JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Metal-Free Regioselective Hypervalent Iodine-Mediated C-2 and C-3 Difunctionalization of *N*-Substituted Indoles

Dongdong Xu,[‡,∥,⊥] Wen-Wu Sun,[†,⊥] Yanli Xie,[‡] Ji-Kai Liu,[*,†] Bin Liu,[*,‡] Yingbi Zhou,[*,‡] and Bin Wu[*,†,§]

[†]School of Pharmaceutical Sciences, South-Central University for Nationalities, Wuhan 430074, China

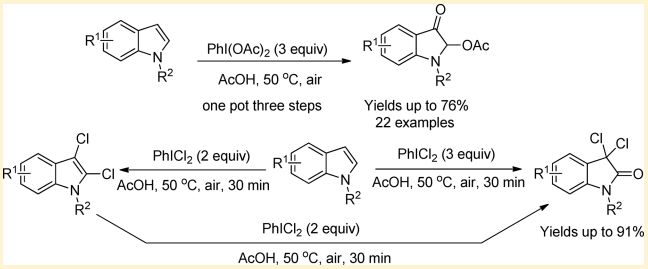
[‡]Cardiovascular Research Center, Shantou University Medical College, 22 Xin-Ling Rd, Shantou, 515041, China

[§]State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences, Kunming 650201, China

[∥]PET/CT Center, The First People's Hospital of Yunnan Province, 157 Jinbi Road, Kunming, 650032, China

Supporting Information

ABSTRACT: Mild, metal-free, highly regioselective hypervalent-iodine mediated C-2 acetoxylation and C-3 oxidations of *N*-substituted indoles with (diacetoxyiodo)benzene [PhI(OAc)$_2$] have been reported. The reaction involves three cascade steps. The quantity of PhI(OAc)$_2$ employed in this reaction plays a key role in the outcome of three types of products (**2a**−**4a**). Furthermore, the mild and highly regioselective C-2 oxidation and C-3 dichlorination of *N*-substituted indoles with PhICl$_2$ have been developed. Extensive studies including in situ IR techniques and H_2O^{18}-labeling experiment were performed to gain insight into the possible reaction mechanism.



INTRODUCTION

Indole and oxindole moieties are key components that are widely present in many pharmaceuticals and biologically active natural products. For example, the core structures of Sumatriptan, zafirlukast and ziprasidone, which are drugs used for migraine treatment, an oral leukotriene receptor antagonist for the treatment of asthma, and an atypical antipsychotic in clinical use for both schizophrenia and bipolar disorder, respectively, possess indole and oxindole skeletons.[1] The chemistry of indoles has been the focus of extensive research involving the preparation, transformation and application of indole-related complex natural product syntheses.[2] In the past few decades, significant advances have been made in transition-metal catalyzed C−H bond activation of indoles to construct C−C and C−O bonds at the C-2 or C-3 position.[3−8] However, despite the important progress in this field, precious metal salts and, in some cases, explosive oxidants are required. Moreover, the site selectivity of the C-2 position versus the C-3 position of indoles is still an issue. Therefore, the development of a mild, highly efficient and regioselective direct functionalization of indoles without transition metals is highly desirable.[9]

Hypervalent iodine compounds, which are used as mild, nontoxic, highly selective and environmentally benign oxidation reagents, have been widely employed in organic synthesis. For example, (diacetoxyiodo)benzene [PhI(OAc)$_2$] is commonly employed for the oxidation of alcohols and alkenes as well as in the α-functionalization of carbonyl compounds.[10] A transition metal-free oxidation reaction with hypervalent iodine reagents offers an alternative, straightforward and efficient synthetic protocol for functionalization of the indoles. Lei[11] and Punji[12] independently reported the C-2,3 diacetoxylation and C-3 acetoxylation of *N*-substituted indoles with PhI(OAc)$_2$ as an oxidant in acetic acid. Huang[13] described the C-3 acetoxylation of free NH-indoles with PhI(OAc)$_2$ and base. Herein, we report the metal-free highly regioselective C-2 acetoxylation and C-3 oxidation of *N*-substituted indoles with PhI(OAc)$_2$. Moreover, mild and highly regioselective C-2 oxidation and C-3 dichlorination of *N*-substituted indoles with PhICl$_2$ have been developed. Extensive studies involving in situ IR techniques and H_2O^{18}-labeling experiment have been performed to gain insight into the possible reaction mechanism.

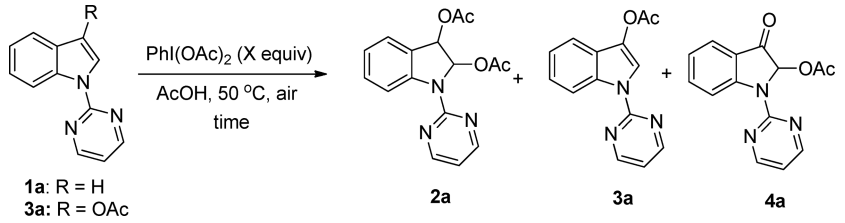
RESULTS AND DISCUSSION

Initially, our studies focused on the acetoxylation reaction at the C-3 position of *N*-pyrimidinylindole **1a** under the following conditions: Co(OAc)$_2$·4H$_2$O (10 mol %) and PhI(OAc)$_2$ (3 equiv) in AcOH at 50 °C for 20 h. Surprisingly, acetoxylation at the C-2 position and oxidation at the C-3 position of indole simultaneously occurred to afford **4a** in 63% yield (entry 1, Table 1). A controlled experiment indicated that the cobalt salt was not necessary for this reaction. **4a** was formed in 68% yield with 3 equiv of PhI(OAc)$_2$ in AcOH, and a small amount of C-3 acetoxylation product **3a** was also detected (entry 2, Table 1). Increasing the reaction temperature to refluxing conditions disfavored the production of **4a** (entry 3, Table 1). In

Received: August 23, 2016
Published: October 28, 2016

DOI: 10.1021/acs.joc.6b02078
J. Org. Chem. 2016, 81, 11081−11094

Table 1. Effect of $PhI(OAc)_2$ on the Distribution of the Products (2a–4a)

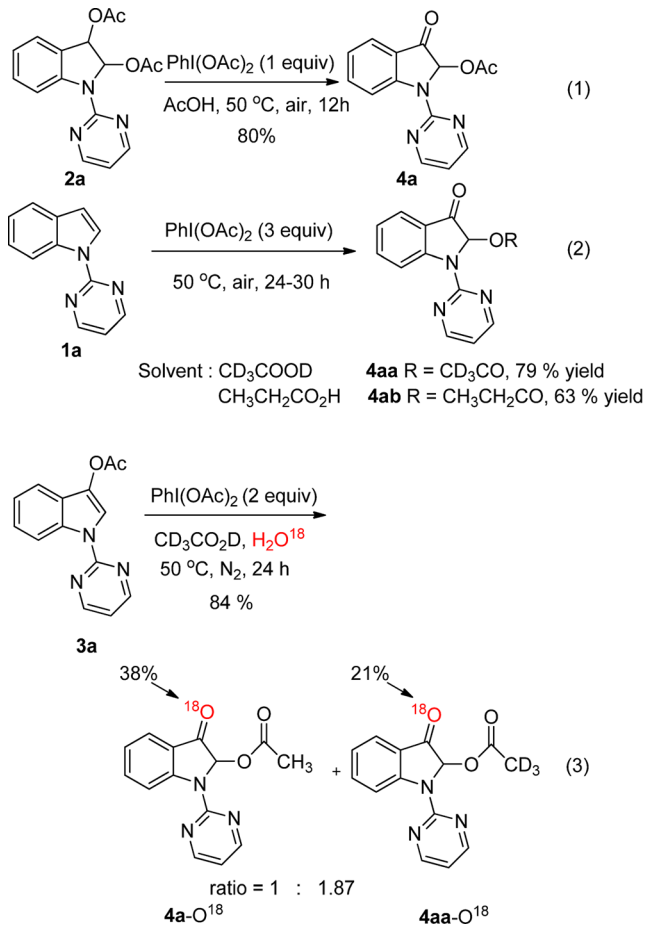


entry	substrate	$PhI(OAc)_2$ (equiv)	time (h)	yield of **2a** (%)	yield of **3a** (%)	yield of **4a** (%)
1	**1a**	3	20	–	–	63
2	**1a**	3	15	–	6	68
3	**1a**	3	2	–	11	48
4	**1a**	0.8	3	4	47	–
5	**1a**	0.9	3	14	52	–
6	**1a**	1	25 min	53	10	–
7	**1a**	1.1	3	–	66	8
8	**1a**	1.2	3	–	64	16
9	**1a**	2	22	–	35	46
10	**3a**	1.2	12	–	9	74
11	**3a**	1.4	12	–	8	77
12	**3a**	1.6	12	–	9	74
13	**3a**	1.9	12	–	8	78
14	**3a**	2.2	12	–	7	79

comparison to Punji's report[12] where the formation of **3a** from substrate **1a** used 1 equiv of $PhI(OAc)_2$ in acetic acid, we reasoned that the quantity of $PhI(OAc)_2$ employed in this type of reaction may be a key factor that governs the outcome of products **2a**–**4a**. Therefore, the effect of $PhI(OAc)_2$ was investigated using 0.8 to 2 equiv in the reaction with **1a** as a typical substrate (entries 4–9, Table 1). When less than 1 equiv of $PhI(OAc)_2$ was used, the initial major product was **2a**, and **2a** was converted to **3a** with a longer reaction time (entries 4–5, Table 1). When more than 1 equiv and less than 2 equiv of $PhI(OAc)_2$ was used, the major product was **3a** along with a small amount of **4a** (entries 7–8, Table 1). The relationship between **3a** and **4a** was investigated with **3a** as the substrate (entries 10–14, Table 1). These results indicated that **4a** was formed via oxidation by $PhI(OAc)_2$ from **3a**. In addition, **2a** led to the formation of **4a** in 80% yield with 1 equiv of $PhI(OAc)_2$ (eq 1). Finally, the optimal conditions for product **4a** were $PhI(OAc)_2$ (3 equiv) in AcOH at 50 °C under air for 15 h. It is important to conduct the reactions under air. A controlled experiment was conducted with substrate **1a** and 3 equiv of $PhI(OAc)_2$ in AcOH at 50 °C under N_2 for 15 h. It gave the products **4a** and **3a** in 50% and 20% yield, respectively. The structure of **4a** was confirmed by X-ray single-crystal diffraction.[14]

By exchanging the solvent to CD_3CO_2D and *n*-propionic acid, **4aa** and **4ab** were formed in 79% and 63% yields, respectively (eq 2). A H_2O^{18}-labeling experiment was carried out with 2 equiv of $PhI(OAc)_2$ in a mixed solvent consisting of CD_3CO_2D and H_2O^{18} at 50 °C under N_2 for 24 h. The result indicated that the oxygen at the C-3 position of the corresponding products (**4a** and **4aa**) partially stemmed from H_2O^{18} (eq 3).

To further investigate the mechanism, additional reactions were performed using in situ IR spectroscopy to monitor the oxidation reaction of **1a** with 1, 2 and 3 equiv of $PhI(OAc)_2$ in acetic acid. The results are shown in Figures 1, 2 and S1 (see the Supporting Information). In comparison to the authentic



samples (see SI), the signals at 1492, 1458, and 1469 cm^{-1} were assigned to **2a**, **3a** and **4a**, respectively. When 1 equiv of $PhI(OAc)_2$ was employed in this reaction, the absorbance of $PhI(OAc)_2$ quickly decreased to baseline (Figure 1). Once $PhI(OAc)_2$ was added to the reaction mixture, the intensity of

DOI: 10.1021/acs.joc.6b02078
J. Org. Chem. 2016, 81, 11081–11094

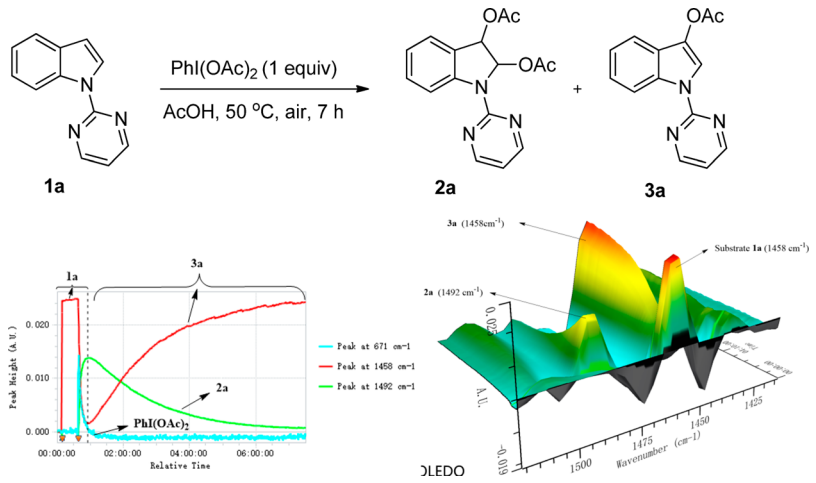


Figure 1. One equivalent of $PhI(OAc)_2$ mediated oxidation reaction of **1a**.

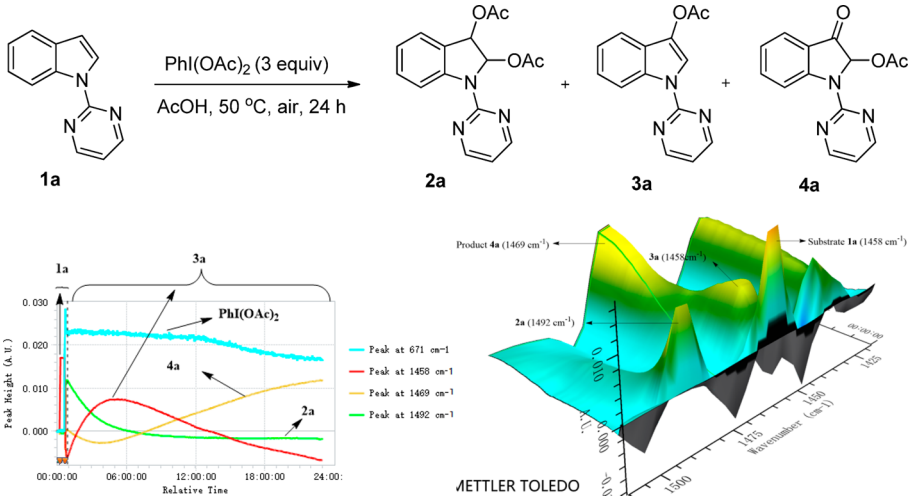


Figure 2. Three equivalents of $PhI(OAc)_2$ mediated oxidation reaction of **1a**.

the signal at 1492 cm^{-1} (assigned to **2a**) quickly increased to its highest level and then decreased with time, and the intensity of the signal at 1458 cm^{-1} (assigned to **3a**) increased with time. These results indicated that **2a** was formed quickly and then transformed to **3a** (Figure 1). When 3 equiv of $PhI(OAc)_2$ was used in the reaction, the absorbance of **2a** decreased quickly, and the absorbance of **3a** originally increased to its highest level and then decreased with time. The intensity of the peak at 1469 cm^{-1} (assigned to **4a**) increased with time (Figure 2). These results indicated that the formation of **4a** proceeded through three cascade steps from **1a**.

