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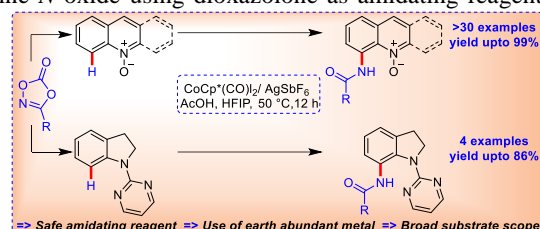
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Supporting Information

ABSTRACT: A cobalt(III)-catalyzed C8 selective C-H amidation of quinoline *N*-oxide using dioxazolone as amidating reagent under mild condition is disclosed. The reaction proceeds efficiently with excellent functional group compatibility. The utility of current method is demonstrated by gram scale synthesis of C-8 amide quinoline *N*-oxide and by converting this amidated product into functionalized quinolines. Further, developed catalytic method is also applicable for C-7 amidation of *N*-pyrimidylindolines and *ortho*-amidation of benzamides.

KEYWORDS: $Cp^*Co(III)$, C-H activation, amidation, quinoline *N*-oxide, indoline



INTRODUCTION

Quinoline is one of the important structural motifs encountered in medicinal,¹ synthetic² and material chemistry,³ and exhibits numerous biological activities. Therefore, researchers have continuously developed new synthetic methods to access novel quinoline derivatives, and during past few years transition metal-catalyzed C-H functionalization is turn out to be an effective approach for quinoline modification by C-H alkylation,⁴ alkenylation,⁵ arylation,^{4d, 6} halogenation⁷ and amidation^{7, 8} using *N*-oxide as a directing group. Among the various functionalization of quinoline, the C(8)-H amidation attracted great attention due to the abundance of 8-aminoquinoline derivatives in pharmaceutical drugs (Fig. 1).⁹ Amidation at the C8 position of quinoline is always a challenge and very few methods have been reported till date. Recent methods for C-8 amidation of quinoline *N*-oxide involved the use of Ir(III)/tosyl azide,^{7a} and use of dioxazolones,^{8a} amidobenziodoxolones,^{8b} trifluoromethylacetamide^{8c} as an amidating reagent with Rh(III) catalyst. In 2019, our group also reported the C-8 amidation of quinoline *N*-oxide with Rh(III) catalyst where NFSI was explored as a new amidating reagent (Scheme 1a).^{7b}

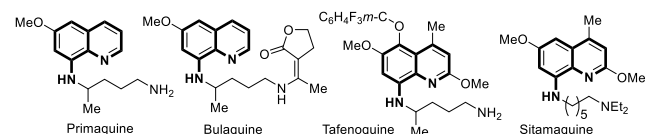
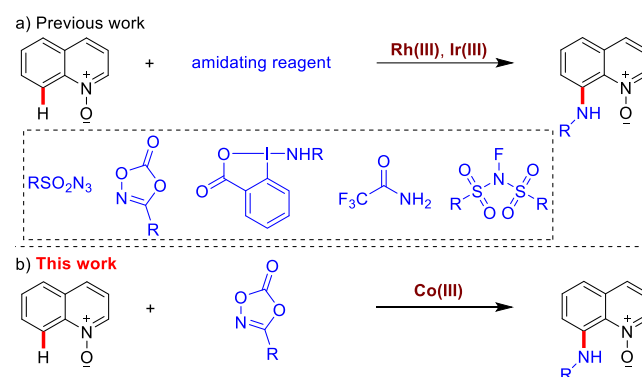


Figure 1. Structure of 8-Aminoquinoline Based Drug Molecules

Despite the high regioselectivity, broad substrate scope and excellent yield of products, all of these methods require expensive noble metal catalysts and their replacement with relatively cheap earth abundant metal is still a big challenge. Although, $CoCp^*(CO)I_2$ /dioxazolones combination has been explored for the amidation of various heterocyclic compounds such as pyridones,¹⁰ isoquinolones,¹⁰ indole,¹¹ thiophene,¹² benzo[*h*]quinoline,^{12a, 12b} and 8-methylquinoline,¹³ C-8 amidation of quinoline *N*-oxide and C-7 amidation of indoline with this combination is not disclosed till date. Incentivized from these developments and our previous work, herein, we

report the foremost $CoCp^*(CO)I_2$ -catalyzed C-8 amidation of quinoline *N*-oxide and C-7 amidation of indoline with dioxazolones under mild reaction condition.



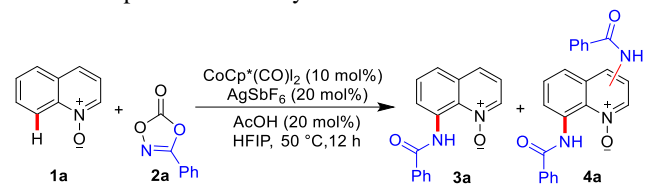
Scheme 1. C-8 Amidation of Quinoline *N*-oxides

RESULTS AND DISCUSSION

Initially quinoline *N*-oxide (**1a**) was reacted with 3-phenyl-1,4,2-dioxazol-5-one (**2a**) in the presence of $CoCp^*(CO)I_2$ (10 mol%)/ $AgSbF_6$ (20 mol%) in HFIP at 50 °C for 12 h to afford the desired C8 amidated product (**3a**) in 10% isolated yield (Table 1, entry 2). Isolated product was characterized on the basis of 1D NMR and ESI-MS spectroscopy, and finally with single-crystal X-ray diffraction (See the supporting information).¹⁴ Further, to surge the desired product yield, different bases and acids as an additive in catalytic as well as in stoichiometric amount were screened.¹⁴ Among various additives, acetic acid (20 mol%) displayed significant improvement in yield along with the formation of di-amidated product in traces (Table 1, entry 1). Di-amidated product was observed in LC-MS analysis of crude reaction mixture and isolated by further scaling up the reaction but the position of 2nd C-H amidation other than the C8 position on the quinoline moiety could not be confirmed. Lowering of temperature curtailed product yield even after increased reaction time (Table 1, entry 7). Also, change of the solvent to TFE resulted in 66% yield of **3a** (Table 1, entry 6).¹⁴ Other silver salts such as $AgNTf_2$ and $AgBF_4$ were found to be inferior

to AgSbF₆ (Table 1, entry 8–9). The control experiment indicated the indispensable role of cobalt catalyst for the amidation reaction (Table 1, entry 10). It was further noted that [IrCp*Cl₂]₂ and [Ru(*p*-cymene)Cl₂]₂ were unproductive under current reaction conditions (Table 1, entry 11–12).

Table 1. Optimization Study^a



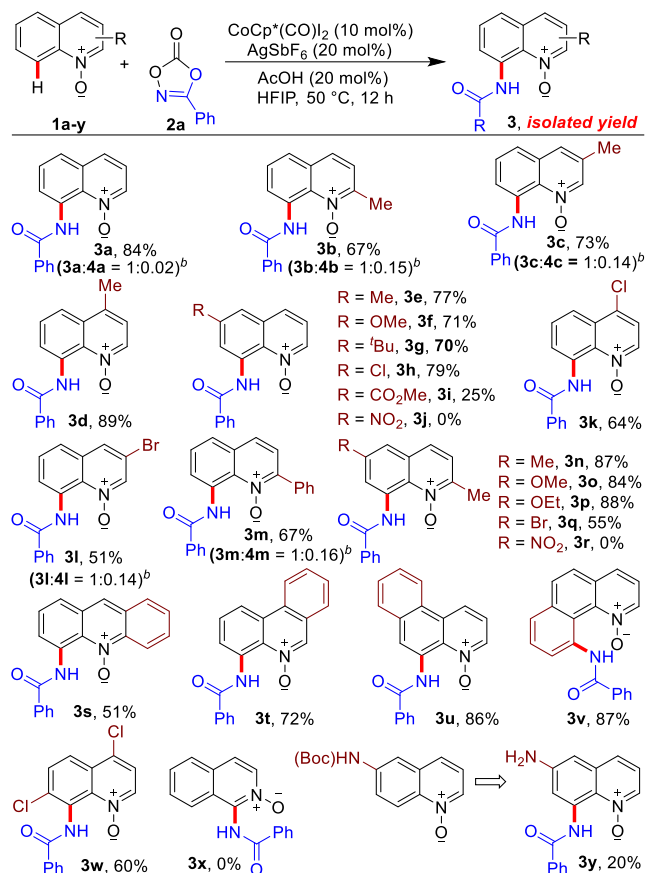
entry	variation from standard condition	3a yield (%) ^b	4a yield (%) ^b
1	none	88 (84) ^c	<5
2	without AcOH	15 (10) ^c	n.d.
3	without AgSbF ₆ and AcOH	n.r.	n.r.
4	NaOAc in place of AcOH	10	n.d.
5	AcOH (1.0 equiv.)	80	traces
6	TFE in place of HFIP	66	n.d.
7	rt for 24 h	60	n.d.
8	AgNTf ₂ in place of AgSbF ₆	76	traces
9	AgBF ₄ in place of AgSbF ₆	<10	n.d.
10	without Cp*Co(CO)I ₂	n.r.	n.r.
11	[IrCp*Cl ₂] ₂ in place of CoCp*(CO)I ₂	n.r.	n.r.
12	[Ru(<i>p</i> -cymene)Cl ₂] ₂ in place of CoCp*(CO)I ₂	n.r.	n.d.

^areaction conditions: **1a** (0.2 mmol), **2a** (1.1 equiv.), CoCp*(CO)I₂ (10 mol%), AgSbF₆ (20 mol%), AcOH (20 mol%), HFIP (0.5 mL), 50 °C, 12 h.

^bNMR yield by using TCE (1,1,2,2-tetrachloroethane) as an internal standard. ^cisolated yield in parenthesis. n.r.: no reaction, n.d.: not detected.

With best optimized conditions, substrate scope was studied with a series of quinoline *N*-oxides (Table 2). Methyl group on different positions of quinoline *N*-oxide (**1b–e**) provided the corresponding amidated products in 67–89% yields (**3b–e**). Quinoline *N*-oxide bearing -OMe, -*t*Bu and -Cl at C6-position were fully compatible and produced the desired product in 70–79% yields (**3f–h**). Although, poor conversion was observed with methylester at C6 position (**3i**) quinoline *N*-oxide with nitro group at C6 position failed to provide even the traces of the amidated product (**3j**). Halogen substituted quinoline *N*-oxide provided corresponding desired product in 51–64% yield (**3k–l**). Similar reactivity was observed with 2-phenylquinoline *N*-oxide (**3m**, 67%). Amidation of 2,6-di-substituted quinoline *N*-oxide proceeded well to afford the final product in good to excellent yields (**3n–q**). Alike 6-nitroquinoline *N*-oxide, 6-nitroquinoline *N*-oxide also failed to provide the desired product (**3r**). Polyheteroarenes (**1s–v**) also afforded amidated products in good to excellent yields (51–87%, **3s–v**). In the case of 4,7-dichloroquinoline *N*-oxide, the corresponding product **3w** was obtained in 60% yield. Isoquinoline *N*-oxide was found unsuitable under the developed reaction condition (**3x**). Moreover, -NH(Boc) protected 6-aminoquinoline *N*-oxide delivered 6-amino-8-benzamidoquinoline *N*-oxide (**3y**) in 20% yield. Along with required amidated product, the diaminated product was also obtained in case of 2-Me, 3-Me, 3-Br and 2-phenylquinoline *N*-oxides (**4a–c**, **1–m**).

Table 2. Substrate Scope with Quinoline *N*-oxides^a

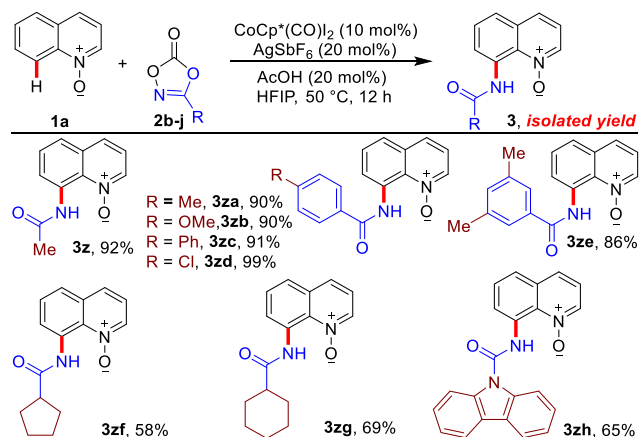


^areaction conditions: **1a** (0.2 mmol), **2a** (1.1 equiv.), CoCp*(CO)I₂ (10 mol%), AgSbF₆ (20 mol%), AcOH (20 mol%), HFIP (0.5 mL), 50 °C, 12 h.

^bratio is calculated on the basis of isolated yield.

Next, the substrate scope with 3-substituted dioxazolones was examined (Table 3).

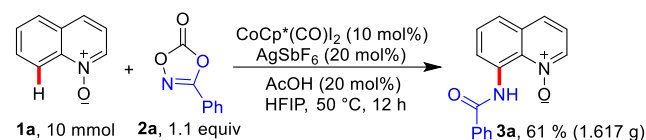
Table 3. Substrate Scope with 3-Substituted-1,4,2-dioxazol-5-one^a



^areaction conditions: **1a** (0.2 mmol), **2a** (1.1 equiv.), CoCp*(CO)I₂ (10 mol%), AgSbF₆ (20 mol%), AcOH (20 mol%), HFIP (0.5 mL), 50 °C, 12 h.

3-Methyl dioxazolone gave 92% yield of the corresponding amidated product (**3z**). Various *meta*- and *para*-substituted phenyl dioxazolones were well tolerated and provided excellent yield (86–99%) of the desired products (**3za–e**). The amidation

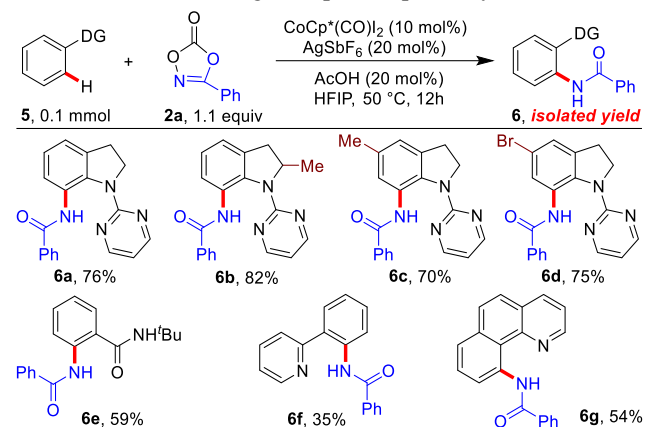
was further extended with cyclopentane and cyclohexane dioxazolone and products were isolated in good yields (**3zf–g**). Additionally, 9-carbazole dioxazolone afforded **3zh** in 65% yield. Notably, the product **3a** was isolated in 61% yield in a gram-scale synthesis (10 mmol) which shows the synthetic applicability of current work (Scheme 2).



