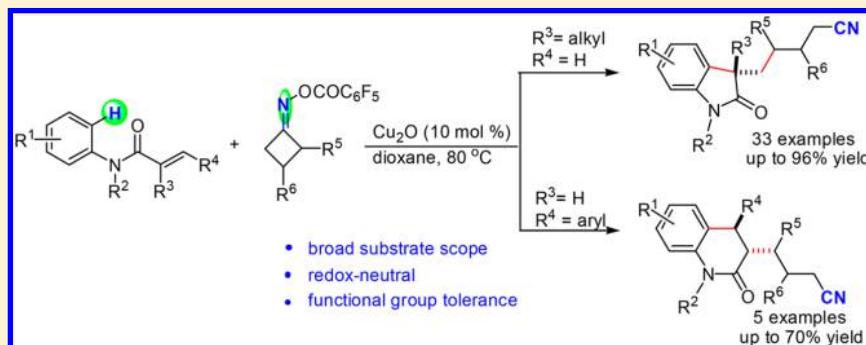


Copper-Catalyzed Redox-Neutral Cyanoalkylarylation of Activated Alkenes with Cyclobutanone Oxime Esters

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Supporting Information



ABSTRACT: The copper-catalyzed cyclization of activated alkenes with cyclobutanone *O*-acyl oximes under redox-neutral conditions has been reported. This facile protocol provided an efficient approach to a variety of cyanoalkylated oxindoles and dihydroquinolin-2(1*H*)-ones with a broad substrate scope and excellent functional group tolerance. In this reaction, sequential C–C bond cleavage, radical addition, and cyclization processes were involved, wherein multiple bonds were constructed in a one-pot reaction. Mechanistic studies suggest that the reaction probably proceeded via a radical pathway.

In modern organic synthesis, catalytic C–C bond activation reactions have become one of the most attractive research areas, which provide a novel strategy for C–C and C–heteroatom bond formations.¹ In this field, C–C bond cleavage of cyclobutanone oxime esters has proven to be an efficient protocol to access structurally diverse nitriles, which are important and versatile building blocks in organic chemistry as well as in medicinal chemistry.² In the early 1990s, Zard and co-workers reported a series of radical C–C bond cleavage of cyclobutanone derivatives under different conditions.³ Later on, Nishimura and Uemura et al. disclosed a palladium-catalyzed ring cleavage of cyclobutanone *O*-benzoyloximes through β -carbon elimination, which provided another alternative for the C–C bond activation of cyclobutanone derivatives.⁴ In recent years, the radical ring-opening of cyclobutanone oxime esters has attracted much attention and several important works have been reported, respectively.^{4c–f} In this aspect, we described a nickel-catalyzed direct C–H cyanoalkylation of heteroaromatic *N*-oxides and quinones with cyclobutanone *O*-acyl oximes via C–C bond cleavage.^{4f} Although some advances have been made, the studies on ring-opening reactions of cyclobutanone oxime esters are still at an early stage. It remains important to explore new catalytic systems and versatile transformations of the ring-opening cleavage of cyclobutanone oxime esters.

In recent years, the radical cyclization reactions have received considerable attention and have been developed as a powerful tool for the synthesis of structurally diverse

heterocycles.⁵ For instance, the cyclization of acrylamides with diverse radicals has been efficiently applied for the construction of functionalized oxindoles, which are important core structures in a wide range of bioactive natural products and pharmaceutical molecules.⁶ In these reactions, a variety of compounds including alcohols, aldehydes, ketones, benzyl hydrocarbons, alkanes, etc. have been successfully served as carbon-centered radical precursors through direct C–H bond cleavage.⁷ Furthermore, we and others have also developed the α -keto acids as acyl radical sources via the decarboxylative C–C bond cleavage process.⁸ In addition, our group has also successfully demonstrated the radical cyclization of acrylamides with tertiary cycloalkanols through C–C bond cleavage.⁹ Although these established protocols are useful and efficient, they still suffer from some limitations including the use of noble metals and harsh reaction conditions (high temperature and strong oxidants). As we know, the ring-opening cleavage of cyclobutanone oxime esters could lead to reactive γ -cyanoalkyl radicals through single-electron reduction.^{3,4} Thus, we believed that it is possible to achieve the cyclization of *N*-arylacrylamides with cyclobutanone *O*-acyl oximes under redox-neutral reaction conditions. Herein, we wish to report an efficient Cu-catalyzed radical cyclization of

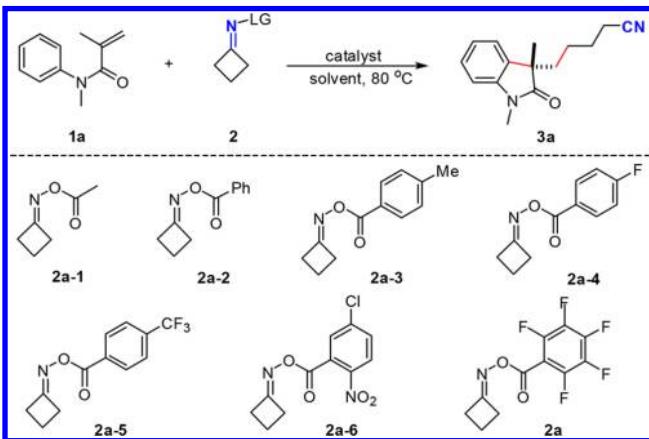
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N-arylacrylamides with cyclobutanone O-acyl oximes. In this reaction, no external oxidants are required.

Initially, the reactions of *N*-methyl-*N*-phenylmethacrylamide (**1a**) with various cyclobutanone O-acyloximes **2** were examined in the presence of a catalyst. To our delight, treatment of **1a** with cyclobutanone O-acyl oximes **2a–1** in the presence of 10 mol % Cu₂O in dioxane at 80 °C afforded the desired oxindole **3a** in 50% yield (Table 1, entry 1).

Table 1. Optimization of the Reaction Conditions^a



entry	2	catalyst (mol %)	solvent	yield (%) ^b
1	2a-1	Cu ₂ O (10%)	dioxane	50
2	2a-2	Cu ₂ O (10%)	dioxane	43
3	2a-3	Cu ₂ O (10%)	dioxane	15
4	2a-4	Cu ₂ O (10%)	dioxane	53
5	2a-5	Cu ₂ O (10%)	dioxane	55
6	2a-6	Cu ₂ O (10%)	dioxane	52
7	2a	Cu ₂ O (10%)	dioxane	65
8	2a	CuCl (10%)	dioxane	17
9	2a	CuBr (10%)	dioxane	26
10	2a	Cu(OAc) ₂ (10%)	dioxane	28
11	2a	CuO (10%)	dioxane	20
12	2a	Fe(OAc) ₂ (10%)	dioxane	45
13	2a	FeBr ₂ (10%)	dioxane	41
14	2a	Cu ₂ O (10%)	diglyme	trace
15	2a	Cu ₂ O (10%)	toluene	23
16	2a	Cu ₂ O (10%)	PhCF ₃	24
17	2a	Cu ₂ O (10%)	EtOAc	31
18	2a	Cu ₂ O (10%)	DME	49
19	2a	Cu ₂ O (5%)	dioxane	61
20	2a	Cu ₂ O (15%)	dioxane	67
21	2a	Cu ₂ O (10%)	dioxane	43 ^c
22	2a	Cu ₂ O (10%)	dioxane	54 ^d

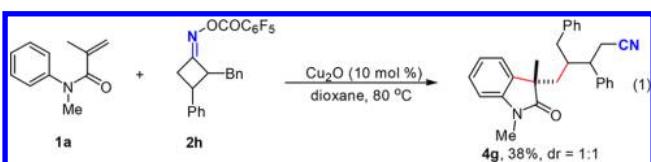
^aReaction conditions: catalyst (10 mol %), **1a** (0.2 mmol, 1.0 equiv), **2** (0.24 mmol, 1.2 equiv), solvent (2 mL) at 80 °C for 24 h under nitrogen. ^bYield of isolated product. ^cAt 50 °C. ^dAt 100 °C.

The use of *O*-benzyloxime **2a-2** also led to a similar yield (entry 2). However, only 15% yield of **3a** was obtained when cyclobutanone *O*-acyl oxime **2a-3** was used, implying that the electron-rich substituent might disfavor this tandem radical cyclization reaction (entry 3). Thus, several *O*-aroxyloximes having an electron-withdrawing group at the aromatic moiety were subjected to this reaction (entries 4–7). As expected, the more electron-deficient cyclobutanone pentafluorobenzoyloxime **2a** gave the best result. Further investigation revealed that Cu₂O is a superior catalyst compared with other

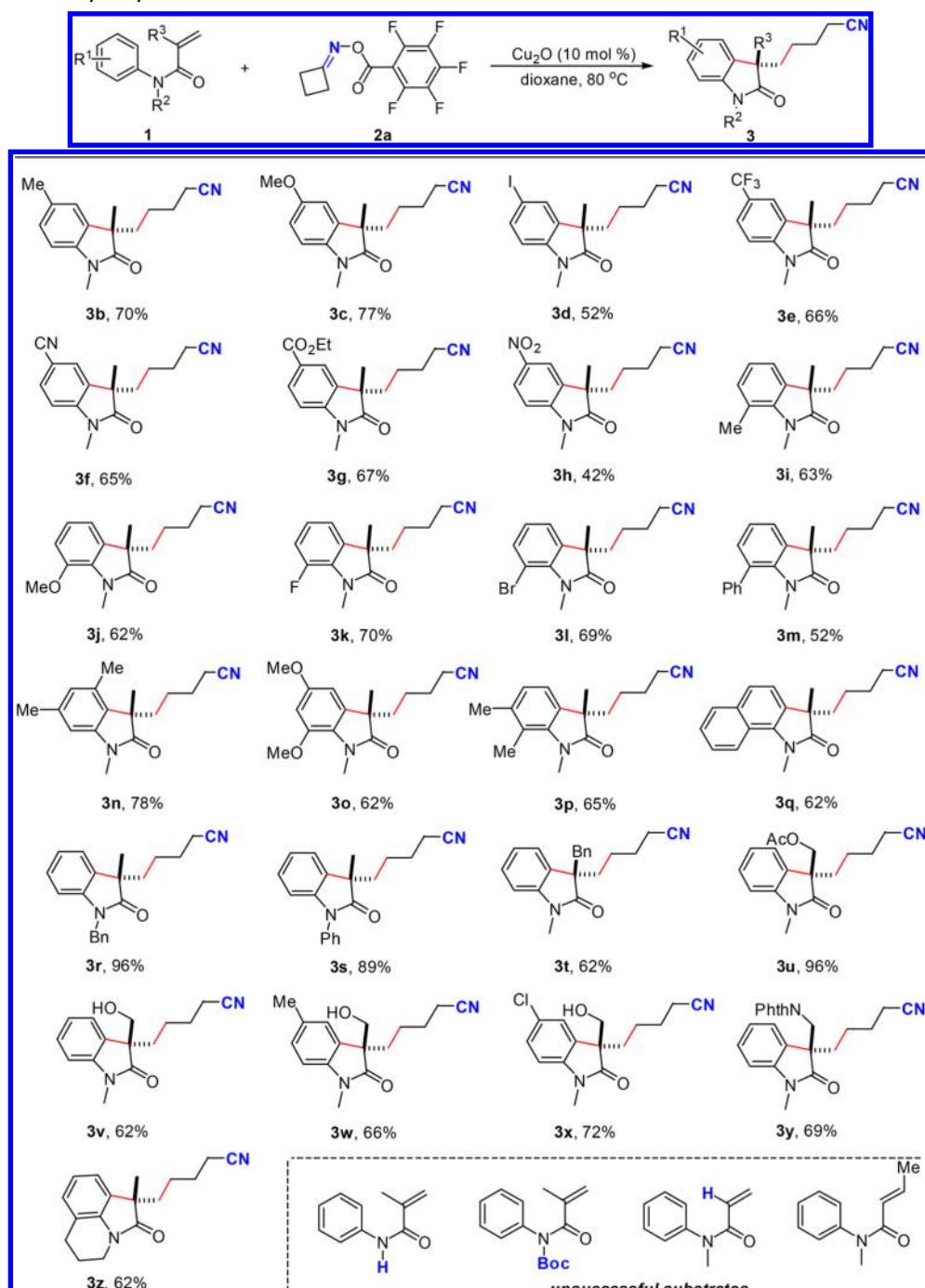
copper and iron catalysts (entries 8–13). Among the solvents screened, dioxane was found to be the optimal one (entries 14–18). Decreasing the Cu₂O loading to 5 mol % or increasing it to 15 mol % both resulted in comparable yields (entries 19 and 20). Finally, it was found that the reaction efficiency was also affected by temperature, and 80 °C was found to be optimal (entries 21 and 22).

