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Azo-Compound-Mediated Cyanoalkylation of Alkenes by Copper Catalysis: General Access to Cyano-Substituted Oxindoles

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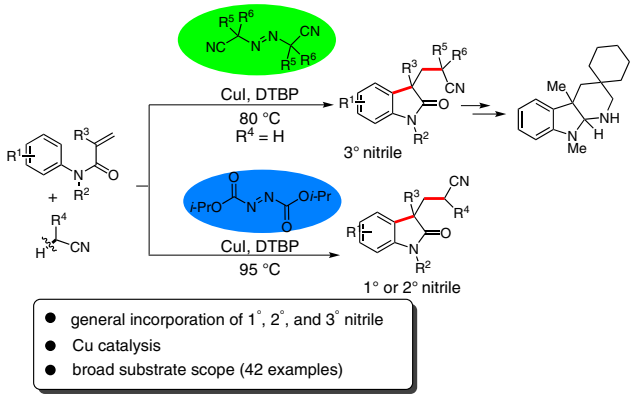

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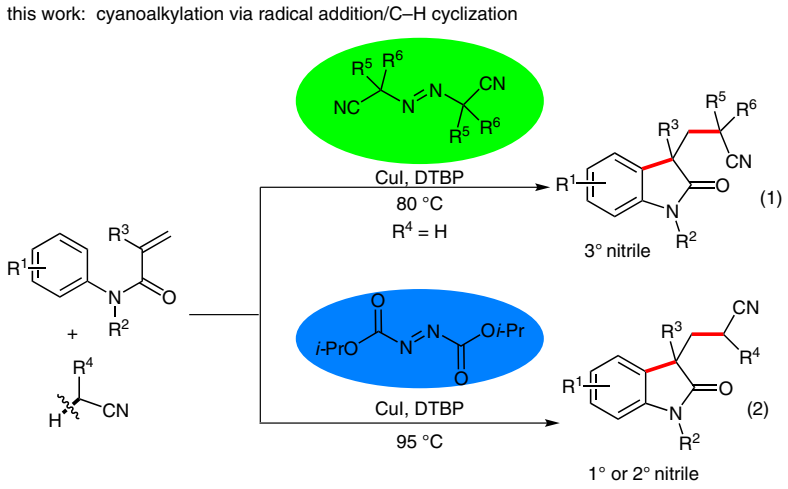
Abstract A practical and highly efficient azo-compound-mediated/promoted radical cyanoalkylation of activated alkenes by copper catalysis was developed, which allowed for general synthesis of oxindoles bearing various nitrile moieties, especially the rarely reported 3° nitrile moiety via cascade radical addition/C(sp^2)–H cyclization. This protocol demonstrates that DIAD served for a new promoter instead of usual Ag salts or bases in the C(sp^3)–H functionalization of acetonitrile for the first time. The use of readily available AIBN and beyond as the radical sources, and inexpensive copper as the catalyst, as well as the simplicity of operation and handling, make this protocol an attractive access to therapeutically important cyano-substituted oxindoles.

Key words azo compounds, cyanoalkylation, alkenes, radical, copper catalysis

The efficient construction of multiple C–C bonds in a cascade process is a perennial topic of interest for organic chemists.[1] In this regard, inexpensive metal-catalyzed radical biscarbonation of alkenes to form dual C–C bond simultaneously attracted increasing attention, where various aryl/alkyl radical precursors, such as aryl diazonium salts, carbazates, diaryliodonium salts, CF_3 reagents, C–H reactants, etc. were successfully utilized to involve the tandem addition/interception process.[2] Aliphatic azo compounds (e.g., AIBN and DEAD), a type of widespread reagent in organic and polymer synthesis, decompose softly to give radical species that can be applied for C–H functionalization.[3] Therefore, we envisaged that the difunctionalization of alkenes with 2,2′-azobisisobutyronitrile (AIBN) is, by judicious design, possible to generate oxindoles bearing a tertiary-alkyl nitrile moiety via tandem radical addition/C(sp^2)–H cyclization (Scheme 1, eq. 1). Remarkably, AIBN in combination with Bu_3SnH was commonly used as an initiator for radical addition of alkyl halide onto alkene,[4] whereas direct addition of electrophilic radical produced by AIBN onto the double bond of an electron-poor alkene (e.g., acrylamides) was usually slow and thus less commonly encountered.[4c] Moreover, despite significant advances in alkene difunctionalization research (including Heck-type and free radical reactions), the direct construction of α-functionalized quaternary carbon center via simple alkene biscarbonation step remains rare and challenging.[5] It can be expected that this strategy would undoubtedly represent a highly interesting approach to oxindole scaffold with an α-cyano quaternary carbon center. Nevertheless, the alkylarylation of activated alkenes with AIBN involving C(sp^2)–H bond activation has, to our best knowledge, rarely been reported.[6]

In earlier studies, the C–H bond activation of acetonitrile by a stoichiometric amount of transition metal (e.g., Ir, Rh, Ni, Fe, etc.) has been well documented.[7] Recent years have also witnessed considerable advances on catalytic α-C–H functionalization of acetonitriles.[8] Nevertheless, success in this field is limited mainly to those cases requiring a strong base for the deprotonation [p*Ka* (MeCN) ~31.3] or stoichiometric Lewis acid AgF as an activator. Therefore, the development of alternative environment-friendly activators instead of commonly encountered strong bases or Ag reagents for α-C–H functionalization of nitriles is still well-desired. Due to economic and environmental benefits, copper has recently gained much popularity as a catalyst in oxidative cross-dehydrogenative coupling and difunctionalization of alkenes.[9,10] However, base-free copper-catalyzed difunctionalization of alkenes via C(sp^3)–H functionalization of acetonitrile was developed later.[8d,e] Oxindoles are common structural motifs in pharmaceutical agents and natural products,[11] and, given that cyano-containing molecules exhibit important functions in materials, synthetic intermediates and pharmaceuticals, the incorporation of cyano-substituted groups into oxindole scaffold via simple



Scheme 1 Azo compound-mediated cyanoalkylation of alkenes; DTBP = di-*tert*-butyl peroxide.

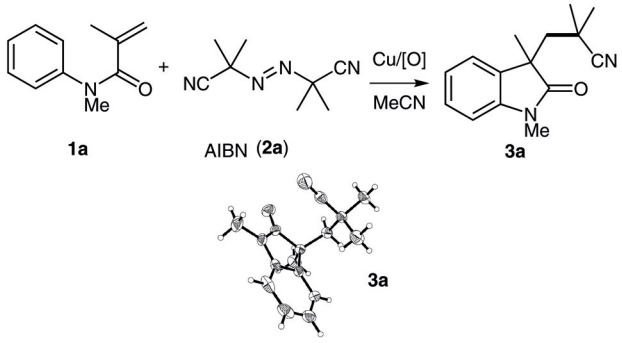
alkene difunctionalization is still of great interest, which is still rare (only a few examples to date).[12] For example, Liu and co-workers,[12a] in early stage, reported a pioneering Pd-catalyzed oxidative alkylarylation of alkene with the aid of a stoichiometric AgF (4 equiv). Just recently, You and co-workers[12b] developed an elegant copper-catalyzed oxidative radical cyanomethylation of activated alkenes using a catalytic combination of CuCl and *t*-BuOO*t*-Bu (3 equiv). Regardless of substantial achievements in this regard, apparent limitations remain: (1) requirement of either the combination of Pd catalyst with stoichiometric AgF or an elevated temperature (≥120 °C)[12b,c] and (2) in general inefficiency for the incorporation of 3° nitrile moiety into oxindole via α-C(sp^3)–H functionalization of the 3° nitrile (possibly due to steric hindrance or lower reactivity of α-C(sp^3)–H bond of 3° nitriles).[12a] As a continuation of our interest in oxindole synthesis,[13] we herein demonstrate an alternative AIBN and beyond-mediated/promoted oxidative cyanoalkylation reaction of *N*-arylacrylamides by copper catalysis, which could allow for general incorporation of 1°, 2°, and 3° alkyl nitrile moieties into oxindoles through cascade radical addition/C(sp^2)–H cyclization (Scheme 1, eq. 1) or double C–H cleavage of an arene and acetonitrile (Scheme 1, eq. 2).

Initially, the reaction between *N*-methyl-*N*-phenylacrylamide (**1a**) and AIBN was employed as the model reaction to explore the optimal conditions to prepare oxindoles with a 3° nitrile moiety (Table 1). Delightedly, we observed the formation of the desired cyclization product **3a** in a 23% yield when the reaction was conducted without the use of metal catalyst (Table 1, entry 1). Encouraged by this result, various inexpensive copper(I) and iron(II) salts were subsequently used as the catalyst to enhance the yield (entries 2–8). Among the metals examined, CuI turned out to be the most effective one, and afforded **3a** in a yield of 78% when using DTBP as an oxidant (entry 4). In this process, adding an oxidant improved the reaction and using DTBP is optimal. Other oxidants, such as TBHP, $K_2S_2O_8$, $PhI(OAc)_2$, and $PhI(OTF)_2$ resulted in unparallel yields (entries 9–13). Sequential screening of solvents revealed MeCN as the best choice (entries 14–16). The optimal temperature effect for the current reaction was 80 °C (entries 17 and 18).

