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Preparation of 2,2-disubstituted 1,2-dihydro-3*H*-indol-3-ones via oxidation of 2-substituted indoles and Mannich-type reaction

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ABSTRACT

A novel preparative method for 2,2-disubstituted 1,2-dihydro-3*H*-indol-3-ones through the oxidation of 2-arylindoles followed by a Mannich-type reaction with carbon nucleophiles is described.

1. Introduction

2,2-Disubstituted 1,2-dihydro-3*H*-indol-3-ones are useful synthetic intermediates for natural products, such as austamide,[1] brevianamides,[2] aristotelone,[3] and duocarmycin A.[4] Therefore, the preparation of 2,2-disubstituted 1,2-dihydro-3*H*-indol-3-ones in a concise manner is highly desirable. Several reported methods for the preparation of 2,2-disubstituted 1,2-dihydro-3*H*-indol-3-ones have utilized acid-, base-, or thermal-induced rearrangements of 2,3-dihydroxyindolines[5] and 3*H*-indol-3-ols,[6] oxidative rearrangement of 2,3-disubstituted indoles,[7] alkylation of 2-substituted 3*H*-indol-3-ones,[8] cyclization of *o*-nitrogenated acetophenones,[9] and so on.[10] Recently, the acid-mediated substitution of 2-alkoxy-1,2-dihydro-3*H*-indol-3-one with aromatic, organosilicon, and organoboron compounds as carbon nucleophiles has been disclosed.[11] Here, we report the details of a new methodology for the preparation of 2,2-disubstituted 1,2-dihydro-3*H*-indol-3-ones **3** through the successive oxidation of indoles **1** and Mannich-type reaction of 2-hydroxy-1,2-dihydro-3*H*-indol-3-ones **2** with various carbon nucleophiles (Fig. 1).[12]

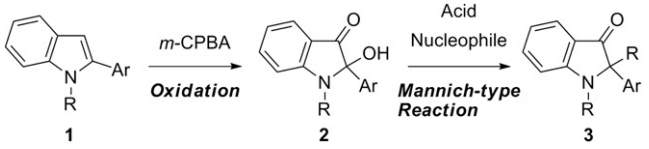

Figure 1. Preparation of 2,2-substituted 1,2-dihydro-3*H*-indol-3-ones.

2. Results and discussion

2.1. Oxidation of 2-substituted indoles

In order to prepare 2-hydoroxy-1,2-dihydro-3*H*-indol-3-ones, the precursor of the subsequent Mannich-type reaction, we investigated the oxidation of 2-substituted indoles. Many oxidations of 2-substituted indoles have been reported;[13–21] however, there are few examples of the production of 2-hydoroxy-1,2-dihydro-3*H*-indol-3-ones from 2-arylindoles.[17b] Previously, we performed MoO_5 oxidation of *N*-acetyl-2-phenylindole to provide 2,3-dioxigenated indolines.[14b] Based on this result, the oxidation of 2-(2-nitrophenyl)indoles **1** was examined (Table 1). However, oxidation of the *N*-acetyl derivative **1a** did not proceed at all (entry 1). Treatment of the *N*-unsubstituted indole **1b** produced the oxidative dimer **5** in 72% yield (entry 2).[14b] In order to accelerate the oxidation, we used the electron-donating methoxymethyl (MOM) substituent on the indole nitrogen and found that the desired reaction occurred to produce **4c** in 21% yield (entry 3).

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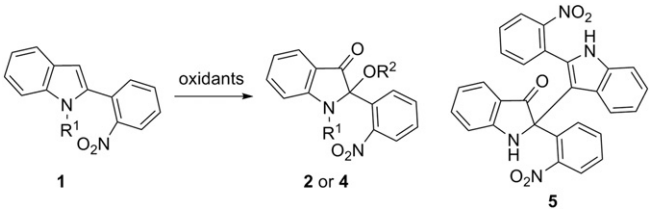
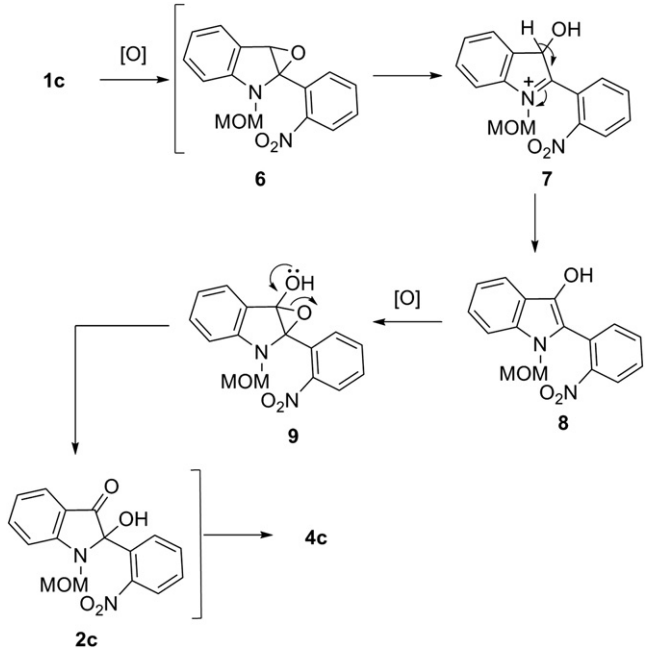
Table 1
Oxidation of 2-substituted indole



Entry	1	R^1	Oxidants (equiv)	Solvents	Time	Results
1	**a**	Ac	$MoO_5 \cdot HMPA \cdot H_2O$ (1.0)	MeOH	2 weeks	No reaction
2	**b**	H	$MoO_5 \cdot HMPA \cdot H_2O$ (1.0)	MeOH	5 days	**5** (72%)
3	**c**	MOM	$MoO_5 \cdot HMPA \cdot H_2O$ (1.0)	MeOH	4 weeks	**4c** (R^2=Me, 21%)
4	**c**	MOM	*m*-CPBA (2.5)	THF	2 h	**2c** (R^2=H, 76%)

A plausible mechanism for the generation of **4c** is as follows (Scheme 1). The 2,3-bond on the indole nucleus of **1c** is oxidized and generates an oxirane ring that opens to furnish iminium **7**. After deprotonation at the 3-position, secondary oxidation occurs at the 2,3-position of **8**. Finally, the oxirane ring in **9** opens to form **2c** and substitution by methanol at the 2-position affords **4c**.



Scheme 1. Plausible mechanism.

Secondary oxidation is faster than primary oxidation as shown in Scheme 1, and Greci et al.[15d] has reported that treatment of *N*-ethyl-2-phenylindole with 1.2 equiv of *m*-CPBA furnished a dimer like **5** in 52% yield. Therefore, we envisioned that treatment of **1c** with 2.5 equiv of *m*-CPBA would effectively furnish aminal **2c** or **4c**. We examined the oxidation of **1c** with 2.5 equiv of *m*-CPBA in THF instead of MoO_5 reagent (Table 1, entry 4).[22] To our delight, 2-hydroxy-1,2-dihydro-3*H*-indol-3-one **2c** was obtained in 76% yield without formation of dimer **5**.

We also found that *p*-methoxybenzyl (PMB) and benzyl (Bn) substituents were best suited for this oxidation in terms of yield and reaction time (Table 2, entries 1,2). *p*-Nitrobenzyl (PNB) derivative **1f** (entry 3) resulted in slightly lower yield than the PMB and Bn derivatives. In entries 4–6, the effects of the substituent at the C2-position of **1** were studied. Phenyl and *o*-methoxyphenyl derivatives **1g**,**h** required shorter reaction times compared with *o*-nitrophenyl **1d** to give **2g**,**h** in 88% and 90% yields, respectively (entries 1 vs 4,5). Oxidation of *p*-methoxyphenyl derivative **1i**, due to the decrease in the bulkiness around the 2,3-position of the indole nucleus, proceeded more smoothly than *o*-methoxy derivative **1h** (entry 5 vs 6). 2-Ethoxycarbonyl indole **1j** bearing a much stronger electron-withdrawing substituent was successfully reacted to afford **2j** (63%), although a prolonged reaction time was required (entry 7). The results listed in Tables 1 and 2 indicate that the electron density on the indole nucleus controlled by the properties of the 1- and 2-substituents affects the reactivity of this oxidation. With compounds **2** readily available, we proceeded to investigate the Mannich-type reaction to assemble the quaternary carbon center.

