A Bench-Stable Vilsmeier Reagent for in-situ Alcohol Activation: Synthetic Application in the Synthesis of 2-Amino-2-Thiazolines

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General Information

Methods: Unless otherwise noted, all reactions were carried out with magnetic stirring under nitrogen atmosphere with no effort to preclude moisture. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 400 MHz spectrometer. Chemical shifts for 1H NMR spectra are recorded in parts per million with the solvent resonance as the internal standard CHCl₃ (δ = 7.26 ppm), DMSO (δ = 2.50 ppm), or Acetone (δ = 2.05 ppm). 1H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, qt = quintet, sept = septuplet, oct = octuplet, m = multiplet), coupling constants (Hz), and integration. Chemical shifts for 13C NMR spectra are recorded in parts per million using the central peak of CHCl₃ (δ = 77.00 ppm), DMSO (δ = 39.51 ppm), or Acetone (δ = 29.92 ppm) as the internal standard. All 13C NMR and 19F NMR spectra were obtained with complete proton decoupling. Melting points (mp) were measured using a Büchi B-545 melting point apparatus. High resolution mass spectrometry (HRMS) was performed on a Thermo Scientific Q-Exactive instrument operated in positive ion mode coupled with ESI and calibrated using NaTF prior to sample analysis. Analytical thin-layer chromatography (TLC) was performed on precoated, glass-backed silica gel (Merck 60 F₂₅₄) and visualization was accomplished with UV light. Flash column chromatography was performed using an automated purification system (Teledyne Isco CombiFlash Rf 200i). Pre-packed normal phase silica gel
columns were used for separation of products using Teledyne Isco RediSep Rf High Performance Gold columns.

**Materials:** \(N,N\)-Dimethylformamide (DMF), 1,2-dimethoxyethane (DME), and dimethyl sulfate were obtained from Sigma-Aldrich SureSeal bottles. All other reagents were purchased from commercial sources and were used as received unless otherwise noted.

**Preparation of Vilsmeier Reagent 3**

Prepared employing a modification to the previously reported *Org. Synth.* procedure.\(^1\) A jacketed 1L reactor with a reflux/return condenser set to 5°C was charged with dimethyl sulfate (200.0mL, 2.11 mol, 1.00 equiv.) at ambient temperature under a \(N_2\) atmosphere. The stirred solution was warmed to 60°C. DMF (200.0mL, 2.59 mol, 1.20 equiv.) was charged into the reactor via syringe pump at a rate of 3.3mL/min over 60 minutes. The rate of addition is controlled such that the internal temperature of the reaction is maintained below 70°C. After addition of DMF, the reaction mixture was aged for 60 minutes at 60°C to ensure complete consumption of dimethyl sulfate. After the reaction was adjudged complete by \(^1\)H NMR, the reaction was cooled to ambient temperature. The contents of the reactor were drained to afford Vilsmeier reagent 3 (402.6g, 2.02 mol, 96% yield) as an 83wt% solution in DMF as determined by \(^1\)H NMR in CDCl\(_3\) employing benzyl benzoate as an internal standard. The spectral properties are in agreement with those previously reported in the literature.\(^2\) The Vilsmeier reagent 3 can be stored in an amber bottle at ambient temperature with no effort to preclude oxygen or moisture for >6 months with no detectable change in titer.

**General Procedure A for the Vilsmeier Salt Promoted Condensation/Cyclization of Isothiocyanates and Amino Alcohols with NaOAc**

To a stirred solution of amino alcohol 5 (8.80 mmol, 1.10 equiv.) in DMF (16.0 mL, 0.5M) at room temperature was added isothiocyanate 4 (8.00 mmol, 1.00 equiv.). After stirring for 2
minutes at room temperature, Vilsmeier salt 3 (12.00 mmol, 1.50 equiv.) and NaOAc (12.00 mmol, 1.50 equiv.) were added sequentially. The reaction mixture was allowed to stir at room temperature until adjudged complete by TLC, generally 4 hours. The reaction was diluted with EtOAc (50mL) and sequentially washed with sat. aq. NaHCO₃ (25mL) and brine (25mL). The organic layer was dried over MgSO₄, polish filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (100% heptane to 80% EtOAc in heptane gradient) to give 6.

General Procedure B for the Vilsmeier Salt Promoted Condensation/Cyclization of Isothiocyanates and Amino Alcohols with iPr₂NEt

To a stirred solution of amino alcohol 5 (8.80 mmol, 1.10 equiv.) in DMF (16.0 mL, 0.5M) at room temperature was added isothiocyanate 4 (8.00 mmol, 1.00 equiv.). After stirring for 2 minutes at room temperature, Vilsmeier salt 3 (12.00 mmol, 1.50 equiv.) and iPr₂NEt (12.00 mmol, 1.50 equiv.) were added sequentially. The reaction mixture was allowed to stir at 75°C until adjudged complete by TLC, generally 4 hours. The reaction was diluted with EtOAc (50mL) and sequentially washed with sat. aq. NaHCO₃ (25mL) and brine (25mL). The organic layer was dried over MgSO₄, polish filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (100% heptane to 80% EtOAc in heptane gradient) to give 6.

