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A Copper-Catalyzed Friedel–Crafts Alkylation/Cyclization Sequence: an Approach to Functionalized Pyrrolo[1,2-*a*]indole Spirooxindoles and 9*H*-Pyrrolo[1,2-*a*]indoles

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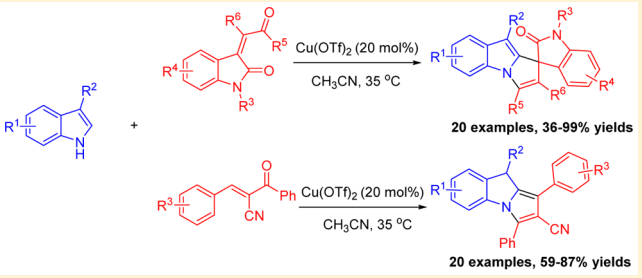
Supporting Information

ABSTRACT: An efficient $Cu(OTf)_2$-catalyzed Friedel–Crafts alkylation/cyclizaiton sequence of 3-substituted indoles with isatin-derived oxodienes was developed, and a series of structurally complex and diverse pyrrolo[1,2-*a*]indole spirooxindoles were first obtained in up to 99% yields. This protocol proved to be quite general and was also robust for the synthesis of 9*H*-pyrrolo[1,2-*a*]indoles.



INTRODUCTION

Pyrrolo[1,2-*a*]indoles and their analogues are an important class of privileged structural units with a 6–5–5 tricyclic core skeleton, which are prevalent in many natural products and pharmaceuticals and exhibit significant bioactivities (Figure 1).[1] For instance, JTT-10 is a protein kinase C-β-selective inhibitor.[1b,c] Flinderole A, isolated from the plant *flindersia acuminate*, and related molecules flinderoles B and C show selective antimalarial activities.[1d−g] In addition, they are also useful intermediates for the synthesis of structurally complex and diverse polycycles.[2] Consequently, considerable efforts have been devoted to the development of efficient approaches for the construction of this skeleton, and many successful examples have been achieved, including the radical cyclization of *N*-substituted indoles,[3] an intramolecular Friedel–Crafts alkylation of *N*-substituted indoles,[4] [6 + 2]-cycloaddition of indolyl-2-benzylic alcohol,[5] [3 + 2]-cycloaddition of 1*H*-indole-2-carbaldehyde[6a−e] or nitrovinylindoles,[6f,g] and C-2 functionalization/annulation sequence of indoles,[7] and so forth. Among them, a C-2 functionalization/annulation sequence of indoles has been proven to be an efficient and rapid strategy for the construction of these useful compounds. For instance, Kumar[7a] and Chen[7b] independently reported the Friedel–Crafts alkylation/annulation sequence of indoles and enones derived from aldehyde, allowing the synthesis of 9*H*-pyrrolo[1,2-*a*]indoles. In 2013, Feng[7c] and Xiao[7d] documented the asymmetric Friedel–Crafts alkylation/*N*-hemiacetalization cascade reaction between indoles and β,γ-unsaturated α-ketoesters, respectively. Although these outstanding discoveries have been reported, the enones are usually derived from aldehydes, and a method employing isatin-derived enones has been less studied.[8] In light of the importance of pyrrolo[1,2-*a*]indoles, it is still highly desirable and challenging to explore more efficient and accessible methods for rapid establishment of these pyrrolo[1,2-*a*]indole skeletons with novel and complex structures under mild conditions.

On the other hand, spirooxindole also represents an interesting structural motif, which constitutes the core unit of many naturally occurring products and pharmacologically active compounds.[9] In light of the importance of these two intriguing scaffolds of pyrrolo[1,2-*a*]indole and spirooxindole, the combination of them into one molecule would deliver a new collection of interesting compounds, which may exhibit new or improved bioactivities. However, to the best of our knowledge, studies on the construction of this kind of compound are fewer, and only one report was documented during our submission of this manuscript.[8]

As a continuation of our interest in the construction of novel and diverse spirooxindoles[10a−c] and indole-related compounds,[10d] we envisioned that C2-functionalization of 3-alkyl-substituted indoles with isatin-derived oxodienes might be achieved under certain appropriate conditions, and subsequently, an intramolecular cyclization occurs, thus leading to pyrrolo[1,2-*a*]indole spirooxindoles (Scheme 1). Notably, challenges still exist in this transformation, such as the relatively low reactivity and more steric hindrance of isatin-derived enones. Herein, we wish to report our preliminary results.

RESULTS AND DISCUSSION

For the feasibility of our hypothesis to be tested, 3-methylindole **1a** and *N*-methyl isatin-derived oxodiene **2a**

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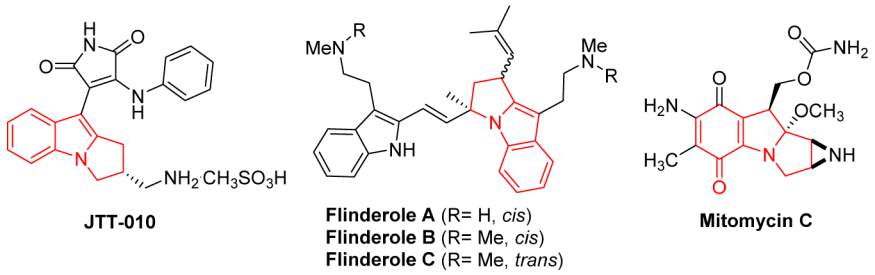
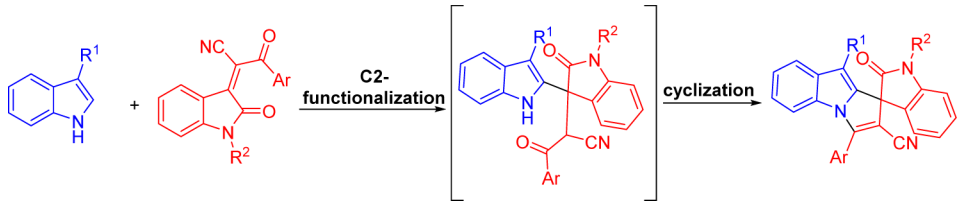


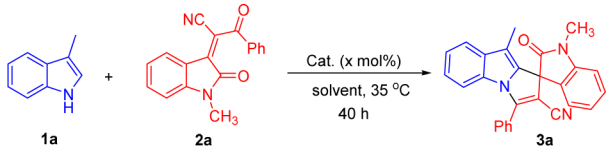
Figure 1. Selected bioactive compounds containing the pyrrolo[1,2-*a*]indole motif.

Scheme 1. Our Synthetic Design toward the Synthesis of Pyrrolo[1,2-*a*]indole Spirooxindoles



were chosen as the model substrates. To our delight, pyrrolo[1,2-*a*]indole spirooxindole **3a** was afforded in 99% yield in the presence of $Cu(OTf)_2$ in CH_3CN at 35 °C (Table 1, entry 1). To improve the synthetic efficiency, then, we examined some other Lewis acids and protonic acids, but all gave inferior yields (Table 1, entries 2–8). Thus, $Cu(OTf)_2$ was chosen as the catalyst to screen the reaction media, and the results indicated that it has a significant effect on the yield. When the reaction was conducted in toluene, EtOAc, and $CHCl_3$, the yields decreased significantly (Table 1, entries 1 vs 9–11). Among the solvents tested, CH_3CN proved to be the best (Table 1, entry 1). Notably, when the reaction was conducted in CH_3CN, product **3a** was precipitated and only filtration was needed to purify the product. This would avoid the use of column chromatography and greatly simply the purification process. Finally, the catalyst loadings were investigated, and the results revealed that they had some influence on the yields (Table 1, entries 12 and 13). When 15 mol % $Cu(OTf)_2$ was used, the yield was dropped to 94% (Table 1, entry 12). Further decreasing the catalyst loading to 10 mol % resulted in an 85% yield of **3a** (Table 1, entry 13). Consequently, the following reaction conditions were recommended: 0.16 mmol **1a** and 0.13 mmol **2a** with 20 mol % $Cu(OTf)_2$ in 0.8 mL of CH_3CN at 35 °C.

Table 1. Optimization of Reaction Conditions[a]



1a 2a 3a

entry	cat.	solvent	*x*	**3a**/ yield[b] (%)
1	$Cu(OTf)_2$	CH_3CN	20	99[c]
2	$In(OTf)_3$	CH_3CN	20	60
3	$Sc(OTf)_3$	CH_3CN	20	97
4	$Cu(OAc)_2{\cdot}4H_2O$	CH_3CN	20	15
5	$CuBr_2$	CH_3CN	20	66
6	*p*-TSA	CH_3CN	20	59
7	TfOH	CH_3CN	20	81
8	$MeSO_3H$	CH_3CN	20	58
9	$Cu(OTf)_2$	toluene	20	59
10	$Cu(OTf)_2$	EtOAc	20	25
11	$Cu(OTf)_2$	$CHCl_3$	20	25
12	$Cu(OTf)_2$	CH_3CN	15	94[c]
13	$Cu(OTf)_2$	CH_3CN	10	85[c]

[a]Unless otherwise noted, the reaction was conducted on a scale of 0.16 mmol **1a** and 0.13 mmol **2a** in 0.8 mL of solvent at 35 °C. [b]Isolated yields after silica gel column chromatography. [c]Isolated yields by directly filtrating the precipitate.

With the optimal conditions established, the substrate scope was explored by using various 3-alkyl-substituted indoles with isatin-derived oxodienes, and the results are listed in Table 2. This domino reaction could tolerate a wide range of oxodienes **2**, and all of the cases delivered the desired products (**3a–l**) in moderate to excellent yields (36–99% yields). The N-protecting groups on the oxodienes **2** were first studied, and the results revealed that they had minimal impact on the yields (**3a–c**, 94–99%). Then, the influence of the positions and the electronic nature of the substitution patterns on the aromatic rings of oxodienes **2** were examined. Substrates with electron-donating substituents exhibit higher reactivity than those with electron-withdrawing ones, affording the desired products in much higher yields (**3d** vs **3e–h**). In addition, varying the position of the substituents resulted in some changes in the yields (**3f–h**). Not only is a phenyl group beside the carbonyl group applicable in this reaction, a *p*-Cl-substituted phenyl group is also tolerated, allowing the synthesis of **3i** in 53% yield. The cyano group is not indispensable in this reaction. It could be switched to esters, and the corresponding products **3j** and **3k** could be obtained in 36 and 49% yields, respectively. Notably, when cyano group was replaced by a H atom, a Friedel–Crafts alkylation/*N*-hemiketalization/Friedel–Crafts alkylation sequence occurred, affording indole-substituted pyrrolo[1,2-*a*]indole spirooxindole **3l** in 59% yield, which is similar to that of Wang's work.[8] Subsequently, the effect of the C3 substituents of indoles was tested, and all of the reactions proceeded smoothly to give the products in moderate to excellent yields (**3m–t**, 61–98% yields). The C3 substituents are not only limited alkyl groups, an aryl group is also tolerable. When 3-phenyl indole was employed, product **3n** with more steric hindrance was generated in 67% yield. However, for no

