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Ligand-Enabled, Copper-Promoted Regio- and Chemoselective Hydroxylation of Arenes, Aryl Halides, and Aryl Methyl Ethers

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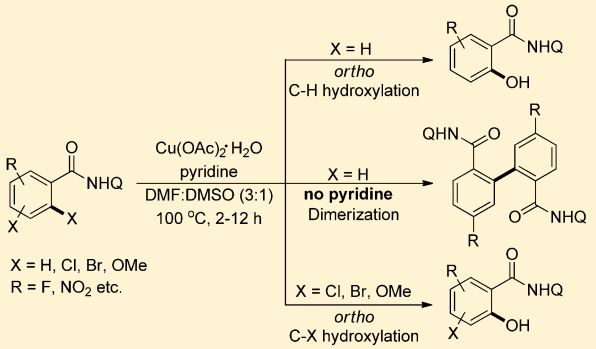
Supporting Information

ABSTRACT: We report here a practical method for the *ortho* C−H hydroxylation of benzamides with inexpensive copper(II) acetate monohydrate and a pyridine ligand. An intra- and intermolecular ligand combination was explored to achieve regio- and chemoselective hydroxylation. Interestingly, typical regiochemical scrambling associated with the C−H activation was further resolved by introducing a ligand-directed *ortho* hydroxylation of haloarenes and aryl methyl ethers.



INTRODUCTION

A paradigm shift from "innate" to "guided" C−H activation has been observed in the past couple of decades for the development of high-utility synthetic methods.[1] The use of ligands to control reactivity and selectivity in transition-metal-catalyzed C−H functionalization is emerging.[2] While the intramolecular ligands direct the site of C−H functionalization,[3] the external ligands control the chemoselectivity[4] and stereoselectivity[5] of the transformations. Owing to their importance in the pharmaceutical, agrochemical, polymer, and materials industries, considerable attention has been dedicated to the synthesis of phenolic compounds directly from hydrocarbons (Figure 1).[6] Following the seminal report by Jintoku, Fujiwara, and co-workers, catalyses using numerous noble metals such as Pd and Ru of direct acetylation/hydroxylation of arenes have been reported.[7] However, expensive noble metal catalysts are not attractive for the large-scale industrial processes. Alternatively, copper has attracted much attention due to its earth abundance and low cost and the distinct reactivity of copper-containing metalloenzymes toward oxidation.[8] The Yu group reported a copper(II)-mediated *ortho* C−H acetoxylation/hydroxylation using a nonremovable pyridine moiety[9a] and a removable oxazolyamide group with moderate yields.[9b] A copper(II)-mediated *ortho* hydroxylation of arenes and heteroarene carboxylates using a removable 2-(pyridine-2-yl)isopropyl (PIP) ligand was reported by the Shi group.[10] However, this method is limited due to the use of an expensive directing group, superstoichiometric silver(I) salt, and moisture-sensitive tetrabutylammonium salt. In recent years, a plethora of copper-catalyzed/mediated C(sp^2)−H functionalizations using cheap and commercially available 8-aminoquinoline have been reported.[11] In fact, a discrete example of copper(II)/silver(I)-mediated C(sp^2)−H acetoxylation in moderate yield (40%) using 8-aminoquinoline was also reported by the Kuninobu and Kanai group.[11g]

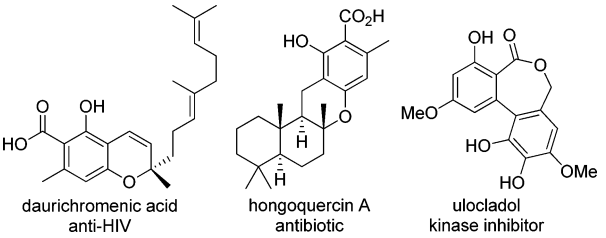


Figure 1. Biologically active salicylic acid derivatives.

We report here a practical, operationally simple, and commercially available 8-aminoquinoline-directed *ortho* hydroxylation of benzamides using inexpensive copper(II) acetate monohydrate and a pyridine ligand without any additional oxidants or additives. We also report for the first time a highly *ortho* selective hydrolysis of bromo, chloro, and methoxy groups, keeping the other regioisomers intact (Scheme 1).

RESULTS AND DISCUSSION

Considering the ability of bidentate monoanionic ligands to stabilize higher oxidation states of metals, we chose Daugulis's 8-aminoquinoline-derived benzamide, **1a**, as a model substrate

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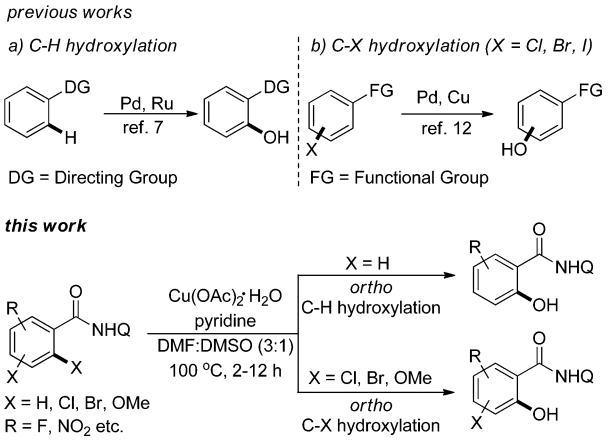
Scheme 1. Regio- and Chemoselective Hydroxylation

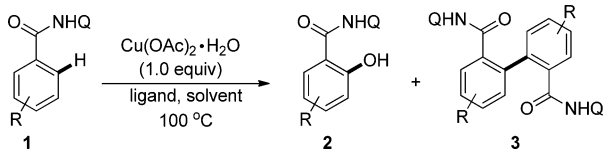


for reaction optimization.[3a] Heating a mixture of **1a** with 1.0 equiv of copper(II) acetate monohydrate in acetonitrile at 100 °C afforded 15% of the desired hydroxylation product. After rigorous screening, we found that the hydroxylation product was formed almost quantitatively in DMSO. We also observed that substitution on the benzamide has a prominent effect on the chemoselectivity. Although *o*-CF_3 resulted in the hydroxylation product exclusively, the *m*-CF_3 afforded a mixture of the hydroxylation and homocoupling products, and the *p*-CF_3 provided the homocoupling product exclusively. We hypothesized that coordinatively unsaturated copper may undergo further intermolecular C−H insertion and reductive elimination to form the homocoupling product. Therefore, addition of external ligands may stabilize the monomeric species and facilitate intramolecular reductive elimination to provide the acetoxylation product first, which will hydrolyze in situ to provide phenolic compounds. Gratifyingly, using 1,10-phenanthroline (2.0 equiv), the hydroxylation product was formed almost quantitatively (entry 10, Table 1). Considering the industrial viability, expensive 1,10-phenanthroline was successfully replaced by the cheap and abundant pyridine ligand. The DMSO was found to be essential for this transformation, and the yield of the desired hydroxylation product was improved to some extent by using a mixture of DMSO and DMF (1:3) (entry 7 vs entry 8, Table 1). Finally, heating the reaction mixture with excess (10 equiv) pyridine in a mixture of DMSO/DMF (1:3) at 100 °C afforded the desired hydroxylation product quantitatively and selectively (entry 13, Table 1).

Under the optimized reaction conditions, we explored the substrate scope of C−H hydroxylation. A wide variety of substituents at the *para* position, such as alkyl, phenyl, alkoxy, trifluoromethyl, acyl, and even halogens such as fluoro, chloro, bromo, and iodo, were compatible under the reaction conditions (Scheme 2). Various substituents at the *ortho* position, such as trifluoromethyl, fluoro, nitro, methyl, and thiomethyl, were also intact (**2f−2j**, Scheme 2). Interestingly, pyridine-4-carboxamide afforded the hydroxylation product in high yield. Of note, in all cases the monohydroxylation products were formed exclusively even with higher copper loading. The halogen substituents on the product could be useful for further manipulations.

During the course of this study, we observed that the steric and electronic parameters of the *meta* substitution play an important role in the product selectivity. For example, electron-donating groups such as methyl, methoxy, and even bromo led to the formation of both regioisomers of the hydroxylation products (Scheme 3). Interestingly, the electron-withdrawing trifluoromethyl group provided a single hydroxylation product quantitatively. The bulky aryl substituents also afforded a single isomer of the desired hydroxylation product at the sterically less hindered side.

Table 1. Optimization of the Reaction Conditions[a,b]



entry	R	ligand	solvent	yield (%)	2:3[c]
1	H		DMF	0	
2	H		CH_3CN	15	>20:1
3	H		DMSO	99	>20:1
4	*o*-CF_3		DMSO	80	>20:1
5	*m*-CF_3		DMSO	70	1:20
6	*p*-CF_3		DMSO	65	>1:20
7	*p*-CF_3	1,10-phen (1.2 equiv)	DMSO	85	7:1
8	*p*-CF_3	1,10-phen (1.2 equiv)	DMSO/DMF (1:3)	88	10:1
9	*p*-CF_3	1,10-phen (1.5 equiv)	DMSO/DMF (1:3)	91	20:1
10	*p*-CF_3	1,10-phen (2.0 equiv)	DMSO/DMF (1:3)	96	>20:1
11	*p*-CF_3	pyridine (2.0 equiv)	DMSO/DMF (1:3)	85	2:1
12	*p*-CF_3	pyridine (5.0 equiv)	DMSO/DMF (1:3)	90	3:1
13	***p*-CF_3**	**pyridine (10 equiv)**	**DMSO/DMF (1:3)**	**96**	**>20:1**
14	*m*-CF_3	pyridine (10 equiv)	DMSO/DMF (1:3)	98	>20:1
15	H	pyridine (10 equiv)	DMSO/DMF (1:3)	99	>20:1

[a]All reactions were carried out on a 0.1 mmol scale, 0.1 M. Q = 8-quinoline. [b]Yields referred to here are overall isolated yields. [c]The product distribution was determined by ^{1}H NMR of the crude product.

To overcome this regioselectivity issue, we introduced the concept of ligand-directed C−X hydroxylation. We observed that *o*-chloro- or *o*-bromo-containing benzamides hydrolyzed to the corresponding phenol in preference to the C−H hydroxylation under the optimized reaction conditions. However, *o*-iodo resulted in a complex mixture of products. More interestingly, the *o*-methoxy group also hydrolyzed to the corresponding phenol in high yield. Being encouraged by these unprecedented results, we intended to extend this ligand-directed C−X hydroxylation to the dihalo- and inexpensive polymethoxybenzamides. Contrary to the conventional C−X hydroxylation,[12] it was observed that chloro, bromo, or methoxy groups were hydrolyzed selectively at the *ortho* position, while the same functional groups at the *meta* and *para* positions remain intact. This directed C−X hydroxylation strategy could be a potential solution to the regiochemical scrambling as observed in C−H hydroxylation (**1v−1x**, Scheme 3, vs entries 7 and 8, Table 2). Particularly, 3-bromobenzamide **1x** furnished an inseparable mixture of **2x** and **2x′** (Scheme 3) which is not synthetically useful, but 2,5-dibromobenzamide (entry 8, Table 2) afforded a single hydroxylation product in

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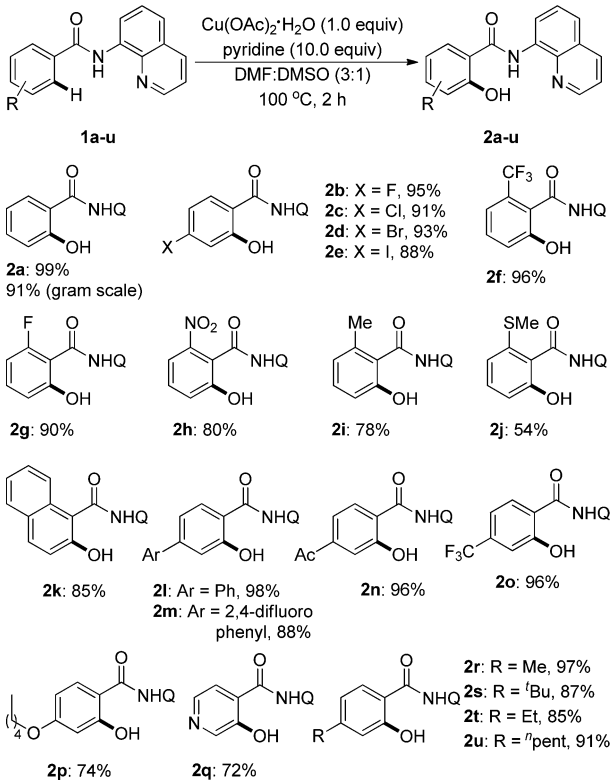
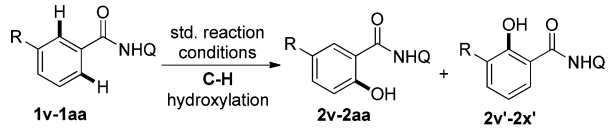
Scheme 2. Scope of Benzamides in C−H Hydroxylation[a,b]



[a]Reagents and conditions: benzamides (0.2 mmol), $Cu(OAc)_2·H_2O$ (0.2 mmol), pyridine (2.0 mmol), DMF/DMSO (3:1; 2 mL), 100 °C, 2 h. [b]Yields refer to the average isolated yields of at least two experiments.

