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Copper(II)-Mediated Intermolecular C(sp^2)−H Amination of Benzamides with Electron-Rich Anilines

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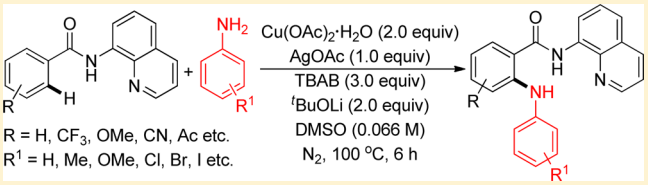
Supporting Information

ABSTRACT: Despite significant progress, copper-catalyzed/mediated C−H amination reactions with electron-rich anilines remain an unsolved problem due to catalyst deactivation and deleterious side reactions. Herein, we report a copper(II)-mediated C(sp^2)−H amination of benzamides with electronically neutral or electron-rich anilines. A dramatic influence of silver(I) and tetrabutylammonium bromide was observed on the reaction outcome. The present protocol also demonstrates the synthesis of a number of nonsteroidal anti-inflammatory drugs.



INTRODUCTION

Diarylamines are ubiquitously found in numerous biologically active natural products, medicinally relevant scaffolds, pharmaceuticals, agrochemicals, dyes, and functionalized materials (Figure 1).[1] Conventionally, they are synthesized

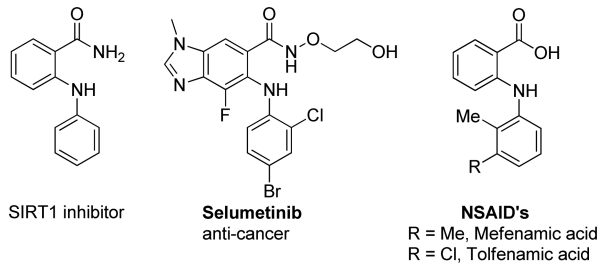


Figure 1. Biologically active diarylamines.

through a palladium- or copper-catalyzed Goldberg cross-coupling between aryl halides and amines.[2] In recent years, a metal-catalyzed C−H activation strategy provides a direct access to the functionalized amines, obviating the need for aryl halides.[3] In this vein, Pd, Ir, and Rh catalyses have been explored with amines[4] and highly energetic azides.[5] To circumvent the metal poisoning issues with amines,[6] the use of inexpensive first row transition metals such as manganese,[7] iron,[8] cobalt,[9] nickel,[10] and copper[11] is emerging. A seminal report on copper-mediated sp^2 C−H amidation using a nonremovable 2-pyridine moiety was disclosed by the Yu group.[12] Subsequently, they accomplished a bidentate auxiliary-directed C(sp^2)−H amination with electron-poor anilines.[13] The Daugulis group also reported an 8-aminoquinoline-directed Cu(II)/Ag(I)-catalyzed C(sp^2)−H amination with aliphatic amines.[14] However, sp^2 C−H amination with readily available and inexpensive anilines to afford diarylamines is extremely rare.[15,4b] Notably, the Chang group also reported iridium[4b]- and rhodium-catalyzed[16] C−H amination with electron-deficient anilines and aryl azides, respectively. This could be attributed due to the deleterious side reactions, especially azoarene formation and catalyst deactivation with nucleophilic amine derivatives.[6]

Very recently, the Daugulis group reported examples of copper-mediated C−H amination with 2,4,6-trimethylanilne.[17] However, other electron-rich anilines such as 4-methoxy aniline, etc., are not stable under this condition, which clearly demonstrates the challenges associated with this transformation. Therefore, development of a general C(sp^2)−H amination reaction conditions for electron-rich anilines is in high demand. We report herein a general copper-mediated C−H amination of benzamides with electronically neutral and electron-rich anilines (Scheme 1) to afford diarylamines in good to high yields. This methodology will enable direct access to a plethora of biologically active compounds (Figure 1).

RESULTS AND DISCUSSION

Under the Yu's conditions,[13] the 8-aminoquinoline-protected benzamide **1** afforded amination product with *p*-nitroaniline (**3ab**, Scheme 2) in 60% yield. Gratifyingly, when the base was changed from sodium carbonate to lithum *tert*-butoxide and the reaction vessel was purged with oxygen, the yield was increased to 96%. Unfortunately, electron-rich *p*-methoxy aniline, **2**, did not furnish any amination product under these conditions, but a mixture of C−H hydroxylation (20%)[18] and azoarene **5** (9%)[19] was isolated as side products. Gratifyingly, 30% amination product along with azoarene **5** (45%) was isolated with the addition of 1.0 equiv of silver(I) acetate under a nitrogen atmosphere (entry 1, Table 1). Remarkably,

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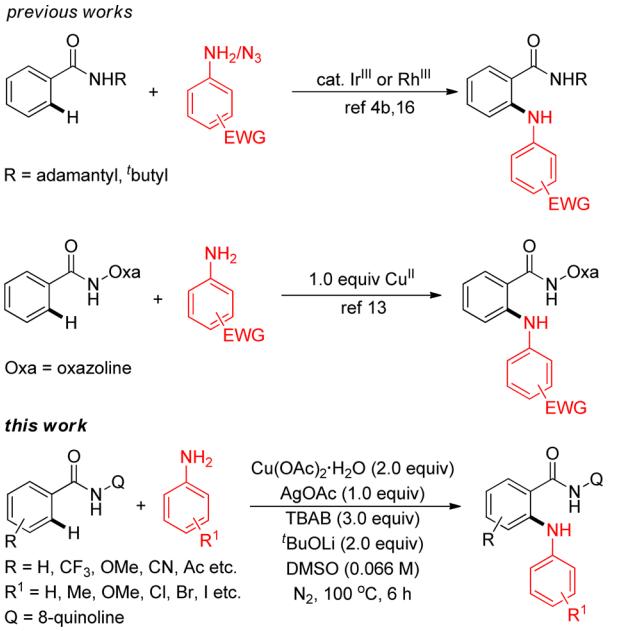
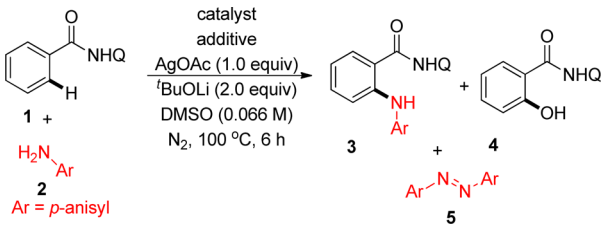
Scheme 1. C−H Amination of Benzamides with Aromatic Amines and Azides



the hydroxylation and azoarene formation were suppressed substantially with the addition of tetrabutylammonium bromide (TBAB) (entry 2, Table 1). When the amount of TBAB was increased (3.0 equiv), the azoarene and hydroxylation formation were completely diminished (entry 10, Table 1). However, the role of TBAB is not clear at this moment. TBAB may form a soluble TBA(OAc) *in situ*, leading to a rapid precipitation of silver(I)bromide. To test this, the reaction was performed with 3.0 equiv of TBA(OAc) in lieu of TBAB. We isolated 52% and 22% of amination product along with azo compounds in the presence and absence of silver(I)acetate, respectively (entries 14 and 15, Table 1). TBAB may be involved in the OAc/Br ion exchange on the copper salt. However, no amination product was formed using 1.0 equiv of copper(II)bromide, leaving a doubt on the exact role of TBAB. In fact, the Daugulis group also found that TBAI was useful for C−H amination reaction, which was proved inferior in this case (entry 5, Table 1).[17] The yield of the desired amination product was further increased to 65% (80% based on recovered starting material) with 2.0 equiv of copper(II) acetate (entry 11, Table 1). From the control experiment, it was confirmed that a catalytic amount of copper(II) acetate is not effective for this transformation. During optimization, it was also observed that, depending upon the electronic nature of the anilines, judicious choice of oxidant is crucial for the reaction outcome. For example, in the case of electron-deficient anilines, oxygen promotes amination reaction and no external oxidant is required. However, in the case of electronically neutral or electron-rich anilines, even a trace amount of oxygen was proved to be detrimental and silver(I) acetate was found to be optimal (entry 13, Table 1). Therefore, the amination reaction with electron-rich anilines was performed under a nitrogen atmosphere with 1.0 equiv of silver(I) acetate.

