2-Substituted-2,3-dihydro-1*H*-quinolin-4-ones *via* acid catalyzed tandem Rupe rearrangement/Donnelly-Farrell ring-closure of 2-(3'-hydroxypropynyl)anilines

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Dedicated to Prof. Alberto Brandi on the occasion of his 60th birthday.

Table of contents

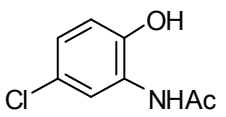
General directions

Solvents were distilled as follows: THF and Et_2O over Na-benzophenone ketyl, toluene over Na and CH_2Cl_2 over CaH_2. Reagents were used as commercially supplied unless otherwise stated and handled in accordance with COSHH regulations. Flash chromatography (FC) was carried out on Silica gel (BDH Silica gel for FC). NMR spectra were recorded at 400 MHz on a Bruker AV-400 or Bruker DX-400 instrument or at 500 MHz on a Bruker AV-500 instrument. Chemical shifts (δ) are given in parts per million (ppm) as referenced to the appropriate residual solvent peak. Broad signals are assigned as br. ^{13}C chemical shifts (δ) are assigned as s, d, t, and q, for C, CH, CH_2, and CH_3 respectively. Infrared spectra were recorded as thin films, on Perkin-Elmer Paragon 1000 Fourier transform spectrometer or as solids, on Pelkin-Elmer Spectrum 100 Fourier transform spectrometer. Only selected absorbances (ν_{max}) are reported. Low resolution and high-resolution mass spectra were recorded on a VG Prospec spectrometer, with molecular ions and major peaks being reported. Intensities are given as percentages of the base peak. HRMS values are valid to ±5 ppm. Melting points were determined on a Khofler hot stage.

General procedure for the aniline protection

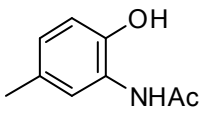
Acetic anhydride (1.5 eq) was added to a stirred solution of the aniline (1 eq) in acetic acid (1 M) at room temperature. The solution was then heated at 60 °C for 2 h. Water was added and the solid precipitate was collected and dried *in vacuo*.

***N*-(5-Chloro-2-hydroxy-phenyl)-acetamide**: Orange solid (84% yield); m.p. 152.5 – 155.6 °C; HR-MS (ESI) Calcd for $C_8H_9ClNO_2$: 186.0322, found 186.0327 (Δ 2.7 ppm); MS (ESI): *m/z* (%) 186 [MH^+] (100); ^1H NMR (400 MHz, d_6-DMSO) 10.13 (s, 1H; OH), 9.27 (s, 1H; NH), 7.95 (d, *J* = 2.5, 1H; 6-H), 6.95 (dd, *J* = 8.5, 2.5, 1H; 4-H), 6.85 (d, *J* = 8.5, 1H; 3-H), 2.10 (s, 3H; Me); ^{13}C NMR (126 MHz, DMSO) δ 169.1 (s; CO), 146.2 (s; Ar), 127.8 (s; Ar),

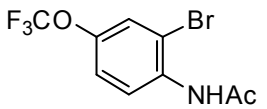


123.5 (d; Ar), 122.1 (s; Ar), 121.0 (d; Ar), 116.3 (d; Ar), 23.8 (q; Me); IR: ν_{max} 3386, 2971, 1739, 1662, 1532, 1415, 1366, 1117, 804 cm^{-1}.

N-(2-Hydroxy-5-methyl-phenyl)-acetamide: white solid (1.19 g, 89 %); m.p. 128.6 – 129.8 °C; HR-MS (ESI) Calcd for $C_9H_{12}NO_2$: 166.0868, found 166.0866 (Δ –1.2 ppm); MS (ESI): *m*/*z* (%) 166 [MH^+] (100); ^1H NMR (400 MHz, d_6-DMSO) δ 9.49 (s, 1H; OH), 9.27 (s, 1H; NH), 7.48 (s, 1H; 6-H), 6.77–6.70 (m, 2H; 3-H, 4-H), 2.18 (s, 3H; Me), 2.10 (s, 3H; Me); ^{13}C NMR (126 MHz, DMSO) δ 169.0 (s; CO), 145.6 (s; Ar), 127.5 (s; Ar), 126.1 (s; Ar), 125.0 (d; Ar), 122.8 (d; Ar), 115.8 (d; Ar), 23.6 (q, Me), 20.4 (q, Me); IR: ν_{max} 3261, 3085, 1739, 1550, 1377, 1206 cm^{-1}.



