

Pyridone Methylsulfone Hydroxamate LpxC Inhibitors for the Treatment of Serious Gram-Negative Infections

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General Suzuki-Miyaura Coupling:

Method A: Palladium (II) Encat™ BINAP(10 mol%, 0.30 mmol/g) was added to a mixture of the aryl halide (1.0 eq), the boronate species (1.5 eq), and K_2CO_3 (3.0 eq) in ethanol:water (9:1, 1.0 M), the suspension was heated to 70 °C, and the reaction mixture was stirred at this temperature until complete conversion was achieved as monitored by TLC and/or LC. The reaction mixture was allowed to cool to rt. The solids were removed via filtration, washed with dichloromethane (2x20 mL), and the combined filtrates were concentrated *in vacuo*. The crude material was purified via flash chromatography on silica to afford the desired product.

Method B: Siliacat® DPP-Pd (10 mol%, 0.27 mmol/g) was added to a mixture of the aryl halide (1.0 eq), the boronate species (1.5 eq), and K_2CO_3 (2.0 eq) in ethanol:water (9:1, 1.0 M). The reaction was heated to 70 °C and stirred at this temperature for 16 h. The reaction was filtered and concentrated *in vacuo*. The crude material was purified via flash chromatography on silica to afford the desired product.

General Saponification Procedure:

Lithium hydroxide (6 mmol) was added to a solution of the ester (1.0 mmol) in tetrahydrofuran:methanol:water (2:1:1, 1 M) at rt and the mixture was stirred until complete conversion was achieved as monitored by TLC and/or LC. The pH of the reaction mixture was adjusted to 3 using aq 1 N HCl and the reaction mixture was extracted with ethyl acetate. The organic layers were combined, dried, filtered, and concentrated *in vacuo* to afford the desired product.

General Amide Coupling:

Method A: Triethylamine (1.8 eq) was added to a solution of the carboxylic acid (1.0 eq), *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (1.5 eq), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (1.4 eq), and *N*-hydroxybenzotriazole (1.8 eq) in dichloromethane (1 M) and the reaction was stirred until complete conversion was achieved as monitored by TLC and/or LC. The reaction was quenched with water and extracted with dichloromethane. The organic layers

were combined, dried, filtered, and concentrated *in vacuo*. The crude material was purified via flash chromatography on silica to afford the desired product.

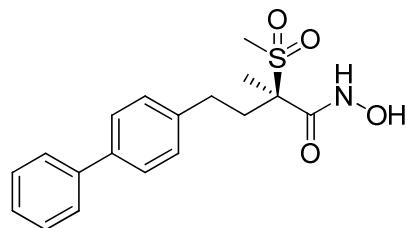
Method B: *N*-Methylmorpholine (1.6 eq) was added to a solution of 2-chloro-4,6-dimethoxy-1,3,5-triazine (1.4 eq) and the carboxylic acid (1.0 eq) in 2-methyltetrahydrofuran (1 M) and the reaction mixture was stirred for 1 h. *O*-(Tetrahydro-2*H*-pyran-2-yl)hydroxylamine (1.6 eq) was added to the reaction mixture and stirred overnight at rt. The crude reaction was filtered through celite (~1 inch) and the filter pad was washed with dichloromethane. The combined filtrates were concentrated *in vacuo*. The crude material was purified via flash chromatography on silica to afford the desired product.

General Tetrahydropyranyl Deprotection:

Method A: Hydrochloric acid (4 M in 1,4-dioxane) was added to a solution of the tetrahydropyranyl protected-hydroxamate (1.0 eq) in dichloromethane:methanol (4:1, 1.0 M) at rt and the reaction was stirred until complete conversion was achieved as monitored by TLC and/or LC. The desired product was purified via trituration, recrystallization, and/or chromatography.

Method B: Pyridinium *p*-toluenesulfonate (0.20 eq) was added to a solution of the tetrahydrylpypyranyl protected-hydroxamate (1.0 eq) in ethanol (1.0 M). The reaction mixture was heated to 50 °C and was stirred at this temperature until complete conversion was achieved as monitored by TLC and/or LC. The desired product was purified via trituration, recrystallization, and/or chromatography.

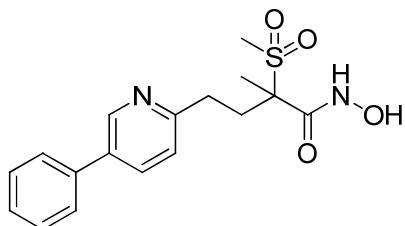
Preparation of (+)-(2*R*)-4-biphenyl-4-yl-*N*-hydroxy-2-methyl-2-(methylsulfonyl)butanamide (1).



(+)-(2*R*)-4-Biphenyl-4-yl-*N*-hydroxy-2-methyl-2-(methylsulfonyl)butanamide (1). The title compound was synthesized according to the previously reported procedure.¹ ¹H NMR (400

MHz, CD₃OD) δ 7.51 - 7.61 (m, 4 H) 7.37 - 7.44 (m, 2 H) 7.27 - 7.34 (m, 3 H) 3.05 (s, 3 H) 2.70 - 2.81 (m, 1 H) 2.50 - 2.64 (m, 2 H) 2.04 - 2.13 (m, 1 H) 1.66 (s, 3 H). HRMS: *m/z* calc'd for C₁₈H₂₁NO₄S [M + H]⁺ 348.1264, found 348.126.

Preparation of *N*-hydroxy-2-methyl-2-(methylsulfonyl)-4-(5-phenylpyridin-2-yl)butanamide (7a).



Ethyl 4-(5-bromopyridin-2-yl)-2-(methylsulfonyl)butanoate. Sodium hydride (60% in mineral oil, 471 mg, 11.8 mmol) was added to a solution of ethyl (methylsulfonyl)acetate (**4, R₂ = H**, 1.96 g, 11.8 mmol) in *N,N*-dimethylformamide (20 mL) at 0 °C. The mixture was allowed to warm to rt and stirred for 10 min. 5-Bromo-2-(2-iodoethyl)pyridine (**3a**)² was added to the mixture and the reaction was stirred at rt overnight. The reaction mixture was quenched with brine and extracted with ethyl acetate. The organic layers were combined, washed with water, dried (MgSO₄), filtered, and concentrated *in vacuo*. The crude material was purified via chromatography on silica (80 g) using a gradient of 0-100% ethyl acetate in *n*-heptane to afford the title compound (2.37 g, 63%). LCMS: *m/z* 351.9 [M-H]⁻.

Ethyl 4-(5-bromopyridin-2-yl)-2-methyl-2-(methylsulfonyl)butanoate (5a, R₁ = Br**).**

Iodomethane (596 μL, 9.35 mmol) was added to a suspension of ethyl 4-(5-bromopyridin-2-yl)-2-(methylsulfonyl)butanoate (2.73 g, 7.80 mmol) and Cs₂CO₃ (3.05 g, 9.35 mmol) in *N,N*-dimethylformamide (30 mL) at rt. The reaction mixture was stirred at rt overnight and then diluted with water and ethyl acetate. The organic layer was separated, washed with water, dried (MgSO₄), filtered, and concentrated. The crude material was purified via chromatography on silica (80 g) with a gradient of 0-100% ethyl acetate in *n*-heptane to afford the title compound (2.64 g, 93%). ¹H NMR (400 MHz, CDCl₃) δ 8.58 (d, *J* = 2.34 Hz, 1H), 7.64 - 7.81 (m, 1H),

7.01 - 7.16 (m, 1H), 4.28 (q, 2H), 3.08 (s, 3H), 2.86 - 2.98 (m, 1H), 2.55 - 2.77 (m, 2H), 2.29 - 2.43 (m, 1H), 1.70 (s, 3H), 1.34 (t, 3H). LCMS: m/z 365.9 [M-H]⁻.

4-(5-Bromopyridin-2-yl)-2-methyl-2-(methylsulfonyl)butanoic acid. Lithium hydroxide (451 mg, 18.3 mmol) was added to a mixture of ethyl 4-(5-bromopyridin-2-yl)-2-methyl-2-(methylsulfonyl)butanoate (**5a**, **R₁** = **Br**) in tetrahydrofuran:water (2:1, 15 mL) at rt. The reaction mixture was allowed to stir at rt overnight. The pH of the reaction mixture was adjusted to 3 using aq HCl and the reaction mixture was extracted with 2-methyltetrahydrofuran. The organic layers were combined, dried (MgSO₄), filtered, and concentrated *in vacuo* to afford the title compound as a solid (471 mg, 46%). LCMS: m/z 333.9 [M-H]⁻.

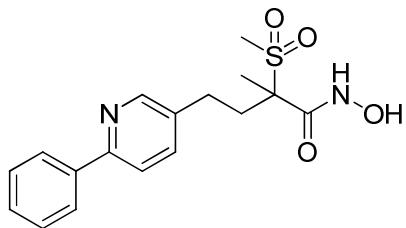
4-(5-Bromopyridin-2-yl)-2-methyl-2-(methylsulfonyl)-N-(tetrahydro-2H-pyran-2-yloxy)butanamide. 1,1'-Carbonyldiimidazole (101.4 mg, 0.60 mmol) was added to a solution of 4-(5-bromopyridin-2-yl)-2-methyl-2-(methylsulfonyl)butanoic acid (200 mg, 0.60 mmol) in *N,N*-dimethylformamide at rt and the mixture was stirred at this temperature for 30 minutes. *O*-(Tetrahydro-2*H*-pyran-2-yl)hydroxylamine (71 mg, 0.60 mmol) was added to the reaction mixture and stirred at rt for 2 h. The reaction mixture was diluted with ethyl acetate, washed with brine, dried (MgSO₄), filtered, and concentrated *in vacuo*. The crude material was purified via silica chromatography (40 g) using an eluent of ethyl acetate in hexanes (0-100%) to afford the title compound (286 mg). The material was carried forward without further purification. LCMS: m/z 434.0 [M-H]⁻.

***N*-Hydroxy-2-methyl-2-(methylsulfonyl)-4-(5-phenylpyridin-2-yl)butanamide (7a).**

SiliaCat® DPP-Pd (167 mg, 0.045 mmol) was added to a mixture of 4-(5-bromopyridin-2-yl)-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (260 mg, 0.60 mmol), phenylboronic acid (146 mg, 1.19 mmol), and K₂CO₃ (248 mg, 1.79 mmol) in ethanol:water (9:1, 5.0 mL). The reaction mixture was heated to 70 °C and was stirred at this temperature for 4 h. The reaction mixture was allowed to cool to rt, filtered, and the filtrate was concentrated *in vacuo* to afford a yellow residue. The residue was dissolved in dichloromethane (4 mL) and methanol (2 mL) was treated with HCl (4.0 M in 1,4-dioxane, 1 mL, 4.0 mmol), and was stirred

at rt for 3 h. The reaction mixture was concentrated *in vacuo* and the crude material was purified via preparatory HPLC to afford an orange residue. The residue was triturated in 1:1 ether:pentane and filtered to afford an orange solid (50 mg, 24%). ^1H NMR (400 MHz, DMSO- d_6) δ 10.97 (s, 1H), 9.22 (br. s., 1H), 8.80 (d, J = 1.76 Hz, 1H), 8.01 (dd, J = 2.35, 8.02 Hz, 1H), 7.66 - 7.76 (m, 2H), 7.46 - 7.54 (m, 2H), 7.36 - 7.46 (m, 2H), 3.07 (s, 3H), 2.79 - 2.92 (m, 1H), 2.55 - 2.69 (m, 2H), 2.06 - 2.18 (m, 1H), 1.55 (s, 3H). HRMS: m/z calc'd for $\text{C}_{17}\text{H}_{21}\text{N}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$: 349.1217; found: 349.1221.

Preparation of *N*-hydroxy-2-methyl-2-(methylsulfonyl)-4-(6-phenylpyridin-3-yl)butanamide (7b).