Scheme 2. Gram Scale Synthesis

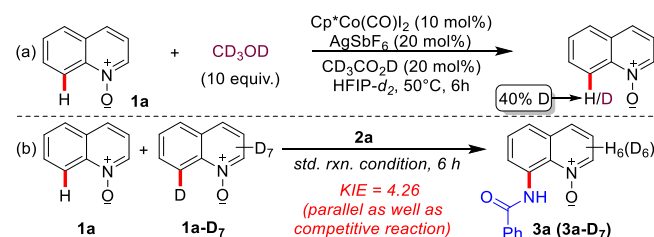
We also scrutinized one more important heterocyclic compound *i.e.* indoline under developed reaction conditions (Table 4). Here C-7 amidation was found to be favored regardless of the position of the substituent on *N*-(2-pyrimidyl) indoline affording the corresponding product (**6a–d**) in high yields (Table 4). This is first report Co(III)-catalyzed C-7 amidation of indolines.^{15–16} The structure of amidated indoline was confirmed by comparing the spectral data with literature.¹⁵ Encouraged by these initial findings, other directing group *N*Bu amide, pyridine and quinoline were also tested under current developed reaction condition for C–H amidation (Table 4) and decent yields were observed in these cases (**6e–g**).

Table 4. Other Directing Groups Compatibility^a



^areaction condition: **1a** (0.2 mmol), **2a** (1.1 equiv.), CoCp*(CO)I₂ (10 mol%), AgSbF₆ (20 mol%), AcOH (20 mol%), HFIP (0.5 mL), 50 °C, 12 h.

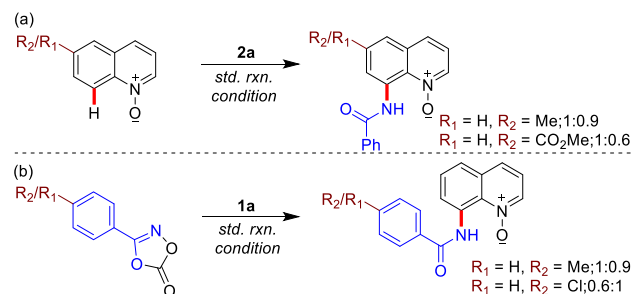
For the mechanism understanding, deuterium labeling experiments were conducted (Scheme 3).



Scheme 3. Deuterium Labeling Experiments

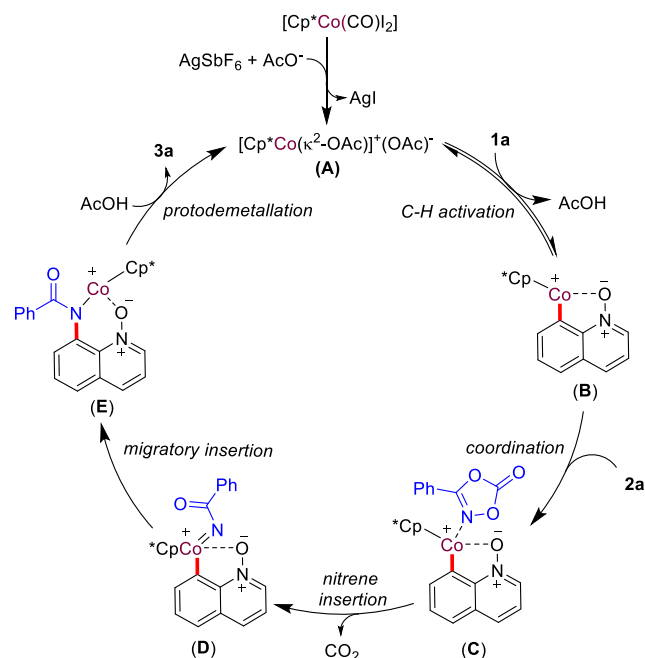
In deuterium labeling experiments, 40% deuteration was detected on the C8 position in the presence of Co(III)-catalyst without **2a**, suggesting that the C–H activation step could be reversible in nature (Scheme 3a). Competitive and parallel experiments were also carried out by reacting **1a** and **1a–D₇** with

2a (Scheme 3b). The competitive as well as parallel experiment gave *P_H/P_D* ratio 4.26 suggesting that the C–H bond cleavage might be the rate determining step. Competition experiments were conducted with electron-rich as well as electron-deficient 3-phenyl-1,4,2-dioxazolones and quinoline *N*-oxides. These experiments revealed that electron-rich quinoline *N*-oxides and electron-deficient dioxazolone are more-favored under current reaction condition (Scheme 4).



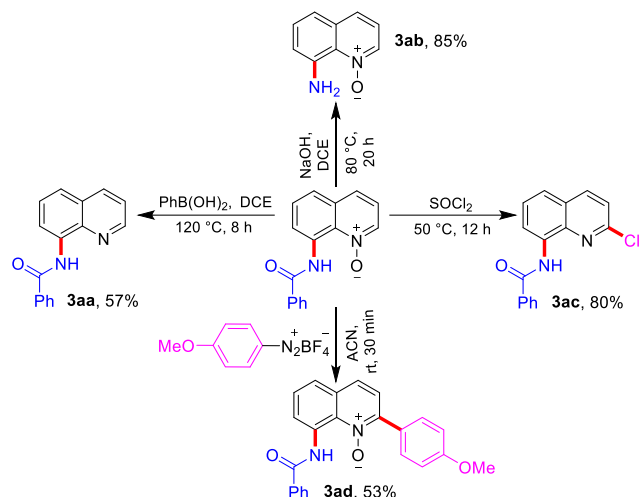
Scheme 4. Competition Experiment

On the basis of preliminary experiments and literature reports a probable mechanism was proposed (Scheme 5).^{4b, 6, 12c, 16} The reaction may proceed through reversible C8–H activation of **1a** with Co(III)-catalyst producing an intermediate **B**. The subsequent coordination of **2a** with **B** resulted in the formation of intermediate **C**. Then **2a** might undergo nitrene insertion through CO₂ extrusion in intermediate **C** to form intermediate **D**. Thereafter, migration insertion delivers the amido-inserted species **E** which on protodemetalation of **E** may give product **3a** along with the regeneration of the active cobalt species (**A**).



Scheme 5. Proposed Mechanism

Final product **3a** could be easily converted to *N*-(quinolin-8-yl)benzamide (**3aa**), 8-aminoquinoline *N*-oxide (**3ab**), *N*-(2-chloroquinolin-8-yl)benzamide (**3ac**) and 2-aryl-8-amidoquinoline *N*-oxide (**3ad**) in moderate to good yield by following the reported procedures.^{22–25}



Scheme 6. Synthetic Transformation of 3a

CONCLUSIONS

In summary, we have developed an efficient Co(III)-catalyzed coupling of quinoline *N*-oxide and indoline with diaoxazolones under mild reaction condition. The method tolerated a variety of functional groups with good to excellent yields.

EXPERIMENTAL SECTION

General Information. All reactions were carried out under air atmosphere in screw cap reaction vials, unless otherwise stated. All solvents were bought from Sigma Aldrich and TCI in sure-seal bottle and used as such. All chemicals were bought from Sigma Aldrich, Alfa-aesar and TCI. For column chromatography, silica gel (230-400 mesh) from Merck was used. A gradient elution using *n*-hexane and ethyl acetate was performed based on Merck aluminum TLC sheets (silica gel 60F₂₅₄).

Analytical information. The melting points were recorded on a Bronsted Electro thermal 9100 and Labindia visual melting range. All isolated compounds were characterized by ¹H NMR, ¹³C NMR, LC-MS and IR. In addition, all the compounds were further characterized by HRMS. Mass spectra were recorded on Water Q-ToF-Micro Micromass, maXis Impact mass spectrometers and high-resolution 6560 Ion Mobility Q-TOF LC/MS (Agilent, Santa Clara, USA). IR was analyzed by Shimadzu IR Prestige-21 with ZnSe Single reflection ATR accessory. Nuclear magnetic resonance spectra were recorded either on a Bruker-Avance 600 or 300 MHz instrument. All ¹H NMR experiments were reported in units, parts per million (ppm) and were measured relative to the signals for residual chloroform (7.26) and DMSO-*d*₆ (2.50) in the deuterated solvents. All ¹³C{¹H} NMR spectra were reported in ppm relative to deuterated chloroform (77.16) and DMSO-*d*₆ (39.52), all were obtained with ¹H decoupling. Optimization studies were done by NMR and NMR yield were calculated by using TCE (tetrachloroethane) as an internal standard.

General procedure for the synthesis of quinoline *N*-oxides.^{7b, 17} All solid reactants, *m*-CPBA (4.0 mmol) and quinoline (2.0 mmol) were added in schlenk tube and put under vacuum for 2 h, then CH₂Cl₂ (4 mL) was added at 0 °C. The reaction was allowed to stir at room temperature for 12 h. On completion, the reaction mixture was extracted with ethyl acetate and organic extract was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (230-400 mesh size) with *n*-hexane/EtOAc to afford desired *N*-oxide. Almost all synthesized *N*-oxides are known compounds. [(1a, 1b, 1c, 1d, 1e, 1f, 1h, 1i, 1j, 1l, 1v)^{17g}, (1n)^{17d} (1o, 1p)^{7b} (1k, 1q),

17e (1r)^{17a} (1s)^{17f} (1u, 1v)^{17c} (1x, 1t, 1w)^{17b}. Other quinoline *N*-oxides were used from commercially available sources and 1y was synthesized from above procedure and characterization data is given below.

Characterization Data. 6-methoxy-2-methylquinoline *N*-oxide (1y). Off white solid, Yield = 364.0 mg (70%). Isolated from flash chromatography (100% EtOAc). ¹H NMR (600 MHz, CDCl₃, δ): 8.64 (d, *J* = 9.0 Hz, 1H), 8.44 (dd, *J* = 6.0, 0.6 Hz, 1H), 8.30 (s, 1H), 8.25 (br, s, 1H, NH), 7.68 (d, *J* = 8.4 Hz, 1H), 7.66 (d, *J* = 9.0 Hz, 1H), 7.23 (dd, *J* = 8.4, 6.0 Hz, 1H), 1.47 (s, 9H). ¹³C{¹H} NMR (150 MHz, CDCl₃, δ): 153.0, 139.4, 137.7, 134.3, 131.7, 126.6, 123.7, 121.4, 120.6, 113.6, 81.2, 28.4. IR (ZnSe): ν_{max} (cm⁻¹) 3120, 2976, 1718, 1595, 1465, 1365, 1244, 1157, 1095, 970, 871, 788, 638. HRMS (ESI-TOF) (*m/z*): [M+H]⁺ calcd for C₁₄H₁₇N₂O₃, 261.1234; found, 261.1230.

General procedure for the synthesis of 3-substituted-1,4,2-dioxazol-5-ones from acid chloride.^{8a, 16d, 18} A flask was charged with hydroxylamine hydrochloride (1 equiv.), potassium carbonate (1 equiv.) and solvent (diethyl ether/water; 7.5:1). The reaction was cooled to 0 °C with vigorous stirring before addition of acid chloride (1 equivalent) dropwise. The reaction was stirred overnight, diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude hydroxamic acid product was purified by washing with pentane/diethyl ether if necessary. To the above hydroxamic acid in freshly distilled dichloromethane (50 mL) was added carbonyldiimidazole (0.50 g, 5 mmol). The reaction mixture was stirred at room temperature (10-30 min) until a high conversion was reached (as indicated by TLC). Then, a cold 1 N aqueous solution of HCl (25 mL) was added, and the mixture was extracted with dichloromethane, dried over magnesium sulfate and concentrated under reduced pressure to give the 3-substituted-1,4,2-dioxazol-5-one. Almost all synthesized dioxazolones were known compounds. (2a, 2b),^{18b} (2d)¹²ⁱ (2c, 2f)^{8a} (2i)^{18c}. Compound 2g, 2h and 2j were synthesized from above procedure and characterization data is given below.

Characterization Data. 3-(3,5-dimethylphenyl)-1,4,2-dioxazol-5-one (2g). White solid, Yield = 624.0 mg (65%). Mp 72-75 °C. Isolated from flash chromatography (10% EtOAc). ¹H NMR (600 MHz, CDCl₃, δ): 7.45 (d, *J* = 0.6 Hz, 2H), 7.26 (s, 1H), 2.39 (s, 6H). ¹³C{¹H} NMR (150 MHz, CDCl₃, δ): 163.9, 154.1, 139.4, 135.7, 124.3, 119.9, 21.3. IR (ZnSe): ν_{max} (cm⁻¹) 3153, 2906, 1793, 1502, 1438, 1382, 1232, 1192, 1083, 929, 862, 798.

3-cyclopentyl-1,4,2-dioxazol-5-one (2h). viscous liquid, Yield = 232.5 mg (30%). Isolated from flash chromatography (10% EtOAc). ¹H NMR (600 MHz, CDCl₃, δ): 3.03-3.08 (m, 1H), 2.01-2.06 (m, 2H), 1.81-1.87 (m, 2H), 1.75-1.79 (m, 2H), 1.66-1.72 (m, 2H). ¹³C{¹H} NMR (150 MHz, CDCl₃, δ): 169.6, 154.5, 35.2, 29.4, 25.5. IR (ZnSe): ν_{max} (cm⁻¹) 3153, 2956, 2872, 1793, 1670, 1440, 1247, 1192, 1093, 987, 775, 694.

3-(9H-carbazol-9-yl)-1,4,2-dioxazol-5-one (2j). White Solid, Yield = 453.6 mg (36%). Isolated from flash chromatography (10% EtOAc). ¹H NMR (600 MHz, CDCl₃, δ): 8.04 (t, *J* = 8.4 Hz, 4H), 7.53-7.56 (m, 2H), 7.44-7.47 (m, 2H). ¹³C{¹H} NMR (150 MHz, CDCl₃, δ): 157.4, 151.7, 136.5, 128.0, 126.2, 124.6, 120.6, 114.8. IR (ZnSe): ν_{max} (cm⁻¹) 3219, 2916, 1761, 1666, 1442, 1327, 1213, 1182, 1024, 985, 850, 744, 617.

