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Article

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2-Oxindole Acts as a Synthon of 2-Aminobenzoyl Anion in the K_2CO_3-Catalyzed Reaction with Enones: Preparation of 1,4-Diketones Bearing an Amino Group and Their Further Transformations

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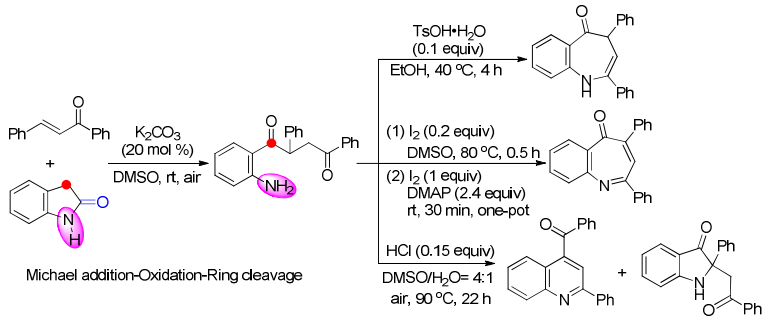


Abstract

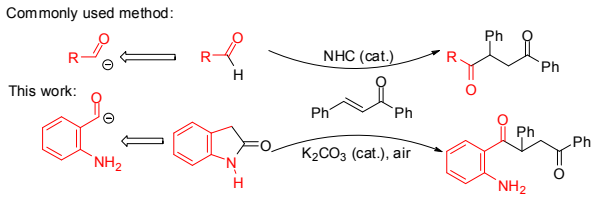
A convenient approach for the synthesis of 1,4-diketones bearing an amino group has been developed through the K_2CO_3-catalyzed reaction of 2-oxindoles with enones with the assistance of atmospheric O_2 *via* sequential Michael addition–oxidation–ring cleavage process. The further intramolecular reaction leads to the formation of benzoazepinone, quinoline, and 3-oxindole derivatives.

Introduction

1,4-Diketones are useful precursors to a variety of synthetically valuable compounds such as pyrroles, furans, thiophenes,[1] pyridazines,[2] and cyclopentenones.[3] A number of reactions have been developed to construct this important structural pattern.[4] Among them, the conjugate

addition of aldehydes onto α,β-unsaturated ketones catalyzed by *N*-heterocyclic carbenes (NHCs), known as the Stetter reaction, was one of the most important methods to access 1,4-diketone skeletons (Scheme 1).[5] An acyl anion equivalent was generated through umpolung of aldehydes catalyzed by NHCs, which was often generated *in situ* from a five membered nitrogen-containing heterocyclic core like thiazolium, triazolium, imidazolium, and imidazolinium salts in the presence of a base. Recently, the Gravel's group developed a novel bis(amino)cyclopropenylidene catalyst as a candidate of NHCs, which even showed high efficiency toward those well-known unreactive substrates in the Stetter reaction catalyzed by NHCs.[6] Notably, a drawback of the Stetter reaction was that most of the aldehyde moieties could not contain amino or hydroxyl groups, which reduced the opportunity for further functionalization of the generated products.

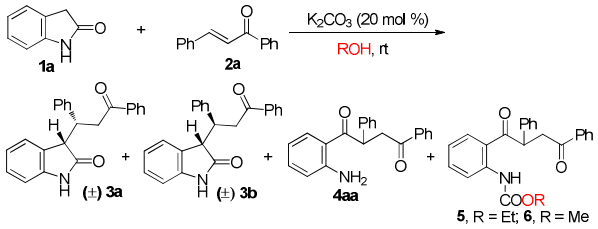
Scheme 1 2-Oxindole as an Equivalent of ortho-Aminobenzoyl Anion.



3-Monosubstituted 2-oxindole as a good nucleophile is easy to take place Michael addition,[7] and Michael addition initiated cascade reaction.[8] In terms of 3-unsubstituted oxindole, it is liable to take place condensation reaction with ketonic compounds[9] or double Michael addition reaction with bisenones[10] to form 3-alkylideneoxindoles or spirooxindoles, respectively. The Michael addition reaction of 3-unsubstituted 2-oxindole with enone to give 3-monosubstituted 2-oxindole has only been reported in few literatures in the presence of sodium ethoxide, piperidine, or proline.[11] Here we reported a base-catalyzed reactions of 2-oxindoles with enones for the preparation of 1,4-diketones bearing an amino group through cascade Michael addition-oxidation-ring cleavage process. The 2-oxindole was used as an equivalent of

ortho-aminobenzoyl anion for the first time (Scheme 1).

Table 1 Primary result.



entry	solvent	time	yield[a]		
			3a + **3b**	**4aa**	**5** or **6**
1	EtOH	1 h	71%	trace	0
2	EtOH	6 h	78%	5%	trace
3	EtOH	24 h	61%	18%	3%
4	EtOH	48 h	49%	30%	6%
5	MeOH	1 h	80%	6%	trace
6	MeOH	6 h	69%	12%	4%
7	MeOH	24 h	54%	19%	10%

[a] Isolated yield.

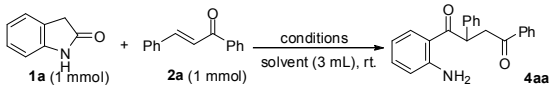
Results and Discussion

Initially, the K_2CO_3-catalyzed addition reaction of oxindole **1a** with chalcone **2a** was carried out in ethanol at room temperature (Table 1). The Michael adducts **3a** and **3b** were obtained as the main products 1 h later.[12] With the extension of reaction time, two new products **4aa** and **5** were generated and the amounts of **3a** and **3b** decreased gradually. The **4aa** and **5** could be isolated in 30% and 6% yield 48 hs later, respectively. Undoubtedly, the ethoxyl in carbamate group of **5** was derived from the ethanol solvent. Changing the solvent from ethanol to methanol gave similar result. The product **6** was produced instead of **5** and the ratio of **4**/**6** is about 2.5 times of the ratio of **4**/**5**.

The product **4aa** looked like a Michael adduct of ortho-aminobenzoyl anion with **2a**. To the best of our knowledge, the umpolung of 2-aminobenzaldehyde to ortho-aminobenzoyl anion in Stetter

reaction has never been realized. On the other hand, an oxidative process was involved with O_2 as the oxidant and only a catalytic amount of K_2CO_3 was enough to achieve this interesting sequential transformation. Molecular oxygen as an ideal green oxidant has attracted considerable attention in organic transformation owing to its abundance, no cost, nontoxic, and free of contamination.[13] Moreover, the introduction of an amino group into 1,4-diketone skeletones made their further transformation more diverse. These inspired us to investigate this interesting transformation in-depth.

