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Synthesis of tetracyclic indolin-3-ones through Pd-catalyzed intramolecular deacetylative dearomatization of 3-acetoxy-indoles†

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An efficient palladium-catalyzed intramolecular deacetylative dearomatization reaction of 3-acetoxyindoles has been developed. A range of tetracyclic indolin-3-ones bearing C2-quaternary stereocenters are achieved in good yields, showing a wide substrate scope for this reaction. A preliminary enantioselective reaction is established to furnish the product in 63% ee by using (*R*,*R*,*R*)-phosphoramide-PE as a chiral ligand.

Introduction

The indolin-3-one containing C2-quaternary stereocenter is an intriguing structural motif that widely appears in natural products and synthetic pharmaceuticals. Representative biologically active molecules include (−)-isatisine A, (−)-isatisine A acetonide, strobilanthoside A, (+)-austamide, and halichrome A (Fig. 1).[1] Considerable attention has been directed to the construction of such a unique framework. A number of reliable synthetic methods have been established, which mainly rely on

Fig. 1 Selected biologically active compounds containing indolin-3-one core.

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the transformations of the pre-existing 3-indolinone ring system.[2] The development of a new strategy for the synthesis of structurally diverse C2-disubstituted indolin-3-ones by using readily available starting materials is still highly desirable.

Transition-metal-catalyzed dearomatization of heteroarenes has become a reliable strategy to access heteroalicyclic compounds having carbon-based stereocenters on the ring.[3] In this context, a number of dearomatizing transformations of indoles, benzofurans, pyrroles, and furans have been intensely established over the past few years.[3,4] Amongst them, the palladium-catalyzed intramolecular dearomatizing arylation of indoles through a Heck reaction pathway has turned out to be very efficient in approaching fused- or spiro-indoline derivatives containing carbon stereocenters at C2 and/or C3 position of indoline ring. Documented examples included the intramolecular dearomatizing Heck reactions,[5] reductive-Heck reactions,[6] and domino dearomatizing Heck/anionic capture sequences involving the capture of benzyl-Pd species with a range of external nucleophiles,[7] such as cyanide,[7a] organoboron reagents,[7b–d] alkynes,[7e–h] and azoles. Nevertheless, the aforementioned methods have not been applied to the construction of C2-disubstituted indolin-3-one substructure, which possesses a cyclic ketone unit at C3. On the other hand, the palladium-catalyzed dearomatizing cross-coupling of phenolates has recently been established as an powerful access to cyclohexenone molecules, in which keto–enol tautomerism of phenols under the basic conditions facilitates the dearomatization, rendering the formation of cyclic ketone motif reliable (Scheme 1a).[8,9] Inspired by these transformations, as well as the Pd-catalyzed deacetylative arylation reactions of acetoxy-dihydronaphthalene derivatives developed by Zhou's group,[10] we envisioned that a similar dearomatization of 3-acetoxyindole derivatives would provide a straightforward approach to C2-disubstituted indolin-3-ones. Herein, we report the palladium-catalyzed intramolecular deacetylative dearomatization of 3-acetoxyindoles, which results in tetracyclic indolin-3-one
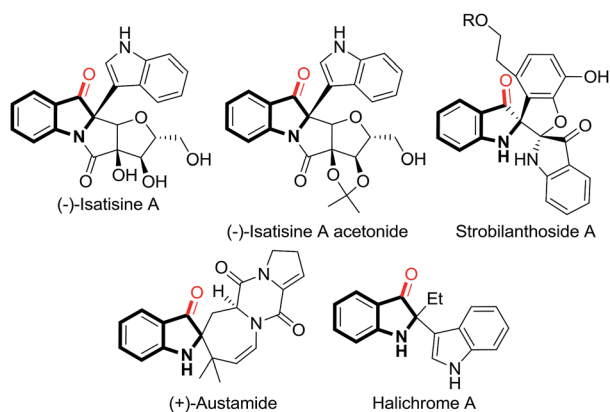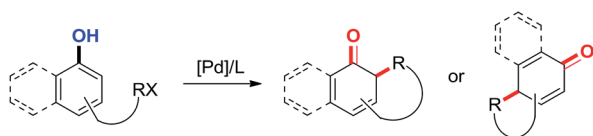
a) Previous work: Pd-catalyzed dearomative cross-coupling of phenols

b) This work: Pd-catalyzed deacetylative dearomatization of 3-acetoxyindoles

Scheme 1 Pd-catalyzed dearomatizing arylation of phenols and 3-acetoxyindoles.

derivatives in good yields (Scheme 1b). It represents a new dearomatizing transformation of indoles.

Results and discussion

We commenced the investigation by exploring the conditions for the intramolecular deacetylative dearomatization reaction with *N*-(2-iodobenzoyl)-3-acetoxyindole **1a** as the model substrate. Initial test using 5 mol% Pd(OAc)$_2$ as a catalyst, PPh$_3$ as a ligand, and K$_2$CO$_3$ as a base in the presence of two

Table 1 Reaction condition optimization[a]

Entry	L	Base	Solvent	Yield[b] (%)
1	PPh$_3$	K$_2$CO$_3$	THF	15
2	PPh$_3$	K$_2$CO$_3$	MeOH	ND
3	PPh$_3$	K$_2$CO$_3$	1,4-Dioxane	20
4	PPh$_3$	K$_2$CO$_3$	Toluene	10
5	PPh$_3$	K$_2$CO$_3$	DMF	45
6	PPh$_3$	K$_2$CO$_3$	NMP	40
7	PPh$_3$	Na$_2$CO$_3$	DMF	54
8	PPh$_3$	NaHCO$_3$	DMF	24
9	PPh$_3$	NEt$_3$	DMF	46
10	PPh$_3$	TMEDA	DMF	20
11	(*o*-Tol)$_3$P	Na$_2$CO$_3$	DMF	50
12	^{t}Bu$_3$P·HBF$_4$	Na$_2$CO$_3$	DMF	30
13	JohnPhos	Na$_2$CO$_3$	DMF	72
14	^{t}Bu-XPhos	Na$_2$CO$_3$	DMF	84
15	RuPhos	Na$_2$CO$_3$	DMF	75
16	DavePhos	Na$_2$CO$_3$	DMF	65
17[c]	^{t}Bu-XPhos	Na$_2$CO$_3$	DMF	16

[a] Reaction conditions: **1a** (0.2 mmol), 5 mol% Pd(OAc)$_2$, **L** (10 mol%), base (2.0 equiv.), H$_2$O (2.0 equiv.), and solvent (2.0 mL) at 100 °C for 12 h. [b] Isolated yield. [c] No additional water and 100 mg 4 Å molecular sieves was added.

