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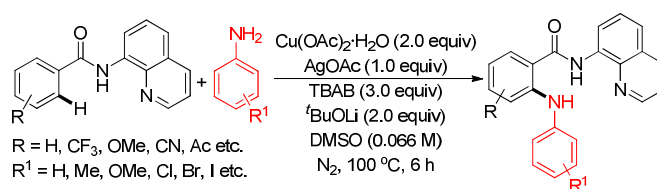
Copper(II)-mediated Intermolecular C(sp²)-H Amination of Benzamides with Electron-rich Anilines

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ABSTRACT: Despite significant progress, copper-catalyzed/mediated C-H amination reactions with electron-rich anilines remains an unsolved problem due to catalyst deactivation and deleterious side reactions. Herein we report, a copper(II)-mediated C(sp²)-H amination of benzamides with electronically neutral or electron-rich anilines. A dramatic influence of silver(I) and tetrabutylammonium bromide (TBAB), was observed on the reaction outcome. The present protocol also demonstrates the synthesis of a number of non-steroidal anti-inflammatory drugs (NSAID's).

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 through a palladium- or copper-catalyzed Goldberg cross-coupling between aryl halides and amines.² In recent years, 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, Rh catalysis have been explored with amines⁴ 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 copper¹¹ is emerging. A seminal report on copper-mediated sp^2 C-H amidation using non-removable 2-pyridine moiety was disclosed by the Yu group.¹² Subsequently, they accomplished a bidentate auxiliary-directed $\text{C}(\text{sp}^2)$ -H amination with electron-poor anilines.¹³ The Daugulis group also reported a 8-aminoquinoline-directed $\text{Cu}(\text{II})/\text{Ag}(\text{I})$ catalyzed $\text{C}(\text{sp}^2)$ -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-catalyzed¹⁶ 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

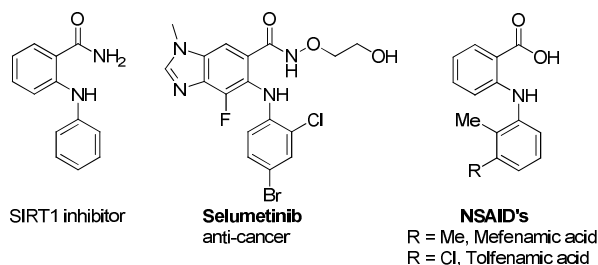
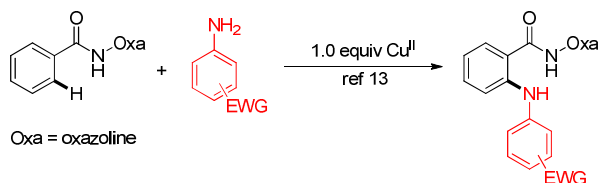
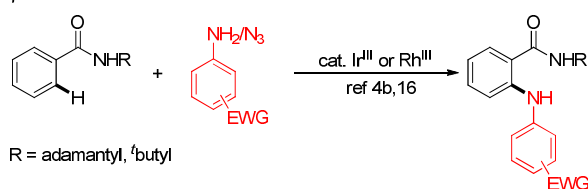


Figure 1. Biologically-active diarylamines

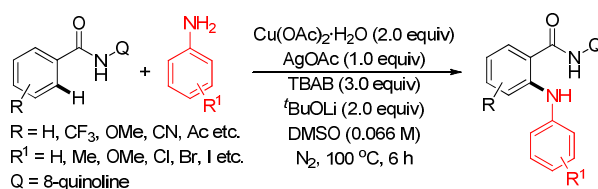
Very recently, the Daugulis group reported an examples of copper-mediated C-H amination with 2,4,6-trimethylaniline.¹⁷ However, other electron-rich anilines such as 4-methoxy aniline etc. are not stable under this condition, which clearly demonstrates the challenges associated with this transformation. Therefore, development of a general $\text{C}(\text{sp}^2)$ -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).

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

previous works



this work

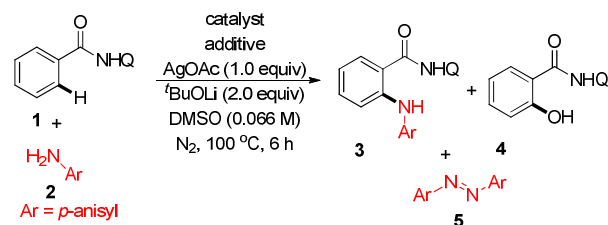


RESULTS AND DISCUSSION

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, changing the base from sodiumcarbonate to lithium *tert*-butoxide and purging the reaction vessel 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 nitrogen atmosphere (entry 1, Table 1). Remarkably, the hydroxylation and azoarene formation was suppressed substantially with the addition of tetrabutylammonium bromide (TBAB) (entry 2, Table 1). Increasing the amount of TBAB (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 a rapid precipitation of silver(I)bromide. To test this the reaction was performed with 3.0 equiv 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 (entry 14 and 15, Table 1).