***N*-(2-Bromo-4-trifluoromethoxy-phenyl)-acetamide** (**1d**): White solid (98% yield); m.p. 91.4 – 92.1°C; HR-MS (ESI) Calcd for $C_9H_8BrF_3NO_2$: 297.9690, found 297.9684 (Δ –2.0 ppm); MS (ESI): *m*/*z* (%) 298 [MH^+] (100); ^1H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, *J* = 9.1, 1H; 6-H), 7.60 (s, 1H; NH), 7.47 (d, *J* = 2.1, 1H; 3-H), 7.23 (dd, *J* = 9.0, 1.8, 1H; 5-H), 2.20 (s, 3H; Me); ^{13}C NMR (126 MHz, DMSO) δ 168.8 (s; CO), 145.1 (s; Ar), 136.0 (s; Ar), 128.1 (s; Ar), 125.4 (d; Ar), 120.8 (d; Ar), 120.0 [q; (q, J_{CF} = 256.9); OCF_3], 118.2 (d; Ar), 23.2 (q; Me); IR: ν_{max} 3287, 1662, 1529, 1478, 1205, 1148, 1014 cm^{-1}.

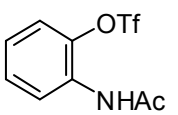


General procedure for the preparation of triflates

The alcohols (1 eq) were dissolved in dry CH_2Cl_2 (0.1 M) at 0 °C and pyridine (3 eq) and then Tf_2O (3 eq) were added in turn. The mixture was stirred for 30 min at 0 °C, then allowed to warm to rt and quenched with water. Phases were separated and the aqueous layer was extracted with CH_2Cl_2 twice. The combined organic phases were

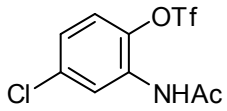
dried over $MgSO_4$, filtered and concentrated *in vacuo*. The desired triflates were purified by flash chromatography.

Trifluoromethanesulfonic acid 2-acetylaminophenyl ester (**1a**): colorless oil (83%



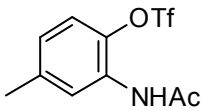
yield); HR-MS (ESI) Calcd for $C_9H_9F_3NO_4S$: 284.0204, found 284.0212 (Δ 2.8 ppm); MS (ESI): m/z (%) 284 [MH^+] (100); ^{1}H NMR (400 MHz, CDCl3) δ 8.25 (d, *J* = 8.1, 1H; 3-H), 7.41 (t, *J* = 7.8, 1H; 4-H), 7.37 – 7.31 (m, 2H; 5-H, NH), 7.22 (t, *J* = 7.7, 1H; 6-H), 2.25 (s, 3H; Me); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9 (s; CO), 140.3 (s; Ar), 130.2 (s; Ar), 128.9 (d; Ar), 125.7 (d; Ar), 125.0 (d; Ar), 121.5 (d; Ar), 118.5 [q (q, J_{CF} = 320.4); CF_3], 24.0 (q, Me); IR: ν_{max} 3521, 1672, 1613, 1542, 1426, 1209, 1142, 760 cm^{-1}.

Trifluoromethanesulfonic acid 2-acetylamino-4-chloro-phenyl ester (**1b**): White



solid (59% yield); m.p. 91.8 – 92.3 °C; HR-MS (ESI) Calcd for $C_9H_8F_3ClNO_4S$: 317.9815, found 317.9821 (Δ 1.9 ppm); MS (ESI): m/z (%) 318 [MH^+] (15); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (app s, 1H; 3-H), 7.71 (br s, 1H; N-H), 7.19 (d, *J* = 9.0, 1H; 6-H), 7.12 (dd, *J* = 9.0, 2.5, 1H; 5-H), 2.20 (s, 3H; MeCON); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7 (s; CO), 137.8 (s; Ar), 134.7 (s; Ar), 131.3 (s; Ar), 125.2 (d; Ar), 124.0 (d; Ar), 122.4 (d; Ar), 118.5 [q (q, J_{CF} = 320.4); CF_3], 24.2 (q; Me); IR: ν_{max} 3238, 1672, 1427, 1206, 1103, 810, 733 cm^{-1}.

Trifluoromethanesulfonic acid 2-acetylamino-4-methyl-phenyl ester (**1c**): Dark-



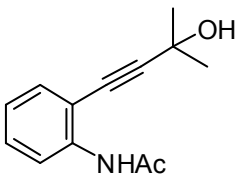
brown oil (38% yield); HR-MS (ESI) Calcd for $C_{10}H_{11}F_3NO_4S$: 298.0361, found 298.0359 (Δ 0.7 ppm); MS (ESI): *m/z* (%) 298 [MH^+] (65); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H, 3-H), 7.47 (br s, 1H; N-H), 7.17 (d, *J* = 8.5, 1H; 6-H), 6.99 (d, *J* = 8.5, 1H; 5-H), 2.37 (s, 3H; 4-Me), 2.22 (s, 3H; MeCONH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6 (s; CO), 139.5 (s; Ar), 137.7 (s;

Ar), 129.8 (s; Ar), 126.1 (d; Ar), 124.9 (d; Ar), 121.1 (d; Ar), 118.6 [q, (q, J_{CF} = 320.4); CF_3], 24.3 (q; $COCH_3$), 21.2 (q; Me); IR: ν_{max} 3188, 3016, 2922, 1738, 1660, 1420, 1204, 1138, 873 cm^{-1}.

