Supporting Information

Addition of α-Lithiated Nitriles to Azaheterocycles

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Preparation of Dihydroquinazolines

General Procedure:

To an oven dried round bottom flask was added the nitrile (12 mmol, 1.2 eq.) and THF (50 ml). The solution was cooled to -78 °C and stirred under a N₂ atmosphere. After 5 minutes, LiHMDS (12 ml of 1M in THF, 12 mmol, 1.2 eq.) was added dropwise. After 5 additional minutes of stirring, quinazoline (1.3 g, 10 mmol, 1.0 eq.) was added, the cooling bath was removed and the reaction mixture stirred for 1 hour. The reaction was then cooled to -78°C and quenched with 1N HCl. The reaction mixture was concentrated then partitioned between saturated aqueous NaHCO₃ and EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc (4x). The combined organic layers were washed with brine, dried (Na₂SO₄), filtered and evaporated to dryness to give a yellow-brown oil. The crude residue was purified via silica gel column chromatography (40 g Isco cartridge; 0-10% MeOH in DCM) to provide the desired product.

Compound Characterization

2-(3,4-Dihydroquinazolin-4-yl)acetonitrile (2a)

$^1$H NMR (400 MHz, CDCl₃) $\delta$ 7.37 (s, 1H), 7.26 – 7.21 (m, 1H), 7.13 – 7.04 (m, 2H), 6.84 (dd, $J$ = 7.9, 0.8 Hz, 1H), 5.02 (t, $J$ = 5.9 Hz, 1H), 2.74 (d, $J$ = 5.9 Hz, 2H). $^{13}$C NMR (101 MHz, CDCl₃) $\delta$ 145.72, 136.74, 129.03, 126.32, 124.78, 119.78, 117.84, 117.38, 51.95, 28.03.
2-(3,4-Dihydroquinazolin-4-yl)propanenitrile (2b)

$^1$H NMR (mix of diastereomers) (400 MHz, CDCl$_3$) $\delta$ 7.41 (d, $J = 5.3$ Hz, 1H), 7.23 (dd, $J = 7.7$, 5.4, 2.3 Hz, 1H), 7.09 (qd, $J = 5.7$, 1.1 Hz, 1H), 7.00 – 6.83 (m, 2H), 4.91 (dd, $J = 75.8$, 4.5 Hz, 1H), 2.97 – 2.87 (m, 1H), 1.31 (dd, $J = 26.7$, 7.2 Hz, 3H).

$^{13}$C NMR (mix of diastereomers) (101 MHz, CDCl$_3$) $\delta$ 146.24, 145.92, 138.31, 137.18, 129.08, 128.98, 127.07, 126.68, 124.76, 124.53, 121.48, 121.46, 118.81, 118.62, 57.19, 56.23, 35.08, 34.72, 13.72, 12.30.
2-(3,4-Dihydroquinazolin-4-yl)-2-methylpropanenitrile (2c)

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.58 – 7.57 (m, 1H), 7.32 – 7.27 (m, 1H), 7.14 (d, $J = 4.0$ Hz, 2H), 6.98 (d, $J = 7.9$ Hz, 1H), 4.74 (s, 1H), 1.35 (s, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 146.10, 138.82, 129.13, 128.48, 124.40, 124.32, 118.79, 117.35, 60.68, 41.19, 22.27, 21.85.
One Pot Addition / Oxidation

General Procedure:

To a solution of the nitrile / sulfone (1.2 mmol) in THF (5 ml) at -78 °C (under an N₂ atmosphere) was added LiHMDS (1.2 mL of 1 M in THF, 1.2 mmol) dropwise and the reaction mixture was stirred at this temperature for 5 minutes. The heterocycle (1 mmol, 1 eq.) was added while the reaction mixture was at -78°C, the cooling bath was removed and the reaction mixture was stirred until the reaction was judged complete by LCMS analysis (generally 1 h). Solid KMnO₄ (316 mg, 2 mmol, 2 eq.) and acetonitrile (1 ml) were added and the reaction mixture was stirred at room temperature until the reaction was judged complete by LCMS analysis (generally 4-6 h). The reaction mixture was poured into saturated aqueous NaHCO₃ and the layers separated. The aqueous layer was then extracted with EtOAc (3x). All organics were combined, washed with water, brine, dried (Na₂SO₄) and evaporated to dryness. Purification by silica gel column chromatography (12 g Isco silica cartridge) using hexanes and EtOAc gave the desired products.
Compound Characterization