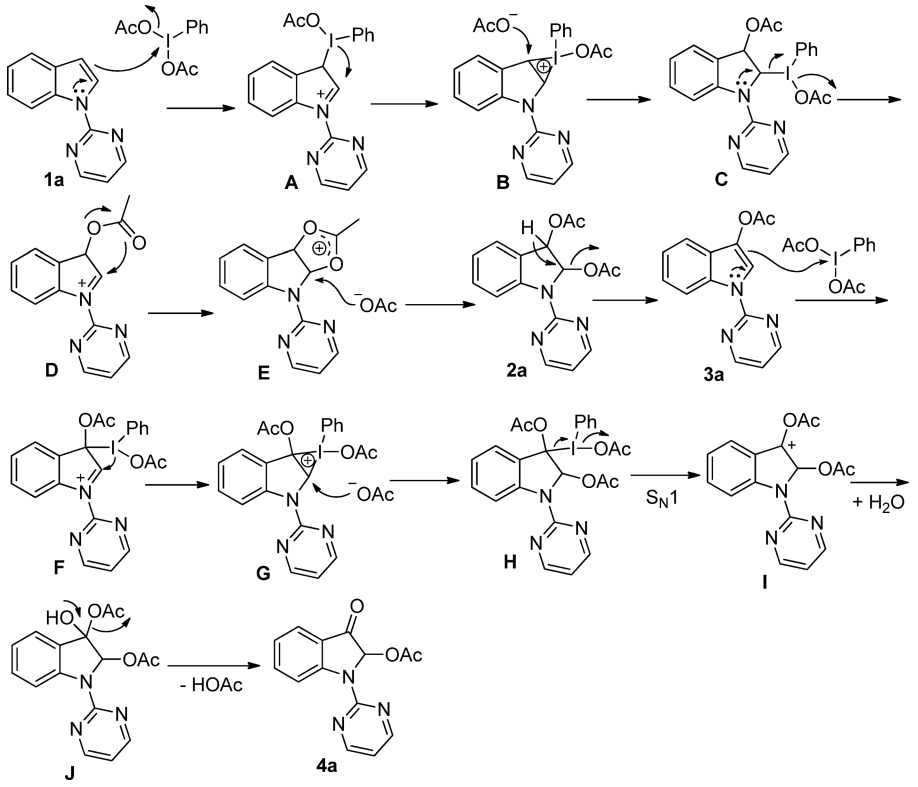
On the basis of our results and the related work from the Lei[11] group, a possible reaction mechanism has been proposed in Scheme 1. A similar reaction pathway for the formation of **2a** from **1a** in the presence of 1 equiv of $PhI(OAc)_2$ was reported by Lei[11] group. Here, we focus on the possible pathway from **2a** to **4a**. **3a** is obtained via aromatization by losing one molecule of acetic acid and further converted to intermediate **F** via nucleophilic attack of **3a** on $PhI(OAc)_2$. Intramolecular nucleophilic attack of iodine in **F** leads to formation of iodonium salt **G**, which is attacked by the acetate anion at the C-2 position to afford **H**. **H** undergoes S_N1 reaction to afford **I**. H_2O acts as a nucleophile and attacks **I** at the C-3 position to afford intermediate **J**, and **J** is further converted to final product **4a** by loss of one acetic acid.

With the optimized conditions in hand, we explored the substrate scope shown in Table 2. On the basis of the mechanism, the reaction undergoes three cascade steps to form final product **4**. The reaction tolerated a broad range of substituents on the phenyl ring including both electron-donating and -withdrawing groups, such as methyl, ether, chloro, bromo, fluoro, and nitro moieties. Even more bulky substituents on the phenyl ring led to the corresponding products (**4m** and **4n**) in synthetically useful yields. The positions of the substituents (e.g., **4b**−**4d** and **4f**−**4h**) did not affect the outcomes of the products. For other types of substrates bearing substituents on the C-3 position of the indoles, the reaction occurred at the C-2 position. For example, substrate **1o** afforded C-2 acetoxylated product **4o** in 88% yield. However, substrate **1p** did not provide any product, which is most likely due to the inhibition effect via coordination of the nucleophilic nitrogen to the electrophilic hypervalent iodine.

The effect of the substituents of the indole nitrogen on this reaction was also investigated. The results are shown in Table 3. Both electron-donating and -withdrawing groups on the pyrimidine led to corresponding products **4q**−**4t** in good

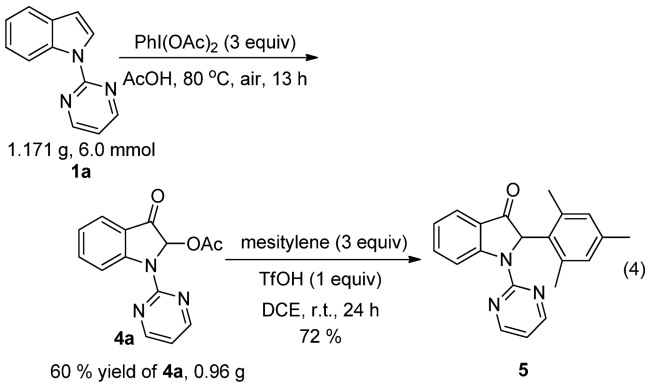
DOI: 10.1021/acs.joc.6b02078
J. Org. Chem. 2016, 81, 11081−11094

Scheme 1. Proposed Mechanism for C-2 Acetoxylation and C-3 Oxidation Reactions of *N*-Substituted Indoles



yields. A set of *N*-2-pyridinyl indole substrates afforded **4u**–**4w** in synthetically useful yields.

Gram scale reaction was carried out with **1a** as the substrate using our standard conditions to afford product **4a** in 60% yield. When **4a** was treated with 3 equiv of mesitylene in the presence of 1 equiv of TsOH in 1,2-dichloroethane, the reactant was converted to the corresponding 2-aryl indole-3-one product **5** in 72% yield (eq 4).[15]



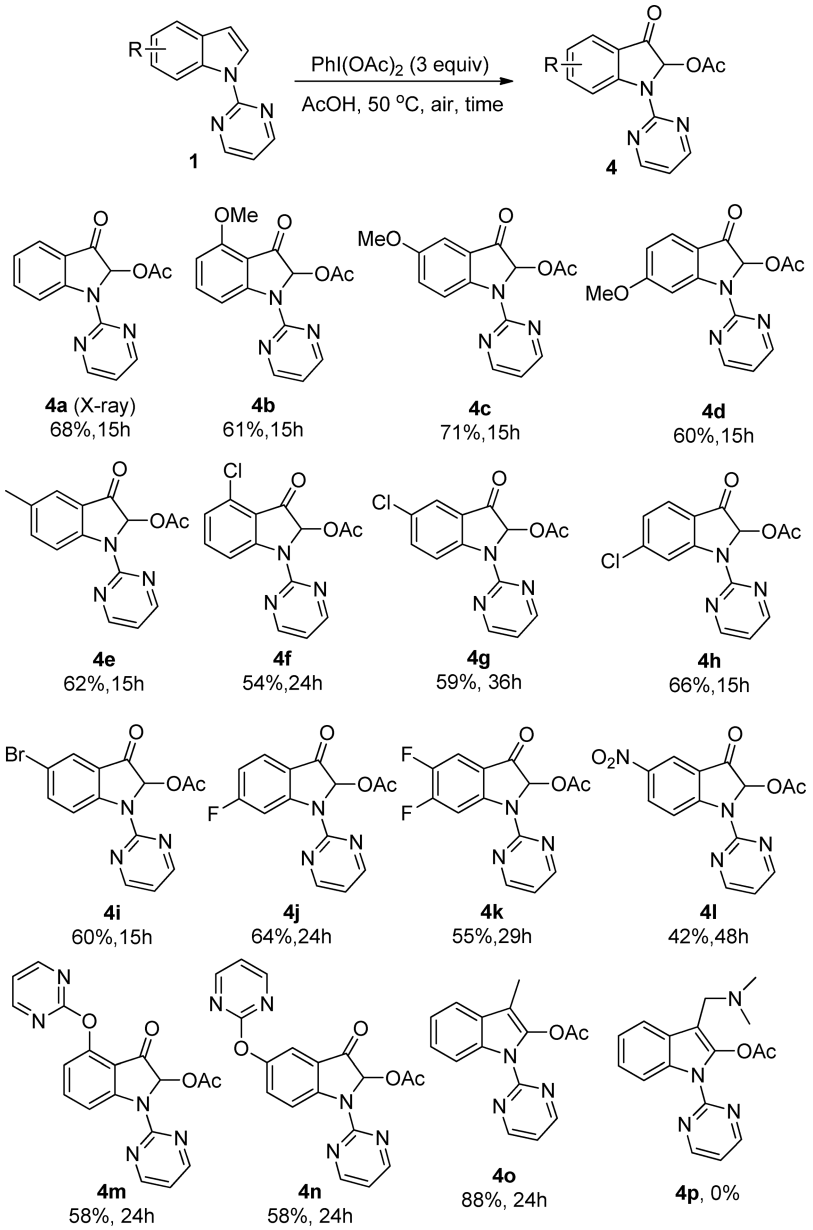
On the basis of the similar reactivity of hypervalent iodine reagents, such as $PhI(OAc)_2$ and $PhICl_2$,[10] and mechanistic considerations, we envisioned that the chlorination reaction could proceed with *N*-pyrimidinyl indole substrates in the presence of $PhICl_2$. Initially, we tested this hypothesis with 3 equiv of $PhICl_2$ in acetic acid at 50 °C using **1a** as the substrate. *N*-pyrimidinyl 3,3-dichloroindole-2-one **7a** was obtained in 81% yield along with a small amount of *N*-pyrimidinyl 2,3-dichloroindole **6a** (entry 4, Table 4).[16] Interestingly, when less than 3 equiv of $PhICl_2$ were used, **6a** was the major product in this reaction (entries 1–3, Table 4). When **6a** was treated with 2 equiv of $PhICl_2$, **7a** was obtained in 87% yield (entry 6, Table 4). Finally, the optimal conditions for **6a** included 2 equiv of $PhICl_2$ in acetic acid at 50 °C under air for 30 min, and the optimal conditions for the preparation of **7a** included 3 equiv of $PhICl_2$ in acetic acid at 50 °C under air for 30 min.

On the basis of these results, a possible mechanism for the chlorination reaction of *N*-substituted indoles is proposed in Scheme 2. First, intermediate **A′** is obtained through nucleophilic attack of **1a** on one molecule of $PhICl_2$ and further converted to the iodonium salt **B′**. A chlorine anion attacks the C-3 position of **B′** to deliver **C′**, and **D′** is obtained via intramolecular nucleophilic attack. Aromatization of **D′** affords **E′**, which reacts with another $PhICl_2$ to gield **F′**. Another chlorine anion attacks the C-2 position of iodonium salt **G′** to afford **H′**, which undergoes aromatization to form **6a**. **6a** reacts with a third $PhICl_2$ to afford **I′**. The third chlorine anion attacks the C-3 position of **J′** to afford **K′**. **K′** undergoes intramolecular nucleophilic attack to afford **L′**. **L′** is attacked by H_2O followed by removal of one HCl to yield final product **7a**. This proposed mechanism explains why 3 equiv of $PhICl_2$ is the optimal condition for the production of **7a** and 2 equiv of $PhICl_2$ is the optimal condition for the production of **6a**.

Next, the substrate scope and limitations in the production of **7** with 3 equiv of $PhICl_2$ were studied (Table 5). Substrates with electron-withdrawing groups on the phenyl ring led to corresponding product **7** in good to excellent yields. However, substrates bearing methoxyl groups on the phenyl ring, such as **1b**–**1d**, produced complicated mixtures. For substrate **1o** bearing a methyl group at the C-3 position of the indole, monochlorinated product **7o** was obtained in 96% yield using our standard conditions. The structure of the product was unambiguously established by X-ray single-crystal diffraction of **7g**.

DOI: 10.1021/acs.joc.6b02078
J. Org. Chem. 2016, 81, 11081–11094

Table 2. Regioselective C-2 Acetoxylation and C-3 Oxidation Reactions of *N*-Pyrimidinyl Indoles



Compounds **6** were prepared, and the results are shown in Table 6. The reactions with substrates bearing electron-withdrawing groups on the phenyl ring underwent C-2,3 dichlorination reaction to afford corresponding product **6** in good yields. Interestingly, for substrate **1o**, product **7o** was obtained in 87% yield even with 2 equiv of $PhICl_2$, and no C-2,3 dichlorination product was formed.

CONCLUSION

In conclusion, we have developed an efficient and highly regioselective method for the construction of 2-acetoxy indole-3-ones via a tandem acetoxylation-oxidation reaction of *N*-substituted indoles using $PhI(OAc)_2$ as the oxidant in acetic acid. The reaction tolerates a broad range of functional groups. The quantity of $PhI(OAc)_2$ employed in this reaction has an important effect on the distribution of the products. Moreover, a mild and highly efficient approach was developed to produce 3,3-dichloro indole-2-ones with $PhICl_2$. Various 2,3-dicloroindole derivatives were obtained in good yields by controlling the amount of $PhICl_2$ in the reaction. Extensive studies including in situ IR spectroscopy and H_2O^{18}-labeling experiments provide insight into the possible reaction mechanism.

