

3g, 90% **3h**, 78% **3i**, 70%

3j, 82% **3k**, 85% **3l**, 60%

3m, 35% **3n**, 94% **3o**, 80%

3p, 41% **3q**, 93% **3r**, 86%

3s, 83% **3t**, 80% **3u**, 76%

3v, 46% **3w**, 63%

3x, 51% **3y**, 70%

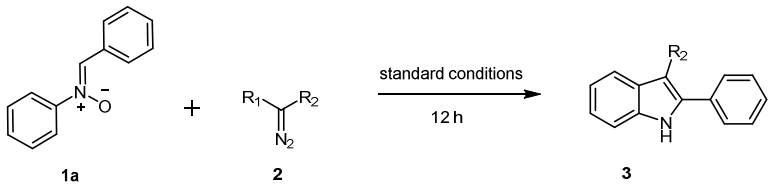
[a]Reaction condition: **1** (0.20 mmol), **2a** (0.40 mmol), $[RhCp^*Cl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), NaOAc (1 equiv), $Cu(OAc)_2$ (2 equiv), and DCE (2 mL) at 120 °C for 12 h under air in a sealed reaction tube.

Under the optimal reaction conditions, a variety of nitrones were used as substrate to investigate the scope of the reaction. As we know, nitrones can be prepared from readily available nitroarenes and aromatic aldehydes. So we examined variation of arylaldehydes at first. As shown in Table 2, arylaldehydes bearing an electron-donating or electron-withdrawing group at *para*, or *meta*-position of the phenyl ring proceeded smoothly to give the ideal products in 78%-93% yields (**3a**, **3b**, **3d**, **3e**, **3g**, **3h**, **3j**, **3k**). According to the experimental results, we found that electronic effects are weak for this reaction. The yields of the *ortho*-position are relatively lower than others which may be due to the steric effect (**3c**, **3f**, **3i**). To our delight, arylaldehydes bearing 2-furyl (**1m**) and 1-naphthyl (**1l**) groups also can be expected to give a moderate yield of the corresponding products (**3m**, **3l**). In addition, the structure of **3a** was confirmed by X-ray crystal structure analysis (see the Supporting Information).

Subsequently, we set out to explore the scope of nitrones bearing kinds of *N*-aryl substituents as summarized in Table 2. It was worth noting that the *N*-aryl moiety bearing both electron-rich groups and electron-deficient groups were all successfully engaged with good yields in this catalytic

methodology. A cyano- group on the *N*-aryl moiety was well tolerated under this reaction but afforded the target product with a lower yield (**3v**). Notably, substrates substituted by methyl, fluorine, chlorine, bromine, methoxyl, trifluoromethyl and even acetyl groups on the *para*-position all could provide very excellent yields (**3n**, **3q-3u**, **3w**). Meanwhile, the *meta*-methyl-substituted *N*-aryl led to a regioselective formation of the desired product which was at a less hindered position (**3o**), whereas the *meta*-fluoro substrate was occurred at the more hindered position (**3y**).[12] When a *ortho*-substituent is present, a slightly lower yield was observed (**3p**). At last, when we reacted **1x** with **2a**, we also got the corresponding product in a good yield (**3x**).

Table 3. Reactions with Different Diazo Compounds.[a]



1a 2 3

Entry	R_1	R_2	Yield(%)
1	-Ac (**2z**)	-C(O)OMe	**3z**, 74
2	-Ac (**2aa**)	-C(O)O^{t}Bu	**3aa**, 65
3	-C(O)Ph (**2ab**)	-C(O)OMe	**3z**, 84
4	-C(O)Ph (**2ac**)	-C(O)OEt	**3a**, 92
5	-P(O)(OMe)$_2$ (**2ad**)	-C(O)OEt	**3a**, 25
6	-P(O)(OEt)$_2$ (**2ae**)	-C(O)O^{t}Bu	**3aa**, 34
7	-P(O)(OEt)$_2$ (**2af**)	-C(O)OEt	**3a**, 59