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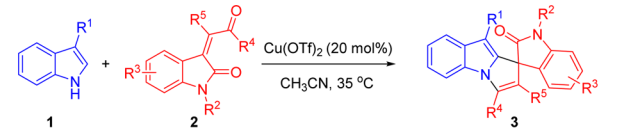
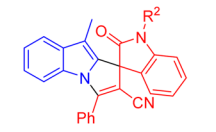
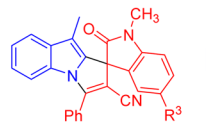
Table 2. Scope of Substrates[a]

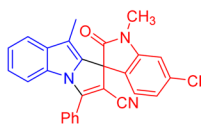




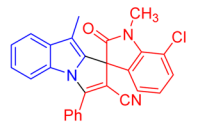
3a, R^2= Me, 40 h, 99% yield[c]
3b, R^2= Et, 40 h, 97% yield[c]
3c, R^2= allyl, 40 h, 94% yield[c]



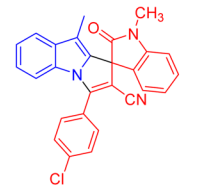
3d, R^3= Me, 40 h, 97% yield[c]
3e, R^3= F, 40 h, 86% yield[b]
3f, R^3= Cl, 40 h, 68% yield[b]



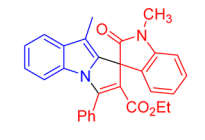
3g, 40 h, 70% yield[b]



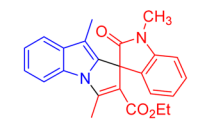
3h, 40 h, 48% yield[b]



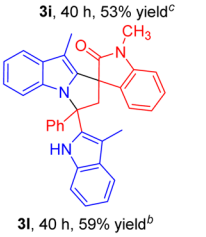
3i, 40 h, 53% yield[c]



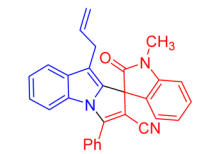
3j, 60 h, 36% yield[b,d]



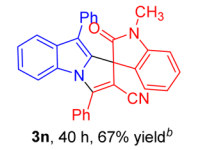
3k, 40 h, 49% yield[c]



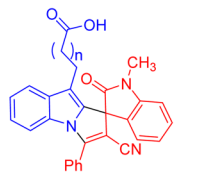
3l, 40 h, 59% yield[b]



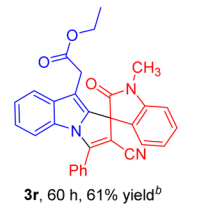
3m, 38 h, 68% yield[b]



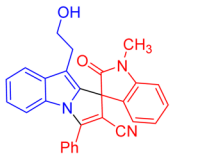
3n, 40 h, 67% yield[b]



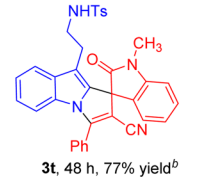
3o, n= 0, 60 h, 86% yield[b]
3p, n= 1, 60 h, 96% yield[c]
3q, n= 2, 40 h, 98% yield[c]



3r, 60 h, 61% yield[b]



3s, 60 h, 67% yield[b]



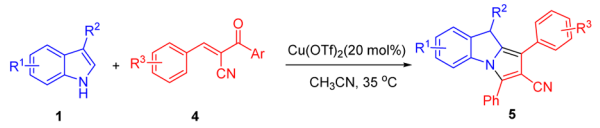
3t, 48 h, 77% yield[b]

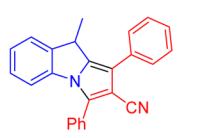
[a]Unless otherwise noted, the reaction was conducted on a scale of 0.16 mmol **1** and 0.13 mmol **2** in 0.8 mL of CH_3CN at 35 °C. [b]Isolated yields after silica gel column chromatography. [c]Isolated yields by directly filtrating the precipitate. [d]At 60 °C.

C3-substituted indole, only Friedel−Crafts alkylation occurred, and the reactive site is the C3 position rather than the C2 position. Remarkably, this method could be applicable to indoles **1o−q** bearing a carboxylic acid functional group, and the chain lengths have nearly no effect on the yields (**3o−l**). Some other functional groups, such as ester, hydroxyl, and amino groups, are also tolerable (**3r−t**), which highlights the application of this reaction because these functional groups could undergo further transformation to obtain more complex molecules.

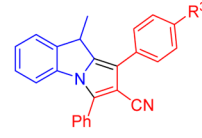
Next, we attempted the reaction of 3-methylindole **1a** with benzaldehyde-derived oxodiene **4a** under the same optimal conditions. Surprisingly, isomerization of the C=C double bond in the indolic cycle took place, and the corresponding 9*H*-pyrrolo[1,2-*a*]indole **5a** was obtained in 86% yield. It was complementary to the method with isatin-derived oxodienes as substrates, and two kinds of different heterocycles could be obtained. Then, the scope with respect to various C3-substituted indoles **1** and aromatic aldehyde-derived oxodienes **4** was studied. As shown in Table 3, when *para*-substituted

Table 3. Scope of Indoles with Aromatic Aldehyde-Derived Oxodienes[a]

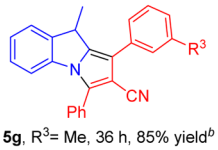




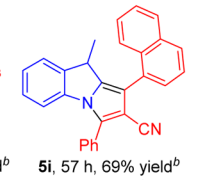
5a, 36 h, 86% yield[c]



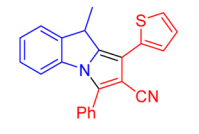
5b, R^3= Me, 36 h, 84% yield[b]
5c, R^3= OMe, 36 h, 71% yield[b]
5d, R^3= F, 36 h, 80% yield[c]
5e, R^3= Cl, 36 h, 71% yield[b]
5f, R^3= Br, 36 h, 69% yield[c]



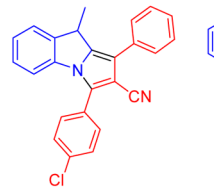
5g, R^3= Me, 36 h, 85% yield[b]
5h, R^3= Br, 36 h, 65% yield[c]



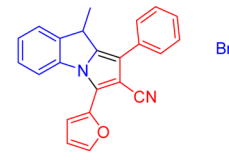
5i, 57 h, 69% yield[b]
d.r.= 2:1[d]



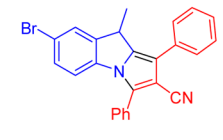
5j, 36 h, 86% yield[c]



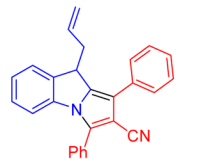
5k, 36 h, 88% yield[b]



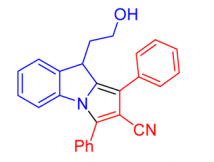
5l, 36 h, 84% yield[c]



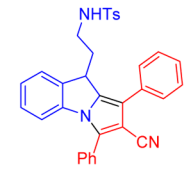
5m, 36 h, 85% yield[c]



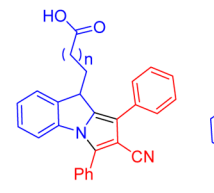
5n, 40 h, 65% yield[b]



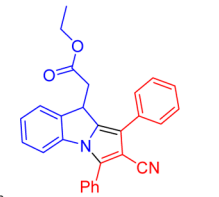
5o, 36 h, 83% yield[b]



5p, 36 h, 87% yield[b]



5q, n= 0, 36 h, 81% yield[c]
5r, n= 1, 36 h, 83% yield[c]
5s, n= 2, 36 h, 59% yield[b]



5t, 58 h, 67% yield[b]

[a]Unless otherwise noted, the reaction was conducted on a scale of 0.16 mmol **1** and 0.13 mmol **4** in 0.8 mL of CH_3CN at 35 °C. [b]Isolated yields after silica gel column chromatography. [c]Isolated yields by directly filtrating the precipitate. [d]The dr value of the inseparable diastereoisomers was determined by ^1H NMR.

oxodienes **4b−f** were used, 69−84% yields were obtained. It seemed that the electronic nature had no obvious effect on the yield, but the bulk of the substituents affected the yield because 4-methyl-substituted substrate **4b** delivered a higher yield than that of the 4-OMe-substituted substrate **4c**. Moreover, this phenomenon was also observed in substrates **4d−f**. When the substituents were located at the meta position of the phenyl ring, an electron-rich substituent gave a better yield than that of

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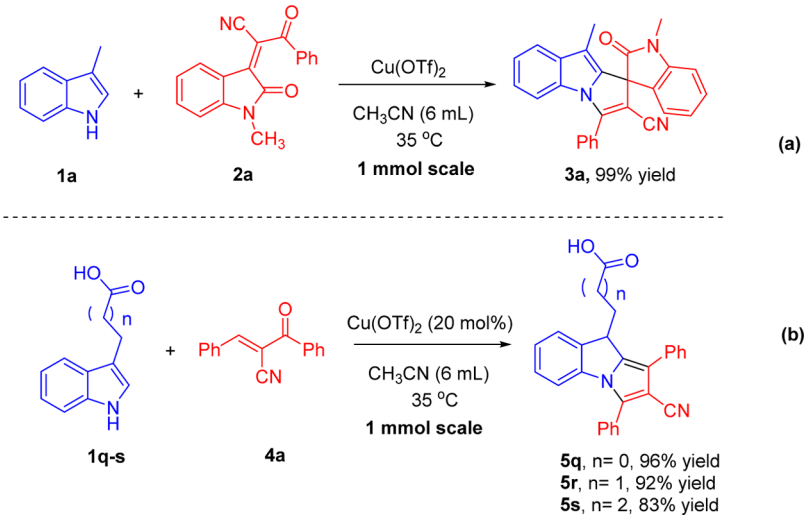
Scheme 2. Gram-Scale Preparation of 3a and 5q−s

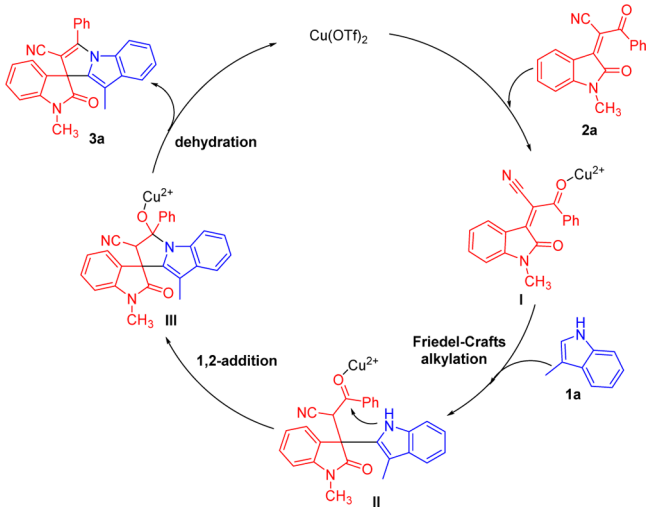


an electron-poor one (**5g** vs **5h**). Furthermore, the naphthyl- and thienyl-substituted oxodienes also proved to be suitable reaction partners for this reaction, giving 9*H*-pyrrolo[1,2-*a*]indoles **5i** and **5j** in 69 and 86% yields, respectively. It is noteworthy that when **4i** was employed as the substrate, a 2:1 dr value was observed in product **5i**. This may be because of steric hindrance that led to the atropisomers.[11] Subsequently, the aryl group beside the carbonyl group of **4** was investigated. It revealed that not only was the phenyl group applicable in this reaction, *p*-Cl-substituted phenyl and 2-furyl groups were also tolerated, affording the corresponding 9*H*-pyrrolo[1,2-*a*]-indoles **5k** and **5l** in 88 and 84% yields, respectively. Finally, the effect of the substituents on the indolic rings was examined, and moderate to good yields were obtained in all cases (**5m−t**, 59−87% yields). Gratifyingly, when alkenyl, hydroxyl, amino, carboxylic acid, and ester were introduced into the C3 position of indoles, this reaction could also be tolerable. Obviously, the lengths of the chain of 3-carboxylic acid-substituted indoles had some influence on the yields. When the length increases, the yields greatly decreased (**5r** vs **5s**). The structures of compounds **3a** and **5a** were unambiguously determined by X-ray crystallographic analysis[12] (for details, see the Supporting Information).