With the optimized reaction conditions in hand, we first examined the scope of the *N*-arylacrylamides (Table 2). Generally, *N*-arylacrylamides bearing electron-donating or electron-withdrawing substituents on the *para* position of the anilides worked well with **2a** to give the corresponding oxindoles **3b–h** in moderate to good yields. Notably, a series of functional groups such as iodo, cyano, ester, and nitro groups were fully compatible with the reaction conditions, which offers good opportunities for further functionalization of the oxindoles (**3d**, **3f–h**). Furthermore, the sterically congested, *ortho*-substituted *N*-arylacrylamides were also efficiently annulated with **2a** to afford the corresponding products **3i–m** in 52–70% yields. Polysubstituted acrylamides **1n–p** also participated well in the reaction to give the corresponding oxindoles in good yields. *N*-Methyl-*N*-naphthylacrylamide also reacted smoothly with **2a**, producing the desired product **3q** in 62% yield. In addition, acrylamides containing a benzyl- or phenyl-protecting group on the *N* tether were also suitable substrates, providing the oxindoles **3r** and **3s** in 96% and 89% yields, respectively. Besides the methyl group, acrylamides having a benzyl, acetoxyethyl, hydroxymethyl, or phthalimide group at the *α*-position of the acrylamide moiety also delivered the corresponding products **3t–y** in 62–96% yields. When substrate **1z** derived from tetrahydroisoquinoline was subjected to the reaction, the corresponding tricyclic oxindole derivative **3z** was obtained in 62% yield. However, unprotected, Boc-protected acrylamides and *N*-methyl-*N*-phenyl-2-butenamide did not furnish any desired products under the reaction conditions. It should be noted that the substituent at the *α*-position of acrylamide is essential for the success of this reaction.

Encouraged by the above results, we next investigated the scope of cyclobutanone *O*-acyl oximes **2** under optimal conditions. As shown in Table 3, the reaction of 3-phenyl cyclobutanone oxime ester with **1a** furnished the desired oxindole **4a** in 68% yield. Moreover, the electron-withdrawing or electron-donating group on the *para* position of the phenyl ring did not affect the reaction efficiency and afforded the corresponding products **4b–e** in good yields. Notably, 3-oxetanone oxime ester could also deliver the desired product **4f**, albeit in a somewhat low yield. Unfortunately, the less-strained substrates derived from cyclopentanone and camphor failed to give any desired products. In addition, cyclobutanone oxime ester having 2,3-disubstituted groups produced the corresponding product **4g** in 38% yield with excellent regioselectivity (eq 1).



To further expand the scope of this protocol, we focused our attention to other activated alkenes, such as cinnamamides **5** (Table 4). Satisfactorily, the reaction of *N*-methyl-*N*-

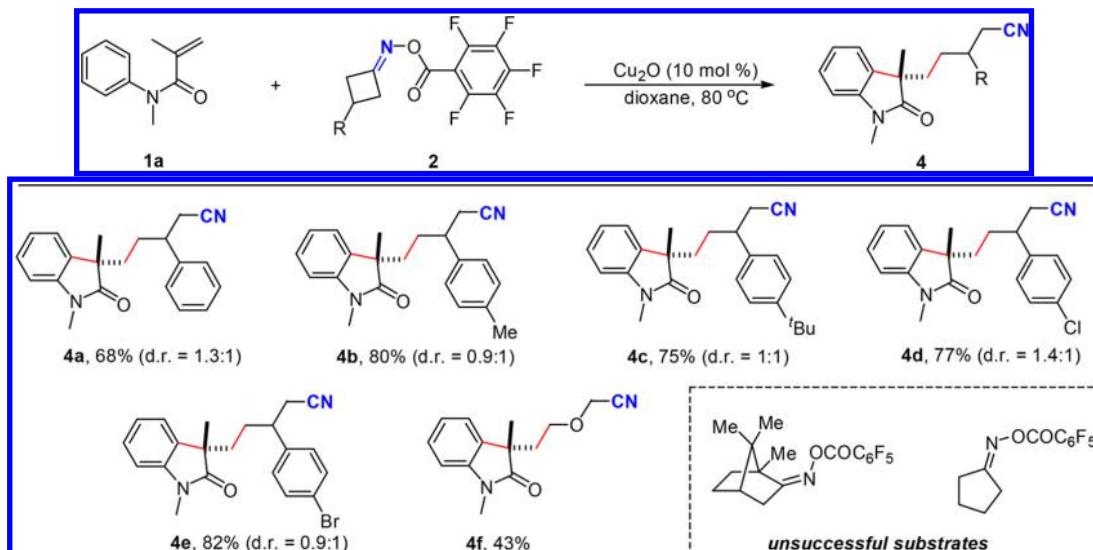
Table 2. Scope of *N*-Arylacrylamides^a

^aReaction conditions: 10 mol % Cu₂O, acrylamide **1** (0.2 mmol, 1 equiv), cyclobutanone O-acyl oxime **2a** (0.24 mmol, 1.2 equiv), dioxane (2.0 mL) at 80 °C for 24 h under nitrogen. Yield of isolated product.

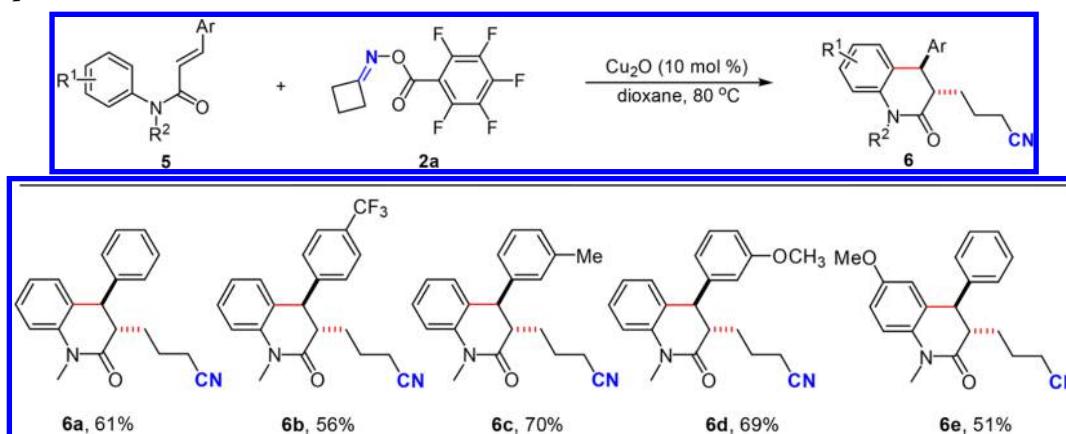
phenylcinnamamide **5a** with **2a** gave the desired dihydroquinolin-2(1*H*)-one **6a** in 61% yield under the present conditions. Substrates having electron-rich or electron-poor groups on the cinnamic acid moiety also furnished the desired products in moderate to good yields (**6b–d**). Additionally, cinnamamide containing a methoxyl group at the *para* position of the anilide moiety was also the effective substrate to afford the desired product **6e** in 51% yield. Remarkably, all of these reactions exhibited excellent stereoselectivities, giving the *anti*-isomers as sole products.

To probe the synthetic utility of the oxindole product, some derivatization reactions of product **3a** were performed (Scheme 1). The CN group of **3a** could easily be converted to the corresponding carboxylic acid **7a** in 78% yield via basic hydrolysis. In addition, the CN group could also undergo [3+2] cycloaddition reaction with NaN₃ to give the tetrazole **8a** in 42% yield in the presence of ZnCl₂.

To gain some insight into the reaction mechanism, several control experiments were conducted. When 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), a well-known radical-trapping reagent, was added to the reaction of **1a** and **2a**, only a

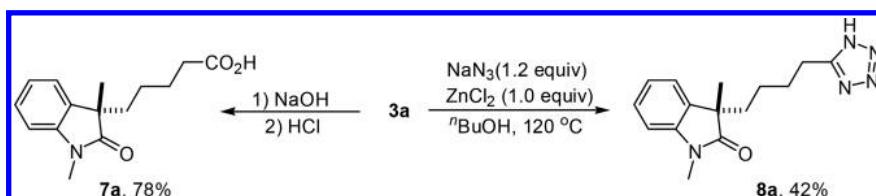
Table 3. Scope of Cyclobutanone O-Acyl Oximes^a

^aReaction conditions: 10 mol % Cu₂O, acrylamide **1a** (0.2 mmol, 1 equiv), cyclobutanone O-acyl oxime **2** (0.24 mmol, 1.2 equiv), dioxane (2.0 mL) at 80 °C for 24 h under nitrogen. Yield of isolated product.

Table 4. Scope of Cinnamamides^a

^aReaction conditions: 10 mol % Cu₂O, cinnamamides **5** (0.2 mmol, 1 equiv), cyclobutanone O-acyl oxime **2a** (0.24 mmol, 1.2 equiv), dioxane (2.0 mL) at 80 °C for 24 h under nitrogen. Yield of isolated product. Only *trans* isomers were observed. For details, see the Supporting Information.

