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# Copper-Catalyzed Electrochemical Selective Bromination Of 8-Aminoquinoline Amide Using $NH_4Br$ as the Brominating Reagent

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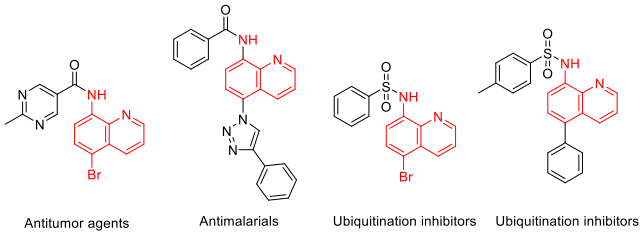
*Supporting Information Placeholder*

**ABSTRACT:** A simple and mild protocol for copper-catalyzed bromination of quinoline at C5 site of quinoline by anodic oxidation was developed, affording the desired remote C–H activation products with isolated yields of up to about 90%. The reaction proceeds with low-cost $NH_4Br$ and shows a mild and green conditions (electricity as green oxidant; $NH_3$ and $H_2$ as byproducts). At the same time, a gram-scale bromination reaction was also successfully fulfilled, showing its potential applicable value in organic synthesis. Moreover the CV chart further demonstrated the proposed catalytic cycle.

## Introduction

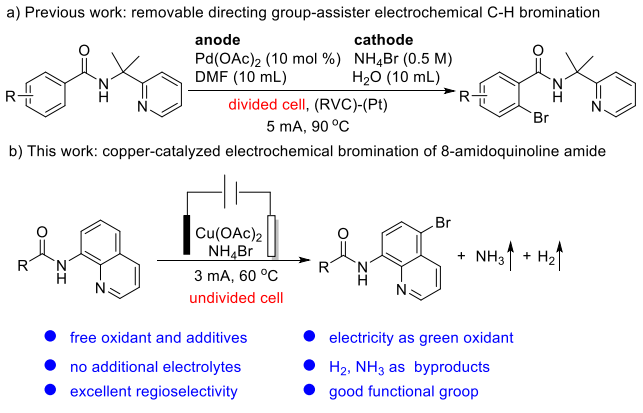
Aromatic and heterocyclic aromatic halids are an important intermediate of natural products, medicine, dyestuff, agrochemicals and pharmaceuticals.[1] Meanwhile, they were synthesized via electrophlic aromatic substitution,[2] directed ortho lithiation[3] or Sandmeyer reaction.[4] Although the above-mentioned traditional ways are widely used in organic chemistry, there are still many limitions, including harsh reaction conditions, poor functional group toluence and metal salts as byproduct etc. Therefore it is of great scientific significance to develop effective and universal strategies for the synthesis of aromatic chlorides.

**Scheme 1. Structures of Some Biologically Active Compounds Containing Quinoline Motifs**




The quinoline and motified quinoline have attracted considerable attentions during the past few years due their biological and pharmacological activities,[5] which exist in natural products and marketed drugs[6] (**Scheme 1**). In the past few years, Stahl, Zhang, Huang, etc reported C5 chlorination of 8-aminoquinoline that is geomatically difficulted to afford[7]. However, there are some limitions and drawbacks. For example, (i) most of reactions need expensive and toxic stoichiometric oxidant such as $PhI(OAc)_2$, $K_2S_2O_8$, Oxone, etc. (ii) Some of reactions also use additives, such as PivOH, $NH_2SO_3H$, $NaHCO_3$ and $CH_3(CH_2)_5COOH$. (iii) There was usage of halide salts (LiX, NaX, KCl) or stoichiometric CuX as halogenation reagents which generated metal salts as byproduct. (iv) Some of reactions require higher temperature and inert atmosphere to progress. Accordingly, we still explore an inexpensive and atom economical synthetic manners which is in line with the green chemistry.

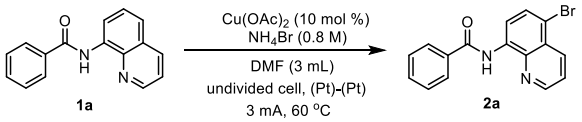
**Scheme 2. Catalytic Bromination of 8-Aminoquinoline Amide**




The past decade has witnessed a renaissane in electrochemical organic synthesis and the study on electro-synthesis has become one of the fascinating fields recently.[8] The rise of electrochemical synthesis has become a promising alternative to traditional chemical oxidants because it uses electrons

which are safety, green, enviroment amity of reagents as oxidant or reductant more importantly. Meanwhile, we can change the electricity and potential to control reaction rate and chemoselectivity. In recent years, electronchemical bromination of arenes has been developed. For example, Thasan, Fachigami and Lei, etc reported electrochemical bromination of aromatic compounds.[9] In 2018, our group reported copper-catalyzed electrochemical C−H amination of arenes with secondary amines which proceeded via a single-electron-transfer (SET) process.[10] Later, we described palladium-catalyzed electrochemical C−H bromination with divided cell[11] (**Scheme 2a**), but the reaction device was complex and the reaction temperature was higher. So we assumed if we could realize the copper-catalyzed regioselective bromination of 8-amidquinoline amide under anodic oxidation using $NH_4Br$ as the brominating source with undivided cell (**Scheme 2b**).

**Table 1. Reaction Optimization with Substrate 1a**[a]




**1a** **2a**

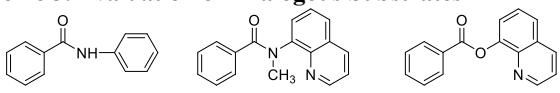
| entry | variation from standard conditions above | yield (%)[b] |
|---|---|---|
| 1 | none | 99 (94)[c] |
| 2 | no $Cu(OAc)_2$ | 10 |
| 3 | CuI instead of $Cu(OAc)_2$ | 32 |
| 4 | $Cu(OTf)_2$ instead of $Cu(OAc)_2$ | 88 |
| 5 | $NH_4Br$ (10 equiv) instead of $NH_4Br$ (12 equiv) | 85 |
| 6 | $NH_4Br$ (14 equiv) instead of $NH_4Br$ (12 equiv) | 88 |
| 7 | DMSO instead of DMF | 73 |
| 8 | $H_2O$ instead of DMF | 42 |
| 9 | LiBr instead of $NH_4Br$ | 83 |
| 10 | *n*-$Bu_4NBr$ instead of $NH_4Br$ | nr |
| 11 | 40 °C instead of 60 °C | 60 |
| 12 | 6 mA instead of 3 mA (12 h) | 87 |
| 13 | C anode instead of Pt anode | 80 |
| 14 | no electric current | nr |

[a]Reaction conditions: **1a** (0.20 mmol), $Cu(OAc)_2$ (10 mol %), DMF (3 mL) $NH_4Br$ (0.8 M) in undivided cell with two platinum eletrodes (1.0×1.0 $cm^2$), 3 mA, 60 °C, 30 h (16.8 F/mol). [b]Yield was determined by $^1H$ NMR analysis with $CH_2Br_2$ as the internal standard. [c]Isolated yield in parentheses.

## Result and Discussion

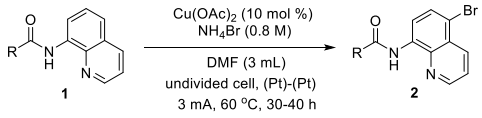
we began our investivation with the electrochemical bromination of arylation of 8-aminoquinoline amide (**1a**) under various reaction conditions (**Table 1**, and see Tables S1–S6 in the Supporting Information). Through a lot of research, the results are shown in table 1. 99% yield of the desired product (**2a**) could be obtained under constant-current electrolysis at 3.0 mA in the presence of 10 mol% $Cu(OAc)_2$ and $NH_4Br$ in DMF without other electrolyte at 60 °C with platinum electrodes (entry 1). There is only 10% yield without catalyst (en-