8	-C(O)OMe (**2ag**)	-C(O)OMe	NR

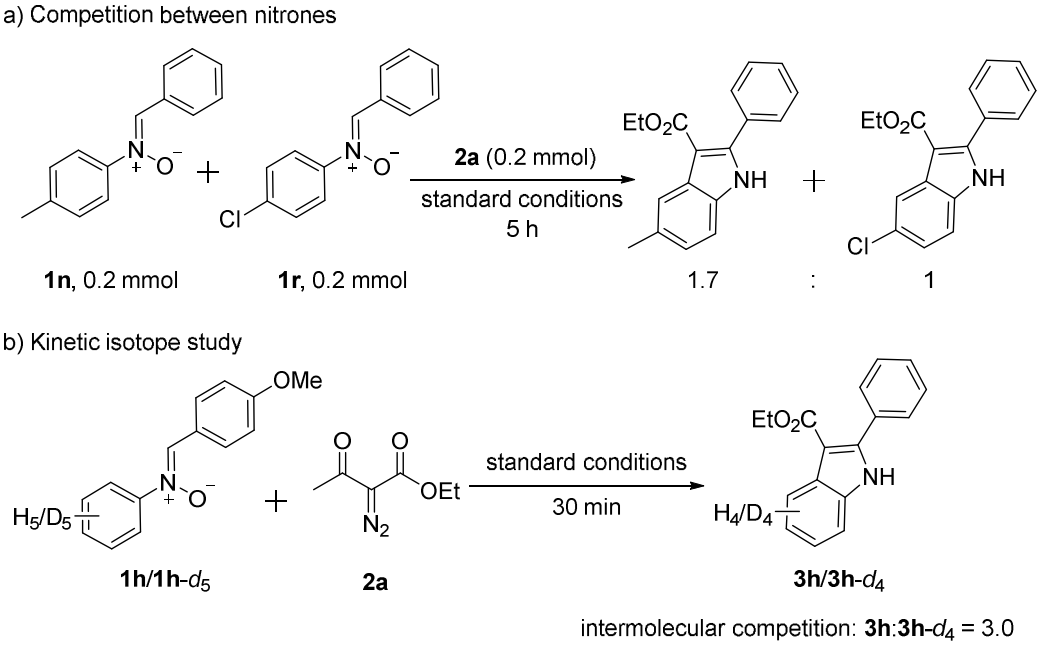
[a]Reaction conditoin: **1a** (0.20 mmol), **2** (0.40 mmol), $[RhCp^*Cl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), NaOAc (1 equiv), $Cu(OAc)_2$ (2 equiv), and DCE (2 mL) at 120 ^oC for 12 h under air in a sealed reaction tube.

Then, we investigated the feasibility of different diazo esters (Table 3). We found that the diazo compounds bearing both ester and ketone groups (**2z**, **2aa**, **2ab, 2ac**) were successfully reacted with **1a** to afford the corresponding products with the cleavage of C-C bond, but bearing only ester groups (**2ag**) were not engaged in this transformation to form 2,3-disubstituted NH indole. To our delight, when we reacted **1a** with other different diazo esters **(2ad–2af)**, we could get the same products with the cleavage of the C-P bonds in the diazo compound.

Additionally, to gain insight into the mechanism of this cyclization process, a series of experiments were performed. First, a competitive reaction was carried out to probe the electronic effect of the *N*-aryl ring (Scheme 2). An equimolar mixture of **1n**, **1r**, and **2a** was allowed to react under standard conditions for 5h. The products **3n** and **3r** were generated in a 1.7:1 ratio by NMR analysis. We found that the reaction is more favorable for *N*-aryl bearing an electron-donating substituent. The results indicated that an electrophilic C-H activation is involved in the reaction mechanism of this reaction (Scheme 2a). Moreover, To further probe the C-H activation process, the kinetic isotope effect(KIE) was determined by intermolecular competition experiments using an equimolar mixture of **1h**

and [**D$_5$**]-**1h**. ^{1}H NMR analysis of the product mixture gave an average **3h**:**3h-*d*4** ratio of 3.0. This result indicated that cleavage of the C-H bond activation is involved in the rate-limiting step (Scheme 2b).[14]

