A New Synthesis of Naphthyridinones and Quinolinones: Palladium Catalyzed Amidation of Ortho-Carbonyl Substituted Aryl Halides

Peter J. Manley* and Mark T. Bilodeau

Department of Medicinal Chemistry, Merck & Co., Inc. P. O. Box 4, West Point, PA
19486.

peter_manley@merck.com

Supplementary Information

General Methods.

General experimental information: Proton and carbon NMR spectra were recorded on Varian Unity 400 or VRX-400 spectrometers (400 MHz) or Varian Unity or Varian Plus (500 MHz) spectrometers. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as an internal standard. Samples provided for accurate mass measurement were taken up in acetonitrile:water:glacial acetic acid (50:50:0.1%v/v). The solutions were analyzed by use of electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI) on either a Bruker Daltonics 3T or 7T Fourier transform ion cyclotron resonance (FTICR) mass spectrometer. External calibration was accomplished with polypropylene glycol (425 or 750). Toluene was distilled from CaH_2 . Anhydrous 1,4-dioxane was obtained from Aldrich in Sure/SealTM bottles and used without further purification. Tris(dibenzylideneacetone)dipalladium(0) ($\text{Pd}_2(\text{dba})_3$) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (xantphos) were obtained from Strem Chemical as used without further purification. Other solvents and reagents were obtained from commercial sources and used without further purification. The reported yields are the actual isolated yields of purified material and are not optimized. Flash column

chromatography was performed on an Isco Combiflash system employing pre-packed silica columns (Isco Redi-Sep columns or Applied Separations Spe-ed cartridges). Preparative reverse phase HPLC was performed on an automated Gilson system using a gradient of 5% MeCN/H₂O to 95% MeCN/H₂O (0.1 % TFA) over 20 min on a Supelcosil ABZ-Plus column (10 cm x 21.2 mm, 5μM). Analytical HPLC: Waters' LC/MS comprised of a 2695 LC with a gradient from 7% MeCN/H₂O to 100% MeCN (0.05% TFA) in 3 minutes, using a YMC PRO LC 3 x 50 mm column. UV analysis was performed at 215 nM. Data is reported in the format: retention time (% purity).

3-Phenyl-1,8-naphthyridin-2(1*H*)-one (1). 2-Bromonicotinaldehyde (100 mg, 0.54 mmol), 2-phenylacetamide (87 mg, 0.65 mmol), Cs₂CO₃ (245 mg, 0.75 mmol), Pd₂(dba)₃ (5 mg, 0.005 mmol), and xantphos (9 mg, 0.016 mmol) were combined in dry toluene (2 mL). The mixture was degassed (3 x pump/N₂) then heated to reflux. After 1 hr the mixture was cooled, diluted with H₂O, and extracted with CH₂Cl₂ (3x). The combined organic layers were dried (MgSO₄), filtered, and concentrated. Flash column (30% EtOAc/CHCl₃) gave the title compound (109 mg, 91%) as a white solid: ¹H-NMR (500 MHz, CDCl₃) δ 11.38 (bs, 1 H), 8.72 (dd, J = 1.71 and 3.17 Hz, 1 H), 7.97 (dd, J = 1.71 and 6.11 Hz, 1 H), 7.84 (s, 1 H), 7.76 (m, 2 H), 7.49-7.40 (m, 3 H), 7.24 (m, 1 H); ¹³C-NMR (100 MHz, d₆-DMSO) δ 162.6, 150.9, 149.9, 137.2, 136.4, 133.4, 129.5, 128.8, 128.7, 119.1, 115.4; HRMS calc for C₁₄H₁₁N₂O 223.0866, found 223.0869; Analytical HPLC 1.64 min (100%).