General procedure for the Sonogashira couplings with 2-methyl-3-butyn-2-ol.

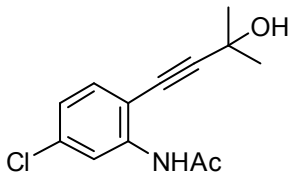
The iodo-, bromo- or triflate-aniline **1a-f** was dissolved in Et_3N/pyridine (1:1, 0.1 M) and nitrogen was bubbled through for 10 min at room temperature. 2-Methyl-3-butyn-2-ol (1.5 eq) was added and the solution was stirred for 10 min with nitrogen bubbling through. CuI (0.05 eq), PPh_3 (0.5 eq) and $(PPh_3)_2PdCl_2$ (0.05 eq) were then added, and the resulting suspension was heated at 90 ºC for 1.5–3 h (see Table 1). The reaction mixture was cooled down to rt and quenched with a saturated solution of NaCl. The mixture was then extracted twice with ethyl acetate, and the combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The desired products were purified by FC.

***N*-[2-(3-Hydroxy-3-methylbut-1-ynyl)-phenyl]-acetamide** (**3a**): colorless oil (76%



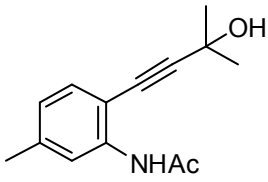
yield); HR-MS (ESI) Calcd for $C_{13}H_{15}NO_2Na$: 240.1000, found 240.1001 (Δ 0.4 ppm); MS (ESI): *m*/*z* (%) 240 [MNa^+] (95), 200 (100); ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 8.3, 1H; 6-H), 7.81 (br s, 1H; NH), 7.31 (dd, *J* = 7.7, 1.3, 1H; 3-H), 7.26 (dt, *J* = 8.3, 1.5, 1H; 5-H), 6.96 (t, *J* = 7.4, 1H; 4-H), 2.15 (s, 3H; *Me*CONH), 1.61 (s, 6H; C*Me*$_2$OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4 (s; CO), 138.9 (s; Ar), 131.5 (d; Ar), 129.7 (d; Ar), 123.4 (d; Ar), 119.4 (d; Ar), 111.4 (s; Ar), 101.5 (s, 2C; C≡), 65.7 (s; *C*Me$_2$OH), 31.5 (q, 2C; C*Me*$_2$OH), 24.8 (q; *Me*CO); IR: ν_{max} 3360, 2924, 2853, 2400, 1662, 1523, 1447 cm^{-1}.

***N*-[5-Chloro-2-(3-hydroxy-3-methyl-but-1-ynyl)-phenyl]-acetamide** (**3b**): Brown



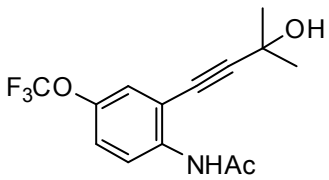
oil (57% yield); HR-MS (Voltage CI+) Calcd for $C_{13}H_{15}ClNO_2$: 252.0791, found 252.0792 (Δ 0.3 ppm); MS (Voltage CI+): m/z (%) 252 [MH^+] (100); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H; 6-H), 7.94 (br s; 1H; NH), 7.22 (d, *J* = 8.0, 1H; 4-H), 6.98 (d, *J* = 8.0, 1H; 3-H), 2.17 (s, 3H; MeCON), 1.64 (s, 6H; C*Me*$_2$OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6 (s; CO), 139.6 (s; Ar), 135.4 (s; Ar), 132.2 (d; C-5), 123.7 (d; C-6), 119.6 (d; C-3), 109.9 (s; Ar), 102.4 (s; C≡), 76.4 (s; C≡), 65.6 (s; *C*Me$_2$OH), 31.4 (q, 2C; C*Me*$_2$OH), 24.7 (q; CH_3CO); IR: ν_{max} 3386, 2982, 2933, 1738, 1680, 1411, 1370 cm^{-1}.