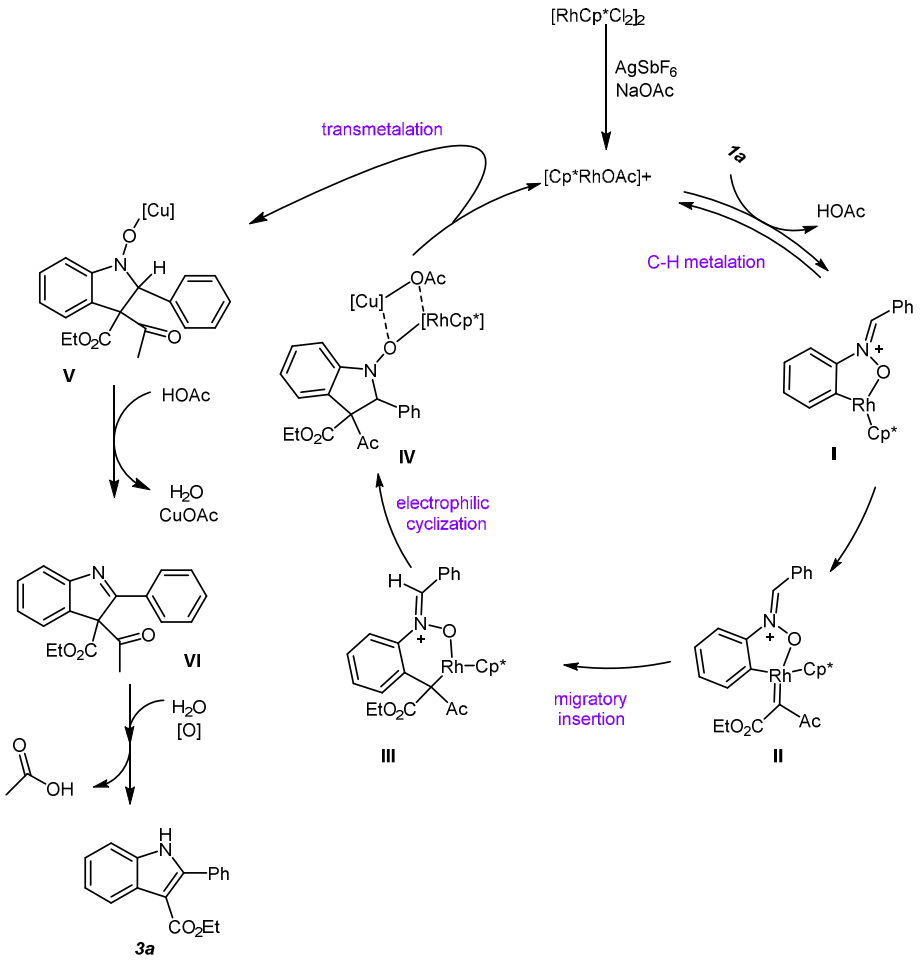
Scheme 2. Experiments for Mechanistic Studies.



Referring to the preceding literature reports, and our experimental findings. We propose a plausible reaction mechanism (Scheme 3). At the first step, the cyclorhodium intermediate **I** is formed through C-H bond activation of nitrone **1a** reaction with the catalytically active rhodium species which is initiated by $AgSbF_6$ and NaOAc. Then, α-acyldiazoacetate (**2a**) reacts with the rhodacycle **I** to form a rhodium (III) carbene intermediate **II**. Migratory insertion of the Rh-C bond into the activated carbene generates the six-membered rhodacyclic intermeditate **III**. Intermediate **IV** is furnished by intramolecular electrophilic attack of the imino moiety.[15] Then transmetalation of the Rh

catalyst with the copper salt and subsequent *β*-hydride elimination releases intermediate **VI**.[16] At last, with the elimination of one acetic acid unit, the desired product is obtained.

Scheme 3. Proposed Catalytic Cycle.



Conclusion

In summary, we have developed a mild and efficient Rh(III)-catalyzed one-pot synthesis of 2,3-disubstituted *NH* indoles from arylnitrones and diazo compounds. The scope of the nitrones substrates are sufficiently

broad to deliver structurally diverse indoles in high yields. Based on the above studies, further applications of this method in natural product synthesis and a detailed mechanistic investigation are in progress.

Experimental Section

General remarks. ^{1}H NMR and ^{13}C NMR spectra were recorded on 300MHz and 100MHz in $CDCl_3$. All chemical shifts are given as δ value (ppm) with reference to tetramethylsilane (TMS) as an internal standard. The high-resolution mass spectra (HRMS) were recorded on an FT-ICR mass spectrometer using electrospray ionization (ESI). Products were purified by flash chromatogrgraphy on 200-300 mesh silica gel. All melting points were determined without correction. Unless otherwise noted, commercially available reagents were used without further purification.

The procedure for the synthesis of Arylnitrones: In a 100 ml round bottomed flask, Nitroarene (1.0 equiv), aldehyde (1.1 equiv) and NH_4Cl (1.4 equiv) were added to a mixture of EtOH (2 mL/mmol of starting material) and H_2O (2 mL/mmol of starting material). Then the resulting mixture was cooled to 0 °C. Then, zinc powder (2.0 equiv) was added at 0 °C, and the reaction mixture was allowed to warm to room temperature and stirred over 1 d. The reaction mixture was filtered through a celite pad and washed with CH_2Cl_2. The filtrate was extracted with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$, filtered and

concentrated to give the crude nitrones. Pure nitrones were obtained by recrystallization from ethanol.[17]

The procedure for the synthesis of Diazo Compounds: To a solution of ketonic ester or 1,3 di-ketone (5 mmol) in CH_3CN, 6 mmol TsN_3 was added. Then the reaction mixture was cooled to 0 ^oC and a solution of DBU (6mmol) in CH_3CN was added dropwise. Next, the reaction temperature was raised to room temperature. After stirring for 5 hours, the residue was extracted with ethyl acetate for 3 times. The combined organic layers were washed with water and brine sequentially, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography on silica gel to afford the corresponding product in 70-90% yields.[18]