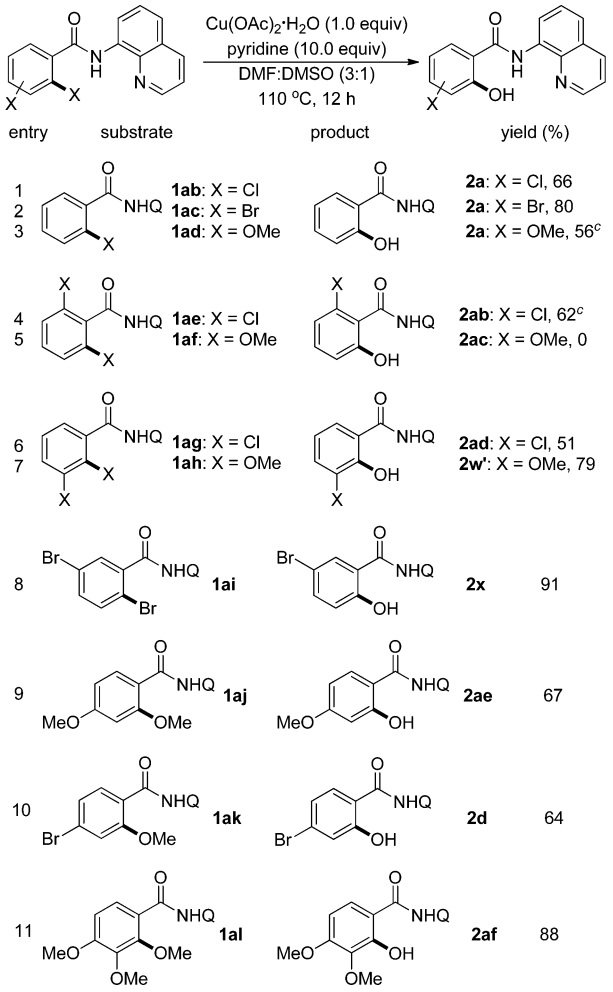
Scheme 3. Regiochemical Scrambling in C−H Hydroxylation[a]



R = Me, 94% yield, (**2v**:**2v'** = 60:40)
R = OMe, 70% yield (**2w**:**2w'** = 57:43)
R= Br, 88% yield (**2x**:**2x'** = 50:50)
R = CF_3, 98% yield, **2y** only
R = *p*-tolyl, 98% yield, **2z** only
R = 2,4-difluorophenyl, 94% yield, **2aa** only

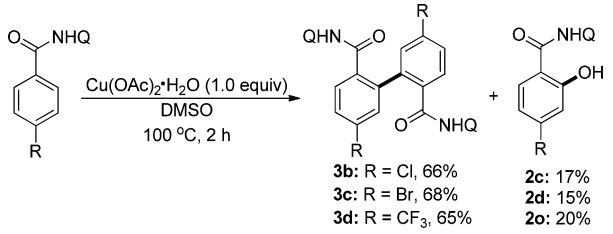
[a]Reagents and conditions: benzamides (0.2 mmol), $Cu(OAc)_2·H_2O$ (0.2 mmol), pyridine (2.0 mmol), DMF/DMSO (3:1; 2 mL), 100 °C, 2 h.

Table 2. Scope of *ortho* C−X Hydroxylation[a,b]



[a]Reagents and conditions: benzamides (0.2 mmol), $Cu(OAc)_2·H_2O$ (0.2 mmol), pyridine (2.0 mmol), DMF/DMSO (3:1; 2 mL), 100 °C, 12 h. [b]Yields refer to the average isolated yields of at least two experiments. [c]Unreacted starting materials were recovered.

Scheme 4. Scope of Directed Homocoupling



excellent yield. More interestingly, 2,3-dichloro- and 2,4,5-trimethoxybenzamides provided hydroxylation selectively at the sterically more hindered side (entries 6 and 11, Table 2), whereas, in such situations, C−H hydroxylation occurs preferably at the less hindered side.

The Miura group reported a copper-mediated homocoupling of thiophene-2-carboxylates using 8-aminoquinoline as the directing group.[13] We also examined the ligand-directed dimerization of benzamides. As expected, in the absence of pyridine, the *para*-substituted substrates afforded dimerization products in good yields with minor hydroxylation products (Scheme 4).[14]

To demonstrate the synthetic utility of the present protocol, the hydroxylation product **2aa** was heated in concd HCl to provide a nonsteroidal anti-inflammatory drug (NSAID), diflunisal, **4a**, in excellent yield. The 8-aminoquinoline was also recovered in almost quantitative yield (Scheme 5).

INVESTIGATION OF THE REACTION MECHANISM

We have performed several control experiments to clarify the mechanism of the hydroxylation reaction (see Scheme 6). The kinetics of the hydroxylation reaction was measured with **1a** and the corresponding **1a**-d_5. The high value of the intermolecular kinetic isotope effect (k_H/k_D = 3.6) indicates

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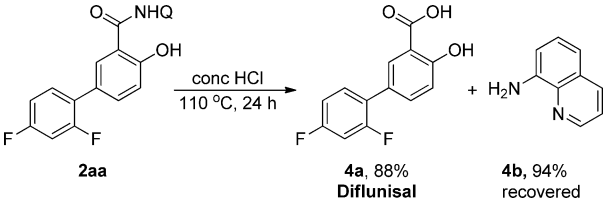
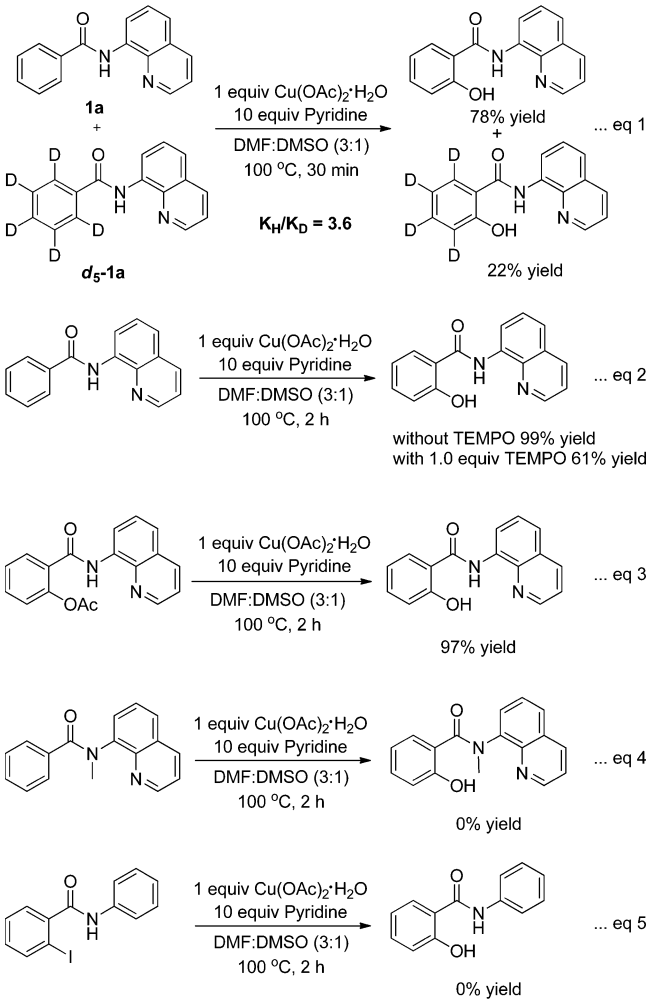
Scheme 5. Synthesis of Diflunisal



Scheme 6. Control Experiments



that the reaction may involve a rate-limiting concerted metalation−deprotonation (CMD) (eq 1, Scheme 6). In addition, 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) has no significant effect on the reaction outcome, eliminating the radical pathway (eq 2, Scheme 6). The OAc group was hydrolyzed under the reaction conditions but not during workup, indicating that initially C−H acetoxylation occurs, and the acetate is hydrolyzed to the corresponding phenol in situ (eq 3, Scheme 6). The 8-aminoquinoline as the directing group is crucial for the chemo- and regioselective hydroxylation under the present reaction conditions since no hydroxylation product was obtained from the corresponding *N*-phenylbenzamide or 2-iodo-*N*-phenylbenzamide (eqs 4 and 5, Scheme 6). Presumably, the directing group helps to bring copper in close proximity to the C−X (X = Cl, Br, I) bonds for the oxidative addition. Subsequently, reductive elimination of the copper species results in the acetoxylation product, which is hydrolyzed in situ to provide the desired hydroxylation product. From a control experiment, it was evident that in the absence of a pyridine ligand no hydroxylation product from the corresponding aryl methyl ether was observed, which could be indicative of copper/pyridine-mediated hydrolysis of the methyl ether. However, the exact mechanism of methyl ether hydrolysis and dimerization is not clear at this moment.

CONCLUSION

In conclusion, we have developed a regio- and chemoselective hydroxylation of benzamides combining ligand-directed and ligand-enabled strategies. The inherent regiochemical scrambling associated with C−H bond activation was resolved via ligand-directed *ortho* C−X (X = Cl, Br, OMe) bond hydroxylation. The use of an external ligand also enables a switch from the homocoupling to the hydroxylation product. The inexpensive catalyst, reproducibility on the gram scale, removal and recovery of the directing group, etc. are the attractive features of the present protocol.

EXPERIMENTAL SECTION

General Information. Melting points were determined in open end capillary tubes and are uncorrected. TLC was performed on silica gel plates (Merck silica gel 60, f254), and the spots were visualized with UV light (254 and 365 nm) and $KMnO_4$ stain. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 solvent using TMS as the internal standard. HRMS data (m/z) were measured using the EI (magnetic sector, positive ion) and ESI (Q-TOF, positive ion) techniques. Infrared (IR) spectra were recorded on a Fourier transform infrared spectrometer; only intense peaks are reported.

General Experimental Procedure for Amide Formation. The benzamides were prepared following the previous literature procedure:[15] A solution of *N*′-(3-(dimethylamino)propyl)-*N*-ethylcarbodimide, hydrochloride salt (EDC·HCl) (1.3 equiv), 4-(*N*,*N*-dimethylamino)pyridine (DMAP) (0.1 equiv), and carboxylic acid (1.2 equiv) in CH_2Cl_2 (5.0 mL, for 1 mmol of 8-aminoquinoline) was stirred under a nitrogen atmosphere followed by slow addition of 8-aminoquinoline (720 mg, 5 mmol, 1.0 equiv) at room temperature. The resulting reaction mixture was stirred overnight. After completion of the reaction as indicated by TLC, the reaction mixture was quenched with 1 N HCl followed by extraction with a CH_2Cl_2 and brine solution. The organic layer was separated and washed with a saturated aqueous solution of $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4. The solvent was evaporated under vacuum. The crude residue was purified using column chromatography on silica gel.

The benzamides (**1a**, **1b**, **1d**, **1f**, **1h**, **1i**, **1k**, **1y**, **1ab**,[11i] **1c**, **1l**, **1s**, **1t**,[11d] **1e**,[23] **1g**,[21] **1o**, **1ac**,[22] **1q**, **1r**, **1v**,[11l] **1w**, **1x**,[20] **1ad**,[19] **1ag**,[11n] **1h**,[7o] **1aj**,[11j] **1am**,[17] **1ap**,[16] **1aq**[18]) were synthesized according to the above general procedure, and the spectral data are consistent with the reported values.