Under the optimized reaction conditions, the substrate scope of the C−H amination reaction was explored. A wide range of benzamides containing functional groups were found to be amenable for C−H amination. Besides alkyl and alkoxyl groups, trifluoromethyl, aryl, and cyano groups remained intact under these reaction conditions. More interestingly, an acetyl group containing benzamide afforded the corresponding

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	additive	yield (%) of 3[b]	3:4:5[c]
1	$Cu(OAc)_2·H_2O$ (1 equiv)		30	15:0:23
2	$Cu(OAc)_2·H_2O$ (1 equiv)	TBAB (1 equiv)	42	21:4:8
3	$Cu(OAc)_2·H_2O$ (1 equiv)	TBAF (1 equiv)	15	15:0:0
4	$Cu(OAc)_2·H_2O$ (1 equiv)	TBACl (1 equiv)	16	16:0:0
5	$Cu(OAc)_2·H_2O$ (1 equiv)	TBAI (1 equiv)	18	9:0:10
6	$Cu(OAc)_2·H_2O$ (1 equiv)	$K_2S_2O_8$ (1 equiv)	5	5:0:12
7	$CuBr_2$ (1 equiv)	TBAB (1 equiv)	0	
8	$CuCl_2$ (1 equiv)	TBAB (1 equiv)	0	
9	$CuSO_4·5H_2O$ (1 equiv)	TBAB (1 equiv)	0	
10	$Cu(OAc)_2·H_2O$ (1 equiv)	TBAB (3 equiv)	51	51:0:0
11	**$Cu(OAc)_2·H_2O$** (2 equiv)	**TBAB (3 equiv)**	**65(80)**[d]	**65:0:0**
12		TBAB (3 equiv)	0	
13[e]	$Cu(OAc)_2·H_2O$ (3 equiv)	TBAB (3 equiv)	10	10:0:0
14	$Cu(OAc)_2·H_2O$ (2 equiv)	TBA(OAc) (3 equiv)	52	13:0:3
15[f]	$Cu(OAc)_2·H_2O$ (2 equiv)	TBA(OAc) (3 equiv)	22	11:0:8

[a]All reactions were carried out in 0.1 mmol scale. [b]Yields referred to here are isolated yields. [c]Product distribution was measured by ^{1}H NMR. [d]Yield in the parentheses is based on the starting material recovery. [e]Purged with O_2 instead of N_2. [f]Without silver(I)acetate.

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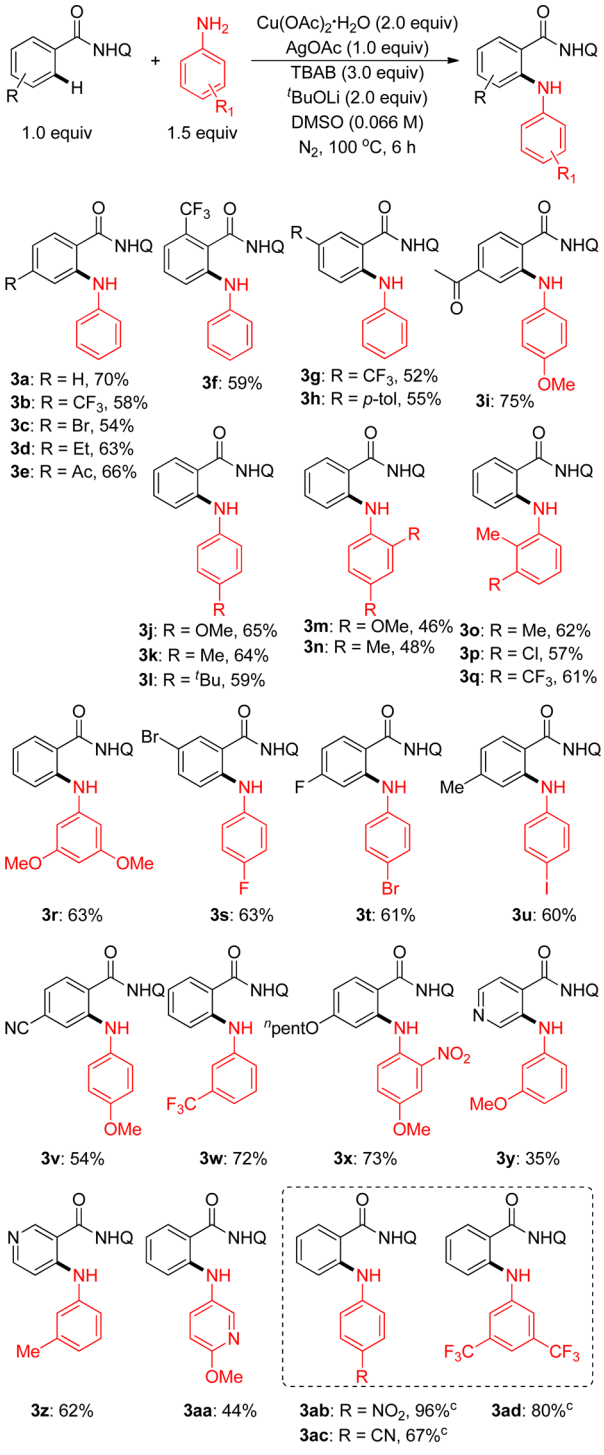
Scheme 2. Substrate Scope[a,b]

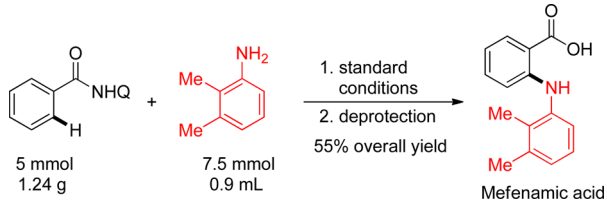


[a]All reactions were carried out in 0.2 mmol scale. [b]Yields refer to the average of isolated yields of at least two experiments. [c]Reaction conditions: 0.2 mmol of $Cu(OAc)_2·H_2O$, 0.4 mmol of ^tBuOLi, O_2, 110 °C, 3 h.

amination product in high yields, which prefers facile imine formation with anilines under slightly acidic conditions (**3e**, Scheme 2). Halogen substituents such as fluoro, chloro, bromo, and even iodo on the benzamide or anilines remained intact, which is useful for further cross-coupling reactions to achieve molecular complexity. A number of amide protected nonsteroidal anti-inflammatory drugs (NSAIDs) such as mefenamic acid, **3o**, tolfenamic acid, **3p**, and flufenamic acid, **3w**, were synthesized in good to high yields. Heteroaromatic benzamide and aniline also provided C−H amination product in moderate to good yields (**3y**−**3aa**, Scheme 2). In most of the cases with electron-rich anilines, the unreacted benzamides were isolated. It was not consumed completely even after the addition of anilines in excess. Prolonged heating also did not improve the yield; rather, product decomposition was observed. As discussed earlier, contrary to the electron-rich anilines, electron-deficient anilines such as *p*-nitro, *p*-cyano, or 3,5-ditrifluoromethyl anilines provided the corresponding amination products in excellent yields using oxygen as terminal oxidant (**3ab**−**3ad**, Scheme 2).

Substituted diarylamines are useful synthetic precursors to a range of *N*-heterocycles such as 9*H*-carbazoles, quinazolinone, indazolol, acridone, acridine, etc.[20] The *o*-carboxylic acid substituted diarylamines also constitute various biologically active compounds such as SIRT1 inhibitor, MEK inhibitor, nonsteroidal anti-inflammatory drugs (NSAIDs), etc.[21] As an illustrative example, the present protocol was applied for the gram-scale synthesis of mefenamic acid. Under the standard conditions, the amination reaction between benzamide **1** and 2,3-dimethyl aniline was performed in 1.2 g scale, and an almost identical yield (60%) of the corresponding amination product was isolated. Refluxing the amination product in alkaline ethanol furnished the mefenamic acid in 90% yield (Scheme 3).

Scheme 3. Gram-Scale Synthesis of Mefenamic Acid



INVESTIGATION OF THE REACTION MECHANISM

Several control experiments were performed to understand the underlying mechanism of this amination reaction. The kinetics of the amination reaction with benzamide **1** and d_5-**1** was observed as k_H/k_D = 4.3, suggesting that the amination reaction may involve a concerted-metalation deprotonation (CMD) in the rate-limiting step (Scheme 4a). The *N*-methylated benzamide did not furnish any amination product, which indicates that coordination of the copper center in bidentate fashion is crucial for the reaction to occur (Scheme 4b). A competition reaction between equimolar amounts of electron-rich *p*-methoxyaniline and electron-deficient *p*-nitroaniline afforded the corresponding amination products in 30% and 55% yields, respectively (Scheme 4c), whereas the respective reactions afforded higher yields, 65% (**3j**) and 98% (**3ab**) yields individually. This result suggests that not only the electron-rich anilines are difficult substrates for amination but also there may have catalyst inhibition by the amination products. For further clarification, the amination reaction was performed in the presence of an amination product, **3k** (Scheme 4d). Only 15% of the amination product **3j** was isolated, suggesting that the catalyst is deactivated presumably via chelation with the amination product. This