**Scheme 3. Evaluation of Analogous Substrates**

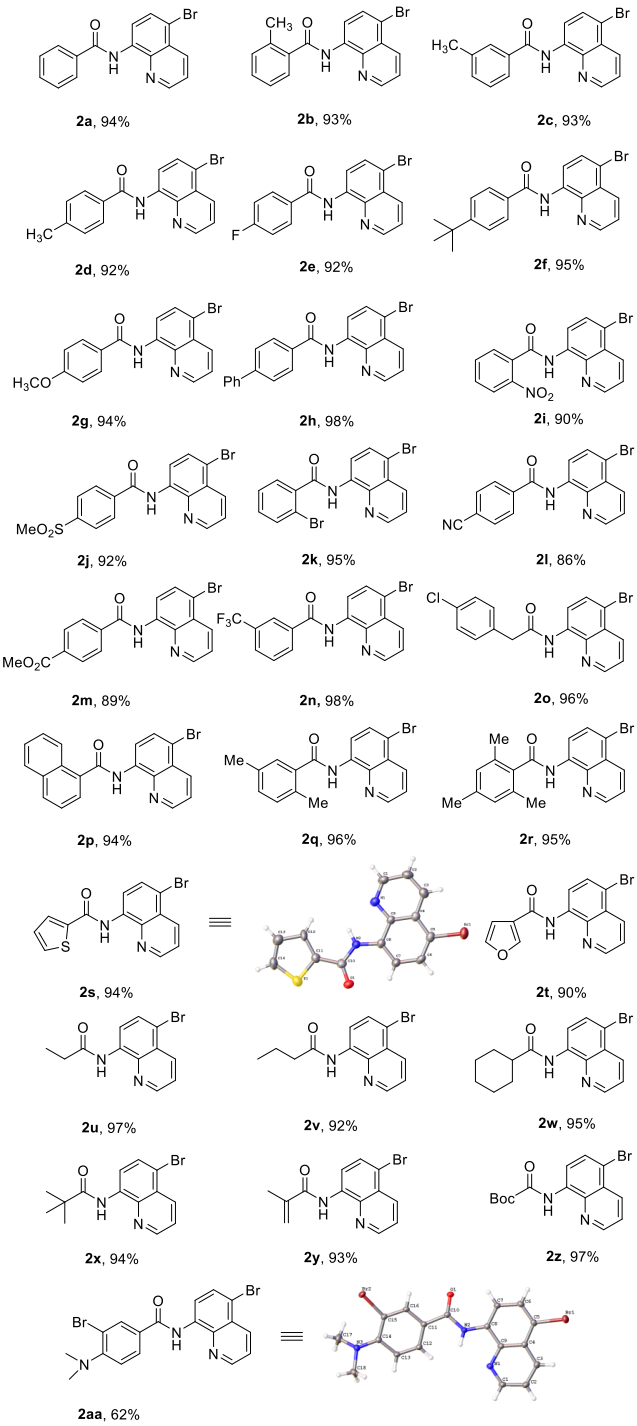


**1ab**, nr **1ac**, nr **1ad**, nr

**Table 2. Evaluation of 8-Aminoquinoline Amide**[a]




**1** **2**




[a]Reaction conditions: the reactions were run on **1b**–**1z** (0.20 mmol), $Cu(OAc)_2$ (10 mol %), DMF (3 mL), $NH_4Br$ (0.8 M) in undivided cell with two platinum eletrodes (1.0×1.0 $cm^2$), 3 mA, 60 °C, 30-40 h.

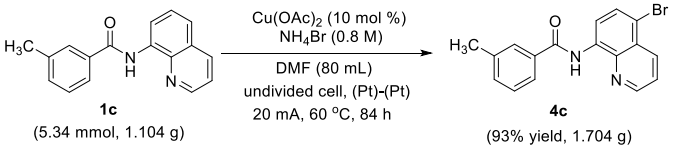
try 2) and the CuI as catalyst give the worse yield (entry 3). However, $Cu(OTf)_2$ led to slightly reduced yield (entry 4). When we decreased or increased the amount of $NH_4Br$, the yields also redeced (entries 5 and 6) because increasing the amount of $NH_4Br$ gave 5,7-dibrominated product. Different solvents were examined and DMF afforded the best yield (entries 7-8). Inorganic bromide salts including LiBr resulted in good yields (entry 9). However, the *n*-$Bu_4NBr$ kept the reaction from beginning (entry 10). Lower temperatures result in lower yields (entry 11). Increasing the electric current gave lower yield because of 5,7-dibrominated product as byprodruct (entry 12). The use of C anode instead of Pt anode gave lightly lower yield (entry 13). Electrical current was necessary for this reaction on the basis of control experiments (entry 14).

With the optimized reaction conditions in hand, next, we explored the analogous substrates (**Scheme 3**). Such as, none of the substrates produced the corresponding products under the standard conditions. In summary, the bidentate nitrogen structure was very critical for the process and a free NH was necessary.

Following, we proceeded to investigate the substrate scope and limitation of the reaction. As shown in （**Table 2**）, diversified aryl substituted carboxamides were tested as substrates Arenes substituted with a variety of functional groups such as alkyl, fluoro, nitro, sulfonyl, bromo, phenyl, nitrile, ester, trifluoromethyl, and Chloro were tolerated (**2a**-**2p**), affording good to excellent yields. Meanwhile, multisubstituted gropes also get good yields (**2q, 2r**). To our delight, the heterocyclic amide could afford the brominated products in 90-94% yields (**2s**, **2t**). It was worth noting, aliphatic amides could also afford the bromated products in higher yields (**2u**-**2y**). Remarkablely, this bromination protocol could also be applied to 8-aminoquinoline protected by $(Boc)_2O$ (**2z**), affording brominated product in excellent yields. Unexpected, the substrate **1aa** give the dibrominated products **2aa**.The structures of **2s** and **2aa** were unambiguously confirmed by X-ray analysis.

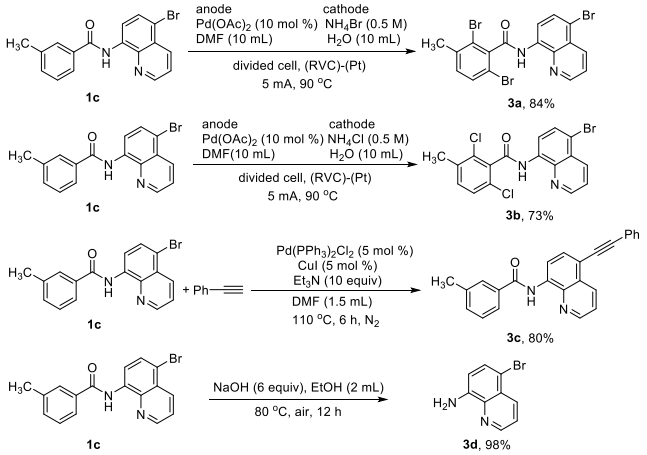
Next, the scalability of this copper-catalyzed electrochemical C–H bromination furnished the desired product in 93% isolated yield by using a reaction contioning 5.34 mmol of **1c**, which showcases the preparative utility of this electrochemical C−H bromination (**Scheme 4**).

**Scheme 4. Gram-scale Experiment**



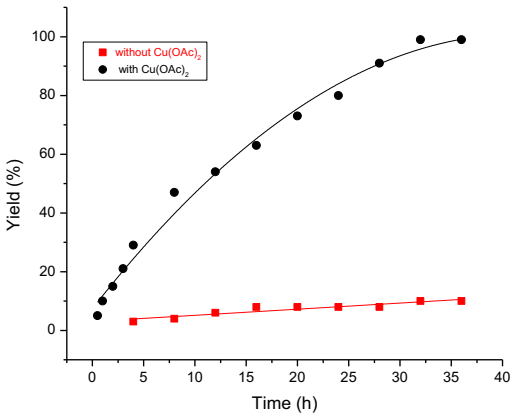

To further demonstrate the advantage of using this method (**Scheme 5**), we found that the 5-brominated product also as a new directing group, chlorination and bromination could be achieved under palladium-catalyzed anodic oxidation conditions. To our delight, the dibominated products were obtained with substratecontaining two ortho C−H bonds in excellent yields and the dichlorinated product showed moderated yields. The structures of **3a** were unambiguously confirmed by X-ray analysis (see Supporting Information). Furthermore, remote alkynylation of 8-aminoquinoline scaffolds at C5 position was achieved in good yield (Sonogashira cross-coupling reaction). At the same time, the amide bond could be easily hydrolyzed into C5 brominated 8-aminoquinoline in 98% yield.

**Scheme 5. Preparation of quinoline derivatives**

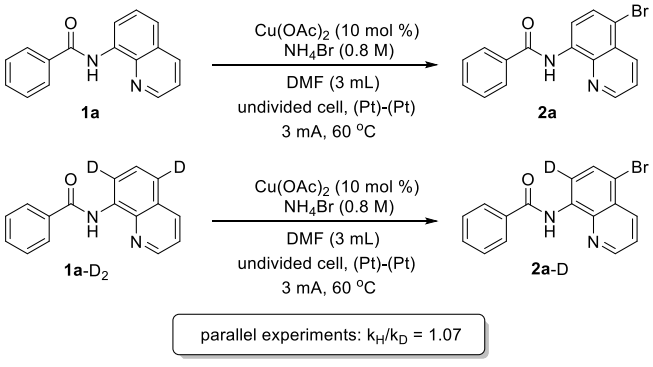



To gain more insight into the reaction, we compared the reactions with and without copper catalyst. It further proved that copper is indispensable (**Figure 1**). Moreover, a kinetic isotope effect (KIE) value of 1.07 was observed by comparing the global reaction rates of **1a** versus **1a**−$D_2$, which in indicated that the C–H bond activation is not the rate-limiting step (**Scheme 6**).

**Figure 1.The Reaction Condition with or without Copper**




**Scheme 6. KIE Experiment**




Studies were performed to obtain insight into the reaction mechanism. We carried out cyclic voltammetry (CV) experiments. individual components (**Figure 2**) showed that substrate **1a** (curve b, 1.71 V), $NH_4Br$ (curve c, 0.76 V, 1.12 V),

which probably associated with with $Br^{3-}/Br^{-}$ and $Br^{3-}/Br^{2}$ redox couples,[11,12] $Cu(OAc)_2$ (curve d), no oxidation potentials. Then we observed that there was no change when added substrate **1a** and $NH_4Br$ (**Figure 3**, curve b). To our delight, a new oxidation wave is Ep = 1.0 V when mixed substrate **1a** and $Cu(OAc)_2$ (**Figure 3**, curve c), which probably generated complex **A**, fllowing the $NH_4Br$ added, the oxidation potentials of $NH_4Br$ (Ep = 1.12 V) disappeared, it maybe formed complex **C**. However, the wave of 1.0 v still exist (**Figure 3**, curve c), which indicated Cu(II) complex still exist, so we assumed that complex **C** quickly transformed into **D** under anodic oxidation.

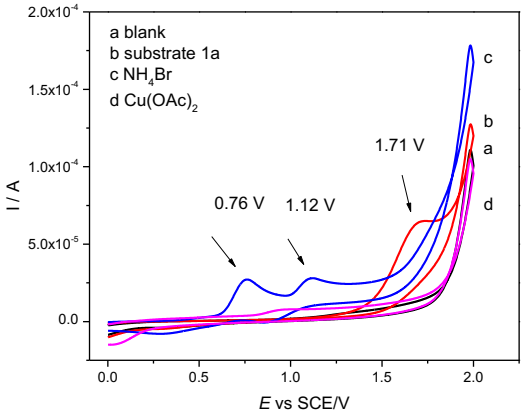



**Figure 2.** Cyclic voltammograms recorded on a Pt electrode (area = 0.03 $cm^2$): (a) DMF containing 0.1 M *n*-$Bu_4NPF_6$; (b) solution (a) after addition of 5 mM substrate **1a**; (c) solution (a) after addition of 5 mM $NH_4Br$; (d) solution (a) after addition of 5 mM $Cu(OAc)_2$.