3-Phenylquinolin-2(1*H*)-one (Table 1, entry 1a and entry 1b). **1a:** 2-Bromobenzaldehyde (100 mg, 0.54 mmol), 2-phenylacetamide (88 mg, 0.65 mmol), Cs₂CO₃ (247 mg, 0.76 mmol), Pd₂(dba)₃ (5 mg, 0.005 mmol), and xantphos (9 mg, 0.016

mmol) were combined in dry toluene (2 mL). The mixture was degassed (3 x pump/N₂) then heated to reflux. After 2 hr the mixture was cooled, diluted with H₂O, and extracted with CH₂Cl₂ (3x). The combined organic layers were dried (MgSO₄), filtered, and concentrated. Flash column (15% EtOAc/CHCl₃) gave the title compound (112 mg, 94%) as an off-white solid: ¹H-NMR (500 MHz, CDCl₃) δ 10.79 (bs, 1 H), 7.92 (s, 1 H), 7.79 (m, 2 H), 7.61 (dd, J = 1.22 and 6.59 Hz, 1 H), 7.52-7.47 (m, 3 H), 7.43-7.39 (m 1 H), 7.30-7.22 (m, 2 H); ¹³C-NMR (100 MHz, d₆-DMSO) δ 161.7, 139.1, 138.3, 137.0, 132.2, 130.8, 129.4, 128.8, 128.6, 128.5, 122.5, 120.2, 115.4; HRMS calc for C₁₅H₁₂NO 222.0914, found 222.0918.

1b: 2-Chlorobenzaldehyde (100 mg, 0.71 mmol), 2-phenylacetamide (115 mg, 0.85 mmol), Cs₂CO₃ (324 mg, 1.0 mmol), Pd₂(dba)₃ (7 mg, 0.007 mmol), and xantphos (12 mg, 0.021 mmol) were combined in dry toluene (2 mL). The mixture was degassed (3 x pump/N₂) then heated to reflux. After 6 hr the mixture was cooled, diluted with H₂O, and extracted with CH₂Cl₂ (3x). The combined organic layers were dried (MgSO₄), filtered, and concentrated. Flash column (25% EtOAc/hexanes) gave the title compound (119 mg, 76%) as a cream-colored solid. Spectra were identical to **1a**.

3-Phenyl-1,5-naphthyridin-2(1H)-one (Table 1, entry 2). 3-Bromopyridine-2-carbaldehyde (134 mg, 0.72 mmol), 2-phenylacetamide (117 mg, 0.86 mmol), Cs₂CO₃ (329 mg, 1.01 mmol), Pd₂(dba)₃ (7 mg, 0.007 mmol), and xantphos (13 mg, 0.022 mmol) were combined in dry toluene (4 mL). The mixture was degassed (3 x pump/N₂) then heated to reflux. After 2 hr the mixture was cooled, diluted with H₂O, and extracted with EtOAc (3x). The combined organic layers were dried (MgSO₄), filtered, and concentrated. Flash column (30% EtOAc/CHCl₃) gave the title compound (110 mg, 69%, yield in table is average of 2 runs) as a pale yellow solid. ¹H-NMR (500 MHz, CDCl₃) δ

11.31 (bs, 1 H), 8.59 (dd, $J = 1.47$ and 3.17 Hz, 1 H), 8.19 (d, 1 H), 7.83 (dd, $J = 1.46$ and 7.08 Hz, 2 H), 7.65 (d, $J = 8.06$ Hz, 1 H), 7.53-7.27 (m, 4 H).

3-Phenyl-1,7-naphthyridin-2(1H)-one (Table 1, entry 3). 3-Bromoisonicotinaldehyde (100 mg, 0.54 mmol), 2-phenylacetamide (87 mg, 0.65 mmol), Cs_2CO_3 (245 mg, 0.75 mmol), $\text{Pd}_2(\text{dba})_3$ (5 mg, 0.005 mmol), and xantphos (9 mg, 0.016 mmol) were combined in dry toluene (2 mL). The mixture was degassed (3 x pump/ N_2) then heated to 100°C . After 18 hr the mixture was cooled to RT, diluted with H_2O , and extracted with CH_2Cl_2 (3x). The combined organic layers were dried (MgSO_4), filtered, and concentrated. Flash column (80% EtOAc/hexanes) gave the title compound (90 mg, 75%) as a yellow solid: $^1\text{H-NMR}$ (500 MHz, d_6 -DMSO) δ 12.22 (bs, 1 H), 8.69 (s, 1 H), 8.35 (d, $J = 3.66$ Hz, 1 H), 8.15 (s, 1 H), 7.77 (d, $J = 6.84$ Hz, 2 H), 7.68 (d, $J = 5.13$ Hz, 7.46 (m, 3 H); HRMS calc for $\text{C}_{14}\text{H}_{11}\text{N}_2\text{O}$ 223.0866, found 223.0868.