Ethyl 4-(6-bromopyridin-3-yl)-2-(methylsulfonyl)butanoate. The title compound (1.08 g, 76%) was obtained from 2-bromo-5-(2-iodoethyl)pyridine¹ (**3b**, $\text{R}_1 = \text{Br}$; 1.26 g, 4.04 mmol) and ethyl (methylsulfonyl)acetate (**4**, $\text{R}_2 = \text{H}$; 738 mg, 4.44 mmol) following a procedure analogous to that described for the synthesis of ethyl 4-(5-bromopyridin-2-yl)-2-(methylsulfonyl)butanoate. ^1H NMR (400 MHz, CDCl_3) δ 8.19 - 8.26 (m, 1H), 7.38 - 7.48 (m, 2H), 4.22 - 4.39 (m, 2H), 3.02 (s, 3H), 2.62 - 2.83 (m, 2H), 2.31 - 2.50 (m, 2H), 1.35 (t, J = 1.00 Hz, 3H). LCMS: m/z 351.9 $[\text{M}+\text{H}]^+$.

Ethyl 4-(6-bromopyridin-3-yl)-2-methyl-2-(methylsulfonyl)butanoate (5b**, $\text{R}_1 = \text{Br}$).** The title compound (802 mg, 72%) was synthesized from ethyl 4-(6-bromopyridin-3-yl)-2-(methylsulfonyl)butanoate (1.08 g, 3.08 mmol) following a procedure analogous to that described for the synthesis of ethyl 4-(5-bromopyridin-2-yl)-2-methyl-2-(methylsulfonyl)butanoate (**5a**, $\text{R}_1 = \text{Br}$). ^1H NMR (400 MHz, CDCl_3) δ 8.20 - 8.26 (m, 1H), 7.37 - 7.46 (m, 2H), 4.21 - 4.38 (m, 2H), 3.05 (s, 3H), 2.70 - 2.82 (m, 1H), 2.52 - 2.62 (m, 1H),

2.41 - 2.51 (m, 1H), 2.15 - 2.26 (m, 1H), 1.71 (s, 3H), 1.32 - 1.38 (m, 3H). LCMS: m/z 365.9 [M+H]⁺.

Ethyl 2-methyl-2-(methylsulfonyl)-4-(6-phenylpyridin-3-yl)butanoate (5b, R₁ = Ph).

Aqueous 3 M K₃PO₄ (1.19 mL, 3.58 mmol) was added to a degassed mixture of ethyl 4-(6-bromopyridin-3-yl)-2-methyl-2-(methylsulfonyl)butanoate (**5b, R₁ = Br**) (435 mg, 1.19 mmol), phenylboronic acid (175 mg, 1.43 mmol) and Pd(dppf)Cl₂ (87 mg, 0.12 mmol). The mixture was heated to 70 °C and was stirred at this temperature for 1 h. The mixture was diluted with water and ethyl acetate. The combined organic layers were separated, washed with water, dried (MgSO₄), filtered, and concentrated *in vacuo*. The crude material was purified via flash chromatography using a silica column (40 g) and a gradient of 0-100% ethyl acetate in *n*-heptane to afford the title compound (274 mg, 63%). ¹H NMR (400 MHz, CDCl₃) δ 8.54 (d, *J* = 1.95 Hz, 1H), 7.94 - 8.02 (m, 2H), 7.64 - 7.73 (m, 1H), 7.57 - 7.63 (m, 1H), 7.45 - 7.52 (m, 2H), 7.37 - 7.45 (m, 1H), 4.21 - 4.34 (m, 2H), 3.05 (s, 3H), 2.76 - 2.89 (m, 1H), 2.47 - 2.68 (m, 2H), 2.18 - 2.33 (m, 1H), 1.75 (s, 3H), 1.36 (t, *J* = 1.00 Hz, 3H). LCMS: m/z 362.1 (M⁺).

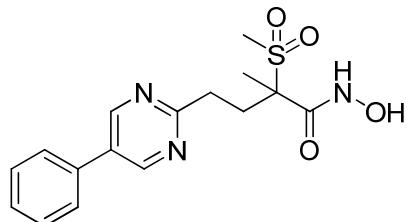
2-Methyl-2-(methylsulfonyl)-4-(6-phenylpyridin-3-yl)-N-(tetrahydro-2*H*-pyran-2-yl)butanamide. Lithium hydroxide (49.2 mg, 2.0 mmol) was added to a mixture of ethyl 2-methyl-2-(methylsulfonyl)-4-(6-phenylpyridin-3-yl)butanoate (**5b, R₁ = Ph**) (120 mg, 0.33 mmol) in tetrahydrofuran:water (1:1, 20 mL). The reaction mixture was stirred at rt overnight. The mixture was acidified with aq 1 M HCl and was extracted with ethyl acetate. The organic layers were combined, dried (MgSO₄), filtered, and concentrated to afford the crude carboxylic acid. The crude material was dissolved in 2-methyltetrahydrofuran (20 mL) and 2-chloro-4,6-dimethoxy-1,3,5-triazine (92 mg, 0.50 mmol) was added followed by the addition of *N*-methylmorpholine (101 mg, 1.00 mmol). The reaction mixture was stirred for 30 min, at which time *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (59.5 mg, 0.50 mmol) was added and the reaction was stirred at rt for 2 h. The mixture was diluted with ethyl acetate and the organics were washed with water. The organics were dried (MgSO₄), filtered, and concentrated. The crude material was purified via flash chromatography using silica (40 g) and a gradient of 0-

100% ethyl acetate in *n*-heptane to afford the title compound (70 mg, 49%). LCMS: m/z 433.1 (M⁺).

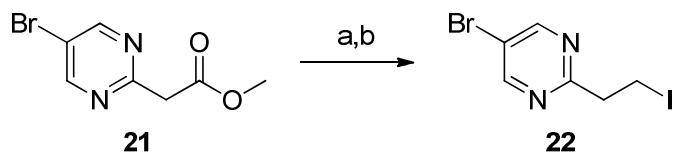
N-Hydroxy-2-methyl-2-(methylsulfonyl)-4-(6-phenylpyridin-3-yl)butanamide (7b).

Aqueous 1 M HCl (1.0 mL, 1.0 mmol) was added to a solution of 2-methyl-2-(methylsulfonyl)-4-(6-phenylpyridin-3-yl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (70 mg, 0.16 mmol) in methanol (1.0 mL) at rt. The reaction mixture was stirred at rt for 3 h and then was concentrated *in vacuo*. The crude material was purified via preparatory HPLC to afford the title compound as a solid (30 mg, 53%). ¹H NMR (400 MHz, CD₃OD) δ 8.50 (s, 1H), 7.88 - 7.94 (m, 2H), 7.77 - 7.84 (m, 2H), 7.38 - 7.52 (m, 3H), 3.07 (s, 3H), 2.76 - 2.91 (m, 1H), 2.53 - 2.68 (m, 2H), 2.04 - 2.20 (m, 1H), 1.71 (s, 3H). HRMS: m/z calc'd for C₁₇H₂₀N₂O₄S [M+H]⁺: 347.1071; found: 347.1070.

Preparation of *N*-hydroxy-2-methyl-2-(methylsulfonyl)-4-(5-phenylpyrimidin-2-yl)butanamide (7c).



Scheme 1. Synthesis of 5-bromo-2-(2-iodoethyl)pyrimidine (**3c**, R₁ = Br).^a



^a Reagents and conditions: (a) DIBAL-H, 0 °C to rt, (b) I₂, PPh₃, imidazole, DCM, rt.

2-(5-Bromopyrimidin-2-yl)ethanol (22). Diisobutylaluminium hydride (1.0 M in hexanes, 86.6 mL, 86.6 mmol) was added to a solution of methyl (5-bromopyrimidin-2-yl)acetate³ (**21**, 8.0 g, 30 mmol) in tetrahydrofuran (50 mL) at 0 °C. The reaction mixture was stirred for 2 h as the ice bath was allowed to expire. The reaction mixture was cooled to 0 °C and quenched with water

(250 mL). Ethyl acetate (250 mL) was added to the reaction mixture and the suspension was filtered. The aqueous layer was separated and extracted with ethyl acetate (100 mL). The organic layers were combined, washed with water (100 mL), brine (100 mL), dried (MgSO_4), filtered and concentrated *in vacuo*. The crude material was purified via flash chromatography using a Biotage SNAP Cartridge (KP-Sil 100g) and an eluent of ethyl acetate:*n*-heptane (6:4) to afford the title compound as a yellow solid (1.0 g, 10%). ^1H NMR (400 MHz, CDCl_3) δ 8.74 (s, 2H), 4.08 (q, $J = 5.85$ Hz, 2H), 3.42 (t, $J = 6.24$ Hz, 1H), 3.07 - 3.27 (m, 2H).

5-Bromo-2-(2-iodoethyl)pyrimidine (3c, $\text{R}_1 = \text{Br}$).

2-(5-Bromopyrimidin-2-yl)ethanol (**22**, 1.00 g, 4.93 mmol) in anhydrous dichloromethane (38 mL) was added via an addition funnel to a suspension of iodine (1.40 g, 5.50 mmol), triphenylphosphine (1.44 g, 5.50 mmol), and imidazole (376 mg, 5.52 mmol) in anhydrous dichloromethane (50 mL) at rt. The reaction mixture was stirred at rt overnight. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The crude material was purified via flash chromatography using a ReadySep 40g silica gel column with an eluent of 1% ethyl acetate in dichloromethane to afford the title compound as an off-white solid (1.33 g, 86%). LCMS: m/z 313.9 $[\text{M}+\text{H}]^+$.

Ethyl 4-(5-bromopyrimidin-2-yl)-2-methyl-2-(methylsulfonyl)butanoate (5c, $\text{R}_1 = \text{Br}$).

Cesium carbonate (3.05 g, 9.35 mmol) was added to a solution of ethyl 2-(methylsulfonyl)propanoate (**4**, $\text{R}_2 = \text{Me}$, 842 mg, 4.68 mmol) and 5-bromo-2-(2-iodoethyl)pyrimidine (**3c, R**₁ = **Br**, 1.33 g, 4.25 mmol) in *N,N*-dimethylformamide (42.5 mL). The reaction mixture was heated to 90 °C and was stirred at this temperature for 90 min. The reaction mixture was allowed to cool to rt and stirred overnight. The reaction mixture was diluted with ethyl acetate (150 mL) and washed with a solution of saturated aq NaHCO_3 :brine:water (1:1:1, 150 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified via flash chromatography using a ReadySep silica gel column (40g) and an eluent of 15% ethyl acetate in dichloromethane to afford the title compound as a clear oil (1.55 g, 71%). LCMS: m/z 367.0 $[\text{M}+\text{H}]^+$.

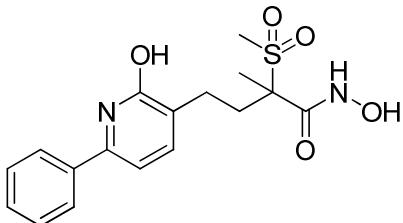
4-(5-Bromopyrimidin-2-yl)-2-methyl-2-(methylsulfonyl)butanoic acid. The title compound (1.02 g, 100%) was obtained as an off-white solid from ethyl 4-(5-bromopyrimidin-2-yl)-2-methyl-2-(methylsulfonyl)butanoate (**5c**, $R_1 = Br$) following a procedure analogous to that described in the General Saponification Procedure. LCMS: m/z 338.0 $[M+H]^+$.

4-(5-Bromopyrimidin-2-yl)-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide. The title compound (1.33 g, 75%) was obtained as a solid from 4-(5-bromopyrimidin-2-yl)-2-methyl-2-(methylsulfonyl)butanoic acid using a procedure analogous to that described in the General Amide Coupling, Method A. LCMS: m/z 435.0 $[M-H]^-$.

2-Methyl-2-(methylsulfonyl)-4-(5-phenylpyrimidin-2-yl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide. The title compound (104.7 mg, 35%) was obtained as a off-white solid using a procedure analogous to that described in the Suzuki-Miyaura Coupling, Method A. LCMS: m/z 434.2 $[M+H]^+$.

***N*-Hydroxy-2-methyl-2-(methylsulfonyl)-4-(5-phenylpyrimidin-2-yl)butanamide (7c).** Hydrochloric acid (4 M in 1,4-dioxane, 1.82 mL, 7.28 mmol) and methanol (200 μ L) was added to 2-methyl-2-(methylsulfonyl)-4-(5-phenylpyrimidin-2-yl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (104.7 mg, 0.24 mmol) and the reaction mixture was stirred at rt for 15 min. The reaction mixture was concentrated *in vacuo* and the crude material was triturated in diethyl ether for 1 h. The solid was collected via filtration and dried *in vacuo* to afford the title compound as a solid (71.2 mg, 84%). 1H NMR (400 MHz, CD_3OD) δ 9.38 (s, 2H), 7.79 - 7.85 (m, 2H), 7.53 - 7.63 (m, 3H), 3.33 - 3.38 (m, 1H), 3.10 - 3.21 (m, 1H), 3.08 (s, 3H), 2.88 - 2.99 (m, 1H), 2.49 (m, 1H), 1.71 (s, 3H). HRMS: m/z calc'd for $C_{16}H_{19}N_3O_4S$ $[M+H]^+$: 350.1169; found: 350.1175.