2-(Methylthio)-N-(quinolin-8-yl)benzamide, ***1j.*** Column chromatography (SiO_2, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a white solid (1.29 g, 88%): ^1H NMR (300 MHz, $CDCl_3$) δ 10.48 (s, 1H), 8.97 (dd, J = 7.2, 1.8 Hz, 1H), 8.80 (dd, J = 4.2, 1.8 Hz, 1H), 8.18 (dd, J = 8.4, 1.8 Hz, 1H), 7.77 (dd, J = 7.5, 1.2 Hz, 1H), 7.63−7.56 (m, 2H), 7.54−7.39 (m, 3H), 7.32−7.27(m, 1H), 2.51 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 148.2, 138.7, 138.6, 136.3, 135.1, 134.6, 130.9, 128.1, 127.9, 127.4, 126.7, 124.9, 121.8, 121.6, 116.7, 16.5; HRMS (ESI, m/z) calcd for $C_{17}H_{14}N_2OSNa$ $[M + Na]^+$ 317.0725, found 317.0723.

2′,4′-Difluoro-N-(quinolin-8-yl)-[1,1′-biphenyl]-4-carboxamide, ***1m.*** 4-Bromo-*N*-(quinolin-8-yl)benzamide (327 mg, 1.0 mmol) was taken in an oven-dried round-bottom flask which was connected through a condenser under a N_2 atmosphere and dissolved with 3 mL of DMF, and then (2,4-difluorophenyl)boronic acid (316 mg, 2.0 mmol, 2.0 equiv), K_2CO_3 (207 mg, 1.5 mmol, 1.5 equiv), and

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$Pd(PPh_3)_4$ (57.8 mg, 0.05 equiv) were added under a nitrogen atmosphere at room temperature. Then the mixture was stirred overnight at 120 °C. The reaction mixture was extracted with an ethyl acetate and brine solution. The desired organic phase was dried over Na_2SO_4, filtered, and evaporated in vacuo. The crude mixture was purified by column chromatography (SiO_2, eluting with 8:2 hexane/ethyl acetate) to afford the desired product as a white solid (306 mg, 85%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.81 (s, 1H), 8.96 (d, J = 7.2 Hz, 1H), 8.87 (s, 1H), 8.22−8.16 (m, 3H), 7.71−7.44 (m, 6H), 7.04−6.93 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9, 148.3, 138.7, 138.4, 136.4, 134.3 (d, J = 18.0 Hz), 131.4, 131.3, 131.3, 129.2 (d, J = 3.0 Hz), 128.0, 127.5 (d, J = 6.0 Hz), 121.74, 121.69, 116.5, 111.8 (d, J = 25.5 Hz),104.6 (t, 25.5 Hz); HRMS (ESI, m/z) calcd for $C_{22}H_{14}F_2N_2ONa$ $[M + Na]^+$ 383.0972, found 383.0972.

4-Acetyl-N-(quinolin-8-yl)benzamide, ***1n.*** Column chromatography (SiO_2, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a white solid (1.16 g, 80%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.82 (s, 1H), 8.94 (dd, J = 6.9, 2.1 Hz, 1H), 8.87 (dd, J = 4.5, 1.8 Hz, 1H), 8.28−8.11 (m, 5H), 7.65−7.57 (m, 2H), 7.51 (dd, J = 8.4, 4.2 Hz, 1H), 2.69 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.4, 164.3, 148.4, 139.3, 138.9, 138.7, 136.4, 134.2, 128.7, 128.0, 127.6, 127.4, 122.1, 121.8, 116.7, 26.9; HRMS (ESI, m/z) calcd for $C_{18}H_{14}N_2O_2Na$ $[M + Na]^+$ 313.0953, found 313.0936.

4-(Pentyloxy)-N-(quinolin-8-yl)benzamide, ***1p.*** Column chromatography (SiO_2, eluting with 8:2 hexane/ethyl acetate) afforded the desired product as a white solid (1.40 g, 84%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.68 (s, 1H), 8.91 (dd, J = 7.5, 0.9 Hz, 1H), 8.85 (dd, J = 4.2, 1.2 Hz, 1H), 8.18 (dd, J = 6.5, 1.2 Hz, 1H), 8.05 (d, J = 8.7 Hz, 2H), 7.62−7.54 (m, 2H), 7.51−7.45 (m, 1H), 7.02 (d, J = 8.7 Hz, 2H), 4.04 (t, J = 6.6 Hz, 2H), 1.88−1.79 (m, 2H), 1.52−1.35 (m, 4H), 0.95(t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0, 162.1, 148.2, 138.7, 136.3, 134.8, 129.1, 128.0, 127.5, 127.1, 121.6, 121.3, 116.3, 114.4, 68.2, 28.8, 28.1, 22.4, 14.0; HRMS (ESI, m/z) calcd for $C_{21}H_{22}N_2O_2Na$ $[M + Na]^+$ 357.1579, found 357.1581.

4-Pentyl-N-(quinolin-8-yl)benzamide, ***1u.*** Column chromatography (SiO_2, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a white solid (1.37 g, 86%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.73 (s, 1H), 8.94 (dd, J = 7.2, 0.9 Hz, 1H), 8.85 (dd, J = 4.2, 1.2 Hz, 1H), 8.18 (dd, J = 8.4, 2.1 Hz, 1H), 8.01 (d, J = 8.1 Hz, 2H), 7.62−7.52 (m, 2H), 7.50−7.45 (m, 1H), 7.35 (d, J = 8.1 Hz, 2H), 2.70 (t, J = 7.5 Hz, 2H), 1.69−1.62 (m, 2H), 1.37−1.32 (m, 4H), 0.91 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 148.2, 147.3, 138.7, 136.3, 134.7, 132.7, 132.5, 128.8, 127.9, 127.4, 127.34, 127.28, 121.6, 121.5, 116.4, 35.8, 31.42, 30.9, 22.5, 14.0; HRMS (ESI, m/z) calcd for $C_{21}H_{22}N_2ONa$ $[M + Na]^+$ 341.1630, found 341.1640.

4′-Methyl-N-(quinolin-8-yl)-[1,1′-biphenyl]-3-carboxamide, ***1z.*** 3-Bromo-*N*-(quinolin-8-yl)benzamide (327 mg, 1.0 mmol) was taken in an oven-dried round-bottom flask which was connected through a condenser under a N_2 atmosphere and dissolved with 3 mL of DMF, and then *p*-tolylboronic acid (272 mg, 2.0 mmol, 2.0 equiv), K_2CO_3 (207 mg, 1.5 mmol, 1.5 equiv), and $Pd(PPh_3)_4$ (57.8 mg, 0.05 equiv) were added under a nitrogen atmosphere at room temperature. Then the mixture was stirred overnight at 120 °C. The reaction mixture was extracted with an ethyl acetate and brine solution. The desired organic phase was dried over Na_2SO_4, filtered, and evaporated in vacuo. The crude mixture was purified by column chromatography (SiO_2, eluting with 8:2 hexane/ethyl acetate) to afford the desired product as a white solid (284 mg, 84%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.79 (s, 1H), 8.97 (d, J = 6.0 Hz, 1H), 8.85 (d, J = 3.9 Hz, 1H), 8.23 (s, 1H), 8.20 (d, J = 8.4 Hz, 1H), 8.02 (d, J = 7.5 Hz, 1H), 7.79 (d, J = 7.5 Hz, 1H), 7.63−7.54 (m, 5H), 7.48 (dd, J = 8.4, 4.2 Hz, 1H), 7.31 (d, J = 7.8 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 148.2, 141.6, 138.6, 137.5, 137.2, 136.2, 135.6, 134.4, 130.2, 129.5, 129.0, 127.8, 127.3, 126.9, 125.9, 125.4, 121.62, 121.55, 116.4, 21.0; HRMS (ESI, m/z) calcd for $C_{23}H_{18}N_2ONa$ $[M + Na]^+$ 361.1317, found 361.1317.

2′,4′-Difluoro-N-(quinolin-8-yl)-[1,1′-biphenyl]-3-carboxamide, ***1aa.*** 3-Bromo-*N*-(quinolin-8-yl)benzamide (327 mg, 1.0 mmol) was taken in an oven-dried round-bottom flask which was connected through a condenser under a N_2 atmosphere and dissolved with 3 mL of DMF, and then (2,4-difluorophenyl)boronic acid (316 mg, 2.0 mmol, 2.0 equiv), K_2CO_3 (207 mg, 1.5 mmol, 1.5 equiv), and $Pd(PPh_3)_4$ (57.8 mg, 0.05 equiv) were added under a nitrogen atmosphere at room temperature. Then the mixture was stirred overnight at 120 °C. The reaction mixture was extracted with ethyl acetate and brine solution. The desired organic phase was dried over Na_2SO_4, filtered, and evaporated in vacuo. The crude mixture was purified by column chromatography (SiO_2, eluting with 8:2 hexane/ethyl acetate) to afford the desired product as a white solid (293 mg, 82%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.80 (s, 1H), 8.97 (dd, J = 7.2, 1.5 Hz, 1H), 8.88 (dd, J = 4.2, 1.5 Hz, 1H), 8.24−8.21 (m, 2H), 8.11−8.07 (m, 1H), 7.77−7.73 (m, 1H), 7.68−7.57 (m, 3H), 7.55−7.49 (m, 2H), 7.06−6.95 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.2, 162.6 (dd, J = 247.5, 11.9 Hz), 159.8 (dd, J = 249.0, 12.0 Hz), 148.3, 138.8, 136.4, 135.7 (d, J = 3.0 Hz), 134.5, 132.3 (d, J = 4.5 Hz), 131.5 (dd, J = 9.0, 4.5 Hz), 128.9, 128.0 (d, J = 1.5 Hz), 127.4, 126.3, 124.4 (dd, J = 13.5, 4.5 Hz), 121.8, 121.7, 116.6, 111.8 (dd, J = 21.0, 3.0 Hz), 104.5 (t, J = 25.5 Hz); HRMS (ESI, m/z) calcd for $C_{22}H_{14}F_2N_2ONa$ $[M + Na]^+$ 383.0972, found 383.0972.

2,6-Dichloro-N-(quinolin-8-yl)benzamide, ***1ae.*** In an oven-dried 100 mL round-bottom (rb) flask, 2,6-dichlorobenzoic acid (764 mg, 4.0 mmol) was taken, and 10 mL of DCM and DMF (5 drops) were added. An ice bath was kept under the rb flask. Then oxyl chloride (0.4 mL, 4.8 mmol, 1.2 equiv) was slowly added. After completion of addition, the reaction mixture was stirred at room temperature for 3 h. Then the solvent and excess oxyl chloride were removed in vacuo. Then 15 mL of DCM and Et_3N (1.2 mL, 8.0 mmol, 2 equiv) were added followed by 8-aminoquinoline (692 mg, 4.8 mmol, 1.2 equiv) at 0 °C, and the mixture was stirred overnight at rt. The reaction mixture was quenched with satd aq $NaHCO_3$, and the organic layer was separated and washed with 1 N aq HCl (50 mL). Then the organic layer was dried over Na_2SO_4, filtered, and evaporated in vacuo. The desired crude was purified through column chromatography (SiO_2, eluting with 9:1 hexane/ethyl acetate) to afford the desired product as a white solid (822 mg, 65%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.05 (s, 1H), 8.97 (dd, J = 6.3, 2.7 Hz, 1H), 8.78 (dd, J = 3.6, 1.5 Hz, 1H), 8.20 (dd, J = 8.4, 1.8 Hz, 1H), 7.66−7.59 (m, 2H), 7.47 (dd, J = 8.4, 4.2 Hz, 1H), 7.43−7.40 (m, 2H), 7.37−7.31 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7, 148.4, 138.4, 136.4, 136.2, 134.0, 132.5, 130.9, 128.2, 128.0, 127.4, 122.5, 121.8, 117.2; HRMS (ESI, m/z) calcd for $C_{16}H_{10}Cl_2N_2ONa$ $[M + Na]^+$ 339.0068, found 339.0068.