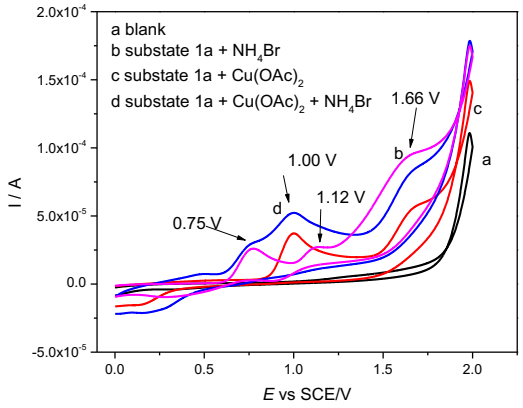
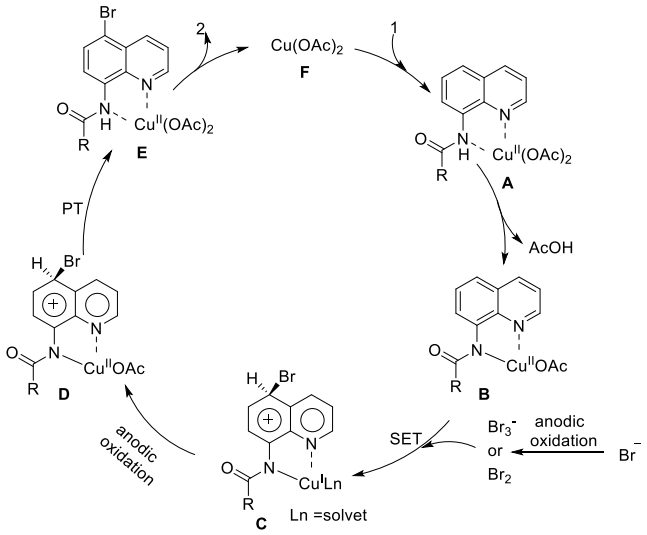



**Figure 3**. Cyclic voltammograms recorded on a Pt electrode (area = 0.03 $cm^2$): (a) DMF containing 0.1 M *n*-$Bu_4NPF_6$; (b) solution (a) after addition of 5 mM substrate **1a** and 5 mM $NH_4Br$; (c) solution (a) after addition of 5 mM substrate **1a** and 5 mM $Cu(OAc)_2$ ; (d) solution (c) after addition of 5 mM substrate $NH_4Br$.

Based on our experimental results and previous work, a plausible mechanism is presented for Cu-catalyzed electrochemical regioselective bromination of 8-amidquinolines (**Scheme 7**). Substrate **1** and $Cu(II)(OAc)_2$ generated the aryl-Cu(II) complex A, which was deprotonated by $AcO^-$ to form complex B. Then, the bromine radical attacked complex B and turned into complex C by single electron transfer (SET), followed by the complex C transformed into D by anodic oxidation. After generation of the intermediate E through the proton transfer process (PT), finally metal dissociation to give product, thereby completing the catalytic cycle.

**Scheme 7. Proposed Catalytic Cycle**




## Conclusion

In conclusion, we have developed a simple, mild and environmental-friendly protocol for the C5 bromination of 8-aminoquinoline amides promoted by a dual catalysis of transition metal and electricity. Note that this method afforded C5 brominated 8-aminoquinoline amides with high regioselectivity. The strategy for the construction of C5 functionalized quinolines also has a good application foreground. Moreover, the CV chart further demonstrated the proposed catalytic cycle in our laboratory.

## EXPERIMENTAL SECTION

**General Experimental Section.** All the electrochemical oxidations were performed in an undivided cell equipped with two platinum electrodes (1.0×1.0 $cm^2$) unless otherwise noted. Solvents and commercially available reagents were used without purification. Column chromatography was performed using either 100-200 Mesh or 300-400 Mesh silica gel. All commercial reagents were purchased from Macklin, TCI, Sigma-Aldrich, Adamas-beta of the highest purity grade. Cyclic voltammograms were recorded on a CHI 660E potentiostat. $^1H$ NMR and $^{13}C$ NMR spectra were recorded on Agilent AV 400, Varian Inova 400 (400 MHz and 100 MHz, respectively). $^{19}F$ NMR spectra were recorded on Agilent AV 400, Varian Inova 400 (376 MHz) instrument and are reported relative to the $CFCl_3$ as the internal standard. The peaks were internally referenced to TMS (0.00 ppm) or residual undeuterated solvent signal. The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. Infrared spectra were ob-

tained on a Bio-Rad FTS-185 instrument. High resolution mass spectra were recorded at the Center for Mass Spectrometry, Shanghai Institute of Organic Chemistry. Analytical and spectral data of all those known compounds are exactly matching with the reported values.

**General Procedure for compounds 1a-1aa**. To a solution of mixture of 8-aminoquinoline (10 mmol, 1 equiv, 1.442 g) and $Et_3N$ (15 mmol, 1.5 equiv, 1.518 g) in anhydrous $CH_2Cl_2$ (30 mL) at ice bath cooling, RCOCl (11 mmol, 1.1 equiv) was added slowly. After addition, the mixture was gradually warmed to room temperature and stirred overnight. The mixture was quenched with water (30 mL) and extracted with $CH_2Cl_2$ (3 x 20 mL). Combined organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel flash chromatography to give the desired product.

**General Procedure for compounds 1w**. A mixture of 8-aminoquinoline (2.08 mmol, 1.0 equiv, 299.8 mg), di-tert-butyl dicarbonate (4.16 mmol, 2.0 equiv, 907.9 mg) and 1,4-dioxane (10 mL) was stirred at 102 °C in an oil bath for 6 h. The solvent was removed under reduced pressure. The resulting residue was purified by silica gel flash chromatography to give the desired product.

**General Procedure for compounds 1ab-1ad worked as General Procedure for compounds 1a-1aa**.

**General Procedure for compounds 1ac**. To a suspension of sodium hydride (1.24 mmol, 2.05 equiv, 29.8 mg) in dry DMF (3 mL), was added a solution of N-(quinolin-8-yl)benzamide (0.604 mmol, 1 equiv, 149.8 mg) in dry DMF (3 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 3 h. Then, methyl iodide (0.785 mmol, 1.3 equiv, 111.4 mg) was added dropwise and the reaction was stirred at room temperature for 1 h. The reaction was diluted with DCM (20 mL) and the organic layer was washed with water (3 x 12 mL), dried over anhydrous $Na_2SO_4$ and concentrated to dryness under reduced pressure. Pale yellow oil was obtained and purified by column chromatography on silica gel.

Compounds **1a-1i** , **1k-1z** and **1aa-1ad** were known compounds and were prepared according the literature procedure[7e,7i,13].

*N-(quinolin-8-yl)-4-(methylsulfonyl)benzamide (**1j**)[new].* Following the general procedure for compounds **1a-1y** to get desired product **1j** which was purified by column chromatography on silica gel (petroleum ether : ethyl acetate = 1 : 1) to title compound (2.6732g, 82%) as a white solid. M.p.: 171.1-171.7 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 10.76 (s, 1H), 8.86 (dd, $J$ = 5.8, 3.0 Hz, 1H), 8.84-8.80 (m, 1H), 8.25-8.19 (m, 2H), 8.17 (d, $J$ = 8.4 Hz, 1H), 8.12-8.07 (m, 2H), 7.60-7.53 (m, 2H), 7.47 (dd, $J$ = 8.2, 4.2 Hz, 1H), 3.10 (s , 3H). $^{13}$C{1H} NMR (100 MHz, $CDCl_3$) 163.6, 148.6, 143.3, 140.0, 138.7, 136.6, 134.0, 128.4, 128.1, 127.4, 122.5, 122.0, 116.9, 44.5. IR (neat): 3341, 2996, 1664, 1535, 1483, 1421, 1386, 1314, 1151, 968, 759, 734, 643, 629 cm$^{-1}$. HRMS (ESI-TOF) Calcd for $C_{17}H_{15}N_2O_3S$, $[M+H]^+$: 327.0798, found 327.0796.

**General Procedure for Electrochemical C–H Bromination of 8-Aminoquinoline Amide.** The electrocatalysis was carried out in an undivided cell equipped with two platinum electrodes (1.0×1.0 cm$^2$). 8-Aminoquinoline Amide **1a-1aa** (0.2 mmol, 1 equiv), $NH_4Br$ (2.4 mmol, 12 equiv), $Cu(OAc)_2$ (10 mol %, 3.62 mg), DMF (3 mL) were added to the electrochemical cell. Electrocatalysis was preformed at 60 °C in an oil bath with a constant current of 3 mA. The progress of the reaction was monitored by TLC. After the completion of reaction, it was quenched by ice cold water and extracted with EtOAc. The combined organic extracts were dried over anhydrous sodium sulphate and filtered. Then, the solvent was evaporated under reduced pressure to give the crude product which was subjected to purify by silica gel column chromatography to afford desired product **2a-2aa**.