The procedure for the synthesis of Compounds 3: A sealed reaction tube was charged with nitrones (0.20 mmol), diazo compounds (0.40 mmol), $[RhCp^*Cl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), NaOAc (0.2 mmol) and $Cu(OAc)_2$ (0.4 mmol) in DCE (2.0 mL). The mixture was stirred at 120 ^oC for 12 h under air. After that, the solvent was removed under vacuum and the residue was purified by silica gel chromatography using ethyl acetate/petroleum ether (20:1) to afford product **3**.

ethyl 2-phenyl-1H-indole-3-carboxylate (3a). White solid (48.5 mg, 92%); m.p. 157 – 159 ^oC; ^1H NMR (300 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.22 (dd, J = 6.0, 3.1 Hz, 1H), 7.68 – 7.57 (m, 2H), 7.46 – 7.37 (m, 3H),

7.37 – 7.30 (m, 1H), 7.29 – 7.22 (m, 2H), 4.28 (q, J = 7.1 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 144.8, 135.4, 132.3, 129.8, 129.4, 128.3, 127.8, 123.4, 122.4, 122.3, 111.3, 104.9, 60.0, 14.6; HRMS (ESI) calcd for $C_{17}H_{16}NO_2$ $[M+H]^+$ 266.1176; found: 266.1176.

ethyl 2-(p-tolyl)-1H-indole-3-carboxylate (3b). Yellow solid (48.1 mg, 86%); m.p. 175 – 178 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.19 (d, J = 6.8 Hz, 1H), 7.50 (d, J = 7.9 Hz, 2H), 7.35 – 7.22 (m, 3H), 7.17 (d, J = 7.9 Hz, 2H), 4.28 (q, J = 7.1 Hz, 2H), 2.35 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 144.8, 139.1, 135.1, 129.4, 128.9, 128.7, 127.6, 122.9, 122.0, 121.9, 111.0, 104.2, 59.6, 21.3, 14.3; HRMS (ESI) calcd for $C_{18}H_{18}NO_2$ $[M+H]^+$ 280.1332; found: 280.1333.

ethyl 2-(o-tolyl)-1H-indole-3-carboxylate (3c). White solid (34.5 mg, 62%); m.p. 76 – 79 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.98 (s, 1H), 8.19 (d, J = 7.9 Hz, 1H), 7.29 – 7.14 (m, 7H), 4.03 (q, J = 7.1 Hz, 2H), 2.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 144.4, 137.4, 135.1, 132.4, 129.7, 129.6, 128.9, 126.8, 125.1, 122.7, 121.8, 121.5, 111.3, 105.6, 59.4, 19.7, 14.0; HRMS (ESI) calcd for $C_{18}H_{18}NO_2$ $[M+H]^+$ 280.1132; found: 280.1132.

ethyl 2-(4-chlorophenyl)-1H-indole-3-carboxylate (3d). White solid (55.7 mg, 93%); m.p. 152 – 155 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.84 (s, 1H), 8.24 – 8.15 (m, 1H), 7.52 (d, J = 8.5 Hz, 2H), 7.37 – 7.29 (m, 3H), 7.26 (dd, J = 6.5, 2.8 Hz, 2H), 4.27 (q, J = 7.1 Hz, 2H), 1.32 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 142.9, 135.0, 130.6, 130.1, 128.0, 127.2, 123.1, 121.9, 110.9, 104.6, 59.6, 14.1; HRMS (ESI) calcd for $C_{17}H_{15}ClNO_2$ $[M+H]^+$ 300.0786; found: 300.0786.

ethyl 2-(3-chlorophenyl)-1H-indole-3-carboxylate (3e). White solid (51.3 mg, 86%); m.p.180 – 182 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.28 – 8.17 (m, 1H), 7.63 (d, J = 1.8 Hz, 1H), 7.53 (dt, J = 6.8, 1.5 Hz, 1H), 7.41 – 7.32 (m, 3H), 7.31 – 7.22 (m, 2H), 4.30 (q, J = 7.1 Hz, 2H), 1.32 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9, 142.3, 135.0, 133.7, 133.5, 129.5, 129.1, 128.9, 127.7, 127.3, 123.3, 122.0, 110.9, 105.0, 59.7, 14.1; HRMS (ESI) calcd for $C_{17}H_{15}ClNO_2$ $[M+H]^+$ 300.0786; found: 300.0786.