***N*-[2-(3-Hydroxy-3-methyl-but-1-ynyl)-5-methyl-phenyl]-acetamide** (**3c**): Pale



yellow oil (43% yield); HR-MS (Voltage CI+) Calcd for $C_{14}H_{18}NO_2$: 232.1338, found 232.1341 (Δ 1.5 ppm); MS (Voltage CI+): m/z (%) 232 [MH^+] (100); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H; 6-H), 7.88 (s, 1H; N-H), 7.22 (d, *J* = 8.0, 1H; 4-H), 6.81 (d, *J* = 8.0, 1H; 3-H), 2.84 (s, 1H; OH), 2.32 (s, 3H; 5-Me), 2.17 (s, 3H; MeCO), 1.64 (s, 6H; C*Me*$_2$OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6 (s; CO), 140.2 (s; Ar), 138.8 (s; Ar), 131.3 (d; Ar), 128.7 (d; Ar), 120.2 (d; Ar), 108.8 (s; Ar), 100.9 (s, 2C; C≡), 65.7 (s; *C*Me$_2$OH), 31.6 (q, 2C; C*Me*$_2$OH), 24.8 (q; MeCO), 21.9 (q; Me-5); IR: ν_{max} 3380, 2980, 2928, 21.82, 1673, 1529, 1022 cm^{-1}.

***N*-[2-(3-Hydroxy-3-methyl-but-1-ynyl)-4-trifluoromethoxy-phenyl]-acetamide**



(**3d**): Pale yellow oil (67 % yield); HR-MS (Voltage CI+) Calcd for $C_{14}H_{15}F_3NO_3$: 302.1004, found 302.1008 (Δ 1.3 ppm); MS (Voltage CI+): m/z (%) 302 [MH^+] (100); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, *J* = 9.1, 1H; 6-H), 7.92 (br s, 1H; NH), 7.24 (d, *J* = 2.0, 1H; 3-H), 7.18 (dd, *J* = 9.1, 2.2, 1H; 5-H), 2.23 (s, 3H; MeCO), 1.69 (s, 6H; C*Me*$_2$OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4 (s; CO), 144.1 (s; Ar), 137.6 (s; Ar), 123.9 (d; Ar), 122.6 (d; Ar), 120.6 (d; Ar), 120.4 [q, (q, J_{CF} = 257.7); OCF_3], 112.8 (s; Ar), 102.6 (s; C≡), 76.2 (s; C≡), 65.7 (s; *C*Me$_2$OH), 31.4 (q, 2C; C*Me*$_2$OH), 24.7 (q; CH_3CO); IR: ν_{max} 3387, 2929, 2856, 2208, 1738, 1681, 1522, 1254 cm^{-1}.

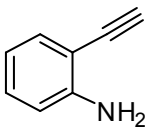
2-(3-Hydroxy-3-methyl-but-1-ynyl)-4-trifluoromethyl aniline (**3e**): Yellow oil (42 % yield); HR-MS (Voltage CI+) Calcd for $C_{12}H_{13}F_3NO$: 244.0949, found 244.0952 (Δ 1.1 ppm); MS (Voltage CI+): m/z (%) 244 [MH^+] (100); ^{1}H NMR (400 MHz, CDCl3) δ 7.52 (d, *J* = 1.4, 1H; 3-H), 7.34 (dd, *J* = 8.5, 1.6, 1H; 5-H), 6.72 (d, *J* = 8.5, 1H; 6-H), 4.63 – 3.72 (br s, 2H; NH_2), 1.66 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2 (s; Ar), 129.6 (d; Ar), 126.6 (d; Ar), 124.30 [q (q, J_{CF} = 281.6); CF_3], 119.9 (s; Ar), 113.7 (d; Ar), 106.9 (s; Ar), 100.4 (s; C≡), 77.4 (s; C≡), 65.78 (s; *C*Me$_2$OH), 30.04 (q, 2C; C*Me*$_2$OH); IR: ν_{max} 2923, 2854, 1572, 1462,1377, 1116, 1066 cm^{-1}.

4-(2-Amino-phenyl)-2-methyl-but-3-yn-2-ol (**3f**): Brown oil (63 % yield); HR-MS (Voltage CI+) Calcd for $C_{11}H_{14}NO$: 176.1075, found 176.1081 (Δ 3.2 ppm); MS (Voltage CI+): *m/z* (%) 176 [MH^+] (100); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (dd, *J* = 8.0, 1.0, 1H; 3-H), 7.15 (td, *J* = 8.2, 1.5, 1H; 4-H), 6.72–6.66 (m, 2H; 5-H, 6-H), 1.65 (s, 6H; C*Me*$_2$OH); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 147.7 (s; Ar), 132.1 (d; Ar), 129.6 (d; Ar), 118.0 (d; Ar), 114.4 (d; Ar), 107.5 (s; Ar), 99.6 (s; C≡), 78.6 (s; C≡), 65.7 (s; *C*Me_2OH), 31.7 (q, 2C; C*Me*$_2$OH); IR: ν_{max} 3361, 2980, 2927, 2216, 1615, 1492, 1157, 747 cm^{-1}.