TBAB may involve 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 control experiment it was confirmed that 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 case of electron-deficient anilines, oxygen promotes amination reaction and no external oxidant is required. However, in 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 nitrogen atmosphere with 1.0 equiv of silver(I) acetate.

Table 1. Optimization of the Reaction Conditions^a



entry	catalyst	additive	yield (%) of 3 ^b	3:4:5 ^c
1	Cu(OAc) ₂ ·H ₂ O (1 equiv)	-	30	15:0:23
2	Cu(OAc) ₂ ·H ₂ O (1 equiv)	TBAB (1 equiv)	42	21:4:8
3	Cu(OAc) ₂ ·H ₂ O (1 equiv)	TBAF (1 equiv)	15	15:0:0
4	Cu(OAc) ₂ ·H ₂ O (1 equiv)	TBACl (1 equiv)	16	16:0:0
5	Cu(OAc) ₂ ·H ₂ O	TBAI	18	9:0:10

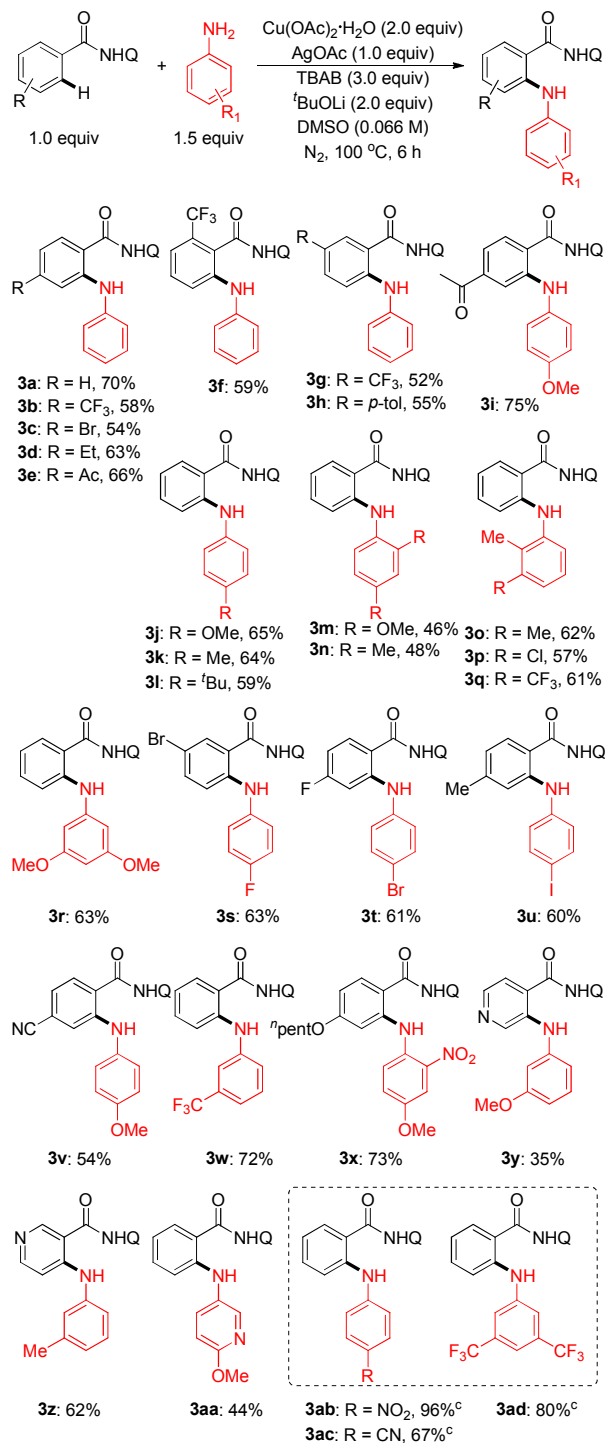
	(1 equiv)	(1 equiv)		
6	Cu(OAc) ₂ .H ₂ O	K ₂ S ₂ O ₈	5	5:0:12
	(1 equiv)	(1 equiv)		
7	CuBr ₂ (1 equiv)	TBAB	0	-
		(1 equiv)		
8	CuCl ₂ (1 equiv)	TBAB	0	-
		(1 equiv)		
9	CuSO ₄ .5H ₂ O	TBAB	0	-
	(1 equiv)	(1 equiv)		
10	Cu(OAc) ₂ .H ₂ O	TBAB	51	51:0:0
	(1 equiv)	(3 equiv)		
11	Cu(OAc)₂.H₂O	TBAB	65(80)^d	65:0:0
	(2 equiv)	(3 equiv)		
12	-	TBAB	0	-
		(3 equiv)		
13 ^e	Cu(OAc) ₂ .H ₂ O	TBAB	10	10:0:0
	(3 equiv)	(3 equiv)		
14	Cu(OAc) ₂ .H ₂ O	TBA(OAc)	52	13:0:3
	(2 equiv)	(3 equiv)		
15 ^f	Cu(OAc) ₂ .H ₂ O	TBA(OAc)	22	11:0:8
	(2 equiv)	(3 equiv)		