After establishing the optimal reaction conditions, the scope of *N*-arylacrylamides was investigated in the difunctionalization reaction using AIBN as α-cyanoalkyl radical source (Scheme 2). Initial screening revealed that N-substituents of acrylamides had obvious effect on the reaction. For example, *N*-arylacrylamides with a benzyl or ethyl group on the N-atom were found to be well compatible with the reaction conditions, whereas unprotected *N*-arylacrylamide (R^2 = H) was less efficient in the cyclization (**3b** and **3c** vs **3d**). Next, the substitution effect on the N-aryl moiety in the reaction was investigated. Gratifyingly, a wide array of substituents including Me, MeO, Cl, F, and CF_3 at the 4-, 3- or 2-position of the aromatic ring displayed good reactivity, and the reactive order is: poor electron-withdrawing and electron donating groups > strong electron-withdrawing groups (**3e**–**o**). Notably, the halo groups, such as Cl and F on the 3- or 4-position of the *N*-aryl moiety, were intact in the reaction, whereas Br substituent at 2-position was very reactive and lead to unidentified by-products. The reaction of *meta*-methyl-substituted *N*-arylacrylamide afforded a mixture of two regioselective products **3j** and **3j′**. *Ortho*-substituted *N*-arylacrylamides were also tolerated, but the yield decreased to some extent possibly owing to the steric hindrance (**3k** and **3i**). Remarkably, a polycyclic oxindole derivative was successfully synthesized by this protocol, and the N-containing ligand (1,10-phenanthroline) was found to be useful to achieve good yield (**3p**). Sequential investigations revealed that several groups (Ph and CH_2OAc) at the 2-position of the acrylamide moiety were compatible with the optimal conditions to afford **3q** and **3s**, respective-

ly, whereas hydroxymethyl ($R^3 = CH_2OH$) and mono-substituted olefins ($R^3 = H$) were inefficient for the cyclization process (**3r** and **3t**). Unfortunately, the β-phenyl substituted acrylamides failed to be tolerated in our current reaction conditions (**3u**).

Table 1 Optimization of Reaction Conditions[a]



Entry	Metal	Oxidant	Solvent	Yield (%)[b]
1	none	DTBP	MeCN	23
2	CuCl	DTBP	MeCN	53
3	CuBr	DTBP	MeCN	74
4	CuI	DTBP	MeCN	78
5	CuCN	DTBP	MeCN	65
6	$FeSO_4·7H_2O$	DTBP	MeCN	45
7	$FeBr_2$	DTBP	MeCN	57
8	$Fe(NH_4)_2(SO_4)_2·6H_2O$	DTBP	MeCN	46
9	CuI	TBHP	MeCN	61
10	CuI	$K_2S_2O_8$	MeCN	51
11	CuI	$PhI(OAc)_2$	MeCN	46
12	CuI	$PhI(OTFA)_2$	MeCN	42
13	CuI	none	MeCN	14
14	CuI	DTBP	1,4-dioxane	62
15	CuI	DTBP	toluene	55
16	CuI	DTBP	DCE	39
17[c]	CuI	DTBP	MeCN	42
18[d]	CuI	DTBP	MeCN	64

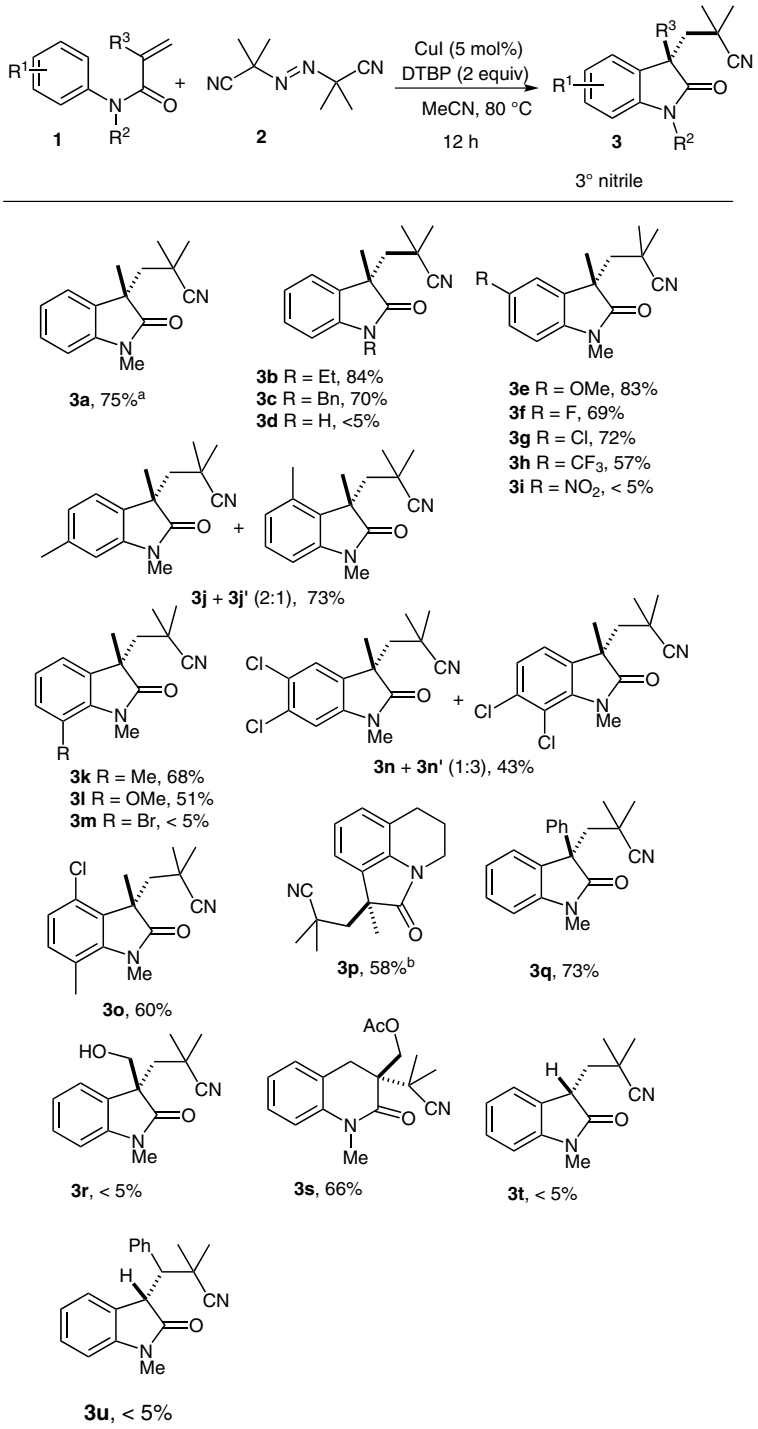
[a] Reaction conditions: **1a** (0.5 mmol), AIBN (2 equiv), oxidant (2 equiv), metal (5 mol%), and solvent (2 mL) at 80 °C for 12 h. TBHP: *tert*-Butyl hydrogen peroxide (70% aq solution); DCE: 1,2-Dichloroethane.
[b] Yield of the isolated product.
[c] Reaction conducted at 60 °C.
[d] Reaction conducted at 100 °C.

Next, the scope of α-cyanoazo compounds was investigated. Besides AIBN, other α-cyanoazo compounds could serve as viable substrate for the alkylarylation reaction to give the desired oxindoles with various 3° nitrile moieties (Scheme 3). Notably, irrespective of electronic and steric character of the substituent groups on the aromatic ring of acrylamides, the α-cyanoazo compound **2b** bearing a cyclohexyl ring underwent the C–H cyclization to yield corresponding oxindoles in good to excellent yields (**3u**–**v**). However, azo compound **2c** [CAS Reg. No. 2638-94-0] bearing carboxylic group failed to give the desired oxindole (**3y**).

Our initial attempt to introduce the ethoxylcarbonyl moiety into oxindole scaffold using diethyl azodicarboxylate (DEAD) under the above standard conditions unexpectedly did not result in the desired product **5**[2a] efficiently, but led to the oxindole **4a** via C(sp^3)–H functionalization of acetonitrile (Table 2). With these results in mind, we wondered whether the DEAD was really involved in this cyclization reaction through dual C–H bond cleavage of an arene and acetonitrile. After brief screenings, the dialkyl azodicarboxylate was observed to be crucial for this transformation, and the use of diisopropyl azodicarboxylate (DIAD) was optimal. Notably, the reaction failed to lead to desired oxindole **4a** in the absence an azodicarboxylate reagent under current temperature conditions (95 °C),[14] which might be attributed to the fact that azodicarboxylate could serve as a radical initiator to promote the C–H activation of acetonitrile (for detail screenings see Supporting information).

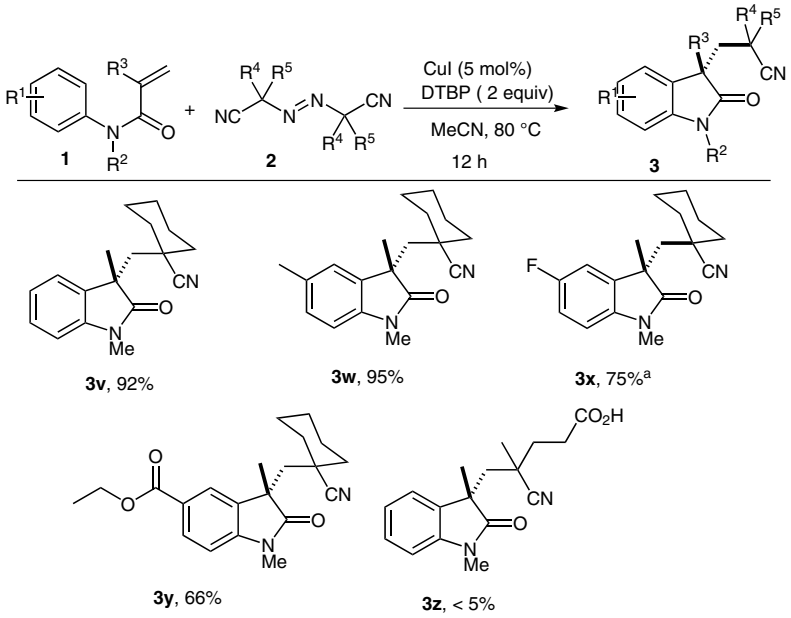
Subsequently, the substrate scope in this reaction involving C–H cleavage of acetonitrile were investigated (Scheme 4). Rewardingly, a series of substituents, such as *p*-Me, *o*-Me, Cl, F, CF_3 displayed good reactivity in most cases to yield various oxindoles with 1° nitrile moiety irrespective of steric and electronic character of the substituent groups (**4a**–**f**). Of more importance, this protocol could also be utilized to prepare complex and pharmaceutically interesting oxindoles. For example, the polycyclic oxindole **4r** could be synthesized through the C–H cyclization of *N*-arylacrylamide **1r**. In addition, the *N*-pyridylacrylamide **1s** was also a viable substrate for the reaction, and afforded synthetically important heterocycle **4s**. Next, the compatibility of other nitriles as C–H reactant under the standard conditions was examined. *n*-Butyl nitrile was also a viable C–H reactant for the cyanoalkylation to *N*-methyl-*N*-phenylacrylamide (**1a**), but the yield decreasing to some extent (**4t**). Nevertheless, the 3° nitrile proved to be an inefficient reactant to be involved in the cyanoalkylation promoted by DIAD (**4u**).