Synthesis of 2-ethynyl-phenylamine (6)

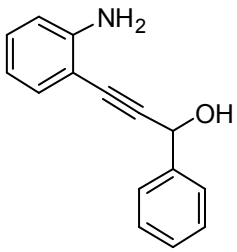
A solution of 2-iodoaniline (**1f**, 2.0 g, 9.13 mmol), $Pd(PPh_3)_4$ (130 mg, 0.18 mmol), PPh_3 (100 mg, 0.38 mmol) and CuI (36 mg, 0.19 mmol) in toluene (15 mL) was evacuated and purged with nitrogen repeatedly. *i*Pr_2NH (3 mL, 21.4 mmol) was then added and the reaction mixture was evacuated and purged with nitrogen repeatedly and then stirred at rt for 20 min. TMS-acetylene (2.6 mL, 18.4 mmol) was added under nitrogen and the reaction mixture was stirred 18 h at rt. KOH (2.5 g, 44.6 mmol) in water (2 mL) and MeOH (5 mL) was then added and the reaction mixture was stirred at rt for 1.5 h, quenched with NH_4Cl (50 mL) and extracted with CH_2Cl_2 (3 × 100 mL). Combined organic layers were washed with water (50 mL) and brine (50 mL) and dried over $MgSO_4$. The crude mixture was purified by FC (5% AcOEt in Hexane) to give the title compound (408 mg, 38 %) as a yellow oil.



HR-MS (Voltage CI+) Calcd for C_8H_8N: 118.0657, found 118.0662 (Δ 4.5 ppm); MS (Voltage CI+): m/z (%) 118 [MH^+] (100); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 7.8, 1.5, 1H; 6-H), 7.19 (td, *J* = 7.8, 1.5, 1H; 5-H), 6.79 – 6.67 (m, 2H; 3-H, 4-H), 4.29 (s, 2H; NH_2), 3.43 (s, 1H; ≡CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.6 (s; C-1), 132.6 (d; C-6), 130.2 (d; C-4), 117.8, 114.4 (d; C-3, C-5), 106.6 (s; C-2), 110.0 (d; ≡CH), 106.6 (s; *C*≡CH); IR: ν_{max} 3476, 3382, 3294, 3079, 2118, 1615, 1488, 1545, 1247, 839, 747 cm^{-1}.

Synthesis of 3-(2-Aminophenyl)-1-phenylprop-2-yn-1-ol (3g)

*n*BuLi (1.6 M in hexane, 1.4 mL, 2.24 mmol) was added dropwise to a solution of 2-ethynylaniline (**6**, 100 mg, 0.85 mmol) in dry THF (12 mL) at –5 °C. The mixture was stirred at –5 °C for 20 min then benzaldehyde (90 μL, 0.85 mmol) in dry THF (12 mL) was added and the mixture was stirred 1 h at rt. The reaction was followed by TLC (20% AcOEt/hexane). Further portions of benzaldehyde (50 μL, 0.47 mmol) were added at –5 °C until the disappearance of the starting material. The reaction was quenched with water (50 mL), extracted with diethyl ether (3 × 50 mL) and dried over $MgSO_4$. The crude product was purified by FC to give the title product (50 mg, 26 %) as yellow oil.

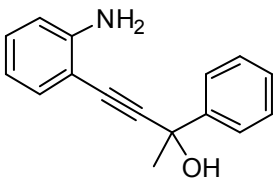


HR-MS (Voltage CI+) Calcd for $C_{15}H_{14}NO$: 224.1075, found 224.1075 (Δ –3.7 ppm); MS (Voltage CI+): m/z (%) 206 [M^+ – H_2O] (100), 224 [MH^+] (13), 241 [MNH_4^+] (9); ^{1}H NMR (400 MHz, CDCl3) δ 7.69 – 7.63 (m, 2H; Ph), 7.48 – 7.36 (m, 3H; Ph), 7.34 (dd, *J* = 8.1, 1.5, 1H; 3'-H), 7.17 (td, *J* = 8.0, 1.5, 1H; 5'-H), 6.75 – 6.66 (m, 2H; 4'-H, 6'-H), 5.78 (d, *J* = 6.2, 1H; 1-H), 4.21 (br s, 1H; NH_2), 2.30 (d, *J* = 6.2, 1H; OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.1 (s; C-2'), 140.8 (s; C-1'), 132.4 (d; C-3'), 130.1 (d; C-5'), 128.8 (d, 2C; Ph), 128.5 (d; Ph), 126.7 (d, 2C; Ph), 118.0, 114.5 (d; C-4', C-6'), 107.1 (s; Ph), 94.3, 83.4 (s; C-2, C-3), 65.24 (d; C-1); IR: ν_{max} 3363, 3030, 2923, 2218, 1614, 1491, 1454, 1312, 1157, 747, 697 cm^{-1}.