EXPERIMENTAL SECTION

General Techniques. All melting points are uncorrected. Preparative chromatographic separations were performed on silica gel (300−400 mesh). Reactions were followed by TLC analysis using silica plates with a fluorescent indicator (254 nm) and visualized with a UV lamp, $KMnO_4$ or phosphomolybdic acid. ^1H and ^{13}C NMR spectra were recorded in Fourier transform mode at the field strength specified on a 400, or 500 MHz spectrometer. Spectra were obtained on $CDCl_3$ solution in 5 mm diameter tubes, and chemical shifts in ppm (part per million) are quoted relative to the residual signals of chloroform (δ_H 7.26 ppm, or δ_C 77.00 ppm). *J* values are given in hertz. IR spectra were measured for samples as KBr pellets in a FT-IR spectrophotometer. High resolution mass spectra (HRMS) were measured at 70 eV using a double focusing magnetic sector mass analyzer with an EI source. Crystallographic data were collected using graphite mono-

DOI: 10.1021/acs.joc.6b02078
J. Org. Chem. 2016, 81, 11081−11094

Table 3. Effect of Substituents of the Indole Nitrogen on the Reaction

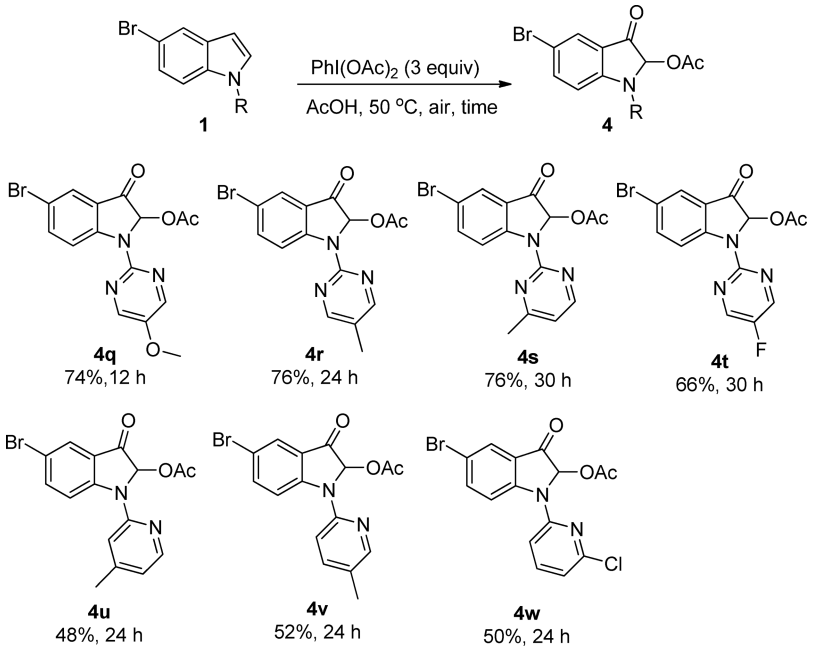
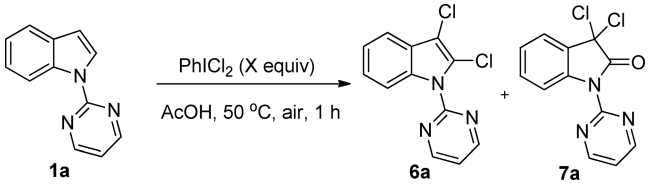


Table 4. Optimization Studies for the Chlorination of *N*-Substituted Indoles



entry	substrate	$PhICl_2$ (equiv)	yield of **6a** (%)	yield of **7a** (%)
1	**1a**	1.5	33	5
2	**1a**	2	61	9
3	**1a**	2.5	59	32
4	**1a**	3	11	81
5	**1a**	5	2	83
6	**6a**	2	–	87

chromated Mo Kα radiation (λ = 0.71073 Å) for the compounds **4a** and **7g**. *N*-pyrimidinyl indoles were prepared according to the literature procedure.[17] Among them, substrates **1a**, **1b**, **1c**, **1d**, **1e**, **1f**, **1g**, **1h**, **1i**, **1j**, **1l**, and **1o** were known.[17,18] *N*-pyridinyl indoles were prepared according to the literature procedure.[19] The data of products **6a**, **6e** and **6i** are consistent with those in the ref 20.

General Procedure to Synthesize *N*-Pyrimidinyl Indoles 1k, 1m, 1n, 1p–1t. NaH (60% dispersion in mineral oil, 400 mg, 10.0 mmol) was added in portions to a stirred solution of indole (5.0 mmol) in DMF (10 mL) at 0 °C. After stirring at 0 °C for 1 h, 2-chloropyrimidine (7.5 mmol) was added and the mixture was stirred at 130 °C for 24 h. Then, the reaction mixture was cooled to ambient temperature, poured into H_2O (100 mL) and extracted with EtOAc (4 × 100 mL). The combined organic phase was dried over Na_2SO_4. After filtration and evaporation of the solvents under reduced pressure, the crude product was purified by column chromatography on silica gel (Petroleum ether/EtOAc = 20/1) to give the desired indole derivatives.

5,6-Difluoro-1-(pyrimidin-2-yl)-1H-indole (***1k***). White solid; mp 124–125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77–8.64 (m, 3H), 8.29 (d, J = 3.6 Hz, 1H), 7.34 (dd, J = 10.1 and 8.1 Hz, 1H), 7.09 (t, J = 4.8 Hz, 1H), 6.63 (d, J = 3.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 157.2, 149.0 (dd, J_{C-F} = 76.0 and 14.7 Hz), 146.6 (dd, J_{C-F} = 76.5 and 14.7 Hz), 130.4 (d, J_{C-F} = 11.2 Hz), 126.9 (d, J_{C-F} = 4.0 Hz), 126.6 (dd, J_{C-F} = 8.0 and 1.8 Hz), 116.5, 107.3 (dd, J_{C-F} = 19.0 and 0.9 Hz), 106.3 (dd, J_{C-F} = 3.6 and 1.6 Hz), 105.2 (d, J_{C-F} = 24.4 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −141.7 (d, J = 21.7 Hz), −144.8 (d, J = 20.8 Hz); HRMS (EI) Calcd for $C_{12}H_7N_3F_2$ [M^+] 231.0608, found 231.0612; IR (KBr) ν(cm^{-1}) 1585, 1562, 1470, 1384, 1140, 847, 801.

1-(Pyrimidin-2-yl)-4-(pyrimidin-2-yloxy)-1H-indole (***1m***). White solid; mp 167–168 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, J = 8.4 Hz, 1H), 8.69 (d, J = 4.8 Hz, 2H), 8.57 (d, J = 4.8 Hz, 2H), 8.23 (d, J = 3.7 Hz, 1H), 7.38 (t, J = 8.1 Hz, 1H), 7.10 (d, J = 7.8 Hz, 1H), 7.07–7.00 (m, 2H), 6.55 (d, J = 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 159.8, 158.1, 157.6, 145.4, 137.1, 125.9, 124.6, 124.2, 116.4, 116.0, 114.3, 114.1, 103.5; HRMS (EI) Calcd for $C_{16}H_{11}N_5O$ [M^+] 289.0964, found 289.0966; IR (KBr) ν(cm^{-1}) 1623, 1574, 1455, 1406, 1383, 1308, 1208, 947, 809, 756.

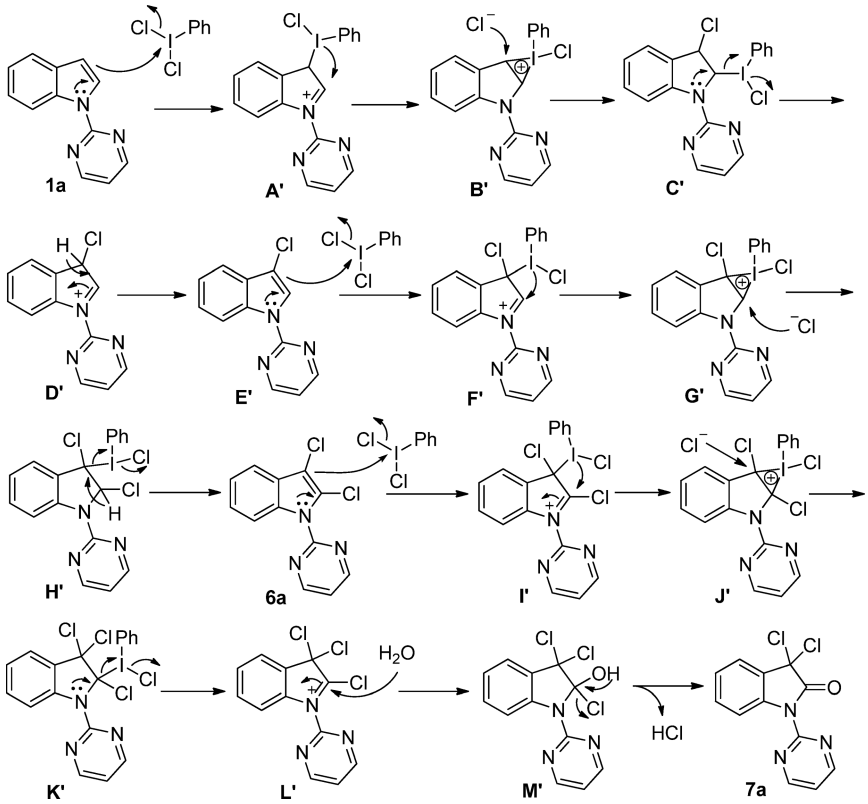
1-(Pyrimidin-2-yl)-5-(pyrimidin-2-yloxy)-1H-indole (***1n***). White solid; mp 174–175 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (d, J = 9.0 Hz, 1H), 8.69 (d, J = 4.8 Hz, 2H), 8.56 (d, J = 4.8 Hz, 2H), 8.31 (d, J = 3.6 Hz, 1H), 7.44 (d, J = 2.2 Hz, 1H), 7.17 (dd, J = 9.0 and 2.3 Hz, 1H), 7.05 (t, J = 4.8 Hz, 1H), 7.01 (t, J = 4.8 Hz, 1H), 6.69 (d, J = 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 159.7, 158.1, 157.6, 148.1, 133.0, 132.1, 126.9, 117.6, 117.2, 116.2, 115.8, 113.0, 106.9; HRMS (EI) Calcd for $C_{16}H_{11}N_5O$ [M^+] 289.0964, found 289.0967; IR (KBr) ν(cm^{-1}) 1580, 1567, 1469, 1453, 1435, 1407, 1304, 1157, 807.

N,N-Dimethyl-1-(1-(pyrimidin-2-yl)-1H-indol-3-yl)methanamine (***1p***). Brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (d, J = 8.3 Hz, 1H), 8.69 (d, J = 4.8 Hz, 2H), 8.19 (s, 1H), 7.74 (d, J = 7.7 Hz, 1H), 7.38–7.31 (m, 1H), 7.29–7.23 (m, 1H), 7.02 (t, J = 4.8 Hz, 1H), 3.66 (s, 2H), 2.33 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 157.7, 135.8, 131.3, 124.7, 123.8, 122.0, 119.6, 117.5, 116.2, 115.9, 54.7, 45.5; HRMS (EI) Calcd for $C_{15}H_{16}N_4$ [M^+] 252.1375, found 252.1371; IR (KBr) ν(cm^{-1}) 1580, 1565, 1460, 1384, 1356, 1312, 1226, 1135, 1083, 1019, 801, 747.

5-Bromo-1-(5-methoxypyrimidin-2-yl)-1H-indole (***1q***). White solid; mp 157–158 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, J = 8.9 Hz, 1H), 8.37 (s, 2H), 8.18 (d, J = 3.6 Hz, 1H), 7.74 (d, J = 1.8 Hz, 1H), 7.39 (dd, J = 8.9 and 1.9 Hz, 1H), 6.60 (d, J = 3.5 Hz, 1H), 3.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7, 150.2, 144.2, 133.8, 132.6, 127.0, 126.1, 123.2, 117.0, 114.9, 105.2, 56.3; HRMS (EI) Calcd for $C_{13}H_{10}N_3OBr$ [M^+] 303.0007, found 303.0032; IR (KBr) ν(cm^{-1}) 1571, 1458, 1431, 1275, 1151, 1011, 977, 820, 779, 727.

DOI: 10.1021/acs.joc.6b02078
J. Org. Chem. 2016, 81, 11081–11094

Scheme 2. Proposed Mechanism for the C-2 Oxidation and the C-3 Dichlorination of *N*-Substituted Indoles



*5-Bromo-1-(5-methylpyrimidin-2-yl)-1H-indole (**1r**).* White solid; mp 119−120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, J = 8.9 Hz, 1H), 8.48 (s, 2H), 8.23 (d, J = 3.6 Hz, 1H), 7.73 (d, J = 1.6 Hz, 1H), 7.39 (dd, J = 8.9 and 1.6 Hz, 1H), 6.60 (d, J = 3.5 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 155.8, 133.9, 132.8, 126.9, 126.1, 125.6, 123.2, 117.5, 115.1, 105.5, 15.0; HRMS (EI) Calcd for $C_{13}H_{10}N_3Br$ [M^+] 287.0058, found 287.0051; IR (KBr) ν(cm^{-1}) 1596, 1458, 1348, 1294, 1192, 1147, 785.

*5-Bromo-1-(4-methylpyrimidin-2-yl)-1H-indole (**1s**).* White solid; mp 85−86 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, J = 8.9 Hz, 1H), 8.52 (d, J = 5.0 Hz, 1H), 8.29 (d, J = 3.6 Hz, 1H), 7.73 (d, J = 1.7 Hz, 1H), 7.40 (dd, J = 8.9 and 1.8 Hz, 1H), 6.91 (d, J = 5.0 Hz, 1H), 6.61 (d, J = 3.5 Hz, 1H), 2.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 157.6, 157.2, 134.0, 133.0, 127.0, 126.2, 123.2, 117.8, 116.0, 115.2, 105.7, 24.3; HRMS (EI) Calcd for $C_{13}H_{10}N_3Br$ [M^+] 287.0058, found 287.0060; IR (KBr) ν(cm^{-1}) 1586, 1562, 1452, 1366, 1198, 1161,724.

*5-Bromo-1-(5-fluoropyrimidin-2-yl)-1H-indole (**1t**).* White solid; mp 129−130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61−8.50 (m, 3H), 8.17 (d, J = 3.6 Hz, 1H), 7.73 (d, J = 1.6 Hz, 1H), 7.40 (dd, J = 8.9 and 1.7 Hz, 1H), 6.61 (d, J = 3.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 153.6, 153.4, 145.7(d, J_{C-F} = 21.9 Hz), 133.8, 132.8, 127.1, 126.5, 123.4, 117.2, 115.5, 106.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −145.4; HRMS (EI) Calcd for $C_{12}H_7N_3FBr$ [M^+] 290.9807, found 290.9814; IR (KBr) ν(cm^{-1}) 1632, 1578, 1464, 1445, 1385, 1245, 1154, 780, 764.

General Procedure to Synthesize *N*-Pyridinyl Indoles 1u−1w. A mixture of 5-bromoindole (2.0 mmol), 2-chloro-5-methylpyridine (3.0 mmol), and KOH (400 mg, 6 mmol) in dimethyl sulfoxide (DMSO, 2 mL) was vigorously stirred at 120 °C under N_2 atmosphere for 24 h. After cooling down to ambient temperature, the mixture was poured into H_2O (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic phase was dried over Na_2SO_4. After filtration and evaporation of the solvents in vacuum, the crude product was purified by column chromatography on silica gel (petroleum ether/EtOAc = 20/1) to give the desired indole derivatives.