*N-(5-bromoquinolin-8-yl)benzamide(**2a**).*[7k] Following the general procedure, reaction between Substrate **1a** (0.2 mmol, 1 equiv, 49.6 mg) with ammonium bromide (2.4 mmol, 12 equiv, 232.8 mg) afforded the corresponding Bromination of 8-Aminoquinoline Amide **2a**, which was purified by column chromatography on silica gel (petroleum ether : ethyl acetate = 10 : 1) to afford title compound (61.6 mg, 94%) as a white solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 10.60 (s, 1H), 8.77–8.73 (m, 2H), 8.41(dd, $J$ = 8.8, 1.6 Hz, 1H), 8.03–8.01 (m, 2H), 7.74 (d, $J$ = 8.0 Hz, 1H), 7.57–7.46 (m, 4H);$^{13}$C{1H} NMR (100 MHz, $CDCl_3$) $\delta$ 165.3, 148.7, 139.3, 135.9, 134.7, 134.4, 132.0, 130.9, 128.8, 127.2, 127.1, 122.7, 116.9, 114.4.

*N-(5-bromoquinolin-8-yl)-2-methylbenzamide (**2b**).*[7k] Following the general procedure, reaction between Substrate **1b** (0.2 mmol, 1 equiv, 52.6 mg) with ammonium bromide (2.4 mmol, 12 equiv, 232.8 mg) afforded the corresponding Bromination of 8-Aminoquinoline Amide **3b**, which was purified by column chromatography on silica gel (petroleum ether : ethyl acetate = 10 : 1) to title compound (63.2 mg, 93%) as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 10.18 (s, 1H), 8.83 (d, $J$ = 8.4 Hz, 1H), 8.77 (d, $J$ = 4.0 Hz, 1H), 8.51 (dd, $J$ = 8.6, 1.2 Hz, 1H), 7.83 (d, $J$ = 8.4 Hz,1H), 7.68 (d, $J$ = 7.2 Hz, 1H),7.54 (dd, $J$ = 8.6, 4.4 Hz, 1H), 7.41 (t, $J$ = 7.2 Hz, 1H), 7.32 (t, $J$ = 8.0 Hz, 2H), 2.60 (s, 3H). $^{13}$C{1H} NMR (100 MHz, $CDCl_3$) $\delta$ 168.1, 148.7, 139.2, 136.8,

136.3, 135.9, 134.6, 131.5, 130.9, 130.5, 127.23, 127.19, 126.1, 122.7, 116.9, 114.5, 20.3.

*N-(5-bromoquinolin-8-yl)-3-methylbenzamide (**2c**).*[7k] Following the general procedure, reaction between Substrate **1c** (0.2 mmol, 1 equiv, 52.6 mg), with Ammonium bromide (2.4 mmol, 12 equiv, 232.8 mg) afforded the corresponding Bromination of 8-Aminoquinoline Amide **2c**, which was purified by column chromatography on silica gel (petroleum ether : ethyl acetate = 10 : 1) to afford title compound (63.2 mg, 93%) as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 10.57 (s, 1H), 8.78 (dd, $J$ = 4.2, 1.2 Hz, 1H), 8.75 (d, $J$ = 8.4 Hz, 1H), 8.42 (dd, $J$ =8.6, 1.2 Hz, 1H), 7.84-7.73 (m, 3H), 7.48 (dd, $J$ = 8.2, 4.4 Hz, 1H), 7.42-7.32 (m, 2H), 2.45 (s, 3H). $^{13}$C{1H} NMR (100 MHz, $CDCl_3$) $\delta$ 165.4, 148.7, 139.2, 138.7, 135.8, 134.7, 134.4, 132.7, 130.8, 128.6, 128.0, 127.0, 124.1, 122.6, 116.9, 114.3, 21.5.

*N-(5-bromoquinolin-8-yl)-4-methylbenzamide (**2d**).*[7k] Following the general procedure, reaction between Substrate **1d** (0.2 mmol, 1 equiv, 52.6 mg) with Ammonium bromide (2.4 mmol, 12 equiv, 232.8 mg) afforded the corresponding Bromination of 8-Aminoquinoline Amide **2d**, which was purified by column chromatography on silica gel (petroleum ether : ethyl acetate = 10 : 1) to title compound (62.5 mg, 92%) as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 10.63 (s, 1H), 8.82 (dd, $J$ = 4.0 , 1.2 Hz, 1H), 8.79 (d, $J$ = 8.4 Hz, 1H), 8.49 (dd, $J$ = 8.6 , 1 Hz, 1H), 7.94 (d, $J$ = 8.2 Hz, 2H), 7.79 (d, $J$ = 8.4 Hz, 1H), 7.54 (dd, $J$ = 8.4, 4.0 Hz, 1H), 7.32 (d, $J$ = 8.0 Hz, 2H), 2.44 (s, 3H). $^{13}$C{1H} NMR (100 MHz, $CDCl_3$) $\delta$ 165.3, 148.7, 142.5, 139.3, 135.9, 134.6, 132.0, 130.9, 129.5, 127.3,127.2, 122.7, 116.9, 114.2, 21.6.

*N-(5-bromoquinolin-8-yl)-4-fluorobenzamide (**2e**).*[7k] Following the general procedure, reaction between Substrate **1e** (0.2 mmol, 1 equiv, 53.2 mg) with Ammonium bromide (2.4 mmol, 12 equiv, 232.8 mg) afforded the corresponding Bromination of 8-Aminoquinoline Amide **2e**, which was purified by column chromatography on silica gel (petroleum ether : ethyl acetate = 10 : 1) to afford title compound (63.2 mg, 92%) as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 10.63 (s, 1H), 8.85 (dd, $J$ = 4 , 1.2 Hz, 1H), 8.79 (d, $J$ = 8.4 Hz , 1H), 8.54 (dd, $J$ = 8.8 , 4 Hz, 1H), 8.06 (dd, $J$ = 8.8, 5.2 Hz, 2H), 7.83 (d, $J$ = 8.4 Hz, 1H), 7.58 (dd, $J$ = 8.8, 4.0 Hz, 1H), 7.22 (t, $J$ = 8.4 Hz, 2H). $^{13}$C{1H} NMR (100 MHz, $CDCl_3$) $\delta$ 166.1 (d, $J$ = 251.4 Hz), 164.2, 148.8, 139.3, 136.1, 134.3, 131.0 (d, $J$ = 3.1 Hz), 130.9, 129.7 (d, $J$ = 9.0 Hz), 127.2, 122.8, 117.0, 115.9 (d, $J$ = 21.8 Hz), 114.5.

*N-(5-bromoquinolin-8-yl)-4-tertiary butylbenzamide (**2f**).*[new] Following the general procedure, reaction between Substrate **1f** (0.2 mmol, 1 equiv, 60.8 mg) with ammonium bromide (2.4 mmol, 12 equiv, 232.8 mg) afforded the corresponding Bromination of 8-Aminoquinoline Amide **2f**, which was purified by column chromatography on silica gel (petroleum ether : ethyl acetate = 10 : 1) to afford title compound (73.2 mg, 95%) as a white solid. M.p.: 86.0-90.6 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 10.66 (s, 1H), 8.84-8.87 (m, 2H), 8.50 (dd, $J$ = 8.8, 1.6 Hz, 1H), 8.01-7.97 (m, 2H), 7.80 (d, $J$ = 8.4 Hz, 1H), 7.58-7.52 (m, 3H), 1.36 (s , 9H). $^{13}$C {1H}NMR (100 MHz, $CDCl_3$) $\delta$ 165.4, 155.6, 148.7, 139.6, 135.9, 134.6, 132.0, 130.9, 127.2, 127.1, 125.8, 122.7, 116.9, 114.2, 35.0, 31.2. IR (neat): 3346, 2959, 1670, 1538, 1510, 1474, 1385, 1363, 1262, 917, 840, 806, 783, 653 cm$^{-1}$. HRMS (ESI-TOF) Calcd for $C_{20}H_{19}BrN_2O$, $[M+H]^+$: 383.0754, found 383.0757.

*N-(5-bromoquinolin-8-yl)-4-methoxybenzamide (**2g**).*[7k] Following the general procedure, reaction between Substrate **1g** (0.2 mmol, 1 equiv, 55.8 mg) with ammonium bromide (2.4 mmol, 12 equiv, 232.8 mg) afforded the corresponding Bromination of 8-Aminoquinoline Amide **2g**, which was purified by column chromatography on silica gel (petroleum ether : ethyl acetate = 10 : 1) to afford title compound (66.9 mg, 94%) as a white solid. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 10.63 (s, 1H), 8.85 (d, $J$ = 4.0 Hz, 1H), 8.81 (d, $J$ = 8.4 Hz, 1H), 8.53 (dd, $J$ = 8.4 , 0.8 Hz, 1H), 8.04 (d, $J$ = 8.8 Hz, 2H), 7.83 (d, $J$ = 8.4 Hz, 1H), 7.57 (dd, $J$ = 8.4, 4.4 Hz, 1H), 7.03 (d, $J$ = 8.8 Hz, 2 H), 3.89 (s, 3H). $^{13}$C{1H} NMR (100 MHz, $CDCl_3$) $\delta$ 164.9, 162.6, 148.7, 139.4, 136.0, 134.7, 131.0, 129.2, 127.2, 127.1, 122.7, 116.8, 114.1, 114.0, 55.5.