Table 2
Oxidation of 2-substituted indoles

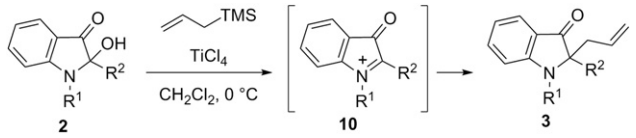
Entry	1	R^1	R^2	Time	Yield (%)
1	**d**	PMB	*o*-$O_2NC_6H_4$	1 h	94
2	**e**	Bn	*o*-$O_2NC_6H_4$	50 min	96
3	**f**	PNB	*o*-$O_2NC_6H_4$	1 h	76
4	**g**	PMB	C_6H_5	50 min	88
5	**h**	PMB	*o*-$MeOC_6H_4$	40 min	90
6	**i**	PMB	*p*-$MeOC_6H_4$	25 min	90
7	**j**	PMB	EtO_2C	5 h	63

PMB: *p*-$MeOC_6H_4CH_2$–, PNB: *p*-$O_2NC_6H_4CH_2$–.

2.2. Mannich-type reaction of 2-hydroxy-1,2-dihydro-3*H*-indol-3-one

As shown in Table 3, when a solution of **2d** and allyltrimethylsilane in CH_2Cl_2 was treated with $TiCl_4$ at 0 °C, the desired reaction proceeded smoothly to afford 2,2-substituted 1,2-dihydro-3*H*-indol-3-one **3d** in 98% yield (entry 1). This result indicates that 2-hydroxy-1,2-dihydro-3*H*-indol-3-one **2** under acidic conditions generates *C*-acyliminium intermediate **10**, which reacts efficiently with allyltrimethylsilane. Although there are many known examples of *N*-acyliminium species in Mannich-type reactions,[23] **10** is a rare type of *C*-acyliminium species.[24] The reaction of benzyl derivative **2e** provided **3e** in high yield (entry 2). In the case of *p*-nitrobenzyl derivative **2f**, the desired product **3f** was obtained in 80% yield together with *N*-dealkylated product **3k** (19%) (entry 3). Next, the effect of the substituent (R^2) at the 2-position was studied. The reaction of 2-aryl derivatives **2g**–**i** proceeded smoothly to

Table 3
Mannich-type reaction of 2-hydroxy-1,2-dihydro-3*H*-indol-3-one



2 10 3

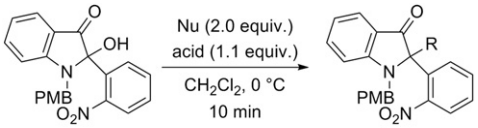
Entry	**2**	R^1	R^2	Time	Yield (%)
1	**d**	PMB	*o*-$O_2NC_6H_4$	5 min	98
2	**e**	Bn	*o*-$O_2NC_6H_4$	5 min	95
3	**f**	PNB	*o*-$O_2NC_6H_4$	5 min	80[a]
4	**g**	PMB	C_6H_5	5 min	90
5	**h**	PMB	*o*-$MeOC_6H_4$	5 min	93
6	**i**	PMB	*p*-$MeOC_6H_4$	5 min	91
7	**j**	PMB	EtO_2C	24 h	35

[a] **3k** (R^1=H, R^2=*o*-$O_2NC_6H_4$) was obtained in 19% yield.

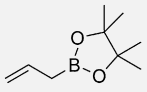
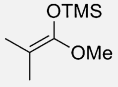
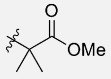
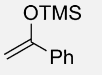
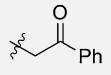
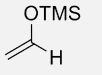
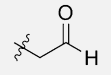
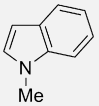
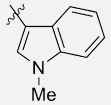
produce the corresponding **3g–i** in excellent yields (entries 4–6); however, ester **2j** required a prolonged reaction time and gave **3j** in low yield (entry 7).

We subsequently explored the scope and the limitations of the Mannich-type reaction of 2-hydroxy-1,2-dihydro-3*H*-indol-3-one **2d** with various carbon nucleophiles (Table 4). A modified Petasis–boronic acid–Mannich reaction with allylboronic ester[25] produced **3d** in 98% yield (entry 1). Alkylations with silylketenacetal and silylenolate also furnished the corresponding carbonyl compounds **3l** and **3m** in high yields, respectively (entries 2,3). When using labile vinyloxytrimethylsilane as a nucleophile under acidic conditions, **3n** was given in low yield (entry 4). The use of camphor sulfonic acid (CSA) instead of $TiCl_4$ improved the yield of **3n** to 56% with recovery of 41% of the starting material **2d** (entry 5). Furan and *N*-methyl indole also worked efficiently in the reaction of **2d** with CSA to provide **3o** and **3p** in excellent yields, respectively (entries 6,7).

Table 4
Mannich-type reaction with various nucleophiles



2d 3d, l-p

Entry	Nu	Acid	R	Yield (%)
1		$TiCl_4$		**d** 98
2		$TiCl_4$		**l** 93
3		$TiCl_4$		**m** 98
4		$TiCl_4$		**n** 39
5		CSA		**n** 56[a]
6		CSA		**o** 98
7		CSA		**p** 98

[a] **2d** was recovered in 41% yield.

3. Conclusions

We have developed a general preparative method for 2,2-disubstituted 1,2-dihydro-3*H*-indol-3-ones via *m*-CPBA oxidation of 2-arylindoles followed by a Mannich-type reaction with various carbon nucleophiles. This method is effective for the construction of the quaternary carbon center of indoline derivatives. Using this methodology, we have also completed the total synthesis of (±)-hinckdentine A.[12] Further application of this methodology to other alkaloid syntheses and the enantioselective preparation for 2,2-disubstituted 1,2-dihydro-3*H*-indol-3-ones are now under investigation in our laboratory.

4. Experimental section

4.1. General

All melting points were measured on a Yanagimoto micro melting point apparatus and were uncorrected. IR spectra were recorded on a Shimadzu IRPrestige-21 spectrophotometer. ^1H and ^{13}C NMR spectra were measured on a JEOL JNM-AL300 (300 MHz), JEOL JMN-AL400 (400 MHz) or JEOL JNM-LA500 (500 MHz) spectrometer with tetramethylsilane as an internal standard. *J*-Values are given in Hertz. Mass spectra were recorded on a JEOL JMS-DX302 or JEOL JMS 700 instrument with a direct inlet system. Elemental analyses were obtained using a Yanaco MT-6 elemental analyzer. Column chromatography was carried out on a silica gel [Kanto Chemical Co. Inc. (Silica Gel 60 N, Spherical, neutral 40–50 μm) and Merck Ltd. (Silica Gel 60, 230–400 mesh)].

4.2. Preparation of 2-aryindoles 1a–j

*4.2.1. 1-Acetyl-2-(2-nitrophenyl)-1H-indole (**1a**).* To a solution of 2-(2-nitrophenyl)indole (**1b**)[26] (5.5 g, 23 mmol), Bu_4NHSO_4 (81 mg, 2.3 mmol), and NaOH (powder 5.4 g, 133 mmol) in CH_2Cl_2 (54 mL) was slowly dropped a solution AcCl (3.7 mL, 52 mmol) in CH_2Cl_2 (28 mL) via pressure equalizing dropping funnel at 0 °C. After stirring 30 min at the same temperature, the reaction mixture was filtered and the filtrate was washed with brine. The organic layer was dried over anhydrous $MgSO_4$ and the filtrate was concentrated. The residue was purified by column chromatography (*n*-hexane–AcOEt=5:1) to give **1a** (3.5 g, 54%) as yellow amorphous: IR ($CHCl_3$) ν 1705, 1530, 1371, 1348, 1311 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.41 (3H, s), 6.54 (1H, s), 7.28 (1H, t, *J*=7.2 Hz), 7.35 (1H, d, *J*=8.4 Hz), 7.48 (1H, d, *J*=7.6 Hz), 7.50–7.58 (2H, m), 7.64 (1H, d, *J*=7.2 Hz), 8.05 (1H, d, *J*=8.4 Hz), 8.10 (1H, d, *J*=8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.7, 111.4, 115.3, 120.9, 123.3, 124.3, 125.0, 129.3, 129.4, 129.9, 132.2, 132.8, 135.1, 136.2, 148.0, 169.3; HRMS (EI) calcd for $C_{16}H_{12}N_2O_3$ 280.0848, found 280.0842.

*4.2.2. General Procedure for Synthesis of **1c–j**.* A solution of 2-substituted indole in DMF was added NaH at 0 °C. After 10 min stirring, to the mixture was added tetrabutylammonium iodide (TBAI) and alkyl halide (R^1-X) and the mixture was stirred at room temperature until starting material consumption monitored by TLC. The mixture was added satd aqueous NH_4Cl and extracted with Et_2O. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. The concentrated residue was purified by column chromatography with *n*-hexane–AcOEt as an eluent to give **1**.