Preparation of *N*-hydroxy-4-(2-hydroxy-6-phenylpyridin-3-yl)-2-methyl-2-(methylsulfonyl)butanamide (10).



Ethyl 2-methyl-2-(methylsulfonyl)-4-(1-oxido-6-phenylpyridin-3-yl)butanoate (8). *meta*-Chloroperbenzoic acid (370 mg, 1.65 mmol) was added to a solution of ethyl 2-methyl-2-(methylsulfonyl)-4-(6-phenylpyridin-3-yl)butanoate (**6b**, 149 mg, 0.41 mmol) in dichloromethane (5 mL). The reaction mixture was stirred overnight and quenched with saturated aq NaHCO₃. The organic phase was separated, dried (CaCl₂), filtered, and concentrated *in vacuo*. The crude material was purified via flash chromatography using silica with a gradient 50-100% of ethyl acetate in *n*-heptane followed by a gradient of 0-20% methanol in ethyl acetate to afford the title compound (103 mg, 33%). LCMS: m/z 378.1 [M+H]⁺.

Ethyl 4-(2-acetoxy-6-phenylpyridin-3-yl)-2-methyl-2-(methylsulfonyl)butanoate. A solution of ethyl 2-methyl-2-(methylsulfonyl)-4-(1-oxido-6-phenylpyridin-3-yl)butanoate (**8**, 60 mg, 0.16 mmol) in acetic anhydride (2 mL) was heated to 130 °C and was stirred at this temperature overnight. The reaction mixture was concentrated *in vacuo* and the crude material was purified via flash chromatography using silica with a gradient of 20-100% ethyl acetate in *n*-heptane followed by a gradient of 0-20% methanol in ethyl acetate to afford the title compound as an orange residue (50 mg, 75%). ¹H NMR (400 MHz, CDCl₃) δ 7.87 - 8.05 (m, 2H), 7.59 - 7.77 (m, 2H), 7.35 - 7.54 (m, 3H), 4.32 (q, 2H), 3.07 (s, 3H), 2.66 - 2.79 (m, 1H), 2.45 - 2.61 (m, 2H), 2.43 (s, 3H), 2.13 - 2.27 (m, 1H), 1.71 - 1.75 (m, 3H), 1.36 (t, *J* = 7.12 Hz, 3H). LCMS: m/z 420.1 [M+H]⁺.

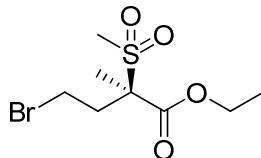
4-(2-Hydroxy-6-phenylpyridin-3-yl)-2-methyl-2-(methylsulfonyl)butanoic acid (9). Lithium hydroxide (28.5 mg, 1.19 mmol) was added to a solution of ethyl 4-(2-acetoxy-6-phenylpyridin-3-yl)-2-methyl-2-(methylsulfonyl)butanoate (50 mg, 0.12 mmol) in tetrahydrofuran:methanol:water (3:1:1, 2.5 mL) and the reaction mixture was stirred overnight at rt. The reaction was concentrated *in vacuo* and the residue was dissolved in water (2 mL). The

solution was acidified to a pH of 1 using aq 1.0 N HCl. The precipitate was filtered, washed with water, and dried *in vacuo* to afford a tan solid (24 mg, 57%). LCMS: m/z 350.1 [M+H]⁺.

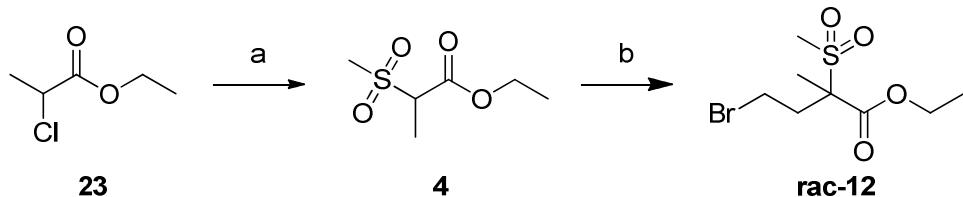
4-(2-Hydroxy-6-phenylpyridin-3-yl)-2-methyl-2-(methylsulfonyl)-N-(tetrahydro-2H-pyran-2-yloxy)butanamide. Hunig's base (30 μ L, 0.17 mmol) was added to a solution of 4-(2-hydroxy-6-phenylpyridin-3-yl)-2-methyl-2-(methylsulfonyl)butanoic acid (24 mg, 0.07 mmol) and HATU (39.9 mg, 0.10 mmol) in *N,N*-dimethylformamide at rt. The reaction mixture was stirred at rt for 4 h. The reaction mixture was diluted with water (2 mL) and ethyl acetate (5 mL) and then was stirred vigorously for 5 min. The aqueous layer was separated and extracted with ethyl acetate:*n*-heptane (1:1, 5 mL). The organic layers were combined, washed with water (2 mL), dried (CaCl_2), filtered, and concentrated *in vacuo*. The crude material was purified via flash chromatography using silica and a gradient of 20-100% ethyl acetate in *n*-heptane followed by a gradient of 0-20% methanol in ethyl acetate to afford the title compound as a clear residue (20 mg, 65%). LCMS: m/z 447.2 [M-H]⁻.

***N*-Hydroxy-4-(2-hydroxy-6-phenylpyridin-3-yl)-2-methyl-2-(methylsulfonyl)butanamide (10).** The title compound (5.3 mg, 33%) was obtained as a an off-white powder from 4-(2-hydroxy-6-phenylpyridin-3-yl)-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2H-pyran-2-yloxy)butanamide following a procedure analogous to that describe in the General Tetrahydropyranyl Deprotection, Method A. ^1H NMR (400 MHz, CD_3OD) δ 7.62 - 7.70 (m, 2H), 7.56 (d, 1H), 7.45 - 7.52 (m, 3H), 6.60 (d, 1H), 3.09 (s, 3H), 2.66 - 2.80 (m, 1H), 2.36 - 2.54 (m, 2H), 2.09 - 2.24 (m, 1H), 1.68 (s, 3H). HRMS: *m/z* calc'd for $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}_5\text{S}$ [M+H]⁺: 365.1166; found: 365.1162.

Synthesis and chiral separation of ethyl(2*R*)-4-bromo-2-methyl-2-(methylsulfonyl)butanoate (12).



Scheme 2. Synthesis of ethyl 4-bromo-2-methyl-2-(methylsulfonyl)butanoate (**rac-12**).^a



^a Reagents and conditions: (a) MeSO₂Na, EtOH, 77 °C. (b) NaH, BrCH₂CH₂Br, DMF, 0 °C.

Ethyl 2-(methylsulfonyl)propanoate (4, R₂ = Me). Sodium methanesulfinate (103 g, 937 mmol) was added to ethyl 2-chloropropionate (**23**, 109 g, 892 mmol) in ethanol (350 mL). The reaction mixture was heated to 77 °C and stirred at this temperature for 20 h. The reaction mixture was allowed to cool to rt. The solids were removed by filtration through celite, and the filter pad was washed with ethanol. The filtrates were combined and concentrated *in vacuo*. The crude product was suspended in diethyl ether (250 mL), and the solids were removed by filtration. The filtrate was concentrated *in vacuo* to afford the title compound as a pale yellow oil (51 g, 73%). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.32 (t, J=7.05 Hz, 3 H) 1.67 (d, J=7.47 Hz, 3 H) 3.05 (s, 3 H) 3.83 - 3.92 (m, 1 H) 4.18 - 4.37 (m, 2 H).

Ethyl 4-bromo-2-methyl-2-(methylsulfonyl)butanoate (rac-12). Sodium hydride (60% dispersion in mineral oil, 2.33 g, 58.3 mmol) was washed with hexanes (2x10 mL) under nitrogen and then was suspended in *N,N*-dimethylformamide (30 mL). The suspension was treated dropwise with ethyl 2-(methylsulfonyl)propanoate (**4, R₂ = Me**, 10.0 g, 55.49 mmol) in *N,N*-dimethylformamide (10 mL). The mixture was stirred 30 min at rt, cooled to 0 °C, and treated drop-wise with 1,2-dibromoethane (5.17 mL, 58.8 mmol). The mixture was allowed to warm to rt while stirring overnight. The mixture was quenched with saturated NH₄Cl (100 mL) and extracted with diethyl ether (4x50 mL). The organic layers were combined then washed with water:brine (1:1, 4x50 mL), dried (MgSO₄), and concentrated *in vacuo*. The crude material

was purified via silica chromatography (350 g) and a gradient of 10-20% ethyl acetate in hexanes to afford the title compound as a pale yellow oil (7.9 g, 50%). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.33 (t, J=7.05 Hz, 3 H) 1.64 (s, 3 H) 2.49 - 2.59 (m, 1 H) 2.78 (m, 1 H) 3.05 (s, 3 H) 3.33 - 3.41 (m, 1 H) 3.46 - 3.54 (m, 1 H) 4.22 - 4.37 (m, 2 H).

Chiral separation of ethyl 4-bromo-2-methyl-2-(methylsulfonyl)butanoate (rac-12). Crude ethyl 4-bromo-2-methyl-2-(methylsulfonyl)butanoate (**rac-12**, 1.82 kg) was purified via flash chromatography using an LP-600 column and an eluent of toluene to afford pure ethyl 4-bromo-2-methyl-2-(methylsulfonyl)butanoate (**rac-12**, 1.63 kg). The purified material was dissolved in ethanol (75 g/L) and resolved via chiral column chromatography (conditions listed in Table 1) on MCC-2 to afford enantiomer #1 (738.4 g, rt = 4.719 min, $[\alpha]_{589}^{20} = +14.1^\circ$) at 99% ee and enantiomer #2 (763.8 g, rt = 4.040 min) at 95% ee. Purity of the enantiomers was determined via chiral HPLC, 4.6x250 mm Chiralpak AD, 10μ column, 215 nm wavelength, mobile phase: ethanol, isocratic elution at 1mL/min at ambient temperature.

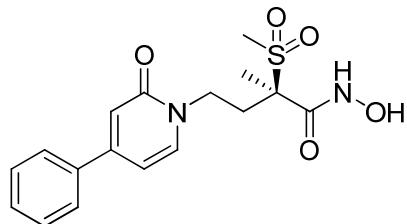
Table 1:

Stationary Phase	ChiralPak AD, 20μ
Column Dimension/Temp	5x10 cm/30 °C
Mobile Phase	100% ethanol
Feed Concentration	75 g/L in mobile phase
Feed Rate	4.0 mL/min
Eluent Rate	90.5 mL/min
Raffinate Rate	35.6 mL/min
Extract Rate	58.9 mL/min
Recycling Rate	262 mL/min
Period Time	1.0 min

Enantiomer 1 was determined to be ethyl (2*R*)-4-bromo-2-methyl-2-(methylsulfonyl)butanoate (**12**) via the co-crystallization of pyridone **2a** in complex with *Pseudomonas aeruginosa* LpxC shown in **Figure 2**. (2*R*)-*N*-Hydroxy-2-methyl-2-(methylsulfonyl)-4-(2-oxo-4-phenylpyridin-

1(2*H*)-yl)butanamide (**2a**) was synthesized from ethyl (2*R*)-4-bromo-2-methyl-2-(methylsulfonyl)butanoate (**12**).

Preparation of (2*R*)-N-hydroxy-2-methyl-2-(methylsulfonyl)-4-(2-oxo-4-phenylpyridin-1(2*H*)-yl)butanamide. (2a).