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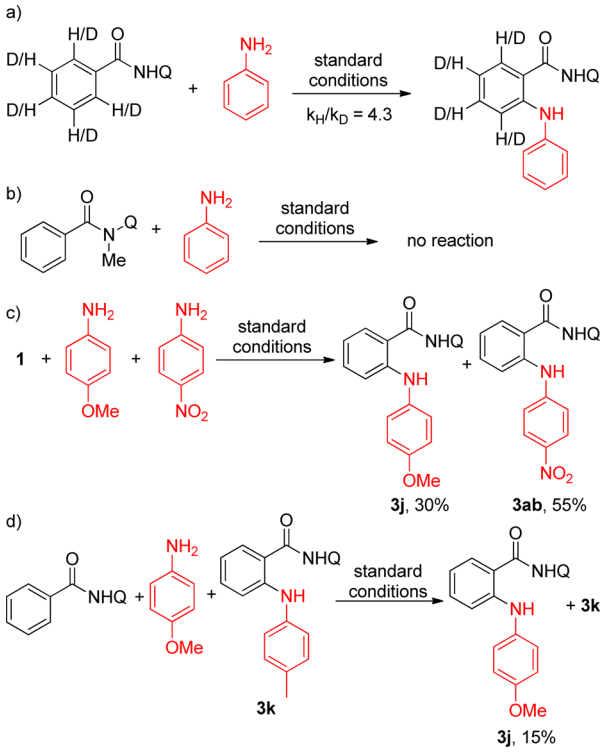
Scheme 4. Control Expeiments



also explains the requirement of stoichiometric copper salt for the present transformation. These control experiments suggest that the Cu^{II} complex may undergo a chelation-assisted C−H insertion to generate aryl-Cu^{III} species[22] which reacts with *N*-nucleophiles to provide the amination products.[23]

CONCLUSION

In conclusion, we have developed a copper(II)-mediated C(sp^2)−H amination of benzamides with electronically neutral or electron-rich anilines. The present transformation is extremely challenging due to the formation of deleterious side reactions and catalyst inhibition by the amination product. This protocol provides direct access to the nonsteroidal anti-inflammatory drugs (NSAIDs).

EXPERIMENTAL SECTION

General Information. Melting points were determined in open end capillary tubes and are uncorrected. TLC was performed on silica gel plates (Merck silica gel 60, f254), and the spots were visualized with UV light (254 and 365 nm) and $KMnO_4$ stain. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as the internal standard. HRMS (*m*/*z*) were measured using EI (magnetic sector, positive ion) and ESI (Q-TOF, positive ion) techniques. Infrared (IR) spectra were recorded on Fourier transform infrared spectroscopy; only intense peaks were reported.

General Experimental Procedure for Benzamide Formation. The benzamides were synthesized according to the literature procedure, and the spectral data are consistent with the reported values.[18]

General Experimental Procedure for C−H Amination Reaction with Electron-Rich Anilines. In a 15 mL sealed tube, the substrates (0.2 mmol), $Cu(OAc)_2·H_2O$ (80 mg, 0.4 mmol, 2 equiv), AgOAc (33.5 mg, 0.2 mmol, 1 equiv), ^tBuOLi (32 mg, 0.4 mmol, 2 equiv), TBAB (196.7 mg, 0.6 mmol, 3 equiv), and anilines (0.3 mmol, 1.5 equiv) were added, followed by DMSO (3 mL). The nitrogen gas was passed to the reaction mixture for 1 min. Then, the tube was charged with a preheated oil bath at 100 °C for 6 h. The reaction mixture was diluted with 10 mL of ethyl acetate and quenched with 20 mL of aq. ammonium solution. Then, it was filtered through Celite-545 and the aqueous phase was extracted with ethyl acetate (2 × 20 mL). The combined organic phase was washed with 20 mL of saturated sodium hydroxide solution and collected, dried over Na_2SO_4, and concentrated under vacuum. The crude was purified by column chromatography on silica gel with a gradient of elution of pet ether and ethyl acetate to give the desired amination product.

Note: Aerial oxygen is detrimental to the amination reaction with electron-rich anilines.

2-(Phenylamino)-N-(quinolin-8-yl)benzamide, ***3a****, Scheme 2.* Column chromatography (SiO_2, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a white solid (48 mg, 70%): mp 144−146 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 10.74 (s,1H), 9.57 (s, 1H),8.88−8.86 (m, 2H),8.21 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.89 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.61 (t, *J* = 7.8 Hz, 1H), 7.57 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.50 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.44−7.42 (m, 1H), 7.38−7.32 (m, 3H), 7.29−7.27 (m, 2H), 7.06−7.03 (m, 1H), 6.95−6.92 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.9, 148.3, 146.2, 141.4, 138.8, 136.4, 134.6, 132.6, 129.3, 128.04, 128.02, 127.4, 122.6, 121.69, 121.66, 121.2, 118.5, 118.0, 116.4, 115.6; IR (neat) υ_{max} 3345, 2923, 1644, 1583, 1520, 1261; HRMS (ESI, *m*/*z*) calcd for $C_{22}H_{18}N_3O$ $[M + H]^+$ 340.1450, found 340.1473.

2-(Phenylamino)-N-(quinolin-8-yl)-4-(trifluoromethyl)benzamide, ***3b****, Scheme 2.* Column chromatography (SiO_2, eluting with 8:2 hexane/ethyl acetate) afforded the desired product as a white solid (47 mg, 58%): mp 156−158 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 10.75 (s, 1H), 9.66 (s, 1H), 8.86−8.83 (m, 2H), 8.20 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.63−7.56 (m, 3H), 7.50 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.40−7.35 (m, 2H), 7.28−7.24 (m, 2H), 7.14−7.09 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 148.4, 146.7, 140.3, 138.7, 136.4, 134.16, 134.19 (q, *J* = 33.80 Hz), 129.6, 128.8, 128.6, 128.0, 127.3, 123.8, 123.7 (q, *J* = 275.3), 122.1, 121.8, 120.5, 116.6, 113.9 (q, *J* = 3.7 Hz), 111.7 (q, *J* = 3.7 Hz); IR (neat) υ_{max} 3351, 3046, 1655, 1589, 1536, 1428, 1335, 1175, 1119; HRMS (EI, *m*/*z*) calcd for $C_{23}H_{16}F_3N_3O$ $[M]^+$ 407.1245, found 407.1248.

4-Bromo-2-(phenylamino)-N-(quinolin-8-yl)benzamide, ***3c****, Scheme 2.* Column chromatography (SiO_2, eluting with 8:2 hexane/ethyl acetate) afforded the desired product as a white solid (45 mg, 54%): mp 168−170 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 10.70 (s, 1H), 9.71 (s, 1H), 8.87 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.84 (dd, *J* = 7.8, 1.8 Hz, 1H), 8.21 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.62−7.57 (m, 2H), 7.52−7.50 (m, 2H),7.40−7.37 (m, 2H), 7.28−7.27 (m, 2H), 7.12 (t, *J* = 7.8, 1H), 7.02 (dd, *J* = 8.4, 1.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.3, 148.4, 147.7, 140.3, 138.8, 136.4, 134.3, 129.5, 129.2, 128.0, 127.4, 127.3, 123.7, 122.2, 121.9, 121.8, 120.7, 117.5, 116.5, 116.4; IR (neat) υ_{max} 3445, 3356, 2924, 2854, 1648, 1586, 1530, 1413; HRMS (ESI, *m*/*z*) calcd for $C_{22}H_{16}BrN_3ONa$ $[M + Na]^+$ 440.0374, found 440.0377.

4-Ethyl-2-(phenylamino)-N-(quinolin-8-yl)benzamide, ***3d****, Scheme 2.* Column chromatography (SiO_2, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a white solid (46 mg, 63%): mp 82−85 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 10.71 (s, 1H), 9.68 (s, 1H), 8.87−8.83 (m, 2H), 8.17 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.82 (d, *J* = 8.1 Hz, 1H), 7.62−7.51 (m, 3H), 7.47 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.38−7.33 (m, 2H), 7.31−7.27 (m, 2H), 7.08−7.02 (m, 1H), 6.78 (dd, *J* = 8.1, 1.8 Hz, 1H), 2.62 (q, *J* = 7.5 Hz, 2H), 1.28 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 149.5, 148.2, 146.4, 141.6, 138.8, 136.3, 134.7, 129.3, 128.2, 128.0, 127.4, 122.4, 121.7, 121.5, 121.1, 118.1, 116.3, 116.0, 114.7, 29.1, 15.2; IR (neat) υ_{max} 3351, 3046, 2963, 2926, 1727, 1650, 1528, 1262; HRMS (ESI, *m*/*z*) calcd for $C_{24}H_{21}N_3ONa$ $[M + Na]^+$ 390.1582, found 390.1562.

4-Acetyl-2-(phenylamino)-N-(quinolin-8-yl)benzamide, ***3e****, Scheme 2.* Column chromatography (SiO_2, eluting with 8:2 hexane/ethyl acetate) afforded the desired product as a yellow solid (50 mg, 66%): mp 144−146 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 10.78 (s, 1H), 9.58 (s, 1H), 8.88−8.86 (m, 2H), 8.22 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.97−7.94 (m, 2H), 7.63−7.58 (m, 2H), 7.51 (dd, *J* =

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8.4, 4.2 Hz, 1H), 7.46 (dd, J = 8.4, 1.8 Hz, 1H), 7.39−7.36 (m, 2H), 7.30−7.28 (m, 2H), 7.10 (t, J = 7.2 Hz, 1H), 2.58 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.8, 167.0, 148.4, 146.4, 140.8, 140.1, 138.7, 136.4, 134.2, 129.5, 128.4, 128.0, 127.3, 123.3, 122.1, 121.8,121.7, 121.3,117.3, 116.6, 115.1, 26.9; IR (neat) υ_{max} 3357, 2923, 1688, 1652, 1527, 1381, 1307; HRMS (ESI, m/z) calcd for $C_{24}H_{19}N_3O_2Na$ $[M + Na]^+$ 404.1375, found 404.1371.