2,6-Dimethoxy-N-(quinolin-8-yl)benzamide, ***1af.*** In an oven-dried 100 mL rb flask, 2,6-dimethoxybenzoic acid (728 mg, 4.0 mmol) was taken, and 10 mL of DCM and DMF (5 drops) were added. An ice bath was kept under the rb flask. Then oxyl chloride (0.4 mL, 4.8 mmol, 1.2 equiv) was slowly added. After completion of addition, the reaction mixture was stirred at room temperature for 3 h. Then the solvent and excess oxyl chloride were removed in vacuo. Then 15 mL of DCM and Et_3N (1.2 mL, 8.0 mmol, 2 equiv) were added followed by 8-aminoquinoline (692 mg, 4.8 mmol, 1.2 equiv) at 0 °C, and the mixture was stirred overnight at rt. The reaction mixture was quenched with satd aq $NaHCO_3$, and the organic layer was separated and washed with 1 N aq HCl (50 mL). Then the organic layer was dried over Na_2SO_4, filtered, and evaporated in vacuo. The desired crude was purified through column chromatography (SiO_2, eluting with 7:3 hexane/ethyl acetate) to afford the desired product as a white solid (739 mg, 60%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.07 (s, 1H), 9.04 (dd, J = 7.8, 1.5 Hz, 1H), 8.76 (dd, J = 4.2, 1.5 Hz, 1H), 8.16 (dd, J = 8.1, 1.5 Hz, 1H), 7.63−7.51 (m, 2H), 7.43 (dd, J = 8.4, 4.2 Hz, 1H), 7.35 (t, J = 8.4 Hz, 1H), 6.65 (d, J = 8.4 Hz, 2H), 3.85 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.3, 157.7, 157.6, 148.0, 138.4, 136.2, 136.2, 134.9, 131.0, 127.9, 127.5, 121.5, 121.4, 116.7, 116.3, 104.05, 104.03, 55.99, 55.96; HRMS (ESI, m/z) calcd for $C_{18}H_{16}N_2O_3Na$ $[M + Na]^+$ 331.1059, found 331.1065.

2,5-Dibromo-N-(quinolin-8-yl)benzamide, ***1ai.*** Column chromatography (SiO_2, eluting with 8:2 hexane/ethyl acetate) afforded the desired product as a white solid (1.85 g, 91%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.29 (s, 1H), 8.91 (dd, J = 6.0, 2.7 Hz, 1H), 8.80 (dd, J = 4.2, 1.5 Hz, 1H), 8.18 (dd, J = 8.4, 1.8 Hz, 1H), 7.83 (d, J = 2.4 Hz, 1H), 7.63−7.57 (m, 2H), 7.55−7.52 (m, 1H), 7.49−7.44 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.3, 148.4, 139.8, 138.5, 136.4, 135.0,

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134.4, 134.0, 132.4, 128.0, 127.3, 122.4, 121.8, 121.6, 118.3, 117.0; HRMS (EI, m/z) calcd for $C_{16}H_{10}Br_2N_2O$ $[M]^+$ 405. 9139, found 405.9181.

4-Bromo-2-methoxy-N-(quinolin-8-yl)benzamide, ***1ak.*** Column chromatography (SiO_2, eluting with 8:2 hexane/ethyl acetate) afforded the desired product as a white solid (1.27 g, 71%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.24 (s, 1H), 9.02 (dd, J = 8.1, 1.5 Hz, 1H), 8.87 (dd, J = 4.2, 1.5 Hz, 1H), 8.24−8.17 (m, 2H), 7.62−7.52 (m, 2H), 7.47 (dd, J = 8.4, 4.2 Hz, 1H), 7.31−7.28 (m, 1H), 7.23 (d, J = 1.5 Hz, 1H), 4.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6, 157.9, 148.2, 139.1, 136.2, 135.5, 133.6, 128.0, 127.5, 127.1, 124.6, 121.7, 121.5, 121.3, 117.3, 115.1, 100.0, 56.5; HRMS (ESI, m/z) calcd for $C_{17}H_{13}BrN_2O_2Na$ $[M + Na]^+$ 379.0058, found 379.0058.

2,3,4-Trimethoxy-N-(quinolin-8-yl)benzamide, ***1al.*** Column chromatography (SiO_2, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a white solid (1.28 g, 76%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.41 (s, 1H), 9.03 (dd, J = 3.9, 0.9 Hz, 1H), 8.91−8.90 (m, 1H), 8.19−8.17 (m, 1H), 8.11 (d, J = 4.5 Hz, 1H), 7.60−7.57 (m, 1H), 7.53−7.51 (m, 1H), 7.48−7.46 (m, 1H), 6.85 (dd, J = 4.5, 0.3 Hz, 1H), 4.27 (s, 3H), 3.96 (s, 3H), 3.95 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.1, 156.8, 152.8, 148.2, 141.8, 139.3, 136.2, 135.8, 128.1, 127.5, 127.1, 121.42, 121.41, 119.3, 117.4, 107.4, 62.0, 61.0, 56.0; HRMS (ESI, m/z) calcd for $C_{19}H_{19}N_2O_4$ $[M + H]^+$ 339.1345, found 339.1345.

N-Methyl-N-(quinolin-8-yl)benzamide, ***1an.*** A solution of *N*-(quinolin-8-yl)benzamide (248 mg, 1.0 mmol) in 3 mL of DMF was taken in a dried round-bottom flask. Sodium hydride (36 mg, 1.5 mmol, 1.5 equiv) was added followed by the slow addition of methyl iodide (0.9 mL, 1.5 mmol, 1.5 equiv) at 0 °C, and the mixture was stirred overnight at rt. The reaction mixture was extracted with an ethyl acetate and brine solution. The organic layer was separated, dried over Na_2SO_4, filtered, and evaporated in vacuo. The desired crude product was purified by column chromatography (SiO_2, eluting with 9:1 hexane/ethyl acetate) to afford the desired product as a white solid (231 mg, 88%). This compound is known.[11j] ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.01 (dd, J = 4.2, 1.5 Hz, 1H), 8.14 (dd, J = 8.1, 1.5 Hz, 1H), 7.69 (dd, J = 7.2, 2.1 Hz, 1H), 7.44 (dd, J = 8.4, 4.2 Hz, 1H), 7.41−7.34 (m, 2H), 7.31−7.28 (m, 2H), 7.10−7.07 (m, 1H), 7.02−6.97 (m, 2H), 3.62 (s, 3H).

2-(Quinolin-8-ylcarbamoyl)phenyl Acetate, ***1ao.*** A solution of 2-hydroxy-*N*-(quinolin-8-yl)benzamide (264 mg, 1.0 mmol) in 3 mL of DCM was taken in a dried round-bottom flask. Et_3N (0.29 mL, 2.0 mmol, 2.0 equiv) was added followed by the slow addition of acetyl chloride (0.1 mL, 1.5 mmol, 1.5 equiv) at 0 °C, and the mixture was stirred overnight at rt. The reaction mixture was extracted with a DCM and brine solution. The organic layer was separated, dried over Na_2SO_4, filtered, and evaporated in vacuo. The desired crude product was purified by column chromatography (SiO_2, eluting with 9:1 hexane/ethyl acetate) to afford the desired product as a white solid (225 mg, 85%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.99 (s, 1H), 9.01 (dd, J = 7.2, 2.1 Hz, 1H), 8.85 (dd, J = 4.2, 1.5 Hz, 1H), 8.22 (dd, J = 8.1, 1.5 Hz, 1H), 8.17 (dd, J = 8.1, 1.8 Hz, 1H), 7.62−7.55 (m, 3H), 7.50 (dd, J = 8.4, 4.2 Hz, 1H), 7.45−7.40 (m, 1H), 7.28−7.25 (m, 1H), 2.45 (s, 3H).

Compound ***2a****-d*$_5$. Column chromatography (SiO_2, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a white solid (1.15 g, 91%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 10. 76 (s, 1H), 8.95 (dd, J = 7.5, 1.2 Hz, 1H), 8.85 (dd, J = 4.2, 1.5 Hz, 1H), 8.19 (dd, J = 8.1, 1.2 Hz, 1H), 7.63−7.53 (m, 2H), 7.48 (dd, J = 8.4, 4.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1, 148.0, 138.4, 136.1, 134.7, 134.3, 131.5, 131.1, 130.8, 128.4, 128.1, 127.7, 127.2, 127.0, 126.6, 126.3, 121.49, 121.46, 116.2; HRMS (ESI, m/z) calcd for $C_{16}H_7D_5N_2ONa$ $[M + Na]^+$ 276.1161, found 276.1167.

General Experimental Procedure for the C−H Hydroxylation Reaction. In a 15 mL sealed tube, the substrate (0.2 mmol, 1 equiv), $Cu(OAc)_2{\cdot}H_2O$ (40 mg, 0.2 mmol, 1equiv), and pyridine (10 equiv) were added followed by the solvent DMF/DMSO (3:1; 2 mL). The tube was charged with a preheated oil bath at 100 °C for 2 h. The reaction mixture was diluted with ethyl acetate and quenched with 20 mL of a saturated solution of $Na_2S_2O_3{\cdot}5H_2O$ or Na_2S. Then the aqueous phase was extracted with ethyl acetate (2 × 10). The combined organic phase was washed with 1 N HCl (50 mL), collected, dried over Na_2SO_4, and concentrated under vacuum. The crude was purified by column chromatography on silica gel with a gradient of elution of petroleum ether and ethyl acetate to give the desired hydroxylation product.

2-Hydroxy-N-(quinolin-8-yl)benzamide, ***2a****, Scheme 2.* Column chromatography (SiO_2, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a white solid (52 mg, 99%): mp 120−122 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.33 (s, 1H), 11.00 (s, 1H), 8.90 (dd, J = 4.2, 1.2 Hz, 1H), 8.84 (dd, J = 5.7, 3.0 Hz, 1H), 8.22 (dd, J = 8.4, 1.5 Hz, 1H), 7.87 (dd, J = 7.2, 0.9 Hz, 1H), 7.64−7.58 (m, 2H), 7.54−7.46 (m, 2H), 7.09−7.00 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 162.1, 148.5, 138.8, 136.5, 134.6, 133.5, 128.0, 127.3, 126.1, 122.3, 121.9, 119.0, 118.8, 116.9, 115.2; IR (neat) υ_{max} 3347, 1651, 1543, 1491; HRMS (ESI, m/z) calcd for $C_{16}H_{12}N_2O_2Na$ $[M + Na]^+$ 287.0796, found 287.0791.

4-Fluoro-2-hydroxy-N-(quinolin-8-yl)benzamide, ***2b****, Scheme 2.* Column chromatography (SiO_2, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a white solid (54 mg, 95%): mp 147−149 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.65 (s, 1H), 10.88 (s, 1H), 8.88 (dd, J = 4.2, 1.5 Hz, 1H), 8.79 (dd, J = 5.1, 3.9 Hz, 1H), 8.21 (dd, J = 8.4, 1.8 Hz, 1H), 7.87−7.82 (m, 1H), 7.60−7.57 (m, 2H), 7.51 (dd, J = 8.4, 4.2 Hz, 1H), 6.77−6.69 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 166.3 (d, J = 252.0 Hz), 164.2 (d, J = 13.5 Hz), 148.4, 138.6, 136.4, 133.3, 127.91, 127.92 (d, J = 11.3 Hz), 127.2, 122.3, 121.8, 116.9, 111.8 (d, J = 3.0 Hz), 107.0 (d, J = 23.3 Hz), 105.3 (d, J = 24.0 Hz); IR (neat) υ_{max} 3431, 3338, 3066, 1627, 1551; HRMS (ESI, m/z) calcd for $C_{16}H_{11}FN_2O_2Na$ $[M + Na]^+$ 305.0702, found 305.0693.

4-Chloro-2-hydroxy-N-(quinolin-8-yl)benzamide, ***2c****, Scheme 2.* Column chromatography (SiO_2, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a white solid (55 mg, 91%): mp 181−183 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.49 (s, 1H), 10.91 (s, 1H), 8.88 (dd, J = 4.2, 1.5 Hz, 1H), 8.80- 8.77 (m, 1H), 8.11 (dd, J = 8.1, 1.5 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.59−7.58 (m, 2H), 7.51 (dd, J = 8.4, 4.2 Hz, 1H), 7.06 (d, J = 2.1 Hz, 1H), 6.97 (dd, J = 8.4, 1.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.7, 162.8, 148.5, 140.1, 138.7, 136.5, 133.3, 127.3, 127.0, 122.5, 121.9, 119.5, 118.8, 117.0, 113.7; IR (neat) υ_{max} 3418, 3334, 1641, 1546, 1491; HRMS (ESI, m/z) calcd for $C_{16}H_{11}ClN_2O_2Na$ $[M + Na]^+$ 321.0407, found 321.0394.