General procedure for the synthesis of 1-(pyrimidin-2-yl) indoline derivatives (5a-5d).¹⁹ The indoline (2.0 mmol) and 2-chloropyrimidine (2.4 mmol, 1.2 equiv.) were dissolved in a mixture of EtOH and water (2 mL) in 4:1 ratio. Concentrated hydrochloric acid (0.2 mL or 200 μL) was added to the mixture. Then, the resulting solution was refluxed overnight. EtOH was then removed under reduced pressure, and the aqueous phase was extracted twice with ethyl acetate. The combined organic layers were dried over

Na₂SO₄, filtered, and evaporated under reduced pressure. The purification was performed by flash column chromatography on silica gel with *n*-hexane/EtOAc eluent.

1-(pyrimidin-2-yl)indoline (5a). Viscous brown, Yield = 334.9 mg (85%). Isolated from flash chromatography (5% EtOAc). ¹H NMR (600 MHz, CDCl₃, δ): 8.49 (d, *J* = 4.2 Hz, 2H), 8.41 (d, *J* = 8.4 Hz, 1H), 7.20–7.25 (m, 2H), 6.93–6.96 (m, 1H), 6.67–6.69 (m, 1H), 4.22–4.25 (m, 2H), 3.18–3.21 (m, 2H). ¹³C{¹H} NMR (150 MHz, CDCl₃, δ): 159.3, 157.5, 143.7, 132.3, 127.3, 124.7, 121.6, 115.4, 111.5, 48.8, 27.3. IR (ZnSe): ν_{max} (cm⁻¹) 3037, 2897, 1577, 1446, 1386, 1282, 1182, 991, 860. HRMS (ESI-TOF) (*m/z*): [M+H]⁺ calcd for C₁₂H₁₂N₃, 198.1026; found, 198.1022.

2-methyl-1-(pyrimidin-2-yl)indoline (5b). Viscous brown, Yield = 295.4 mg (70%). Isolated from flash chromatography (2% EtOAc). ¹H NMR (600 MHz, CDCl₃, δ): 8.48 (d, *J* = 4.2 Hz, 2H), 8.40–8.42 (m, 1H), 7.26–7.29 (m, 1H), 7.24 (d, *J* = 7.8 Hz, 1H), 6.98–7.00 (m, 1H), 6.65 (t, *J* = 4.8 Hz, 1H), 4.99–5.04 (m, 1H), 3.43–3.47 (m, 1H), 2.73 (d, *J* = 15.6 Hz, 1H), 1.39 (d, *J* = 6.6 Hz, 3H). ¹³C{¹H} NMR (150 MHz, CDCl₃, δ): 158.9, 157.5, 142.5, 131.1, 127.2, 124.9, 121.7, 116.2, 111.3, 55.8, 35.7, 20.0. IR (ZnSe): ν_{max} (cm⁻¹) 3037, 1581, 1487, 1346, 1280, 1118, 1078, 975, 854, 756, 640. HRMS (ESI-TOF) (*m/z*): [M+H]⁺ calcd for C₁₃H₁₄N₃, 212.1182; found, 212.1180.

5-methyl-1-(pyrimidin-2-yl)indoline (5c). Light brown solid, Yield = 337.6 mg (80%). Mp 50–52 °C. Isolated from flash chromatography (5% EtOAc). ¹H NMR (600 MHz, CDCl₃, δ): 8.47 (d, *J* = 4.8 Hz, 2H), 8.27–8.29 (m, 1H), 7.02–7.04 (m, 2H), 6.64–6.65 (m, 1H), 4.20–4.23 (m, 2H), 3.15–3.18 (m, 2H), 2.33 (s, 3H). ¹³C{¹H} NMR (150 MHz, CDCl₃, δ): 159.3, 157.5, 141.4, 132.4, 131.0, 127.7, 125.5, 115.2, 111.1, 48.9, 27.3, 20.9. IR (ZnSe): ν_{max} (cm⁻¹) 2922, 1579, 1492, 1444, 1388, 1280, 1188, 1078, 970, 815, 790, 636. HRMS (ESI-TOF) (*m/z*): [M+H]⁺ calcd for C₁₃H₁₄N₃, 212.1182; found, 212.1179.

5-bromo-1-(pyrimidin-2-yl)indoline (5d). Brown solid, Yield = 412.5 mg (76%). Mp 92–95 °C. Isolated from flash chromatography (5% EtOAc). ¹H NMR (600 MHz, CDCl₃, δ): 8.48 (d, *J* = 4.8 Hz, 2H), 8.27 (d, *J* = 9.0 Hz, 1H), 7.29–7.30 (m, 2H), 6.71 (t, *J* = 4.8 Hz, 1H), 4.22–4.24 (m, 2H), 3.16–3.19 (m, 2H). ¹³C{¹H} NMR (150 MHz, CDCl₃, δ): 159.2, 157.6, 142.9, 134.7, 130.1, 127.7, 116.8, 113.8, 111.9, 48.9, 27.1. IR (ZnSe): ν_{max} (cm⁻¹) 2922, 1577, 1494, 1342, 1278, 1172, 1078, 948, 823, 786. HRMS (ESI-TOF) (*m/z*): [M+H]⁺ calcd for C₁₂H₁₁BrN₃, 276.0131; found, 276.0129.

General procedure for the synthesis of 8-amidoquinoline *N*-oxides. To a solution of various substituted quinoline *N*-oxide (**1a–y**) (0.2 mmol) in HFIP (0.5 mL per mmol) in a reaction vial equipped with magnetic stir bar, 3-substituted-1,4,2-dioxazol-5-one (**2a–j**) (1.1 equiv.), [CoCOP*₂I₂] (10 mol%), AgSbF₆ (20 mol%) and AcOH (20 mol%) were added. The reaction mixture was stirred at 50 °C for 12 h on a heating block, filtered through a pad of celite using ethyl acetate solvent. After that, filtrate was transferred to round bottom flask and organic solvents were removed under reduced pressure. The residue was purified by flash chromatography on silica gel (mesh 230–400) to give the desired product. Eluting solvents for chromatography are indicated under the specific compound headings.

Gram scale experiment for preparation of 3a. In a round-bottom flask equipped with magnetic stir bar, quinoline *N*-oxide (**1a**) (1.810 g, 10 mmol) in HFIP (50 mL, 0.5 mL per mmol), 3-phenyl-1,4,2-dioxazol-5-one (**2a**) (1.793 g, 1.1 equiv.), [CoCp*(CO)I₂] (0.476 g, 10 mol%), AgSbF₆ (0.687 g, 20 mol%) and AcOH (115 μL, 20 mol%) were added. The reaction mixture was stirred at 50 °C for 12 h, filtered through a pad of celite using ethyl acetate solvent. After that filtrate was transferred to round bottom flask and organic solvents were removed under reduced pressure. The crude product was purified by column chromatography on silica gel (230–400) with 60% EtOAc/*n*-hexane to obtain 1.617 gram of **3a**, yield 61%.

Characterization Data. **8-benzamidoquinoline *N*-oxide** (Table 2, entry **3a**).¹⁶ Brown solid, Yield = 44.5 mg (84%). Mp 137–140 °C. Isolated from flash chromatography (60% EtOAc/*n*-hexane). ¹H NMR (600 MHz, CDCl₃, δ): 15.19 (br, s, 1H, NH), 9.27 (d, *J* = 7.8 Hz, 1H), 8.40 (d, *J* = 6.0 Hz, 1H), 8.08 (d, *J* = 7.2 Hz, 2H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.60–7.63 (m, 1H), 7.50–7.55 (m, 4H), 7.40 (dd, *J* = 7.8, 6.6 Hz, 1H). ¹³C{¹H} NMR (150 MHz, CDCl₃, δ): 165.7, 137.6, 135.2, 134.8, 132.4, 131.9, 131.2, 129.9, 129.7, 128.9, 127.5, 122.3, 120.8, 119.7. IR (ZnSe): ν_{max} (cm⁻¹) 3076, 2852, 2326, 1654, 1537, 1489, 1344, 1257, 1159, 1033, 883, 746, 646. HRMS (ESI-TOF) (*m/z*): [M+H]⁺ calcd for C₁₆H₁₃N₂O₂, 265.0974; found, 265.0974.

8-benzamido-2-methylquinoline *N*-oxide (Table 2, entry **3b**).²⁰ Brown solid, Yield = 37.3 mg (67%). Mp 142–145 °C. Isolated from flash chromatography (40% EtOAc/*n*-hexane). ¹H NMR (600 MHz, CDCl₃, δ): 15.41 (br, s, 1H, NH), 9.26 (d, *J* = 8.4 Hz, 1H), 8.10–8.12 (m, 2H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.56–7.58 (m, 1H), 7.51–7.55 (m, 3H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 1H), 2.69 (s, 3H). ¹³C{¹H} NMR (150 MHz, CDCl₃, δ): 165.7, 147.6, 135.5, 134.5, 131.8, 131.4, 131.2, 128.9, 128.8, 128.2, 127.5, 122.9, 122.4, 119.7, 19.3. IR (ZnSe): ν_{max} (cm⁻¹) 3053, 2848, 2328, 1653, 1537, 1435, 1355, 1257, 1170, 1074, 877, 750, 651. HRMS (ESI-TOF) (*m/z*): [M+H]⁺ calcd for C₁₇H₁₅N₂O₂, 279.1128; found, 279.1129.

8-benzamido-3-methylquinoline *N*-oxide (Table 2, entry **3c**). Brown solid, Yield = 40.6 mg (73%). Mp 212–214 °C. Isolated from flash chromatography (35% EtOAc/*n*-hexane). ¹H NMR (600 MHz, CDCl₃, δ): 15.14 (br, s, 1H, NH), 9.18 (d, *J* = 7.8 Hz, 1H), 8.28 (s, 1H), 8.08 (d, *J* = 8.4 Hz, 2H), 7.54–7.58 (m, 2H), 7.53 (d, *J* = 6.6 Hz, 1H), 7.49–7.52 (m, 2H), 7.41 (d, *J* = 7.8 Hz, 1H), 2.43 (s, 3H). ¹³C{¹H} NMR (150 MHz, CDCl₃, δ): 165.6, 138.8, 135.3, 134.6, 132.2, 131.9, 131.2, 129.8, 129.4, 129.1, 128.9, 127.5, 121.7, 118.7, 18.5. IR (ZnSe): ν_{max} (cm⁻¹) 3061, 2920, 2326, 1662, 1535, 1450, 1384, 1261, 1190, 1056, 993, 873, 788, 690. HRMS (ESI-TOF) (*m/z*): [M+H]⁺ calcd for C₁₇H₁₅N₂O₂, 279.1128; found, 279.1130.

8-benzamido-4-methylquinoline *N*-oxide (Table 2, entry **3d**). Brown solid, Yield = 49.5 mg (89%). Mp 183–185 °C. Isolated from flash chromatography (35% EtOAc/*n*-hexane). ¹H NMR (600 MHz, CDCl₃, δ): 15.53 (br, s, 1H, NH), 9.30 (d, *J* = 7.8 Hz, 1H), 8.30–8.32 (m, 1H), 8.09 (d, *J* = 5.4 Hz, 2H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.51–7.52 (m, 3H), 7.13–7.15 (m, 1H), 2.63 (s, 3H). ¹³C{¹H} NMR (150 MHz, CDCl₃, δ): 165.7, 137.9, 136.7, 135.4, 131.9, 131.6, 129.7, 128.9, 127.5, 121.6, 119.7, 118.6, 19.5. IR (ZnSe): ν_{max} (cm⁻¹) 3047, 2816, 2328, 1656, 1535, 1487, 1305, 1159, 893, 707, 630. HRMS (ESI-TOF) (*m/z*): [M+H]⁺ calcd for C₁₇H₁₅N₂O₂, 279.1128; found, 279.1130.

8-benzamido-6-methylquinoline *N*-oxide (Table 2, entry **3e**). Brown solid, Yield = 42.8 mg (77%). Mp 208–210 °C. Isolated from flash chromatography (35% EtOAc/*n*-hexane). ¹H NMR (600 MHz, CDCl₃, δ): 15.16 (br, s, 1H, NH), 9.14 (s, 1H), 8.33 (d, *J* = 5.4 Hz, 1H), 8.07–8.09 (m, 2H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.50–7.55 (m, 3H), 7.27 (s, 1H), 7.23 (dd, *J* = 8.4, 6.6 Hz, 1H), 2.52 (s, 3H). ¹³C{¹H} NMR (150 MHz, CDCl₃, δ): 165.6, 140.5, 136.8, 135.2, 134.4, 132.5, 131.9, 129.8, 128.93, 128.87, 127.4, 121.5, 121.4, 120.8, 22.0. IR (ZnSe): ν_{max} (cm⁻¹) 3116, 2918, 2850, 1653, 1573, 1481, 1371, 1296, 1138, 1041, 985, 879, 707, 682. HRMS (ESI-TOF) (*m/z*): [M+H]⁺ calcd for C₁₇H₁₅N₂O₂, 279.1128; found, 279.1133.

8-benzamido-6-methoxyquinoline *N*-oxide (Table 2, entry **3f**). Brown solid, Yield = 41.7 mg (71%). Mp 200–204 °C. Isolated from flash chromatography (50% EtOAc/*n*-hexane). ¹H NMR (600 MHz, CDCl₃, δ): 15.28 (br, s, 1H, NH), 9.03–9.05 (m, 1H), 8.25–8.27 (m, 1H), 8.07–8.09 (m, 2H), 7.68 (t, *J* = 7.2 Hz, 1H), 7.53–7.56 (m, 1H), 7.50–7.53 (m, 2H), 7.21–7.25 (m, 1H), 6.82–6.83 (m, 1H), 3.95 (s, 3H). ¹³C{¹H} NMR (150 MHz, CDCl₃, δ): 165.8, 159.8, 136.1, 135.5, 135.1, 133.7, 131.9, 128.9, 128.4, 127.5,

121.1, 110.3, 101.8, 55.9. IR (ZnSe): ν_{\max} (cm⁻¹) 3558, 2922, 2850, 2337, 1620, 1548, 1423, 1174, 1031, 837, 642. HRMS (ESI-TOF) (m/z): [M+H]⁺ calcd for C₁₇H₁₅N₂O₃, 295.1077; found, 295.1069.