Table 2 Screening of the Reaction Conditions

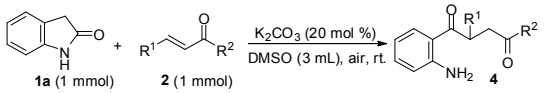


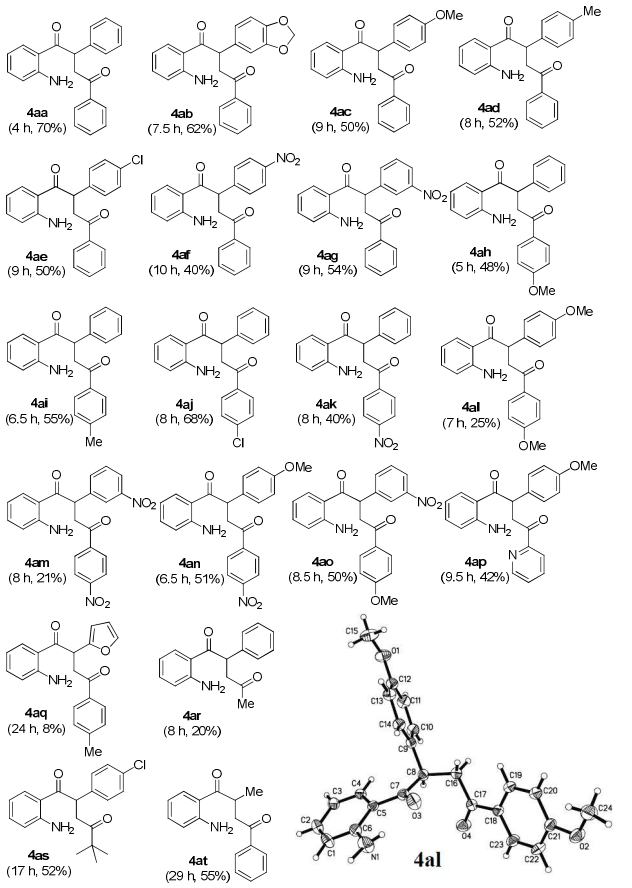
entry	base (equiv)	solvent	time (h)	yield (%)[a]
1	K_2CO_3 (0.2)	CH_3CN	24	17
2	K_2CO_3 (0.2)	THF	28	trace
3	K_2CO_3 (0.2)	acetone	20	11
4	K_2CO_3 (0.2)	toluene	28	trace
5	K_2CO_3 (0.2)	DCE	28	trace
6	**K_2CO_3 (0.2)**	**DMSO**	**4**	**70**
7	K_2CO_3 (1)	DMSO	2.5	67
8	K_2CO_3 (0.05)	DMSO	12	59
9	K_2CO_3 (0.2)	DMF	12	69
10	K_2CO_3 (0.2)	NMP	24	32
11[b]	K_2CO_3 (0.2)	DMSO	24	4
12	NaOH (0.2)	DMSO	3	52
13	Et_3N (0.2)	DMSO	24	8
14	DMAP (0.2)	DMSO	24	9
15	piperidine (0.2)	DMSO	24	9
16	DBU (0.2)	DMSO	4	47

[a] Isolated yield. [b] Carried out under N_2 atomosphere.

The influence of solvent and base was investigated carefully (Table 2). Different solvents were evaluated by employing 20 mol % of K_2CO_3 as the catalyst. Conducting the reaction in THF, DCE, or toluene only afforded trace of **4aa** (Entries 2, 4, and 5). Using NMP (*N*-methylpyrrolidone) as solvent gave 32% yield of 4**aa** (Entry 10) and much lower yield was obtained in acetonitrile and acetone (Entries 1 and 3). Upon switching the solvent to DMSO, the yield of **4aa** was dramatically improved to 70% (Entry 6). Although DMF also gave a comparative yield as that of DMSO, the reaction took much longer time to complete (Entry 9). Further screening different bases for this transformation in DMSO revealed that organic bases such as Et_3N, DMAP, and piperidine afforded very low yield of **4aa** (Entries 13-15) and the NaOH or DBU only gave moderate yield of **4aa** (Entries 12 and 16). The O_2 was proved to be crucial to the reaction and only 4% of **4aa** could be obtained under N_2 atmosphere after 24 h (Entry 11). Reducing the loading of K_2CO_3 to 5 mol % led to longer reaction time and slightly lower yield (Entry 8). Although employing 1 equiv of K_2CO_3 could shorten the reaction time, no noticeable enhancement on the yield was got (Entry 7).

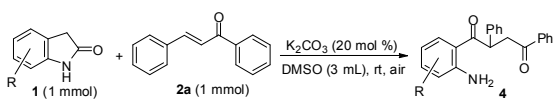
Table 3 Substrate Scope of the Enones

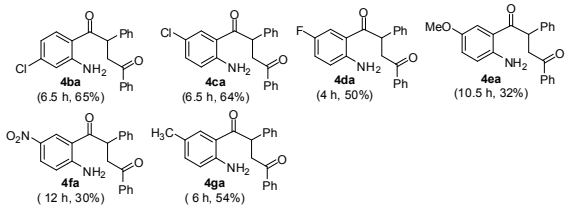




With the optimal conditions in hand (Table 2, entry 6), the scope of the reaction was then investigated (Table 3). The R^1 and R^2 substituent of substrate **2** may be either electron-rich or electron-deficient aryl, and alkyl groups. Most of the reactions gave moderate yield of products. When both of the Aryl groups of R^1 and R^2 linked with strong electron-donating or strong electron-withdrawing group, the yield was unsatisfied (**4al** and **4am**). When R^2 was a methyl group, only 20% yield of product (**4ar**) was obtained. Replacing the methyl group by tert-butyl group increased the yield to 52% (**4as**). Pyridyl group was also tolerated in the transformation, producing the product **4ap** in 42% yield. Furyl group gave very low yield of product **4aq**. The structure of product **4al** was further established by single crystal X-ray crystallographic analysis.

Table 4 Substrate Scope of the Oxindoles

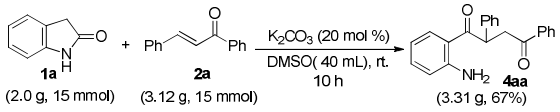




The applicability of other 2-oxindoles in this conversion was also evaluated by performing the reaction of them with chalcone **2a** (Table 4). The results showed that an obvious electronic substrate effect existed. Either strong electron-donating or strong electron-withdrawing group substituted 2-oxindole gave low yield of the product.

To show the practicality of this protocol, a large scale experiment was carried out by performing the reaction of **1a** (2.0 g, 15 mmol) with **3a** (3.12 g, 15 mmol) in 40 mL of DMSO in the presence of 3 mmol of K_2CO_3 (Scheme 2). In order to increase the concentration of oxygen in the solvent, air was simultaneously bubbled into the reaction mixture through a glass dropper. This transformation proceeded smoothly to afford **4aa** in 67% yield within 10 h.

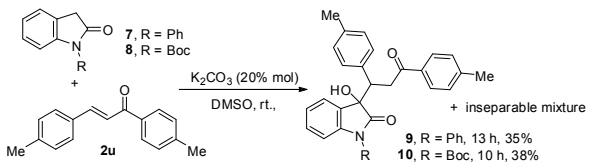
Scheme 2 Large Scale Synthesis of **4aa**



Among the above investigated reactions, there was no substituent on the nitrogen atom of 2-oxindole. Next, the reactivity of *N*-substituted 2-oxindoles was considered (Scheme 3). For the reaction of *N*-phenyl-2-oxindole (**7**) with enone **2u** under the standard conditions, although the TLC indicated that full conversion to two almost equal amounts of products had occurred, the ^{1}H NMR analysis showed that both of them were not the anticipated product. The product with higher polarity was assigned as the hydroxylated Michael adduct **9** (35%)[14] but not the hydroperoxide. Because the characteristic chemical shifts for -OO*H* at 9-10 ppm[15] was not observed in the ^{1}H NMR spectrum of **9**. The product with lower polarity was proved to be a mixture of three

inseparable compounds. *N*-Boc protected 2-oxindole (**8**) gave a similar result as that of *N*-phenyl 2-oxindole.

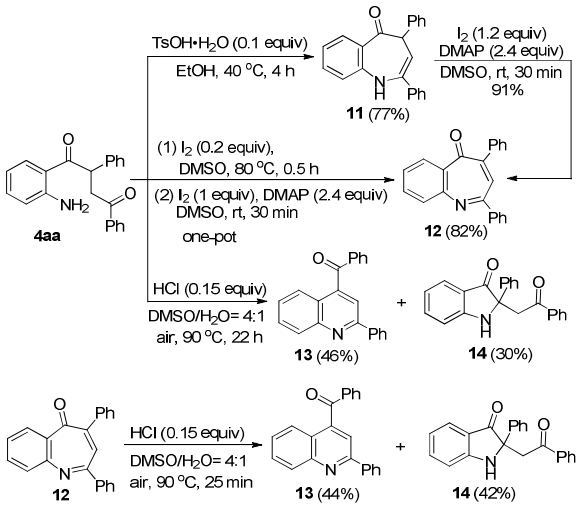
Scheme 3 Reaction of *N*-Substituted-2-Oxindoles with Enone.