4-Bromo-2-hydroxy-N-(quinolin-8-yl)benzamide, ***2d****, Scheme 2 and Entry 10, Table 2.* Column chromatography (SiO_2, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a white solid (64 mg, 93%): mp 191−193 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.47 (s, 1H), 10.93 (s, 1H), 8.88 (dd, J = 4.2, 2.7 Hz, 1H), 8.82−8.76 (m, 1H), 8.21 (dd, J = 8.4, 1.5 Hz, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.61 (dd, J = 8.7, 4.5 Hz, 2H), 7.52 (dd, J = 8.4, 4.2 Hz, 1H), 7.24 (d, J = 1.5 Hz, 1H), 7.13 (dd, J = 8.7, 1.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.8, 162.7, 148.6, 138.7, 136.5, 133.3, 128.5, 128.0, 127.3, 127.0, 122.5, 122.4, 121.9, 117.1, 114.1; IR (neat) υ_{max} 3401, 3333, 1640, 1545, 1487; HRMS (ESI, m/z) calcd for $C_{16}H_{12}BrN_2O_2$ $[M + H]^+$ 343.0082, found 343.0082.

2-Hydroxy-4-iodo-N-(quinolin-8-yl)benzamide, ***2e****, Scheme 2.* Column chromatography (SiO_2, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a white solid (69 mg, 88%): mp 185−187 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.38 (s, 1H), 10.94 (s, 1H), 8.88 (d, J = 4.2 Hz, 1H), 8.79 (dd, J = 8.7, 4.5 Hz, 1H), 8.21 (d, J = 8.1 Hz, 1H), 7.60−7.59 (m, 2H), 7.54−7.50 (m, 2H), 7.46 (s, 1H), 7.34 (dd, J = 8.4, 1.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 162.2, 148.6, 138.7, 136.5, 133.3, 128.2, 128.03, 127.96, 127.3, 126.8, 122.5, 121.9, 117.0, 114.6, 101.0; IR (neat) υ_{max} 3429, 3313, 3092, 1619, 1592, 1554; HRMS (ESI, m/z) calcd for $C_{16}H_{11}IN_2O_2Na$ $[M + Na]^+$ 412.9763, found 412.9763.

2-Hydroxy-N-(quinolin-8-yl)-6-(trifluoromethyl)benzamide, ***2f****, Scheme 2.* Column chromatography (SiO_2, eluting with 8:2 hexane/ethyl acetate) afforded the desired product as a white solid (64 mg, 96%): mp 250−252 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.74 (s, 1H), 10.19 (s, 1H), 8.87−8.85 (m, 1H), 8.73 (d, J = 7.5 Hz, 1H), 8.45 (dd, J = 8.1, 1.2 Hz, 1H), 7.75 (d, J = 7.8, 1H), 7.68−7.63 (m, 2H), 7.53 (t, J = 7.8, 1H), 7.27 (d, J = 7.2 Hz, 2H); ^{13}C NMR (75 MHz,

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DMSO-d_6) δ 163.8, 155.4, 149.5, 138.1, 137.2, 134.5, 131.4, 128.2, 127.9, 127.5 (q, J = 5.6 Hz), 124.2 (q, J = 271.6 Hz), 123.4, 122.8, 120.8, 116.9 (q, J = 5.2 Hz), 116.7; IR (neat) υ_{max} 3344, 3234, 1653, 1527, 1482; HRMS (EI, m/z) calcd for $C_{17}H_{11}F_3N_2O_2$ $[M]^+$ 332.0773, found 332.0779.

2-Fluoro-6-hydroxy-N-(quinolin-8-yl)benzamide, ***2g****, Scheme 2.* Column chromatography (SiO_2, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a white solid (51 mg, 90%): mp 115−118 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.19 (s, 1H), 11.54 (d, J = 19.8 Hz, 1H), 8.89 (dd, J = 4.2, 1.5 Hz, 1H), 8.87 (dd, J = 3.6, 1.8 Hz, 1H), 8.19 (dd, J = 8.1, 1.5 Hz, 1H), 7.60−7.55 (m, 2H), 7.49 (dd, J = 8.4, 4.2 Hz, 1H), 7.41−7.34 (m, 1 H), 6.86 (d, J = 8.4 Hz, 1H), 6.76−6.69 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4 (d, J = 3.0 Hz), 164.0 (d, J = 3.8 Hz), 161.2 (d, J = 247.5 Hz), 148.7, 138.9, 136.3, 134.0, 133.9, 128.0, 127.2, 122.7, 121.8, 118.0, 114.7 (d, J = 1.5 Hz), 105.9 (d, J = 25.5 Hz), 104.6 (d, J = 12.7 Hz); IR (neat) υ_{max} 3413, 3321, 1616, 1545, 1455; HRMS (EI, m/z) calcd for $C_{16}H_{11}FN_2O_2$ $[M]^+$ 282.0805, found 282.0804.

2-Hydroxy-6-nitro-N-(quinolin-8-yl)benzamide, ***2h****, Scheme 2.* Column chromatography (SiO_2, eluting with 6:4 hexane/ethyl acetate) afforded the desired product as a white solid (50 mg, 80%): mp 252−254 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.38 (s, 1H), 10.79 (s, 1H), 8.87 (d, J = 4.2 Hz, 1H), 8.72 (d, J = 7.5 Hz, 1H), 8.43 (d, J = 8.1 Hz, 1H), 7.74−7.71 (m, 1H), 7.65−7.60 (m, 2H), 7.57−7.52 (m, 2H), 7.39−7.33 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.2, 156.1, 149.5, 149.0, 138.4, 137.1, 134.8, 131.8, 128.3, 127.5, 122.8, 122.7, 122.0, 119.0, 117.1, 115.1; IR (neat) υ_{max} 3344, 3233, 1654, 1528, 1325; HRMS (EI, m/z) calcd for $C_{16}H_{11}N_3O_4$ $[M]^+$ 309.0750, found 309.0744.

2-Hydroxy-6-methyl-N-(quinolin-8-yl)benzamide, ***2i****, Scheme 2.* Column chromatography (SiO_2, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a white solid (43 mg, 78%): mp 198−200 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.91 (s, 1H), 10.62 (s, 1H), 8.90 (dd, J = 6.0, 3.0 Hz, 1H), 8.81 (dd, J = 4.2, 1.5 Hz, 1H), 8.20 (dd, J = 8.1, 1.5 Hz, 1H), 7.64−7.57 (m, 2H), 7.48 (dd, J = 8.4, 4.2 Hz, 1H), 7.31−7.26 (m, 1H), 6.90 (d, J = 8.4 Hz, 1H), 6.83 (d, J = 7.5 Hz, 1H), 2.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 160.4, 148.5, 138.7, 136.4, 136.0, 133.9, 132.5, 128.0, 127.3, 122.9, 122.4, 121.8, 118.5, 117.2, 115.7, 22.8; IR (neat) υ_{max} 3359, 3197, 1646, 1521, 1480; HRMS (EI, m/z) calcd for $C_{17}H_{14}N_2O_2$ $[M]^+$ 278.1055, found 278.1053.

2-Hydroxy-6-(methylthio)-N-(quinolin-8-yl)benzamide, ***2j****, Scheme 2.* Column chromatography (SiO_2, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a white solid (34 mg, 54%): mp 144−146 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.09 (s, 1H), 11.81 (s, 1H), 8.91−8.84 (m, 2H), 8.18 (d, J = 8.1 Hz, 1H), 7.59 (d, J = 4.2 Hz, 2H), 7.47 (dd, J = 8.4, 4.2 Hz, 1H), 7.31−7.26 (m, 1H), 7.02 (d, J = 7.8, 1H), 6.93 (d, J = 8.4 Hz, 1H), 2.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 162.0, 148.6, 139.3, 136.5, 136.2, 134.2, 132.5, 128.1, 127.2, 122.8, 122.0, 121.7, 118.2, 116.9, 18.9; IR (neat) υ_{max} 3336, 3166, 1634, 1528, 1429; HRMS (ESI, m/z) calcd for $C_{17}H_{14}N_2O_2SNa$ $[M + Na]^+$ 333.0674, found 333.0674.

2-Hydroxy-N-(quinolin-8-yl)-1-naphthamide, ***2k****, Scheme 2.* Column chromatography (SiO_2, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a white solid (54 mg, 85%): mp 118−120 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.51 (s, 1H), 10.92 (s, 1H), 8.96 (dd, J = 7.2, 2.1 Hz, 1H), 8.75 (dd, J = 4.2, 1.5 Hz, 1H), 8.48 (d, J = 8.7 Hz, 1H), 8.21 (dd, J = 8.4, 1.5 Hz, 1H), 7.92−7.85 (m, 2H), 7.68−7.57 (m, 3H), 7.47 (dd, J = 8.4, 4.2 Hz, 1H), 7.42 (d, J = 7.2 Hz, 1H), 7.25−7.22 (m, J, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 160.2, 148.6, 136.4, 134.5, 134.0, 130.7, 129.4, 128.9, 128.4, 128.0, 127.4, 123.7, 123.3, 122.4, 121.8, 119.4, 117.4, 110.5; IR (neat) υ_{max} 3411, 3316, 2921, 1641, 1521, 1463; HRMS (ESI, m/z) calcd for $C_{20}H_{14}N_2O_2Na$ $[M + Na]^+$ 337.0953, found 337.0953.

3-Hydroxy-N-(quinolin-8-yl)-[1,1′-biphenyl]-4-carboxamide, ***2l****, Scheme 2.* Column chromatography (SiO_2, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a white solid (67 mg, 98%): mp 138−140 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.41 (s, 1H), 11.02 (s, 1H), 8.92−8.90 (m, 1H), 8.87−8.84 (m, 1H), 8.23 (d, J = 8.4 Hz, 1H), 7.94 (d, J = 8.1 Hz, 1H), 7.68−7.60 (m, 4H), 7.55−7.39 (m, 4H), 7.23−7.24 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 162.3, 148.5, 147.3, 139.6, 138.7, 136.4, 133.6, 128.9, 128.3, 128.0, 127.3, 127.1, 126.5, 122.2, 121.8, 117.9, 116.9, 116.8, 113.9; IR (neat) υ_{max} 3413, 3352, 1645, 1536, 1485; HRMS (ESI, m/z) calcd for $C_{22}H_{16}N_2O_2Na$ $[M + Na]^+$ 363.1109, found 363.1110.

2′,4′-Difluoro-3-hydroxy-N-(quinolin-8-yl)-[1,1′-biphenyl]-4-carboxamide, ***2m****, Scheme 2.* Column chromatography (SiO_2, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a white solid (66 mg, 88%): mp 191−193 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.40 (s, 1H), 11.03 (s, 1H), 8.91−8.89 (m, 1H), 8.85 (dd, J = 5.7, 3.3 Hz, 1H), 8.24−8.21 (m, 1H), 7.92 (d, J = 8.1 Hz, 1H), 7.65−7.60 (m, 2H), 7.55−7.44 (m, 2H), 7.20 (d, J = 3.6 Hz, 1H), 7.16 (s, 1H), 7.02−6.91 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 162.0, 148.5, 141.2, 138.8, 136.5, 133.5, 131.3 (dd, J = 9.8, 4.5 Hz), 128.0, 127.3, 126.2, 122.4, 121.9, 119.7 (d, J = 3.0 Hz), 118.9 (d, J = 2.3 Hz), 116.9, 114.3, 111.8 (dd, J = 21.0, 3.8 Hz),104.6 (t, J = 25.5 Hz); IR (neat) υ_{max} 3416, 3352, 1655, 1545, 1492; HRMS (EI, m/z) calcd for $C_{22}H_{14}F_2N_2O_2$ $[M]^+$ 376.1023, found 376.1013.