To demonstrate the synthetic robustness of this reaction, we carried out a gram scale experiment with 1.2 mmol **1a** and 1.0 mmol **2a**. This reaction proceeded smoothly without comprising the yield, furnishing **3a** in 99% yield (Scheme 2a). Similarly, **5q−s** bearing a carboxylic acid chain could also be prepared on a 1 mmol scale (Scheme 2b), and increased yields were obtained for all cases (**5q**, 96 vs 81%; **5r**, 92 vs 83%; **5s**, 83 vs 59%).

On the basis of the experimental results, a plausible reaction mechanism was provided (Scheme 3). Initially, *N*-methyl isatin-derived oxodiene **2a** was activated by Lewis acid $Cu(OTf)_2$ to generate intermediate **I**, which was then attacked by the C2 position of 3-methylindole **1a** via the Friedel−Crafts alkylation to afford intermediate **II**. Subsequently, the N atom of indole served as an electrophile to attack the carbonyl group neighboring the benzene ring, thus leading to intermediate **III**, Finally, product **3a** was formed by the dehydration of intermediate **III**, accompanied by the release of the catalyst. As for the aromatic aldehyde-derived oxodienes **4**, an additional

Scheme 3. Plausible Reaction Mechanism



isomerization proceeded to give the corresponding 9*H*-pyrrolo[1,2-*a*]indoles **5** (not shown in Scheme 3).

In summary, we have first developed an efficient $Cu(OTf)_2$-catalyzed Friedel−Crafts alkylation/cyclization sequence of C3-substituted indoles and isatin-derived oxodienes, which provides an efficient approach to access functionalized pyrrolo[1,2-*a*]indole spirooxindoles with complex structures in moderate-to-excellent yields. Furthermore, this protocol proved to be quite general and robust for the synthesis of 9*H*-pyrrolo[1,2-*a*]indoles. Further research to extend the asymmetric synthesis of pyrrolo[1,2-*a*]indole spirooxindoles and study their bioactivities will be our focus in the future.

EXPERIMENTAL SECTION

General Methods. NMR spectra were recorded with tetramethylsilane as the internal standard. ^{1}H NMR spectra were recorded at 400 MHz, and ^{13}C NMR spectra were recorded at 100 MHz (Bruker Avance). ^{1}H NMR chemical shifts (δ) are reported in ppm relative to tetramethylsilane (TMS) with the solvent signal as the internal standard ($CDCl_3$ at 7.26 ppm, $(CD_3)_2SO$ at 2.50 ppm). ^{13}C NMR chemical shifts are reported in ppm from tetramethylsilane (TMS) with the solvent resonance as the internal standard ($CDCl_3$ at 77.00 ppm, $(CD_3)_2SO$ at 39.52 ppm). Data are given as s (singlet), d (doublet), t (triplet), q (quartet), dd (double of doublet), br (broad),

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or m (multiplets), coupling constants (Hz), and integration. Flash column chromatography was carried out using silica gel eluting with ethyl acetate and petroleum ether. High-resolution mass spectra were obtained with a Q-TOF-Premier mass spectrometer. Reactions were monitored by TLC and visualized with ultraviolet light. IR spectra were recorded on a Thermo Fisher Nicolet Avatar 360 FTIR spectrometer on a KBr beam splitter. All of the solvents were used directly without any purification.

General Procedure for the Synthesis of Functionalized Pyrrolo[1,2-*a*]indole Spirooxindoles 3. To a 5.0 mL vial were successively added indole **1** (0.16 mmol), isatin-derived α,β-unsaturated ketone **2** (0.13 mmol), $Cu(OTf)_2$ (9.4 mg, 0.026 mmol), and 0.8 mL of CH_3CN. The resulting mixture was stirred at 35 °C until almost full consumption of **2** as monitored by thin layer chromatography, and then the reaction mixture was directly subjected to flash column chromatography on silica gel (petroleum ether/ethyl acetate) to afford the corresponding products **3**. In some cases, the precipitate was generated, and only a simple filtration was needed to purify the product.

*1,9′-Dimethyl-2-oxo-3′-phenylspiro[indoline-3,1′-pyrrolo[1,2-a]indole]-2′-carbonitrile (**3a**).* White solid obtained by filtration of the precipitate: 51.6 mg, 99% yield; reaction time = 40 h; mp 212.3−213.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 8.0 Hz, 2H), 7.63 (d, J = 8.0 Hz, 3H), 7.47 (d, J = 8.0 Hz, 1H), 7.41 (t, J = 8.0 Hz, 1H), 7.13 (dd, $J_1 = J_2$ = 4.0 Hz, 5H), 7.01 (d, J = 8.0 Hz, 1H), 3.39 (s, 3H), 1.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 156.2, 144.3, 138.0, 134.8, 131.8, 130.2, 129.2, 129.2, 126.9, 125.6, 124.4, 123.8, 123.5, 122.0, 119.8, 111.9, 111.4, 109.0, 96.0, 57.5, 27.2, 7.9; IR (KBr) ν 3432, 3057, 2922, 2205, 1723, 1608, 1452, 1396, 1216, 1125, 746 cm^{-1}; HRMS (ESI) calcd for $C_{27}H_{20}N_3O$ $[M + H]^+$ 402.1601, found 402.1612.

*1-Ethyl-9′-methyl-2-oxo-3′-phenylspiro[indoline-3,1′-pyrrolo[1,2-a]indole]-2′-carbonitrile (**3b**).* White solid obtained by filtration of the precipitate: 52.3 mg, 97% yield; reaction time = 40 h; mp 236.7−237.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.0 Hz, 2H), 7.59−7.52 (m, 3H), 7.39 (d, J = 8.0 Hz, 1H), 7.32 (t, J = 8.0 Hz, 1H), 7.10−6.98 (m, 5H), 6.94 (d, J = 8.0 Hz, 1H), 3.91−3.78 (m, 2H), 1.79 (s, 3H), 1.31 (t, J = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 156.0, 143.4, 138.0, 134.8, 131.8, 131.7, 130.1, 129.2, 129.1, 127.0, 125.9, 124.7, 123.6, 123.5, 121.9, 119.8, 114.8, 111.9, 111.3, 109.1, 96.1, 57.6, 35.8, 12.8, 7.9; IR (KBr) ν 3430, 3059, 2930, 2206, 1721, 1606, 1455, 1404, 1353, 1222, 1137, 746 cm^{-1}; HRMS (ESI) calcd for $C_{28}H_{22}N_3O$ $[M + H]^+$ 416.1757, found 416.1755.

*1-Allyl-9′-methyl-2-oxo-3′-phenylspiro[indoline-3,1′-pyrrolo[1,2-a]indole]-2′-carbonitrile (**3c**).* White solid obtained by filtration of the precipitate: 52.5 mg, 94% yield; reaction time = 40 h; mp 223.3−224.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.0 Hz, 2H), 7.56−7.53 (m, 3H), 7.39 (d, J = 8.0 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.08−7.00 (m, 5H), 6.91 (d, J = 8.0 Hz, 1H), 5.87−5.80 (m, 1H), 5.25 (dd, J_1 = 16.0 Hz, J_2 = 8.0 Hz, 2H), 4.41 (d, J = 4.0 Hz, 2H), 1.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 154.9, 142.4, 136.8, 133.7, 130.7, 130.6, 129.6, 129.0, 128.1, 128.0, 125.8, 124.5, 123.5, 122.7, 122.5, 120.9, 118.8, 117.2, 113.8, 110.8, 110.4, 108.9, 95.1, 52.4, 42.1, 6.9; IR (KBr) ν 3435, 3057, 2921, 2859, 2206, 1723, 1608, 1455, 1407, 1349, 1221, 1187, 747, 704 cm^{-1}; HRMS (ESI) calcd for $C_{29}H_{21}N_3NaO$ $[M + Na]^+$ 450.1577, found 450.1555.

*1,5,9′-Trimethyl-2-oxo-3′-phenylspiro[indoline-3,1′-pyrrolo[1,2-a]indole]-2′-carbonitrile (**3d**).* White solid obtained by filtration of the precipitate: 52.2 mg, 97% yield; reaction time = 40 h; mp 269.1−269.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.0 Hz, 2H), 7.65−7.61 (m, 3H), 7.47 (d, J = 8.0 Hz, 1H), 7.21−7.09 (m, 4H), 6.90 (t, J = 8.0 Hz, 2H), 5.87−5.80 (m, 1H), 3.37 (s, 3H), 2.29 (s, 3H), 1.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 156.0, 141.9, 138.2, 134.8, 133.5, 131.8, 131.7, 130.4, 129.2, 129.1, 127.0, 125.6, 125.1, 123.5, 121.9, 119.8, 115.0, 111.9, 111.3, 108.7, 96.2, 53.5, 27.2, 21.1, 8.0; IR (KBr) ν 3434, 3056, 2921, 2861, 2208, 1721, 1630, 1497, 1453, 1405, 1351, 1225, 744, 701 cm^{-1}; HRMS (ESI) calcd for $C_{28}H_{21}N_3NaO$ $[M + Na]^+$ 438.1577, found 438.1562.

*5-Fluoro-1,9′-dimethyl-2-oxo-3′-phenylspiro[indoline-3,1′-pyrrolo[1,2-a]indole]-2′-carbonitrile (**3e**).* White solid obtained by column chromatography (petroleum ether/ethyl acetate = 10:1 to 5:1); 47.0 mg, 86% yield; reaction time = 40 h; mp 243.1−243.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.0 Hz, 2H), 7.57−7.52 (m, 3H), 7.39 (d, J = 8.0 Hz, 1H), 7.08−7.01 (m, 4H), 6.86 (dd, $J_1 = J_2$ = 4.0 Hz, 1H), 6.81 (dd, $J_1 = J_2$ = 2.4 Hz, 1H), 3.28 (s, 3H), 1.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 159.7 (d, J = 241.0 Hz, 1C), 156.4, 140.3, 137.3, 134.7, 132.0, 131.9, 129.2, 127.3 (d, J = 8.0 Hz, 1C), 126.7, 123.8, 122.2, 119.9, 116.8, 116.5, 114.7, 112.7, 112.4, 111.9 (d, J = 8.0 Hz, 1C), 109.7 (d, J = 8.0 Hz, 1C), 95.4, 53.5, 27.4, 8.0; IR (KBr) ν 3433, 3058, 2924, 2857, 2206, 1727, 1619, 1493, 1452, 1402, 1344, 1270, 1123, 741, 699 cm^{-1}; HRMS (ESI) calcd for $C_{27}H_{18}FN_3NaO$ $[M + Na]^+$ 442.1326, found 442.1308.