To investigate the mechanism of the cascade addition/C(sp^2)–H cyclization process, the inter- and intra-molecular kinetic isotope control experiments were performed (Scheme 5). For the cyanopropylation using AIBN, small kinetic isotopic effects (the intramolecular $K_H/K_D = 1.3$ and intermolecular $K_H/K_D = 1.0$) were observed. Comparative kinetic isotopic effects (the intramolecular $K_H/K_D = 1.3$ and intermolecular $K_H/K_D = 1.0$) were also observed in the DIAD-promoted cyanomethylation involving C–H activation of acetonitrile, which suggested that either the S_EAr mechanism or the free radical mechanism was involved in the two reactions.[15] Interestingly, when the reaction of **1a** was conducted in a 1:1 mixture of MeCN–CD_3CN using DIAD, a large primary isotope effect ($K_H/k_D = 4.5$) was



Scheme 2 Scope of *N*-arylacrylamines. *Reaction conditions*: 1 (0.5 mmol), AIBN (2 equiv), DTBP (2 equiv), CuI (5 mol%), and MeCN (2 mL) at 80 °C for 12 h. [a] Reaction was carried out on a 2 mmol scale. [b] 1,10-phenanthroline (10 mol%) was added.

obtained (Scheme 5, eq. 1). A similar KIE value (3.0) was also observed in individual reaction in CH_3CN and CD_3CN, which suggested that a C(sp^3)–H bond cleavage of acetonitrile contributed to the rate-determining step. Notably, the



Scheme 3 Scope of α-cyanoazo compounds. *Reaction conditions*: **1** (0.5 mmol), **2** (2 equiv), DTBP (2 equiv), CuI (5 mol%), and MeCN (2 mL) at 80 °C for 12 h. [a] Reaction was carried out on a 2 mmol scale.

free radical mechanism was supported by the control experiment: a stoichiometric amount of TEMPO (4 equiv), a well-known radical inhibitor, was used in the reactions of **1a** with either AIBN or DIAD, and the formation of the corresponding oxindoles was suppressed seriously (Scheme 5, eq. 2 and 3).

Based on the experimental results and previously reported mechanism,[2–8] a possible mechanism is proposed as outlined in Scheme 6 for this alkylarylation process of *N*-arylacrylamides. First, the copper(II) alkoxide [Cu^{II}]O*t*-Bu and *t*-BuO$^{\bullet}$ were generated by the reaction of [Cu^{I}] with *t*-BuOO*t*-Bu.[16] For the C–H cyclization using AIBN, at first, the AIBN decomposes to give the nitrile-stabilized radical **A**, followed by its addition onto the C=C bond of *N*-methyl-*N*-phenylacrylamide (**1a**) generating an alkyl radical **B**. Intramolecular cyclization of intermediate **B** with an aryl ring forms radical intermediate **C**, and then abstraction of an aryl hydrogen in the intermediate **C** by [Cu^{II}]-species takes place to afford desired oxindole **3a**. Regarding the cyclization involving C–H functionalization of acetonitrile, at first the DIAD decomposes to generate radical *i*-PrO_2C$^{\bullet}$ under heat, and then *i*-PrO_2C$^{\bullet}$ abstracts a hydrogen from acetonitrile to generate $^{\bullet}CH_2CN$.[17] The resulting $^{\bullet}CH_2CN$ adds onto C=C bond of **1a** to give intermediate **D**, followed by cyclization of intermediate **D** generating **E**. Finally, the abstraction of an aryl hydrogen by the [Cu^{II}] species produced by the oxidative reaction of [Cu^{I}] salt with *t*-BuOO*t*-Bu takes place to give the corresponding oxindole **4a**.

Finally, to utilize the copper-catalyzed difunctionalization of alkene for the modification of pharmaceutically interesting scaffold, diverse synthetic transformations of the above-obtained cyano-containing oxindoles were explored (Scheme 7). Delightedly, the product **3w** could be reduced by $LiAlH_4$ to afford spirocyclic indoline **6** in 73% yield.[18] In addition, aliphatic carboxylic acid **7** resulted by the hydrolysis of **3a** under alkaline conditions was an interesting synthetic precursor for the construction of an interesting bisoxindole scaffold **8** via an additional cyclization process developed by Zhu.[2k]

In summary, we have developed a highly practical azo compound-mediated radical cyanoalkylation of activated alkenes by inexpensive CuI, which allowed for general preparation of various oxindoles bearing various nitrile moieties, especially the rare-reported ones bearing an α-cyano quaternary carbon center. In addition, this protocol discovered that DIAD could be used as a novel promoter instead of commonly encountered Ag reagents or strong base for the α-C(sp^3)–H functionalization of acetonitrile, which would open a new door for the application of azo compound in the C–H functionalization of nitriles. The use of environment-friendly and readily available azo compound and inexpensive copper as the catalyst, as well as the simplicity of preparation and handling, make this protocol a highly attractive complement for the construction of pharmaceutically interesting cyano-substituted oxindoles. The detailed mechanism and application of the novel reaction to more complex targets are currently under investigation in our laboratory.

All manipulations of oxygen- and moisture-sensitive materials were conducted with a Schlenk technique or in a dry box under a N_2 or argon atmosphere. Flash column chromatography was performed using EM Silica gel 60 (300—400 mesh). Visualization was accomplished with UV light (254 nm) and/or an aqueous alkaline $KMnO_4$ solution followed by heating. ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 400 (^1H NMR, 400 MHz; ^{13}C NMR 101 MHz) spectrometer with solvent resonance as the internal standard (^1H NMR, $CHCl_3$ at 7.26 ppm; ^{13}C NMR, $CDCl_3$ at 77.0 ppm). Unless otherwise noted, reagents were commercially available and were used without further purification. *N*-Arylacrylamides **1** were prepared according to literature procedures.[12a]

Oxindoles Bearing 3° Nitrile Moiety; General Procedure

To a mixture of *N*-arylacrylamide **1** (0.5 mmol), AIBN or its analogue (2.0 equiv), CuI (5 mol%) in MeCN (2.0 mL) was added *t*-BuOO*t*-Bu (2.0 equiv) dropwise, and then the resulting solution was stirred at the indicated temperature for 12 h. The solvent was evaporated under reduced pressure and the resulted mixture was filtered through a Florisil pad, diluted with Et_2O (50 mL), and the Et_2O layer was washed with H_2O (10 mL) and then brine (10 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography on silica gel to afford the corresponding oxindole with 3° alkyl nitrile moiety in a yield listed in Scheme 1 and 2.

3-(1,3-Dimethyl-2-oxoindolin-3-yl)-2,2-dimethylpropanenitrile (3a)

Yield: 94.0 mg (78%); colorless solid; mp 100–101 °C.

IR (KBr): 2234, 1716, 1610, 1432, 1378, 1335 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.40–7.25 (m, 2 H), 7.09 (t, *J* = 7.5 Hz, 1 H), 6.90 (d, *J* = 8.0 Hz, 1 H), 3.23 (s, 3 H), 2.32 (d, *J* = 14.4 Hz, 1 H), 2.16 (d, *J* = 14.5 Hz, 1 H), 1.34 (s, 3 H), 1.13 (s, 3 H), 1.08 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 179.5, 143.1, 130.9, 128.6, 124.6, 123.9, 122.4, 108.5, 47.0, 46.5, 30.7, 29.6, 27.4, 26.8, 26.4.

MS (EI, 70 eV): *m*/*z* (%) = 242 ([M^+], 32), 160 (100).

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{19}N_2O$ [M + H]$^+$: 243.1492; found: 243.1495.

3-(1-Ethyl-3-methyl-2-oxoindolin-3-yl)-2,2-dimethylpropanenitrile (3b)

Yield: 107.5 mg (84%); colorless solid; mp 71–72 °C.

IR (KBr): 2247, 1713, 1611, 1431. 1376, 1337 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.31 (m, 2 H), 7.09 (t, *J* = 7.2 Hz, 1 H), 6.90 (d, *J* = 8.0 Hz, 2 H), 3.90–3.70 (m, 2 H), 2.32 (d, *J* = 14.4 Hz, 1 H), 2.16 (d, *J* = 14.4 Hz, 1 H), 1.32 (s, 3 H), 1.27 (t, *J* = 7.2 Hz, 3 H), 1.20 (s, 3 H), 1.05 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 179.2, 142.1, 131.0, 128.5, 125.0, 124.2, 122.2, 108.6, 46.0, 46.1, 30.8, 29.8, 27.9, 26.1, 25.8, 12.2.

MS (EI, 70 eV): *m*/*z* (%) = 256 ([M^+], 27), 174 (100).

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{21}N_2O$ [M + H]$^+$: 257.1649; found: 257.1653.