4-Acetyl-2-hydroxy-N-(quinolin-8-yl)benzamide, ***2n****, Scheme 2.* Column chromatography (SiO_2, eluting with 8:2 hexane/ethyl acetate) afforded the desired product as a white solid (59 mg, 96%): mp 170−172 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.35 (s, 1H), 11.06 (s, 1H), 8.89 (dd, J = 4.5, 1.8 Hz, 1H), 8.81 (dd, J = 5.1, 3.9 Hz, 1H), 8.21 (dd, J = 8.4, 1.5 Hz, 1H), 7.93 (d, J = 9.0 Hz, 1H), 7.62−7.55 (m, 4H), 7.52 (dd, J = 8.4, 4.2 Hz, 1H), 2.63 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.4, 167.4, 162.0, 148.6, 141.5, 138.7, 136.5, 133.2, 127.9, 127.3, 126.4, 122.7, 122.0 119.0, 118.4, 118.1, 117.1, 26.9; IR (neat) υ_{max} 3348, 3310, 1685, 1655, 1546, 1496; HRMS (EI, m/z) calcd for $C_{18}H_{14}N_2O_3$ $[M]^+$ 306.1004, found 306.1004.

2-Hydroxy-N-(quinolin-8-yl)-4-(trifluoromethyl)benzamide, ***2o****, Scheme 2.* Column chromatography (SiO_2, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a white solid (64 mg, 96%): mp 140−142 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.47 (s, 1H), 11.07 (s, 1H), 8.91 (dd, J = 4.2, 1.5 Hz, 1H), 8.86−8.81 (m, 1H), 8.24 (dd, J = 8.4, 1.2 Hz, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.64−7.59 (m, 2H), 7.55 (dd, J = 8.4, 4.2 Hz, 1H), 7.33 (s, 1H), 7.28−7.24 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 162.0, 148.6, 138.7, 136.6, 133.1, 129.0 (q, J = 271.0 Hz), 128.0, 126.8, 122.8, 122.0, 117.8, 117.2, 116.1 (q, J = 8.0 Hz), 115.3 (q, J = 3.7 Hz), 100.0; IR (neat) υ_{max} 3418, 3337, 1652, 1548, 1422; HRMS (EI, m/z) calcd for $C_{17}H_{11}F_3N_2O_2$ $[M]^+$ 332.0773, found 332.0767.

2-Hydroxy-4-(pentyloxy)-N-(quinolin-8-yl)benzamide, ***2p****, Scheme 2.* Column chromatography (SiO_2, eluting with 8:2 hexane/ethyl acetate) afforded the desired product as a white solid (52 mg, 74%): mp 85−87 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.64 (s, 1H), 10.80 (s, 1H), 8.88 (dd, J = 4.2, 1.5 Hz, 1H), 8.80 (dd, J = 6.9, 2.1 Hz, 1H), 8.20 (dd, J = 8.4, 1.5 Hz, 1H), 7.75 (d, J = 9.0 Hz, 1H), 7.61−7.53 (m, 2H), 7.50 (dd, J = 8.4, 4.2 Hz, 1H), 6.57−6.51 (m, 2H), 4.01 (t, J = 6.6 Hz, 2H), 1.86−1.58 (m, 2H), 1.50−1.34 (m, 4H), 0.95 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 164.3, 148.4, 138.7, 136.4, 133.8, 128.0, 127.3, 121.8, 121.8, 116.6, 107.9, 107.8, 102.1, 68.2, 28.7, 28.1, 22.4, 14.02; IR (neat) υ_{max} 3446, 3368, 2929, 1646, 1543; HRMS (ESI, m/z) calcd for $C_{21}H_{22}N_2O_3Na$ $[M + Na]^+$ 373.1528, found 373.1528.

3-Hydroxy-N-(quinolin-8-yl)isonicotinamide, ***2q****, Scheme 2.* Column chromatography (SiO_2, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a white solid (38 mg, 72%): mp 190−192 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.90 (s, 1H), 11.16 (s, 1H), 8.94−8.92 (m, 1H), 8.87−8.84 (m, 1H), 8.57 (s, 1H), 8.35 (d, J = 5.4 Hz, 1H), 8.26 (d, J = 8.4 Hz, 1H), 7.68−7.64 (m, 3H), 7.28 (d, J = 3.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.6, 156.2, 148.7, 143.1, 140.2, 138.7, 136.6, 132.8, 128.0, 127.3, 123.1, 122.1, 120.5, 118.2, 117.4; IR (neat) υ_{max} 3449, 3284, 1667, 1546, 1491, 1329; HRMS (ESI, m/z) calcd for $C_{15}H_{11}N_3O_2$ $[M]^+$ 265.0851, found 265.0830.

2-Hydroxy-4-methyl-N-(quinolin-8-yl)benzamide, ***2r****, Scheme 2.* Column chromatography (SiO_2, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a white solid (54 mg, 97%): mp 158−160 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.29 (s, 1H), 10.89 (s, 1H), 8.87(dd, J = 4.2, 1.5 Hz, 1H), 8.80 (dd, J = 6.6, 2.7 Hz, 1H), 8.19 (dd, J = 8.4, 1.5 Hz, 1H), 7.72 (d, J = 8.1 Hz, 1H), 7.61−7.54 (m, 2H), 7.49

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(dd, J = 8.4, 4.2 Hz, 1H), 6.86 (s, 1H), 6.81 (d, J = 8.4 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.5, 162.1, 148.4, 145.7, 138.8, 136.4, 133.7, 128.0, 127.3, 125.9, 122.0, 121.8, 120.2, 118.9, 116.8, 112.6, 21.7; IR (neat) υ_{max} 3446, 3341, 1641, 1541; HRMS (ESI, m/z) calcd for $C_{17}H_{14}N_2O_2Na$ $[M + Na]^+$ 301.0953, found 301.0948.

4-(tert-Butyl)-2-hydroxy-N-(quinolin-8-yl)benzamide, ***2s****, Scheme 2*. Column chromatography (SiO_2, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a white solid (57 mg, 87%): mp 140−142 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.25 (s, 1H), 10.93 (s, 1H), 8.87 (dd, J = 4.2, 1.2 Hz, 1H), 8.82 (dd, J = 6.6, 2.4 Hz, 1H), 8.20 (dd, J = 8.4, 1.5 Hz, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.60−7.57 (m, 2H), 7.50 (dd, J = 8.4, 4.2 Hz, 1H), 7.07 (s, 1H), 7.04 (d, J = 1.8 Hz, 1H), 1.35 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 161.9, 158.8, 148.4, 138.7, 136.4, 133.6, 127.9, 127.3, 125.7, 122.0, 121.8, 116.8, 116.7, 115.5, 112.5, 35.1, 30.9; IR (neat) υ_{max} 3426, 3336, 2959, 1643, 1612, 1546; HRMS (ESI, m/z) calcd for $C_{20}H_{20}N_2O_2Na$ $[M + Na]^+$ 343.1422, found 343.1422.

4-Ethyl-2-hydroxy-N-(quinolin-8-yl)benzamide, ***2t****, Scheme 2*. Column chromatography (SiO_2, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a white solid (50 mg, 85%): mp 108−110 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.30 (s, 1H), 10.90 (s, 1H), 8.87−8.86 (m, 1H), 8.80 (dd, J = 6.3, 2.4 Hz, 1H), 8.18 (d, J = 8.1 Hz, 1H), 7.75 (d, J = 5.1, 1H), 7.60−7.54 (m, 2H), 7.49 (dd, J = 8.4, 4.2 Hz, 1H), 6.89 (s, 1H), 6.84 (d, J = 8.1 Hz, 1H), 2.67 (q, J = 7.5 Hz, 2H), 1.27 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 162.2, 151.9, 148.4, 138.7, 136.4, 133.6, 127.9, 127.2, 126.0, 122.0, 121.8, 119.0, 117.6, 116.8, 112.7, 28.9, 14.9; IR (neat) υ_{max} 3421, 3352, 2963, 1542, 1422; HRMS (ESI, m/z) calcd for $C_{18}H_{16}N_2O_2$ $[M + Na]^+$ 315.1109, found 315.1096.

2-Hydroxy-4-pentyl-N-(quinolin-8-yl)benzamide, ***2u****, Scheme 2*. Column chromatography (SiO_2, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a white solid (61 mg, 91%): mp 96−98 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ12.29 (s, 1H), 10.92 (s, 1H), 8.89−8.88 (m, 1H), 8.82 (dd, J = 6.6, 2.4 Hz, 1H), 8.20 (d, J = 8.1 Hz, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.62−7.56 (m, 2H), 7.50 (dd, J = 8.4, 4.2 Hz, 1H), 6.88−6.82 (m, 2H), 2.63 (t, J = 7.5 Hz, 2H), 1.68−1.61 (m, 2H), 1.36−1.34 (m, 4H), 0.93−0.88 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 162.1, 150.7, 148.4, 138.7, 136.4, 133.7, 128.0, 127.3, 125.9, 122.0, 121.8, 119.6, 118.2, 116.8, 112.7, 35.9, 31.4, 30.4, 22.5, 14.0; IR (neat) υ_{max} 3409, 3331, 2921, 1649, 1545; HRMS (ESI, m/z) calcd for $C_{21}H_{22}N_2O_2Na$ $[M + Na]^+$ 357.1579, found 357.1579.

2-Hydroxy-5-methyl-N-(quinolin-8-yl)benzamide, ***2v****, Scheme 3*. Column chromatography (SiO_2, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a white solid (32 mg, 57%): mp 120−122 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.09 (s, 1H), 10.92 (s, 1H), 8.91 (dd, J = 4.2, 1.5 Hz, 1H), 8.84 (dd, J = 6.0, 3.0 Hz, 1H), 8.21 (dd, J = 8.4, 1.8 Hz, 1H), 7.63−7.57 (m, 3H), 7.52 (dd, J = 8.4, 4.2 Hz, 1H), 7.31−7.26 (m, 1H), 6.97 (d, J = 8.4 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 159.9, 148.5, 138.8, 136.5, 135.6, 133.6, 128.2, 128.0, 127.3, 125.8, 122.2, 121.8, 118.6, 117.0, 114.8, 20.8; IR (neat) υ_{max} 3912, 3342, 1641, 1544, 1486; HRMS (ESI, m/z) calcd for $C_{17}H_{15}N_2O_2$ $[M + H]^+$ 279.1134, found 279.1147.

2-Hydroxy-3-methyl-N-(quinolin-8-yl)benzamide, ***2v′****, Scheme 3*. Column chromatography (SiO_2, eluting with 8:2 hexane/ethyl acetate) afforded the desired product as a white solid (21 mg, 37%): mp 153−155 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.55 (s, 1H), 10.96 (s, 1H), 8.88 (dd, J = 4.2, 1.8 Hz, 1H), 8.83 (dd, J = 6.3, 2.4 Hz, 1H), 8.19 (dd, J = 8.1, 1.2 Hz, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.62−7.55 (m, 2H), 7.49 (dd, J = 8.4, 4.2 Hz, 1H), 7.34 (d, J = 7.2 Hz, 1H), 6.90 (t, J = 7.5 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 160.6, 148.5, 138.9, 136.4, 135.3, 133.8, 128.0, 127.8, 127.4, 123.6, 122.1, 121.8, 118.3, 116.9, 114.4, 15.8; IR (neat) υ_{max} 3418, 3341, 1641, 1544, 1486; HRMS (ESI, m/z) calcd for $C_{17}H_{14}N_2O_2Na$ $[M + Na]+$ 301.0953, found 301.0945.

2-Hydroxy-5-methoxy-N-(quinolin-8-yl)benzamide, ***2w****, Scheme 3*. Column chromatography (SiO_2, eluting with 8:2 hexane/ethyl acetate) afforded the desired product as a white solid (24 mg, 40%): mp 168−170 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.77 (s, 1H), 10.92 (s, 1H), 8.89 (dd, J = 4.2, 1.5 Hz, 1H), 8.83 (dd, J = 5.7, 3.6 Hz, 1H), 8.22 (dd, J = 8.4, 1.8 Hz, 1H), 7.64−7.59 (m, 2H), 7.52 (dd, J = 8.4, 4.2 Hz, 1H), 7.36 (d, J = 2.7 Hz, 1H), 7.14−7.10 (m, 1H), 7.01 (d, J = 9.0 Hz, 1H), 3.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 156.1, 151.8, 148.5, 138.7, 136.4, 133.5, 127.9, 127.2, 122.2, 121.8, 121.0, 119.4, 116.9, 115.0, 110.5, 56.1; IR (neat) υ_{max} 3443, 3345, 1649, 1546, 1493; HRMS (ESI, m/z) calcd for $C_{17}H_{14}N_2O_3Na$ $[M + Na]^+$ 317.0902, found 317.0920.