**N-Phenyl-4,5-dihydrothiazol-2-amine (6a):** The title compound was prepared according to General Procedure A using phenyl isothiocyanate (2.40mL, 20.0 mmol), ethanolamine (1.35mL, 22.4 mmol), Vilsmeier salt 3 (7.20g, 30.0 mmol, 83wt%), NaOAc (2.51g, 30.6 mmol), and DMF (40.0mL) affording 6a (3.31g, 18.57 mmol, 93% yield) as a white solid (mp: 153°C). Analytical data for 6a: **¹H NMR (400 MHz, CDCl₃)**: δ 7.31-7.24 (m, 2H), 7.16-7.08 (m, 2H), 7.04-7.01 (m, 1H), 6.36 (br s, 1H), 3.78 (t, J = 7.04 Hz, 2H), 3.27 (t, J = 7.04 Hz, 2H); **¹³C NMR (101 MHz, CDCl₃)**: δ 161.83, 147.59, 128.89, 123.10, 121.12, 50.44, 31.81; **HRMS (ESI):** calcd. for C₉H₁₁N₂S [M+H]+: 179.06349 m/z, found 179.06375 m/z. **TLC** (1:1 EtOAc:Heptane): Rf = 0.22. The spectral properties are in agreement with those previously reported in the literature.²
(S)-4-Benzyl-N-cyclopropyl-4,5-dihydrothiazol-2-amine (6b): The title compound was prepared according to General Procedure A using cyclopropyl isothiocyanate (1.00mL, 10.3 mmol), (S)-(−)-2-amino-3-phenyl-1-propanol (1.82g, 11.8 mmol), Vilsmeier salt 3 (3.70g, 15.0 mmol, 83wt%), NaOAc (1.33g, 16.2 mmol) and DMF (20.0mL) affording 6b (2.04g, 8.78 mmol, 85% yield) as a white solid (mp: 74°C). Analytical data for 6b: $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.33-7.26 (m, 2H), 7.25-7.17 (m, 3H), 5.56 (br s, 1H), 4.46-4.33 (m, 1H), 3.19 (dd, $J$ = 7.2, 10.8 Hz, 1H), 3.09 (dd, $J$ = 5.2, 13.4 Hz, 1H), 3.01 (dd, $J$ = 6.3, 10.8 Hz, 1H), 2.72 (dd, $J$ = 9.0, 13.4 Hz, 1H), 2.66-2.58 (m, 1H), 0.74-0.65 (m, 2H), 0.62-0.52 (m, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 163.27, 138.86, 129.17, 128.44, 126.29, 71.80, 41.30, 37.86, 27.30, 7.51; HRMS (ESI): calcd. for C$_{13}$H$_{17}$N$_2$S [M+H]$^+$: 233.11017 m/z, found 233.11070 m/z. TLC (1:1 EtOAc:Heptane): $R_f$ = 0.07.

(S)-Ethyl (4-benzyl-4,5-dihydrothiazol-2-yl)carbamate (6c): The title compound was prepared according to General Procedure A using ethoxycarbonyl isothiocyanate (1.00mL, 8.47 mmol), (S)-(−)-2-amino-3-phenyl-1-propanol (1.43g, 9.27 mmol), Vilsmeier salt 3 (3.10g, 12.9 mmol, 83wt%), NaOAc (1.06g, 12.9 mmol), and DMF (17.0mL) affording 6c (2.11g, 7.98 mmol, 94% yield) as a white solid (mp: 123°C). Analytical data for 6c: $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 10.82 (br s, 1H), 7.34-7.22 (m, 3H), 7.20-7.14 (m, 2H), 4.26-4.08 (m, 3H), 3.21 (dd, $J$ = 7.9, 11.3 Hz, 1H), 3.13 (dd, $J$ = 5.6, 13.5 Hz, 1H), 2.98 (dd, $J$ = 4.9, 11.3 Hz, 1H), 2.86 (dd, $J$ = 8.4, 13.5 Hz, 1H), 1.27 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 175.07, 161.46, 136.52, 129.00, 128.45, 126.72, 61.04, 58.99, 39.61, 33.55, 14.46; HRMS (ESI): calcd. for C$_{13}$H$_{17}$N$_2$O$_2$S [M+H]$^+$: 265.10053 m/z, found 265.10010 m/z. TLC (1:1 EtOAc:Heptane): $R_f$ = 0.36.

(S)-4-((4-Benzyl-4,5-dihydrothiazol-2-yl)amino)benzonitrile (6d): The title compound was prepared according to General Procedure A using 4-cyanophenyl isothiocyanate (1.00g, 6.12 mmol), (S)-(−)-2-amino-3-phenyl-1-propanol (1.06g, 6.87 mmol), Vilsmeier salt 3 (2.30g, 9.58 mmol, 83wt%), NaOAc (0.80g, 9.75 mmol), and DMF (15.0mL) affording 6d (1.63g, 5.56 mmol, 91% yield) as an off-white solid (mp: 136°C). Analytical data for 6d: $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.54 (d, $J$ = 8.4 Hz, 2H), 7.36-7.29 (m, 2H), 7.29-7.23 (m, 1H), 7.22-7.15 (m, 2H), 7.11 (d, $J$ = 8.3 Hz, 2H), 6.59 (br s, 1H), 4.17 (quin, $J$ = 6.9 Hz, 1H), 3.32 (dd, $J$ = 6.7, 10.8 Hz, 1H), 2.98 (dd, $J$ = 5.6, 13.5 Hz, 1H), 1.27 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 175.07, 161.46, 136.52, 129.00, 128.45, 126.72, 61.04, 58.99, 39.61, 33.55, 14.46; HRMS (ESI): calcd. for C$_{13}$H$_{17}$N$_2$O$_2$S [M+H]$^+$: 265.10053 m/z, found 265.10010 m/z. TLC (1:1 EtOAc:Heptane): $R_f$ = 0.36.
(S)-1-(4-((4-Benzyl-4,5-dihydrothiazol-2-yl)amino)phenyl)ethanone (6e): The title compound was prepared according to General Procedure A using 4-acetylphenyl isothiocyanate (1.00g, 5.36 mmol), (S)-(−)-2-amino-3-phenyl-1-propanol (0.93g, 6.15 mmol), Vilsmeier salt 3 (1.95g, 8.12 mmol, 83wt%), NaOAc (0.70g, 8.53 mmol), and DMF (12.0mL) affording 6e (1.45g, 4.67 mmol, 87% yield) as an off-white semi solid. Analytical data for 6e: $^1$H NMR (400 MHz, CDCl$_3$): δ 7.89 (d, $J = 8.6$ Hz, 2H), 7.35-7.27 (m, 2H), 7.27-7.12 (m, 5H), 4.17 (quin, $J = 6.8$ Hz, 1H), 3.27 (dd, $J = 6.7$, 10.8 Hz, 1H), 3.06 (dd, $J = 6.6$, 10.8 Hz, 1H), 2.98-2.90 (m, 1H), 2.89-2.81 (m, 1H), 2.55 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 197.08, 160.84, 152.74, 137.32, 131.98, 129.70, 129.05, 128.83, 128.69, 120.95, 62.64, 40.83, 35.60, 26.32; HRMS (ESI): calcd. for C$_{18}$H$_{19}$N$_2$O$_2$S [M+H]$^+$: 311.12126 m/z, found 311.12053 m/z. TLC (1:1 EtOAc:Heptane): $R_f = 0.68$.

