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Zinc-Mediated C-3 α-Prenylation of Isatins with Prenyl Bromide: Access to 3-Prenyl-3-hydroxy-2-oxindoles and Its Application

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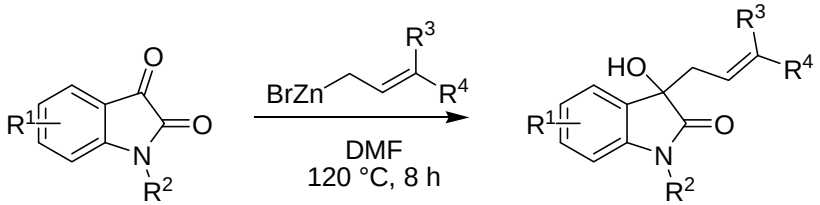


R^1 = H, CH_3, CH_3O, F, Cl, Br, NO_2
R^2 = H, CH_3, C_2H_5, allyl, substituted benzyl
R^3 = R^4 = CH_3 or R^3 = H, R^4 = phenyl

28 examples
up to 98% yield

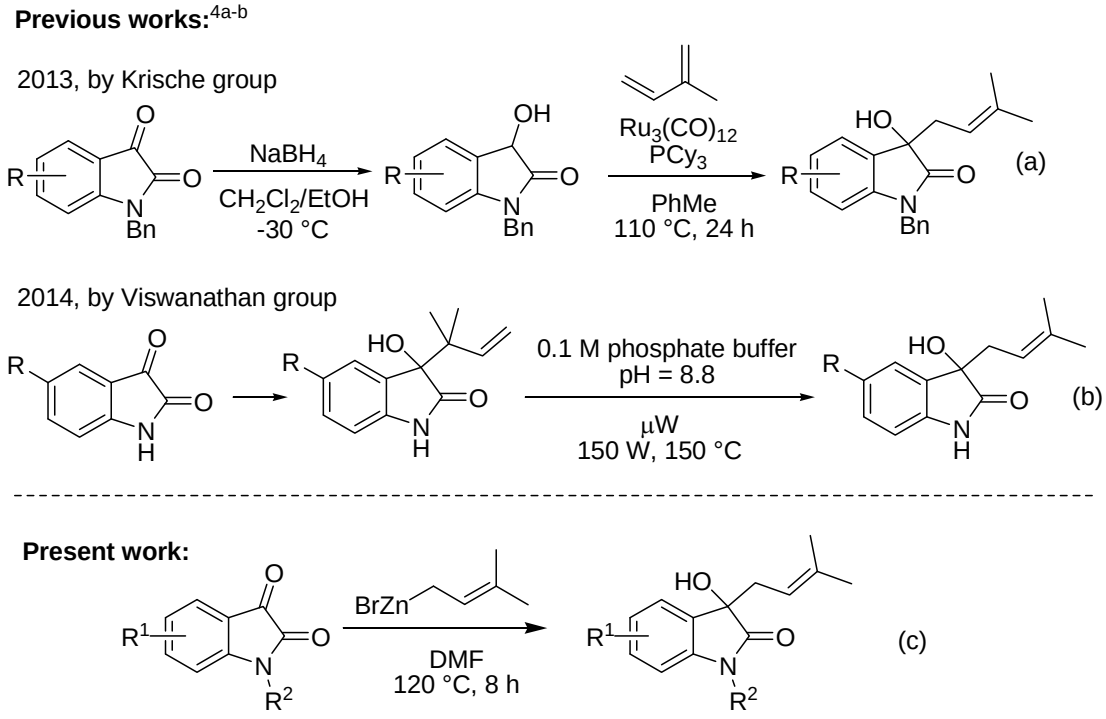
Abstract A convenient and highly α-regioselective strategy for the synthesis of 3-prenyl-3-hydroxy-2-oxindoles has been developed starting from isatins and prenylzinc with good to excellent yield. This protocol provides a straightforward and practical way to introduce an α-prenyl moiety to the C-3 position of isatins. The advantages of this reaction are use of the cheap and readily available reagents, operational simplicity, and wide substrate scope. Furthermore, this transformation was applied to the synthesis of several oxindole-containing natural products, which further demonstrated the synthetic utility of this methodology.

INTRODUCTION

3-Substituted-3-hydroxy-2-oxindoles have attracted increasing interest because of their potential biological activities and their role as key precursors in the synthesis of bioactive molecules and natural products.[1] Among those oxindole derivatives, 3-allyl-3-hydroxy-2-oxindoles are one of the most versatile building blocks to access various alkaloids and molecules with biological importance.[2] Accordingly, over the decades, many methods have been reported for the synthesis of this class of compounds via the reactions of isatins with allyl metal reagents such as indiums[3a, 3b], stannanes[3c, 3g], and silanes[3d, 3e, 3f] as nucleophilic allyl sources. However, in contrast to the well-established allylation of isatins, the analogous prenylation of isatins for the generation of 3-prenyl-3-hydroxy-2-oxindoles has rarely been explored due to the challenging issue of regioselectivity. Generally, α-regioselective prenylation of isatins is difficult to achieve when using α-substituted allylmetal reagents such as prenylmetal.[3a, 3b, 3d] Consequently, these oxindole derivatives are often assembled in a stepwise fashion by the initial preparation of a 3-substituted-2-oxindole intermediate, which is then further elaborated to the target (Scheme 1a).[4a] In 2014, Viswanathan and coworkers reported a potentially rate-accelerated "anionic-oxy-Cope" rearrangement for prenylating the C4-position of oxindoles. Coincidentally they observed an internal prenyl migratory event leading to C3-normal prenylated derivatives (Scheme 1b).[4b] Considering the importance of the prenyl moiety, which represents an important natural product substructure[5] and plays a significant role in metabolism of living organisms,[6] it is conceivable that the development of a simple and general method for the synthesis of 3-prenyl-3-hydroxy-2-oxindoles via a one-step procedure featuring facile operation and

readily available starting materials will be highly desirable.

Scheme 1. Methods for the Preparation of 3-Prenyl-3-hydroxy-2-oxindoles



one-step preparation of 3-prenyl-3-hydroxy-2-oxindoles using cheap and readily available reagents with a broader substrate scope

In the recent past, our research group was interested in the development of methodologies towards simple and efficient regioselective prenylation using prenylzinc as the allyl metal reagent for the synthesis of various α-prenylated compounds[7] and their applications.[8] As a logical extension of our previous work and to explore the use of prenylzinc in the preparation of structurally interesting compounds that may otherwise be inaccessible, we report herein a powerful zinc-mediated prenylation reaction that allows direct access to 3-prenyl-3-hydroxy-2-oxindoles from simple and commercially available stating materials (Scheme 1c). This method has several significant advantages. First, it provides a straightforward route to these structurally interesting molecules in a single step, which represents high synthetic efficiency. Second, the reaction shows a broader substrate scope,

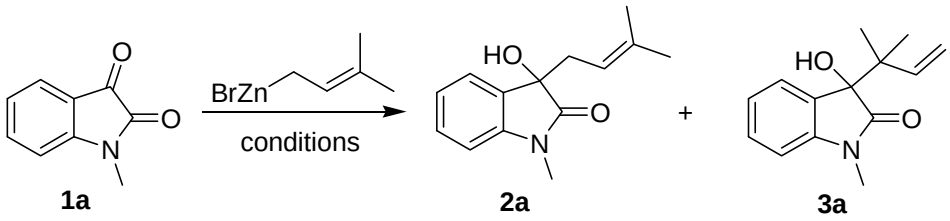
tolerating different types of substituted isatins. Third, isatins, prenyl bromide, and zinc as well as *N*,*N*-dimethylformamide (DMF) are all cheap and readily available chemicals, which brings great efficiency and convenience for the construction of the corresponding compound library. Fourth, a Bn-protecting group at the N1 position is necessary for oxindoles in Scheme 1a. For the synthetic method reported in this paper, a Bn-protecting group (or any group) is unnecessary. This is a practical advantage as it is well known that removal of such a protecting group (especially late in a multi-step synthetic effort) may prove to be a challenge in reality and that many oxindole-containing natural products do not carry a protecting group at N1.[9]