*5-Bromo-1-(4-methylpyridin-2-yl)-1H-indole (**1u**).* White solid; mp 51−52 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, J = 5.0 Hz, 1H), 8.12 (d, J = 8.8 Hz, 1H), 7.77 (d, J = 1.8 Hz, 1H), 7.67 (d, J = 3.4 Hz, 1H), 7.36 (dd, J = 8.8 and 1.8 Hz, 1H), 7.24 (s, 1H), 7.01 (d, J = 4.9 Hz, 1H), 6.63 (d, J = 3.4 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 150.0, 148.6, 133.8, 132.0, 127.0, 125.8, 123.4, 121.6, 115.1, 114.8, 114.3, 104.6, 21.3; HRMS (EI) Calcd for $C_{14}H_{11}N_2Br$ [M^+] 286.0106, found 286.0101; IR (KBr) ν(cm^{-1}) 1608, 1558, 1522,1484, 1454, 1434, 1328, 1201, 846, 722.

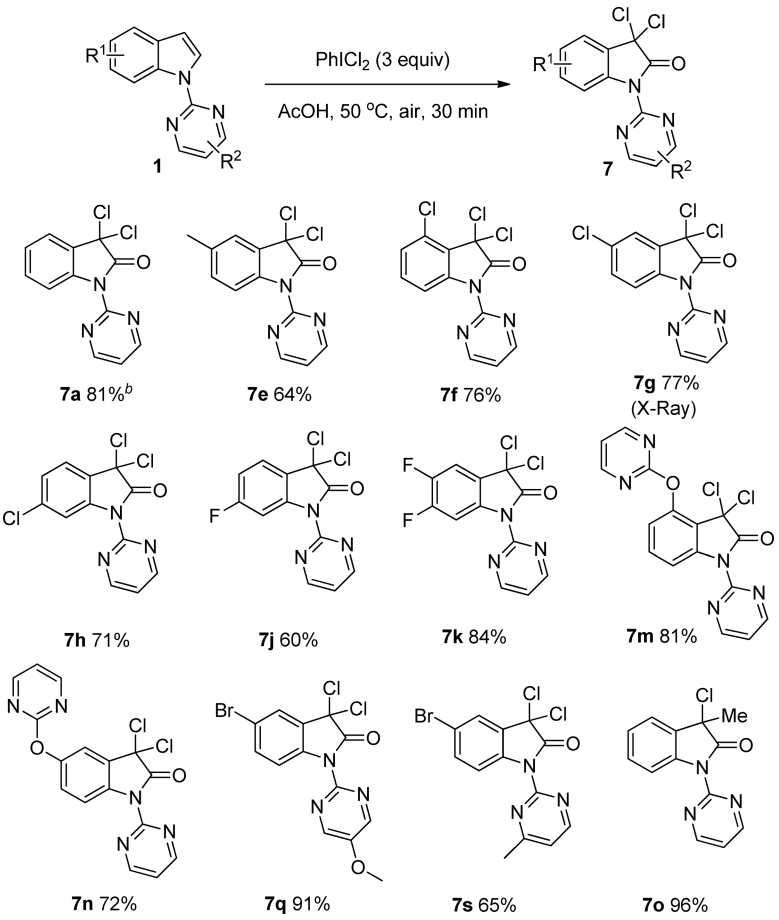
*5-Bromo-1-(5-methylpyridin-2-yl)-1H-indole (**1v**).* Brown solid; mp 68−69 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 8.06 (d, J = 8.8 Hz, 1H), 7.77 (d, J = 1.7 Hz, 1H), 7.65 (d, J = 3.4 Hz, 1H), 7.61 (dd, J = 8.3 and 1.8 Hz, 1H), 7.35 (dd, J = 8.9 and 1.8 Hz, 1H), 7.32 (d, J = 8.3 Hz, 1H), 6.62 (d, J = 3.3 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 149.0, 139.1, 133.8, 131.8, 130.0, 127.0, 125.7, 123.4, 114.4, 114.2, 114.1, 104.4, 17.8; HRMS (EI) Calcd for $C_{14}H_{11}N_2Br$ [M^+] 286.0106, found 286.0114; IR (KBr) ν(cm^{-1}) 1602, 1578, 1522, 1491, 1449, 1389, 1335, 1298, 1200, 1115, 960, 808, 757.

*5-Bromo-1-(6-chloropyridin-2-yl)-1H-indole (**1w**).* White solid; mp 86−87 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 8.9 Hz, 1H), 7.84−7.70 (m, 2H), 7.65 (d, J = 3.5 Hz, 1H), 7.40 (dd, J = 8.9 and 1.8 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.18 (d, J = 7.8 Hz, 1H), 6.64 (d, J = 3.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8, 150.2, 140.7, 133.7, 132.2, 126.4, 123.6, 120.1, 115.3, 115.0, 111.6, 105.8; HRMS (EI) Calcd for $C_{13}H_8N_2ClBr$ [M^+] 305.9559, found 305.9558; IR (KBr) ν(cm^{-1}) 1584, 1459, 1164, 1138, 1121, 874, 781, 713.

General Procedure for the C-2 Acetoxylation and C-3 Oxidation Reaction of *N*-Protected Indole Derivatives (1) Using PhI(OAc)$_2$ as the Oxidant. To a 25 mL of round-bottom flask equipped with a stirrer was charged with substrate **1** (0.1 mmol), $PhI(OAc)_2$ (0.3 mmol). Acetic acid (1 mL) was added to the reaction flask via a syringe. The reaction flask was charged with condenser. The reaction mixture was stirred at 50 °C under air for 24 h and monitored by TLC. Then, the reaction mixture was cooled down to room temperature, diluted with aqueous NH_3 (5 M, 5 mL) and brine, and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phase was

DOI: 10.1021/acs.joc.6b02078
J. Org. Chem. 2016, 81, 11081−11094

Table 5. Scope and Limitations of the C-2 Oxidation and the C-3 Dichlorination of *N*-Substituted Indoles[a]



[a]Reaction conditions: Substrate (0.1 mmol), $PhICl_2$ (0.3 mmol) in AcOH (1 mL) at 50 °C under air for 30 min. [b]Reaction time was 1 h.

dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was then purified by preparative TLC plate (petroleum ether:ethyl acetate = 3:1 as eluent) to get the product **4**.

*3-Oxo-1-(pyrimidin-2-yl)indolin-2-yl acetate (**4a**).* The general procedure described above was followed using substrate **1a** (19.5 mg, 0.1 mmol), $PhI(OAc)_2$ (96.6 mg, 0.3 mmol) and AcOH (1 mL). The residue was purified by preparative TLC plate (petroleum ether:ethyl acetate = 3:1 as eluent) to get the product **4a** (18.2 mg, 68% yield). Yollow solid; mp 122−124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, J = 8.4 Hz, 1H), 8.58 (d, J = 4.8 Hz, 2H), 7.75 (d, J = 7.6 Hz, 1H), 7.67 (t, J = 7.8 Hz, 1H), 7.14 (t, J = 7.4 Hz, 1H), 6.93 (t, J = 4.8 Hz, 1H), 6.88 (s, 1H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.2, 169.3, 157.9, 153.8, 137.7, 124.5, 122.8, 122.1, 117.3, 114.6, 79.6, 20.7; HRMS (EI) Calcd for $C_{14}H_{11}N_3O_3$ [M^+] 269.0800, found 269.0801; IR (KBr) ν(cm^{-1}) 1751, 1725, 1609, 1582, 1467, 1430, 1224, 1149, 1016, 760.

*4-Methoxy-3-oxo-1-(pyrimidin-2-yl)indolin-2-yl acetate (**4b**).* The general procedure described above was followed using substrate **1b** (22.5 mg, 0.1 mmol), $PhI(OAc)_2$ (96.6 mg, 0.3 mmol) and AcOH (1 mL). The residue was purified by preparative TLC plate (petroleum ether:ethyl acetate = 3:1 as eluent) to get the product **4b** (18.3 mg, 61% yield). Yollow solid; mp 188−190 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, J = 4.8 Hz, 2H), 8.30 (d, J = 8.3 Hz, 1H), 7.59 (t, J = 8.3 Hz, 1H), 6.92 (t, J = 4.8 Hz, 1H), 6.86 (s, 1H), 6.58 (d, J = 8.3 Hz, 1H), 3.96 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.3, 169.2, 158.7, 157.8, 154.9, 139.4, 114.6, 110.6, 109.2, 104.8, 79.6, 56.0, 20.7; HRMS (EI) Calcd for $C_{15}H_{13}N_3O_4$ [M^+] 299.0906, found 299.0902; IR (KBr) ν(cm^{-1})1758, 1719, 1601, 1459, 1419, 1221, 1111, 1018, 783.

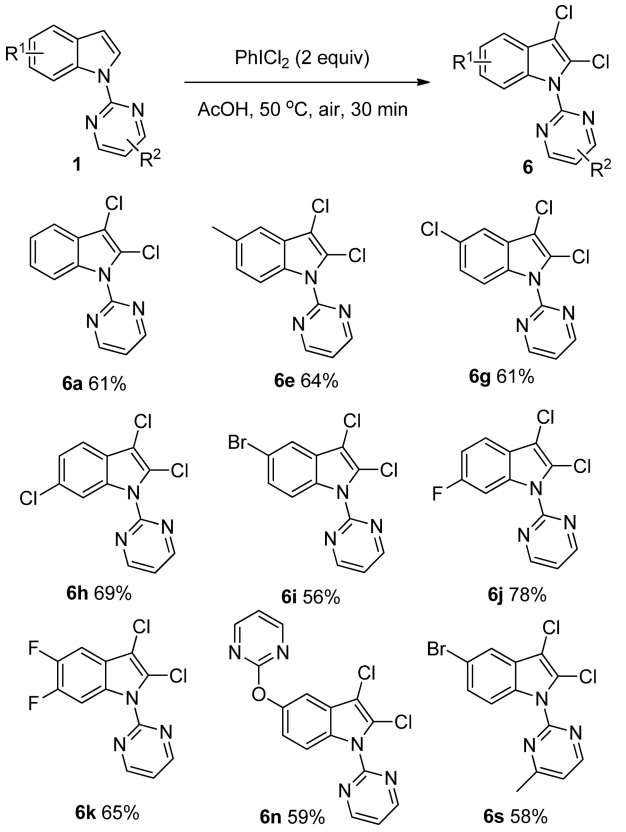
*5-Methoxy-3-oxo-1-(pyrimidin-2-yl)indolin-2-yl acetate (**4c**).* The general procedure described above was followed using substrate **1c** (22.5 mg, 0.1 mmol), $PhI(OAc)_2$ (96.6 mg, 0.3 mmol) and AcOH (1 mL). The residue was purified by preparative TLC plate (petroleum ether:ethyl acetate = 3:1 as eluent) to get the product **4c** (21.2 mg, 71% yield). Yollow solid; mp 176−177 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, J = 9.1 Hz, 1H), 8.55 (d, J = 4.8 Hz, 2H), 7.28 (dd, J = 9.1 and 2.8 Hz 1H), 7.20 (d, J = 2.7 Hz, 1H), 6.89 (t, J = 4.8 Hz, 1H), 6.85 (s, 1H), 3.84 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.2, 169.3, 157.8, 155.7, 148.8, 126.4, 122.7, 118.7, 114.2, 105.5, 80.2, 55.8, 20.7; HRMS (EI) Calcd for $C_{15}H_{13}N_3O_4$ [M^+] 299.0906, found 299.0909; IR (KBr) ν(cm^{-1})1723, 1627, 1583, 1473, 1428, 1050.

*6-Methoxy-3-oxo-1-(pyrimidin-2-yl)indolin-2-yl acetate (**4d**).* The general procedure described above was followed using substrate **1d** (22.5 mg, 0.1 mmol), $PhI(OAc)_2$ (96.6 mg, 0.3 mmol) and AcOH (1 mL). The residue was purified by preparative TLC plate (petroleum ether:ethyl acetate = 3:1 as eluent) to get the product **4d** (17.9 mg, 60% yield). Yollow solid; mp 172−174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 4.8 Hz, 2H), 8.30 (d, J = 2.0 Hz, 1H), 7.68 (d, J = 8.5 Hz, 1H), 6.93 (t, J = 4.8 Hz, 2H), 6.67 (dd, J = 8.6 and 2.1 Hz, 1H), 3.96 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.8, 169.3, 167.8, 157.8, 156.0, 126.2, 115.4, 114.6, 110.6, 101.7, 80.2, 55.9, 20.8; HRMS (EI) Calcd for $C_{15}H_{13}N_3O_4$ [M^+] 299.0906, found 299.0909; IR (KBr) ν(cm^{-1})1751, 1716, 1609, 1565, 1443, 1280, 1217, 1014, 966.

*5-Methyl-3-oxo-1-(pyrimidin-2-yl)indolin-2-yl acetate (**4e**).* The general procedure described above was followed using substrate **1e** (20.9 mg, 0.1 mmol), $PhI(OAc)_2$ (96.6 mg, 0.3 mmol) and AcOH (1 mL). The residue was purified by preparative TLC plate (petroleum ether:ethyl acetate = 3:1 as eluent) to get the product **4e** (17.5 mg, 62% yield). Yollow solid; mp 159−161 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J = 8.6 Hz 1H), 8.56 (d, J = 4.8 Hz, 2H), 7.54 (s,

DOI: 10.1021/acs.joc.6b02078
J. Org. Chem. 2016, 81, 11081−11094

Table 6. Preparation of the 2,3-Dichloro *N*-Substituted Indoles



1H), 7.48 (d, J = 8.5 Hz, 1H), 6.90 (t, J = 4.8 Hz, 1H), 6.85 (s, 1H), 2.37 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.3, 169.3, 157.8, 151.9, 138.7, 132.7, 124.2, 122.1, 117.1, 114.3, 79.9, 20.7, 20.6; HRMS (EI) Calcd for $C_{15}H_{13}N_3O_3$ [M^+] 283.0957, found 283.0949; IR (KBr) ν(cm^{-1})1758, 1721, 1621, 1585, 1563, 1490, 1454, 1193, 1016, 805.