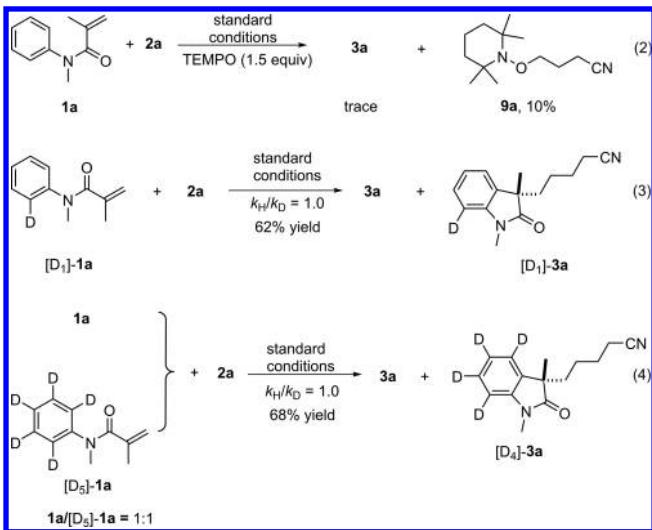
Scheme 1. Derivatization of Product 3a



trace amount of **3a** was observed along with TEMPO-CH₂CH₂CH₂CN **9a** isolated in 10% yield (*eq 2*). The adduct **9a** was also obtained in 42% yield in the absence of **1a**. (For details, see the Supporting Information.) These results suggest that the γ -cyanoalkyl radical intermediate should be involved in the reaction. Then, the intra- and intermolecular kinetic isotope effect (KIE) experiments were performed under the standard conditions, and negligible KIEs ($k_H/k_D = 1.0$) for the intra- and intermolecular competition experiments were observed, respectively (*eq 3* and *eq 4*). On the basis of these results and previous reports,^{3–6} a possible mechanism is proposed in Scheme 2. First, single-electron

transfer (SET) from Cu(I) catalyst to **2a** gives the iminyl radical **I**,¹⁰ which undergoes C–C bond cleavage and rearrangement to form γ -cyanoalkyl radical **II**. Subsequently, the radical **II** attacks to the C=C bond of acrylamide to generate a new tertiary alkyl radical **III**, which undergoes an intramolecular cyclization to give radical intermediate **IV**. Finally, a Cu(II)-promoted single-electron oxidation of radical **IV** into the corresponding carbocation **V**, followed by the loss of H⁺, leads to the desired product **3a** and regenerates Cu(I).

In summary, we have developed a simple and efficient copper-catalyzed cyanoalkylation of activated alkenes. A



series of cyanoalkyl groups with long aliphatic chains have been successfully incorporated in diverse oxindoles and dihydroquinolin-2(1*H*)-ones via a tandem ring-opening and ring-closing process. Besides a broad substrate scope and excellent functional group tolerance, the most remarkable feature of this protocol is avoiding the use of stoichiometric amounts of external oxidants. Mechanistic investigation indicates that the γ -cyanoalkyl radical intermediate should be involved in this transformation.

EXPERIMENTAL SECTION

General Methods. All reactions were carried out in oven-dried Schlenk tubes filled with nitrogen. Column chromatography was carried out on silica gel. ^1H NMR and ^{13}C NMR spectra were recorded on a 400 M spectrometer in solvents as indicated. Chemical shifts are reported in ppm with the solvent resonance as internal standard (CDCl_3 , ^1H NMR δ 7.26; ^{13}C NMR δ 77.0). IR spectra were recorded on a spectrometer, and only major peaks were reported in cm^{-1} . HRMS were obtained on a Q-TOF micro spectrometer. All of the acrylamides **1** were synthesized according to the literature, and the NMR spectra were in full accordance with the data in the literature.¹¹ All of the cyclobutanone *O*-acyl oximes **2** were synthesized from the corresponding cyclobutanones and carboxylic acids according to the literature.^{4b} The substituted cyclobutanones were prepared according to the reported procedure.¹² All of the commercially available compounds were used without further purification.

General Procedure for the Cyclization of Acrylamides with Cyclobutanone *O*-acyl oximes. Acrylamides **1** (0.2 mmol, 1.0 equiv), Cu_2O (2.8 mg, 10 mol %), and cyclobutanone *O*-acyl oximes **2** (0.24 mmol, 1.2 equiv) were added into an oven-dried Schlenk

tube. The tube was evacuated and backfilled with nitrogen (three times). Then, dioxane (2.0 mL) was injected into the tube by syringe. The reaction mixture was then stirred at 80 °C for 24 h. The resulting mixture was diluted with EtOAc , and the organic phase was washed successively with H_2O (three times) and brine (one time), then dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient eluent of $\text{EtOAc}/\text{petroleum ether}$ 1:20 to 1:10) to give the corresponding products **3** or **4** in yields listed in Tables 2 and 3.

5-(1,3-Dimethyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-pentanenitrile (3a): colorless liquid (65%, 31.5 mg); R_f 0.20 ($\text{EtOAc}/\text{petroleum ether}$ = 1:3); ^1H NMR (400 MHz, CDCl_3) δ 7.25–7.20 (m, 1H), 7.12 (dd, J = 7.2, 0.8 Hz, 1H), 7.02 (td, J = 7.6, 0.8 Hz, 1H), 6.81 (d, J = 8.0 Hz, 1H), 3.17 (s, 3H), 2.18–2.14 (m, 2H), 1.91–1.83 (m, 1H), 1.76–1.68 (m, 1H), 1.53–1.43 (m, 2H), 1.30 (s, 3H), 1.07–0.97 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 180.0, 142.9, 133.2, 127.7, 122.4, 122.2, 119.2, 107.9, 47.9, 37.1, 25.9, 25.2, 23.6, 23.5, 16.6 ppm; IR (KBr) ν_{max} 2245, 1719, 1614, 1497, 1342, 1261 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{18}\text{N}_2\text{NaO}$ [$\text{M} + \text{Na}]^+$ 265.1311, found 265.1322.

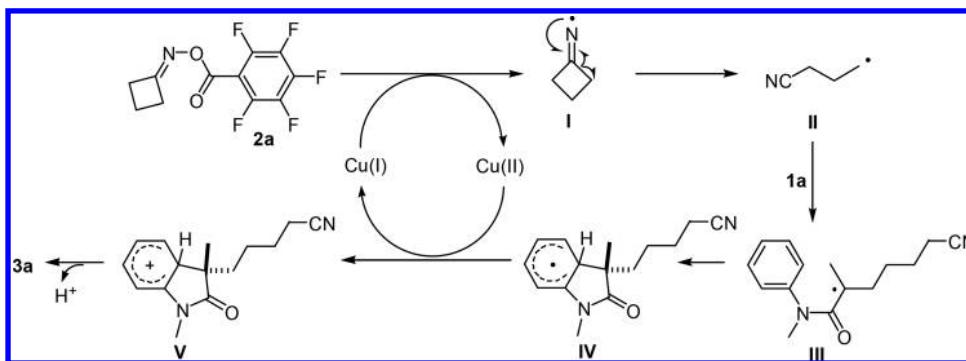
5-(1,3,5-Trimethyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-pentanenitrile (3b): colorless liquid (70%, 35.9 mg); R_f 0.5 ($\text{EtOAc}/\text{petroleum ether}$ = 1:1); ^1H NMR (400 MHz, CDCl_3) δ 7.07 (dd, J = 8.0, 0.8 Hz, 1H), 6.97 (s, 1H), 6.74 (d, J = 7.6 Hz, 1H), 3.19 (s, 3H), 2.35 (s, 3H), 2.24–2.19 (m, 2H), 1.94–1.87 (m, 1H), 1.77–1.69 (m, 1H), 1.58–1.59 (m, 2H), 1.33 (s, 3H), 1.10–1.02 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 180.3, 140.8, 133.5, 132.2, 128.1, 123.2, 119.4, 107.8, 48.2, 37.4, 26.2, 25.4, 23.9, 23.8, 21.1, 16.8 ppm; IR (KBr) ν_{max} 2245, 1710, 1620, 1499, 1350, 1245 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{21}\text{N}_2\text{O}$ [$\text{M} + \text{H}]^+$ 257.1643, found 257.1648.

5-(5-Methoxy-1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-pentanenitrile (3c): colorless liquid (77%, 41.9 mg); R_f 0.3 ($\text{EtOAc}/\text{petroleum ether}$ = 1:1); ^1H NMR (400 MHz, CDCl_3) δ 6.80–6.74 (m, 3H), 3.80 (s, 3H), 3.19 (s, 3H), 2.23–2.19 (m, 2H), 1.96–1.88 (m, 1H), 1.76–1.69 (m, 1H), 1.56–1.48 (m, 2H), 1.34 (s, 3H), 1.08–1.01 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 180.1, 156.2, 136.6, 134.9, 119.4, 111.7, 110.2, 108.4, 55.7, 48.6, 37.4, 26.2, 25.4, 23.9, 23.7, 16.8 ppm; IR (KBr) ν_{max} 2245, 1701, 1600, 1497, 1356, 1289, 1219 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{21}\text{N}_2\text{O}_2$ [$\text{M} + \text{H}]^+$ 273.1598, found 273.1599.

5-(5-Iodo-1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-pentanenitrile (3d): colorless liquid (52%, 38.3 mg); R_f 0.2 ($\text{EtOAc}/\text{petroleum ether}$ = 1:3); ^1H NMR (400 MHz, CDCl_3) δ 7.59 (dd, J = 8.0, 1.6 Hz, 1H), 7.43 (d, J = 1.6 Hz, 1H), 6.64 (d, J = 8.4 Hz, 1H), 3.19 (s, 3H), 2.23 (t, J = 7.2 Hz, 2H), 1.95–1.87 (m, 1H), 1.75–1.68 (m, 1H), 1.58–1.51 (m, 2H), 1.34 (s, 3H), 1.08–1.02 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 179.5, 143.0, 136.8, 136.0, 131.3, 119.3, 110.2, 85.2, 48.2, 37.4, 26.2, 25.4, 23.8, 23.7, 16.9 ppm; IR (KBr) ν_{max} 2247, 1710, 1602, 1487, 1415, 1340, 1261 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{17}\text{IN}_2\text{NaO}$ [$\text{M} + \text{Na}]^+$ 391.0278, found 391.0275.

