JOC The Journal of Organic Chemistry
Article
pubs.acs.org/joc

Metal-Free Synthesis of 2-Oxindoles via PhI(OAc)$_2$-Mediated Oxidative C−C Bond Formation

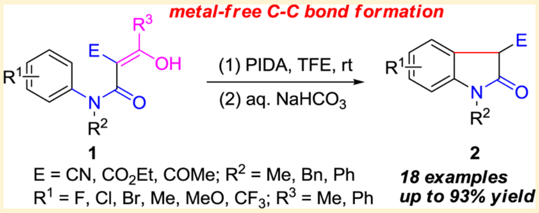
Jinglei Lv,[†] Daisy Zhang-Negrerie,[†] Jun Deng,[†] Yunfei Du,[†,‡,]* and Kang Zhao*[,†]

[†]Tianjin Key Laboratory for Modern Drug Delivery & High-Efficiency, School of Pharmaceutical Science and Technology, Tianjin University, Tianjin 300072, People's Republic of China

[‡]Collaborative Innovation Center of Chemical Science and Engineering (Tianjin) Tianjin University, Tianjin 300072, People's Republic of China

S Supporting Information

ABSTRACT: The series of 3-monofunctionalized 2-oxindoles **2** were conveniently synthesized from reactions between anilide **1** and phenyliodine(III) diacetate (PIDA) through hypervalent iodine mediated C(sp^2)−C(sp^2) bond formation followed by a subsequent deacylation reaction. This metal-free method, shown to provide direct access to an important oxindole intermediate, could be applied to the total synthesis of naturally occurring horsfiline.

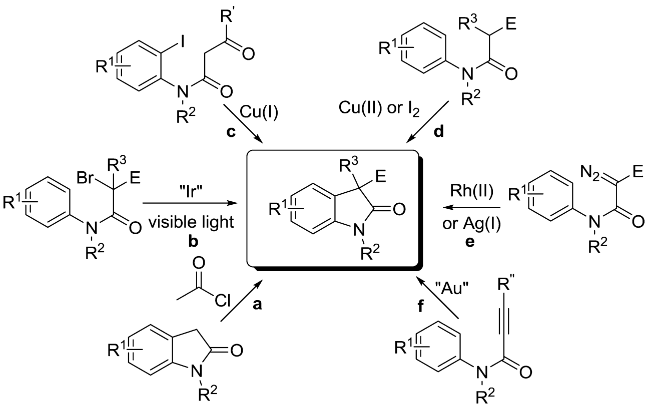


■ INTRODUCTION

Oxindoles have received enduring synthetic interest from organic chemists, since they are versatile building blocks for the synthesis of natural products and biologically active molecules.[1] Specifically, 3-monofunctionalized 2-oxindoles have been identified as indispensable intermediates in the total synthesis of the naturally occurring horsfiline, welwitindolinone C, CPC-1, etc.[1g−j]

According to a literature survey, a handful of strategies have been established to construct the oxindole skeleton. The most commonly used approach is through the condensation of oxindoles with activated ortho esters or acyl derivatives (Scheme 1, route **a**).[2] Another route is through Ir- or Cu-catalyzed intramolecular cyclization of β-keto amide derivatives (Scheme 1, routes **b** and **c**).[3] However, for the cyclization to occur, both methods require specifically functionalized precursors and the presence of either an ortho aromatic halogen or an α-halogen. Recently, Taylor and Bisai realized the conversion of anilides to 3,3-disubstituted oxindoles through Cu- and I$_2$- mediated aromatic C(sp^2)−C(sp^3) coupling (Scheme 1, route **d**).[4] Moreover, Ag-, or Rh-catalyzed aromatic C−H functionalization of α-diazoamides is another effective way to construct 3-monofunctionalized oxindoles (Scheme 1, route **e**),[5] and starting from *N*-arylpropiolamides, 3-acyloxindoles can also be synthesized via Au-mediated aromatic C(sp^2)−C(sp) bond formation (Scheme 1, route **f**).[6] In the past 50 years, hypervalent iodine reagents, such as phenyliodine diacetate (PIDA) and phenyliodine bis(trifluoroacetate) (PIFA), have been proven to be a class of effective and environmentally friendly oxidative reagents in mediating the formation of C−C bonds, without the involvement of a toxic, transition-metal-containing reagent.[7] To our knowledge, there are few examples describing the synthesis of 3-monofunctionalized 2-oxindoles via oxidative C(sp^2)−C(sp^2) bond formation from anilide derivatives.[8] Herein, we report a new application of hypervalent iodine: that is, in constructing 3-monofunctionalized 2-oxindole frameworks through its role of facilitating an intramolecular cyclization of anilide derivatives via an exclusive C(sp^2)−C(sp^2) bond-forming reaction.

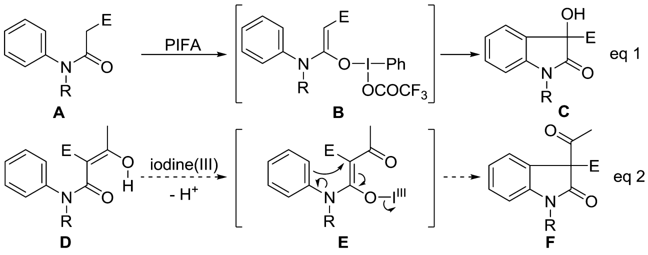
Scheme 1. Existing Routes To Access 3-Functionalized 2-Oxindoles



In our previous work, we successfully realized the construction of the oxindole scaffold **C** through PIDA-mediated oxidative cyclization of anilide **A** (Scheme 2, eq 1).[9] Enthused by this work, we envisaged the formation of another oxindole compound **F** through the same reaction pattern by starting with the functionalized anilide derivative **D**, the structure of which bears a terminal enol functionality (Scheme 2, eq 2).[10] We argued that, upon treatment of **D** with an iodine(III) oxidant, the analogous O−I intermediate **E** should be furnished, which would likely trigger a similar C(sp^2)−C(sp^2) bond-forming process and thus produce the oxindole compound **F**. The acetyl group in **F** could

Received: November 18, 2013
Published: January 10, 2014

Scheme 2. Proposed Route To Access 3-Functionalized Oxindoles Based on the Previously Reported PIFA-Mediated Synthesis of 3-Hydroxy-2-oxindoles

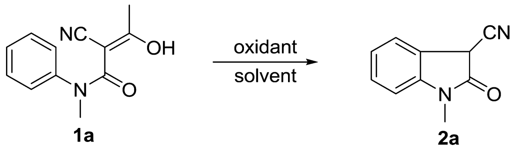


act as a protecting group to avoid overoxidation of the oxindole at the 3-position.

■ RESULTS AND DISCUSSION

To test the feasibility of the proposed conversion, (*Z*)-2-cyano-3-hydroxy-*N*-methyl-*N*-phenylbut-2-enamide (**1a**), readily prepared via condensation of cyanoacetanilide with acetyl chloride,[10a] was selected as the model substrate. However, to our surprise, 3-cyano-2-oxindole **2a** was formed instead, after mixing **1a** and PIDA in MeCN for 72 h at room temperature. The result showed that an unexpected deacylation reaction had occurred following the expected C(sp^2)−C(sp^2) bond formation. Later on, other iodine(III) oxidants, i.e., PIFA and PhIO, were put to the test and were also found to be effective in affording the same product, albeit in slightly lower yields (Table 1, entries 2 and 3). Using PIDA as the oxidant, we next investigated other solvents, including MeCN, DCM, THF, TFE, DMF, DMSO, and MeOH (Table 1, entries 4−9). The results revealed that TFE was the leading solvent for this cyclization reaction (Table 1, entry 6). Considering the long reaction time of 72 h, we made further attempts to speed up the reaction, first by raising the reaction temperature to reflux temperature. The higher temperature indeed resulted in a greatly reduced reaction time, 7 h, but was unfortunately accompanied by a reduced yield of 76% (Table 1, entry 10). The cyclized product **2a** was obtained in 76% yield.

Table 1. Optimization of Reaction Conditions[a]



entry	oxidant	solvent	temp	time (h)	yield (%)[b]
1	PIDA	MeCN	room temp	72	84
2	PIFA	MeCN	room temp	72	71
3	PhIO	MeCN	room temp	72	72
4	PIDA	DCM	room temp	72	55
5	PIDA	THF	room temp	72	ND
6	PIDA	TFE	room temp	72	92
7	PIDA	DMF	room temp	48	74
8	PIDA	DMSO	room temp	72	52
9	PIDA	MeOH	room temp	72	ND
10	PIDA	TFE	reflux	7	76
11[c]	PIDA	TFE	room temp	2	88

[a] Reaction conditions: **1a** (1.0 mmol), oxidant (1.1 mmol) in solvent unless otherwise stated. [b] Isolated yields. [c] Aqueous NaHCO$_3$ (3.0 mmol) was used after the addition of PIDA.

Another modification that drastically improved the reaction efficiency was the introduction of aqueous NaHCO$_3$ after the addition of PIDA at room temperature. This modification not only further reduced the reaction time to only 2 h but also brought back the yield to 90% (Table 1, entry 11).[11]

Under the optimal conditions (Table 1, entry 11), a range of substituted anilide derivatives were studied to explore the scope as well as limitations of this newly developed method. We were delighted to see that the method could be well applied to substrates bearing either electron-donating or electron-withdrawing aromatic substituents to afford the expected oxindoles in moderate to good yields (Table 2, entries 2−5, 8, and 9), with higher yields occurring in the former class of substrates, giving higher yields of the products. Switching the methyl group on N to other substituents, such as benzyl and phenyl groups, did not affect the yield to any significant degree (Table 2, entries 6 and 7). As expected, meta-substituted substrates provided two regioisomeric products (Table 2, entries 8 and 9), the ratio of which implied the cyclization to preferably occur at the less hindered position. However, total regioselectivity was observed for **1l**, as **2l** was obtained as the sole regioisomeric product (Table 2, entry 12). Because of its strong electron-withdrawing effect, the cyano group in substrates **1a**−**j** is understood to be crucial for maintaining the terminal enol structure through preventing the keto tautomer structure.[10] In light of this, we investigated the functional group tolerance of this methodology by replacing the cyano group with other electron-withdrawing groups, such as carboxylic ester (Table 2, entries 11−13) and acetyl groups (Table 2, entries 14−18).[12] To our delight, substrates bearing either the ester or acetyl group also furnished the desired oxindole products in satisfactory yields of 72−93%.[13]

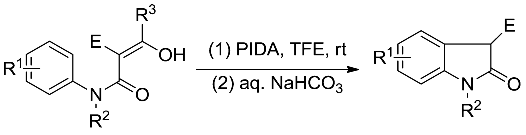
It is worth noting that the method worked equally well for substrates **1j**,**m**,**q**, readily derived from tetrahydroquinoline, to deliver the tricyclic oxindoles **2j**,**m**,**q** in satisfactory yields, respectively (Table 2, entries 10, 13, and 17).[14]