8-benzamido-6-(tert-butyl)quinoline N-oxide (Table 2, entry **3g**). Brown solid. Yield = 44.8 mg (70%). Mp 204–206 °C. Isolated from flash chromatography (40% EtOAc/*n*-hexane). ¹H NMR (600 MHz, CDCl₃, δ): 15.15 (br, s, 1H, NH), 9.48 (d, *J* = 2.4 Hz, 1H), 8.36 (d, *J* = 6.0 Hz, 1H), 8.09–8.11 (m, 2H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.53–7.54 (m, 1H), 7.50–7.52 (m, 2H), 7.45 (d, *J* = 1.8 Hz, 1H), 7.27 (dd, *J* = 8.4, 6.0 Hz, 1H), 1.45 (s, 9H). ¹³C{¹H} NMR (150 MHz, CDCl₃, δ): 165.7, 153.4, 136.9, 135.3, 134.4, 132.4, 131.9, 129.8, 129.6, 128.9, 127.4, 120.6, 118.8, 117.8, 35.5, 31.1. IR (ZnSe): ν_{\max} (cm⁻¹) 3082, 2958, 2326, 1664, 1523, 1481, 1357, 1296, 1166, 1039, 862, 742. HRMS (ESI-TOF) (m/z): [M+H]⁺ calcd for C₂₀H₂₁N₂O₂, 321.1598; found, 321.1599.

8-benzamido-6-chloroquinoline N-oxide (Table 2, entry **3h**). Brown solid. Yield = 47.1 mg (79%). Mp 232–235 °C. Isolated from flash chromatography (30% EtOAc/*n*-hexane). ¹H NMR (600 MHz, CDCl₃, δ): 15.23 (br, s, 1H, NH), 9.33 (d, *J* = 2.4 Hz, 1H), 8.38 (dd, *J* = 6.0, 0.6 Hz, 1H), 8.06–8.08 (m, 2H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.57 (t, *J* = 7.2 Hz, 1H), 7.52 (t, *J* = 7.2 Hz, 2H), 7.49 (d, *J* = 1.8 Hz, 1H), 7.32 (dd, *J* = 8.4, 6.0 Hz, 1H). ¹³C{¹H} NMR (150 MHz, CDCl₃, δ): 165.8, 137.5, 136.2, 136.1, 134.7, 132.9, 132.3, 129.9, 128.9, 128.4, 127.5, 121.8, 120.6, 119.7. IR (ZnSe): ν_{\max} (cm⁻¹) 3120, 2922, 2852, 2328, 1656, 1527, 1477, 1396, 1286, 1165, 1097, 908, 835, 707. HRMS (ESI-TOF) (m/z): [M+Na]⁺ calcd for C₁₆H₁₁ClN₂NaO₂, 321.0401; found, 321.0423.

8-benzamido-6-(methoxycarbonyl)quinoline N-oxide (Table 2, entry **3i**). Brown solid. Yield = 16.1 mg (25%). Mp 237–241 °C. Isolated from flash chromatography (50% EtOAc/*n*-hexane). ¹H NMR (600 MHz, CDCl₃, δ): 15.02 (br, s, 1H, NH), 9.79 (d, *J* = 1.8 Hz, 1H), 8.50 (dd, *J* = 6.0, 0.6 Hz, 1H), 8.26 (d, *J* = 1.8 Hz, 1H), 8.07–8.08 (m, 2H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.54–7.57 (m, 1H), 7.50–7.53 (m, 2H), 7.39 (dd, *J* = 8.4, 6.0 Hz, 1H), 4.01 (s, 3H). ¹³C{¹H} NMR (150 MHz, CDCl₃, δ): 165.8, 165.7, 139.2, 135.3, 134.8, 132.8, 132.2, 132.0, 131.4, 130.8, 128.9, 127.5, 124.5, 121.7, 118.8, 52.9. IR (ZnSe): ν_{\max} (cm⁻¹) 3120, 3076, 2920, 1728, 1653, 1537, 1409, 1286, 1174, 1093, 999, 879, 704, 655. HRMS (ESI-TOF) (m/z): [M+Na]⁺ calcd for C₁₈H₁₄N₂NaO₄, 345.0846; found, 345.0845.

8-benzamido-4-chloroquinoline N-oxide (Table 2, entry **3k**). Brown solid. Yield = 38.1 mg (64%). Mp 177–179 °C. Isolated from flash chromatography (50% EtOAc/*n*-hexane). ¹H NMR (600 MHz, CDCl₃, δ): 15.19 (br, s, 1H, NH), 9.35–9.37 (m, 1H), 8.29–8.31 (m, 1H), 8.06 (d, *J* = 7.8 Hz, 2H), 7.87–7.89 (m, 1H), 7.71–7.75 (m, 1H), 7.53–7.56 (m, 1H), 7.50–7.52 (m, 2H), 7.38–7.40 (m, 1H). ¹³C{¹H} NMR (150 MHz, CDCl₃, δ): 165.7, 136.7, 135.4, 135.0, 133.7, 132.1, 131.6, 130.9, 129.7, 128.9, 127.5, 121.1, 120.5, 118.9. IR (ZnSe): ν_{\max} (cm⁻¹) 2897, 2850, 1674, 1579, 1381, 1257, 1197, 1089, 920, 831, 794, 688. HRMS (ESI-TOF) (m/z): [M+H]⁺ calcd for C₁₆H₁₂ClN₂O₂, 299.0582; found, 299.0586.

8-benzamido-3-bromoquinoline N-oxide (Table 2, entry **3l**). Brown solid. Yield = 34.9 mg (51%). Mp 180–183 °C. Isolated from flash chromatography (30% EtOAc/*n*-hexane). ¹H NMR (600 MHz, CDCl₃, δ): 14.75 (br, s, 1H, NH), 9.25 (dd, *J* = 8.4, 1.2 Hz, 1H), 8.47 (d, *J* = 1.2 Hz, 1H), 8.04–8.06 (m, 2H), 7.92 (d, *J* = 1.2 Hz, 1H), 7.61–7.64 (m, 1H), 7.54–7.57 (m, 1H), 7.50–7.53 (m, 2H), 7.41 (dd, *J* = 7.8, 0.6 Hz, 1H). ¹³C{¹H} NMR (150 MHz, CDCl₃, δ): 165.7, 146.6, 138.6, 134.9, 132.2, 132.1, 130.83, 130.80, 130.1, 128.9, 127.5, 121.4, 119.7, 113.9. IR (ZnSe): ν_{\max} (cm⁻¹) 2964, 1660, 1552, 1479, 1352, 1294, 1159, 1072, 889, 748, 694. HRMS (ESI-TOF) (m/z): [M+H]⁺ calcd for C₁₆H₁₂BrN₂O₂, 343.0077; found, 343.0072.

8-benzamido-2-phenylquinoline N-oxide (Table 2, entry **3m**). Brown solid. Yield = 45.6 mg (67%). Mp 202–205 °C. Isolated from flash chromatography (15% EtOAc/*n*-hexane). ¹H NMR (600 MHz, CDCl₃, δ): 15.34 (br, s, 1H, NH), 9.32 (d, *J* = 8.4 Hz, 1H),

8.06–8.08 (m, 2H), 7.88–7.89 (m, 2H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.61–7.64 (m, 1H), 7.53–7.56 (m, 2H), 7.50–7.51 (m, 3H), 7.47–7.49 (m, 2H), 7.42 (d, *J* = 8.4 Hz, 1H). ¹³C{¹H} NMR (150 MHz, CDCl₃, δ): 165.7, 146.9, 135.4, 135.3, 133.4, 131.8, 131.7, 131.6, 129.9, 129.8, 129.5, 128.8, 128.6, 128.5, 127.6, 123.5, 122.4, 120.2. IR (ZnSe): ν_{\max} (cm⁻¹) 3064, 2962, 1660, 1552, 1479, 1352, 1294, 1159, 1079, 848, 748, 677. HRMS (ESI-TOF) (m/z): [M+H]⁺ calcd for C₂₂H₁₇N₂O₂, 341.1285; found, 341.1276.

8-benzamido-2,6-dimethylquinoline N-oxide (Table 2, entry **3n**). Brown solid. Yield = 50.8 mg (87%). Mp 172–175 °C. Isolated from flash chromatography (40% EtOAc/*n*-hexane). ¹H NMR (600 MHz, CDCl₃, δ): 15.37 (br, s, 1H, NH), 9.08 (d, *J* = 1.8 Hz, 1H), 8.08–8.09 (m, 2H), 7.49–7.53 (m, 4H), 7.16–7.18 (m, 2H), 2.62 (s, 3H), 2.46 (s, 3H). ¹³C{¹H} NMR (150 MHz, CDCl₃, δ): 165.5, 146.6, 138.9, 135.4, 133.9, 131.7, 131.1, 129.8, 128.8, 127.7, 127.4, 122.8, 121.6, 121.3, 21.8, 19.1. IR (ZnSe): ν_{\max} (cm⁻¹) 3061, 2916, 2850, 2335, 1651, 1577, 1440, 1398, 1294, 1182, 1105, 1033, 881, 707, 644. HRMS (ESI-TOF) (m/z): [M+H]⁺ calcd for C₁₈H₁₇N₂O₂, 293.1285; found, 293.1298.

8-benzamido-6-methoxy-2-methylquinoline N-oxide (Table 2, entry **3o**). Brown solid. Yield = 51.7 mg (84%). Mp 200–203 °C. Isolated from flash chromatography (60% EtOAc/*n*-hexane). ¹H NMR (600 MHz, CDCl₃, δ): 15.45 (br, s, 1H, NH), 8.94 (d, *J* = 3.0 Hz, 1H), 8.07–8.08 (m, 2H), 7.50–7.53 (m, 3H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.14 (d, *J* = 8.4 Hz, 1H), 6.71 (d, *J* = 2.4 Hz, 1H), 3.88 (s, 3H), 2.59 (s, 3H). ¹³C{¹H} NMR (150 MHz, CDCl₃, δ): 165.6, 158.8, 145.2, 135.6, 135.3, 132.2, 131.8, 128.8, 127.4, 127.35, 127.32, 123.2, 109.9, 101.9, 55.7, 18.9. IR (ZnSe): ν_{\max} (cm⁻¹) 3008, 2922, 2848, 2339, 1660, 1573, 1454, 1327, 1288, 1180, 1049, 921, 867, 798, 651. HRMS (ESI-TOF) (m/z): [M+H]⁺ calcd for C₁₈H₁₇N₂O₃, 309.1234; found, 309.1236.

8-benzamido-6-ethoxy-2-methylquinoline N-oxide (Table 2, entry **3p**). Brown solid. Yield = 56.7 mg (88%). Mp 171–173 °C. Isolated from flash chromatography (60% EtOAc/*n*-hexane). ¹H NMR (600 MHz, CDCl₃, δ): 15.45 (br, s, 1H, NH), 8.99–9.02 (m, 1H), 8.09 (d, *J* = 7.2 Hz, 2H), 7.50–7.55 (m, 4H), 7.17–7.20 (m, 1H), 6.75–6.77 (m, 1H), 4.13–4.16 (m, 2H), 2.62 (s, 3H), 1.45–1.47 (m, 3H). ¹³C{¹H} NMR (150 MHz, CDCl₃, δ): 165.7, 158.3, 145.1, 135.6, 135.4, 132.3, 131.8, 128.9, 127.5, 127.41, 127.36, 123.2, 110.4, 102.8, 64.1, 18.9, 14.8. IR (ZnSe): ν_{\max} (cm⁻¹) 3099, 2985, 2868, 2349, 1651, 1577, 1492, 1375, 1292, 1271, 1170, 1051, 869, 705, 642. HRMS (ESI-TOF) (m/z): [M+H]⁺ calcd for C₁₉H₁₉N₂O₃, 323.1390; found, 323.1398.

8-benzamido-6-bromo-2-methylquinoline N-oxide (Table 2, entry **3q**). Brown solid. Yield = 39.3 mg (55%). Mp 227–229 °C. Isolated from flash chromatography (40% EtOAc/*n*-hexane). ¹H NMR (600 MHz, CDCl₃, δ): 15.44 (br, s, 1H, NH), 9.43 (d, *J* = 2.4 Hz, 1H), 8.08 (dd, *J* = 7.8, 1.2 Hz, 2H), 7.60 (d, *J* = 2.4 Hz, 1H), 7.55–7.58 (m, 2H), 7.53–7.55 (m, 2H), 7.31 (d, *J* = 8.4 Hz, 1H), 2.66 (s, 3H). ¹³C{¹H} NMR (150 MHz, CDCl₃, δ): 165.7, 147.9, 135.6, 134.9, 132.1, 131.9, 130.3, 128.9, 127.5, 127.0, 124.0, 123.9, 122.9, 122.2, 19.3. IR (ZnSe): ν_{\max} (cm⁻¹) 2922, 1654, 1595, 1489, 1355, 1280, 1176, 1043, 889, 761, 694. HRMS (ESI-TOF) (m/z): [M+H]⁺ calcd for C₁₇H₁₄BrN₂O₂, 357.0233; found, 357.0230.

4-benzamidoacridine N-oxide (Table 2, entry **3s**). Orange solid. Yield = 32.0 mg (51%). Mp 195–197 °C. Isolated from flash chromatography (20% EtOAc/*n*-hexane). ¹H NMR (600 MHz, CDCl₃, δ): 15.55 (br, s, 1H, NH), 9.29 (d, *J* = 7.8 Hz, 1H), 8.83 (d, *J* = 9.0 Hz, 1H), 8.33 (s, 1H), 8.17–8.18 (m, 2H), 7.97 (d, *J* = 8.4 Hz, 1H), 7.81–7.84 (m, 1H), 7.60–7.65 (m, 2H), 7.55–7.57 (m, 4H). ¹³C{¹H} NMR (150 MHz, CDCl₃, δ): 165.7, 140.2, 135.5, 134.1, 132.0, 131.9, 131.3, 129.3, 129.0, 128.9, 128.4, 128.1, 127.9, 127.6, 127.2, 122.8, 119.5, 119.1. IR (ZnSe): ν_{\max} (cm⁻¹) 3282, 2924, 2346, 1616, 1537, 1438, 1396, 1184, 1093, 896, 734, 653. HRMS (ESI-TOF) (m/z): [M+H]⁺ calcd for C₂₀H₁₅N₂O₂, 315.1128; found, 315.1122.

4-benzamidophenanthridine N-oxide (Table 2, entry **3t**). Brown solid, Yield = 45.2 mg (72%). Mp 217–219 °C. Isolated from flash chromatography (60% EtOAc/*n*-hexane). ¹H NMR (600 MHz, CDCl₃, δ): 15.41 (br, s, 1H, NH), 9.38 (dd, *J* = 7.8, 1.2 Hz, 1H), 8.78 (s, 1H), 8.49 (d, *J* = 8.4 Hz, 1H), 8.28 (dd, *J* = 7.8, 0.6 Hz, 1H), 8.11–8.12 (m, 2H), 7.78–7.81 (m, 3H), 7.68–7.71 (m, 1H), 7.52–7.56 (m, 3H). ¹³C{¹H} NMR (150 MHz, CDCl₃, δ): 165.8, 136.9, 136.1, 135.5, 131.9, 130.9, 130.4, 129.4, 128.9, 128.6, 128.0, 127.6, 127.3, 126.5, 125.9, 122.8, 120.4, 116.9. IR (ZnSe): ν_{max} (cm⁻¹) 3061, 2924, 2854, 1660, 1548, 1475, 1368, 1159, 1072, 889, 750, 694. HRMS (ESI-TOF) (*m/z*): [M+H]⁺ calcd for C₂₀H₁₅N₂O₂, 315.1128; found, 315.1128.