^aAll reactions were carried out in 0.1 mmol scale. ^bYields refer to here are isolated yields. ^cproduct distribution was measured by ¹H NMR. ^dyield in the parenthesis is based on the starting material recovery. ^ePurged with O₂ instead of N₂. ^fwithout 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, cyano groups remained intact under these reaction conditions. More interestingly, an acetyl group containing benzamide afforded the corresponding 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 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 non-steroidal anti-inflammatory drug (NSAID's) such as mefenamic acid, **3o**, tolfenamic acid, **3p**, flufenamic acid, **3w** were synthesized in

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2
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4 good to high yields. Heteroaromatic benzamide and aniline also provided C-H amination product in
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6 moderate to good yields (**3y-3aa**, Scheme 2). Most of the cases with electron-rich anilines the unreacted
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8 benzamides were isolated. It was not consumed completely even after the addition of anilines in excess.
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10 Prolonged heating also did not improve the yield rather product decomposition was observed. As
11
12 discussed earlier, contrary to the electron-rich anilines electron-deficient anilines such as *p*-nitro, *p*-
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14 cyano, or 3,5-ditrifluoromethyl anilines provided the corresponding amination products in excellent
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16 yields using oxygen as terminal oxidant (**3ab-3ad**, Scheme 2).
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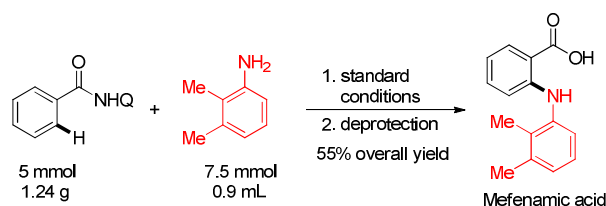
19 **Scheme 2. Substrate Scope^{a,b}**
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^aAll reactions were carried out in 0.2 mmol scale. ^bYields refer to the average of isolated yields of at least two experiments. ^cReaction conditions: 0.2 mmol $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$, 0.4 mmol $t\text{BuOLi}$, O_2 , 110°C , 3 h.

Substituted diarylamines are useful synthetic precursor 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 a various biologically active compounds such as SIRT1 inhibitor, MEK inhibitor, non-steroidal anti-inflammatory drugs (NSAID's) 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 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

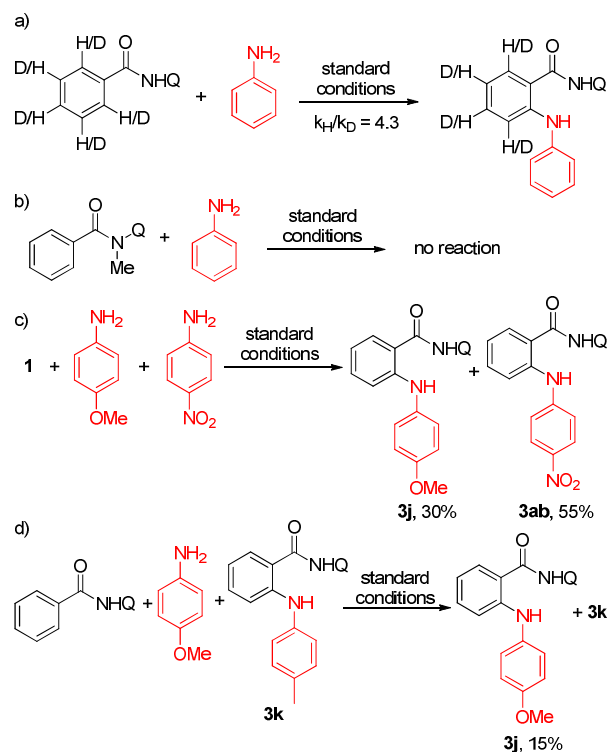


INVESTIGATION OF THE RECTION MECHANISM

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 amount 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 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 also explains the requirement of stoichiometric copper salt for the present transformation. These control experiments suggest that Cu^{II} complex may undergo a chelation-assisted C-H insertion to generate aryl- Cu^{III} species²² which reacts with *N*-nucleophiles to provide the amination products.²³

Scheme 4. Control Experiments



CONCLUSION

In conclusion, we have developed a copper(II)-mediated $\text{C}(\text{sp}^2)\text{-H}$ 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 non-steroidal anti-inflammatory drugs (NSAID's).