Due to the simultaneous existence of amino and carbonyl group, the synthetic potential of the products **4** through the intramolecular reaction was investigated (Scheme 4). No reaction occurred by heating **4aa** in ethanol with 20% mol of acetic acid or directly in acetic acid at reflux. When the HOAc was replaced by $TsOH{\cdot}H_2O$, the **4aa** was smoothly converted to benzoazepinone **11** in 77% yield in ethanol at 40 ºC. It seems that **4aa** are liable to convert to **12** through a condensation-oxidation process. However, several oxidation conditions like $Cu(OAc)_2$, $PhI(OAc)_2$, DDQ, and $K_2S_2O_8$ could not realize this simple looking conversion. Finally, a concise route to access **12** through two-step one-pot reaction was explored**.** In the presence of 1.2 equiv of I_2 and 2.4 equiv of DMAP, **11** could turn into the single product **12** in excellent yield. Surprisely, the iodine could also catalyze the transformation of **4aa** to **11** in DMSO at 80 ºC. It could be explained by that the formation of HI in the iodination catalyzed the conversion. Thus, a simple one-pot conversion of **4aa** to **12** was realized. A mixture of **4aa** and 0.2 equiv of I_2 were stirred in DMSO at 80 ºC for 0.5 h. After cooling to room temperature, 1.0 equiv of I_2 and 2.4 equiv of DMAP were added and the mixture was further stirred at room temperature for 30 min to give **12** in 82% yield. The structure of product **12** was unambiguously determined on the basis of single crystal X-ray diffraction analysis (see Supporting Information). It was noteworthy that direct reaction of **4aa** with 1.2 equiv of I_2 and 2.4 equiv of DMAP lead to a complex mixture with very low conversion.

To the best our knowledge, the benzoazepinone skeleton like **11** and **12** was rather rare.[16] If heating **4aa** in a mixed solvent of DMSO/H_2O (4:1) in the presence of catalytic amounts of hydrochloric acid at 90 ^oC for 22 h, two interesting cyclization products **13**[17] and **14** were provided in 46% and 30% yield, respectively. During the reaction, **11** was quickly formed as the intermediate. However, the conversion of **11** to **13** and **14** needed very long time.

Scheme 4 Further Transformation of **4aa**.

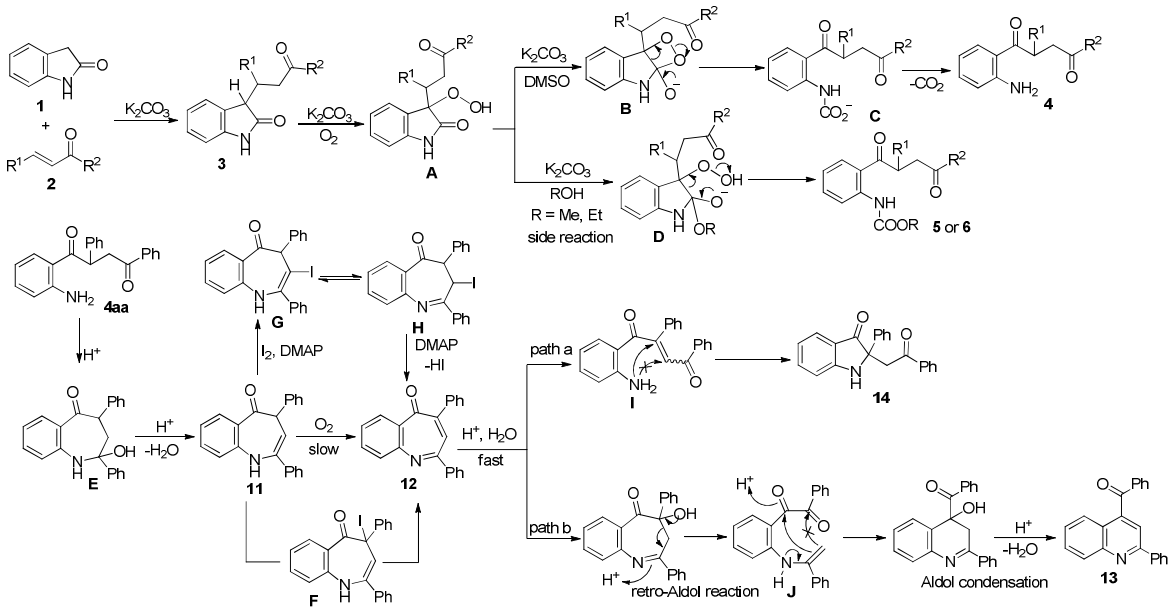


A possible mechanism is depicted in Scheme 5. Initially, Michael addition of 2-oxindole to enone affords the Michael adduct **3**. Under basic condition, the reaction of **3** with O_2 generates peroxide **A**.[15a,18] Intramolecular attacks of peroxide anion on the amide group produce the dioxetane intermediate **B**, which undergoes dissociation to generate **C**. Decarboxylation of **C** form the product **4**. This type of cleavage of an oxindole ring under basic oxidative conditions has precedence in the literature.[19] However, either large excess amount of NaH (3 equiv) or NaOH (> 10 equiv) was needed[19a,b,d] or a mixture was generated.[19c,d] If the reaction was carried out in methanol or ethanol, the competing intermolecular attack of alkoxy anion at the amide group provides the intermediate **D**, which undergoes sequential C-C and O-O bond cleavage to generate the side product **5** or **6**. At present, we had no a definite explaination to the generation of different

products for *N*-protected 2-oxindoles. It was possible that the substituent on the nitrogen atom was not benificial to the attack of peroxide anion on the amide group. As a consequence, the oxidation of starting material by the generated peroxide led to the formation of hydroxylated product.

Under acid conditions, the intramoleclar reaction of amino group with the carbonyl affords the enamine product **11**. The iodination of **11** in the presence of DMAP provides the intermediate **F**. Another iodinated product G also could not be exluded.[20] Extrusion of HI from F or the imine **H** (equilibrates to **G**) by DMAP would afford the product **12**. This indirect route (one-pot, two-step) could synthesize **12** in good yield within short time. At high temperature, **11** is slowly oxidized by O_2 to generate **12**. Two possible reaction pathways exist for the rapid hydrolysis of **12** in the presence of H_2O under acid conditions. In path a, C=N bond cleavage gives the intermediate **I**, which undergoes selective intramolecular Michael addition to afford the product **14**. In path b, the retro-Aldol condensation generates the intermediate **J**. The follow-up selective Aldol condensation produces the quinoline product **13**. The water was essential to the hydrolysis of **12**, if water was not added as the co-solvent, the hydrolysis is very slow. The hydrolysis of **12** is so fast that we cannot observe the intermediate **12** on TLC during the hydrochloric acid-catalyzed reaction of **4aa** in DMSO/H_2O. In order to prove this, the reaction of **12** in the presence of catalytic amount of hydrochloric acid was conducted in DMSO/H_2O at 90 ºC (Scheme 4). Full conversion of **12** was completed within 25 min along with the formation of **13** and **14** with the ratio of 1:1.

Scheme 5 Proposed Mechanism



In summary, the K_2CO_3-catalyzed reaction of 2-oxindoles with enones for the preparation of a variety of 1,4-diketones bearing an amino group was disclosed. Simple experimental procedures and mild reaction conditions were used for the successive Michael addition–oxidation–ring cleavage reactions. The further intramolecular reaction of the 1,4-diketone produced the benzoazepinone, quinoline, and 3-oxindole derivatives. Only atmospheric oxygen was needed in the oxidative process among these transformations.

Experimental Section

General Information.

^{1}H and ^{13}C NMR spectra were recorded on 300 MHz and 500 MHz (75 and 100 MHz for ^{13}C NMR) spectrometer. Melting points were determined on a micromelting point apparatus without corrections. Flash column chromatography was performed over silica gel (200−300 mesh).

Preparation of Starting Materials

2-Oxindoles **1a**–**g**, **7**, and **2r** are commercially availible. *N*-Boc-2-oxindole **8** was prepared from **1a** and $(Boc)_2O$ according to reported procedure.[21] Enones **2a**–**q** and **2s** were synthesized from corresponding ketones and aldehydes catalyzed by NaOH.[22] (E)-1-Phenyl-2-buten-1-one **2t** was

prepared through the Fridel-Craft reacition of benzene with (E)-2-butenoylchlorid.[23]

K_2CO_3-Catalyzed Reaction of 2-Oxindole (1a) with Chalcone (2a) in Ethanol or Methanol

A mixture of 2-oxindole (133 mg, 1 mmol), chalcone **2a** (208 mg, 1 mmol), and K_2CO_3 (28 mg, 0.2 mmol) was stirred in 3 mL of ethanol or methanol in a tube (Φ18 × 150 mm) under open air at room temperature for 48 h or 24 h, respectively. 30 mL of water was added and the mixture was extracted with dichloromethane (20 mL× 3). The combined organic phases were dried over anhydrous sodium sulfate and concentrated in *vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate/petroleum ether) to provide the corresponding products **5** (or **6**), **4aa**, and **3a+3b**.