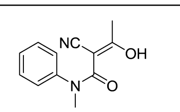
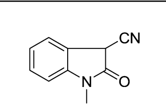
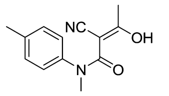
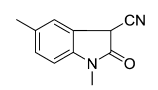
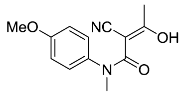
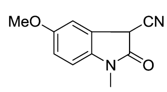
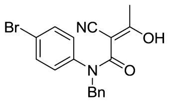
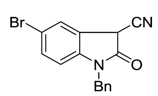
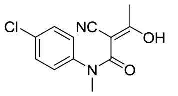
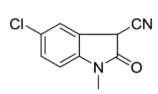
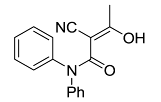
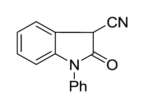
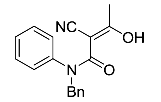
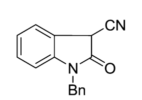
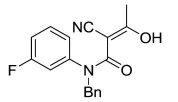
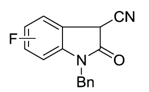
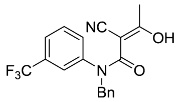
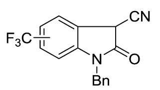
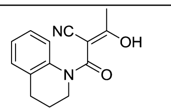
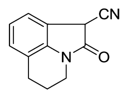
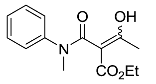
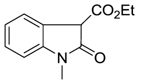
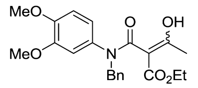
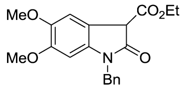
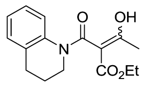
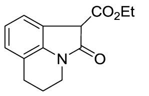
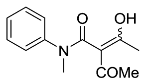
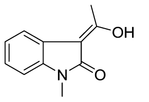
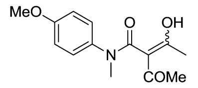
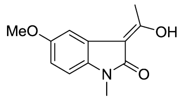
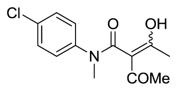
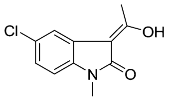
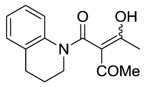
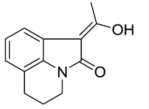
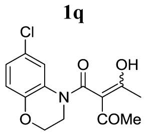
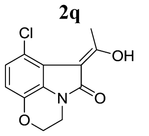
At the early stages, anilide **D** probably underwent exactly the pathway we proposed in Scheme 2 and indeed gave the 3-acetyl oxindole intermediate **F** through intermediates **E** and **G** (Scheme 3). We believe that intermediate **F**, bearing an acetyl group and a strong electron-withdrawing group on the same carbon atom, should have a strong tendency to undergo deacylation through a nucleophilic attack on the carbonyl group by the released acetate anion. Finally, the formed carbanion **H** captures one proton to furnish the desired 3-functionalized 2-oxindole.

In order to confirm this assumption, anilide **1s** was prepared and treated with PIDA in TFE, without further treatment with aqueous NaHCO$_3$ (Scheme 4). In this reaction, intermediate **F′** was detected by crude HRMS analysis, although it could not be purified by silica gel column chromatography due to its extreme instability.[15] As expected, in addition to the desired cyclized product **2a**, the mixed anhydride **3** was also isolated. This result adequately supports the deacylation mechanism proposed above. It also led to the conclusion that the presence of NaHCO$_3$ in the reaction system effectively accelerates the final deacylation process.

Back in 2006, Trost and Brennan reported a total synthesis of the oxindole alkaloid horsfiline,[1g] in which oxindole **L** acts as an important intermediate. Here, we report the synthesis of intermediate **L**, by applying our newly developed method, starting from the readily available amine **I.** As described in Scheme 5, amine **I** was conveniently converted to anilide **J** through condensation with 2-ethoxycarbonylacetyl chloride, which was further transformed into **K** by the general acylation

Table 2. Synthesis of 3-Monofunctionalized 2-Oxindoles by PIDA[a]



entry	substrate 1	product 2	yield (%)[b]
1	 1a	 2a	88
2	 1b	 2b	89
3	 1c	 2c	88
4	 1d	 2d	78
5	 1e	 2e	64
6	 1f	 2f	80
7	 1g	 2g	83
8[c]	 1h	 2h: 5-F/2h': 3-F	49
9[d]	 1i	 2i: 5-CF_3/2i': 3-CF_3	43
10[e]	 1j	 2j	88
11	 1k	 2k	84
12	 1l	 2l	72
13[e]	 1m	 2m	84
14	 1n	 2n	82
15	 1o	 2o	86
16	 1p	 2p	75
17	 1q	 2q	93
18	 1r	 2r	82

[a]General conditions: **1** (1.0 equiv), PIDA (1.1 equiv) in TFE at room temperature for 1 h unless otherwise stated; then aqueous $NaHCO_3$ (3.0 equiv) was added. [b]Isolated yields. [c]The two regioisomers were inseparable: **2h**/**2h′** = 2:1. [d]The two regioisomers were inseparable: **2i**/**2i′** = 1.2:1. [e]**1** (1.0 equiv) and PIDA (1.1 equiv) in TFE at room temperature for 72 h without treatment with aqueous $NaHCO_3$.

approach. To our delight, upon treatment with PIDA in MeCN,[16] the expected intramolecular oxidative cyclization/deacylation occurred in **K** and gave the oxindole intermediate, which was captured by TIPSOTf in the presence of Et_3N to give the desired intermediate **L** in moderate yield. This result demonstrates that our method can provide an alternative and effective access to the natural product horsfiline.

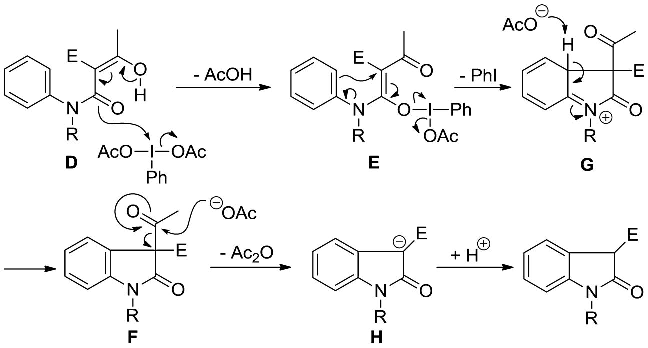
CONCLUSION

In conclusion, we have developed an efficient approach for the synthesis of 3-monofunctionalized 2-oxindoles via PIDA-mediated C(sp^2)−C(sp^2) bond formation and a deacylation reaction. The highlights of the reported method, in comparison to the currently existing methods for the synthesis of oxindole products, include the mild reaction conditions, good functional group tolerance, the metal-free feature, and environmentally friendly characteristics.

EXPERIMENTAL SECTION

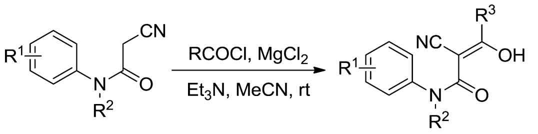
I. General Information. All reactions were stirred magnetically without precaution of air and carried out at room temperature. ^1H and ^{13}C NMR spectra were recorded on a 400 or 600 MHz spectrometer at 25 °C. Chemical shift values are given in ppm and referenced to the internal standard TMS at 0.00 ppm. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet; br,

Scheme 3. Proposed Mechanism



broad; dd, doublet of doublets. The coupling constants *J* are reported in hertz (Hz). High-resolution mass spectra (HRMS) were obtained on a Q-TOF micro spectrometer. Melting points were determined with a national micromelting point apparatus without corrections. TLC plates were visualized by exposure to ultraviolet light. Reagents and solvents were purchased as reagent grade and were used without further purification. Flash column chromatography was performed over silica gel 200−300 m, and the eluent was a mixture of ethyl acetate (EA) and petroleum ether (PE).

II. General Procedure for the Synthesis of 2-Cyano-3-hydroxy-*N*-substituted Amides (1a−j,s).[10]



S_X **1X**

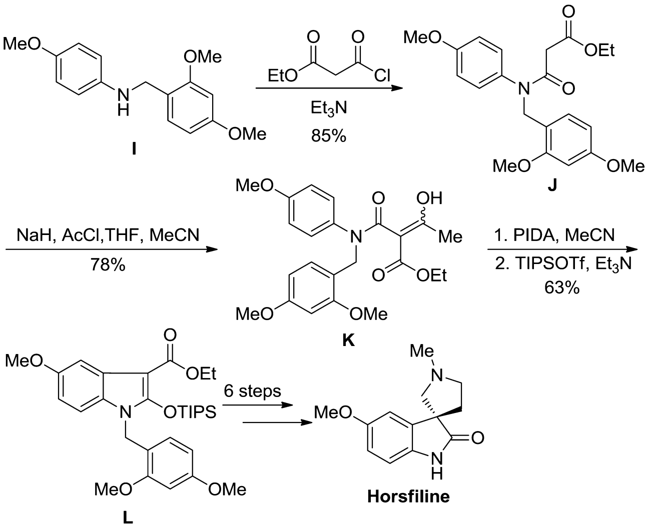
The cyanoacetanilides were prepared by the known procedures.[17] The novel cyanoacetanilide derivatives S_d, S_h, and S_i thus obtained were characterized as follows.

N-Benzyl-N-(4-bromophenyl)-2-cyanoacetamide (S_d). The amide was purified by silica gel chromatography (20% EA/PE): yield 84%, white solid, mp 101−103 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.54 (d, J = 8.4 Hz, 2H), 7.30 (m, 3H), 7.18 (m, 2H), 6.91 (d, J = 8.4 Hz, 2H), 4.88 (s, 2H), 3.24 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 161.5, 139.5, 135.8, 133.5, 130.0, 129.1, 128.7, 128.1, 123.3, 113.9, 53.7, 25.8; HRMS (ESI) calcd for $C_{16}H_{13}BrN_2NaO^+$ [M + Na$^+$] 351.0103, found 351.0107; IR (KBr) 2251, 1667, 1489, 1455, 1417, 1198, 837 cm^{-1}.

N-Benzyl-2-cyano-N-(3-fluorophenyl)acetamide (S_h). The amide was purified by silica gel chromatography (40% EA/PE): yield 81%, white solid, mp 119−121 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.41 (m, 1H), 7.30 (m, 3H), 7.20 (m, 2H), 7.12 (t, J = 8.0 Hz, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.79 (d, J = 8.8 Hz, 1H), 4.90 (s, 2H), 3.27 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 163.0 (d, J_{C-F} = 251.8 Hz), 161.8, 161.6, 141.9 (d, J_{C-F} = 8.2 Hz), 135.8, 131.5 (d, J_{C-F} = 9.1 Hz), 129.0, 128.7 128.1, 124.3 (d, J_{C-F} = 2.8 Hz), 116.5 (d, J_{C-F} = 21.4 Hz), 115.8 (d, J_{C-F} = 22.3 Hz), 113.9, 53.7, 25.8; ^{19}F NMR (566 MHz, CDCl$_3$) δ −108.83 (s, 1F); HRMS (ESI) calcd for $C_{16}H_{13}FN_2NaO^+$ [M + Na$^+$] 291.0904, found 291.0904; IR (KBr) 2250, 1665, 1606, 1487, 1412, 1217 cm^{-1}.