5-benzamidobenzof[quinoline N-oxide (Table 2, entry **3u**). Brown solid, Yield = 54.0 mg (86%). Mp 196–198 °C. Isolated from flash chromatography (70% EtOAc/*n*-hexane). ¹H NMR (600 MHz, CDCl₃, δ): 15.30 (br, s, 1H, NH), 9.62 (s, 1H), 8.72 (d, *J* = 8.4 Hz, 1H), 8.55 (d, *J* = 6.6 Hz, 1H), 8.46 (d, *J* = 8.4 Hz, 1H), 8.12 (dd, *J* = 7.8, 1.2 Hz, 2H), 7.94 (d, *J* = 7.8 Hz, 1H), 7.68–7.70 (m, 1H), 7.61–7.64 (m, 1H), 7.52–7.57 (m, 4H). ¹³C{¹H} NMR (150 MHz, CDCl₃, δ): 165.9, 138.5, 136.7, 135.3, 133.0, 132.8, 131.9, 131.3, 130.7, 129.5, 128.9, 127.4, 126.9, 125.1, 124.2, 123.0, 121.4, 119.6. IR (ZnSe): ν_{max} (cm⁻¹) 2850, 1726, 1649, 1523, 1408, 1355, 1274, 1176, 1080, 977, 881, 754, 671. HRMS (ESI-TOF) (*m/z*): [M+H]⁺ calcd for C₂₀H₁₅N₂O₂, 315.1128; found, 315.1123.

10-benzamidobenzof[quinoline N-oxide (Table 2, entry **3v**). Brown solid, Yield = 54.6 mg (87%). Mp 218–220 °C. Isolated from flash chromatography (80% EtOAc/*n*-hexane). ¹H NMR (600 MHz, CDCl₃, δ): 12.91 (br, s, 1H, NH), 8.70 (dd, *J* = 6.6, 1.2 Hz, 1H), 8.32 (dd, *J* = 7.8, 1.2 Hz, 1H), 8.21–8.23 (m, 2H), 7.87–7.90 (m, 2H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.74 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.55 (d, *J* = 4.8 Hz, 1H), 7.53–7.54 (m, 2H), 7.52 (d, *J* = 1.2 Hz, 1H), 7.50–7.51 (m, 1H). ¹³C{¹H} NMR (150 MHz, CDCl₃, δ): 165.9, 140.0, 139.0, 138.0, 136.5, 135.7, 132.2, 131.6, 131.4, 129.9, 128.6, 128.1, 128.0, 125.9, 124.4, 124.2, 121.9, 117.9. IR (ZnSe): ν_{max} (cm⁻¹) 3066, 2922, 2850, 2339, 1658, 1566, 1485, 1390, 1290, 1163, 1001, 916, 842, 796, 626. HRMS (ESI-TOF) (*m/z*): [M+H]⁺ calcd for C₂₀H₁₅N₂O₂, 315.1128; found, 315.1133.

8-benzamido-4,7-dichloroquinoline N-oxide (Table 2, entry **3w**). Brown solid, Yield = 39.9 mg (60%). Mp 193–195 °C. Isolated from flash chromatography (20% EtOAc/*n*-hexane). ¹H NMR (600 MHz, CDCl₃, δ): 13.28 (br, s, 1H, NH), 8.29 (d, *J* = 6.6 Hz, 1H), 8.08–8.09 (m, 2H), 7.98 (d, *J* = 9.0 Hz, 1H), 7.81 (d, *J* = 9.0 Hz, 1H), 7.55–7.58 (m, 1H), 7.49–7.52 (m, 2H), 7.39 (d, *J* = 6.6 Hz, 1H). ¹³C{¹H} NMR (150 MHz, CDCl₃, δ): 164.8, 137.7, 135.9, 134.1, 132.9, 132.60, 132.57, 132.4, 131.4, 128.9, 128.30, 128.27, 121.7, 121.4. IR (ZnSe): ν_{max} (cm⁻¹) 3523, 2922, 2326, 1672, 1510, 1452, 1330, 1273, 1174, 1056, 921, 821, 792, 621. HRMS (ESI-TOF) (*m/z*): [M+H]⁺ calcd for C₁₆H₁₁Cl₂N₂O₂, 333.0192, found 333.0193.

6-amino-8-benzamidoquinoline N-oxide (Table 2, entry **3y**). Brown solid, Yield = 11.2 mg (20%). Mp 124–126 °C. Isolated from flash chromatography (50% EtOAc/*n*-hexane). ¹H NMR (600 MHz, DMSO-*d*₆, δ): 15.51 (br, s, 1H, NH), 8.49 (d, *J* = 2.4 Hz, 1H), 8.06 (d, *J* = 5.4 Hz, 1H), 7.84 (d, *J* = 7.2 Hz, 2H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.49–7.52 (m, 1H), 7.46 (t, *J* = 7.2 Hz, 2H), 7.16 (dd, *J* = 8.4, 6.0 Hz, 1H), 6.48 (d, *J* = 2.4 Hz, 1H), 5.94 (br, s, 2H, NH₂). ¹³C{¹H} NMR (150 MHz, DMSO-*d*₆, δ): 164.1, 149.1, 134.9, 134.5, 134.1, 133.4, 132.0, 129.0, 127.2, 126.9, 123.6, 121.6, 109.0, 100.6. IR (ZnSe): ν_{max} (cm⁻¹) 3593, 1726, 1641, 1541, 1409, 1365, 1240, 1151, 1039, 896, 734, 653. HRMS (ESI-TOF) (*m/z*): [M+H]⁺ calcd for C₁₆H₁₄N₃O₂, 280.1081; found, 280.1079.

8-acetamidoquinoline N-oxide (Table 3, entry **3z**).²⁰ Black solid, Yield = 37.2 mg (92%). Isolated from flash chromatography (70% EtOAc/*n*-hexane). ¹H NMR (600 MHz, CDCl₃, δ): 14.08 (br, s, 1H, NH), 9.01 (dd, *J* = 8.4, 1.2 Hz, 1H), 8.35 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.54–7.57 (m, 1H), 7.46 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.25–7.27 (m, 1H), 2.26 (s, 3H). ¹³C{¹H} NMR (150

MHz, CDCl₃, δ): 169.2, 137.5, 134.5, 132.4, 131.0, 129.7, 129.3, 122.1, 120.7, 119.5, 26.0. IR (ZnSe): ν_{max} (cm⁻¹) 3383, 2968, 1651, 1535, 1492, 1375, 1192, 815, 788, 626, 555.

8-(4-methylbenzamido)quinoline N-oxide (Table 3, entry **3za**). Brown solid, Yield = 50.0 mg (90%). Mp 193–195 °C. Isolated from flash chromatography (70% EtOAc/*n*-hexane). ¹H NMR (600 MHz, CDCl₃, δ): 15.10 (br, s, 1H, NH), 9.28 (d, *J* = 7.8 Hz, 1H), 8.41 (d, *J* = 6.0 Hz, 1H), 7.98 (d, *J* = 7.8 Hz, 2H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.61–7.63 (m, 1H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 6.6 Hz, 1H), 2.42 (s, 3H). ¹³C{¹H} NMR (150 MHz, CDCl₃, δ): 165.7, 142.4, 137.5, 135.0, 132.5, 132.4, 131.3, 129.9, 129.6, 129.5, 127.5, 122.1, 120.7, 119.6, 21.7. IR (ZnSe): ν_{max} (cm⁻¹) 3392, 2981, 1656, 1550, 1485, 1348, 1192, 1055, 817, 744, 653. HRMS (ESI-TOF) (*m/z*): [M+H]⁺ calcd for C₁₇H₁₅N₂O₂, 279.1128; found, 279.1125.

8-(4-methoxybenzamido)quinoline N-oxide (Table 3, entry **3zb**). Brown solid, Yield = 52.9 mg (90%). Mp 164–166 °C. Isolated from flash chromatography (90% EtOAc/*n*-hexane). ¹H NMR (600 MHz, CDCl₃, δ): 15.04 (br, s, 1H, NH), 9.25 (d, *J* = 7.8 Hz, 1H), 8.36 (d, *J* = 3.6 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 2H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.60–7.63 (m, 1H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.28–7.31 (m, 1H), 6.99 (d, *J* = 8.4 Hz, 2H), 3.86 (s, 3H). ¹³C{¹H} NMR (150 MHz, DMSO-*d*₆, δ): 163.9, 162.3, 138.3, 134.2, 132.2, 129.9, 129.7, 129.3, 128.9, 126.9, 122.5, 122.0, 117.9, 114.3, 55.6. IR (ZnSe): ν_{max} (cm⁻¹) 2916, 2850, 1658, 1579, 1460, 1371, 1249, 1176, 1024, 906, 779, 651. HRMS (ESI-TOF) (*m/z*): [M+H]⁺ calcd for C₁₇H₁₅N₂O₃, 295.1077; found, 295.1079.

8-([1,1'-biphenyl]-4-carboxamido)quinoline N-oxide (Table 3, entry **3zc**). Brown solid, Yield = 61.9 mg (91%). Mp 201–203 °C. Isolated from flash chromatography (50% EtOAc/*n*-hexane). ¹H NMR (600 MHz, CDCl₃, δ): 15.26 (br, s, 1H, NH), 9.31 (dd, *J* = 8.4, 1.2 Hz, 1H), 8.43 (dd, *J* = 6.0, 1.2 Hz, 1H), 8.17 (dd, *J* = 6.6, 1.8 Hz, 2H), 7.82 (d, *J* = 7.8 Hz, 1H), 7.74 (dd, *J* = 6.6, 1.8 Hz, 2H), 7.63–7.66 (m, 3H), 7.52–7.54 (m, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.39 (t, *J* = 7.2 Hz, 1H), 7.31 (dd, *J* = 8.4, 6.0 Hz, 1H). ¹³C{¹H} NMR (150 MHz, CDCl₃, δ): 165.4, 144.7, 140.3, 137.5, 134.9, 133.9, 132.5, 131.3, 129.9, 129.5, 129.0, 128.1, 128.0, 127.6, 127.4, 122.3, 120.8, 119.7. IR (ZnSe): ν_{max} (cm⁻¹) 3564, 2918, 2850, 1653, 1541, 1485, 1384, 1257, 1165, 1089, 818, 742, 692. HRMS (ESI-TOF) (*m/z*): [M+H]⁺ calcd for C₂₂H₁₇N₂O₂, 341.1285; found, 341.1288.

8-(4-chlorobenzamido)quinoline N-oxide (Table 3, entry **3zd**). Brown solid, Yield = 59.0 mg (99%). Mp 170–172 °C. Isolated from flash chromatography (70% EtOAc/*n*-hexane). ¹H NMR (600 MHz, CDCl₃, δ): 15.27 (br, s, 1H, NH), 9.24 (dd, *J* = 8.4, 1.2 Hz, 1H), 8.39 (d, *J* = 6.0 Hz, 1H), 8.01 (d, *J* = 8.4 Hz, 2H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.52–7.53 (m, 1H), 7.47 (dd, *J* = 6.6, 1.8 Hz, 2H), 7.32 (dd, *J* = 8.4, 6.0 Hz, 1H). ¹³C{¹H} NMR (150 MHz, DMSO-*d*₆, δ): 163.1, 138.3, 136.9, 133.8, 133.5, 132.2, 129.9, 129.8, 129.1, 128.8, 123.0, 122.1, 118.2. IR (ZnSe): ν_{max} (cm⁻¹) 3070, 2920, 2852, 1662, 1541, 1485, 1350, 1259, 1163, 1022, 813, 742, 673. HRMS (ESI-TOF) (*m/z*): [M+H]⁺ calcd for C₁₆H₁₂ClN₂O₂, 299.0582; found, 299.0594.

8-(3,5-dimethylbenzamido)quinoline N-oxide (Table 3, entry **3ze**). Brown solid, Yield = 50.2 mg (86%). Mp 190–192 °C. Isolated from flash chromatography (50% EtOAc/*n*-hexane). ¹H NMR (600 MHz, CDCl₃, δ): 15.02 (br, s, 1H, NH), 9.27–9.29 (m, 1H), 8.42 (d, *J* = 6.0 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.68 (s, 2H), 7.61–7.64 (m, 1H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.29 (dd, *J* = 8.4, 6.0 Hz, 1H), 7.18 (s, 1H), 2.42 (s, 6H). ¹³C{¹H} NMR (150 MHz, CDCl₃, δ): 166.2, 138.5, 137.5, 135.3, 134.9, 133.6, 132.5, 131.4, 129.9, 129.4, 125.3, 122.2, 120.7, 119.7, 21.6. IR (ZnSe): ν_{max} (cm⁻¹) 3101, 2850, 2779, 1654, 1533, 1489, 1379, 1228, 1155, 1039, 920, 815, 786, 669. HRMS (ESI-TOF) (*m/z*): [M+Na]⁺ calcd for C₁₈H₁₆NaN₂O₂, 315.1104; found, 315.1105.

8-(cyclopentanecarboxamido)quinoline N-oxide (Table 3, entry **3zf**). Brown viscous, Yield = 39.7 mg (58%). Isolated from flash

chromatography (80% EtOAc/*n*-hexane). ¹H NMR (600 MHz, CDCl₃, δ): 14.14 (br, s, 1H, NH), 9.08 (d, *J* = 7.8 Hz, 1H), 8.35 (d, *J* = 6.0 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.54–7.57 (m, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.25 (dd, *J* = 8.4 Hz, 6.0 Hz, 1H), 2.85 (p, *J* = 8.4 Hz, 1H), 1.99–2.05 (m, 2H), 1.90–1.96 (m, 2H), 1.76–1.82 (m, 2H), 1.61–1.67 (m, 2H). ¹³C{¹H} NMR (150 MHz, CDCl₃, δ): 175.5, 137.4, 134.8, 132.4, 131.2, 129.8, 129.2, 121.8, 120.6, 119.4, 48.4, 30.4, 26.0. IR (ZnSe): ν_{max} (cm⁻¹) 2958, 2864, 1672, 1581, 1489, 1369, 1290, 1159, 1091, 848, 746, 609. HRMS (ESI-TOF) (*m/z*): [M+H]⁺ calcd for C₁₅H₁₇N₂O₂, 257.1285; found, 257.1283.

