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Copper-Catalyzed Intermolecular C(sp^2)−H Amination with Electrophilic *O*-Benzoyl Hydroxylamines

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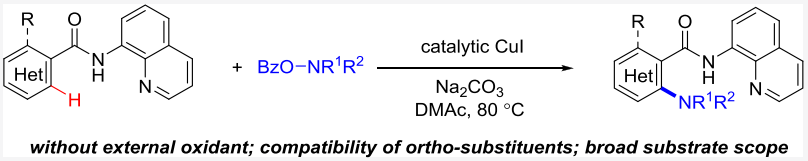

without external oxidant; compatibility of ortho-substituents; broad substrate scope

ABSTRACT: A copper-catalyzed intermolecular electrophilic amination of benzamides with *O*-benzoyl hydroxylamines was achieved with the assistance of an 8-aminoquinolyl group. With this protocol, good compatibility was observed for a variety of aryl amides and heteroaryl amides, and excellent tolerance with various functional groups was achieved. Significantly, the monoaminated product was overwhelmingly delivered under the simple reaction conditions. Preliminary mechanistic investigations suggested that a radical pathway should be excluded and C−H activation be potentially the rate-determining step.

INTRODUCTION

Over the past decades, C−H amination has received considerable attention.[1] To achieve excellent regioselectivity and reactivity, the strategy of auxiliary-assisted transition-metal catalysis tends to be adopted.[2] Compared with directed C−H amination under precious metal catalysis, base-metal copper has shown excellent catalytic performance due to low cost and low toxicity. In this area, Yu and Chatani's group independently developed copper-mediated selective C−H amination of 2-phenylpyridines with tosylamines and anilines.,[3a3b] Nicholas's group have later developed a similar C−H amination protocol.[3c] Inspired by these seminal works, several different approaches for aromatic C−H amination or amidation with nucleophilc amino sources including tosylamides, aromatic amides, aromatic or alkyl amines, anilines, and azides have been later reported. For example, Zhu's group accomplished several elegant works on pyridine-directed copper-mediated aryl C−H amination with azides.[4] Daugulis's group pioneered 8-aminoquinolyl or picolinyl group-directed copper-mediated/catalyzed arene C−H amination with a series of nucleophilic amines (Scheme 1A)[5] and recently realized *N*-aminopyridinium ylide-directed copper-promoted amination of benzamides with pyrazoles, imidazoles, and sulfonamides.[6] Jana and coworkers later developed a copper-mediated intermolecular C(sp^2)−H amination of benzamides with electron-rich anilines.[7] Yu and Dai accomplished several examples of directed copper-mediated ortho-C−H amination/amidation of benzamides with a broad array of nucleophilic amine donors.[8] Chen and Carretero's group independently accomplished picolinamide-directed copper-catalyzed amination of aromatic C−H bonds with simple amines.[9] Recently, Koley and coworkers reported pyrimidyl or pyridyl group-directed copper-catalyzed ortho C−H diarylamination of indoles, indolines, anilines, and *N*-aryl-7-azaindoles with diaryl amines.[10] Moreover, copper, nickel, or cobalt-catalyzed (electrochemical) versions of aromatic C−H amination with nucleophilic amines have been developed.[11]

In contrast to directed nucleophilic amination versions, copper-catalyzed electrophilic amination of C(sp^2)−H bonds is still underexplored.[12] Yu et al. developed an efficient copper-mediated C−H amination reaction with oximes as amino donors to introduce free NH$_2$ groups directly.[12a] Very recently, Jana et al. reported a practical copper-catalyzed, 2-picolinamide directed ortho C−H amination of anilines with hydroxylamines.[12b] These electrophilic aminations proceed smoothly without any external oxidant or additives. Early in 2014, an elegant work on iron-catalyzed ortho-amination of 8-aminoquinolyl aromatic carboxamides with *N*-chloroamines was described by Nakamura's group (Scheme 1B).[13] However, the use of air and moisture-sensitive phenyl magnesium bromide and incompatibility of ortho-substituted benzamides, to some extent, hampered its practicability. Enlightened by these elegant works, we envisioned that an electrophilic amination protocol for C(sp^2)−H of benzamides would be realized by using hydroxylamines with the strategy of directed copper-

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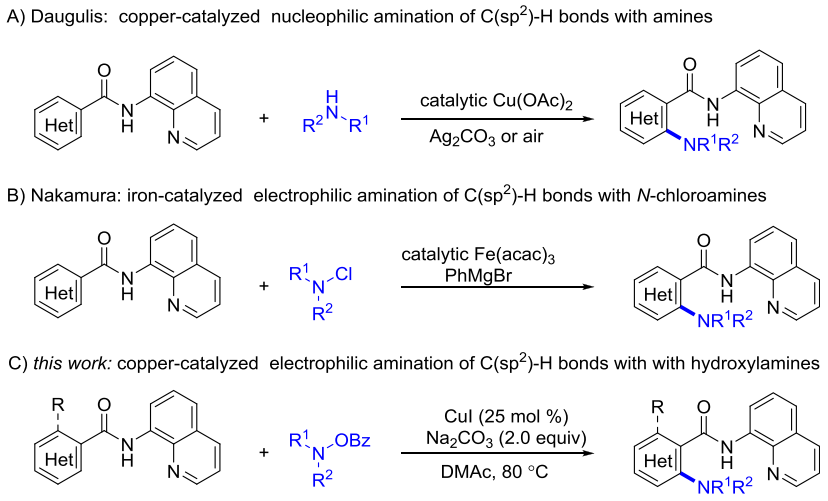
Scheme 1. Different Scenario of Copper-Catalyzed Electrophilic Amination of C(sp^2)−H Bonds

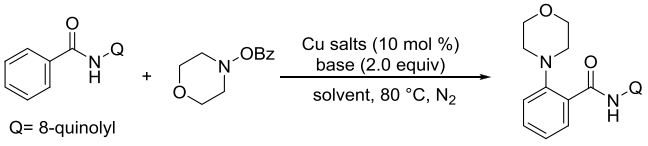


catalyzed C−H activation, in virtue of the significant success of electrophilic hydroxylamines in the amination reaction.[14] We here report a copper-catalyzed intermolecular electrophilic amination of C(sp^2)−H with hydroxylamines with the assistance of an 8-aminoquinolyl group (Scheme 1C). Significantly, mono-selective ortho-amination was obtained and compatibility of ortho-substituted benzamides was observed with the protocol.

RESULTS AND DISCUSSION

We commenced our optimization study with the reaction of *N*-(quinolin-8-yl)benzamide (**1a**) and *O*-benzoyl hydroxylmorpholine (**2a**) as model substrates (Table 1). We first evaluated

Table 1. Optimization of the Reaction Conditions[a]



entry	Cu salts	base	solvent	yield (%)[b]
1	$Cu(OAc)_2$	Na_2CO_3	DMF	56
2	$Cu(OAc)_2$	Na_2CO_3	DMAc	64
3	$Cu(OAc)_2$	Na_2CO_3	NMP	42
4	$Cu(OAc)_2$	Na_2CO_3	DCE	trace
5	$Cu(OAc)_2$	Na_2CO_3	toluene	trace
6	$Cu(OAc)_2$	Na_2CO_3	dioxane	trace
7	CuBr	Na_2CO_3	DMAc	32
8	CuI	Na_2CO_3	DMAc	66
9[c]	CuI	Na_2CO_3	DMAc	78(74)[d]
10	$Cu_2(OH)_2CO_3$	Na_2CO_3	DMF	0
11	CuI	Li_2CO_3	DMAc	46
12	CuI	K_2CO_3	DMAc	48
13	CuI	K_3PO_4	DMAc	trace
14	CuI	NaOAc	DMAc	56
15	CuI	KOAc	DMAc	50

[a]Reaction conditions: **1a** (0.3 mmol), Cu salts (0.03 mmol, 10 mol %), base (0.6 mmol, 2 equiv), **2a** (0.45 mmol, 1.5 equiv) in 3 mL of solvent at 80 °C for 2 h under nitrogen. [b]Yield determined by ^1H NMR using CH_2Br_2 as the internal standard. [c]With 25 mol % CuI. [d]Isolated yield in parentheses.

several solvents in the presence of catalytic copper acetate and excess Na_2CO_3 (entries 1−6). Experiments showed that amide-type solvent was generally superior to other tested solvents, and DMAc afforded the desired product **3a** in 64% yield (entry 2). After the extensive screening of various copper salts (entries 7 and 10), we were pleased to find that product **3a** could be produced in 66% yield in the presence of CuI as a catalyst. To our delight, the desired product **3a** could be afforded in 78% yield (74% isolated yield) when the loading amount of CuI was increased to 25 mol %. Further experiments showed that Na_2CO_3 worked better than other tested bases (entries 11−15). Overall, the desired product **3a** was obtained in 74% yield with 25 mol % CuI in DMAc at 80 °C for 2 h (entry 9).

With the optimized conditions in hand, we explored the aromatic amide scope. As shown in Scheme 2, a broad variety of aromatic amides were compatible with the protocol. Para-substituted aromatic amides generally proceeded smoothly. Amination of electron-rich or -deficient substrates afforded the desired products **3b-3k** in moderate to high yields. The amination reaction of ortho-substituted benzamides generally proceeded at a higher temperature (**3l-3o**), presumably caused by a high steric hindrance arising from the ortho-substituents. Meta-substituents including methyl (**3p**), chloro (**3r**), bromo (**3s**), and trifluoromethyl (**3t**) groups at the aromatic ring could be also well tolerated. Notably, the selective mono-amination occurred exclusively at the ortho site. Meanwhile, amination of benzamide with a small fluoro substituent at the meta site delivered regioisomers **3q** with a 1:1 regioselectivity. The amination reaction of electron-rich 2-naphthamide occurred at the C3 site of the naphthyl ring to afford the amination product **3u** in moderate yield. The protocol could be extended to the ortho-amination of 1-naphthamide, and the corresponding product **3v** was obtained in 64% yield. Moreover, heteroaromatic amides including nicotinamide, isonicotinamide, thiophene-2-carboxamide, and thiophene-3-carboxamide could be selectively aminated at the ortho site to afford the corresponding product **3w**−**3z** in 52%−61% yields.