Ethyl (2*R*)-2-methyl-2-(methylsulfonyl)-4-(2-oxo-4-phenylpyridin-1(2*H*)-yl)butanoate (13a, $\mathbf{R}_4 = \mathbf{Ph}$). Cesium carbonate (68.3 g, 210 mmol) was added to a solution ethyl (2*R*)-4-bromo-2-methyl-2-(methylsulfonyl)butanoate (**12**, 34.2 g, 119 mmol) and 4-phenylpyridin-2-ol⁴ (**11a, R₄ = Ph**, 17 g, 99 mmol) in tetrahydrofuran (250 mL). The suspension was heated to 65 °C and stirred at this temperature overnight. The reaction mixture was allowed to cool to rt and filtered through celite (~1 inch). The filter pad was washed with 2-methyltetrahydrofuran (250 mL) and ethyl acetate (250 mL). The filtrates were combined and concentrated *in vacuo*. The crude residue was diluted with water (75 mL) and extracted with ethyl acetate (3x400 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified via flash chromatography using a Biotage SNAP Cartridge (KP-Sil 340g) and a gradient of 25-100% ethyl acetate in *n*-heptane to afford the title compound as a white solid (25 g, 67%). LCMS: m/z 378.1 [M+H]⁺.

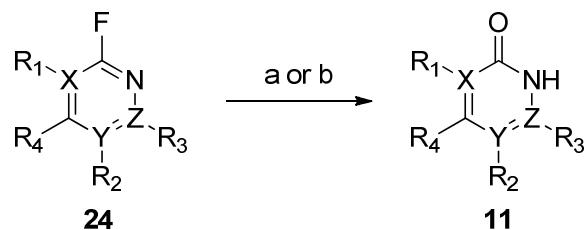
(2*R*)-2-Methyl-2-(methylsulfonyl)-4-(2-oxo-4-phenylpyridin-1(2*H*)-yl)butanoic acid. A white solid (31.0 g, 98%) was obtained from ethyl (2*R*)-2-methyl-2-(methylsulfonyl)-4-(2-oxo-4-phenylpyridin-1(2*H*)-yl)butanoate (**13a, R₄ = Ph**) using the General Saponification Procedure. ¹H NMR (400 MHz, DMSO-d₆) δ 7.76 (d, *J* = 7.22 Hz, 1H), 7.67 - 7.74 (m, 2H), 7.41 - 7.54 (m,

3H), 6.67 (d, J = 1.95 Hz, 1H), 6.61 (dd, J = 2.05, 7.12 Hz, 1H), 4.02 - 4.17 (m, 1H), 3.84 - 4.01 (m, 1H), 3.17 (s, 3H), 2.40 - 2.48 (m, 1H), 2.14 - 2.26 (m, 1H), 1.58 (s, 3H). LCMS: m/z 350.1 [M+H]⁺.

(2*R*)-2-Methyl-2-(methylsulfonyl)-4-(2-oxo-4-phenylpyridin-1(2*H*)-yl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (14a). The title compound (5.10 g, 75%) was obtained as a white gum from (2*R*)-2-methyl-2-(methylsulfonyl)-4-(2-oxo-4-phenylpyridin-1(2*H*)-yl)butanoic acid using the General Amide Coupling, Method A. LCMS: m/z 447.8 [M-H]⁻.

(2*R*)-*N*-Hydroxy-2-methyl-2-(methylsulfonyl)-4-(2-oxo-4-phenylpyridin-1(2*H*)-yl)butanamide (2a). The title compound (3.10 g, 75%) was obtained as an off-white solid from (2*R*)-2-methyl-2-(methylsulfonyl)-4-(2-oxo-4-phenylpyridin-1(2*H*)-yl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (14a) using the General Tetrahydropyranyl Deprotection Procedure, Method B. ¹H NMR (400 MHz, CD₃OD) δ 7.75 - 7.81 (m, 1H), 7.66 - 7.74 (m, 2H), 7.47 - 7.55 (m, 3H), 6.80 - 6.88 (m, 2H), 4.27 - 4.43 (m, 1H), 3.92 - 4.05 (m, 1H), 3.13 (s, 3H), 2.55 - 2.70 (m, 1H), 2.32 - 2.46 (m, 1H), 1.72 (s, 3H). HRMS: m/z calc'd for C₁₇H₂₀N₂O₅S [M+H]⁺: 365.1166; found: 365.1158.

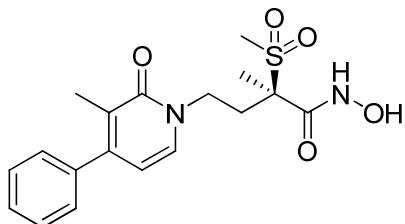
Scheme 3. Synthesis of 4-iodo-3-methylpyridin-2(1*H*)-one (11b, R₄ = I).



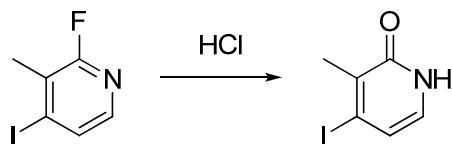
- b.** R₁=Me, R₄ = I, R₂,R₃ = H, X,Y,Z = C
- c.** R₂=Me, R₄ = I, R₁,R₃ = H, X,Y,Z = C
- d.** R₃=Me, R₄ = I, R₁,R₂ = H, X,Y,Z = C
- e.** R₁=F, R₄ = I, R₂,R₃ = H, X,Y,Z = C
- f.** R₂=F, R₄ = I, R₁,R₂ = H, X,Y,Z = C

^aReagents and conditions. (a) Conc. HCl, 1,4-dioxane, H₂O. (b) KOH, 1,4-dioxane, H₂O.

Preparation of (2*R*)-*N*-hydroxy-2-methyl-4-(3-methyl-2-oxo-4-phenylpyridin-1(2*H*)-yl)-2-(methylsulfonyl)butanamide (2b).



Scheme 3. Synthesis of 4-iodo-3-methylpyridin-2(1*H*)-one (11b, R₄ = I).



4-Iodo-3-methylpyridin-2(1*H*)-one (11b, R₄ = I). Concentrated HCl (100 mL) was added to a solution of 2-fluoro-4-iodo-3-methylpyridine (24b, 49.50 g, 208.85 mmol) in 1,4-dioxane:water (1:1, 200 mL). The reaction mixture was heated to 100 °C and was stirred at this temperature for 2 h. The reaction mixture was allowed to cool to rt and was diluted with water (300 mL) causing a precipitate to form. The suspension was stirred overnight at rt, and the solid was collected via filtration. The solid was washed with water and dried *in vacuo* to afford the title compound as a tan solid (49.08 g, 88%). ¹H NMR (400 MHz, DMSO-d₆) δ 11.68 (br. s., 1H), 6.96 (d, *J* = 6.80 Hz, 1H), 6.55 (d, *J* = 6.83 Hz, 1H). LCMS: m/z 236.1 [M+H]⁺.

Ethyl (2*R*)-4-(4-iodo-3-methyl-2-oxopyridin-1(2*H*)-yl)-2-methyl-2-(methylsulfonyl)butanoate (13b, R₄ = I). Cesium carbonate (2.10 g, 6.45 mmol) was added to a solution of 4-iodo-3-methylpyridin-2(1*H*)-one (11b, R₄ = I, 1.00 g, 4.26 mmol) and (+)-ethyl (2*R*)-4-bromo-2-methyl-2-(methylsulfonyl)butanoate (12, 2.44 g, 8.51 mmol) in *t*-butanol:tetrahydrofuran (9:1, 40 mL). The resulting suspension was heated to 50 °C and was stirred at this temperature overnight. The reaction mixture was allowed to cool to rt, filtered, and concentrated *in vacuo*. The crude material was purified via flash chromatography using a Biotage SNAP Cartridge (KP-Sil 10g) and a gradient of 0-100% ethyl acetate in hexanes to

afford the title compound as a clear gum (1.69 g, 90%). ^1H NMR (400 MHz, CDCl_3) δ 6.85 (dd, $J = 0.68, 7.22$ Hz, 1H), 6.55 - 6.68 (m, 1H), 4.27 (q, 2H), 4.17 - 4.24 (m, 1H), 3.88 - 3.98 (m, 1H), 3.10 (s, 3H), 2.40 - 2.59 (m, 2H), 2.34 (s, 3H), 1.75 (s, 3H), 1.31 - 1.38 (m, 3H). LCMS: m/z 442.0 $[\text{M}+\text{H}]^+$.

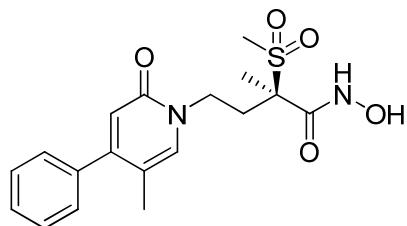
(2*R*)-2-Methyl-4-(3-methyl-2-oxo-4-phenylpyridin-1(2*H*)-yl)-2-(methylsulfonyl)butanoic acid. Palladium(II) EncatTM BINAP(452 mg, 0.14 mmol, 0.30 mmol Pd/g) was added to a mixture of the ethyl (2*R*)-4-(4-iodo-3-methyl-2-oxopyridin-1(2*H*)-yl)-2-methyl-2-(methylsulfonyl)butanoate (**13b**, **R**₄ = **I**, 590 mg, 1.34 mmol), phenylboronic acid (252 mg, 2.07 mmol), and K_2CO_3 (565 mg, 4.09 mmol) in ethanol:water (9:1, 10 mL). The reaction mixture was heated to 70 °C and was stirred at this temperature overnight. Potassium hydroxide (512 mg, 9.12 mmol) was added to the suspension and heated at 70 °C for 3 h. The reaction mixture was allowed to cool to rt and was diluted with water (50 mL). The aqueous layer was washed with ethyl acetate (3x40 mL) and acidified to a pH of 3 using aq 3 N HCl. The aqueous layer was extracted with ethyl acetate (3x60 mL). The organic layers were combined, washed with brine (50 mL), dried (MgSO_4), filtered, and concentrated to afford the title compound as a yellow solid (449 mg, 92%). ^1H NMR (400 MHz, CDCl_3) δ 6.85 (dd, $J = 0.68, 7.22$ Hz, 1H), 6.55 - 6.68 (m, 1H), 4.27 (q, 2H), 4.17 - 4.24 (m, 1H), 3.88 - 3.98 (m, 1H), 3.10 (s, 3H), 2.40 - 2.59 (m, 2H), 2.34 (s, 3H), 1.75 (s, 3H), 1.31 - 1.38 (m, 3H). LCMS: m/z 364.1 $[\text{M}+\text{H}]^+$.

(2*R*)-2-Methyl-4-(3-methyl-2-oxo-4-phenylpyridin-1(2*H*)-yl)-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (14b**).** The title compound (352 mg, 62%) was obtained as a clear solid from (2*R*)-2-methyl-4-(3-methyl-2-oxo-4-phenylpyridin-1(2*H*)-yl)-2-(methylsulfonyl)butanoic acid using a procedure analogous to that described in the General Amide Coupling, Method B. LCMS: m/z 461.2 $[\text{M}-\text{H}]^-$.

(2*R*)-*N*-Hydroxy-2-methyl-4-(3-methyl-2-oxo-4-phenylpyridin-1(2*H*)-yl)-2-(methylsulfonyl)butanamide (2b**).** The title compound (54 mg, 46%) was obtained as an off-white solid from (2*R*)-2-methyl-4-(3-methyl-2-oxo-4-phenylpyridin-1(2*H*)-yl)-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide using a procedure analogous to

that described in the General Tetrahydropyranyl Deprotection, Method B. ^1H NMR (400 MHz, DMSO-d₆) δ 11.19 (s, 1H), 9.25 (s, 1H), 7.59 (d, J = 6.44 Hz, 1H), 7.45 - 7.52 (m, 2H), 7.38 - 7.45 (m, 1H), 7.32 - 7.38 (m, 2H), 6.21 (d, J = 7.02 Hz, 1H), 4.15 (td, J = 5.07, 11.90 Hz, 1H), 3.76 (td, J = 5.46, 12.68 Hz, 1H), 3.12 (s, 3H), 2.36 - 2.48 (m, 1H), 2.19 (td, J = 4.98, 12.24 Hz, 1H), 1.96 (s, 3H), 1.59 (s, 3H). HRMS: *m/z* calc'd for C₁₈H₂₂N₂O₅S [M+H]⁺: 379.1322; found: 379.1324.

Preparation of (2*R*)-*N*-hydroxy-2-methyl-4-(5-methyl-2-oxo-4-phenylpyridin-1(2*H*)-yl)-2-(methylsulfonyl)butanamide (2c).