*4-Chloro-3-oxo-1-(pyrimidin-2-yl)indolin-2-yl acetate (**4f**).* The general procedure described above was followed using substrate **1f** (22.9 mg, 0.1 mmol), $PhI(OAc)_2$ (96.6 mg, 0.3 mmol) and AcOH (1 mL). The residue was purified by preparative TLC plate (petroleum ether:ethyl acetate = 3:1 as eluent) to get the product **4f** (16.2 mg, 54% yield). Yollow solid; mp 166−167 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (d, J = 8.4 Hz, 1H), 8.59 (d, J = 4.8 Hz, 2H), 7.55 (t, J = 8.2 Hz, 1H), 7.07 (d, J = 7.9 Hz, 1H), 6.97 (t, J = 4.8 Hz, 1H), 6.87 (s, 1H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.4, 169.1, 157.9, 157.6, 155.0, 137.6, 132.5, 124.1, 118.7, 115.5, 115.0, 79.6, 20.7; HRMS (EI) Calcd for $C_{14}H_{10}N_3O_3Cl$ [M^+] 303.0411, found 303.0420; IR (KBr) ν(cm^{-1})1756, 1731, 1600, 1578, 1455, 1416, 1210, 1144, 1023, 963, 784.

*5-Chloro-3-oxo-1-(pyrimidin-2-yl)indolin-2-yl acetate (**4g**).* The general procedure described above was followed using substrate **1g** (22.9 mg, 0.1 mmol), $PhI(OAc)_2$ (96.6 mg, 0.3 mmol) and AcOH (1 mL). The residue was purified by preparative TLC plate (petroleum ether:ethyl acetate = 3:1 as eluent) to get the product **4g** (17.7 mg, 59% yield). Yollow solid; mp 160−161 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (d, J = 8.9 Hz, 1H), 8.58 (d, J = 4.8 Hz, 2H), 7.69 (d, J = 2.1 Hz, 1H), 7.59 (dd, J = 8.9 and 2.2 Hz, 1H), 6.96 (t, J = 4.8 Hz, 1H), 6.83 (s, 1H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.1, 169.1, 157.9, 157.6, 152.1, 137.2, 128.4, 123.8, 123.3, 118.7, 114.9, 79.9, 20.6; HRMS (EI) Calcd for $C_{14}H_{10}N_3O_3Cl$ [M^+] 303.0411, found 303.0408; IR (KBr) ν(cm^{-1}) 1755, 1737, 1608, 1581, 1468, 1419, 1221, 1191, 1144, 1018, 833.

*6-Chloro-3-oxo-1-(pyrimidin-2-yl)indolin-2-yl acetate (**4h**).* The general procedure described above was followed using substrate **1h** (22.9 mg, 0.1 mmol), $PhI(OAc)_2$ (96.6 mg, 0.3 mmol) and AcOH (1 mL). The residue was purified by preparative TLC plate (petroleum ether:ethyl acetate = 3:1 as eluent) to get the product **4h** (19.6 mg, 66% yield). Yollow solid; mp 157−158 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (d, J = 1.3 Hz, 1H), 8.61 (d, J = 4.8 Hz, 2H), 7.68 (d, J = 8.2 Hz, 1H), 7.13 (dd, J = 8.1 and 1.5 Hz, 1H), 6.98 (t, J = 4.8 Hz, 1H), 6.87 (s, 1H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.9, 169.1, 158.0, 157.6, 154.2, 144.1, 125.3, 123.4, 120.6, 117.6, 115.1, 79.9, 20.7; HRMS (EI) Calcd for $C_{14}H_{10}N_3O_3Cl$ [M^+] 303.0411, found 303.0407; IR (KBr) ν(cm^{-1}) 1755, 1732, 1609, 1579, 1468, 1430, 1217, 1068, 1016, 959.

*5-Bromo-3-oxo-1-(pyrimidin-2-yl)indolin-2-yl acetate (**4i**).* The general procedure described above was followed using substrate **1i** (54.8 mg, 0.2 mmol), $PhI(OAc)_2$ (193.3 mg, 0.6 mmol) and AcOH (2 mL). The residue was purified by preparative TLC plate (petroleum ether:ethyl acetate = 3:1 as eluent) to get the product **4i** (42.0 mg, 60% yield). Yollow solid; mp 138−139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, J = 8.9 Hz, 1H), 8.58 (d, J = 4.8 Hz, 2H), 7.82 (d, J = 1.9 Hz, 1H), 7.71 (dd, J = 8.9 and 2.0 Hz, 1H), 6.96 (t, J = 4.8 Hz, 1H), 6.81 (s, 1H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.9, 169.1, 157.9, 157.6, 152.4, 139.9, 126.8, 123.7, 119.0, 115.6, 114.9, 79.7, 20.6; HRMS (EI) Calcd for $C_{14}H_{10}N_3O_3Br$ [M^+] 346.9906, found 346.9909; IR (KBr) ν(cm^{-1}) 1756, 1736, 1605, 1578, 1563, 1466, 1415, 1217, 1017, 830.

*6-Fluoro-3-oxo-1-(pyrimidin-2-yl)indolin-2-yl acetate (**4j**).* The general procedure described above was followed using substrate **1j** (42.6 mg, 0.2 mmol), $PhI(OAc)_2$ (193.3 mg, 0.6 mmol) and AcOH (2 mL). The residue was purified by preparative TLC plate (petroleum ether:ethyl acetate = 3:1 as eluent) to get the product **4j** (36.2 mg, 64% yield). Yollow solid; mp 166−168 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, J = 4.8 Hz, 2H), 8.46 (dd, J = 11.0 and 2.0 Hz, 1H), 7.73 (dd, J = 8.4 and 5.9 Hz, 1H), 6.97 (t, J = 4.8 Hz, 1H), 6.87 (s, 1H), 6.82 (td, J = 8.5, 2.0 Hz, 1H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.3, 169.1, 168.9 (d, J_{C-F} = 254.8 Hz), 157.9, 157.5, 155.5 (d, J_{C-F} = 14.8 Hz), 126.5 (d, J_{C-F} = 12.0 Hz), 118.5, 115.0, 110.8 (d, J_{C-F} = 24.3 Hz), 105.1 (d, J_{C-F} = 29.9 Hz), 79.9, 20.6; ^{19}F NMR (470 MHz, $CDCl_3$) δ −96.04; HRMS (EI) Calcd for $C_{14}H_{10}N_3O_3F$ [M^+] 287.0706, found 287.0705; IR (KBr) ν(cm^{-1})1752, 1724, 1623, 1593, 1581, 1489, 1459, 1489, 1169, 1017, 796.

*5,6-Difluoro-3-oxo-1-(pyrimidin-2-yl)indolin-2-yl acetate (**4k**).* The general procedure described above was followed using substrate **1k** (23.1 mg, 0.1 mmol), $PhI(OAc)_2$ (96.6 mg, 0.3 mmol) and AcOH (1 mL). The residue was purified by preparative TLC plate (petroleum ether:ethyl acetate = 3:1 as eluent) to get the product **4k** (16.6 mg, 55% yield). Yollow solid; mp 155−156 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (dd, J = 11.9 and 6.6 Hz, 1H), 8.59 (d, J = 4.8 Hz, 2H), 7.53 (t, J = 8.1 Hz, 1H), 6.98 (t, J = 4.8 Hz, 1H), 6.82 (s, 1H), 2.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.2 (d, J_{C-F} = 2.5 Hz), 169.1, 158.0, 157.8 (d, J_{C-F} = 85.1 Hz), 153.0 (dd, J_{C-F} = 584.8 and 13.3 Hz), 147.0 (dd, J_{C-F} = 247.5 and 14.5 Hz), 117.8 (dd, J_{C-F} = 5.2 and 2.4 Hz), 115.1, 114.5, 112.1 (dd, J_{C-F} = 18.6 and 3.2 Hz), 107.1 (d, J_{C-F} = 25.5 Hz), 79.7, 20.6; ^{19}F NMR (470 MHz, $CDCl_3$) δ −119.1 (d, J = 20.7 Hz), −142.4 (d, J = 20.5 Hz); HRMS (EI) Calcd for $C_{14}H_9N_3O_3F_2$ [M^+] 305.0612, found 305.0608; IR (KBr) ν(cm^{-1}) 1735, 1582, 1486, 1450, 1288, 1215, 1174, 1152, 1015.

*5-Nitro-1-(pyrimidin-2-yl)-1H-indol-2-yl acetate (**4l**).* The general procedure described above was followed using substrate **1l** (24 mg, 0.1 mmol), $PhI(OAc)_2$ (96.6 mg, 0.3 mmol) and AcOH (1 mL). The residue was purified by preparative TLC plate (petroleum ether:CH_2Cl_2 = 1:1 as eluent) to get the product **4l** (13.0 mg, 42% yield). Yollow solid; mp 193−194 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (d, J = 1.7 Hz, 1H), 8.76 (d, J = 4.8 Hz, 2H), 8.70 (s, 1H), 8.14 (dd, J = 8.7 and 1.8 Hz, 1H), 7.63 (d, J = 8.7 Hz, 1H), 7.16 (t, J = 4.8 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 158.4, 157.0, 145.2, 132.8, 131.1, 128.1, 119.8, 117.6, 117.4, 117.2, 113.4, 20.9; HRMS (EI) calcd for $C_{14}H_{10}N_4O_5$ [M^+] 314.0651, found 314.0642; IR (KBr) ν(cm^{-1}) 1764, 1573, 1520, 1456, 1429, 1342, 1204, 817, 731.

*3-Oxo-1-(pyrimidin-2-yl)-4-(pyrimidin-2-yloxy)indolin-2-yl acetate (**4m**).* The general procedure described above was followed using substrate **1m** (28.9 mg, 0.1 mmol), $PhI(OAc)_2$ (96.6 mg, 0.3

DOI: 10.1021/acs.joc.6b02078
J. Org. Chem. 2016, 81, 11081−11094

mmol) and AcOH (1 mL). The residue was purified by preparative TLC plate (CH_2Cl_2 as eluent) to get the product **4m** (20.9 mg, 58% yield). Yollow solid; mp 163−165 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, J = 8.5 Hz, 1H), 8.58 (d, J = 4.8 Hz, 2H), 8.53 (d, J = 4.7 Hz, 2H), 7.73 (t, J = 8.2 Hz, 1H), 7.05 (t, J = 4.7 Hz, 1H), 6.98−6.91 (m, 2H), 6.85 (s, 1H), 2.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.8, 169.0, 164.8, 159.6, 157.9, 157.7, 154.7, 149.9, 139.1, 116.6, 115.9, 114.8, 114.6, 114.5, 79.5, 20.6; HRMS (EI) Calcd for $C_{18}H_{13}N_5O_4$ [M^+] 363.0968, found 363.0975; IR (KBr) ν(cm^{-1}) 1754, 1724, 1615, 1576, 1462, 1403, 1289, 1213, 1011, 791.

*3-Oxo-1-(pyrimidin-2-yl)-5-(pyrimidin-2-yloxy)indolin-2-yl acetate (**4n**).* The general procedure described above was followed using substrate **1n** (28.9 mg, 0.1 mmol), $PhI(OAc)_2$ (96.6 mg, 0.3 mmol) and AcOH (1 mL). The residue was purified by preparative TLC plate (CH_2Cl_2 as eluent) to get the product **4n** (21.0 mg, 58% yield). Yollow solid; mp 197−200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (d, J = 9.0 Hz, 1H), 8.57 (t, J = 5.1 Hz, 4H), 7.60 (d, J = 2.4 Hz, 1H), 7.52 (dd, J = 9.0 and 2.5 Hz, 1H), 7.07 (t, J = 4.8 Hz, 1H), 6.96−6.91 (m, 2H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.6, 169.2, 165.1, 159.8, 157.9, 157.7, 151.2, 148.2, 131.2, 123.0, 118.5, 117.0, 116.6, 114.7, 80.0, 20.7; HRMS (EI) Calcd for $C_{18}H_{13}N_5O_4$ [M^+] 363.0968, found 363.0958; IR (KBr) ν(cm^{-1})1756,1727, 1621, 1577, 1486, 1471, 1406, 1303, 1020, 922, 814.

*3-Methyl-1-(pyrimidin-2-yl)-1H-indol-2-yl acetate (**4o**).* The general procedure described above was followed using substrate **1o** (20.9 mg, 0.1 mmol), $PhI(OAc)_2$ (96.6 mg, 0.3 mmol) and AcOH (1 mL). The residue was purified by preparative TLC plate (petroleum ether:ethyl acetate = 3:1 as eluent) to get the product **4o** (23.6 mg, 88% yield). Yollow solid; mp 121−122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (d, J = 4.8 Hz, 2H), 7.75 (d, J = 8.4 Hz, 1H), 7.34 (t, J = 6.5 Hz, 2H), 7.26 (t, J = 4.8 Hz, 1H), 7.16 (t, J = 7.5 Hz, 1H), 2.07 (s, 3H), 1.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 169.0, 158.5, 158.0, 155.9, 140.6, 129.4, 128.5, 124.1, 122.1, 118.8, 113.2, 23.6, 20.4; HRMS (EI) Calcd for $C_{15}H_{13}N_3O_2$ [M^+] 267.1008, found 267.0986; IR (KBr) ν(cm^{-1}) 1745, 1614, 1567, 1484, 1411, 1370, 1247, 1191, 1100, 768.

*5-Bromo-1-(5-methoxypyrimidin-2-yl)-3-oxoindolin-2-yl acetate (**4q**).* The general procedure described above was followed using substrate **1q** (30.4 mg, 0.1 mmol), $PhI(OAc)_2$ (96.6 mg, 0.3 mmol) and AcOH (1 mL). The residue was purified by preparative TLC plate (petroleum ether:ethyl acetate = 3:1 as eluent) to get the product **4q** (28.1 mg, 74% yield). Yollow solid; mp 148−149 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54−8.49 (m, 1H), 8.29 (s, 2H), 7.80 (s, 1H), 7.68 (d, J = 8.8 Hz, 1H), 6.76 (s, 1H), 3.89 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.1, 169.2, 152.9, 152.0, 149.2, 144.7, 144.3, 139.9, 126.8, 123.3, 118.1, 114.9, 80.1, 56.4, 20.7; HRMS (EI) Calcd for $C_{15}H_{12}N_3O_4Br$ [M^+] 377.0011, found 377.0013; IR (KBr) ν(cm^{-1}) 1766, 1723, 1607, 1469, 1423, 1275, 1194, 1117, 1009, 824.

*5-Bromo-1-(5-methylpyrimidin-2-yl)-3-oxoindolin-2-yl acetate (**4r**).* The general procedure described above was followed using substrate **1r** (28.8 mg, 0.1 mmol), $PhI(OAc)_2$ (96.6 mg, 0.3 mmol) and AcOH (1 mL). The residue was purified by preparative TLC plate (petroleum ether:ethyl acetate = 3:1 as eluent) to get the product **4r** (27.4 mg, 76% yield). Yollow solid; mp 155−157 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J = 8.9 Hz, 1H), 8.40 (s, 2H), 7.81 (s, 1H), 7.69 (d, J = 8.8 Hz, 1H), 6.78 (s, 1H), 2.26 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.1, 169.1, 157.9, 156.0, 152.7, 139.9, 126.8, 123.9, 123.5, 118.7, 115.2, 79.8, 20.6, 14.9; HRMS (EI) Calcd for $C_{15}H_{12}N_3O_3Br$ [M^+] 361.0062, found 361.0063; IR (KBr) ν(cm^{-1}) 1762, 1732, 1597, 1470, 1424, 1204, 1015, 827.