Subsequently, we turned our attention to examine the scope of electrophilic *O*-benzoyl hydroxylamines (Scheme 3). The catalytic amination of **1b** with these *O*-benzoyl hydroxylamines, derived from 6-membered cyclic amines including piperidines and piperazine proceeded smoothly to provide the

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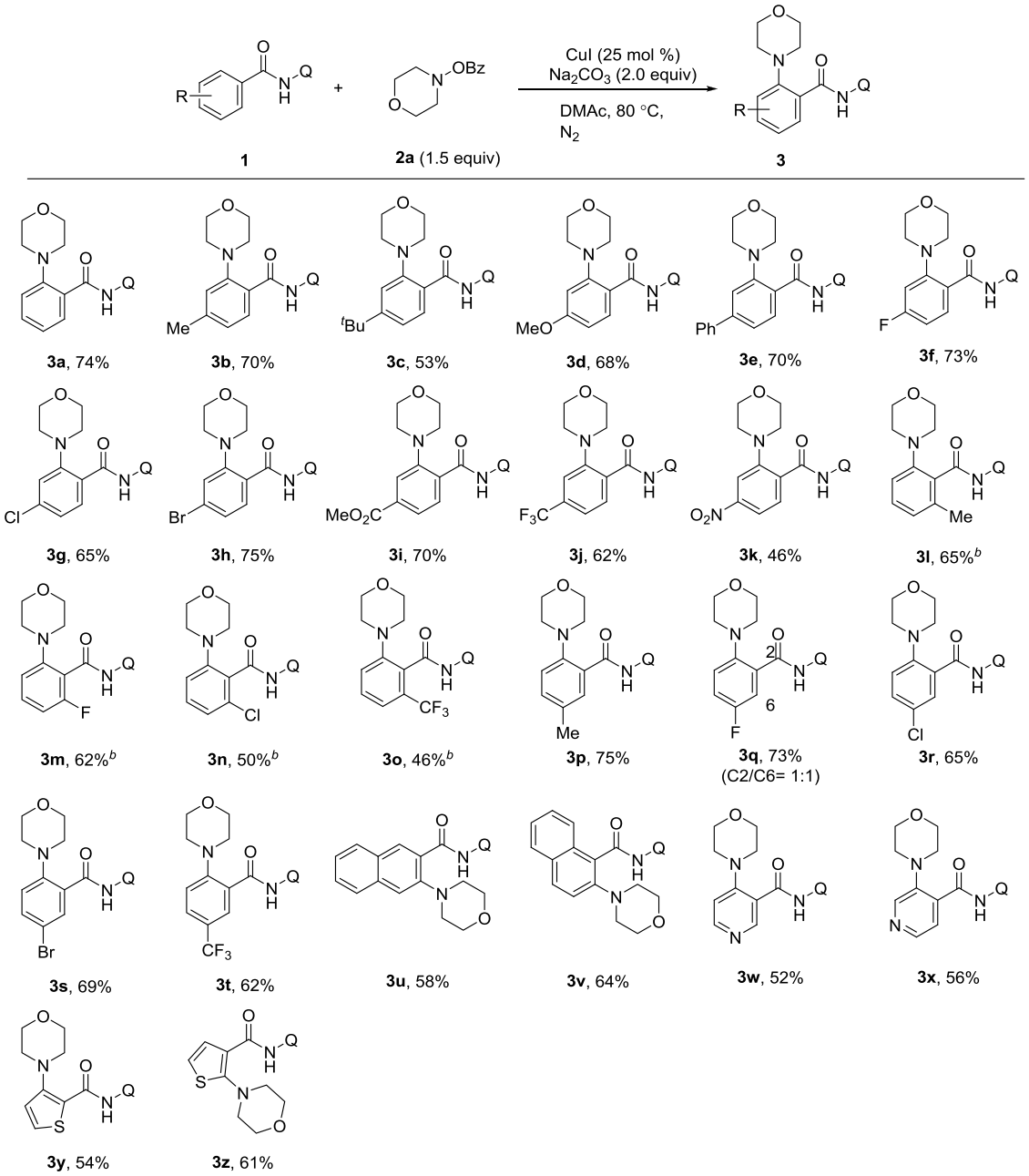
Scheme 2. Ortho-C−H Amination of Substituted 8-Aminoquinonyl Benzamides with 2a[a]



[a]Unless otherwise mentioned, all of the reactions were carried out with **1** (0.3 mmol), **2a** (0.45 mmol), CuI (25 mol %), Na_2CO_3 (0.6 mmol) in the DMAc (3.0 mL) at 80 °C for 2 h under N_2. Isolated yields. [b]Under 100 °C.

desired aminated product **4a**−**4e** in acceptable to good yields. Notably, the ester, ketal, and Boc groups are well tolerated. A 7-membered cyclic azepane donor coupled well with **1b** to give the aminated product **4f** in 50% yield. However, a 5-membered cyclic pyrrolidine donor (**4g**) was not tolerated. The reactions with acyclic diethyl amine- and dipropyl amine-derived *O*-benzoyl hydroxylamines (**4h**-**4i**) could also render the installation of the dialkyl amine units, albeit in low yields.

A gram-scale synthesis of **3a** was carried out, and **3a** was isolated in 69% yield along with 20% recovery of **1a** (Scheme 4a), demonstrating the potential application of the protocol into large-scale production. To examine the viability of this transformation, the removal of 8-aminoquinolyl directing group was conducted (Scheme 4b). The amide cleavage was realized under basic conditions to provide the carboxylic acid **5** in 89% isolated yield.[5a]

Considering that the preparation of *O*-benzoyl hydroxylamines required an additional synthetic step, we wondered whether the one-pot amination of benzamides with the combination of morpholine and BzOOBz was feasible. With this in mind, the ortho-amination of **1a** with the combination of morpholine and BzOOBz instead of **2a** was performed (Scheme 5). Unfortunately, the yield of **3a** was only 30% based on crude ^{1}H NMR analysis (see Supporting Information for details), which suggested that *O*-benzoyl hydroxylamines was superior to the combination of morpholine and BzOOBz in the amination reaction.

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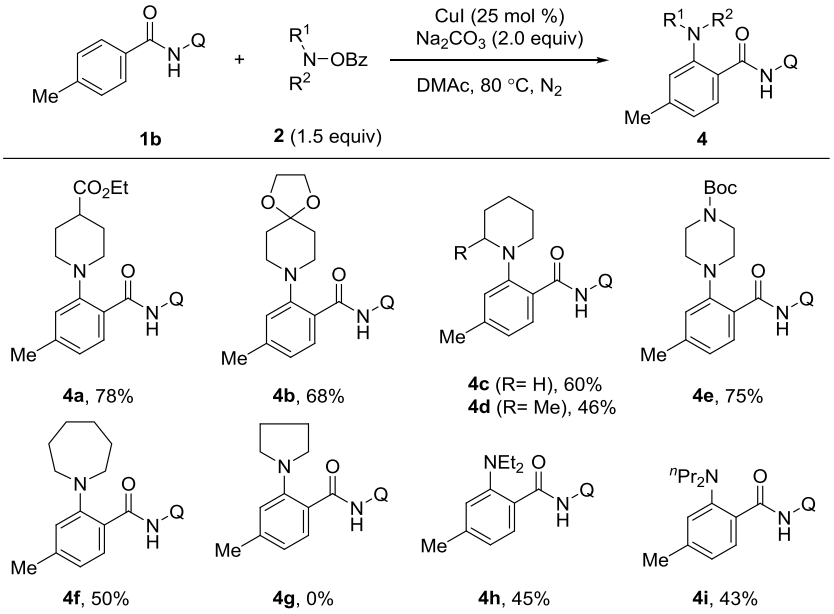
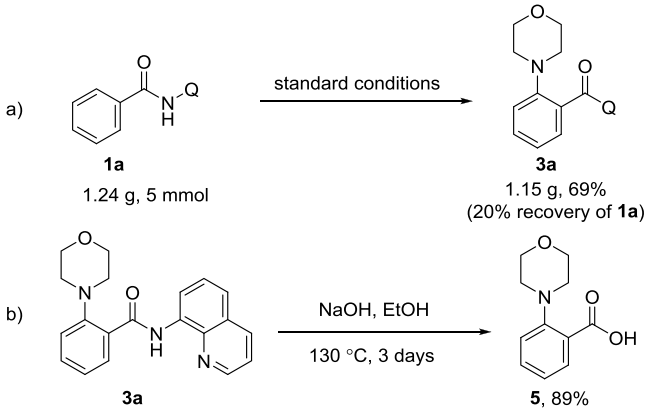
Scheme 3. Scope of *O*-Benzoyl Hydroxylamines[a]

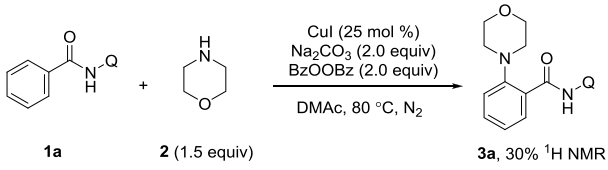


[a]Reaction conditions: **1b** (0.3 mmol), **2** (0.45 mmol), CuI (25 mol %), Na_2CO_3 (0.6 mmol) in the DMAc (3.0 mL) at 80 °C for 2 h under N_2. Isolated yields.

Scheme 4. Gram-Scale Synthesis of 3a and Removal of 8-Aminoquinoline Auxiliary



Scheme 5. Amination of 1a with the Combination of Morpholine and BzOOBz



To further get insight into the reaction mechanism, preliminary mechanistic investigations were conducted. Radical scavenger experiments with 1.0 or 2.0 equiv of TEMPO or 2.0 equiv of BHT as a radical inhibitor showed that the transformation was not completely inhibited (Scheme 6a), suggesting that a radical pathway should not be involved in the amination process. Subsequent competition experiments were performed to probe the reactivity of substrates (Scheme 6b). Competitive reaction of benzamide (**1a**) and 3-methylbenzoic amide derivatives (**1p**) with *O*-benzoyl hydroxylmorpholine (**2a**) afforded a 1.8:1 ratio of the products, which showed that the electron-deficient amide was favored. The 1.75:1 ratio of products **4c** and **3b** in the competitive coupling reaction of *O*-benzoyl hydroxylmorpholine (**2a**) and *O*-benzoyl hydroxylpiperidine (**2b**) with 4-methylbenzoic amide derivative (**1b**) showed that less electrophilic *O*-benzoyl hydroxylpiperidine (**2b**) was favored. Furthermore, intramolecular and intermolecular KIE were determined to be 3.8 and 4.0, respectively (Scheme 6c,d), indicating that C−H cleavage could potentially be involved in the rate-determining step.