*N-(5-bromoquinolin-8-yl)-[1,1'-biphenyl]-4-carboxamide (**2h**).*[7j] Following the general procedure, reaction between Substrate **1h** (0.2 mmol, 1 equiv, 64.8 mg) was brominated following the general procedure, with ammonium bromide (2.4 mmol, 12 equiv, 232.8 mg) afforded the corresponding Bromination of 8-Aminoquinoline Amide **2h**, which was purified by column chromatography on silica gel (petroleum ether : ethyl acetate = 10 : 1) to afford title compound (79.3 mg, 98%) as a white solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 10.70 (s, 1H), 8.84 (dd, $J$ = 4.0, 1.2 Hz, 1H), 8.81 (d, $J$ = 8.4 Hz, 1H), 8.49 (dd, $J$ = 8.4, 1.2 Hz, 1H), 8.12 (d, $J$ = 8.0 Hz, 2H), 7.81 (d, $J$ = 8.0 Hz, 1H), 7.74 (d, $J$ = 8.4 Hz, 2H), 7.76 (d, $J$ = 7.2Hz, 2H), 7.54 (dd, $J$ = 8.4, 4.0 Hz, 1H), 7.48 (t, $J$ = 7.2 Hz, 2H), 7.41 (t, $J$ = 7.2 Hz, 1H). $^{13}$C{1H} NMR (101 MHz, $CDCl_3$) $\delta$ 163.9, 147.7, 143.7, 138.8, 138.3, 134.9, 133.4, 132.3, 129.9, 127.9, 127.1, 126.8, 126.4, 126.2, 126.1, 121.7, 115.9, 113.4.

*N-(5-bromoquinolin-8-yl)-2-nitrobenzamide (**2i**).*[12k] Following the general procedure, reaction between Substrate **1i** (0.2 mmol, 1 equiv, 58.6 mg) was brominated following the general procedure, with ammonium bromide (2.4 mmol, 12 equiv, 232.8 mg) afforded the corresponding Bromination of 8-Aminoquinoline Amide **2i**, which was purified by column chromatography on silica

gel (petroleum ether : ethyl acetate = 5 : 1) to afford title compound (66.9 mg, 90%) as a yellow solid. $^1$H NMR (600 MHz, $CDCl_3$) δ 10.14 (s, 1H), 8.85-8.75 (m, 2H), 8.56 (d, $J$ = 8.4 Hz, 1H), 8.15 (d, $J$ = 8.4 Hz, 1H), 7.87 (d, $J$ = 8.4 Hz, 1H), 7.80-7.74 (m, 2H), 7.71-7.64 (m, 1H), 7.58 (dd, $J$ = 8.6, 4.2 Hz, 1H). $^{13}$C{1H} NMR (100 MHz, $CDCl_3$) $\delta$ 164.4, 149.0, 139.9, 139.2, 136.2, 134.2, 133.9, 133.8, 133.0, 131.0, 128.7, 127.4, 124.9, 122.9, 117.7, 115.4.

*N-(5-bromoquinolin-8-yl)-4-(methylsulfonyl)benzamide(**2j**).*[new]. Following the general procedure, reaction between Substrate **1j** (0.2 mmol, 1 equiv, 65.2 mg) was brominated following the general procedure, with ammonium bromide (2.4 mmol, 12 equiv, 232.8 mg) afforded the corresponding Bromination of 8-Aminoquinoline Amide **2j**, which was purified by column chromatography on silica gel (petroleum ether : ethyl acetate = 1 : 1) to afford title compound (74.3 mg, 92%) as a white solid. M.p.: 186.8-188.3 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 10.74 (s, 1H), 8.87 (d, $J$ = 4.0 Hz, 1H), 8.78 (d, $J$ = 8.4 Hz, 1H), 8.56 (d, $J$ = 8.8 Hz, 1H), 8.20-8.27 (m, 2H), 8.16-8.09 (m, 2H), 7.85 (d, $J$ = 8.4 Hz, 1H),7.61 (dd, $J$ = 8.4, 4.0 Hz, 1H), 3.12 (s, 3H); $^{13}$C{1H} NMR (101 MHz, $CDCl_3$): $\delta$ 163.4, 149.0, 143.4 139.6, 139.2, 136.1, 133.8, 130.9, 128.3, 128.0, 127.3, 122.9, 117.2, 115.2, 44.4. IR (neat): 3342, 1671,1535, 1473, 1387, 1368, 1309, 1292, 1146, 968, 918, 782, 662, 569 cm$^{-1}$. HRMS (ESI-TOF) Calcd for $C_{17}H_{14}BrN_2O_3S$, $[M+H]^+$: 404.9903, found 404.9899

*N-(5-bromoquinolin-8-yl)-1-bromobenzamide (**2k**).*[new] Following the general procedure, reaction between Substrate **1k** (0.2 mmol, 1 equiv, 65.2 mg) with ammonium bromide (2.4 mmol, 12 equiv, 232.8 mg) afforded the corresponding Bromination of 8-Aminoquinoline Amide **2k**, which was purified by column chromatography on silica gel (petroleum ether : ethyl acetate = 10 : 1) to afford title compound (77.5 mg, 95%) as a white solid. M.p.: 154.0-156.4 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 10.28 (s, 1H), 8.83 (d, $J$ = 8.4 Hz, 1H), 8.79 (d, $J$ = 3.6 Hz, 1H), 8.51 (d, $J$ = 8.4 Hz, 1H), 7.84 (d, $J$ = 8.4 Hz, 1H)), 7.71 (d, $J$ = 7.2 Hz, 1H), 7.68 (d, $J$ = 8.0 Hz, 1H), 7.55 (dd, $J$ = 8.4 , 4 Hz, 1H), 7.44 (t, $J$ = 7.4 Hz, 1H), 7.34 (t, $J$ = 7.4 Hz, 1H). $^{13}$C{1H} NMR (100 MHz, $CDCl_3$): $\delta$ 165.8, 148.8, 139.2, 138.0, 135.9, 134.2, 133.7, 131.6, 130.9, 129.6, 127.7, 127.2, 122.8, 119.6, 117.3, 115.0. IR (neat): 3334, 1668, 1519, 1474, 1383, 1361, 1318, 1019, 918, 847, 778, 741, 711, 663 cm$^{-1}$. HRMS (ESI-TOF) Calcd for $C_{16}H_{11}Br_2N_2O$, $[M+H]^+$: 404.9233, found 404.9240.

*N-(5-bromoquinolin-8-yl)-4-cyanobenzamide (**2l**).*[new] Following the general procedure, reaction between Substrate **1l** (0.2 mmol, 1 equiv, 54.6 mg) with ammonium bromide (2.4 mmol, 12 equiv, 232.8 mg) afforded the corresponding Bromination of 8-Aminoquinoline Amide **2l**, which was purified by column chromatography on silica gel (petroleum ether : ethyl acetate = 10 : 1) to afford title compound (60.4 mg, 86%) as a white solid. M.p.: 236.0-239.2 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 10.75 (s, 1H), 8.88 (d, $J$ = 4.0 Hz, 1H), 8.79 (d, $J$ = 8.4 Hz, 1H), 8.57 (d, $J$ = 8.4 Hz, 1H), 8.16 (d, $J$ = 8.0 Hz, 2H)), 7.86(m, 3H), 7.62(dd, $J$ = 8.6, 4.2 Hz, 1H). $^{13}$C{1H} NMR (100 MHz, $CDCl_3$): $\delta$ 163.4, 149.0, 139.3, 138.6, 136.2, 133.8, 132.7, 130.9, 127.9, 127.3, 122.9, 117.9, 117.3, 115.5, 115.3. IR (neat): 3335, 1673, 1521, 1475, 1384, 1321, 1258, 1098, 917, 832, 782, 756, 672, 577 cm$^{-1}$. HRMS (ESI-TOF) Calcd for $C_{17}H_{11}BrN_3O$, $[M+H]^+$: 352.0080, found 352.0069.

*Methyl-4-(5-bromoquinolin-8-yicarbamoyl)-benzoate (**2m**).*[7i] Following the general procedure, reaction between Substrate **1m** (0.2 mmol, 1 equiv, 61.2mg) with ammonium bromide (2.4 mmol, 12 equiv, 232.8 mg) afforded the corresponding Bromination of 8-Aminoquinoline Amide **2m**, which was purified by column chromatography on silica gel (petroleum ether : ethyl acetate = 10 : 1) to afford title compound (68.5 mg, 89%) as a white solid. $^1$H NMR (400 MHz, $CDCl_3$): 10.78 (s,1H), 8.92 (d, J = 4.0 Hz, 1H), 8.86 (d, J = 8.4 Hz, 1H), 8.59 (d, J = 8.4 Hz, 1H), 8.29-8.21 (m, 2H), 8.20-8.13 (m, 2H), 7.89 (d, J = 8.4 Hz, 1H), 7.65 (dd, J = 8.4, 4.0 Hz, 1H), 4.03 (s, 3H); $^{13}$C{1H} NMR (100 MHz, $CDCl_3$): δ 166.2, 164.3, 148.9, 139.3, 138.5, 136.1, 134.1, 133.1, 130.9, 130.0, 127.3, 127.2, 122.8, 117.1, 114.8, 52.5.

*N-(5-bromoquinolin-8-yl)-3-(trifluoromethyl)benzamide (**2n**).*[7k] Following the general procedure, reaction between Substrate **1n** (0.2 mmol, 1 equiv, 63.2 mg) was brominated following the general procedure, with ammonium bromide (2.4 mmol, 12 equiv, 232.8 mg) afforded the corresponding Bromination of 8-Aminoquinoline Amide **2n**, which was purified by column chromatography on silica gel (petroleum ether : ethyl acetate = 10 : 1) to afford title compound (77.9 mg, 98%) as a white solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 10.65 (s, 1H), 8.82 (dd, $J$ = 4, 1.6 Hz, 1H), 8.73 (d, $J$ = 8.4 Hz, 1H), 8.48 (dd, $J$ = 8.4, 1.2 Hz, 1H), 8.30 (s, 1H), 8.18 (d, $J$ = 7.6 Hz, 1H), 7.77 (d, $J$ = 8.0 Hz, 1H), 7.78 (d, $J$ = 8.4 Hz, 1H), 7.66 (t, $J$ = 8.0 Hz, 1H), 7.55 (dd, $J$ = 8.8, 4.4 Hz, 1H). $^{13}$C{1H} NMR (100 MHz, $CDCl_3$): $\delta$ 163.7, 148.9, 139.2, 136.0, 135.6, 133.9, 131.4 (q, $J$ = 32.7 Hz), 130.8, 130.2,129.4, 128.5 (q, $J$ = 3.6 Hz), 127.1, 124.5 (q, $J$ = 3.8 Hz), 123.7 (q, $J$ = 271.2 Hz), 122.8, 117.1, 114.9. $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ -62.7.