RESULTS AND DISCUSSION

Exposure of 1-methyl isatin **1a** as a model substrate to the previously reported reaction conditions[7a] that involve heating the reaction mixture to 120 °C in hexamethylphosphoramide (HMPA) resulted in the formation of the desired product **2a** in excellent yield (Table 1, entry 1). Under the previous conditions, a high yield of **2a** was attained, but the carcinogenic solvent HMPA was employed. The use of hazardous and toxic solvents in chemical laboratories is considered a very important problem for the health and safety of chemists. Furthermore, the solvent is the major source of waste in a chemical reaction, therefore, the replacement of toxic solvents with greener alternatives is a crucial point in designing environmentally improved methods toward functionalized molecules. Thus, other polar aprotic solvents including 1,3-dimethyl-2-imidazolidinone (DMI) (entry 2), tetramethylurea (TMU) (entry 3), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)pyrimidinone (DMPU) (entry 4), and

DMF (entry 5) were evaluated, and DMI and DMF were proven to be optimal, affording **2a** in 93% and 92% yields, respectively. Compared with DMI, which is relatively expensive and can be difficult to process due to its high boiling point (222 °C), DMF has obvious economic and operational attractiveness. Consequently, DMF was chosen as the optimal solvent for the reaction. We also noticed that a temperature of 120 °C was necessary to achieve the highly α-regioselective result. When the reaction temperature was decreased from 120 °C to 110 °C, the yield of the desired product **2a** was reduced to 69% and was accompanied by 15% of γ-adduct **3a** (entry 6). When the temperature was decreased to 80 °C, the γ-isomer was almost exclusively formed (entry 7). An attempt to conduct the reaction for a shorter reaction time gave a decreased yield of **2a** as well as a trace amount of **3a** (entry 8). Therefore, we decided to perform the subsequent reactions of isatins and prenylzinc at 120 °C in DMF for 8 h.

Table 1. Optimization of the Reaction Conditions[a]



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

entry	solvent	T (°C)	t (*h*)	**2a** (%)[b]	**3a** (%)[b]
1	HMPA	120	8	95	0
2	DMI	120	8	93	0
3	TMU	120	8	52	0
4	DMPU	120	8	67	0
5	DMF	120	8	92	0
6	DMF	110	8	69	15

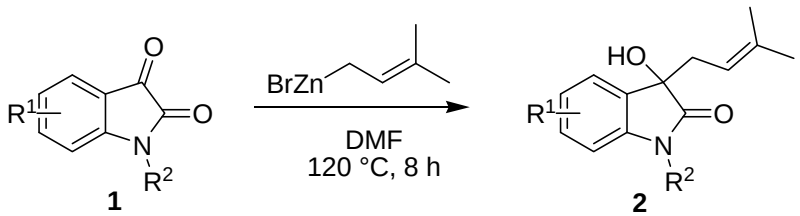
7	THF/DMF	80	8	trace	80
8	DMF	120	6	84	trace

[a] Reactions were performed with **1a** (0.5 mmol), prenyl bromide (1.0 mmol), and zinc (1.5 mmol). [b] Isolated yield.

With the optimal conditions in hand, the reaction scope was examined by using various isatins (Table 2). Initial investigation of the scope of the reaction was focused on varying the substituents on the phenyl ring of isatins. Pleasingly, the reaction tolerated well all the *N*-methylisatin derivatives with either an electron-donating or an electron-withdrawing group, giving the corresponding α-prenylated products in good to excellent yields (entries 1-5). For instance, *N*-methylisatin substrates with a methyl (**1b**) or a methoxy group (**1c**) at C-5 position led to the corresponding products **2b** and **2c** in 85% and 90% yields, respectively (entries 1 and 2). Similarly, 5-bromo-*N*-methylisatin worked equally well (entry 3). More importantly, the conditions showed noteworthy tolerance to the nitro group, albeit with a decreased yield (entry 4). In addition, we assessed the influence of a bromo group at the C-4 position of *N*-methylisatin. Despite the possible steric interaction, the reaction of **1f** proceeded smoothly to afford **2f** in 75% yield (entry 5). Further exploration into different *N*-protective groups reveals that various groups such as ethyl, allyl, and benzyl were appropriate for the reaction. For example, when the *N*-methyl protective group at the isatin framework (**1a**) was changed into an *N*-ethyl (**1g**), *N*-allyl (**1i**), or *N*-benzyl groups (**1m**), the corresponding isatins were smoothly converted into the 3-prenyl-3-hydroxy-2-oxindoles **2g**, **2i**, and **2m** in 81%, 90%, and 85% yields, respectively (entries 6, 8, and 12). Moreover, almost all isatins with

N-ethyl groups (**1g-h**), *N*-allyl groups (**1i-l**) and *N*-benzyl groups (**1m-o**) gave the desired products in excellent yields (entries 6-14) with the exception of adducts **2o** containing a nitro group (entry 14) for which the isolated yields were somewhat lower but still acceptable. It is noteworthy that the *N*-unprotected isatins **1p-w** were also suitable reaction partners for this regioselective prenylation and afforded the corresponding α-products **2p-w** with good yields (entries 15-22). This is particularly advantageous because the introduction and removal of protective groups imposes extra labor on the synthesis of target compounds. These results show that the reaction is quite general and the variation of the protective group on the *N* atom or substituents on the phenyl ring of isatins have no significant influence on the reaction efficiency. This methodology thus provides a practical and efficient means of realizing the rapid introduction of an α-prenyl moiety to the C-3 position of isatins. All the products were identified through NMR and HRMS. The structure of **2p** was further confirmed by X-ray crystallography (see the Supporting Information).

Table 2. Formation of 3-Prenyl-3-hydroxy-2-oxindoles from Various Isatins 1 under the Zinc-Mediated Prenylation Conditions



1 **2**

entry	**1**	R^1, R^2	**2**	yield (%)[a]	α/γ[b]
1	**1b**	5-CH_3, CH_3	**2b**	85	> 95:5
2	**1c**	5-OCH_3, CH_3	**2c**	90	> 95:5
3	**1d**	5-Br, CH_3	**2d**	84	> 95:5

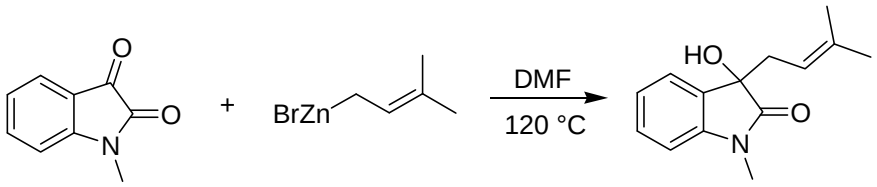
4	**1e**	5-NO_2, CH_3	**2e**	60	> 95:5
5	**1f**	4-Br, CH_3	**2f**	75	> 95:5
6	**1g**	H, C_2H_5	**2g**	81	> 95:5
7	**1h**	5-CH_3, C_2H_5	**2h**	92	> 95:5
8	**1i**	H, allyl	**2i**	90	> 95:5
9	**1j**	5-CH_3, allyl	**2j**	91	> 95:5
10	**1k**	5-OCH_3, allyl	**2k**	85	> 95:5
11	**1l**	5-Br, allyl	**2l**	98	> 95:5
12	**1m**	H, 4-$FC_6H_4CH_2$	**2m**	85	> 95:5
13	**1n**	H, 4-$BrC_6H_4CH_2$	**2n**	89	> 95:5
14	**1o**	H, 4-$NO_2C_6H_4CH_2$	**2o**	53	> 95:5
15	**1p**	H, H	**2p**	83	> 95:5
16	**1q**	5-CH_3, H	**2q**	80	> 95:5
17	**1r**	5-OCH_3, H	**2r**	71	> 95:5
18	**1s**	5-F, H	**2s**	62	> 95:5
19	**1t**	5-Br, H	**2t**	73	> 95:5
20	**1u**	5-NO_2, H	**2u**	55	> 95:5
21	**1v**	4-Cl, H	**2v**	72	> 95:5
22	**1w**	4-Br, H	**2w**	82	> 95:5

[a] Isolated yield. [b] Determined by NMR.