equivalents of water led to the target tetracyclic indolin-3-one **2a** in 15% yield in THF at 100 °C for 12 h (Table 1, entry 1). Solvent effect was then investigated to improve the yield. No desired product **2a** was detected in protonic solvent MeOH, while comparable yields were observed for the reactions occurred in 1,4-dioxane and toluene (Table 1, entries 2–4). To our delight, the yield was improved to 45% and 40% in DMF and NMP solvent, respectively (Table 1, entries 5 and 6). The influence of the base was then examined in DMF solvent. Na$_2$CO$_3$ proved to be better than K$_2$CO$_3$, which led to **2a** in 54% yield (Table 1, entry 7). In comparison, NaHCO$_3$ and organic bases (NEt$_3$ and TMEDA) resulted in lower yields (Table 1, entries 8–10). Moreover, ligand effect was investigated. Although (*o*-Tol)$_3$P and ^{t}Bu$_3$P turned out to be unsuitable ligands (Table 1, entries 11 and 12), the yield of **2a** was markedly improved to 72% for JohnPhos and to 84% for ^{t}Bu-XPhos, respectively (Table 1, entries 13 and 14). This observation might imply that JohnPhos and ^{t}Bu-XPhos matched the electronically and sterically demanding of the oxidative addition and reductive elimination processes. In addition, RuPhos and DavePhos also furnished product **2a** in satisfactory yields (Table 1, entries 15 and 16). Of note, bidentate phosphine ligands, such as dppe and XantPhos, fully suppressed the reaction. Moreover, water proved to be critical to the reaction as the reaction yield was dramatically decreased to 16% when adding 4 Å molecular sieves to the mixture in the absence of water (Table 1, entry 17). Other tests showed that no reaction occurred in pure water and a diminished yield (58%) in a mixed solvent of DMF/H$_2$O (10 : 1). Moreover, lowering the temperature remarkably decreased the yields even prolonging the reaction time to 48 h (62% for 80 °C and 30% for 60 °C, respectively).

With the optimal reaction conditions in hand, we then investigated the scope of the intramolecular deacetylative dearomatization reaction. As shown in Scheme 2, a range of *N*-(2-iodobenzoyl)-3-acetoxyindoles were tested and all the reactions proceeded smoothly to afford the desired tetracyclic indolin-3-one products **2** in moderate to excellent yields. The analogous bromo-substrate led to a relatively lower yield (74%) of product **2a**. Either electron-withdrawing or electron-donating substituents on the benzene ring of 2-iodobenzoyl moiety were well tolerated, furnishing indolin-3-ones **2b–2g** in the yields ranging from 72% to 92%. The electron-donating substituents resulted in relatively higher yields. Note that a longer reaction time (18 h) was needed for the *ortho*-methyl product **2g**. The effect of substituted groups attached on the indole ring was then examined. A range of functionalities at C5 of indole, including methyl, halide, methoxyl, –CF$_3$, and –CO$_2$Me, were compatible to this deacetylative dearomatization reaction, which smoothly delivered products **2h–2n** in moderate to good yields, albeit relatively lower yields were observed for those substrates bearing electron-withdrawing substituents. It's worthy to note that a bromine atom of product **2l** survived under the reaction conditions, which kept the potential for further functionalization. In addition, substrates having substituents at C6 also led to the desired products **2o–2q** in good yields.
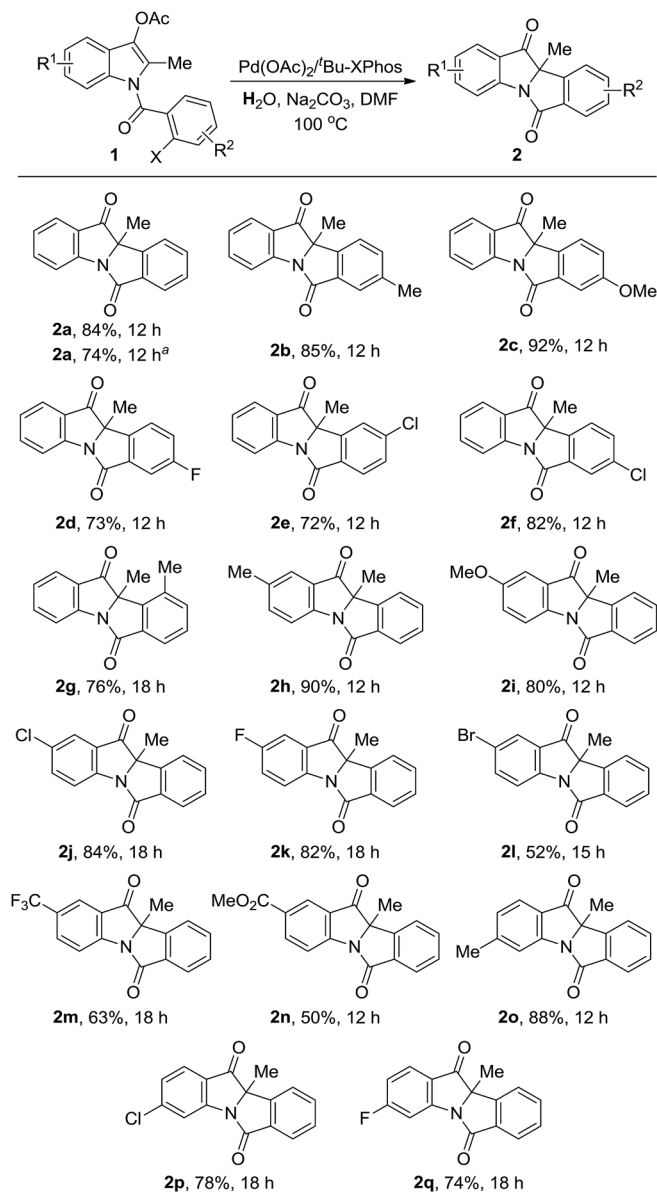
To demonstrate the synthetic utility of the reaction, several transformations of the indolin-3-one products were then

Scheme 2 Substrate scope. Reaction conditions: 1 (0.2 mmol), 5 mol% Pd(OAc)$_2$, ^{t}Bu-XPhos (10 mol%), Na$_2$CO$_3$ (2.0 equiv.), H$_2$O (2.0 equiv.), and DMF (2.0 mL) at 100 °C for indicated time (X = I). ^{a}X = Br.