In summary, we developed a copper-catalyzed intermolecular electrophilic amination of benzamides with *O*-benzoyl hydroxylamines. The amination occurred at the *ortho* site selectively with the assistance of a 8-aminoquinolyl group. A variety of aryl amides and heteroaryl amides are compatible with the protocol, and excellent tolerance with various functional groups was achieved. Significantly, the monoaminated product was overwhelmingly delivered under the simple reaction conditions.

EXPERIMENTAL SECTION

General Information. NMR spectra were recorded on a JNM-ECZ600R/S3 at 600 MHz (for ^1H NMR) and 150 MHz (for ^{13}C NMR) using TMS as the internal standard. Chemical shifts are given relative to the residual solvents of $CDCl_3$ (7.26 ppm for ^1H NMR, 77.16 ppm for $^{13}C\{^1H\}$ NMR) unless otherwise noted. HRMS for new compounds were recorded on a MicroMass Waters Xevo G2-XS QTof, Xinyang Normal University. Melting points were measured on a SGW X-4A melting point apparatus and are uncorrected. For column chromatography, silica gel (300−400 mesh) was used as the stationary phase. Unless otherwise noted, all commercial materials were used without further purification. Solvents were used after purification directed by Purification of Laboratory Chemicals, 6th Ed.

Synthesis of Starting Materials. The benzamides **1a−1z** were synthesized from the corresponding carboxylic acids and 8-aminoquinoline according to the literature.[5a] All *O*-benzoyl hydroxylamines **2** were synthesized from the corresponding amines and benzoyl peroxide according to the literature.[15] **1a-d_1 and 1a-d_5** were prepared

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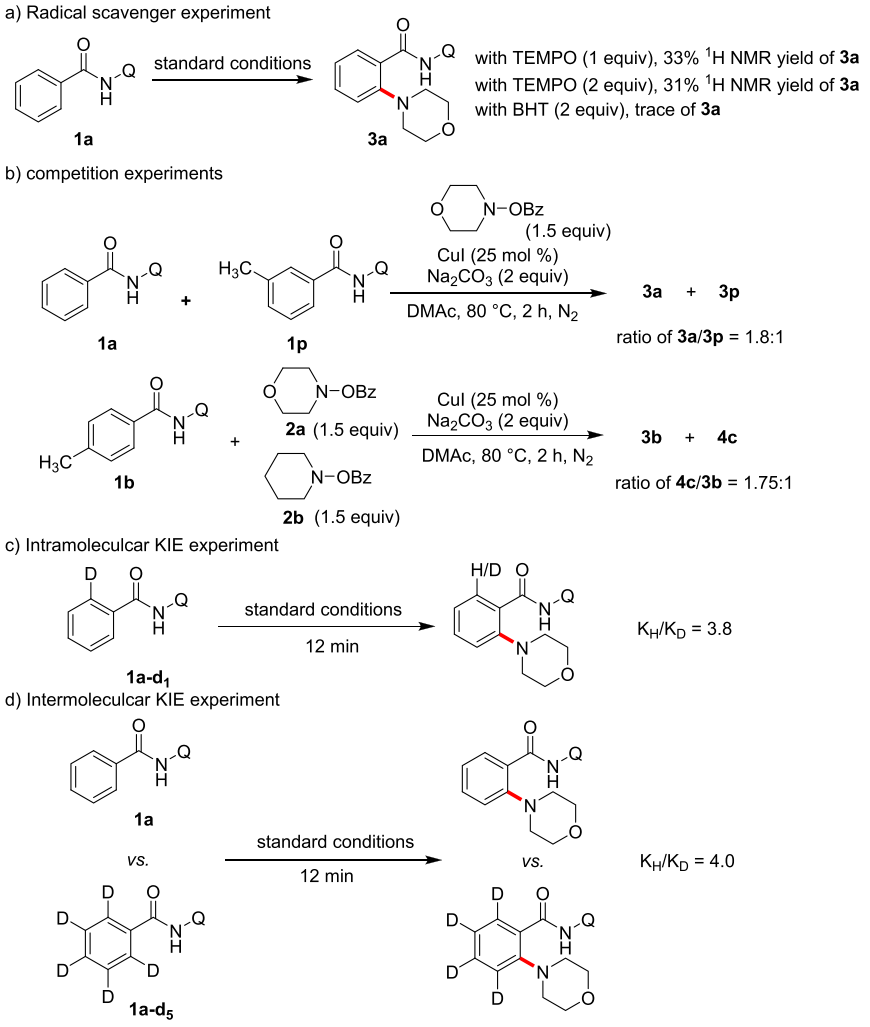
Scheme 6. Mechanistic Investigations



according to the literature.[16] All of the NMR spectra of the known compounds were in accordance with the data in the literature.

General Procedure for the *Ortho*-Amination of Benzamides. Take the reaction of **1a** with **2a** for example: To a 30 mL Schlenk flask were added **1a** (75 mg, 0.3 mmol), CuI (14 mg, 0.075 mmol), **2a** (93 mg, 0.45 mmol, 1.5 equiv), Na_2CO_3 (64 mg, 0.6 mmol, 2 equiv), and DMAc (3.0 mL). The flask was then charged with N_2 via two-times N_2 vacuum exchanges, and the mixture was stirred at 80 °C (oil bath) for 2 h. After being allowed to cool to room temperature, the reaction was diluted with DCM (10 mL) and treated with saturated aqueous solution of Na_2S. Then, the mixture was stirred at room temperature for 10 min and was filtered through a short pad of Celite, which was washed with copious DCM. Evaporation of the organic solvent and purification by silica gel column chromatography (petroleum ether: EtOAc = 4:1) gave the desired product **3a** as a white solid (74 mg) in 74% yield.

Gram-Scale Synthesis of 3a. To a 100 mL vial were added **1a** (1.24 g, 5 mmol), CuI (0.237 g, 1.25 mmol), **2a** (1.55 g, 0.45 mmol, 1.5 equiv), Na_2CO_3 (1.06 mg, 10 mmol, 2 equiv), and DMAc (50 mL). The flask was then charged with N_2 via two-times N_2-vacuum exchanges, and the mixture was stirred at 80 °C (oil bath) for 2 h. After being allowed to cool to room temperature, the reaction was diluted with DCM (10 mL) and treated with saturated aqueous solution of Na_2S. Then, the mixture was stirred at room temperature for 10 min and was filtered through a short pad of Celite, which was washed with copious DCM. Evaporation of the organic solvent and purification by silica gel column chromatography (petroleum ether: EtOAc = 4:1) gave the desired product **3a** as a white solid (1.15 g) in 69% yield and the residual starting material **1a** (0.25 g) as a white solid in 20% yield.

Removal of the 8-Aminoquinolyl Auxiliary. The removal of 8-aminoquinolyl auxiliary was conducted according the literature.[5a] A 30 mL Schlenk flask equipped with a stir bar was charged with **3a** (100 mg, 0.3 mmol), NaOH (180 mg, 4.5 mmol), and EtOH (3 mL). The resulting mixture was stirred at 130 °C (oil bath). After 3 days, the reaction mixture was cooled down to room temperature, diluted with 50 mL ethyl acetate, and washed with HCl (4 × 20 mL of 0.5 N aqueous solution). The aqueous layers were combined and extracted with EtOAc (3 × 20 mL). Combined organic layers were dried over $MgSO_4$. Evaporation of the organic solvent and purification by silica gel column chromatography (petroleum ether: EtOAc = 7:1) gave the desired product **5** as a yellowish oil (55 mg) in 89% yield.

Mechanistic Investigation. *Radical Scavenger Experiment.* To a 30 mL Schlenk flask were added **1a** (75 mg, 0.3 mmol), CuI (14 mg, 0.075 mmol), **2a** (93 mg, 0.45 mmol, 1.5 equiv), Na_2CO_3 (64 mg, 0.6 mmol, 2 equiv), TEMPO (1.0 or 2.0 equiv), or BHT (2.0 equiv) and DMAc (3.0 mL). The flask was then charged with N_2 via two-times N_2-vacuum exchanges, and the mixture was stirred at 80 °C (oil bath) for 2 h. After being allowed to cool to room temperature, the reaction was diluted with DCM (10 mL) and treated with saturated aqueous solution of Na_2S. Then, the mixture was stirred at room temperature for 10 min and was filtered through a short pad of Celite, which was washed with copious DCM. Evaporation of the organic solvent afforded the crude product, and subsequent ^{1}H NMR analysis of the crude product with CH_2Br_2 as an internal standard gave a 33% yield

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of **3a** with 1.0 equiv of TEMPO, a 31% yield of **3a** with 2.0 equiv of TEMPO, and a trace of **3a** with 2.0 equiv of BHT, respectively.

Competition experiments of **1a** and **1p** with **2a**: To a 30 mL Schlenk flask were added **1a** (25 mg, 0.1 mmol), **1p** (26 mg, 0.1 mmol), CuI (10 mg, 0.05 mmol), **2a** (62 mg, 0.3 mmol, 1.5 equiv), Na_2CO_3 (43 mg, 0.4 mmol, 2 equiv), and DMAc (2.0 mL). The flask was then charged with N_2 via two-times N_2 vacuum exchanges, and the mixture was stirred at 80 °C (oil bath) for 2 h. After being allowed to cool to room temperature, the reaction was diluted with DCM (10 mL) and treated with saturated aqueous solution of Na_2S. Then, the mixture was stirred at room temperature for 10 min and was filtered through a short pad of Celite, which was washed with copious DCM. Evaporation of the organic solvent afforded the crude product, and subsequent ^{1}H NMR analysis of the crude product gave a 1.8:1 ratio of products **3a** and **3p**.

*Competition Experiment of **2a** and **2b** with **1b**.* To a 30 mL Schlenk flask were added **1b** (53 mg, 0.2 mmol), CuI (10 mg, 0.05 mmol), **2a** (62 mg, 0.3 mmol, 1.5 equiv), **2b** (62 mg, 0.3 mmol, 1.5 equiv), Na_2CO_3 (43 mg, 0.4 mmol, 2 equiv), and DMAc (2.0 mL). The flask was then charged with N_2 via two-times N_2 vacuum exchanges, and the mixture was stirred at 80 °C (oil bath) for 2 h. After being allowed to cool to room temperature, the reaction was diluted with DCM (10 mL) and treated with saturated aqueous solution of Na_2S. Then, the mixture was stirred at room temperature for 10 min and was filtered through a short pad of Celite, which was washed with copious DCM. Evaporation of the organic solvent afforded the crude product, and subsequent ^{1}H NMR analysis of the crude product gave a 1.75:1 ratio of products **4c** and **3b**.