N-Benzyl-2-cyano-N-(3-(trifluoromethyl)phenyl)acetamide (S_i). The amide was purified by silica gel chromatography (30% EA/PE): yield 87%, light yellow solid, mp 122−124 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.69 (d, J = 7.7 Hz, 1H), 7.56 (t, J = 7.9 Hz, 1H), 7.30 (m, 4H), 7.24 (d, J = 7.8 Hz, 1H), 7.18 (m, 2H), 4.92 (s, 2H), 3.23 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 161.5, 141.1, 135.6, 132.8 (q, J_{C-F} = 32.8 Hz), 132.6, 132.1, 131.0, 129.1, 128.8, 128.2, 126.1 (q, J_{C-F} = 2.8 Hz), 125.4 (q, J_{C-F} = 3.2 Hz), 123.1 (q, J_{C-F} = 274.0 Hz), 113.7, 53.8, 25.9; ^{19}F NMR (566 MHz, CDCl$_3$) δ −62.82 (s, 3F); HRMS (ESI) calcd for $C_{17}H_{13}F_3N_2NaO^+$ [M + Na$^+$] 341.0872, found 341.0872; IR (KBr) 1667, 1593, 1410, 1322, 1125 cm^{-1}.

Scheme 5. Preparation of a Horsfiline Precursor L



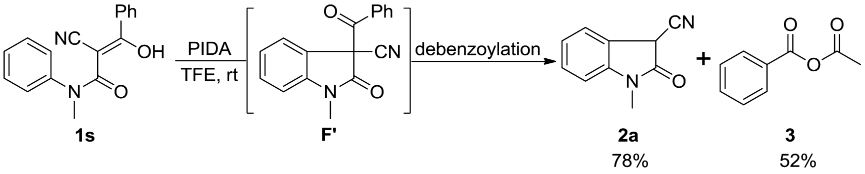
To a suspension of anhydrous MgCl$_2$ (952 mg, 10 mmol) and cyanoacetanilide (10 mmol) in MeCN (40 mL) was added anhydrous Et$_3$N (2.79 mL, 20 mmol) at room temperature. Stirring was continued at room temperature for 45 min, and then acid chloride (11 mmol) was added to the mixture at 0 °C. The resulting mixture was stirred for another 4 h at room temperature (the reaction was monitored by TLC). Upon completion of the reaction, the mixture was acidified with HCl (1 N, 30 mL). The aqueous layer was extracted with EA (50 mL × 3), and the combined organic layer was washed with brine (70 mL), dried over Na$_2$SO$_4$, and evaporated under reduced pressure to remove the solvent. Purification of the crude solid by flash column chromatography on silica gel (EA/PE) afforded the desired amides.

*(Z)-2-Cyano-3-hydroxy-N-methyl-N-phenylbut-2-enamide (**1a**).* **1a** was purified by silica gel chromatography (30% EA/PE): yield 1.75 g, 81%, white solid, mp 91−94 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 17.04 (s, 1H), 7.48−7.44 (m, 3H), 7.27−7.25 (m, 2H), 3.37 (s, 3H), 2.23 (s, 3H).

*(Z)-2-Cyano-3-hydroxy-N-methyl-N-(p-tolyl)but-2-enamide (**1b**).* **1b** was purified by silica gel chromatography (30% EA/PE): yield 1.75 g, 76%, white solid, mp 99−100 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 17.02 (s, 1H), 7.26 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 7.8 Hz, 2H), 3.33 (s, 3H), 2.41 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 191.0, 169.6, 139.4, 130.6, 127.4, 115.4, 79.1, 39.2, 22.3, 21.3 (one carbon peak was missing due to overlapping); HRMS (ESI) calcd for $C_{13}H_{14}N_2NaO_2^+$ [M + Na$^+$] 253.0947, found 253.0947; IR (KBr) 2209, 1574, 1512, 1482, 1450, 1380, 1300, 837, 754, 633 cm^{-1}.

*(Z)-2-Cyano-3-hydroxy-N-(4-methoxyphenyl)-N-methylbut-2-enamide (**1c**).* **1c** was purified by silica gel chromatography (30% EA/PE): yield 2.02 g, 82%, white solid, mp 91−92 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 17.09 (s, 1H), 7.16 (d, J = 9 Hz, 2H), 6.95 (d, J = 9 Hz, 2H), 3.84 (s, 3H), 3.32 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 191.1, 169.8, 160.3, 134.6, 128.9, 115.4, 115.1, 79.0, 55.5, 39.3, 22.4; HRMS (ESI) calcd for $C_{13}H_{14}N_2NaO_3^+$ [M + Na$^+$] 269.0897, found

Scheme 4. Specific Reaction for Mechanism Elucidation



269.0902; IR (KBr) 2209, 1579, 1510, 1463, 1299, 1254, 1026, 836, 756, 641, 568 cm^{-1}.

*(Z)-N-Benzyl-N-(4-bromophenyl)-2-cyano-3-hydroxybut-2-enamide (**1d**).* **1d** was purified by silica gel chromatography (40% EA/PE): yield 3.01 g, 81%, white solid, mp 100−102 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 16.82 (s, 1H), 7.49 (d, J = 8.4 Hz, 2H), 7.29−7.17 (m, 5H, H$_{\text{arom}}$), 6.93 (d, J = 9 Hz, 2H), 4.90 (s, 2H), 2.24 (s, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 191.6, 169.3, 139.1, 135.6, 133.0, 130.3, 128.9, 128.7, 128.1, 123.5, 115.2, 79.3, 54.6, 22.4; HRMS (ESI) calcd for $C_{18}H_{15}{}^{79}BrN_2NaO_2^+$ [M + Na$^+$] 393.0209, found 393.0209; IR (KBr) 2210, 1591, 1564, 1466, 1218, 1081, 1005, 701, 546 cm^{-1}.

*(Z)-N-(4-Chlorophenyl)-2-cyano-3-hydroxy-N-methylbut-2-enamide (**1e**).* **1e** was purified by silica gel chromatography (40% EA/PE): yield 1.98 g, 79%, white solid, mp 110−113 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 16.78 (s, 1H), 7.43 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H), 3.34 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 191.3, 169.6, 140.5, 135.2, 130.2, 129.0, 115.4, 79.2, 39.1, 22.3; HRMS (ESI) calcd for $C_{12}H_{11}{}^{35}ClN_2NaO_2^+$ [M + Na$^+$] 273.0401, found 273.0403; IR (KBr) 2213, 1587, 1493, 1345, 1299, 1106, 1018, 850, 556 cm^{-1}.

*(Z)-2-Cyano-3-hydroxy-N,N-diphenylbut-2-enamide (**1f**).* **1f** was purified by silica gel chromatography (30% EA/PE): yield 1.92 g, 69%, white solid, mp 123−124 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 16.45 (s, 1H), 7.43−7.24 (m, 10H, H$_{\text{arom}}$), 2.30 (s, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 191.9, 170.4, 141.6, 129.7, 128.2, 127.6, 114.9, 80.6, 22.5; HRMS (ESI) calcd for $C_{17}H_{14}N_2NaO_2^+$ [M + Na$^+$] 301.0947, found 301.0964; IR (KBr) 2210, 1586, 1493, 1441, 754, 740, 556 cm^{-1}.

*(Z)-N-Benzyl-2-cyano-3-hydroxy-N-phenylbut-2-enamide (**1g**).* **1g** was purified by silica gel chromatography (40% EA/PE): yield 2.31 g, 79%, white solid, mp 92−95 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 17.04 (s, 1H), 7.42−7.06 (m, 10H, H$_{\text{arom}}$), 4.93 (s, 2H), 2.23 (s, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 191.5, 169.4, 140.2, 135.9, 129.8, 129.5, 128.9, 128.8, 128.6, 127.9, 115.1, 79.3, 54.8, 22.4; HRMS (ESI) calcd for $C_{18}H_{16}N_2NaO_2^+$ [M + Na$^+$] 315.1104, found 315.1107; IR (KBr) 2214, 1569, 1443, 1293, 755, 693, 564 cm^{-1}.

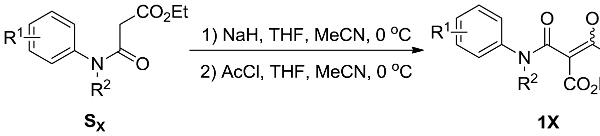
*(Z)-N-Benzyl-2-cyano-N-(3-fluorophenyl)-3-hydroxybut-2-enamide (**1h**).* **1h** was purified by silica gel chromatography (20% EA/PE): yield 2.23 g, 72%, white solid, mp 89−90 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 16.84 (s, 1H), 7.33−6.81 (m, 9H, H$_{\text{arom}}$), 4.93 (s, 2H), 2.25 (s, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 191.6, 169.4, 163.8 (d, $J_{\text{C−F}}$ = 249.2 Hz), 141.5 (d, $J_{\text{C−F}}$ = 9.9 Hz), 135.6, 130.9 (d, $J_{\text{C−F}}$ = 9.4 Hz), 128.8, 128.7, 128.1, 124.7 (d, $J_{\text{C−F}}$ = 2.4 Hz), 116.7 (d, $J_{\text{C−F}}$ = 21.0 Hz), 116.3 (d, $J_{\text{C−F}}$ = 22.7 Hz), 115.0, 79.4, 54.6, 22.4; HRMS (ESI) calcd for $C_{18}H_{15}FN_2NaO_2^+$ [M + Na$^+$] 333.1010, found 333.1010; IR (KBr) 3072, 2215, 1572, 1445, 1336, 1297, 756, 702, 515 cm^{-1}.

*(Z)-N-Benzyl-2-cyano-3-hydroxy-N-(3-(trifluoromethyl)phenyl)-but-2-enamide (**1i**).* **1i** was purified by silica gel chromatography (20% EA/PE): yield 2.41 g, 67%, white solid, mp 105−108 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 16.83 (s, 1H), 7.67 (d, J = 7.8 Hz, 1H), 7.49 (t, J = 8.4 Hz, 1H), 7.30−7.29 (m, 4H, H$_{\text{arom}}$), 7.24 (d, J = 9.0 Hz, 1H), 7.18 (m, 2H), 4.95 (s, 2H), 2.24 (s, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 191.9, 169.3, 140.6, 135.4, 132.4 (q, $J_{\text{C−F}}$ = 33.2 Hz), 132.3, 130.4, 128.9, 128.7, 128.2, 126.2 (q, $J_{\text{C−F}}$ = 3.7 Hz), 126.1 (q, $J_{\text{C−F}}$ = 3.8 Hz), 122.4 (q, $J_{\text{C−F}}$ = 272.8 Hz), 114.9, 79.2, 54.7, 22.4; HRMS (ESI) calcd for $C_{19}H_{15}F_3N_2NaO_2^+$ [M + Na$^+$] 383.0978, found 383.0984; IR (KBr) 3064, 2207, 1571, 1497, 1426, 1325, 1170, 1136, 787, 704 cm^{-1}.