conducted. A reduction of indolin-3-one **2a** with LiAlH$_4$ gave 3-hydroxylindoline **3** in 87% yield as a single isomer, which provides an efficient method to access tetracyclic indolin-3-ol in high diastereoselectivity (Scheme 3, eqn (1)). The Suzuki and Sonogashira reactions of product **2l** having a bromide group were established, which furnished the coupling products **4** and **5** in 86% and 92% yields, respectively (Scheme 3, eqn (2) and (3)). The extended conjugate structure might find potential application as material molecules. In addition, a preliminary enantioselective reaction was also studied. As elucidated in Scheme 4, (*R,R,R*)-MONOPHOS-PE proved to be a potential ligand in the reaction of **1a′**, leading to optically active indolin-3-one **2a** in 63% ee albeit with a lower yield.
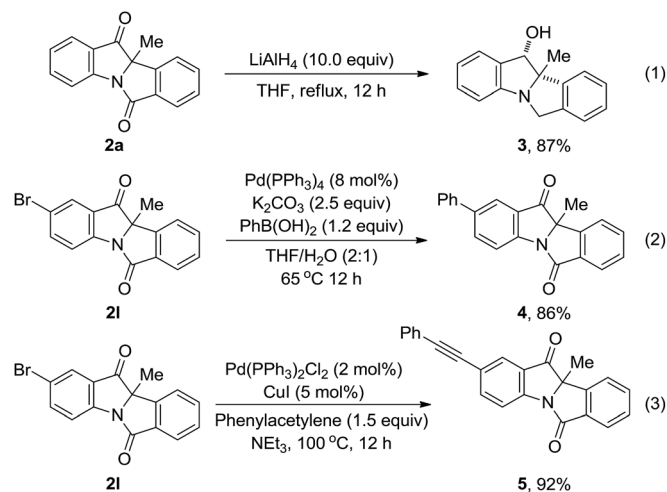
Scheme 3 Synthetic transformations.
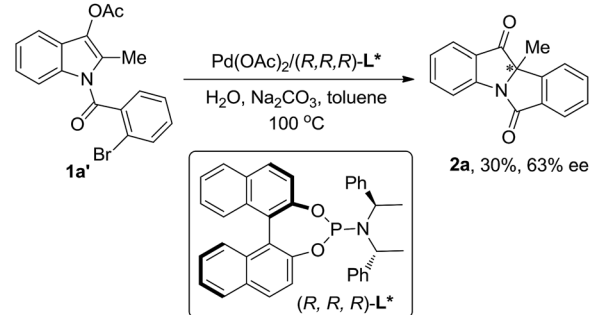
Scheme 4 Preliminary result of the enantioselective reaction.
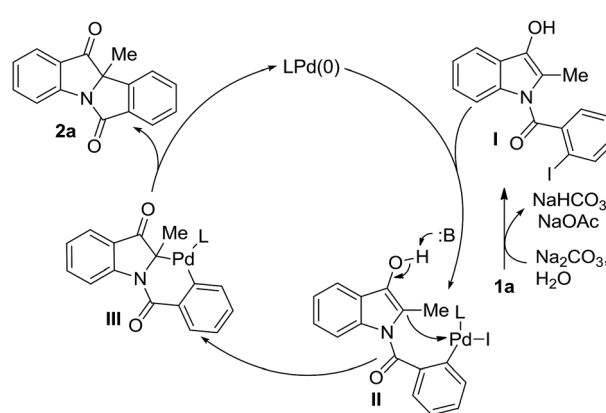
Scheme 5 A plausible reaction mechanism.

A tentative mechanism is depicted in Scheme 5. Considering the key role of water in this reaction (Table 1, entry 17), an initial hydrolysis of 3-acetoxy indole **1a** in the presence of base is proposed to deliver 3-hydroxyindole **I**. An adduct **II** was then achieved through oxidative addition of Pd(0) to compound **I**. Facilitated by a base-mediated keto–enol tautomerism, nucleophilic attack of indole at C2 to Pd-center furnishes

organopalladium **III**. Subsequent reductive elimination affords product **2a** and fulfils the catalytic cycle.

Conclusions

In summary, we have developed an efficient intramolecular deacetylative dearomatization reaction of 3-acetoxyindoles by employing the complex of Pd(OAc)$_2$/^{t}Bu-XPhos as a catalyst. This protocol provides a rapid access to a range of tetracyclic indolin-3-ones in moderate to good yields. Meanwhile, a preliminary enantioselective reaction is developed to afford the product in 63% ee by using (*R*,*R*,*R*)-phosphoramide-PE as a chiral ligand.

Experimental section

General information

Reactions and manipulations involving organometallic or moisture sensitive compounds were carried out under dry nitrogen and glassware heated under oven for two hours prior to use. ^{1}H NMR spectra were recorded on 500 MHz in CDCl$_3$, ^{13}C NMR spectra were recorded on 125 MHz in CDCl$_3$. Melting points were determined on a microscopic apparatus and were uncorrected. Commercial reagents were used as received without further purification unless otherwise noticed. HRMS were recorded on a TOF LC/MS mass spectrometer equipped with an ESI source. Column chromatography was carried out using silica gel (200–300 mesh). Anhydrous THF, 1,4-dioxane, and toluene were freshly distilled over Na and benzophenone. Anhydrous methanol was freshly distilled over Mg. Anhydrous DMF and NMP were freshly distilled over calcium hydride under reduced pressure. 3-Acetoxyindoles **1** was prepared (5.0 mmol scale) according to the known method.[11]

Synthesis of 3-acetoxyindole derivatives 1

According to the known methods,[11] to a stirred solution of *N*-2-iodobenzoyl indole derivatives[6a] (5.0 mmol) in HOAc (20 mL) was added PhI(OAc)$_2$ (3.22 g, 10.0 mmol). The mixture was then stirred in oil-bath at 70 °C for 12 h. After the reaction was completed, HOAc was removed under vacuum. H$_2$O (5 mL) was added and the solution was extracted with EtOAc (3 × 20 mL). The combined organic layer was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude was purified by column chromatography on silica gel (ethyl acetate/petroleum ether, v/v = 1/20–1/5) to give **1**.

1-(2-Iodobenzoyl)-2-methyl-1*H*-indol-3-yl acetate (1a)

628 mg, 30% yield, yellow solid, mp 107–109 °C; purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1 : 20 (v/v); R_f = 0.2. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.93 (d, *J* = 8.0 Hz, 1H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.44 (m, 1H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.29 (d, *J* = 7.7 Hz, 1H), 7.25–7.19 (m, 2H), 7.14 (t, *J* = 7.6 Hz, 1H), 2.40 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 168.8, 168.5, 142.0, 140.0, 134.0, 133.8, 132.1, 129.1, 128.6, 126.2, 124.7, 124.0, 123.8, 116.9, 115.3, 93.1,

20.5, 12.1. HRMS *m/z* (ESI+): calculated for C$_{18}$H$_{15}$INO$_3$ ([M + H]$^+$): 441.9911, found 441.9900.

1-(2-Iodo-5-methylbenzoyl)-2-methyl-1*H*-indol-3-yl acetate (1b)

650 mg, 30% yield, yellow solid, mp 112–114 °C; purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1 : 20 (v/v); R_f = 0.2. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.78 (d, *J* = 8.1 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 1H), 7.28 (m, 2H), 7.25–7.19 (m, 1H), 7.17–7.12 (m, 1H), 7.06 (dd, *J* = 8.0, 1.7 Hz, 1H), 2.40 (s, 3H), 2.35 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 168.9, 168.5, 141.8, 139.7, 139.0, 134.0, 133.7, 133.1, 129.7, 126.2, 124.7, 124.0, 123.7, 116.9, 115.3, 89.0, 20.9, 20.5, 12.1. HRMS *m/z* (ESI+): calculated for C$_{19}$H$_{16}$INO$_3$Na ([M + Na]$^+$): 456.0067, found 456.0058.

