

# **An unexpected copper(II)-catalyzed three-component reaction of quinazoline 3-oxide, alkylidenecyclopropane, and water**

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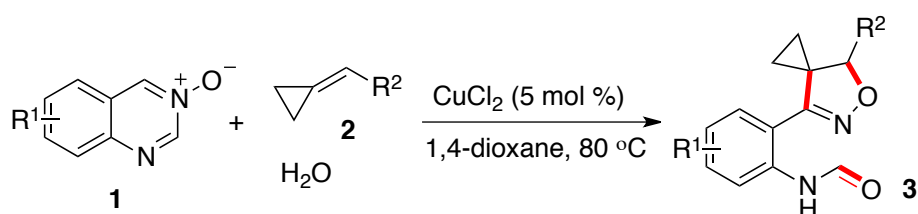
## **Supporting Information**

1. General experimental methods (S2).
2. General experimental procedure and characterization data (S2-S7).
3. <sup>1</sup>H and <sup>13</sup>C NMR spectra of compound **3** (S8-S31).

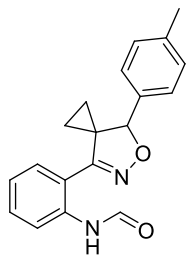
## General Materials and Methods:

Unless otherwise stated, all commercial reagents were used as received. Flash column chromatography was performed using silica gel (60-Å pore size, 32-63µm, standard grade). Analytical thin-layer chromatography was performed using glass plates pre-coated with 0.25 mm 230-400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin layer chromatography plates were visualized by exposure to ultraviolet light. Organic solutions were concentrated on rotary evaporators at ~20 Torr at 25-35°C. Nuclear magnetic resonance (NMR) spectra are recorded in parts per million from internal tetramethylsilane on the  $\delta$  scale.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded in  $\text{CDCl}_3$  on a Bruker DRX-400 spectrometer operating at 400 MHz and 100 MHz, respectively. All chemical shift values are quoted in ppm and coupling constants quoted in Hz. High resolution mass spectrometry (HRMS) spectra were obtained on a micrOTOF II Instrument.

*General procedure for the copper(II)-catalyzed three-component reaction of quinazoline 3-oxide, alkylidenecyclopropane, and water*

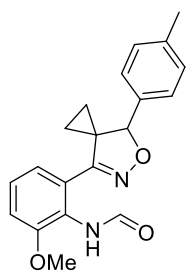


Alkylidenecyclopropane **2** (0.4 mmol, 2 equiv) was added to a solution of quinazoline-N-oxide **1** (0.2 mmol) and CuCl<sub>2</sub>(0.01 mmol, 1.4 mg) in non-distilled 1,4-dioxane (2.0 mL Analytical Reagent) under air atmosphere. The solution was stirred at 80 °C for 8-10 hours. After completion of the reaction as indicated by TLC, the mixture was purified directly by flash column chromatograph (PE:EA, 4:1) to give the desired product **3**.



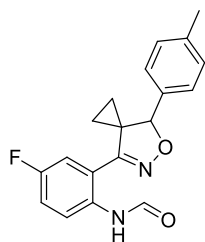
*N*-(2-(4-(*p*-Tolyl)-5-oxa-6-azaspiro[2.4]hept-6-en-7-yl)phenyl)formamide (**3a**)

Yield: 76%; Yellow oil; IR: 3310.9, 3007.6, 2921.6, 2870.2, 1697.1, 1517.1, 1463.1  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.63-0.69 (m, 1H), 0.87-0.99 (m, 2H), 1.33-1.37 (m, 1H), 2.37 (s, 3H), 5.48 (s, 1H), 7.13 (d,  $J = 4.2$  Hz, 2H), 7.20 (s, 4H), 7.39-7.43 (m, 1H), 8.45-8.47 (m, 2H), 9.38 (s, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  11.0, 11.8, 21.2, 36.8, 87.7, 119.1, 122.8, 124.1, 127.1, 127.3, 129.5, 130.7, 130.9, 134.1, 136.0, 138.8, 159.4, 162.1; HRMS (ESI) calcd for  $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_2$ : 307.1441 ( $\text{M}+\text{H}^+$ ), found: 307.1412.