Intramolecular KIE Experiment. To a 30 mL Schlenk flask were added **1a-d$_1$** (100 mg, 0.4 mmol), CuI (19 mg, 0.1 mmol), **2a** (124 mg, 0.6 mmol, 1.5 equiv), Na_2CO_3 (168 mg, 0.8 mmol, 2.0 equiv), and DMAc (4.0 mL). The flask was then charged with N_2 via twice N_2-vacuum exchanges, and the mixture was stirred at 80 °C (oil bath) for 12 min. After being allowed to cool to room temperature, the reaction was diluted with DCM (15 mL) and treated with saturated aqueous solution of Na_2S. Then, the mixture was stirred at room temperature for 10 min and was filtered through a pad of Celite, which was washed with copious DCM. Evaporation of the organic solvent and purification by flash chromatography (toluene: EtOAc = 6:1) gave the desired product in 10% yield. The KIE value was calculated to be K_H/K_D = 3.8.

Intermolecular KIE Experiment. To a 30 mL Schlenk flask were added **1a-d$_5$** (50.6 mg, 0.2 mmol), **1a** (50.0 mg, 0.2 mmol), CuI (19 mg, 0.1 mmol), **2a** (124 mg, 0.6 mmol, 1.5 equiv), Na_2CO_3 (168 mg, 0.8 mmol, 2.0 equiv), and DMAc (4.0 mL). The flask was then charged with N_2 via two-times N_2 vacuum exchanges, and the mixture was stirred at 80 °C (oil bath) for 12 min. After being allowed to cool to room temperature, the reaction was diluted with DCM (15 mL) and treated with saturated aqueous solution of Na_2S. Then, the mixture was stirred at room temperature for 10 min and was filtered through a pad of Celite, which was washed with copious DCM. Evaporation of the organic solvent and purification by flash chromatography (toluene:EtOAc = 8:1) gave the desired product in 12% yield. The KIE value was calculated to be K_H/K_D = 4.0.

Characterization of Compounds. *2-Morpholino-N-(quinolin-8-yl)benzamide (**3a**).* The compound **3a** was prepared according to the **GP** and purified by silica column chromatography in petroleum ether:ethyl acetate = 4:1. **3a** was obtained as a white solid (74 mg, 74%). This compound is known.[5b] Melting point: 122−124 °C. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 12.67 (s, 1H), 9.13 (d, *J* = 7.8 Hz,1H), 8.82 (dd, *J* = 3.6, 1.8 Hz, 1H), 8.19 (dd, *J* = 7.8, 1.8 Hz, 1H), 8.11 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.55 (t, *J* = 7.8 Hz, 1H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.46 (td, *J* = 7.8, 1.2 Hz, 1H), 7.41 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.23 (d, *J* = 7.2 Hz, 1H), 7.20 (d, *J* = 8.4 Hz, 1H), 3.93 (t, *J* = 4.2 Hz, 4H), 3.10 (t, *J* = 4.2 Hz, 4H). ^{13}C{^{1}H} NMR (150 MHz, Chloroform-*d*) δ 165.6, 151.1, 148.1, 138.7, 136.3, 135.5, 132.3, 132.1, 128.8, 128.2, 127.5, 124.2, 121.7, 121.6, 119.2, 117.7, 66.0, 53.8. HRMS (ESI-TOF): *m/z* calcd for $C_{20}H_{20}N_3O_2$ [M + H]$^+$ 334.1550, found 334.1550.

*4-Methyl-2-morpholino-N-(quinolin-8-yl)benzamide (**3b**).* The compound **3b** was prepared according to the **GP** and purified by silica column chromatography in petroleum ether:ethyl acetate = 6:1. **3b** was obtained as a white solid (73 mg, 70%). This compound is known.[13] Melting point: 184−185 °C. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 12.69 (s, 1H), 9.13 (dd, *J* = 7.8, 1.2 Hz, 1H), 8.86 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.16 (dd, *J* = 8.4, 1.2 Hz, 1H), 8.09 (d, *J* = 7.8 Hz, 1H), 7.58 (t, *J* = 7.8 Hz, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.46 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.10−6.98 (m, 2H), 3.97 (t, *J* = 4.2 Hz, 4H), 3.13 (t, *J* = 4.2 Hz, 4H), 2.41 (s, 3H). ^{13}C{^{1}H} NMR (150 MHz, Chloroform-*d*) δ 165.9, 151.2, 148.2, 143.0, 138.9, 136.5, 135.8, 132.3, 128.4, 127.7, 126.1, 125.2, 121.7, 121.7, 120.1, 117.8, 66.2, 54.0, 21.7. HRMS (ESI-TOF): *m/z* calcd for $C_{21}H_{22}N_3O_2$ [M + H]$^+$ 348.1707, found 348.1710.

*4-(tert-Butyl)-2-morpholino-N-(quinolin-8-yl)benzamide (**3c**).* The compound **3c** was prepared according to the **GP** and purified by silica column chromatography in petroleum ether:ethyl acetate = 4:1. **3c** was obtained as a white solid (62 mg, 53%). This compound is known.[5a] Melting point: 132−134 °C. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 12.71 (s, 1H), 9.13 (d, *J* = 7.8 Hz, 1H), 8.87 (dd, *J* = 4.2, 1.2 Hz, 1H), 8.19 (d, *J* = 7.8 Hz, 1H), 8.13 (d, *J* = 7.8 Hz, 1H), 7.60 (t, *J* = 7.8 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.48 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.32−7.27 (m, 2H), 3.99 (t, *J* = 4.2 Hz, 4H), 3.18 (t, *J* = 4.2 Hz, 4H), 1.37 (s, 9H). ^{13}C{^{1}H} NMR (150 MHz, Chloroform-*d*) δ 165.9, 156.1, 151.0, 148.2, 139.0, 136.5, 135.9, 132.0, 128.4, 127.7, 126.1, 121.7, 121.6, 121.5, 117.9, 116.3, 66.3, 54.1, 35.3, 31.3. HRMS (ESI-TOF): *m/z* calcd for $C_{24}H_{28}N_3O_2$ [M + H]$^+$ 390.2176, found 390.2174.

*4-Methoxy-2-morpholino-N-(quinolin-8-yl)benzamide (**3d**).* Compound **3d** was prepared according to the **GP** and purified by silica column chromatography in petroleum ether:ethyl acetate = 6:1. **3d** was obtained as a white solid (74 mg, 68%). This compound is known.[5a] Melting point: 171−173 °C. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 12.62 (s, 1H), 9.12 (dd, *J* = 7.8, 1.2 Hz, 1H), 8.86 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.23−8.10 (m, 2H), 7.58 (t, *J* = 7.8 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.46 (dd, *J* = 8.4, 4.2 Hz, 1H), 6.77−6.75 (m, 2H), 3.97 (t, *J* = 4.2 Hz, 4H), 3.87 (s, 3H), 3.12 (t, *J* = 4.2 Hz, 4H). ^{13}C{^{1}H} NMR (150 MHz, Chloroform-*d*) δ 165.5, 163.0, 153.1, 148.1, 138.9, 136.5, 135.9, 134.1, 128.4, 127.7, 121.7, 121.6, 121.6, 117.8, 108.4, 106.2, 66.2, 55.6, 54.0. HRMS (ESI-TOF): *m/z* calcd for $C_{21}H_{22}N_3O_3$ [M + H]$^+$ 364.1656, found 364.1653.

*3-Morpholino-N-(quinolin-8-yl)-[1,1′-biphenyl]-4-carboxamide (**3e**).* Compound **3e** was prepared according to the **GP** and purified by silica column chromatography in petroleum ether:ethyl acetate = 5:1. **3e** was obtained as a white solid (86 mg, 70%). This compound is known.[11a] Melting point: 168−170 °C. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 12.73 (s, 1H), 9.17 (dd, *J* = 7.8, 1.2 Hz, 1H), 8.89 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.28 (d, *J* = 7.8 Hz, 1H), 8.19 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.68−7.64 (m, 2H), 7.61 (t, *J* = 7.8 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.52−7.47 (m, 4H), 7.46 (d, *J* = 1.8 Hz, 1H), 7.44−7.39 (m, 1H), 4.00 (t, *J* = 4.2 Hz, 4H), 3.23 (t, *J* = 4.2 Hz, 4H). ^{13}C{^{1}H} NMR (150 MHz, Chloroform-*d*) δ 165.6, 151.6, 148.2, 145.4, 140.3, 138.9, 136.5, 135.7, 132.8, 129.0, 128.4, 128.2, 127.7, 127.6, 127.3, 123.0, 121.9, 121.7, 118.2, 117.9, 66.2, 54.1. HRMS (ESI-TOF): *m/z* calcd for $C_{26}H_{23}NaN_3O_2$ [M + Na]$^+$ 432.1682, found 432.1683.

*4-Fluoro-2-morpholino-N-(quinolin-8-yl)benzamide (**3f**).* Compound **3f** was prepared according to the **GP** and purified by silica column chromatography in petroleum ether:ethyl acetate = 4:1. **3f** was obtained as a white solid (77 mg, 73%). This compound is known.[5a] Melting point: 177−179 °C. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 12.5 (s, 1H), 9.09 (dd, *J* = 7.8, 1.2 Hz, 1H), 8.88 (d, *J* = 2.4 Hz, 1H), 8.20 (dd, *J* = 8.4, 1.8 Hz, 1H), 8.17 (dd, *J* = 9.6, 6.6 Hz, 1H), 7.60 (t, *J* = 7.8 Hz, 1H), 7.56 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.50 (dd, *J* = 8.4, 4.2 Hz, 1H), 6.94 (m, *J* = 7.8 Hz, 1H), 6.93 (dd, *J* = 6.6, 2.4 Hz, 1H), 3.96 (t, *J* = 4.2 Hz, 4H), 3.14 (t, *J* = 4.2 Hz, 4H). ^{13}C{^{1}H} NMR (150 MHz, Chloroform-*d*) δ 165.1 (d, *J* = 251.25 Hz, 1C), 164.8, 153.3 (d, *J* = 8.4 Hz, 1C), 148.2, 138.7, 136.5, 135.4, 134.4 (d, *J* = 9.9 Hz, 1C), 128.4, 127.6, 125.0, 121.9, 121.7, 117.7, 111.0 (d, *J* = 21.15 Hz, 1C), 106.7 (d, *J* = 23.25 Hz, 1C), 66.0, 53.8.