Synthesis of 4-(2-Aminophenyl)-2-phenylbut-3-yn-2-ol (3h)

$CeCl_3 \cdot 7H_2O$ was placed under vacuum and while stirring heated slowly from rt to 140 °C over 2 h. Then it was stirred at 140 °C for 16 h. The anhydrous $CeCl_3$ (350 mg, 1.42 mmol) was slurried in dry THF (2 mL) for 1 h at room temperature. Meanwhile,

a solution of 2-ethynylaniline (**6**, 50 mg, 0.43 mmol) in dry THF (1.5 mL) was cooled to –78 °C before the dropwise addition of *n*BuLi (1.6 M in hexane, 0.80 mL, 1.28 mmol), and the mixture stirred at –78 °C for 20 min. The $CeCl_3$ slurry was cooled to –78 °C and *n*BuLi (1.6 M in hexane) was added dropwise until a pale yellow color persisted (~0.3-0.4 mL). The solution of lithiated alkyne was then transferred *via* syringe to the $CeCl_3$ slurry, and the mixture stirred at –78 °C for 10 min before the dropwise addition of a solution of acetophenone (207 mg, 1.72 mmol) in dry THF (1.5 mL). The reaction mixture was stirred at –78 °C for 2 h and then, after allowing to warm to rt, quenched with a saturated solution of NH_4Cl (15 mL). The mixture was extracted with EtOAc (3 x 10 mL) and the combined organic layers dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by FC (20% EtOAc in hexane) to give the title compound (61 mg, 60 %) as a pale yellow oil.

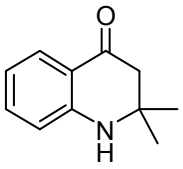


HR-MS (ESI) Calcd for $C_{16}H_{14}N$ [– H_2O]: 220.1126, found 220.1130 (Δ 1.8 ppm); MS (ESI): m/z (%) 220 [M^+ – H_2O] (100); ^{1}H NMR (400 MHz, CDCl3) δ 7.74 (d, *J* = 7.4, 2H; Ph), 7.39 (t, *J* = 7.6, 2H; Ph), 7.32 (m, 2H; Ph), 7.14 (td, *J* = 7.7, 1.1, 1H; Ph), 6.70 (m, 2H; Ph), 4.18 (br s, 2H; NH_2), 2.82 (br s, 1H; OH), 1.89 (s, 3H; CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.9 (s), 145.7 (s), 132.2 (d, Ph), 129.9 (d, Ph), 128.4 (d, 2C, Ph), 127.7 (d, Ph), 124.9 (d, 2C, Ph), 117.9 (d, Ph), 114.4 (d, Ph), 107.2 (s), 98.1 (s), 81.5 (s), 70.5 (s), 33.5 (q); IR: ν_{max} 3372, 2983, 2929, 2224, 1614, 1491, 1447, 1312, 1088, 750, 700 cm^{-1}.

General procedure for the acid catalyzed cyclization

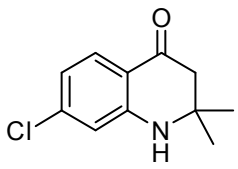
Sonogashira coupling product **3a-h** was dissolved in *c*HCl/H_2O (1:1, v/v; 0.1 M) and heated at 120 °C for 1.5–8 h (see Table 2). The reaction mixture was then concentrated *in vacuo.* Water was then added followed by K_2CO_3 up to pH = 11. The mixture was extracted twice with ethyl acetate and the combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Final quinolinones were purified by FC.

2,2-Dimethyl-2,3-dihydro-1*H*-quinolin-4-one (**4a**): yellow oil (70-98% yield); HR-



MS (ESI) Calcd for $C_{11}H_{14}NO$: 176.1075, found 176.1071 (Δ –2.3 ppm); MS (ESI): *m*/*z* (%) 176 [MH^+] (78), 120 (100); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 1.4, 7.9, 1H; Ar), 7.35 – 7.27 (m, 1H; Ar), 6.71 (m, 1H; Ar), 6.63 (d, *J* = 8.2, 1H; Ar), 4.18 (s, 1H; NH), 2.61 (s, 2H; 3-H), 1.35 (s, 6H; Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.0 (s; CO), 149.8 (s; Ar), 135.4 (d; Ar), 127.2 (d; Ar), 118.1 (d; Ar), 117.5 (d; Ar), 115.8 (s; Ar), 53.6 (s; 2-C), 50.6 (t, 3-C), 27.7 (q, 2C; Me); IR: ν_{max} 3333, 2924, 2853, 1659, 1613, 1481 cm^{-1}.