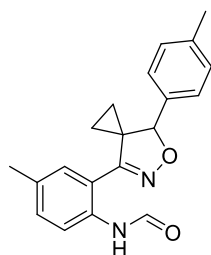
*N*-(2-Methoxy-6-(4-(*p*-tolyl)-5-oxa-6-azaspiro[2.4]hept-6-en-7-yl)phenyl)formamide (**3b**)

Yield: 68%; Yellow solid; m.p. 50.5-51.4  $^{\circ}\text{C}$ ; IR: 3259.8, 3003.9, 2923.7, 2875.8, 1697.1, 1580.8, 1474.7, 1276.5  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.51-0.53 (m, 2H), 0.8-1.01 (m, 2H), 2.35 (s, 3H), 3.86 (s, 3H), 5.53 (s, 1H), 6.84 (d,  $J = 7.7$  Hz, 1H), 7.01 (d,  $J = 7.5$  Hz, 1H), 7.18-7.26 (m, 5H), 7.63-7.67 (m, 1H), 8.58 (d,  $J = 11.2$  Hz, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  10.5, 10.9, 21.2, 37.4, 56.1, 113.0, 120.7, 122.0, 126.4, 127.1, 128.1, 129.4, 138.5, 159.5, 164.7; HRMS(ESI) calcd for  $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_3$ : 337.1547 ( $\text{M} + \text{H}^+$ ), found: 337.1558.



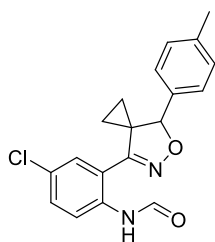
*N*-(4-Fluoro-2-(4-(*p*-tolyl)-5-oxa-6-azaspiro[2.4]hept-6-en-7-yl)phenyl)formamide (**3c**)

Yield: 85%; White solid; m.p. 113.2-113.9 °C; IR: 3313.7, 3010.2, 2923.7, 2872.6, 1697.3, 1517.9, 1425.1, 1165.7 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.67-0.69 (m, 1H), 0.91-0.96 (m, 2H), 1.36-1.38 (m, 1H) 2.37 (s, 3H), 5.49 (s, 1H), 6.84 (dd, *J*<sub>1</sub> = 2.9 Hz, *J*<sub>2</sub> = 9.1 Hz, 1H), 7.11-7.22 (m, 5H), 8.41-8.45 (m, 2H), 9.35 (s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 11.1, 11.8, 21.3, 36.6, 88.0, 114.2 (d, <sup>2</sup>*J*<sub>CF</sub> = 24.2 Hz), 117.4(d, <sup>2</sup>*J*<sub>CF</sub> = 21.6 Hz), 121.4, 124.7 (d, <sup>3</sup>*J*<sub>CF</sub> = 7.8 Hz), 127.1, 129.5, 132.3, 133.7, 139.0, 157.3, 158.5, 159.3, 161.0 (d, <sup>1</sup>*J*<sub>CF</sub> = 238.2 Hz); HRMS (ESI) calcd for C<sub>19</sub>H<sub>17</sub>FN<sub>2</sub>O<sub>2</sub>: 325.1347 (M + H<sup>+</sup>), found: 325.1348.