*4.2.2.1. 1-Methoxymethyl-2-(2-nitrophenyl)-1H-indole (**1c**).* 2-(2-Nitrophenyl)indole (1.0 g, 4.2 mmol); MOMCl (474 μL, 6.3 mmol); NaH (252 mg, 60%, 6.3 mmol); TBAI (155 mg, 0.42 mmol); DMF (42 mL); 10 min; *n*-hexane–AcOEt=5:1; **1c** (1.1 g, 93%); orange oil: IR ($CHCl_3$) ν 1531, 1456, 1348 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.16 (3H, s), 5.24 (2H, s), 6.53 (1H, s), 7.15–7.20

(1H, m), 7.27 (1H, t, J=7.2 Hz), 7.49–7.65 (5H, m), 7.98 (1H, d, J=8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.8, 74.9, 104.3, 109.9, 120.6, 120.7, 122.6, 124.0, 126.8, 127.9, 129.6, 132.1, 133.4, 135.2, 137.6, 149.6; HRMS (EI) calcd for $C_{16}H_{14}N_2O_3$ 282.1004, found 282.1000.

*4.2.2.2. 1-(4-Methoxybenzyl)-2-(2-nitrophenyl)-1H-indole (**1d**).* 2-(2-Nitrophenyl)indole (10.0 g, 42 mmol); PMBCl (6.9 mL, 50 mmol); NaH (2.5 g, 60%, 63 mmol); DMF (0.42 L); TBAI (1.6 g, 4.2 mmol); 2.5 h; *n*-hexane–AcOEt=10:1; **1d** (13.5 g, 90%); yellow crystals: mp 131–133 °C; IR ($CHCl_3$) ν 1530, 1512, 1348 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (3H, s), 5.13 (2H, s), 6.52 (1H, s), 6.71 (2H, d, J=8.4 Hz), 6.83 (2H, d, J=8.4 Hz), 7.12 (1H, tt, J=6.8, 1.6 Hz), 7.17 (1H, tt, J=6.8, 1.6 Hz), 7.23 (1H, d, J=7.6 Hz), 7.31–7.37 (1H, m), 7.48–7.54 (2H, m), 7.63 (1H, d, J=7.6 Hz), 7.95 (1H, dt, J=9.6, 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 47.5, 55.2, 103.1, 110.4, 113.8, 120.0, 120.7, 122.2, 123.9, 127.2, 127.4, 127.9, 129.4, 132.0, 133.3, 135.1, 137.2, 149.7, 158.6. Anal. Calcd for $C_{22}H_{18}N_2O_3$: C, 73.73; H, 5.06; N, 7.82. Found: C, 73.95; H, 5.19; N, 7.83; HRMS (EI) calcd for $C_{22}H_{18}N_2O_3$ 358.1317, found 358.1312.

*4.2.2.3. 1-Benzyl-2-(2-nitrophenyl)-1H-indole (**1e**).* 2-(2-Nitrophenyl)indole (1.0 g, 4.2 mmol); BnBr (0.55 mL, 5.0 mmol); NaH (252 mg, 60%, 6.3 mmol); DMF (42 mL); TBAI (155 mg, 0.42 mmol); 45 min; *n*-hexane–AcOEt=5:1; **1e** (1.2 g, 89%); orange solids: IR ($CHCl_3$) ν 1529, 1460, 1348 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.18 (2H, s), 6.53 (1H, s), 6.86–6.93 (2H, m), 7.09–7.23 (6H, m), 7.30–7.33 (1H, m), 7.44–7.48 (2H, m), 7.63 (1H, d, J=6.8 Hz), 7.89–7.94 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 47.9, 103.2, 110.3, 120.0, 120.7, 122.2, 123.9, 126.1, 127.0, 127.1, 127.8, 128.4, 129.4, 132.0, 133.2, 135.1, 137.2, 137.3, 149.7; HRMS (EI) calcd for $C_{21}H_{16}N_2O_2$ 328.1212, found 328.1217.

*4.2.2.4. 1-(4-Nitrobenzyl)-2-(2-nitrophenyl)-1H-indole (**1f**).* 2-(2-Nitrophenyl)indole (300 mg, 1.3 mmol); PNBBr (300 mg, 1.4 mmol); NaH (76 mg, 60%, 1.9 mmol); DMF (13 mL); 3 h; *n*-hexane–AcOEt=4:1; **1f** (240 mg, 51%); orange amorphous: IR ($CHCl_3$) ν 1529, 1458, 1348 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.29 (2H, s), 6.59 (1H, s), 7.07 (2H, d, J=8.8 Hz), 7.13 (1H, dd, J=1.2, 7.6 Hz), 7.15–7.23 (2H, m), 7.33–7.38 (1H, m), 7.54–7.60 (2H, m), 7.64–7.68 (1H, m), 7.95–8.00 (1H, m), 8.06 (2H, d, J=8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 47.4, 104.0, 109.9, 120.5, 121.1, 122.7, 123.8, 124.2, 126.6, 126.9, 128.0, 129.9, 132.2, 133.1, 134.9, 137.0, 144.6, 147.1, 149.8; HRMS (EI) calcd for $C_{21}H_{15}N_3O_4$ 373.1063, found 373.1058.

*4.2.2.5. 1-(4-Methoxybenzyl)-2-phenyl-1H-indole (**1g**).* 2-Phenylindole (1.0 g, 5.2 mmol); PMBCl (0.7 mL, 5.2 mmol); NaH (250 mg, 60%, 5.2 mmol); TBAI (192 mg, 0.52 mmol); DMF (52 mL); 3 h; *n*-hexane–CH_2Cl_2=1:2; **1g** (960 mg, 60%); colorless crystals: mp 161–164 °C; IR ($CHCl_3$) ν 1612, 1512, 1462, 1346, 1248 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.74 (3H, s), 5.30 (2H, s), 6.63 (1H, s), 6.78 (2H, d, J=8.4 Hz), 6.93 (2H, d, J=8.4 Hz), 7.09–7.22 (3H, m), 7.33–7.45 (5H, m), 7.63–7.68 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 47.2, 55.3, 102.2, 110.5, 114.0, 120.0, 120.4, 121.7, 127.0, 127.8, 128.2, 128.4, 129.1, 130.1, 132.6, 137.8, 141.6, 158.5; HRMS (EI) calcd for $C_{22}H_{19}NO$ 313.1467, found 313.1468.

*4.2.2.6. 1-(4-Methoxybenzyl)-2-(2-methoxyphenyl)-1H-indole (**1h**).* 2-(2-Methoxyphenyl)indole[27] (2.5 g, 11 mmol); PMBCl (1.8 mL, 13 mmol); NaH (672 mg, 60%, 17 mmol); TBAI (406 mg, 0.11 mmol); DMF (0.11 L); 30 min; *n*-hexane–AcOEt=10:1; **1h** (2.7 g, 71%); colorless oil: IR ($CHCl_3$) ν 1512, 1460, 1248 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.53 (3H, s), 3.60 (3H, s), 5.07 (2H, s), 6.53 (1H, s), 6.66 (2H, d, J=8.7 Hz), 6.83 (2H, d, J=8.7), 6.85 (1H, d, J=8.7 Hz), 6.93 (1H, td, J=7.2, 0.9 Hz), 7.00–7.11 (2H, m), 7.12–7.19 (1H, m), 7.26–7.34 (2H, m), 7.57–7.65 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 47.2, 54.96, 55.00, 102.4, 110.4, 110.6, 113.6, 119.4, 120.3, 120.5, 121.3, 121.8, 127.5, 128.3, 130.0, 130.2, 132.6, 137.0, 138.4, 157.3, 158.3; HRMS (EI) calcd for $C_{23}H_{21}NO_2$ 343.1572, found 343.1569.

*4.2.2.7. 1-(4-Methoxybenzyl)-2-(4-methoxyphenyl)-1H-indole (**1i**).* 2-(4-Methoxyphenyl)indole[28] (66 mg, 0.30 mmol); PMBCl (44 μL, 0.33 mmol); NaH (18 mg, 60%, 0.44 mmol); TBAI (11 mg, 30 μmol); DMF (3.0 mL); 2.5 h; *n*-hexane–CH_2Cl_2=1:1; **1i** (46 mg, 46%); white solids: IR ($CHCl_3$) ν 1612, 1512, 1499, 1460, 1248 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.75 (3H, s), 3.82 (3H, s), 5.27 (2H, s), 6.57 (1H, s), 6.79 (2H, d, J=9.0 Hz), 6.87–6.96 (4H, m), 7.00–7.21 (3H, m), 7.35 (2H, d, J=9.0 Hz), 7.60–7.67 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 47.1, 55.3, 55.4, 101.6, 110.4, 113.9, 114.0, 119.9, 120.2, 121.4, 125.0, 127.0, 128.2, 130.2, 130.3, 137.6, 141.4, 158.5, 159.3; HRMS (EI) calcd for $C_{23}H_{21}NO_2$ 343.1572, found 343.1578.