2-(Phenylamino)-N-(quinolin-8-yl)-6-(trifluoromethyl)benzamide, ***3f****,* Scheme 2. Column chromatography (SiO_2, eluting with 8:2 hexane/ethyl acetate) afforded the desired product as a white solid (48 mg, 59%): mp 169−171 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.31 (s, 1H), 8.96 (dd, J = 8.4, 3.3 Hz, 1H), 8.78 (dd, J = 4.2, 1.5 Hz, 1H), 8.18 (dd, J = 8.4, 1.8 Hz, 1H), 7.62−7.55 (m, 3H), 7.46 (dd, J = 8.4, 4.2 Hz, 1H), 7.39 (t, J = 8.1 Hz, 1H), 7..32−7.24 (m, 3H), 7.15−7.11 (m, 2H), 7.04−6.98 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 148.4, 143.3, 141.1, 138.5, 136.3, 134.1, 130.3 (q, J = 4.5 Hz), 130.25, 129.8, 129.4, 128.3(q, J = 30.8 Hz), 128.0, 127.2, 123.8 (q, J = 272.3 Hz), 123.2, 122.8, 122.7, 121.8, 120.3, 119.4, 117.2 (q, J = 5.3 Hz), 117.1; IR (neat) υ_{max} 3337, 3040, 2926, 1665, 1591, 1527, 1326, 1126; HRMS (EI, m/z) calcd for $C_{23}H_{16}F_3N_3O$ $[M]^+$ 407.1245, found 407.1241.

2-(Phenylamino)-N-(quinolin-8-yl)-5-(trifluoromethyl)benzamide, ***3g****,* Scheme 2. Column chromatography (SiO_2, eluting with 8:2 hexane/ethyl acetate) afforded the desired product as a yellow solid (42 mg, 52%): mp 171−172 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.74 (s, 1H), 9.86 (s, 1H), 8.90 (dd, J = 4.2, 1.8 Hz, 1H), 8.83 (dd, J = 7.2, 2.4 Hz, 1H), 8.23 (dd, J = 8.4, 1.8 Hz, 1H), 8.09 (d, J = 1.8 Hz, 1H), 7.64−7.59 (m, 2H), 7.55−7.52 (m, 2H), 7.41−7.37 (m, 3H), 7.30−7.29 (m, 2H), 7.16 (t, J = 7.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.0, 149.3, 148.6, 139.9, 138.8, 136.4, 134.2, 129.51, 129.3 (q, J = 3.0 Hz), 128.0, 127.2, 125.4 (q, J = 3.0 Hz), 124.2 (q, J = 270.0), 124.3, 122.8, 122.1, 121.9, 119.0 (q, J = 33.0), 117.0, 116.6, 114.6; IR (neat) υ_{max} 3348, 3216, 2923, 2853, 1654, 1534; HRMS (EI, m/z) calcd for $C_{23}H_{16}F_3N_3O$ $[M]^+$ 407.1245, found 407.1248.

4′-Methyl-4-(phenylamino)-N-(quinolin-8-yl)-[1,1′-biphenyl]-3-carboxamide, ***3h****,* Scheme 2. Column chromatography (SiO_2, eluting with 8:2 hexane/ethyl acetate) afforded the desired product as a yellow solid (47 mg, 55%): mp 286−288 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.77 (s, 1H), 9.47 (s, 1H), 8.89 (dd, J = 7.8, 1.8 Hz, 1H), 8.85 (dd, J = 4.2, 1.8 Hz, 1H), 8.21(dd, J = 8.4 Hz, 1.8 Hz, 1H), 8.08 (d, J = 2.4 Hz, 1H), 7.64−7.56 (m, 5H), 7.52−7.48 (m, 2H), 7.37−7.34 (m, 2H), 7.31−7.29 (m, 4H), 7.06 (t, J = 7.2 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.0, 148.4, 145.0, 141.4, 138.8, 137.5, 136.6, 136.3, 134.6, 131.10, 131.06, 129.6, 129.3, 128.0, 127.3, 126.3, 126.2, 122.6, 121.8, 121.7, 121.0, 119.3, 116.5, 116.1, 21.1; IR (neat) υ_{max} 3358, 3294, 2922, 1657, 1597, 1533, 1328; HRMS (ESI, m/z) calcd for $C_{29}H_{24}N_3O$ $[M + H]^+$ 430.1919, found 430.1906.

4-Acetyl-2-((4-methoxyphenyl)amino)-N-(quinolin-8-yl)benzamide, ***3i****,* Scheme 2. Column chromatography (SiO_2, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a yellow solid (62 mg, 75%): mp 138−140 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.77 (s, 1H), 9.44 (s, 1H), 8.88−8.84 (m, 2H), 8.20 (dd, J = 8.4, 1.8 Hz, 1H),7.92 (d, J = 8.1 Hz, 1H), 7.68 (d, J = 1.5 Hz, 1H), 7.60−7.56 (m, 2H),7.50 (dd, J = 8.4, 4.2 Hz, 1H), 7.36 (dd, J = 8.1, 1.5 Hz, 1H), 7.23−7.19 (m, 2H), 6.94−6.91 (m, 2H), 3.83 (s, 3H), 2.53 (s,3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.0, 167.2, 156.5, 148.4, 148.2, 140.2, 138.7, 136.4, 134.3, 133.4, 128.3, 128.0, 127.3, 124.9, 122.0, 121.8, 120.0, 116.5, 116.1, 114.8, 114.0, 55.5, 26.9; IR (neat) υ_{max} 3345, 2924, 2853, 1685, 1653, 1517, 1242; ; HRMS (ESI, m/z) calcd for $C_{25}H_{21}N_3O_3Na$ $[M + Na]^+$ 434.1481, found 434.1456.

2-((4-Methoxyphenyl)amino)-N-(quinolin-8-yl)benzamide, ***3j****,* Scheme 2. Column chromatography (SiO_2, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a yellow solid (48 mg, 65%): mp 120−122 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.73 (s, 1H), 9.44 (s, 1H), 8.88−8.86 (m, 1H), 8.86−8.85 (m, 1H), 8.20 (dd, J = 8.1, 1.5 Hz, 1H), 7.86 (dd, J = 8.1, 1.8 Hz, 1H), 7.62−7.53 (m, 2H), 7.49 (dd, J = 8.4, 4.2 Hz, 1H), 7.33−7.27 (m, 1H), 7.23−7.11 (m, 3H), 6.93−6.81 (m, 3H), 3.82 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.0, 156.2, 148.3, 148.2, 138.6, 136.4, 134.7, 134.0, 132.7, 128.0, 127.9, 127.4, 125.0, 121.7, 121.5, 116.84, 116.77, 116.3, 114.6, 114.4, 55.5; IR (neat) υ_{max} 3348, 2923, 1648, 1580, 1515, 1242; HRMS (ESI, m/z) calcd for $C_{23}H_{19}N_3O_2Na$ $[M + Na]^+$ 392.1375, found 392.1380.

N-(Quinolin-8-yl)-2-(p-tolylamino)benzamide, ***3k****,* Scheme 2. Column chromatography (SiO_2, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a yellow solid (45 mg, 64%): mp 146−148 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.7 (s, 1H), 9.5 (s, 1H), 8.88−8.83 (m, 2H), 8.18 (dd, J = 8.4, 1.8 Hz, 1H), 7.86 (d, J = 7.8 Hz, 1H), 7.62−7.52 (m, 2H), 7.48 (dd, J = 8.1, 4.2 Hz, 1H), 7.33−7.30 (m, 2H),7.19−7.12 (m, 4H), 6.90−6.84 (m, 1H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 148.3, 147.1, 138.8, 138.6, 136.4, 134.6, 132.63, 132.57, 129.8, 128.0, 127.3, 122.1, 121.7, 121.6, 117.7, 117.4, 116.3, 115.0, 20.8; IR (neat) υ_{max} 3350, 3025, 2923, 2859, 1726, 1650, 1519, 1262; HRMS (ESI, m/z) calcd for $C_{23}H_{19}N_3ONa$ $[M + Na]^+$ 376.1426, found 376.1419.