6-Methoxy-3-phenylquinolin-2(1H)-one (Table 1, entry 4). 2-Bromo-5-methoxybenzaldehyde (125 mg, 0.58 mmol), 2-phenylacetamide (94 mg, 0.7 mmol), Cs_2CO_3 (265 mg, 0.8 mmol), $\text{Pd}_2(\text{dba})_3$ (5 mg, 0.006 mmol), and xantphos (10 mg, 0.017 mmol) were combined in dry toluene (2.5 mL). The mixture was degassed (3 x pump/ N_2) then heated to 100°C . After 24 hr the mixture was cooled to RT, diluted with H_2O , and extracted with CH_2Cl_2 (3x). The combined organic layers were dried (MgSO_4), filtered, and concentrated. Flash column (25% EtOAc/ CHCl_3) gave the title compound (69 mg, 47%) as a pale yellow solid: $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 10.89 (bs, 1 H), 7.86 (s, 1 H), 7.81 (s, 1H), 7.79 (s, 1 H), 7.48 (m, 2 H), 7.42 (m, 1 H), 7.23 (d, $J = 9.03$ Hz, 1 H), 7.14 (dd, $J = 2.69$ and 6.1 Hz, 1 H), 7.04 (d, $J = 2.69$ Hz, 1 H), 3.88 (s, 3 H); $^{13}\text{C-NMR}$ (100 MHz, d_6 -DMSO) δ 160.7, 154.3, 137.4, 136.6, 133.1, 132.0, 128.8, 128.0, 127.9, 120.3,

119.6, 116.1, 109.6, 55.6; HRMS calc for $C_{16}H_{14}NO_2$ 252.1019, found 252.1027; Analytical HPLC 1.89 min (96%).

4-Methyl-3-phenylquinolin-2(1*H*)-one (Table 2, entry 1). 1-(2-Bromophenyl)ethanone (100 mg, 0.5 mmol), 2-phenylacetamide (81 mg, 0.6 mmol), Cs_2CO_3 (229 mg, 0.7 mmol), $Pd_2(dba)_3$ (5 mg, 0.005 mmol), and xantphos (9 mg, 0.015 mmol) were combined in dry toluene (2 mL). The mixture was degassed (3 x pump/ N_2) then heated to 100°C. After 18 hr the mixture was cooled, diluted with EtOAc, filtered through Celite®, and concentrated. Flash column (gradient, 35-70% EtOAc/hexanes) gave the title compound (77 mg, 65%) as a cream solid: 1H -NMR (500 MHz, $CDCl_3$) δ 10.92 (bs, 1 H), 7.74 (d, J = 7.57 Hz, 1 H), 7.50-7.46 (m, 3 H), 7.41 (t, J = 7.08 Hz, 1 H), 7.34 (d, J = 7.08 Hz, 2 H), 7.25 (m, 5 H), 2.36 (s, 3 H); ^{13}C -NMR (100 MHz, $CDCl_3$) δ 163.2, 144.7, 137.5, 136.1, 132.2, 130.3, 130.0, 128.2, 127.5, 124.8, 122.3, 120.8, 116.3, 16.9; HRMS calc for $C_{16}H_{14}NO$ 236.1070, found 236.1078; Analytical HPLC 1.96 min (98%).

3,4-Diphenylquinolin-2(1*H*)-one (Table 2, entry 2). (2-Bromophenyl)(phenyl)methanone (140 mg, 0.54 mmol), 2-phenylacetamide (87 mg, 0.64 mmol), Cs_2CO_3 (245 mg, 0.75 mmol), $Pd_2(dba)_3$ (5 mg, 0.005 mmol), and xantphos (9 mg, 0.015 mmol) were combined in dry toluene (2 mL). The mixture was degassed (3 x pump/ N_2) then heated to 100°C. After 18 hr the mixture was cooled, diluted with EtOAc, filtered through Celite®, and concentrated. Flash column (20% EtOAc/ $CHCl_3$) gave the title compound (88 mg, 55%) as a white solid. 1H -NMR (500 MHz, d_6 -DMSO) δ 12.07 (bs, 1 H), 7.52 (t, J = 7.08 Hz, 1 H), 7.50 (d, J = 1.22 Hz, 1 H), 7.30 (m, 3 H), 7.11 (m, 8 H), 7.01 (d, J = 8.05 Hz, 1 H); ^{13}C -NMR (100 MHz, d_6 -DMSO) δ 161.3, 148.3, 138.4,

136.3, 135.9, 132.1, 130.8, 130.3, 129.7, 128.1, 127.7, 127.3, 127.0, 126.7, 121.9, 120.1, 115.3; HRMS calc for $C_{21}H_{15}NO$ 298.1226, found 298.1232; Analytical HPLC 2.27 min (94%).