3-(1-Benzyl-3-methyl-2-oxoindolin-3-yl)-2,2-dimethylpropanenitrile (3c)

Yield: 111.3 mg (70%); yellow solid; mp 80–81 °C.

IR (KBr): 2233, 1701, 1610, 1432, 1376, 1332 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.20 (m, 7 H), 7.05 (t, *J* = 7.2 Hz, 1 H), 6.83 (d, *J* = 8.0 Hz, 2 H), 5.12 (d, *J* = 15.6 Hz, 1 H), 4.72 (d, *J* = 15.6 Hz, 1 H), 2.36 (d, *J* = 14.8 Hz, 1 H), 2.22 (d, *J* = 14.4 Hz, 1 H), 1.40 (s, 3 H), 1.19 (s, 3 H), 1.03 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 179.7, 142.3, 130.8, 128.7, 128.5, 127.7, 127.6, 124.8, 124.1, 122.4, 119.9, 109.5, 47.0, 46.2, 44.1, 30.8, 29.7, 28.1, 26.3.

MS (EI, 70 eV): *m*/*z* (%) = 318 ([M^+], 22), 236 (100).

HRMS: *m*/*z* (ESI) calcd for $C_{21}H_{23}N_2O$ [M + H]$^+$: 319.1805; found: 319.1801.

3-(1-Ethyl-5-methoxy-3-methyl-2-oxoindolin-3-yl)-2,2-diethylpropanenitrile (3e)

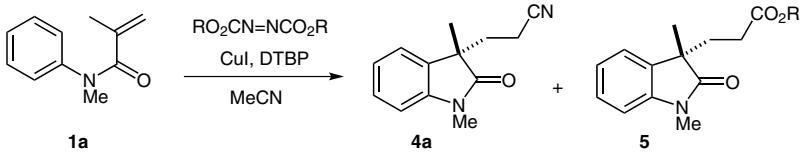
Yield: 118.6 mg (83%); yellow solid; mp 111–112 °C.

IR (KBr): 2237, 1702, 1596, 1431, 1384, 1337 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.95 (s, 1 H), 6.86–6.79 (m, 2 H), 3.84–3.67 (m, 2 H), 3.80 (s, 3 H), 2.30 (d, *J* = 14.8 Hz, 1 H), 2.17 (s, *J* = 14.8 Hz, 1 H), 1.31 (s, 3 H), 1.29–1.20 (m, 6 H), 1.04 (s, 3 H).

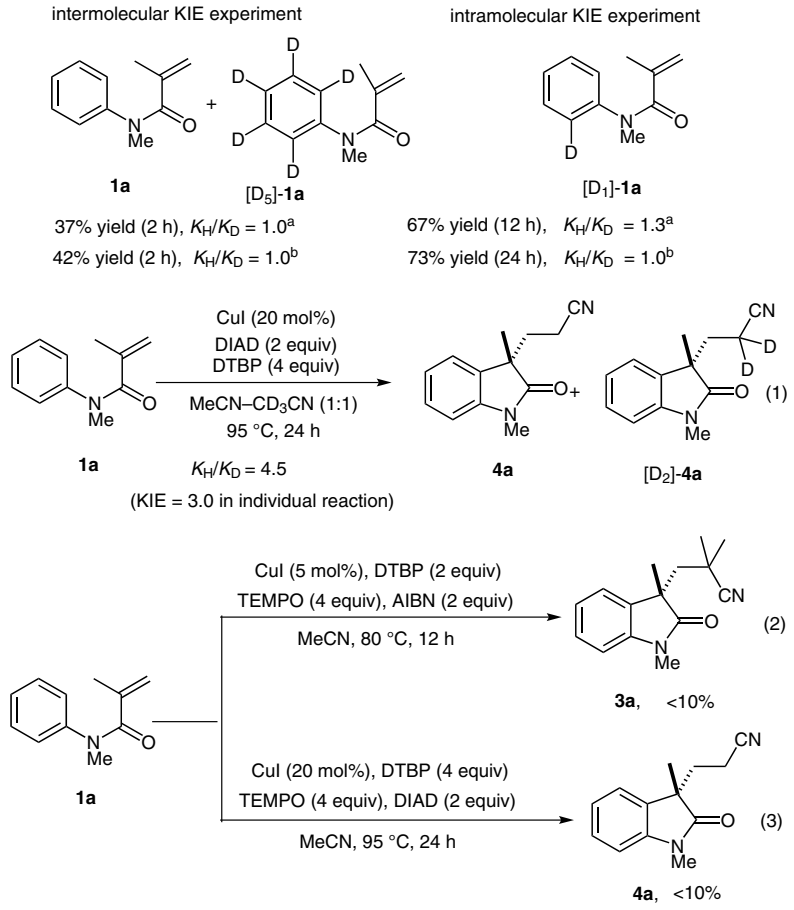
^{13}C NMR (101 MHz, $CDCl_3$): δ = 178.9, 166.7, 135.5, 132.3, 124.3, 113.2, 112.4, 108.9, 55.9, 47.3, 46.0, 30.8, 29.8, 29.7, 28.0, 25.8, 12.2.

Table 2 Screening of Azodicarboxylic Reagents[a]



Entry	$RO_2CN=NCO_2R$	Yield of **4a**(%)[b]	Yield of **5** (%)[c]
1	none	<5	0
2	R = Me (DMAD)	35	trace
3	R = Et (DEAD)	43	trace
4	R = *i*-Pr (DIAD)	85	trace

[a] Reaction conditions: **1a** (0.5 mmol), $RO_2CN=NCO_2R$ (2 equiv), DTBP (4 equiv), CuI (20 mol%), and MeCN (2 mL) at 95 °C for 24 h.
[b] Yield of the isolated product.
[c] Determined by GC/MS.



Scheme 5 Control experiments. [a] Under standard conditions using AIBN. [b] Under standard conditions using DIAD.

MS (EI, 70 eV): *m*/*z* (%) = 286 ([M⁺], 17), 204 (100).

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{23}N_2O_2$ [M + H]⁺: 287.1755; found: 287.1752.

3-(5-Fluoro-1,3-dimethyl-2-oxoindolin-3-yl)-2,2-dimethylpropanenitrile (3f)

Yield: 89.75 mg (69%); pale yellow solid; mp 107–108 °C.

IR (KBr): 2234, 1718, 1617, 1435, 1383, 1335 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.10–7.00 (m, 2 H), 6.60–6.71 (m, 1 H), 3.21 (s, 3 H), 2.32 (d, *J* = 14.8 Hz, 1 H), 2.11 (d, *J* = 14.8 Hz, 1 H), 1.34 (s, 3 H), 1.16 (s, 3 H), 1.10 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 179.2, 159.2 (d, *J* = 204.4 Hz), 139.1, 132.6, 123.7, 114.8 (d, *J* = 23.4 Hz), 112.7 (d, *J* = 24.5 Hz), 109.0, 47.4, 46.5, 30.6, 29.1, 23.3, 26.9, 26.5.

MS (EI, 70 eV): *m*/*z* (%) = 260 ([M⁺], 17), 178 (100).

HRMS: *m*/*z* (ESI) calcd for $C_{15}H_{18}FN_2O$ [M + H]⁺: 261.1397; found: 261.1399.

3-(5-Chloro-1,3-dimethyl-2-oxoindolin-3-yl)-2,2-dimethylpropanenitrile (3g)

Yield: 99.3 mg (72%); pale yellow solid; mp 128–129 °C.

IR (KBr): 2233, 1715, 1610, 1432, 1383, 1345 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.25 (m, 2 H), 6.81 (d, *J* = 8.0 Hz, 1 H), 3.21 (s, 3 H), 2.32 (d, *J* = 14.4 Hz, 1 H), 2.10 (d, *J* = 14.4 Hz, 1 H), 1.34 (s, 3 H), 1.15 (s, 3 H), 1.10 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 179.0, 141.7, 132.7, 127.9, 125.0, 123.9, 123.6, 109.4, 47.2, 46.6, 30.5, 29.6, 27.3, 27.1, 26.5.

MS (EI, 70 eV): *m*/*z* (%) = 276 ([M⁺], 12), 194 (100).

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{18}ClN_2O$ [M + H]⁺: 277.1103; found: 277.1106.

3-(1,3-Dimethyl-2-oxo-5-(trifluoromethyl)indolin-3-yl)-2,2-dimethylpropanenitrile (3h)

Yield: 88.3 mg (57%); yellow solid; mp 114–115 °C.

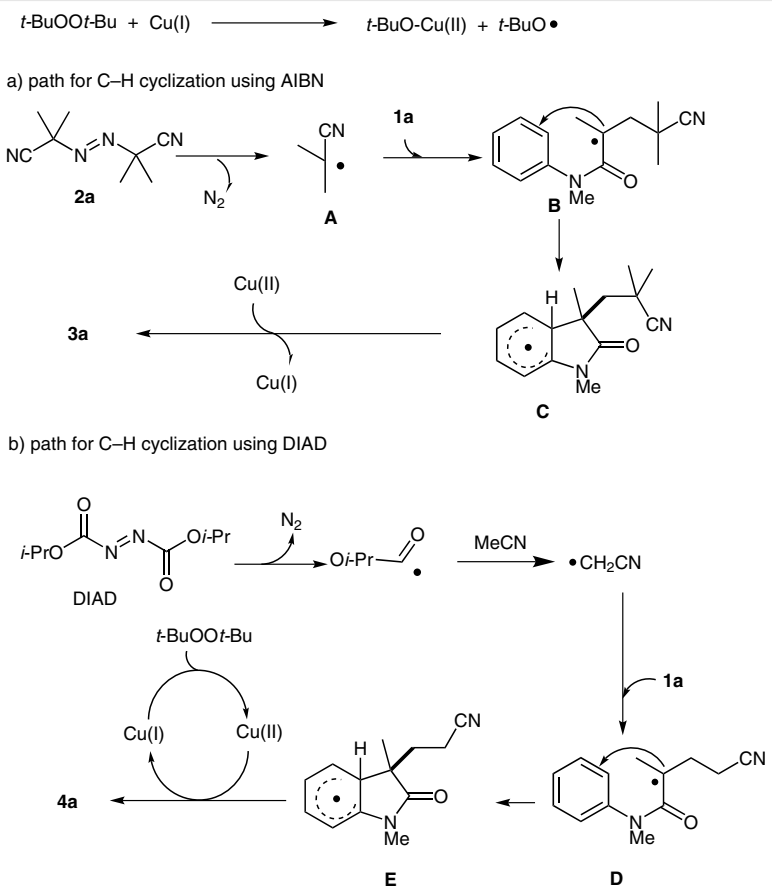
IR (KBr): 2235, 1715, 1624, 1432, 1385, 1327 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 8.4 Hz, 1 H), 7.52 (s, 1 H), 6.96 (d, *J* = 8.4 Hz, 1 H), 3.26 (s, 3 H), 2.33 (d, *J* = 14.8 Hz, 1 H), 2.15 (d, *J* = 14.8 Hz, 1 H), 1.37 (s, 3 H), 1.11 (s, 6 H).