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 KMnO₄ stain. ¹H and ¹³C NMR spectra were recorded in CDCl₃ 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.H₂O (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) was added followed by DMSO (3 mL). The nitrogen gas was passed to the reaction mixture for 1 minute. Then, the tube was charged with preheated oil bath at 100 °C for 6 h. The reaction mixture was diluted with 10 mL ethyl acetate and quenched with 20 ml aq. ammonium solution. Then, it was filtered through celite-545 and aqueous phase was extracted with ethyl acetate (2x20). The combined organic phase was washed with 20 mL saturated sodium hydroxide solution and collected, dried over Na₂SO₄ and concentrated under vacuum. The crude was purified by column chromatography on silica gel with 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 (SiO₂, 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, CDCl₃) 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) ν_{max} 3345, 2923, 1644, 1583, 1520, 1261; HRMS (ESI, m/z) calcd for $\text{C}_{22}\text{H}_{18}\text{N}_3\text{O}$ $[\text{M} + \text{H}]^+$ 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) ν_{max} 3351, 3046, 1655, 1589, 1536, 1428, 1335, 1175, 1119; HRMS (EI, m/z) calcd for $\text{C}_{23}\text{H}_{16}\text{F}_3\text{N}_3\text{O}$ $[\text{M}]^+$ 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, $J = 7.8, 1\text{H}$), 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) ν_{max} 3445, 3356, 2924, 2854, 1648, 1586, 1530, 1413; HRMS (ESI, m/z) calcd for $\text{C}_{22}\text{H}_{16}\text{BrN}_3\text{O}$ $[\text{M} + \text{Na}]^+$ 440.0374, found 440.0377.

4-Ethyl-2-(phenylamino)-*N*-(quinolin-8-yl)benzamide, 3d, Scheme 2

Column chromatography (SiO₂, 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, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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) ν_{max} 3351, 3046, 2963, 2926, 1727, 1650, 1528, 1262; HRMS (ESI, *m/z*) calcd for C₂₄H₂₁N₃ONa [M + Na]⁺ 390.1582, found 390.1562.

4-Acetyl-2-(phenylamino)-*N*-(quinolin-8-yl)benzamide, 3e, Scheme 2

Column chromatography (SiO₂, 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, CDCl₃) 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* = 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); ¹³C NMR (150 MHz, CDCl₃) 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) ν_{max} 3357, 2923, 1688, 1652, 1527, 1381, 1307; HRMS (ESI, *m/z*) calcd for C₂₄H₁₉N₃O₂Na [M + Na]⁺ 404.1375, found 404.1371.

2-(Phenylamino)-*N*-(quinolin-8-yl)-6-(trifluoromethyl)benzamide, 3f, Scheme 2

Column chromatography (SiO₂, eluting with 8:2 hexane/ethyl acetate) afforded the desired product as a white solid (48 mg, 59%): mp 169 – 171 °C; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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) ν_{\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 (SiO₂, eluting with 8:2 hexane/ethyl acetate) afforded the desired product as a yellow solid (42 mg, 52 %): mp 171 – 172 °C; ¹H NMR (600 MHz, CDCl₃) 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); ¹³C NMR (150 MHz, CDCl₃) 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) ν_{\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 (SiO₂, eluting with 8:2 hexane/ethyl acetate) afforded the desired product as a yellow solid (47 mg, 55 %): mp 286 – 288 °C; ¹H NMR (600 MHz, CDCl₃) 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); ¹³C NMR (150 MHz, CDCl₃) 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) ν_{\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 (SiO₂, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a yellow solid (62 mg, 75 %): mp 138 – 140 °C; ¹H NMR (300 MHz, CDCl₃) 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) ν_{max} 3345, 2924, 2853, 1685, 1653, 1517, 1242; ; HRMS (ESI, m/z) calcd for $\text{C}_{25}\text{H}_{21}\text{N}_3\text{O}_3\text{Na}$ $[\text{M} + \text{Na}]^+$ 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 $^\circ\text{C}$; ^1H 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) ν_{max} 3348, 2923, 1648, 1580, 1515, 1242; HRMS (ESI, m/z) calcd for $\text{C}_{23}\text{H}_{19}\text{N}_3\text{O}_2\text{Na}$ $[\text{M} + \text{Na}]^+$ 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 $^\circ\text{C}$; ^1H 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) ν_{max} 3350, 3025, 2923, 2859, 1726, 1650, 1519, 1262; HRMS (ESI, m/z) calcd for $\text{C}_{23}\text{H}_{19}\text{N}_3\text{ONa}$ $[\text{M} + \text{Na}]^+$ 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 orange solid (47 mg, 59 %): mp 280 – 284 $^\circ\text{C}$; ^1H 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) ν_{max} 3351, 2959, 2926, 1651, 1590, 1520, 1324; HRMS (EI, m/z) calcd for $\text{C}_{26}\text{H}_{25}\text{N}_3\text{O}$ $[\text{M}]^+$ 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; ^1H 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) ν_{max} 3337, 3313, 2949, 2830, 1643, 1540, 1511, 1211, 1159; HRMS (ESI, m/z) calcd for $\text{C}_{24}\text{H}_{22}\text{N}_3\text{O}_3$ $[\text{M} + \text{H}]^+$ 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; ^1H 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) ν_{\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 (SiO₂, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a white solid (46 mg, 62 %): mp 139 – 141 °C; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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) ν_{\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 (SiO₂, 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, CDCl₃) 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, 1H), 6.94-6.91 (m, 1H), 2.43 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) 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) ν_{\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 (SiO₂, 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, CDCl₃) 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) ν_{max} 3432, 3352, 2923, 1652, 1583, 1325; HRMS (EI, m/z) calcd for $\text{C}_{24}\text{H}_{18}\text{F}_3\text{N}_3\text{O}$ $[\text{M}]^+$ 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) ν_{max} 3347, 2928, 1650, 1597, 1521, 1155; HRMS (ESI, m/z) calcd for $\text{C}_{24}\text{H}_{22}\text{N}_3\text{O}_3$ $[\text{M} + \text{H}]^+$ 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) ν_{max} 3443, 3343, 2923, 1653, 1541, 1511, 1390, 1206; HRMS (ESI, m/z) calcd for $\text{C}_{22}\text{H}_{16}\text{N}_3\text{BrFO}$ $[\text{M} + \text{H}]^+$ 436.0461, found 436.0476.