*(Z)-3-Hydroxy-2-(1,2,3,4-tetrahydroquinoline-1-carbonyl)but-2-enenitrile (**1j**).* **1j** was purified by silica gel chromatography (40% EA/PE): yield 2.08 g, 86%, white solid, mp 134−136 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 16.33 (s, 1H), 7.25−7.20 (m, 4H, H$_{\text{arom}}$), 3.84 (m, 2H), 2.75 (t, J = 6.6 Hz, 2H), 2.32 (s, 3H), 2.01 (m, 2H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 190.71, 169.8, 137.2, 133.4, 128.7, 126.7, 126.5, 124.6, 115.9, 80.8, 44.7, 26.3, 23.9, 22.3; HRMS (ESI) calcd for $C_{14}H_{14}N_2NaO_2^+$ [M + Na$^+$] 265.0947, found 265.0956; IR (KBr) 2962, 2212, 1597, 1493, 1432, 1334, 755, 566 cm^{-1}.

*(Z)-2-Cyano-3-hydroxy-N-methyl-N,3-diphenylacrylamide (**1s**).* **1s** was purified by silica gel chromatography (20% EA/PE): yield 2.20 g, 79%, white solid, mp 122−125 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 17.07 (s, 1H), 7.78 (d, J = 6.0 Hz, 2H), 7.49−7.46 (m, 3H, H$_{\text{arom}}$), 7.43 (t, J = 6.0 Hz, 1H), 7.38 (t, J = 6.0 Hz, 2H), 7.32 (d, J = 6.0 Hz, 2H), 3.43 (s, 3H).

III. General Procedure for the Synthesis of Ethyl 3-Hydroxy-2-(*N*-substituted carbamoyl)but-2-enoate (1k−m). The ethyl



3-(substituted (aryl) amino)-3-oxopropanoates were prepared by the known procedures.[17] The novel ethyl 3-(substituted (aryl) amino)-3-oxopropanoate (S$_\text{l}$) thus obtained was characterized as follows.

Ethyl 3-(Benzyl(3,4-dimethoxyphenyl)amino)-3-oxopropanoate (S$_l$). The amide was purified by silica gel chromatography (40% EA/PE): yield 86%, light yellow oil; ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.29−7.23 (m, 5H), 6.77 (d, J = 8.5 Hz, 1H), 6.59 (d, J = 8.4 Hz, 1H), 6.42 (s, 1H), 4.88 (s, 2H), 4.14 (q, J = 7.1 Hz, 2H), 3.86 (s, 3H), 3.68 (s, 3H), 3.24 (s, 2H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 167.9, 166.3, 149.3, 148.9, 137.2, 134.5, 129.1, 128.4, 127.5, 120.5, 111.7, 111.2, 61.2, 55.9, 55.9, 53.1, 41.7, 14.1; HRMS (ESI) calcd for $C_{20}H_{23}NNaO_5^+$ [M + Na$^+$] 380.1468, found 380.1467; IR (KBr) 2966, 1745, 1650, 1514, 1407, 1260 cm^{-1}.

To a suspension of NaH (60% in mineral oil, 600 mg, 15 mmol) in THF and MeCN (35 mL, 1/1 $v_{\text{THF}}/v_{\text{MeCN}}$) was added a solution of ethyl 3-(substituted (aryl) amino)-3-oxopropanoate (10 mmol) in THF and MeCN (35 mL, 1/1 $v_{\text{THF}}/v_{\text{MeCN}}$) dropwise at 0 °C. Stirring was continued at room temperature for 15 min, and acetyl chloride (778 μL, 11 mmol) was added to the mixture at 0 °C. The resulting mixture was stirred for another 4 h at room temperature (the reaction was monitored by TLC). Upon completion, the mixture was acidified with HCl (1 N, 60 mL). The aqueous layer was extracted with EA (60 mL × 3), and the combined organic layer was washed with brine (90 mL), dried over Na$_2$SO$_4$, and evaporated under reduced pressure to remove the solvent. Purification of the crude oil by flash column chromatography on silica gel (EA/PE) afforded the desired amides.

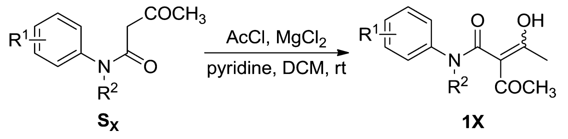
*Ethyl 3-Hydroxy-2-(methyl(phenyl)carbamoyl)but-2-enoate (**1k**).* **1k** was purified by silica gel chromatography (30% EA/PE): yield 2.21 g, 84% (enol:ketone = 3:2), light yellow oil; ^{1}H NMR (600 MHz, CDCl$_3$) major isomer (**1k**) δ 12.44 (s, 1H), 7.46−7.42 (m, 1H, peak of two isomers overlapped), 7.32 (t, J = 6.0 Hz, 2H), 7.09 (d, 12 Hz, 2H), 4.13 (q, J = 7.2 Hz, 2H), 3.40 (s, 3H), 2.02 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H), minor isomer (**1k′**) δ 7.40−7.38 (m, 1H, peak of two isomers overlapped), 7.24 (t, J = 7.2 Hz, 2H), 7.20 (d, J = 7.2 Hz, 2H), 4.37 (s, 1H), 4.18−4.16 (q, J = 6.0 Hz, 2H), 3.33 (s, 3H), 2.22 (s, 3H), 1.23 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 198.3, 174.6, 169.8, 166.3, 165.5, 164.4, 164.1, 143.9, 142.7, 130.2, 129.9, 129.1, 128.7, 128.3, 127.6, 127.3, 126.1, 102.9, 64.5, 62.0, 60.9, 37.7, 37.3, 29.1, 19.8, 14.2, 14.0; HRMS (ESI) calcd for $C_{14}H_{17}NNaO_4^+$ [M + Na$^+$] 286.1050, found 286.1044; IR (KBr) 3062, 2846, 1741, 1629, 1580, 1492, 1383, 1069, 846, 666 cm^{-1}.

*Ethyl 2-(Benzyl(3,4-dimethoxyphenyl)carbamoyl)-3-hydroxybut-2-enoate (**1l**).* **1l** was purified by silica gel chromatography (30% EA/PE): yield 2.65 g, 82% (enol:ketone = 1:1.4), light yellow oil; ^{1}H NMR (600 MHz, CDCl$_3$) major isomer (**1l′**) δ7.29−7.24 (m, 5H, H$_{\text{arom}}$, peak of two isomers overlapped), 6.76 (d, J = 8.4 Hz, 1H), 6.54 (d, J = 8.4 Hz, 1H), 6.32 (d, 1H, peak of two isomers overlapped), 5.22−4.71 (m, 2H, peak of two isomers overlapped), 4.39 (s, 1H), 4.20 (m, 2H, peak of two isomers overlapped), 3.86 (s, 3H), 3.66 (s, 3H), 1.25 (t, J = 7.2 Hz, 3H), minor isomer (**1l**) δ 12.29 (s, 1H), 7.29−7.24 (m, 5H, H$_{\text{arom}}$, peak of two isomers overlapped), 6.68 (d, J = 8.4 Hz, 1H), 6.50 (d, J = 8.4 Hz, 1H), 6.32 (d, 1H, peak of two isomers overlapped), 5.22−4.71 (m, 2H, peak of two isomers overlapped), 4.20 (m, 2H, peak of two isomers overlapped), 3.83 (s, 3H), 3.62 (s, 3H), 2.02 (s, 3H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 198.5, 173.7, 169.7, 166.3, 165.7, 164.5, 149.4, 149.2, 148.7, 148.4, 137.6, 136.9, 135.1, 133.6, 129.0, 128.9, 128.5, 128.4, 127.6, 127.5, 120.8, 119.5, 111.8, 111.3, 111.0, 110.7, 103.1, 64.6, 62.0, 60.9, 56.0, 55.9, 55.8, 55.7, 53.3, 53.1, 29.2, 19.8, 14.2, 14.0; HRMS (ESI) calcd for $C_{22}H_{25}NNaO_6^+$ [M + Na$^+$] 422.1574, found 422.1579; IR (KBr) 2982, 1745, 1631, 1580, 1461, 1241, 1051, 909, 678 cm^{-1}.

*Ethyl 3-Hydroxy-2-(1,2,3,4-tetrahydroquinoline-1-carbonyl)but-2-enoate (**1m**).* **1m** was purified by silica gel chromatography (20% EA/PE): yield 2.43 g, 84% (enol:ketone = 1:0.3), light yellow oil;

^{1}H NMR (600 MHz, $CDCl_3$) major isomer (**1m**) δ 12.86 (s, 1H), 7.28−6.89 (m, 4H, H_{arom}, peak of two isomers overlapped), 4.31−3.33 (m, 4H, peak of two isomers overlapped), 2.86 (m, 2H, peak of two isomers overlapped), 2.29−1.90 (m, 5H, peak of two isomers overlapped), 0.98 (m, 3H), minor isomer (**1m′**) 7.28−6.89 (m, 4H, H_{arom}, peak of two isomers overlapped), 4.31−3.33 (m, 4H, peak of two isomers overlapped), 2.86 (m, 2H, peak of two isomers overlapped), 2.29−1.90 (m, 5H, peak of two isomers overlapped), 1.22 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.1, 169.8, 165.8, 139.1, 132.5, 128.3, 126.0, 125.0, 123.5, 103.2, 60.8, 43.3, 27.3, 23.7, 19.9, 13.8; HRMS (ESI) calcd for $C_{16}H_{19}NNaO_4^+$ [M + Na$^+$] 312.1206, found 312.1206; IR (KBr) 2935, 1740, 1630, 1492, 1241, 764 cm^{-1}.

IV. General Procedure for the Synthesis of 2-Acetyl-3-hydroxy-*N*-substituted Amide (1n−r).[12a] The acetoacetanilides were prepared by the known procedures.[17] The novel acetoacetanilides (S_o, S_q) thus obtained were characterized as follows.



N-(4-Methoxyphenyl)-N-methyl-3-oxobutanamide (S_o). The amide was purified by silica gel chromatography (40% EA/PE): yield 69% (ketone:enol = 3.75:1), colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) major isomer (ketone) δ 7.11 (d, J = 8.9 Hz, 2H), 6.92 (d, J = 8.9 Hz, 2H), 3.83 (s, 3H), 3.30 (s, 2H), 3.27 (s, 3H), 2.10 (s, 3H), minor isomer (enol) δ 14.28 (s, 1H), 7.12 (m, 2H, peak of two isomers overlapped), 6.93 (m, 2H, peak of two isomers overlapped), 4.66 (s, 1H), 3.84 (s, 3H), 3.26 (s, 3H), 1.79 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.4, 172.1, 167.0, 159.2, 136.4, 128.5, 128.3, 115.0, 114.8, 88.9, 55.6, 49.9, 37.4, 36.4, 30.3, 21.6 (four carbon peaks were missing due to overlapping); HRMS (ESI) calcd for $C_{12}H_{15}NNaO_3^+$ [M + Na$^+$] 244.0944, found 244.0941; IR (KBr) 1655, 1514, 1423, 1357, 1108, 795 cm^{-1}.