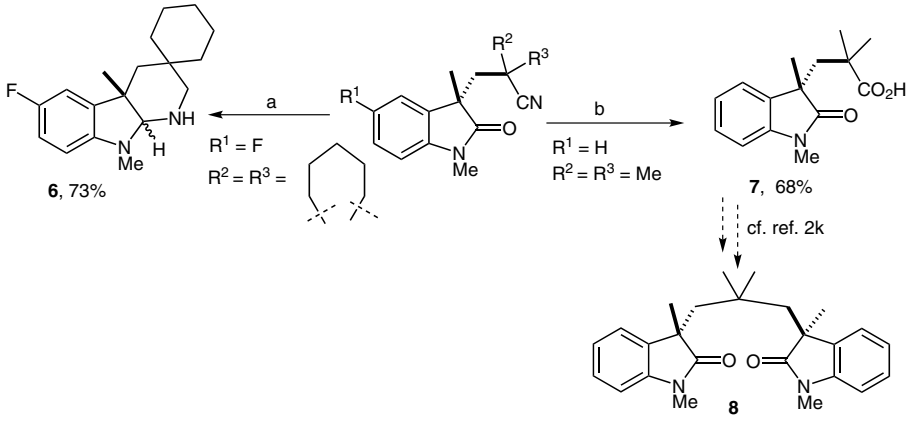
^{13}C NMR (101 MHz, $CDCl_3$): δ = 179.4, 146.1, 131.6, 126.3 (q, *J* = 3.9 Hz), 124.0 (q, *J* = 32.8 Hz), 123.4, 121.6 (q, *J* = 3.5 Hz), 120.2, 108.3, 47.0, 46.5, 30.5, 29.5, 27.2, 27.1, 26.6.

MS (EI, 70 eV): *m*/*z* (%) = 310 ([M⁺], 32), 228 (100).

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{18}F_3N_2O$ [M + H]⁺: 311.1366; found: 311.1367.



Scheme 6 Proposed mechanism for the formation of oxindoles



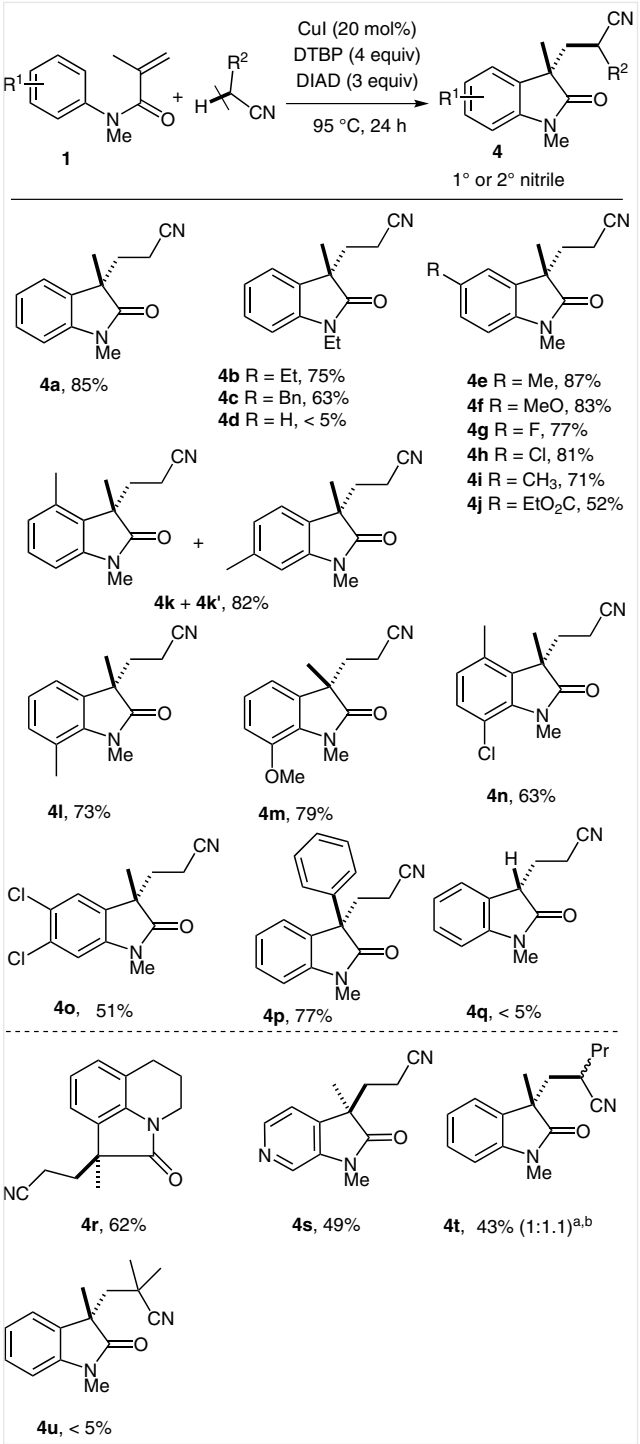
Scheme 7 Synthetic transformation of cyano-containing oxindoles. *Reagent and conditions*: (a) $LiAlH_4$ (4 equiv), THF, 1 h, then reflux, 0.5 h; (b) NaOH (5 equiv), ethylene glycol, 110 °C, 12 h, then aq 1 M HCl, 0 °C to r.t.

2,2-Dimethyl-3-(1,3,6-trimethyl-2-oxoindolin-3-yl)propanenitrile (3j) and 2,2-Dimethyl-3-(1,3,4-trimethyl-2-oxoindolin-3-yl)propanenitrile (3j')

Yield **3j**/**3j'** (2:1): 93.4 mg (73%).

IR (KBr): 2233, 1702, 1610, 1434, 1372, 1327 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.15 (m, 3 H), 6.90–6.83 (m, 3 H), 6.74–6.70 (m, 3 H), 2.20 (s, 9 H), 2.42 (s, 6 H), 2.36 (s, 3 H), 2.36–2.22 (m, 5 H), 2.12 (d, *J* = 14.8 Hz, 1 H), 2.39 (s, 6 H), 2.30 (s, 3 H), 1.15 (s, 6 H), 1.13 (s, 3 H), 1.07 (s, 6 H), 1.05 (s, 3 H).



Scheme 4 Scope of *N*-arylacrylamides. Reaction conditions: **1** (0.5 mmol), DIAD (2 equiv), DTBP (4 equiv), CuI (20 mol%), and MeCN (2 mL) at 95 °C for 24 h. [a] *n*-Butyl nitrile (2 mL) instead of MeCN. [b] The ratio in the parentheses is the diasteroselectivity of the reaction as determined by ^{1}H NMR spectroscopy.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 180.0, 179.6, 143.3, 143.1, 138.7, 135.8, 128.5, 128.1, 125.3, 124.4, 123.4, 122.9, 109.4, 106.2, 46.8, 46.4, 45.1, 44.2, 30.8, 30.7, 30.5, 30.3, 29.6, 29.1, 27.5, 26.6, 26.4, 24.7.

MS (EI, 70 eV): *m*/*z* (%) = 256 ([M$^+$], 26), 174 (100).

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{21}N_2O$ [M + H]$^+$: 257.1649; found: 257.1654.

2,2-Dimethyl-3-(1,3,7-trimethyl-2-oxoindolin-3-yl)propanenitrile (3k)

Yield: 87.0 mg (68%); yellow solid; mp 84–85 °C.

IR (KBr): 2232, 1702, 1600, 1432, 1363, 1327 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.12 (d, *J* = 7.6 Hz, 1 H), 7.04 (d, *J* = 7.6 Hz, 1 H), 6.99 (t, *J* = 7.6 Hz, 1 H), 3.51 (s, 3 H), 2.59 (s, 3 H), 2.21 (d. *J* = 14.4 Hz, 1 H), 2.11 (d, *J* = 14.4 Hz, 1 H), 1.31 (s, 3 H), 1.14 (s, 3 H), 1.10 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 180.3, 140.9, 132.3, 131.6, 123.9, 122.5, 122.3, 120.1, 46.7, 46.3, 30.7, 29.7, 29.6, 27.8, 26.8, 19.1.

MS (EI, 70 eV): *m*/*z* (%) = 256 ([M$^+$], 22), 174 (100).

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{21}N_2O$ [M + H]$^+$: 257.1649; found: 257.1652.

3-(7-Methoxy-1,3-dimethyl-2-oxoindolin-3-yl)-2,2-dimethylpropanenitrile (3l)

Yield: 69.4 mg (51%); yellow solid; mp 93–94 °C.