2-((4-Bromophenyl)amino)-4-fluoro-*N*-(quinolin-8-yl)benzamide, 3t, Scheme 2

Column chromatography (SiO₂, 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, CDCl₃): 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); ¹³C NMR (75 MHz, CDCl₃): 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) ν_{\max} 3350, 3310, 1649, 1592, 1534, 1486; HRMS (ESI, *m/z*) calcd for C₂₂H₁₅N₃BrFONa [M + Na]⁺ 458.0280, found 458.0271.

2-((4-Iodophenyl)amino)-4-methyl-*N*-(quinolin-8-yl)benzamide, 3u, Scheme 2

Column chromatography (SiO₂, 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, CDCl₃) 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); ¹³C NMR (150 MHz, CDCl₃) 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) ν_{\max} 3449, 3334, 1646, 1526, 1482, 1256; HRMS (ESI, *m/z*) calcd for C₂₃H₁₈N₃IONa [M + Na]⁺ 502.0392, found 502.0369.

4-Cyano-2-((4-methoxyphenyl)amino)-*N*-(quinolin-8-yl)benzamide, 3v, Scheme 2

Column chromatography (SiO₂, 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, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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) ν_{\max} 3420, 3320, 2910, 2229, 1659; HRMS (ESI, m/z) calcd for $\text{C}_{24}\text{H}_{18}\text{N}_4\text{O}_2\text{Na}$ $[\text{M} + \text{Na}]^+$ 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) ν_{\max} 3356, 3219, 1659, 1595, 1532, 1333; HRMS (EI, m/z) calcd for $\text{C}_{23}\text{H}_{16}\text{F}_3\text{N}_3\text{O}$ $[\text{M}]^+$ 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) ν_{\max} 3350, 2928, 2859, 1655, 1514, 1254, 1148; HRMS (ESI, m/z) calcd for $\text{C}_{28}\text{H}_{29}\text{N}_4\text{O}_5$ $[\text{M} + \text{H}]^+$ 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), 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) ν_{max} 3367, 3344, 2921, 2852, 1669, 1598, 1562, 1534, 1025; HRMS (ESI, m/z) calcd for $\text{C}_{22}\text{H}_{18}\text{N}_4\text{O}_2\text{Na}$ $[\text{M} + \text{Na}]^+$ 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; ^1H 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) ν_{max} 3370, 3353, 3045, 1648, 1603, 1535, 1326, 1195; HRMS (ESI, m/z) calcd for $\text{C}_{22}\text{H}_{19}\text{N}_4\text{O}$ $[\text{M} + \text{H}]^+$ 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; ^1H 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) ν_{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), $tBuOLi$ (32 mg, 0.4 mmol, 2 equiv), and anilines 2 (0.3 mmol, 1.5 equiv) was added followed by DMSO (3 mL). The oxygen gas was passed to the reaction mixture for 1 minute. Then, the tube was charged with preheated oil bath at 100 °C for 3 h. The reaction mixture was diluted with 10 mL ethyl acetate and quenched with 20 mL aq. ammonium solution. Then, it was filtered through celite-545 and aqueous phase was extracted with ethyl acetate (2x20). 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 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; 1H 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) ν_{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; 1H 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) ν_{max} 3357, 2214, 1653, 1587, 1514, 1326, 1171; HRMS (EI, m/z) calcd. for $\text{C}_{23}\text{H}_{16}\text{N}_4\text{O}$ $[\text{M}]^+$ 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; ^1H 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) ν_{max} 3351, 3205, 1648, 1530, 1387, 1279; HRMS (EI, m/z) calcd. for $\text{C}_{24}\text{H}_{15}\text{F}_6\text{N}_3\text{O}$ $[\text{M}]^+$ 475.1119, found 475.1121.