(5)-4-Benzyl-N-(3-nitrophenyl)-4,5-dihydrothiazol-2-amine (6f): The title compound was prepared according to General Procedure A using 3-nitrophenyl isothiocyanate (1.51g, 8.21 mmol), (S)-(−)-2-amino-3-phenyl-1-propanol (1.42g, 9.20 mmol), Vilsmeier salt 3 (3.03g, 12.6 mmol, 83wt%), NaOAc (1.06g, 12.9 mmol), and DMF (16.0mL) affording 6f (2.32g, 7.40 mmol, 90% yield) as a viscous yellow oil. Analytical data for 6f: $^1$H NMR (400 MHz, CDCl$_3$): δ 7.91-7.80 (m, 2H), 7.63 (br s, 1H), 7.41-7.35 (m, 1H), 7.33-7.25 (m, 1H), 7.25-7.19 (m, 1H), 7.24-7.14 (m, 2H), 4.12 (quin, $J = 6.7$ Hz, 1H), 3.28 (dd, $J = 6.7$, 10.9 Hz, 1H), 3.06 (dd, $J = 6.3$, 10.9 Hz, 1H), 2.95-2.80 (m, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$): δ 162.89, 150.51, 148.59, 136.86, 129.43, 128.97, 128.62, 126.82, 128.04, 117.66, 116.59, 60.60, 40.71, 35.13; HRMS (ESI): calcd. for C$_{16}$H$_{16}$N$_3$O$_2$S [M+H]$^+$: 314.09577 m/z, found 314.09464 m/z. TLC (1:1 EtOAc:Heptane): $R_f = 0.66$. 

Hz, 1H), 3.10 (dd, $J = 6.8$, 10.8 Hz, 1H), 2.98-2.85 (m, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$): δ 161.20, 152.91, 137.10, 133.16, 129.01, 128.84, 127.03, 121.97, 119.40, 105.89, 61.68, 40.83, 35.53; HRMS (ESI): calcd. for C$_{17}$H$_{16}$N$_3$S [M+H]$^+$: 294.10594 m/z, found 294.10535 m/z.
(R)-N-(2,5-Dibromophenyl)-4-isopropyl-4,5-dihydrothiazol-2-amine (6g): The title compound was prepared according to General Procedure A using 3,5-dibromophenyl isothiocyanate (3.01g, 10.1 mmol), (S)-(−)-2-amino-3-methyl-1-butanol (1.30mL, 11.1 mmol), Vilsmeier salt 3 (3.60g, 15.0 mmol, 83wt%), NaOAc (1.30g, 15.8 mmol), and DMF (20.0mL) affording 6g (3.54g, 9.36 mmol, 93% yield) as a white solid (mp: 121°C). Analytical data for 6g:

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.49-7.26 (m, 2H), 7.02 (d, $J = 8.5$ Hz, 1H), 6.39 (br s, 1H), 3.71 (q, $J = 7.4$ Hz, 1H), 3.35-3.21 (m, 1H), 3.14-3.01 (m, 1H), 1.90-1.73 (m, 1H), 0.96 (dd, $J = 6.8$, 14.7 Hz, 6H); $^{13}$C NMR (101 MHz, CDCl$_3$): δ 162.71, 149.50, 133.61, 127.05, 125.75, 121.07, 116.09, 65.77, 33.62, 32.56, 19.33, 18.55; HRMS (ESI): calcd. for C$_{12}$H$_{15}$Br$_2$N$_2$S [M+H]$^+$: 378.92967 m/z, found 378.92898 m/z.

TLC (1:1 EtOAc:Heptane): $R_f = 0.65$.

(R)-N-(4-Bromo-2-chlorophenyl)-4-isopropyl-4,5-dihydrothiazol-2-amine (6h): The title compound was prepared according to General Procedure A using 2-chloro-4-bromophenyl isothiocyanate (2.52g, 10.0 mmol), (S)-(−)-2-amino-3-methyl-1-butanol (1.30mL, 11.1 mmol), Vilsmeier salt 3 (3.62g, 15.1 mmol, 83wt%), NaOAc (1.31g, 16.0 mmol), and DMF (20.0mL) affording 6h (3.06g, 9.17 mmol, 91% yield) as a white solid (mp: 95°C). Analytical data for 6h:

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.49 (s, 1H), 7.28 (br d, $J = 8.9$ Hz, 1H), 7.12 (br d, $J = 7.7$ Hz, 1H), 6.45 (br s, 1H), 3.71 (q, $J = 7.4$ Hz, 1H), 3.35-3.17 (m, 1H), 3.16-2.95 (m, 1H), 1.81 (qd, $J = 6.7$, 13.5 Hz, 1H), 0.95 (dd, $J = 6.8$, 14.4 Hz, 6H); $^{13}$C NMR (101 MHz, CDCl$_3$): δ 162.71, 149.50, 133.61, 127.05, 125.75, 121.07, 116.09, 65.77, 33.62, 32.56, 19.33, 18.55; HRMS (ESI): calcd. for C$_{12}$H$_{15}$BrClN$_2$S [M+H]$^+$: 332.98224 m/z, found 332.98160 m/z.