*5-Bromo-1-(4-methylpyrimidin-2-yl)-3-oxoindolin-2-yl acetate (**4s**).* The general procedure described above was followed using substrate **1s** (28.8 mg, 0.1 mmol), $PhI(OAc)_2$ (96.6 mg, 0.3 mmol) and AcOH (1 mL). The residue was purified by preparative TLC plate (petroleum ether:ethyl acetate = 3:1 as eluent) to get the product **4s** (27.4 mg, 76% yield). Yollow solid; mp 158−159 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, J = 8.8 Hz, 1H), 8.41 (d, J = 4.9 Hz, 1H), 7.82 (s, 1H), 7.71 (d, J = 8.7 Hz, 1H), 6.86 (s, 1H), 6.82 (d, J = 5.0 Hz, 1H), 2.48 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.2, 169.1, 168.4, 157.4, 152.7, 139.9, 126.9, 123.6, 119.0, 115.4, 114.4, 79.6, 24.2, 20.6; HRMS (EI) Calcd for $C_{15}H_{12}N_3O_3Br$ [M^+] 361.0062, found 361.0058; IR (KBr) ν(cm^{-1}) 1763, 1730, 1606, 1585, 1563, 1468, 1405, 1225, 1089, 828.

*5-Bromo-1-(5-fluoropyrimidin-2-yl)-3-oxoindolin-2-yl acetate (**4t**).* The general procedure described above was followed using substrate **1t** (29.2 mg, 0.1 mmol), $PhI(OAc)_2$ (96.6 mg, 0.3 mmol) and AcOH (1 mL). The residue was purified by preparative TLC plate (petroleum ether:ethyl acetate = 3:1 as eluent) to get the product **4t** (24.1 mg, 66% yield). Yollow solid; mp 144−146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (dd, J = 8.8 and 2.4 Hz, 1H), 8.48 (s, 2H), 7.84 (s, 1H), 7.80−7.70 (m, 1H), 6.78 (d, J = 2.1 Hz, 1H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.6, 169.0, 155.1, 153.9, 152.6, 152.3, 145.7 (d, J_{C-F} = 22.0 Hz), 140.0, 127.0, 123.6, 118.4, 115.8, 79.9, 20.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −147.6; HRMS (EI) Calcd for $C_{14}H_9N_3O_3FBr$ [M^+] 364.9811, found 364.9810; IR (KBr) ν(cm^{-1})1764, 1728, 1603, 1471, 1423, 1246, 1205, 1135, 1121, 1014.

*5-Bromo-1-(4-methylpyridin-2-yl)-3-oxoindolin-2-yl acetate (**4u**).* The general procedure described above was followed using substrate **1u** (28.7 mg, 0.1 mmol), $PhI(OAc)_2$ (96.6 mg, 0.3 mmol) and AcOH (1 mL). The residue was purified by preparative TLC plate (petroleum ether:CH_2Cl_2 = 1:3 as eluent) to get the product **4u** (17.3 mg, 48% yield). Yollow solid; mp 149−150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, J = 8.9 Hz, 1H), 8.26 (d, J = 5.0 Hz, 1H), 7.80 (s, 1H), 7.67 (dd, J = 8.9 and 1.7 Hz, 1H), 6.86 (d, J = 4.9 Hz, 1H), 6.76 (s, 1H), 6.32 (s, 1H), 2.37 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0, 169.4, 154.3, 152.8, 149.7, 147.8, 139.9, 126.9, 123.0, 119.6, 118.3, 114.4, 111.3, 80.6, 21.5, 20.6; HRMS (EI) Calcd for $C_{16}H_{13}N_2O_3Br$ [M^+] 360.0110, found 360.0106; IR (KBr) ν(cm^{-1})-1750, 1725, 1604, 1463, 1413, 1210, 1179, 1098, 1016.

*5-Bromo-1-(5-methylpyridin-2-yl)-3-oxoindolin-2-yl acetate (**4v**).* The general procedure described above was followed using substrate **1v** (28.7 mg, 0.1 mmol), $PhI(OAc)_2$ (96.6 mg, 0.3 mmol) and AcOH (1 mL). The residue was purified by preparative TLC plate (petroleum ether:CH_2Cl_2 = 1:3 as eluent) to get the product **4v** (18.7 mg, 52% yield). Yollow solid; mp 98−99 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, J = 8.9 Hz, 1H), 8.23 (s, 1H), 7.79 (d, J = 1.9 Hz, 1H), 7.65 (dd, J = 8.9 and 2.1 Hz, 1H), 7.50 (dd, J = 8.5 and 1.9 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 6.31 (s, 1H), 2.31 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0, 169.5, 154.4, 150.5, 148.1, 139.9, 139.0, 127.7, 126.9, 122.8, 117.8, 114.2, 110.7, 80.7, 20.6, 17.7; HRMS (EI) Calcd for $C_{16}H_{13}N_2O_3Br$ [M^+] 360.0110, found 360.0124; IR (KBr) ν(cm^{-1}) 1740, 1601, 1487, 1463, 1391, 1287, 1186, 1123, 823.

*5-Bromo-1-(6-chloropyridin-2-yl)-3-oxoindolin-2-yl acetate (**4w**).* The general procedure described above was followed using substrate **1w** (29.1 mg, 0.1 mmol), $PhI(OAc)_2$ (96.6 mg, 0.3 mmol) and AcOH (1 mL). The residue was purified by preparative TLC plate (petroleum ether:CH_2Cl_2 = 1:3 as eluent) to get the product **4w** (18.2 mg, 50% yield). Yollow solid; mp 122−124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, J = 8.8 Hz, 1H), 7.82 (s, 1H), 7.74 (d, J = 8.9 Hz, 1H), 7.64 (t, J = 7.9 Hz, 1H), 7.02 (d, J = 7.7 Hz, 1H), 6.82 (d, J = 8.2 Hz, 1H), 6.27 (s, 1H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.1, 169.3, 153.1, 152.1, 149.5, 140.6, 140.2, 126.9, 123.1, 118.8, 117.7, 115.4, 108.1, 80.1, 20.5; HRMS (EI) Calcd for $C_{15}H_{10}N_2O_3ClBr$ [M^+] 379.9563, found 379.9556; IR (KBr) ν(cm^{-1}) 1755, 1732, 1583, 1463, 1430, 1369, 1218, 1105, 980, 781.

*Procedure for the Preparation of **4a** from Substrate **2a** with PhI(OAc)$_2$.* To a 25 mL of round-bottom flask equipped with a stirrer was charged with **2a** (15.7 mg, 0.05 mmol), $PhI(OAc)_2$ (16.1 mg, 0.05 mmol). Acetic acid (0.5 mL) was added to the reaction flask via a syringe. The reaction flask was charged with condenser. The reaction mixture was stirred at 50 °C under air for 12 h and monitored by TLC. The reaction mixture was cooled down to room temperature, diluted with aqueous NH_3 (5 M, 5 mL) and brine, and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was then purified by preparative TLC plate (petroleum ether:ethyl acetate = 3:1 as eluent) to get the product **4a** (10.8 mg, 80% yield).

General Procedure for the Preparation of 4aa or 4ab from *N*-Protected Indole Derivative (1a) with PhI(OAc)$_2$. To a 25 mL of round-bottom flask equipped with a stirrer was charged with **1a** (0.1

DOI: 10.1021/acs.joc.6b02078
J. Org. Chem. 2016, 81, 11081−11094

mmol), $PhI(OAc)_2$ (0.3 mmol). One mL of CD_3COOD (or CH_3CH_2COOH) was then added to the reaction flask via a syringe. The reaction flask was charged with condenser. The reaction mixture was stirred at 50 °C under air and monitored by TLC. The reaction mixture was cooled down to room temperature, diluted with aqueous NH_3 (5 M, 5 mL) and brine, and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was then purified by preparative TLC plate (petroleum ether:ethyl acetate = 3:1 as eluent) to get the product **4aa** (or **4ab**).

*[D_3]-3-Oxo-1-(pyrimidin-2-yl)indolin-2-yl acetate (**4aa**).* The general procedure described above was followed using **1a** (19.5 mg, 0.1 mmol), $PhI(OAc)_2$ (96.6 mg, 0.3 mmol) and 1 mL of CD_3COOD. The residue was then purified by preparative TLC plate (petroleum ether:ethyl acetate = 3:1 as eluent) to get the product **4aa** (21.3 mg, 79%). ^1H NMR (600 MHz, $CDCl_3$) δ 8.73 (d, J = 8.4 Hz, 1H), 8.59 (d, J = 4.8 Hz, 2H), 7.76 (d, J = 7.6 Hz, 1H), 7.72−7.64 (m, 1H), 7.15 (t, J = 7.4 Hz, 1H), 6.94 (t, J = 4.8 Hz, 1H), 6.89 (s, 1H); ^{13}C NMR (150 MHz, CDCl3) δ 193.3, 169.3, 157.9, 157.8, 153.8, 137.7, 124.5, 122.9, 122.1, 117.3, 114.6, 79.6.

*3-Oxo-1-(pyrimidin-2-yl)indolin-2-yl propionate (**4ab**).* The general procedure described above was followed using **1a** (19.5 mg, 0.1 mmol), $PhI(OAc)_2$ (96.6 mg, 0.3 mmol) and 1 mL of CH_3CH_2COOH. The residue was then purified by preparative TLC plate (petroleum ether:ethyl acetate = 3:1 as eluent) to get the product **4ab** (17.9 mg, 63%). Yollow solid; mp 113−114 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, J = 8.4 Hz, 1H), 8.58 (d, J = 4.7 Hz, 2H), 7.76 (d, J = 7.5 Hz, 1H), 7.67 (t, J = 7.7 Hz, 1H), 7.14 (t, J = 7.4 Hz, 1H), 6.93 (t, J = 4.7 Hz, 1H), 6.88 (s, 1H), 2.39 (q, J = 7.5 Hz, 2H), 1.14 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.4, 172.8, 157.8, 153.8, 137.6, 124.4, 122.8, 122.1, 117.3, 114.6, 79.7, 27.3, 8.9; HRMS (EI) Calcd for $C_{15}H_{13}N_3O_3$ [M^+] 283.0957, found 283.0954; IR (KBr) ν(cm^{-1}) 1753, 1729, 1610, 1581, 1470, 1434, 1137, 1081, 761.

Gram Scale Reaction (eq 4). To a 50 mL of round-bottom flask equipped with a stirrer was charged with substrate **1a** (1.171 g, 6.0 mol) and $PhI(OAc)_2$ (5.796 g, 18.0 mol). Acetic acid (10 mL) was added to the reaction flask via a syringe. The reaction flask was charged with condenser. The reaction mixture was stirred at 80 °C under air for 13 h and monitored by TLC. Then, the reaction mixture was cooled down to room temperature, diluted with aqueous NH_3 and brine, and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phase was dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was purified by flash chromatography (Silica gel, eluent: petroleum ether:ethyl acetate = 10:1) to afford the product **4a** as a yellow solid (0.96 g, 60% yield).

To a 25 mL of round-bottom flask equipped with a stirrer was charged with substrate **4a** (269.0 mg, 1.0 mol), Mesitylene (150.0 mg, 1.0 mol) and DCE (5 mL). Then, TfOH (240 mg, 4.0 mol) was added to the reaction flask via a syringe. The reaction mixture was stirred at room temperature for 24 h and monitored by TLC. Then, the reaction mixture was diluted with aqueous NH_3 and brine, and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phase was dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was purified by flash chromatography (Silica gel, eluent: petroleum ether:ethyl acetate = 10:1) to afford the product **5** as a yellow solid (238.3 mg, 72% yield).

*2-Mesityl-1-(pyrimidin-2-yl)indolin-3-one (**5**).* Yollow solid; mp 160−161 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.79 (d, J = 8.5 Hz, 1H), 8.45 (d, J = 4.8 Hz, 2H), 7.81 (d, J = 7.6 Hz, 1H), 7.69 (t, J = 7.3 Hz, 1H), 7.15 (t, J = 7.4 Hz, 1H), 6.93 (s, 1H), 6.77 (t, J = 4.8 Hz, 1H), 6.63 (s, 1H), 6.00 (s, 1H), 2.73 (s, 3H), 2.22 (s, 3H), 1.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.4, 158.3, 157.5, 154.4, 139.5, 137.1, 136.9, 135.7, 130.3, 130.2, 129.2, 124.3, 123.6, 122.1, 116.9, 113.8, 66.7, 21.1, 20.8, 19.8; HRMS (EI) Calcd for $C_{21}H_{19}N_3O$ [M^+] 329.1528, found 329.1530; IR (KBr) ν(cm^{-1}) 1708, 1609, 1577, 1470, 1438, 1313, 1151, 756.

General Procedure for the Synthesis of the C-3 Dichlorinated Oxindoles (7) from *N*-Protected Indole Derivatives (1) Using $PhICl_2$ Reagent. To a 25 mL of round-bottom flask equipped with a stirrer was charged with substrate **1** (0.1 mmol), $PhICl_2$ (0.3 mmol). Acetic acid (1 mL) was added to the reaction flask via a syringe. The reaction flask was charged with condenser. The reaction mixture was stirred at 50 °C under air for 30 min and monitored by TLC. Then, the reaction mixture was cooled down to room temperature, diluted with aqueous NH_3 (5 M, 5 mL) and brine, and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was then purified by preparative TLC plate (petroleum ether:ethyl acetate = 3:1 as eluent) to get the product **7**.

*3,3-Dichloro-1-(pyrimidin-2-yl)indolin-2-one (**7a**).* The general procedure described above was followed using substrate **1a** (19.5 mg, 0.1 mmol), $PhICl_2$ (82.5 mg, 0.3 mmol) and AcOH (1 mL). The residue was purified by preparative TLC plate (petroleum ether:ethyl acetate = 3:1 as eluent) to get the product **7a** (22.5 mg, 81% yield). White solid; mp 81−82 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.90 (d, J = 4.8 Hz, 2H), 7.77−7.68 (m, 2H), 7.42 (t, J = 7.8 Hz, 1H), 7.35 (t, J = 4.8 Hz, 1H), 7.29 (t, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 158.8, 155.2, 138.1, 131.7, 128.6, 125.4, 125.0, 119.6, 113.7, 74.5; HRMS (EI) Calcd for $C_{12}H_7N_3OCl_2$ [M^+] 278.9966, found 278.9971; IR (KBr) ν(cm^{-1})1767, 1609, 1567, 1483, 1468, 1409, 1365, 1176, 753.