4-Hydroxy-3-phenylquinolin-2(1H)-one (Table 2, entry 3). Methyl 2-bromobenzoate (100 mg, 0.47 mmol), 2-phenylacetamide (75 mg, 0.56 mmol), Cs_2CO_3 (212 mg, 0.65 mmol), $Pd_2(dba)_3$ (4 mg, 0.005 mmol), and xantphos (8 mg, 0.016 mmol) were combined in dry toluene (2 mL). The mixture was degassed (3 x pump/ N_2) then heated to 100°C. After 5 hr the mixture was heated to reflux. After 18 hr the mixture was cooled to RT, diluted with 1M NaOH and washed with EtOAc (3x). The aqueous was filtered and the pH adjusted to 4. The resulting solid was collected by filtration, washed with H_2O and air dried. The solid was crystallized from HOAc to give the title compound (40 mg, 36%) as a pale yellow solid: 1H -NMR (500 MHz, d_6 -DMSO) δ 11.46 (bs, 1 H), 10.06 (bs, 1 H), 7.94 (d, J = 8.06 Hz, 1 H), 7.51 (t, J = 7.08 Hz, 1 H), 7.41-7.36 (m, 4 H), 7.32-7.22 (m, 2 H), 7.18 (t, J = 7.33 Hz, 1 H); ^{13}C -NMR (100 MHz, d_6 -DMSO) δ 162.6, 157.3, 138.0, 133.3, 131.2, 130.5, 127.6, 126.8, 123.1, 121.1, 115.4, 114.9, 112.6; HRMS calc for $C_{15}H_{12}NO_2$ 238.0863, found 238.0846; Analytical HPLC 1.47 min (100%).

4-Hydroxy-3,6-diphenylquinolin-2(1H)-one (Table 2, entry 4). Methyl 4-bromobiphenyl-3-carboxylate (200 mg, 0.69 mmol), 2-phenylacetamide (111 mg, 0.82 mmol), Cs_2CO_3 (313 mg, 0.96 mmol), $Pd_2(dba)_3$ (6 mg, 0.007 mmol), and xantphos (12 mg, 0.021 mmol) were combined in dry toluene (3 mL). The mixture was degassed (3 x pump/ N_2) then heated to 100°C. After 18 hr the mixture was heated to reflux. After 24 hr the mixture was cooled, diluted with 1M NaOH, and washed with EtOAc (3x). The combined organic layers were extracted with 1M NaOH (3x). The combined aqueous

layers were filtered and the pH was adjusted to 4. The resulting white solid was collected by filtration, washed with H₂O, and dried *in vacuo* to give the title compound (160 mg, 74%): ¹H-NMR (500 MHz, d₆-DMSO) δ 11.48 (bs, 1 H), 10.25 (bs, 1 H), 8.26 (s, 1 H), 7.84 (d, J = 8.31 Hz, 1 H), 7.71 (d, J = 8.06 Hz, 2 H), 7.48 (t, J = 7.82 Hz, 2 H), 7.43-7.28 (m, 7 H); ¹³C-NMR (100 MHz, d₆-DMSO) δ 162.7, 158.1, 139.7, 137.5, 133.8, 132.9, 131.2, 129.0, 128.9, 127.5, 127.1, 126.6, 126.4, 121.0, 116.1, 115.6, 112.6; HRMS calc for C₂₁H₁₆NO₂ 314.1176, found 314.1157; Analytical HPLC 2.08 min (100%).