2-Hydroxy-3-methoxy-N-(quinolin-8-yl)benzamide, ***2w′****, Scheme 3 and Entry 7, Table 2*. Column chromatography (SiO_2, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a white solid (18 mg, 30%): mp 132−134 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.24 (s, 1H), 11.07 (s, 1H), 8.89 (dd, J = 4.2, 1.5 Hz, 1H), 8.67−8.85 (m, 1H), 8.21 (dd, J = 8.4, 1.5 Hz, 1H), 7.64−7.59 (m, 2H), 7.53−7.49 (m, 2H), 7.07 (d, J = 7.2 Hz, 1H), 6.97 (t, J = 8.1 Hz, 1H), 3.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 151.9, 149.1, 148.4, 138.7, 136.4, 133.6, 127.9, 127.2, 122.2, 121.8, 118.4, 117.7, 117.0, 115.5, 115.0, 56.1; IR (neat) υ_{max} 3417, 3340, 1642, 1589, 1546, 1464; HRMS (ESI, m/z) calcd for $C_{17}H_{14}N_2O_3Na$ $[M + Na]^+$ 317.0902, found 317.0905.

3-Bromo-2-hydroxy-N-(quinolin-8-yl)benzamide, ***2x****, with 5-Bromo-2-hydroxy-N-(quinolin-8-yl)benzamide,* ***2x′*** *(1:1), Scheme 3*. Column chromatography (SiO_2, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a white solid (61 mg, 88%): mp 128−130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.09 (s, 1H), 12.28 (s, 1H), 11.01 (s, 1H), 10.86 (s, 1H), 8.91 (dd, J = 4.2, 1.5 Hz, 1H), 8.87 (dd, J = 4.2, 1.2 Hz, 1H), 8.80 (dd, J = 9.00, 4.5 Hz, 1H), 8.77−8.74 (m, 1H), 8.21 (dd, J = 7.2, 0.9 Hz, 2H), 7.90 (d, J = 2.1 Hz, 1H), 7.81 (dd, J = 7.8, 0.6 Hz, 1H), 7.74 (d, J = 7.4 Hz, 1H), 7.59−7.48 (m, 4H), 7.34−7.32 (m, 3H), 6.96−6.87 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.6, 167.1, 161.1, 158.6, 148.7, 148.6, 138., 137.8, 137.3, 136.49, 136.46, 133.18, 133.17, 128.5, 127.9, 127.3, 127.2, 125.2, 122.6, 122.6, 122.0, 121.9, 120.7, 119.6, 117.2, 117.1, 116.7, 116.2, 112.6, 110.5; IR (neat) υ_{max} 3418, 3416, 3353, 3322, 1649, 1579, 1544, 1485, 1429, 1367; HRMS (EI, m/z) calcd for $C_{16}H_{11}BrN_2O_2$ $[M]^+$ 343.9983, found 343.9940.

2-Hydroxy-N-(quinolin-8-yl)-5-(trifluoromethyl)benzamide, ***2y****, Scheme 3*. Column chromatography (SiO_2, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a white solid (65 mg, 98%): mp 141−143 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.72 (s, 1H), 11.00 (s, 1H), 8.91 (dd, J = 4.2, 1.5 Hz, 1H), 8.79 (dd, J = 5.4, 3.3 Hz, 1H), 8.22 (dd, J = 8.4, 1.5 Hz, 1H), 8.07 (s, 1H), 7.70 (dd, J = 8.7, 1.5 Hz, 1H), 7.61−7.60 (m, 2H), 7.53 (dd, J = 8.4, 4.2 Hz, 1H), 7.15 (d, J = 8.7 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.4, 164.6, 148.8, 138.7, 136.5, 133.1, 131.1 (q, J = 3.3 Hz), 128.0, 127.2, 123.9 (q, J = 270.9 Hz), 123.6 (q, J = 3.0 Hz), 122.8, 122.0, 119.5 (q, J = 34.0 Hz), 117.2, 115.0; IR (neat) υ_{max} 3432, 3311, 1651, 1602, 1551; HRMS (EI, m/z) calcd For $C_{17}H_{11}F_3N_2O_2$ $[M]^+$ 332.0773, found 332.0779.

4-Hydroxy-4′-methyl-N-(quinolin-8-yl)-[1,1′-biphenyl]-3-carboxamide, ***2z****, Scheme 3*. Column chromatography (SiO_2, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a white solid (70 mg, 98%): mp 197−199 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.27 (s, 1H), 11.04 (s, 1H), 8.89−8.84 (m, 2H), 8.22 (dd, J = 8.4, 1.8 Hz, 1 H), 8.01 (d, J = 2.1 Hz, 1H), 7.69 (dd, J = 8.7, 2.4 Hz, 1H), 7.62−7.58 (m, 2H), 7.56−7.49 (m, 3H), 7.32 (d, J = 7.8 Hz, 2H), 7.13 (d, J = 8.7 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 161.3, 148.6, 138.7, 137.4, 136.9, 136.4, 133.5, 133.4, 132.3, 129.7, 128.0, 127.3, 126.7, 124.2, 122.4, 121.8, 119.1, 117.0, 115.3, 21.1; IR (neat) υ_{max} 3425, 3313, 2922, 1643, 1544, 1463; HRMS (ESI, m/z) calcd for $C_{23}H_{18}N_2O_2Na$ $[M + Na]^+$ 377.1266, found 377.1266.

2′,4′-Difluoro-4-hydroxy-N-(quinolin-8-yl)-[1,1′-biphenyl]-3-carboxamide, ***2aa****, Scheme 3*. Column chromatography (SiO_2, eluting with 8:2 hexane/ethyl acetate) afforded the desired product as a white solid (71 mg, 94%): mp 200−202 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.39 (s, 1H), 11.03 (s, 1H), 8.89 (dd, J = 4.2, 1.5 Hz, 1H), 8.86 (dd, J = 5.4, 3.3 Hz, 1H), 8.24 (dd, J = 8.4, 1.8 Hz, 1H), 7.99−7.98 (m, 1H), 7.65−7.61 (m, 3H), 7.55−7.45 (m, 2H), 7.16 (d, J = 8.7 Hz, 1H), 7.07−6.96 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.2, 162.3 (dd, J = 247.5, 12.0 Hz), 161.7, 159.8 (dd, J = 247.5, 12.0 Hz), 148.6, 138.8, 136.5, 135.1 (d, J = 3.0 Hz), 133.4, 131.1 (dd, J = 9, 4.5 Hz), 128.0, 127.3, 126.4 (d, J = 3.0 Hz), 125.8, 124.3 (dd, J = 13.5, 4.5 Hz), 122.4,

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121.9, 119.0, 117.1, 115.3, 111.7 (dd, J = 21.0, 3.0 Hz), 104.5 (t, J = 27.0 Hz); IR (neat) υ_{max} 3412, 3341, 1656, 1547, 1487, 1371; HRMS (ESI, m/z) calcd for $C_{22}H_{14}F_2N_2O_2Na$ $[M + Na]^+$ 399.0921, found 399.0921.

General Experimental Procedure for the C−X Hydroxylation Reaction. In a 15 mL sealed tube, the substrate (0.2 mmol, 1 equiv), $Cu(OAc)_2{\cdot}H_2O$ (40 mg, 0.2 mmol, 1equiv), and pyridine (10 equiv) were added followed by the solvent DMF/DMSO (3:1; 4 mL). The tube was charged with a preheated oil bath at 110 °C for 12 h. The reaction mixture was diluted with ethyl acetate and quenched with 20 mL of a saturated solution of $Na_2S_2O_3{\cdot}5H_2O$ or Na_2S. Then the aqueous phase was extracted with ethyl acetate (2 × 10). The combined organic phase was dried over Na_2SO_4 and concentrated under vacuum. The crude was purified by column chromatography on silica gel with a gradient of elution of petroleum ether and ethyl acetate to give the desired hydroxylation product.

2-Chloro-6-hydroxy-N-(quinolin-8-yl)benzamide, ***2ab****, Table 2.* Column chromatography (SiO_2, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a white solid (37 mg, 62%): mp 208−210 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.15 (s, 1H), 11.68 (s, 1H), 8.91 (dd, J = 5.4, 3.9 Hz, 1H), 8.87 (dd, J = 4.2, 1.5 Hz, 1H), 8.21 (dd, J = 8.4, 1.8 Hz, 1H), 7.64−7.60 (m, 2H), 7.50 (dd, J = 8.4, 4.2 Hz, 1H), 7.31 (t, J = 8.1 Hz, 1H), 7.05−6.97 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 163.6, 149.3, 139.6, 136.9, 134.6, 133.6, 131.8, 128.6, 127.8, 123.5, 122.5, 122.4, 118.6, 118.0; IR (neat) υ_{max} 3436, 3344, 3149, 1650, 1593, 1524; HRMS (ESI, m/z) calcd for $C_{16}H_{11}ClN_2O_2Na$ $[M + Na]^+$ 321.0407, found 321.0444.

3-Chloro-2-hydroxy-N-(quinolin-8-yl)benzamide, ***2ad****, Table 2.* Column chromatography (SiO_2, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a white solid (31 mg, 51%): mp 180−182 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.99 (s, 1H), 11.05 (s, 1H), 8.90−8.78 (m, 2H), 8.23 (d, J = 7.5 Hz, 1H), 7.81 (d, J = 8.1 Hz, 1H), 7.62 (d, J = 4.2, 1H), 7.57−7.46 (m, 3H), 6.98 (t, J = 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 157.9, 148.6, 138.8, 136.5, 134.6, 133.3, 128.0, 127.3, 124.5, 123.4, 122.6, 122.0, 119.0, 117.2, 116.4; IR (neat) υ_{max} 3449, 3333, 2923, 2852, 1649, 1544, 1433; HRMS (ESI, m/z) calcd for $C_{16}H_{11}ClN_2O_2Na$ $[M + Na]^+$ 321.0407, found 321.0408.

5-Bromo-2-hydroxy-N-(quinolin-8-yl)benzamide, ***2x****, Scheme 3 and Entry 8, Table 2.* Column chromatography (SiO_2, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a white solid (63 mg, 91%): mp 143−145 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.30 (s, 1H), 10.90 (s, 1H), 8.93 (dd, J = 4.2, 1.5 Hz, 1H), 8.80 (dd, J = 5.4, 3.4 Hz, 1H), 8.23 (dd, J = 8.1, 1.2 Hz, 1H), 7.94 (d, J = 2.1 Hz, 1H), 7.63−7.52 (m, 4H), 6.97 (d, J = 9.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 161.0, 148.7, 138.6, 137.3, 136.4, 133.2, 128.5, 127.9, 127.2, 122.6, 122.0, 120.7, 117.1, 116.6, 110.5; IR (neat) υ_{max} 3419, 3321, 1650, 1546, 1484; HRMS (ESI, m/z) calcd for $C_{16}H_{11}BrN_2O_2Na$ $[M + Na]^+$ 364.9902, found 364.9902.

2-Hydroxy-4-methoxy-N-(quinolin-8-yl)benzamide, ***2ae****, Table 2.* Column chromatography (SiO_2, eluting with 8:2 hexane/ethyl acetate) afforded the desired product as a white solid (40 mg, 67%): mp 140−142 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.68 (s, 1H), 10.82 (s, 1H), 8.88 (dd, J = 4.2, 1.5 Hz, 1H), 8.81 (dd, J = 6.6, 2.4 Hz, 1H), 8.20 (dd, J = 8.4, 1.8 Hz, 1H), 7.78 (d, J = 8.7 Hz, 1H), 7.62−7.57 (m, 2H), 7.51 (dd, J = 8.4, 4.2 Hz, 1H), 6.59−6.53 (m, 2H), 3.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 164.6, 164.3, 148.3, 138.7, 136.4, 133.7, 127.9, 127.33, 127.28, 121.8, 121.7, 116.6, 108.1, 107.4, 101.6, 55.4; IR (neat) υ_{max} 3421, 3351, 1652, 1601, 1547; HRMS (ESI, m/z) calcd for $C_{17}H_{14}N_2O_3Na$ $[M + Na]^+$ 317.0902, found 317.0919.