4-Iodo-5-methylpyridin-2(1*H*)-one (11c, R₄ = I). Concentrated HCl (10 mL) was added to a mixture of 2-fluoro-4-iodo-5-methylpyridine (**24c**, 5.00 g, 21.10 mmol) in 1,4-dioxane:water (1:1, 20 mL). The mixture was heated to 100 °C and stirred at this temperature for 2 h. The reaction mixture was allowed to cool to rt and was diluted with water (30 mL) forming a precipitate. The suspension was triturated for 1 h, cooled in an ice bath, and the solid was collected via filtration. The precipitate was washed with diethyl ether, and dried *in vacuo* to afford the title compound as a yellow solid (2.89 g, 58%). LCMS: *m/z* 236.9 [M+H]⁺.

Ethyl (2*R*)-4-(4-iodo-5-methyl-2-oxopyridin-1(2*H*)-yl)-2-methyl-2-(methylsulfonyl)butanoate (13c, R₄ = I). Cesium carbonate (8.41 g, 25.8 mmol) was added to a solution of 4-iodo-5-methylpyridin-2(1*H*)-one (**11c**, R₄ = I, 2.89 g, 12.30 mmol) and ethyl (+)-(2*R*)-4-bromo-2-methyl-2-(methylsulfonyl)butanoate (**12**, 3.53 g, 12.3 mmol) in tetrahydrofuran (75 mL). The suspension was heated to 60 °C and was stirred at this temperature overnight. The reaction mixture was allowed to cool to rt and was diluted with ethyl acetate and water. The aqueous layer was extracted with ethyl acetate. The organic layers were combined, washed with brine, dried (MgSO₄), filtered, and concentrated *in vacuo*. The crude material was purified via

flash chromatography using a silica column (80 g) and a gradient of 0-100% ethyl acetate in *n*-heptane to afford the title compound as a solid (5.43 g, 31%). ^1H NMR (400 MHz, CDCl_3) δ 7.24 (s, 1H), 7.05 (s, 1H), 4.27 (q, $J = 7.22$ Hz, 2H), 4.07 - 4.24 (m, 1H), 3.79 - 4.01 (m, 1H), 3.10 (s, 3H), 2.36 - 2.57 (m, $J = 5.56, 9.95, 13.63, 13.63$ Hz, 2H), 2.16 (s, 3H), 1.75 (s, 3H), 1.30 - 1.40 (m, 3H). LCMS: m/z 442.0 $[\text{M}+\text{H}]^+$.

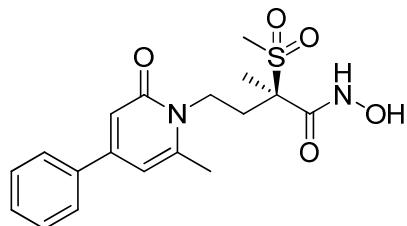
(2*R*)-2-Methyl-4-(5-methyl-2-oxo-4-phenylpyridin-1(2*H*)-yl)-2-(methylsulfonyl)butanoic acid. Palladium(II) EncatTM BINAP (**13c**, $\text{R}_4 = \text{I}$, 965 mg, 290 mmol, 0.30 mmol/g) was added to a mixture of ethyl (2*R*)-4-(4-iodo-5-methyl-2-oxopyridin-1(2*H*)-yl)-2-methyl-2-(methylsulfonyl)butanoate (**13c**, $\text{R}_4 = \text{I}$, 1.69 g, 3.83 mmol), phenylboronic acid (495 mg, 4.06 mmol), K_2CO_3 (1.62 g, 11.74 mmol) in ethanol:water (9:1, 30 mL). The suspension was heated to 70 °C and stirred at this temperature overnight. The reaction mixture was allowed to cool and diluted with ethyl acetate and aq 1 N HCl. The reaction mixture was filtered, and the aqueous layer was extracted with ethyl acetate. The organic layers were combined, washed with brine, dried (MgSO_4), filtered and concentrated. The crude material was purified via flash chromatography using a silica column (40 g) and a gradient of 0-20% methanol in dichloromethane to afford the title compound as a tan solid (895.4 mg, 64%). LCMS: m/z 364.0 $[\text{M}+\text{H}]^+$.

(2*R*)-2-Methyl-4-(5-methyl-2-oxo-4-phenylpyridin-1(2*H*)-yl)-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (14c**).** The title compound (1.05 g, 92%) was obtained as a tan solid from (2*R*)-2-methyl-4-(5-methyl-2-oxo-4-phenylpyridin-1(2*H*)-yl)-2-(methylsulfonyl)butanoic acid using a procedure analogous to that described in the General Amide Coupling, Method A. LCMS: m/z 463.2 $[\text{M}+\text{H}]^+$.

(2*R*)-*N*-Hydroxy-2-methyl-4-(5-methyl-2-oxo-4-phenylpyridin-1(2*H*)-yl)-2-(methylsulfonyl)butanamide (2c**).** The title compound (650 mg, 79%) as a tan solid was obtained from (2*R*)-2-methyl-4-(5-methyl-2-oxo-4-phenylpyridin-1(2*H*)-yl)-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (**14c**) using a procedure analogous to that described in the General Tetrahydropyranyl Deprotection, Method A. ^1H NMR (400 MHz, CD_3OD) δ 7.89

(s, 1H), 7.45 - 7.56 (m, 3H), 7.40 (d, J = 7.41 Hz, 2H), 6.72 (d, J = 0.78 Hz, 1H), 4.35 - 4.54 (m, 1H), 4.04 - 4.24 (m, 1H), 3.10 (s, 3H), 2.64 - 2.84 (m, 1H), 2.34 - 2.52 (m, 1H), 2.14 (s, 3H), 1.73 (s, 3H). HRMS: m/z calc'd for $C_{18}H_{22}N_2O_5S$ [M+H]⁺: 379.1322; found: 379.1326.

Preparation of (2*R*)-*N*-hydroxy-2-methyl-4-(6-methyl-2-oxo-4-phenylpyridin-1(2*H*)-yl)-2-(methylsulfonyl)butanamide (2d).



4-Iodo-6-methylpyridin-2(1*H*)-one (11d, R_4 = I). Potassium hydroxide (485 mg, 8.64 mmol) was added to a solution of 2-fluoro-4-iodo-6-methylpyridine (**24d**, 1.0 g, 4.2 mmol) in water (2.5 mL) and 1,4-dioxane (250 μ L). The solution was heated to reflux and stirred at this temperature overnight. The reaction mixture was allowed to cool to rt and was acidified with acetic acid (3 mL). The mixture was stirred for 30 minutes. The solid was collected via filtration, washed with water (20 mL) and hexanes (20 mL), and was dried *in vacuo* to afford the title compound as a white solid (663 mg, 68%). LCMS: m/z 235.9 [M+H]⁺. 1H NMR (400 MHz, DMSO-d₆) δ 11.79 (br. s., 1H), 6.66 (s, 1H), 6.37 (s, 1H).

Ethyl (2*R*)-4-(4-Iodo-6-methyl-2-oxopyridin-1(2*H*)-yl)-2-methyl-2-(methylsulfonyl)butanoate (13d, R_4 = I). Cesium carbonate (662 mg, 2.03 mmol) was added to a solution of the 4-iodo-6-methylpyridin-2(1*H*)-one (315 mg, 1.34 mmol) and ethyl (+)-4-bromo-2-methyl-2-(methylsulfonyl)butanoate (**12**, 770 mg, 2.68 mmol) in *t*-butanol:tetrahydrofuran (9:1 10 mL). The resulting suspension was heated to 50 °C and was stirred at this temperature overnight. Excess ethyl (+)-4-bromo-2-methyl-2-(methylsulfonyl)butanoate (770 mg, 2.68 mmol) was added to the reaction mixture and was stirred at 50 °C for 3 days. The reaction mixture was allowed to cool to rt, filtered, and concentrated *in vacuo*. The crude material was purified via flash chromatography using a Biotage SNAP Cartridge (KP-Sil 10g) and a gradient of 0-100% ethyl acetate in hexanes to afford the title compound as a viscous yellow oil (155 mg, 26%). 1H NMR (400 MHz, CDCl₃) δ 6.99 (d, J = 1.66 Hz, 1H), 6.42 (dd, J = 0.78, 1.85 Hz, 1H),

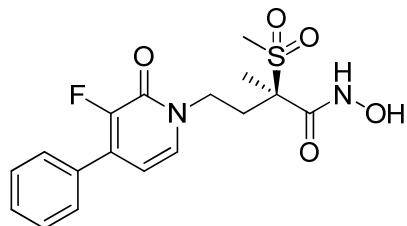
4.24 - 4.42 (m, 3H), 3.96 - 4.10 (m, 1H), 3.11 (s, 3H), 2.28 - 2.48 (m, 5H), 1.79 (s, 3H), 1.36 (t, 3H). LCMS: m/z 442.0 [M+H]⁺.

(2R)-2-Methyl-4-(6-methyl-2-oxo-4-phenylpyridin-1(2H)-yl)-2-(methylsulfonyl)butanoic acid. Palladium(II) EncatTM BINAP (165 mg, 0.050 mmol, 0.30 mmol Pd/g) was added to a mixture of ethyl (2R)-4-(4-iodo-6-methyl-2-oxopyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoate (**13d, R₄ = I**, 250 mg, 0.48 mmol), phenylboronic acid (90 mg, 0.74 mmol), and K₂CO₃ (205 mg, 1.48 mmol) in ethanol:water (9:1, 5.0 mL). The reaction mixture was heated to 70 °C and stirred at this temperature overnight. The reaction mixture was allowed to cool to rt, filtered, and the filtrate was concentrated *in vacuo*. The crude material was purified via flash chromatography using a Biotage SNAP cartridge (KP Sil 10g) and a gradient of 0-100% ethyl acetate in hexanes to afford the title compound as a yellow solid (100 mg, 78%). LCMS: m/z 364.1 [M+H]⁺.

(2R)-N-Hydroxy-2-methyl-4-(6-methyl-2-oxo-4-phenylpyridin-1(2H)-yl)-2-(methylsulfonyl)butanamide (14d). The title compound (110 mg, 87%) was obtained as a clear solid from (2R)-2-methyl-4-(6-methyl-2-oxo-4-phenylpyridin-1(2H)-yl)-2-(methylsulfonyl)butanoic acid using a procedure analogous to that described in the General Amide Coupling, Method A. LCMS: m/z 461.2 [M-H]⁻.

(2R)-N-hydroxy-2-methyl-4-(6-methyl-2-oxo-4-phenylpyridin-1(2H)-yl)-2-(methylsulfonyl)butanamide (2d). The title compound (44.2 mg, 46%) was obtained as a white solid from (2R)-N-hydroxy-2-methyl-4-(6-methyl-2-oxo-4-phenylpyridin-1(2H)-yl)-2-(methylsulfonyl)butanamide (**14d**) using a procedure analogous to that described in the General Tetrahydropyranyl Deprotection, Method B. ¹H NMR (400 MHz, CD₃CN) δ 7.63 - 7.73 (m, 2H), 7.43 - 7.54 (m, 3H), 6.70 (d, *J* = 1.95 Hz, 1H), 6.59 (s, 1H), 4.13 - 4.28 (m, 1H), 3.97 - 4.13 (m, 1H), 3.12 (s, 3H), 2.45 - 2.51 (m, 3H), 2.19 - 2.41 (m, 2H), 1.63 - 1.69 (m, 3H). HRMS (ESI) *m/z* calc'd for C₁₈H₂₂N₂O₅S [M+H]⁺: 379.1322; found: 379.1326.

Prepartion of (2R)-4-(3-fluoro-2-oxo-4-phenylpyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide (2e).



3-Fluoro-4-iodopyridin-2(1H)-one (11e, R₄ = I). Potassium hydroxide (973 mg, 17.3 mmol) was added to a solution of the 2,3-difluoro-4-iodopyridine (**24e**, 2.0 g, 8.43 mmol) in water (5 mL) and 1,4-dioxane (500 μ L). The solution was heated to reflux and was stirred at this temperature overnight. The reaction mixture was allowed to cool to rt and acidified with acetic acid (6 mL). The mixture was stirred for 30 minutes and the solid was collected via filtration. The solid was washed with water (20 mL) and hexanes (20 mL). The solids were dried *in vacuo* to afford the title compound as a white solid (1.44 g, 73%). LCMS: m/z 239.9 [M+H]⁺.