*4.2.2.8. Ethyl 1-(4-methoxybenzyl)-1H-indole-2-carboxylate (**1j**).* Ethyl indole-2-carboxyrate (1.0 g, 5.3 mmol); PMBCl (0.79 mL, 5.8 mmol); NaH (316 mg, 60%, 63 mmol); TBAI (196 mg, 0.53 mmol); DMF (52 mL); 1.5 h; *n*-hexane–AcOEt=10:1; **1j** (1.5 g, 91%); colorless oil: IR ($CHCl_3$) ν 1703, 1612, 1514, 1458, 1248 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (3H, t, J=7.2 Hz), 3.68 (3H, s), 4.31 (2H, q, J=7.2 Hz), 5.74 (2H, s), 6.74 (2H, d, J=8.8 Hz), 7.00 (2H, d, J=8.4 Hz), 7.12 (1H, t, J=7.2 Hz), 7.27 (1H, ddd, J=1.2, 6.8, 8.0 Hz), 7.34 (1H, d, J=9.2 Hz), 7.36 (1H, s), 7.67 (1H, d, J=8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 47.3, 55.1, 60.5, 110.7, 110.8, 113.8, 120.6, 122.4, 125.0, 126.0, 127.5, 130.2, 139.2, 158.4, 161.7; HRMS (EI) calcd for $C_{19}H_{19}NO_3$ 309.1365, found 309.1366.

4.3. Oxidation of 2-substituted indoles

4.3.1. Representative procedure for MoO_5 HMPA H_2O oxidation of 2-arylindoles.

*4.3.1.1. 2-(2-Nitrophenyl)-2-[2-(2-nitrophenyl)-1H-indol-3-yl]1,2-dihydro-3H-indol-3-one (**5**).* A solution of **1b** (23.8 mg, 0.1 mmol) in MeOH (1.0 mL) was added MoO_5 HMPA H_2O (36.6 mg, 0.1 mmol) and the mixture was stirred at room temperature for five days. The mixture was quenched with satd aqueous Na_2SO_3 and concentrated under reduced pressure. The residue was extracted with AcOEt and the organic layer was washed by brine and dried over anhydrous $MgSO_4$. The concentrated residue was purified by column chromatography (*n*-hexane–AcOEt=5:1) to give **5** (17.7 mg, 72%) as yellow crystals: mp 248–250 °C; IR ($CHCl_3$) ν 3456, 1714, 1616, 1530, 1358 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.40–7.70 (16H, m), 8.10 (1H, m), 11.29 (1H, s). Anal. Calcd for $C_{28}H_{18}N_4O_5$: C, 68.57; H, 3.70; N, 11.42. Found: C, 68.37; H, 3.95; N, 11.31; HRMS (FAB) calcd for $C_{28}H_{18}N_4O_5$ 490.1277, found 490.1360.

*4.3.1.2. 2-Methoxy-1-methoxymethyl-2-(2-nitrophenyl)-1,2-dihydro-3H-indol-3-one (**4c**).* Compound **1c** (36.3 mg, 0.13 mmol); MoO_5 HMPA H_2O (36.6 mg, 0.1 mmol); MeOH (1.3 mL); four weeks; *n*-hexane–AcOEt=5:1; **4c** (8.9 mg, 21%); orange oil: IR ($CHCl_3$) ν 1722, 1614, 1531, 1362 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.22 (3H, s), 3.25 (3H, s), 4.39 (1H, d, J=11.1 Hz), 4.64 (1H, d, J=10.8 Hz), 6.90–6.99 (2H, m), 7.40–7.69 (5H, m), 8.12 (1H, d, J=7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.7, 56.0, 74.7, 91.2, 108.7, 119.2, 120.4, 123.4, 124.2, 129.3, 129.8, 130.7, 131.8, 137.9, 148.5, 158.9, 196.7; HRMS (EI) calcd for $C_{17}H_{16}N_2O_5$ 328.1059, found 328.1057.

4.3.2. General procedure for m-CPBA oxidation of 2-arylindole. *m*-CPBA was added to a solution of indole **1** in THF. After stirring at room temperature, the mixture was cooled with ice bath, quenched with satd aqueous Na_2SO_3, and neutralized with satd aqueous $NaHCO_3$. The resulting precipitate was filtered off and rinsed with AcOEt. The filtrate was washed with brine, dried over anhydrous

$MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography with *n*-hexane–AcOEt as an eluent to afford **2c–j**.

*4.3.2.1. 2-Hydroxy-1-methoxymethyl-2-(2-nitrophenyl)-1,2-dihydro-3H-indol-3-one (**2c**).* Compound **1c** (951 mg, 3.4 mmol); *m*-CPBA (1.9 g, 77%, 8.5 mmol); THF (34 mL); 2 h; *n*-hexane–AcOEt=5:1–1:1; **2c** (807 mg, 76%); orange oil: IR ($CHCl_3$) ν 1724, 1614, 1531 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.25 (3H, s), 4.16 (1H, s), 4.42 (1H, d, J=10.8 Hz), 4.82 (1H, d, J=10.8 Hz), 6.96 (1H, d, J=8.4 Hz), 7.03 (1H, td, J=7.2, 0.8 Hz), 7.51–7.58 (2H, m), 7.67–7.77 (3H, m), 8.24 (1H, dd, J=1.6, 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.1, 75.3, 87.9, 109.6, 118.6, 121.1, 123.8, 125.5, 129.8, 130.1, 130.8, 132.2, 136.9, 148.0, 157.0, 195.0; HRMS (EI) calcd for $C_{16}H_{14}N_2O_5$ 314.0903, found 314.0898.

*4.3.2.2. 2-Hydroxy-1-(4-methoxybenzyl)-2-(2-nitrophenyl)-1,2-dihydro-3H-indol-3-one (**2d**).* Compound **1d** (11.5 g, 31 mmol); *m*-CPBA (21.1 g, 77%, 94 mmol); THF (0.31 L); 2 h; *n*-hexane–AcOEt=5:1–3:1; **2d** (11.8 g, 94%); yellow crystals: mp 143–145 °C; IR ($CHCl_3$) ν 1703, 1612, 1529, 1512, 1483 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.16 (1H, s), 3.75 (3H, s), 4.25 (1H, d, J=16.4 Hz), 4.35 (1H, d, J=16.4 Hz), 6.65 (1H, d, J=8.0 Hz), 6.74 (2H, d, J=8.8 Hz), 6.92 (1H, t, J=7.2 Hz), 7.05 (2H, d, J=8.4 Hz), 7.44 (1H, t, J=8.0 Hz), 7.49 (1H, t, J=7.2 Hz), 7.64 (1H, t, J=7.6 Hz), 7.72 (2H, t, J=7.6 Hz), 8.11 (1H, d, J=8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 46.5, 55.3, 88.4, 110.1, 113.8, 118.5, 119.8, 124.4, 125.5, 128.4, 128.8, 129.7, 130.5, 131.0, 132.5, 137.5, 148.0, 158.5, 159.8, 196.8. Anal. Calcd for $C_{22}H_{18}N_2O_5$: C, 67.69; H, 4.65; N, 7.18. Found: C, 67.90; H, 4.72; N, 7.17; HRMS (EI) calcd for $C_{22}H_{18}N_2O_5$ 390.1216, found 390.1212.

*4.3.2.3. 1-Benzyl-2-hydroxy-2-(2-nitrophenyl)-1,2-dihydro-3H-indol-3-one (**2e**).* Compound **1e** (1.0 g, 3.1 mmol); *m*-CPBA (2.3 g, 77%, 9.2 mmol); THF (30 mL); 50 min; *n*-hexane–AcOEt=3:1; **2e** (1.1 g, 96%); orange crystals: mp 141–143 °C; IR ($CHCl_3$) ν 1703, 1612, 1530, 1483 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.17 (1H, s), 4.32 (1H, d, J=16.0 Hz), 4.42 (1H, d, J=16.4 Hz), 6.62 (1H, d, J=8.0 Hz), 6.93 (1H, t, J=7.6 Hz), 7.10–7.22 (5H, m), 7.44 (1H, ddd, J=1.2, 7.2, 8.4 Hz), 7.48 (1H, dt, J=1.2, 7.6 Hz), 7.64 (1H, dt, J=1.2, 7.6 Hz), 7.72 (2H, dt, J=1.2, 7.6 Hz), 8.13 (1H, dd, J=1.2, 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 47.0, 88.4, 110.1, 118.5, 119.9, 124.5, 125.5, 127.0, 127.1, 128.4, 129.8, 130.5, 131.0, 132.5, 136.9, 137.6, 147.9, 159.7, 196.7. Anal. Calcd for $C_{21}H_{16}N_2O_4$: C, 69.99; H, 4.48; N, 7.77. Found: C, 69.83; H, 4.72; N, 7.77; HRMS (EI) calcd for $C_{21}H_{16}N_2O_4$ 360.1110, found 360.1106.