To demonstrate the practicality of this protocol, a gram-scale synthesis of **2a** was carried

out under the standard conditions. As shown in Scheme 2, when 1.61 g of **1a** was utilized, 1.86 g of product **2a** was obtained in 81% yield without significant loss of efficiency (small scale 92%, entry 5 in Table 1). Thus, this simple, one-step protocol could be extended as a practical and efficient method to prepare various potentially bioactive 3-prenyl-3-hydroxy-2-oxindoles. The straightforward one-step process constitutes an important practical feature of this method.

Scheme 2. Gram-Scale α-Prenylation of Isatin 1a



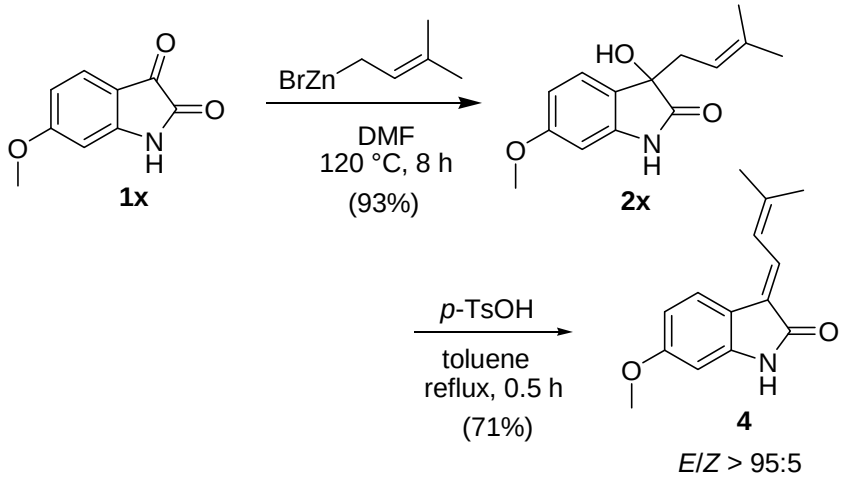
1a 1.61 g **2a** 1.86 g, 81%

The synthesis of natural products constitutes one of the most demanding tests of the viability of a new synthetic methodology. Therefore, a synthesis of soulieotine **4** was undertaken in order to further test the viability of our zinc-mediated prenylation procedure as an entry into some natural products.

Soulieotine **4** is an alkaloid isolated from the rhizomes of *Souliea vaginata*, a widely distributed plant in China used as an anti-inflammatory analgesic.[9d] Taylor and coworkers described the first synthesis of **4** by starting from 2-bromo-5-methoxybenzenamine via a four-step procedure in an overall yield of 22%.[10] More recently, Curti and coworkers have synthesized soulieotine through a condensation of 6-methoxyoxindole with 3-methyl-2-butenal in 50% yield.[11] In contrast, using our novel method, soulieotine **4** can be obtained via **2x**, prepared from commercially available 6-methoxyisatin **1x**, in two steps with

an overall yield of 66% (Scheme 3). More importantly, our procedure is highly stereoselective to produce almost exclusively *E* geometry (soulieotine). This is particularly advantageous because it is not always an easy task to prepare certain natural products with specific geometry. For example, Taylor's procedure resulted in the formation of a mixture of soulieotine (*E* geometry) and its *Z* isomer in a 2:1 ratio, although they could be separated by chromatography.[10] Curti's procedure yielded a 3:1 (*E/Z*) mixture of soulienotine.[11] This result thus highlights the usefulness of our procedure for synthesis of oxindole-containing natural products.

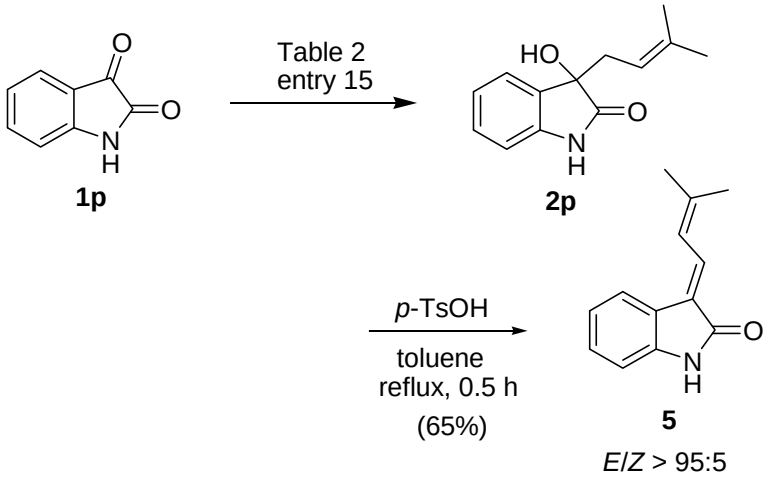
Scheme 3. Synthesis of Soulieotine via the Zinc-mediated Prenylation of 6-Methoxyisatin



Encouraged by the efficiency and high stereoselectivity observed in the synthesis of soulieotine, we sought to examine the effects of this chemistry with respect to other oxindole-containing natural products. (*E*)-3-(3-Methyl-2-butenylidene)-2-indolinone **5** was isolated from the rhizomes of *Cimicifuga foetida*, a traditional Chinese medicine "Shengma".[12] It has in the past been synthesized through Wittig reaction of isatin with γ,γ-dimethylallylphosphonium bromide via a short route.[13] Unfortunately, the practical use of

this route is limited by low yield (12%) and low stereoselectivity (*E*/*Z* = 2:1) in the Wittig reaction. In our laboratory, zinc-mediated prenylation of isatin **1p** followed by dehydration of **2p** provided a 54% overall yield of (*E*)-3-(3-methyl-2-butenylidene)-2-indolinone **5** (Scheme 4). No stereoisomer was found in the reaction product, thus demonstrating the stereospecific character of the process.