4-Amino-3-phenylquinolin-2(1H)-one (Table 2, entry 5). 2-Bromobenzonitrile (100 mg, 0.55 mmol), 2-phenylacetamide (89 mg, 0.66 mmol), Cs₂CO₃ (251 mg, 0.77 mmol), Pd₂(dba)₃ (5mg, 0.005 mmol), and xantphos (10 mg, 0.016 mmol) were combined in dry toluene (2 mL). The mixture was degassed (3 x pump/N₂) then heated to 100°C. After 18 hr the mixture was heated to reflux. After 18 hr the mixture was cooled and concentrated. The residue was taken up in DMF, filtered, and concentrated. Preparative reverse phase HPLC (gradient, 5% MeCN/H₂O to 95% MeCN/H₂O (0.1 % TFA) gave the title compound (67 mg, 52%) as a white solid: ¹H-NMR (500 MHz, d₆-DMSO) δ 11.00 (s, 1 H), 7.99 (d, J = 8.30 Hz, 1 H), 7.44 (m, 3 H), 7.31 (m, 3 H), 7.24 (d, J = 8.30 Hz, 1 H), 7.11 (t, J = 7.57 Hz, 1 H), 5.86 (bs, 2 H); ¹³C-NMR (100 MHz, d₆-DMSO) δ 161.6, 148.4, 138.4, 135.1, 130.0, 128.4, 126.6, 123.2, 120.5, 115.1, 113.5, 106.0; HRMS calc for C₁₅H₁₃N₂O 237.1023, found 237.1032; Analytical HPLC 1.33 min (100%).

3-(4-Methoxyphenyl)quinolin-2(1H)-one (Table 3, entry 1). 2-Bromobenzaldehyde (100 mg, 0.54 mmol), 2-(4-methoxyphenyl)acetamide (107 mg, 0.65 mmol), Cs₂CO₃ (247 mg, 0.76 mmol), Pd₂(dba)₃ (5 mg, 0.005 mmol), and xantphos (9 mg, 0.016 mmol) were combined in dry toluene (2 mL). The mixture was degassed (3 x pump/N₂) then heated to

100°C. After 18 hr the mixture was cooled to RT, diluted with CH₂Cl₂, filtered, and concentrated. Flash column (25% EtOAc/CHCl₃) gave the title compound (123 mg, 91%) as a pale yellow solid: ¹H-NMR (500 MHz, CDCl₃) δ 10.57 (bs, 1 H), 7.86 (s, 1 H), 7.76 (d, J = 8.55 Hz, 2 H), 7.60 (d, J = 7.81 Hz, 1 H), 7.47 (t, J = 7.81 Hz, 1 H), 7.27 (m, 1 H), 7.22 (t, J = 7.57 Hz, 1 H), 7.01 (d, J = 8.30 Hz, 2 H), 3.88 (s, 3 H); ¹³C-NMR (100 MHz, d₆-DMSO) δ 161.2, 159.0, 138.1, 136.3, 131.0, 129.9, 129.8, 128.5, 127.8, 121.8, 119.7, 114.6, 113.3, 55.1; HRMS calc for C₁₆H₁₄NO₂ 252.1019, found 252.1009; Analytical HPLC 1.94 min (100%).

1-Methyl-3-phenylquinolin-2(1H)-one (Table 3, entry 2). 2-Bromobenzaldehyde (100 mg, 0.54 mmol), *N*-methyl-2-phenylacetamide (97 mg, 0.65 mmol), Cs₂CO₃ (247 mg, 0.76 mmol), Pd₂(dba)₃ (5 mg, 0.005 mmol), and xantphos (9 mg, 0.016 mmol) were combined in dry toluene (2 mL). The mixture was degassed (3 x pump/N₂) then heated to 100°C. After 18 hr the mixture was cooled to RT, diluted with CH₂Cl₂, filtered through Celite®, and concentrated. Flash column (15% EtOAc/hexanes) gave the title compound (76 mg, 60%) as a white solid: ¹H-NMR (500 MHz, CDCl₃) δ 7.81 (s, 1 H), 7.72 (d, J = 1.46 Hz, 1 H), 7.71 (d, J = 0.49 Hz, 1 H), 7.61 (dd, J = 1.46 and 6.60 Hz, 1 H), 7.58 (m, 1 H), 7.44 (m, 2 H), 7.39 (m, 2 H), 7.27-7.24 (m 1 H), 5.30 (s, 3 H); ¹³C-NMR (100 MHz, CDCl₃) δ 161.5, 139.6, 136.8, 136.7, 132.5, 130.2, 128.9, 128.8, 128.1, 122.1, 120.8, 113.9, 29.9; HRMS calc for C₁₆H₁₄NO 236.1070, found 236.1080; Analytical HPLC 2.23 min (100%).