*5-Chloro-1,9′-dimethyl-2-oxo-3′-phenylspiro[indoline-3,1′-pyrrolo[1,2-a]indole]-2′-carbonitrile (**3f**).* White solid obtained by column chromatography (petroleum ether/ethyl acetate = 20:1 to 10:1); 38.3 mg, 68% yield; reaction time = 40 h; mp 275.9−277.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 8.0 Hz, 2H), 7.64 (dd, J_1 = 4.0 Hz, J_2 = 4.0 Hz, 3H), 7.48 (d, J = 8.0 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.20−7.08 (m, 4H), 6.94 (d, J = 8.0 Hz, 1H), 3.38 (s, 3H), 1.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 156.4, 142.9, 137.2, 134.7, 131.9, 131.8, 130.2, 129.2, 129.1, 127.4, 126.7, 124.8, 123.8, 122.2, 119.9, 114.7, 111.9, 111.8, 110.0, 95.3, 57.3, 27.4, 8.1; IR (KBr) ν 3436, 3057, 2924, 2206, 1729, 1601, 1452, 1404, 1345, 1097, 1060, 738 cm^{-1}; HRMS (ESI) calcd for $C_{27}H_{18}ClN_3O$ $[M + H]^+$ 436.1211, found 436.1223.

*6-Chloro-1,9′-dimethyl-2-oxo-3′-phenylspiro[indoline-3,1′-pyrrolo[1,2-a]indole]-2′-carbonitrile (**3g**).* White solid obtained by column chromatography (petroleum ether/ethyl acetate = 25:1 to 20:1); 39.8 mg, 70% yield; reaction time = 40 h; mp 248.1−249.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 8.0 Hz, 2H), 7.67−7.62 (m, 3H), 7.48 (d, J = 8.0 Hz, 1H), 7.20−7.03 (m, 6H), 3.38 (s, 3H), 1.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 156.3, 145.4, 137.3, 136.0, 134.7, 131.9, 131.8, 129.3, 129.1, 126.7, 125.4, 124.0, 123.7, 123.6, 122.1, 119.9, 114.7, 111.9, 111.7, 109.8, 95.5, 58.5, 27.3, 8.0; IR (KBr) ν 3444, 3065, 2922, 2206, 1731, 1605, 1453, 1400, 1361, 1069, 979, 743 cm^{-1}; HRMS (ESI) calcd for $C_{27}H_{18}ClN_3O$ $[M + H]^+$ 436.1211, found 436.1213.

*7-Chloro-1,9′-dimethyl-2-oxo-3′-phenylspiro[indoline-3,1′-pyrrolo[1,2-a]indole]-2′-carbonitrile (**3h**).* White solid obtained by column chromatography (petroleum ether/ethyl acetate = 30:1); 27.2 mg, 48% yield; reaction time = 40 h; mp 98.6−99.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 8.0 Hz, 2H), 7.66−7.63 (m, 3H), 7.48 (d, J = 8.0 Hz, 1H), 7.35−7.32 (m, 1H), 7.18 (t, J = 8.0 Hz, 1H), 7.13−7.07 (m, 2H), 7.01 (d, J = 4.0 Hz, 1H), 7.00 (s, 1H), 3.75 (s, 3H), 1.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 156.2, 140.2, 137.6, 134.7, 132.5, 131.9, 131.8, 129.2, 128.5, 126.7, 124.5, 123.8, 123.0, 122.1, 119.9, 116.3, 114.7, 111.9, 111.8, 95.8, 57.2, 30.7, 8.1; IR (KBr) ν 3433, 3057, 2923, 2207, 1728, 1602, 1456, 1407, 1326, 1227, 1106, 742 cm^{-1}; HRMS (ESI) calcd for $C_{27}H_{18}ClN_3O$ $[M + Na]^+$ 458.1031, found 458.1034.

*3′-(4-Chlorophenyl)-1,9′-dimethyl-2-oxospiro[indoline-3,1′-pyrrolo[1,2-a]indole]-2′-carbonitrile (**3i**).* White solid obtained by filtration of the precipitate: 30.0 mg, 53% yield; reaction time = 40 h; mp 297.5−298.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 8.0 Hz, 2H), 7.62 (d, J = 8.0 Hz, 2H), 7.48−7.40 (m, 2H), 7.20−7.00 (m, 6H), 3.39 (s, 3H), 1.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 154.8, 144.3, 138.1, 137.9, 134.8, 131.7, 130.6, 130.2, 129.6, 125.4, 125.3, 124.4, 123.8, 123.7, 122.1, 119.9, 114.6, 111.7, 109.0, 96.5, 57.6, 27.2, 7.9; IR (KBr) ν 3419, 3059, 2914, 2204, 1722, 1607, 1452, 1413, 1346, 1212, 1085, 751 cm^{-1}; HRMS (ESI) calcd for $C_{27}H_{19}ClN_3O$ $[M + H]^+$ 436.1211, found 436.1239.

*Ethyl 1,9′-Dimethyl-2-oxo-3′-phenylspiro[indoline-3,1′-pyrrolo-[1,2-a]indole]-2′-carboxylate (**3j**).* White solid obtained by column chromatography (petroleum ether/ethyl acetate = 20:1 to 10:1); 21.0 mg, 36% yield; reaction time = 60 h; mp 206.5−207.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.61−7.56 (m, 3H), 7.42 (d, J = 8.0 Hz, 1H), 7.36−7.32 (m, 1H), 7.09 (t, J = 8.0 Hz, 1H), 7.03−6.95 (m, 4H), 6.56 (d, J = 8.0 Hz, 1H), 3.85−3.75 (m, 2H), 3.40 (s, 3H), 1.83 (s, 3H), 0.77 (t, J = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 162.7, 153.1, 144.8,

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138.7, 134.4, 131.7, 130.2, 129.5, 129.4, 128.9, 128.5, 128.2, 123.4, 123.0, 122.8, 121.4, 119.4, 116.2, 111.4, 109.3, 108.2, 59.7, 56.8, 27.0, 13.5, 7.8; IR (KBr) ν 3425, 3058, 2927, 2858, 1718, 1610, 1457, 1375, 1342, 1242, 1094, 750 cm^{-1}; HRMS (ESI) calcd for $C_{29}H_{25}N_2O_3$ $[M + H]^+$ 449.1860, found 449.1866.

*Ethyl 1,3′,9′-Trimethyl-2-oxospiro[indoline-3,1′-pyrrolo[1,2-a]indole]-2′-carboxylate (**3k**).* White solid obtained by filtration of the precipitate: 24.8 mg, 49% yield; reaction time = 40 h; mp 219.9−220.6 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.32 (t, J = 8.0 Hz, 1H), 7.26 (t, J = 8.0 Hz, 1H), 7.17 (t, J = 8.0 Hz, 1H), 6.99−6.88 (m, 3H), 3.94 (q, J = 4.0 Hz, 2H), 3.37 (s, 3H), 3.07 (s, 3H), 1.78 (s, 3H), 0.94 (t, J = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 163.7, 153.1, 144.7, 138.6, 134.4, 131.5, 129.1, 128.7, 123.3, 123.1, 122.9, 121.4, 119.7, 114.6, 111.1, 108.6, 108.0, 59.6, 56.4, 26.9, 13.8, 13.6, 7.7; IR (KBr) ν 3430, 2924, 1720, 1695, 1601, 1464, 1387, 1291, 1218, 1160, 1071, 744 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{23}N_2O_3$ $[M + H]^+$ 387.1703, found 387.1687.

*1,9′-Dimethyl-3′-(3-methyl-1H-indol-2-yl)-3′-phenyl-2′,3′-dihydrospiro[indoline-3,1′-pyrrolo[1,2-a]indol]-2-one (**3l**).* White solid obtained by column chromatography (petroleum ether/ethyl acetate = 30:1 to 25:1); 24.1 mg, 59% yield; reaction time = 40 h; mp 328.3−329.5 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.67 (s, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 8.0 Hz, 6H), 7.24−7.16 (m, 2H), 7.05 (t, J = 8.0 Hz, 1H), 6.98−6.93 (m, 2H), 6.86−6.74 (m, 4H), 6.38 (d, J = 8.0 Hz, 1H), 4.27 (d, J = 12.0 Hz, 1H), 3.39 (d, J = 16.0 Hz, 1H), 3.31 (s, 3H), 1.84 (s, 3H), 1.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 144.2, 142.9, 139.0, 135.4, 133.6, 133.0, 132.4, 132.3, 129.5, 129.0, 128.6, 128.0, 126.6, 124.0, 123.7, 122.3, 121.5, 119.4, 119.0, 118.9, 118.8, 111.2, 111.1, 110.1, 108.4, 102.6, 68.5, 59.6, 52.5, 26.8, 10.3, 7.3; IR (KBr) ν 3437, 3256, 2921, 1690, 1611, 1451, 1373, 1336, 1264, 1094, 742 cm^{-1}; HRMS (ESI) calcd for $C_{35}H_{30}N_3O$ $[M + H]^+$ 508.2383, found 508.2385.

*9′-Allyl-1-methyl-2-oxo-3′-phenylspiro[indoline-3,1′-pyrrolo[1,2-a]indole]-2′-carbonitrile (**3m**).* White solid obtained by column chromatography (petroleum ether/ethyl acetate = 60:1 to 50:1); 37.9 mg, 68% yield; reaction time = 38 h; mp 240.7−241.9 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 4.0 Hz, 2H), 7.67−7.61 (m, 3H), 7.50 (d, J = 4.0 Hz, 1H), 7.44−7.39 (m, 1H), 7.16−7.07 (m, 5H), 6.98 (d, J = 8.0 Hz, 1H), 5.60−5.50 (m, 1H), 4.81−4.73 (m, 2H), 3.35 (s, 3H), 3.10 (dd, J_1 = J_2 = 8.0 Hz, 1H), 2.98 (dd, J_1 = J_2 = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 155.8, 144.4, 138.2, 134.5, 133.9, 131.8, 130.2, 129.2, 129.1, 126.9, 125.9, 124.5, 123.7, 123.6, 122.0, 120.1, 115.9, 114.7, 113.8, 111.9, 109.0, 96.6, 58.5, 28.3, 27.2; IR (KBr) ν 3425, 3063, 2896, 2204, 1721, 1610, 1457, 1408, 1346, 1216, 1127, 1075, 986, 749, 698 cm^{-1}; HRMS (ESI) calcd for $C_{29}H_{21}N_3NaO$ $[M + Na]^+$ 450.1577, found 450.1555.