8-(cyclohexanecarboxamido)quinoline *N*-oxide (Table 3, entry **3zg**). Brown solid, Yield = 37.3 mg (69%). Mp 101–103 °C. Isolated from flash chromatography (60% EtOAc/*n*-hexane). ¹H NMR (600 MHz, CDCl₃, δ): 14.12 (br, s, 1H, NH), 9.09 (d, *J* = 8.4 Hz, 1H), 8.35 (d, *J* = 6.0 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.54–7.57 (m, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.24–7.27 (m, 1H), 2.35–2.40 (m, 1H), 2.06–2.08 (m, 2H), 1.82–1.85 (m, 2H), 1.69–1.71 (m, 1H), 1.53–1.59 (m, 2H), 1.31–1.38 (m, 2H), 1.25–1.29 (m, 1H). ¹³C{¹H} NMR (150 MHz, CDCl₃, δ): 175.5, 137.4, 134.8, 132.4, 131.2, 129.8, 129.3, 121.9, 120.6, 119.6, 47.7, 29.7, 25.9. IR (ZnSe): ν_{max} (cm⁻¹) 3086, 2916, 2850, 1660, 1577, 1460, 1381, 1294, 1159, 933, 798, 696. HRMS (ESI-TOF) (*m/z*): [M+H]⁺ calcd for C₁₆H₁₉N₂O₂, 271.1441; found, 271.1450.

8-(9H-carbazole-9-carboxamido)quinoline *N*-oxide (Table 3, entry **3zh**). Brown solid, Yield = 45.9 mg (65%). Mp 190–192 °C. Isolated from flash chromatography (90% EtOAc/*n*-hexane). ¹H NMR (600 MHz, CDCl₃, δ): 14.91 (br, s, 1H, NH), 8.95 (d, *J* = 7.2 Hz, 1H), 8.33 (d, *J* = 5.4 Hz, 1H), 8.26 (d, *J* = 8.4 Hz, 2H), 8.03 (d, *J* = 7.8 Hz, 2H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.67 (t, *J* = 7.8 Hz, 1H), 7.50–7.54 (m, 3H), 7.35–7.37 (m, 2H), 7.23–7.25 (m, 1H). ¹³C{¹H} NMR (150 MHz, CDCl₃, δ): 150.6, 146.6, 140.6, 138.3, 137.2, 134.2, 132.4, 129.6, 129.4, 127.1, 125.6, 122.6, 122.4, 121.0, 120.8, 120.2, 120.0, 114.7. IR (ZnSe): ν_{max} (cm⁻¹) 3097, 1687, 1533, 1479, 1290, 1159, 935, 821, 740, 605. HRMS (ESI-TOF) (*m/z*): [M+H]⁺ calcd for C₂₂H₁₆N₃O₂, 354.1237; found, 354.1234.

Synthesis of various substituted *N*-(1-(pyrimidin-2-yl)indolin-7-yl)benzamides (6a–d). To a solution of various substituted 1-(pyrimidin-2-yl)indoline (**5a–d**) (0.2 mmol) in HFIP (0.5 mL per mmol) in a reaction vial equipped with magnetic stir bar, 3-Phenyl-1,4,2-dioxazol-5-one **2a** (1.1 equiv.), [CoCOP*₂] (10 mol%), AgSbF₆ (20 mol%) and AcOH (20 mol%) were added. The reaction mixture was stirred at 50 °C for 12 h on a heating block, filtered through a pad of celite using ethyl acetate solvent. After that filtrate was transferred to round bottom flask and organic solvents were removed under reduced pressure. The residue was purified by flash chromatography on silica gel (mesh 230–400) to give the desired product. Eluting solvents for chromatography are indicated under the specific compound headings.

Characterization Data. ***N*-(1-(pyrimidin-2-yl)indolin-7-yl)benzamide** (Table 4, entry **6a**).¹⁵ Brown solid, Yield = 48.0 mg (76%). Mp 153–155 °C. Isolated from flash chromatography (10% EtOAc/*n*-hexane). ¹H NMR (600 MHz, CDCl₃, δ): 11.42 (br, s, 1H, NH), 8.44 (d, *J* = 4.8 Hz, 2H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.84–7.85 (m, 2H), 7.47–7.50 (m, 1H), 7.41–7.44 (m, 2H), 7.15–7.17 (m, 1H), 7.07 (dd, *J* = 7.2, 1.2 Hz, 1H), 6.70 (t, *J* = 4.8 Hz, 1H), 4.47 (t, *J* = 7.8 Hz, 2H), 3.10–3.12 (m, 2H). ¹³C{¹H} NMR (150 MHz, CDCl₃, δ): 165.9, 159.5, 157.9, 136.3, 136.1, 134.7, 131.5, 128.6, 127.4, 127.3, 124.7, 123.9, 121.3, 111.6, 51.9, 28.9. IR (ZnSe): ν_{max} (cm⁻¹) 3161, 2891, 1660, 1577, 1473, 1379, 1278, 1186, 1049, 991, 848, 781, 690. HRMS (ESI-TOF) (*m/z*): [M+H]⁺ calcd for C₁₉H₁₇N₄O, 317.1397; found, 317.1395.

***N*-(2-methyl-1-(pyrimidin-2-yl)indolin-7-yl)benzamide** (Table 4, entry **6b**).¹⁵ Brown solid, Yield = 54.1 mg (82%). Mp 151–153 °C. Isolated from flash chromatography (25% EtOAc/*n*-hexane). ¹H NMR (600 MHz, CDCl₃, δ): 11.42 (br, s, 1H, NH), 8.45 (d, *J* = 4.8 Hz, 2H), 7.97 (d, *J* = 7.8 Hz, 1H), 7.86 (d, *J* = 7.2 Hz, 2H), 7.48–

7.50 (m, 1H), 7.42–7.44 (m, 2H), 7.16–7.19 (m, 1H), 7.07 (d, *J* = 7.2 Hz, 1H), 6.71 (t, *J* = 4.8 Hz, 1H), 5.19–5.24 (m, 1H), 3.43–3.47 (m, 1H), 2.58 (d, *J* = 15.0 Hz, 1H), 1.32 (d, *J* = 6.6 Hz, 3H). ¹³C{¹H} NMR (150 MHz, CDCl₃, δ): 165.8, 159.0, 157.9, 136.2, 134.8, 133.1, 131.5, 128.5, 127.7, 127.4, 124.8, 123.6, 121.8, 111.6, 59.2, 36.1, 20.4. IR (ZnSe): ν_{max} (cm⁻¹) 2926, 2850, 1658, 1577, 1456, 1371, 1261, 1222, 1190, 974, 779, 696. HRMS (ESI-TOF) (*m/z*): [M+Na]⁺ calcd for C₂₀H₁₈N₄NaO, 353.1373; found, 353.1379.

***N*-(5-methyl-1-(pyrimidin-2-yl)indolin-7-yl)benzamide** (Table 4, entry **6c**).¹⁵ Brown solid, Yield = 46.2 mg (70%). Mp 174–176 °C. Isolated from flash chromatography (20% EtOAc/*n*-hexane). ¹H NMR (600 MHz, CDCl₃, δ): 11.46 (br, s, 1H, NH), 8.41 (d, *J* = 4.8 Hz, 2H), 7.84–7.85 (m, 2H), 7.77 (s, 1H), 7.48 (t, *J* = 7.2 Hz, 1H), 7.41–7.43 (m, 2H), 6.88 (s, 1H), 6.67 (t, *J* = 4.8 Hz, 1H), 4.44 (t, *J* = 7.8 Hz, 2H), 3.05 (t, *J* = 7.8 Hz, 2H), 2.37 (s, 3H). ¹³C{¹H} NMR (150 MHz, CDCl₃, δ): 165.8, 159.4, 157.9, 146.6, 136.2, 136.1, 134.7, 132.3, 131.4, 128.5, 127.4, 126.9, 123.9, 122.2, 111.3, 51.9, 28.8, 21.1. IR (ZnSe): ν_{max} (cm⁻¹) 2789, 1664, 1581, 1465, 1377, 1267, 1184, 1080, 844, 790, 642. HRMS (ESI-TOF) (*m/z*): [M+H]⁺ calcd for C₂₀H₁₉N₄O, 331.1553; found, 331.1548.

***N*-(5-bromo-1-(pyrimidin-2-yl)indolin-7-yl)benzamide** (Table 4, entry **6d**).¹⁵ Brown solid, Yield = 59.3 mg (75%). Mp 180–182 °C. Isolated from flash chromatography (20% EtOAc/*n*-hexane). ¹H NMR (600 MHz, CDCl₃, δ): 11.60 (br, s, 1H, NH), 8.42 (d, *J* = 4.8 Hz, 2H), 8.16 (s, 1H), 7.81 (d, *J* = 7.8 Hz, 2H), 7.48–7.51 (m, 1H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.16 (d, *J* = 0.6 Hz, 1H), 6.72–6.74 (m, 1H), 4.44–4.46 (m, 2H), 3.06–3.09 (m, 2H). ¹³C{¹H} NMR (150 MHz, CDCl₃, δ): 165.8, 159.2, 157.9, 137.8, 135.8, 133.8, 131.7, 128.6, 128.2, 127.4, 126.1, 124.1, 116.9, 111.9, 52.0, 28.6. IR (ZnSe): ν_{max} (cm⁻¹) 2889, 1666, 1581, 1450, 1373, 1296, 1124, 1080, 910, 864, 790, 640, 599. HRMS (ESI-TOF) (*m/z*): [M+H]⁺ calcd for C₁₉H₁₆BrN₄O, 395.0502; found, 395.0492.

Synthesis of 2-benzamido-*N*-(tert-butyl)benzamide. To a solution of *N*-(tert-butyl)benzamide (**5e**) (0.2 mmol) in HFIP (0.5 mL per mmol) in a reaction vial equipped with magnetic stir bar, 3-Phenyl-1,4,2-dioxazol-5-one **2a** (1.1 equiv.), [CoCOP*₂] (10 mol%), AgSbF₆ (20 mol%) and AcOH (20 mol%) were added. The reaction mixture was stirred at 50 °C for 12 h on a heating block, filtered through a pad of celite using ethyl acetate solvent. After that filtrate was transferred to round bottom flask and organic solvents were removed under reduced pressure. The residue was purified by flash chromatography on silica gel (mesh 230–400) to give the desired product. Eluting solvents for chromatography are indicated under the specific compound headings.

2-benzamido-*N*-(tert-butyl)benzamide (Table 4, entry **6e**).^{8a} Brown solid, Yield = 34.9 mg (59%). Mp 185–187 °C. Isolated from flash chromatography (25% EtOAc/*n*-hexane). ¹H NMR (600 MHz, CDCl₃, δ): 11.92 (br, s, 1H, NH), 8.73 (d, *J* = 8.4 Hz, 1H), 8.02–8.03 (m, 2H), 7.53–7.55 (m, 1H), 7.50–7.52 (m, 2H), 7.46–7.49 (m, 1H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.03–7.05 (m, 1H), 6.19 (br, s, 1H, NH), 1.50 (s, 9H). ¹³C{¹H} NMR (150 MHz, CDCl₃, δ): 169.2, 165.6, 139.6, 134.9, 132.3, 131.9, 128.9, 127.5, 126.7, 122.9, 122.5, 121.8, 52.3, 28.9. IR (ZnSe): ν_{max} (cm⁻¹) 3296, 2966, 1647, 1550, 1479, 1325, 1222, 1074, 885, 748, 653. HRMS (ESI-TOF) (*m/z*): [M+Na]⁺ calcd for C₁₈H₂₀N₂NaO₂, 319.1417; found, 319.1420.

***N*-(2-(pyridin-2-yl)phenyl)benzamide** (Table 4, entry **6f**).²¹ To a solution of 2-phenylpyridine (**5f**) (0.2 mmol) in HFIP (0.5 mL per mmol) in a reaction vial equipped with magnetic stir bar, 3-Phenyl-1,4,2-dioxazol-5-one **2a** (1.1 equiv.), [CoCOP*₂] (10 mol%), AgSbF₆ (20 mol%) and AcOH (20 mol%) were added. The reaction mixture was stirred at 50 °C for 12 h on a heating block, filtered through a pad of celite using ethyl acetate solvent. After that filtrate was transferred to round bottom flask and organic solvents were removed under reduced pressure. The residue was purified by flash chromatography on silica gel (mesh 230–400) to give the desired

product. Eluting solvents for chromatography are indicated under the specific compound headings. White solid, Yield = 19.2 mg (35%). Mp 114–117 °C. Isolated from flash chromatography (10% EtOAc/*n*-hexane). ¹H NMR (600 MHz, CDCl₃, δ): 13.31 (br, s, 1H, NH), 8.80 (d, *J* = 8.4 Hz, 1H), 8.67 (d, *J* = 4.8 Hz, 1H), 8.03–8.05 (m, 2H), 7.83–7.86 (m, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.73 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.46–7.55 (m, 4H), 7.28–7.30 (m, 1H), 7.19–7.22 (m, 1H). ¹³C{¹H} NMR (150 MHz, CDCl₃, δ): 165.7, 158.5, 147.4, 138.3, 137.9, 135.9, 131.6, 130.4, 128.9, 128.7, 127.5, 125.7, 123.7, 123.1, 122.1, 122.0. IR (ZnSe): ν_{max} (cm⁻¹) 2927, 2850, 2335, 1664, 1585, 1475, 1313, 1278, 1091, 947, 889, 754, 696. HRMS (ESI-TOF) (*m/z*): [M+H]⁺ calcd for C₁₈H₁₅N₂O, 275.1179; found, 275.1153.

N-(benzo[*h*]quinolin-10-yl)benzamide (Table 4, entry 6g).²¹ To a solution of benzo[*h*]quinoline (**5g**) (0.2 mmol) in HFIP (0.5 mL per mmol) in a reaction vial equipped with magnetic stir bar, 3-Phenyl-1,4,2-dioxazol-5-one **2a** (1.1 equiv.), [CoCOP*₂] (10 mol%), AgSbF₆ (20 mol%) and AcOH (20 mol%) were added. The reaction mixture was stirred at 50 °C for 12 h on a heating block, filtered through a pad of celite using ethyl acetate solvent. After that filtrate was transferred to round bottom flask and organic solvents were removed under reduced pressure. The residue was purified by flash chromatography on silica gel (mesh 230–400) to give the desired product. Eluting solvents for chromatography are indicated under the specific compound headings. Brown solid, Yield = 32.2 mg (54%). Mp 158–160 °C. Isolated from flash chromatography (15% EtOAc/*n*-hexane). ¹H NMR (600 MHz, CDCl₃, δ): 15.77 (br, s, 1H, NH), 9.37–9.38 (m, 1H), 8.94 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.26–8.29 (m, 3H), 7.84 (d, *J* = 9.0 Hz, 1H), 7.77 (t, *J* = 7.8 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.59–7.60 (m, 2H), 7.57–7.59 (m, 2H). ¹³C{¹H} NMR (150 MHz, CDCl₃, δ): 166.7, 148.0, 145.8, 139.9, 136.9, 136.7, 135.3, 131.6, 129.8, 129.3, 128.8, 127.8, 125.3, 123.4, 120.9, 118.7, 118.1. IR (ZnSe): ν_{max} (cm⁻¹) 2885, 1662, 1544, 1489, 1342, 1288, 1182, 1093, 835, 709, 601. HRMS (ESI-TOF) (*m/z*): [M+H]⁺ calcd for C₂₀H₁₅N₂O, 299.1179; found, 299.1177.