TLC (1:1 EtOAc:Heptane): $R_f = 0.77$.

(R)-4-Isopropyl-N-(pyridin-3-yl)-4,5-dihydrothiazol-2-amine (6i): The title compound was prepared according to General Procedure A using 3-pyridyl isothiocyanate (1.00g, 7.20 mmol), (S)-(−)-2-amino-3-methyl-1-butanol (1.00mL, 8.56 mmol), Vilsmeier salt 3 (2.60g, 10.8 mmol, 83wt%), NaOAc (0.91g, 11.1 mmol), and DMF (15.0mL) affording 6i (1.39g, 6.28 mmol, 87% yield) as an off-white solid (mp: 113°C). Analytical data for 6i: $^1$H NMR (400 MHz, CDCl$_3$): δ
8.34 (d, J = 2.6 Hz, 1H), 8.27 (dd, J = 1.5, 4.7 Hz, 1H), 7.42 (br d, J = 8.2 Hz, 1H), 7.19 (dd, J = 4.7, 8.1 Hz, 1H), 3.69 (q, J = 7.3 Hz, 1H), 3.25 (dd, J = 6.9, 10.8 Hz, 1H), 3.05 (dd, J = 8.3, 10.7 Hz, 1H), 1.81 (qd, J = 6.8, 13.5 Hz, 1H), 0.94 (dd, J = 6.8, 12.6 Hz, 6H); 13C NMR (101 MHz, CDCl3): δ 162.92, 145.92, 143.91, 143.78, 128.69, 123.31, 65.81, 33.24, 32.22, 19.22, 18.28; HRMS (ESI): calcd. for C11H16N3S [M+H]+: 222.10594 m/z, found 222.10558 m/z.

TLC (1:1 EtOAc:Heptane): Rf = 0.13.

(S)-4-((1H-Indol-3-yl)methyl)-N-phenyl-4,5-dihydrothiazol-2-amine (6j): The title compound was prepared according to General Procedure A using phenyl isothiocyanate (0.55mL, 4.60 mmol), L-tryptophanol (1.00g, 5.10 mmol), Vilsmeier salt 3 (1.69g, 7.04 mmol, 83wt%), NaOAc (0.59g, 7.19 mmol), and DMF (10.0mLmL) affording 6j (1.28g, 4.16 mmol, 91% yield) as a white solid (mp: 152°C). Analytical data for 6j: 1H NMR (400 MHz, Acetone-d6): δ 10.06 (br s, 1H), 7.81 (br s, 1H), 7.64 (d, J = 7.9 Hz, 1H), 7.40 (t, J = 7.8 Hz, 3H), 7.30-7.19 (m, 3H), 7.16-7.07 (m, 1H), 7.07-6.99 (m, 1H), 6.95 (t, J = 7.3 Hz, 1H), 4.57-4.42 (m, 1H), 3.31-2.98 (m, 4H); 13C NMR (101 MHz, Acetone-d6): δ 158.55, 147.51, 138.14, 129.94, 129.30, 124.66, 123.27, 122.65, 121.04, 120.06, 119.89, 113.08, 112.68, 69.27, 37.62, 31.93; HRMS (ESI): calcd. for C18H18N3S [M+H]+: 308.12159 m/z, found 308.12073 m/z.

TLC (1:1 EtOAc:Heptane): Rf = 0.23.

(S)-4-((2-((4-(Trifluoromethyl)phenyl)amino)-4,5-dihydrothiazol-4-yl)methyl)phenol (6k): The title compound was prepared according to General Procedure A using 4-(trifluoromethyl)phenyl isothiocyanate (0.89g, 4.24 mmol), L-tyrosinol hydrochloride (1.00g, 4.81 mmol), Vilsmeier salt 3 (1.50g, 6.25 mmol, 83wt%), NaOAc (0.92g, 11.2 mmol), and DMF (9.0mL) affording 6k (1.38g, 3.92 mmol, 92% yield) as a white solid (mp: 67°C). Analytical data for 6k: 1H NMR (400 MHz, CDCl3): δ 7.54 (d, J = 8.2 Hz, 2H), 7.14 (d, J = 8.2 Hz, 2H), 7.01 (d, J = 8.2 Hz, 2H), 6.97-6.99 (br s, 2H), 6.73 (d, J = 8.2 Hz, 2H), 4.16-4.02 (m, 1H), 3.40 (dd, J = 6.6, 10.8 Hz, 1H), 3.10 (dd, J = 6.7, 10.8 Hz, 1H), 2.91-2.73 (m, 2H); 13C NMR (101 MHz, CDCl3): δ 163.67, 155.76, 151.80, 130.03, 127.99, 126.28 (q, J = 3.7 Hz, 1C), 125.75 (q, J = 32.8 Hz, 1C), 122.25, 124.37, (q, J = 271.9 Hz, 1C), 115.93, 60.24, 39.96, 35.24; 19F NMR (377 MHz, CDCl3): δ -61.85; HRMS (ESI): calcd. for C17H18F3N2OS [M+H]+: 353.09299 m/z, found 353.09201 m/z. TLC (1:1 EtOAc:Heptane): Rf = 0.49.
(2-(Phenylamino)-4,5-dihydrothiazol-4-yl)methanol (6l). The title compound was prepared according to General Procedure A using phenyl isothiocyanate (1.00mL, 8.36 mmol), 2-amino-1,3-propanediol (0.86g, 9.25 mmol), Vilsmeier salt (3.06g, 12.7 mmol, 83wt%), NaOAc (1.07g, 13.0 mmol), and DMF (17.0mL) affording 6l (1.66g, 7.96 mmol, 95% yield) as a pale yellow viscous oil. Analytical data for 6l: ¹H NMR (400 MHz, CDCl₃): δ 7.31-7.19 (m, 2H), 7.13-7.01 (m, 3H), 5.90 (br s, 2H), 4.21-4.08 (m, 1H), 3.73-3.56 (m, 2H), 3.24 (dd, J = 7.5, 10.8 Hz, 1H), 3.05 (dd, J = 6.9, 10.9 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃): δ 162.67, 146.51, 128.91, 123.57, 121.55, 64.42, 63.88, 32.62; HRMS (ESI): calcd. for C₁₀H₁₃N₂OS [M+H]⁺: 209.07431 m/z, found 209.07401 m/z. TLC (1:1 EtOAc:Heptane): Rf = 0.08.