5-(1,3-Dimethyl-2-oxo-5-trifluoromethyl-2,3-dihydro-1*H*-indol-3-yl)-pentanenitrile (3e): colorless liquid (66%, 41.0 mg); R_f 0.40

Scheme 2. Proposed Mechanism



(EtOAc/petroleum ether = 1:1); ^1H NMR (400 MHz, CDCl_3) δ 7.56 (dd, $J = 8.0, 0.8$ Hz, 1H), 7.38 (d, $J = 1.2$ Hz, 1H), 6.92 (d, $J = 8.4$ Hz, 1H), 3.24 (s, 3H), 2.22 (t, $J = 7.2$ Hz, 2H), 1.99–1.91 (m, 1H), 1.82–1.74 (m, 1H), 1.59–1.50 (m, 2H), 1.37 (s, 3H), 1.11–0.93 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 180.1, 146.2, 134.1, 125.8, 125.7, 124.4 (q, $J_{\text{C}-\text{F}} = 260.2$ Hz), 123.0, 119.4, 119.3, 119.2, 107.9, 48.1, 37.3, 26.3, 25.3, 23.7, 23.6, 16.8 ppm; IR (KBr) ν_{max} 2246, 1721, 1623, 1461, 1326, 1256 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{17}\text{F}_3\text{N}_2\text{NaO}$ [M + Na]⁺ 333.1185, found 333.1184.

3-(4-Cyano-butyl)-1,3-dimethyl-2-oxo-2,3-dihydro-1H-indole-5-carbonitrile (3f**):** colorless liquid (65%, 34.7 mg); R_f 0.3 (EtOAc/petroleum ether = 1:1); ^1H NMR (400 MHz, CDCl_3) δ 7.61 (dd, $J = 8.0, 1.6$ Hz, 1H), 7.41 (d, $J = 1.2$ Hz, 1H), 6.92 (d, $J = 8.0$ Hz, 1H), 3.24 (s, 3H), 2.23 (t, $J = 7.2$ Hz, 2H), 1.98–1.91 (m, 1H), 1.80–1.73 (m, 1H), 1.59–1.50 (m, 2H), 1.37 (s, 3H), 1.11–0.97 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 179.9, 147.0, 134.5, 133.4, 125.8, 119.2, 119.1, 108.6, 105.8, 48.0, 37.2, 26.4, 25.2, 23.6, 16.8 ppm; IR (KBr) ν_{max} 2245, 2222, 1719, 1614, 1496, 1460, 1342, 1260 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{17}\text{N}_3\text{NaO}$ [M + Na]⁺ 290.1264, found 290.1274.

3-(4-Cyano-butyl)-1,3-dimethyl-2-oxo-2,3-dihydro-1H-indole-5-carboxylic Acid Ethyl Ester (3g**):** colorless liquid (67%, 42.1 mg); R_f 0.5 (EtOAc/petroleum ether = 1:1); ^1H NMR (400 MHz, CDCl_3) δ 8.03 (dd, $J = 8.0, 1.6$ Hz, 1H), 7.82 (d, $J = 1.6$ Hz, 1H), 6.88 (d, $J = 8.0$ Hz, 1H), 4.40–4.34 (m, 2H), 3.24 (s, 3H), 2.20 (t, $J = 7.2$ Hz, 2H), 1.98–1.91 (m, 1H), 1.83–1.76 (m, 1H), 1.58–1.49 (m, 2H), 1.42–1.37 (m, 6H), 1.10–0.96 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 180.5, 166.4, 147.2, 133.4, 130.6, 124.9, 123.6, 119.3, 107.6, 60.9, 48.0, 37.3, 26.3, 25.4, 23.8, 23.7, 16.8, 14.4 ppm; IR (KBr) ν_{max} 2245, 1716, 1616, 1498, 1458, 1374, 1346, 1267, 1236 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{22}\text{N}_2\text{NaO}_3$ [M + Na]⁺ 337.1523, found 337.1521.

5-(1,3-Dimethyl-5-nitro-2-oxo-2,3-dihydro-1H-indol-3-yl)-pentanenitrile (3h**):** colorless liquid (42%, 24.1 mg); R_f 0.2 (EtOAc/petroleum ether = 1:3); ^1H NMR (400 MHz, CDCl_3) δ 8.27 (dd, $J = 8.8, 2.4$ Hz, 1H), 8.06 (d, $J = 2.4$ Hz, 1H), 6.94 (d, $J = 8.8$ Hz, 1H), 3.29 (s, 3H), 2.24 (t, $J = 7.2$ Hz, 2H), 2.03–1.95 (m, 1H), 1.86–1.79 (m, 1H), 1.61–1.52 (m, 2H), 1.41 (s, 3H), 1.12–1.00 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 180.3, 148.8, 143.5, 134.3, 125.4, 119.1, 118.3, 107.7, 48.2, 37.3, 26.6, 25.2, 23.7, 23.6, 16.9 ppm; IR (KBr) ν_{max} 2245, 1725, 1613, 1519, 1495, 1461, 1335, 1293 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{18}\text{N}_3\text{O}_3$ [M + H]⁺ 288.1343, found 288.1343.

5-(1,3,7-Trimethyl-2-oxo-2,3-dihydro-1H-indol-3-yl)-pentanenitrile (3i**):** colorless liquid (63%, 32.3 mg); R_f 0.5 (EtOAc/petroleum ether = 1:3); ^1H NMR (400 MHz, CDCl_3) δ 7.00–6.93 (m, 3H), 3.50 (s, 3H), 2.59 (s, 3H), 2.23–2.19 (m, 2H), 1.95–1.87 (m, 1H), 1.75–1.68 (m, 1H), 1.58–1.48 (m, 2H), 1.32 (s, 3H), 1.07–0.98 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 181.0, 140.9, 134.1, 131.6, 122.6, 120.3, 119.7, 119.4, 47.4, 37.7, 29.5, 25.4, 24.3, 23.8, 19.0, 16.8 ppm; IR (KBr) ν_{max} 2245, 1705, 1601, 1460, 1365, 1338, 1244 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{20}\text{N}_2\text{NaO}$ [M + Na]⁺ 279.1468, found 279.1465.

5-(7-Methoxy-1,3-dimethyl-2-oxo-2,3-dihydro-1H-indol-3-yl)-pentanenitrile (3j**):** colorless liquid (62%, 33.8 mg); R_f 0.5 (EtOAc/petroleum ether = 1:1); ^1H NMR (400 MHz, CDCl_3) δ 7.03–6.99 (m, 1H), 6.83 (d, $J = 8.0$ Hz, 1H), 6.77 (dd, $J = 7.6, 0.8$ Hz, 1H), 3.86 (s, 3H), 3.48 (s, 3H), 2.28–2.18 (m, 2H), 1.94–1.87 (m, 1H), 1.75–1.67 (m, 1H), 1.58–1.48 (m, 2H), 1.32 (s, 3H), 1.09–0.99 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 180.5, 145.3, 135.2, 130.9, 123.2, 119.4, 115.0, 111.6, 55.8, 48.2, 37.5, 29.4, 25.4, 24.2, 23.8, 16.8 ppm; IR (KBr) ν_{max} 2245, 1700, 1653, 1615, 1491, 1473, 1364, 1338, 1259 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{20}\text{N}_2\text{NaO}_2$ [M + Na]⁺ 295.1417, found 295.1415.

5-(7-Fluoro-1,3-dimethyl-2-oxo-2,3-dihydro-1H-indol-3-yl)-pentanenitrile (3k**):** colorless liquid (70%, 36.4 mg); R_f 0.3 (EtOAc/petroleum ether = 1:3); ^1H NMR (400 MHz, CDCl_3) δ 7.01–6.93 (m, 3H), 3.42 (d, $J = 2.8$ Hz, 3H), 2.28–2.16 (m, 2H), 1.96–1.89 (m, 1H), 1.78–1.70 (m, 1H), 1.59–1.49 (m, 2H), 1.35 (s, 3H), 1.11–1.01 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 179.9, 147.7

($J = 242.3$ Hz), 136.5 ($J = 2.9$ Hz), 129.7 ($J = 7.9$ Hz), 123.2 ($J = 6.2$ Hz), 119.3, 118.2 ($J = 3.2$ Hz), 115.9 ($J = 19.1$ Hz), 48.5 ($J = 1.4$ Hz), 37.5, 28.6 ($J = 5.6$ Hz), 25.3, 24.1, 23.7, 16.8 ppm; IR (KBr) ν_{max} 2246, 1716, 1634, 1488, 1372, 1338, 1261, 1236, 1101 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{17}\text{FN}_2\text{NaO}$ [M + Na]⁺ 283.1217, found 283.1216.

5-(7-Bromo-1,3-dimethyl-2-oxo-2,3-dihydro-1H-indol-3-yl)-pentanenitrile (3l**):** colorless liquid (69%, 44.3 mg); R_f 0.4 (EtOAc/petroleum ether = 1:3); ^1H NMR (400 MHz, CDCl_3) δ 7.37 (dd, $J = 8.0, 1.2$ Hz, 1H), 7.07 (dd, $J = 7.2, 0.8$ Hz, 1H), 6.91 (dd, $J = 8.0, 7.2$ Hz, 1H), 3.59 (s, 3H), 2.28–2.18 (m, 2H), 1.97–1.89 (m, 1H), 1.76–1.69 (m, 1H), 1.59–1.49 (m, 2H), 1.34 (s, 3H), 1.07–1.01 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 180.6, 140.5, 136.7, 133.6, 123.8, 121.4, 119.3, 102.5, 47.9, 37.6, 29.7, 25.4, 24.3, 23.7, 16.8 ppm; IR (KBr) ν_{max} 2245, 1716, 1606, 1576, 1457, 1365, 1332, 1251 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{17}\text{BrN}_2\text{NaO}$ [M + Na]⁺ 343.0416, found 343.0406.

5-(1,3-Dimethyl-2-oxo-7-phenyl-2,3-dihydro-1H-indol-3-yl)-pentanenitrile (3m**):** colorless liquid (52%, 33.1 mg); R_f 0.3 (EtOAc/petroleum ether = 1:3); ^1H NMR (400 MHz, CDCl_3) δ 7.41–7.34 (m, 5H), 7.17–7.08 (m, 3H), 2.73 (s, 3H), 2.27–2.21 (m, 2H), 1.99–1.92 (m, 1H), 1.82–1.75 (m, 1H), 1.62–1.52 (m, 2H), 1.40 (s, 3H), 1.18–1.08 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 181.3, 140.1, 138.9, 134.5, 130.9, 129.9, 127.8, 127.6, 125.5, 121.9, 121.4, 119.4, 47.4, 37.7, 30.1, 25.4, 24.2, 23.7, 16.9 ppm; IR (KBr) ν_{max} 2245, 1716, 1598, 1457, 1337, 1260 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{22}\text{N}_2\text{NaO}$ [M + Na]⁺ 341.1624, found 341.1620.

5-(1,3,4,6-Tetramethyl-2-oxo-2,3-dihydro-1H-indol-3-yl)-pentanenitrile (3n**):** colorless liquid (78%, 42.2 mg); R_f 0.3 (EtOAc/petroleum ether = 1:3); ^1H NMR (400 MHz, CDCl_3) δ 6.66 (s, 1H), 6.52 (s, 1H), 3.19 (s, 3H), 2.34 (s, 3H), 2.31 (s, 3H), 2.26–2.17 (m, 2H), 1.99–1.95 (m, 2H), 1.60–1.46 (m, 2H), 1.40 (s, 3H), 0.98–0.90 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 180.7, 143.5, 137.8, 133.7, 127.0, 125.7, 119.4, 106.9, 49.0, 35.4, 26.2, 25.4, 24.2, 22.5, 21.5, 18.0, 16.8 ppm; IR (KBr) ν_{max} 2246, 1716, 1620, 1457, 1335, 1297, 1240 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{23}\text{N}_2\text{O}$ [M + H]⁺ 341.1620, found 341.1620.