1,3-Diphenylquinolin-2(1H)-one (Table 3, entry 3). 2-Bromobenzaldehyde (95 mg, 0.51 mmol), *N*-phenyl-2-phenylacetamide (217 mg, 1.03 mmol), K₂CO₃ (142 mg, 1.03 mmol), CuI (10 mg, 0.051 mmol), and *N,N'*-dimethylethylenediamine (0.011 mL, 0.103

mmol) were combined in dry toluene (0.75 mL) in a sealed tube. The mixture was degassed (3 x pump/N₂) then heated in an oil bath at 150°C. After 18 hr approximately 50% conversion. After an additional 24 hr no change in conversion. The mixture was cooled to RT, diluted with MeOH, filtered through Celite®, and concentrated. Flash column (10% EtOAc/hexanes) gave the title compound (51 mg, 33%) as a pale yellow solid: ¹H-NMR (500 MHz, CDCl₃) δ 7.96 (s, 1 H), 7.80 (d, J = 1.47 Hz, 2 H), 7.65 (dd, J = 0.97 and 6.60 Hz, 1 H), 7.61 (t, J = 7.32 Hz, 2 H), 7.52 (t, J = 7.32 Hz, 1 H), 7.43-7.32 (m, 6 H), 7.22 (t, J = 7.57 Hz, 1 H), 6.68 (d, J = 8.54 Hz, 1 H); ¹³C-NMR (100 MHz, CDCl₃) δ 161.5, 140.7, 138.1, 137.3, 136.2, 132.6, 130.1, 129.8, 129.0, 128.8, 128.7, 128.4, 128.2, 128.0, 122.4, 120.6, 115.8; HRMS calc for C₂₁H₁₆NO 298.1227, found 298.1226; Analytical HPLC 2.58 min (100%).

3-Pyridin-3-ylquinolin-2(1H)-one (Table 3, entry 4). 2-Bromobenzaldehyde (100 mg, 0.54 mmol), 2-pyridin-3-ylacetamide (88 mg, 0.65 mmol), Cs₂CO₃ (247 mg, 0.76 mmol), Pd₂(dba)₃ (5 mg, 0.005 mmol), and xantphos (9 mg, 0.016 mmol) were combined in dry toluene (2 mL). The mixture was degassed (3 x pump/N₂) then heated to 100°C. After 30 min the mixture had become gummy. Dry, degassed dioxane (1 mL) was added and heating continued. After 18 hr the mixture was diluted with MeOH, adsorbed directly onto silica gel, and flash chromatographed (gradient, 0-5% MeOH/CH₂Cl₂) to give the title compound (71 mg, 59%) as an off-white solid: ¹H-NMR (500 MHz, d₆-DMSO) δ 12.05 (s, 1 H), 8.93 (s, 1 H), 8.56 (d, J = 4.64 Hz, 1 H), 8.25 (s, 1 H), 8.17 (d, J = 7.82 Hz, 1 H), 7.74 (d, J = 7.81 Hz, 1 H), 7.54 (t, J = 7.32 Hz, 1 H), 7.46 (dd, J = 4.89 and 2.98 Hz, 1 H), 7.35 (d, J = 8.30 Hz, 1 H), 7.22 (t, J = 7.57 Hz, 1 H); ¹³C-NMR (100 MHz, d₆-DMSO) δ 160.8, 149.1, 148.7, 148.5, 138.6, 138.4, 138.3, 136.1, 132.0, 130.6,

128.5, 128.3, 122.9, 122.0, 119.4, 114.8; HRMS calc for $C_{14}H_{11}N_2O$ 223.0866, found 223.0869; Analytical HPLC 0.78 min (100%).