3a: white solid, mp 129-130 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, J = 7.1 Hz, 2H), 7.65 (s, br, 1H), 7.57 (tt, J = 7.3, 1.3 Hz, 1H), 7.46 (t, J = 7.4 Hz, 2H), 7.31 (d, J = 7.3 Hz, 1H), 7.08-7.16 (m, 6H), 7.01 (td, J = 7.6, 1.0 Hz, 1H), 6.64 (d, J = 7.6 Hz, 1H), 4.17-4.29 (m, 2H), 3.88 (d, J = 3.4 Hz, 1H), 3.56 (dd, J = 20.6 Hz, 8.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.0, 178.4, 141.0, 139.7, 137.2, 133.3, 128.8, 128.5, 128.4, 128.3, 128.2, 128.0, 127.0, 124.9, 122.4, 109.3, 50.1, 42.0, 39.8; HRMS (ESI-Q-TOF) m/z: $[M+Na]^+$ Calcd for $C_{23}H_{19}NNaO_2$ 364.1313; Found 364.1309.

5: yellow solid, 24.2 mg, 6%, mp 42-43 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.09 (s, 1H), 8.46 (dd, J = 8.6, 1.0 Hz, 1H), 8.10 (dd, J = 8.2, 1.5 Hz, 1H), 7.99 (d, J = 7.1 Hz, 2H), 7.58 (tt, J = 7.4, 1.3 Hz, 1H), 7.28-7.36 (m, 4H), 7.19-7.28 (m, 1H), 7.16-7.25 (m, 1H), 7.00 (ddd, J = 8.2, 7.4, 1.2 Hz, 1H), 5.37 (dd, J = 10.3, 3.5 Hz, 1H), 4.21 (dd, J = 18.2 Hz, 10.3 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.29 (dd, J = 18.2, 3.5 Hz, 1H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.6, 198.0, 154.0, 142.3, 138.8, 136.5, 134.9, 133.5, 131.6, 129.5, 128.8, 128.3, 128.1, 127.7, 121.4, 120.9, 119.3, 61.3, 49.5, 44.2, 14.6; HRMS (ESI-Q-TOF) m/z: $[M+Na]^+$ Calcd for $C_{25}H_{23}NNaO_4$

424.1525; Found 424.1521.

6: yellow solid, 37.9 mg, 10%, mp 97-99 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.13 (s, 1H), 8.44 (dd, J = 8.5, 0.8 Hz, 1H), 8.10 (dd, J = 8.2, 1.3 Hz, 1H), 7.98 (d, J = 7.1 Hz, 2H), 7.57 (tt, J = 7.4, 1.3 Hz, 1H), 7.20-7.36 (m, 5H), 7.00 (ddd, J = 8.2, 7.3, 1.1 Hz, 1H), 5.36 (dd, J =10.4, 3.5 Hz, 1H), 4.21 (dd, J = 18.1, 10.4 Hz, 1H), 3.74 (s, 3H), 3.28 (dd, J = 18.1, 3.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.6, 198.0, 154.3, 142.1, 138.7, 136.3, 134.9, 133.5, 131.6, 129.4, 128.7, 128.3, 128.0, 127.6, 121.5, 120.9, 119.2, 52.3, 49.5, 44.2; HRMS (ESI-Q-TOF) m/z: $[M+Na]^+$ Calcd for $C_{24}H_{21}NNaO_4$ 410.1368; Found 410.1366.

General Procedure for the K_2CO_3-Catalyzed Reaction of 2-Oxindoles (1) with Enones (2) in DMSO for the Preparation of 4.

A mixture of 2-oxindoles **1** (1 mmol), enones **2** (1 mmol), and K_2CO_3 (0.2 mmol) was stirred in 3 mL of DMSO in a tube (Φ18 × 150 mm) under open air at room temperature for a given time. Upon completion of the reaction as determined by TLC, 30 mL of water was added and the mixture was extracted with dichloromethane (20 mL× 3). The combined organic phases were dried over anhydrous sodium sulfate and concentrated in *vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate/petroleum ether) to provide the corresponding products **4**.

4aa: yellow solid, 230 mg, 70%, mp 77-79 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, J = 7.1 Hz, 2H), 7.91 (d, J = 7.7 Hz, 1H), 7.55 (tt, J = 7.3 Hz, 1.3 Hz, 1H), 7.44 (t, J = 7.5 Hz, 2H), 7.28-7.39 (m, 4H), 7.14-7.25 (m, 2H), 6.53-6.63 (m, 2H), 6.21 (s, br, 2H), 5.34 (dd, J = 10.0, 3.8 Hz, 1H), 4.19 (dd, J = 18.0, 10.0 Hz, 1H), 3.23 (dd, J = 17.9, 3.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.7, 198.3, 151.2, 139.9, 136.7, 134.3, 133.3, 131.8, 129.2, 128.7, 128.3, 128.1, 127.2, 117.5, 116.0, 48.9, 43.9; HRMS (+ESI) m/z: $[M+H]^+$ Calcd for $C_{22}H_{20}NO_2$ 330.1494; Found

330.1490.

4ab: yellow solid, 231 mg, 62%, mp 120-121 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, J = 7.1 Hz, 2H), 7.91 (dd, J = 8.6, 1.4 Hz, 1H), 7.56 (tt, J = 7.3, 1.3 Hz, 1H), 7.44 (t, J = 7.5 Hz, 2H), 7.20 (ddd, J = 8.3, 7.3, 1.4 Hz, 1H), 6.84 (s, 1H), 6.82 (dd, J = 8.3, 1.9 Hz, 1H), 6.74 (dd, J = 7.5, 0.9 Hz, 1H), 6.55-6.63 (m, 2H), 6.20 (s, br, 2H), 5.92 (d, J = 1.4 Hz, 1H), 5.90 (d, J = 1.4 Hz, 1H), 5.26 (dd, J = 9.8, 4.0 Hz, 1H), 4.12 (dd, J = 18.0, 9.8 Hz, 1H), 3.21 (dd, J = 18.0, 3.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.7, 198.3, 151.2, 148.2, 146.8, 136.7, 134.3, 133.6, 133.3, 131.7, 128.7, 128.3, 121.4, 117.5, 117.4, 116.0, 108.9, 108.4, 101.2, 48.4, 43.9; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{23}H_{20}NO_4$ 374.1392; Found 374.1384.

4ac: yellow solid, 180 mg, 50%, mp 135-136 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, J = 7.1 Hz, 2H), 7.91 (dd, J = 8.6, 1.6 Hz, 1H), 7.55 (tt, J = 7.4, 1.3 Hz, 1H), 7.44 (t, J = 7.5 Hz, 2H), 7.27 (d, J = 8.9 Hz, 2H), 7.17 (ddd, J = 8.3, 7.3, 1.5 Hz, 1H), 6.84 (d, J = 8.9 Hz, 2H), 6.54-6.62 (m, 2H), 6.20 (s, br, 2H), 5.29 (dd, J = 9.8, 4.0 Hz, 1H), 4.14 (dd, J = 17.9, 9.8 Hz, 1H), 3.75 (s, 3H), 3.21 (dd, J = 17.9, 4.0Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.9, 198.4, 158.7, 151.2, 136.6, 134.2, 133.2, 131.8, 131.7, 129.1, 128.6, 128.2, 117.44, 117.35, 115.9, 114.5, 55.3, 47.9, 43.9; HRMS (ESI-Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{22}NO_3$ 360.1600; Found 360.1596.