*N-(5-bromoquinolin-8-yl)-2-(4-chlorophenyl)acetamide (**2o**).*[new] Following the general procedure, reaction between Substrate **1o** (0.2 mmol, 1 equiv, 59.2 mg) with ammonium bromide (2.4 mmol, 12 equiv, 232.8 mg) afforded the corresponding Bromination of 8-

Aminoquinoline Amide **2o**, which was purified by column chromatography on silica gel (petroleum ether : ethyl acetate = 10 : 1) to afford title compound (71.9 mg, 96%) as a white solid. M.p.: 127.1-127.9 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 9.83 (s, 1H), 8.69 (dd, $J$ = 4.4, 1.6 Hz, 1H), 8.60 (d, $J$ = 8.4 Hz, 1H), 8.43 (dd, $J$ = 8.4, 1.2 Hz, 1H), 7.72 (d, $J$ = 8.4 Hz, 1H), 7.48 (dd, $J$ = 8.4, 4.0 Hz, 1H)), 7.40-7.29 (m, 4H), 3.84 (s, 2H). $^{13}$C{1H} NMR (100 MHz, $CDCl_3$): δ 168.9, 148.7, 138.9, 135.8, 134.0, 133.3, 132.9, 130.9, 130.7, 129.1, 127.0, 122.6, 116.8, 114.4, 44.4. IR (neat): 3361, 1663, 1534, 1501, 1473, 1358, 1026, 952, 921, 853, 808, 778, 747, 638 cm$^{-1}$. HRMS (ESI-TOF) Calcd for $C_{17}H_{13}BrN_2OCl$, $[M+H]^+$: 374.9894, found 374.9887.

*N-(5-bromoquinolin-8-yl)-1-naphthamide* ***(2p)***.[7k] Following the general procedure, reaction between Substrate **1p** (0.2 mmol, 1 equiv, 59.6 mg) was brominated following the general procedure, with ammonium bromide (2.4 mmol, 12 equiv, 232.8 mg) afforded the corresponding Bromination of 8-Aminoquinoline Amide **2p**, which was purified by column chromatography on silica gel (petroleum ether : ethyl acetate = 10 : 1) to afford title compound (71.0 mg, 94%) as a white solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 10.40 (s, 1H), 8.94 (d, $J$ = 8.4 Hz, 1H), 8.75 (dd, $J$ = 4.4, 1.6 Hz, 1H), 8.56-8.50 (m, 2H), 8.01 (d, $J$ = 8.4 Hz, 1H), 7.95-7.86 (m, 3H), 7.62-7.51 (m, 4H); $^{13}$C{1H} NMR (101 MHz, $CDCl_3$): $\delta$ 167.7, 148.8, 139.3, 136.0, 134.7, 134.3, 133.9, 131.3, 130.9, 130.3, 128.4, 127.4, 127.3, 126.6, 125.6, 125.5, 124.8, 122.8, 117.2, 114.7.

*N-(5-bromoquinolin-8-yl)-2,5-dimethylbenzamide* ***(2q)***.[new] Following the general procedure, reaction between Substrate **1q** (0.2 mmol, 1 equiv, 55.2 mg) with ammonium bromide (2.4 mmol, 12 equiv, 232.8 mg) afforded the corresponding Bromination of 8-Aminoquinoline Amide **2q**, which was purified by column chromatography on silica gel (petroleum ether : ethyl acetate = 10 : 1) to afford title compound (68.2 mg, 96%) as a white solid. M.p.: 141.7-143.5 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 10.16 (s, 1H), 8.83 (d, $J$ = 8.4 Hz, 1H), 8.78 (dd, $J$ = 4.0, 3.2 Hz, 1H), 8.51 (dd, $J$ = 8.4, 1.2 Hz, 1H), 7.83 (d, $J$ = 8.4 Hz, 1H), 7.54 (dd, $J$ = 8.6, 4.2 Hz, 1H)), 7.48 (s, 1H), 7.23-7.16 (m, 2H), 2.55 (s, 3H), 2.40 (s, 3H). $^{13}$C{1H} NMR (100 MHz, $CDCl_3$): δ 168.3, 148.7, 139.3, 136.2, 135.9, 135.6, 134.7, 133.4, 131.3, 131.2, 130.9, 127.8, 127.2, 122.7, 117.0, 114.4, 21.0, 19.8. IR (neat): 3349, 1680, 1527, 1472, 1375, 1320, 1256, 1153, 935, 832, 806, 784, 699, 673 cm$^{-1}$. HRMS (ESI-TOF) Calcd for $C_{18}H_{16}BrN_2O$, $[M+H]^+$: 355.0441, found 355.0454.

*N-(5-bromoquinolin-8-yl)-2,4,6-trimethylbenzamide* ***(2r)***.[7e] Following the general procedure, reaction between Substrate **1r** (0.2 mmol, 1 equiv, 58.0 mg) with ammonium bromide (2.4 mmol, 12 equiv, 232.8 mg) afforded the corresponding Bromination of 8-Aminoquinoline Amide **2r**, which was purified by column chromatography on silica gel (petroleum ether : ethyl acetate = 10 : 1) to afford title compound (70.1 mg, 95%) as a white solid. $^1$H NMR (400 MHz, $CDCl_3$): δ 9.91 (s, 1H), 8.90 (d, J = 8.4 Hz, 1H), 8.74 (dd, J = 4.2, 1.4 Hz, 1H), 8.52 (dd, J = 8.6, 1.4 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.53 (dd, J = 8.4, 4.4 Hz, 1H), 6.93 (s, 2H), 2.40 (s, 6H), 2.34 (s, 3H). $^{13}$C{1H} NMR (100 MHz, $CDCl_3$): δ 169.1, 148.7, 139.2, 138.9, 135.9, 135.1, 134.5, 134.4, 130.9, 128.5, 127.2, 122.7, 117.2, 114.6, 21.2, 19.4.

*N-(5-bromoquinolin-8-yl)thiophene-2-carboxamide* ***(2s)***.[7k] Following the general procedure, reaction between Substrate **1s** (0.2 mmol, 1 equiv, 50.8 mg) was brominated following the general procedure, with ammonium bromide (2.4 mmol, 12 equiv, 232.8 mg) afforded the corresponding Bromination of 8-Aminoquinoline Amide **2s**, which was purified by column chromatography on silica gel (petroleum ether : ethyl acetate = 10 : 1) to afford title compound (62.9 mg, 94%) as a yellow solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 10.48 (s, 1H), 8.81 (dd, $J$ = 4.2, 0.6 Hz, 1H), 8.68 (d, $J$ = 8.4 Hz, 1H), 8.48 (dd, $J$ = 8.4, 0.8 Hz, 1H), 7.81-7.75 (m, 2H), 7.58 (d, $J$ = 4.8 Hz, 1H), 7.54 (dd, $J$ = 8.6, 4.2 Hz, 1H);7.18-7.15 (m, 1H) . $^{13}$C{1H} NMR (100 MHz, $CDCl_3$): $\delta$ 159.9, 148.8, 139.7, 139.0, 135.9, 134.1, 131.2, 130.9, 128.5, 127.9, 127.1, 122.7, 116.9, 114.4.

*N-(5-bromoquinolin-8-yl)furan-3-carboxamide* ***(2t)***.[new] Following the general procedure, reaction between Substrate **1s** (0.2 mmol, 1 equiv, 47.6 mg) was brominated following the general procedure, with ammonium bromide (2.4 mmol, 12 equiv, 232.8 mg) afforded the corresponding Bromination of 8-Aminoquinoline Amide **2s**, which was purified by column chromatography on silica gel (petroleum ether : ethyl acetate = 10 : 1) to afford title compound (57.0 mg, 90%) as a white solid. M.p.: 155.8-156.9 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 10.20 (s, 1H), 8.80 (dd, $J$ = 4.4, 1.6 Hz, 1H), 8.70 (d, $J$ = 8.4 Hz, 1H), 8.48 (dd, $J$ = 8.6, 1.4 Hz, 1H), 8.16 (d, $J$ = 1.2, 0.8 Hz, 1H)), 7.77 (d, $J$ = 8.4 Hz, 1H), 7.56-7.50 (m, 2H), 6.89 (dd, $J$ = 1.6, 0.8 Hz, 1H). $^{13}$C{1H} NMR (100 MHz, $CDCl_3$): $\delta$ 160.6, 148.7, 145.3, 144.1, 139.0, 135.9, 134.1, 130.9, 127.1, 123.4, 122.7, 116.9, 114.3, 108.5. IR (neat): 3341, 1668, 1570, 1527, 1472, 1385, 1366, 1319, 1161, 1080, 1017, 911, 870, 853, 784, 730, 677, 600 cm$^{-1}$. HRMS (ESI-TOF) Calcd for $C_{14}H_{10}BrN_2O_2$, $[M+H]^+$: 316.9920, found 316.9923.