Gram-Scale Synthesis of Compound 3o

The compound *N*-(quinolin-8-yl)benzamide (1.24 gm, 5 mmol) was taken in an oven dried two way 250 mL round bottom flask which was connected through condenser under N_2 ballon and dissolved with 60 mL DMSO, then it was degassed two times followed by $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (1.99 gm, 10 mmol, 2 equiv), AgOAc (0.83 gm, 5 mmol, 1 equiv), TBAB (4.83 gm, 15 mmol, 3 equiv), LiO^tBu (.80 gm, 10 mmol, 2 equiv), and 2,3-dimethylaniline (0.9 ml, 7.5 mmol, 1.5 equiv) was 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 ethyl acetate and quenched with 200 mL aq. ammonium solution. Then, it was filtered through celite-545 and aqueous phase was extracted with ethyl acetate (4x50). 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 gradient of elution of pet ether and ethyl acetate to give the desired white amination product **3o** with 1.1 gm 60% yield.

Synthesis of Mefenamic Acid, Scheme 3

In a 15 mL sealed tube, the substrate 3o (73.4 mg, 0.2 mmol), KOH (448 mg, 40 equiv) was added followed by ethanol (2 mL). Then, the tube was charged with preheated oil bath at 110 °C for 18 h. After completion of reaction, the solvent was evaporated by vacuum and added EtOAc (25 mL x 4) to extract. The organic phased was dried over Na₂SO₄ 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 1N HCl to PH 3-4, and extracted with ethyl acetate followed by organic fraction was dried over Na₂SO₄ 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 (SiO₂, eluting with 6:4 hexane/ethyl acetate) afforded the desired product as a white solid (43 mg, 90 %): mp 228 – 230 °C; ¹H NMR (600 MHz, CDCl₃) 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); ¹³C NMR (150 MHz, CDCl₃) 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) ν_{max} 3341, 3311, 2860, 1650, 1575, 1506, 1445, 1254; HRMS (EI, *m/z*) calcd. for C₁₅H₁₅NO₂ [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 (24.8mg, 0.1 mmol), d₅-1 (25.3 mg, 0.1 mmol) Cu(OAc)₂·H₂O (79.7 mg, 0.4 mmol, 2 equiv), AgOAc (33.3 mg, 0.2 mmol, 1 equiv), ^tBuOLi (32 mg, 0.4 mmol, 2 equiv), TBAB (193.4 mg, 0.6 mmol, 3 equiv) and aniline (27μL, 0.3 mmol, 1.5 equiv) was added followed by DMSO (3 mL). The nitrogen gas was passed to the reaction mixture for 1 minute. Then, the tube was charged with preheated oil bath at 100 °C for 45 minutes. The reaction mixture was diluted with 10 mL ethyl acetate and quenched with 20 ml aq. ammonium solution. Then, it was filtered

through celite-545 and aqueous phase was extracted with ethyl acetate (2x20). The combined organic phase was washed with 20 mL saturated sodium hydroxide solution and collected, dried over Na₂SO₄ and concentrated under vacuum. The crude was purified by column chromatography on silica gel with gradient of elution of pet ether and ethyl acetate to give the desired amination product, The product was analyzed by ¹H NMR (300 MHz, CDCl₃).

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·H₂O (40 mg, 0.2 mmol, 2 equiv), AgOAc (17 mg, 0.1 mmol, 1 equiv), ^tBuOLi (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) was added followed by DMSO (2 mL). The nitrogen gas was passed to the reaction mixture for 1 minute. Then, the tube was charged with preheated oil bath at 100 °C for 6 h. The reaction mixture was diluted with 10 mL ethyl acetate and quenched with 20 ml aq. ammonium solution. Then, it was filtered through celite-545 and aqueous phase was extracted with ethyl acetate (2x20). The combined organic phase was washed with 20 mL saturated sodium hydroxide solution and collected, dried over Na₂SO₄ and concentrated under vacuum. The crude was purified by column chromatography on silica gel with gradient of elution of pet ether and ethyl acetate and from ¹H 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·H₂O (40 mg, 0.2 mmol, 2 equiv), AgOAc (17 mg, 0.1 mmol, 1 equiv), ^tBuOLi (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), 4-nitroaniline (20.7 mg, 0.15 mmol, 1.5 equiv) was added followed by DMSO (3 mL). The nitrogen gas was passed to the reaction mixture for 1 minute. Then, the tube was charged with preheated oil bath at 100 °C for 6 h. The reaction mixture was diluted with 10 mL ethyl acetate and quenched with 20 ml aq. ammonium