*4.3.2.4. 2-Hydroxy-1-(4-nitrobenzyl)-2-(2-nitrophenyl)-1,2-dihydro-3H-indol-3-one (**2f**).* Compound **1f** (500 mg, 1.3 mmol); *m*-CPBA (925 mg, 77%, 4.0 mmol); THF (13 mL); 1 h; *n*-hexane–AcOEt=3:1; **2f** (414 mg, 76%); yellow crystals: mp 137–138 °C; IR ($CHCl_3$) ν 1722, 1612, 1528, 1477, 1348, 1261 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.84 (1H, s), 4.46 (1H, d, J=16.8 Hz), 4.51 (1H, d, J=17.2 Hz), 6.54 (1H, d, J=8.0 Hz), 6.98 (1H, t, J=7.6 Hz), 7.31 (2H, d, J=8.0 Hz), 7.45–7.74 (5H, m), 8.05 (2H, d, J=8.8 Hz), 8.10 (1H, d, J=8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 46.6, 88.2, 109.8, 118.7, 120.5, 123.6, 124.6, 125.8, 127.8, 130.1, 130.3, 130.7, 132.7, 137.8, 144.5, 147.0, 147.9, 159.1, 196.3. Anal. Calcd for $C_{21}H_{15}N_3O_6$: C, 62.22; H, 3.73; N, 10.37. Found: C, 62.37; H, 3.72; N, 10.28; HRMS (EI) calcd for $C_{21}H_{15}N_3O_6$ 405.0961, found 405.0964.

*4.3.2.5. 2-Hydroxy-1-(4-methoxybenzyl)-2-phenyl-1,2-dihydro-3H-indol-3-one (**2g**).* Compound **1g** (300 mg, 0.93 mmol); *m*-CPBA (526 mg, 77%, 2.4 mmol); THF (9.3 mL); 50 min; *n*-hexane–AcOEt=4:1; **2g** (292 mg, 88%); yellow crystals: mp 136–138 °C; IR ($CHCl_3$) ν 3564, 1713, 1614, 1512, 1485 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.34 (1H, s), 3.77 (3H, s), 4.31 (1H, d, J=16.0 Hz), 4.36 (1H, d, J=16.4 Hz), 6.59 (1H, d, J=8.4 Hz), 6.75 (1H, t, J=7.6 Hz), 6.81 (2H, d, J=8.8 Hz), 7.22 (2H, d, J=8.4 Hz), 7.28–7.46 (6H, m), 7.55 (1H, d, J=7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.3, 48.1, 55.6, 76.7, 109.4, 114.1, 117.9, 119.7, 120.2, 125.4, 126.8, 128.2, 128.7, 129.1, 129.7, 131.8, 137.7, 158.9, 161.8, 201.3. Anal. Calcd for $C_{22}H_{19}NO_3$: C, 76.50; H, 5.54; N, 4.06. Found: C, 76.55; H, 5.64; N, 4.11; HRMS (EI) calcd for $C_{22}H_{19}NO_3$ 345.1365, found 345.1361.

*4.3.2.6. 2-Hydroxy-1-(4-methoxybenzyl)-2-(2-methoxyphenyl)-1,2-dihydro-3H-indol-3-one (**2h**).* Compound **1h** (1.5 g, 4.4 mmol); *m*-CPBA (2.4 g, 77%, 10.9 mmol); THF (44 mL); 40 min; *n*-hexane–AcOEt=5:1; **2h** (1.5 g, 90%); yellow crystals: mp: 139–141 °C; IR ($CHCl_3$) ν 3543, 1715, 1614, 1489 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.48 (1H, s), 3.56 (3H, s), 3.75 (3H, s), 4.28 (1H, d, J=16.0 Hz), 4.33 (1H, d, J=16.0 Hz), 6.51 (1H, d, J=8.4 Hz), 6.73–6.80 (1H, m), 6.75 (2H, d, J=8.8 Hz), 6.83 (1H, d, J=8.4 Hz), 7.00 (1H, t, J=7.2 Hz), 7.10 (2H, d, J=8.4 Hz), 7.31 (1H, t, J=7.6 Hz), 7.36 (1H, t, J=7.6 Hz), 7.63 (1H, d, J=7.6 Hz), 7.71 (1H, d, J=7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 46.0, 55.3, 55.7, 89.1, 108.9, 111.5, 113.7, 117.8, 118.6, 120.9, 124.8, 126.1, 128.0, 128.4, 130.0, 130.1, 137.3, 156.6, 158.4, 159.3, 200.0. Anal. Calcd for $C_{23}H_{21}NO_4$: C, 73.58; H, 5.64; N, 3.73. Found: C, 73.74; H, 5.85; N, 3.74; HRMS (EI) calcd for $C_{23}H_{21}NO_4$ 375.1471, found 375.1467.

*4.3.2.7. 2-Hydroxy-1-(4-methoxybenzyl)-2-(4-methoxyphenyl)-1,2-dihydro-3H-indol-3-one (**2i**).* Compound **1i** (1.0 g, 2.9 mmol); *m*-CPBA (1.6 g, 77%, 7.3 mmol); THF (29 mL); 25 min; *n*-hexane–AcOEt=3:1; **2i** (1.1 g, 90%); yellow oil: IR ($CHCl_3$) ν 3564, 1710, 1614, 1512, 1249 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.40 (1H, s), 3.76 (3H, s), 3.79 (3H, s), 4.33 (2H, s), 6.57 (1H, d, J=8.0 Hz), 6.74 (1H, t, J=7.2 Hz), 6.81 (2H, d, J=8.4 Hz), 6.87 (2H, d, J=8.8 Hz), 7.22 (2H, d, J=8.4 Hz), 7.35 (2H, d, J=8.8 Hz), 7.40 (1H, d, J=8.0 Hz), 7.54 (1H, d, J=7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 46.6, 55.29, 55.34, 91.4, 108.8, 113.9, 114.1, 117.5, 118.2, 125.8, 127.3, 128.2, 129.6, 132.2, 138.3, 158.5, 159.8, 160.3, 199.5; HRMS (EI) calcd for $C_{23}H_{21}NO_4$ 375.1471, found 375.1467.

*4.3.2.8. Ethyl 2-hydroxy-1-(4-methoxybenzyl)-3-oxo-1,2-dihydro-3H-indol-2-carboxylate (**2j**).* Compound **1j** (500 mg, 1.6 mmol); *m*-CPBA (907 mg, 77%, 4.1 mmol); THF (16 mL); 5 h; *n*-hexane:AcOEt=5:1; **2j** (350 mg, 63%); yellow crystals: mp 79–82 °C; IR ($CHCl_3$) ν 3497, 1740, 1722, 1614, 1512, 1483 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.13 (3H, t, J=7.2 Hz), 3.78 (3H, s), 4.01 (1H, ddd, J=6.8, 10.4, 14.4 Hz), 4.11 (1H, ddd, J=7.2, 10.4, 14.4 Hz), 4.40 (1H, d, J=16.0 Hz), 4.46 (1H, d, J=16.0 Hz), 6.65 (1H, d, J=8.0 Hz), 6.79 (1H, t, J=7.2 Hz), 6.85 (2H, d, J=8.8 Hz), 7.27 (2H, d, J=7.6 Hz), 7.41 (1H, ddd, J=1.6, 7.6, 8.8 Hz), 7.57 (1H, d, J=7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 46.0, 55.3, 63.4, 87.6, 109.3, 113.8, 117.8, 118.8, 125.4, 128.4, 128.6, 138.2, 158.8, 161.0, 168.9, 195.3. Anal. Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.73; H, 5.72; N, 4.19; HRMS (EI) calcd for $C_{19}H_{19}NO_5$ 341.1263, found 341.1266.