*N-(5-bromoquinolin-8-yl)propionamide* ***(2u)***.[7g] Following the general procedure, reaction between Substrate **1u** (0.2 mmol, 1 equiv, 40.0 mg) was brominated following the general procedure, with ammonium bromide (2.4 mmol, 12 equiv, 232.8 mg) afforded the corresponding Bromination of 8-Aminoquinoline Amide

**2u**, which was purified by column chromatography on silica gel (petroleum ether : ethyl acetate = 10 : 1) to afford title compound (54.5 mg, 97%) as a white solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 9.75 (s, 1H), 8.77 (d, $J$ = 4.0 Hz, 1H), 8.64 (d, $J$ = 8.4 Hz, 1H), 8.46 (d, $J$ = 8.4 Hz, 1H), 7.74 (d, $J$ = 8.4 Hz, 1H), 7.51 (dd, $J$ = 8.6, 4.2 Hz, 1H), 2.58 (q, $J$ = 7.6 Hz, 2H), 1.32 (t, $J$ = 7.6 Hz, 3H). $^{13}$C{1H} NMR (100 MHz, $CDCl_3$): $\delta$ 172.4, 148.5, 138.9, 135.9, 134.4, 130.9, 127.1, 122.6, 116.8, 113.9, 31.2, 9.6.

*N-(5-Bromoquinolin-8-yl)butyramide (**2v**).*[7g] Following the general procedure, reaction between Substrate 1v (0.2 mmol, 1 equiv, 42.8 mg) was brominated following the general procedure, with ammonium bromide (2.4 mmol, 12 equiv, 232.8 mg) afforded the corresponding Bromination of 8-Aminoquinoline Amide **2v**, which was purified by column chromatography on silica gel (petroleum ether : ethyl acetate = 10 : 1) to afford title compound (53.9 mg, 92%) as a white solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 9.75 (s, 1H), 8.79 (dd, $J$ = 4.2, 1.4 Hz, 1H), 8.66 (d, $J$ = 8.4 Hz, 1H), 8.48 (dd, $J$ = 8.4, 1.2 Hz, 1H), 7.76 (d, $J$ = 8.4 Hz, 1H), 7.53 (dd, $J$ = 8.6, 4.2 Hz, 1H), 2.53 (t, $J$ = 7.6 Hz, 2H), 1.90-1.75 (m, 2H), 1.05 (t, $J$ = 7.4 Hz, 3H). $^{13}$C{1H} NMR (100 MHz, $CDCl_3$): $\delta$ 171.8, 148.5, 139.0, 135.9, 134.4, 130.9, 127.1, 122.6, 116.8, 114.0, 40.1, 19.1, 13.8.

*N-(5-bromoquinolin-8-yl)cyclohexanecarboxamide (**2w**).*[7k] Following the general procedure, reaction between Substrate **1w** (0.2 mmol, 1 equiv, 50.8 mg) was brominated following the general procedure, with ammonium bromide (2.4 mmol, 12 equiv, 232.8 mg) afforded the corresponding Bromination of 8-Aminoquinoline Amide **2w**, which was purified by column chromatography on silica gel (petroleum ether : ethyl acetate = 10 : 1) to afford title compound (63.08 mg, 95%) as a white solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 9.84 (s, 1H), 8.81 (d, $J$ = 4.4 Hz, 1H),, 8.67 (d, $J$ = 8.4 Hz, 1H), 8.49 (d, $J$ = 8.4 Hz, 1H), 7.76 (d, $J$ = 8.4 Hz, 1H), 7.53 (dd, $J$ = 8.4, 4.4 Hz, 1H), 2.52-2.43 (m, 1H), 2.07 (d, $J$ = 12.4 Hz, 2H), 1.87 (d, $J$ = 12.8 Hz, 2H), 1.78-1.56 (m, 3H), 1.44-1.22 (m, 3H), $^{13}$C{1H} NMR (100 MHz, $CDCl_3$): $\delta$ 174.8, 148.5, 139.1, 135.9, 134.5, 130.9, 127.1, 122.6, 116.9, 113.9, 46.9, 29.7, 25.74, 25.71.

*N-(5-Bromoquinolin-8-yl)pivalamide (**2x**).*[7k] Following the general procedure, reaction between Substrate **1x** (0.2 mmol, 1 equiv, 45.6 mg) was brominated following the general procedure, with ammonium bromide (2.4 mmol, 12 equiv, 232.8 mg) afforded the corresponding Bromination of 8-Aminoquinoline Amide **2x**, which was purified by column chromatography on silica gel (petroleum ether : ethyl acetate = 10 : 1) to afford title compound (57.52 mg, 94%) as a white solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 10.20 (s, 1H), 8.70 (dd, $J$ = 4.2, 1.4 Hz, 1H), 8.66 (d, $J$ = 8.4 Hz, 1H), 8.47 (dd, $J$ = 8.8, 1.6 Hz, 1H), 7.75 (d, $J$ = 8.4 Hz, 1H), 7.52 (dd, $J$ = 8.6, 4.2 Hz, 1H), 1.40 (s, 9H). $^{13}$C{1H} NMR (100 MHz, $CDCl_3$): $\delta$ 177.2, 148.6, 139.4, 135.9, 134.6, 130.9, 127.1, 122.5, 116.7, 113.9, 40.4, 27.7.

*N-(5-bromoquinolin-8-yl)methacrylamide (**2y**).*[7e] Following the general procedure, reaction between Substrate **1y** (0.2 mmol, 1 equiv, 42.4 mg) was brominated following the general procedure, with ammonium bromide (2.4 mmol, 12 equiv, 232.8 mg) afforded the corresponding Bromination of 8-Aminoquinoline Amide **2y**, which was purified by column chromatography on silica gel (petroleum ether : ethyl acetate = 10 : 1) to afford title compound (54.1 mg, 93%) as a yiellow solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 10.31 (s, 1H), 8.81 (dd, $J$ = 4.2, 1.0 Hz, 1H), 8.70 (d, $J$ = 8.4 Hz, 1H), 8.50 (dd, $J$ = 8.4, 1.2 Hz, 1H), 7.78 (d, $J$ = 8.4 Hz, 1H), 7.54 (dd, $J$ = 8.4, 4.4 Hz, 1H), 6.04 (s, 1H), 5.57 (s, 1H), 2.18 (s, 3H). $^{13}$C{1H} NMR (100 MHz, $CDCl_3$): $\delta$ 166.6, 148.7, 140.5, 139.3, 135.9, 134.3, 130.9, 127.1, 122.6, 120.9, 116.9, 114.3, 18.6.

*tert-Butyl (5-bromoquinolin-8-yl)carbamate (**2z**).*[7m] Following the general procedure, reaction between Substrate **1z** (0.2 mmol, 1 equiv, 48.8 mg) was brominated following the general procedure, with ammonium bromide (2.4 mmol, 12 equiv, 232.8 mg) afforded the corresponding Bromination of 8-Aminoquinoline Amide **2a**, which was purified by column chromatography on silica gel (petroleum ether : ethyl acetate = 10 : 1) to afford title compound (68.3 mg, 97%) as a white solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.99 (s, 1H),8.77 (dd, $J$ = 4.0, 1.2 Hz, 1H), 8.46 (dd, $J$ = 8.4, 1.2 Hz, 1H), 8.29 (d, $J$ = 8 Hz, 1H), 7.74 (d, $J$ = 8.4 Hz, 1H), 7.50 (dd, $J$ = 8.6, 4.2 Hz, 1H), 1.58 (s, 9H). $^{13}$C{1H} NMR (100 MHz, $CDCl_3$): $\delta$ 152.6, 148.4, 138.8, 135.7, 135.1, 130.8, 127.1, 122.5, 114.9, 112.6, 80.7, 28.4.

*N-(5-bromoquinolin-8-yl)-4-(dimethyl-amino) 3-bromobenzamide (**2aa**).*[new] Following the general procedure, reaction between Substrate **1aa** (0.2 mmol, 1 equiv, 58.2 mg) with ammonium bromide (2.4 mmol, 12 equiv, 232.8 mg) afforded the corresponding Bromination of 8-Aminoquinoline Amide **2aa**, which was purified by column chromatography on silica gel (petroleum ether : ethyl acetate = 30 : 1) to afford title compound (56.3 mg, 62%) as a white solid. M.p.: 127.5-133.4 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 10.55 (s, 1H), 8.84 (dd, $J$ = 4.0, 1.2 Hz, 1H), 8.76 (d, $J$ = 8.0 Hz, 1H), 8.51 (dd, $J$ = 8.4, 1.2 Hz, 1H), 8.24 (d, $J$ = 2.0 Hz, 1H)), 7.92 (dd, $J$ = 8.4, 2.0 Hz, 1H), 7.80 (d, $J$ = 8.4 Hz, 1H), 7.56 (dd, $J$ = 8.6 , 4.2 Hz, 1H), 7.13 (d, $J$ = 8.4 Hz, 1H), 2.91 (s, 6H). $^{13}$C{1H} NMR (100 MHz, $CDCl_3$): $\delta$ 163.7, 155.0, 148.7, 139.3, 136.0, 134.4, 133.5, 130.9, 129.2, 127.2, 127.1, 122.7, 119.7, 117.7, 116.9, 114.3, 43.7. IR (neat): 3362, 1662, 1596, 1535, 1473, 1380, 1359, 1318, 1245,

1227, 1135, 952, 853, 778, 747, 675, 637 $cm^{-1}$. HRMS (ESI-TOF) Calcd for $C_{18}H_{16}Br_2N_3O$, $[M+H]^+$: 447.9655, found 447.9647.

*[Gram Scale synthesis]* The electrocatalysis was carried out in an undivided cell equipped with two platinum electrodes (4.0×4.0 $cm^2$). 8-Aminoquinoline Amide **1c** (5.34 mmol, 1 equiv, 1.104 g), $NH_4Br$ (64.08 mmol, 12 equiv, 6.23 g), $Cu(OAc)_2$ (10 mol %, 96.73 mg), DMF (80 mL) were added to the electrochemical cell. Electrocatalysis was preformed at 60 °C in an oil bath with a constant current of 20 mA, maintaining 84 h. After the completion of reaction, it was quenched by ice cold water and extracted with EtOAc. The combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated. The resulting residue was purified by silica gel column chromatography to give the product **4c** as white solid with 93% yield.