5-(5,7-Dimethoxy-1,3-dimethyl-2-oxo-2,3-dihydro-1H-indol-3-yl)-pentanenitrile (3o**):** colorless liquid (62%, 37.5 mg); R_f 0.20 (EtOAc/petroleum ether = 1:3); ^1H NMR (400 MHz, CDCl_3) δ 6.41 (d, $J = 2.4$ Hz, 1H), 6.35 (d, $J = 2.0$ Hz, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.43 (s, 3H), 2.26–2.17 (m, 2H), 1.93–1.86 (m, 1H), 1.71–1.64 (m, 1H), 1.58–1.48 (m, 2H), 1.31 (s, 3H), 1.08–1.00 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 180.1, 156.7, 145.9, 135.8, 124.4, 119.5, 100.2, 98.8, 55.8, 48.8, 37.6, 29.3, 25.4, 24.3, 23.8, 16.8 ppm; IR (KBr) ν_{max} 2245, 1699, 1607, 1496, 1457, 1363, 1331, 1266, 1208, 1154, 1103, 1038 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{23}\text{N}_2\text{O}_3$ [M + H]⁺ 303.1703, found 303.1696.

5-(1,3,6,7-Tetramethyl-2-oxo-2,3-dihydro-1H-indol-3-yl)-pentanenitrile (3p**):** colorless liquid (65%, 35.2 mg); R_f 0.3 (EtOAc/petroleum ether = 1:3); ^1H NMR (400 MHz, CDCl_3) δ 6.88 (s, 2H), 3.52 (s, 3H), 2.48 (s, 3H), 2.30 (s, 3H), 2.26–2.17 (m, 2H), 1.89 (td, $J = 11.6, 5.2$ Hz, 1H), 1.70 (td, $J = 12.8, 4.8$ Hz, 1H), 1.60–1.46 (m, 2H), 1.31 (s, 3H), 1.11–0.98 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 181.6, 141.2, 137.7, 132.1, 124.3, 119.6, 119.5, 118.9, 47.1, 37.7, 30.4, 25.5, 24.5, 23.8, 20.9, 16.9, 14.2 ppm; IR (KBr) ν_{max} 2246, 1705, 1608, 1457, 1364, 1266 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{23}\text{N}_2\text{O}$ [M + H]⁺ 271.1805, found 271.1796.

5-(1,3-Dimethyl-2-oxo-2,3-dihydro-1H-benzo[g]indol-3-yl)-pentanenitrile (3q**):** colorless liquid (62%, 36.3 mg); R_f 0.3 (EtOAc/petroleum ether = 1:3); ^1H NMR (400 MHz, CDCl_3) δ 7.73 (d, $J = 8.0$ Hz, 1H), 7.72–7.52 (m, 2H), 7.46–7.40 (m, 2H), 6.96 (d, $J = 7.2$ Hz, 1H), 3.54 (s, 3H), 2.44–2.37 (m, 1H), 2.19–2.14 (m, 2H), 1.92–1.85 (m, 1H), 1.67 (s, 3H), 1.59–1.48 (m, 2H), 1.19–1.05 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 173.1, 137.6, 136.6, 133.3, 127.1, 126.4, 126.1, 122.6, 122.5, 119.6, 119.4, 108.4, 47.4, 43.1, 31.3, 29.6, 25.5, 24.8, 16.8 ppm; IR (KBr) ν_{max} 2246, 1662, 1585, 1465, 1380, 1316 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{20}\text{KN}_2\text{O}$ [M + K]⁺ 331.1207, found 331.1203.

5-(1-Benzyl-3-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-pentanenitrile (3r**):** colorless liquid (96%, 61.1 mg); R_f 0.4 (EtOAc/petroleum ether = 1:2); ^1H NMR (400 MHz, CDCl_3) δ 7.34–7.25 (m, 5H), 7.18–7.15 (m, 2H), 7.04 (td, J = 7.6, 0.8 Hz, 1H), 6.76 (dd, J = 7.2, 1.2 Hz, 1H), 4.96 (d, J = 15.6 Hz, 1H), 4.87 (d, J = 16.0 Hz, 1H), 2.26–2.14 (m, 2H), 2.03–1.96 (m, 1H), 1.84–1.77 (m, 1H), 1.59–1.49 (m, 2H), 1.42 (s, 3H), 1.18–1.02 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 180.4, 142.3, 136.0, 133.5, 128.8, 127.8, 127.6, 127.3, 122.7, 122.5, 119.3, 109.1, 48.1, 43.6, 37.5, 25.4, 24.2, 23.9, 16.9 ppm; IR (KBr) v_{\max} 2245, 1709, 1612, 1488, 1467, 1356, 1173 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{22}\text{KN}_2\text{O}$ [M + K]⁺ 357.1364, found 357.1360.

5-(3-Methyl-2-oxo-1-phenyl-2,3-dihydro-1*H*-indol-3-yl)-pentanenitrile (3s**):** colorless liquid (89%, 54.2 mg); R_f 0.35 (EtOAc/petroleum ether = 1:3); ^1H NMR (400 MHz, CDCl_3) δ 7.55–7.51 (m, 2H), 7.42–7.39 (m, 3H), 7.25–7.19 (m, 2H), 7.14–7.10 (m, 1H), 6.85 (d, J = 8.0 Hz, 1H), 2.27–2.18 (m, 2H), 2.08–2.00 (m, 1H), 1.89–1.82 (m, 1H), 1.64–1.54 (m, 2H), 1.48 (s, 3H), 1.30–1.15 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 179.8, 143.1, 134.4, 133.2, 129.6, 128.0, 127.8, 126.4, 123.1, 122.7, 119.3, 109.4, 48.2, 37.8, 25.4, 24.1, 23.8, 16.8 ppm; IR (KBr) v_{\max} 2245, 1718, 1610, 1499, 1458, 1374, 1201 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{21}\text{N}_2\text{O}$ [M + H]⁺ 305.1648, found 305.1638.

5-(3-Benzyl-1-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-pentanenitrile (3t**):** colorless liquid (62%, 39.5 mg); R_f 0.3 (EtOAc/petroleum ether = 1:3); ^1H NMR (400 MHz, CDCl_3) δ 7.19 (td, J = 7.2, 1.2 Hz, 1H), 7.13 (dd, J = 6.8, 0.8 Hz, 1H), 7.08–7.01 (m, 4H), 6.79 (dd, J = 7.6, 1.6 Hz, 2H), 6.59 (d, J = 7.6 Hz, 1H), 3.11 (d, J = 12.8 Hz, 1H), 2.99 (d, J = 13.2 Hz, 1H), 2.95 (s, 3H), 2.44–2.06 (m, 3H), 1.94–1.87 (m, 1H), 1.64–1.51 (m, 2H), 1.12–0.99 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 178.8, 143.7, 135.5, 130.6, 129.8, 128.0, 127.4, 126.4, 123.3, 122.2, 119.4, 107.8, 54.5, 44.4, 35.9, 25.8, 25.5, 23.8, 16.9 ppm; IR (KBr) v_{\max} 2246, 1707, 1612, 1494, 1470, 1377, 1346, 1256 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{23}\text{N}_2\text{O}$ [M + H]⁺ 319.1805, found 319.1802.

Acetic Acid 3-(4-Cyano-butyl)-1-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-ylmethyl Ester (3u**):** colorless liquid (96%, 57.7 mg); R_f 0.20 (EtOAc/petroleum ether = 1:1); ^1H NMR (400 MHz, CDCl_3) δ 7.32 (td, J = 7.6, 1.2 Hz, 1H), 7.20 (d, J = 6.8 Hz, 1H), 7.08 (td, J = 7.6, 0.8 Hz, 1H), 6.87 (d, J = 8.0 Hz, 1H), 4.48 (d, J = 10.8 Hz, 1H), 4.14 (d, J = 10.8 Hz, 1H), 3.24 (s, 3H), 2.28–2.16 (m, 2H), 1.98–1.80 (m, 5H), 1.60–1.50 (m, 2H), 1.13–1.01 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 177.1, 170.3, 144.0, 129.0, 128.7, 123.3, 122.8, 119.2, 108.2, 67.2, 52.2, 32.6, 26.3, 25.3, 23.0, 20.5, 16.8 ppm; IR (KBr) v_{\max} 2246, 1747, 1711, 1613, 1494, 1470, 1376, 1234 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{20}\text{N}_2\text{NaO}_3$ [M + Na]⁺ 323.1366, found 323.1357.

5-(3-Hydroxymethyl-1-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-pentanenitrile (3v**):** colorless liquid (62%, 32.0 mg); R_f 0.1 (EtOAc/petroleum ether = 1:2); ^1H NMR (400 MHz, CDCl_3) δ 7.30 (td, J = 7.6, 1.2 Hz, 1H), 7.20 (d, J = 6.8 Hz, 1H), 7.11 (t, J = 7.2 Hz, 1H), 6.89 (d, J = 7.6 Hz, 1H), 3.86–3.82 (m, 1H), 3.72 (d, J = 10.8 Hz, 1H), 3.24 (s, 3H), 2.28–2.21 (m, 3H), 2.11–2.06 (m, 1H), 1.89–1.81 (m, 1H), 1.61–1.52 (m, 2H), 1.13–1.07 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 179.0, 144.1, 129.4, 128.7, 123.0, 122.9, 119.3, 108.5, 67.1, 54.2, 32.0, 26.2, 25.4, 23.3, 16.9 ppm; IR (KBr) v_{\max} 3450, 2246, 1703, 1612, 1493, 1468, 1378, 1260 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{18}\text{N}_2\text{NaO}_2$ [M + Na]⁺ 281.1260, found 281.1258.

5-(3-Hydroxymethyl-1,5-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-pentanenitrile (3w**):** colorless liquid (66%, 35.9 mg); R_f 0.15 (EtOAc/petroleum ether = 1:2); ^1H NMR (400 MHz, CDCl_3) δ 7.11 (dd, J = 8.0, 0.4 Hz, 1H), 7.00 (s, 1H), 6.77 (d, J = 8.0 Hz, 1H), 3.82 (dd, J = 10.8, 9.6 Hz, 1H), 3.70 (dd, J = 10.8, 3.2 Hz, 1H), 3.21 (s, 3H), 2.38–2.34 (m, 4H), 2.28–2.18 (m, 2H), 2.11–2.04 (m, 1H), 1.85–1.77 (m, 1H), 1.59–1.49 (m, 2H), 1.12–1.06 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 178.9, 141.7, 132.5, 129.4, 128.9, 123.7, 119.4, 108.1, 67.2, 54.2, 32.1, 26.2, 25.4, 23.3, 21.2, 16.8 ppm; IR (KBr) v_{\max} 3447, 2247, 1716, 1699, 1684, 1559,

1498, 1363, 1261 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{20}\text{N}_2\text{NaO}_2$ [M + Na]⁺ 295.1417, found 295.1412.