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^{19}F NMR (565 MHz, Chloroform-*d*) δ −106.3. HRMS (ESI-TOF): *m/z* calcd for $C_{20}H_{18}FNaN_3O_2$ $[M + Na]^+$ 374.1275, found 374.1276.

*4-Chloro-2-morpholino-N-(quinolin-8-yl)benzamide (**3g**).* Compound **3g** was prepared according to the **GP** and purified by silica column chromatography in petroleum ether:ethyl acetate = 6:1. **3 g** was obtained as a white solid (72 mg, 65%). This compound is known.[5b] Melting point: 148−150 °C. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 12.47 (s, 1H), 9.08 (dd, *J* = 7.8, 1.8 Hz, 1H), 8.86 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.48 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.21 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.19 (d, *J* = 1.8 Hz, 1H), 3.94 (t, *J* = 4.2 Hz, 4H), 3.13 (t, *J* = 4.2 Hz, 4H). ^{13}C{^{1}H} NMR (150 MHz, Chloroform-*d*) δ 164.8, 152.2, 148.3, 138.8, 138.2, 136.6, 135.4, 133.5, 128.4, 127.7, 127.4, 124.4, 122.1, 121.8, 119.8, 117.8, 66.1, 53.8. HRMS (ESI-TOF): *m/z* calcd for $C_{20}H_{19}ClN_3O_2$ $[M + H]^+$ 368.1160, found 368.1156.

*4-Bromo-2-morpholino-N-(quinolin-8-yl)benzamide (**3h**).* Compound **3h** was prepared according to the **GP** and purified by silica column chromatography in petroleum ether:ethyl acetate = 4:1. **3h** was obtained as a white solid (93 mg, 75%). This compound is known.[13] Melting point: 148 °C (decomp). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 12.47 (s, 1H), 9.08 (dd, *J* = 7.8, 1.2 Hz, 1H), 8.87 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.20 (dd, *J* = 8.4, 1.8 Hz, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.60 (t, *J* = 7.8 Hz, 1H), 7.56 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.50 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.39 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.36 (d, *J* = 2.4 Hz, 1H), 3.95 (t, *J* = 4.8 Hz, 4H), 3.15 (t, *J* = 4.8 Hz, 4H). ^{13}C{^{1}H} NMR (150 MHz, Chloroform-*d*) δ 164.9, 152.1, 148.3, 138.8, 136.6, 135.3, 133.7, 128.4, 127.8, 127.7, 127.4, 126.7, 122.8, 122.1, 121.8, 117.8, 66.0, 53.9. HRMS (ESI-TOF): *m/z* calcd for $C_{20}H_{19}BrN_3O_2$ $[M + H]^+$ 412.0655 found 412.0653.

*Methyl-3-morpholino-4-(quinolin-8-ylcarbamoyl)benzoate (**3i**).* Compound **3i** was prepared according to the **GP** and purified by silica column chromatography in petroleum ether:ethyl acetate = 4:1. **3i** was obtained as a white solid (82 mg, 70%). This compound is known.[5a] Melting point: 183−185 °C. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 12.57 (s, 1H), 9.08 (d, *J* = 7.8 Hz, 1H), 8.85 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.20 (d, *J* = 7.8 Hz, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 7.89 (s, 1H), 7.87 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.62−7.55 (m, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.46 (ddd, *J* = 8.4, 4.2, 1.8 Hz, 1H), 3.93 (t, *J* = 4.2 Hz, 4H), 3.16 (t, *J* = 4.2 Hz, 4H). ^{13}C{^{1}H} NMR (150 MHz, Chloroform-*d*) δ 166.4, 164.9, 151.0, 148.3, 138.8, 136.5, 135.2, 133.4, 132.8, 132.3, 128.4, 127.6, 125.1, 122.2, 121.8, 120.4, 117.9, 66.1, 53.8, 52.5. HRMS (ESI-TOF): *m/z* calcd for $C_{22}H_{22}N_3O_4$ $[M + H]^+$ 392.1605, found 392.1597.

*2-Morpholino-N-(quinolin-8-yl)-4-(trifluoromethyl)benzamide (**3j**).* Compound **3j** was prepared according to the **GP** and purified by silica column chromatography in petroleum ether:ethyl acetate = 4:1. **3j** was obtained as a white solid (75 mg, 62%). This compound is known.[13] Melting point: 172−174 °C. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 12.45 (s, 1H), 9.09 (dd, *J* = 7.8, 1.8 Hz, 1H), 8.86 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.24 (d, *J* = 7.8 Hz, 1H), 8.19 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.60 (t, *J* = 7.8 Hz, 1H), 7.56 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.49 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.45 (s, 1H), 3.94 (t, *J* = 4.2 Hz, 4H), 3.18 (t, *J* = 4.2 Hz, 4H). ^{13}C{^{1}H} NMR (150 MHz, Chloroform-*d*) δ 164.6, 151.4, 148.4, 138.8, 136.6, 135.1, 133.9 (q, *J* = 32.1 Hz, 1C), 132.9, 132.1, 128.4, 127.6, 123.7, 122.3, 121.9, 121.0, 120.7, 117.9, 116.0, 66.1, 53.7. ^{19}F NMR (565 MHz, Chloroform-*d*) δ −62.75. HRMS (ESI-TOF): *m/z* calcd for $C_{21}H_{18}NaF_3N_3O_2$ $[M + Na]^+$ 424.1243, found 424.1249.

*2-Morpholino-4-nitro-N-(quinolin-8-yl)benzamide (**3k**).* Compound **3k** was prepared according to the **GP** and purified by silica column chromatography in petroleum ether:ethyl acetate = 4:1. **3k** was obtained as a yellowish solid (52 mg, 46%). Melting point: 116−118 °C. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 12.37 (s, 1H), 9.06 (dd, *J* = 7.2, 1.8 Hz, 1H), 8.87 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.29−8.24 (m, 1H), 8.21 (dd, *J* = 8.4, 1.8 Hz, 1H), 8.05 (s, 1H), 8.04 (dd, *J* = 7.8, 2.4 Hz, 1H), 7.64−7.57 (m, 2H), 7.51 (dd, *J* = 8.4, 4.2 Hz, 1H), 4.01−3.74 (m, 4H), 3.29−2.96 (m, 4H). ^{13}C{^{1}H} NMR (150 MHz, Chloroform-*d*) δ 163.9, 151.9, 150.2, 148.5, 138.7, 136.7, 134.8, 134.5, 133.4, 128.5, 127.7, 122.7, 122.0, 118.6, 118.0, 114.3, 66.0, 53.7. HRMS (ESI-TOF): *m/z* calcd for $C_{20}H_{19}N_4O_4$ $[M + H]^+$ 379.1401, found 379.1405.

*2-Methyl-6-morpholino-N-(quinolin-8-yl)benzamide (**3l**).* Compound **3l** was prepared according to the **GP** and purified by silica column chromatography in petroleum ether:ethyl acetate = 4:1. **3l** was obtained as a white solid (67 mg, 65%). This compound is known.[5a] Melting point: 126−128 °C. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 10.62 (s, 1H), 9.00 (dd, *J* = 7.8, 1.8 Hz, 1H), 8.77 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.18 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.64−7.58 (m, 1H), 7.55 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.45 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 7.01 (d, *J* = 7.8 Hz, 1H), 6.98 (d, *J* = 7.8 Hz, 1H), 3.51 (t, *J* = 4.2 Hz, 4H), 3.08 (t, *J* = 4.2 Hz, 4H), 2.50 (s, 3H). ^{13}C{^{1}H} NMR (150 MHz, Chloroform-*d*) δ 168.0, 150.1, 148.3, 138.6, 138.4, 136.5, 135.0, 131.9, 130.2, 128.3, 127.6, 126.0, 121.8, 116.7, 116.5, 67.0, 53.1, 20.5. HRMS (ESI-TOF): *m/z* calcd for $C_{21}H_{22}N_3O_2$ $[M + H]^+$ 348.1707, found 348.1712.

*2-Fluoro-6-morpholino-N-(quinolin-8-yl)benzamide (**3m**).* Compound **3m** was prepared according to the **GP** and purified by silica column chromatography in petroleum ether:ethyl acetate = 4:1. **3m** was obtained as a white solid (65 mg, 62%). Melting point: 145−147 °C. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 10.93 (s, 1H), 8.99 (d, *J* = 7.8 Hz, 1H), 8.78 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.17 (dt, *J* = 8.4, 1.8 Hz, 1H), 7.58 (td, *J* = 7.8, 3.0 Hz, 1H), 7.54 (dt, *J* = 8.4, 1.8 Hz, 1H), 7.45 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.40−7.33 (m, 1H), 6.89−6.85 (m, 2H), 3.64 (t, *J* = 3.6 Hz, 4H), 3.12 (t, *J* = 3.6 Hz, 4H). ^{13}C{^{1}H} NMR (150 MHz, Chloroform-*d*) δ 162.9, 161.6 (d, *J* = 251.25 Hz, 1C), 151.5 (d, *J* = 4.2 Hz, 1C), 148.3, 138.5, 136.5, 134.6, 131.8 (d, *J* = 10.5 Hz, 1C), 128.2, 127.6, 122.1, 121.8, 119.1 (d, *J* = 13.8 Hz, 1C), 117.0, 114.0, 111.0 (d, *J* = 22.5 Hz, 1C), 66.6, 52.9. ^{19}F NMR (565 MHz, Chloroform-*d*) δ −113.2. HRMS (ESI-TOF): *m/z* calcd for $C_{20}H_{19}FN_3O_2$ $[M + H]^+$ 352.1456, found 352.1449.

*2-Chloro-6-morpholino-N-(quinolin-8-yl)benzamide (**3n**).* Compound **3n** was prepared according to the **GP** and purified by silica column chromatography in petroleum ether:ethyl acetate = 6:1. **3n** was obtained as a white solid (55 mg, 50%). Melting point: 116−118 °C. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 12.68 (s, 1H), 9.13 (dd, *J* = 7.8, 1.2 Hz, 1H), 8.87 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.19 (dd, *J* = 3.6, 1.8 Hz, 1H), 8.18 (dd, *J* = 4.2, 1.8 Hz, 1H), 7.60 (t, *J* = 7.8 Hz, 1H), 7.54 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.51 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.48 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.28−7.22 (m, 2H), 3.97 (t, *J* = 4.2 Hz, 4H), 3.15 (t, *J* = 4.2 Hz, 4H). ^{13}C{^{1}H} NMR (150 MHz, Chloroform-*d*) δ 165.9, 151.2, 148.2, 138.9, 136.5, 135.7, 132.5, 132.3, 129.0, 128.4, 127.7, 124.4, 121.9, 121.7, 119.3, 117.9, 66.3, 54.0. HRMS (ESI-TOF): *m/z* calcd for $C_{20}H_{19}ClN_3O_2$ $[M + H]^+$ 368.1160, found 368.1170.