IR (KBr): 2233, 1700, 1612, 1439, 1365, 1333 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.01 (t, *J* = 8.4 Hz, 2 H), 6.90–6.71 (m, 2 H), 3.85 (s, 3 H), 3.49 (s, 3 H), 2.28 (d, *J* = 14.8 Hz, 1 H), 2.12 (d, *J* = 14.8 Hz, 1 H), 1.30 (s, 3 H), 1.17 (s, 3 H), 1.08 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 179.8, 146.6, 132.6, 130.9, 123.9, 122.9, 117.3, 112.2, 55.8, 46.9, 46.5, 30.7, 29.7, 27.7, 26.4, 25.8.

MS (EI, 70 eV): *m*/*z* (%) = 272 ([M$^+$], 35), 190 (100).

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{21}N_2O_2$ [M + H]$^+$: 273.1598; found: 273.1603.

3-(5,6-Dichloro-1,3-dimethyl-2-oxoindolin-3-yl)-2,2-dimethylpropanenitrile (3n) and 3-(4,5-Dichloro-1,3-dimethyl-2-oxoindolin-3-yl)-2,2-dimethylpropanenitrile (3n′)

Yield **3n**/**3n′** (1:3): 66.7 mg (43%).

IR (KBr): 2235, 1723, 1602, 1473, 1376, 1325 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (d, *J* = 8.4 Hz, 1 H), 7.36 (s, 0.3 H), 6.98 (s, 0.3 H), 6.77 (d, *J* = 14.4 Hz, 1 H), 3.21 (s, 3 H), 3.20 (s, 1 H), 2.68 (d, *J* = 14.4Hz, 1 H), 2.31 (d, *J* = 14.4 Hz, 0.3 H), 2.21 (d, *J* = 14.4 Hz, 1 H), 2.10 (d, *J* = 14.4 Hz, 0.3 H), 1.48 (s, 3 H), 1.33 (s, 1 H), 1.18 (s, 4 H), 1.12 (s, 3 H), 1.09 (s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 178.9, 178.4, 143.3, 142.7, 130.9, 130.4, 130.3, 129.7, 126.5, 123.9, 123.6, 121.5, 123.1, 110.9, 107.8, 47.0, 46.4, 44.2, 43.4, 30.6, 30.5, 30.4, 30.3, 29.7, 28.2, 28.0, 27.3, 26.9, 26.6, 25.8.

MS (EI, 70 eV): *m*/*z* (%) = 310 ([M$^+$], 35), 227 (100).

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{17}Cl_2N_2O$ [M + H]$^+$: 311.0713; found: 311.0717.

3-(4-Chloro-1,3,7-trimethyl-2-oxoindolin-3-yl)-2,2-dimethylpropanenitrile (3o)

Yield: 87.0 mg (60%); yellow solid; mp 78–79 °C.

IR (KBr): 2231, 1717, 1636, 1457, 1384 1337 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.98 (d, *J* = 8.4 Hz, 1 H), 6.88 (d, *J* = 8.4 Hz, 1 H), 3.5 (s, 3 H), 2.60 (d, *J* = 14.4 Hz, 1 H), 2.57 (s, 3 H), 2.19 (d, *J* = 14.4 Hz, 1 H), 1.47 (s, 3 H), 1.18 (s, 3 H), 1.13 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 179.6, 142.7, 123.5, 129.8, 129.1, 128.5, 128.1, 118.8, 47.6, 44.1, 30.7, 29.7, 28.2, 28.0, 23.8, 19.0.

MS (EI, 70 eV): *m*/*z* (%) = 290 ([M^+], 23), 208 (100).

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{20}ClN_2O$ [M + H]$^+$: 291.1259; found: 291.1256.

2,2-Dimethyl-3-(1-methyl-2-oxo-2,4,5,6-tetrahydro-1*H*-pyrrolo[3,2,1-*ij*]quinolin-1-yl)propanenitrile (3p)

Yield: 77.7 mg (58%); yellow oil.

IR (neat): 2232, 1710, 1608, 1473, 1372, 1341 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.20 (d, *J* = 7.2 Hz, 1 H), 7.13 (d, *J* = 7.6 Hz, 1 H), 7.04 (t, *J* = 7.6 Hz, 1 H), 3.85–3.74 (m, 2 H), 2.93–2.79 (m, 2 H), 2.38 (d, *J* = 14.4 Hz, 1 H), 2.19 (d, *J* = 14.4 Hz, 1H), 2.11–2.09 (m, 2 H), 1.41 (s, 3 H), 1.22 (s, 3 H), 1.18 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 179.3, 139.8, 130.3, 128.1, 124.8, 123.3, 122.6, 121.4, 49.1, 47.2, 31.6, 30.4, 27.9, 27.7, 25.4, 21.9.

MS (EI, 70 eV): *m*/*z* (%) = 268 ([M^+], 29), 186 (100).

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{21}N_2O$ [M + H]$^+$: 269.1649; found: 269.1653.

2,2-Dimethyl-3-(1-methyl-2-oxo-3-phenylindolin-3-yl)propanenitrile (3q)

Yield: 110.9 mg (73%); yellow solid; mp 121–122 °C.

IR (KBr): 2234, 1713, 1611, 1470, 1372, 1341 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.48 (m, 7 H), 7.18 (t, *J* = 8.0 Hz, 1 H), 6.96 (d, *J* = 8.0 Hz, 1 H), 3.22 (s, 3 H), 2.82 (d, *J* = 14.4 Hz, 1 H), 2.49 (d, *J* = 14.4 Hz, 1 H), 1.23 (s, 3 H), 1.18 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 177.4, 144.1, 140.7, 140.4, 129.4, 128.0, 127.5, 125.4, 124.2, 123.8, 122.5, 108.9, 54.6, 46.6, 30.7, 30.2, 29.0, 28.7.

MS (EI, 70 eV): *m*/*z* (%) = 304 ([M^+], 35), 222 (100).

HRMS (ESI): *m*/*z* calcd for $C_{20}H_{21}N_2O$ [M + H]$^+$: 305.1649; found: 305.1647.

[3-(2-Cyano-2-methylpropyl)-1-methyl-2-oxoindolin-3-yl]methyl Acetate (3s)

Yield: 99.0 mg (66%); yellow oil.

IR (neat): 2234, 1732, 1710, 1614, 1491, 1378, 1340 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.37 (m, 2 H), 7.07 (t, *J* = 7.6 Hz, 1 H), 6.90 (d, *J* = 8.4 Hz, 1 H), 4.34 (d, *J* = 10.4 Hz, 1 H), 4.00 (d, *J* = 10.8 Hz, 1 H), 3.24 (s, 3 H), 2.28 (s, 2 H), 1.90 (s, 3 H), 1.17 (s, 3 H), 1.10 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 176.3, 170.2, 143.9, 129.4, 125.9, 123.7, 122.5, 108.5, 68.5, 50.9, 41.6, 30.3, 27.8, 26.8, 26.5, 20.5.

MS (EI, 70 eV): *m*/*z* (%) = 300 ([M^+], 14), 242 (30), 174 (100).

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{21}N_2O_3$ [M + H]$^+$: 301.1547; found: 301.1546.

1-[(1,3-Dimethyl-2-oxoindolin-3-yl)methyl]cyclohexanecarbonitrile (3v)

Yield: 129.7 mg (92%); yellow solid; mp 158–159 °C.

IR (KBr): 2231, 1701, 1614, 1471 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.28 (m, 2 H), 7.06 (t, *J* = 7.6 Hz, 1 H), 6.87 (d, *J* = 8.0 Hz, 1 H), 3.21 (s, 3 H), 2.39 (d, *J* = 14.4 Hz, 1 H), 2.14 (d, *J* = 14.4 Hz, 1 H), 1.64–1.03 (m, 10 H), 1.31 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 179.8, 143.0, 131.3, 128.5, 124.6, 122.4, 122.1, 108.5, 46.7, 46.6, 38.1, 37.0, 35.0, 27.7, 26.4, 24.8, 22.8, 22.5.

MS (EI, 70 eV): *m*/*z* (%) = 282 ([M^+], 15), 160 (100).

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{23}N_2O$ [M + H]$^+$: 283.1805; found: 283.1808.

1-[(1,3,5-Trimethyl-2-oxoindolin-3-yl)methyl]cyclohexanecarbonitrile (3w)

Yield: 140.6 mg (95%); yellow solid; mp 145–146 °C.

IR (KBr): 2233, 1706, 1617, 1496 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.11 (s, 1 H), 7.07 (d, *J* = 7.6 Hz, 1 H), 6.74 (d, *J* = 8.0 Hz, 1 H), 3.17 (s, 3 H), 2.31 (s, 3 H), 2.25 (d, *J* = 14.8 Hz, 1 H), 2.11 (d, *J* = 14.8 Hz, 1 H), 1.28–1.09 (m, 10 H), 1.28 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 179.8, 140.6, 131.8, 131.2, 128.6, 125.5, 122.2, 108.1, 46.7, 46.5, 38.1, 37.0, 34.8, 27.8, 26.4, 24.8, 22.7, 22.5, 21.2.

MS (EI, 70 eV): *m*/*z* (%) = 296 ([M^+], 15), 174 (100).

HRMS (ESI): *m*/*z* calcd for $C_{19}H_{25}N_2O$ [M + H]$^+$: 297.1962; found: 297.1965.

1-[(5-Fluoro-1,3-dimethyl-2-oxoindolin-3-yl)methyl]cyclohexanecarbonitrile (3x)

Yield: 450.0 mg (75% on a 2 mmol scale); yellow solid; mp 150–151 °C.