5-(5-Chloro-3-hydroxymethyl-1-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-pentanenitrile (3x**):** colorless liquid (72%, 42.2 mg); R_f 0.20 (EtOAc/petroleum ether = 1:1); ^1H NMR (400 MHz, CDCl_3) δ 7.30 (dd, J = 8.4, 2.0 Hz, 1H), 7.19 (d, J = 2.0 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 3.85–3.72 (m, 2H), 3.22 (s, 3H), 2.26–2.22 (m, 3H), 2.10–2.02 (m, 1H), 1.84–1.77 (m, 1H), 1.62–1.52 (m, 2H), 1.17–1.02 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 178.3, 142.7, 131.4, 128.5, 128.4, 123.5, 119.2, 109.3, 67.0, 54.7, 32.0, 26.3, 25.4, 23.2, 16.9 ppm; IR (KBr) v_{\max} 3446, 2247, 1707, 1610, 1541, 1364 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{17}\text{ClN}_2\text{NaO}_2$ [M + Na]⁺ 315.0871, found 315.0868.

5-[3-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)methyl]-1-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-pentanenitrile (3y**):** colorless liquid (69%, 53.5 mg); R_f 0.25 (EtOAc/petroleum ether = 1:3); ^1H NMR (400 MHz, CDCl_3) δ 7.77–7.74 (m, 2H), 7.67–7.65 (m, 2H), 7.24–7.15 (m, 2H), 6.98 (td, J = 7.6, 0.4 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 4.02 (d, J = 14.0 Hz, 1H), 3.96 (d, J = 14.0 Hz, 1H), 3.20 (s, 3H), 2.22–2.06 (m, 3H), 1.98–1.92 (m, 1H), 1.58–1.49 (m, 2H), 1.06–0.97 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 177.4, 167.9, 143.8, 134.3, 133.9, 131.6, 128.7, 128.6, 123.6, 123.4, 123.3, 122.4, 119.3, 108.2, 52.5, 43.2, 34.3, 26.3, 25.3, 23.4, 16.8 ppm; IR (KBr) v_{\max} 2248, 1717, 1612, 1470, 1395, 1340, 1259 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{21}\text{N}_3\text{NaO}_3$ [M + Na]⁺ 410.1475, found 410.1460.

5-(1-Methyl-2-oxo-1,2,5,6-tetrahydro-4*H*-pyrrolo[3,2,1-ij]quinolin-1-yl)-pentanenitrile (3z**):** colorless liquid (62%, 33.3 mg); R_f 0.25 (EtOAc/petroleum ether = 1:3); ^1H NMR (400 MHz, CDCl_3) δ 7.04–6.94 (m, 3H), 3.72 (t, J = 6.0 Hz, 2H), 2.8 (t, J = 6.0 Hz, 2H), 2.25–2.21 (m, 2H), 2.04–1.98 (m, 2H), 1.90–1.86 (m, 1H), 1.80–1.72 (m, 1H), 1.60–1.51 (m, 2H), 1.36 (s, 3H), 1.16–1.10 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 179.2, 138.9, 132.0, 126.7, 122.0, 120.3, 120.1, 119.4, 49.4, 38.7, 37.1, 25.4, 24.6, 23.8, 23.5, 21.2, 16.8 ppm; IR (KBr) v_{\max} 2245, 1703, 1625, 1507, 1261 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{20}\text{N}_2\text{NaO}$ [M + Na]⁺ 291.1468, found 291.1460.

5-(1,3-Dimethyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-3-phenyl-pentanenitrile (4a**):** colorless liquid (68%, 43.3 mg); R_f 0.30 (EtOAc/petroleum ether = 1:3); ^1H NMR (400 MHz, CDCl_3) δ 7.34–7.27 (m, 4H), 7.16–7.07 (m, 4H), 6.86 (d, J = 7.6 Hz, 1H), 3.22 (s, 3H), 2.76–2.71 (m, 1H), 2.47 (d, J = 6.8 Hz, 2H), 1.81–1.74 (m, 1H), 1.69–1.62 (m, 1H), 1.55–1.45 (m, 1H), 1.43–1.35 (m, 1H), 1.29 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 180.1, 143.2, 141.0, 133.5, 129.0, 128.0, 127.5, 127.2, 122.7, 122.4, 118.2, 108.2, 48.0, 42.2, 35.8, 29.4, 26.2, 25.1, 23.9 ppm; IR (KBr) v_{\max} 2246, 1706, 1654, 1492, 1375, 1258 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{22}\text{N}_2\text{NaO}$ [M + Na]⁺ 341.1624, found 341.1627.

4a': ^1H NMR (400 MHz, CDCl_3) δ 7.35–7.26 (m, 4H), 7.08–7.04 (m, 3H), 6.96 (dd, J = 7.2, 0.8 Hz, 1H), 6.86 (d, J = 7.6 Hz, 1H), 3.23 (s, 3H), 2.84–2.78 (m, 1H), 2.50–2.38 (m, 2H), 1.88–1.81 (m, 1H), 1.56–1.37 (m, 2H), 1.29–1.22 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 180.2, 143.2, 140.8, 133.3, 128.9, 127.9, 127.5, 127.2, 122.6, 122.3, 118.1, 108.1, 48.0, 42.2, 35.6, 29.4, 26.2, 25.5, 24.0 ppm.

5-(1,3-Dimethyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-3-p-tolyl-pentanenitrile (4b**):** colorless liquid (80%, 53.2 mg); R_f 0.3 (EtOAc/petroleum ether = 1:3); ^1H NMR (400 MHz, CDCl_3) δ 7.29 (td, J = 7.6, 1.2 Hz, 1H), 7.16–7.06 (m, 4H), 7.00 (d, J = 8.0 Hz, 2H), 6.85 (d, J = 8.0 Hz, 1H), 3.21 (s, 3H), 2.74–2.66 (m, 1H), 2.44 (d, J = 6.8 Hz, 2H), 2.32 (s, 3H), 1.82–1.74 (m, 1H), 1.68–1.61 (m, 1H), 1.50–1.43 (m, 1H), 1.41–1.32 (m, 1H), 1.29 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 180.1, 143.2, 137.9, 137.1, 133.6, 129.6, 127.9, 127.0, 122.7, 122.4, 118.3, 108.1, 48.0, 41.8, 35.8, 29.5, 26.2, 25.2, 23.8, 21.0 ppm; IR (KBr) v_{\max} 2248, 1716, 1613, 1492, 1472, 1376, 1258 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{24}\text{N}_2\text{NaO}$ [M + Na]⁺ 355.1781, found 355.1779.

4b': ^1H NMR (400 MHz, CDCl_3) δ 7.29 (td, J = 7.6, 1.2 Hz, 1H), 7.12 (d, J = 7.6 Hz, 2H), 7.06 (td, J = 7.6, 0.4 Hz, 1H), 6.98 (dd, J = 7.2, 0.8 Hz, 1H), 6.93 (d, J = 8.0 Hz, 2H), 6.86 (d, J = 8.0

Hz, 1H), 3.23 (s, 3H), 2.82–2.74 (m, 1H), 2.47–2.35 (m, 2H), 2.34 (s, 3H), 1.83 (td, $J = 12.4, 4.0$ Hz, 1H), 1.54 (td, $J = 12.4, 4.0$ Hz, 1H), 1.47–1.38 (m, 1H), 1.29–1.18 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 180.3, 143.2, 137.7, 137.2, 133.4, 129.6, 127.9, 127.1, 122.6, 122.3, 118.2, 108.1, 48.1, 41.8, 35.7, 29.4, 26.2, 25.6, 24.0, 21.0 ppm.

3-(4-*tert*-Butyl-phenyl)-5-(1,3-dimethyl-2-oxo-2,3-dihydro-1H-indol-3-yl)-pentanenitrile (4c**):** colorless liquid (75%, 56.2 mg); R_f 0.3 (EtOAc/petroleum ether = 1:3); ^1H NMR (400 MHz, CDCl_3) δ 7.33–7.26 (m, 3H), 7.16 (dd, $J = 7.2, 0.8$ Hz, 1H), 7.09 (td, $J = 7.6, 0.8$ Hz, 1H), 7.04 (d, $J = 8.4$ Hz, 2H), 6.86 (d, $J = 8.0$ Hz, 1H), 3.22 (s, 3H), 2.75–2.68 (m, 1H), 2.50–2.41 (m, 2H), 1.82 (td, $J = 13.2, 4.8$ Hz, 1H), 1.67 (td, $J = 13.2, 4.8$ Hz, 1H), 1.55–1.45 (m, 1H), 1.40–1.30 (m, 12H); ^{13}C NMR (100 MHz, CDCl_3) δ 180.2, 150.2, 143.2, 137.9, 133.6, 127.9, 126.7, 125.8, 122.7, 122.4, 118.3, 108.1, 48.0, 41.6, 35.8, 34.4, 31.3, 29.3, 26.2, 25.1, 23.9 ppm; IR (KBr) ν_{\max} 2247, 1717, 1613, 1457, 1376, 1253 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{30}\text{N}_2\text{NaO}$ [M + Na]⁺ 397.2250, found 397.2251.

4c': ^1H NMR (400 MHz, CDCl_3) δ = 7.33–7.26 (m, 3H), 7.06 (t, $J = 7.2$ Hz, 1H), 6.99–6.96 (m, 3H), 6.86 (d, $J = 7.6$ Hz, 1H), 3.23 (s, 3H), 2.82–2.75 (m, 1H), 2.48–2.37 (m, 2H), 1.84 (td, $J = 12.4, 4.4$ Hz, 1H), 1.58 (td, $J = 13.2, 4.0$ Hz, 1H), 1.49–1.42 (m, 1H), 1.35–1.28 (m, 12H); ^{13}C NMR (100 MHz, CDCl_3) δ 180.3, 150.3, 143.2, 137.7, 133.4, 127.9, 126.8, 125.7, 122.6, 122.4, 118.3, 108.1, 48.1, 41.7, 35.6, 34.5, 31.3, 29.3, 26.2, 25.5, 23.9 ppm.