4ad: yellow solid, 178 mg, 52%, mp 61-63 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, J = 7.1 Hz, 2H), 7.91 (dd, J = 8.5, 1.3 Hz, 1H), 7.52 (tt, J = 7.3, 1.3 Hz, 1H), 7.41 (t, J = 7.5 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 7.15 (ddd, J = 8.3, 7.2, 1.5 Hz, 1H), 7.10 (d, J = 8.0 Hz, 2H), 6.52-6.59 (m, 2H), 6.20 (s, br, 2H), 5.30 (dd, J = 10.0, 3.8 Hz, 1H), 4.16 (dd, J = 18.0, 10.0 Hz, 1H), 3.19 (dd, J = 18.0, 3.8 Hz, 1H) , 2.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.8, 198.3, 151.1, 136.8, 136.7, 136.6, 134.1, 133.1, 131.7, 129.8, 128.6, 128.1, 127.8, 117.4, 117.3, 115.8, 48.4, 43.9, 21.0; HRMS (ESI-Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{22}NO_2$ 344.1651; Found 344.1642.

4ae: yellow solid, 182 mg, 50%, mp 99-101 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, J = 7.1 Hz, 2H), 7.86 (d, J = 8.2 Hz, 1H), 7.55 (tt, J = 7.3, 1.3 Hz, 1H), 7.44 (t, J = 7.5 Hz, 2H), 7.25-7.32 (m, 4H), 7.19 (ddd, J = 8.3, 7.3, 1.5 Hz, 1H), 6.54-6.62 (m, 2H), 6.22 (s, br, 2H), 5.33 (dd, J = 9.7, 4.1 Hz, 1H), 4.13 (dd, J = 18.0, 9.7 Hz, 1H), 3.22 (dd, J = 17.9, 4.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.2, 197.9, 151.2, 138.3, 136.4, 134.4, 133.3, 133.0, 131.5, 129.4, 129.2, 128.6, 128.1, 117.5, 117.0, 115.8, 47.9, 43.6; HRMS (ESI-Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{19}ClNO_2$ 364.1104; Found 364.1097.

4af: yellow solid, 150 mg, 40%, mp 137-139 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, J = 8.8 Hz, 2H), 7.98 (d, J = 7.1 Hz, 2H), 7.83 (dd, J = 8.3 Hz, 1.3 Hz, 1H), 7.52-7.61 (m, 3H), 7.46 (t, J = 7.5 Hz, 2H), 7.22 (ddd, J = 8.3, 7.3, 1.5 Hz, 1H), 6.56-6.65 (m, 2H), 6.26 (s, br, 2H), 5.48 (dd, J = 9.2 Hz, 4.4 Hz, 1H), 4.16 (dd, J = 17.9 Hz, 9.2 Hz, 1H), 3.30 (dd, J = 17.9 Hz, 4.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.3, 197.4, 151.5, 147.4, 147.1, 136.3, 134.9, 133.6, 131.3, 129.1, 128.8, 128.3, 124.4, 117.7, 116.9, 116.1, 48.4, 43.4; HRMS (ESI-Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{19}N_2O_4$ 375.1345; Found 375.1336.

4ag: yellow solid, 202 mg, 54%, mp 141-142 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (t, J = 1.9 Hz, 1H), 8.09 (ddd, J = 8.2, 2.2, 1.0 Hz, 1H), 7.99 (d, J = 7.1 Hz, 2H), 7.87 (dd, J = 8.7, 1.5 Hz, 1H), 7.73 (dt, J = 7.7, 1.3 Hz, 1H), 7.58 (tt, J = 7.3, 1.3 Hz, 1H), 7.42-7.53 (m, 3H), 7.23 (ddd, J = 8.5, 7.2, 1.4 Hz, 1H), 6.58-6.66 (m, 2H), 6.27 (s, br, 2H), 5.49 (dd, J = 9.3, 4.5 Hz, 1H), 4.18 (dd, J = 18.0, 9.3 Hz, 1H), 3.33 (dd, J = 18.0, 4.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.4, 197.5, 151.5, 148.7, 141.9, 136.3, 134.8, 134.5, 133.6, 131.3, 130.1, 128.8, 128.2, 123.1, 122.4, 117.7, 116.8, 116.1, 47.9, 43.5; HRMS (ESI-Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{19}N_2O_4$ 375.1345; Found 375.1341.

4ah: yellow solid, 172 mg, 48%, mp 77-78 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, J = 9.0

Hz, 2H), 7.91(d, *J* = 8.0 Hz, 1H), 7.27-7.39 (m, 4H), 7.13-7.24 (m, 2H), 6.90 (d, *J* = 9.0 Hz, 2H), 6.53-6.61 (m, 2H), 6.21 (s, br, 2H), 5.33 (dd, *J* = 10.0, 3.8 Hz, 1H), 4.13 (dd, *J* = 17.8, 10.0 Hz, 1H), 3.85 (s, 3H), 3.19 (dd, *J* = 17.8, 3.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.8, 196.8, 163.6, 151.2, 140.0, 134.2, 131.7, 130.5, 129.7, 129.1, 128.0, 127.1, 117.45, 117.41, 115.9, 113.7, 55.5, 48.8, 43.6; HRMS (ESI-Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{22}NO_3$ 360.1600; Found 360.1592.

4ai: yellow solid, 189 mg, 55%, mp 69-71 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86-7.94 (m, 3H), 7.27-7.38 (m, 4H), 7.13-7.25 (m, 4H), 6.53-6.62 (m, 2H), 6.21 (s, br, 2H), 5.33 (dd, *J* = 10.0, 3.8 Hz, 1H), 4.16 (dd, *J* = 17.9, 10.0 Hz, 1H), 3.21 (dd, *J* = 17.9, 3.8 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.7, 197.8, 151.2, 143.9, 139.9, 134.13, 134.10, 131.7, 129.2, 129.1, 128.3, 128.0, 127.1, 117.4, 117.3, 115.7, 48.7, 43.7, 21.6; HRMS (ESI-Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{22}NO_2$ 344.1651; Found 344.1647.

4aj: yellow solid, 247 mg, 68%, mp 115-116 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85-7.92 (m, 3H), 7.37 (d, *J* = 8.6 Hz, 2H), 7.24-7.35 (m, 4H), 7.09-7.24 (m, 2H), 6.49-6.58 (m, 2H), 6.22 (s, br, 2H), 5.31 (dd, *J* = 10.0, 3.7 Hz, 1H), 4.12 (dd, *J* = 17.9, 10.1 Hz, 1H), 3.15 (dd, *J* = 18.0, 3.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.5, 197.1, 151.2, 139.8, 139.6, 135.0, 134.3, 131.7, 129.7, 129.2, 128.9, 128.0, 127.3, 117.5, 117.3, 115.9, 48.9, 43.8; HRMS (ESI-Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{19}ClNO_2$ 364.1104; Found 364.1095.

4ak: yellow solid, 150 mg, 40%, mp 135-136 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (d, *J* = 9.0 Hz, 2H), 8.14 (d, *J* = 9.0 Hz, 2H), 7.87 (dd, *J* = 8.2 Hz, 1.1 Hz, 1H), 7.29-7.38 (m, 4H), 7.16-7.27 (m, 2H), 6.53-6.64 (m, 2H), 6.23 (s, br, 2H), 5.34 (dd, *J* = 10.1, 3.7 Hz, 1H), 4.19 (dd, *J* = 18.0, 10.1 Hz, 1H), 3.21 (dd, *J* = 17.9, 3.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.2, 197.1, 151.3, 150.4, 141.1, 139.5, 134.5, 131.8, 129.4, 129.3, 128.0, 127.5, 123.9, 117.5, 117.1, 116.0, 49.2, 44.3;

HRMS (ESI-Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{19}N_2O_4$ 375.1345; Found 375.1338.

4al: yellow solid, 97 mg, 25%, mp 132 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, J = 9.0 Hz, 2H), 7.92 (dd, J = 8.7 Hz, 1.5 Hz, 1H), 7.27 (d, J = 8.9 Hz, 2H), 7.17 (ddd, J = 8.3, 7.3, 1.4 Hz, 1H), 6.91 (d, J = 9.0 Hz, 2H), 6.83 (d, J = 8.8 Hz, 2H), 6.54-6.61 (m, 2H), 6.20 (s, br, 2H), 5.28 (dd, J = 9.8, 4.0 Hz, 1H), 4.09 (dd, J = 17.7, 9.8 Hz, 1H), 3.85 (s, 3H), 3.75 (s, 3H), 3.17 (dd, J = 17.7, 4.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.2, 197.0, 163.6, 158.7, 151.2, 134.2, 132.0, 131.8, 130.5, 129.9, 129.1, 117.6, 117.5, 116.0, 114.6, 113.8, 55.6, 55.3, 48.0, 43.6; HRMS (ESI-Q-TOF) m/z: $[M+Na]^+$ Calcd for $C_{24}H_{23}NNaO_4$ 412.1525; Found 412.1516.