Ethyl (2R)-4-(3-fluoro-4-iodo-2-oxopyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoate. (13e, R₄ = I). Cesium carbonate (3.03 g, 9.29 mmol) was added to a solution of 3-fluoro-4-iodopyridin-2(1H)-one (**11e, R₄ = I**, 1.44 g, 6.02 mmol) and ethyl (+)-(2R)-4-bromo-2-methyl-2-(methylsulfonyl)butanoate (**12**, 3.52 g, 12.3 mmol) in *t*-butanol:tetrahydrofuran (9:1 50 mL). The resulting suspension was heated to 50 °C and stirred at this temperature for 3 days. The reaction mixture was filtered and concentrated *in vacuo*. The crude material was purified via flash chromatography using a Biotage SNAP Cartridge (KP-Sil 50g) and a gradient of 0-100% ethyl acetate in hexanes to afford the title compound as a clear gum (2.32 g, 87%). LCMS: m/z 446.0 [M+H]⁺.

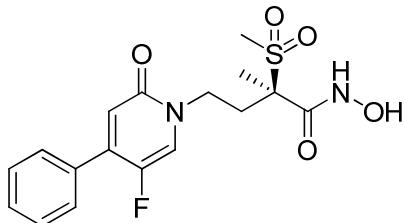
(2R)-4-(3-Fluoro-2-oxo-4-phenylpyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoic acid. Palladium(II) Encat™ BINAP(440 mg, 0.13 mmol, 0.30 mmol Pd/g) was added to a mixture of ethyl (2R)-4-(3-fluoro-4-iodo-2-oxopyridin-1(2H)-yl)-2-methyl-2-

(methylsulfonyl)butanoate (**13e**, **R₄** = **I**, 580 mg, 1.30 mmol), phenylboronic acid (242 mg, 1.98 mmol), and K₂CO₃ (552 mg, 3.99 mmol) in ethanol:water (9:1, 10 mL). The reaction mixture was heated to 70 °C and was stirred at this temperature overnight. Potassium hydroxide (452 mg, 8.06 mmol) was added to the suspension and stirred at 70 °C for 3 h. The reaction mixture was allowed to cool to rt and was diluted with aq 1 N NaOH (50 mL). The aqueous layer was washed with ethyl acetate (3x40 mL) and then acidified to a pH of 3 using aq 3 N HCl. The aqueous layer was extracted with ethyl acetate (3x60 mL) and the organic layers were combined, washed with brine (50 mL), dried (MgSO₄), filtered, and concentrated to afford the title compound as a yellow solid (394 mg, 83%). LCMS: m/z 368.0 [M+H]⁺.

(2R)-4-(3-Fluoro-2-oxo-4-phenylpyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)-N-(tetrahydro-2H-pyran-2-yloxy)butanamide (14e). The title compound (366 mg, 73%) was obtained as an orange solid from (2R)-4-(3-fluoro-2-oxo-4-phenylpyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoic acid using a procedure analogous to that described in the General Amide Coupling, Method B. LCMS: m/z 465.1 [M-H]⁻.

(2R)-4-(3-Fluoro-2-oxo-4-phenylpyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide (2e). The title compound (196.2 mg, 65%) was obtained as a white solid from (2R)-4-(3-fluoro-2-oxo-4-phenylpyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)-N-(tetrahydro-2H-pyran-2-yloxy)butanamide (**14e**) using a procedure analogous to that described in the General Tetrahydropyranyl Deprotection, Method B. ¹H NMR (400 MHz, CD₃OD) δ 7.60 - 7.66 (m, 2H), 7.44 - 7.56 (m, 4H), 6.50 - 6.57 (m, 1H), 4.26 - 4.42 (m, 1H), 3.11 (s, 3H), 2.60 - 2.70 (m, 1H), 2.35 - 2.45 (m, 1H), 1.72 (s, 3H). HRMS: m/z calc'd for C₁₇H₁₉FN₂O₅S [M+H]⁺: 383.1071; found: 383.1076.

Preparation of (2R)-4-(5-fluoro-2-oxo-4-phenylpyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide (2f).



5-Fluoro-4-iodopyridin-2(1H)-one (11f, R₄ = I). Potassium hydroxide (2.05 g, 8.51 mmol) was added to a solution of 2,5-difluoro-4-iodopyridine (2.05 g, 8.51 mmol) in *tert*-butanol (20 mL) and the reaction mixture was heated to reflux and stirred at this temperature for 4 h. The reaction mixture was allowed to cool to rt and concentrated *in vacuo*. The crude residue was triturated in aq 1N HCl (20 mL) overnight. The solids were collected via filtration, washed with water (10 mL), then with hexanes (10 mL), and dried *in vacuo* to afford the title compound as a yellowish solid (940 mg, 46.2%). ¹H NMR (400 MHz, DMSO-d₆) δ 11.50 (br. s., 1H), 7.68 (d, *J* = 2.34 Hz, 1H), 7.02 (d, *J* = 5.07 Hz, 1H). LCMS: m/z 239.9[M+H]⁺.

The filtrates were extracted with ethyl acetate (3x60 mL). The organic layers were washed with brine (100 mL), dried (MgSO₄), filtered and concentrated *in vacuo* to afford the title compound as a yellow solid (1.05 g, 51.6%). ¹H NMR (400 MHz, DMSO-d₆) δ 11.50 (br. s., 1H), 7.68 (d, *J* = 2.34 Hz, 1H), 7.02 (d, *J* = 5.07 Hz, 1H). LCMS: m/z 239.9[M+H]⁺.

Ethyl (2*R*)-4-(5-fluoro-4-iodo-2-oxopyridin-1(2*H*)-yl)-2-methyl-2-(methylsulfonyl)butanoate (13f, R₄ = I). Cesium carbonate (1.77 g, 5.44 mmol) was added to a solution of 5-fluoro-4-iodopyridin-2(1*H*)-one (11f, R₄ = I, 1.00 g, 4.2 mmol) and ethyl (+)-(2*R*)-4-bromo-2-methyl-2-(methylsulfonyl)butanoate (12, 1.56 g, 5.44 mmol) in anhydrous tetrahydrofuran (45 mL). The reaction mixture was heated to 70 °C and was stirred at this temperature overnight. The reaction mixture was quenched with water (100 mL) then was extracted with ethyl acetate (2x100 mL). The organic layers were combined, washed with brine (100 mL), dried (MgSO₄), filtered, and concentrated *in vacuo*. The crude material was purified via flash chromatography using a Varian SF15-24g column and a gradient of 30-80% ethyl acetate in *n*-heptane to afford the title compound as a yellow residue (691mg, 37%). ¹H NMR (400 MHz, CDCl₃) δ 7.20 (d, *J* = 3.32 Hz, 1H), 7.15 (d, *J* = 5.85 Hz, 1H), 4.16 - 4.33 (m, 3H),

3.88 - 3.98 (m, 1H), 3.10 (s, 3H), 2.40 - 2.56 (m, 2H), 1.76 (s, 3H), 1.35 (t, J = 7.12 Hz, 3H). LCMS: m/z 446.0[M+H]⁺.

Ethyl (2*R*)-4-(5-fluoro-2-oxo-4-phenylpyridin-1(2*H*)-yl)-2-methyl-2-(methylsulfonyl)butanoate (13f, R = Ph).

[1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (484 mg, 0.593 mmol) was added to a solution of ethyl (2*R*)-4-(5-fluoro-4-iodo-2-oxopyridin-1(2*H*)-yl)-2-methyl-2-(methylsulfonyl)butanoate (**13f, R = I**, 2.20 g, 4.94 mmol) phenylboronic acid (904 mg, 7.41 mmol) and tribasic potassium phosphate (3.95 g, 114.8 mmol) in 2-methyltetrahydrofuran:water (5:1, 60 mL). The reaction mixture was heated to 60 °C and vigorously stirred at this temperature for 1 h. The reaction mixture was allowed to cool to rt. The aqueous layer was separated and extracted with ethyl acetate (2x30 mL). The organic layers were combined, washed with deionized water (20 mL) and brine (20 mL), dried (MgSO_4), filtered, and concentrated *in vacuo*. The crude material was purified via flash chromatography using an Analogix SF25-40g column and a gradient of 0-60% ethyl acetate in hexanes to afford a brown solid (1.70 g, 87%). ¹H NMR (400 MHz, CDCl_3) δ 7.50 - 7.56 (m, 2H), 7.44 - 7.50 (m, 3H), 7.32 (d, J = 5.66 Hz, 1H), 6.63 (d, J = 7.61 Hz, 1H), 4.19 - 4.39 (m, 4H), 3.90 - 4.05 (m, 1H), 3.13 (s, 3H), 2.42 - 2.66 (m, 2H), 1.78 (s, 3H), 1.36 (t, J = 7.12 Hz, 3H). LCMS: m/z 396.0[M+H]⁺.

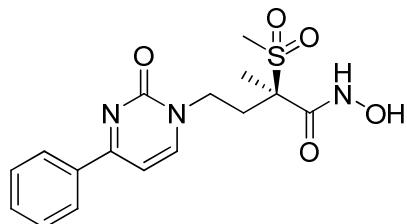
(2*R*)-4-(5-Fluoro-2-oxo-4-phenylpyridin-1(2*H*)-yl)-2-methyl-2-(methylsulfonyl)butanoic acid. Potassium hydroxide (1.70 g, 30.3 mmol) was added to a solution of ethyl (2*R*)-4-(5-fluoro-2-oxo-4-phenylpyridin-1(2*H*)-yl)-2-methyl-2-(methylsulfonyl)butanoate (**13f, R = Ph**, 1.70 g, 4.30 mmol) in 2-methyltetrahydrofuran:water (2:1 45 mL) and the solution was stirred at rt overnight. The reaction mixture was diluted with aq 1 N NaOH (100 mL) and washed with ethyl acetate (3x60 mL). The aqueous layer was acidified to a pH of 3 using aq 3 N HCl. The precipitate was collected via filtration, washed with water (20 mL) and hexanes (20 mL) and

dried *in vacuo* to afford the title compound as an off-white solid (1.29 g, 82%). ^1H NMR (400 MHz, DMSO-d₆) δ 13.88 (br. s., 1H), 8.05 (d, J = 6.63 Hz, 1H), 7.53 - 7.62 (m, 2H), 7.46 - 7.53 (m, 3H), 6.49 (d, J = 7.61 Hz, 1H), 3.89 - 4.10 (m, 2H), 3.17 (s, 3H), 2.43 - 2.57 (m, 1H), 2.12 - 2.27 (m, 1H), 1.58 (s, 3H). LCMS: m/z 368.0 [M+H]⁺.

(2*R*)-4-(5-Fluoro-2-oxo-4-phenylpyridin-1(2*H*)-yl)-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (14f). The title compound (1.21 g, 75%) was obtained as a white solid from (2*R*)-4-(5-fluoro-2-oxo-4-phenylpyridin-1(2*H*)-yl)-2-methyl-2-(methylsulfonyl)butanoic acid (1.28 g, 3.48 mmol) using the General Amide Coupling, Method B. LCMS: m/z 465.2 [M-H]⁻.

(2*R*)-4-(5-Fluoro-2-oxo-4-phenylpyridin-1(2*H*)-yl)-*N*-hydroxy-2-methyl-2-(methylsulfonyl)butanamide (2f). The title compound (204.5 mg, 21%) was obtained as a white solid from (2*R*)-4-(5-fluoro-2-oxo-4-phenylpyridin-1(2*H*)-yl)-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (14f, 1.21 g, 2.59 mmol) using a procedure analogous to that described in the General Tetrahydropyranyl Deprotection, Method B. ^1H NMR (400 MHz, CD₃OD) δ 7.85 (d, J = 5.85 Hz, 1H), 7.55 - 7.62 (m, 2H), 7.46 - 7.53 (m, 3H), 6.62 (d, J = 7.22 Hz, 1H), 4.27 (m Hz, 1H), 3.95 (m, 2H), 3.13 (s, 3H), 2.63 (m, 2H), 2.38 (m, 2H), 1.65 - 1.77 (m, 4H). HRMS: *m/z* calc'd for C₁₇H₁₉N₂O₅S [M-H]⁺: 383.1076; found: 383.1076.