4.4. General procedure for Mannich-type reaction of 2-hydroxy-1,2-dihydro-3*H*-indol-3-ones 2

To a solution of **2** in CH_2Cl_2 was added nucleophile and acids at 0 °C. After starting material consumption monitored by TLC, the resulting mixture was neutralized with satd aqueous $NaHCO_3$ at 0 °C and extracted with CH_2Cl_2. Combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and then concentrated under reduced pressure. The residue was purified by column chromatography with *n*-hexane–AcOEt as an eluent to afford **3d–p**.

*4.4.1. 2-Allyl-1-(4-methoxybenzyl)-2-(2-nitrophenyl)-1,2-dihydro-3H-indol-3-one (**3d**).* Compound **2d** (100 mg, 0.26 mmol);

allyltrimethylsilane (81 μL, 0.51 mmol); $TiCl_4$ (0.28 mL, 1.0 M in CH_2Cl_2, 0.28 mmol); CH_2Cl_2 (2.6 mL); *n*-hexane–AcOEt=4:1; **3d** (104 mg, 98%); yellow crystals: mp 110–112 °C; IR ($CHCl_3$) ν 1703, 1612, 1530, 1512 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.90 (1H, dd, *J*=6.8, 13.6 Hz), 3.09 (1H, dd, *J*=7.2, 13.6 Hz), 3.75 (3H, s), 4.22 (1H, d, *J*=16.0 Hz), 4.44 (1H, d, *J*=16.0 Hz), 4.86 (1H, dd, *J*=1.6, 10.0 Hz), 5.00 (1H, dd, *J*=1.6, 16.8 Hz), 5.33, (1H, tdd, *J*=6.8, 10.0, 16.8 Hz), 6.73 (2H, d, *J*=8.8 Hz), 6.76 (1H, d, *J*=8.0 Hz), 6.87 (1H, t, *J*=7.6 Hz), 7.03 (2H, d, *J*=8.8 Hz), 7.40–7.48 (2H, m), 7.52–7.59 (2H, m), 7.64–7.68 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.6, 47.3, 55.3, 73.0, 108.9, 113.7, 118.8, 119.7, 120.8, 124.3, 124.6, 128.7, 129.0, 129.8, 130.2, 130.3, 130.5, 131.7, 136.8, 149.3, 158.8, 159.6, 199.5. Anal. Calcd for $C_{25}H_{22}N_2O_4$: C, 72.45; H, 5.35; N, 6.76. Found: C, 72.40; H, 5.47; N, 6.73; HRMS (EI) calcd for $C_{25}H_{22}N_2O_4$ 414.1580, found 414.1579.

*4.4.2. 2-Allyl-1-benzyl-2-(2-nitrophenyl)-1,2-dihydro-3H-indol-3-one (**3e**).* Compound **2e** (100 mg, 0.28 mmol); allyltrimethylsilane (88 μL, 0.56 mmol); $TiCl_4$ (0.31 mL, 1.0 M in CH_2Cl_2, 0.31 mmol); CH_2Cl_2 (2.8 mL); *n*-hexane–AcOEt=4:1; **3e** (107 mg, 95%); orange crystals: mp 102–104 °C; IR ($CHCl_3$) ν 1703, 1612, 1530, 1483, 1358, 1323 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.91 (1H, dd, *J*=6.4, 14.0 Hz), 3.09 (1H, dd, *J*=7.2, 14.0 Hz), 4.28 (1H, d, *J*=16.0 Hz), 4.50 (1H, d, *J*=16.4 Hz), 4.87 (1H, dd, *J*=1.2, 10.4 Hz), 4.98 (1H, dd, *J*=1.2, 16.8 Hz), 5.35 (1H, tdd, *J*=6.8, 10.0, 16.8 Hz), 6.74 (1H, d, *J*=8.4 Hz), 6.87 (1H, t, *J*=7.2 Hz), 7.12 (2H, dd, *J*=3.6, 7.2 Hz), 7.17–7.22 (3H, m), 7.39–7.48 (2H, m), 7.54 (1H, dd, *J*=1.2, 6.8 Hz), 7.56 (1H, dd, *J*=1.2, 7.6 Hz), 7.67 (2H, d, *J*=7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.5, 47.9, 73.1, 109.0, 118.9, 119.7, 120.9, 124.3, 124.7, 127.4, 127.6, 128.3, 129.1, 130.28, 130.34, 131.8, 136.77, 136.80, 149.3, 159.5, 199.3. Anal. Calcd for $C_{24}H_{20}N_2O_3$: C, 74.98; H, 5.24; N, 7.29. Found: C, 75.27; H, 5.43; N, 7.32; HRMS (EI) calcd for $C_{24}H_{20}N_2O_3$ 384.1474, found 384.1477.

*4.4.3. 2-Allyl-1-(4-nitrobenzyl)-2-(2-nitrophenyl)-1,2-dihydro-3H-indol-3-one (**3f**) and 2-allyl-2-(2-nitrophenyl)-1,2-dihydro-3H-indol-3-one (**3k**).* Compound **2f** (30 mg, 74 μmol); allyltrimethylsilane (23 μL, 0.15 mmol); $TiCl_4$ (81 μL, 1.0 M in CH_2Cl_2, 81 μmol); CH_2Cl_2 (0.74 mL); *n*-hexane–AcOEt=5:1–2:1; **3f** (26 mg, 80%); **3k** (5 mg, 19%).

Compound **3f**: yellow crystals: mp 151–153 °C; IR ($CHCl_3$) ν 1709, 1612, 1530, 1348 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.99 (1H, dd, *J*=7.2, 14.4 Hz), 3.14 (1H, dd, *J*=7.2, 14.4 Hz) 4.49 (1H, d, *J*=16.8 Hz), 4.57 (1H, d, *J*=16.8 Hz), 4.93 (1H, dd, *J*=1.2, 10.4 Hz), 5.06 (1H, dd, *J*=1.2, 16.8 Hz), 5.40 (1H, tdd, *J*=6.8, 10.0, 16.8 Hz), 6.61 (1H, d, *J*=8.4 Hz), 6.95 (1H, t, *J*=7.6 Hz), 7.29 (2H, d, *J*=8.4 Hz), 7.42–7.51 (2H, m), 7.57 (2H, d, *J*=7.6 Hz), 7.71 (2H, t, *J*=6.8 Hz), 8.06 (2H, d, *J*=8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.4, 47.4, 73.0, 108.9, 119.6, 120.2, 121.3, 123.6, 124.6, 125.0, 128.0, 129.5, 130.1, 130.4, 132.1, 137.0, 144.3, 147.1, 149.2, 158.9, 198.4. Anal. Calcd for $C_{24}H_{19}N_3O_5$: C, 67.38; H, 4.59; N, 9.76. Found: C, 67.13; H, 4.46; N, 9.79; HRMS (EI) calcd for $C_{24}H_{19}N_3O_5$ 429.1325, found 429.1328.

Compound **3k**: yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 2.75 (1H, dd, *J*=7.5, 14.1 Hz), 3.17 (1H, dd, *J*=6.6, 14.1 Hz) 4.99 (1H, s), 4.57 (1H, d, *J*=16.8 Hz), 5.11 (1H, dt, *J*=0.9, 10.2 Hz), 5.19 (1H, dd, *J*=1.5, 16.8 Hz), 5.59 (1H, tdd, *J*=7.5, 10.2, 16.8 Hz), 6.88–6.95 (2H, m), 7.39 (1H, td, *J*=1.2, 7.2 Hz), 7.44–7.53 (2H, m), 7.56 (1H, td, *J*=1.5, 7.2 Hz), 7.63 (1H, d, *J*=7.5 Hz), 8.07 (1H, dd, *J*=0.9, 7.8 Hz).