*1-Methyl-2-oxo-3′,9′-diphenylspiro[indoline-3,1′-pyrrolo[1,2-a]indole]-2′-carbonitrile (**3n**).* White solid obtained by column chromatography (petroleum ether/ethyl acetate = 30:1 to 15:1); 40.4 mg, 67% yield; reaction time = 40 h; mp 245.4−246.8 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 8.0 Hz, 2H), 7.66 (q, J = 8.0 Hz, 4H), 7.35 (t, J = 8.0 Hz, 1H), 7.22−7.13 (m, 7H), 7.05 (t, J = 8.0 Hz, 1H), 6.99−6.97 (m, 2H), 6.83 (d, J = 8.0 Hz, 1H), 3.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 155.9, 144.4, 138.3, 133.2, 132.2, 131.9, 131.7, 130.2, 129.3, 129.2, 128.5, 128.3, 127.3, 126.9, 126.8, 124.2, 123.9, 123.6, 122.6, 120.9, 118.0, 114.6, 112.1, 109.1, 96.9, 58.2, 27.0; IR (KBr) ν 3433, 3057, 2926, 2209, 1724, 1611, 1451, 1401, 1367, 1257, 1091, 749 cm^{-1}; HRMS (ESI) calcd for $C_{32}H_{22}N_3O$ $[M + H]^+$ 464.1757, found 464.1774.

*2-(2′-Cyano-1-methyl-2-oxo-3′-phenylspiro[indoline-3,1′-pyrrolo[1,2-a]indol]-9′-yl)acetic Acid (**3o**).* White solid obtained by column chromatography (petroleum ether/ethyl acetate = 1:1 to 0:1); 49.5 mg, 86% yield; reaction time = 60 h; mp 297.6−298.4 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 7.90 (t, J = 4.0 Hz, 2H), 7.80−7.74 (m, 3H), 7.59 (d, J = 8.0 Hz, 1H), 7.46 (t, J = 4.0 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H), 7.14−7.09 (m, 3H), 6.92 (d, J = 8.0 Hz, 1H), 3.28 (s, 3H), 3.05 (d, J = 16.0 Hz, 1H), 2.76 (d, J = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.8, 156.4, 144.9, 138.6, 134.6, 132.5, 131.6, 130.7, 129.8, 129.4, 126.9, 125.2, 125.1, 123.9, 122.2, 121.7, 121.9, 115.3, 112.1, 111.4, 110.0, 109.9, 96.1, 57.7, 27.6, 19.0; IR (KBr) ν 3433, 2922, 2860, 2208, 1714, 1616, 1454, 1394, 1261, 1175, 748, 697 cm^{-1}; HRMS (ESI) calcd for $C_{28}H_{19}N_3NaO_3$ $[M + Na]^+$ 468.1319, found 468.1298.

*3-(2′-Cyano-1-methyl-2-oxo-3′-phenylspiro[indoline-3,1′-pyrrolo[1,2-a]indol]-9′-yl)propanoic Acid (**3p**).* White solid obtained by filtration of the precipitate: 57.6 mg, 96% yield; reaction time = 60 h; mp 253.7−254.9 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 12.2 (s, 1H), 7.95 (d, J = 4.0 Hz, 2H), 7.78−7.74 (m, 3H), 7.67 (d, J = 8.0 Hz, 1H), 7.52 (t, J = 8.0 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.31 (d, J = 4.0 Hz, 1H), 7.22−7.14 (m, 3H), 6.98 (d, J = 8.0 Hz, 1H), 3.37 (s, 3H), 2.58−2.51 (m, 1H), 2.46−2.39 (m, 1H), 2.18−2.04 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.6, 172.1, 156.4, 144.6, 138.7, 133.6, 132.6, 131.6, 131.0, 129.8, 129.5, 126.8, 125.5, 125.1, 124.2, 122.6, 120.8, 115.2, 114.5, 111.8, 110.3, 96.2, 57.6, 33.8, 27.6, 18.9; IR (KBr) ν 3428, 3061, 2940, 2207, 1733, 1691, 1609, 1453, 1407, 1369, 1270, 1160, 1084, 752, 700 cm^{-1}; HRMS (ESI) calcd for $C_{29}H_{21}N_3NaO_3$ $[M + Na]^+$ 482.1475, found 482.1452.

*4-(2′-Cyano-1-methyl-2-oxo-3′-phenylspiro[indoline-3,1′-pyrrolo[1,2-a]indol]-9′-yl)butanoic Acid (**3q**).* White solid obtained by filtration of the precipitate: 60.5 mg, 98% yield; reaction time = 40 h; mp 252.6−253.2 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 12.1 (s, 1H), 7.95 (d, J = 4.0 Hz, 2H), 7.75 (d, J = 4.0 Hz, 3H), 7.64 (d, J = 8.0 Hz, 1H), 7.51 (t, J = 8.0 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.29 (d, J = 4.0 Hz, 1H), 7.22−7.14 (m, 3H), 6.98 (d, J = 8.0 Hz, 1H), 3.38 (s, 3H), 2.37−2.30 (m, 1H), 2.24−2.17 (m, 1H), 2.08−1.92 (m, 2H), 1.47 (t, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.5, 172.3, 156.3, 144.6, 138.6, 134.0, 132.5, 131.5, 130.9, 129.8, 129.5, 126.8, 125.7, 125.0, 124.1, 124.0, 122.5, 120.6, 115.3, 115.1, 111.9, 110.3, 96.1, 57.6, 33.6, 27.5, 24.8, 22.9; IR (KBr) ν 3422, 3057, 2944, 2203, 1716, 1613, 1578, 1457, 1414, 1339, 1214, 1133, 1084, 749, 696 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{23}N_3NaO_3$ $[M + Na]^+$ 496.1632, found 496.1612.

*Ethyl 2-(2′-Cyano-1-methyl-2-oxo-3′-phenylspiro[indoline-3,1′-pyrrolo[1,2-a]indol]-9′-yl)acetate (**3r**).* White solid obtained by column chromatography (petroleum ether/ethyl acetate = 15:1 to 8:1); 38.0 mg, 62% yield; reaction time = 60 h; mp 197.2−198.6 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.0 Hz, 2H), 7.60−7.56 (m, 3H), 7.51 (d, J = 8.0 Hz, 1H), 7.38−7.33 (m, 1H), 7.14−7.10 (m, 1H), 7.07−7.00 (m, 4H), 6.95 (d, J = 8.0 Hz, 1H), 3.86 (q, J = 8.0 Hz, 2H), 3.32 (s, 3H), 3.21 (d, J = 16.0 Hz, 1H), 3.07 (d, J = 16.0 Hz, 1H), 1.03 (t, J = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 168.6, 155.1, 143.6, 138.3, 132.6, 130.8, 130.7, 129.3, 128.2, 128.1, 125.7, 123.7, 123.6, 122.7, 122.6, 121.3, 119.1, 113.5, 111.0, 108.0, 107.3, 95.9, 60.0, 28.9, 26.3, 17.4, 13.1; IR (KBr) ν 3423, 3059, 2928, 2208, 1727, 1607, 1456, 1403, 1371, 1256, 1166, 1030, 977, 749, 699 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{23}N_3NaO_3$ $[M + Na]^+$ 496.1632, found 496.1635.

*9′-(2-Hydroxyethyl)-1-methyl-2-oxo-3′-phenylspiro[indoline-3,1′-pyrrolo[1,2-a]indole]-2′-carbonitrile (**3s**).* White solid obtained by column chromatography (petroleum ether/ethyl acetate = 3:1 to 1:1); 37.7 mg, 67% yield; reaction time = 60 h; mp 240.3−241.4 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 7.92 (d, J = 8.0 Hz, 2H), 7.79−7.73 (m, 3H), 7.61 (d, J = 8.0 Hz, 1H), 7.52 (t, J = 8.0 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.21−7.13 (m, 3H), 6.95 (d, J = 8.0 Hz, 1H), 4.62 (t, J = 8.0 Hz, 1H), 3.36 (s, 3H), 3.22−3.15 (m, 2H), 2.48−2.43 (m, 1H), 2.32−2.25 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.3, 156.3, 144.7, 139.0, 134.4, 132.6, 131.5, 130.9, 129.8, 129.5, 126.8, 125.7, 125.0, 124.1, 122.5, 120.9, 115.2, 113.0, 111.7, 110.2, 96.1, 60.7, 57.6, 27.6, 27.5; IR (KBr) ν 3453, 3058, 2932, 2205, 1719, 1610, 1456, 1405, 1355, 1218, 1126, 1062, 748, 697 cm^{-1}; HRMS (ESI) calcd for $C_{28}H_{21}N_3NaO_2$ $[M + Na]^+$ 454.1526, found 454.1517.

*N-(2-(2′-Cyano-1-methyl-2-oxo-3′-phenylspiro[indoline-3,1′-pyrrolo[1,2-a]indol]-9′-yl)ethyl)-4-methylbenzenesulfonamide (**3t**).* White solid obtained by column chromatography (petroleum ether/ethyl acetate = 5:1 to 4:1); 58.9 mg, 78% yield; reaction time = 48 h; mp 85.8−86.9 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 4.0 Hz, 2H), 7.59−7.51 (m, 3H), 7.47 (d, J = 8.0 Hz, 2H), 7.34−7.27 (m, 2H), 7.09 (d, J = 8.0 Hz, 2H), 7.03−6.93 (m, 6H), 4.59 (t, J = 8.0 Hz,

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1H), 3.30 (s, 3H), 2.87−2.72 (m, 2H), 2.53−2.46 (m, 1H), 2.32 (t, J = 8.0 Hz, 1H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 155.9, 144.4, 143.3, 139.2, 136.9, 133.5, 131.9, 131.8, 130.5, 129.6, 129.2, 129.1, 127.0, 126.6, 125.4, 124.2, 124.0, 123.8, 122.3, 119.8, 114.5, 112.1, 111.7, 109.6, 96.8, 57.8, 42.4, 27.6, 24.8, 21.5; IR (KBr) ν 3278, 3056, 2926, 2861, 2207, 1714, 1606, 1455, 1406, 1326, 1219, 1157, 1088, 982, 814, 748, 665 cm^{-1}; HRMS (ESI) calcd for $C_{35}H_{28}N_4NaO_3S$ [M + Na]$^+$ 607.1774, found 607.1779.

General Procedure for the Synthesis of 9*H*-Pyrrolo[1,2-*a*]indoles 5. To a 5.0 mL vial were successively added indole **1** (0.16 mmol), aromatic aldehyde-derived oxodiene **4** (0.13 mmol), Cu(OTf)$_2$ (9.4 mg, 0.026 mmol), and 0.8 mL of CH_3CN. The resulting mixture was stirred at 35 °C until almost full consumption of **4** monitored by thin layer chromatography, and then the reaction mixture was directly subjected to flash column chromatography on silica gel (petroleum ether/ethyl acetate) to afford the corresponding products **5**. In some cases, the precipitate was generated, and only a simple filtration was needed to purify the product.

*9-Methyl-1,3-diphenyl-9H-pyrrolo[1,2-a]indole-2-carbonitrile (**5a**).* White solid obtained by filtration of the precipitate: 38.6 mg, 86% yield; reaction time = 36 h; mp 173.8−174.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73−7.67 (m, 4H), 7.58−7.52 (m, 3H), 7.47 (t, J = 8.0 Hz, 2H), 7.42 (d, J = 8.0 Hz, 1H), 7.36−7.32 (m, 1H), 7.21−7.12 (m, 2H), 7.03 (d, J = 8.0 Hz, 1H), 4.47 (q, J = 8.0 Hz, 1H), 1.45 (d, J = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2, 139.1, 138.4, 135.1, 132.3, 129.8, 129.6, 128.9, 128.8, 128.7, 127.7, 127.5, 127.2, 125.4, 125.1, 120.4, 117.2, 112.7, 96.0, 36.0, 16.9; IR (KBr) ν 3426, 3054, 2930, 2214, 1604, 1475, 758, 702 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{18}N_2Na$ [M + Na]$^+$ 369.1362, found 369.1348.