N-(quinolin-8-yl)benzamide (Scheme 6, 3aa).²² To an oven-dried screw cap reaction vial charged with a spinvane magnetic stir-bar, 8-benzamidoquinoline *N*-oxide (**3a**, 0.1 mmol), phenylboronic acid (1.5 equiv.) and 0.5 mL DCE were added. The reaction mixture was allowed to stir at 120 °C for 12 h on a heating block. After completion, the reaction mixture was diluted with DCM and washed with water three times. Combined organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure and the products were isolated by flash chromatography using silica gel (mesh 230–400). Eluting solvents for chromatography are indicated under the specific compound headings. White solid, Yield = 14.1 mg (57%). Isolated from flash chromatography (10% EtOAc/*n*-hexane). Mp 83–85 °C. ¹H NMR (600 MHz, CDCl₃, δ): 10.75 (br, s, 1H, NH), 8.94–8.96 (m, 1H), 8.84 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.17 (dd, *J* = 8.4, 1.2 Hz, 1H), 8.09–8.10 (m, 2H), 7.53–7.61 (m, 5H), 7.47 (dd, *J* = 8.4, 4.2 Hz, 1H). ¹³C{¹H} NMR (150 MHz, CDCl₃, δ): 165.6, 148.4, 146.6, 138.9, 136.5, 135.3, 134.7, 131.9, 128.9, 128.1, 127.6, 127.4, 121.8, 116.7. IR (ZnSe): ν_{max} (cm⁻¹) 3350, 1670, 1523, 1483, 1388, 1267, 1128, 970, 898, 796, 673. HRMS (ESI-TOF) (*m/z*): [M+Na]⁺ calcd for C₁₆H₁₂N₂NaO, 271.0842; found, 271.0840.

8-aminoquinoline *N*-oxide (Scheme 6, 3ab).²³ To an oven-dried sealed tube charged with 8-benzamidoquinoline *N*-oxide (**3a**) (26.4 mg, 0.1 mmol, 100 mol %) and NaOH (224.0 mg, 5.6 mmol, 56 equiv.) was added EtOH (3 mL) at room temperature. The reaction mixture was allowed to stir at 80 °C for 20 h on a heating block. The reaction mixture was concentrated in vacuo. The reaction residue was diluted with EtOAc and quenched with AcOH to adjust pH = ~9. The organic layer was washed with H₂O. The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo. Yellow solid, Yield = 13.6 mg (85%). Mp 102–104 °C. Isolated from flash chromatography (100% EtOAc/*n*-hexane). ¹H

NMR (600 MHz, CDCl₃, δ): 8.14 (d, *J* = 5.4 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.24 (t, *J* = 7.8 Hz, 1H), 7.04 (dd, *J* = 8.4, 6.0 Hz, 1H), 6.94 (d, *J* = 7.8 Hz, 1H), 6.82 (br, s, 2H, NH₂), 6.67 (d, *J* = 7.8 Hz, 1H). ¹³C{¹H} NMR (150 MHz, CDCl₃, δ): 143.5, 135.6, 133.6, 130.9, 129.5, 127.9, 120.5, 115.1, 113.4. IR (ZnSe): ν_{max} (cm⁻¹) 3365, 3244, 3062, 2922, 1903, 1593, 1462, 1398, 1296, 1134, 1043, 964, 804, 740, 634. HRMS (ESI-TOF) (*m/z*): [M+H]⁺ calcd for C₉H₉N₂O, 161.0709; found, 161.0695.

N-(2-chloroquinolin-8-yl)benzamide (Scheme 6, 3ac).²⁴ To an oven-dried screw cap reaction vial charged with a spinvane magnetic stir-bar, 8-benzamidoquinoline *N*-oxide (**3a**, 0.1 mmol) and thionyl chloride (2.0 mL) were added. The reaction mixture was allowed to stir at 50 °C for 12 h on a heating block. After completion, the reaction mixture was collected in round bottom flask and reaction vial was washed with DCM. Collected DCM fraction of crude reaction mixture was evaporated under reduced pressure and the products were isolated by flash chromatography using silica gel (mesh 230–400). Eluting solvents for chromatography are indicated under the specific compound headings. Off white solid, Yield = 22.6 mg (80%). Mp 134–136 °C. Isolated from flash chromatography (10% EtOAc/*n*-hexane). ¹H NMR (600 MHz, CDCl₃, δ): 10.29 (br, s, 1H, NH), 8.96–8.98 (m, 1H), 8.11 (d, *J* = 9.0 Hz, 1H), 8.06–8.07 (m, 2H), 7.55–7.61 (m, 4H), 7.52–7.53 (m, 1H), 7.43 (d, *J* = 9.0 Hz, 1H). ¹³C{¹H} NMR (150 MHz, CDCl₃, δ): 165.6, 149.4, 139.4, 138.4, 135.0, 134.0, 132.1, 129.0, 128.0, 127.4, 126.7, 122.9, 121.6, 118.0. IR (ZnSe): ν_{max} (cm⁻¹) 3377, 3061, 1680, 1535, 1475, 1388, 1251, 1118, 1097, 896, 746, 682. HRMS (ESI-TOF) (*m/z*): [M+Na]⁺ calcd for C₁₆H₁₁ClN₂NaO, 305.0452; found, 305.0454.

8-benzamido-2-(4-methoxyphenyl) quinoline *N*-oxide (Scheme 6, 3ad).²⁵ To an oven-dried screw cap reaction vial charged with a spinvane magnetic stir-bar, aryldiazonium tetrafluoroborate salt (0.1 mmol), 8-benzamidoquinoline *N*-oxide (**3a**, 3 equiv.) and sodium acetate (2 equiv.) were added in MeCN (5 mL) and stir for 6 h at room temperature. After completion, reaction mixture was diluted with ethyl acetate and washed with brine solution three times. Organic layer was dried over anhydrous Na₂SO₄ and evaporated under reduced pressure and the products were isolated by flash chromatography using silica gel (mesh 230–400). Eluting solvents for chromatography are indicated under the specific compound headings. Orange solid, Yield = 19.6 mg (53%). Mp 184–186 °C. Isolated from flash chromatography (40% EtOAc/*n*-hexane). ¹H NMR (600 MHz, CDCl₃, δ): 15.42 (br, s, 1H, NH), 9.31 (d, *J* = 8.4 Hz, 1H), 8.09 (d, *J* = 6.6 Hz, 2H), 7.92 (d, *J* = 9.0 Hz, 2H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.60–7.63 (m, 1H), 7.48–7.52 (m, 4H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.06 (d, *J* = 8.4 Hz, 2H), 3.90 (s, 3H). ¹³C{¹H} NMR (150 MHz, CDCl₃, δ): 165.8, 160.9, 146.8, 135.4, 135.2, 131.8, 131.5, 131.3, 129.3, 128.8, 128.5, 127.6, 125.4, 123.4, 122.4, 120.2, 114.1, 55.6. IR (ZnSe): ν_{max} (cm⁻¹) 2850, 1660, 1577, 1485, 1485, 1381, 251, 1176, 974, 696. HRMS (ESI-TOF) (*m/z*): [M+H]⁺ calcd for C₂₃H₁₉N₂O₃, 371.1390; found, 371.1385.

Deuterium labeling experiment. To a screw capped vial with a stirbar quinoline *N*-oxide (0.1 mmol), [Cp*Co(CO)I₂]₂ (10 mol%), AgSbF₆ (20 mol%), CD₃CO₂D (20 mol%), HFIP-*d*₂ (500 μL) and CD₃OD (10 equiv.) were added. The reaction was stirred at 50 °C for 6 hours. After cooling to room temperature, the mixture was dried under reduced pressure and extracted with EtOAc (3 x 10 mL). The combined organic phase was washed with saturated NaCl solution (3 x 5 mL), dried over Na₂SO₄, and filtered. EtOAc was removed under reduced pressure to obtain the crude product of C8 deuterated quinoline *N*-oxide. The percentage of *d*-incorporation was determined by ¹H NMR. Peak areas at 8.72 ppm and 8.61 ppm were compared to obtain the deuterium incorporation. Deuterium incorporation was detected to be 40% by ¹H NMR (Scheme 3a).

Parallel Reaction for KIE Study. In two different screw capped vial with a stirbar separately placed quinoline *N*-oxide (**1a**) and D7-quinoline *N*-oxide (**1a-D7**), (0.1 mmol), [Cp*Co(CO)I₂]₂ (10

mol%), AgSbF₆ (20 mol%), AcOH (20 mol%), HFIP were added, then both the mixtures were stirred at 50 °C for 6 hours on a heating block at the same time. The k_H/k_D = 4.26 was calculated by ¹H NMR spectroscopy (Scheme 3b).

Competitive Reaction for KIE Study. To a screw capped vial with a stirbar consecutively placed 0.05 mmol of quinoline *N*-oxide (**1a**) and 0.05 mmol of D₇-quinoline *N*-oxide (**1a-D₇**), [Cp*Co(CO)I₂] (10 mol%), AgSbF₆ (20 mol%), AcOH (20 mol%), HFIP were added, then the mixtures were stirred at 50 °C for 6 hours on a heating block. The k_H/k_D = 4.26 was calculated by ¹H NMR. (Scheme 3b).

Competition experiment with quinoline *N*-oxide. To a screw capped vial with a stirbar consecutively placed 0.05 mmol of quinoline *N*-oxide (**1a**) and 0.05 mmol of 6-methylquinoline *N*-oxide (**1e**), after that 0.1 mmol of 3-phenyl-1,4,2-dioxazol-5-one (**2a**) [Cp*Co(CO)I₂] (10 mol%), AgSbF₆ (20 mol%), AcOH (20 mol%), HFIP were added, then the mixtures were stirred at 50 °C for 12 hours on a heating block. The product ratio was calculated by ¹H NMR. In another reaction vial, 0.05 mmol of quinoline *N*-oxide (**1a**) and 0.05 mmol of 6-(methoxycarbonyl) quinoline *N*-oxide (**1i**), [Cp*Co(CO)I₂] (10 mol%), AgSbF₆ (20 mol%), AcOH (20 mol%), HFIP were stirred at 50 °C for 12 hours. The product ratio was calculated by ¹H NMR. (Scheme 4a).

Competition experiment with dioxazolones. To a screw capped vial with a stirbar consecutively placed 0.055 mmol of 3-phenyl-1,4,2-dioxazol-5-one (**2a**) and 0.05 mmol of 3-*p*-methylphenyl-1,4,2-dioxazol-5-one (**2c**), after that 0.1 mmol of quinoline *N*-oxide (**1a**) [Cp*Co(CO)I₂] (10 mol%), AgSbF₆ (20 mol%), AcOH (20 mol%), HFIP were added. Then the mixtures were stirred at 50 °C for 12 hours on a heating block. The product ratio was calculated by ¹H NMR. In another reaction vial, 0.05 mmol 3-phenyl-1,4,2-dioxazol-5-one (**2a**) and 0.05 mmol of 3-*p*-chlorophenyl-1,4,2-dioxazol-5-one (**2e**), 0.1 mmol of quinoline *N*-oxide (**1a**), [Cp*Co(CO)I₂] (10 mol%), AgSbF₆ (20 mol%), AcOH (20 mol%), HFIP were stirred at 50 °C on a heating block for 12 hours. The product ratio was calculated by ¹H NMR. (Scheme 4b).

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, details of optimization studies, characterization data for all synthesized compounds including ¹H and ¹³C spectra. FAIR Data is available as Supporting Information for Publication and includes the primary NMR FID files for compounds [**1y**, **2g-j**, **5a-d**, **3a-i**, **3k-q**, **3s-w**, **3y-z**, **3za-zh**, **6a-g**, **3aa-3ad**]