2-Methyl-2-(quinazolin-4-yl)propanenitrile (3):

\[ ^1H \text{NMR (400 MHz, CDCl}_3 \] \( \delta \) 9.22 (s, 1H), 8.61 (d, \( J = 8.6 \) Hz, 1H), 8.07 (d, \( J = 8.4 \) Hz, 1H), 7.89 (ddd, \( J = 8.4, 6.9, 1.3 \) Hz, 1H), 7.68 (ddd, \( J = 8.4, 6.9, 1.3 \) Hz, 1H), 1.92 (s, 6H).

\[ ^{13}C \text{NMR (101 MHz, CDCl}_3 \] \( \delta \) 166.18, 153.72, 151.09, 133.87, 130.10, 128.06, 124.67, 123.81, 122.02, 37.51, 27.59.
1-(Quinazolin-4-yl)cyclohexanecarbonitrile (Table 3, Entry 1)

\[ \text{H NMR (400 MHz, CDCl}_3\text{)} \] \( \delta \) 9.29 (s, 1H), 8.70 (d, \( J = 8.6 \text{ Hz, 1H} \)), 8.13 (d, \( J = 8.2 \text{ Hz, 1H} \)), 7.94 (ddd, \( J = 8.4, 6.9, 1.3 \text{ Hz, 1H} \)), 7.72 (ddd, \( J = 8.4, 6.9, 1.3 \text{ Hz, 1H} \)), 2.52 (d, \( J = 12.3 \text{ Hz, 2H} \)), 2.17 – 2.08 (m, 2H), 2.02 – 1.95 (m, 4H), 1.93 – 1.87 (m, 1H), 1.40 – 1.28 (m, 1H). \[ \text{C NMR (101 MHz, CDCl}_3\text{)} \] \( \delta \) 166.61, 153.75, 151.05, 133.79, 130.02, 127.89, 124.73, 122.31, 121.92, 44.40, 35.58, 25.06, 22.97.
2-(Quinazolin-4-yl)bicyclo[2.2.1]heptane-2-carbonitrile (Table 3, Entry 2)

\[ \text{\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3})} \delta 9.28 (s, 1H), 8.44 (dd, J = 8.6, 0.6 Hz, 1H), 8.12 (d, J = 8.2 Hz, 1H), 7.94 (ddd, J = 8.4, 6.9, 1.3 Hz, 1H), 7.73 (ddd, J = 8.4, 7.0, 1.2 Hz, 1H), 3.35 (d, J = 2.9 Hz, 1H), 3.04 (ddd, J = 12.9, 4.2, 2.7 Hz, 1H), 2.49 (s, 1H), 2.32 – 2.24 (m, 1H), 2.21 (dd, J = 12.9, 2.0 Hz, 1H), 1.89 – 1.73 (m, 2H), 1.64 – 1.56 (m, 2H), 1.47 – 1.38 (m, 2H);
\text{\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3})} \delta 166.06, 153.28, 151.26, 133.83, 129.91, 127.95, 125.15, 123.40, 122.34, 47.28, 45.88, 44.23, 37.15, 37.02, 28.84, 25.88.\]
4-(Quinazolin-4-yl)tetrahydro-2H-pyran-4-carbonitrile (Table 3, Entry 3)

\[
\begin{align*}
\text{H NMR (400 MHz, CDCl}_3\text{) } & \delta 9.32 (s, 1H), 8.63 (d, J = 8.3 Hz, 1H), 8.17 (d, J = 8.4 Hz, 1H), 7.97 (ddd, J = 8.4, 6.9, 1.3 Hz, 1H), 7.75 (ddd, J = 8.4, 6.9, 1.3 Hz, 1H), 4.18 - 4.03 (m, 4H), 2.52 (ddd, J = 14.1, 11.6, 4.6 Hz, 2H), 2.41 (dd, J = 14.1, 2.2 Hz, 2H); \\
\text{C NMR (101 MHz, CDCl}_3\text{) } & \delta 164.77, 153.79, 151.19, 134.01, 130.27, 128.21, 124.20, 122.08, 121.01, 64.28, 42.05, 34.94.
\end{align*}
\]
4-(Quinazolin-4-yl)piperidine-4-carbonitrile (Table 3, Entry 4)