1-(2-Iodo-5-methoxybenzoyl)-2-methyl-1*H*-indol-3-yl ace-tate (1c)

562 mg, 25% yield, yellow solid, mp 104–106 °C; purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1 : 10 (v/v); R_f = 0.2. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.76 (d, *J* = 8.8 Hz, 1H), 7.36 (m, 1H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.23 (m, 1H), 7.19–7.12 (m, 1H), 6.99 (d, *J* = 3.0 Hz, 1H), 6.83 (dd, *J* = 8.8, 3.1 Hz, 1H), 3.80 (s, 3H), 2.40 (s, 3H), 2.13 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 168.6, 168.5, 160.1, 142.7, 140.7, 134.0, 133.9, 126.2, 124.8, 124.0, 123.8, 118.9, 116.9, 115.3, 114.3, 81.4, 55.7, 20.5, 12.1. HRMS *m/z* (ESI+): calculated for C$_{19}$H$_{16}$INO$_4$Na ([M + Na]$^+$): 472.0016, found 472.0013.

1-(5-Fluoro-2-iodobenzoyl)-2-methyl-1*H*-indol-3-yl acetate (1d)

590 mg, 27% yield, yellow solid, mp 128–130 °C; purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1 : 20 (v/v); R_f = 0.2. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.87 (m, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 7.5 Hz, 1H), 7.27–7.24 (m, 1H), 7.19 (m, 2H), 7.03–6.97 (m, 1H), 2.40 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 168.4, 167.4, 162.8 (d, *J* = 250.0 Hz), 143.5 (d, *J* = 6.3 Hz), 141.6 (d, *J* = 7.5 Hz), 134.1, 133.9, 125.9, 124.9, 124.1, 124.0, 119.7 (d, *J* = 21.3 Hz), 117.1, 116.6 (d, *J* = 23.8 Hz), 115.2, 86.2 (d, *J* = 3.8 Hz), 20.5, 12.1. HRMS *m/z* (ESI+): calculated for C$_{18}$H$_{13}$FINO$_3$Na ([M + Na]$^+$): 459.9816, found 459.9805.

1-(4-Chloro-2-iodobenzoyl)-2-methyl-1*H*-indol-3-yl acetate (1e)

680 mg, 30% yield, yellow solid, mp 52–53 °C; purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1 : 20 (v/v); R_f = 0.3. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.95 (d, *J* = 1.9 Hz, 1H), 7.49 (m, 1H), 7.36 (m, 2H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.25–7.21 (m, 1H), 7.19–7.14 (m, 1H), 2.40 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 168.4, 168.0, 140.4, 139.6, 137.3, 134.0, 133.9, 129.9, 129.0, 126.0, 124.8, 124.1, 123.9, 117.1, 115.1, 93.5, 20.5, 12.2. HRMS *m/z* (ESI+): calculated for C$_{18}$H$_{13}$ClINO$_3$Na ([M + Na]$^+$): 475.9521, found 475.9512.

1-(5-Chloro-2-iodobenzoyl)-2-methyl-1H-indol-3-yl acetate (1f)

680 mg, 30% yield, yellow solid, mp 112–113 °C; purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1 : 20 (v/v); R_f = 0.2. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.83 (d, J = 8.4 Hz, 1H), 7.44 (d, J = 2.5 Hz, 1H), 7.40 (d, J = 6.6 Hz, 1H), 7.30 (d, J = 7.6 Hz, 1H), 7.26–7.21 (m, 2H), 7.19 (m, 1H), 2.40 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 168.4, 167.4, 143.4, 141.1, 135.3, 134.1, 133.9, 132.2, 129.0, 125.9, 124.9, 124.1, 124.0, 117.1, 115.2, 90.2, 20.5, 12.2. HRMS m/z (ESI+): calculated for C$_{18}$H$_{13}$ClINO$_3$Na ([M + Na]$^+$): 475.9521, found 475.9513.

1-(2-Iodo-3-methylbenzoyl)-2-methyl-1H-indol-3-yl acetate (1g)

650 mg, 30% yield, yellow solid, mp 119–120 °C; purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1 : 20 (v/v); R_f = 0.2. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.39 (s, 2H), 7.37 (d, J = 7.6 Hz, 1H), 7.29 (d, J = 7.6 Hz, 1H), 7.24 (d, J = 7.3 Hz, 1H), 7.22–7.19 (m, 1H), 7.15 (t, J = 7.5 Hz, 1H), 2.52 (s, 3H), 2.40 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 169.4, 168.5, 143.4, 143.3, 134.1, 133.8, 131.4, 128.7, 126.3, 126.1, 124.7, 124.0, 123.8, 116.9, 115.5, 99.6, 28.8, 20.5, 12.2. HRMS m/z (ESI+): calculated for C$_{19}$H$_{16}$INO$_3$Na ([M + Na]$^+$): 456.0067, found 456.0069.

1-(2-Iodobenzoyl)-2,5-dimethyl-1H-indol-3-yl acetate (1h)

606 mg, 28% yield, yellow solid, mp 116–118 °C; purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1 : 20 (v/v); R_f = 0.2. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.92 (d, J = 7.7 Hz, 1H), 7.49 (m, 1H), 7.44–7.41 (m, 1H), 7.25–7.15 (m, 2H), 7.09–6.90 (m, 2H), 2.40 (s, 3H), 2.39 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 168.7, 168.6, 142.1, 141.9, 139.9, 133.5, 132.3, 131.9, 129.0, 128.6, 128.0, 126.0, 124.2, 116.8, 115.0, 93.1, 21.3, 20.5, 12.1. HRMS m/z (ESI+): calculated for C$_{19}$H$_{16}$INO$_3$Na ([M + Na]$^+$): 456.0067, found 456.0060.

1-(2-Iodobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl ace-tate (1i)

404 mg, 18% yield, yellow solid, mp 132–134 °C; purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1 : 10 (v/v); R_f = 0.2. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.92 (d, J = 7.9 Hz, 1H), 7.49 (t, J = 7.5 Hz, 1H), 7.43 (m, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.23 (m, 1H), 6.77–6.70 (m, 2H), 3.82 (s, 3H), 2.40 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 168.5, 168.4, 156.6, 142.1, 139.9, 133.8, 131.9, 128.9, 128.59, 128.55, 126.8, 125.0, 116.4, 113.0, 99.9, 93.1, 55.6, 20.5, 12.2. HRMS m/z (ESI+): calculated for C$_{19}$H$_{16}$INO$_4$Na ([M + Na]$^+$): 472.0016, found 472.0006.

5-Chloro-1-(2-iodobenzoyl)-2-methyl-1H-indol-3-yl acetate (1j)

454 mg, 20% yield, yellow solid, mp 117–119 °C; purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1 : 20 (v/v); R_f = 0.2. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.93 (d, J = 7.6 Hz, 1H), 7.51 (td, J = 7.6, 0.8 Hz, 1H), 7.44 (dd, J = 7.6, 1.6 Hz, 1H), 7.34 (d, J = 8.8 Hz, 1H), 7.27 (d, J =

1.9 Hz, 1H), 7.26–7.24 (m, 1H), 7.11 (dd, J = 8.9, 2.1 Hz, 1H), 2.40 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 168.6, 168.4, 141.6, 140.0, 132.9, 132.4, 132.3, 129.6, 129.1, 128.7, 127.7, 125.3, 124.8, 116.8, 116.4, 93.0, 20.5, 12.2. HRMS m/z (ESI+): calculated for C$_{18}$H$_{13}$ClINO$_3$Na ([M + Na]$^+$): 475.9521, found 475.9515.