3-(4-Chloro-phenyl)-5-(1,3-dimethyl-2-oxo-2,3-dihydro-1H-indol-3-yl)-pentanenitrile (4d**):** colorless liquid (77%, 54.3 mg); R_f 0.25 (EtOAc/petroleum ether = 1:3); ^1H NMR (400 MHz, CDCl_3) δ 7.31–7.26 (m, 3H), 7.15–7.05 (m, 4H), 6.86 (d, $J = 8.0$ Hz, 1H), 3.22 (s, 3H), 2.76–2.69 (m, 1H), 2.44 (d, $J = 6.8$ Hz, 2H), 1.75 (td, $J = 12.0, 5.2$ Hz, 1H), 1.64 (td, $J = 13.2, 4.4$ Hz, 1H), 1.50–1.32 (m, 2H), 1.29 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 180.0, 143.2, 139.3, 133.4, 133.3, 129.2, 128.5, 128.0, 122.7, 122.4, 117.8, 108.2, 47.9, 41.6, 35.7, 29.4, 26.2, 25.1, 23.8 ppm; IR (KBr) ν_{\max} 2248, 1705, 1613, 1492, 1376, 1349, 1260 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{21}\text{ClN}_2\text{NaO}$ [M + Na]⁺ 375.1235, found 375.1237.

4d': ^1H NMR (400 MHz, CDCl_3) δ = 7.31–7.26 (m, 3H), 7.06 (t, $J = 7.6$ Hz, 1H), 7.00–6.95 (m, 3H), 6.87 (d, $J = 8.0$ Hz, 1H), 3.23 (s, 3H), 2.84–2.77 (m, 1H), 2.49–2.35 (m, 2H), 1.87–1.78 (m, 1H), 1.52–1.40 (m, 2H), 1.27–1.18 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 180.1, 143.2, 139.2, 133.4, 133.2, 129.1, 128.6, 128.1, 122.7, 122.2, 117.8, 108.2, 48.0, 41.7, 35.6, 29.4, 26.2, 25.4, 23.9 ppm.

3-(4-Bromo-phenyl)-5-(1,3-dimethyl-2-oxo-2,3-dihydro-1H-indol-3-yl)-pentanenitrile (4e**):** colorless liquid (82%, 65.2 mg); R_f 0.25 (EtOAc/petroleum ether = 1:3); ^1H NMR (400 MHz, CDCl_3) δ 7.46–7.44 (m, 2H), 7.29 (td, $J = 7.6, 1.6$ Hz, 1H), 7.14 (dd, $J = 7.2, 0.8$ Hz, 1H), 7.08 (td, $J = 7.2, 0.8$ Hz, 1H), 7.00 (d, $J = 8.4$ Hz, 2H), 6.86 (d, $J = 8.0$ Hz, 1H), 3.22 (s, 3H), 2.72–2.68 (m, 1H), 2.44 (d, $J = 6.8$ Hz, 2H), 1.78–1.71 (m, 1H), 1.67–1.60 (m, 1H), 1.50–1.35 (m, 2H), 1.29 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 180.0, 143.2, 139.8, 133.4, 132.1, 128.9, 128.1, 122.7, 122.4, 121.4, 117.8, 108.2, 47.9, 41.7, 35.7, 29.3, 26.2, 25.0, 23.8 ppm; IR (KBr) ν_{\max} 2248, 1702, 1613, 1490, 1377, 1349, 1260 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{21}\text{BrN}_2\text{NaO}$ [M + Na]⁺ 419.0729, found 419.0731.

4e': ^1H NMR (400 MHz, CDCl_3) δ 7.45 (d, $J = 8.4$ Hz, 2H), 7.29 (td, $J = 7.6, 0.8$ Hz, 1H), 7.06 (t, $J = 7.6$ Hz, 1H), 6.97–6.92 (m, 3H), 6.87 (d, $J = 7.6$ Hz, 1H), 3.23 (s, 3H), 2.81–2.77 (m, 1H), 2.48–2.35 (m, 2H), 1.86–1.81 (m, 1H), 1.49–1.42 (m, 2H), 1.27–1.20 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 180.1, 143.2, 139.7, 133.2, 132.1, 129.0, 128.0, 122.7, 122.2, 117.8, 108.2, 48.0, 41.7, 35.5, 29.3, 26.2, 25.3, 23.9 ppm.

[2-(1,3-Dimethyl-2-oxo-2,3-dihydro-1H-indol-3-yl)-ethoxy]-acetone (4f**):** colorless liquid (43%, 21.0 mg); R_f 0.3 (EtOAc/petroleum ether = 1:2); ^1H NMR (400 MHz, CDCl_3) δ 7.29 (td, $J = 7.6, 1.2$ Hz, 1H), 7.17 (dd, $J = 7.2, 0.4$ Hz, 1H), 7.08 (td, $J = 7.6, 0.8$ Hz, 1H), 6.87 (d, $J = 8.0$ Hz, 1H), 4.00 (d, $J = 16.0$ Hz, 1H), 3.95 (d, $J = 16.0$ Hz, 1H), 3.37–3.33 (m, 1H), 3.29–3.24 (m, 1H), 3.22 (s, 3H), 2.40–2.34 (m, 1H), 2.03–1.98 (m, 1H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 180.2, 143.3, 132.7, 128.1, 122.6,

122.5, 115.6, 108.3, 68.1, 55.8, 46.3, 36.8, 26.2, 24.4 ppm; IR (KBr) ν_{\max} 1706, 1612, 1493, 1470, 1377, 1349, 1260, 1108 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{16}\text{KN}_2\text{O}_2$ [M + K]⁺ 283.0843, found 283.0850.

4-Benzyl-5-(1,3-dimethyl-2-oxoindolin-3-yl)-3-phenylpentanenitrile (4g**):** colorless liquid (38%, 31.6 mg); R_f 0.30 (EtOAc/petroleum ether = 1:3); ^1H NMR (400 MHz, CDCl_3) δ 7.29–7.26 (m, 3H), 7.25 (s, 1H), 7.22 (d, $J = 7.4$ Hz, 2H), 7.15 (d, $J = 7.2$ Hz, 1H), 6.85 (t, $J = 7.9$ Hz, 4H), 6.79 (d, $J = 7.2$ Hz, 2H), 6.26 (d, $J = 7.3$ Hz, 1H), 3.19 (s, 3H), 2.90–2.81 (m, 1H), 2.63 (d, $J = 8.0$ Hz, 2H), 2.51 (dd, $J = 14.5, 4.1$ Hz, 1H), 2.33 (dd, $J = 14.4, 11.0$ Hz, 1H), 1.90 (dd, $J = 13.8, 9.4$ Hz, 1H), 1.79–1.62 (m, 1H), 1.60 (d, $J = 8.9$ Hz, 1H), 1.23 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 180.6, 142.9, 139.7, 139.5, 132.5, 128.7, 128.5, 128.4, 127.8, 127.6, 127.0, 126.3, 122.8, 122.6, 118.9, 107.9, 47.3, 42.6, 42.3, 37.4, 36.4, 26.2, 25.4, 15.8; IR (neat): ν_{\max} 2926, 2249, 1706, 1613, 1492, 1470, 1379, 1260 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{29}\text{N}_2\text{O}$ [M + H]⁺ 409.2274, found 409.2273.

4g': ^1H NMR (400 MHz, CDCl_3) δ 7.40–7.36 (m, 1H), 7.36–7.28 (m, 3H), 7.21 (dd, $J = 12.5, 4.9$ Hz, 3H), 7.16 (d, $J = 6.3$ Hz, 2H), 7.03 (d, $J = 6.9$ Hz, 2H), 6.92 (d, $J = 7.8$ Hz, 1H), 6.78 (d, $J = 7.2$ Hz, 2H), 3.16 (s, 3H), 2.74–2.73 (m, 1H), 2.45–2.41 (m, 3H), 2.21 (dd, $J = 14.8, 9.3$ Hz, 1H), 1.98–1.84 (m, 3H), 1.34 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 180.5, 143.2, 139.8, 138.8, 133.0, 128.6, 128.4, 127.5, 126.2, 123.0, 123.0, 118.4, 108.4, 47.5, 43.7, 40.4, 38.4, 37.1, 26.3, 25.8, 21.3.

General Procedure for the Cyclization of Cinnamamides with Cyclobutanone O-Acyl Oximes. Cinnamamides **5** (0.2 mmol, 1.0 equiv), Cu_2O (2.8 mg, 10 mol %), and cyclobutanone *O*-acyl oxime **2a** (0.24 mmol, 1.2 equiv) were added into an oven-dried Schlenk tube. The tube was evacuated and backfilled with nitrogen (three times). Then, dioxane (2.0 mL) was injected into the tube by syringe. The reaction mixture was then stirred at 80 °C for 24 h. The resulting mixture was diluted with EtOAc, and the organic phase was washed successively with H_2O (three times) and brine (one time), then dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient eluent of EtOAc/petroleum ether 1:20 to 1:10) to give the corresponding products **6** in yields listed in Table 4.

4-(1-Methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro-quinolin-3-yl)-butyronitrile (6a**):** colorless liquid (61%, 37.1 mg); R_f 0.20 (EtOAc/petroleum ether = 1:3); ^1H NMR (400 MHz, CDCl_3) δ 7.34–7.24 (m, 4H), 7.07–6.97 (m, 5H), 4.00 (d, $J = 6.4$ Hz, 1H), 3.39 (s, 3H), 2.92–2.90 (m, 1H), 2.35–2.30 (m, 2H), 1.80–1.64 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.4, 140.8, 139.4, 129.2, 128.9, 128.3, 128.1, 127.6, 127.2, 123.4, 119.3, 114.8, 47.2, 47.0, 29.7, 29.1, 22.9, 17.0 ppm; IR (KBr) ν_{\max} 2246, 1669, 1468, 1376, 1264 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{NaO}$ [M + Na]⁺ 327.1468, found 327.1469.

4-[1-Methyl-2-oxo-4-(4-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-quinolin-3-yl]-butyronitrile (6b**):** colorless liquid (56%, 41.7 mg); R_f 0.25 (EtOAc/petroleum ether = 1:3); ^1H NMR (400 MHz, CDCl_3) δ 7.55 (d, $J = 8.4$ Hz, 2H), 7.38–7.34 (m, 1H), 7.17 (d, $J = 8.0$ Hz, 2H), 7.10–7.00 (m, 3H), 4.06 (d, $J = 5.2$ Hz, 1H), 3.39 (s, 3H), 2.95–2.90 (m, 1H), 2.39–2.33 (m, 2H), 1.82–1.63 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.9, 145.0, 139.4, 129.4, 128.6, 127.9, 125.9, 123.7, 115.1, 47.4, 47.0, 29.7, 29.4, 23.0, 16.9 ppm; IR (KBr) ν_{\max} 2246, 1673, 1601, 1468, 1365, 1326, 1263 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{19}\text{F}_3\text{N}_2\text{NaO}$ [M + Na]⁺ 395.1342, found 395.1346.

