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Graphical Abstract

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Ruthenium(II)-Catalyzed Facile Synthesis of 3-(Phenylamino)-1H-indole-2-carboxylates from Anilines and Diazo Pyruvates Promoted by $FeCl_3$

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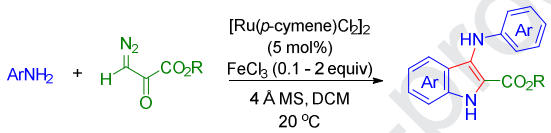

* unprecedented annulation * biologically active indole scaffolds
* anti-cancer activity with IC_{50} values up to 0.05 μM

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Ruthenium(II)-Catalyzed Facile Synthesis of 3-(Phenylamino)-1H-indole-2-carboxylates from Anilines and Diazo Pyruvates Promoted by $FeCl_3$

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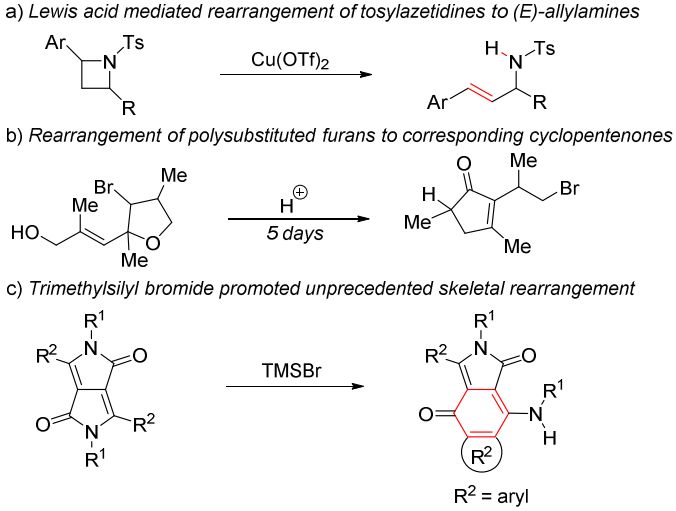
ABSTRACT

An unprecedented synthetic route towards a variety of 3-anilino-1H-indoles is accomplished from diazo pyruvates and anilines via a domino ruthenium-catalyzed annulation and subsequent iron promoted fragmentation and rearrangement. The current strategy was amenable to deliver diversely substituted indole esters, which were subjected to in vitro anti-cancer activity assessment using CCK-8 assay. Compound **4i** displayed the best inhibition activity with IC_{50} value of 0.05 µM, triggering the initiation towards discovering promising lead compounds in the future.

1. Introduction

Development of novel expedite routes, via multiple bonds formation or reorganization, for the synthesis of molecular frameworks of biological importance has been a long-standing objective in organic chemistry. These routes prove their efficiency in avoiding the isolation of intermediate products, thus leading to time and cost-effectiveness [1]. Significance of such protocols has been illustrated in unprecedented reaction patterns, such as, molecular rearrangements/bond reorganizations [2].



Scheme 1: Rearrangement of Compounds lead to form different class of compounds.

Among the various serendipitous restructuring arrays, it was found that the sensitivity of the substrate towards the employed reaction conditions played a vital role. A few of such notable examples include the formation of (*E*)-allylamines from aryl-*N*-tosylazetidines through ring-opening and reorganization mechanism by $Cu(OTf)_2$ as Lewis acid (Scheme 1a) [3a], while the treatment of diversely substituted tetrahydrofurans under mild acidic conditions led to corresponding cyclopentenone analogs (Scheme 1b) [3b]. In yet another example, trimethylsilyl bromide facilitated a unique skeletal rearrangement of diketopyrrolopyrroles into isoindol-diones (Scheme 1c) [3c]. It is notable that the reports highlight the role of Lewis acids in contributing to rearrangements and heretofore transformations in suitable precursors leading to various heterocycles.

Indole derivatives have attracted a considerable attention from synthetic chemists over the decades for their existence as core-part in molecules possessing anti-cancer, anti-hypertensive, anti-histaminic, anti-oxidant, anti-HIV, anti-diabetic, photochemotherapeutic, anti-depressant, anti-convulsant, tranquilizing, anti-inflammatory, anti-fungal, anti-microbial, anti-viral and insecticidal properties [4]. For example, the indole-3-acetic acid **A** possesses potent cytotoxic activity [5a], whereas, the *N*-morpholine amide derivative of indole **B** showed excellent inhibition property against all the tested tumor cell lines (GI50 11-17 M) [5b], melatonin **C** is used as medicine for sleep improvement [5c], while the fused pyrimido[5,4-b]indole tricyclic **D** was found to be anti-HIV in nature [5d] and the indole imine **E** acted as analgesic & anti-inflammatory [5e] (Figure 1).