5-Fluoro-1-(2-iodobenzoyl)-2-methyl-1H-indol-3-yl acetate (1k)

437 mg, 20% yield, yellow solid, mp 114–116 °C; purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1 : 20 (v/v); R_f = 0.2. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.95–7.91 (m, 1H), 7.52–7.49 (m, 1H), 7.44 (m, J = 7.6, 1.6 Hz, 2H), 7.25 (m, J = 7.6, 6.0 Hz, 1H), 6.96 (dd, J = 8.2, 2.6 Hz, 1H), 6.89 (td, J = 9.1, 2.6 Hz, 1H), 2.39 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 168.6, 168.3, 159.7 (d, J = 241.3 Hz), 141.8, 140.0, 133.4 (d, J = 3.8 Hz), 132.2, 130.3, 129.0, 128.6, 127.8, 125.2 (d, J = 8.8 Hz), 116.7 (d, J = 8.8 Hz), 112.4 (d, J = 23.8 Hz), 103.0 (d, J = 25.0 Hz), 93.0, 20.5, 12.2. HRMS m/z (ESI+): calculated for C$_{18}$H$_{13}$FINO$_3$Na ([M + Na]$^+$): 459.9816, found 459.9813.

5-Bromo-1-(2-iodobenzoyl)-2-methyl-1H-indol-3-yl acetate (1l)

697 mg, 28% yield, yellow solid, mp 143–145 °C; purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1 : 20 (v/v); R_f = 0.3. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.93 (d, J = 7.7 Hz, 1H), 7.51 (td, J = 7.5, 0.7 Hz, 1H), 7.46–7.41 (m, 2H), 7.28–7.23 (m, 3H), 2.40 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 168.6, 168.3, 141.6, 140.0, 132.7, 132.7, 132.3, 129.1, 128.7, 127.6, 127.5, 125.7, 119.8, 117.2, 116.7, 93.0, 20.5, 12.1. HRMS m/z (ESI+): calculated for C$_{18}$H$_{13}$BrINO$_3$Na ([M + Na]$^+$): 519.9016, found 519.9003.

1-(2-Iodobenzoyl)-2-methyl-5-(trifluoromethyl)-1H-indol-3-yl acetate (1m)

487 mg, 20% yield, white solid, mp 139–141 °C; purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1 : 20 (v/v); R_f = 0.2. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.97–7.92 (m, 1H), 7.57 (s, 1H), 7.55–7.50 (m, 1H), 7.46 (dd, J = 7.8, 1.5 Hz, 2H), 7.42–7.38 (m, 1H), 7.30–7.26 (m, 1H), 2.43 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 168.8, 168.4, 141.4, 140.2, 135.5, 133.4, 132.5, 129.3, 128.8, 128.3, 126.1 (q, J = 32.5 Hz), 124.4 (q, J = 270.0 Hz), 123.9, 121.5 (q, J = 3.8 Hz), 115.5, 114.6 (q, J = 5.0 Hz), 93.0, 20.5, 12.2. HRMS m/z (ESI+): calculated for C$_{19}$H$_{13}$F$_3$INO$_3$Na ([M + Na]$^+$): 509.9784, found 509.9776.

Methyl 3-acetoxy-1-(2-iodobenzoyl)-2-methyl-1H-indole-5-carboxylate (1n)

597 mg, 25% yield, white solid, mp 148–150 °C; purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1 : 5 (v/v); R_f = 0.2. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.02 (d, J = 1.2 Hz, 1H), 7.94 (d, J = 8.1 Hz, 1H), 7.85 (dd, J = 8.8, 1.6 Hz, 1H), 7.52 (t, J = 7.4 Hz, 1H), 7.47 (m, 1H), 7.35 (d, J = 8.8 Hz, 1H), 7.27 (m, 1H), 3.92 (s, 3H), 2.43 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 168.7, 168.4, 166.9,

141.4, 140.1, 136.5, 133.6, 132.4, 129.2, 128.7, 127.8, 125.9, 125.6, 123.9, 119.1, 114.8, 93.0, 52.1, 20.5, 12.1. HRMS m/z (ESI+): calculated for $C_{20}H_{16}INO_5Na$ ([M + Na]$^+$): 499.9965, found 499.9953.

1-(2-Iodobenzoyl)-2,6-dimethyl-1H-indol-3-yl acetate (1o)

433 mg, 20% yield, yellow solid, mp 57–58 °C; purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1 : 20 (v/v); R_f = 0.2. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.94–7.91 (m, 1H), 7.50–7.41 (m, 3H), 7.23 (m, 1H), 7.17 (d, J = 7.9 Hz, 1H), 7.07 (d, J = 8.0 Hz, 1H), 2.38 (s, 3H), 2.35 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 168.9, 168.4, 142.1, 139.8, 134.9, 134.5, 134.0, 131.9, 129.0, 128.5, 125.2, 124.9, 121.7, 116.5, 116.0, 93.2, 22.0, 20.5, 12.1. HRMS m/z (ESI+): calculated for $C_{19}H_{16}INO_3Na$ ([M + Na]$^+$): 456.0067, found 456.0059.

6-Chloro-1-(2-iodobenzoyl)-2-methyl-1H-indol-3-yl acetate (1p)

408 mg, 18% yield, yellow solid, mp 110–112 °C; purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1 : 20 (v/v); R_f = 0.2. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.92 (d, J = 7.7 Hz, 1H), 7.65 (s, 1H), 7.50 (m, 1H), 7.43 (m, 1H), 7.27–7.19 (m, 3H), 2.37 (s, 3H), 1.95 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 168.6, 168.3, 141.5, 139.9, 134.3, 133.4, 132.2, 130.8, 129.0, 128.6, 126.5, 124.4, 122.5, 117.7, 115.9, 93.0, 20.4, 12.1. HRMS m/z (ESI+): calculated for $C_{18}H_{13}ClINO_3Na$ ([M + Na]$^+$): 475.9521, found 475.9512.

6-Fluoro-1-(2-iodobenzoyl)-2-methyl-1H-indol-3-yl acetate (1q)

437 mg, 20% yield, yellow solid, mp 96–98 °C; purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1 : 20 (v/v); R_f = 0.2. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.94 (d, J = 7.9 Hz, 1H), 7.52 (m, 1H), 7.44 (m, 1H), 7.28 (d, J = 1.5 Hz, 1H), 7.26–7.19 (m, 2H), 7.00 (td, J = 8.8, 2.2 Hz, 1H), 2.39 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 168.6, 168.3, 160.9 (d, J = 240.0 Hz), 141.5, 139.9, 134.1 (d, J = 11.3 Hz), 133.3, 132.2, 128.7 (d, J = 40.0 Hz), 126.1, 126.0, 120.3, 117.6 (d, J = 10.0 Hz), 111.9 (d, J = 23.8 Hz), 103.2 (d, J = 28.8 Hz), 92.9, 20.4, 12.0. HRMS m/z (ESI+): calculated for $C_{18}H_{13}$-FINO$_3$Na ([M + Na]$^+$): 459.9816, found 459.9809.