2-((4-(tert-Butyl)phenyl)amino)-N-(quinolin-8-yl)benzamide, ***3l****,* Scheme 2. Column chromatography (SiO_2, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a organge solid (47 mg, 59%): mp 280−284 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.72 (s, 1H), 9.54 (s, 1H), 8.88−8.87 (m, 1H), 8.86 (dd, J = 4.2, 1.8 Hz, 1H), 8.20 (dd, J = 8.4, 1.8 Hz, 1H), 7.88 (dd, J = 7.8, 1.8 Hz, 1H), 7.62−7.60 (m, 1H), 7.57−7.55 (m, 1H), 7.50 (dd, J = 8.4, 4.2 Hz, 1H), 7.40−7.34 (m, 4H), 7.24−7.21 (m, 2H),6.91−6.86 (m, 1H), 1.35 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.9, 148.3, 146.8, 145.8, 138.8, 138.6, 136.4, 134.6, 132.6, 128.01, 127.99, 127.4,126.1, 121.7, 121.8,121.3, 117.9, 117.5,116.4,115.3, 34.3, 31.4; IR (neat) υ_{max} 3351, 2959, 2926, 1651, 1590, 1520, 1324; HRMS (EI, m/z) calcd for $C_{26}H_{25}N_3O$ $[M]^+$ 395.1998, found 395.2007.

2-((2,4-Dimethoxyphenyl)amino)-N-(quinolin-8-yl)benzamide, ***3m****,* Scheme 2. Column chromatography (SiO_2, eluting with 8:2 hexane/ethyl acetate) afforded the desired product as a white solid (37 mg, 46%): mp 252−254 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.72 (s, 1H), 9.24 (s, 1H), 8.92 (dd, J = 7.2, 1.2 Hz, 1H), 8.86−8.85 (m, 1H), 8.20−8.18 (m, 1H), 7.87 (dd, J = 7.8, 1.2 Hz, 1H), 7.61−7.59 (m, 1H), 7.55−7.54 (m, 1H), 7.50−7.47 (m, 1H), 7.33−7.28 (m, 2H), 7.12−7.10 (m, 1H), 6.86−6.84 (m, 1H), 6.58(d, J = 3.0 Hz, 1H), 6.49 (dd, J = 8.4, 2.4 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.9, 156.8, 153.8, 148.2, 147.8, 138.8, 136.3, 134.8, 132.5, 127.99, 127.96, 127.4, 123.7, 123.4, 121.6, 121.4, 117.6, 116.9, 116.4, 114.6, 103.8, 99.5, 55.8, 55.5; IR (neat) υ_{max} 3337, 3313, 2949, 2830, 1643, 1540, 1511, 1211, 1159; HRMS (ESI, m/z) calcd for $C_{24}H_{22}N_3O_3$ $[M + H]^+$ 400.1661, found 400.1651.

2-((2,4-Dimethylphenyl)amino)-N-(quinolin-8-yl)benzamide, ***3n****,* Scheme 2. Column chromatography (SiO_2, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a white solid (35 mg, 48%): mp 134−136 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.76 (s, 1H), 9.37 (s, 1H), 8.90 (dd, J = 7.8, 1.2 Hz, 1H), 8.88 (dd, J = 4.2, 1.8 Hz, 1H), 8.21 (dd, J = 8.4, 1.8 Hz, 1H), 7.89 (dd, J = 7.8, 1.2 Hz, 1H), 7.61 (t, J = 8.4 Hz, 1H), 7.57−7.55 (m, 1H), 7.50 (dd, J = 8.4, 4.2 Hz, 1H), 7.32−7.29 (m, 1H), 7.25−7.24 (m, 1H), 7.11−7.10 (m, 1H), 7.03−7.02 (m, 1H), 6.97−6.96 (m, 1H), 6.86−6.84 (m, 1H), 2.35 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.0, 148.2, 148.1, 138.8, 136.8, 136.4, 134.7, 133.8, 132.71, 132.68, 131.7, 128.0, 127.9, 127.4, 127.1, 123.8, 121.7, 121.5, 116.8, 116.7, 116.3, 114.7, 20.9, 18.0; IR (neat) υ_{max} 3358, 3286, 1642, 1520, 1483, 1322; HRMS (ESI, m/z) calcd for $C_{24}H_{21}N_3ONa$ $[M + Na]^+$ 390.1582, found 390.1565.

2-((2,3-Dimethylphenyl)amino)-N-(quinolin-8-yl)benzamide, ***3o****,* Scheme 2. Column chromatography (SiO_2, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a white solid (46 mg, 62%): mp 139−141 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.77 (s, 1H), 9.45 (s, 1H), 8.92−8.91 (m, 1H), 8.89 (dd, J = 4.2, 1.8 Hz, 1H), 8.22 (dd, J = 8.4, 1.8 Hz, 1H), 7.90 (dd, J = 8.1, 1.5 Hz, 1H), 7.65−7.55 (m, 2H), 7.51 (dd, J = 8.4, 4.2 Hz, 1H), 7.34−7.28 (m, 1H), 7.24−7.22 (m, 1H), 7.12 (t, J = 7.5 Hz, 1H), 7.02−6.94 (m, 2H), 6.89−6.84 (m, 1H), 2.36 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (75

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J. Org. Chem. 2016, 81, 4295−4303

MHz, $CDCl_3$) δ 168.0, 148.2, 148.0, 139.3, 138.8, 138.0, 136.4, 134.7, 132.7, 131.5, 128.0, 127.9, 127.4, 126.0, 125.8, 121.8, 121.7, 121.5, 116.9, 116.9, 116.3, 114.9, 20.6, 14.0; IR (neat) υ_{max} 3343, 2923, 1647, 1578, 1520, 1320; HRMS (ESI, m/z) calcd for $C_{24}H_{21}N_3ONa$ $[M + Na]^+$ 390.1582, found 390.1566.

2-((3-Chloro-2-methylphenyl)amino)-N-(quinolin-8-yl)benzamide, ***3p****, Scheme 2*. Column chromatography (SiO_2, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a white solid (44 mg, 57%): mp 130−132 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 10.77 (s, 1H), 9.53 (s, 1H), 8.89 (dd, J = 7.8, 1.8 Hz, 1H), 8.88 (dd, J = 4.2, 1.8 Hz, 1H), 8.21 (dd, J = 8.4, 1.8 Hz, 1H), 7.91 (dd, J = 7.8, 1.8 Hz, 1H), 7.63−7.60 (m, 1H), 7.58−7.56 (m, 1H), 7.51 (dd, J = 8.4, 4.2 Hz, 1H) 7.36−7.33 (m, 1H), 7.30−7.28 (m, 1H), 7.17 (dd, J = 7.8, 1.8 Hz, 1H), 7.13−7.10 (m, 1H), 7.03 (dd, J = 8.4, 1.2 Hz, 1 H), 6.94−6.91 (m, 1H), 2.43 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.8, 148.3, 146.9, 141.1, 138.8, 136.4, 135.4, 134.5, 132.7, 130.4, 128.02, 127.98, 127.4, 126.7, 124.6, 121.71, 121.70 121.1, 117.9, 117.8, 116.4, 115.4, 15.0; IR (neat) υ_{max} 3435, 3358, 2921, 1657, 1590, 1528, 1324; HRMS (EI, m/z) calcd for $C_{23}H_{18}ClN_3O$ $[M]^+$ 387.1138, found 387.1132.

2-((2-Methyl-3-(trifluoromethyl)phenyl)amino)-N-(quinolin-8-yl)-benzamide, ***3q****, Scheme 2*. Column chromatography (SiO_2, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a white solid (51 mg, 61%): mp 142−144 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 10.79 (s, 1H), 9.56 (s, 1H), 8.90−8.89 (m, 1H), 8.88 (dd, J = 4.2, 1.8 Hz, 1H), 8.22 (dd, J = 8.4, 1.8 Hz, 1H), 7.93 (dd, J = 7.8, 1.8 Hz, 1H), 7.63−7.60 (m, 1H), 7.58−7.56 (m, 2H), 7.51(dd, J = 8.4, 4.2 Hz, 1H), 7.42−7.41 (m, 1H),7.38−7.35 (m, 1H) 7.28−7.26 (m, 1H), 7.04(dd, J = 8.4, 1.8 Hz, 1H), 6.97−6.94 (m, 1H), 2.48(s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.8, 148.3, 146.7, 141.4, 138.8, 136.4, 134.5, 130.52 (q, J = 30.0 Hz), 130.51, 128.1, 128.0, 127.4, 126.1, 125.7, 124.48 (q, J = 271.5 Hz), 121.76, 121.73, 121.10 (q, J = 3.0 Hz), 118.18, 118.16, 116.4,115.4, 13.8 (d, J = 3.0 Hz); IR (neat) υ_{max} 3432, 3352, 2923, 1652, 1583, 1325; HRMS (EI, m/z) calcd for $C_{24}H_{18}F_3N_3O$ $[M]^+$ 421.1402, found 421.1400.