4-(1-Methyl-2-oxo-4-m-tolyl-1,2,3,4-tetrahydro-quinolin-3-yl)-butyronitrile (6c**):** colorless liquid (70%, 44.6 mg); R_f 0.25 (EtOAc/petroleum ether = 1:3); ^1H NMR (400 MHz, CDCl_3) δ 7.33–7.29 (m, 1H), 7.18 (t, $J = 7.2$ Hz, 1H), 7.07–6.97 (m, 4H), 6.90 (s, 1H), 6.82 (d, $J = 8.0$ Hz, 1H), 3.95 (d, $J = 6.0$ Hz, 1H), 3.39 (s, 3H), 2.92–2.87 (m, 1H), 2.40–2.27 (m, 5H), 1.83–1.58 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.5, 140.7, 139.4, 138.5, 129.2, 128.8, 128.4, 128.0, 127.4, 124.6, 123.3, 119.3, 114.7, 47.2, 46.9, 29.7, 29.1, 23.0, 21.5, 17.0 ppm; IR (KBr) ν_{\max} 2245, 1663, 1600, 1457, 1362, 1261 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{22}\text{N}_2\text{NaO}$ [M + Na]⁺ 341.1624, found 341.1627.

4-[4-(3-Methoxy-phenyl)-1-methyl-2-oxo-1,2,3,4-tetrahydro-quinolin-3-yl]-butyronitrile (6d**):** colorless liquid (69%, 46.1 mg); R_f 0.20 (EtOAc/petroleum ether = 1:3); ^1H NMR (400 MHz, CDCl_3) δ 7.33–7.29 (m, 1H), 7.22 (t, J = 8.0 Hz, 1H), 7.07–6.99 (m, 3H), 6.78 (dd, J = 8.4, 2.4 Hz, 1H), 6.66 (d, J = 7.6 Hz, 1H), 6.59 (t, J = 2.0 Hz, 1H), 3.96 (d, J = 6.0 Hz, 1H), 3.75 (s, 3H), 3.39 (s, 3H), 2.92–2.87 (m, 1H), 2.38–2.27 (m, 2H), 1.83–1.60 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.4, 159.9, 142.4, 139.4, 129.9, 129.2, 128.1, 127.1, 123.4, 119.9, 119.3, 114.8, 113.9, 112.0, 55.1, 47.2, 47.0, 29.7, 29.1, 23.0, 17.0 ppm; IR (KBr) v_{\max} 2245, 1666, 1598, 1463, 1365, 1261 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{22}\text{N}_2\text{NaO}_2$ [M + Na]⁺ 357.1573, found 357.1576.

4-(6-Methoxy-1-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro-quinolin-3-yl)-butyronitrile (6e**):** colorless liquid (51%, 34.1 mg); R_f 0.25 (EtOAc/petroleum ether = 1:3); ^1H NMR (400 MHz, CDCl_3) δ 7.32–7.23 (m, 3H), 7.05 (d, J = 7.2 Hz, 2H), 6.99 (d, J = 8.8 Hz, 1H), 6.84 (dd, J = 8.8, 2.8 Hz, 1H), 6.56 (d, J = 2.8 Hz, 1H), 3.94 (d, J = 5.6 Hz, 1H), 3.74 (s, 3H), 3.36 (s, 3H), 2.90–2.85 (m, 1H), 2.39–2.27 (m, 2H), 1.83–1.58 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.9, 155.7, 140.7, 133.1, 129.0, 128.7, 127.6, 127.3, 119.3, 115.8, 115.3, 112.6, 55.4, 47.4, 29.8, 29.3, 23.0, 17.0 ppm; IR (KBr) v_{\max} 2246, 1662, 1590, 1505, 1455, 1377, 1299, 1249 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{22}\text{N}_2\text{NaO}_2$ [M + Na]⁺ 357.1573, found 357.1572.

Derivatization of Product **3a. Hydrolysis of Product **3a**.** ^{13a} To a solution of aqueous NaOH (1.0 M, 1 mL) was added nitrile **3a** (48.4 mg, 0.2 mmol). The flask was placed into a preheated 100 °C oil bath and stirred for 24 h. After cooling down to room temperature and the aqueous phase was acidified with concentrated HCl (pH = 2), the mixture was extracted with EtOAc (3 × 10 mL) and the combined organic layers were washed with brine, dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure by rotary evaporation. Purification by flash column chromatography on silica gel (EtOAc/MeOH = 20:1) afforded the title compound as a colorless liquid

7a: colorless liquid (78%, 40.8 mg); R_f 0.25 (EtOAc/petroleum ether = 1:1); ^1H NMR (400 MHz, CDCl_3) δ 7.26 (td, J = 7.6, 1.2 Hz, 1H), 7.16 (d, J = 6.8 Hz, 1H), 7.06 (t, J = 7.6 Hz, 1H), 6.84 (d, J = 7.6 Hz, 1H), 3.21 (s, 3H), 2.20 (t, J = 7.6 Hz, 2H), 1.91 (td, J = 13.2, 4.8 Hz, 1H), 1.74 (td, J = 12.4, 4.4 Hz, 1H), 1.53–1.45 (m, 2H), 1.34 (s, 3H), 1.05–0.86 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 180.7, 178.7, 143.2, 133.9, 127.7, 122.6, 122.4, 108.0, 48.3, 37.9, 33.6, 26.1, 24.6, 23.9, 23.8 ppm; IR (KBr) v_{\max} 1708, 1611, 1492, 1467, 1381, 1261 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{19}\text{NNaO}_3$ [M + Na]⁺ 284.1257, found 284.1265.

2. [3+2]Cycloaddition of Product **3a.** ^{13b} A 10 mL oven-dried Schlenk tube was charged with **3a** (0.2 mmol, 1.0 equiv), ZnCl_2 (0.2 mmol, 1.0 equiv), and NaN_3 (0.24 mmol, 1.2 equiv). ³BuOH (1 mL) was then injected into the tube by syringe. The resulting mixture was stirred vigorously for 20 h at 120 °C. Upon completion of the reaction, the mixture was diluted with EtOAc. The solvent was then removed under vacuo. The usual workup with 5% aq NaOH afforded the desired thiotetrazole **8a**.

8a: colorless liquid (42%, 24.0 mg); R_f 0.1 (EtOAc); ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.28–7.24 (m, 2H), 7.05–6.98 (m, 2H), 3.11 (s, 3H), 2.72 (t, J = 7.2 Hz, 2H), 1.81–1.68 (m, 2H), 1.54 (t, J = 7.2 Hz, 2H), 1.23 (s, 3H), 0.94–0.71 (m, 2H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 179.5, 155.8, 143.0, 133.3, 127.7, 122.5, 122.2, 108.3, 47.5, 37.1, 25.8, 23.6, 23.5 ppm; IR (KBr) v_{\max} 2923, 1688, 1611, 1517, 1492, 1375, 1125 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{19}\text{N}_5\text{NaO}$ [M + Na]⁺ 308.1482, found 308.1489.

Characterization of New Starting Materials. 2a-2: ^1H NMR (400 MHz, CDCl_3) δ 7.94 (d, J = 8.4 Hz, 2H), 7.47–7.33 (m, 3H), 3.03–3.01 (m, 4H), 2.00–1.98 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.2, 163.9, 133.1, 129.4, 128.9, 128.4, 31.7, 14.2; IR (KBr) v_{\max} 1736, 1451, 1262, 1079, 1023 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{11}\text{H}_{12}\text{NO}_2$ [M + H]⁺ 190.0863, found 190.0862.

2a-3: ^1H NMR (400 MHz, CDCl_3) δ 7.93 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 3.13 (t, J = 8.4 Hz, 4H), 2.41 (s, 3H), 2.13–2.09 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.0, 164.1,

143.9, 129.6, 129.2, 126.2, 31.9, 31.8, 21.7, 14.3; IR (KBr) v_{\max} 1734, 1611, 1313, 1265, 1180, 1069 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{14}\text{NO}_2$ [M + H]⁺ 204.1019, found 204.1018.

2a-4: ^1H NMR (400 MHz, CDCl_3) δ 8.06–8.01 (m, 2H), 7.13–7.08 (m, 2H), 3.14–3.09 (m, 4H), 2.15–2.06 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.4, 167.0, 164.5, 163.0, 132.1, 125.1, 31.7, 14.2; IR (KBr) v_{\max} 1737, 1595, 1505, 1413, 1261, 1098 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{11}\text{H}_{11}\text{FNO}_2$ [M + H]⁺ 208.0768, found 208.0767.

2a-5: ^1H NMR (400 MHz, CDCl_3) δ 8.15 (d, J = 8.0 Hz, 2H), 7.72 (d, J = 8.0 Hz, 2H), 3.15 (t, J = 8.0 Hz, 4H), 2.18–2.10 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.7, 162.8, 134.8 (q, $J_{\text{C}-\text{F}}$ = 219.5 Hz), 130.0, 125.5, 122.2, 31.8, 14.3; IR (KBr) v_{\max} 1739, 1414, 1330, 1159, 1091 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{11}\text{F}_3\text{NO}_2$ [M + H]⁺ 258.0736, found 258.0735.

2a-6: ^1H NMR (400 MHz, CDCl_3) δ 7.95 (d, J = 8.1 Hz, 1H), 7.73 (d, J = 2.0 Hz, 1H), 7.95 (dd, J = 8.1, 2.0 Hz, 1H), 3.09 (t, J = 7.6 Hz, 2H), 3.01 (t, J = 7.6 Hz, 2H), 2.12–2.04 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.9, 162.5, 140.1, 131.7, 130.1, 12.5, 125.4, 31.8, 31.7, 14.1; IR (KBr) v_{\max} 1755, 1570, 1530, 1343, 1238 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{11}\text{H}_9\text{ClN}_2\text{NaO}_4$ [M + Na]⁺ 291.0143, found 291.0145.

2g: ^1H NMR (400 MHz, CDCl_3) δ 5.46–5.44 (m, 2H), 5.39–5.37 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 165.1, 155.8, 78.2, 77.9; ^{19}F NMR (376 MHz, CDCl_3) δ -136.6 (m, 2F), -146.4 (m, 1F), -159.4 (m, 2F) ppm; IR (KBr) v_{\max} 1770, 1494, 1342, 1220, 1098, 999 cm^{-1} . High-resolution mass spectral data could not be obtained for this compound.

2h: ^1H NMR (400 MHz, CDCl_3) δ 7.29 (dd, J = 6.7, 5.5 Hz, 2H), 7.25–7.17 (m, 6H), 6.98 (d, J = 7.0 Hz, 2H), 3.75 (dd, J = 13.4, 5.6 Hz, 1H), 3.49–3.29 (m, 3H), 3.09 (ddd, J = 16.6, 11.3, 5.4 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.8, 141.8, 137.7, 129.2, 128.5, 126.8, 126.6, 126.3, 54.6, 38.5, 37.2, 36.6; IR (KBr) v_{\max} 1760, 1523, 1497, 1325 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{16}\text{F}_5\text{NNaO}_2$ [M + Na]⁺ 468.0993, found 468.0993.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.joc.7b02714](https://doi.org/10.1021/acs.joc.7b02714).

^1H and ^{13}C spectra of all new compounds; the primary mechanistic and KIE studies of the reactions ([PDF](#))

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Notes

The authors declare no competing financial interest.

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