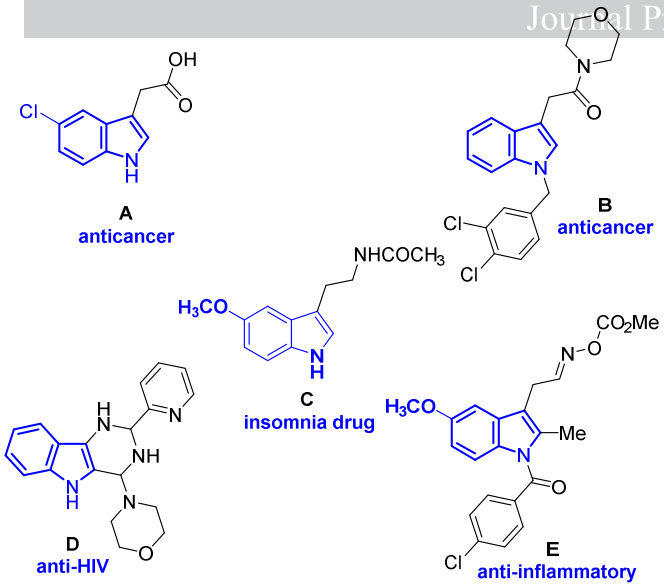
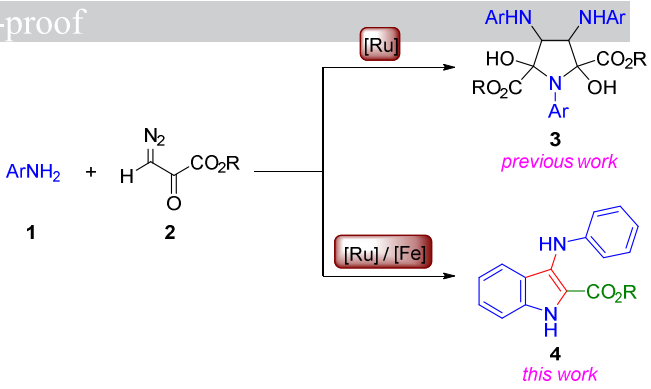


Figure 1: Representative examples of biologically active indoles.

As a result, numerous approaches were established towards the preparation of indole, such as Fisher indole synthesis [6], transition metal-catalyzed C-H activation of anilines with alkyne [7], C-H activation carbene insertion [8], C-H amination of vinyl or aryl azides [9], annulations of suitable *ortho*- alkyne [10a-c] or olefin substituted anilines [10d-g], coupling reactions [11], and diazo carbene transformations [12] are some of the powerful strategies for the efficient construction of indoles. However, these protocols required prefunctionalized substrates, expensive metal catalysts, harsh reaction conditions and stoichiometric amounts of reagents. Despite the handful indole derivatives explored for biological assays, the demand has been high for the development of new indole derivatives, using catalytic amount of reagents commencing from easily accessible synthons leading to high atom economy, to be identified as potential lead candidates for various targets.

Inspired by the diversity in multi-component reactions (MCRs) over the recent decade [13], metal-carbene induced trapping strategies were developed efficiently towards the stereoselective synthesis of elegant molecular scaffolds [14,15]. In continuation of our research interests in the construction of heterocycle moieties of biological interest, very recently we have disclosed an unprecedented and efficient ruthenium-catalyzed highly diastereoselective synthesis of fully substituted pyrrolidines bearing four contiguous stereocenters from easily-



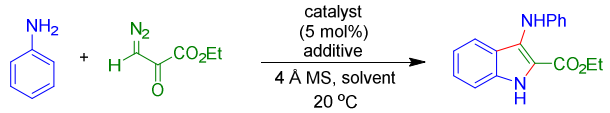
Scheme 2: Our approaches towards polysubstituted pyrrolidines **3** and amino indole esters **4**.

accessible anilines and diazo pyruvates [16]. Inspired by this unusual finding, we have explored the reaction under different conditions to investigate the versatile reactivity, which delightfully led us to unveil a hitherto unknown [Ru(*p*-cymene)Cl_2]$_2$/$FeCl_3$ promoted synthesis of indoles from easily accessible starting materials (Scheme 2).

2. Results and discussion

With the requisite starting materials, aniline **1a** and the diazo pyruvate **2a**, a thorough examination was explored under different reaction conditions by employing various catalysts in combination with additives. Interestingly, 5 mol% [Ru(*p*-cymeneCl_2)]$_2$ catalyst and copper(II)triflate as additive in DCM at room temperature yielded a poly-functionalized indole **4a**, albeit in poor yield, (Table 1, entry 1). Intrigued by the novel product **4a** formation, we performed the reaction by using different additives such as $Cu(OAc)_2$, DDQ, TBHP, Na_2CO_3, Al_2O_3 and *p*-TSA, which resulted in trace amounts of the product **4a** (Table 1, entries 2 to 9). Interestingly, $FeCl_3$ additive displayed better efficiency, thus provided the desired product **4a** in fair yield (Table 1, entry 10). The reaction outcome was similar in other solvents such as THF and toluene with slightly lower yields (Table 1, entries 11 & 12), while attempts with other catalysts $RuCl_3.xH_2O$, $Rh_2(OAc)_4$ and $Cu(OTf)_2$, performed poorly and gave the desired product in less yields (Table 1, entries 13–15). Other efforts on condition optimizations, including increasing the amount of **1a**, extending the reaction time, or increasing the temperature, gave no improvement on the yield of the desired product. No desired product **4a** was observed in the absence of [Ru(*p*-cymeneCl_2)]$_2$, indicating the inevitable role of ruthenium catalyst in the transformation (Table 1, entry 16).

Table 1: Optimization of indole **4a** formation from aniline **1a** and ethyl diazo pyruvate **2a**.[a,b]