2-((3,5-Dimethoxyphenyl)amino)-N-(quinolin-8-yl)benzamide, ***3r****, Scheme 2*. Column chromatography (SiO_2, eluting with 8:2 hexane/ethyl acetate) afforded the desired product as a white solid (50 mg, 63%): mp 124−126 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 10.72 (s, 1H), 9.55 (s, 1H), 8.87−8.86 (m, 2H), 8.20 (dd, J = 8.4, 1.8 Hz, 1H), 7.88 (dd, J = 7.8, 1.8 Hz, 1H), 7.61 (t, J = 7.8 Hz, 1H), 7.57−7.53 (m, 2H), 7.49 (dd, J = 8.4, 4.2 Hz, 1H), 7.40−7.38 (m, 1H), 6.97−6.94 (m, 1H), 6.46−6.45 (m, 2H), 6.18 (t, J = 1.8 Hz, 1H), 3.80(s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.8, 161.4, 148.3, 145.6, 143.4, 138.8, 136.4, 134.5, 132.5, 128.0, 127.3, 121.74, 121.71, 119.1, 118.5, 116.6, 116.4, 98.8, 94.9, 55.3; IR (neat) υ_{max} 3347, 2928, 1650, 1597, 1521, 1155; HRMS (ESI, m/z) calcd for $C_{24}H_{22}N_3O_3$ $[M + H]^+$ 400.1661, found 400.1647.

5-Bromo-2-((4-fluorophenyl)amino)-N-(quinolin-8-yl)benzamide, ***3s****, Scheme 2*. Column chromatography (SiO_2, eluting with 8:2 hexane/ethyl acetate) afforded the desired product as a yellow solid (55 mg, 63%): mp 190−192 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 10.62 (s, 1H), 9.38 (s, 1H), 8.88 (dd, J = 8.4, 1.5 Hz, 1H), 8.80 (dd, J = 6.0, 3.0 Hz, 1H), 8.20 (dd, J = 8.4, 1.8 Hz, 1H), 7.92 (d, J = 2.4 Hz, 1H), 7.59−7.55 (m, 2H), 7.50 (dd, J = 8.4, 4.2 Hz, 1H), 7.40−7.36 (m, 1H), 7.20−7.16 (m, 2H), 7.09−7.01 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 159.2 (d, J = 241.5 Hz), 148.5, 146.1, 138.7, 136.7 (d, J = 2.3 Hz), 136.4, 135.4, 134.2, 130.4, 128.0, 127.2, 124.3, 124.2, 122.0, 121.8, 119.3, 116.6, 116.4, 116.1(d, J = 22.5 Hz), 108.9; IR (neat) υ_{max} 3443, 3343, 2923, 1653, 1541, 1511, 1390, 1206; HRMS (ESI, m/z) calcd for $C_{22}H_{16}N_3BrFO$ $[M + H]^+$ 436.0461, found 436.0476.

2-((4-Bromophenyl)amino)-4-fluoro-N-(quinolin-8-yl)benzamide, ***3t****, Scheme 2*. Column chromatography (SiO_2, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a white solid (53 mg, 61%): mp 278−280 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 10.64 (s, 1H), 9.86 (s, 1H), 8.84 (dd, J = 4.2, 1.5 Hz, 1H), 8.79 (dd, J = 6.9, 2.4 Hz, 1H), 8.19 (dd, J = 8.4, 1.8 Hz, 1H), 7.88−7.83 (m, 1H), 7.61−7.53 (m, 2H), 7.49 (dd, J = 8.4, 4.2 Hz, 1H), 7.46−7.42 (m, 2H), 7.15−7.10 (m, 2H), 6.98−6.93 (m, 1H), 6.63−6.56 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.1, 165.6 (d, J = 248.2 Hz), 148.5, 148.3, 139.5, 138.7, 136.4, 134.3, 132.4, 130.3, 130.2, 128.0, 127.3, 123.5, 121.8 (d, J = 5.2 Hz), 116.4, 115.9, 114.3 (d, J = 1.5 Hz), 114.26, 105.5 (d, J = 22.5 Hz), 101.2 (d, J = 26.2 Hz); IR (neat) υ_{max} 3350, 3310, 1649, 1592, 1534, 1486; HRMS (ESI, m/z) calcd for $C_{22}H_{15}N_3BrFONa$ $[M + Na]^+$ 458.0280, found 458.0271.

2-((4-Iodophenyl)amino)-4-methyl-N-(quinolin-8-yl)benzamide, ***3u****, Scheme 2*. Column chromatography (SiO_2, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a yellow solid (58 mg, 60%): mp 158−160 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 10.71 (s, 1H), 9.65 (s, 1H), 8.86 (dd, J = 3.6, 1.8 Hz, 1H), 8.85−8.83 (m, 1H), 8.20−8.19 (m, 1H), 7.79 (dd, J = 7.8, 1.8 Hz, 1H), 7.62−7.54 (m, 3H), 7.50−7.48 (m, 1H), 7.44−7.28 (m, 1H), 7.21−7.15 (m, 1H), 7.05−7.04 (m, 2H), 6.78 (d, J = 8.4 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.7, 148.3, 145.5, 143.4, 141.4, 138.8, 138.1, 136.4, 134.6, 132.2, 128.1, 128.0, 127.3, 122.8, 122.7, 121.7, 121.6, 119.9, 116.33, 116.30, 115.9, 84.5, 21.9; IR (neat) υ_{max} 3449, 3334, 1646, 1526, 1482, 1256; HRMS (ESI, m/z) calcd for $C_{23}H_{18}N_3IONa$ $[M + Na]^+$ 502.0392, found 502.0369.

4-Cyano-2-((4-methoxyphenyl)amino)-N-(quinolin-8-yl)benzamide, ***3v****, Scheme 2*. Column chromatography (SiO_2, eluting with 8:2 hexane/ethyl acetate) afforded the desired product as a yellow solid (43 mg, 54%): mp 154−156 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 10.74 (s, 1H), 9.48 (s, 1H), 8.86 (dd, J = 4.5, 1.5 Hz, 1H), 8.82 (dd, J = 5.7, 3.6 Hz, 1H), 8.21 (dd, J = 8.4, 1.8 Hz,1H), 7.86 (d, J = 8.1 Hz, 1H), 7.60−7.56 (m, 2H), 7.51 (dd, J = 8.4, 4.2 Hz, 1H), 7.26 (s, 1H), 7.19−7.16 (m, 2H), 7.02 (dd, J = 8.1, 1.5 Hz, 1H), 6.96−6.93 (m, 2H), 3.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 157.2, 148.6, 148.5, 138.7, 136.5, 134.0, 132.2, 128.6, 128.0, 127.3, 125.9, 122.2, 121.9, 119.5, 119.0, 118.5, 117.4, 116.6, 115.8, 115.0, 55.5; IR (neat) υ_{max} 3420, 3320, 2910, 2229, 1659; HRMS (ESI, m/z) calcd for $C_{24}H_{18}N_4O_2Na$ $[M + Na]^+$ 417.1327, found 417.1335.

N-(Quinolin-8-yl)-2-((3-(trifluoromethyl)phenyl)amino)benzamide, ***3w****, Scheme 2*. Column chromatography (SiO_2, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a white solid (59 mg, 72%): mp 140−142 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 10.77 (s, 1H), 9.73 (s, 1H), 8.88−8.85 (m, 2H), 8.22 (dd, J = 8.1, 1.8 Hz, 1H), 7.91 (dd, J = 7.2, 1.5 Hz, 1H), 7.65−7.55 (m, 2H), 7.53−7.48 (m, 2H), 7.46−7.39 (m, 4H), 7.28−7.23 (m, 1H), 7.06−7.00 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 148.4, 144.8, 142.2, 138.6, 136.4, 134.4, 132.7, 131.7 (q, J = 31.5 Hz), 129.8, 128.2, 128.0, 127.3, 124.02 (q, J = 270.0 Hz), 123.1, 121.9, 121.8, 119.6, 119.3, 118.5 (q, J = 3.7 Hz), 116.5 (q, J = 3.7 Hz), 116.4, 116.0; IR (neat) υ_{max} 3356, 3219, 1659, 1595, 1532, 1333; HRMS (EI, m/z) calcd for $C_{23}H_{16}F_3N_3O$ $[M]^+$ 407.1245, found 407.1242.

2-((4-Methoxy-2-nitrophenyl)amino)-4-(pentyloxy)-N-(quinolin-8-yl)benzamide, ***3x****, Scheme 2*. Column chromatography (SiO_2, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a red solid (73 mg, 73%): mp 110−112 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 10.95 (s, 1H), 10.76 (s, 1H), 8.90 (dd, J = 7.8, 1.8 Hz, 1H), 8.80 (dd, J = 4.2, 1.8 Hz, 1H), 8.26 (dd, J = 8.4, 1.8 Hz, 1H), 7.95 (d, J = 9.0 Hz, 1H), 7.63−7.61(m, 2H), 7.58−7.56 (m, 1H), 7.52−7.50 (m, 2H), 7.11(dd, J = 9.6, 3.0 Hz, 1H), 6.91 (d, J = 2.4 Hz, 1H), 6.70 (dd, J = 9.0, 2.4 Hz, 1H), 3.98 (t, J = 6.6 Hz, 2H), 3.83(s, 3H), 1.81−1.79 (m, 2H), 1.46−1.39 (m, 4H), 0.95 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.3, 162.4, 152.7, 147.5, 143.4, 137.9, 137.7, 137.4, 134.0, 133.9, 130.6, 128.1, 127.9, 124.0, 121.9, 121.5, 121.0, 118.6, 116.8, 108.6, 107.9, 105.5, 68.3, 55.8, 28.8, 28.1, 22.4, 14.0; IR (neat) υ_{max} 3350, 2928, 2859, 1655, 1514, 1254, 1148; HRMS (ESI, m/z) calcd for $C_{28}H_{29}N_4O_5$ $[M + H]^+$ 501.2138, found 501.2133.