IR (KBr): 2234, 1713, 1621, 1451 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.05–6.97 (m, 2 H), 6.81–6.77 (m, 1 H), 3.20 (s, 3 H), 2.39 (d, *J* = 14.8 Hz, 1 H), 2.19 (d, *J* = 14.8 Hz, 1 H), 1.52–0.99 (m, 10 H), 1.31 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 179.4, 159.1 (d, *J* = 241 Hz), 139.0, 133.0 (d, *J* = 7.8 Hz), 121.9, 114.6, 112.6 (d, *J* = 24.5 Hz), 108.9 (d, *J* = 7.1 Hz), 47.1, 46.6, 38.1, 36.9, 35.3, 27.6, 26.5, 24.5, 22.7, 22.5.

MS (EI, 70 eV): *m*/*z* (%) = 300 ([M^+], 19), 178 (100).

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{22}FN_2O$ [M + H]$^+$: 301.1711; found: 301.1714.

Ethyl 3-[(1-Cyanocyclohexyl)methyl]-1,3-dimethyl-2-oxoindoline-5-carboxylate (3y)

Yield: 116.8 mg (66%); yellow solid; mp 140–141 °C.

IR (KBr): 2235, 1726, 1701, 1612, 1475 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.05 (dd, *J* = 8.4, 1.6 Hz, 1 H), 7.90 (s, 1 H), 6.90 (d, *J* = 8.4 Hz, 1 H), 4.34 (q, *J* = 6.8 Hz, 2 H), 3.25 (s, 3 H), 2.32 (d, *J* = 14.4 Hz, 1 H), 2.25 (d, *J* = 14.4 Hz, 1 H), 1.61–0.98 (m, 10 H), 1.37 (t, *J* = 7.2 Hz, 3 H), 1.35 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 179.9, 166.3, 147.2, 131.5, 131.1, 125.4, 124.6, 121.6, 108.0, 60.9, 46.7, 46.6, 37.9, 36.9, 36.1, 27.5, 26.6, 24.8, 22.7, 22.5, 14.3.

MS (EI, 70 eV): *m*/*z* (%) = 354 ([M^+], 13), 232 (100).

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{27}N_2O_3$ [M + H]$^+$: 355.2017; found: 355.2019.

Oxindoles Bearing 1° and 2° Nitrile Moiety; General Procedure

To a mixture of *N*-arylacrylamide **1** (0.5 mmol), CuI (20 mol%), DIAD (2.0 equiv) in MeCN (2.0 mL) was added *t*-BuOO*t*-Bu (4.0 equiv) dropwise, and then the resulting solution was stirred at the indicated temperature (Scheme 3) for 24 h. The solvent was evaporated under reduced pressure and the resulting mixture was filtered through a Florisil pad. The pad was washed with with Et_2O (50 mL), and the Et_2O layer was washed with H_2O (10 mL) and brine (10 mL). The Et_2O layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography on silica gel to afford the corresponding oxindole with 1° and 2° nitrile moiety in a yield listed in Scheme 3.

3-(1,3-Dimethyl-2-oxoindolin-3-yl)propanenitrile (4a)[12]

Yield: 90.9 mg (85%); yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (t, *J* = 7.6 Hz, 1 H), 7.16 (d, *J* = 7.2 Hz, 1 H), 7.09 (t, *J* = 7.6 Hz, 1 H), 6.85 (d, *J* = 8.0 Hz, 1 H), 3.19 (s, 3 H), 2.37–2.25 (m, 1 H), 2,12–1.96 (m, 3 H), 1.37 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 178.9, 143.1, 131.6, 128.7, 127.0, 122.6, 118.8, 108.5, 47.3, 33.4, 26.3, 23.4, 12.7.

3-(1-Ethyl-3-methyl-2-oxoindolin-3-yl)propanenitrile (4b)

Yield: 85.5 mg (75%); yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (t, *J* = 7.2 Hz, 1 H), 7.18 (d, *J* = 6.4 Hz, 1 H), 7.09 (t, *J* = 7.6 Hz, 1 H), 6.88 (d, *J* = 7.6 Hz, 1 H), 5.83–5.68 (m, 2 H), 2.37–2.26 (m, 1 H), 2,14–1.99 (m, 3 H), 1.37 (s, 3 H), 1.25 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 178.4, 142.2, 131.9, 128.6, 127.0, 122.8, 122.8, 118.8, 108.6, 49.2, 34.7, 33.5, 23.4, 12.7, 12.7.

MS (EI, 70 eV): *m*/*z* (%) = 228 ([M$^+$], 27), 174 (100).

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{17}N_2O$ [M + H]$^+$: 229.1336; found: 229.1332.

3-(1-Benzyl-3-methyl-2-oxoindolin-3-yl)propanenitrile (4c)[12]

Yield: 91.3 mg (63%); yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.17 (m, 7 H), 7.07 (t, *J* = 7.6 Hz, 1 H), 6.79 (d, *J* = 7.6 Hz, 1 H), 4.90 (d, *J* = 7.2 Hz, 2 H), 2.43–2.32 (m, 1 H), 2,22–1.97 (m, 3 H), 1.44 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 179.0, 142.2, 135.7, 131.6, 128.9, 128.6, 128.0, 127.3, 123.1, 122.7, 118.8, 109.5, 47.3, 43.8, 33.6, 23.8, 12.8.

3-(1,3,5-Trimethyl-2-oxoindolin-3-yl)propanenitrile (4e)[12]

Yield: 99.1 mg (87%); yellow solid; mp 91–92 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.09 (d, *J* = 7.6 Hz, 1 H), 6.98 (s, 1 H), 6.75 (d, *J* = 7.6 Hz, 1 H), 3.18 (s, 3 H), 2.35 (s, 3 H), 2.55–2.24 (m, 1 H), 2.12–1.93 (m, 3 H), 1.37 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 178.8, 140.7, 132.7, 131.7, 128.9, 123.4, 118.9, 108.2, 47.4, 33.5, 26.3, 23.5, 21.1, 12.8.

3-(5-Methoxy-1,3-dimethyl-2-oxoindolin-3-yl)propanenitrile (4f)[12]

Yield: 101.2 mg (83%); yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.87–6.72 (m, 3 H), 3.77 (s, 3 H), 3.18 (s, 3 H), 2.36–2.23 (m, 1 H), 2.17–1.96 (m, 3 H), 1.36 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 178.5, 156.4, 136.5, 133.1, 118.8, 112.6, 110.3, 108.8, 55.8, 47.7, 33.5, 26.4, 23.5, 12.8.

3-(5-Fluoro-1,3-dimethyl-2-oxoindolin-3-yl)propanenitrile (4g)[12]

Yield: 89.3 mg (77%); yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.00 (td, *J* = 8.8, 2.4 Hz, 1 H), 6.93 (dd, *J* = 7.6, 2.5 Hz, 1 H), 6.78 (dd, *J* = 8.4, 4.0 Hz, 1 H), 3.18 (s, 3 H), 2.35–2.24 (m, 1 H), 2.15–1.89 (m, 3 H), 1.38 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 178.5, 159.4 (d, *J* = 240.6 Hz), 129.1, 133.3 (d, *J* = 7.7 Hz), 118.5, 114.9 (d, *J* = 23.4 Hz), 110.8 (d, *J* = 24.5 Hz), 109.0 (d, *J* = 8.0 Hz), 47.7, 33.2, 26.4, 23.4, 12.8.

3-(5-Chloro-1,3-dimethyl-2-oxoindolin-3-yl)propanenitrile (4h)[12]

Yield: 100.4 mg (81%); yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.16 (s, 1 H), 6.80 (d, *J* = 8.4 Hz, 1 H), 3.20 (s, 3 H), 2.37–2.23 (m, 1 H), 2.09–1.97 (m, 3 H), 1.39 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 178.3, 141.7, 133.4, 128.6, 128.5, 123.2, 118.4, 109.5, 47.5, 33.3, 26.4, 23.4, 12.8.

3-(1,3-Dimethyl-2-oxo-5-(trifluoromethyl)indolin-3-yl)propanenitrile (4i)[12]

Yield: 100.0 mg (71%); yellow solid; mp 61–62 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 8.0 Hz, 1 H), 7.42 (s, 1 H), 6.96 (d, *J* = 8.0 Hz, 1 H), 3.25 (s, 3 H), 2.41–2.30 (m, 1 H), 2.16–2.02 (m, 3 H), 1.43 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 178.3, 148.1, 132.4, 126.5 (q, *J* = 2.1 Hz), 126.3 (q, *J* = 33 Hz), 119.7 (q, *J* = 4.1 Hz), 125.2, 118.3, 108.3, 47.2, 33.1, 26.5, 23.4, 12.8.

Ethyl 3-(2-Cyanoethyl)-1,3-dimethyl-2-oxoindoline-5-carboxylate (4j)[12]

Yield: 74.3 mg (52%); yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (dd, *J* = 8.0, 0.8 Hz, 1 H), 7.83 (s, 1 H), 6.89 (d, *J* = 8.4 Hz, 1 H), 4.36 (q, *J* = 7.6 Hz, 2 H), 3.23 (s, 3 H), 2.38–2.26 (s, 1 H), 2.14–1.97 (m, 3 H), 1.40 (s, 3 H), 1.39 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 179.2, 166.1, 147.2, 131.7, 131.4, 125.3, 123.9, 118.5, 108.1, 61.1, 47.2, 33.2, 26.6, 23.5, 14.4, 12.9.

3-(1,3,6-Trimethyl-2-oxoindolin-3-yl)propanenitrile (4k) and 3-(1,3,4-Trimethyl-2-oxoindolin-3-yl)propanenitrile (4k')[12]

Yield **4k**/**4k'** (1:2): 93.4 mg (82%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20 (t, *J* = 7.6 Hz, 2 H), 7.06 (d, *J* = 7.6 Hz, 1 H), 6.94–6.83 (m, 3 H), 6.71–6.66 (m, 3 H), 3.20 (s, 6 H), 3.19 (s, 3 H), 2.38 (s, 6 H), 2.37 (s, 3 H), 2.42–2.23 (m, 3 H), 2.09–1.85 (m, 9 H), 1.45 (s, 6 H), 1.36 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 179.2, 178.9, 143.4, 143.2, 138.9, 134.4, 128.6, 128.5, 128.1, 125.5, 123.5, 122.3, 118.8, 118.6, 109.4, 106.3, 48.4, 47.1, 32.5, 31.5, 25.4, 25.2, 23.5, 21.8, 18.1, 13.0, 12.8.