3-Pyridin-4-ylquinolin-2(1H)-one (Table 3, entry 5). 2-Bromobenzaldehyde (100 mg, 0.54 mmol), 2-pyridin-4-ylacetamide (88 mg, 0.65 mmol), Cs_2CO_3 (247 mg, 0.76 mmol), $Pd_2(dba)_3$ (5 mg, 0.005 mmol), and xantphos (9 mg, 0.016 mmol) were combined in dry toluene (2 mL). The mixture was degassed (3 x pump/ N_2) then heated to 100°C. After 30 min the mixture had become gummy. Dry, degassed dioxane (1 mL) was added and heating continued. After 18 hr the mixture was diluted with MeOH, adsorbed directly onto silica gel, and flash chromatographed (gradient, 0-5% MeOH/ CH_2Cl_2) to give the title compound (44 mg, 37%) an off-white solid: 1H -NMR (500 MHz, d_6 -DMSO) δ 12.09 (s, 1 H), 8.62 (d, J = 5.86 Hz, 2 H), 8.35 (s, 1 H), 7.82 (d, J = 6.10 Hz, 2 H), 7.77 (d, J = 7.57 Hz, 1 H), 7.56 (t, J = 7.32 Hz, 1 H), 7.36 (d, J = 8.30 Hz, 1 H), 7.24 (t, J = 7.32 Hz, 1 H); ^{13}C -NMR (100 MHz, d_6 -DMSO) δ 160.5, 149.4, 143.5, 139.3, 138.8, 131.1, 128.6, 128.5, 123.0, 122.1, 119.1, 114.8; HRMS calc for $C_{14}H_{11}N_2O$ 223.0866, found 223.0868; Analytical HPLC 0.86 min (92%).

3-Pyridin-2-ylquinolin-2(1H)-one (Table 3, entry 6). 2-Bromobenzaldehyde (95 mg, 0.51 mmol), 2-pyridin-2-ylacetamide (140 mg, 1.03 mmol), K_2CO_3 (142 mg, 1.03 mmol), CuI (10 mg, 0.051 mmol), and N,N' -dimethylethylenediamine (0.011 mL, 0.103 mmol) were combined in dry toluene (0.5 mL) in a sealed tube. The mixture was degassed (3 x pump/ N_2) then heated in an oil bath at 150°C. After 18 hr the mixture was cooled to RT, diluted with MeOH, adsorbed directly onto silica gel, and flash chromatographed (50% EtOAc/ $CHCl_3$) to give the title compound (71 mg, 62%) as a cream-colored solid: 1H -NMR (500 MHz, d_6 -DMSO) δ 12.07 (s, 1 H), 8.78 (s, 1 H), 8.69 (d, J = 4.64 Hz, 1 H), 8.52 (d, J = 8.06 Hz, 1 H), 7.86 (m, 2 H), 7.55 (t, J = 8.30 Hz, 1 H), 7.38 (m, 2 H), 7.23 (t,

$J = 7.57$ Hz, 1 H); ^{13}C -NMR (100 MHz, d_6 -DMSO) δ 161.1, 152.6, 149.2, 139.3, 138.8, 136.2, 131.0, 128.8, 123.8, 123.0, 122.0, 119.2, 114.7; HRMS calc for $\text{C}_{14}\text{H}_{11}\text{N}_2\text{O}$ 223.0866, found 223.0869; Analytical HPLC 0.82 min (100%).

3-Methoxyquinolin-2(1H)-one (Table 3, entry 7). 2-Bromobenzaldehyde (100 mg, 0.54 mmol), 2-methoxyacetamide (58 mg, 0.65 mmol), Cs_2CO_3 (247 mg, 0.76 mmol), $\text{Pd}_2(\text{dba})_3$ (5 mg, 0.005 mmol), and xantphos (9 mg, 0.016 mmol) were combined in dry toluene (2 mL). The mixture was degassed (3 x pump/ N_2) then heated to 100°C . After 3 hr LC/MS indicated complete conversion to the amide coupled product. NaOtBu in $t\text{BuOH}$ (2 mL of a 25 mg/mL solution) was added and heating continued. After 90 minutes the mixture was cooled to RT, diluted with saturated NH_4Cl and extracted with CH_2Cl_2 (3x). The combined organic layers were dried (MgSO_4), filtered, and concentrated. Flash column (gradient, 50-75% EtOAc/hexanes) gave the title compound (48 mg, 51%) as a pale pink solid: ^1H -NMR (500 MHz, CDCl_3) δ 10.92 (bs, 1 H), 7.50 (d, $J = 7.32$ Hz, 1 H), 7.38 (m, 2 H), 7.22 (t, $J = 6.83$ Hz, 1 H), 7.00 (s, 1 H), 3.98 (s, 3 H); ^{13}C -NMR (100 MHz, CDCl_3) δ 159.8, 148.6, 133.5, 127.5, 126.1, 123.0, 120.2, 116.1, 112.0, 56.0; HRMS calc for $\text{C}_{10}\text{H}_{10}\text{NO}_2$ 176.0706, found 176.0713; Analytical HPLC 1.18 min (100%).