General procedure for the deacetylative dearomatization of 3-acetoxyindoles

To a Schlenk tube were added Pd(OAc)$_2$ (5 mol%), ^{t}Bu-XPhos (10 mol%), Na$_2$CO$_3$ (2.0 equiv., 0.4 mmol), indole **1** (0.2 mmol), and 2.0 mL anhydrous DMF under N$_2$, after which H$_2$O (2.0 equiv., 0.4 mmol) was added to the reaction mixture by a syringe. The mixture was then stirred in oil-bath at 100 °C for 12–18 h. When the reaction was completed, the mixture was extracted with EtOAc (3 × 10 mL) and the combined organic layer was concentrated under reduced pressure. The residue was then purified by column chromatography on silica gel (ethyl acetate/petroleum ether, v/v = 1/20–1/10) to give products **2**.

10b-Methyl-6H-isoindolo[2,1-a]indole-6,11(10bH)-dione (2a)

42.0 mg, 84% yield, white solid, mp 135–136 °C; purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1 : 20 (v/v); R_f = 0.3. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.98 (d, J = 8.0 Hz, 1H), 7.83 (m, 2H), 7.78–7.73 (m, 2H), 7.73–7.68 (m, 1H), 7.53 (m, 1H), 7.29 (t, J = 7.5 Hz, 1H), 1.81 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 197.4, 169.6, 151.7, 145.6, 137.4, 134.4, 131.1, 129.5, 127.5, 125.3, 125.24, 125.16, 122.8, 118.6, 73.6, 25.9. HRMS m/z (ESI+): calculated for $C_{16}H_{11}NO_2Na$ ([M + Na]$^+$): 272.0682, found 272.0672. For the reaction with (R,R,R)-phosphoramide-PE as a chiral ligand: 30% yield, 63% ee [Daicel Chiralpak AD-H column (25 cm × 0.46 cm ID), ^{n}hexane/^{i}PrOH = 95/5, 0.7 mL min^{-1}, 254 nm; t_{major} = 18.6 min, t_{minor} = 21.4 min].

8,10b-Dimethyl-6H-isoindolo[2,1-a]indole-6,11(10bH)-dione (2b)

44.7 mg, 85% yield, yellow solid, mp 105–107 °C; purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1 : 20 (v/v); R_f = 0.3. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.97 (d, J = 8.1 Hz, 1H), 7.78–7.72 (m, 2H), 7.69 (d, J = 7.8 Hz, 1H), 7.64 (s, 1H), 7.53–7.50 (m, 1H), 7.29 (d, J = 7.4 Hz, 1H), 2.44 (s, 3H), 1.78 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 197.8, 169.9, 151.8, 143.1, 139.9, 137.4, 135.6, 131.3, 127.6, 125.4, 125.3, 125.2, 122.5, 118.7, 73.5, 26.0, 21.4. HRMS m/z (ESI+): calculated for $C_{17}H_{14}NO_2$ ([M + H]$^+$): 264.1019, found 264.1016.

8-Methoxy-10b-methyl-6H-isoindolo[2,1-a]indole-6,11(10bH)-dione (2c)

51.4 mg, 92% yield, white solid, mp 110–112 °C; purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1 : 10 (v/v); R_f = 0.4. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.97 (d, J = 8.0 Hz, 1H), 7.79–7.73 (m, 2H), 7.70 (d, J = 8.4 Hz, 1H), 7.31–7.27 (m, 2H), 7.27–7.25 (m, 1H), 3.86 (s, 3H), 1.77 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 197.7, 169.8, 161.1, 151.6, 138.2, 137.4, 132.5, 127.8, 125.4, 125.2, 123.7, 122.9, 118.7, 107.6, 73.3, 55.8, 25.9. HRMS m/z (ESI+): calculated for $C_{17}H_{13}NO_3Na$ ([M + Na]$^+$): 302.0788, found 302.0788.

8-Fluoro-10b-methyl-6H-isoindolo[2,1-a]indole-6,11(10bH)-dione (2d)

39.0 mg, 73% yield, yellow solid, mp 108–110 °C; purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1 : 20 (v/v); R_f = 0.3. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.96 (d, J = 7.9 Hz, 1H), 7.78 (m, 3H), 7.50 (dd, J = 7.4, 2.4 Hz, 1H), 7.41 (td, J = 8.6, 2.4 Hz, 1H), 7.34–7.28 (m, 1H), 1.80 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 197.0, 168.43, 168.41, 163.6 (d, J = 248.8 Hz), 151.3, 141.2 (d, J = 1.3 Hz), 137.5, 133.3 (d, J = 7.5 Hz), 127.5, 125.4 (d, J = 6.3 Hz), 124.4 (d, J = 8.8 Hz), 122.1, 121.9, 118.6, 111.7 (d, J = 22.5 Hz), 73.2, 25.9. HRMS m/z (ESI+): calculated for $C_{16}H_{11}FNO_2$ ([M + H]$^+$): 268.0768, found 268.0768.

9-Chloro-10b-methyl-6H-isoindolo[2,1-a]indole-6,11(10bH)-dione (2e)

40.8 mg, 72% yield, yellow solid, mp 159–161 °C; purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1 : 20 (v/v); R_f = 0.4. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.96 (d, J = 8.0 Hz, 1H), 7.81 (d, J = 1.6 Hz, 1H), 7.76 (m, 3H), 7.50 (dd, J = 8.2, 1.8 Hz, 1H), 7.30 (m, 1H), 1.80 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 196.7, 168.5, 151.5, 147.0, 141.1, 137.6, 130.3, 129.6, 127.3, 126.4, 125.4, 123.3, 118.6, 73.1, 25.9. HRMS m/z (ESI+): calculated for C$_{16}$H$_{11}$ClNO$_2$ ([M + H]$^+$): 284.0473, found 284.0466.

8-Chloro-10b-methyl-6H-isoindolo[2,1-a]indole-6,11(10bH)-dione (2f)

46.5 mg, 82% yield, yellow solid, mp 125–127 °C; purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1 : 20 (v/v); R_f = 0.3. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.96 (d, J = 8.4 Hz, 1H), 7.81 (d, J = 1.8 Hz, 1H), 7.79–7.74 (m, 3H), 7.67 (m, 1H), 7.31 (t, J = 7.5 Hz, 1H), 1.80 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 196.8, 168.2, 151.3, 143.7, 137.6, 136.0, 134.5, 132.9, 127.5, 125.5, 125.4, 125.2, 124.0, 118.6, 73.3, 25.9. HRMS m/z (ESI+): calculated for C$_{16}$H$_{10}$ClNO$_2$Na ([M + Na]$^+$): 306.0292, found 306.0286.

10,10b-Dimethyl-6H-isoindolo[2,1-a]indole-6,11(10bH)-dione (2g)

40.0 mg, 76% yield, yellow solid, mp 40–41 °C; purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1 : 20 (v/v); R_f = 0.3. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.98 (d, J = 8.0 Hz, 1H), 7.78–7.71 (m, 2H), 7.68 (d, J = 7.5 Hz, 1H), 7.47 (d, J = 7.5 Hz, 1H), 7.39 (t, J = 7.5 Hz, 1H), 7.28 (t, J = 5.0 Hz, 1H), 2.84 (s, 3H), 1.88 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 197.5, 169.0, 150.7, 143.5, 137.3, 136.5, 135.0, 132.0, 129.4, 127.8, 125.2, 125.0, 122.6, 118.3, 74.9, 24.4, 19.3. HRMS m/z (ESI+): calculated for C$_{17}$H$_{14}$NO$_2$ ([M + H]$^+$): 264.1019, found 264.1011.