*2-Morpholino-N-(quinolin-8-yl)-6-(trifluoromethyl)benzamide (**3o**).* Compound **3o** was prepared according to the **GP** and purified by silica column chromatography in petroleum ether:ethyl acetate = 4:1. **3o** was obtained as a white solid (55 mg, 46%). Melting point: 135−137 °C. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 10.26 (s, 1H), 8.91 (dd, *J* = 7.8, 1.8 Hz, 1H), 8.75 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.20 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.61 (t, *J* = 7.8 Hz, 1H), 7.58 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.46 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.37 (d, *J* = 7.8 Hz, 1H), 3.53 (t, *J* = 4.2 Hz, 4H), 3.09 (t, *J* = 4.2 Hz, 4H). ^{13}C{^{1}H} NMR (150 MHz, Chloroform-*d*) δ 165.4, 151.0, 148.4, 138.5, 136.6, 134.6, 131.9, 130.7, 129.6 (q, *J* = 31.5 Hz, 1C), 128.3, 127.7, 124.0, 123.7 (d, *J* = 272.7 Hz, 1C), 122.2, 121.9, 121.6 (q, *J* = 4.65 Hz, 1C), 117.0, 67.0, 53.1. ^{19}F NMR (565 MHz, Chloroform-*d*) δ −58.75. HRMS (ESI-TOF): *m/z* calcd for $C_{21}H_{18}NaF_3N_3O_2$ $[M + Na]^+$ 424.1243, found 424.1249.

*5-Methyl-2-morpholino-N-(quinolin-8-yl)benzamide (**3p**).* Compound **3p** was prepared according to the **GP** and purified by silica column chromatography in petroleum ether:ethyl acetate = 4:1. **3p** was obtained as a white solid (78 mg, 75%). This compound is known.[13] Melting point: 149−151 °C. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 12.80 (s, 1H), 9.13 (dd, *J* = 7.8, 1.2 Hz, 1H), 8.87 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.18 (dd, *J* = 8.4, 1.8 Hz, 1H), 8.03 (d, *J* = 2.4 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.54 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.47 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.30 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 4.07−3.86 (m, 4H), 3.25−3.03 (m, 4H),

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2.38 (s, 3H). $^{13}C\{^1H\}$ NMR (150 MHz, Chloroform-*d*) δ 165.9, 148.9, 148.2, 139.0, 136.5, 135.8, 134.1, 133.0, 132.7, 128.6, 128.4, 127.7, 121.8, 121.7, 119.5, 117.9, 66.3, 54.1, 20.8. HRMS (ESI-TOF): *m/z* calcd for $C_{21}H_{22}N_3O_2$ $[M + H]^+$ 348.1707, found 348.1710.

*5-Fluoro-2-morpholino-N-(quinolin-8-yl)benzamide (**3q**).* Compound **3q** was prepared according to the **GP** and purified by silica column chromatography in petroleum ether:ethyl acetate = 4:1. **3q** was obtained as a white solid (38 mg, 36%). This compound is known.[5b] Melting point: 158−159 °C. ^1H NMR (600 MHz, Chloroform-*d*) δ 12.91 (s, 1H), 9.10 (dd, *J* = 7.8, 1.8 Hz, 1H), 8.88 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.19 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.95 (dd, *J* = 9.6, 3.0 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.56 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.49 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.26 (dd, *J* = 9.0, 4.8 Hz, 1H), 7.19 (ddd, *J* = 9.0, 7.2, 3.0 Hz, 1H), 4.00 (t, *J* = 4.2 Hz, 4H), 3.11 (t, *J* = 4.2 Hz, 4H). $^{13}C\{^1H\}$ NMR (150 MHz, Chloroform-*d*) δ 164.2, 159.7 (d, *J* = 242.7 Hz, 1C), 148.3, 147.4, 139.0, 136.6, 135.5, 131.0 (d, *J* = 6.9 Hz, 1C), 128.5, 127.7, 122.3, 121.8, 121.6 (d, *J* = 8.0 Hz, 1C), 119.1 (d, *J* = 22.5 Hz, 1C), 118.8 (d, *J* = 24.2 Hz, 1C), 118.3, 66.2, 54.3. ^{19}F NMR (565 MHz, Chloroform-*d*) δ −117.50. HRMS (ESI-TOF): *m/z* calcd for $C_{20}H_{19}FN_3O_2$ $[M + H]^+$ 352.1456, found 352.1449.

*3-Fluoro-2-morpholino-N-(quinolin-8-yl)benzamide (**3q′**).* Compound **3q′** was prepared according to the **GP** and purified by silica column chromatography in petroleum ether:ethyl acetate = 4:1. **3q′** was obtained as a white solid (39 mg, 37%). This compound is known.[5b] Melting point: 131−133 °C. ^1H NMR (600 MHz, Chloroform-*d*) δ 12.73 (s, 1H), 9.07 (dd, *J* = 7.8, 1.8 Hz, 1H), 8.89 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.20 (dd, *J* = 8.4, 1.8 Hz, 1H), 8.09 (d, *J* = 7.8 Hz, 1H), 7.60 (t, *J* = 7.8 Hz, 1H), 7.57 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.49 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.29 (td, *J* = 8.4, 5.4 Hz, 1H), 7.24 (ddd, *J* = 12.6, 7.8, 1.8 Hz, 1H), 4.07 (t, *J* = 4.2 Hz, 4H), 3.36 (t, *J* = 4.2 Hz, 4H). $^{13}C\{^1H\}$ NMR (150 MHz, Chloroform-*d*) δ 164.5, 161.0 (d, *J* = 250.5 Hz, 1C), 148.2, 139.2, 137.1 (d, *J* = 9.9 Hz, 1C), 136.6, 135.5, 133.3 (d, *J* = 2.7 Hz, 1C), 128.4, 127.6, 126.8 (d, *J* = 8.9 Hz, 1C), 122.4, 121.8, 120.2 (d, *J* = 21.8 Hz, 1C), 118.9, 66.5, 52.0, 52.0. ^{19}F NMR (565 MHz, Chloroform-*d*) δ −117.5. HRMS (ESI-TOF): *m/z* calcd for $C_{20}H_{19}FN_3O_2$ $[M + H]^+$ 352.1456, found 352.1449.

*5-Chloro-2-morpholino-N-(quinolin-8-yl)benzamide (**3r**).* Compound **3r** was prepared according to the **GP** and purified by silica column chromatography in petroleum ether:ethyl acetate = 4:1. **3r** was obtained as a white solid (72 mg, 65%). This compound is known.[11a] Melting point: 147−149 °C. ^1H NMR (600 MHz, Chloroform-*d*) δ 12.64 (s, 1H), 9.08 (dd, *J* = 7.6, 1.4 Hz, 1H), 8.86 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.21−8.17 (m, 2H), 8.16 (d, *J* = 2.7 Hz, 1H), 7.59 (t, *J* = 7.9 Hz, 1H), 7.55 (d, *J* = 7.4 Hz, 1H), 7.48 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.43 (dd, *J* = 8.6, 2.7 Hz, 1H), 7.17 (d, *J* = 8.6 Hz, 1H), 4.11−3.74 (m, 5H), 3.22−2.98 (m, 5H). $^{13}C\{^1H\}$ NMR (150 MHz, Chloroform-*d*) δ 164.3, 149.7, 148.3, 138.8, 136.6, 135.3, 132.2, 132.1, 130.4, 130.1, 128.4, 127.6, 122.2, 121.8, 121.0, 118.0, 66.1, 56.0. HRMS (ESI-TOF): *m/z* calcd for $C_{20}H_{19}ClN_3O_2$ $[M + H]^+$ 368.1160, found 368.1170.

*5-Bromo-2-morpholino-N-(quinolin-8-yl)benzamide (**3s**).* Compound **3s** was prepared according to the **GP** and purified by silica column chromatography in petroleum ether:ethyl acetate = 8:1. **3s** was obtained as a white solid (85 mg, 69%). Melting point: 155−157 °C. ^1H NMR (600 MHz, Chloroform-*d*) δ 12.58 (s, 1H), 9.08 (dd, *J* = 7.8, 1.8 Hz, 1H), 8.85 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.29 (d, *J* = 2.4 Hz, 1H), 8.18 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.61−7.58 (m, 1H), 7.58−7.56 (m, 1H), 7.54 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.47 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.10 (d, *J* = 8.4 Hz, 1H), 3.95 (d, *J* = 4.2 Hz, 4H), 3.10 (d, *J* = 4.2 Hz, 4H). $^{13}C\{^1H\}$ NMR (150 MHz, Chloroform-*d*) δ 164.2, 150.1, 148.3, 138.8, 136.6, 135.3, 135.1, 135.0, 130.7, 128.4, 127.6, 122.2, 121.8, 121.2, 118.0, 117.6, 66.1, 53.9. HRMS (ESI-TOF): *m/z* calcd for $C_{20}H_{19}BrN_3O_2$ $[M + H]^+$ 412.0655 found 412.0644.

*2-Morpholino-N-(quinolin-8-yl)-5-(trifluoromethyl)benzamide (**3t**).* Compound **3t** was prepared according to the **GP** and purified by silica column chromatography in petroleum ether:ethyl acetate = 4:1. **3t** was obtained as a white solid (75 mg, 62%). This compound is known.[5a] Melting point: 144−146 °C. ^1H NMR (600 MHz, Chloroform-*d*) δ 12.36 (s, 1H), 9.09 (dd, *J* = 7.8, 1.2 Hz, 1H), 8.87 (d, *J* = 2.4 Hz, 1H), 8.41 (d, *J* = 2.4 Hz, 1H), 8.21 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.73 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.65−7.60 (m, 1H), 7.58 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.51 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 3.95 (t, *J* = 4.2 Hz, 4H), 3.21 (t, *J* = 4.2 Hz, 4H). $^{13}C\{^1H\}$ NMR (150 MHz, Chloroform-*d*) δ 164.6, 153.8, 148.4, 138.8, 136.7, 135.1, 129.7 (d, *J* = 3.5 Hz, 1C), 129.30, 129.1 (d, *J* = 2.6 Hz, 1C), 128.5, 127.7, 126.1 (q, *J* = 33.2 Hz, 1C), 125.8, 125.0 (q, *J* = 270.3 Hz, 1C), 123.2, 122.3, 121.9, 119.3, 117.9, 66.1, 53.7. ^{19}F NMR (565 MHz, Chloroform-*d*) δ −62.08. HRMS (ESI-TOF): *m/z* calcd for $C_{21}H_{18}NaF_3N_3O_2$ $[M + Na]^+$ 424.1243, found 424.1249.