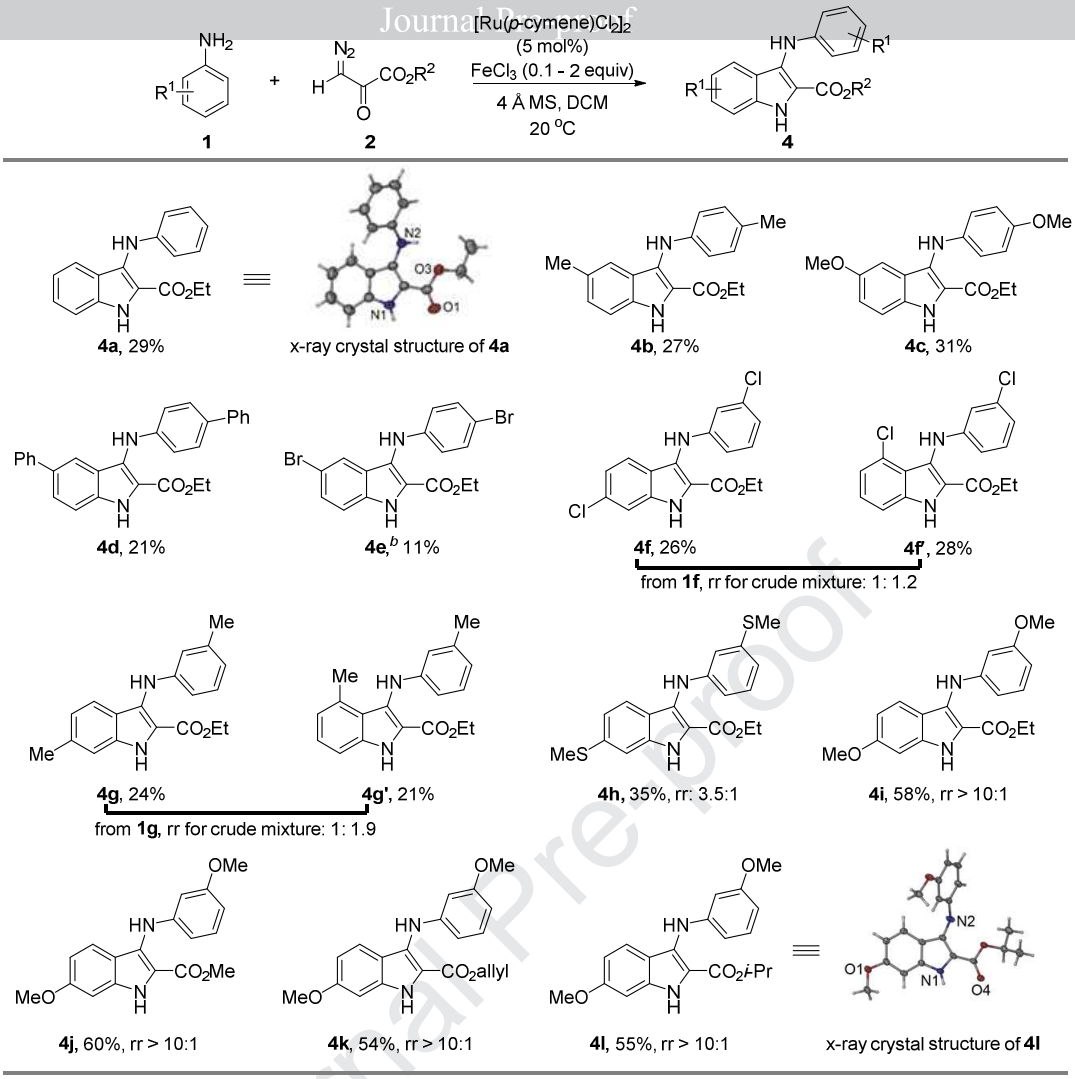
Entry	Catalyst (5 mol%)	Solvent	Additive (equiv)	Time (h)	Yield of **4a** (%)
1	[Ru(*p*-cymene)Cl_2]$_2$	DCM	$Cu(OTf)_2$ (0.1)	1	8
2	[Ru(*p*-cymene)Cl_2]$_2$	DCM	$Cu(OAc)_2$ (0.1)	1	--
3	[Ru(*p*-cymene)Cl_2]$_2$	DCM	DDQ (0.5)	15	--

4	[Ru(*p*-cymene)Cl_2]$_2$	DCM	TBHP (1.0)	15	< 5
5	[Ru(*p*-cymene)Cl_2]$_2$	DCM	Na_2CO_3 (0.5)	15	--
6	[Ru(*p*-cymene)Cl_2]$_2$	DCM	Na_2CO_3 (1.0)	15	--
7	[Ru(*p*-cymene)Cl_2]$_2$	DCM	Al_2O_3 (0.5)	15	--
8	[Ru(*p*-cymene)Cl_2]$_2$	DCM	*p*-TSA (0.5)	15	--
9	[Ru(*p*-cymene)Cl_2]$_2$	DCM	*p*-TSA (1.0)	15	--
10	[Ru(*p*-cymene)Cl_2]$_2$	DCM	$FeCl_3$ (1.0)	1	29
11	[Ru(*p*-cymene)Cl_2]$_2$	THF	$FeCl_3$ (1.0)	1	27
12	[Ru(*p*-cymene)Cl_2]$_2$	Toluene	$FeCl_3$ (1.0)	1	25
13	$RuCl_3.xH_2O$	DCM	$FeCl_3$ (1.0)	1	18
14	$Rh_2(OAc)_4$	DCM	$FeCl_3$ (1.0)	1	12
15	$Cu(OTf)_2$	DCM	$FeCl_3$ (1.0)	1	< 5
16	--	DCM	$FeCl_3$ (1.0)	1	--

[a]Reaction Conditions: Unless noted down, all the optimizations were performed by using **1a (**0.3 mmol, 1.5 equiv), **2a** (0.2 mmol, 1 equiv) and 5 mol% of catalyst in 2 mL of solvent at 20 ^oC. [b]Isolated yields of chromatographically pure product **4a**.