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Notes

The authors declare no competing financial interests

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REFERENCES

- (a) Kaur, K.; Jain, M.; Reddy, R. P.; Jain, R., Quinolines and Structurally Related Heterocycles as Antimalarials. *Eur. J. Med. Chem.* **2010**, *45*, 3245-3264; (b) Michael, J. P., Quinoline, Quinazoline and Acridone Alkaloids. *Nat. Prod. Rep.* **2008**, *25*, 166-187; (c) Kumar, S.; Bawa, S.; Gupta, H., Biological Activities of Quinoline Derivatives. *Mini-Rev. Med. Chem.* **2009**, *9*, 1648-1654; (d) Edmont, D.; Rocher, R.; Plisson, C.; Chenault, J., Synthesis and Evaluation of Quinoline Carboxyguanidines as Antidiabetic Agents. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1831-1834; (e) Musiol, R.; Jampilek, J.; Buchta, V.; Silva, L.; Niedbala, H.; Podeszwa, B.; Palka, A.; Majerz-Maniecka, K.; Oleksyn, B.; Polanski, J., Antifungal Properties of New Series of Quinoline Derivatives. *Bioorg. Med. Chem.* **2006**, *14*, 3592-3598.
- Kimyonok, A.; Wang, X. Y.; Weck, M., Electroluminescent Poly (Quinoline)s and Metalloquinolates. *J. Macromol Sci Polymer Rev* **2006**, *46*, 47-77.
- (a) Chen, C. H.; Shi, J., Metal Chelates as Emitting Materials for Organic Electroluminescence. *Coord. Chem. Rev.* **1998**, *171*, 161-174; (b) Hughes, G.; Bryce, M. R., Electron-Transporting Materials for Organic Electroluminescent and Electrophosphorescent Devices. *J. Mater. Chem.* **2005**, *15*, 94-107.
- (a) Kalsi, D.; Laskar, R. A.; Barsu, N.; Premkumar, J. R.; Sundararaju, B., C-8-Selective Allylation of Quinoline: A Case Study of β -Hydride vs β -Hydroxy Elimination. *Org. Lett.* **2016**, *18*, 4198-4201; (b) Barsu, N.; Sen, M.; Premkumar, J. R.; Sundararaju, B., Cobalt (III) Catalyzed C-8 Selective C-H and C-O Coupling of Quinoline *N*-oxide with Internal Alkynes via C-H Activation and Oxygen Atom Transfer. *ChemComm* **2016**, *52*, 1338-1341; (c) Sharma, R.; Kumar, I.; Kumar, R.; Sharma, U., Rhodium-Catalyzed Remote C-8 Alkylation of Quinolines with Activated and Unactivated Olefins: Mechanistic Study and Total Synthesis of EP4 Agonist. *Adv. Synth. Catal.* **2017**, *359*, 3022-3028; (d) Wang, B.; Li, C.; Liu, H., Cp* Rh(III)-Catalyzed Directed C-H Methylation and Arylation of Quinoline *N*-oxides at the C-8 Position. *Adv. Synth. Catal.* **2017**, *359*, 3029-3034; (e) You, C.; Pi, C.; Wu, Y.; Cui, X., Rh (III)-Catalyzed Selective C8-H Acylmethylation of Quinoline *N*-oxides. *Adv. Synth. Catal.* **2018**, *360*, 4068-4072;
- (a) Shibata, T.; Matsuo, Y., Directed C-H Alkenylation of Quinoline *N*-Oxides at the C-8 Position Using a Cationic Rhodium(I) Catalyst. *Adv. Synth. Catal.* **2014**, *356*, 1516-1520; (b) Sharma, R.; Kumar, R.; Kumar, I.; Sharma, U., Rh(III)-Catalyzed Dehydrogenative Coupling of Quinoline *N*-Oxides with Alkenes: *N*-Oxide as Traceless Directing Group for Remote C-H Activation. *Eur. J. Org. Chem.* **2015**, 7519-7528; (c) Sharma, R.; Kumar, R.; Sharma, U., Rh/O₂-Catalyzed C8 Olefination of Quinoline *N*-oxides with Activated and Unactivated Olefins. *J. Org. Chem.* **2019**, *84*, 2786-2797.
- Kwak, J.; Kim, M.; Chang, S., Rh(NHC)-Catalyzed Direct and Selective Arylation of Quinolines at the 8-Position. *J. Am. Chem. Soc.* **2011**, *133*, 3780-3783.
- (a) Hwang, H.; Kim, J.; Jeong, J.; Chang, S., Regioselective Introduction of Heteroatoms at the C-8 position of Quinoline *N*-oxides: Remote C-H Activation using *N*-oxide as a Stepping Stone. *J. Am. Chem. Soc.* **2014**, *136*, 10770-10776; (b) Dhiman, A. K.; Gupta, S. S.; Sharma, R.; Kumar, R.; Sharma, U., Rh (III)-Catalyzed C (8)-H Activation of Quinoline *N*-Oxides: Regioselective C-Br and C-N Bond Formation. *J. Org. Chem.* **2019**, *84*, 12871-12880.
- (a) Park, Y.; Park, K. T.; Kim, J. G.; Chang, S., Mechanistic Studies on the Rh (III)-Mediated Amido Transfer Process Leading to Robust C-H Amination with a New Type of Amidating Reagent. *J. Am. Chem. Soc.* **2015**, *137*, 4534-4542; (b) Hu, X.-H.; Yang, X.-F.; Loh, T.-P., Chelation-Assisted Rhodium-Catalyzed Direct Amidation with Amidobenziodoxolones: C(sp³)-H, C(sp³)-H, and Late-Stage Functionalizations. *ACS Catal.* **2016**, *6*, 5930-5934; (c) You, C.; Yuan, T.; Huang, Y.; Pi, C.; Wu, Y.; Cui, X., Rhodium-Catalyzed Regioselective C8-H Amination of Quinoline *N*-oxides with Trifluoroacetamide at Room Temperature. *Org. Biomol. Chem.* **2018**, *16*, 4728-4733;
- (a) Greenwood, D., Historical perspective. *Conflicts of Interest: the genesis of synthetic antimalarial agents in peace and war. J. Antimicrob. Chemother* **1995**, *36*, 857-872; (b) Lell, B.; Faucher, J.-F.; Missinou, M. A.; Borrmann, S.; Dangelmaier, O.; Horton, J.; Kremsner, P. G., Malaria Chemoprophylaxis with Tafenoquine: A Randomised Study. *Lancet* **2000**, *355*, 2041-2045; (c) Schwartz, E.; Parise, M.; Kozarsky, P.; Cetron, M., Delayed Onset of Malaria-Implications for Chemoprophylaxis in Travelers. *N. Engl. J. Med.* **2003**, *349*, 1510-1516; (d) Tekwani, B. L.; Walker, L. A., 8-Aminoquinolines: Future Role as Antiprotozoal Drugs. *Curr. Opin.*

- Infect. Dis.* **2006**, *19*, 623-631; (e) Peng, H.-K.; Lin, C.-K.; Yang, S.-Y.; Tseng, C.-K.; Tzeng, C.-C.; Lee, J.-C.; Yang, S.-C., Synthesis and Anti-HCV Activity Evaluation of Anilinoquinoline Derivatives. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 1107-1110.
10. Gao, F.; Han, X.; Li, C.; Liu, L.; Cong, Z.; Liu, H., Cobalt (III)-Catalyzed Site-Selective C-H Amidation of Pyridones and Isoquinolones. *RSC Adv.* **2018**, *8*, 32659-32663.
11. (a) Mei, R.; Loup, J.; Ackermann, L., Oxazolinyl-Assisted C-H Amidation by Cobalt(III) Catalysis. *ACS Catal.* **2016**, *6*, 793-797; (b) Cheng, H.; Hernández, J. G.; Bolm, C., Mechanochemical Cobalt-Catalyzed C-H Bond Functionalizations by Ball Milling. *Adv. Synth. Catal.* **2018**, *360*, 1800-1804; (c) Shi, X.; Xu, W.; Wang, R.; Zeng, X.; Qiu, H.; Wang, M., Ketone-Directed Cobalt (III)-Catalyzed Regioselective C2 Amidation of Indoles. *J. Org. Chem.* **2020**, *85*, 3911-3920.
12. (a) Park, J.; Chang, S., Comparative Catalytic Activity of Group 9 [Cp* M^{III}] Complexes: Cobalt-Catalyzed C-H Amidation of Arenes with Dioxazolones as Amidating Reagents. *Angew. Chem. Int. Ed.* **2015**, *54*, 14103-14107; (b) Liang, Y.; Liang, Y. F.; Tang, C.; Yuan, Y.; Jiao, N., Cationic Cobalt(III)-Catalyzed Aryl and Alkenyl C-H Amidation: A Mild Protocol for the Modification of Purine Derivatives. *Chem. Eur. J.* **2015**, *21*, 16395-16399; (c) Bera, S. S.; Sk, M. R.; Maji, M. S., Weakly Coordinating, Ketone-Directed (η^5 -Pentamethylcyclopentadienyl) cobalt (III)- and (η^5 -Pentamethylcyclopentadienyl) rhodium(III)-Catalyzed C-H Amidation of Arenes: A Route to Acridone Alkaloids. *Chem. Eur. J.* **2019**, *25*, 1806-1811.
13. Barsu, N.; Rahman, M. A.; Sen, M.; Sundararaju, B., Cp*Co(III)-Catalyzed C(sp³)-H Bond Amidation of 8-Methylquinoline. *Chem.: Eur. J.* **2016**, *22*, 9135-9138.
14. See the supporting information.
15. Banerjee, S.; De, P. B.; Pradhan, S.; Shah, T. A.; Punniyamurthy, T., Ru(II)-Catalyzed Regioselective C-N Bond Formation of Indolines and Carbazole with Acyl Azides. *Eur. J. Org. Chem.* **2019**, *2019*, 1677-1684.
16. (a) Zhang, L.; Zheng, X.; Chen, J.; Cheng, K.; Jin, L.; Jiang, X.; Yu, C., Ru(II)-Catalyzed C6-Selective C-H Amidation of 2-Pyridones. *Org. Chem. Front.* **2018**, *5*, 2969-2973; (b) Wu, X.; Sun, S.; Xu, S.; Cheng, J., Rh-Catalyzed Annulation of *ortho*-C-H Bonds of 2-Arylimidazoles with 1,4,2-dioxazol-5-ones toward 5-arylimidazo [1, 2-c] quinazolines. *Adv. Synth. Catal.* **2018**, *360*, 1111-1115; (c) Ding, J.; Jiang, W.; Bai, H.-Y.; Ding, T.-M.; Gao, D.; Bao, X.; Zhang, S.-Y., Experimental and Computational Studies on H₂O-Promoted, Rh-Catalyzed Transient-Ligand-Free *ortho*-C(sp³)-H amidation of benzaldehydes with dioxazolones. *ChemComm* **2018**, *54*, 8889-8892; (d) Lei, H.; Rovis, T., Ir-Catalyzed Intermolecular Branch-Selective Allylic C-H Amidation of Unactivated Terminal Olefins. *J. Am. Chem. Soc.* **2019**, *141*, 2268-2273; (e) Bera, S. S.; Maji, M. S., Carbamates: A Directing Group for Selective C-H Amidation and Alkylation under Cp*Co(III) Catalysis. *Org. Lett.* **2020**, *22*, 2615-2620.
17. (a) Butera, J. A.; Spinelli, W.; Anantharaman, V.; Marcopulos, N.; Parsons, R. W.; Moubarak, I. F.; Cullinan, C.; Bagli, J. F., Synthesis and Selective Class III Antiarrhythmic Activity of Novel *N*-heteroaralkyl-Substituted 1-(aryloxy)-2-Propanolamine and Related Propylamine Derivatives. *J. Med. Chem.* **1991**, *34*, 3212-3228; (b) Larionov, O. V.; Stephens, D.; Mfuh, A. M.; Arman, H. D.; Naumova, A. S.; Chavez, G.; Skenderi, B., Insights into the Mechanistic and Synthetic Aspects of the Mo/P-Catalyzed Oxidation of *N*-Heterocycles. *Org. Biomol. Chem.* **2014**, *12*, 3026-3036; (c) Nishida, T.; Fukazawa, A.; Yamaguchi, E.; Oshima, H.; Yamaguchi, S.; Kanai, M.; Kuninobu, Y., Synthesis of Pyridine *N*-oxide-BF₃CF₃ Complexes and Their Fluorescence Properties. *Chem.: Asian J.* **2014**, *9*, 1026-1030; (d) Li, G.; Yang, S.; Lv, B.; Han, Q.; Ma, X.; Sun, K.; Wang, Z.; Zhao, F.; Lv, Y.; Wu, H., Metal-Free Methylation of a Pyridine *N*-oxide C-H Bond by using Peroxides. *Org. Biomol. Chem.* **2015**, *13*, 11184-11188; (e) Ma, X.; Dang, H.; Rose, J. A.; Rablen, P.; Herzon, S. B., Hydroheteroarylation of Unactivated Alkenes using *N*-Methoxyheteroarene Salts. *J. Am. Chem. Soc.* **2017**, *139*, 5998-6007; (f) Zhang, Q.-W.; Hartwig, J. F., Synthesis of Heteroaromatic Trifluoromethyl Ethers with Trifluoromethyl Triflate as the Source of the Trifluoromethoxy Group. *ChemComm* **2018**, *54*, 10124-10127; (g) Zhang, Y.; Zhang, S.; Xu, G.; Li, M.; Tang, C.; Fan, W., Cu-Catalyzed Carbamoylation versus Amination of Quinoline *N*-oxide with Formamides. *Org. Biomol. Chem.* **2019**, *17*, 309-314.
18. (a) Shi, H.; Dixon, D. J., Dithiane-Directed Rh (III)-Catalyzed Amidation of Unactivated C(sp³)-H Bonds. *Chem. Sci.* **2019**, *10*, 3733-3737; (b) Bizet, V.; Buglioni, L.; Bolm, C., Light-Induced Ruthenium-Catalyzed Nitrene Transfer Reactions: A Photochemical Approach towards *N*-Acyl Sulfimides and Sulfoximines. *Angew. Chem. Int. Ed.* **2014**, *53*, 5639-5642; (c) Lei, H.; Rovis, T., Ir-Catalyzed Intermolecular Branch-Selective Allylic C-H Amidation of Unactivated Terminal Olefins. *J. Am. Chem. Soc.* **2019**, *141*, 2268-2273.
19. Xie, W.; Li, B.; Wang, B., Rh(III)-Catalyzed C7-thiolation and Selenation of Indolines. *J. Org. Chem.* **2016**, *81*, 396-403.
20. Sen, C.; Ghosh, S. C., Transition-Metal-Free Regioselective Alkylation of Quinoline *N*-oxides via Oxidative Alkyl Migration and C-C Bond Cleavage of *tert*-/sec-Alcohols. *Adv. Synth. Catal.* **2018**, *360*, 905-910.
21. Liang, Y.-F.; Li, X.; Wang, X.; Yan, Y.; Feng, P.; Jiao, N., Aerobic Oxidation of Pd^{II} to Pd^{IV} by Active Radical Reactants: Direct C-H Nitration and Acylation of Arenes via Oxygenation Process with Molecular Oxygen. *ACS Catal.* **2015**, *5*, 1956-1963.
22. Gupta, S.; Sureshbabu, P.; Singh, A. K.; Sabiah, S.; Kandasamy, J., Deoxygenation of Tertiary Amine *N*-oxides under Metal Free Condition using Phenylboronic Acid. *Tetrahedron Lett.* **2017**, *58*, 909-913.
23. Qiao, H.; Sun, S.; Yang, F.; Zhu, Y.; Kang, J.; Wu, Y.; Wu, Y., Merging Photoredox Catalysis with Iron(III) Catalysis: C5-H Bromination and Iodination of 8-Aminoquinoline Amides in Water. *Adv. Synth. Catal.* **2017**, *359*, 1976-1980.
24. Stephens, D. E.; Lakey-Beitia, J.; Atesin, A. C.; Ateşin, T. I. A.; Chavez, G.; Arman, H. D.; Larionov, O. V., Palladium-Catalyzed C8-Selective C-H Arylation of Quinoline *N*-Oxides: Insights into the Electronic, Steric, and Solvation Effects on the Site Selectivity by Mechanistic and DFT Computational Studies. *ACS Catal.* **2015**, *5*, 167-175.
25. Kumar, R.; Kumar, R.; Dhiman, A. K.; Sharma, U., Regioselective Metal-Free C2-H Arylation of Quinoline *N*-oxides with Aryldiazonium Salts/Anilines under Ambient Conditions. *Asian J. Org. Chem.* **2017**, *6*, 1043-1053.