*1-Morpholino-N-(quinolin-8-yl)-2-naphthamide (**3u**).* Compound **3u** was prepared according to the **GP** and purified by silica column chromatography in petroleum ether: ethyl acetate = 5:1. **3u** was obtained as a white solid (67 mg, 58%). This compound is known.[5a] Melting point: 212−214 °C. ^1H NMR (600 MHz, Chloroform-*d*) δ 10.66 (s, 1H), 9.13 (dd, *J* = 7.8, 1.2 Hz, 1H), 8.74 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.29 (d, *J* = 9.0 Hz, 1H), 8.20 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.65 (t, *J* = 7.8 Hz, 1H), 7.58 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.52 (ddd, *J* = 8.4, 6.6, 1.2 Hz, 1H), 7.45 (dd, *J* = 7.8, 4.2 Hz, 1H), 7.44−7.42 (m, 1H), 7.41 (d, *J* = 9.0 Hz, 1H), 3.63 (t, *J* = 4.2 Hz, 4H), 3.24 (t, *J* = 4.2 Hz, 4H). $^{13}C\{^1H\}$ NMR (150 MHz, Chloroform-*d*) δ 167.7, 148.3, 147.5, 138.6, 136.5, 135.1, 131.8, 131.4, 130.4, 128.3, 128.1, 127.7, 127.6, 127.0, 125.1, 125.0, 122.0, 121.9, 118.8, 116.8, 67.1, 53.0. HRMS (ESI-TOF): *m/z* calcd for $C_{24}H_{22}N_3O_2$ $[M + H]^+$ 384.1707, found 384.1704.

*2-Morpholino-N-(quinolin-8-yl)-1-naphthamide (**3v**).* Compound **3v** was prepared according to the **GP** and purified by silica column chromatography in petroleum ether:ethyl acetate = 6:1. **3v** was obtained as a brown oil (74 mg, 64%). ^1H NMR (600 MHz, Chloroform-*d*) δ 10.67 (s, 1H), 9.13 (dd, *J* = 7.8, 1.2 Hz, 1H), 8.74 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.29 (d, *J* = 8.4 Hz, 1H), 8.19 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.94 (d, *J* = 9.0 Hz, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.65 (t, *J* = 7.8 Hz, 1H), 7.58 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.52 (ddd, *J* = 8.4, 6.6, 1.2 Hz, 1H), 7.45 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.44−7.42 (m, 1H), 7.41 (d, *J* = 9.0 Hz, 1H), 3.63 (t, *J* = 4.2 Hz, 4H), 3.24 (t, *J* = 4.2 Hz, 4H). $^{13}C\{^1H\}$ NMR (150 MHz, Chloroform-*d*) δ 167.7, 148.3, 147.5, 138.6, 136.5, 135.1, 131.8, 131.4, 130.4, 128.3, 128.1, 127.7, 127.6, 127.0, 125.1, 125.0, 121.9, 121.8, 118.8, 116.8, 67.1, 53.0. HRMS (ESI-TOF): *m/z* calcd for $C_{24}H_{22}N_3O_2$ $[M + H]^+$ 384.1707, found 384.1706.

*4-Morpholino-N-(quinolin-8-yl)nicotinamide (**3w**).* Compound **3w** was prepared according to the **GP** and purified by silica column chromatography in petroleum ether:ethyl acetate = 1:3. **3w** was obtained as an off-white solid (52 mg, 52%). This compound is known.[5b] Melting point: 188−190 °C. ^1H NMR (600 MHz, Chloroform-*d*) δ 11.69 (s, 1H), 9.05 (s, 1H), 9.02 (dd, *J* = 7.8, 1.8 Hz, 1H), 8.82 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.56 (d, *J* = 5.4 Hz, 1H), 8.18 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.60−7.56 (m, 1H), 7.55 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.48 (dd, *J* = 8.4, 4.2 Hz, 1H), 6.98 (d, *J* = 5.4 Hz, 1H), 3.98−3.74 (m, 4H), 3.32−3.08 (m, 4H). $^{13}C\{^1H\}$ NMR (151 MHz, Chloroform-*d*) δ 164.5, 153.0, 152.8, 148.4, 138.5, 136.6, 134.8, 128.3, 127.7, 123.5, 122.2, 121.9, 117.4, 112.6, 65.9, 52.3. HRMS (ESI-TOF): *m/z* calcd for $C_{19}H_{19}N_4O_2$ $[M + H]^+$ 335.1503, found 335.1510.

*3-Morpholino-N-(quinolin-8-yl)isonicotinamide (**3x**).* Compound **3x** was prepared according to the **GP** and purified by silica column chromatography in petroleum ether:ethyl acetate = 1:1. **3x** was obtained as a yellowish solid (56 mg, 56%). This compound is known.[5b] Melting point: 217−219 °C. ^1H NMR (600 MHz, Chloroform-*d*) δ 12.52 (s, 1H), 9.07 (dd, *J* = 7.2, 2.4 Hz, 1H), 8.87 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.62 (s, 1H), 8.55 (d, *J* = 4.8 Hz, 1H), 8.20 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.97 (d, *J* = 4.8 Hz, 1H), 7.65−7.55 (m, 2H), 7.50 (dd, *J* = 8.4, 4.2 Hz, 1H), 4.10−3.82 (m, 4H), 3.38−3.11 (m, 4H). $^{13}C\{^1H\}$ NMR (150 MHz, Chloroform-*d*) δ 163.6, 148.5, 146.3, 145.2, 142.5, 138.8, 136.6, 135.4, 134.9, 128.4, 127.6, 124.7, 122.6, 121.9, 118.1, 66.1, 53.6. HRMS (ESI-TOF): *m/z* calcd for $C_{19}H_{19}N_4O_2$ $[M + H]^+$ 335.1503, found 335.1506.

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*3-Morpholino-N-(quinolin-8-yl)thiophene-2-carboxamide (**3y**).* Compound **3y** was prepared according to the **GP** and purified by silica column chromatography in petroleum ether:ethyl acetate = 4:1. **3y** was obtained as an off-white solid (55 mg, 54%). This compound is known.[5b] Melting point: 170−171 °C. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 12.60 (s, 1H), 9.04 (dd, *J* = 7.8, 1.2 Hz, 1H), 8.93 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.19 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.58 (t, *J* = 7.8 Hz, 1H), 7.54 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.52 (d, *J* = 5.4 Hz, 1H), 7.50 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.20 (d, *J* = 5.4 Hz, 1H), 4.15 (t, *J* = 4.2 Hz, 4H), 3.11 (t, *J* = 4.2 Hz, 4H). ^{13}C{^{1}H} NMR (150 MHz, Chloroform-*d*) δ 160.7, 152.3, 148.1, 139.0, 136.5, 135.8, 130.3, 130.2, 128.4, 127.7, 122.3, 121.8, 121.7, 118.1, 66.6, 54.4. HRMS (ESI-TOF): *m*/*z* calcd for $C_{18}H_{17}NaN_3O_2S$ [M + Na]$^+$ 362.0934, found 362.0927.

*2-Morpholino-N-(quinolin-8-yl)thiophene-3-carboxamide (**3z**).* Compound **3z** was prepared according to the **GP** and purified by silica column chromatography in petroleum ether:ethyl acetate = 4:1. **3z** was obtained as a white solid (62 mg, 61%). Melting point: 151−153 °C. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 12.35 (s, 1H), 9.06 (dd, *J* = 7.8, 1.2 Hz, 1H), 8.89 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.17 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.57 (d, *J* = 6.0 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 7.51 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.48 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.00 (d, *J* = 5.4 Hz, 1H), 4.11 (t, *J* = 4.2 Hz, 4H), 3.13 (t, *J* = 4.2 Hz, 4H). ^{13}C{^{1}H} NMR (150 MHz, Chloroform-*d*) δ 161.3, 160.2, 148.1, 139.0, 136.6, 135.9, 128.3, 128.2, 127.7, 127.6, 121.7, 121.7, 118.8, 117.8, 66.4, 56.5. HRMS (ESI-TOF): *m*/*z* calcd for $C_{18}H_{17}NaN_3O_2S$ [M + Na]$^+$ 362.0934, found 362.0927.

*Ethyl-1-(5-methyl-2-(quinolin-8-ylcarbamoyl)phenyl)piperidine-4-carboxylate (**4a**).* Compound **4a** was prepared according to the **GP** and purified by silica column chromatography in petroleum ether:ethyl acetate = 4:1. **4a** was obtained as a white solid (97 mg, 78%). Melting point: 125−127 °C. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 12.8 (s, 1H), 9.16 (dd, *J* = 7.8, 1.2 Hz, 1H), 8.88 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.14 (dd, *J* = 8.4, 1.8 Hz, 1H), 8.12 (d, *J* = 7.8 Hz, 1H), 7.57 (t, *J* = 7.8 Hz, 1H), 7.51 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.44 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.03 (s, 1H), 7.04 (d, *J* = 7.8 Hz, 1H), 4.05 (q, *J* = 7.2 Hz, 2H), 3.40 (d, *J* = 12.0 Hz, 2H), 2.98−2.79 (m, 2H), 2.43−2.38 (m, 1H), 2.40 (s, 3H), 2.32−2.22 (m, 2H), 2.05−1.93 (m, 2H), 1.15 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (150 MHz, Chloroform-*d*) δ 174.9, 165.9, 152.1, 148.3, 142.8, 139.1, 136.3, 136.1, 132.2, 128.4, 127.5, 126.1, 125.0, 121.6, 121.5, 120.4, 117.9, 60.4, 54.0, 41.0, 27.7, 21.7, 14.3. HRMS (ESI-TOF): *m*/*z* calcd for $C_{25}H_{28}N_3O_3$ [M + H]$^+$ 418.2125, found 418.2128.