*4.4.4. 2-Allyl-1-(4-methoxybenzyl)-2-phenyl-1,2-dihydro-3H-indol-3-one (**3g**).* Compound **2g** (100 mg, 0.29 mmol); allyltrimethylsilane (92 μL, 0.58 mmol); $TiCl_4$ (0.32 mL, 1.0 M in CH_2Cl_2, 0.32 mmol); CH_2Cl_2 (2.9 mL); *n*-hexane–AcOEt=4:1; **3g** (97 mg, 90%); yellow crystals: mp 133–134 °C; IR ($CHCl_3$) ν 1695, 1612, 1512, 1487, 1321, 1246 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.94 (1H, dd, *J*=7.2, 14.0 Hz), 3.17 (1H, dd, *J*=6.8, 14.0 Hz), 3.77 (3H, s), 4.23 (1H, d, *J*=16.4 Hz), 4.50 (1H, d, *J*=16.4 Hz), 4.91 (1H, dd, *J*=10.0 Hz), 5.02 (1H, dd, *J*=1.2, 16.8 Hz), 5.50 (1H, tdd, *J*=7.2, 10.4, 17.2 Hz), 6.70 (1H, d, *J*=8.4 Hz), 6.75 (1H, d, *J*=7.2 Hz), 6.79 (2H, d, *J*=8.4 Hz), 7.09 (2H, d, *J*=8.8 Hz), 7.19–7.34 (5H, m), 7.41 (1H, ddd, *J*=1.2, 7.2, 8.4 Hz), 7.61 (1H, d, *J*=8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.3, 48.1, 55.6, 76.7, 109.4, 114.1, 117.9, 119.7, 120.2, 125.4, 126.8, 128.2, 128.7, 129.1, 129.7, 131.8, 137.7 (2C), 158.9, 161.8, 201.3. Anal. Calcd for $C_{25}H_{23}NO_2$: C, 81.27; H, 6.27; N, 3.79. Found: C, 81.53; H, 6.46; N, 3.77; HRMS (EI) calcd for $C_{25}H_{23}NO_2$ 369.1729, found 369.1731.

*4.4.5. 2-Allyl-1-(4-methoxybenzyl)-2-(2-methoxyphenyl)-1,2-dihydro-3H-indol-3-one (**3h**).* Compound **2h** (30 mg, 80 μmol); allyltrimethylsilane (88 μL, 0.16 mmol); $TiCl_4$ (88 μL, 1.0 M in CH_2Cl_2, 8 μmol); CH_2Cl_2 (0.80 mL); *n*-hexane–AcOEt=4:1; **3h** (30 mg, 93%); green-yellow crystals: mp 104–105 °C; IR ($CHCl_3$) ν 1695, 1614, 1512, 1489, 1319, 1247 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.93 (1H, dd, *J*=7.2, 14.0 Hz), 3.02 (1H, dd, *J*=7.2, 13.6 Hz), 3.38 (3H, s), 3.73 (3H, s), 4.19 (1H, d, *J*=16.0 Hz), 4.31 (1H, d, *J*=16.0 Hz), 4.93 (1H, dd, *J*=0.8, 10.0 Hz), 5.08 (1H, dd, *J*=1.6, 17.2 Hz), 5.53 (1H, tdd, *J*=7.2, 10.0, 17.2 Hz), 6.57 (1H, d, *J*=8.4 Hz), 6.68–6.73 (1H, m), 6.71 (2H, d, *J*=8.4 Hz), 6.76 (1H, d, *J*=8.0 Hz), 6.91–6.99 (1H, m), 6.94 (2H, d, *J*=8.8 Hz), 7.23–7.29 (1H, m), 7.30–7.36 (1H, m), 7.45 (1H, dd, *J*=1.6, 8.0 Hz), 7.63 (1H, d, *J*=7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.1, 46.7, 55.1, 55.2, 73.0, 108.6, 111.6, 113.6, 116.5, 119.0, 120.6, 122.0, 123.5, 127.0, 128.2, 128.7, 129.5, 130.0, 131.4, 136.0, 157.2, 158.3, 159.6, 202.7. Anal. Calcd for $C_{26}H_{25}NO_3$: C, 78.17; H, 6.31; N, 3.51. Found: C, 78.39; H, 6.44; N, 3.71; HRMS (EI) calcd for $C_{26}H_{25}NO_3$ 399.1834, found 399.1839.

*4.4.6. 2-Allyl-1-(4-methoxybenzyl)-2-(4-methoxyphenyl)-1,2-dihydro-3H-indol-3-one (**3i**).* Compound **2i** (300 mg, 0.80 mmol); allyltrimethylsilane (253 μL, 1.6 mmol); $TiCl_4$ (880 μL, 1.0 M in CH_2Cl_2, 0.88 mmol); CH_2Cl_2 (8.0 mL); *n*-hexane–AcOEt=4:1; **3i** (292 mg, 91%); green-yellow oil: IR ($CHCl_3$) ν 1694, 1612, 1512, 1485, 1465, 1319 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.90 (1H, dd, *J*=7.2, 14.4 Hz), 3.12 (1H, dd, *J*=6.8, 14.0 Hz), 3.73 (3H, s), 3.74 (3H, s), 4.22 (1H, d, *J*=16.4 Hz), 4.47 (1H, d, *J*=16.4 Hz), 4.89 (1H, dd, *J*=1.6, 10.8 Hz), 5.00 (1H, dd, *J*=1.2, 16.8 Hz), 5.49 (1H, tdd, *J*=6.8, 10.0, 16.8 Hz), 6.69 (1H, d, *J*=8.8 Hz), 6.73 (1H, d, *J*=7.2 Hz), 6.79 (2H, d, *J*=8.4 Hz), 6.82 (2H, d, *J*=9.2 Hz), 7.09 (2H, d, *J*=8.8 Hz), 7.13 (2H, d, *J*=9.2 Hz), 7.38 (1H, ddd, *J*=1.2, 7.2, 8.4 Hz), 7.59 (1H, d, *J*=7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.0, 47.5, 55.1, 75.8, 109.0, 113.6, 114.0, 117.3, 119.1, 119.7, 124.9, 127.6, 128.3, 129.2, 129.4, 131.5, 137.2, 158.5, 159.0, 160.0, 161.3, 201.2; HRMS (EI) calcd for $C_{26}H_{25}NO_3$ 399.1834, found 399.1840.

*4.4.7. Ethyl 2-allyl-1-(4-methoxybenzyl)-3-oxo-1,2-dihydro-3H-indol-2-carboxylate (**3j**).* Compound **2j** (400 mg, 1.2 mmol); allyltrimethylsilane (371 μL, 2.3 mmol); $TiCl_4$ (1.3 mL, 1.0 M in CH_2Cl_2, 1.3 mmol); CH_2Cl_2 (12 mL); *n*-hexane–AcOEt=6:1; **3j** (148 mg, 35%); pale-yellow oil; IR ($CHCl_3$) ν 1736, 1701, 1612, 1512, 1485, 1321, 1246 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.15 (3H, t, *J*=7.2 Hz), 2.94 (1H, dd, *J*=7.2, 14.8 Hz), 3.02 (1H, dd, *J*=6.8, 14.8 Hz), 3.80 (3H, s), 4.01 (1H, ddd, *J*=7.2, 10.8, 14.4 Hz), 4.08 (1H, ddd, *J*=7.2, 10.8, 14.4 Hz), 4.47 (1H, d, *J*=16.0, Hz), 4.56 (1H, d, *J*=16.4 Hz), 4.96 (1H, d, *J*=10.0 Hz), 5.03 (1H, d, *J*=17.2 Hz), 5.45 (1H, tdd, *J*=7.2, 10.0, 17.2 Hz), 6.65 (1H, d, *J*=8.4 Hz), 6.78 (1H, t, *J*=7.2 Hz), 6.86 (2H, d, *J*=7.2 Hz), 7.24 (2H, d, *J*=8.4 Hz), 7.39 (1H, t, *J*=7.2 Hz), 7.60 (1H, d, *J*=8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 37.0, 48.2, 55.3, 62.1, 109.8, 113.9, 118.1, 119.8, 119.9, 124.9, 128.3, 128.8, 130.6, 137.5, 158.8, 161.6, 167.3, 195.5; HRMS (EI) calcd for $C_{22}H_{23}NO_4$ 365.1627, found 365.1632.

*4.4.8. 2-Allyl-1-(4-methoxybenzyl)-2-(2-nitrophenyl)-1,2-dihydro-3H-indol-3-one (**3d**).* Compound **2d** (200 mg, 0.51 mmol);

allylboronic acid pinacol ester (0.19 mL, 1.0 mmol); $TiCl_4$ (0.56 mL, 1.0 M in CH_2Cl_2, 0.56 mmol); *n*-hexane–AcOEt (3:1); **3d** (208 mg, 98%).