1-(3,4-Dihydroquinolin-1(2H)-yl)butane-1,3-dione (S_q). The amide was purified by silica gel chromatography (30% EA/PE): yield 76% (ketone:enol = 2:1), colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) major isomer δ 7.20−7.06 (m, 4H, peak of two isomers overlapped), 3.81 (m, 2H, peak of two isomers overlapped), 3.69 (s, 2H), 2.72 (m, 2H, peak of two isomers overlapped), 2.21 (s, 3H), 1.99 (m, 2H, peak of two isomers overlapped), minor isomer δ 14.38 (s, 1H), 7.29 (d, J = 6.54 Hz, 1H), 7.18−7.06 (m, 3H, peak of two isomers overlapped), 5.37 (s, 1H), 3.81 (m, 2H, peak of two isomers overlapped), 2.72 (m, 2H, peak of two isomers overlapped), 1.99 (m, 2H, peak of two isomers overlapped), 1.91 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.6, 174.9, 171.5, 166.5, 138.3, 133.3, 128.6, 128.6, 126.4, 126.0, 125.2, 124.9, 124.0, 89.2, 50.1, 42.8, 42.4, 30.4, 26.8, 26.7, 24.0, 24.0, 21.9 (three carbon peaks were missing due to overlapping); HRMS (ESI) calcd for $C_{13}H_{15}NNaO_2^+$ [M + Na$^+$] 240.0995, found 240.0990; IR (KBr) 1716, 1651, 1579, 1444, 1157, 1029 cm^{-1}.

To a suspension of anhydrous $MgCl_2$ (952 mg, 10 mmol) and acetoacetanilide (10 mmol) in DCM (35 mL) was added anhydrous pyridine (1.61 mL, 20 mmol) at 0 °C. Stirring was continued at room temperature for 45 min, and acetyl chloride (778 μL, 11 mmol) was added to the mixture at 0 °C. The resulting mixture was stirred for another 4 h at room temperature (the reaction was monitored by TLC). Upon completion of the reaction, the mixture was treated with HCl (1 N, 30 mL). The aqueous layer was extracted with DCM (40 mL × 3), and the combined organic layer was washed with brine (100 mL), dried over Na_2SO_4, and evaporated under reduced pressure to remove the solvent. Purification of the crude oil by flash column chromatography on silica gel (EA/PE) afforded the desired amides.

*2-Acetyl-3-hydroxy-N-methyl-N-phenylbut-2-enamide (**1n**).* **1n** was purified by silica gel chromatography (30% EA/PE): yield 1.82 g, 78%, light yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 16.09 (s, 1H), 7.34 (t, J = 7.2 Hz, 2H), 7.33 (t, J = 7.2 Hz, 1H), 7.06 (d, J = 8.4 Hz, 2H), 3.45 (s, 3H), 2.09 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 189.7, 168.1, 143.7, 129.4, 127.3, 125.9, 113.2, 37.5, 23.8 (two carbon peaks were missing due to overlapping); HRMS (ESI) calcd for $C_{13}H_{15}NNaO_3^+$ [M + Na$^+$] 256.0944, found 256.0942; IR (KBr) 3063, 1645, 1493, 1425, 1266, 1013, 840 cm^{-1}.

*2-Acetyl-3-hydroxy-N-(4-methoxyphenyl)-N-methylbut-2-enamide (**1o**).* **1o** was purified by silica gel chromatography (30% EA/PE): yield 2.13 g, 81% (enol:ketone = 11:1), light yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) major isomer **1o** δ 16.07 (s, 1H), 7.07 (d, J = 9.0 Hz, 2H), 6.84 (d, J = 9.0 Hz, 2H), 3.79 (s, 3H), 3.41 (s, 3H), 2.09 (s, 6H), isomer **1o′** δ 7.23−6.93 (m, 4H, H_{arom}, peak of three isomers overlapped), 4.51 (s, 1H), 3.83 (s, 3H), 3.30 (s, 3H), 2.12 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 189.5, 168.3, 158.4, 136.5, 128.7, 127.0, 126.8, 115.3, 114.6, 113.3, 72.1, 55.5, 55.4, 37.7, 29.6, 23.7, 23.2; HRMS (ESI) calcd for $C_{14}H_{17}NNaO_4^+$ [M + Na$^+$] 286.1050, found 286.1055; IR (KBr) 2946, 1635, 1577, 1488, 1208, 777 cm^{-1}.

*2-Acetyl-N-(4-chlorophenyl)-3-hydroxy-N-methylbut-2-enamide (**1p**).* **1p** was purified by silica gel chromatography (30% EA/PE): yield 2.09 g, 78%, colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 16.12 (s, 1H), 7.40 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 7.2 Hz, 2H), 3.43 (s, 3H), 2.07 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 189.7, 168.0, 142.2, 132.9, 130.5, 129.6, 129.0, 127.1, 112.7, 37.4, 23.6; HRMS (ESI) calcd for $C_{13}H_{14}{}^{35}ClNNaO_3^+$ [M + Na$^+$] 290.0554, found 290.0555; IR (KBr) 3093, 1645, 1493, 1374, 1092, 854, 565 cm^{-1}.

*1-(3,4-Dihydroquinolin-1(2H)-yl)-2-(1-hydroxyethylidene)butane-1,3-dione (**1q**).* **1q** was purified by silica gel chromatography (30% EA/PE): yield 2.28 g, 88%, white solid, mp 80−82 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 16.41 (s, 1H), 7.90−6.79 (m, 4H, H_{arom}), 3.93 (m, 2H), 2.77 (m, 2H), 2.16−1.98 (m, 8H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 190.6, 167.4, 138.1, 132.3, 128.7, 126.2, 125.2, 124.2, 113.2, 43.6, 27.2, 23.9, 23.5 (two carbon peaks were missing due to overlapping); HRMS (ESI) calcd for $C_{15}H_{17}NNaO_3^+$ [M + Na$^+$] 282.1101, found 282.1107; IR (KBr) 2968, 1635, 1488, 1387, 754 cm^{-1}.

*1-(6-Chloro-2H-benzo[b][1,4]oxazin-4(3H)-yl)-2-(1-hydroxyethylidene)butane-1,3-dione (**1r**).* **1r** was purified by silica gel chromatography (20% EA/PE): yield 1.98 g, 67%, white solid, mp 138−140 °C; ^{1}H NMR (600 MHz, DMSO) δ 16.26 (s, 1H), 8.22 (s, 1H), 7.12 (d, J = 8.4 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 4.30 (m, 2H), 4.03 (m, 2H), 2.12 (s, 6H); ^{13}C NMR (150 MHz, DMSO) δ 190.0, 166.3, 145.1, 126.1, 125.2, 123.2, 122.7, 118.4, 111.6, 65.8, 44.3, 30.1, 23.4 (one carbon peak was missing due to overlapping); HRMS (ESI) calcd for $C_{14}H_{14}{}^{35}ClNNaO_4^+$ [M + Na$^+$] 318.0504, found 318.0512; IR (KBr) 3039, 1650, 1492, 1384, 1045, 823, 740 cm^{-1}.

V. Preparation of 3-Monofunctionalized 2-Oxindole Products 2. Anilide **1** (2 mmol) was dissolved in TFE (30 mL), and then a solution of PIDA (711 mg, 2.2 mmol) in TFE (10 mL) was added dropwise over 5 min. The reaction mixture was stirred at room temperature for 40 min, then aqueous $NaHCO_3$ (5 mL 144 mg, 6 mmol) was added, and the resulting mixture was stirred at room temperature until TLC indicated the total consumption of anilide **1**. The solvent was removed under vacuum. The residue was extracted with EA (50 mL), and the combined organic layer was washed with water (50 mL), dried with anhydrous Na_2SO_4, and concentrated by a rotary evaporator. The residue was purified by silica gel chromatography, using a mixture of PE and EA as eluent, to give the desired product **2**.

*1-Methyl-2-oxoindoline-3-carbonitrile (**2a**).* **2a** was purified by silica gel chromatography (30% EA/PE): yield 303.1 mg, 88%, white solid, mp 95−97 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 (d, J = 7.8 Hz, 1H), 7.41 (t, J = 7.8 Hz, 1H), 7.17 (t, J = 7.8 Hz, 1H), 6.90 (d, J = 7.8 Hz, 1H), 4.54 (s, 1H), 3.26 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.1, 143.8, 130.5, 124.8, 123.8, 120.1, 114.1, 109.3, 77.3, 77.1, 76.9, 36.6, 27.1.

*1,5-Dimethyl-2-oxoindoline-3-carbonitrile (**2b**).* **2b** was purified by silica gel chromatography (30% EA/PE): yield 331.4 mg, 89%, white solid, mp 115−118 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26 (s, 1H), 7.21 (d, J = 8.4 Hz, 1H), 6.78 (d, J = 7.8 Hz, 1H), 4.51 (s, 1H), 3.23 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.0, 141.4, 133.7, 130.7, 125.5, 120.1, 114.2, 109.0, 36.7, 27.1, 21.0; HRMS (ESI) calcd for $C_{11}H_{10}N_2NaO^+$ [M + Na$^+$] 209.0685, found 209.0685; IR (KBr) 2947, 2211, 1625, 1558, 1531, 1308, 799 cm^{-1}.

*5-Methoxy-1-methyl-2-oxoindoline-3-carbonitrile (**2c**).* **2c** was purified by silica gel chromatography (30% EA/PE): yield 355.8 mg, 88%, white solid, mp 136−138 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.05 (s, 1H), 6.94 (d, J = 8.4 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 4.53 (s, 1H), 3.81 (s, 3H), 3.23 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.7, 156.7, 137.1, 121.2, 115.2, 114.1, 111.8, 109.8, 56.0, 37.0, 27.1; HRMS (ESI) calcd for $C_{11}H_{10}N_2NaO_2^+$ [M + Na^+] 225.0634, found 225.0635; IR (KBr) 2945, 2218, 1689, 1562, 1487, 1268, 1230, 760 cm^{-1}.

1-Benzyl-5-bromo-2-hydroxy-1H-indole-3-carbonitrile (**2d**). **2d** was purified by silica gel chromatography (30% EA/PE): yield Yield: 510.4 mg, 78%, white solid, mp 225−227 °C; ^{1}H NMR (600 MHz, DMSO) δ 7.44 (s, 1H), 7.33−7.18 (m, 7H, H_{arom}), 5.27 (s, 2H); ^{13}C NMR (150 MHz, DMSO) δ 158.4, 136.6, 129.6, 128.7, 128.0, 127.5, 126.9, 123.4, 118.6, 115.8, 113.9, 112.0, 63.3, 44.3; HRMS (ESI) calcd for $C_{16}H_{11}{}^{79}BrN_2NaO^+$ [M + Na^+] 348.9947, found 348.9947; IR (KBr) 2945, 2227, 1612, 1592, 1466, 1183, 800, 700 cm^{-1}.