solution. Then, it was filtered through celite-545 and aqueous phase was extracted with ethyl acetate (2x20). The combined organic phase was washed with 20 mL saturated sodium hydroxide solution and collected, dried over Na₂SO₄ and concentrated under vacuum. The crude was purified by column chromatography on silica gel with 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·H₂O (40 mg, 0.2 mmol, 2 equiv), AgOAc (17 mg, 0.1 mmol, 1 equiv), ^tBuOLi (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), was added followed by DMSO (3 mL). The nitrogen gas was passed to the reaction mixture for 1 minute. Then, the tube was charged with preheated oil bath at 100 °C for 6 h. The reaction mixture was diluted with 10 mL ethyl acetate and quenched with 20 ml aq. ammonium solution. Then, it was filtered through celite-545 and aqueous phase was extracted with ethyl acetate (2x20). The combined organic phase was washed with 20 mL saturated sodium hydroxide solution and collected, dried over Na₂SO₄ and concentrated under vacuum. The crude was purified by column chromatography on silica gel with gradient of elution of pet ether and ethyl acetate to give the desired amination product 6 mg, 15% yield.

ASSOCIATED CONTENT

Supporting Information

¹H, ¹³C NMR, and kinetic isotope study ¹H NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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REFERENCES

- (1) (a) Ricci, A. *Amino Group Chemistry: From Synthesis to the Life Sciences*; Wiley-VCH: Weinheim, Germany, 2008. (b) Lawrence, S. A. *Amines: Synthesis Properties and Applications*; Cambridge University Press, Cambridge, UK, 2004.
- (2) (a) Okano, K.; Tokuyama, H.; Fukuyama, T. *Chem. Commun.* **2014**, 50, 13650-13663. (b) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, 47, 6338-6361. (c) Hartwig, J. F. *Acc. Chem. Res.* **2008**, 41, 1534-1544.
- (3) For recent reviews, see: (a) Kim, H.; Chang, S. *ACS Catal.* **2016**, 6, 2341-2351. (b) Jiao J.; Murakami, K.; Itami, K. *ACS Catal.* **2016**, 6, 610-633. (c) Louillat, M.-L.; Patureau, F. W. *Chem. Soc. Rev.* **2014**, 43, 901-910. (d) Armstrong, A.; Collins, J. C. *Angew. Chem. Int. Ed.* **2010**, 49, 2282-2285.
- (4) For selective examples, see: (a) Zhu, D.; Yang, G.; He, J.; Chu, L.; Chen, G.; Gong, W.; Chen, K.; Eastgate, M. D.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2015**, 54, 2497-2500. (b) Kim, H.; Shin, K.; Chang, S. *J. Am. Chem. Soc.* **2014**, 136, 5904-5907. (c) Allen, L. J.; Cabrera, P. J.; Lee, M.; Sanford, M. S. *J. Am. Chem. Soc.* **2014**, 136, 5607-5610. (d) Shin, K.; Baek, Y. Chang, S. *Angew. Chem. Int. Ed.* **2013**, 52, 8031-8036. (e) Grohmann, C.; Wang, H.; Glorius, F. *Org. Lett.* **2012**, 14, 656-659.
- (5) For reviews, see: (a) Shin, K.; Kim, H.; Chang, S. *Acc. Chem. Res.* **2015**, 48, 1040-1052. (b) Intrieri, D.; Zardi, P.; Caselli, A.; Gallo, E. *Chem. Commun.* **2014**, 50, 11440-11453. For selective examples, see: (c) Park, S. H.; Kwak, J.; Shin, K.; Ryu, J.; Park, Y.; Chang, S. *J. Am. Chem. Soc.* **2014**, 136, 2492-2502. (d) Kim, J.; Chang, S. *Angew. Chem. Int. Ed.* **2014**, 53, 2203-2207. (e) Ryu, J.; Kwak, J.; Shin, K.; Lee, D.; Chang, S. *J. Am. Chem. Soc.* **2013**, 135, 12861-12868. (f) Lee, D.; Kim, Y.; Chang, S. *J. Org. Chem.* **2013**, 78, 11102-11109. (g) Thirunavukkarasu, V. S.; Raghuvanshi, K.; Ackermann, L.