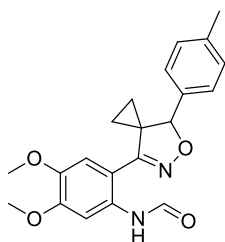


*N*-(4-Methyl-2-(4-(*p*-tolyl)-5-oxa-6-azaspiro[2.4]hept-6-en-7-yl)phenyl)formamide (**3d**)

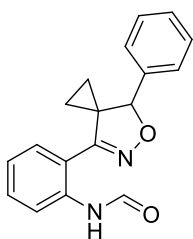
Yield: 75%; Yellow oil; IR: 3322.0, 3003.8, 2952.1, 2922.9, 1719.8, 1517.5, 1425.1 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.67-0.71 (m, 1H), 0.92-1.09 (m, 2H), 1.47-1.49 (m, 1H) 2.37 (s, 3H), 3.91 (s, 3H), 5.49 (s, 1H), 7.20 (s, 4H), 7.83 (s, 1H), 8.05 (dd, *J*<sub>1</sub> = 1.8 Hz, *J*<sub>2</sub> = 8.7 Hz, 1H), 8.51 (s, 1H), 8.66 (d, *J* = 4.4 Hz, 1H), 9.94(s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 11.4, 12.0, 21.3, 29.7, 36.5, 88.0, 116.3, 121.7, 125.3, 127.2, 128.6, 129.5, 132.0, 133.7, 139.0, 140.3, 158.8, 159.7, 165.9; HRMS (ESI) calcd for C<sub>20</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>: 321.1598 (M + H<sup>+</sup>), found: 321.1584.



*N*-(4-Chloro-2-(4-(*p*-tolyl)-5-oxa-6-azaspiro[2.4]hept-6-en-7-yl)phenyl)formamide (**3e**) Yield: 83%; Yellow solid; m.p. 90.4-91.2 °C; IR: 3300.6, 3003.5, 2922.2, 2874.6, 1700.3, 1511.9, 1412.7 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.67-0.71 (m, 1H), 0.89-0.99 (m, 2H), 1.33-1.36 (m, 1H) 2.37 (s, 3H), 3.91 (s, 3H), 5.49 (s, 1H), 7.09 (d, *J* = 2.4 Hz 1H), 7.16-7.22 (m, 4H), 7.37 (dd, *J*<sub>1</sub> = 2.4 Hz, *J*<sub>2</sub> = 8.9 Hz, 1H), 8.43-8.46 (m, 2H), 9.43 (s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 11.1, 11.9, 21.27, 36.6, 88.0, 118.4, 123.9, 127.1, 129.2, 129.5, 130.6, 133.7, 134.7, 139.0, 158.4, 159.5; HRMS (ESI) calcd for C<sub>19</sub>H<sub>17</sub>ClN<sub>2</sub>O<sub>2</sub>: 341.1051 (M + H<sup>+</sup>), found: 341.1046.

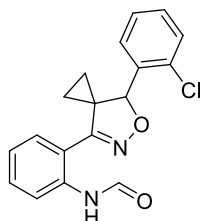


*N*-(4,5-Dimethoxy-2-(4-(*p*-tolyl)-5-oxa-6-azaspiro[2.4]hept-6-en-7-yl)phenyl)formamide (**3f**) Yield: 62%; Yellow oil; IR: 3315.4, 3004.1, 2934.2, 2862.3, 1692.8, 1522.1, 1414.4, 1218.9 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.64-0.66 (m, 1H), 0.87-0.99 (m, 2H), 1.37-1.42 (m, 1H) 2.37 (s, 3H), 3.83 (s, 3H), 3.93 (s, 3H), 5.47 (s, 1H), 6.57 (s, 1H), 7.20 (s, 4H), 8.17 (s, 1H), 8.41 (d, *J* = 1.8 Hz, 1H), 9.42 (s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 11.1, 11.7, 21.3, 36.8, 56.1, 56.3, 87.6, 106.4, 108.5, 109.9, 127.1, 129.5, 130.9, 133.9, 134.0, 138.8, 159.4; HRMS (ESI) calcd for C<sub>21</sub>H<sub>22</sub>N<sub>2</sub>O<sub>4</sub>: 367.1652 (M + H<sup>+</sup>), found: 367.1632.