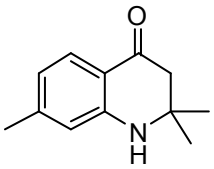
7-Chloro-2,2-dimethyl-2,3-dihydro-1*H*-quinolin-4-one (**4b**): Pale yellow oil (68%



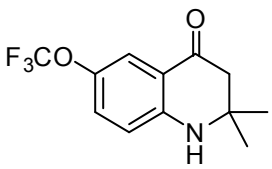
yield); HR-MS (ESI) Calcd for $C_{11}H_{13}ClNO$: 210.0686, found 210.0687 (Δ 0.5 ppm); MS (ESI): m/z (%) 210 [MH^+] (88); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.5, 1H; 5-H), 6.69 (dd, *J* = 8.5, 2.0, 1H; 6-H), 6.65 (d, *J* = 2.0, 1H; 8-H), 4.18 (br s, 1H; NH), 2.61 (s, 2H; 3-H), 1.36 (s, 6H; Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.9 (s; CO), 150.4 (s; Ar), 141.4 (s; Ar), 128.8 (d; Ar), 118.0 (d; Ar), 116.5 (s; Ar), 115.1 (d; Ar), 53.7 (s; C-2), 50.3 (t, C-3), 30.9 (q, 2C; Me); IR: ν_{max} 3318, 2923, 1738, 1660, 1604, 1366, 1217,

798 $cm^{-1.}$

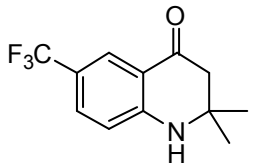
2,2,7-Trimethyl-2,3-dihydro-1*H*-quinolin-4-one (**4c**): Brown oil (70% yield); HR-MS (ES+) Calcd for $C_{12}H_{16}NO$: 190.1232, found 190.1224 (Δ –4.2 ppm); MS (Voltage CI+): *m*/*z* (%) 190 [MH^+] (100); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.0, 1H; 5-H), 6.54 (d, *J* = 8.0, 1H; 6-H), 6.43 (s, 1H; 8-H), 4.10 (br s, 1H; NH), 2.58 (s, 2H; 3-H), 2.29 (s, 3H; Ar-*Me*), 1.33 (s, 6H; $NC(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.6 (s; CO), 150.1 (s; Ar), 146.4 (s; Ar), 127.2 (d; Ar), 119.1 (d; Ar), 116.0 (s; Ar), 115.7 (d; Ar), 53.5 (s; C-2), 50.6 (t, C-3), 27.8 (q, 2C; $NC(CH_3)_2$), 21.9 (q; Ar-*Me*); IR: ν_{max} 3322, 2923, 1738, 1653, 1362, 1212, 795 cm^{-1}.



2,2-Dimethyl-6-trifluoromethoxy-2,3-dihydro-1*H*-quinolin-4-one (**4d**): Brown oil (60% yield); HR-MS (ESI) Calcd for $C_{12}H_{13}F_3NO_2$: 260.0898, found 260.0891 (Δ –2.7 ppm); MS (ESI): m/z (%) 260 [MH^+] (100); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 2.0, 1H; 5-H), 7.18 (dd, *J* = 2.0, 9.0, 1H; 7-H), 6.64 (d, *J* = 9.0, 1H; 8-H), 4.27 (br s, 1H; NH), 2.62 (s, 2H; 3-H), 1.36 (s, 6H; Me); ^{13}C NMR (126 MHz, CDCl3) δ 192.9 (s; CO), 148.4 (s; Ar), 140.4 (s; Ar), 129.0 (d; Ar), 120.6 [q; (q, J_{CF} = 256.5); OCF_3], 119.6 (d; Ar), 117.6 (s; Ar), 116.9 (d; Ar), 53.7 (s; C-2), 50.1 (t; C-3), 27.6 (q, 2C; Me); IR: ν_{max} 3323, 2923, 2853, 1661, 1510, 1209, 1161 $cm^{-1.}$

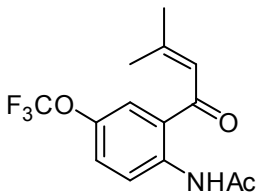


2,2-Dimethyl-6-trifluoromethyl-2,3-dihydro-1*H*-quinolin-4-one (**4e**): Pale yellow



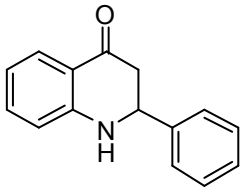
oil (35% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.7, 1H; 8-H), 6.78 – 6.69 (m, 1H; 5-H), 6.63 (d, *J* = 8.7, 1H; 7-H), 4.12 (br s, 1H; NH), 2.62 (s, 2H; 3-H), 1.36 (s, 6H; Me). IR: ν_{max} 3319, 2923, 2854, 2046, 1615, 1464, 1117 cm^{-1}.