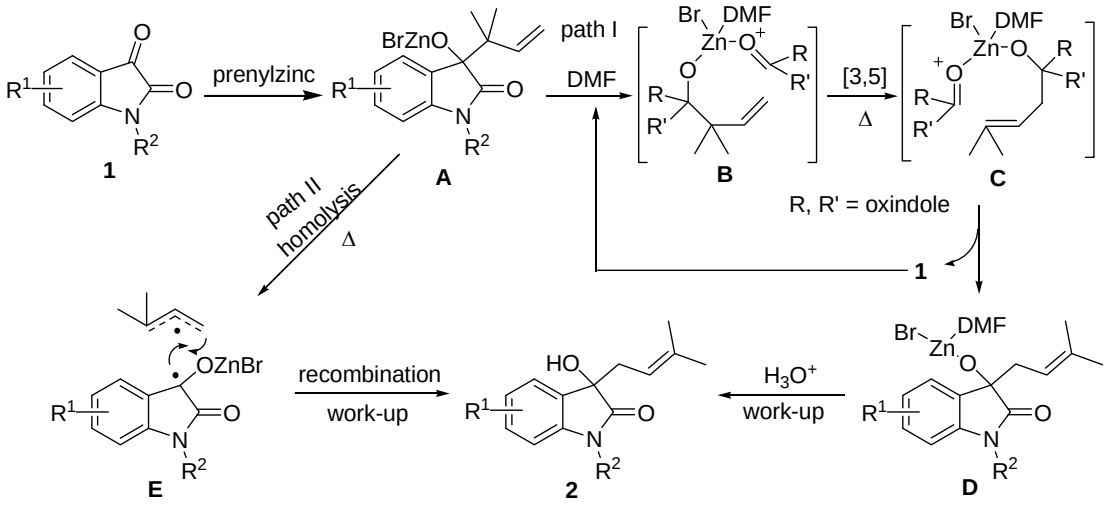
Scheme 4. Synthesis of (*E*)-3-(3-Methyl-2-butenylidene)-2-indolinone



On the basis of the experimental results and previous reports,[4b,7a] two plausible pathways for this one-step method to generate 3-prenyl-3-hydroxy-2-oxindoles were proposed as shown in Scheme 5. Both pathway I and patheway II are initiated by the nucleophilic attack of the γ-carbon of prenylzinc at 3-carbonyl of isatin to yield the zinc alcoholate **A** via a six-membered cyclic transition state (TS) analogous to that reported previously.[14] Then, in path I, DMF acts as a Lewis base interacting with the zinc atom of initially formed zinc alcoholate **A**[15] and the resulting intermediate further coordinates the isatin, which results in the formation of **B**. Subsequently, a metallo[3,5]-sigmatropic shift at an elevated temperature via a eight-membered TS occurs to generate **C**. Finally, elimination of parent isatin from **C**

could produce intermediate **D**, which could convert to the target product **2** after work-up. Alternatively, at high temperature, the thermolysis of zinc alcoholate **A** could also occur leading to the homolytic cleavage of C3-reverse prenyl σ bond to afford the prenyl radical intermediate and a carbon radical as shown in intermediate **E**. Subsequent recombination of these two radicals and final work-up would furnish the α-adduct **2** (path II).

Scheme 5. Two Potential Mechanistic Pathways

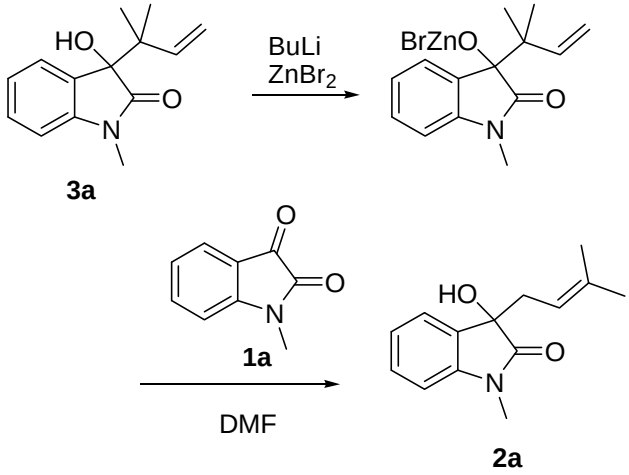


To obtain mechanistic insight, **1p** was treated with hydroquinone or 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) under the standard conditions. It was observed that the addition of the radical-trapping reagents did not inhibit the reaction and **2p** was obtained in 85% and 81% yields, respectively. These results indicate that the radical process might not be involved in the regioselective prenylation (path II) (See the Supporting Information).

For verification of the path I, an experiment involving the reaction of zinc alcoholate A with *N*-methylisatin **1a** was carried out. 3-γ-Prenyl-3-hydroxy-2-oxindoles **3a** was first transformed to its zinc alkoxide in the presence of BuLi and zinc bromide. Then, the zinc

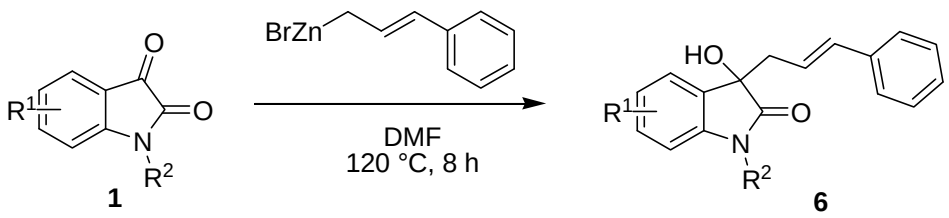
alkoxide was treated with *N*-methylisatin **1a** in DMF in 120 °C, and after 7 h, the α-product **2a** was obtained in 85% yield (Scheme 6). Based on the above observations, we consider that it is possible that the reaction proceeded via the former mechanism.

Scheme 6. Reaction of Zinc Alcoholate and *N*-Methylisatin



Due to the above success, other 3-substituted allylmetal reagents, such as cinnamylzinc bromide, were also investigated in the reaction with isatins. As clearly shown in Table 3, it was also found that cinnamyl bromide worked well for various isatins bearing different substituents on the phenyl ring of isatins including electron-donating (methyl, entries 1 and 3) and electron-withdrawing (bromo, entries 2 and 4) groups as well as different *N*-protective groups such as methyl (entries 1 and 2), ethyl (entry 3), allyl (entry 4), and benzyl groups (entry 5) under the standard reaction conditions to afford the corresponding α-products in good yields.

Table 3. α-Selective Allylation of Isatins 1 Using Cinnamyl Bromide as the Allylation Reagent



entry	**1**	R^1, R^2	**6**	yield (%)[a]	α/γ[b]
1	**1b**	5-CH_3, CH_3	**6b**	80	> 95:5
2	**1d**	5-Br, CH_3	**6d**	72	> 95:5
3	**1h**	5-CH_3, C_2H_5	**6h**	77	> 95:5
4	**1l**	5-Br, allyl	**6l**	75	> 95:5
5	**1n**	H, 4-$BrC_6H_4CH_2$	**6n**	84	> 95:5

[a] Isolated yield. [b] Determined by NMR.

CONCLUSIONS

In conclusion, we show that 3-prenyl-3-hydroxy-2-oxindoles can be directly prepared from isatins and prenyl bromide by means of a convenient and efficient procedure based on a zinc-mediated highly α-regioselective prenylation. A wide range of isatins were tolerated in this method, and all the α-prenylated products could be obtained in good to excellent yields. Due to the easy accessibility and low cost of the reactants and reagents and the simple manipulations of the reaction, this method is very practical and has good economical and environmental advantages. Furthermore, the utility of this reaction has been demonstrated via the syntheses of some natural products and this procedure provides an efficient and stereoselective route to those natural products. Thus, the reaction, obviously, offers significant advantages over the previous protocols for the synthesis of 3-prenyl-3-hydroxy-2-oxindoles

and some related natural products. Moreover, the importance of these compounds would render this protocol attractive for both synthetic and medicinal chemistry.

EXPERIMENTAL SECTION

General Methods Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz in $CDCl_3$ or DMSO-d_6 with chemical shift (δ) given in ppm relative to TMS as internal standard. Multiplicities were indicated, s (singlet), d (doublet), t (triplet), m (multiplet), dd (doublet of doublets), etc; coupling constant (*J*) were given in Hertz (Hz). High resolution mass spectra (HRMS) were recorded using atmospheric pressure chemical ionization (APCI) or electrospray ionization (ESI) and time-of-flight (TOF) mass analysis.