- Org. Lett.* **2013**, *15*, 3286-3289. (h) Stokes, B. J.; Dong, H.; Leslie, B. E.; Pumphrey, A. L. Driver, T. G. *J. Am. Chem. Soc.* **2007**, *129*, 7500-7501.
- (6) Davies, D. L.; Al-Duaij, O.; Giardiello, M.; Hilton, S. T.; Russel, D. R. *Dalton. Trans.* **2003**, 4132-4138.
- (7) Kim, J.; Cho, S. H.; Joseph, J.; Chang, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 9899-9903.
- (8) (a) Alt, I. T.; Plietker, B. *Angew. Chem. Int. Ed.* **2016**, *55*, 1519-1522. (b) Matsubara, T.; Asako, S.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2014**, *136*, 646-649. (c) Liu, Y.; Guan, X.; Wong, E. L.-M.; Liu, P.; Huang, J.-S.; Che, C.-M. *J. Am. Chem. Soc.* **2013**, *135*, 7194-7204. (d) Nguyen, Q.; Nguyen, T.; Driver, T. G. *J. Am. Chem. Soc.* **2013**, *135*, 620-623. (e) Hennessy, E. T.; Betley, T. A. *Science*, **2013**, *340*, 591-595.
- (9) Zhang, L.-B.; Zhang, S.-K.; Wei, D.; Zhu, X.; Hao, X.-Q. Su, J.-H. Niu, J.-L.; Song, M.-P. *Org. Lett.* **2016**, *18*, 1318-1321.
- (10) Yan, Q.; Chen, Z.; Yu, W.; Yin, H.; Liu, Z.; Zhang, Y. *Org. Lett.* **2015**, *17*, 2482-2485.
- (11) (a) Sokolovs, I.; Lubriks, D.; Suna, E. *J. Am. Chem. Soc.* **2014**, *136*, 6920-6928. (b) Kawano, T.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2010**, *132*, 6900-6901. (c) Zhao, H.; Wang, M.; Su, W.; Hong, M. *Adv. Synth. Catal.* **2010**, *352*, 1301-1306. (d) Monguchi, D.; Fujiwara, T.; Furukawa, H.; Mori, A. *Org. Lett.* **2009**, *11*, 1607-1610. (e) Wang, Q.; Schreiber, S. L. *Org. Lett.* **2009**, *11*, 5178-5180.
- (12) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790-6791.
- (13) Shang, M.; Sun, S.-Z.; Dai, H.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 3354-3357.
- (14) Tran, D. L.; Roane, J.; Daugulis, O. *Angew. Chem. Int. Ed.* **2013**, *52*, 6043-6046.
- (15) Uemura, T.; Imoto, S.; Chatani, N. *Chem. Lett.* **2006**, *35*, 842-843.
- (16) Ryu, J.; Shin, K.; Park, S. H.; Kim, J. Y.; Chang, S. *Angew. Chem. Int. Ed.* **2012**, *51*, 9904-9908.
- (17) Roane, J.; Daugulis, O. *J. Am. Chem. Soc.* **2016**, *138*, 4601-4607.
- (18) Singh, B. K.; Jana, R. *J. Org. Chem.* **2016**, *81*, 831-841.
- (19) Zhang, C.; Jiao, N. *Angew. Chem. Int. Ed.* **2010**, *49*, 6174-6177.

- (20) For reviews, see: (a) Schmidt, A. W.; Reddy, K. R.; Knölker, H.-J. *Chem. Rev.* **2012**, *112*, 3193-3328. For selective examples, see: (b) Liégault, B.; Lee, D.; Huestis, M. P.; Stuart, D. R.; Fagnou, K. *J. Org. Chem.* **2008**, *73*, 5022-5028. (c) Koshima, H.; Kutsunai, K. *Heterocycles* **2002**, *57*, 1299-1302. (d) Moloney, G. P.; Kelly, D. P.; Mack, P. *Molecules* **2001**, *6*, 230-243.
- (21) (a) Rice, K. D.; Aay, N.; Anand, N. K.; Blazey, C. M.; Bowles, O. J.; Bussenius, J.; Costanzo, S.; Curtis, J. K.; Defina, S. C.; Dubenko, L.; Engst, S.; Joshi, A. A.; Kennedy, A. R.; Kim, A. I.; Koltun, E. S.; Loughheed, J. C.; Manalo, J.-C. L.; Martini, J.-F.; Nuss, J. M.; Peto, C. J.; Tsang, T. H.; Yu, P.; Johnston, S. *ACS Med. Chem. Lett.* **2012**, *3*, 416-421. (b) Suzuki, T.; Imai, K.; Imai, E.; Iida, S.; Ueda, R.; Tsumoto, H.; Nakagawa, H.; Miyata, N. *Bioorg. Med. Chem.* **2009**, *17*, 5900-5905. (c) Suzuki, T.; Imai, K.; Nakagawa, H.; Miyata, N. *ChemMedChem* **2006**, *1*, 1059-1062.
- (22) Ribas, X.; Jackson, D. A.; Donnadieu, B.; Mahía, J.; Parella, T.; Xifra, R.; Hedman, B.; Hodgson, K. O.; Llobet, A.; Stack, T. D. P. *Angew. Chem. Int. Ed.* **2002**, *41*, 2991-2994.
- (23) (a) King, A. E.; Huffman, L. M.; Casitas, A.; Costas, M.; Ribas, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2010**, *132*, 12068-12073. (b) Huffman, L. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 9196-9197.