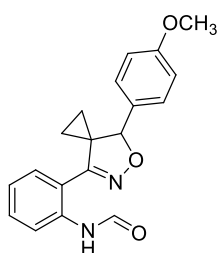
*N*-(2-(4-Phenyl-5-oxa-6-azaspiro[2.4]hept-6-en-7-yl)phenyl)formamide (**3g**)

Yield: 68%; Yellow oil; IR: 3314.5, 3063.9, 2922.3, 2873.5, 1698.1, 1518.6, 1449.7  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.62-0.67 (m, 1H), 0.90-1.00 (m, 2H), 1.33-1.38 (m, 1H) 5.5 (s, 1H), 7.12-7.21 (m, 2H), 7.30-7.44 (m, 6H), 8.44-8.45 (m, 2H), 9.35 (s, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  11.0, 11.9, 37.0, 87.7, 119.2, 122.8, 124.1, 124.9, 127.1, 127.4, 128.8, 129.0, 130.8, 131.0, 136.0, 137.2, 159.5, 162.3; HRMS (ESI) calcd for  $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_2$ : 293.1285 ( $\text{M} + \text{H}^+$ ), found: 293.1259.



*N*-(2-(4-(2-Chlorophenyl)-5-oxa-6-azaspiro[2.4]hept-6-en-7-yl)phenyl)formamide (**3h**)

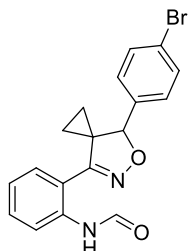
Yield: 54%; Yellow solid; m.p. 101.2-101.8  $^\circ\text{C}$ ; IR: 3310.9, 3067.5, 2889.6, 1770.6, 1519.3, 1449.7  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.82-0.88 (m, 1H), 0.98-1.04 (m, 2H), 1.23-1.27 (m, 1H), 6.05 (s, 1H), 7.08-7.20 (m, 2H), 7.27-7.44 (m, 4H), 7.50-7.52 (m, 1H), 8.44 (s, 1H), 8.68 (s, 1H), 9.08 (s, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  10.3, 13.0, 37.5, 83.7, 119.3, 122.8, 124.2, 124.9, 127.6, 127.7, 128.5, 129.1, 129.7, 129.8, 130.8, 135.9, 159.3, 162.1; HRMS (ESI) calcd for  $\text{C}_{18}\text{H}_{15}\text{ClN}_2\text{O}_2$ : 327.0895 ( $\text{M} + \text{H}^+$ ), found: 327.0850.



*N*-(2-(4-(4-Methoxyphenyl)-5-oxa-6-azaspiro[2.4]hept-6-en-7-yl)phenyl)formamide (**3i**)

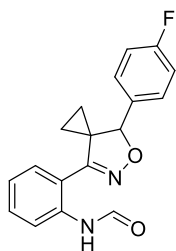
Yield: 72%; Yellow oil; IR: 3314.7, 3002.7, 2934.1, 2837.5, 1697.6, 1514.5, 1450.0, 1250.1  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.63-0.69 (m, 1H), 0.84-0.90 (m, 2H), 1.33-1.39 (m, 1H), 3.82 (s, 3H), 5.48 (s, 1H), 6.92 (d,  $J = 8.6$  Hz, 2H), 7.13 (d,  $J = 4.2$  Hz, 2H), 7.24 (d,  $J = 8.6$  Hz, 2H), 7.39-7.43 (m, 1H), 8.46-8.72 (m, 2H), 9.42

(s, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  11.1, 11.7, 36.7, 55.3, 87.6, 114.2, 119.2, 122.8, 124.1, 124.8, 127.4, 128.7, 128.9, 129.0, 130.7, 130.9, 136.0, 159.5, 162.2; HRMS (ESI) calcd for  $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_3$ : 323.1390 ( $\text{M} + \text{H}^+$ ), found: 323.1398.