3-((3-Methoxyphenyl)amino)-N-(quinolin-8-yl)isonicotinamide, ***3y****, Scheme 2*. Column chromatography (SiO_2, eluting with 6:4 hexane/ethyl acetate) afforded the desired product as a yellow solid (26 mg, 35%): mp 128−130 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 10.85 (s, 1H), 9.16 (s, 1H), 8.90 (dd, J = 7.2, 1.8 Hz, 1H), 8.87 (dd, J = 4.2, 1.8 Hz, 1H), 8.77 (s, 1H), 8.23−8.21 (m, 2H), 7.67 (d, J = 5.4, 1H), 7.63−7.59 (m, 2H), 7.52 (dd, J = 8.4, 4.2 Hz, 1H), 7.43 (dd, J = 7.2, 1.2 Hz, 1H), 7.09−7.06 (m, 1H), 6.99−6.94 (m, 2H),

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J. Org. Chem. 2016, 81, 4295−4303

3.94 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.8, 151.3,148.5, 140.6, 139.9, 139.0, 138.7, 136.4, 134.0, 129.5, 128.0, 127.4, 124.1, 123.7, 122.2, 121.8, 120.6, 120.4, 120.0, 116.8, 111.3, 55.7; IR (neat) υ_{max} 3367, 3344, 2921, 2852, 1669, 1598, 1562, 1534, 1025; HRMS (ESI, m/z) calcd for $C_{22}H_{18}N_4O_2Na$ $[M + Na]^+$ 393.1327, found 393.1334.

N-(Quinolin-8-yl)-4-(m-tolylamino)nicotinamide, ***3z****, Scheme 2.* Column chromatography (SiO_2, eluting with 6:4 hexane/ethyl acetate) afforded the desired product as a yellow solid (44 mg, 62%): mp 160−162 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.87 (s, 1H), 10.11 (s, 1H), 9.04 (s, 1H), 8.88 (dd, J = 4.2, 1.8 Hz, 1H), 8.83 (dd, J = 7.2, 1.8 Hz, 1H), 8.29 (d, J = 6.0 Hz,1H), 8.22 (dd, J = 8.4, 1.8 Hz, 1H), 7.62−7.58 (m, 2H),7.52 (dd, J = 8.4, 4.2 Hz, 1H), 7.32−7.29 (m, 1H), 7.12−7.11 (m, 2H), 7.08 (d, J = 6.0 Hz,1H), 7.04 (d, J = 7.8 Hz,1H), 2.39 (s,3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.6, 152.6, 151.9, 149.1, 148.5, 139.6, 138.7, 138.5, 136.4, 134.2, 129.3, 128.0, 127.2, 126.1, 124.4, 122.0, 121.9, 120.7, 116.5, 113.0, 108.0, 21.4; IR (neat) υ_{max} 3370, 3353, 3045, 1648, 1603, 1535, 1326, 1195; HRMS (ESI, m/z) calcd for $C_{22}H_{19}N_4O$ $[M + H]^+$ 355.1559, found 355.1566.

2-((6-Methoxypyridin-3-yl)amino)-N-(quinolin-8-yl)benzamide, ***3aa****, Scheme 2.* Column chromatography (SiO_2, eluting with 6:4 hexane/ethyl acetate) afforded the desired product as a white solid (33 mg, 44%): mp 108−110 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.77 (s, 1H), 9.46 (s, 1H), 8.88−8.86 (m, 2H), 8.21 (dd, J = 8.4, 1.8 Hz, 1H), 8.15 (d, J = 3.0 Hz, 1H), 7.89 (dd, J = 7.8, 1.8 Hz, 1H), 7.61 (t, J = 7.8 Hz, 1H), 7.57−7.54 (m, 2H), 7.50 (dd, J = 8.4, 4.2 Hz, 1H), 7.34−7.31 (m, 1H), 7.03 (dd, J = 8.4, 1.2 Hz, 1H), 6.90−6.88 (m, 1H), 6.78 (d, J = 8.4 Hz, 1H), 3.97 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.9, 161.0, 148.3, 148.1, 142.4, 138.8, 136.4, 135.6, 134.5, 132.9, 131.3, 128.02, 127.99, 127.3, 121.72, 121.69, 117.4, 117.0, 116.4, 114.1, 111.1, 53.6; IR (neat) υ_{max} 3352, 3290, 2922, 1651, 1583, 1534, 1486, 1273; HRMS (ESI, m/z) calcd for $C_{22}H_{18}N_4O_2Na$ $[M + Na]^+$ 393.1327, found 393.1344.

General Experimental Procedure for C−H Amination Reaction with Electron-Deficient Anilines. In a 15 mL sealed tube, the substrate **1** (0.2 mmol), $Cu(OAc)_2{\cdot}H_2O$ (40 mg, 0.2 mmol, 1 equiv), ^{t}BuOLi (32 mg, 0.4 mmol, 2 equiv), and anilines **2** (0.3 mmol, 1.5 equiv) were added, followed by DMSO (3 mL). The oxygen gas was passed to the reaction mixture for 1 min. Then, the tube was charged with a preheated oil bath at 100 °C for 3 h. The reaction mixture was diluted with 10 mL of ethyl acetate and quenched with 20 mL of aq. ammonium solution. Then, it was filtered through Celite-545 and the aqueous phase was extracted with ethyl acetate (2 × 20 mL). The combined organic phase was collected, dried over Na_2SO_4, and concentrated under vacuum. The crude was purified by column chromatography on silica gel with a gradient of elution of pet ether and ethyl acetate to give the desired amination product.

2-((4-Nitrophenyl)amino)-N-(quinolin-8-yl)benzamide, ***3ab****, Scheme 2.* Column chromatography (SiO_2, eluting with 8:2 hexane/ethyl acetate) afforded the desired product as a yellow solid (74 mg, 96%): mp 204−206 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.76 (s, 1H), 9.98 (s, 1H), 8.87−8.84 (m, 2H), 8.22 (dd, J = 8.4, 1.8 Hz, 1H), 8.17 (d, J = 9.0 Hz, 2H), 7.95 (dd, J = 8.4, 1.8 Hz, 1H), 7.63−7.59 (m, 3H), 7.53−7.50 (m, 2H), 7.24−7.22 (m, 2H), 7.20−7.17 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.1, 148.5, 148.3, 142.2, 140.7, 138.7, 136.5, 134.1, 132.5, 128.3, 128.0, 127.3, 125.9, 122.4, 122.3, 121.9, 121.8, 118.7, 116.6, 116.4; IR (neat) υ_{max} 3347, 1655, 1595, 1528, 1329, 1111; HRMS (ESI, m/z) calcd for $C_{22}H_{16}N_4O_3Na$ $[M + Na]^+$ 407.1120, found 407.1117.

2-((4-Cyanophenyl)amino)-N-(quinolin-8-yl)benzamide, ***3ac****, Scheme 2.* Column chromatography (SiO_2, eluting with 8:2 hexane/ethyl acetate) afforded the desired product as a white solid (49 mg, 67%): mp 192−194 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.74 (s, 1H), 9.80 (s, 1H), 8.86−8.81 (m, 2H), 8.21 (dd, J = 8.1, 1.5 Hz, 1H), 7.92 (dd, J = 7.8, 1.5 Hz, 1H), 7.61−7.44 (m, 7H), 7.25−7.22 (m, 2H), 7.14−7.09 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 148.4, 146.2, 142.7, 138.7, 136.5, 134.2, 133.6, 132.5, 128.3, 128.0, 127.3, 122.2 121.8, 121.8, 121.7, 121.1, 119.7, 118.0, 117.7, 116.6, 103.1; IR (neat) υ_{max} 3357, 2214, 1653, 1587, 1514, 1326, 1171; HRMS (EI, m/z) calcd. for $C_{23}H_{16}N_4O$ $[M]^+$ 364.1324, found 364.1313.

2-((3,5-Bis(trifluoromethyl)phenyl)amino)-N-(quinolin-8-yl)benzamide, ***3ad****, Scheme 2.* Column chromatography (SiO_2, eluting with 8:2 hexane/ethyl acetate) afforded the desired product as a white solid (76 mg, 80%): mp 168−170 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.77 (s, 1H), 9.92 (s, 1H), 8.87−8.82 (m, 2H), 8.20 (dd, J = 6.9, 1.5 Hz, 1H), 7.94 (d, J = 7.8 Hz, 1H), 7.63 (s, 2H), 7.61−7.56 (m, 2H), 7.52−7.46 (m, 3H), 7.42 (s, 1H), 7.14−7.09 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 148.4, 143.4, 143.3, 138.7, 136.4, 134.1, 132.8, 132.4, 128.3, 128.0, 127.2, 123.2, (q, J = 270.8 Hz), 122.1, 121.8, 120.9, 120.7, 118.2 (q, J = 3.8 Hz), 116.7, 116.5, 114.4 (q, J = 3.8 Hz); IR (neat) υ_{max} 3351, 3205, 1648, 1530, 1387, 1279; HRMS (EI, m/z) calcd. for $C_{24}H_{15}F_6N_3O$ $[M]^+$ 475.1119, found 475.1121.