\[ \text{1}^H \text{ NMR (400 MHz, CDCl}_3\text{)} \delta 9.31 \text{ (s, 1H), 8.66 (d, J = 8.5 Hz, 1H), 8.15 (d, J = 8.5 Hz, 1H), 7.95 (ddd, J = 8.4, 7.0, 1.1 Hz, 1H), 7.73 (ddd, J = 8.4, 6.9, 1.2 Hz, 1H), 3.37 – 3.28 (m, 4H), 2.57 – 2.46 (m, 2H), 2.42 – 2.32 (m, 2H); \text{13}^C \text{ NMR (101 MHz, CDCl}_3\text{)} \delta 165.53, 153.85, 151.22, 133.84, 130.21, 128.00, 124.45, 122.16, 121.40, 43.37, 43.20, 35.59.} \]
1-Methyl-4-(quinazolin-4-yl)piperidine-4-carbonitrile (Table 3, Entry 5)

\[
\begin{align*}
\text{\textsuperscript{1}H NMR (400 MHz, CDCl}_3 & \text{) } \delta \ 9.30 \ (s, \ 1H), \ 8.63 \ (d, \ J = 8.4 \ Hz, \ 1H), \ 8.15 \ (d, \ J = 8.1 \ Hz, \ 1H), \ 7.95 \ (ddd, \ J = 8.4, \ 6.9, \ 1.2 \ Hz, \ 1H), \ 7.74 \ (ddd, \ J = 8.4, \ 6.9, \ 1.3 \ Hz, \ 1H), \ 3.16 \ (s \ br, \ 2H), \ 2.79 \ (s \ br, \ 2H), \ 2.63 \ (s \ br, \ 2H), \ 2.54 \ (s \ br, \ 2H), \ 2.51 \ (s, \ 3H); \ \text{\textsuperscript{13}C NMR (101 MHz, CDCl}_3 & \text{) } \delta 165.08, \ 153.84, \ 151.19, \ 133.87, \ 130.24, \ 128.06, \ 124.38, \ 122.26, \ 121.09, \ 51.98, \ 45.89, \ 42.32, \ 34.48.}
\end{align*}
\]
Benzyl 4-cyano-4-(quinazolin-4-yl)piperidine-1-carboxylate (Table 3, Entry 6)

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.29 (s, 1H), 8.64 (d, $J = 8.3$ Hz, 1H), 8.17 (d, $J = 8.1$ Hz, 1H), 7.97 (ddd, $J = 8.4$, 7.0, 1.2 Hz, 1H), 7.76 (ddd, $J = 8.4$, 6.9, 1.2 Hz, 1H), 7.39 – 7.31 (m, 5H), 5.17 (s, 2H), 4.40 (s br, 2H), 3.48 (s br, 2H), 2.43 (s br, 4H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 164.68, 154.99, 153.63, 151.04, 136.43, 134.16, 130.19, 128.59, 128.37, 128.22, 128.03, 124.03, 122.03, 120.55, 67.53, 42.86, 40.69, 34.41.
tert-Butyl 3-cyano-3-(quinazolin-4-yl)pyrrolidine-1-carboxylate (Table 3, Entry 7)

$^1$H NMR (400 MHz, CDCl$_3$) [Mixture of rotamers] $\delta$ 9.28 (s, 1H), 8.51 – 8.45 (m, 1H), 8.19 – 8.15 (m, 1H), 8.02 – 7.97 (m, 1H), 7.82 – 7.77 (m, 1H), 4.49 – 4.24 (m, 2H), 3.81 – 3.71 (m, 1H), 3.70 – 3.63 (m, 1H), 3.27 – 2.92 (m, 1H), 2.87 – 2.74 (m, 1H), 1.47 (s, 9H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 161.98, 153.99-153.90, 153.64, 151.20, 134.33, 130.19-130.10, 128.67, 124.23-124.15, 122.34-122.26, 120.80, 80.53-80.46, 54.96-54.59, 46.35-45.50, 44.37-44.15, 35.71, 28.40.
1-Benzyl-3-(quinazolin-4-yl)pyrrolidine-3-carbonitrile (Table 3, Entry 8)