ethyl 2-(2-chlorophenyl)-1H-indole-3-carboxylate (3f). Yellow solid (49.9 mg, 84%); m.p. 141 – 143 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.27 – 8.18 (m, 1H), 7.44 (dd, J = 10.0, 4.5 Hz, 2H), 7.40 – 7.33 (m, 2H), 7.32 (dd, J = 4.3, 1.8 Hz, 1H), 7.27 (dd, J = 6.0, 3.0 Hz, 2H), 4.19 (q, J = 7.1 Hz, 2H), 1.17 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, CDCl3) δ

164.9, 140.9, 135.1, 133.9, 132.0, 131.7, 130.3, 129.4, 126.7, 126.2, 123.3, 122.0, 121.9, 111.2, 106.6, 59.6, 14.1; HRMS (ESI) calcd for $C_{17}H_{15}ClNO_2$ $[M+H]^+$ 300.0786; found: 300.0786.

ethyl 2-(4-fluorophenyl)-1H-indole-3-carboxylate (3g). White solid (51.0 mg, 90%); m.p. 166 – 168 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.20 (dd, J = 5.4, 3.0 Hz, 1H), 7.66 – 7.52 (m, 2H), 7.34 (dd, J = 7.2, 2.0 Hz, 1H), 7.30 – 7.22 (m, 2H), 7.07 (t, J = 8.7 Hz, 2H), 4.28 (q, J = 7.1 Hz, 2H), 1.32 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, CDCl3) δ 165.4, 164.8, 161.5, 143.4, 135.1, 131.5 (d, J_{CF} = 8.4 Hz), 128.0, 127.4, 123.3, 122.1, 115.1 (d, J_{CF} = 21.8 Hz), 111.0, 104.7, 59.8, 14.3; HRMS (ESI) calcd for $C_{17}H_{15}FNO_2$ $[M+H]^+$ 284.1082; found: 284.1078.

ethyl 2-(4-methoxyphenyl)-1H-indole-3-carboxylate (3h). White solid (46.3 mg, 78%); m.p. 147 – 150 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.20 (dd, J = 5.9, 3.1 Hz, 1H), 7.59 (d, J = 8.8 Hz, 2H), 7.38 – 7.32 (m, 1H), 7.25 (dd, J = 6.4, 3.0 Hz, 2H), 6.93 (d, J = 8.7 Hz, 2H), 4.31 (q, J = 7.1 Hz, 2H), 3.82 (s, 3H), 1.35 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, CDCl3) δ 165.5, 160.3, 144.6, 135.0, 130.9, 127.7, 124.2, 122.9, 122.0, 121.9, 113.5, 110.9, 104.1, 59.6, 55.3, 14.4; HRMS (ESI) calcd for $C_{18}H_{18}NO_3$ $[M+H]^+$ 296.1281; found: 296.1280.

ethyl 2-(2-methoxyphenyl)-1H-indole-3-carboxylate (3i). White solid (41.2 mg, 70%); m.p. 167 – 169 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.87 (s, 1H), 8.28 – 8.14 (m, 1H), 7.56 (dd, J = 7.6, 1.5 Hz, 1H), 7.37 (dd, J = 7.8, 5.9 Hz, 2H), 7.24 (dd, J = 6.2, 2.9 Hz, 2H), 7.01 (dd, J = 16.8, 8.1 Hz, 2H), 4.27 (q, J = 7.1 Hz, 2H), 3.79 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 156.9, 141.0, 135.0, 132.7, 130.6, 127.1, 122.9, 121.8, 121.6, 120.5, 120.2, 111.0, 110.9, 105.5, 59.5, 55.6, 14.3; HRMS (ESI) calcd for $C_{18}H_{18}NO_3$ $[M+H]^+$ 296.1281; found: 296.1287.

ethyl 2-(4-cyanophenyl)-1H-indole-3-carboxylate (3j). White solid (47.5 mg, 82%); m.p. 200 – 202 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.21 (dd, J = 6.2, 2.7 Hz, 1H), 7.75 (d, J = 8.3 Hz, 2H), 7.66 (d, J = 8.1 Hz, 2H), 7.45 – 7.36 (m, 1H), 7.31 (dd, J = 6.2, 3.2 Hz, 2H), 4.33 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1, 141.6, 136.5, 135.5, 131.7, 130.3, 127.2, 124.0, 122.5, 122.4, 118.5, 112.4, 111.2, 105.9, 60.1, 14.3; HRMS (ESI) calcd for $C_{18}H_{15}N_2O_2$ $[M+H]^+$ 291.1128; found: 291.1126.

ethyl 2-(4-(trifluoromethyl)phenyl)-1H-indole-3-carboxylate (3k). White solid (56.4 mg, 85%); m.p. 150 – 152 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.83 (s, 1H), 8.26 – 8.15 (m, 1H), 7.72 (d, J = 8.2 Hz, 2H), 7.63 (d, J = 8.2 Hz, 2H), 7.41 – 7.32 (m, 1H), 7.32 – 7.20 (m, 2H), 4.28 (q, J =