1,3-Dimethylquinolin-2(1H)-one (Table 3, entry 8). 2-Bromobenzaldehyde (100 mg, 0.54 mmol), *N*-methylpropionamide (57 mg, 0.65 mmol), Cs_2CO_3 (247 mg, 0.76 mmol), $\text{Pd}_2(\text{dba})_3$ (5 mg, 0.005 mmol), and xantphos (9 mg, 0.016 mmol) were combined in dry toluene (2 mL). The mixture was degassed (3 x pump/ N_2) then heated to 100°C . After 18 hr the mixture was cooled to RT, diluted with EtOAc, filtered through Celite®, and concentrated. The residue was taken up in $t\text{BuOH}$ (2 mL). NaOtBu (62 mg, 0.65 mmol) was added and the mixture heated to reflux. After 90 min the mixture was cooled to RT,

diluted with H₂O and the pH adjusted to 5. The resulting mixture was extracted with CH₂Cl₂ (4x). The combined organic layers were dried (MgSO₄), filtered, and concentrated. Flash column (15% EtOAc/hexanes) gave the title compound (30 mg, 32%) as a pale yellow solid: ¹H-NMR (500 MHz, CDCl₃) δ 7.56 (s, 1 H), 7.50 (m, 2 H), 7.34 (d, J = 8.79 Hz, 1 H), 7.21 (t, J = 7.32 Hz, 1 H), 3.76 (s, 3 H), 2.27 (d, J = 0.98 Hz, 3 H); ¹³C-NMR (100 MHz, CDCl₃) δ 162.9, 139.1, 135.6, 130.1, 129.2, 127.8, 121.9, 120.7, 113.9, 29.7, 17.7; HRMS calc for C₁₁H₁₂NO 174.0913, found 174.0925; Analytical HPLC 1.63 min (100%).

N-(2-Formylphenyl)propanamide (4). 2-Bromobenzaldehyde (100 mg, 0.54 mmol), propionamide (47 mg, 0.65 mmol), Cs₂CO₃ (247 mg, 0.76 mmol), Pd₂(dba)₃ (5 mg, 0.005 mmol), and xantphos (9 mg, 0.016 mmol) were combined in dry toluene (2 mL). The mixture was degassed (3 x pump/N₂) then heated to 100°C. After 3 hr the mixture was cooled to RT, diluted with EtOAc, filtered through a pad of Celite®, and concentrated. Flash column (gradient, 0-10% EtOAc/hexanes) gave the title compound (79 mg, 82%) as a clear oil: ¹H-NMR (500 MHz, CDCl₃) δ 11.17 (bs, 1 H), 9.94 (s, 1 H), 8.78 (d, J = 8.30 Hz, 1 H), 7.68 (dd, J = 1.47 and 6.10 Hz, 1 H), 7.63 (m, 1 H), 7.24 (t, J = 7.32 Hz, 1 H), 2.51 (q, J = 7.57 Hz, 2 H), 1.31 (t, J = 7.57 Hz, 3 H).

2-Cyclopropyl-N-(2-formylphenyl)acetamide (5). 2-Bromobenzaldehyde (100 mg, 0.54 mmol), 2-cyclopropylacetamide (64 mg, 0.65 mmol), Cs₂CO₃ (247 mg, 0.76 mmol), Pd₂(dba)₃ (5 mg, 0.005 mmol), and xantphos (9 mg, 0.016 mmol) were combined in dry toluene (2 mL). The mixture was degassed (3 x pump/N₂) then heated to 100°C. After 3 hr the mixture was cooled to RT, diluted with EtOAc, filtered through a pad of Celite®, and concentrated. Flash column (gradient, 0-10% EtOAc/hexanes) gave the title compound (103 mg, 94%) as a clear oil: ¹H-NMR (500 MHz, CDCl₃) δ 11.41 (bs, 1 H),

9.96 (s, 1 H), 8.82 (d, $J = 8.30$ Hz, 1 H), 7.70 (dd, $J = 1.71$ and 6.10 Hz, 1 H), 7.64 (m, 1 H), 7.28-7.23 (m, 1 H), 2.40 (d, $J = 7.32$ Hz, 2 H), 1.17 (m, 1 H), 0.76 (m, 2 H), 0.32 (m, 2 H).