*9-Methyl-3-phenyl-1-(p-tolyl)-9H-pyrrolo[1,2-a]indole-2-carbonitrile (**5b**).* White solid obtained by column chromatography (petroleum ether/ethyl acetate = 60:1); 39.3 mg, 84% yield; reaction time = 36 h; mp 198.2−199.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 8.0 Hz, 2H), 7.61 (d, J = 8.0 Hz, 2H), 7.58−7.50 (m, 3H), 7.41 (d, J = 8.0 Hz, 1H), 7.27 (t, J = 8.0 Hz, 2H), 7.20−7.11 (m, 2H), 7.02 (d, J = 4.0 Hz, 1H), 4.45 (q, J = 8.0 Hz, 1H), 2.40 (s, 3H), 1.45 (d, J = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2, 139.1, 138.1, 137.0, 135.0, 129.8, 129.6, 129.5, 129.4, 129.0, 128.9, 127.6, 127.4, 125.3, 125.0, 120.4, 117.2, 112.7, 96.1, 35.9, 21.3, 16.9; IR (KBr) ν 3436, 3059, 2925, 2216, 1604, 1475, 1418, 1105, 751 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{20}N_2Na$ [M + Na]$^+$ 383.1519, found 383.1511.

*1-(4-Methoxyphenyl)-9-methyl-3-phenyl-9H-pyrrolo[1,2-a]indole-2-carbonitrile (**5c**).* White solid obtained by column chromatography (petroleum ether/ethyl acetate = 50:1 to 40:1); 34.9 mg, 71% yield; reaction time = 36 h; mp 191.6−192.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (dd, J_1 = 8.0 Hz, J_2 = 12.0 Hz, 4H), 7.57−7.50 (m, 3H), 7.41 (d, J = 8.0 Hz, 1H), 7.20−7.11 (m, 2H), 7.02 (t, J = 8.0 Hz, 3H), 4.42 (q, J = 8.0 Hz, 1H), 3.85 (s, 3H), 1.44 (d, J = 4.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 141.2, 139.1, 137.8, 134.8, 129.7, 129.5, 129.0, 128.9, 128.7, 127.6, 125.3, 125.0, 124.7, 120.2, 117.3, 114.3, 112.7, 96.0, 55.4, 35.9, 16.9; IR (KBr) ν 3428, 2931, 2208, 1509, 1475, 1420, 1247, 1177, 1030, 750 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{20}N_2NaO$ [M + Na]$^+$ 399.1468, found 399.1472.

*1-(4-Fluorophenyl)-9-methyl-3-phenyl-9H-pyrrolo[1,2-a]indole-2-carbonitrile (**5d**).* White solid obtained by filtration of the precipitate: 37.7 mg, 80% yield; reaction time = 36 h; mp 167.7−168.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69−7.65 (m, 4H), 7.58−7.51 (m, 3H), 7.42 (d, J = 8.0 Hz, 1H), 7.22−7.13 (m, 4H), 7.03 (d, J = 8.0 Hz, 1H), 4.43 (q, J = 8.0 Hz, 1H), 1.44 (d, J = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0 (d, J = 245.0 Hz, 1C), 141.0, 139.0, 138.3, 135.1, 129.7, 129.6, 129.2, 129.1, 128.9, 128.8, 128.4 (d, J = 3.0 Hz, 1C), 127.7, 125.2 (d, J = 36.0 Hz, 1C), 119.5, 117.0, 115.9 (d, J = 21.0 Hz, 1C), 112.8, 96.0, 35.8, 16.9; IR (KBr) ν 3419, 2927, 2215, 1475, 1420, 1229, 1156, 1026, 744 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{17}FN_2Na$ [M + Na]$^+$ 387.1268, found 387.1274.

*1-(4-Chlorophenyl)-9-methyl-3-phenyl-9H-pyrrolo[1,2-a]indole-2-carbonitrile (**5e**).* White solid obtained by column chromatography (petroleum ether/ethyl acetate = 70:1 to 60:1); 34.9 mg, 71% yield; reaction time = 36 h; mp 187.6−189.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66−7.62 (m, 4H), 7.57−7.52 (m, 3H), 7.45−7.41 (m, 3H), 7.20 (t, J = 8.0 Hz, 1H), 7.14 (t, J = 8.0 Hz, 1H), 7.02 (d, J = 8.0 Hz, 1H), 4.43 (q, J = 8.0 Hz, 1H), 1.44 (d, J = 4.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.0, 138.9, 138.6, 135.3, 133.0, 130.9, 129.7, 129.1, 129.0, 128.7, 127.7, 125.5, 125.1, 119.2, 117.0, 112.8, 95.9, 35.9, 16.8; IR (KBr) ν 3425, 2931, 2216, 1477, 1417, 1313, 1095, 749 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{17}ClN_2Na$ [M + Na]$^+$ 403.0972, found 403.0972.

*1-(4-Bromophenyl)-9-methyl-3-phenyl-9H-pyrrolo[1,2-a]indole-2-carbonitrile (**5f**).* White solid obtained by filtration of the precipitate: 38.2 mg, 69% yield; reaction time = 36 h; mp 197.1−197.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 8.0 Hz, 2H), 7.59−7.53 (m, 7H), 7.42 (d, J = 8.0 Hz, 1H), 7.20 (t, J = 8.0 Hz, 1H), 7.15 (t, J = 8.0 Hz, 1H), 7.02 (d, J = 4.0 Hz, 1H), 4.43 (q, J = 8.0 Hz, 1H), 1.44 (d, J = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.0, 138.9, 138.6, 135.3, 132.1, 131.3, 129.7, 129.0, 129.0, 128.7, 127.7, 125.5, 125.1, 121.1, 119.2, 116.9, 112.8, 95.9, 36.0, 16.8; IR (KBr) ν 3431, 2930, 2216, 1605, 1478, 1418, 1314, 1073, 750 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{17}BrN_2Na$ [M + Na]$^+$ 447.0467, found 447.0463.

*9-Methyl-3-phenyl-1-(m-tolyl)-9H-pyrrolo[1,2-a]indole-2-carbonitrile (**5g**).* White solid obtained by column chromatography (petroleum ether/ethyl acetate = 70:1 to 60:1); 39.8 mg, 85% yield; reaction time = 36 h; mp 128.3−130.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 8.0 Hz, 2H), 7.51 (t, J = 8.0 Hz, 5H), 7.38 (d, J = 8.0 Hz, 1H), 7.33 (t, J = 8.0 Hz, 1H), 7.15−7.10 (m, 3H), 7.01 (d, J = 4.0 Hz, 1H), 4.42 (q, J = 8.0 Hz, 1H), 2.41 (s, 3H), 1.43 (d, J = 4.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2, 139.1, 138.5, 138.4, 135.1, 132.3, 129.8, 129.6, 129.0, 128.9, 128.8, 128.2, 128.1, 127.7, 125.4, 125.1, 124.7, 120.5, 117.3, 112.7, 96.1, 36.0, 21.7, 16.9; IR (KBr) ν 3404, 3053, 2925, 2216, 1607, 1477, 1419, 1096, 749 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{20}N_2Na$ [M + Na]$^+$ 383.1519, found 383.1521.

*1-(3-Bromophenyl)-9-methyl-3-phenyl-9H-pyrrolo[1,2-a]indole-2-carbonitrile (**5h**).* White solid obtained by filtration of the precipitate: 36.1 mg, 65% yield; reaction time = 36 h; mp 178.8−179.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (t, J = 8.0 Hz, 1H), 7.66 (d, J = 8.0 Hz, 3H), 7.58−7.51 (m, 3H), 7.44 (dd, J_1 = J_2 = 8.0 Hz, 2H), 7.33 (t, J = 8.0 Hz, 1H), 7.20 (t, J = 8.0 Hz, 1H), 7.14 (t, J = 8.0 Hz, 1H), 7.02 (d, J = 8.0 Hz, 1H), 4.45 (q, J = 8.0 Hz, 1H), 1.45 (d, J = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.0, 138.9, 135.4, 134.5, 130.5, 130.3, 130.2, 129.8, 129.0, 128.7, 127.8, 126.2, 125.6, 125.1, 122.9, 118.9, 116.8, 112.8, 95.9, 35.9, 16.9; IR (KBr) ν 3431, 3056, 2971, 2928, 2214, 1601, 1473, 1414, 1314, 1077, 788, 753, 696 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{17}BrN_2Na$ [M + Na]$^+$ 447.0467, found 447.0474.

*9-Methyl-1-(naphthalen-1-yl)-3-phenyl-9H-pyrrolo[1,2-a]indole-2-carbonitrile (**5i**).* White solid obtained by column chromatography (petroleum ether/ethyl acetate = 70:1 to 60:1); 35.5 mg, 69% yield; reaction time = 57 h; 2:1 dr; mp 115.4−116.2 °C (mixtures of the both isomers); ^{1}H NMR of the major isomer (400 MHz, $CDCl_3$) δ 7.94−7.87 (m, 3H), 7.73 (dd, J_1 = J_2 = 8.0 Hz, 3H), 7.56−7.49 (m, 6H), 7.32 (t, J = 4.0 Hz, 1H), 7.13 (s, 3H), 4.10 (q, J = 8.0 Hz, 1H), 1.05 (d, J = 8.0 Hz, 3H); ^{13}C NMR of the major isomer (100 MHz, $CDCl_3$) δ 141.4, 140.4, 139.4, 134.7, 133.9, 132.6, 131.5, 130.1, 129.8, 129.6, 129.5, 129.0, 128.8, 128.4, 127.7, 126.5, 126.2, 125.6, 125.5, 125.4, 125.2, 119.2, 116.8, 112.8, 98.4, 36.5, 17.6; ^{1}H NMR of the minor isomer (400 MHz, $CDCl_3$) δ 7.94−7.87 (m, 3H), 7.73 (dd, J_1 = J_2 = 8.0 Hz, 3H), 7.56−7.49 (m, 6H), 7.32 (t, J = 4.0 Hz, 1H), 7.13 (s, 3H), 4.25 (q, J = 8.0 Hz, 1H), 1.12 (d, J = 8.0 Hz, 3H); ^{13}C NMR of the minor isomer (100 MHz, $CDCl_3$) δ 141.3, 139.8, 139.5, 134.5, 133.9, 132.6, 131.5, 130.1, 129.8, 129.6, 129.5, 129.1, 128.7, 128.4, 127.4, 126.3, 126.2, 125.6, 125.5, 125.4, 125.1, 119.3, 116.7, 112.8, 98.7, 36.2, 17.2; IR (KBr) ν 3433, 3053, 2972, 2929, 2869, 2217, 1602, 1475, 1413, 1312, 785, 751, 698 cm^{-1}; HRMS (ESI) calcd for $C_{29}H_{20}N_2Na$ [M + Na]$^+$ 419.1519, found 419.1527.