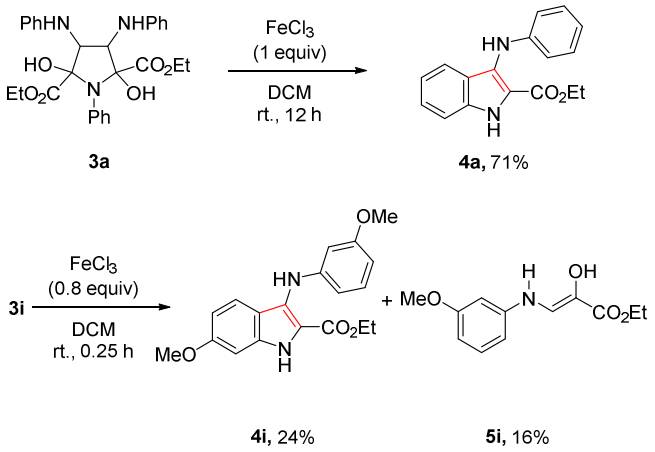
Of all the trials, the reaction parameters of entry 10 of Table 1 turned out be the best to furnish the desired indole product **4a**. Therefore, various anilines **1** and diazo pyruvates **2** with diverse substitutions were applied to the above sequence to evaluate the substrate scope. A series of anilines bearing electron-donating groups such as methyl, methoxy, phenyl, and thiomethyl substituents, halogens such as chloro and bromo as substituents were tolerated well regardless of their electronic features and afforded corresponding indole products in fair to good yields (Table 2, **4b-4l**). An interesting pattern was noticed with the *meta*-substituted anilines that resulted in regioselective products, which might be accounted for the competitive reactivity of both the *ortho*-carbons of aniline towards the annulation, a common phenomenon encountered with *meta*-substituted partners (Table 2, **4f**–**4l**). Weak activating groups like halo and methyl groups were less selective, thus produced the desired products with poor regioselective ratio, whereas, the strong activating methoxy group resulted in single isomeric product. Moreover, methyl, allyl and isopropyl diazo pyruvates were also compatible to the current transformation (Table 2, **4j**–**4l**). *ortho*-substituted anilines were not appropriate to afford the desired product probably owing to steric crowding from the *ortho*-substituent. Notably the amount of $FeCl_3$ and the reaction time varied with respect to the substrates highlighting the sensitivity of protocol. In addition to spectroscopic analysis, the structure of indole was confirmed by single-crystal X-ray diffraction report of both **4a** and **4l** (Table 2).

Table 2: Substrate-scope of the reaction for the formation of indoles **4**.[a]



[a]Reaction conditions: Unless noted down, all the reactions were performed by using 0.3 mmol of **1a**, 0.2 mmol of **2a**, 5 mol% of [Ru(*p*-cymene)Cl_2]$_2$ and $FeCl_3$ (0.1–2.0 equiv) in DCM (2 mL) at 20–48 °C for 0.8–3 h. For detailed amount of $FeCl_3$ being used for each substrate, see the Supporting Information. Isolated yields were reported. Regioisomeric ratios (rr) were determined by ^{1}H NMR of the crude reaction mixture. [b]Reaction was performed at 48 °C.

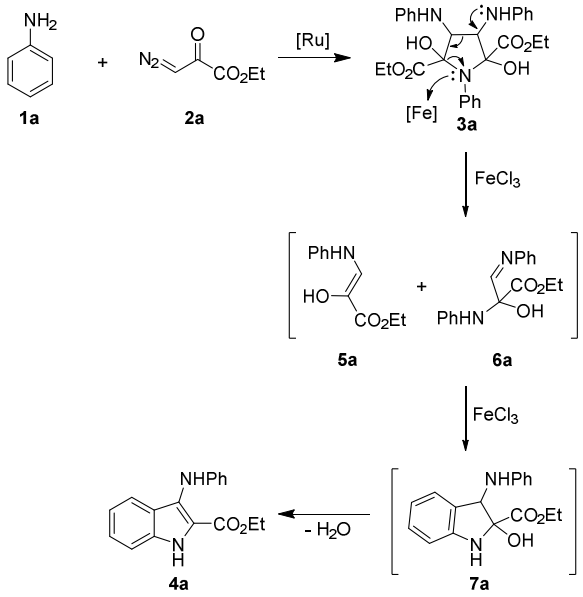
In order to unlock the reaction pathway by determining the reaction intermediate, the pyrrolidine **3a** obtained from our previous report [16] was treated with $FeCl_3$. Delightfully, $FeCl_3$ was able to transform pyrrolidine **3a** to the desired indole evidencing pyrrolidine as the key reaction intermediate. On the other hand, after thorough assessment of different pyrrolidine intermediates with $FeCl_3$, we were able to isolate the enol of methoxy system **5i**, upon controlling the reaction time, which illustrated possibility of reaction through the formation of enol via the cleavage of pyrrolidine **3** [17]. It's noteworthy that the enol substrate is sensitive to the ruthenium catalyst being employed [16] and hence no enol side product was observed in this one-pot strategy (Scheme 3).



Scheme 3: Control experiments.

A plausible reaction pathway was proposed for the surprising formation of indoles **4**. We suppose that after the formation of pyrrolidine **3a** from aniline **1a** and ethyl diazo pyruvate **2a** under ruthenium catalysis [16], the addition of $FeCl_3$ leads to the activation of tertiary amine of pyrrolidine **3a**, triggering the

fragmentation leading to imine **6a** and enol **5a** [18]. On the other hand, the possibility that **6a** was directly formed from **1a** and **2a** under [Ru]/[Fe] catalysis could not be ruled out under current stage. The imine intermediate **6a** might undergo an intramolecular Friedel-Crafts annulation which was facilitated by $FeCl_3$, to give indanol **7a**. Further dehydration of **7a** would deliver the desired indole product **4a**.



Scheme 4: Mechanism for the formation of indole ester **4a**.

As indoles are well-documented to possess varied biological properties, we headed to explore the new compounds for possible anticancer activity. CCK-8 assay was used to validate the cytotoxicity of these compounds in HCT116 cells. The results are summarized in Table 3. Among all the screened derivatives, five compounds showed good growth inhibitory activity when used at 30 µM. Three of these compounds were further measured for their IC_{50} values of cytotoxic effects and provided values ranging from 0.05 to 2.4 µM. Overall it was noticed that compound **4i** showed the most potent inhibitory effect with IC_{50} value of 0.05 µM (Table 3).