5-Chloro-2-hydroxy-1-methyl-1H-indole-3-carbonitrile (**2e**). **2e** was purified by silica gel chromatography (30% EA/PE): yield 264.4 mg, 64%, white solid, mp 195−199 °C; ^{1}H NMR (400 MHz, DMSO) δ 12.80 (s, 1H, OH), 7.27 (d, *J* = 8.0 Hz, 1H), 7.25 (s, 1H), 7.07 (d, *J* = 12 Hz, 1H), 3.49 (s, 3H); ^{13}C NMR (101 MHz, DMSO) δ 158.8, 130.4, 127.7, 126.5, 121.0, 116.3, 116.1, 111.4, 63.7, 28.3; HRMS (ESI) calcd for $C_{10}H_7{}^{35}ClN_2NaO^+$ [M + Na^+] 229.0139, found 229.0137; IR (KBr) 2948, 2218, 1618, 1561, 1531, 1472, 1276, 1108, 844, 798 cm^{-1}.

2-Oxo-1-phenylindoline-3-carbonitrile (**2f**). **2f** was purified by silica gel chromatography (30% EA/PE): yield 412.3 mg, 88%, white solid, mp 154−158 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.55 (t, *J* = 7.8 Hz, 3H), 7.50 (d, *J* = 7.2 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 1H), 7.40 (d, *J* = 7.8 Hz, 2H), 7.33 (t, *J* = 7.8 Hz, 1H), 7.20 (t, *J* = 7.8 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 4.75 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.4, 144.1, 133.4, 130.4, 130.0, 129.0, 126.5, 125.1, 124.2, 120.0, 113.9, 110.5, 37.1; HRMS (ESI) calcd for $C_{15}H_{10}N_2NaO^+$ [M + Na^+] 257.0685, found 257.0688; IR (KBr) 2946, 2810, 2211, 1624, 1558, 1477, 1362, 1109, 760 cm^{-1}.

1-Benzyl-2-oxoindoline-3-carbonitrile (**2g**). **2g** was purified by silica gel chromatography (30% EA/PE): yield 412.2 mg, 83%, white solid, mp 127−130 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44−6.79 (m, 9H, H_{arom}), 4.94 (m, 2H), 4.63 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.3, 143.0, 134.6, 130.4, 129.0, 128.2, 127.5, 124.9, 123.8, 120.2, 114.0, 110.2, 44.7, 36.7; HRMS (ESI) calcd for $C_{16}H_{12}N_2NaO^+$ [M + Na^+] 271.0842, found 271.0843; IR (KBr) 2932, 2810, 2221, 1617, 1559, 1523, 1470, 1307, 743 cm^{-1}.

1-Benzyl-6-fluoro-2-hydroxy-1H-indole-3-carbonitrile (**2h**) *and 1-Benzyl-4-fluoro-2-hydroxy-1H-indole-3-carbonitrile* (**2h′**). **2h** and **2h′** were purified by silica gel chromatography (30% EA/PE): yield 261.0 mg, 49% (**2h**:**2h′** = 2:1), white solid, mp 160−165 °C; ^{1}H NMR (600 MHz, DMSO) major isomer **2h** δ 7.31−7.18 (m, 6H, H_{arom}, peak of two isomers overlapped), 7.04 (d, *J* = 5.4 Hz, 1H), 6.90 (t, *J* = 9.0 Hz, 1H), 5.28 (s, 2H, peak of two isomers overlapped), minor isomer **2h′** δ 7.31−7.18 (m, 7H, H_{arom}, peak of two isomers overlapped), 6.97 (t, *J* = 9.0 Hz, 1H), 5.28 (s, 2H, peak of two isomers overlapped); ^{13}C NMR (150 MHz, DMSO) δ 158.2, 153.9 (d, J_{C-F} = 243.3 Hz), 136.6, 133.1, 128.7, 127.5, 127.0, 126.9, 122.1, 121.6, 117.5, 116.2 (d, J_{C-F} = 31.1 Hz), 113.4, 113.3, 109.0 (d, J_{C-F} = 23.2 Hz), 107.1 (d, J_{C-F} = 18.0 Hz), 106.7, 97.6 (d, J_{C-F} = 25.3 Hz), 63.4, 60.7, 44.6, 44.4 (six carbon peaks were missing due to overlapping and the extremely poor solubility in NMR solvents); HRMS (ESI) calcd for $C_{16}H_{11}FN_2NaO^+$ [M + Na^+] 289.0748, found 289.0744; IR (KBr) 2948, 2810, 2217, 1618, 1561, 1471, 1212, 1065, 844, 693 cm^{-1}.

1-Benzyl-2-hydroxy-6-(trifluoromethyl)-1H-indole-3-carbonitrile (**2i**) *and 1-Benzyl-2-hydroxy-4-(trifluoromethyl)-1H-indole-3-carbonitrile* (**2i′**). **2i** and **2i′** were purified by silica gel chromatography (30% EA/PE): yield 272.0 mg, 43% (**2i**:**2i′** = 1.2:1), white solid, mp 175−179 °C; ^{1}H NMR (600 MHz, DMSO) isomer **2i** δ 10.31 (s, 1H), 7.77 (s, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.44 (t, *J* = 8.4 Hz, 1H), 7.37−7.34 (m, 4H, H_{arom}), 5.42 (s, 2H); isomer **2i′** δ 10.31 (s, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.30−7.20 (m, 7H, H_{arom}), 5.39 (s, 2H); ^{13}C NMR (150 MHz, DMSO) δ 160.5, 159.7, 136.6, 136.5, 131.7, 130.1, 129.6, 128.7, 128.7, 127.5, 127.5, 126.9, 126.8, 125.0 (q, J_{C-F} = 270.0 Hz), 124.4 (q, J_{C-F} = 270.2 Hz), 121.5 (q, J_{C-F} = 33.0 Hz), 120.0, 118.6 (q, J_{C-F} = 3.4 Hz), 118.3 (q, J_{C-F} = 3.3 Hz), 117.3 (q, J_{C-F} = 30.0 Hz), 116.7, 115.9, 115.7, 114.0, 107.1, 107.1, 64.2, 44.4, 44.3 (one carbon peak was missing due to overlapping); HRMS (ESI) calcd for $C_{17}H_{11}F_3N_2NaO^+$ [M + Na^+] 339.0716, found 339.0718; IR (KBr) 3024, 2932, 2796, 2221, 1559, 1523, 1496, 1202, 997, 743 cm^{-1}.

2-Oxo-2,4,5,6-tetrahydro-1H-pyrrolo[3,2,1-ij]quinoline-1-carbonitrile (**2j**). **2j** was purified by silica gel chromatography (30% EA/PE): yield 348.8 mg, 88%, white solid, mp 160−165 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27 (d, *J* = 7.5 Hz, 1H), 7.16 (d, *J* = 7.7 Hz, 1H), 7.04 (t, *J* = 7.6 Hz, 1H), 4.51 (s, 1H), 3.75 (m, 2H), 2.79 (m, 2H), 2.04 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.0, 139.8, 129.1, 123.2, 122.5, 121.5, 119.0, 114.2, 39.8, 37.3, 24.2, 20.9; HRMS (ESI) calcd for $C_{12}H_{10}N_2NaO^+$ [M + Na^+] 221.0685, found 221.0684; IR (KBr) 2969, 2213, 1734, 1555, 1526, 1471, 1303, 743 cm^{-1}.

Ethyl 1-Methyl-2-oxoindoline-3-carboxylate (**2k**). **2k** was purified by silica gel chromatography (40% EA/PE): yield 368.3 mg, 84% (ketone:enol = 6:1), tan solid, mp 109−111 °C; ^{1}H NMR (600 MHz, $CDCl_3$) major isomer (ketone) δ 7.35 (d, *J* = 7.2 Hz, 1H), 7.34(t, *J* = 8.4 Hz, 1H), 7.08 (t, *J* = 7.2 Hz, 1H), 6.85 (d, *J* = 7.8 Hz, 1H), 4.42 (s, 1H), 4.25 (m, 2H), 3.24 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H), minor isomer (enol) δ 7.74 (m, 1H), 7.21−7.16 (m, 3H), 4.42 (m, 2H, peak of two isomers overlapped), 3.62 (s, 3H), 1.45 (t, *J* = 7.2 Hz, 3H).

Ethyl 1-Benzyl-5,6-dimethoxy-2-oxoindoline-3-carboxylate (**2l**). **2l** was purified by silica gel chromatography (40% EA/PE): yield 402.2 mg, 72% (ketone:enol = 9.6:1), tan solid, mp 142−145 °C; ^{1}H NMR (600 MHz, $CDCl_3$) major isomer (ketone) δ 7.31−7.26 (m, 5H, H_{arom}, peak of two isomers overlapped), 6.95 (s, 1H), 6.30 (s, 1H), 5.07−4.77 (m, 2H), 4.31−4.21 (m, 2H), 3.83 (s, 3H), 3.73 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H), minor isomer (enol) δ 7.29−7.19 (m, 6H, H_{arom}, peak of two isomers overlapped), 6.65 (s, 1H), 5.20 (s, 2H), 4.44 (m, 2H, peak of two isomers overlapped), 3.93 (s, 3H), 3.80 (s, 3H), 1.46 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.3, 167.3, 150.2, 145.3, 137.6, 135.5, 128.8, 127.8, 127.7, 127.1, 126.9, 114.2, 109.4, 95.6, 62.1, 56.8, 56.6, 56.5, 56.3, 52.7, 45.1, 44.0, 14.6, 14.1; HRMS (ESI) calcd for $C_{20}H_{21}NNaO_5^+$ [M + Na^+] 378.1312, found 378.1311; IR (KBr) 2973, 1731, 1615, 1510, 1381, 1040, 731 cm^{-1}.

Ethyl 2-Oxo-2,4,5,6-tetrahydro-1H-pyrrolo[3,2,1-ij]quinoline-1-carboxylate (**2m**). **2m** was purified by silica gel chromatography (30% EA/PE): yield 412.1 mg, 84% (ketone:enol = 8.35:1), tan solid, mp 58−60 °C; ^{1}H NMR (600 MHz, $CDCl_3$) major isomer **2m** δ 7.17 (d, *J* = 7.2 Hz, 1H), 7.08 (d, *J* = 7.2 Hz, 1H), 6.96 (t, *J* = 7.2 Hz, 1H), 4.40 (s, 1H), 4.25 (m, 2H), 3.74 (t, *J* = 6.0 Hz, 2H), 2.77 (m, 2H), 2.02 (m, 2H), 1.30 (t, *J* = 7.2 Hz, 3H), minor isomer **2m′** δ 7.49 (d, *J* = 7.8 Hz, 1H), 7.09 (m, 1H, peak of two isomers overlapped), 6.88 (d, *J* = 7.8 Hz, 1H), 4.40 (m, 2H, peak of two isomers overlapped), 4.02 (t, *J* = 6.0 Hz, 2H), 2.93 (t, *J* = 6.0 Hz, 2H), 2.18 (m, 2H), 1.43 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.6, 167.1, 140.5, 127.9, 122.3, 121.9, 121.0, 120.6, 119.0, 116.8, 84.6, 62.0, 59.9, 53.2, 40.0, 39.2, 24.5, 24.4, 22.0, 21.1, 14.6, 14.1; HRMS (ESI) calcd for $C_{14}H_{15}NNaO_3^+$ [M + Na^+] 268.0944, found 268.0944; IR (KBr) 2993, 2943, 1713, 1509, 1452, 1320, 1083, 731, 686 cm^{-1}.