4am: yellow solid, 88 mg, 21%, mp 78-79 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (d, J = 9.0 Hz, 2H), 8.26 (t, J =2.0 Hz, 1H), 8.16 (d, J = 9.0 Hz, 2H), 8.12 (ddd, J = 8.2, 2.2, 1.0 Hz, 1H), 7.82 (dd, J = 8.2, 1.1 Hz, 1H), 7.72 (dt, J = 7.9, 1.3 Hz, 1H), 7.52 (t, J =8.0 Hz, 1H), 7.24 (ddd, J = 8.4 Hz, 7.1 Hz, 1.4 Hz, 1H), 6.58-6.66 (m, 2H), 6.29 (s, br, 2H), 5.48 (dd, J = 9.7, 4.2 Hz, 1H), 4.23 (dd, J = 18.0, 9.6 Hz, 1H), 3.29 (dd, J = 18.0, 4.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.9, 196.3, 151.6, 150.5, 148.8, 141.5, 140.7, 135.0, 134.3, 131.3, 130.3, 129.3, 124.0, 123.0, 122.6, 117.8, 116.4, 116.2, 48.2, 43.9; HRMS (ESI-Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{18}N_3O_6$ 420.1196; Found 420.1189.

4an: yellow solid, 206 mg, 51%, mp 177-178 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (d, J = 9.0 Hz, 2H), 8.14 (d, J = 9.0 Hz, 2H), 7.87 (dd, J = 8.2 Hz, 1.1 Hz, 1H), 7.26 (d, J = 8.9 Hz, 2H), 7.20 (ddd, J = 8.3, 7.0, 1.5 Hz, 1H), 6.85 (d, J = 8.8 Hz, 2H), 6.55-6.63 (m, 2H), 6.21 (s, br, 2H), 5.29 (dd, J = 10.0, 3.9 Hz, 1H), 4.15 (dd, J = 18.0, 10.0 Hz, 1H), 3.76 (s, 3H), 3.19 (dd, J = 17.9, 3.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.5, 197.2, 158.9, 151.3, 150.4, 141.2, 134.5, 131.8, 131.4, 129.3, 129.0, 123.9, 117.5, 117.1, 116.0, 114.7, 55.4, 48.3, 44.3; HRMS (ESI-Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{21}N_2O_5$ 405.1450; Found 405.1440.

4ao: yellow solid, 202 mg, 50%, mp 158 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (t, J = 1.9 Hz, 1H), 8.08 (ddd, J = 8.2, 2.2, 1.0 Hz, 1H), 7.97 (d, J = 9.0 Hz, 2H), 7.88 (dd, J = 8.6 Hz, 1.3 Hz, 1H), 7.73 (dt, J = 7.8 Hz, 1.3 Hz, 1H), 7.48 (t, J = 8.0 Hz, 1H), 7.22 (ddd, J = 8.3, 7.1, 1.4 Hz, 1H), 6.93 (d, J = 8.9 Hz, 2H), 6.58-6.65 (m, 2H), 6.27 (s, br, 2H), 5.48 (dd, J = 9.2, 4.5 Hz, 1H), 4.12 (dd, J = 17.8, 9.3 Hz, 1H), 3.87 (s, 3H), 3.29 (dd, J = 17.7, 4.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.6, 195.9, 163.8, 151.5, 148.7, 142.0, 134.8, 134.5, 131.3, 130.6, 130.0, 129.4, 123.1, 122.4, 117.7, 116.9, 116.1, 113.9, 55.6, 48.0, 43.2; HRMS (ESI-Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{21}N_2O_5$ 405.1450; Found 405.1442.

4ap: yellow solid, 151 mg, 42%, mp 118-120 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (d, J = 4.4 Hz, 1H), 8.00 (d, J = 7.8 Hz, 1H), 7.93 (dd, J = 8.7 Hz, 1.4 Hz, 1H), 7.80 (td, J = 7.7 Hz, 1.7 Hz, 1H), 7.45 (ddd, J = 7.5 Hz, 4.8 Hz, 1.2 Hz, 1H), 7.27 (d, J = 8.7 Hz, 2H), 7.18 (ddd, J = 8.4, 7.3, 1.4 Hz, 1H), 6.82 (d, J = 8.7 Hz, 2H), 6.55-6.63 (m, 2H), 6.20 (s, br, 2H), 5.27 (dd, J = 10.1, 4.0 Hz, 1H), 4.41 (dd, J = 18.8, 10.2 Hz, 1H), 3.75 (s, 3H), 3.47 (dd, J = 18.8, 4.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.1, 200.1, 158.6, 153.1, 151.1, 149.1, 136.9, 134.1, 131.9, 131.8, 129.2, 127.3, 121.9, 117.4, 115.8, 114.4, 55.3, 48.0, 43.2; HRMS (ESI-Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{21}N_2O_3$ 361.1552; Found 361.1544.

4aq: yellow solid, 27 mg, 8%, mp 69 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (dd, J = 8.2, 1.3 Hz, 1H), 7.91 (d, J = 8.2 Hz, 2H), 7.33 (dd, J = 1.8, 0.8 Hz, 1H), 7.21-7.28 (m, 3H), 6.60-6.69 (m, 2H), 6.28 (dd, J = 3.2, 1.9 Hz, 1H), 6.20 (s, br, 2H), 6.15 (d, J = 3.2 Hz, 1H), 5.48 (dd, J = 9.7, 4.1 Hz, 1H), 4.14 (dd, J = 17.9, 9.7 Hz, 1H), 3.39 (dd, J = 17.9, 4.1Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.3, 197.5, 152.7, 151.3, 144.2, 142.1, 134.6, 134.1, 131.7, 129.4, 128.4, 117.5, 117.2, 116.1, 110.8, 107.1, 42.2, 40.4, 21.8; HRMS (ESI-Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{21}H_{20}NO_3$ 334.1443; Found 334.1433.

4ar: yellow solid, 53 mg, 20%, mp 257 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (dd, J = 8.2 Hz, 1.4 Hz, 1H), 7.23-7.30 (m, 4H), 7.12-7.22 (m, 2H), 6.58 (dd, J = 8.3, 0.9 Hz, 1H), 6.53 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H), 6.22 (s, br, 2H), 5.12 (dd, J = 9.9, 4.2 Hz, 1H), 3.55 (dd, J = 17.8, 9.8Hz, 1H), 2.71 (dd, J = 17.8, 4.2Hz, 1H), 2.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.2, 200.7, 151.2, 139.9, 134.3, 131.8, 129.2, 127.9, 127.2, 117.4, 117.3, 115.9, 49.0, 48.3, 30.2; HRMS (ESI-Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{18}NO_2$ 268.1338; Found 268.1330.

4as: yellow solid, 178 mg, 52%, mp 99-101 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, J = 8.2 Hz, 1H), 7.18-7.25 (m, 4H), 7.13 (t, J = 7.5 Hz, 1H), 6.53 (t, J = 7.6 Hz, 2H), 6.23 (s, br, 2H), 5.13 (dd, J = 9.5, 4.4 Hz, 1H), 3.59 (dd, J = 18.0, 9.6Hz, 1H), 2.76 (dd, J = 18.0, 4.4 Hz, 1H), 1.13 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.0, 200.3, 151.1, 138.4, 134.3, 132.8, 131.4, 129.3, 129.1, 117.4, 117.0, 115.8, 47.7, 43.9, 41.9, 26.4; HRMS (ESI-Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{20}H_{23}ClNO_2$ 344.1417; Found 344.1406.