2,10b-Dimethyl-6H-isoindolo[2,1-a]indole-6,11(10bH)-dione (2h)

47.4 mg, 90% yield, yellow solid, mp 97–98 °C; purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1 : 20 (v/v); R_f = 0.3. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.89–7.78 (m, 3H), 7.69 (t, J = 7.5 Hz, 1H), 7.56 (d, J = 8.5 Hz, 2H), 7.52 (t, J = 7.5 Hz, 1H), 2.40 (s, 3H), 1.79 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 197.4, 169.6, 149.7, 145.6, 138.4, 135.2, 134.2, 131.2, 129.4, 127.6, 125.1, 125.0, 122.7, 118.2, 73.8, 25.9, 20.9. HRMS m/z (ESI+): calculated for C$_{17}$H$_{13}$NO$_2$Na ([M + Na]$^+$): 286.0838, found 286.0829.

2-Methoxy-10b-methyl-6H-isoindolo[2,1-a]indole-6,11(10bH)-dione (2i)

44.7 mg, 80% yield, white solid, mp 87–88 °C; purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1 : 10 (v/v); R_f = 0.3. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.89 (d, J = 8.8 Hz, 1H), 7.82 (dd, J = 14.8, 7.7 Hz, 2H), 7.70 (td, J = 7.7, 1.0 Hz, 1H), 7.53 (m, 1H), 7.35 (dd, J = 8.8, 2.7 Hz, 1H), 7.19 (d, J = 2.7 Hz, 1H), 3.83 (s, 3H), 1.80 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 197.5, 169.9, 157.5, 146.2, 145.5, 134.3, 131.2, 129.5, 128.3, 126.1, 125.2, 122.7, 119.6, 106.5, 74.3, 55.9, 25.9. HRMS m/z (ESI+): calculated for C$_{17}$H$_{13}$NO$_3$Na ([M + Na]$^+$): 302.0788, found 302.0778.

2-Chloro-10b-methyl-6H-isoindolo[2,1-a]indole-6,11(10bH)-dione (2j)

47.6 mg, 84% yield, yellow solid, mp 118–120 °C; purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1 : 20 (v/v); R_f = 0.3. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.93 (d, J = 8.5 Hz, 1H), 7.85 (d, J = 7.7 Hz, 1H), 7.80 (d, J = 7.7 Hz, 1H), 7.74–7.68 (m, 3H), 7.57–7.52 (m, 1H), 1.80 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 196.4, 169.5, 150.1, 145.4, 137.3, 134.7, 131.2, 130.9, 129.8, 128.8, 125.5, 125.0, 122.8, 119.8, 74.2, 26.0. HRMS m/z (ESI+): calculated for C$_{16}$H$_{11}$ClNO$_2$ ([M + H]$^+$): 325.2420, found 325.2411.

2-Fluoro-10b-methyl-6H-isoindolo[2,1-a]indole-6,11(10bH)-dione (2k)

43.8 mg, 82% yield, yellow solid, mp 180–182 °C; purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1 : 20 (v/v); R_f = 0.3. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.96 (dd, J = 8.8, 4.1 Hz, 1H), 7.83 (m, 2H), 7.74–7.70 (m, 1H), 7.55 (t, J = 7.5 Hz, 1H), 7.48 (td, J = 8.7, 2.7 Hz, 1H), 7.43 (dd, J = 6.9, 2.7 Hz, 1H), 1.81 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 196.8, 169.7, 160.1 (d, J = 246.3 Hz), 148.0, 145.4, 134.6, 131.0, 129.7, 128.7 (d, J = 8.8 Hz), 125.4, 124.8 (d, J = 25.0 Hz), 122.8, 120.0 (d, J = 7.5 Hz), 111.1 (d, J = 23.8 Hz), 74.4, 25.9. HRMS m/z (ESI+): calculated for C$_{16}$H$_{11}$FNO$_2$ ([M + H]$^+$): 268.0768, found 268.0762.

2-Bromo-10b-methyl-6H-isoindolo[2,1-a]indole-6,11(10bH)-dione (2l)

34.1 mg, 52% yield, white solid, mp 103–105 °C; purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1 : 20 (v/v); R_f = 0.4. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.88 (m, 2H), 7.86–7.82 (m, 2H), 7.80 (d, J = 7.7 Hz, 1H), 7.72 (td, J = 7.6, 0.9 Hz, 1H), 7.55 (m, 1H), 1.80 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 196.2, 169.4, 150.5, 145.3, 140.0, 134.7, 130.9, 129.7, 129.2, 128.0, 125.4, 122.8, 120.1, 118.4, 73.9, 25.9. HRMS m/z (ESI+): calculated for C$_{16}$H$_{10}$BrNO$_2$Na ([M + Na]$^+$): 349.9787, found 349.9796.

10b-Methyl-2-(trifluoromethyl)-6H-isoindolo[2,1-a]indole-6,11(10bH)-dione (2m)

40.0 mg, 63% yield, white solid, mp 52–54 °C; purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1 : 20 (v/v); R_f = 0.3. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.11 (d, J = 8.5 Hz, 1H), 8.05 (s, 1H), 8.00 (dd, J = 8.4, 1.5 Hz, 1H), 7.87 (d, J = 7.7 Hz, 1H), 7.83 (d, J = 7.7 Hz, 1H), 7.75 (m, 1H), 7.59–7.54 (m, 1H), 1.83 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 196.4, 169.2, 153.7, 145.3, 134.9, 134.1 (q, J = 3.8 Hz), 130.7, 129.9, 127.7, 127.6 (q, J = 33.8 Hz), 125.6, 124.6, 122.88,

122.85, 119.0, 74.1, 26.0. HRMS m/z (ESI+): calculated for $C_{17}H_{10}F_3NO_2Na$ ([M + Na]+): 347.2224, found 347.2226.

Methyl 10b-methyl-6,11-dioxo-10b,11-dihydro-6H-isoindolo[2,1-a]indole-2-carboxylate (2n)

30.7 mg, 50% yield, white solid, mp 125–127 °C; purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1 : 10 (v/v); R_f = 0.2. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.47–8.41 (m, 2H), 8.03 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 7.6 Hz, 1H), 7.83 (d, J = 7.7 Hz, 1H), 7.76–7.71 (m, 1H), 7.56 (m, 1H), 3.95 (s, 3H), 1.82 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 196.6, 169.1, 165.7, 154.4, 145.5, 138.5, 134.8, 130.8, 129.8, 127.6, 127.3, 127.2, 125.5, 122.8, 118.2, 74.1, 52.5, 26.1. HRMS m/z (ESI+): calculated for $C_{18}H_{14}NO_4$ ([M + H]+): 308.0917, found 308.0903.