General Procedure for the Synthesis of 2 and 6. Allyl bromide (1.0 mmol) was added into a suspension of activated zinc powder (1.5 mmol) in dry THF (10 ml); the reaction mixture was stirred for 1 h at room temperature (reflux 1 h for cinnamyl bromide). Filtered the solution through a Schlenk filter and kept under N_2 for the following reaction. A solution of isatins **1** (0.5 mmol) in dry THF (3 ml) was added to the solution of allylzinc bromide prepared above. Then DMF (1.5 ml) was added to the reaction mixture, followed by removal of initial reaction solvent (THF). The mixture was heated to 120 °C under N_2 for 8 h. Analysis of the final reaction mixtures by ^{1}H NMR showed that no γ-products were observed. After cooling to room temperature, the residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 3/1) to afford the α-product **2** and **6**.

3-Hydroxy-1-methyl-3-(3-methylbut-2-enyl)indolin-2-one (2a). White solid (106 mg,

92% yield); mp 101-103 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42-7.28 (m, 2H), 7.13-7.04 (m, 1H), 6.82 (d, *J* = 7.8 Hz, 1H), 5.03 (t, *J* = 7.6 Hz, 1H), 3.18 (s, 3H), 3.00 (s, 1H), 2.63 (d, *J* = 7.7 Hz, 2H), 1.65 (s, 3H), 1.54 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.2, 143.4, 137.4, 130.2, 129.6, 124.1, 123.1, 115.9, 108.4, 76.3, 37.5, 26.3, 26.1, 18.1. HRMS (APCI): m/z calcd for $C_{14}H_{18}NO_2$ $[M + H]^+$: 232.1338; found: 232.1341.

3-Hydroxy-1,5-dimethyl-3-(3-methylbut-2-enyl)indolin-2-one (2b). White solid (105 mg, 85% yield); mp 142-144 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.20 (s, 1H), 7.11-7.09 (m, 1H), 6.70 (d, *J* = 7.9 Hz, 1H), 5.08-4.93 (m, 1H), 3.17 (s, 1H), 3.15(s, 3H), 2.68-2.55 (m, 2H), 2.34 (s, 3H), 1.65 (s, 3H), 1.55 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.2, 141.0, 137.2, 132.6, 130.3, 129.7, 124.9, 116.0, 108.1, 76.4, 37.5, 26.3, 26.1, 21.2, 18.1. HRMS (APCI): m/z calcd for $C_{15}H_{20}NO_2$ $[M + H]^+$: 246.1494; found: 246.1524.

3-Hydroxy-5-methoxy-1-methyl-3-(3-methylbut-2-enyl)indolin-2-one (2c). Pale yellow solid (117 mg, 90% yield); mp 148-150 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.01 (d, *J* = 2.6 Hz, 1H), 6.84 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.72 (d, *J* = 8.5 Hz, 1H), 5.04-5.01 (m, 1H), 3.80 (s, 3H), 3.15-3.13 (m, 4H), 2.62 (d, *J* = 7.6 Hz, 2H), 1.66 (s, 3H), 1.54 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.0, 156.4, 137.3, 136.8, 131.5, 116.0, 114.2, 111.3, 108.8, 76.7, 56.0, 37.5, 26.4, 26.1, 18.2. HRMS (APCI): m/z calcd for $C_{15}H_{20}NO_3$ $[M + H]^+$: 262.1443; found: 262.1441.

5-Bromo-3-hydroxy-1-methyl-3-(3-methylbut-2-enyl)indolin-2-one (2d). White solid (130 mg, 84% yield); mp 155-157 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.54-7.39 (m, 2H), 6.70 (d, *J* = 8.2 Hz, 1H), 5.05-5.00 (m, 1H), 3.16 (s, 3H), 2.82 (s, 1H), 2.60 (d, *J* = 7.7 Hz, 2H), 1.68 (s, 3H), 1.56 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.6, 142.5, 138.2, 132.5, 132.2,

127.5, 115.8, 115.3, 109.9, 76.2, 37.5, 26.4, 26.1, 18.2. HRMS (APCI): m/z calcd for $C_{14}H_{17}BrNO_2$ $[M + H]^+$: 310.0443; found: 310.0460.

3-Hydroxy-1-methyl-3-(3-methylbut-2-enyl)-5-nitroindolin-2-one (2e). Yellow solid (83 mg, 60% yield); mp 154-156 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.25 (dd, J = 8.7, 2.4 Hz, 1H), 8.09 (d, J = 2.4 Hz, 1H), 7.18 (d, J = 8.7 Hz, 1H), 4.77-4.76 (m, 1H), 3.13 (s, 3H), 2.69-2.47 (m, 2H), 1.49 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 178.2, 149.7, 143.0, 136.0, 132.7, 126.7, 119.5, 116.6, 109.1, 75.4, 36.6, 26.7, 26.0, 18.2. Negative ion HRMS (ESI): m/z calcd for $C_{14}H_{15}N_2O_4$ $[M - H]^-$: 275.1032; found: 275.1018.

4-Bromo-3-hydroxy-1-methyl-3-(3-methylbut-2-enyl)indolin-2-one (2f). Pale yellow solid (116 mg, 75% yield); mp 136-138 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.22-7.07 (m, 2H), 6.91 (dd, J = 7.6, 0.9 Hz, 1H), 4.40-4.36 (m, 1H), 3.00 (s, 3H), 2.95 (dd, J = 13.6, 7.5 Hz, 1H), 2.52 (dd, J = 13.6, 7.5 Hz, 1H), 1.40 (s, 3H), 1.36 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ: 177.1, 146.0, 135.6, 131.3, 128.9, 126.6, 118.9, 116.5, 108.1, 77.6, 34.2, 26.3, 26.0, 18.3. Negative ion HRMS (ESI): m/z calcd for $C_{14}H_{15}BrNO_2$ $[M - H]^-$: 308.0286; found: 308.0309.

1-Ethyl-3-hydroxy-3-(3-methylbut-2-enyl)indolin-2-one (2g). White solid (99 mg, 81% yield); mp 110-113 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39 (dd, J = 7.3, 0.8 Hz, 1H), 7.36-7.23 (m, 1H), 7.09-7.05 (m, 1H), 6.82 (d, J = 7.8 Hz, 1H), 4.93-4.89 (m, 1H), 3.87-3.78 (m, 1H), 3.65-3.56 (m, 1H), 3.19 (s, 1H), 2.79-2.53 (m, 2H), 1.60 (s, 3H), 1.52 (s, 3H), 1.22 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.9, 142.5, 137.0, 130.5, 129.5, 124.2, 122.86, 116.0, 108.4, 76.4, 37.7, 34.7, 26.0, 18.1, 12.7. HRMS (APCI): m/z calcd for $C_{15}H_{20}NO_2$ $[M + H]^+$: 246.1494; found: 246.1505.

1-Ethyl-3-hydroxy-5-methyl-3-(3-methylbut-2-enyl)indolin-2-one (2h). Pale yellow

solid (119 mg, 92% yield); mp 150-153 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.21 (d, *J* = 1.1 Hz, 1H), 7.10-7.08 (m, 1H), 6.71 (d, *J* = 7.9 Hz, 1H), 4.91-4.89 (m, 1H), 3.84-3.75 (m, 1H), 3.62-3.53 (m, 1H), 3.29-3.26 (m, 1H), 2.72-2.58 (m, 2H), 2.34 (s, 3H), 1.60 (s, 3H), 1.53 (s, 3H), 1.20 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.8, 140.1, 136.9, 132.4, 130.5, 129.7, 125.0, 116.1, 108.2, 76.5, 37.7, 34.7, 26.0, 21.2, 18.1, 12.70. HRMS (APCI): m/z calcd for $C_{16}H_{22}NO_2$ $[M + H]^+$: 260.1651; found: 260.1658.