*3,3-Dichloro-5-methyl-1-(pyrimidin-2-yl)indolin-2-one (**7e**).* The general procedure described above was followed using substrate **1e** (20.9 mg, 0.1 mmol), $PhICl_2$ (82.5 mg, 0.3 mmol) and AcOH (1 mL). The residue was purified by preparative TLC plate (petroleum ether:ethyl acetate = 3:1 as eluent) to get the product **7e** (18.9 mg, 64% yield). White solid; mp 151−152 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.88 (d, J = 4.7 Hz, 2H), 7.65 (d, J = 8.3 Hz, 1H), 7.53 (s, 1H), 7.32 (t, J = 4.7 Hz, 1H), 7.21 (d, J = 8.2 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 158.7, 155.4, 135.7, 135.4, 132.3, 128.5, 125.3, 119.4, 113.6, 74.7, 21.0; HRMS (EI) Calcd for $C_{13}H_9N_3OCl_2$ [M^+] 293.0123, found 293.0130; IR (KBr) ν(cm^{-1})-1761, 1568, 1488, 1405, 1355, 1190, 815.

*3,3,4-Trichloro-1-(pyrimidin-2-yl)indolin-2-one (**7f**).* The general procedure described above was followed using substrate **1f** (23.0 mg, 0.1 mmol), $PhICl_2$ (82.5 mg, 0.3 mmol) and AcOH (1 mL). The residue was purified by preparative TLC plate (petroleum ether:ethyl acetate = 3:1 as eluent) to get the product **7f** (23.9 mg, 76% yield). White solid; mp 168−169 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.92 (d, J = 4.8 Hz, 2H), 7.65 (d, J = 8.1 Hz, 1H), 7.42−7.34 (m, 2H), 7.28−7.22 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 158.9, 154.9, 140.0, 132.8, 132.4, 126.4, 124.5, 119.9, 111.8, 73.7; HRMS (EI) Calcd for $C_{12}H_6N_3OCl_3$ [M^+] 312.9576, found 312.9570; IR (KBr) ν(cm^{-1}) 1761, 1601, 1567, 1449, 1405, 1355, 1162, 785, 676.

*3,3,5-Trichloro-1-(pyrimidin-2-yl)indolin-2-one (**7g**).* The general procedure described above was followed using substrate **1g** (23.0 mg, 0.1 mmol), $PhICl_2$ (82.5 mg, 0.3 mmol) and AcOH (1 mL). The residue was purified by preparative TLC plate (petroleum ether:ethyl acetate = 3:1 as eluent) to get the product **7g** (24.3 mg, 77% yield). White solid; mp 117−118 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.89 (d, J = 4.7 Hz, 2H), 7.77 (d, J = 8.7 Hz, 1H), 7.70 (s, 1H), 7.45−7.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 158.8, 155.1, 136.6, 131.7, 130.8, 130.0, 125.1, 119.7, 115.3, 73.6; HRMS (EI) Calcd for $C_{12}H_6N_3OCl_3$ [M^+] 312.9576, found 312.9582; IR (KBr) ν(cm^{-1}) 1769, 1569, 1476, 1404, 1353, 1171, 823.

*3,3,6-Trichloro-1-(pyrimidin-2-yl)indolin-2-one (**7h**).* The general procedure described above was followed using substrate **1h** (23.0 mg, 0.1 mmol), $PhICl_2$ (82.5 mg, 0.3 mmol) and AcOH (1 mL). The residue was purified by preparative TLC plate (petroleum ether:ethyl acetate = 3:1 as eluent) to get the product **7h** (22.3 mg, 71% yield). White solid; mp 160−161 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.92 (d, J = 4.8 Hz, 2H), 7.85 (s, 1H), 7.66 (d, J = 8.2 Hz, 1H), 7.37 (t, J = 4.8 Hz, 1H), 7.28 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 158.9, 155.1, 139.1, 137.7, 127.0, 126.0, 125.6, 119.8, 114.6, 73.7; HRMS (EI) Calcd for $C_{12}H_6N_3OCl_3$ [M^+] 312.9576, found 312.9579; IR (KBr) ν(cm^{-1}) 1770, 1610, 1570, 1482, 1406, 1363, 1170, 802.

*3,3-Dichloro-6-fluoro-1-(pyrimidin-2-yl)indolin-2-one (**7j**).* The general procedure described above was followed using substrate **1j**

DOI: 10.1021/acs.joc.6b02078
J. Org. Chem. 2016, 81, 11081−11094

(21.3 mg, 0.1 mmol), $PhICl_2$ (82.5 mg, 0.3 mmol) and AcOH (1 mL). The residue was purified by preparative TLC plate (petroleum ether:ethyl acetate = 3:1 as eluent) to get the product **7j** (17.7 mg, 60% yield). White solid; mp 146−147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (d, J = 4.8 Hz, 2H), 7.70 (dd, J = 8.4 and 5.4 Hz, 1H), 7.59 (dd, J = 9.6 and 2.1 Hz, 1H), 7.37 (t, J = 4.8 Hz, 1H), 6.98 (td, J = 8.6 and 2.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 164.3 (d, J_{C-F} = 249.3 Hz), 158.8, 155.1, 139.7 (d, J_{C-F} = 12.6 Hz), 126.6 (d, J_{C-F} = 10.3 Hz), 124.3, 119.7, 112.4 (d, J_{C-F} = 23.3 Hz), 102.8 (d, J_{C-F} = 29.7 Hz), 73.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ −104.60; HRMS (EI) Calcd for $C_{12}H_6N_3OFCl_2$ [M^+] 296.9872, found 296.9878; IR (KBr) ν(cm^{-1})1773, 1606, 1570, 1497, 1405, 1368, 1165, 1092, 799, 770, 659.

*3,3-Dichloro-5,6-difluoro-1-(pyrimidin-2-yl)indolin-2-one (**7k**).* The general procedure described above was followed using substrate **1k** (23.1 mg, 0.1 mmol), $PhICl_2$ (82.5 mg, 0.3 mmol) and AcOH (1 mL). The residue was purified by preparative TLC plate (petroleum ether:ethyl acetate = 3:1 as eluent) to get the product **7k** (26.4 mg, 84% yield). White solid; mp 146−147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (d, J = 4.8 Hz, 2H), 7.88−7.75 (m, 1H), 7.61−7.47 (m, 1H), 7.37 (t, J = 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 158.8, 155.0 (d, J_{C-F} = 4.4 Hz), 152.1 (dd, J_{C-F} = 252.4 and 14.1 Hz), 148.1 (dd, J_{C-F} = 247.3 and 15.8 Hz), 134.5 (d, J_{C-F} = 10.6 Hz), 124.3, 119.7 (d, J_{C-F} = 3.9 Hz), 114.2 (d, J_{C-F} = 20.8 Hz), 105.1 (d, J_{C-F} = 25.2 Hz), 73.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ −129.0 (d, J = 20.8 Hz), −139.7 (d, J = 20.6 Hz); HRMS (EI) Calcd for $C_{12}H_5N_3OF_2Cl_2$ [M^+] 314.9778, found 314.9774; IR (KBr) ν(cm^{-1}) 1775, 1622, 1573, 1499, 1409, 1322, 1138, 786.

*3,3-Dichloro-1-(pyrimidin-2-yl)-4-(pyrimidin-2-yloxy)indolin-2-one (**7m**).* The general procedure described above was followed using substrate **1m** (28.9 mg, 0.1 mmol), $PhICl_2$ (82.5 mg, 0.3 mmol) and AcOH (1 mL). The residue was purified by preparative TLC plate (petroleum ether:ethyl acetate = 1:1 as eluent) to get the product **7m** (30.2 mg, 81% yield). White solid; mp 198−199 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (d, J = 3.9 Hz, 2H), 8.60 (d, J = 3.9 Hz, 2H), 7.65−7.58 (m, 1H), 7.51−7.44 (m, 1H), 7.36 (t, J = 4.8 Hz, 1H), 7.11 (t, J = 4.7 Hz, 1H), 7.06 (d, J = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 164.5, 159.8, 158.8, 155.0, 149.9, 139.6, 132.5, 119.8, 119.52, 119.45, 117.0, 110.5, 72.3; HRMS (EI) Calcd for $C_{16}H_9N_5O_2Cl_2$ [M^+] 373.0133, found 373.0128; IR (KBr) ν(cm^{-1}) 1772, 1622, 1572, 1462, 1404, 1361, 1294, 1256, 1201, 916, 815, 656.

*3,3-Dichloro-1-(pyrimidin-2-yl)-5-(pyrimidin-2-yloxy)indolin-2-one (**7n**).* The general procedure described above was followed using substrate **1n** (28.9 mg, 0.1 mmol), $PhICl_2$ (82.5 mg, 0.3 mmol) and AcOH (1 mL). The residue was purified by preparative TLC plate (petroleum ether:ethyl acetate = 1:1 as eluent) to get the product **7n** (26.9 mg, 72% yield). White solid; mp 216−217 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (d, J = 4.8 Hz, 2H), 8.58 (d, J = 4.7 Hz, 2H), 7.88 (d, J = 8.8 Hz, 1H), 7.61 (d, 1H), 7.34 (t, J = 4.8 Hz, 1H), 7.27 (dd, J = 8.8 and 2.3 Hz, 1H), 7.09 (t, J = 8.8, 4.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 165.0, 159.8, 158.7, 155.3, 150.2, 135.2, 129.6, 125.2, 119.5, 118.7, 116.6, 115.1, 74.0; HRMS (EI) Calcd for $C_{16}H_9N_5O_2Cl_2$ [M^+] 373.0133, found 373.0137; IR (KBr) ν(cm^{-1}) 1763, 1571, 1486, 1405, 1303, 1176, 814.

*5-Bromo-3,3-dichloro-1-(5-methoxypyrimidin-2-yl)indolin-2-one (**7q**).* The general procedure described above was followed using substrate **1q** (30.4 mg, 0.1 mmol), $PhICl_2$ (82.5 mg, 0.3 mmol) and AcOH (1 mL). The residue was purified by preparative TLC plate (petroleum ether:ethyl acetate = 3:1 as eluent) to get the product **7q** (35.3 mg, 91% yield). White solid; mp 157−158 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 2H), 7.81 (s, 1H), 7.49 (d, J = 8.6 Hz, 1H), 7.42 (d, J = 8.5 Hz, 1H), 3.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 152.2, 147.5, 144.7, 137.6, 134.5, 130.2, 127.9, 117.5, 114.6, 73.5, 56.4; HRMS (EI) Calcd for $C_{13}H_8N_3O_2Cl_2Br$ [M^+] 386.9177, found 386.9173; IR (KBr) ν(cm^{-1}) 1766, 1561, 1474, 1451, 1422, 1359, 1283, 1175, 826, 605.

*5-Bromo-3,3-dichloro-1-(4-methylpyrimidin-2-yl)indolin-2-one (**7s**).* The general procedure described above was followed using substrate **1s** (28.8 mg, 0.1 mmol), $PhICl_2$ (82.5 mg, 0.3 mmol) and AcOH (1 mL). The residue was purified by preparative TLC plate (petroleum ether:ethyl acetate = 3:1 as eluent) to get the product **7s** (24.2 mg, 65% yield). White solid; mp 140−141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, J = 5.0 Hz, 1H), 7.83 (d, J = 1.7 Hz, 1H), 7.63 (d, J = 8.7 Hz, 1H), 7.52 (dd, J = 8.7 and 1.8 Hz, 1H), 7.20 (d, J = 5.0 Hz, 1H), 2.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 166.6, 158.3, 154.7, 137.4, 134.6, 130.3, 127.9, 119.4, 117.7, 115.5, 73.6, 24.2; HRMS (EI) Calcd for $C_{13}H_8N_3OCl_2Br$ [M^+] 370.9228, found 370.9241; IR (KBr) ν(cm^{-1}) 1769, 1601, 1472, 1432, 1378, 1174, 833, 667, 550.

*3-Chloro-3-methyl-1-(pyrimidin-2-yl)indolin-2-one (**7o**).* The general procedure described above was followed using substrate **1o** (20.9 mg, 0.1 mmol), $PhICl_2$ (82.5 mg, 0.3 mmol) and AcOH (1 mL). The residue was purified by preparative TLC plate (petroleum ether:ethyl acetate = 3:1 as eluent) to get the product **7o** (24.9 mg, 96% yield). White solid; mp 96−97 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (d, J = 4.7 Hz, 2H), 7.70 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 7.4 Hz, 1H), 7.34 (t, J = 7.8 Hz, 1H), 7.30 (t, J = 4.7 Hz, 1H), 7.21 (t, J = 7.5 Hz, 1H), 2.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 158.6, 155.6, 139.4, 130.3, 130.0, 124.7, 123.9, 119.2, 113.2, 62.0, 26.3; HRMS (EI) Calcd for $C_{13}H_{10}N_3OCl$ [M^+] 259.0512, found 259.0517; IR (KBr) ν(cm^{-1}) 1752, 1613, 1569, 1483, 1409, 1369, 1186, 754.

General Procedure for the Dichlorination Reaction of *N*-Protected Indole Derivatives (1) with $PhICl_2$ Reagent. To a 25 mL of round-bottom flask equipped with a stirrer was charged with substrate **1** (0.1 mmol), $PhICl_2$ (0.2 mmol). Acetic acid (1 mL) was added to the reaction flask via a syringe. The reaction flask was charged with condenser. The reaction mixture was stirred at 50 °C under air for 30 min and monitored by TLC. The reaction mixture was cooled down to room temperature, diluted with aqueous NH_3 (5 M, 5 mL) and brine, and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was then purified by preparative TLC plate (petroleum ether:ethyl acetate = 3:1 as eluent) to get the product **6**.

*2,3-Dichloro-1-(pyrimidin-2-yl)-1H-indole (**6a**).* The general procedure described above was followed using substrate **1a** (19.5 mg, 0.1 mmol), $PhICl_2$ (55 mg, 0.2 mmol) and AcOH (1 mL). The residue was purified by preparative TLC plate (petroleum ether:ethyl acetate = 3:1 as eluent) to get the product **6a** (16.1 mg, 61% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (d, J = 4.8 Hz, 2H), 8.05 (d, J = 7.5 Hz, 1H), 7.64−7.56 (m, 1H), 7.36−7.26 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 156.3, 134.5, 125.6, 124.7, 122.8, 121.7, 118.6, 117.8, 113.0, 109.9.