Preparation of (2*R*)-*N*-hydroxy-2-methyl-2-(methylsulfonyl)-4-(2-oxo-4-phenylpyrimidin-1(2*H*)-yl)butanamide (2g).



Ethyl (2R)-2-methyl-2-(methylsulfonyl)-4-(2-oxo-4-phenylpyrimidin-1(2H)-yl)butanoate (13g). Potassium carbonate (843 mg, 6.10 mmol) was added to a solution of 4-phenylpyrimidin-2(1H)-one⁵ (700 mg, 4.06 mmol) and ethyl (2R)-4-bromo-2-methyl-2-(methylsulfonyl)butanoate (12, 1.20 g, 4.18 mmol) in *N,N*-dimethylformamide (10.0 mL). The reaction mixture was stirred at rt for 5 days. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layers were combined, dried (MgSO_4), filtered, and concentrated *in vacuo*. The crude material was purified via flash chromatography using silica (80 g) and a gradient of ethyl acetate in *n*-heptane to afford the title compound as a yellow solid (586.6 mg, 37%). ^1H NMR (400 MHz, CDCl_3) δ 8.03 - 8.19 (m, 2H), 7.75 (d, J = 7.02 Hz, 1H), 7.42 - 7.60 (m, 3H), 6.82 (dd, J = 1.07, 6.93 Hz, 1H), 4.21 - 4.36 (m, 3H), 4.02 - 4.13 (m, 1H), 3.13 (s, 3H), 2.62 (t, J = 7.61 Hz, 2H), 1.77 (s, 3H), 1.34 (m, 3H).

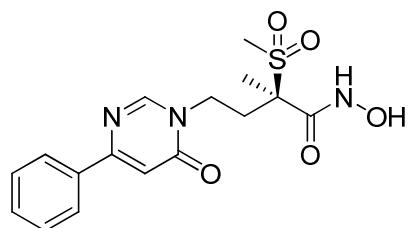
(2R)-2-Methyl-2-(methylsulfonyl)-4-(2-oxo-4-phenylpyrimidin-1(2H)-yl)butanoic acid. The title compound (536 mg, 100%) was obtained as a white solid from ethyl (2R)-2-methyl-2-(methylsulfonyl)-4-(2-oxo-4-phenylpyrimidin-1(2H)-yl)butanoate using a procedure analogous to that described in the General Saponification Procedure. LCMS: m/z 351.4 [M+H]⁺.

(2R)-2-Methyl-2-(methylsulfonyl)-4-(2-oxo-4-phenylpyrimidin-1(2H)-yl)-N-(tetrahydro-2H-pyran-2-yloxy)butanamide (14g). The title compound (565 mg, 84%) was obtained as a yellow oil from (2R)-2-methyl-2-(methylsulfonyl)-4-(2-oxo-4-phenylpyrimidin-1(2H)-yl)butanoic acid using a procedure analogous to that described in the General Amide Coupling, Method A. LCMS: m/z 448.6 [M-H]⁻.

(2R)-N-Hydroxy-2-methyl-2-(methylsulfonyl)-4-(2-oxo-4-phenylpyrimidin-1(2H)-yl)butanamide (2g). The title compound (196.2 mg, 65%) was obtained as a white solid from (2R)-2-methyl-2-(methylsulfonyl)-4-(2-oxo-4-phenylpyrimidin-1(2H)-yl)-N-(tetrahydro-2H-pyran-2-yloxy)butanamide (14g) using a procedure analogous to that described in the General Tetrahydropyranyl Deprotection, Method A. ^1H NMR (400 MHz, DMSO-d_6) δ 8.40 (d, J = 6.83 Hz, 1H), 8.07 - 8.15 (m, 2H), 7.58 - 7.65 (m, 1H), 7.51 - 7.59 (m, 2H), 7.17 (d, 1H), 4.00 - 4.14

(m, 1H), 3.74 - 3.89 (m, 1H), 3.11 (s, 3H), 2.52 - 2.62 (m, 1H), 2.14 - 2.28 (m, 1H), 1.61 (s, 3H).
HRMS: *m/z* calc'd for C₁₆H₁₉N₃O₅S [M+H]⁺: 366.118; found: 366.1128.

Preparation of (2*R*)-*N*-hydroxy-2-methyl-2-(methylsulfonyl)-4-(6-oxo-4-phenylpyrimidin-1(6*H*)-yl)butanamide (2h).



Ethyl (2*R*)-2-methyl-2-(methylsulfonyl)-4-(6-oxo-4-phenylpyrimidin-1(6*H*)-yl)butanoate (13h, R₄ = Ph). Potassium carbonate (201 mg, 1.45 mmol) was added to a suspension of 6-phenylpyrimidin-4(3*H*)-one (11h, R₄ = Ph, 100 mg, 0.58 mmol), ethyl (2*R*)-4-bromo-2-methyl-2-(methylsulfonyl)butanoate (184 mg, 0.64 mmol), and tetra-*n*-butylammonium bromide (19.1 mg, 0.058 mmol) in acetonitrile (10 mL). The suspension was heated to reflux and was stirred at this temperature for 4 h. The reaction mixture was allowed to cool to rt and then was filtered through a silica plug using dichloromethane as the eluent. The filtrate was concentrated and the crude material was purified via flash chromatography using silica and a gradient of 40-100% ethyl acetate in *n*-heptane to afford the title compound as a solid (150 mg, 68%). ¹H NMR (400 MHz, CDCl₃) δ 8.30 (s, 1H), 7.91 - 8.00 (m, 2H), 7.44 - 7.55 (m, 3H), 6.85 (s, 1H), 4.23 - 4.42 (m, 3H), 3.98 - 4.19 (m, 1H), 3.13 (s, 3H), 2.46 - 2.67 (m, 2H), 1.81 (s, 3H), 1.37 (t, 3H). LCMS: *m/z* 379.5 [M+H]⁺.

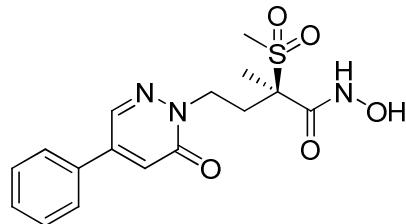
(2*R*)-2-Methyl-2-(methylsulfonyl)-4-(6-oxo-4-phenylpyrimidin-1(6*H*)-yl)butanoic acid. The title compound (130 mg, 94%) was obtained as a solid from ethyl (2*R*)-2-methyl-2-

(methylsulfonyl)-4-(6-oxo-4-phenylpyrimidin-1(6*H*)-yl)butanoate (**13h**, **R₄** = **Ph**) using a procedure analogous to that described in the General Saponification Procedure. ¹H NMR (400 MHz, DMSO-d₆) δ 8.57 (s, 1H), 7.99 - 8.11 (m, 2H), 7.42 - 7.56 (m, 3H), 6.96 (s, 1H), 4.03 - 4.18 (m, 1H), 3.90 - 4.03 (m, 1H), 3.15 (s, 3H), 2.43 - 2.48 (m, 0H), 2.13 - 2.27 (m, 1H), 1.55 (s, 3H). LCMS: m/z 351.2 [M+H]⁺.

(2*R*)-2-Methyl-2-(methylsulfonyl)-4-(6-oxo-4-phenylpyrimidin-1(6*H*)-yl)-N-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (14h). The title compound (110.9 mg, 86%) as a solid from (2*R*)-2-methyl-2-(methylsulfonyl)-4-(6-oxo-4-phenylpyrimidin-1(6*H*)-yl)butanoic acid using a procedure analogous to that described in the General Amide Coupling, Method B. LCMS: m/z 448.7 [M-H]⁻.

(2*R*)-N-Hydroxy-2-methyl-2-(methylsulfonyl)-4-(6-oxo-4-phenylpyrimidin-1(6*H*)-yl)butanamide (2h). The title compound (8 mg, 40%) was obtained as a solid from (2*R*)-2-methyl-2-(methylsulfonyl)-4-(6-oxo-4-phenylpyrimidin-1(6*H*)-yl)-N-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (**14h**) using a procedure analogous to that described in the General Tetrahydropyranyl Deprotection, Method A. ¹H NMR (400 MHz, DMSO-d₆) δ 11.02 (d, *J* = 1.76 Hz, 1H), 9.25 (d, *J* = 1.76 Hz, 1H), 8.54 (d, *J* = 0.78 Hz, 1H), 7.99 - 8.17 (m, 2H), 7.39 - 7.59 (m, 3H), 6.98 (s, 1H), 3.99 - 4.17 (m, 1H), 3.71 - 3.91 (m, 1H), 3.10 (s, 3H), 2.10 - 2.29 (m, 1H), 1.59 (s, 3H). HRMS (ESI) *m/z* calc'd for C₁₆H₁₉N₃O₅S [M+H]⁺: 366.1118; found: 366.1116.

Preparation of (2*R*)-N-hydroxy-2-methyl-2-(methylsulfonyl)-4-(6-oxo-4-phenylpyridazin-1(6*H*)-yl)butanamide (2i).



Ethyl (2*R*)-2-methyl-2-(methylsulfonyl)-4-(6-oxo-4-phenylpyridazin-1(6*H*)-yl)butanoate

(13i, R₄ = Ph). Potassium carbonate (482 mg, 3.49 mmol) was added to a suspension of 5-phenylpyridazin-3(2H)-one (200 mg, 1.16 mmol), ethyl (2*R*)-4-bromo-2-methyl-2-(methylsulfonyl)butanoate (367 mg, 1.28 mmol), and tetra-*n*-butylammonium bromide (38.2 mg, 0.12 mmol) in acetonitrile (9 mL). The suspension was heated to reflux and was stirred at this temperature for 2 h. The reaction mixture was allowed to cool to rt and filtered through silica using dichloromethane as the eluent. The filtrate was concentrated and the crude material was purified via flash chromatography using silica and a gradient of 40-100% ethyl acetate in *n*-heptane to afford the title compound as a solid (150 mg, 68%). LCMS: m/z 379.1 [M+H]⁺.

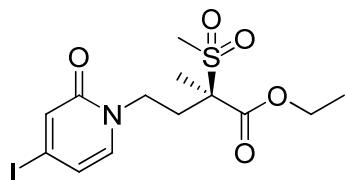
(2*R*)-2-Methyl-2-(methylsulfonyl)-4-(6-oxo-4-phenylpyridazin-1(6*H*)-yl)butanoic acid. The title compound (180 mg, 44%) was obtained as a solid from ethyl (2*R*)-2-methyl-2-(methylsulfonyl)-4-(6-oxo-4-phenylpyridazin-1(6*H*)-yl)butanoate using a procedure analogous to that described in the General Saponification Procedure. LCMS: m/z 351.0 [M+H]⁺.

(2*R*)-2-Methyl-2-(methylsulfonyl)-4-(6-oxo-4-phenylpyridazin-1(6*H*)-yl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (14i). The title compound (60 mg, 47%) was obtained as a solid from (2*R*)-2-methyl-2-(methylsulfonyl)-4-(6-oxo-4-phenylpyridazin-1(6*H*)-yl)butanoic acid using a procedure analogous to that described in the General Amide Coupling, Method B. LCMS: m/z 448.7 [M-H]⁻.

(2*R*)-*N*-Hydroxy-2-methyl-2-(methylsulfonyl)-4-(6-oxo-4-phenylpyridazin-1(6*H*)-yl)butanamide (2i). The title compound (36 mg, 74%) was obtained as a solid from (2*R*)-2-methyl-2-(methylsulfonyl)-4-(6-oxo-4-phenylpyridazin-1(6*H*)-yl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide using a procedure analogous to that described in the General Tetrahydropyranyl Deprotection, Method A. ¹H NMR (400 MHz, DMSO-d₆) δ 10.99 (s, 1H), 8.39 (d, *J* = 2.34 Hz, 1H), 7.77 - 7.92 (m, 2H), 7.45 - 7.60 (m, 3H), 7.22 (d, *J* = 2.15 Hz, 1H), 4.19 - 4.32 (m, 1H), 3.92 - 4.06 (m, 1H), 3.08 (s, 3H), 2.56 - 2.71 (m, 1H), 2.12 - 2.24 (m, 1H), 1.56 (s, 3H). HRMS: m/z calc'd for C₁₆H₁₉N₃O₅S [M+H]⁺: 366.1118; found: 366.1116.