1-Allyl-3-hydroxy-3-(3-methylbut-2-enyl)indolin-2-one (2i). White solid (116 mg, 90% yield); mp 117-118 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.40 (d, *J* = 8.1 Hz, 1H), 7.30-7.26 (m, 1H), 7.10-7.06 (m, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 5.89-5.67 (m, 1H), 5.24-5.12 (m, 2H), 4.94-4.90 (m, 1H), 4.50-4.45 (m, 1H), 4.14-4.08 (m, 1H), 3.20 (s, 1H), 2.75-2.64 (m, 2H), 1.60 (s, 3H), 1.52 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.0, 142.7, 137.3, 131.2, 130.2, 129.5, 124.1, 123.0, 117.3, 116.0, 109.3, 76.5, 42.3, 37.7, 26.0, 18.1. HRMS (APCI): m/z calcd for $C_{16}H_{20}NO_2$ $[M + H]^+$: 258.1494; found: 258.1513.

1-Allyl-3-hydroxy-5-methyl-3-(3-methylbut-2-enyl)indolin-2-one (2j). Pale yellow solid (123 mg, 91% yield); mp 112-114 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.22 (d, *J* = 1.1 Hz, 1H), 7.08-7.05 (m, 1H), 6.67 (d, *J* = 7.9 Hz, 1H), 5.83-5.73 (m, 1H), 5.23-5.11 (m, 2H), 4.91-4.87 (m, 1H), 4.52-4.36 (m, 1H), 4.13-4.02 (m, 1H), 3.38 (s, 1H), 2.76-2.61 (m, 2H), 2.33 (s, 3H), 1.60 (s, 3H), 1.53 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.0, 140.3, 137.1, 132.6, 131.3, 130.18, 129.7, 124.9, 117.2, 116.1, 109.0, 76.6, 42.3, 37.7, 26.0, 21.2, 18.1. HRMS (APCI): m/z calcd for $C_{17}H_{22}NO_2$ $[M + H]^+$: 272.1651; found: 272.1677.

1-Allyl-3-hydroxy-5-methoxy-3-(3-methylbut-2-enyl)indolin-2-one (2k). Pale yellow solid (122 mg, 85% yield); mp 109-111 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.02 (d, *J* = 2.6

Hz, 1H), 6.80 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.70 (d, *J* = 8.5 Hz, 1H), 5.83-5.74 (m, 1H), 5.26-5.10 (m, 2H), 4.94-4.90 (m, 1H), 4.48-4.42 (m, 1H), 4.15-4.01 (m, 1H), 3.80 (s, 3H), 3.15 (s, 1H), 2.79-2.57 (m, 2H), 1.62 (s, 3H), 1.54 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.7, 156.3, 137.3, 136.0, 131.4, 131.4, 117.3, 116.0, 114.3, 111.1, 109.8, 76.8, 56.0, 42.4, 37.8, 26.1, 18.14. HRMS (APCI): m/z calcd for $C_{17}H_{22}NO_3$ $[M + H]^+$: 288.1600; found: 288.1619.

1-Allyl-5-bromo-3-hydroxy-3-(3-methylbut-2-enyl)indolin-2-one (2l). Pale yellow solid (164 mg, 98% yield); mp 93-94 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.51 (d, *J* = 2.0 Hz, 1H), 7.40 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.67 (d, *J* = 8.3 Hz, 1H), 5.82-5.72 (m, 1H), 5.22-5.14 (m, 2H), 4.92-4.89 (m, 1H), 4.49-4.43 (m, 1H), 4.12-4.06 (m, 1H), 3.19 (s, 1H), 2.74-2.61 (m, 2H), 1.62 (s, 3H), 1.54 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.5, 141.7, 138.0, 132.4, 132.2, 130.8, 127.5, 117.6, 115.8, 115.4, 110.8, 76.4, 42.4, 37.7, 26.1, 18.1. HRMS (APCI): m/z calcd for $C_{16}H_{19}BrNO_2$ $[M + H]^+$: 336.0599; found: 336.0583.

1-(4-Fluorobenzyl)-3-hydroxy-3-(3-methylbut-2-enyl)indolin-2-one (2m). Pale yellow solid (138 mg, 85% yield); mp 146-148 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42-7.39 (m, 1H), 7.26-7.17 (m, 3H), 7.09-7.05 (m, 1H), 7.0-6.96 (m, 2H), 6.65 (d, *J* = 7.8 Hz, 1H), 5.07 (d, *J* = 15.7 Hz, 1H), 4.89-4.85 (m, 1H), 4.59 (d, *J* = 15.7 Hz, 1H), 3.31 (s, 1H), 2.83-2.68 (m, 2H), 1.60 (s, 3H), 1.54 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.4, 162.3 (*J* = 244.6 Hz), 142.5, 137.4, 131.5, 131.4, 130.1, 129.6, 129.0, 128.9, 124.2, 123.3, 116.0 (*J* = 3.0 Hz), 115.7, 109.3, 76.5, 43.2, 37.7, 26.1, 18.2. HRMS (APCI): m/z calcd for $C_{20}H_{21}FNO_2$ $[M + H]^+$: 326.1556; found: 326.1562.

1-(4-Bromobenzyl)-3-hydroxy-3-(3-methylbut-2-enyl)indolin-2-one (2n). Pale yellow solid (171 mg, 89% yield); mp 186-188 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.44-7.40 (m, 3H),

7.22-7.18 (m, 1H), 7.13 (d, *J* = 8.4 Hz, 2H), 7.09-7.06 (m, 1H), 6.62 (d, *J* = 7.8 Hz, 1H), 5.06 (d, *J* = 15.9 Hz, 1H), 4.90-4.86 (m, 1H), 4.57 (d, *J* = 15.9 Hz, 1H), 2.99 (s, 1H), 2.82-2.68 (m, 2H), 1.62 (s, 3H), 1.56 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.2, 142.4, 137.6, 134.8, 132.1, 132.1, 130.0, 129.7, 129.0, 129.0, 124.2, 123.3, 121.7, 115.9, 109.3, 76.5, 43.3, 37.7, 26.1, 18.2. HRMS (APCI): m/z calcd for $C_{20}H_{21}BrNO_2$ $[M + H]^+$: 386.0756; found: 386.0742.

3-Hydroxy-3-(3-methylbut-2-enyl)-1-(4-nitrobenzyl)indolin-2-one (2o). Pale yellow solid (93 mg, 53% yield); mp 136-137 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.19-8.15 (m, 2H), 7.62-7.34 (m, 3H), 7.26-7.20 (m, 1H), 7.13-7.08 (m, 1H), 6.58 (d, *J* = 7.8 Hz, 1H), 5.20 (d, *J* = 16.5 Hz, 1H), 4.91-4.87 (m, 1H), 4.73 (d, *J* = 16.5 Hz, 1H), 3.17 (s, 1H), 2.87-2.69 (m, 2H), 1.64 (s, 3H), 1.56 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.4, 147.6, 143.2, 142.1, 137.8, 130.0, 129.8, 127.9, 127.9, 124.5, 124.2, 124.2, 123.7, 115.8, 109.0, 76.5, 43.3, 37.7, 26.2, 18.2. HRMS (APCI): m/z calcd for $C_{20}H_{21}N_2O_4$ $[M + H]^+$: 353.1501; found: 353.1477.