7.1 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 142.5, 135.5, 135.3, 130.0, 127.3, 125.9 (d, J_{CF} = 3.7 Hz), 123.7, 122.3, 122.2, 111.2, 105.5, 60.0, 14.2; HRMS (ESI) calcd for $C_{18}H_{15}F_3NO_2$ [M+H]+ 334.1050; found: 334.1049.

ethyl 2-(naphthalen-1-yl)-1H-indole-3-carboxylate (3l). White solid (37.9 mg, 60%); m.p. 166 – 168 ^{o}C;^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.30 (d, J = 6.8 Hz, 1H), 7.90 (dd, J = 11.3, 8.3 Hz, 2H), 7.66 (d, J = 8.2 Hz, 1H), 7.56 – 7.44 (m, 3H), 7.41 – 7.27 (m, 4H), 3.96 (q, J = 7.1 Hz, 2H), 0.81 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0, 142.5, 135.2, 133.2, 132.2, 130.5, 129.4, 128.2, 127.9, 127.1, 126.5, 126.0, 125.7, 124.8, 123.2, 122.1, 121.8, 111.1, 107.1, 59.3, 13.6; HRMS (ESI) calcd for $C_{21}H_{18}NO_2$ $[M+H]^+$ 316.1332; found: 316.1334.

ethyl 2-(furan-2-yl)-1H-indole-3-carboxylate (3m). White solid (17.9 mg, 35%); m.p. 123 – 126 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.15 (s, 1H), 8.26 – 8.12 (m, 1H), 7.88 (d, J = 3.4 Hz, 1H), 7.51 (s, 1H), 7.43 – 7.34 (m, 1H), 7.26 (dt, J = 4.4, 3.4 Hz, 2H), 6.58 (dd, J = 3.4, 1.7 Hz, 1H), 4.46 (q, J = 7.1 Hz, 2H), 1.49 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 145.6, 142.7, 134.7, 133.8, 127.4, 123.5, 122.4, 122.0, 114.6, 112.7, 110.9, 103.1, 59.9, 14.6; HRMS (ESI) calcd for $C_{15}H_{14}NO_3$ $[M+H]^+$ 256.0968; found: 256.0964.

ethyl 5-methyl-2-phenyl-1H-indole-3-carboxylate (3n). White solid (52.5 mg, 94%); m.p. 136 – 139 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.00 (s, 1H), 7.63 – 7.53 (m, 2H), 7.40 – 7.33 (m, 3H), 7.23 – 7.17 (m, 1H), 7.04 (d, J = 8.3 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H), 2.47 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 144.5, 133.5, 132.2, 131.4, 129.7, 129.5, 128.9, 127.9, 124.6, 121.6, 110.7, 104.0, 59.6, 21.7, 14.2; HRMS (ESI) calcd for $C_{18}H_{18}NO_2$ $[M+H]^+$ 280.1332; found: 280.1331.

ethyl 6-methyl-2-phenyl-1H-indole-3-carboxylate (3o). yellow oil (44.7 mg, 80%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.08 (d, J = 8.2 Hz, 1H), 7.61 (dd, J = 6.6, 3.0 Hz, 2H), 7.42 – 7.36 (m, 3H), 7.14 – 7.05 (m, 2H), 4.26 (q, J = 7.1 Hz, 2H), 2.45 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_{3)}$ δ 165.4, 143.9, 135.5, 133.0, 132.1, 129.5, 128.9, 128.0, 125.4, 123.7, 121.7, 110.9, 104.4, 60.0, 21.6, 14.3; HRMS (ESI) calcd for $C_{18}H_{18}NO_2$ $[M+H]^+$ 280.1332; found: 280.1329.

ethyl 7-methyl-2-phenyl-1H-indole-3-carboxylate (3p). White solid (22.6 mg, 41%); m.p. 155– 157 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (s, 1H), 8.06 (d, J = 8.0 Hz, 1H), 7.64 (d, J = 3.7 Hz, 2H), 7.41 (d, J = 3.7 Hz, 3H), 7.19 (t, J = 7.6 Hz, 1H), 7.06 (d, J = 7.0 Hz, 1H), 4.27 (dd, J = 14.2,

7.1 Hz, 2H), 2.49 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 144.18, 134.7, 132.2, 130.7, 129.6, 129.5, 129.0, 128.8, 128.0, 127.2, 123.7, 122.2, 120.2, 119.8, 105.2, 59.6, 16.5, 14.3; HRMS (ESI) calcd for $C_{18}H_{18}NO_2$ $[M+H]^+$ 280.1332; found: 280.1330.