*4-Methyl-N-(quinolin-8-yl)-2-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)benzamide (**4b**).* Compound **4b** was prepared according to the **GP** and purified by silica column chromatography in petroleum ether:ethyl acetate = 3:1. **4b** was obtained as a white solid (82 mg, 68%). Melting point: 201−203 °C. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 13.08 (s, 1H), 9.16 (dd, *J* = 7.8, 1.2 Hz, 1H), 8.93 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.21−8.10 (m, 2H), 7.58 (t, *J* = 7.8 Hz, 1H), 7.52 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.47 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.15 (s, 1H), 7.06 (d, *J* = 7.8 Hz, 1H), 3.96 (s, 4H), 3.21 (t, *J* = 5.4 Hz, 4H), 2.40 (s, 3H), 2.13 (s, 4H). ^{13}C{^{1}H} NMR (150 MHz, Chloroform-*d*) δ 165.9, 152.0, 148.1, 142.9, 139.2, 136.4, 136.3, 132.2, 128.4, 127.6, 126.1, 125.4, 121.7, 121.7, 121.2, 118.2, 107.2, 64.4, 52.6, 34.7, 21.7. HRMS (ESI-TOF): *m*/*z* calcd for $C_{24}H_{26}N_3O_3$ [M + H]$^+$ 404.1969, found 404.1972.

*4-Methyl-2-(piperidin-1-yl)-N-(quinolin-8-yl)benzamide (**4c**).* Compound **4c** was prepared according to the **GP** and purified by silica column chromatography in petroleum ether:ethyl acetate = 5:1. **4c** was obtained as a white solid (82 mg, 60%). Melting point: 190−192 °C. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 9.14 (dd, *J* = 7.8, 1.2 Hz, 1H), 8.84 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.17 (dd, *J* = 8.4, 1.8 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.52 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.45 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.05 (s, 1H), 7.03−6.97 (m, 1H), 3.07 (s, 4H), 2.40 (s, 3H), 1.91−1.77 (m, 4H), 1.50 (d, *J* = 5.4 Hz, 2H). ^{13}C{^{1}H} NMR (150 MHz, Chloroform-*d*) δ 166.3, 153.0, 147.9, 142.7, 139.2, 136.3, 136.2, 132.0, 128.4, 127.7, 126.0, 124.5, 121.6, 121.5, 120.3, 118.0, 55.5, 25.4, 24.2, 21.8. HRMS (ESI-TOF): *m*/*z* calcd for $C_{22}H_{23}NaN_3O_1$ [M + Na]$^+$ 368.1733, found 368.1733.

*4-Methyl-2-(2-methylpiperidin-1-yl)-N-(quinolin-8-yl)benzamide (**4d**).* Compound **4d** was prepared according to the **GP** and purified by silica column chromatography in petroleum ether:ethyl acetate = 6:1. **4d** was obtained as an off-white solid (50 mg, 46%). Melting point: 196−198 °C. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 13.72 (s, 1H), 9.14 (dd, *J* = 7.8, 1.2 Hz, 1H), 8.86 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.29 (d, *J* = 8.4 Hz, 1H), 8.16 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.52 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.46 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.21 (s, 1H), 7.11 (d, *J* = 7.8 Hz, 1H), 3.28−3.18 (m, 1H), 3.16 (dt, *J* = 11.4, 3.6 Hz, 1H), 2.76 (td, *J* = 11.4, 2.4 Hz, 1H), 2.23−2.11 (m, 1H), 2.06−1.95 (m, 1H), 1.87−1.82 (m, 2H), 1.56−1.44 (m, 1H), 1.29−1.19 (m, 1H), 1.05 (d, *J* = 6.6 Hz, 3H). ^{13}C{^{1}H} NMR (150 MHz, Chloroform-*d*) δ 165.7, 152.1, 147.7, 142.7, 139.7, 136.7, 136.3, 131.9, 128.4, 127.7, 127.6, 126.2, 123.7, 121.6, 121.5, 118.8, 56.7, 33.1, 24.4, 25.8, 21.6, 19.5. HRMS (ESI-TOF): *m*/*z* calcd for $C_{23}H_{26}N_3O$ [M + H]$^+$ 360.2070, found 360.2079.

*tert-Butyl-4-(5-methyl-2-(quinolin-8-ylcarbamoyl)phenyl)-piperazine-1-carboxylate (**4e**).* Compound **4e** was prepared according to the **GP** and purified by silica column chromatography in petroleum ether:ethyl acetate = 4:1. **4e** was obtained as a white solid (100 mg, 75%). Melting point: 146−148 °C. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 12.74 (s, 1H), 9.13 (dd, *J* = 7.8, 1.2 Hz, 1H), 8.79 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.17 (dd, *J* = 8.4, 1.2 Hz, 1H), 8.11 (d, *J* = 7.8 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.45 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.07 (d, *J* = 7.8 Hz, 1H), 7.03 (s, 1H), 3.73 (d, *J* = 50.4 Hz, 1H), 3.09 (s, 4H), 2.41 (s, 3H), 1.43 (s, 9H). ^{13}C{^{1}H} NMR (150 MHz, Chloroform-*d*) δ 165.7, 154.9, 151.3, 148.0, 143.0, 138.9, 136.5, 135.8, 132.3, 128.5, 127.7, 126.2, 125.4, 121.7, 121.7, 120.4, 117.9, 79.9, 28.5, 21.7. HRMS (ESI-TOF): *m*/*z* calcd for $C_{26}H_{30}N_4NaO_3$ [M + Na]$^+$ 469.2210, found 469.2215.

*2-(Azepan-1-yl)-4-methyl-N-(quinolin-8-yl)benzamide (**4f**).* Compound **4f** was prepared according to the **GP** and purified by silica column chromatography in petroleum ether:ethyl ether: ethyl acetate = 5:1:1. **4f** was obtained as an off-white solid (54 mg, 50%). Melting point: 130−132 °C. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 12.73 (s, 1H), 9.09 (dd, *J* = 7.8, 1.2 Hz, 1H), 8.82 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.16 (dd, *J* = 8.4, 1.8 Hz, 1H), 8.05 (d, *J* = 7.8 Hz, 1H), 7.58 (t, *J* = 7.8 Hz, 1H), 7.51 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.44 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.10 (s, 1H), 6.97 (d, *J* = 7.8 Hz, 1H), 3.47−3.25 (m, 4H), 2.39 (s, 3H), 2.05−1.83 (m, 4H), 1.62 (m, 4H). ^{13}C{^{1}H} NMR (150 MHz, Chloroform-*d*) δ 166.4, 153.7, 147.9, 142.5, 139.4, 136.3, 136.1, 131.8, 128.4, 127.7, 125.7, 123.9, 122.0, 121.5, 121.4, 117.9, 57.0, 28.2, 27.2, 21.8. HRMS (ESI-TOF): *m*/*z* calcd for $C_{23}H_{26}N_3O$ [M + H]$^+$ 360.2070, found 360.2079.

*2-(Diethylamino)-4-methyl-N-(quinolin-8-yl)benzamide (**4h**).* Compound **4h** was prepared according to the **GP** and purified by silica column chromatography in petroleum ether:ethyl acetate = 6:1. **4h** was obtained as a light-yellow oil (45 mg, 45%). ^{1}H NMR (600 MHz, chloroform-*d*) δ 14.67 (s, 1H), 9.07 (d, *J* = 7.8 Hz, 1H), 8.83 (dd, *J* = 4.2, 1.2 Hz, 1H), 8.30 (d, *J* = 7.8 Hz, 1H), 8.15 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.57 (t, *J* = 7.8 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.43 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.14 (s, 1H), 7.12 (d, *J* = 8.4 Hz, 1H), 3.25 (q, *J* = 7.2 Hz, 4H), 2.41 (s, 3H), 1.06 (t, *J* = 7.2 Hz, 6H). ^{13}C{^{1}H} NMR (150 MHz, Chloroform-*d*) δ 165.3, 149.2, 148.0, 142.5, 140.0, 136.7, 136.1, 131.6, 128.8, 128.4, 127.7, 126.2, 124.3, 121.4, 121.3, 117.8, 50.0, 21.6, 12.0. HRMS (ESI-TOF): *m*/*z* calcd for $C_{21}H_{24}N_3O$ [M + H]$^+$ 334.1914, found 334.1928.

*2-(Dipropylamino)-4-methyl-N-(quinolin-8-yl)benzamide (**4i**).* Compound **4i** was prepared according to the **GP** and purified by silica column chromatography in petroleum ether:ethyl acetate = 6:1. **4i** was obtained as a white solid (47 mg, 43%). Melting point: 113−115 °C. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 14.55 (s, 1H), 9.08 (dd, *J* = 7.8, 1.2 Hz, 1H), 8.83 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.29 (d, *J* = 8.4 Hz, 1H), 8.15 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.58 (t, *J* = 7.8 Hz, 1H), 7.52−7.48 (m, 1H), 7.43 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.15 (s, 1H), 7.11 (d, *J* = 8.4 Hz, 1H), 3.19−3.05 (m, 4H), 2.41 (s, 3H), 1.60−1.47 (m, 4H), 0.77 (t, *J* = 7.2 Hz, 6H). ^{13}C{^{1}H} NMR (150 MHz, Chloroform-*d*) δ 165.3, 149.8, 147.9, 142.5, 139.9, 136.7, 136.1, 131.6, 128.4,

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128.3, 127.7, 126.0, 124.2, 121.4, 121.3, 117.9, 58.6, 21.7, 19.8, 12.1. HRMS (ESI-TOF): *m/z* calcd for $C_{23}H_{28}N_3O$ $[M + H]^+$ 362.2227, found 362.2224.

*2-Morpholinobenzoic Acid (**5**).* Yellowish oil, Yield 55 mg (89%) at a 0.3 mmol scale. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.28 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.65−7.59 (m, 1H), 7.44 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.41 (td, *J* = 7.8, 1.2 Hz, 1H), 3.94 (s, 4H), 3.07 (s, 4H). ^{13}C{^{1}H} NMR (150 MHz, Chloroform-*d*) δ 166.8, 150.3, 134.2, 132.6, 128.0, 125.2, 122.6, 67.0, 53.6. HRMS (ESI-TOF): *m/z* calcd for $C_{11}H_{14}NO_3$ $[M + H]^+$ 208.0968, found 208.0968.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c01229.

Verification test, copies of all spectral, and full characterization for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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