*9-Methyl-3-phenyl-1-(thiophen-2-yl)-9H-pyrrolo[1,2-a]indole-2-carbonitrile (**5j**).* White solid obtained by filtration of the precipitate: 39.2 mg, 86% yield; reaction time = 36 h; mp 143.5−144.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 4.0 Hz, 2H), 7.57−7.52 (m, 4H), 7.42 (d, J = 8.0 Hz, 1H), 7.30 (d, J = 4.0 Hz, 1H), 7.20−7.10 (m,

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3H), 7.00 (d, J = 8.0 Hz, 1H), 4.35 (q, J = 8.0 Hz, 1H), 1.61 (d, J = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3, 138.8, 138.4, 135.1, 133.9, 129.8, 128.9, 128.7, 127.8, 127.7, 125.5, 125.2, 124.9, 124.2, 117.0, 114.3, 112.8, 95.9, 36.0, 17.6; IR (KBr) ν 3427, 3060, 2978, 2932, 2871, 2215, 1600, 1474, 1415, 752, 705 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{16}N_2NaS$ $[M + Na]^+$ 375.0926, found 375.0929.

*3-(4-Chlorophenyl)-9-methyl-1-phenyl-9H-pyrrolo[1,2-a]indole-2-carbonitrile (**5k**).* White solid obtained by column chromatography (petroleum ether/ethyl acetate = 70:1 to 60:1); 43.6 mg, 88% yield; reaction time = 36 h; mp 188.2−189.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 8.0 Hz, 2H), 7.62 (d, J = 8.0 Hz, 2H), 7.54 (d, J = 8.0 Hz, 2H), 7.48−7.42 (m, 3H), 7.33 (t, J = 8.0 Hz, 1H), 7.23−7.15 (m, 2H), 7.02 (d, J = 8.0 Hz, 1H), 4.46 (q, J = 8.0 Hz, 1H), 1.44 (d, J = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2, 138.9, 138.7, 135.7, 133.6, 131.1, 131.1, 129.3, 128.9, 127.7, 127.5, 127.4, 127.3, 125.5, 125.2, 120.6, 116.9, 112.6, 96.4, 36.0, 16.9; IR (KBr) ν 3433, 2930, 2216, 1605, 1477, 1417, 1161, 1022, 751 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{18}ClN_2$ $[M + H]^+$ 381.1153, found 381.1162.

*3-(Furan-2-yl)-9-methyl-1-phenyl-9H-pyrrolo[1,2-a]indole-2-carbonitrile (**5l**).* Light yellow solid obtained by filtration of the precipitate: 36.9 mg, 84% yield; reaction time = 36 h; mp 160.6−161.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61−7.58 (m, 3H), 7.39−7.32 (m, 4H), 7.27−7.12 (m, 3H), 6.90 (d, J = 4.0 Hz, 1H), 6.56−6.55 (m, 1H), 4.34 (q, J = 8.0 Hz, 1H), 1.32 (d, J = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1, 142.4, 140.9, 139.3, 138.9, 132.0, 128.9, 128.0, 127.5, 127.4, 125.6, 124.8, 124.3, 120.7, 116.7, 113.4, 112.4, 112.2, 96.3, 36.2, 16.8; IR (KBr) ν 3408, 3207, 3139, 3054, 2983, 2934, 2875, 2213, 1965, 1910, 1758, 1600, 1460, 1407, 1311, 1276, 1210, 1153, 1073, 1008, 911, 746, 701 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{17}N_2O$ $[M + H]^+$ 337.1335, found 337.1342.

*7-Bromo-9-methyl-1,3-diphenyl-9H-pyrrolo[1,2-a]indole-2-carbonitrile (**5m**).* White solid obtained by filtration of the precipitate: 47.2 mg, 85% yield; reaction time = 36 h; mp 165.3−166.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.0 Hz, 2H), 7.57 (d, J = 4.0 Hz, 2H), 7.50−7.46 (m, 4H), 7.39 (t, J = 8.0 Hz, 2H), 7.26 (t, J = 8.0 Hz, 1H), 7.19 (d, J = 8.0 Hz, 1H), 6.81 (d, J = 8.0 Hz, 1H), 4.38 (q, J = 8.0 Hz, 1H), 1.36 (d, J = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 138.1, 137.9, 135.2, 131.9, 130.7, 129.8, 129.7, 129.0, 128.9, 128.5, 128.4, 127.5, 127.4, 120.7, 118.4, 116.9, 113.9, 96.5, 36.0, 16.8; IR (KBr) ν 3421, 3053, 2217, 1604, 1476, 1408, 1277, 805, 701 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{17}BrN_2Na$ $[M + Na]^+$ 447.0467, found 447.0475.

*9-Allyl-1,3-diphenyl-9H-pyrrolo[1,2-a]indole-2-carbonitrile (**5n**).* White solid obtained by column chromatography (petroleum ether/ethyl acetate = 60:1 to 50:1); 31.4 mg, 65% yield; reaction time = 40 h; mp 57.6−58.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.65 (m, 4H), 7.56−7.50 (m, 3H), 7.45 (t, J = 8.0 Hz, 3H), 7.32 (t, J = 8.0 Hz, 1H), 7.17−7.10 (m, 2H), 7.03−7.00 (m, 1H), 5.47−5.37 (m, 1H), 4.84−4.75 (m, 2H), 4.53−4.51 (m, 1H), 2.75−2.69 (m, 1H), 2.54−2.47 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6, 139.0, 136.3, 135.2, 133.5, 132.5, 129.8, 129.6, 129.0, 128.9, 128.8, 127.8, 127.6, 127.3, 125.7, 125.2, 120.9, 118.3, 117.1, 112.7, 96.1, 40.7, 35.1; IR (KBr) ν 3393, 3063, 2920, 2215, 1604, 1476, 1417, 1316, 994, 918, 758, 699 cm^{-1}; HRMS (ESI) calcd for $C_{27}H_{21}N_2$ $[M + H]^+$ 373.1699, found 373.1697.

*9-(2-Hydroxyethyl)-1,3-diphenyl-9H-pyrrolo[1,2-a]indole-2-carbonitrile (**5o**).* Amaranthine solid obtained by column chromatography (petroleum ether/ethyl acetate = 20:1); 40.5 mg, 83% yield; reaction time = 36 h; mp 99.7−100.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.73−7.62 (m, 8H), 7.52 (t, J = 8.0 Hz, 2H), 7.38 (t, J = 8.0 Hz, 1H), 7.27−7.20 (m, 2H), 6.91 (d, J = 8.0 Hz, 1H), 4.77 (t, J = 8.0 Hz, 1H), 3.27−3.22 (m, 2H), 2.10−2.06 (m, 1H), 1.81−1.77 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 140.0, 139.0, 137.9, 134.9, 132.4, 130.4, 130.1, 129.5, 129.4, 128.8, 128.2, 127.8, 127.7, 126.6, 126.0, 119.7, 117.2, 112.5, 95.5, 58.3, 37.9, 34.2; IR (KBr) ν 3429, 3057, 2928, 2216, 1605, 1476, 1418, 1314, 1271, 1037, 759, 701 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{20}N_2NaO$ $[M + Na]^+$ 399.1468, found 399.1460.

*N-(2-(2-Cyano-1,3-diphenyl-9H-pyrrolo[1,2-a]indol-9-yl)ethyl)-4-methylbenzenesulfonamide (**5p**).* Yellow solid obtained by column chromatography (petroleum ether/ethyl acetate = 5:1 to 4:1); 59.9 mg, 87% yield; reaction time = 36 h; mp 83.2−84.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65−7.60 (m, 4H), 7.57−7.53 (m, 3H), 7.50 (d, J = 8.0 Hz, 2H), 7.47−7.39 (m, 3H), 7.34 (t, J = 8.0 Hz, 1H), 7.25−7.15 (m, 5H), 7.00 (dd, J_1 = J_2 = 2.0 Hz, 1H), 4.55 (t, J = 4.0 Hz, 1H), 2.74−2.56 (m, 2H), 2.40 (s, 3H), 2.06−1.99 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 139.3, 138.5, 136.5, 135.7, 135.5, 132.2, 129.7, 129.6, 129.1, 128.9, 128.6, 128.1, 127.6, 127.5, 127.0, 126.9, 125.6, 125.5, 120.9, 116.8, 112.9, 96.3, 40.1, 38.2, 31.6, 21.6; IR (KBr) ν 3418, 3280, 3059, 2927, 2867, 2216, 1603, 1477, 1418, 1157, 1090, 758, 701 cm^{-1}; HRMS (ESI) calcd for $C_{33}H_{27}N_3NaO_2S$ $[M + Na]^+$ 552.1716, found 552.1730.

*2-(2-Cyano-1,3-diphenyl-9H-pyrrolo[1,2-a]indol-9-yl)acetic Acid (**5q**).* White solid obtained by filtration of the precipitate: 41.2 mg, 81% yield; reaction time = 36 h; mp 239.1−240.7 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.68 (dd, J_1 = J_2 = 8.0 Hz, 7H), 7.60−7.56 (m, 1H), 7.53 (t, J = 8.0 Hz, 2H), 7.39 (t, J = 8.0 Hz, 1H), 7.26−7.24 (m, 2H), 6.93−6.91 (m, 1H), 4.99 (dd, J_1 = J_2 = 3.0 Hz, 1H), 2.92 (dd, J_1 = J_2 = 4.0 Hz, 1H), 2.54−2.48 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.3, 139.7, 139.3, 136.9, 135.1, 132.1, 130.4, 130.1, 129.6, 129.5, 128.7, 128.5, 128.0, 127.6, 126.1, 126.0, 119.7, 117.1, 112.5, 95.4, 37.0, 35.0; IR (KBr) ν 3424, 3044, 2919, 2218, 1700, 1604, 1476, 1417, 762, 701 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{19}N_2O_2$ $[M + H]^+$ 391.1441, found 391.1453.

*3-(2-Cyano-1,3-diphenyl-9H-pyrrolo[1,2-a]indol-9-yl)propanoic Acid (**5r**).* White solid obtained by filtration of the precipitate: 43.8 mg, 83% yield; reaction time = 36 h; mp 186.2−187.8 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74−7.60 (m, 8H), 7.52 (t, J = 8.0 Hz, 2H), 7.39 (t, J = 8.0 Hz, 1H), 7.28−7.22 (m, 2H), 6.91 (dd, J_1 = J_2 = 4.0 Hz, 1H), 4.83 (t, J = 4.0 Hz, 1H), 2.24−2.15 (m, 1H), 2.09−2.00 (m, 1H), 1.83−1.76 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.1, 139.3, 139.1, 136.9, 135.2, 132.3, 130.4, 130.1, 129.5, 129.4, 128.7, 128.5, 127.9, 127.7, 126.4, 126.1, 120.3, 117.1, 112.5, 95.6, 39.8, 30.1, 26.1; IR (KBr) ν 3425, 3043, 2921, 2216, 1702, 1606, 1477, 1416, 1281, 760, 703 cm^{-1}; HRMS (ESI) calcd for $C_{27}H_{20}N_2NaO_2$ $[M + Na]^+$ 427.1417, found 427.1417.