ethyl 5-fluoro-2-phenyl-1H-indole-3-carboxylate (3q). White solid (52.6 mg, 93%); m.p.153 – 155 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.97 (s, 1H), 7.83 (dd, J = 10.1, 2.3 Hz, 1H), 7.56 (dd, J = 6.5, 2.8 Hz, 2H), 7.42 – 7.28 (m, 3H), 7.19 (dd, J = 8.8, 4.4 Hz, 1H), 6.95 (td, J = 9.0, 2.4 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 159.2 (d, J = 236.4 Hz), 146.2, 131.7 (d, J = 4.1 Hz), 129.5, 129.3, 128.3 (d, J = 11.1 Hz), 128.1, 112.1, 112.0, 111.5(d, J = 26.6 Hz), 107.3 (d, J = 25.3 Hz), 104.6 (d, J = 4.4 Hz), 59.9, 14.3; HRMS (ESI) calcd for $C_{17}H_{15}FNO_2$ $[M+H]^+$ 284.1082; found: 284.1081.

ethyl 5-chloro-2-phenyl-1H-indole-3-carboxylate (3r). White solid (51.4 mg, 86%); m.p. 122 – 125 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.17 (d, J = 1.9 Hz, 1H), 7.64 – 7.55 (m, 2H), 7.39 (dd, J = 4.2, 2.4 Hz, 3H), 7.26 – 7.16 (m, 2H), 4.26 (q, J = 7.1 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0, 145.6, 133.5, 131.5, 129.5, 129.3, 128.6, 128.1, 127.7, 123.4, 121.6, 112.1, 104.3, 59.9, 14.3; HRMS (ESI) calcd for $C_{17}H_{15}ClNO_2$ $[M+H]^+$ 300.0786; found: 300.0784.

ethyl 5-bromo-2-phenyl-1H-indole-3-carboxylate (3s). Yellow solid (57.0 mg, 83%); m.p. 102 – 104 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.86 (s, 1H), 8.34 (d, J = 1.9 Hz, 1H), 7.63 – 7.54 (m, 2H), 7.39 (dd, J = 4.3, 2.3 Hz, 3H), 7.32 (dd, J = 8.6, 1.9 Hz, 1H), 7.18 (d, J = 8.6 Hz, 1H), 4.30 – 4.22 (m, 2H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8, 145.3, 133.6, 131.2, 129.3, 129.2, 129.0, 127.9, 125.9, 124.5, 115.3, 112.3, 104.0, 59.7, 14.1; HRMS (ESI) calcd for $C_{17}H_{15}BrNO_2$ $[M+H]^+$ 344.0281; found: 344.0281.

ethyl 2-phenyl-5-(trifluoromethyl)-1H-indole-3-carboxylate (3t). White solid (53.3 mg, 80%); m.p. 166 – 168 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.17 (d, J = 17.3 Hz, 1H), 8.51 (s, 1H), 7.63 – 7.54 (m, 2H), 7.46 (d, J = 8.5 Hz, 1H), 7.37 (dd, J = 4.5, 2.0 Hz, 4H), 4.27 (dd, J = 7.1, 3.2 Hz, 2H), 1.30 (td, J = 7.1, 1.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0, 146.1, 136.5, 131.2, 129.9, 129.5, 128.8, 128.1, 127.0, 124.4, 119.8, 111.5, 105.1, 60.0, 14.2; HRMS (ESI) calcd for $C_{18}H_{15}F_3NO_2$ $[M+H]^+$ 334.1050; found: 334.1049.

ethyl 5-methoxy-2-phenyl-1H-indole-3-carboxylate (3u). Yellow solid (44.8 mg, 76%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (s, 1H), 7.73 (d, J = 2.4 Hz, 1H), 7.60 (d, J = 3.3 Hz, 2H), 7.39 (d, J = 3.0 Hz, 3H), 7.24 (dd, J

= 7.4, 4.8 Hz, 1H), 6.88 (dd, J = 8.7, 2.4 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 3.88 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 155.7, 144.8, 132.1, 130.2, 129.5, 129.0, 128.5, 127.9, 113.3, 111.9, 104.2, 103.5, 59.6, 55.6, 14.2; HRMS (ESI) calcd for $C_{18}H_{18}NO_3$ $[M+H]^+$ 296.1281; found: 296.1278.

ethyl 5-cyano-2-phenyl-1H-indole-3-carboxylate (3v). White solid (26.8 mg, 46%); m.p. 124 – 126 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.37 (s, 1H), 8.54 (s, 1H), 7.63 (dd, J = 6.6, 3.0 Hz, 2H), 7.47 (dd, J = 8.4, 1.4 Hz, 1H), 7.44 – 7.36 (m, 4H), 4.30 (q, J = 7.1 Hz, 2H), 1.32 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 146.6, 136.9, 130.8, 129.7, 129.5, 128.2, 127.7, 127.3, 126.0, 120.5, 112.1, 105.0, 60.2, 14.3; HRMS (ESI) calcd for $C_{18}H_{15}N_2O_2$ $[M+H]^+$ 291.1128; found: 291.1138.