\[ \text{\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3})} \delta 9.25 (s, 1H), 8.47 (d, J = 8.4 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.93 (ddd, J = 8.4, 7.0, 1.2 Hz, 1H), 7.37 – 7.30 (m, 4H), 7.29 – 7.25 (m, 1H), 3.77 (s, 2H), 3.54 (s, 2H), 3.07 – 2.98 (m, 2H), 2.91 – 2.75 (m, 2H); \text{\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3})} \delta 164.66, 153.53, 151.27, 137.96, 134.02, 129.98, 128.56, 128.48, 128.28, 127.36, 124.85, 123.18, 122.20, 63.12, 59.08, 52.88, 46.60, 37.46. \]
2-(2-Chloroquinazolin-4-yl)-2-methylpropanenitrile (Table 3, Entry 10)

\[
\begin{align*}
\text{NMR (400 MHz, CDCl}_3) & \quad \delta 8.62 (d, J = 8.1 \text{ Hz, 1H}), 8.01 (dd, J = 8.5, 0.6 \text{ Hz, 1H}), 7.91 (ddd, J = 8.4, 6.9, 1.3 \text{ Hz, 1H}), 7.68 (ddd, J = 8.4, 6.9, 1.3 \text{ Hz, 1H}), 1.92 (s, 6H); \\
\text{C NMR (101 MHz, CDCl}_3) & \quad \delta 169.52, 156.21, 153.06, 135.11, 129.25, 128.34, 124.95, 123.19, 120.47, 37.52, 27.54.
\end{align*}
\]
Ethyl 4-(2-cyanopropan-2-yl)quinazoline-2-carboxylate (Table 3, Entry 11)

\[
\begin{align*}
\text{1H NMR (400 MHz, CDCl}_3\text{)} & \, \delta \; 8.69 (d, J = 8.5 \text{ Hz}, 1H), \; 8.29 (d, J = 8.4 \text{ Hz}, 1H), \; 7.96 (ddd, J = 8.4, 7.0, 1.2 \text{ Hz}, 1H), \; 7.79 (ddd, J = 8.4, 7.0, 1.2 \text{ Hz}, 1H), \; 4.52 (q, J = 7.1 \text{ Hz}, 2H), \; 1.97 (s, 6H), \; 1.43 (t, J = 7.1 \text{ Hz}, 3H); \quad \text{13C NMR (101 MHz, CDCl}_3\text{)} & \, \delta \; 167.41, \; 163.89, \; 151.77, \; 151.12, \; 134.53, \; 131.22, \; 129.87, \; 124.70, \; 123.58, \; 122.16, \; 62.77, \; 37.60, \; 27.52, \; 14.29.
\end{align*}
\]
Ethyl 4-(1-cyanocyclohexyl)pyrimidine-5-carboxylate (Table 4, Entry 1)

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.24 (s, 1H), 8.97 (s, 1H), 4.49 (q, $J = 7.2$ Hz, 2H), 2.36 (d, $J = 12.2$ Hz, 2H), 2.14 (td, $J = 13.2$, 4.0 Hz, 2H), 1.94 – 1.77 (m, 5H), 1.44 (t, $J = 7.2$ Hz, 3H), 1.40 – 1.27 (m, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 165.46, 165.37, 159.26, 158.40, 126.15, 120.56, 62.84, 46.33, 34.87, 24.78, 22.81, 13.92.
tert-Butyl 3-(2-bromopyrimidin-4-yl)-3-cyanopyrrolidine-1-carboxylate (Table 4, Entry 2)
$^1$H NMR (400 MHz, CDCl$_3$) [Mixture of rotamers] $\delta$ 8.69 (d, J = 5.1 Hz, 1H), 7.72 (d, J = 4.8 Hz, 1H), 4.17 – 4.05 (m, 1H), 3.97 – 3.89 (m, 1H), 3.86 – 3.66 (m, 2H), 2.85 – 2.70 (m, 1H), 2.61 – 2.47 (m, 1H), 1.50 (s, 9H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 166.02-165.91, 160.72, 153.80, 153.62-153.57, 119.63-119.59, 117.74, 80.72-80.60, 55.93-55.73, 48.59-47.61, 44.86-44.58, 37.66-36.97, 28.40.
1-(2-bromopyrimidin-4-yl)cyclohexanecarbonitrile (Table 4, Entry 3)

\[ \text{[Structural formula]} \]