Gram-Scale Synthesis of Compound 3o. The compound *N*-(quinolin-8-yl)benzamide (1.24 g, 5 mmol) was taken in an oven-dried, two way 250 mL round-bottom flask which was connected through a condenser under a N_2 ballon and dissolved with 60 mL of DMSO; then it was degassed two times. Next, $Cu(OAc)_2{\cdot}H_2O$ (1.99 g, 10 mmol, 2 equiv), AgOAc (0.83 g, 5 mmol, 1 equiv), TBAB (4.83 g, 15 mmol, 3 equiv), LiO^tBu (0.80 g, 10 mmol, 2 equiv), and 2,3-dimethylaniline (0.9 mL, 7.5 mmol, 1.5 equiv) were added in it. Then, it was degassed three times and stirred for 6 h at 100 °C. The reaction mixture was diluted with 80 mL of ethyl acetate and quenched with 200 mL of aq. ammonium solution. Then, it was filtered through Celite-545 and the aqueous phase was extracted with ethyl acetate (4 × 50 mL). The combined organic phase was collected and dried over Na_2SO_4 and concentrated under vacuum. The crude was purified by column chromatography on silica gel with a gradient of elution of pet ether and ethyl acetate to give the desired white amination product **3o** with 1.1 g, 60% yield.

Synthesis of Mefenamic Acid, Scheme 3. In a 15 mL sealed tube, the substrate **3o** (73.4 mg, 0.2 mmol) and KOH (448 mg, 40 equiv) were added, followed by ethanol (2 mL). Then, the tube was charged with a preheated oil bath at 110 °C for 18 h. After completion of reaction, the solvent was evaporated by vacuum and EtOAc (25 mL × 4) was added to extract. The organic phase was dried over Na_2SO_4 and purified by column chromatography on silica gel with a gradient elute of 7:3 hexane/ethyl acetate to give the directing group with 26 mg, yield 91%. Next, the water fraction was acidified with 1 N HCl to pH 3−4, and extracted with ethyl acetate. Next, the organic fraction was dried over Na_2SO_4 and purified by chromatography on silica gel with a gradient elute of 6:4 hexane/ethyl acetate to give Mefenamic acid with 43 mg, 90% yield.

2-((2,3-Dimethylphenyl)amino)benzoic Acid. Column chromatography (SiO_2, eluting with 6:4 hexane/ethyl acetate) afforded the desired product as a white solid (43 mg, 90%): mp 228−230 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.14 (s, 1H), 8.04 (dd, J = 8.4, 1.8 Hz, 1H), 7.31−7.29 (m, 1H), 7.18−7.13 (m, 2H), 7.07 (d, J = 7.2 Hz, 1H), 6.73−6.69 (m, 2H), 2.36 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.0, 150.3, 138.33, 138.28, 135.2, 132.9, 132.4, 127.2, 126.0, 123.7, 116.1, 113.7, 109.2, 20.6, 14.0; IR (neat) υ_{max} 3341, 3311, 2860, 1650, 1575, 1506, 1445, 1254; HRMS (EI, m/z) calcd. for $C_{15}H_{15}NO_2$ $[M]^+$ 241.1103, found 241.1097.

Control Experiments, Scheme 4. *Intermolecular Molecular Kinetic Isotopic effect, Scheme 4a.* In a 15 mL sealed tube, the compound **1** (24.8 mg, 0.1 mmol), d_5-**1** (25.3 mg, 0.1 mmol), $Cu(OAc)_2{\cdot}H_2O$ (79.7 mg, 0.4 mmol, 2 equiv), AgOAc (33.3 mg, 0.2 mmol, 1 equiv), ^{t}BuOLi (32 mg, 0.4 mmol, 2 equiv), TBAB (193.4 mg, 0.6 mmol, 3 equiv), and aniline (27 μL, 0.3 mmol, 1.5 equiv) were added, followed by DMSO (3 mL). The nitrogen gas was passed to the reaction mixture for 1 min. Then, the tube was charged with a preheated oil bath at 100 °C for 45 min. The reaction mixture was diluted with 10 mL of ethyl acetate and quenched with 20 mL of aq. ammonium solution. Then, it was filtered through Celite-545 and the aqueous phase was extracted with ethyl acetate (2 × 20 mL). The combined organic phase was washed with 20 mL of saturated sodium hydroxide solution and collected, dried over Na_2SO_4, and

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concentrated under vacuum. The crude was purified by column chromatography on silica gel with a gradient of elution of pet ether and ethyl acetate to give the desired amination product. The product was analyzed by ^{1}H NMR (300 MHz, $CDCl_3$).

Coordination Effect, Scheme 4b. In a 15 mL sealed tube, the *N*-methyl-*N*-(quinolin-8-yl)benzamide (26.3 mg, 0.1 mmol), $Cu(OAc)_2\cdot H_2O$ (40 mg, 0.2 mmol, 2 equiv), AgOAc (17 mg, 0.1 mmol, 1 equiv), ^{t}BuOLi (16 mg, 0.2 mmol, 2 equiv), TBAB (98 mg, 0.3 mmol, 3 equiv), and aniline (13.5 μL, 0.15 mmol, 1.5 equiv) were added, followed by DMSO (2 mL). The nitrogen gas was passed to the reaction mixture for 1 min. Then, the tube was charged with a preheated oil bath at 100 °C for 6 h. The reaction mixture was diluted with 10 mL of ethyl acetate and quenched with 20 mL of aq. ammonium solution. Then, it was filtered through Celite-545 and the aqueous phase was extracted with ethyl acetate (2 × 20 mL). The combined organic phase was washed with 20 mL of saturated sodium hydroxide solution and collected, dried over Na_2SO_4, and concentrated under vacuum. The crude was purified by column chromatography on silica gel with a gradient of elution of pet ether and ethyl acetate, and from ^{1}H NMR analysis, it was found that no reaction occurred and starting material was recovered.

Competition Reaction, Scheme 4c. In a 15 mL sealed tube, the *N*-(quinolin-8-yl)benzamide (24.8 mg, 0.1 mmol), $Cu(OAc)_2\cdot H_2O$ (40 mg, 0.2 mmol, 2 equiv), AgOAc (17 mg, 0.1 mmol, 1 equiv), ^{t}BuOLi (16 mg, 0.2 mmol, 2 equiv), TBAB (98 mg, 0.3 mmol, 3 equiv), 4-methoxyaniline (18.4 mg, 0.15 mmol, 1.5 equiv), and 4-nitroaniline (20.7 mg, 0.15 mmol, 1.5 equiv) were added, followed by DMSO (3 mL). The nitrogen gas was passed to the reaction mixture for 1 min. Then, the tube was charged with a preheated oil bath at 100 °C for 6 h. The reaction mixture was diluted with 10 mL of ethyl acetate and quenched with 20 mL of aq. ammonium solution. Then, it was filtered through Celite-545 and the aqueous phase was extracted with ethyl acetate (2 × 20 mL). The combined organic phase was washed with 20 mL of saturated sodium hydroxide solution and collected, dried over Na_2SO_4, and concentrated under vacuum. The crude was purified by column chromatography on silica gel with a gradient of elution of pet ether and ethyl acetate to give the desired amination products.

Catalyst Inhibition Experiment, Scheme 4d. In a 15 mL sealed tube, the *N*-(naphthalen-1-yl)-2-(*p*-tolylamino)benzamide (35.2 mg, 0.1 mmol), *N*-(quinolin-8-yl)benzamide (24.8 mg, 0.1 mmol), $Cu(OAc)_2\cdot H_2O$ (40 mg, 0.2 mmol, 2 equiv), AgOAc (17 mg, 0.1 mmol, 1 equiv), ^{t}BuOLi (16 mg, 0.2 mmol, 2 equiv), TBAB (98 mg, 0.3 mmol, 3 equiv), and 4-methoxyaniline (18.4 mg, 0.15 mmol, 1.5 equiv) were added, followed by DMSO (3 mL). The nitrogen gas was passed to the reaction mixture for 1 min. Then, the tube was charged with a preheated oil bath at 100 °C for 6 h. The reaction mixture was diluted with 10 mL of ethyl acetate and quenched with 20 mL of aq. ammonium solution. Then, it was filtered through Celite-545 and the aqueous phase was extracted with ethyl acetate (2 × 20 mL). The combined organic phase was washed with 20 mL of saturated sodium hydroxide solution and collected, dried over Na_2SO_4, and concentrated under vacuum. The crude was purified by column chromatography on silica gel with a gradient of elution of pet ether and ethyl acetate to give the desired amination product 6 mg, 15% yield.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00659.

^{1}H, ^{13}C NMR, and kinetic isotope study ^{1}H NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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