ethyl 5-acetyl-2-phenyl-1H-indole-3-carboxylate (3w). White solid (38.4 mg, 63%); m.p. 184 –186 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.23 (s, 1H), 8.81 (s, 1H), 7.85 (d, J = 8.6 Hz, 1H), 7.57 (s, 2H), 7.32 (d, J = 8.7 Hz, 4H), 4.23 (q, J = 7.0 Hz, 2H), 2.61 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.7, 165.0, 145.9, 137.9, 131.6, 131.4, 129.6, 129.5, 128.1, 127.2, 124.5, 123.1, 111.3, 105.6, 60.0, 26.6, 14.2; HRMS (ESI) calcd for $C_{19}H_{18}NO_3$ $[M+H]^+$ 308.1281; found: 308.1272.

ethyl (E)-2-styryl-1H-indole-3-carboxylate (3x). White solid (29.7 mg, 51%); m.p.136 –139 ^{o}C; NMR (300 MHz, $CDCl_3$) δ 8.95 (s, 1H), 8.24 – 8.05 (m, 2H), 7.51 (d, J = 6.8 Hz, 2H), 7.40 – 7.15 (m, 6H), 7.06 (d, J = 16.9 Hz, 1H), 4.45 (q, J = 7.1 Hz, 2H), 1.48 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 141.5, 136.2, 135.7, 131.3, 128.8, 128.6, 127.5, 126.9, 123.8, 122.1, 121.9, 118.0, 110.7, 59.9, 14.6; HRMS (ESI) calcd for $C_{19}H_{18}NO_2$ $[M+H]^+$ 292.1332; found: 292.1331.

ethyl 4-fluoro-2-(4-methoxyphenyl)-1H-indole-3-carboxylate (3y). White solid (43.9 mg, 70%); m.p.168 –170 ^{o}C; ^{1}H NMR (400 MHz,) δ 9.02 (s, 1H), 7.42 (d, J = 8.5 Hz, 2H), 7.10 (ddd, J = 19.4, 9.9, 6.2 Hz, 2H), 6.92 – 6.83 (m, 1H), 6.79 (d, J = 8.5 Hz, 2H), 4.24 (q, J = 7.1 Hz, 2H), 3.75 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5, 160.2, 157.2, 154.7, 143.4, 137.8 (d, J_{CF} = 10.2 Hz), 130.5, 123.4 (d, J_{CF} = 8.0 Hz), 115.6 (d, J_{CF} = 18.9 Hz), 113.6 ,107.6, 107.2 (d, J_{CF} = 3.8 Hz), 103.5, 60.4, 55.2, 14.0; HRMS (ESI) calcd for $C_{18}H_{17}FNO_3$ $[M+H]^+$ 314.1187; found: 314.1187.

methyl 2-phenyl-1H-indole-3-carboxylate 3z). White solid (37.3 mg, 74%); m.p.136 –139 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.87 (s, 1H), 8.23 – 8.13 (m, 1H), 7.63 – 7.53 (m, 2H), 7.36 (dd, J = 6.8, 3.6 Hz, 3H), 7.30 (dd, J = 6.5, 2.4 Hz, 1H), 7.27 – 7.18 (m, 2H), 3.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 144.7, 135.1, 131.8, 129.4, 129.1, 128.0, 127.4,

123.1, 122.0, 111.1, 104.1, 50.8; HRMS (ESI) calcd for $C_{16}H_{14}NO_2$ $[M+H]^+$ 252.1019; found: 252.1019.

tert-butyl 2-phenyl-1H-indole-3-carboxylate (3aa). White solid (38.1 mg, 65%); m.p.189 – 192 ^oC; ^1H NMR (300 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.26 – 8.17 (m, 1H), 7.59 (dd, J = 6.4, 3.0 Hz, 2H), 7.40 (dd, J = 4.9, 1.7 Hz, 3H), 7.37 – 7.31 (m, 1H), 7.29 – 7.20 (m, 2H), 1.49 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 143.9, 135.0, 132.4, 129.6, 128.9, 128.0, 127.7, 123.0, 122.0, 121.8, 110.9, 106.1, 80.0, 28.4; HRMS (ESI) calcd for $C_{19}H_{20}NO_2$ $[M+H]^+$ 294.1489; found: 294.1488.

Supporting Information

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

Copies of ^1H and ^{13}C NMR spectra for all reaction products.

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

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