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.60 (d, $J = 5.1$ Hz, 1H), 7.64 (d, $J = 5.1$ Hz, 1H), 2.05 (dd, $J = 9.2$, 3.3 Hz, 4H), 1.94 – 1.74 (m, 5H), 1.41 – 1.28 (m, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 171.01, 160.40, 153.35, 120.57, 116.98, 46.74, 35.19, 24.45, 22.91.
1-(5-fluoropyrimidin-4-yl)cyclohexanecarbonitrile (Table 4, Entry 4)

\[
\begin{align*}
\text{H NMR (400 MHz, CDCl}_3\text{) } &\delta 9.04 (d, J = 2.7 \text{ Hz, } 1\text{H}), \ 8.64 (d, J = 3.0 \text{ Hz, } 1\text{H}), \ 2.33 - 2.26 (m, 2\text{H}), \ 2.07 - 1.98 (m, 2\text{H}), \ 1.93 - 1.88 (m, 4\text{H}), \ 1.88 - 1.82 (m, 1\text{H}), \ 1.40 - 1.29 (m, 1\text{H}); \\
\text{C NMR (101 MHz, CDCl}_3\text{) } &\delta 157.28, \ 154.60-154.52, \ 154.28-154.21, \ 146.08-145.86, \ 119.67, \ 43.23-43.18, \ 33.42-33.40, \ 24.73, \ 22.61.
\end{align*}
\]
tert-butyl 3-(5-chloropyrimidin-4-yl)-3-cyanopyrrolidine-1-carboxylate (Table 4, Entry 5)

$^1$H NMR (400 MHz, CDCl$_3$) [Mixture of Rotomers] $\delta$ 9.08 (s, 1H), 8.81 (s, 1H), 4.35 – 3.98 (m, 2H), 3.75 – 3.56 (m, 2H), 2.98 – 2.70 (m, 2H), 1.47 (s, 9H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 158.54, 158.32, 155.99, 153.92, 153.89, 153.80, 131.00, 130.87, 118.45, 80.59, 80.48, 53.43, 46.35, 45.57, 44.29, 44.00, 34.77, 34.14, 28.39.
1-(5-nitropyridin-2-yl)cyclohexanecarbonitrile (Table 4, Entry 7)

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.91 (s, 1H), 8.81 (d, $J = 5.4$ Hz, 1H), 7.61 (d, $J = 5.4$ Hz, 1H), 2.41 – 2.33 (m, 2H), 1.96 – 1.84 (m, 7H), 1.36 – 1.27 (m, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 153.33, 146.53, 146.20, 141.78, 121.90, 118.97, 43.41, 35.55, 24.54, 23.12.
4-(2-(Phenylsulfonyl)propan-2-yl)quinazoline (Table 5, Entry 1)

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.02 (s, 1H), 8.97 (dd, $J = 8.8$, 0.6 Hz, 1H), 8.11 (dd, $J = 8.5$, 0.9 Hz, 1H), 7.94 (ddd, $J = 8.3$, 6.9, 1.3 Hz, 1H), 7.74 (ddd, $J = 8.5$, 6.9, 1.4 Hz, 1H), 7.58 – 7.52 (m, 1H), 7.40 – 7.31 (m, 4H), 2.09 (s, 6H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 166.35, 152.27, 150.96, 135.10, 133.93, 133.86, 129.84, 129.02, 128.55, 128.30, 127.81, 124.59, 71.95, 25.08.
5-Chloro-4-(2-(phenylsulfonyl)propan-2-yl)pyrimidine (Table 4, Entry 2)

\[ ^{1}H\text{ NMR (400 MHz, CDCl}_{3}\delta 8.84 \text{ (s, 1H), 8.68 (s, 1H), 7.64 – 7.60 (m, 1H), 7.55 – 7.51 (m, 2H), 7.46 – 7.41 (m, 2H), 2.01 (s, 6H);} \]

\[ ^{13}C\text{ NMR (101 MHz, CDCl}_{3}\delta 160.32, 159.49, 154.73, 135.26, 134.05, 132.76, 130.23, 128.66, 70.27, 22.95.} \]
I-(quinazolin-4-yl)ethanone (4)

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 9.46 (s, 1H), 8.81 (dd, \(J = 8.6, 0.6\) Hz, 1H), 8.14 (d, \(J = 8.5\) Hz, 1H), 8.01 – 7.96 (m, 1H), 7.81 – 7.72 (m, 1H), 2.89 (s, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 201.97, 158.91, 154.04, 152.17, 134.26, 129.52, 128.83, 126.53, 120.89, 28.14.