**General Procedure for 2,6-Dibromo-N-(5-bromoquinolin-8-yl)-3-methylbenzamide (3a)**.*new* Substrate **2c** (0.25 mmol, 1 equiv, 85.75 mg) was brominated following the general procedure, with ammonium bromide (5.0 mmol, 20 equiv, 489.7 mg) at 90 °C in an oil bath for 9 h. Purification by column chromatography on silica gel (petroleum ether : ethyl acetate = 10 : 1) to afford **3a** (104.16 mg, 84%) as a white solid. M.p.: 211.5-212.7 °C. $^1H$ NMR (400 MHz, $CDCl_3$): δ 9.97 (s, 1 H), 8.86 (d, *J* = 8.4 Hz, 1 H), 8.77 (dd, *J* = 4.0, 1.6 Hz, 1 H), 8.51 (dd, *J* = 8.4, 1.6 Hz, 1 H), 7.86 (d, *J* = 8.4 Hz, 1 H), 7.55 (dd, *J* = 8.6, 4.2 Hz, 1 H), 7.47 (d, *J* = 8.4 Hz, 1 H),7.18 (d, *J* = 8.0 Hz, 1 H), 2.40 (s, 3 H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.0, 148.9, 140.0, 139.1, 138.4, 136.0, 133.9, 132.3, 131.5, 130.9, 127.3, 122.9, 122.8, 117.6, 117.2, 115.3, 23.1. IR (neat): 3330, 2919, 1676, 1513, 1471, 1436, 1365, 1316, 842, 808, 781, 760, 665 $cm^{-1}$. HRMS (ESI-TOF) Calcd for $C_{17}H_{12}Br_3N_2O$, $[M+H]^+$: 496.8494, found 496.8502.

**General Procedure for 2,6-Dichloro-N-(5-chloroquinolin-8-yl)-3-methylbenzamide (3b)**. *new-* Substrate **2c** (0.25 mmol, 1 equiv, 85.75 mg,) was chlorinated following the general procedure, with ammonium chloride (5.0 mmol, 20 equiv, 267.5 mg) at 90 °C in an oil bath for 9 h. Purification by column chromatography on silica gel (petroleum ether : ethyl acetate = 80 : 1) to afford **3b** (74.76 mg, 73%) as a white solid. M.p.: 206.8-207.6 °C. $^1H$ NMR (400 MHz, $CDCl_3$): δ 10.02 (s, 1 H), 8.89 (d, *J* = 8.4 Hz, 1 H), 8.79 (dd, *J* = 4.0, 1.2 Hz, 1 H), 8.55 (dd, *J* = 8.4, 1.2 Hz, 1 H), 7.89 (d, *J* = 8.4 Hz, 1 H), 7.57 (dd, *J* = 8.4, 4.0 Hz, 1 H), 7.29 (d, *J* = 3.2 Hz, 2 H),2.41 (s, 3 H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): δ 163.2, 148.8, 139.1, 136.04, 135.99, 135.9, 133.9, 132.2, 132.1, 130.9, 129.4, 127.8, 127.3, 122.8, 117.6, 115.2, 20.0. IR (neat): 3331, 1677, 1514, 1473, 1444, 1383, 1366, 1317, 939, 910, 811, 780, 645 $cm^{-1}$. HRMS (ESI-TOF) Calcd for $C_{17}H_{12}BrCl_2N_2O$, $[M+H]^+$: 408.9505, found 408.951.

**General Procedure for 3-methyl-N-(5-(phenylethynyl)quinolin-8-yl)benzamide (3c)**.*new* Substrate **2c** (0.25 mmol, 1 equiv, 85.75 mg) added copper(I) iodide (5 mol %), $Pd(PPh_3)_2Cl_2$ (5 mol %), triethylamine (2.5 mmol), phenylacetylene (0.5 mmol, 2 equiv, 51 mg) and DMF (1.5 mL) under $N_2$ atmosphere. The reaction mixture was placed in a pre-heated oil bath at 50 °C and vigorously stirred for 6 h. Subsequently it was cooled down to room temperature, filtered through a plug of celite and then washed saturated brine and extracted by with ethyl acetate. The solvents were removed under reduced pressure and the crude reaction mixture was purified by chromatography on silica gel using (petroleum ether : ethyl acetate = 50:1) as eluent to obtain the desired product **3c** (72.4 mg, 80%) as yellow solid. M.p.: 131.6-132.8 °C. $^1H$ NMR (400 MHz, $CDCl_3$): δ 10.79 (s, 1H), 8.93 (d, *J* = 8.4 Hz, 1H), 8.89 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.73 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.92-7.84 (m, 3H), 7.67-7.62 (m, 2H), 7.58 (dd, *J* = 8.4, 4.4 Hz, 1H), 7.48–7.36 (m, 5H), 2.50 (s, 3H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.6, 147.6, 137.7, 137.4, 134.11, 134.08, 133.8, 131.8, 130.8, 130.6, 127.7, 127.5, 127.2, 127.1, 123.2, 122.1, 121.2, 115.0, 113.8, 93.1, 85.4, 20.5. IR (neat): 3354, 1670, 1527, 1486, 1375, 1329, 1267, 1189, 846, 806, 729, 685, 657, 497 $cm^{-1}$. HRMS (ESI-TOF) Calcd for $C_{25}H_{19}N_2O$, $[M+H]^+$: 363.1492, found 363.1497.

**General Procedure for 4-bromoquinolin-8-amine (3d)**.*7k* Substrate **2c** (0.25 mmol, 1 equiv, 85.75 mg) in EtOH (2 mL), was added NaOH (1.5 mmol, 6 equiv, 0.06 g). The mixture was heated at 80 °C in an oil bath for 12 h. Then, the mixture was concentrated under reduced pressure. The residue was purified by chromatography silica gel (petroleum ether : ethyl acetate = 5: 1) to afford the desired product **3d** (54.3 mg, 98% ). $^1H$ NMR (400 MHz, $CDCl_3$): δ 8.75 (dd, *J* = 4.0, 1.2 Hz, 1 H), 8.40 (dd, *J* = 8.4, 1.6 Hz, 1 H), 7.55 (d, *J* = 8.4 Hz, 1 H), 7.45 (dd, *J* = 8.4, 4.0 Hz, 1 H), 6.78 (d, *J* = 8.0 Hz, 1 H), 5.05 (s, 2H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): δ 147.8, 144.0, 138.9, 135.4, 130.8, 127.7, 122.4, 110.1, 107.3.

**General Procedure for N-(5,7-dideuteroquinolin-8-yl)benzamide (1a-$D_2$)**.*7c* In a 50 mL Schlenk tube with a magnetic stir bar, 8-aminoquinoline (2.0 mmol, 1 equiv, 288.0 mg) was added, followed by conc. DCl in $D_2O$ (1 equiv, 2.0 mL). The tube was capped and sealed and heated for 12 h at 150 °C in an oil bath. When it was completed, the reaction was cooled to room temperature and diluted with water (25 mL). Extracted with EtOAc (3 x 15 mL) and the combined organic layer was washed with 1 M $NaHCO_3$ aqueous solution (3 x 15 mL),

brine (50 mL), dried with $Na_2SO_4$, and filtered through a pad of Celite. The solvent was removed under reduced pressure to afford the deuterated aniline product Q-D. Then the reaction worked as reported methode to afford N-(5,7-dideuteroquinolin-8-yl)benzamide (**1a-$D_2$**). $^1$H NMR (400 MHz, $CDCl_3$): δ 10.74 (s, 1H), 8.83 (d, *J* = 2.0 Hz, 1H), 8.20-8.12 (m, 1H), 8.09 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.60-7.51 (m, 4H), 7.49-7.21 (m, 1H). $^{13}$C{1H} NMR (100 MHz, $CDCl_3$): δ 164.4, 147.3, 137.7, 135.3, 134.1, 133.5, 130.8, 127.8, 126.9, 126.3, 126.2, 120.7, 120.4, 120.2, 115.5, 115.2, 115.0.

**Parallel experiments**.The electrocatalysis was carried out in an undivided cell equipped with two platinum electrodes (1.0×1.0 $cm^2$). 8-Aminoquinoline Amide **1a** (0.2 mmol, 1 equiv, 49.6 mg), $NH_4Br$ (2.4 mmol, 12 equiv, 232.8 mg), $Cu(OAc)_2$ (10 mol %, 3.62 mg,), DMF (3 mL) were added to the electrochemical cell. Electrocatalysis was preformed at 60 °C in an oil bath with a constant current of 3 mA, and stopped respectively at 0.5 h, 1 h, 2 h, 3 h and 4 h. In similar, substrate **1a-[$D_2$]** (0.20 mmol, 1 equiv, 50.0 mg) was used instead of 1a for the reaction .The yield of products was determined by 1H NMR with $CH_2Br_2$ as internal standard and the reaction rate was obtained by plotting the percentage yield of the product versus time. The kinetic isotope effect ($k_H/k_D$) was determined to be 1.07.

**Electrochemical Procedure for Cyclic Voltammetry.** Cyclic voltammograms were recorded with a CHI660E potentiostat at room temperature in DMF. *n*-$Bu_4NPF_6$ (0.1 M) was used as the supporting electrolyte, and a Pt electrode (area = 0.03 $cm^2$) was used as the working electrode. The auxiliary electrode was a Pt wire. All potentials are referenced against the SCE redox couple. The scan rate was 100 mV/s.

## ASSOCIATED CONTENT

### Supporting Information

reaction optimization, compare the reaction with or withot copper, mechanistic studies, X-ray crystallography data, CIF files, $^1$H and $^{13}$C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interests.

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