3-(1,3,7-Trimethyl-2-oxoindolin-3-yl)propanenitrile (4l)[12]

Yield: 83.2 mg (73%); yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.06–6.95 (m, 3 H), 3.49 (s, 3 H), 2.58 (s, 3 H), 2.36–2.26 (m, 1 H), 2.12–1.91 (m, 3 H), 1.36 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 179.6, 140.9, 132.3, 122.9, 120.4, 120.2, 118.9, 108.2, 46.6, 33.7, 29.6, 23.9, 19.0, 12.9.

3-(7-Methoxy-1,3-dimethyl-2-oxoindolin-3-yl)propanenitrile (4m)[12]

Yield: 96.4 mg (79%); yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.03 (t, *J* = 7.6 Hz, 1 H), 6.84 (d, *J* = 8.4 Hz, 1 H), 6.77 (d, *J* = 7.6 Hz, 1 H), 3.84 (s, 3 H), 3.46 (s, 3 H), 2.35–2.23 (m, 1 H), 2.11–1.91 (m, 3 H), 1.34 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 179.1, 145.6, 133.3, 130.8, 123.7, 118.9, 115.4, 112.3, 56.9, 47.4, 33.6, 29.6, 23.7, 12.8.

3-(4-Chloro-1,3,7-trimethyl-2-oxoindolin-3-yl)propanenitrile (4n)

Yield: 82.5 mg (63%); yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.96 (d, *J* = 8.4 Hz, 1 H), 6.89 (d, *J* = 8.0 Hz, 1 H), 3.48 (s, 3 H), 2.58–2.49 (m, 4 H), 2.39–2.29 (m, 1 H), 2.05–1.90 (m, 3 H), 1.49 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 179.2, 142.8, 133.6, 128.6, 127.8, 123.7, 118.9, 118.5, 48.4, 30.4, 29.8, 22.0, 21.7, 21.5, 18.9, 13.2.

MS (EI, 70 eV): *m*/*z* (%) = 262 ([M$^+$], 27), 208 (100).

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{16}ClN_2O$ [M + H]$^+$: 263.0951; found: 263.0948.

3-(5,6-Dichloro-1,3-dimethyl-2-oxoindolin-3-yl)propanenitrile (4o)

Yield: 71.9 mg (51%); yellow solid; mp 120–121 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 8.0 Hz, 1 H), 6.75 (d, *J* = 8.4 Hz, 1 H), 3.21 (s, 3 H), 2.57–2.48 (m, 1 H), 2.45–2.345 (m, 1 H), 2.12–1.95 (m, 2 H), 1.52 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 178.0, 143.3, 120.4, 129.3, 129.3, 127.4, 118.0, 107.7. 49.8, 30.1, 26.6, 21.1, 13.2.

MS (EI, 70 eV): *m*/*z* (%) = 282 ([M$^+$], 27), 228 (100).

HRMS (ESI): *m*/*z* calcd for $C_{13}H_{14}Cl_2N_2O$ [M + H]$^+$: 283.0400; found: 283.0403.

3-(1-Methyl-2-oxo-3-phenylindolin-3-yl)propanenitrile (4p)[12]

Yield: 106.3 mg (77%); yellowish solid; mp 106–107 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.25 (m, 7 H), 7.16 (t, *J* = 7.6 Hz, 1 H), 6.94 (d, *J* = 8.0 Hz, 1 H), 3.14 (s, 3 H), 2.87–2.76 (m, 1 H), 2.64–2.43 (m, 1 H), 2.15 (dt, *J* = 10.4, 6.0 Hz, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 177.3, 144.0, 138.7, 130.3, 129.2, 128.2, 126.9, 125.0, 123.5, 119.0, 10.2, 55.7, 33.5, 26.9, 13.4.

3-(1-Methyl-2-oxo-2,4,5,6-tetrahydro-1*H*-pyrrolo[3,2,1-*ij*]quinolin-1-yl)propanenitrile (4r)[12]

Yield: 74.4 mg (62%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.06–6.93 (m, 3 H), 3.74–3.65 (m, 2 H), 2.77 (t, *J* = 6.0 Hz, 2 H), 2.52–2.25 (m, 1 H), 2.13–1.95 (m, 5 H), 1.37 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 177.8, 138.9, 130.2, 127.4, 122.5, 120.7, 120.5, 118.9, 48.7, 38.9, 33.2, 24.5, 23.2, 21.1, 12.9.

3-(1,3-Dimethyl-2-oxo-2,3-dihydro-1*H*-pyrrolo[2,3-*c*]pyridin-3-yl)propanenitrile (4s)

Yield: 52.7 mg (49%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23 (d, *J* = 8.8 Hz, 1 H), 7.20 (dd, *J* = 8.0, 5.2 Hz, 1 H), 7.09 (d, *J* = 7.6 Hz, 1 H), 3.22 (s, 3 H), 2.34–2.10 (m, 4 H), 1.42 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 177.7, 163.1, 143.3, 138.3, 123.2, 118.6, 114.6, 43.3, 31.6, 26.1, 21.5, 12.7.

MS (EI, 70 eV): *m*/*z* (%) = 215 ([M$^+$], 27), 161 (100).

HRMS (ESI): *m*/*z* calcd for $C_{12}H_{14}N_3O$ [M + H]$^+$: 216.1132; found: 216.1136.

2-[(1,3-Dimethyl-2-oxoindolin-3-yl)methyl]pentanenitrile (4t)

Yield: 52.2 mg (43%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–6.95 (m, 4 H), 3.21 (s, 3 H), 2.37–1.89 (m, 3 H), 1.62–1.51 (m, 7 H), 0.85 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 179.4, 179.2, 143.4, 143.1, 132.2, 131.5, 128.5, 123.5, 123.0, 122.6, 122.4, 122.3, 121.0, 108.6, 108.4, 47.6, 46.9, 39.8, 35.2, 27.5, 27.0, 26.3, 24.9, 24.4, 19.9, 13.4.

MS (EI, 70 eV): *m*/*z* (%) = 256 ([M$^+$], 27), 160 (100).

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{21}N_2O$ [M + H]$^+$: 257.1649; found: 257.1646.

Spirocyclic Indole 6

A suspension of **3w** (150 mg, 0.5 mmol) and $LiAlH_4$ (76 mg, 2.0 mmol) in THF (10 mL) was stirred under a N_2 atmosphere at r.t. for 1 h, and then heated at reflux temperature for 0.5 h. The reaction was quenched with THF–H_2O (10:1, 2 mL) at 0 °C, and the resulting mixture was diluted with CH_2Cl_2 and filtered through a glass filter. The resulting precipitates were washed thoroughly with CH_2Cl_2 and the filtrate was concentrated in vacuo. The residue was dissolved in EtOAc (10 mL) and added aq 1 M HCl (5 mL). After stirring for 5 min, the solution was neutralized by adding solid K_2CO_3, and then extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), filtered through a Celite pad, and concentrated in vacuo. The residue was purified by flash column chromatography to give the title compound as a yellowish oil; yield: 105.1 mg (73%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.83–6.73 (m, 2 H), 6.41 (dd, *J* = 8.0, 4.0 Hz, 1 H), 3.87 (s, 1 H), 2.77 (s, 3 H), 2.69 (d, *J* = 12.8 Hz, 1 H), 2.58 (d, *J* = 12.8 Hz, 1 H), 1.97 (br, 1 H), 1.70–1.50 (m, 10 H), 1.39 (s, 3 H), 1.17–1.04 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.4 (d, *J* = 234.4 Hz), 146.5, 141.4, 113.5 (d, *J* = 23.4 Hz), 110.1 (d, *J* = 23.7 Hz), 107.9 (d, *J* = 7.1 Hz), 87.5, 49.1, 45.3, 41.4, 38.5, 35.9, 32.8, 32.1, 27.4, 26.9, 22.6, 22.3.

MS (EI, 70 eV): *m*/*z* (%) = 270 ([M$^+$], 100).

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{26}FN_2$ [M + H]$^+$: 289.2075; found: 289.2079.

Aliphatic Carboxylic Acid 7

A solution of **3a** (121 mg, 0.5 mmol) and NaOH (100 mg, 2.5 mmol) in ethylene glycol (5 mL) were stirred under a N_2 atmosphere at 110 °C for 12 h. Then, the reaction mixture was treated with aq 1 M HCl slowly at 0 °C until the pH of solution was between 2 and 3. The resulting mixture was extracted with EtOAc (3 × 20 mL), and the combined organic layers were washed with H_2O (10 mL) and brine (10 mL), and dried ($MgSO_4$). After concentration in vacuo, the residue was purified by flash chromatography on silica gel to afford the title compound as a white solid; yield: 88.7 mg (68%); mp 113–114 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.13 (m, 2 H), 6.88 (t, *J* = 7.6 Hz, 1 H), 6.80 (d, *J* = 8.0 Hz, 1 H), 3.19 (s, 3 H), 2.46 (d, *J* = 14.4 Hz, 1 H), 2.27 (d, *J* = 14.4 Hz, 1 H), 1.30 (s, 3 H), 1.07 (s, 3 H), 0.83 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 180.2, 178.0, 140.6, 129.1, 126.4, 121.9, 119.4, 105.5, 44.6, 44.2, 38.9, 26.1, 24.9, 23.7, 19.9.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{20}NO_3$ [M + H] $^+$: 262.1438; found: 262.1437.

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Supporting Information

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