*4-(2-Cyano-1,3-diphenyl-9H-pyrrolo[1,2-a]indol-9-yl)butanoic Acid (**5s**).* White solid obtained by column chromatography (petroleum ether/ethyl acetate = 6:1 to 3:1); 32.2 mg, 59% yield; reaction time = 36 h; mp 196.6−197.8 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.71 (d, J = 8.0 Hz, 4H), 7.66−7.62 (m, 3H), 7.58 (d, J = 8.0 Hz, 1H), 7.51 (t, J = 8.0 Hz, 2H), 7.38 (t, J = 8.0 Hz, 1H), 7.28−7.21 (m, 2H), 6.92 (d, J = 8.0 Hz, 1H), 4.76 (t, J = 4.0 Hz, 1H), 1.98−1.90 (m, 3H), 1.85−1.76 (m, 1H), 1.18−1.06 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.4, 139.7, 139.2, 137.5, 135.0, 132.3, 130.4, 130.1, 129.5, 129.4, 128.7, 128.3, 127.9, 127.7, 126.3, 126.1, 120.1, 117.1, 112.5, 95.6, 40.5, 33.8, 30.1, 20.8; IR (KBr) ν 3057, 2929, 2217, 1707, 1605, 1476, 1417, 759, 701 cm^{-1}; HRMS (ESI) calcd for $C_{28}H_{23}N_2O_2$ $[M + H]^+$ 419.1754, found 419.1754.

*Ethyl 2-(2-Cyano-1,3-diphenyl-9H-pyrrolo[1,2-a]indol-9-yl)-acetate (**5t**).* White solid obtained by column chromatography (petroleum ether/ethyl acetate = 50:1 to 30:1); 36.3 mg, 67% yield; reaction time = 58 h; mp 44.7−45.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71−7.66 (m, 4H), 7.59−7.53 (m, 3H), 7.49−7.45 (m, 3H), 7.34 (t, J = 8.0 Hz, 1H), 7.18−7.14 (m, 2H), 7.05−7.00 (m, 1H), 4.92 (dd, J_1 = J_2 = 4.0 Hz, 1H), 4.12−4.02 (m, 2H), 2.98 (dd, J_1 = J_2 = 4.0 Hz, 1H), 2.48 (q, J = 8.0 Hz, 1H), 1.17 (t, J = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 139.4, 138.9, 135.5, 135.4, 131.9, 129.8, 129.7, 129.1, 128.9, 128.7, 128.2, 127.5, 127.4, 125.7, 125.5, 120.7, 116.9, 112.8, 96.4, 60.9, 37.1, 36.1, 14.1; IR (KBr) ν 3433, 3059, 2927, 2861, 2214, 1732, 1604, 1476, 1413, 1166, 1028, 759, 700 cm^{-1}; HRMS (ESI) calcd for $C_{28}H_{22}N_2NaO_2$ $[M + Na]^+$ 441.1573, found 441.1570.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00488.

Copies of NMR spectra for the products (PDF)

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Single-crystal X-ray crystallographic data for products **3a** (CIF) and **5a** (CIF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) For a selected review, see: (a) Bass, P. D.; Gubler, D. A.; Judd, T. C.; Williams, R. M. *Chem. Rev.* **2013**, *113*, 6816. For selected examples, see: (b) Tanaka, M.; Sagawa, S.; Hoshi, J. I.; Shimoma, F.; Yasue, K.; Ubukata, M.; Ikemoto, T.; Hase, Y.; Takahashi, M.; Sasase, T.; Ueda, N.; Matsushita, M.; Inaba, T. *Bioorg. Med. Chem.* **2006**, *14*, 5781. (c) Tanaka, M.; Ubukata, M.; Matsuo, T.; Yasue, K.; Matsumoto, K.; Kajimoto, Y.; Ogo, T.; Inaba, T. *Org. Lett.* **2007**, *9*, 3331. (d) Fernandez, L. S.; Buchanan, M. S.; Carroll, A. R.; Feng, Y. J.; Quinn, R. J.; Avery, V. M. *Org. Lett.* **2009**, *11*, 329. (e) Dethe, D. H.; Erande, R. D.; Ranjan, A. *J. Am. Chem. Soc.* **2011**, *133*, 2864. (f) Zeldin, R. M.; Toste, F. D. *Chem. Sci.* **2011**, *2*, 1706. (g) Vallakati, R.; May, J. A. *J. Am. Chem. Soc.* **2012**, *134*, 6936.

(2) For selected examples, see: (a) Colandrea, V. J.; Rajaraman, S.; Jimenez, L. S. *Org. Lett.* **2003**, *5*, 785. (b) Dethe, D. H.; Erande, R. D.; Ranjan, A. *J. Org. Chem.* **2013**, *78*, 10106.

(3) For selected examples, see: (a) Lu, S. C.; Duan, X. Y.; Shi, Z. J.; Li, B.; Ren, Y. W.; Zhang, W.; Zhang, Y. H.; Tu, Z. F. *Org. Lett.* **2009**, *11*, 3902. (b) Tucker, J. W.; Narayanam, J. M. R.; Krabbe, S. W.; Stephenson, C. R. J. *Org. Lett.* **2010**, *12*, 368. (c) Kaldas, S. J.; Cannillo, A.; McCallum, T.; Barriault, L. *Org. Lett.* **2015**, *17*, 2864. (d) Tejeda, J. E. C.; Landschoot, B. K.; Kerr, M. A. *Org. Lett.* **2016**, *18*, 2142. (e) Chen, S.; Zhang, P. B.; Shu, W. Y.; Gao, Y. Z.; Tang, G.; Zhao, Y. F. *Org. Lett.* **2016**, *18*, 5712. (f) Zhang, H. L.; Li, W. P.; Zhu, C. J. *J. Org. Chem.* **2017**, *82*, 2199. (g) Xu, J.; Yu, X. X.; Song, Q. L. *Org. Lett.* **2017**, *19*, 980.

(4) Patil, D. V.; Cavitt, M. A.; France, S. *Org. Lett.* **2011**, *13*, 5820.

(5) (a) Dethe, D. H.; Boda, R.; Das, S. *Chem. Commun.* **2013**, *49*, 3260. (b) Dethe, D. H.; Boda, R. *Org. Biomol. Chem.* **2016**, *14*, 5843. (c) Bera, K.; Schneider, C. *Chem. - Eur. J.* **2016**, *22*, 7074.

(6) For selected examples, see: (a) Hong, L.; Sun, W. S.; Liu, C. X.; Wang, L.; Wang, R. *Chem. - Eur. J.* **2010**, *16*, 440. (b) Li, L. X.; Du, D.; Ren, J.; Wang, Z. W. *Eur. J. Org. Chem.* **2011**, *2011*, 614. (c) Lu, H.; Lin, J. B.; Liu, J. Y.; Xu, P. F. *Chem. - Eur. J.* **2014**, *20*, 11659. (d) Dethe, D. H.; Boda, R. *Chem. - Eur. J.* **2016**, *22*, 106. (e) Saleh, N.; Voituriez, A. *J. Org. Chem.* **2016**, *81*, 4371. (f) Enders, D.; Wang, C.; Yang, X. N.; Raabe, G. *Synlett* **2011**, *2011*, 469. (g) Ni, Q. J.; Zhang, H.; Grossmann, A.; Loh, C. C. J.; Merkens, C.; Enders, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 13562.

(7) For selected examples, see: (a) Wood, K.; Black, D. S.; Kumar, N. *Tetrahedron Lett.* **2009**, *50*, 574. (b) Sun, Y. Q.; Qiao, Y.; Zhao, H. Y.; Li, B. G.; Chen, S. F. *J. Org. Chem.* **2016**, *81*, 11987. (c) Zhang, Y. L.; Liu, X. H.; Zhao, X. H.; Zhang, J. L.; Zhou, L.; Lin, L. L.; Feng, X. M. *Chem. Commun.* **2013**, *49*, 11311. (d) Cheng, H. G.; Lu, L. Q.; Wang, T.; Yang, Q. Q.; Liu, X. P.; Li, Y.; Deng, Q. H.; Chen, J. R.; Xiao, W. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 3250.

(8) During submission of this manuscript, Wang and co-workers developed a chiral diphosphine-palladium-catalyzed double Friedel–Crafts alkylation/*N*-hemiketalization sequence between oxindolyl β,γ-unsaturated α-ketoesters and two molecule 3-alkylindoles, see: Li, N. K.; Zhang, J. Q.; Sun, B. B.; Li, H. Y.; Wang, X. W. *Org. Lett.* **2017**, *19*, 1954.

(9) For selected reviews, see: (a) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748. (b) Singh, G. S.; Desta, Z. Y. *Chem. Rev.* **2012**, *112*, 6104. (c) Hong, L.; Wang, R. *Adv. Synth. Catal.* **2013**, *355*, 1023. (d) Cheng, D. J.; Ishihara, Y.; Tan, B.; Barbas, C. F., III *ACS Catal.* **2014**, *4*, 743. For selected examples on their synthesis, see: (e) Chen, W. B.; Wu, Z. J.; Pei, Q. L.; Cun, L. F.; Zhang, X. M.; Yuan, W. C. *Org. Lett.* **2010**, *12*, 3132. (f) Zhao, Y. Y.; Zhao, S.; Xie, J. K.; Hu, X. Q.; Xu, P. F. *J. Org. Chem.* **2016**, *81*, 10532. (g) Wang, Y. M.; Zhang, H. H.; Li, C.; Fan, T.; Shi, F. *Chem. Commun.* **2016**, *52*, 1804.

(10) (a) Wang, Q. L.; Peng, L.; Wang, F. Y.; Zhang, M. L.; Jia, L. N.; Tian, F.; Xu, X. Y.; Wang, L. X. *Chem. Commun.* **2013**, *49*, 9422. (b) Wang, Q. L.; Cai, T.; Zhou, J.; Tian, F.; Xu, X. Y.; Wang, L. X. *Chem. Commun.* **2015**, *51*, 10726. (c) Zhu, Y. S.; Wang, W. B.; Yuan, B. B.; Li, Y. N.; Wang, Q. L.; Bu, Z. W. *Org. Biomol. Chem.* **2017**, *15*, 984. (d) Wang, W. B.; Zhu, Y. S.; Guo, S. Q.; Wang, Q. L.; Bu, Z. W. *Org. Biomol. Chem.* **2016**, *14*, 4420.

(11) For selected examples, see: (a) Bruhn, T.; Pescitelli, G.; Jurinovich, S.; Schaumlöffel, A.; Witterauf, F.; Ahrens, J.; Bröring, M.; Bringmann, G. *Angew. Chem., Int. Ed.* **2014**, *53*, 14592. (b) Goel, A.; Kumar, V.; Hemberger, Y.; Singh, F. V.; Nag, P.; Knauer, M.; Kant, R.; Raghunandan, R.; Maulik, P. R.; Bringmann, G. *J. Org. Chem.* **2016**, *81*, 10721. (c) Wernerova, M.; Hudlicky, T. *Synlett* **2010**, *2010*, 2701.

(12) CCDC 1532712 (**3a**) and 1532710 (**5a**).

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