2-Hydroxy-3,4-dimethoxy-N-(quinolin-8-yl)benzamide, ***2af****, Table 2.* Column chromatography (SiO_2, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a white solid (57 mg, 88%): mp 137−139 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.11 (s, 1H), 10.93 (s, 1H), 8.87 (dd, J = 4.2, 1.5 Hz, 1H), 8.83 (dd, J = 6.6, 2.4 Hz, 1H), 8.20 (dd, J = 8.4, 1.5 Hz, 1H), 7.66 (d, J = 9.0 Hz, 1H), 7.59−7.55 (m, 2H), 7.50 (dd, J = 8.4, 4.2 Hz, 1H), 6.62 (d, J = 8.7 Hz, 1H), 3.95 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 156.8, 155.8, 148.4, 138.7, 137.0, 136.4, 133.8, 127.9, 127.3, 122.2, 122.0, 121.7, 116.8, 110.2, 103.0, 60.7, 56.0; IR (neat) υ_{max} 3432, 3344, 1640, 1544, 1498; HRMS (ESI, m/z) calcd for $C_{18}H_{16}N_2O_4Na$ $[M + Na]^+$ 347.1008, found 347.1008.

General Experimental Procedure for the Homocoupling Reaction. In a 15 mL sealed tube, the substrate (0.2 mmol, 1 equiv) and $Cu(OAc)_2{\cdot}H_2O$ (40 mg, 0.2 mmol, 1 equiv) were added followed by 2 mL of DMSO. The tube was charged with a preheated oil bath at 100 °C for 2 h. The reaction mixture was diluted with ethyl acetate and quenched with 30 mL of a saturated solution of $Na_2S_2O_3{\cdot}5H_2O$ or Na_2S. Then the aqueous phase was extracted with ethyl acetate (2 × 10). The combined organic phase was dried over Na_2SO_4 and concentrated under vacuum. The crude was purified by column chromatography on silica gel with a gradient of elution of petroleum ether and ethyl acetate to give a mixture of products, i.e., the homocoupling product (major) and the hydroxylation product (minor).

5,5′-Dichloro-N^2,N$^{2′}$-bis(quinolin-8-yl)-[1,1′-biphenyl]-2,2′-dicarboxamide, ***3b****, Scheme 4.* Column chromatography (SiO_2, eluting with 6:4 hexane/ethyl acetate) afforded the desired product as a white solid (37 mg, 66%): mp 143−145 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.23 (s, 2H), 8.58 (dd, J = 5.4, 3.6 Hz, 2H), 8.48−8.47 (m, 2H), 7.90 (dd, J = 6.9, 1.2 Hz, 2H), 7.75 (d, J = 8.1 Hz, 2H), 7.50 (d, J = 1.5 Hz, 2H), 7.44 (dd, J = 8.1, 1.8 Hz, 2H), 7.29 (d, J = 4.2 Hz, 2H), 7.18−7.16 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.8, 147.7, 140.4, 138.0, 136.7, 135.7, 134.6, 134.1, 130.7, 129.2, 128.4, 127.2, 126.8, 121.5, 121.3, 116.5; IR (neat) υ_{max} 3425, 3327, 1671, 1526, 1482; HRMS (ESI, m/z) calcd for $C_{32}H_{20}Cl_2N_4O_2Na$ $[M + Na]^+$ 585.0861, found 585.0851.

5,5′-Dibromo-N^2,N$^{2′}$-bis(quinolin-8-yl)-[1,1′-biphenyl]-2,2′-dicarboxamide, ***3c****, Scheme 4.* Column chromatography (SiO_2, eluting with 5:5 hexane/ethyl acetate) afforded the desired product as a white solid (45 mg, 68%): mp 241−243 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.22 (s, 2H), 8.58−8.55 (m, 2H), 8.48 (dd, J = 4.2, 1.5 Hz, 2H), 7.91 (dd, J = 8.1, 1.5 Hz, 2H), 7.69−7.66 (m, 4H), 7.62−7.58 (m, 2H), 7.29 (d, J = 4.2 Hz, 2H), 7.16−7.15 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.9, 147.7, 140.4, 137.9, 135.7, 135.1, 134.1, 133.6, 131.4, 129.2, 127.2, 126.8, 125.0, 121.5, 121.3, 116.4; IR (neat) υ_{max} 3414, 3334, 1667, 1525, 1482; HRMS (ESI, m/z) calcd for $C_{32}H_{20}Br_2N_4O_2Na$ $[M + Na]^+$ 672.9851, found 672.9851.

N^2,N$^{2′}$-Bis(quinolin-8-yl)-5,5′-bis(trifluoromethyl)-[1,1′-biphenyl]-2,2′-dicarboxamide, ***3d****, Scheme 4.* Column chromatography (SiO_2, eluting with 4:6 hexane/ethyl acetate) afforded the desired product as a white solid (41 mg, 65%): mp 230−232 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.28 (s, 2H), 8.53−8.51 (m, 2H), 8.47 (dd, J = 4.2, 1.2 Hz, 2H), 7.93−7.90 (m, 4H), 7.79−7.74 (m, 4H), 7.29 (dd, J = 8.4, 4.2 Hz, 2H), 7.14−7.12 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 147.9, 139.6, 137.99, 137.96, 135.9, 133.9, 132.8 (q, J = 32.3 Hz), 128.3, 127.9, 127.3, 126.9, 125.5, 125.4, 121.8, 121.5, 116.7; IR (neat) υ_{max} 3401, 3308, 1923, 1677, 1536, 1483; HRMS (ESI, m/z) calcd for $C_{34}H_{20}F_6N_4O_2Na$ $[M + Na]^+$ 653.1388, found 653.1388.

Experimental Procedure for the Reaction on a Gram Scale. *N*-(Quinolin-8-yl)benzamide (1.1 g, 4.5 mmol) was taken in an oven-dried round-bottom flask which was connected through a condenser under a N_2 atmosphere and dissolved with DMF/DMSO (3:1; 100 mL). Then $Cu(OAc)_2{\cdot}H_2O$ (899 mg, 4.5 mmol, 1 equiv) and pyridine (3.6 mL, 10 equiv) were added, and the mixture was stirred for 4 h at 100 °C. The reaction mixture was diluted with ethyl acetate and quenched with 200 mL of a saturated solution of $Na_2S_2O_3{\cdot}5H_2O$ or Na_2S. Then the aqueous phase was extracted with ethyl acetate (4 × 30). The combined organic phase was washed with 1 N HCl (100 mL), collected, dried over Na_2SO_4, and concentrated under vacuum. The crude was purified by column chromatography on silica gel with a gradient of elution of petroleum ether and ethyl acetate to give 1.08 g (91% yield) of the desired white hydroxylation product.

Experimental Procedure for the Deprotection of the Directing Group. 2-Hydroxy-*N*-(quinolin-8-yl)benzamide (40 mg, 0.15 mmol) was taken in an oven-dried round-bottom flask which was connected through a condenser under a N_2 atmosphere, and 3 mL of 12 M HCl was added. Then the mixture was stirred for 24 h at 110 °C followed by cooling. EtOAc (15 mL) and satd aq $NaHCO_3$ (50 mL) were added. The aqueous layer was extracted with EtOAc (2 × 5 mL).

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The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 8-aminoquinoline (yellow solid, 21 mg, 97%). Then 1 M HCl was added to the aqueous layer until pH 4. The aqueous layer was extracted with EtOAC (2 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatograpy on silica gel to afford the desired carboxylic acid (white solid, 20 mg, 96%).

2-Hydroxybenzoic Acid. Column chromatography (SiO_2, eluting with 7:3 hexane/ethyl acetate) afforded the desired product as a white solid (20 mg, 96%): mp 155−157 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.39 (s, 1H), 7.96 (dd, J = 8.1, 1.8 Hz, 1H), 7.58−7.52 (m, 1H), 7.05−6.94 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.9, 162.2, 136.8, 130.8, 119.5, 117.8, 111.2; IR (neat) υ_{max} 3428, 3238, 2857, 1659, 1611, 1442, 1296, 1246; HRMS (EI, m/z) calcd for $C_7H_6O_3$ $[M]^+$ 138.0317, found 138.0285.

Data for quinolin-8-amine, ***4b****, Scheme 5:* ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78 (dd, J = 4.2, 1.8 Hz, 1H), 8.08 (dd, J = 8.4, 1.8 Hz, 1H), 7.40−7.32 (m, 2H), 7.18−7.15 (m, 1H), 6.95 (dd, J = 7.5, 1.2 Hz, 1H), 4.99 (s, 2H).

Experimental Procedure for the Synthesis of Diflunisal. *Step 1. Experimental Procedure for the Synthesis of 2′,4′-Difluoro-4-hydroxy-N-(quinolin-8-yl)-[1,1′-biphenyl]-3-carboxamide,* ***2aa****, from* ***1aa****.* 2′,4′-Difluoro-*N*-(quinolin-8-yl)-[1,1′-biphenyl]-3-carboxamide, **yy** (144 mg, 0.4 mmol), was taken in an oven-dried round-bottom flask which was connected through a condenser under a N_2 atmosphere and dissolved with DMF/DMSO (3:1, 8 mL). Then $Cu(OAc)_2{\cdot}H_2O$ (80 mg, 0.4 mmol, 1 equiv) and pyridine (0.3 mL, 10 equiv) were added, and the mixture was stirred for 2 h at 100 °C. The reaction mixture was diluted with ethyl acetate and quenched with 50 mL of a saturated solution of $Na_2S_2O_3{\cdot}5H_2O$ or Na_2S. Then the aqueous phase was extracted with ethyl acetate (2 × 30 mL). The combined organic phase was washed with 1 N HCl (50 mL), collected, dried over Na_2SO_4, and concentrated under vacuum. The crude was purified by column chromatography on silica gel with a gradient of elution of petroleum ether and ethyl acetate to give 141 mg (94% yield) of the desired white hydroxylation product.

Step 2. Deprotection of ***2aa*** *to Diflunisal,* ***4aa****.* 2′,4′-Difluoro-4-hydroxy-*N*-(quinolin-8-yl)-[1,1′-biphenyl]-3-carboxamide (57 mg, 0.15 mmol) was taken in an oven-dried round-bottom flask which was connected through a condenser under a N_2 atmosphere, and 3 mL of 12 M HCl was added. Then the mixture was stirred for 24 h at 110 °C followed by cooling. EtOAc (15 mL) and satd aq $NaHCO_3$ (50 mL) were added. The aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to afford the 8-aminoquinoline (yellow solid, 20 mg, 94%). Then 1 M HCl was added to the aqueous layer until pH 4. The aqueous layer was extracted with EtOAC (2 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatograpy on silica gel to afford the desired drug molecule diflunisal (white solid, 33 mg, 88%): mp 210−212 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.89 (s, 1H), 7.56−7.52 (m, 2H), 7.35−7.31 (m, 1H), 7.17−7.14 (m, 2H), 6.95 (d, J = 4.5 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) 171.8, 162.0, 161.7 (dd, J = 244.5, 12.0 Hz), 159.4 (dd, J = 246.0, 12.0 Hz), 134.9, 131.9 (dd, J = 9.0, 4.5 Hz), 130.72, 130.70, 124.8, 124.4, 117.6, 112.5 (d, J = 4.5 Hz), 112.3 (d, J = 4.5 Hz), 104.9 (t, J = 22.5 Hz); IR (neat) υ_{max} 3447, 2925, 2855, 1673, 1486, 1448, 1245; HRMS (EI, m/z) calcd for $C_{13}H_8F_2O_3$ $[M]^+$ 250.0442, found 250.0447.

Compound ***2a****-d_4.* Column chromatography (SiO_2, eluting with 9:1 hexane/ethyl acetate) afforded the desired product as a white solid (49 mg, 91%): mp 132−134 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.31 (s, 1H), 10.99 (s, 1H), 8.89 (dd, J = 4.2, 1.5 Hz, 1H), 8.87−8.82 (m, 1H), 8.21 (dd, J = 8.1, 1.2 Hz, 1H), 7.61−7.57 (m, 2H), 7.52 (dd, J = 8.4, 4.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 162.0, 148.5, 138.7, 136.4, 133.5, 128.0, 127.3, 122.2, 121.9, 116.9, 115.1; IR (neat) υ_{max} 3411, 3348, 1647, 1541, 1487; HRMS (ESI, m/z) calcd for $C_{16}H_8D_4N_2O_2Na$ $[M + Na]^+$ 291.1048, found 291.1038.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02302.

X-ray crystallographic data for **3d** (CIF)
X-ray crystallographic data for **2r** (CIF)
Mechanistic investigation, spectral data, and crystal structures of **2r** and **3d** (PDF)

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Notes

The authors declare no competing financial interest.

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