3-Hydroxy-3-(3-methylbut-2-enyl)indolin-2-one (2p). Pale yellow solid (90 mg, 83% yield); mp 144-146 ºC. This compound has been previously reported and ^{1}H and ^{13}C NMR spectral data match described.[4b] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.08 (s, 1H), 7.37 (d, *J* = 7.4 Hz, 1H), 7.28-7.23 (m, 1H), 7.06 (td, *J* = 7.6, 0.9 Hz, 1H), 6.86 (d, *J* = 7.7 Hz, 1H), 5.06-5.02 (m, 1H), 3.13 (s, 1H), 2.65 (d, *J* = 7.6 Hz, 2H), 1.65 (s, 3H), 1.55 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 180.4, 140.4, 137.6, 130.7, 129.7, 124.5, 123.1, 115.7, 110.3, 76.7, 37.4, 26.1, 18.1. HRMS (APCI): m/z calcd for $C_{13}H_{16}NO_2$ $[M + H]^+$: 218.1181; found: 218.1178.

3-Hydroxy-5-methyl-3-(3-methylbut-2-enyl)indolin-2-one (2q). Pale yellow solid (92 mg, 80% yield); mp 194-196 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.70 (s, 1H), 7.18 (s, 1H),

7.05 (d, *J* = 7.8 Hz, 1H), 6.74 (d, *J* = 7.9 Hz, 1H), 5.03 (t, *J* = 7.2 Hz, 1H), 2.93 (s, 1H), 2.76-2.50 (m, 2H), 2.33 (s, 3H), 1.66 (s, 3H), 1.62 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 179.5, 139.7, 134.5, 132.4, 130.6, 129.4, 125.1, 117.8, 109.5, 76.1, 37.0, 26.1, 21.2, 18.3. HRMS (APCI): m/z calcd for $C_{14}H_{18}NO_2$ $[M + H]^+$: 232.1338; found: 232.1333.

3-Hydroxy-5-methoxy-3-(3-methylbut-2-enyl)indolin-2-one (2r). Pale yellow solid (87 mg, 71% yield); mp 142-144 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.51 (s, 1H), 6.97 (s, 1H), 6.77 (d, *J* = 1.9 Hz, 2H), 5.03-5.0 (m, 1H), 3.78 (s, 3H), 3.66 (s, 1H), 2.64 (d, *J* = 8.6 Hz, 2H), 1.64 (s, 3H), 1.53 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 180.8, 156.2, 137.3, 133.7, 132.0, 115.8, 114.6, 111.1, 110.9, 77.5, 55.9, 37.4, 26.1, 18.1. HRMS (APCI): m/z calcd for $C_{14}H_{18}NO_3$ $[M + H]^+$: 248.1287; found: 248.1291.

5-Fluoro-3-hydroxy-3-(3-methylbut-2-enyl)indolin-2-one (2s). Pale yellow solid (72 mg, 62% yield); mp 188-190 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.12 (s, 1H), 7.02 (dd, *J* = 8.2, 2.7 Hz, 1H), 6.95-6.90 (m, 1H), 6.67 (dd, *J* = 8.4, 4.3 Hz, 1H), 4.70-4.64 (m, 1H), 2.42-2.34 (m, 2H), 1.44 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 179.47, 158.4 (*J* = 235.4 Hz), 138.3, 135.0, 134.2 (*J* = 7.4 Hz), 117.3, 115.4 (*J* = 23.1 Hz), 112.2 (*J* = 24.1 Hz), 110.5 (*J* = 7.8 Hz), 76.3, 36.8, 26.1, 18.2. Negative ion HRMS (ESI): m/z calcd for $C_{13}H_{13}FNO_2$ $[M - H]^-$: 234.0930; found: 234.0936.

5-Bromo-3-hydroxy-3-(3-methylbut-2-enyl)indolin-2-one (2t). Pale yellow solid (107 mg, 73% yield); mp 214-216 ºC. This compound has been previously reported and ^{13}C NMR spectral data match described.[4b] The proton signals were not quite superimposed with those of previously reported compound since a different solvent was used in the NMR measurement. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.25 (s, 1H), 7.41-7.21 (m, 2H), 6.67 (d, *J* = 8.1 Hz, 1H),

4.71-4.67 (m, 1H), 2.43-2.36 (m, 2H),1.54 (s, 3H), 1.43 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 179.0, 141.4, 135.2, 134.8, 131.9, 127.4, 117.2, 113.6, 111.8, 76.2, 36.8, 26.1, 18.3. HRMS (APCI): m/z calcd for $C_{13}H_{15}BrNO_2$ $[M + H]^+$: 296.0286; found: 296.0316.

3-Hydroxy-3-(3-methylbut-2-enyl)-5-nitroindolin-2-one (2u). Pale yellow solid (72 mg, 55% yield); mp 231-233 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.87 (s, 1H), 8.11 (dd, J = 8.6, 2.4 Hz, 1H), 8.03 (d, J = 2.4 Hz, 1H), 6.92 (d, J = 8.6 Hz, 1H), 4.75-4.72 (m, 1H), 2.57-2.44 (m, 2H), 1.47 (s, 3H), 1.33 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 179.8, 148.7, 142.5, 135.9, 133.3, 126.7, 120.0, 116.8, 110.1, 75.8, 36.6, 26.1, 18.2. HRMS (APCI): m/z calcd for $C_{13}H_{15}N_2O_4$ $[M + H]^+$: 263.1032; found: 263.1058.

4-Chloro-3-hydroxy-3-(3-methylbut-2-enyl)indolin-2-one (2v). Pale yellow solid (90 mg, 72% yield); mp 211-213 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.33 (s, 1H), 7.12 (t, J = 8.0 Hz, 1H), 6.85 (dd, J = 8.2, 0.8 Hz, 1H), 6.66 (dd, J = 7.7, 0.8 Hz, 1H), 4.45 (s, 1H), 2.85 (dd, J = 13.5, 7.4 Hz, 1H), 2.51 (dd, J = 13.5, 7.7 Hz, 1H), 1.40 (s, 3H), 1.38 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 178.6, 144.4, 135.4, 131.1, 130.8, 127.9, 122.8, 116.9, 108.8, 77.2, 34.4, 26.1, 18.2. Negative ion HRMS (ESI): m/z calcd for $C_{13}H_{13}ClNO_2$ $[M - H]^-$: 250.0635; found: 250.0650.

4-Bromo-3-hydroxy-3-(3-methylbut-2-enyl)indolin-2-one (2w). White solid (121 mg, 82% yield); mp 208-210 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03 (s, 1H), 7.18 (dd, J = 8.2, 0.9 Hz, 1H), 7.11 (t, J = 7.9 Hz, 1H), 6.80 (dd, J = 7.6, 0.9 Hz, 1H), 4.84-4.80 (m, 1H), 3.10-2.97 (m, 2H), 2.91 (dd, J = 13.6, 8.5 Hz, 1H), 1.60 (s, 3H), 1.59 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 178.7, 144.6, 135.3, 131.3, 129.5, 125.9, 119.2, 116.9, 109.3, 77.8, 34.2, 26.1, 18.3. HRMS (APCI): m/z calcd for $C_{13}H_{15}BrNO_2$ $[M + H]^+$: 296.0286; found:

296.0303.