(5)-N-(2-Bromophenyl)-4-(2-(methylthio)ethyl)-4,5-dihydrothiazol-2-amine (6m): The title compound was prepared according to General Procedure A using 2-bromophenyl isothiocyanate (1.00mL, 7.43 mmol), (5)-(−)-methioninol (1.13g, 8.36 mmol), Vilsmeier salt (2.70g, 11.2 mmol, 83wt%), NaOAc (1.03g, 12.6 mmol), and DMF (15.0mL) affording 6m (2.31g, 6.97 mmol, 94% yield) as a white solid (mp: 121°C). Analytical data for 6m: ¹H NMR (400 MHz, CDCl₃): δ 7.75 (br s, 1H), 7.53 (dd, J = 1.4, 8.0 Hz, 1H), 7.34-7.18 (m, 2H), 6.91 (dt, J = 1.8, 7.6 Hz, 1H), 4.13 (quin, J = 6.7 Hz, 1H), 3.36 (dd, J = 6.9, 10.7 Hz, 1H), 2.97 (dd, J = 7.0, 10.7 Hz, 1H), 2.54-2.36 (m, 2H), 1.96 (s, 3H), 1.86-1.74 (m, 1H); ¹³C NMR (101 MHz, CDCl₃): δ 162.23, 147.36, 132.54, 128.04, 124.37, 122.98, 116.98, 60.11, 35.83, 34.08, 30.65, 15.30; HRMS (ESI): calcd. for C₁₂H₁₆BrN₂S₂ [M+H]⁺: 330.99328 m/z, found 330.99277 m/z. TLC (1:1 EtOAc:Heptane): Rf = 0.65.

(5)-N,4-Diphenyl-4,5-dihydrothiazol-2-amine (6n): The title compound was prepared according to General Procedure A using phenyl isothiocyanate (1.00mL, 8.36 mmol), (S)-(−)-2-phenylglycinol (1.27g, 9.26 mmol), Vilsmeier salt (3.02g, 12.6 mmol, 83wt%), NaOAc (1.08g, 13.2 mmol), and DMF (17.0mL) affording 6n (1.67g, 6.56 mmol, 79% yield) as a white solid (mp: 134°C). Analytical data for 6n: ¹H NMR (400 MHz, CDCl₃): δ 8.02-7.50 (br s, 1H), 7.41-7.18 (m, 7H), 7.05-6.97 (m, 3H), 5.01 (t, J = 7.7 Hz, 1H), 3.51 (dd, J = 7.0, 10.7 Hz, 1H), 3.14 (dd, J = 8.5, 10.7 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃): δ 161.44, 147.38, 141.11, 128.79, 128.63, 127.95, 126.30, 123.16, 121.31, 65.94, 39.34; HRMS (ESI): calcd. for C₁₅H₁₅N₂S
[M+H]^+: 255.09505 m/z, found 295.09520 m/z. TLC (1:1 EtOAc:Heptane): R_f = 0.70. The spectral properties are in agreement with those previously reported in the literature.\(^2\)

4,4-Dimethyl-N-phenyl-4,5-dihydrothiazol-2-amine (6o): The title compound was prepared according to General Procedure A using phenyl isothiocyanate (1.00mL, 8.36 mmol), 2-amino-2-methyl-1-propanol (1.00mL, 9.91 mmol), Vilsmeier salt 3 (3.11g, 13.0 mmol, 83wt%), NaOAc (108g, 13.2 mmol), and DMF (17.0mL) affording 6o (1.48g, 7.17 mmol, 86% yield) as a white solid (mp: 154°C). Analytical data for 6o: ^1H NMR (400 MHz, CDCl\(_3\)): δ 7.27 (t, J = 7.2 Hz, 2H), 7.11-6.99 (m, 3H), 3.03 (s, 2H), 1.33 (s, 6H); ^13C NMR (101 MHz, CDCl\(_3\)): δ 160.68, 149.10, 128.79, 123.03, 121.87, 61.88, 42.84, 27.62; HRMS (ESI): calcd. for C\(_{11}\)H\(_{15}\)N\(_2\)S [M+H]^+: 207.09505 m/z, found 207.09488 m/z. TLC (1:1 EtOAc:Heptane): R_f = 0.45. The spectral properties are in agreement with those previously reported in the literature.\(^2\)

N,5-Diphenyl-4,5-dihydrothiazol-2-amine (6p): The title compound was prepared according to General Procedure A using phenyl isothiocyanate (1.00mL, 8.36 mmol), phenylethanolamine (1.52g, 9.42 mmol), Vilsmeier salt 3 (3.03g, 12.6 mmol, 83wt%), NaOAc (1.06g, 12.9 mmol), and DMF (17.0mL) affording 6p (1.79g, 7.04 mmol, 84% yield) as a viscous pale yellow oil. Analytical data for 6p: ^1H NMR (400 MHz, CDCl\(_3\)): δ 8.10-7.50 (br s, 1H), 7.41-7.35 (m, 2H), 7.33-7.22 (m, 5H), 7.15 (d, J = 7.8 Hz, 2H), 7.04-6.98 (m, 1H), 4.88 (t, J = 7.4 Hz, 1H), 4.06 (dd, J = 7.3, 11.3 Hz, 1H), 3.83 (dd, J = 7.4, 11.3 Hz, 1H); ^13C NMR (101 MHz, CDCl\(_3\)): δ 161.27, 147.19, 139.45, 128.88, 128.68, 127.94, 127.37, 123.14, 121.14, 58.32, 52.42; HRMS (ESI): calcd. for C\(_{15}\)H\(_{15}\)N\(_2\)S [M+H]^+: 255.09505 m/z, found 255.09451 m/z. TLC (1:1 EtOAc:Heptane): R_f = 0.61. The spectral properties are in agreement with those previously reported in the literature.\(^2\)