4at: yellow solid, 147 mg, 55%, mp 76-77 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, J = 7.1 Hz, 2H), 7.91 (dd, J = 8.2, 1.1 Hz, 1H), 7.55 (tt, J = 7.3, 1.3 Hz, 1H), 7.45 (t, J = 7.4 Hz, 2H), 7.26 (ddd, J = 8.4, 7.1, 1.4 Hz, 1H), 6.62-6.72 (m, 2H), 6.22 (s, br, 2H), 4.12-4.28 (m, 1H), 3.69 (dd, J = 18.0, 8.1 Hz, 1H), 3.06 (dd, J = 18.0, 5.2 Hz, 1H), 1.29 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.4, 198.7, 151.1, 136.8, 134.3, 133.2, 131.2, 128.6, 128.2, 117.6, 116.8, 116.0, 42.4, 36.4, 18.6; HRMS (ESI-Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{18}NO_2$ 268.1338; Found 268.1330.

4ba: yellow solid, 236 mg, 65%, mp 59-60 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, J = 7.1 Hz, 2H), 7.82 (d, J = 8.8 Hz, 1H), 7.55 (tt, J = 7.3, 1.3 Hz, 1H), 7.43 (t, J = 7.4 Hz, 2H), 7.19-7.35 (m, 5H), 6.57 (d, J = 2.0 Hz, 1H), 6.52 (dd, J = 8.7 Hz, 2.0 Hz, 1H), 6.31 (s, br, 2H), 5.25 (dd, J = 10.2, 3.7 Hz, 1H), 4.18 (dd, J = 18.0, 10.2 Hz, 1H), 3.21 (dd, J = 18.0, 3.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.0, 198.3, 152.0, 140.1, 139.6, 136.5, 133.4, 133.1, 129.3, 128.7, 128.2, 128.0,

127.4, 116.6, 116.4, 115.9, 49.0, 43.9; HRMS (ESI-Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{19}ClNO_2$ 364.1104; Found 364.1095.

4ca: yellow solid, 232 mg, 64%, mp 126-127 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, J = 7.3 Hz, 2H), 7.87 (d, J = 2.3 Hz, 1H), 7.56 (t, J = 7.3 Hz, 1H), 7.45 (t, J = 7.5 Hz, 2H), 7.21-7.38 (m, 5H), 7.13 (dd, J = 8.8 Hz, 2.3 Hz, 1H), 6.55 (d, J = 8.9 Hz, 1H), 6.21 (s, br, 2H), 5.24 (dd, J = 10.3, 3.5 Hz, 1H), 4.19 (dd, J = 18.0, 10.3 Hz, 1H), 3.24 (dd, J = 18.0, 3.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.8, 198.2, 149.7, 139.2, 136.5, 134.3, 133.4, 130.8, 129.4, 128.7, 128.3, 128.0, 127.5, 120.2, 118.9, 118.0, 48.9, 44.0; HRMS (ESI-Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{19}ClNO_2$ 364.1104; Found 364.1101.

4da: yellow solid, 174 mg, 50%, mp 104 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, J = 7.1 Hz, 2H), 7.52-7.61 (m, 2H), 7.44 (t, J = 7.5 Hz , 2H), 7.20-7.38 (m, 5H), 6.96 (ddd, J = 9.0, 7.7, 2.9 Hz, 1H), 6.55 (dd, J = 9.1, 4.7 Hz, 1H), 6.07 (s, br, 2H), 5.21 (dd, J = 10.3, 3.5 Hz, 1H), 4.19 (dd, J = 18.0, 10.3 Hz, 1H), 3.23 (dd, J = 18.0, 3.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.8 (d, $J_{4,C-F}$ = 2.8 Hz), 198.2, 153.3 (d, $J_{1,C-F}$ = 234.2 Hz), 147.7, 139.2, 136.4, 133.3, 129.3, 128.6, 128.2, 127.9, 127.4, 122.4 (d, $J_{2,C-F}$ = 23.6 Hz), 118.6 (d, $J_{3,C-F}$ = 7.0 Hz), 116.7 (d, $J_{4,C-F}$ = 5.5 Hz), 116.1 (d, $J_{2,C-F}$ = 22.4 Hz), 48.9, 44.0; HRMS (ESI-Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{19}FNO_2$ 348.1400; Found 348.1392.

4ea: yellow solid, 116 mg, 32%, mp 88-90 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, J = 7.1 Hz, 2H), 7.55 (tt, J = 7.3, 1.3 Hz, 1H), 7.44 (t, J = 7.4 Hz, 2H), 7.29-7.39 (m, 5H), 7.18-7.25 (m, 1H), 6.87 (dd, J = 9.0, 2.9 Hz, 1H), 6.56 (d, 9.0 Hz, 1H), 5.93(s, br, 2H), 5.29 (dd, J = 9.9, 3.8 Hz, 1H), 4.18 (dd, J = 18.0, 9.9 Hz, 1H), 3.66 (s, 3 H), 3.22 (dd, J = 17.9, 3.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.1, 198.3, 150.0, 146.0, 140.0, 136.7, 133.3, 129.3, 128.7, 128.3, 128.0, 127.3, 123.6, 118.9, 117.1, 113.8, 55.8, 49.4, 43.9; HRMS (ESI-Q-TOF) m/z: $[M+H]^+$ Calcd for

$C_{23}H_{22}NO_3$ 360.1600; Found 360.1593.

4fa: yellow solid, 112 mg, 30%, mp 196-197 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.99 (d, J = 2.5 Hz, 1H), 7.96-8.06 (m, 3H), 7.58 (tt, J = 7.4, 1.3 Hz, 1H), 7.46 (t, J = 7.5 Hz, 2H), 8.03 (dd, J = 9.2, 2.5 Hz, 1H), 7.99 (d, J = 7.1 Hz, 2H), 7.23-7.31 (m, 1H), 6.98(s, br, 1H), 6.59 (d, J = 9.2 Hz, 1H), 5.33 (dd, J = 10.7, 3.2 Hz, 1H), 4.23 (dd, J = 18.2 Hz, 10.7 Hz, 1H), 3.30 (dd, J = 18.1 Hz, 3.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ200.2, 198.2, 155.5, 138.5, 136.9, 136.3, 133.6, 129.6, 129.4, 129.2, 128.8, 128.3, 128.0, 127.8, 117.3, 115.3, 49.0, 44.0; HRMS (ESI-Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{19}N_2O_4$ 375.1345; Found 375.1340.

4ga: yellow solid, 184 mg, 54%, mp 132 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, J = 7.1 Hz, 2H), 7.71 (s, 1H), 7.52 (t, J = 7.3 Hz, 1H), 7.41 (t, J = 7.5 Hz, 2H), 7.36 (t, J = 7.1 Hz, 2H), 7.29 (t, J = 7.5 Hz, 2H), 7.20 (t, J = 7.1 Hz, 1H), 6.99 (dd, J = 8.4, 1.7 Hz, 1H), 6.50 (d, J = 8.4 Hz, 1H), 6.05 (s, br, 2H), 5.35 (dd, J = 9.9, 3.8 Hz, 1H), 4.18 (dd, J = 17.9, 9.9 Hz, 1H), 3.22 (dd, J = 18.0, 3.9 Hz, 1H), 2.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.4, 198.3, 149.1, 140.0, 136.6, 135.4, 133.1, 131.2, 129.1, 128.5, 128.1, 128.0, 127.1, 124.5, 117.5, 117.2, 48.6, 43.8, 20.5; HRMS (ESI-Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{22}NO_2$ 344.1651; Found 344.1642.

K_2CO_3-Catalyzed Reactions of *N*-Phenyl-2-Oxindole (7) or *N*-Boc-2-Oxindole (8) with Enone 2u.

A mixture of *N*-phenyl 2-oxindole **7** or *N*-phenyl 2-oxindole **8** (1 mmol), enone **2u** (1 mmol), and K_2CO_3 (0.2 mmol) was stirred in 4 mL of DMSO at room temperature under open air condition for given time. After completion of the reaction determined by TLC, 30 mL of water was added and the mixture was extracted with dichloromethane (20 mL× 3). The combined organic phases were dried over anhydrous sodium sulfate and concentrated in *vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate/petroleum ether) to provide two fractions. The

first fraction with low polarity was mixture of three inseparable compounds and the second fraction with high polarity corresponds to product **9** (162 mg, 35%) or **10** (186 mg, 38%).