Table 3: Cytotoxicity Data of Indoles **4a**–**4l**.[a]

Entry	Compound	Inhibition (%)[a]	IC_{50}(µM)
1	**4a**	12.65	-[b]
2	**4b**	95.24	-
3	**4c**	27.99	-
4	**4h**	86.68	-
5	**4i**	97.07	0.05
6	**4j**	84.45	0.7
7	**4k**	88.24	2.4

[a]Inhibition of HCT116 cell proliferation produced by the tested compounds at 30 µM. [b]The IC50 of compounds were not determined since the inhibition rate at 10 µM was lower than 50%.

3. Conclusions

In conclusion, we have developed a unique access to substituted indoles via unprecedented Lewis acid-promoted fragmentation and rearrangement processes from simple starting materials. The transformation tolerates a variety of substrates and yielded variedly substituted indoles. One of the indole **4i**, has demonstrated excellent anti-cancer potency. Further work is under way to fully study the biological effect of these newly synthesized indole molecules.

4. Experimental section:

4.1. General Information:

All the reactions were carried in a flame-dried or oven-dried flask containing a magnetic stir. All ^{1}H-NMR (400 MHz), and ^{13}C-NMR (101 MHz) spectra were recorded on a Bruker spectrometer in $CDCl_3$ and DMSO-d_6. Tetramethylsilane (TMS) served as an internal standard (δ = 0) for ^{1}H-NMR, $CDCl_3$ (δ = 77.0) and DMSO (δ = 39.5) were used as internal standards for ^{13}C-NMR respectively. Chemical shifts (δ) are reported in parts per million (ppm) as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad singlet). HRMS spectra were recorded on an Ion Spec FT-ICR mass spectrometer in ESI mode. Dichloromethane (DCM) was distilled over calcium hydride prior to use. Diazo pyruvates were prepared based on the reported methods [19].

4.2. General procedure (GP-1) for the synthesis of Indoles (4):

To an oven dried 10 mL test tube containing a well stirred mixture of [Ru(*p*-cymene)Cl_2]$_2$ (5 mol%), $FeCl_3$ (0.1-2.0 equiv.), aniline **1** (0.30 mmol) in 1.0 mL of dichlormethane at 20 to 48 ^{o}C, was added diazo compound **2** (0.20 mmol) in 1.0 mL of dichloromethane over 15 minutes via syringe. The tube was sealed with a rubber stopper and the mixture was allowed to stir for 0.8-3 h, monitored the progress of the reaction by TLC until complete consumption of starting materials. Filtered the reaction mixture through celite and concentrated under reduced pressure to obtain the crude residue. The crude mass was purified by flash column chromatography on silica gel (eluent: petroleum ether/ EtOAc = 20:1 to 15:1) to give the pure product **4**.

4.3. Cytotoxicity Data (CCK-8 Assay):

Cancer cell line HCT116 (colon cancer) were used in the study was purchased from Cell bank of China Science Academy (Shanghai, China), and cultured aseptically in 5% CO_2 at 37□ with the corresponding medium supplemented with 10% (V/V) fetal bovine serum and 100 units per ML each of penicillin G and streptomycin. In vitro cytotoxicity of the compounds was evaluated by CCK-8 assay. HCT116 cells were respectively seeded in 96-well plates at a concentration 3000-3500 cells/well and incubated for 24 h before compound administration. Each tested compound was dissolved in DMSO (30 mM) and diluted in media. Then the compound was added to the cells at 30 µM. The control cells were treated with the vehicle DMSO. After 72 h of incubation, the old medium was removed and 100 µL new medium containing 10 µL CCK-8 solution (5 gL-1) was added to each well, incubated for additional 4 h. Finally, the optical density (OD) was measured at 450 nm and 620 nm (reference wavelength) using a microplate reader (spectraMax M5/M5e, Sunnyvale, CA, USA). IC50 value was determined by testing the inhibitory effects of the compound with 10 gradient-dilution concentrations with at least three replicates per concentration.

4.4. Characterization Data of Products:

4.4.1. Ethyl 3-(phenylamino)-1H-indole-2-carboxylate (4a):

This desired compound **4a** (12 mg, 29% yield) as white solid was obtained by following representative procedure using $FeCl_3$ (1.0 equiv), aniline **1a** (0.3 mmol, 29.2 mg) and ethyl diazopyruvate **2a** (0.2 mmol, 28.4 mg) at 20 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.23 (s, 1H), 7.42 – 7.38 (m, 1H), 7.36 – 7.28 (m, 3H), 7.28 – 7.22 (m, 2H), 7.05 (d, *J* = 7.7 Hz, 2H), 7.00 – 6.92 (m, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 162.43, 143.64, 135.87, 128.99, 126.29, 122.96, 121.13, 120.49, 119.05, 118.27, 113.01, 112.02, 60.55, 14.53.
HRMS: Calcd. for $C_{17}H_{16}N_2NaO_2$ [M+Na] =303.1109, found 303.1104.

4.4.2. Ethyl 5-methyl-3-(p-tolylamino)-1H-indole-2-carboxylate (4b):

This desired compound **4b** (12.5 mg, 27% yield) as white solid was obtained by following representative procedure using $FeCl_3$ (0.2 equiv), 4-toluidine **1b** (0.30 mmol, 32 mg) and ethyl diazopyruvate **2a** (0.20 mmol, 27.9 mg) at 20 °C. **^{1}H NMR (400 MHz, DMSO-d_6)** δ 11.02 (s, 1H), 7.33 (s, 1H), 7.14 (d, *J* = 8.4 Hz, 1H), 6.93 (dd, *J* = 8.5, 1.4 Hz, 1H), 6.89 (s, 1H), 6.81 (d, *J* = 8.2 Hz, 2H), 6.59 (d, *J* = 8.4 Hz, 2H), 4.11 (q, *J* = 7.1 Hz, 2H), 2.12 (s, 3H), 2.05 (s, 3H), 1.11 (t, *J* = 7.1 Hz, 3H).**^{13}C NMR (101 MHz, DMSO-d_6)** δ 161.28, 145.72, 138.33, 136.26, 135.41, 129.20, 125.77, 121.48, 119.07, 118.43, 116.14, 115.61, 112.40, 112.02, 108.99, 59.96, 15.10, 14.54, 14.21.
HRMS: Calcd. for $C_{19}H_{21}N_2O_2$ [M+H] =309.1603, found 309.1613.