N-Phenyl-5-(trifluoromethyl)-4,5-dihydrooxazol-2-amine (6q-O): The title compound was prepared according to General Procedure B using phenyl isothiocyanate (0.85mL, 7.10 mmol), 3-amino-1,1,1-trifluoropropan-2-ol (1.00g, 7.51 mmol), Vilsmeier salt 3 (2.59g, 10.8 mmol),
Pr$_2$NEt (1.90mL, 10.9 mmol), and DMF (14.0mL) affording 6q-O (1.30g, 5.65 mmol, 80% yield) as a white solid (mp: 102°C). Analytical data for 6q- O: $^1$H NMR (400 MHz, CDCl$_3$): δ 7.41-7.32 (m, 2H), 7.3 -7.26 (m, 2H), 7.02 (t, $J$ = 7.3 Hz, 1H), 4.81-4.73 (m, 1H), 4.20-4.10 (m, 1H), 4.09-4.00 (m, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$): δ 155.71, 138.41, 129.06, 122.98, 123.60 (q, $J$ = 280.0 Hz, 1C), 118.37, 74.40 (q, $J$ = 34.1 Hz, 1C), 53.75; $^{19}$F NMR (377 MHz, CDCl$_3$): δ -79.66; HRMS (ESI): calcd. for C$_{10}$H$_{10}$ON$_2$F$_3$ [M+H]$^+$: 231.07352 m/z, found 231.07397 m/z. TLC (1:1 EtOAc:Heptane): $R_f$ = 0.70.

N-Phenyl-5,6-dihydro-4H-1,3-thiazin-2-amine (6s): The title compound was prepared according to General Procedure A using phenyl isothiocyanate (1.00mL, 8.36 mmol), 3-amino-1-propanol (0.75mL, 9.85 mmol), Vilsmeier salt 3 (3.00g, 12.5 mmol, 83wt%), NaOAc (1.05g, 12.8 mmol), and DMF (17.0mL) affording 6s (1.45g, 7.54 mmol, 90% yield) as a white solid (mp: 121°C). Analytical data for 6s: $^1$H NMR (400 MHz, CDCl$_3$): δ 7.25 (t, $J$ = 6.9 Hz, 2H), 7.14-6.97 (m, 3H), 6.94-6.20 (br s, 1H), 3.48-3.37 (m, 2H), 2.9 6 (br t, $J$ = 6.1 Hz, 2H), 2.08-1.92 (m, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$): δ 151.34, 146.12, 128.69, 122.60, 121.92, 43.16, 27.01, 22.53; HRMS (ESI): calcd. for C$_{10}$H$_{13}$N$_2$S [M+H]$^+$: 193.07940 m/z, found 193.07924 m/z. TLC (1:1 EtOAc:Heptane): $R_f$ = 0.05.

N-Phenyl-4H-benzo[d][1,3]thiazin-2-amine (6t): The title compound was prepared according to General Procedure A using phenyl isothiocyanate (1.00mL, 8.36 mmol), 2-aminobenzyl alcohol (1.18g, 9.39 mmol), Vilsmeier salt 3 (3.00g, 12.5 mmol, 83wt%), NaOAc (1.00g, 12.2 mmol), and DMF (17.0mL) affording 6t (1.65g, 6.87 mmol, 82% yield) as an off-white solid (mp: 203°C). Analytical data for 6t: $^1$H NMR (400 MHz, CDCl$_3$): δ 7.41 (d, $J$ = 7.5 Hz, 2H), 7.36-7.22 (m, 3H), 7.18-6.99 (m, 5H), 3.92 (s, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$): δ 151.62, 143.17, 142.52, 128.90, 128.39, 126.66, 123.67, 123.61, 122.25, 121.01, 120.10, 30.00; HRMS (ESI): calcd. for C$_{14}$H$_{13}$N$_2$S [M+H]$^+$: 241.07940 m/z, found 241.07875 m/z. TLC (1:1 EtOAc:Heptane): $R_f$ = 0.77.
N-(2-Bromophenyl)-4H-benzo[d][1,3]thiazin-2-amine (6u): The title compound was prepared according to General Procedure A using 2-bromophenyl isothiocyanate (1.00 mL, 7.43 mmol), 2-aminobenzyl alcohol (1.06 g, 8.43 mmol), Vilsmeier salt 3 (2.66 g, 11.1 mmol, 83 wt%), NaOAc (0.92 g, 11.2 mmol), and DMF (15.0 mL) affording 6u (2.04 g, 6.39 mmol, 86% yield) as an off-white solid (mp: 179°C). Analytical data for 6u: 1H NMR (400 MHz, DMSO-d6): δ 10.58 (br s, 1H), 7.58 (d, J = 7.9 Hz, 1H), 7.32-7.17 (m, 3H), 7.10 (d, J = 7.9 Hz, 1H), 6.96 (d, J = 4.7 Hz, 3H), 3.97 (s, 2H); 13C NMR (101 MHz, DMSO-d6): δ 153.81, 139.74, 132.39, 128.03, 128.00, 126.80, 124.48, 123.94, 121.78, 120.44, 116.82, 28.14 (two carbons missing due to overlap); HRMS (ESI): calcd. for C14H12BrN2S [M+H]+: 318.98991 m/z, found 318.98944 m/z. TLC (1:1 EtOAc:Heptane): Rf = 0.79.