9: white solid, mp 201-203 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, J = 8.2 Hz, 2H), 7.59 (dd, J = 7.2, 1.2 Hz, 1H), 7.30-7.40 (m, 3H), 7.21-7.29 (m, 3H), 7.18 (td, J = 7.5, 1.4 Hz, 1H), 6.84-6.92 (m, 2H), 6.69-6.77 (m, 4H), 6.49 (d, J = 7.7 Hz, 1H), 4.00-4.13 (m, 2H), 3.52-3.68 (m, 2H), 2.41 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.6, 177.2, 144.2, 144.1, 137.0, 134.49, 134.47, 133.6, 129.8, 129.5, 129.4, 129.0, 128.6, 128.4, 128.2, 127.8, 126.5, 125.1, 123.1, 109.6, 79.7, 49.2, 38.5, 21.7, 21.0; HRMS (ESI-Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{31}H_{28}NO_3$ 462.2069; Found 462.2059.

10: white solid, mp 77-79 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, J = 8.2 Hz, 2H), 7.59 (d, J = 7.9 Hz, 1H), 7.41 (dd, J = 7.4, 1.0 Hz, 1H), 7.32 (td, J = 7.7, 1.4 Hz, 1H), 7.17-7.25 (m, 3H), 6.85 (d, J = 7.9 Hz, 2H), 6.66 (d, J = 8.1 Hz, 2H), 3.79-4.01 (m, 3H), 3.47-3.61 (m, 1H), 2.39 (s, 3H), 2.18 (s, 3H), 1.48 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.4, 177.0, 148.2, 144.0, 139.8, 136.8, 134.3, 133.7, 129.9, 129.3, 128.7, 128.5, 128.3, 127.0, 124.6, 124.3, 115.0, 83.9, 79.1, 49.4, 38.0, 27.9, 21.7, 21.0; HRMS (ESI-Q-TOF) m/z: $[M+Na]^+$ Calcd for $C_{30}H_{31}NNaO_5$ 508.2100; Found 508.2092.

TsOH•H_2O Catalyzed-Intramolecular Reaction of 4aa for the Synthesis of 11.

A mixture of **4aa** (53 mg, 0.16 mmol) and TsOH•H_2O (3.1 mg, 0.016 mmol) in ethanol (0.4 mL) were stirred at 40 °C for 4 h until the disappearance of **4aa** determined by TLC. Saturated aqueous solution of $NaHCO_3$ (15 mL) was added and the mixture was extracted with dichloromethane (15 mL × 3). The combined organic layers was dried over $MgSO_4$, and concentrated in *vacuo*. Purification on silica gel (ethyl acetate/petroleum ether) afforded the product **11** (38.5 mg, 77%).

11: yellow solid, mp 80-81 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (dd, J = 8.0, 1.6 Hz, 1H),

7.45-7.51 (m, 2H), 7.27-7.45 (m, 9H), 7.10 (d, J = 8.2 Hz, 1H), 6.99 (ddd, J = 8.0, 7.1, 0.9 Hz, 1H), 6.66 (s, br, 1H), 5.29 (dd, J = 7.0, 1.7 Hz, 1H), 4.29 (d, J = 7.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.2, 144.3, 141.5, 137.3, 137.1, 132.7, 131.2, 129.6, 129.4, 129.0, 128.5, 127.3, 125.4, 119.5, 118.3, 105.7, 57.4; HRMS (ESI-Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{18}NO$ 312.1388; Found 312.1380.

One-pot Two-Step Conversion of 4aa to 12.

A mixture of **4aa** (36 mg, 0.11 mmol) and I_2 (5.5 mg, 0.02 mmol) was stirred in 0.4 mL of DMSO at 80 °C for half an hour until the disappearance of **4aa** as determined by TLC. After cooling to room temperature, I_2 (27 mg, 0.11 mmol) and DMAP (32 mg, 0.26 mmol) was added and the mixture was stirred at room temperature for 30 min. Upon completion of the reaction, the mixture was quenched with saturated aqueous solution of $Na_2S_2O_3$ and then extracted with dichloromethane (3× 15 mL). The organic extracts were dried over sodium sulfate and concentrated in *vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate/petroleum ether) to provide the product **12** (27.8 mg, 82%).

12: yellow solid, mp 250 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03-8.10 (m, 2H), 7.94 (dd, J = 7.9, 1.5 Hz, 1H), 7.89 (dd, J = 8.0, 0.9 Hz, 1H), 7.75 (ddd, J = 8.1, 7.2, 1.6 Hz, 1H), 7.65-7.72 (m, 2H), 7.49-7.56 (m, 4H), 7.48 (s, 1H), 7.40-7.47 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.3, 159.9, 151.6, 146.1, 140.8, 137.2, 135.1, 132.9, 131.4, 130.7, 129.6, 128.9, 128.8, 128.8, 128.6, 128.3, 128.2, 125.8; HRMS (ESI-Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{16}NO$ 310.1232; Found 310.1224.

The Hydrochloric Acid-Catalyzed Transformation of 4aa to 13 and 14 in DMSO/H_2O.

Hydrochloric acid (12 mol/L, 2.5 μL, 0.03 mmol) was added to a solution of **4aa** (65.5 mg, 0.2 mmol) in DMSO/H_2O (0.4 mL/0.1 mL). The mixture was stirred at 90 °C under open air condition for 22 h. After completion of the reaction as determined by TLC, the mixture was quenched with

saturated $NaHCO_3$ and then extracted with dichloromethane (20 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated to give a residue, which was purified by column chromatography on silica gel (ethyl acetate/petroleum ether) to afford product **13** (28.4 mg, 46%, lower polarity) and product **14** (19.4 mg, 30%, higher polarity. *The compound **14** has same polarity with **4aa** in the eluent of ethyl acetate/petroleum ether. However, they can be separated on TLC using isopropyl ether/n-hexane = 5:4 as the eluent*).

13: yellow solid, mp 105-106 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (ddd, J = 8.5, 1.1, 0.6 Hz, 1H), 8.13-8.19 (m, 2H), 7.89-7.94 (m, 2H), 7.88 (s, 1H), 7.83-7.89 (m, 1H), 7.78 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H), 7.66 (tt, J = 7.4, 1.3 Hz, 1H), 7.44-7.57 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.4, 156.6, 148.8, 145.4, 139.0, 136.7, 134.3, 130.5, 130.35, 130.33, 129.8, 129.0, 128.9, 127.6, 127.4, 125.2, 124.0, 117.6; HRMS (ESI-Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{16}NO$ 310.1232; Found 310.1223.

14: yellow solid, mp 150 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, J = 7.1 Hz, 2H), 7.52-7.61 (m, 4H), 7.40-7.52 (m, 3H), 7.28 (tt, J = 6.9, 1.5 Hz, 2H), 7.21 (tt, J =7.2, 1.3 Hz, 1H), 6.96 (d, J = 8.3 Hz, 1H), 6.81 (ddd, J =7.8, 7.2, 0.7 Hz, 1H), 6.31 (s, br, 1H), 4.45 (d, J = 18.0 Hz, 1H), 3.18 (d, J = 17.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.8, 197.9, 160.4, 138.1, 137.9, 136.7, 133.9, 128.9, 128.8, 128.2, 127.7, 125.8, 125.4, 119.0, 118.2, 111.9, 69.4, 44.8; HRMS (ESI-Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{18}NO_2$ 328.1338; Found 328.1326.

Conversion of 12 to 13 and 14 with Catalytic Amount of Hydrochloric Acid in DMSO/H_2O.

Hydrochloric acid (12 mol/L, 2.5 μL, 0.03 mmol) was added to a solution of **12** (55 mg, 0.18 mmol) in DMSO/H_2O (0.4 mL/0.1 mL). The mixture was stirred at 90 °C until the completion of reaction as determined by TLC (within 25 min). The resulting mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with dichloromethane (3 × 15 mL). The organic extracts

were dried over sodium sulfate, filtered and concentrated to give a residue, which was purified by column chromatography on silica gel (ethyl acetate/petroleum ether) to afford product **13** (24.4 mg, 44%) and product **14** (24.7 mg, 42%).

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Supporting Information

^{1}H and ^{13}C NMR spectra of the products and X-ray crystallographic data of **3a**, **4al** and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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