3-Acetyl-1-methylindolin-2-one (**2n**). **2n** was purified by silica gel chromatography (30% EA/PE): yield 310.3 mg, 82%, white solid, mp 102−106 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 13.62 (s, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.20 (t, *J* = 8.4 Hz, 1H), 7.08 (t, *J* = 8.4 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 3.30 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.9, 171.0, 138.9, 125.2, 122.2, 122.1, 119.7, 108.6, 101.8, 25.6, 20.3; HRMS (ESI) calcd for $C_{11}H_{11}NNaO_2^+$ [M + Na^+] 212.0682, found 212.0682; IR (KBr) 3025, 1769, 1657, 1491, 1151, 977, 905, 748 cm^{-1}.

(Z)-3-(1-Hydroxyethylidene)-5-methoxy-1-methylindolin-2-one (**2o**). **2o** was purified by silica gel chromatography (40% EA/PE): yield 377.0 mg, 86%, white solid, mp 132−137 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 13.75 (s, 1H), 6.92 (s, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 6.76 (d, *J* = 8.4 Hz, 1H), 3.82 (s, 3H), 3.29 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.1, 170.9, 155.7, 133.1, 123.3, 109.6, 108.4, 107.2, 102.0, 55.9, 25.7, 20.2; HRMS (ESI) calcd for $C_{12}H_{13}NNaO_3^+$ [M + Na^+] 242.0788, found 242.0787; IR (KBr) 2939, 1658, 1589, 1474, 1263, 1145, 1035, 772 cm^{-1}.

(Z)-5-Chloro-3-(1-hydroxyethylidene)-1-methylindolin-2-one (**2p**). **2p** was purified by silica gel chromatography (30% EA/PE): yield 335.4 mg, 75%, white solid, mp 130−132 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 13.70 (s, 1H), 7.28 (s, 1H), 7.17 (d, *J* = 8.4 Hz, 1H), 6.84 (d, *J* = 8.4 Hz, 1H), 3.31 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.3, 170.8, 137.2, 127.5, 124.8, 123.6, 119.6, 109.1, 101.1, 25.7, 20.4; HRMS (ESI) calcd for $C_{11}H_{10}{}^{35}ClNNaO_2^+$ [M + Na^+]

246.0292, found 246.0292; IR (KBr) 1654, 1609, 1486, 1272, 1154, 808 cm^{-1}.

*(Z)-1-(1-Hydroxyethylidene)-5,6-dihydro-1H-pyrrolo[3,2,1-ij]-quinolin-2(4H)-one (**2q**).* **2q** was purified by silica gel chromatography (30% EA/PE): yield 400.3 mg, 93%, light purple solid, mp 155−157 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 13.49 (s, 1H), 7.18 (d, *J* = 7.2 Hz, 1H), 7.00−6.95 (m, 2H), 3.83 (t, *J* = 6.0 Hz, 2H), 2.83 (t, *J* = 6.0 Hz, 2H), 2.42 (s, 3H), 2.06 (m, 2H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 172.8, 169.9, 134.9, 123.9, 121.7, 120.7, 120.4, 117.5, 102.6, 38.4, 24.7, 21.4, 20.2; HRMS (ESI) calcd for $C_{13}H_{13}NNaO_2^+$ [M + Na$^+$] 238.0838, found 238.0838; IR (KBr) 2937, 1742, 1661, 1611, 1362, 1305, 1243, 1099, 747 cm^{-1}.

*(Z)-7-Chloro-6-(1-hydroxyethylidene)-2,3-dihydro[1,4]oxazino-[2,3,4-hi]indol-5(6H)-one (**2r**).* **2r** was purified by silica gel chromatography (30% EA/PE): yield 412.6 mg, 82% (enol:ketone = 5:1) white solid, mp 153−154 °C; ^{1}H NMR (600 MHz, CDCl$_3$) isomer **2r** δ 14.90 (s, 1H), 6.91 (d, *J* = 9.0 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 4.29 (t, *J* = 4.8 Hz, 2H), 3.95 (t, *J* = 4.8 Hz, 2H), 2.78 (s, 3H), isomer **2r′** δ 6.92 (d, *J* = 8.4 Hz, 1H), 6.84 (d, *J* = 9.0 Hz, 1H), 4.64 (s, 1H), 4.27 (t, *J* = 4.8 Hz, 2H), 3.86−3.78 (m, 2H), 2.45 (s, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 197.6, 178.4, 169.1, 167.4, 140.1, 140.0, 130.3, 124.7, 124.2, 123.2, 123.2, 121.7, 119.7, 117.7, 117.4, 113.0, 102.0, 64.8, 64.4, 61.4, 39.4, 38.6, 29.8, 24.8; HRMS (ESI) calcd for $C_{12}H_{10}{}^{35}ClNNaO_3^+$ [M + Na$^+$] 274.0241, found 274.0243; IR (KBr) 1623, 1484, 1445, 1358, 1244, 1206, 1035, 770 cm^{-1}.

VI. Preparation of Horsfiline Precursor L. Substrate **K** was prepared according to the general procedure above.

Anilide **K** (859 mg, 2 mmol) was dissolved in MeCN (40 mL), and then PIDA (711 mg, 2.2 mmol) powder was added in one portion. The reaction mixture was stirred at room temperature for 20 min. Alcohol (6 mL) and sodium acetate (1.64 g, 20 mmol) were then added, and the resulting mixture was stirred at room temperature for 48 h. The solvent was removed, and the residue was treated with water (40 mL) and extracted with EA (30 mL × 3). The combined organic layer was dried with anhydrous Na_2SO_4 and concentrated by a rotary evaporator. The residue was dissolved in anhydrous DCM (8 mL). The solution was then cooled to 0 °C, and TEA (836 μL, 6 mmol) was added followed by TIPSOTf (538 μL, 2 mmol). The mixture was stirred at 0 °C for 10 min before being quenched with water (15 mL) and extracted with DCM (20 mL × 3). The combined organic layer was washed with water (40 mL) and then dried with anhydrous Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by silica gel chromatography, using a mixture of PE and EA as eluent, to give the desired product **L**.

*Ethyl 3-((2,4-Dimethoxybenzyl)(4-methoxyphenyl)amino)-3-oxo-propanoate (**J**).* **J** was purified by silica gel chromatography (40% EA/PE): yield 85%, light yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.26 (d, *J* = 8.4 Hz, 1H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.79 (d, *J* = 8.8 Hz, 2H), 6.43 (d, *J* = 8.4 Hz, 1H), 6.32 (s, 1H), 4.87 (s, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.77 (s, 6H), 3.55 (s, 3H), 3.20 (s, 2H), 1.23 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 167.9, 166.3, 160.3, 159.0, 158.5, 134.8, 131.1, 129.4, 117.6, 114.3, 104.2, 98.2, 61.1, 55.4, 55.3, 55.1, 47.0, 41.9, 14.1; HRMS (ESI) calcd for $C_{21}H_{25}NNaO_6^+$ [M + Na$^+$] 410.1574, found 410.1574; IR (KBr) 2959, 2838, 1738, 1660, 1511, 1400, 1249, 1036, 838 cm^{-1}.

*Ethyl 2-((2,4-Dimethoxybenzyl)(4-methoxyphenyl)carbamoyl)-3-hydroxybut-2-enoate (**K**).* **K** was purified by silica gel chromatography (30% EA/PE): yield 78% (enol:ketone = 0.9:1), light yellow oil; ^{1}H NMR (600 MHz, CDCl$_3$) isomer **K** δ 12.33 (s, 1H), 7.25 (d, *J* = 7.2 Hz, 1H), 6.87−6.82 (m, 2H, peak of two isomers overlapped), 6.69 (d, *J* = 7.8 Hz, 2H), 6.41 (t, *J* = 7.8 Hz, 2H), 5.06−4.80 (m, 2H, peak of two isomers overlapped), 4.18−4.14 (m, 2H, peak of two isomers overlapped), 3.77- 3.76 (m, 6H, peak of two isomers overlapped), 3.61 (s, 3H), 2.03 (s, 3H), 1.33 (t, *J* = 7.2 Hz, 3H), isomer **K′** δ 7.21 (d, *J* = 7.8 Hz, 1H), 6.87−6.82 (m, 2H, peak of two isomers overlapped), 6.78 (d, *J* = 8.4 Hz, 2H), 6.35 (m, 2H), 5.06−4.80 (m, 2H, peak of two isomers overlapped), 4.35 (s, 1H), 4.18−4.14 (m, 2H, peak of two isomers overlapped), 3.76 (s, 3H), 3.73 (s, 3H), 3.57 (s, 3H), 2.24 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 198.7, 173.8, 169.8, 166.2, 165.7, 164.4, 160.4, 160.2, 159.3, 158.5, 158.4, 158.4, 135.0, 133.6, 131.2, 130.8, 129.7, 128.4, 117.6, 117.1, 114.5, 113.7, 104.1, 104.1, 103.3, 98.2, 98.1, 64.9, 62.0, 60.9, 55.4, 55.3, 55.1, 53.5, 47.3, 47.0, 29.2, 19.7, 14.3, 14.0 (two carbon peaks were missing due to overlapping); HRMS (ESI) calcd for $C_{23}H_{27}NNaO_7^+$ [M + Na$^+$] 452.1680, found 452.1681; IR (KBr) 2982, 1741, 1628, 1492, 1241, 1112, 678 cm^{-1}.

*Ethyl 1-(2,4-Dimethoxybenzyl)-5-methoxy-2-((triisopropylsilyl)-oxy)-1H-indole-3-carboxylate (**L**).* **L** was purified by silica gel chromatography (5% EA/PE): yield 682.6 mg, 63%, colorless oil; ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.61 (s, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 6.70 (d, *J* = 8.4 Hz, 1H), 6.48 (d, *J* = 9.0 Hz, 1H), 6.46 (s, 1H), 6.26 (d, *J* = 8.4 Hz, 1H), 5.15 (s, 2H), 4.38 (m, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.72 (s, 3H), 1.49−1.43 (m, 6H), 1.07−1.05 (d, *J* = 7.8 Hz, 18H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 164.8, 160.0, 157.2, 155.5, 153.4, 127.3, 125.9, 125.8, 116.9, 110.0, 109.7, 104.0, 103.8, 98.1, 89.2, 58.9, 55.6, 55.2, 39.6, 17.8, 17.6, 14.7, 14.2.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Figures, tables, and a CIF file giving spectral data for all new compounds and X-ray structural data of **2j**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: duyunfeier@tju.edu.cn (Y.D.); kangzhao@tju.edu.cn (K.Z.).