(3aS,7aR)-N-Phenyl-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazol-2-amine (6v): The title compound was prepared according to General Procedure B using phenyl isothiocyanate (1.00 mL, 8.36 mmol), (1S,2S)-2-aminocyclohexanol (1.13 g, 9.61 mmol), Vilsmeier salt 3 (3.03 g, 126 mmol), iPr2NEt (2.20 mL, 12.6 mmol), and DMF (17.0 mL) affording 6v (1.48 g, 6.37 mmol, 76% yield) as a white solid (mp: 111°C). Analytical data for 6v: 1H NMR (400 MHz, CDCl3): δ 7.29-7.23 (m, 2H), 7.06-7.00 (m, 2H), 3.92-3.85 (m, 1H), 3.70-3.61 (m, 1H), 1.99-1.81 (m, 3H), 1.74-1.58 (m, 3H), 1.44-1.28 (m, 2H); 13C NMR (101 MHz, CDCl3): δ 162.53, 149.82, 128.77, 123.01, 121.88, 58.11, 46.79, 29.78, 28.41, 23.05, 20.53; HRMS (ESI): calcd. for C13H17N2S [M+H]+: 233.11070 m/z, found 233.11029 m/z. TLC (1:1 EtOAc:Heptane): Rf = 0.41.

(4S,5S)-N,4,5-Triphenyl-4,5-dihydrothiazol-2-amine (6w): The title compound was prepared according to General Procedure A using phenyl isothiocyanate (1.00 mL, 8.36 mmol), (1R,2S)-(-)-2-amino-1,2-diphenylethanol (2.03 g, 9.33 mmol), Vilsmeier salt 3 (3.00 g, 12.5 mmol, 83 wt%), NaOAc (1.09 g, 13.3 mmol), and DMF (17.0 mL) affording 6w (2.35 g, 7.11 mmol, 85% yield) in >20:1 dr as a white solid (mp: 118°C). Analytical data for 6w: 1H NMR (400 MHz, CDCl3): δ 8.70 (br s, 1H), 7.49-6.71 (m, 15 H), 4.91 (br d, J = 6.6 Hz, 1H), 4.61 (br d, J = 6.6 Hz, 1H); 13C NMR (101 MHz, CDCl3): δ 160.92, 147.31, 139.68, 137.97, 137.97, 128.77, 123.01, 121.88, 58.11, 46.79, 29.78, 28.41, 23.05, 20.53; HRMS (ESI): calcd. for C21H19N2S [M+H]+: 331.12635 m/z, found 331.12543 m/z. TLC (1:1 EtOAc:Heptane): Rf = 0.75.
(R)-1-((S)-2-(Phenylamino)-4,5-dihydrothiazol-4-yI)ethanol (6x): The title compound was prepared according to General Procedure A using phenyl isothiocyanate (1.00mL, 8.36 mmol), L-threoninol (1.00g, 9.23 mmol), Vilsmeier salt 3 (3.06g, 12.7 mmol, 83wt%), NaOAc (1.05g, 12.8 mmol), and DMF (17.0mL) affording 6x (1.73g, 7.78 mmol, 93% yield) in >20:1 dr as a viscous pale yellow oil. Analytical data for 6x: $^1$H NMR (400 MHz, CDCl$_3$): δ 7.26 (t, $J = 7.8$ Hz, 2H), 7.12 (br d, $J = 7.7$ Hz, 2H), 7.07-7.01 (m, 1H), 5.85 (br s, 1H), 3.89 (q, $J = 7.7$ Hz, 1H), 3.79-3.70 (m, 1H), 3.21 (dd, $J = 7.3$, 10.8 Hz, 1H), 3.21 (dd, $J = 7.3$, 10.8 Hz, 1H), 2.98 (dd, $J = 8.4$, 10.7 Hz, 1H), 1.20 (d, $J = 6.2$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$): δ 161.50, 146.51, 128.86, 123.36, 121.22, 97.77, 69.68, 33.06, 20.02; HRMS (ESI): calcd. for C$_{11}$H$_{15}$N$_2$SO [M+H]$^+$: 223.08996 m/z, found 223.08952 m/z. TLC (1:1 EtOAc:Heptane): $R_f$ = 0.13.

Mechanistic Rationale for Formation of 6q-O

The metathesis of 1,1,1-trifluoromethyl-substituted alcohol 5q is proposed to be slow given the poor nucleophilicity of the carbinol leading to the activation of the thiourea (pro-6q-O). Although intramolecular metathesis from pro-6q-O to pro-6q-S is feasible, the rate of elimination to afford 6q-O proceeds faster at 75°C leading to the selective formation of 6q-O under the reaction conditions.
Preparation of 3-d7 and NMR studies

To a stirred solution of dimethyl sulfate (4.00mL, 42.2 mmol, 2.00 equiv.) at 60°C was added DMF-d₇ (10.0g, 125 mmol, 6.00 equiv.) dropwise over 5 minutes. After stirring for 90 minutes at 60°C, the reaction mixture was allowed to cool to ambient temperature. 4-Chlorobenzyl alcohol (7) (2.99g, 21.0 mmol, 1.00 equiv.) was added to the reaction. The reaction mixture was allowed to stir at room temperature. Aliquots (~0.60mL) were removed from the reaction mixture at various time points (t = 30 minutes, 60 minutes, and 18 hours) and analyzed by ¹H NMR. Conversion of 7 to 8 was determined by integration of the benzylic protons (Hₙ and Hₘ). The ratio of Hₘ to Hₙ was found to be 2:3 at all stages of the reaction, which supports a reversible alcohol metathesis.
Preparation of 6x Employing Vilsmeier Reagent 1