4.4.3. Ethyl 5-methoxy-3-((4-methoxyphenyl)amino)-1H-indole-2-carboxylate (4c):

This desired compound **4c** (16 mg, 31% yield) as yellow solid was obtained by following representative procedure using $FeCl_3$ (0.1 equiv), 4-methoxyaniline **1c** (0.30 mmol, 38 mg) and ethyl diazopyruvate **2a** (0.20 mmol, 27.6 mg) at 20 °C. 4c contains ca. 7% unidentified impurities. **^{1}H NMR (400 MHz, DMSO-d_6)** δ 8.45 (s, 1H), 7.46 – 7.40 (m, 2H), 7.11 – 6.95 (m, 6H), 4.24 (q, J = 7.1 Hz, 2H), 3.81 (s, 3H), 3.78 (s, 3H), 1.14 (t, J = 7.1 Hz, 3H). **^{13}C NMR (101 MHz, DMSO-d_6)** δ 164.72, 160.28, 159.27, 158.79, 155.69, 141.86, 141.42, 124.18, 122.74, 115.11, 114.97, 61.75, 55.86, 14.34.
HRMS: Calcd. for $C_{19}H_{21}N_2O_4$ [M+H] = 341.1501, found 341.1482.

4.4.4. Ethyl 3-([1,1'-biphenyl]-4-ylamino)-5-phenyl-1H-indole-2-carboxylate (4d):

This desired compound **4d** (13.4 mg, 21% yield) as yellow solid was obtained by following representative procedure using $FeCl_3$ (1.0 equiv), 4-aminobiphenyl **1d** (0.30 mmol, 51.1 mg) and ethyl diazopyruvate **2a** (0.20 mmol, 28.1 mg) at 20 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.29 (s, 1H), 7.69 (s, 1H), 7.60 (t, *J* = 9.2 Hz, 3H), 7.52 (d, *J* = 6.8 Hz, 4H), 7.47 – 7.34 (m, 6H), 7.30 (t, *J* = 8.5 Hz, 2H), 7.15 (d, *J* = 8.2 Hz, 2H), 4.43 (q, *J* = 7.1 Hz, 2H), 1.44 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (126 MHz, DMSO-d_6)** δ 161.78, 145.68, 141.53, 140.69, 135.71, 132.04, 130.71, 129.37, 129.25, 127.47, 127.12, 126.63, 126.32, 126.16, 125.49, 122.79, 119.21, 117.63, 115.90, 113.93, 60.59, 14.67.
HRMS: Calcd. for $C_{29}H_{24}N_2NaO_2$ [M+Na] =455.1735, found 455.1732.

4.4.5. Ethyl 5-bromo-3-((4-bromophenyl)amino)-1H-indole-2-carboxylate (4e):

This desired compound **4e** (7.4 mg, 11% yield) as white solid was obtained by following representative procedure using $FeCl_3$ (2 equiv), 4-bromoaniline **1e** (0.30 mmol, 53.1 mg) and ethyl diazopyruvate **2a** (0.20 mmol, 28.2 mg) at 48 °C. **^{1}H NMR (400 MHz, DMSO-d_6)** δ 11.74 (s, 1H), 7.94 (s, 1H), 7.50 (s, 1H), 7.40 (s, 2H), 7.28 (d, *J* = 8.5 Hz, 2H), 6.71 (d, *J* = 8.6 Hz, 2H), 4.25 (q, *J* = 7.1 Hz, 2H), 1.20 (t, *J* = 7.1 Hz, 3H**). ^{13}C NMR (101 MHz, DMSO-d_6)** δ 166.00, 150.42, 139.29, 136.54, 133.21, 128.98, 128.80, 127.78, 123.94, 121.75, 120.29, 116.75, 114.23, 65.51, 19.28.
HRMS: Calcd. for $C_{17}H_{15}Br_2N_2O_2$ [M+H] = 436.9495, found 436.9462.

4.4.6. Ethyl 6-chloro-3-((3-chlorophenyl)amino)-1H-indole-2-carboxylate (4f):

This desired compound **4f** (13.8 mg, 26% yield) as white solid was obtained by following representative procedure using $FeCl_3$ (1.5 equiv), 3-chloroaniline **1f** (0.3 mmol, 39 mg) and ethyl diazopyruvate **2a** (0.2 mmol, 28.0 mg) at 20 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.32 (s, 1H), 7.35 (s, 1H), 7.32 (d, *J* = 8.7 Hz, 1H), 7.25 (m, 1H), 7.16 (t, *J* = 8.0 Hz, 1H), 7.01 (s, 1H), 6.98 (br s, 1H), 6.89 (dd, *J* = 20.3, 8.0 Hz, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 161.97, 144.76, 135.77, 134.79, 132.47, 130.06, 128.59, 123.49, 121.11, 120.54, 119.01, 117.68, 115.92, 114.23, 111.86, 60.90, 14.50.
HRMS: Calcd. for $C_{17}H_{13}N_2O_2Cl_2$ [M–H] =347.0354, found 347.0356.