*4.4.9. Methyl 2-[1-(4-methoxybenzyl)-2-(2-nitrophenyl)-3-oxo-1,2-dihydro-3H-indol-2-yl]-2-methylpropanoate (**3l**).* Compound **2d** (200 mg, 0.51 mmol); *O*-methyl *O*′-trimethylsilyl dimethylketene acetal (0.21 mL, 1.0 mmol); $TiCl_4$ (0.56 mL, 1.0 M in CH_2Cl_2, 0.56 mmol); *n*-hexane–AcOEt (3:1); **3l** (228 mg, 93%) as brownish crystals: mp 102–104 °C; IR ($CHCl_3$) ν 1736, 1612, 1530, 1512 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (3H, s), 1.34 (3H, s), 3.62 (3H, s), 3.72 (3H, s), 4.92 (1H, d, *J*=16.5 Hz), 5.28 (1H, d, *J*=16.8 Hz), 6.68 (2H, d, *J*=9.0 Hz), 6.77 (2H, d, *J*=8.7 Hz), 7.08–7.23 (3H, m), 7.42 (1H, dd, *J*=2.1, 7.5 Hz), 7.53 (1H, dt, *J*=1.8, 7.5 Hz), 7.58 (1H, dt, *J*=1.5, 4.5 Hz), 7.62 (1H, dd, *J*=1.5, 6.6 Hz), 8.08 (1H, dd, *J*=1.5, 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0, 47.5, 52.3, 55.2, 82.0, 110.3, 113.8, 119.0, 119.7, 122.6, 123.3, 124.5, 125.6, 127.1, 127.2, 129.2, 129.3, 131.7, 132.4, 134.1, 134.8, 149.4, 158.5, 173.9. Anal. Calcd for $C_{27}H_{26}N_2O_6$: C, 68.34; H, 5.52; N, 5.90.Found: C, 68.56; H, 5.65; N, 5.86; HRMS (EI) calcd for $C_{27}H_{26}N_2O_6$ 474.1791, found 474.1787.

*4.4.10. 1-(4-Methoxybenzyl)-2-(2-nitrophenyl)-2-(2-oxo-2-phenylethyl)-1,2-dihydro-3H-indol-3-one (**3m**).* Compound **2d** (200 mg, 0.51 mmol); trimethyl(1-phenylvinyloxy)silane (0.21 mL, 1.0 mmol); $TiCl_4$ (0.56 mL, 1.0 M in CH_2Cl_2, 0.56 mmol); *n*-hexane–AcOEt (3:1); **3m** (249 mg, 98%) as yellowish powder: mp 192–194 °C; IR ($CHCl_3$) ν 1711, 1697, 1612, 1528, 1512 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.50 (3H, s), 3.73 (1H, d, *J*=17.1 Hz), 3.96 (1H, d, *J*=17.4 Hz), 4.43 (1H, d, *J*=16.8 Hz), 4.60 (1H, d, *J*=16.8 Hz), 6.42 (2H, d, *J*=8.4 Hz), 6.79 (1H, d, *J*=8.4 Hz), 6.89 (2H, d, *J*=8.7 Hz), 6.91 (1H, t, *J*=7.8 Hz), 7.22–7.30 (2H, m), 7.40–7.56 (8H, m), 7.67 (1H, dd, *J*=0.6, 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.5, 47.0, 55.0, 71.9, 108.8, 113.6, 118.9, 119.1, 123.9, 124.7, 127.5, 127.8, 127.9, 128.9, 129.0, 129.1, 130.4, 131.0, 132.8, 135.8, 137.3, 149.0, 158.2, 160.1, 193.9, 198.5. Anal. Calcd for $C_{30}H_{24}N_2O_5$: C, 73.16; H, 4.91; N, 5.69. Found: C, 73.31; H, 5.12; N, 5.75; HRMS (EI) calcd for $C_{30}H_{24}N_2O_5$ 492.1685, found 492.1685.

*4.4.11. 2-[1-(4-Methoxybenzyl)-2-(2-nitrophenyl)-3-oxo-1,2-dihydro-3H-indol-2-yl]acetaldehyde (**3n**).* For entry 4: **2d** (200 mg, 0.51 mmol); trimethyl(vinyloxy)silane (0.15 mL, 1.0 mmol); $TiCl_4$ (0.56 mL, 1.0 M in CH_2Cl_2, 0.56 mmol); *n*-hexane–AcOEt (3:1); **3n** (79 mg, 39%) as yellowish crystals. For entry 5: **2d** (100 mg, 0.26 mmol); trimethyl(vinyloxy)silane (76 μL, 0.51 mmol); CSA (60 mg, 0.26 mmol); *n*-hexane–AcOEt (4:1); **3n** (60 mg, 56%, 41% of recovered **2d**) as yellowish crystals: mp 154–155 °C; IR ($CHCl_3$) ν 1715, 1612, 1530, 1512 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.00 (1H, dd, *J*=2.4, 15.6 Hz), 3.23 (1H, dd, *J*=2.0, 15.6 Hz), 3.74 (3H, s), 4.22 (1H, d, *J*=16.4 Hz), 4.52 (1H, d, *J*=16.4 Hz), 6.73 (2H, d, *J*=8.4 Hz), 6.80 (1H, d, *J*=8.8 Hz), 6.93 (1H, d, *J*=7.2 Hz), 6.98 (2H, d, *J*=8.8 Hz), 7.43–7.61 (5H, m), 7.73 (1H, dt, *J*=8.0, 0.8 Hz), 9.32 (1H, t, *J*=2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 47.0, 48.6, 55.3, 71.4, 109.3, 114.0, 119.3, 119.5, 124.8, 125.0, 128.2, 128.4, 129.0, 129.6, 130.1, 132.0, 137.6, 148.9, 158.9, 159.2, 197.1, 198.0. Anal. Calcd for $C_{24}H_{20}N_2O_5$: C, 69.22; H, 4.84; N, 6.73. Found: C, 69.25; H, 4.91; N, 6.78; HRMS (EI) calcd for $C_{24}H_{20}N_2O_5$ 416.1372, found 416.1377.

*4.4.12. 2-(2-Furyl)-1-(4-methoxybenzyl)-2-(2-nitrophenyl)-1,2-dihydro-3H-indol-3-one (**3o**).* Compound **2d** (100 mg, 0.26 mmol); furan (37 μL, 0.51 mmol); CSA (65 mg, 0.28 mmol); 1 h; *n*-hexane–AcOEt=3:1; **3o** (110 mg, 98%); orange powder; IR ($CHCl_3$): 1719, 1612, 1530, 1512, 1483 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.68 (3H, s), 4.57 (1H, d, *J*=17.2 Hz), 4.75 (1H, d, *J*=17.2 Hz), 6.34 (1H, dd, *J*=2.0, 3.2 Hz), 6.43 (1H, d, *J*=3.6 Hz), 6.45 (1H, d, *J*=8.4 Hz), 6.63 (4H, s), 6.85 (1H, t, *J*=7.2 Hz), 7.05 (1H, dd, *J*=2.0, 8.0 Hz), 7.22 (1H, d, *J*=1.6 Hz), 7.36 (1H, ddd, *J*=1.2, 7.2, 8.4 Hz), 7.40–7.50 (2H, m), 7.57 (1H, dd, *J*=1.6, 7.6 Hz), 7.73 (1H, d, *J*=7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 47.3, 55.1, 73.8, 110.0, 110.3, 111.3, 113.6, 118.7, 118.9, 123.9, 124.9, 126.9, 128.4, 129.4, 129.7, 131.5, 133.0, 137.2, 143.8, 148.7, 149.0, 158.0, 158.3, 194.7; HRMS (EI) Calcd for $C_{26}H_{20}N_2O_5$ 440.1372, found 440.1371.

*4.4.13. 2-(1-Methyl-3-indolyl)-1-(4-methoxybenzyl)-2-(2-nitrophenyl)-1,2-dihydro-3H-indol-3-one (**3p**).* Compound **2d** (100 mg, 0.26 mmol); *N*-methyl indole (35 μL, 0.28 mmol); CSA (65 mg, 0.28 mmol); column chromatography eluent: CH_2Cl_2; **3p** (128 mg, 98%) as orange powder: mp 255–257 °C; IR ($CHCl_3$) ν 1707, 1612, 1530, 1512, 1481 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.67 (3H, s), 3.70 (3H, s), 4.70 (1H, d, *J*=16.5 Hz), 4.80 (1H, d, *J*=16.5 Hz), 6.50–6.62 (2H, m), 6.72–6.95 (7H, m), 7.08–7.14 (1H, m), 7.18–7.24 (1H, m), 7.33–7.49 (3H, m), 7.57–7.64 (2H, m), 7.83 (1H, br d, *J*=8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.1, 47.3, 55.2, 74.6, 108.6, 109.4, 110.4, 113.4, 118.0, 119.6, 120.3, 122.1, 125.0, 125.3, 125.9, 127.3, 128.9, 129.3, 131.1, 131.9, 134.5, 136.7, 137.7, 149.0, 157.9, 158.1. Anal. Calcd for $C_{31}H_{25}N_3O_4$: C, 73.94; H, 5.00; N, 8.34. Found: C, 74.15; H, 5.24; N, 8.35; HRMS (EI) calcd for $C_{31}H_{25}N_3O_4$ 503.1845, found 503.1843.

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