To a stirred solution of L-threoninol (5x) (1.00g, 9.32 mmol, 1.05 equiv.) in DMF (18.0mL, 0.5M) at room temperature was added phenyl isothiocyanate (4a) (1.10mL, 9.04 mmol, 1.00 equiv.). After stirring for 2 minutes at room temperature, thionyl chloride (0.66mL, 9.06 mmol, 1.00 equiv.) was added dropwise. The reaction mixture was allowed to stir at room temperature for 30 minutes during which time the imidate salt precipitated as a white salt. 1Pr₂NET (3.20mL, 18.3 mmol, 2.00 equiv.) was added dropwise to the reaction. The reaction mixture was allowed to stir at room temperature until adjudged complete by TLC, approximately 4 hours. The reaction was diluted with EtOAc (50mL) and sequentially washed with sat. aq. NaHCO₃ (25mL) and brine (25mL). The organic layer was dried over MgSO₄, polish filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (100% heptane to 80% EtOAc in heptane gradient) to give 6x (774mg, 3.48 mmol, 39% yield) as a viscous pale yellow oil.
General Procedure C for the Cu(I)-Catalyzed Synthesis of Fused Heterocycles

A 40mL vial was charged with 6 (2.00 mmol, 1.00 equiv.), CuI (0.10 mmol, 0.05 equiv.), 1,10-phenanthroline (0.20 mmol, 0.10 equiv.), Cs₂CO₃ (4.00 mmol, 2.00 equiv.), and 1,2-dimethoxyethane (10.0mL, 0.2M) at room temperature. The vial was capped and placed on a heating block preset to 85°C. The reaction mixture was allowed to stir at 85°C until adjudged complete by TLC, generally 1 hour. The vial was cooled to ambient temperature, filtered through a pad of celite washing with EtOAc (~20mL), and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (100% heptane to 60% EtOAc in heptane gradient) to give 11.

(S)-3-(2-(Methylthio)ethyl)-2,3-dihydrobenzo[4,5]imidazo[2,1-b]thiazole (11a): The title compound was prepared according to General Procedure C using 6l (488mg, 1.47 mmol), CuI (15.0mg, 0.0788 mmol), 1,10-phenanthroline (31.0mg, 0.172 mmol), Cs₂CO₃ (1.03g, 3.16 mmol), and 1,2-dimethoxyethane (8.0mL) affording 11a (358mg, 1.43 mmol, 97% yield) as a white solid (mp: 115°C). Analytical data for 11a: ¹H NMR (400 MHz, CDCl₃): δ 7.65-7.56 (m, 1H), 7.32-7.25 (m, 1H), 7.23-7.11 (m, 2H), 4.92-4.81 (m, 1H), 4.13 (dd, J = 7.4, 11.3 Hz, 1H), 3.57 (dd, J = 2.9, 11.3 Hz, 1H), 2.66-2.53 (m, 2H), 2.36-2.24 (m, 1H), 2.14 (s, 3H); ¹³C NMR (101 MHz, CDCl₃): δ 127.69, 149.40, 133.31, 121.88, 121.82, 118.90, 108.71, 55.35, 39.81, 31.55, 30.05, 15.60; HRMS (ESI): calcd. for C₁₂H₁₅N₂S₂ [M+H]⁺: 251.06712 m/z, found 251.06656 m/z. TLC (1:1 EtOAc:Heptane): Rf = 0.32.
(R)-7-Bromo-3-isopropyl-2,3-dihydrobenzo[4,5]imidazo[2,1-b]thiazole (11b): The title compound was prepared according to General Procedure C using 6g (1.07g, 2.83 mmol), CuI (28.0mg, 0.147 mmol), 1,10-phenanthroline (53.0mg, 0.294 mmol), Cs2CO3 (1.93g, 5.92 mmol), and 1,2-dimethoxyethane (15.0mL) affording 11b (807mg, 2.72 mmol, 96% yield) as a white solid (mp: 115°C). Analytical data for 11b: 1H NMR (400 MHz, CDCl3): δ 7.72 (d, J = 1.9 Hz, 1H), 7.23 (dd, J = 1.8, 8.5 Hz, 1H), 7.08 (d, J = 8.5 Hz, 1H), 4.59-4.50 (m, 1H), 3.94 (dd, J = 8.2, 11.4 Hz, 1H), 3.67 (dd, J = 4.4, 11.4 Hz, 1H), 2.66-2.53 (m, 1H), 1.07 (d, J = 7.0 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H); 13C NMR (101 MHz, CDCl3): δ 159.93, 150.69, 132.54, 124.34, 121.52, 114.69, 110.09, 62.00, 35.29, 30.54, 18.94, 16.09; HRMS (ESI): calcd. for C12H14BrN2S [M+H]+: 297.00556 m/z, found 297.00500 m/z. TLC (1:1 EtOAc:Heptane): Rf = 0.53.

5H-Benz[4,5]imidazo[2,1-b][1,3]thiazine (11c): The title compound was prepared according to General Procedure C using 6t (643mg, 2.01 mmol), CuI (19.0mg, 0.100 mmol), 1,10-phenanthroline (36.0mg, 0.200 mmol), Cs2CO3 (1.39g, 4.27 mmol), and 1,2-dimethoxyethane (10.0mL) affording 11c (466mg, 1.96 mmol, 97% yield) as an off-white solid (mp: 116°C). Analytical data for 11c: 1H NMR (400 MHz, CDCl3): δ 7.88-7.78 (m, 2H), 7.78-7.71 (m, 1H), 7.46 (dt, J = 1.6, 7.8 Hz, 1H), 7.43-7.37 (m, 1H), 7.35-7.24 (m, 3H), 4.03 (s, 2H); 13C NMR (101 MHz, CDCl3): δ 150.61, 143.94, 135.41, 132.58, 128.87, 128.06, 125.78, 125.72, 123.38, 122.95, 119.48, 118.12, 111.32, 30.38; HRMS (ESI): calcd. for C14H11N2S [M+H]+: 239.06375 m/z, found 239.06390 m/z. TLC (1:1 EtOAc:Heptane): Rf = 0.58.

References
6j - 1H NMR

6j - 13C NMR
6I - 1H NMR

6I - 13C NMR