***N*-[2-(3-Methyl-but-2-enoyl)-4-trifluoromethoxy-phenyl]-acetamide** (**5**): Brown



oil; HR-MS (ESI) Calcd for $C_{14}H_{15}F_3NO_3$: 302.1004, found 302.1008 (Δ 1.3 ppm); MS (ESI): m/z (%) 302 [MH^+] (100); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.44 (s, 1H; NH), 8.74 (d, *J* = 9.2, 1H; 6-H), 7.68 (d, *J* = 2.6, 1H; 3-H), 7.40 (dd, *J* = 9.2, 1.9, 1H; 5-H), 6.62 (m, 1H; C*H*=CMe_2) 2.27 (s, 3H; *Me*CONH), 2.21 (d, *J* = 1.1, 3H; CH=C*Me*$_2$), 2.08 (d, *J* = 1.1, 3H; CH=C*Me*$_2$).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.9 (s; CO), 148.4 (s; CO), 140.4 (s; Ar), 127.0 (d; Ar), 120.61 [q, (q, J_{CF} = 256.5); OCF_3], 119.5 (d; Ar), 117.8 (s; Ar), 116.9 (d; Ar), 53.7 (s; CH=*C*Me_2), 50.1 (d; *C*H=CMe_2), 29.7 (q; *Me*CONH), 22.7 (q, 2C; CH=C*Me*$_2$); IR: ν_{max} 2970, 1739, 1650, 1589, 1519, 1366, 1257, 1217, 1164 cm^{-1}.

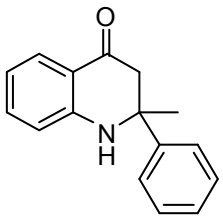
2-Phenyl-2,3,4a,8a-tetrahydro-1*H*-quinolin-4-one (**7a**)**:** colorless oil (50% yield);



HR-MS (ESI) Calcd for $C_{15}H_{12}N$: 206.0970, found 206.0966 (Δ –0.4 ppm); MS (ESI): m/z (%) 206 [$MH^+ - H_2O$] (100); ^{1}H NMR (400 MHz, CDCl3) δ 7.91 (dd, *J* = 8.0, 1.0, 1H; 8-H), 7.50 (dd, *J* = 7.9, 1.2, 2H; Ph), 7.47 – 7.34 (m, 4H; Ph, 6-H), 6.83 (dd, *J* = 11.1, 4.1, 1H; 7-H), 6.74 (d, *J* = 8.2, 1H; 5-H), 4.79 (dd, *J* = 13.7, 3.8, 1H; 2-H), 4.53 (br s, 1H; NH), 2.93 (dd, *J* = 16.3, 13.7, 1H; 3-H_a), 2.81 (ddd, *J* = 16.2, 3.9, 1.7, 1H; 3-H_b); ^{13}C NMR (126 MHz, CDCl3) δ 193.3 (s; CO), 141.1 (s; C-8a), 135.4 (s; C-4a), 129.5 (d; C-6), 129.0

(d, 2C; Ph), 128.5 (d; Ph), 127.6 (d; C-8), 126.6 (d, 2C; Ph), 119.0 (s; Ph), 118.5 (d; C-7), 115.9 (d; C-5), 58.5 (d; C-2), 46.4 (t; C-3); IR: ν_{max} 3362, 2924, 1738, 1613, 1491, 1454, 1313, 1090, 748, 697 cm^{-1}.

2-Phenyl-2,3,4a,8a-tetrahydro-1*H*-quinolin-4-one (**7b**)**:** brown oil (26% yield);



HR-MS (ESI) Calcd for $C_{16}H_{16}NO$: 238.1232, found 238.1236 (Δ 1.7 ppm); MS (ESI): m/z (%) 206 [$MH^+ - H_2O$] (100); ^{1}H NMR (400 MHz, CDCl3) δ 7.75 (dd, *J* = 1.3, 7.9, 1H, Ph), 7.44 (m, 2H, Ph), 7.29 – 7.36 (m, 3H, Ph), 7.24 (m, 1H, Ph), 6.75 – 6.68 (m, 2H, Ph), 4.67 (br s, 1H, NH), 3.14 (d, *J* = 16.2, 1H, CHH), 2.85 (d, *J* = 16.2, 1H, CHH), 1.67 (s, 3H, CH_3); ^{13}C NMR (101 MHz, CDCl3) δ 193.0 (s, CO), 149.9 (s, Ph), 144.9 (s, Ph), 135.5 (d, Ph), 128.7 (d, 2C, Ph), 127.4 (d, Ph), 127.3 (d, Ph), 125.3 (d, 2C, Ph & s, 1C, Ph), 117.8 (d, Ph), 115.6 (d, Ph), 59.1 (s, C-2), 51.0 (t, C-3), 28.4 (q); IR: ν_{max} 3343, 2973, 2926, 1658, 1611, 1494, 1445, 1315, 1094, 755, 699 cm^{-1}.