*2,3-Dichloro-5-methyl-1-(pyrimidin-2-yl)-1H-indole (**6e**).* The general procedure described above was followed using substrate **1e** (20.9 mg, 0.1 mmol), $PhICl_2$ (55.0 mg, 0.2 mmol) and AcOH (1 mL). The residue was purified by preparative TLC plate (petroleum ether:ethyl acetate = 3:1 as eluent) to get the product **6e** (17.7 mg, 64% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (d, J = 4.8 Hz, 2H), 7.95 (d, J = 8.5 Hz, 1H), 7.38 (s, 1H), 7.25 (t, J = 4.7 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 156.4, 132.8, 132.5, 126.2, 125.8, 121.4, 118.4, 117.5, 112.9, 109.7, 21.3.

*2,3,5-Trichloro-1-(pyrimidin-2-yl)-1H-indole (**6g**).* The general procedure described above was followed using substrate **1g** (23.0 mg, 0.1 mmol), $PhICl_2$ (55.0 mg, 0.2 mmol) and AcOH (1 mL). The residue was purified by preparative TLC plate (petroleum ether:ethyl acetate = 3:1 as eluent) to get the product **6g** (18.1 mg, 61% yield). White solid; mp 150−151 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (d, J = 4.8 Hz, 2H), 8.00 (d, J = 8.9 Hz, 1H), 7.57 (d, J = 1.8 Hz, 1H), 7.31 (t, J = 4.8 Hz, 1H), 7.29−7.24 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 156.1, 132.7, 128.7, 126.7, 125.0, 123.1, 118.8, 117.4, 114.6, 109.2; HRMS (EI) Calcd for $C_{12}H_6N_3Cl_3$ [M^+] 296.9627, found 296.9636; IR (KBr) ν(cm^{-1}) 1567, 1440, 1426, 1329, 1210, 1076, 792.

*2,3,6-Trichloro-1-(pyrimidin-2-yl)-1H-indole (**6h**).* The general procedure described above was followed using substrate **1h** (23.0 mg, 0.1 mmol), $PhICl_2$ (55.0 mg, 0.2 mmol) and AcOH (1 mL). The residue was purified by preparative TLC plate (petroleum ether:ethyl acetate = 3:1 as eluent) to get the product **6h** (20.5 mg, 69% yield). White solid; mp 131−132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (d,

DOI: 10.1021/acs.joc.6b02078
J. Org. Chem. 2016, 81, 11081−11094

J = 4.7 Hz, 2H), 8.12 (s, 1H), 7.50 (dd, J = 8.3 and 2.4 Hz, 1H), 7.29 (dd, J = 9.4 and 2.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 156.0, 134.6, 130.8, 124.2, 123.5, 122.3, 118.8, 118.7, 113.5, 109.9; HRMS (EI) Calcd for $C_{12}H_6N_3Cl_3$ [M^+] 296.9627, found 296.9628; IR (KBr) ν(cm^{-1}) 1613, 1575, 1425, 1339, 1211, 796.

*5-Bromo-2,3-dichloro-1-(pyrimidin-2-yl)-1H-indole (**6i**).* The general procedure described above was followed using substrate **1i** (27.4 mg, 0.1 mmol), $PhICl_2$ (55.0 mg, 0.2 mmol) and AcOH (1 mL). The residue was purified by preparative TLC plate (petroleum ether:ethyl acetate = 3:1 as eluent) to get the product **6i** (19.3 mg, 56% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (d, J = 4.8 Hz, 2H), 7.95 (d, J = 8.8 Hz, 1H), 7.73 (s, 1H), 7.40 (dd, J = 8.9 and 1.7 Hz, 1H), 7.31 (t, J = 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 156.1, 133.1, 127.6, 127.2, 123.0, 120.5, 118.9, 116.2, 114.9, 109.1.

*2,3-Dichloro-6-fluoro-1-(pyrimidin-2-yl)-1H-indole (**6j**).* The general procedure described above was followed using substrate **1j** (21.3 mg, 0.1 mmol), $PhICl_2$ (55.0 mg, 0.2 mmol) and AcOH (1 mL). The residue was purified by preparative TLC plate (petroleum ether:ethyl acetate = 3:1 as eluent) to get the product **6j** (22.1 mg, 78% yield). White solid; mp 134−135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (d, J = 4.5 Hz, 2H), 7.85 (d, J = 10.1 Hz, 1H), 7.52 (dd, J = 8.4 and 5.4 Hz, 1H), 7.33−7.27 (m, 1H), 7.06 (t, J = 8.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2 (d, J_{C-F} = 239.7 Hz), 158.5, 156.2, 134.5 (d, J_{C-F} = 13.1 Hz), 122.1, 121.6, 118.8 (d, J_{C-F} = 10.0 Hz), 118.7, 111.5, (d, J_{C-F} = 25.6 Hz), 110.0, 100.7 (d, J_{C-F} = 28.9 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −116.4; HRMS (EI) Calcd for $C_{12}H_6N_3FCl_2$ [M^+] 280.9923, found 280.9924; IR (KBr) ν(cm^{-1}) 1621, 1567, 1488, 1416, 1348, 1209, 1152, 817, 671.

*2,3-Dichloro-5,6-difluoro-1-(pyrimidin-2-yl)-1H-indole (**6k**).* The general procedure described above was followed using substrate **1k** (23.1 mg, 0.1 mmol), $PhICl_2$ (55.0 mg, 0.2 mmol) and AcOH (1 mL). The residue was purified by preparative TLC plate (petroleum ether:ethyl acetate = 3:1 as eluent) to get the product **6k** (19.5 mg, 65% yield). White solid; mp 137−138 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.87 (d, J = 4.8 Hz, 2H), 8.02 (dd, J = 13.9 and 8.6 Hz, 1H), 7.35 (dd, J = 9.6 and 7.7 Hz, 1H), 7.33 (t, J = 4.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.6, 158.3, 156.1, 149.6 (dd, J_{C-F} = 141.0 and 14.8 Hz), 147.7 (dd, J_{C-F} = 140.7 and 14.9 Hz), 129.5 (d, J_{C-F} = 11.8 Hz), 122.6 (d, J_{C-F} = 3.7 Hz), 121.5 (dd, J_{C-F} = 8.6 and 2.1 Hz), 118.9, 105.1 (d, J_{C-F} = 20.7 Hz), 103.0 (d, J_{C-F} = 24.6 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ −139.6 (d, J = 21.1 Hz), 142.5 (d, J = 21.0 Hz); HRMS (EI) Calcd for $C_{12}H_5N_3F_2Cl_2$ [M^+] 298.9829, found 298.9822; IR (KBr) ν(cm^{-1}) 1631, 1598, 1571, 1468, 1428, 1178, 861.

*2,3-Dichloro-1-(pyrimidin-2-yl)-5-(pyrimidin-2-yloxy)-1H-indole (**6n**).* The general procedure described above was followed using substrate **1n** (28.9 mg, 0.1 mmol), $PhICl_2$ (55.0 mg, 0.2 mmol) and AcOH (1 mL). The residue was purified by preparative TLC plate (petroleum ether:CH_2Cl_2 = 1:3 as eluent) to get the product **6n** (21.1 mg, 59% yield). White solid; mp 172−173 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96−8.73 (m, 2H), 8.55 (d, J = 4.6 Hz, 2H), 8.15 (d, J = 9.0 Hz, 1H), 7.43 (d, J = 2.1 Hz, 1H), 7.32−7.27 (m, 1H), 7.16 (dd, J = 9.0 and 2.2 Hz, 1H), 7.03 (t, J = 4.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 159.7, 158.5, 156.3, 148.7, 132.0, 126.4, 122.8, 119.1, 118.7, 116.1, 114.6, 110.4, 109.9; HRMS (EI) Calcd for $C_{16}H_9N_5OCl_2$ [M^+] 357.0184, found 357.0182; IR (KBr) ν(cm^{-1}) 1570, 1475, 1453, 1423, 1406, 1315, 1166.

*5-Bromo-2,3-dichloro-1-(4-methylpyrimidin-2-yl)-1H-indole (**6s**).* The general procedure described above was followed using substrate **1s** (28.8 mg, 0.1 mmol), $PhICl_2$ (55.0 mg, 0.2 mmol) and AcOH (1 mL). The residue was purified by preparative TLC plate (petroleum ether:ethyl acetate = 3:1 as eluent) to get the product **6s** (20.7 mg, 58% yield). White solid; mp 117−118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, J = 4.8 Hz, 1H), 7.91 (d, J = 8.8 Hz, 1H), 7.72 (s, 1H), 7.39 (d, J = 8.8 Hz, 1H), 7.16 (d, J = 4.7 Hz, 1H), 2.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 158.1, 155.7, 133.1, 127.5, 127.1, 123.0, 120.4, 118.5, 116.0, 114.8, 108.6, 24.2; HRMS (EI) Calcd for $C_{13}H_8N_3Cl_2Br$ [M^+] 354.9279, found 354.9281; IR (KBr) ν(cm^{-1}) 1584, 1557, 1532, 1445, 1411, 1312, 1214, 829, 790.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02078.

In situ IR spectroscopy, H_2O^{18}-labeling experiments, X-ray crystallographic analysis, ^{1}H and ^{13}C NMR spectra of new compounds (PDF)

Crystal data (CIF)

Crystal data (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: jkliu@mail.kib.ac.cn.

*E-mail: bliu0210@yahoo.com.

*E-mail: yz_sumc@163.com.

*E-mail: wubin@mail.kib.ac.cn.

Author Contributions

⊥Dongdong Xu and Wen-Wu Sun contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully thank "Hundred Talents Project" of Chinese Academy of Science, "High-end Science and Technology Talents Program" of Yunnan Province (2011HA008), the National Natural Science Foundation of China (Nos. 21472198) and Grant (2014FA039) from Yunnan Province of China for financial support of this work. We thank Dr. Xiaonian Li for the X-ray crystallographic analysis.

■ REFERENCES

(1) (a) Mérour, J.-Y.; Piroëlle, S.; Joseph, B. *Trends Heterocycl. Chem.* **1997**, *5*, 115. (b) Gul, W.; Hamann, M. T. *Life Sci.* **2005**, *78*, 442. (c) Wu, Y.-J. *Top. Heterocycl. Chem.* **2010**, *26*, 1.

(2) (a) Ihara, M.; Fukumoto, K. *Nat. Prod. Rep.* **1994**, *11*, 493. (b) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (c) Lewis, S. E. *Tetrahedron* **2006**, *62*, 8655. (d) Saracoglu, N. *Top. Heterocycl. Chem.* **2007**, *11*, 1.

(3) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichimica Acta* **2007**, *40*, 32.

(4) Wang, X.; Lane, B. S.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 4996.

(5) (a) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 9578. (b) Liu, C.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 10250. (c) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050. (d) Grimster, N. P.; Gauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3125. (e) Bressy, C.; Alberico, D.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 13148. (f) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972. (g) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172. (h) Stuart, D. R.; Villemure, E.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 12072. (i) Lebrasseur, N.; Larrosa, I. *J. Am. Chem. Soc.* **2008**, *130*, 2926. (j) Jiao, L.; Bach, T. *J. Am. Chem. Soc.* **2011**, *133*, 12990.

(6) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172.

(7) Ackermann, L.; Lygin, A. V. *Org. Lett.* **2011**, *13*, 3332.

(8) (a) Mutule, I.; Suna, E.; Olofsson, K.; Pelcman, B. *J. Org. Chem.* **2009**, *74*, 7195. (b) Choy, P. Y.; Lau, C. P.; Kwong, F. Y. *J. Org. Chem.* **2011**, *76*, 80. (c) Liu, Q.; Li, G.; Yi, H.; Wu, P.; Liu, J.; Lei, A.-W. *Chem. - Eur. J.* **2011**, *17*, 2353. (d) Lubriks, D.; Sokolovs, I.; Suna, E. *Org. Lett.* **2011**, *13*, 4324.

(9) (a) Mehta, V. P.; Punji, B. *RSC Adv.* **2013**, *3*, 11957. (b) Sun, C.-L.; Shi, Z.-J. *Chem. Rev.* **2014**, *114*, 9219.

DOI: 10.1021/acs.joc.6b02078
J. Org. Chem. 2016, 81, 11081−11094

(10) (a) *Hypervalent Iodine Chemistry: Preparation, Structure and Synthetic Application of Polyvalent Iodine Compounds*; Zhdankin, V. V., Ed; John Wiley & Sons: Chichester, 2013. (b) Wirth, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3656. (c) Merritt, E. A.; Olofsson, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9052.
(11) Liu, Q.; Zhao, Q.-Y.; Liu, J.; Wu, P.; Yi, H.; Lei, A.-W. *Chem. Commun.* **2012**, *48*, 3239.
(12) Soni, V.; Patel, U. N.; Punji, B. *RSC Adv.* **2015**, *5*, 57472.
(13) Liu, K.-X.; Wen, P.; Liu, J.; Huang, G.-S. *Synthesis* **2010**, *21*, 3623.
(14) The CIF files of **4a** and **7g** have been deposited with Cambridge Crystallographic Data Centre (# CCDC 1475922 and 1475923). These data can be obtained free of charge from CCDC via www.ccdc.cam.ac.uk/data_request/cif.
(15) Sun, Y.; Fan, R.-H. *Chem. Commun.* **2010**, *46*, 6834.
(16) Preparation of 3,3-dichloroindole-2-ones with $PhICl_2$ using 3-diazo-2-oxindoles and isatin-3-hydrazones as the substrates, see: (a) Murphy, G. K.; Abbas, F. Z.; Poulton, A. V. *Adv. Synth. Catal.* **2014**, *356*, 2919. (b) Coffey, K. E.; Moreira, R.; Abbas, F. Z.; Murphy, G. K. *Org. Biomol. Chem.* **2015**, *13*, 682.
(17) Ackermann, L.; Lygin, A. V. *Org. Lett.* **2011**, *13*, 3332.
(18) (a) Ding, Z.; Yoshikai, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 4698. (b) Shi, J.; Zhou, B.; Yang, Y.; Li, Y. *Org. Biomol. Chem.* **2012**, *10*, 8953.
(19) Liang, L.; Fu, S.; Lin, D.; Zhang, X.-Q.; Deng, Y.; Jiang, H.; Zeng, W. *J. Org. Chem.* **2014**, *79*, 9472.
(20) Zhao, J.; Cheng, X.; Le, J.; Yang, W.; Xue, F.; Zhang, X.; Jiang, C. *Org. Biomol. Chem.* **2015**, *13*, 9000.

DOI: 10.1021/acs.joc.6b02078
J. Org. Chem. 2016, 81, 11081−11094