3-Cinnamyl-3-hydroxy-1,5-dimethylindolin-2-one (6b). Yellow oil (117 mg, 80% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32-7.18 (m, 6H), 7.13 (d, *J* = 7.9 Hz, 1H), 6.71 (d, *J* = 7.9 Hz, 1H), 6.46 (d, *J* = 15.9 Hz, 1H), 6.20-5.93 (m, 1H), 3.15 (s, 3H), 3.03-2.76 (m, 2H), 2.77-2.68 (m, 1H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.7, 141.0, 137.2, 135.3, 132.9, 130.1, 129.8, 128.6, 128.6, 127.6, 126.4, 126.4, 125.0, 122.1, 108.4, 76.3, 42.4, 26.4, 21.3. HRMS (APCI): m/z calcd for $C_{19}H_{20}NO_2$ $[M + H]^+$: 294.1494; found: 294.1480.

5-Bromo-3-cinnamyl-3-hydroxy-1-methylindolin-2-one (6d). Yellow oil (129 mg, 72% yield); ^{1}H NMR (400 MHz, CDCl3) δ: 7.53 (d, *J* = 1.9 Hz, 1H), 7.43 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.27-7.12 (m, 5H), 6.66 (d, *J* = 8.3 Hz, 1H), 6.41 (d, *J* = 15.8 Hz, 1H), 6.12-5.78 (m, 1H), 4.12 (s, 1H), 3.09 (s, 3H), 2.89-2.84 (m, 1H), 2.80-2.66 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.8, 177.7, 142.2, 136.9, 135.6, 132.5, 132.1, 132.0, 128.6, 127.6, 127.5, 126.4, 121.3, 116.0, 110.1, 76.5, 42.1, 26.4. HRMS (APCI): m/z calcd for $C_{18}H_{17}BrNO_2$ $[M + H]^+$: 358.0443; found: 358.0458.

3-Cinnamyl-1-ethyl-3-hydroxy-5-methylindolin-2-one (6h). White solid (119 mg, 77% yield); mp 137-139 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.29-7.22 (m, 5H), 7.19 (d, *J* = 8.6 Hz, 1H), 7.11 (d, *J* = 8.8 Hz, 1H), 6.72 (d, *J* = 7.9 Hz, 1H), 6.43 (d, *J* = 15.8 Hz, 1H), 6.04-5.82 (m, 1H), 3.81-3.72 (m, 1H), 3.64-3.55 (m, 1H), 3.04 (dd, *J* = 15.3, 6.0 Hz, 1H), 2.94-2.69 (m, 2H), 2.35 (s, 3H), 1.15 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.4, 140.0, 137.2, 135.2, 132.7, 130.0, 130.0, 128.6, 128.6, 127.5, 126.4, 126.4, 125.2, 122.1, 108.5, 76.5, 42.5, 34.8, 21.2, 12.8. HRMS (APCI): m/z calcd for $C_{20}H_{22}NO_2$ $[M + H]^+$: 308.1651; found: 308.1671.

1-Allyl-5-bromo-3-cinnamyl-3-hydroxyindolin-2-one (6l). White solid (143 mg, 75% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.56 (d, *J* = 1.8 Hz, 1H), 7.41 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.28-7.17 (m, 5H), 6.67 (d, *J* = 8.3 Hz, 1H), 6.44 (d, *J* = 15.8 Hz, 1H), 6.04-5.81 (m, 1H), 5.72-5.62 (m, 1H), 5.08 (dd, *J* = 18.8, 13.9 Hz, 2H), 4.42-4.36 (m, 1H), 4.10 (dd, *J* = 16.9, 4.8 Hz, 1H), 3.40 (s, 1H), 2.92-2.78 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.2, 141.6, 136.8, 135.9, 132.6, 131.8, 130.7 128.6, 128.6, 127.8, 127.6, 126.4, 126.4, 121.1, 118.1, 116.0, 111.1, 76.5, 42.5, 42.5.HRMS (APCI): m/z calcd for $C_{20}H_{19}BrNO_2$ $[M + H]^+$: 384.0599; found: 384.0569.

1-(4-Bromobenzyl)-3-cinnamyl-3-hydroxyindolin-2-one (6n). White solid (182 mg, 84% yield); mp 179-181 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.46 (d, *J* = 7.2 Hz, 1H), 7.27-7.22 (m, 4H), 7.24-7.13 (m, 3H), 7.11 (t, *J* = 7.5 Hz, 1H), 7.05-6.99 (m, 3H), 6.61 (d, *J* = 7.8 Hz, 1H), 6.45 (d, *J* = 15.8 Hz, 1H), 5.94-5.71 (m, 1H), 5.09 (d, *J* = 15.9 Hz, 1H), 4.47 (d, *J* = 15.9 Hz, 1H), 3.36 (s, 1H), 3.07-2.84 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.9, 142.4, 136.8, 135.6, 134.3, 132.0, 132.0, 130.0, 129.6, 128.9, 128.9, 128.7, 128.7, 127.9, 126.5, 126.5, 124.3, 123.6, 121.6, 121.6, 109.5, 76.6, 43.5, 42.5. HRMS (APCI): m/z calcd for $C_{24}H_{21}BrNO_2$ $[M + H]^+$: 434.0756; found: 434.0733.

Synthesis of soulieotine 4. Compound **2x** (100 mg, 0.4 mmol) was dissolved in toluene (5.0 mL). Then *p*-toluenesulfonic acid (0.2 equiv) was added. The mixture was heated to reflux for 0.5 h. After being cooled to room temperature, the solvent was evaporated in vacuum. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 3/1) to afford **4** (66 mg, 71% yield) as a yellow solid. The product was identified as a *E* geometry by a typical trans coupling constant of 12.6 Hz for the double bond. Mp 201-203

ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.72 (br s, 1H), 7.54 (d, *J* = 8.5 Hz, 1H), 7.45 (d, *J* = 12.6 Hz, 1H), 6.73 (ddd, *J* = 12.6, 2.4, 1.2 Hz, 1H), 6.55 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.45 (d, *J* = 2.3 Hz, 1H), 3.83 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.2, 160.4, 150.7, 142.0, 130.2, 124.8, 122.9, 121.5, 116.5, 107.2, 96.8, 55.7, 27.6, 19.1. HRMS (ESI): m/z calcd for $C_{14}H_{16}NO_2$ $[M + H]^+$: 230.1175; found: 230.1134. All spectral data is consistent with that previously reported. [9d, 10]

Synthesis of (*E*)-3-(3-methyl-2-butenylidene)-2-indolinone 5. (*E*)-3-(3-methyl-2-butenylidene)-2-indolinone **5** was prepared according to the procedure for the synthesis soulieotine **4** from commercially available isatin **1p** as the starting material to afford **5** as a yellow solid. The product was identified as a *E* geometry by a typical trans coupling constant of 12.8 Hz for the double bond. Mp 196-198 ºC. (lit.[13] mp 200-203 ºC) ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.88 (brs, 1H), 7.64 (d, *J* = 7.6 Hz, 1H), 7.60 (d, *J* = 12.8 Hz, 1H), 7.19 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.03 (dt, *J* = 7.6, 1.0 Hz, 1H), 6.87 (d, *J* = 7.6 Hz, 1H), 6.78 (ddd, *J* = 12.8, 2.4, 1.2 Hz, 1H), 2.07 (s, 3H), 2.06 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.6, 152.4, 140.5, 132.9, 128.4, 123.8, 123.4, 123.1, 122.1, 121.6, 109.9, 27.7, 19.2. HRMS (ESI): m/z calcd for $C_{13}H_{14}NO$ $[M + H]^+$: 200.1070; found: 200.1036.

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Supporting Information Available Copies of ^{1}H and ^{13}C NMR spectra for all prepared products and X-ray crystal structure of **2p** and crystal data of **2p** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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