3,10b-Dimethyl-6H-isoindolo[2,1-a]indole-6,11(10bH)-dione (2o)

46.3 mg, 88% yield, yellow solid, mp 149–150 °C; purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1 : 20 (v/v); R_f = 0.3. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.87–7.78 (m, 3H), 7.70 (td, J = 7.7, 1.0 Hz, 1H), 7.65 (d, J = 7.9 Hz, 1H), 7.53 (m, 1H), 7.10 (d, J = 7.8 Hz, 1H), 2.52 (s, 3H), 1.79 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 196.8, 169.7, 152.0, 149.5, 145.8, 134.3, 131.2, 129.4, 126.5, 125.2, 125.1, 125.0, 122.7, 118.8, 73.9, 26.1, 22.6. HRMS m/z (ESI+): calculated for $C_{17}H_{14}NO_2$ ([M + H]+): 264.1019, found 264.1009.

3-Chloro-10b-methyl-6H-isoindolo[2,1-a]indole-6,11(10bH)-dione (2p)

44.3 mg, 78% yield, white solid, mp 160–162 °C; purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1 : 20 (v/v); R_f = 0.3. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.99 (d, J = 1.6 Hz, 1H), 7.86 (d, J = 7.7 Hz, 1H), 7.81 (d, J = 7.7 Hz, 1H), 7.73 (m, 1H), 7.69 (d, J = 8.2 Hz, 1H), 7.56–7.53 (m, 1H), 7.26 (m, 1H), 1.80 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 196.2, 169.4, 152.3, 145.6, 144.0, 134.7, 130.8, 129.7, 126.2, 125.92, 125.90, 125.5, 122.8, 118.9, 74.0, 26.0. HRMS m/z (ESI+): calculated for $C_{16}H_{10}ClNO_2Na$ ([M + Na]+): 306.0292, found 306.0280.

3-Fluoro-10b-methyl-6H-isoindolo[2,1-a]indole-6,11(10bH)-dione (2q)

39.6 mg, 74% yield, white solid, mp 168–170 °C; purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1 : 20 (v/v); R_f = 0.3. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.85 (d, J = 7.6 Hz, 1H), 7.81 (d, J = 7.7 Hz, 1H), 7.77 (dd, J = 8.5, 5.5 Hz, 1H), 7.72 (t, J = 7.5 Hz, 1H), 7.66 (dd, J = 8.9, 2.1 Hz, 1H), 7.54 (t, J = 7.5 Hz, 1H), 6.98 (td, J = 8.6, 2.1 Hz, 1H), 1.81 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 195.7, 169.4, 168.7 (d, J = 256.3 Hz), 153.6 (d, J = 13.8 Hz), 145.7, 134.7, 130.7, 129.6, 127.4 (d, J = 12.5 Hz), 125.4, 123.7, 122.8, 113.4 (d, J = 23.8 Hz), 106.1 (d, J = 26.3 Hz), 74.2, 26.0. HRMS m/z (ESI+): calculated for $C_{16}H_{11}FNO_2$ ([M + H]+): 279.2795, found 279.2784.

Reduction of 2a

To a solution of **2a** (1.0 equiv., 0.2 mmol) in THF (2.0 mL) was added LiAlH$_4$ (10.0 equiv., 2.0 mmol) in portions at 0 °C, after which the mixture was stirred at 90 °C for 12 h. The resulting mixture was then quenched with H$_2$O at 0 °C, and extracted with EtOAc. After the solvent EtOAc was removed under vacuum, the residue was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether, v/v = 1/3) to give compound **3** (41.0 mg, 87%) as a white solid, R_f = 0.4. Mp 85–87 °C; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.32–7.25 (m, 2H), 7.20 (m, 3H), 7.14 (d, J = 6.7 Hz, 1H), 6.83 (m, 2H), 5.40 (s, 1H), 4.61 (d, J = 15.2 Hz, 1H), 4.41 (d, J = 15.2 Hz, 1H), 2.31 (brs, 1H), 1.52 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 154.4, 147.1, 138.5, 132.0, 130.3, 128.0, 127.4, 125.9, 122.9, 122.3, 121.5, 113.3, 80.4, 78.6, 56.9, 21.0. HRMS m/z (ESI+): calculated for $C_{16}H_{16}NO$ ([M + H]+): 238.1226, found 238.1223.

Suzuki reaction of 2l with PhB(OH)$_2$

The mixture of PhB(OH)$_2$ (1.2 equiv., 0.24 mmol), Pd(PPh$_3$)$_4$ (8 mol%), K$_2$CO$_3$ (2.5 equiv., 0.5 mmol), and **2l** (1.0 equiv., 0.2 mmol) in THF (2.0 mL) and H$_2$O (1.0 mL) was stirred at 65 °C for 12 h under N$_2$ atmosphere. The resulting mixture was then extracted with EtOAc and the combined organic phases were concentrated under vacuum. The residue was then purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether, v/v = 1/10) to give compound **4** (55.8 mg, 86%) as a white solid, R_f = 0.5. Mp 120–122 °C; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.05 (d, J = 8.3 Hz, 1H), 7.99 (m, 2H), 7.85 (dd, J = 14.9, 7.7 Hz, 2H), 7.72 (t, J = 7.5 Hz, 1H), 7.59–7.52 (m, 3H), 7.46 (t, J = 7.6 Hz, 2H), 7.37 (t, J = 7.3 Hz, 1H), 1.84 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 197.5, 169.7, 150.9, 145.6, 139.4, 138.7, 136.5, 134.5, 131.1, 129.6, 129.0, 128.1, 127.8, 127.0, 125.3, 123.4, 122.8, 118.8, 74.1, 26.0. HRMS m/z (ESI+): calculated for $C_{22}H_{15}NO_2Na$ ([M + Na]+): 348.0995, found 348.0997.

Sonogashira reaction of 2l with phenylacetylene

The mixture of phenylacetylene (1.5 equiv., 0.3 mmol), CuI (5 mol%), Pd(PPh$_3$)$_2$Cl$_2$ (2 mol%), and **2l** (1.0 equiv., 0.2 mmol) in Et$_3$N (2.0 mL) was stirred at 100 °C for 12 h under N$_2$ atmosphere. After the reaction was completed, Et$_3$N was removed under vacuum. The crude was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether, v/v = 1/10) to give compound **5** (64.4 mg, 92%) as a yellow solid, R_f = 0.2. Mp 145–146 °C; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.96 (d, J = 8.3 Hz, 1H), 7.93–7.83 (m, 3H), 7.81 (d, J = 7.6 Hz, 1H), 7.71 (m, 1H), 7.53 (m, 3H), 7.39–7.30 (m, 3H), 1.81 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 196.6, 169.3, 150.8, 145.5, 140.3, 134.5, 131.6, 131.0, 129.6, 128.6, 128.4, 128.2, 127.7, 125.3, 122.74, 122.66, 120.6, 118.5, 90.4, 87.7, 73.8, 26.0. HRMS m/z (ESI+): calculated for $C_{24}H_{16}NO_2$ ([M + H]+): 350.1176, found 350.1178.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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