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge the National Natural Science Foundation of China (#21072148), Foundation (B) for Peiyang Scholar-Young Core Faculty of Tianjin University (2013XR-0144), the Innovation Foundation of Tianjin University (2013XJ-0005), and the National Basic Research Project (2014CB932200) of the MOST for financial support.

■ REFERENCES

(1) (a) Parkes, K. E. B.; Ermert, P.; Fässler, J.; Ives, J.; Martin, J. A.; Merrett, J. H.; Obrecht, D.; Williams, G.; Klumpp, K. *J. Med. Chem.* **2003**, *46*, 1153. (b) Heckel, A.; Roth, G. J.; Kley, J.; Hoerer, S.; Uphues, I. U.S. Patent US 2005203104, 2005. (c) Sipe, J. D.; Bartle, L. M.; Loose, L. D. *J. Immunol.* **1992**, *148*, 480. (d) LaLiberte, R.; Perregaux, D.; Svensson, L.; Pazoles, C. J.; Gabel, C. A. *J. Immunol.* **1994**, *153*, 2180. (e) Golding, S.; Emery, P.; Young, S. P. *J. Immunol.* **1995**, *154*, 5384. (f) Robinson, R. P.; Reiter, L. A.; Barth, W. E.; Campeta, A. M.; Cooker, K.; Cronin, B. J.; Destito, R.; Donahue, K. M.; Falkner, F. C.; Fiese, E. F.; Johnson, D. L.; Kuperman, A. V.; Liston, T. E.; Malloy, D.; Matin, J. J.; Mitchell, D. Y.; Rusek, F. W.; Shamblin, S. L.; Wright, C. F. *J. Med. Chem.* **1996**, *39*, 10. (g) Trost, B. M.; Brennan, M. K. *Org. Lett.* **2006**, *8*, 2027. (h) Liang, J. X.; Chen, J. B.; Liu, J. P.; Li, L.; Zhang, H. B. *Chem. Commun.* **2010**, *46*, 3666. (i) Chen, X. J.; Zhu, W.; Qian, W. K.; Feng, E. G.; Zhou, Y.; Wang, J. F.; Jiang, H. L.; Yao, Z. J.; Liu, H. *Adv. Synth. Catal.* **2012**, *354*, 2151. (j) Kitajima, M.; Mori, I.; Arai, K.; Kogure, N.; Takayama, H. *Tetrahedron Lett.* **2006**, *47*, 3199.

(2) Burgdorf, L. T.; Bruge, D.; Greiner, H.; Kordowicz, M.; Sirrenberg, C.; Zenke, F. (Merck) World Patent WO2006131186 A1, 2006.

(3) (a) Ju, X. H.; Liang, Y.; Jia, P. J.; Li, W. F.; Yu, W. *Org. Biomol. Chem.* **2012**, *10*, 498. (b) Lu, B.; Ma, D. W. *Org. Lett.* **2006**, *8*, 6115.

(4) (a) Perry, A.; Taylor, R. J. K. *Chem. Commun.* **2009**, 3249. (b) Klein, J. E. M. N.; Perry, A.; Pugh, D. S.; Taylor, R. J. K. *Org. Lett.* **2010**, *12*, 3446. (c) Ghosh, S.; De, S.; Kakde, B. N.; Bhunia, S.; Adhikary, A.; Bisai, A. *Org. Lett.* **2012**, *14*, 5864.

(5) (a) Wang, H. L.; Li, Z.; Wang, G. W.; Yang, S. D. *Chem. Commun.* **2011**, *47*, 11336. (b) Miah, S.; Moody, C. J.; Richards, I. C.; Slawin, A.

M. Z. *J. Chem. Soc., Perkin Trans. 1* **1997**, *1*, 2405. (c) Brown, D. S.; Elliott, M. C.; Moody, C. J.; Mowlem, T. J.; Marino, J. P.; Padwa, A. *J. Org. Chem.* **1994**, *59*, 2447. (d) Wee, A. G. H.; Liu, B. S.; Zhang, L. *J. Org. Chem.* **1992**, *16*, 4405. (e) Himbert, V. G.; Ruppmich, M. *Angew. Chem.* **1990**, *102*, 69.

(6) Qian, D. Y.; Zhang, J. L. *Chem. Commun.* **2012**, *48*, 7082.

(7) For selected examples, see: (a) Huang, J.; Liang, Y.; Pan, W.; Yang, Y.; Dong, D. *Org. Lett.* **2007**, *9*, 5345. (b) Dohi, T.; Minamitsuji, Y.; Maruyama, A.; Hirose, S.; Kita, Y. *Org. Lett.* **2008**, *10*, 3559. (c) Kita, Y.; Morimoto, K.; Ito, M.; Ogawa, C.; Goto, A.; Dohi, T. *J. Am. Chem. Soc.* **2009**, *131*, 1668. (d) Liang, J.; Chen, J.; Du, F.; Zeng, X.; Li, L.; Zhang, H. *Org. Lett.* **2009**, *11*, 2820. (e) Desjardins, S.; Andrez, J.; Canesi, S. *Org. Lett.* **2011**, *13*, 3406. (f) Zheng, C.; Fan, R. *Chem. Commun.* **2011**, *47*, 12221. (g) Yu, W. Q.; Du, Y. F.; Zhao, K. *Org. Lett.* **2009**, *11*, 2417. (h) Dohi, T.; Kato, D.; Hyodo, R.; Yamashita, D.; Shiro, M.; Kita, Y. *Angew. Chem., Int. Ed.* **2011**, *50*, 3784. (i) Matousek, V.; Togni, A.; Bizet, V.; Cahard, D. *Org. Lett.* **2011**, *13*, 5762. (j) Ackermann, L.; Dell'Acqua, M.; Fenner, S.; Vicente, R.; Sandmann, R. *Org. Lett.* **2011**, *13*, 2358. (k) Castro, S.; Fernandea, J. J.; Vicente, R.; Fanans, F. J.; Rodriguez, F. *Chem. Commun.* **2012**, *48*, 9089. (l) Matcha, K.; Antonchick, A. P. *Angew. Chem., Int. Ed.* **2013**, *52*, 2082.

(8) For the synthesis of 3,3-disubstituted oxindole derivatives via oxidative C(sp^2)−C(sp^2) bond formation, see: (a) Wei, H. L.; Piou, T.; Dufour, J.; Neuville, L.; Zhu, J. P. *Org. Lett.* **2011**, *13*, 2244. (b) Fabry, D. C.; Stodulski, M.; Hoerner, S.; Gulder, T. *Chem. Eur. J.* **2012**, *18*, 10834. (c) Xie, J.; Xu, P.; Li, H. M.; Xue, Q. C.; Jin, H. M.; Cheng, Y. X.; Zhu, C. J. *Chem. Commun.* **2013**, 5672. (d) Matcha, K.; Narayan, R.; Antonchick, A. P. *Angew. Chem., Int. Ed.* **2013**, *52*, 7985. (e) Wu, T.; Zhang, H.; Liu, G. S. *Tetrahedron Lett.* **2012**, *68*, 5229. (f) Mu, X.; Wu, T.; Wang, H. Y.; G, Y. L.; Liu, G. S. *J. Am. Chem. Soc.* **2012**, *134*, 878. (g) Li, Y. M.; Sun, M.; Wang, H. L.; Tian, Q. P.; Yang, S. D. *Angew. Chem., Int. Ed.* **2013**, *52*, 3972. (h) Wei, W. T.; Zhou, M. B.; Fan, J. H.; Liu, W.; Song, R. J.; Liu, Y.; Hu, M.; Xie, P.; Li, J. H. *Angew. Chem., Int. Ed.* **2013**, *52*, 3638. (i) Li, X. Q.; Xu, X. S.; Hu, P. Z.; Xiao, X. Q.; Zhou, C. J. *Org. Chem.* **2013**, *78*, 7343. (j) Meng, Y.; Guo, L. N.; Wang, H.; Duan, X. H. *Chem. Commun.* **2013**, 7540. (k) Wei, X. H.; Li, Y. M.; Zhou, A. X.; Yang, T. T.; Yang, S. D. *Org. Lett.* **2013**, *15*, 4158. (l) Wu, T.; Mu, X.; Liu, G. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 12578. (m) Jaegli, S.; Dufour, J.; Wei, H. L.; Piou, T.; Duan, X. H.; Vors, J. P.; Neuville, L.; Zhu, J. P. *Org. Lett.* **2010**, *12*, 4498.

(9) Wang, J. W.; Yuan, Y. C.; Xiong, R.; Zhang-Negrerie, D.; Du, Y. F.; Zhao, K. *Org. Lett.* **2012**, *14*, 2210.

(10) (a) Kobayashi, Y.; Katagiri, K.; Azumaya, I.; Harayama, T. *J. Org. Chem.* **2010**, *75*, 2741. (b) Métro, T. X.; Bonnamour, J.; Reidon, T.; Sarpoulet, J.; Martinez, J.; Lamaty, F. *Chem. Commun.* **2012**, *48*, 11781. (c) Davies, M.; Heikkilä, T.; McConkey, G. A.; Fishwick, C. W. G.; Parsons, M. R.; Johnson, A. P. *J. Med. Chem.* **2009**, *52*, 2683.

(11) It was found that other bases, including Na_2CO_3 and NaOAc, could also improve the reaction efficiency but gave relatively lower yields.

(12) (a) Rathke, M. W.; Cowan, P. J. *J. Org. Chem.* **1985**, *50*, 2622. (b) Shen, Q. S.; Huang, W.; Wang, J. L.; Zhou, X. G. *Org. Lett.* **2007**, *9*, 4491. (c) Navarro, I.; Basset, J. F.; Hebbe, S.; Major, S. M.; Werner, T.; Howsham, C.; Bräckow, J.; Barrett, A. G. M. *J. Am. Chem. Soc.* **2008**, *130*, 10293. (d) Shen, Q. S.; Huang, W.; Wang, J. L.; Zhou, X. G. *Org. Lett.* **2007**, *9*, 4491.

(13) When the E group was replaced with a methyl group, the corresponding anilide substrate afforded no desired cyclized product under the identical conditions. For our previous work describing this, see ref 9.

(14) The cyclization reaction in entries 10 and 13 would lead to decreased yields on treatment with N_aHCO_3 after the addition of PIDA.

(15) For details of the crude HRMS spectra of intermediate **F′**, please see S93 in the Supporting Information.

(16) The reaction run in TFE gave product **L** in an inferior yield of 37%.

(17) For the preparation of 2-functionalized acetanilide derivatives including cyanoacetanilides, ethyl 3-(substituted (aryl) amino)-3-oxopropanoates, and acetoacetanilides, see: (a) Kobayashi, Y.; Harayama, T. *Org. Lett.* **2009**, *11*, 1603. (b) Maiti, A.; Reddy, P. V. N.; Sturdy, M.; Marler, L.; Pegan, S. D.; Mesecar, A. D.; Pezzuto, J. M.; Cushman, M. *J. Med. Chem.* **2009**, *52*, 1873. (c) Wee, A. G. H.; McLeod, D. D. *Heterocycles* **2000**, *53*, 637. (d) Anwar, M.; Moloney, M. G. *Tetrahedron Lett.* **2007**, *48*, 7259.