4.4.7. Ethyl 4-chloro-3-((3-chlorophenyl)amino)-1H-indole-2-carboxylate (4f′):

This desired compound **4f′** (14.7 mg, 28% yield) as white solid was obtained by following representative procedure using $FeCl_3$ (1.5 equiv), 3-chloroaniline **1f** (0.3 mmol, 39 mg) and ethyl diazopyruvate **2a** (0.2 mmol, 28.0 mg) at 20 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.76 (s, 1H), 7.35 – 7.20 (m, 2H), 7.10 – 7.06 (m, 2H), 6.81 (d, *J* = 8.0 Hz, 1H), 6.76 (s, 1H), 6.68 (d, *J* = 7.9 Hz, 1H), 6.50 (s, 1H), 4.34 (q, *J* = 7.0 Hz, 2H), 1.28 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 161.34, 148.36, 136.36, 134.61, 129.81, 127.41, 126.72, 125.17, 121.82, 121.12, 119.80, 119.23, 115.53, 113.91, 110.80, 61.23, 14.19.
HRMS: Calcd. for $C_{17}H_{13}N_2O_2Cl_2$ [M–H] =347.0354, found 347.0356.

4.4.8. Ethyl 6-methyl-3-(m-tolylamino)-1H-indole-2-carboxylate (4g):

The desired compound **4g** (11.2 mg, 24% yield) as white solid was obtained by following representative procedure using $FeCl_3$ (1.0 equiv), 3-toluidine **1g** (0.30 mmol, 33.4 mg) and ethyl diazopyruvate **2a** (0.20 mmol, 28.6 mg) at 20 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.06 (s, 1H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.20 – 7.07 (m, 2H), 6.92 – 6.73 (m, 4H), 4.39 (q, *J* = 7.1 Hz, 2H), 2.45 (s, 3H), 2.29 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 162.51, 143.53, 138.87, 136.65, 136.46, 128.82, 122.70, 121.98, 121.14, 119.08, 118.38, 116.54, 115.40, 112.24, 111.61, 60.42, 21.98, 21.56, 14.60.
HRMS: Calcd. for $C_{19}H_{19}N_2O_2$ [M-H] =307.1447, found 307.1436.

4.4.9. thyl 4-methyl-3-(m-tolylamino)-1H-indole-2-carboxylate (4g′):

The desired compound **4g′** (9.8 mg, 21% yield) as white solid was obtained by following representative procedure using $FeCl_3$ (1.0 equiv), 3-toluidine **1g** (0.30 mmol, 33.4 mg) and ethyl diazopyruvate **2a** (0.20 mmol, 28.6 mg) at 20 °C. **4g′** contains ca.

12% of major isomer **4g**. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.46 (s, 1H), 7.25 – 7.17 (m, 2H), 7.04 (t, *J* = 7.7 Hz, 1H), 6.84 (d, *J* = 6.5 Hz, 1H), 6.66 (d, *J* = 7.5 Hz, 1H), 6.62 (s, 1H), 6.56 (d, *J* = 8.0 Hz, 1H), 6.50 (s, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 2.42 (s, 3H), 2.24 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 162.05, 148.02, 138.87, 135.80, 133.55, 128.89, 128.64, 126.33, 123.83, 121.78, 120.82, 117.62, 116.55, 112.83, 109.45, 60.73, 21.55, 18.88, 14.38.
HRMS: Calcd. for $C_{19}H_{20}N_2O_2Na$ [M+Na] =331.1422, found 331.1416.

4.4.10. Ethyl 6-(methylthio)-3-((3-(methylthio)phenyl)amino)-1H-indole-2-carboxylate (4h):

This desired compound **4h** (19.8 mg, 35% yield) as light yellow solid was obtained by following representative procedure using $FeCl_3$ (1.5 equiv), 3-(methylthio)aniline **1h** (0.30 mmol, 42.6 mg) and ethyl diazopyruvate **2a** (0.20 mmol, 28.4 mg) at 20 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.14 (s, 1H), 7.31 (d, *J* = 9.1 Hz, 2H), 7.19 – 7.13 (m, 2H), 6.94 – 6.88 (m, 2H), 6.86 – 6.84 (m, 1H), 6.82 (dd, *J* = 20.7, 7.9 Hz, 1H), 4.40 (q, *J* = 7.1, 2H), 2.53 (s, 3H), 2.41 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H**). ^{13}C NMR (101 MHz, DMSO-d_6)** δ 161.28, 145.71, 138.34, 136.26, 135.41, 129.19, 125.78, 121.46, 119.07, 118.43, 116.16, 115.61, 112.42, 112.03, 109.00, 59.96, 15.11, 14.55, 14.20.
HRMS: Calcd. for $C_{19}H_{21}N_2O_2S_2$ [M+H] = 373.1044, found 373.1056.

4.4.11. Ethyl 6-methoxy-3-((3-methoxyphenyl)amino)-1H-indole-2-carboxylate (4i):

This desired compound **4i** (29.9 mg, 58% yield) as white solid was obtained by following representative procedure using $FeCl_3$ (0.8 equiv), 3-methoxyaniline **1i** (0.30 mmol, 37.6 mg) and ethyl diazopyruvate **2a** (0.20 mmol, 27 mg) at 20 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.15 (s, 1H), 7.41 – 7.30 (m, 2H), 7.15 (t, *J* = 8.1 Hz, 1H), 6.72 (d, *J* = 2.2 Hz, 1H), 6.66 (d, *J* = 2.2 Hz, 1H), 6.64 (d, *J* = 2.1 Hz, 1H), 6.62 (t, *J* = 2.3 Hz, 1H), 6.52 (dd, *J* = 8.0, 2.2 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.84 (s, 3H), 3.73 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H).**^{13}C NMR (101 MHz, $CDCl_3$)** δ 162.33, 160.47, 159.52, 144.87, 137.22, 129.76, 123.96, 114.78, 111.86, 110.93, 110.53, 106.93, 103.81, 93.62, 60.35, 55.45, 55.19, 14.61.
HRMS: Calcd. for $C_{19}H_{21}N_2O_4$ [M+H] = 341.1501, found 341.1482.