*N*-(2-(4-(4-Bromophenyl)-5-oxa-6-azaspiro[2.4]hept-6-en-7-yl)phenyl)formamide (**3j**)

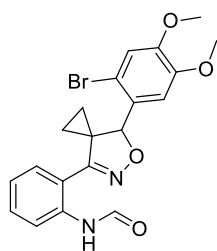
Yield: 65%; Yellow oil; IR: 3315.5, 3035.6, 2935.3, 1691.9, 1518.1, 1448.9  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.61-0.64 (m, 1H), 0.89-1.00 (m, 2H), 1.33-1.36 (m, 1H), 5.47 (s, 1H), 7.09-7.20 (m, 4H), 7.40-7.44 (m, 1H), 7.51-7.53 (m, 2H), 8.42-8.45 (m, 2H), 9.32 (s, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  11.0, 12.0, 37.0, 87.0, 119.4, 122.9, 124.2, 125.0, 127.4, 128.7, 128.9, 130.9, 131.1, 132.0, 136.0, 136.3, 159.5, 162.3; HRMS (ESI) calcd for  $\text{C}_{18}\text{H}_{15}\text{BrN}_2\text{O}_2$ : 371.0390 ( $\text{M} + \text{H}^+$ ), found: 371.0386.



*N*-(2-(4-(4-Fluorophenyl)-5-oxa-6-azaspiro[2.4]hept-6-en-7-yl)phenyl)formamide (**3k**)

Yield: 71%; Yellow oil; IR: 3315.2, 3050.3, 2924.6, 1698.0, 1510.8, 1450.5  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.60-0.64 (m, 1H), 0.88-1.03 (m, 2H), 1.34-1.42 (m, 1H), 5.50 (s, 1H), 7.07-7.22 (m, 4H), 7.29-7.34 (m, 2H), 7.40-7.44 (m, 1H), 8.44-8.46 (m, 2H), 9.35 (s, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  11.0, 11.9, 36.9, 87.1, 115.8 (d,  $^2J_{\text{CF}} = 21.5$  Hz), 116.8, 119.4, 122.9, 124.2, 124.9, 127.4, 129.0 (d,  $^3J_{\text{CF}} = 7.7$  Hz), 130.9 (d,  $^2J_{\text{CF}} = 21.3$  Hz), 133.1, 136.0, 159.5, 162.3, 163.0 (d,  $^1J_{\text{CF}} = 246.7$  Hz).

Hz); HRMS (ESI) calcd for C<sub>18</sub>H<sub>15</sub>FN<sub>2</sub>O<sub>2</sub>: 311.1190 (M + H<sup>+</sup>), found: 311.1188.



*N*-(2-(4-(2-Bromo-4,5-dimethoxyphenyl)-5-oxa-6-azaspiro[2.4]hept-6-en-7-yl)phenyl)formamide (**31**)

Yield: 71%; Yellow solid; m.p. 80.7-81.5 °C; IR: 3318.5, 3010.5, 2934.3, 2840.7, 1700.3, 1509.1, 1450.2, 1260.1 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.77-0.85 (m, 1H), 1.01-1.04 (m, 1H), 1.21-1.29 (m, 2H), 3.87 (dd, *J*<sub>1</sub> = 4.0 Hz, *J*<sub>2</sub> = 7.4 Hz, 6H), 5.98 (s, 1H), 6.94-6.98 (m, 2H), 7.08-7.15 (m, 2H), 7.33-7.43 (m, 1H), 8.42-8.44 (m, 2H), 9.20 (s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 10.6, 12.7, 37.5, 56.2, 85.6, 110.6, 115.1, 115.2, 119.2, 122.8, 124.1, 124.9, 127.4, 128.9, 130.8, 131.0, 136.0, 159.2, 162.0; HRMS (ESI) calcd for C<sub>20</sub>H<sub>19</sub>BrN<sub>2</sub>O<sub>4</sub>: 431.0601 (M + H<sup>+</sup>), found: 431.0583.