4.4.12. Methyl 6-methoxy-3-((3-methoxyphenyl)amino)-1H-indole-2-carboxylate (4j):

This desired compound **4j** (29.3 mg, 60% yield) as white solid was obtained by following representative procedure using $FeCl_3$ (0.8 equiv), 3-methoxyaniline **1i** (0.30 mmol, 37.2 mg) and methyl diazopyruvate **2b** (0.20 mmol, 25 mg) at 20 °C. **^{1}H NMR (400 MHz, DMSO-d_6)** δ 11.22 (s, 1H), 7.74 (s, 1H), 7.17 (d, *J* = 8.9 Hz, 1H), 7.05 (t, *J* = 8.2 Hz, 1H), 6.81 (s, 1H), 6.63 (d, *J* = 8.9 Hz, 1H), 6.47 (d, *J* = 6.6 Hz, 2H), 6.36 (d, *J* = 8.9 Hz, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.64 (s, 3H). **^{13}C NMR (101 MHz, DMSO-d_6)** δ 161.80, 159.97, 158.39, 146.18, 137.10, 129.47, 126.98, 122.37, 115.23, 113.86, 110.43, 108.48, 104.56, 101.45, 93.96, 55.10, 54.70, 51.13.
HRMS: Calcd. for $C_{18}H_{19}N_2O_4$ [M+H] =327.1345, found 327.1349.

4.4.13. Allyl 6-methoxy-3-((3-methoxyphenyl)amino)-1H-indole-2-carboxylate (4k):

This desired compound **4k** (28.7 mg, 54% yield) as white solid was obtained by following representative procedure using $FeCl_3$ (0.8 equiv), 3-methoxyaniline **1i** (0.30 mmol, 37.4 mg) and allyl diazopyruvate **2c** (0.20 mmol, 30.2 mg) at 20 °C. **^{1}H NMR (400 MHz, DMSO-d_6)** δ 11.23 (s, 1H), 7.76 (s, 1H), 7.21 (d, *J* = 8.9 Hz, 1H), 7.06 (t, *J* = 8.1 Hz, 1H), 6.85 (s, 1H), 6.65 (d, *J* = 8.9 Hz, 1H), 6.48 (d, *J* = 8.5 Hz, 2H), 6.36 (d, *J* = 8.8 Hz, 1H), 6.08 – 5.93 (m, 1H), 5.40 (d, *J* = 17.3 Hz, 1H), 5.24 (d, *J* = 10.5 Hz, 1H), 4.79 (d, *J* = 4.9 Hz, 2H), 3.79 (s, 3H), 3.65 (s, 3H). **^{13}C NMR (101 MHz, DMSO-d_6)** δ 160.95, 159.99, 158.47, 146.15, 137.17, 132.87, 129.49, 127.33, 122.34, 117.50, 115.28, 113.73, 110.50, 108.41, 104.55, 101.35, 93.98, 64.08, 55.08, 54.69.
HRMS: Calcd. for $C_{20}H_{21}N_2O_4$ [M+H] =353.1501, found 353.1482.

4.4.14. Isopropyl 6-methoxy-3-((3-methoxyphenyl)amino)-1H-indole-2-carboxylate (4l):

This desired compound **4l** (29.1 mg, 55% yield) as white solid was obtained by following representative procedure using $FeCl_3$ (0.8 equiv), 3-methoxyaniline **1i** (0.30 mmol, 37 mg) and allyl diazopyruvate **2c** (0.20 mmol, 30.2 mg) at 20 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.12 (s, 1H), 7.41 (s, 1H), 7.35 (d, *J* = 9.0 Hz, 1H), 7.15 (t, *J* = 8.0 Hz, 1H), 6.73 (s, 1H), 6.65 (d, *J* = 8.8 Hz, 2H), 6.62 (s, 1H), 6.51 (d, *J* = 8.1 Hz, 1H), 5.25 (h, *J* = 6.4 Hz, 1H), 3.84 (s, 3H), 3.73 (s, 3H), 1.38 (d, *J* = 6.2 Hz, 7H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 161.94, 160.46, 159.45, 144.95, 137.08, 129.75, 123.93, 114.83, 110.81, 110.47, 106.83, 103.67, 93.62, 67.94, 55.45, 55.18, 22.26.
HRMS: Calcd. for $C_{20}H_{23}N_2O_4$ [M+H] =355.1658, found 355.1649.

4.4.15. Ethyl (Z)-2-hydroxy-3-((3-methoxyphenyl)amino)acrylate (5i):

This desired compound **5i** (5.4 mg, 16% yield) as Pale yellow semi-solid was obtained by using pyrrolidine **3i** (0.14 mmol, 83 mg) with $FeCl_3$ (0.8 equiv) in dichloromethane at 25 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.19 (s, 1H), 7.07 (t, *J* = 8.0 Hz, 1H), 6.66 (s, 1H), 6.43 (d, *J* = 8.5 Hz, 1H), 6.30 (d, *J* = 8.2 Hz, 1H), 6.25 (s, 1H), 5.81 (s, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.71 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 163.60, 160.27, 142.81, 132.33, 129.53, 114.15, 110.53, 107.00, 103.95, 62.01, 55.20, 14.08.
HRMS: Calcd. for $C_{12}H_{16}NO_4$ [M+H] =238.1079, found 238.1074.

Declaration of competing interest
The authors have declared that they have no conflict of interest.

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Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.

Highlights

- Domino [Ru]-catalyzed annulation followed by iron promoted fragmentation
- One-pot synthesis of indole esters
- Usage of easily accessible starting materials
- Application to anti-cancer activity