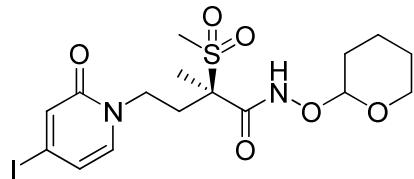
Synthesis of ethyl (2*R*)-4-(4-iodo-2-oxopyridin-1(2*H*)-yl)-2-methyl-2-

(methylsulfonyl)butanoate (13a, R₄ = I)



Ethyl (2R)-4-(4-iodo-2-oxopyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoate (13a, R₄ = I). A solution of ethyl (2R)-4-bromo-2-methyl-2-(methylsulfonyl)butanoate (43.8 g, 153 mmol) in tetrahydrofuran (360 mL) was added to a suspension of 4-iodopyridin-2-ol (**11a, R₄ = I**, 24.1 g, 109 mmol), cesium carbonate (39.5 g, 120 mmol), and tetra-*n*-butylammonium iodide (2.05 g, 10.9 mmol) in *t*-butanol (360 mL). The suspension was heated to 35 °C and was stirred at this temperature for 3 days. The reaction mixture was allowed to cool to rt and then was filtered through a medium fritted funnel. The filter cake was washed with ethyl acetate. The filtrates were washed with water (400 mL) and the aqueous layer was extracted with ethyl acetate (3x400 mL). The organic layers were combined, dried (Na₂SO₄), filtered, and concentrated *in vacuo*. The crude material was purified via flash chromatography using a Biotage SNAP Cartridge (KP-Sil 340g) and a gradient of 30-100% ethyl acetate in *n*-heptane to afford the title compound as a yellow solid (36.0 g, 77%). ¹H NMR (400 MHz, CDCl₃) δ 7.06 (d, *J* = 1.76 Hz, 1H), 6.98 (d, *J* = 7.22 Hz, 1H), 6.50 (dd, *J* = 1.85, 7.12 Hz, 1H), 4.26 (q, *J* = 7.02 Hz, 2H), 4.13 - 4.22 (m, 1H), 3.87 - 3.97 (m, 1H), 3.09 (s, 3H), 2.34 - 2.57 (m, 2H), 1.73 (s, 3H), 1.32 (t, 3H). LCMS: m/z 428.0 [M+H]⁺.

Synthesis of (2R)-4-(4-iodo-2-oxopyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)-N-(tetrahydro-2H-pyran-2-yloxy)butanamide (15).

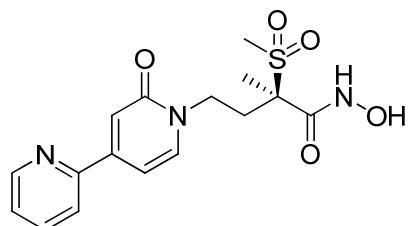


(2R)-4-(4-Iodo-2-oxopyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoic acid. The title compound (40.75 g, 87%) was obtained as a white solid from ethyl (2R)-4-(4-iodo-2-oxopyridin-

1(2*H*)-yl)-2-methyl-2-(methylsulfonyl)butanoate (**13a**, **R**₄ = **I**) using a procedure analogous to that described in the General Saponification Procedure. ¹H NMR (400 MHz, DMSO-d₆) δ 7.46 (d, *J* = 7.02 Hz, 1H), 6.92 (d, *J* = 1.76 Hz, 1H), 6.59 (dd, *J* = 1.85, 7.12 Hz, 1H), 3.94 - 4.05 (m, 1H), 3.79 - 3.92 (m, 1H), 3.14 (s, 3H), 2.34 - 2.47 (m, 1H), 2.05 - 2.21 (m, 1H), 1.54 (s, 3H). LCMS: m/z 399.9 [M+H]⁺.

(2*R*)-4-(4-Iodo-2-oxopyridin-1(2*H*)-yl)-2-methyl-2-(methylsulfonyl)-N-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (15). The title compound (34.6 g, 53%) was obtained as a white solid from (2*R*)-4-(4-iodo-2-oxopyridin-1(2*H*)-yl)-2-methyl-2-(methylsulfonyl)butanoic acid using a procedure analogous to that described in the General Amide Coupling, Method B. LCMS: m/z 448.1 [M-H]⁻.

Preparation of (2*R*)-N-hydroxy-2-methyl-2-(methylsulfonyl)-4-(2'-oxo-2,4'-bipyridin-1'(2*H*)-yl)butanamide-hydrochloride (17a).



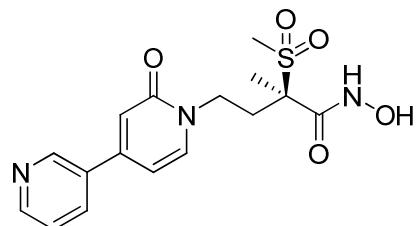
Ethyl (2*R*)-2-methyl-2-(methylsulfonyl)-4-(2'-oxo-2,4'-bipyridin-1'(2*H*)-yl)butanoate. 2-Pyridylzinc bromide (0.5 M in THF, 1.60 mL, 0.80 mmol) was added to a solution of ethyl (2*R*)-4-(4-iodo-2-oxopyridin-1(2*H*)-yl)-2-methyl-2-(methylsulfonyl)butanoate (**15**, 309 mg, 0.72 mmol) and Pd(PPh₃)₄ (76.4 mg, 0.066 mmol) in tetrahydrofuran (2 mL) under N₂. The reaction was stirred at rt for 1 h. The reaction mixture was quenched with saturated aq NH₄Cl and extracted with ethyl acetate. The organic layers were combined, dried (MgSO₄), filtered, and concentrated. The crude material was purified via flash chromatography using silica (40 g) and a gradient of 0-100% ethyl acetate in *n*-heptane followed by a gradient of 0-30% methanol in ethyl acetate to afford the title compound as a solid (83 mg, 33%). LCMS: m/z 379.1 [M+H]⁺.

(2*R*)-2-Methyl-2-(methylsulfonyl)-4-(2'-oxo-2,4'-bipyridin-1'(2'H)-yl)butanoic acid. The title compound (43 mg, 55%) was obtained as a solid from ethyl (+)-(2*R*)-2-methyl-2-(methylsulfonyl)-4-(2'-oxo-2,4'-bipyridin-1'(2'H)-yl)butanoate using a procedure analogous to that described in the General Saponification Procedure, Method A. LCMS: m/z 351.1 [M+H]⁺.

(2*R*)-2-Methyl-2-(methylsulfonyl)-4-(2'-oxo-2,4'-bipyridin-1'(2'H)-yl)-N-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (16a). The title compound (223 mg, 40%) was obtained as a yellow solid from (2*R*)-2-methyl-2-(methylsulfonyl)-4-(2'-oxo-2,4'-bipyridin-1'(2'H)-yl)butanoic acid using a procedure analogous to that described in the General Amide Coupling, Method B. LCMS: m/z 448.1 [M-H]⁻.

(2*R*)-N-Hydroxy-2-methyl-2-(methylsulfonyl)-4-(2'-oxo-2,4'-bipyridin-1'(2'H)-yl)butanamide-hydrochloride (17a). The title compound (150 mg, 72%) was obtained as a yellow solid from (2*R*)-2-methyl-2-(methylsulfonyl)-4-(2'-oxo-2,4'-bipyridin-1'(2'H)-yl)-N-(tetrahydro-2*H*-pyran-2-yloxy)butanamide using a procedure analogous to that described in the General Tetrahydropyranyl Deprotection, Method A. ¹H NMR (400 MHz, CD₃OD) δ 8.99 (dd, *J* = 0.98, 5.85 Hz, 1H), 8.78 (m, 1H), 8.47 (d, *J* = 8.20 Hz, 1H), 8.21 (m, 1H), 8.06 (d, *J* = 7.22 Hz, 1H), 7.19 (d, *J* = 1.95 Hz, 1H), 6.99 (m, 1H), 4.30 - 4.43 (m, 1H), 4.03 - 4.15 (m, 1H), 3.10 (s, 3H), 2.63 - 2.77 (m, 1H), 2.31 - 2.47 (m, 1H), 1.73 (s, 3H). HRMS: m/z calc'd for C₁₆H₁₉N₃O₅S [M+H]⁺: 366.1118; found: 366.1122.

Preparation of (2*R*)-N-hydroxy-2-methyl-2-(methylsulfonyl)-4-(2'-oxo-3,4'-bipyridin-1'(2'H)-yl)butanamide-hydrochloride (17b).

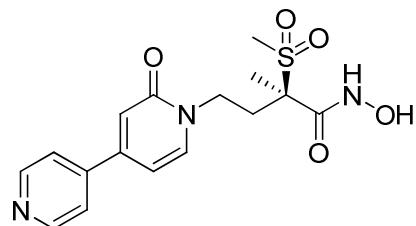


(2*R*)-2-Methyl-2-(methylsulfonyl)-4-(2'-oxo-3,4'-bipyridin-1'(2'H)-yl)-N-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (16b). The title compound (277 mg) was obtained as a yellow solid

from **(2R)-4-(4-iodo-2-oxopyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)-N-(tetrahydro-2H-pyran-2-yloxy)butanamide (15)** and 3-pyridinylboronic acid using a procedure analogous to that described in the General Suzuki-Miyaura Coupling, Method A. The title compound was used without further purification. LCMS: m/z 448.1 [M-H]⁻.

(2R)-N-Hydroxy-2-methyl-2-(methylsulfonyl)-4-(2'-oxo-3,4'-bipyridin-1'(2'H)-yl)butanamide-hydrochloride (17b). The title compound (200 mg, 81%) was obtained as a yellow solid from **(2R)-2-methyl-2-(methylsulfonyl)-4-(2'-oxo-3,4'-bipyridin-1'(2'H)-yl)-N-(tetrahydro-2H-pyran-2-yloxy)butanamide (16b)** using a procedure analogous to that described in the General Tetrahydropyranyl Deprotection, Method A. ¹H NMR (400 MHz, CD₃OD) δ 8.91 (d, *J* = 1.56 Hz, 1H), 8.67 (dd, *J* = 1.56, 4.88 Hz, 1H), 8.25 (dt, *J* = 1.80, 8.29 Hz, 1H), 7.80 (d, *J* = 7.02 Hz, 1H), 7.59 - 7.69 (m, 1H), 6.87 (d, *J* = 1.95 Hz, 1H), 6.79 (dd, *J* = 1.95, 7.02 Hz, 1H), 4.26 - 4.38 (m, 1H), 3.92 - 4.04 (m, 1H), 3.12 (s, 3H), 2.56 - 2.69 (m, 1H), 2.31 - 2.45 (m, 1H), 1.72 (s, 3H). HRMS: *m/z* calc'd for C₁₆H₁₉N₃O₅S [M+H]⁺: 366.1118; found: 366.1116.

Preparation of (2R)-N-hydroxy-2-methyl-2-(methylsulfonyl)-4-(2-oxo-4,4'-bipyridin-1(2H)-yl)butanamide-hydrochloride (17c).

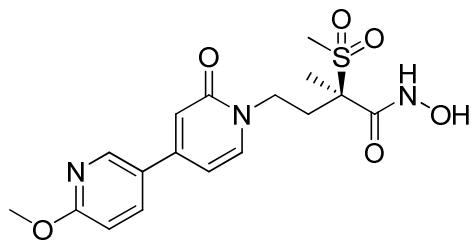


(2R)-2-Methyl-2-(methylsulfonyl)-4-(2-oxo-4,4'-bipyridin-1(2H)-yl)-N-(tetrahydro-2H-pyran-2-yloxy)butanamide (16c). The title compound (277 mg) was obtained as a yellow solid from **(2R)-4-(4-iodo-2-oxopyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)-N-(tetrahydro-2H-pyran-2-yloxy)butanamide (15)** and 4-pyridinylboronic acid using a procedure analogous to that described in the General Suzuki-Miyaura Coupling, Method A. The title compound was used without further purification. LCMS: m/z 448.1 [M-H]⁻.

(2R)-N-Hydroxy-2-methyl-2-(methylsulfonyl)-4-(2-oxo-4,4'-bipyridin-1(2H)-yl)butanamide-

hydrochloride (17c). The title compound (201 mg, 64%) was obtained as a yellow solid from (2*R*)-2-methyl-2-(methylsulfonyl)-4-(2-oxo-4,4'-bipyridin-1(2*H*)-yl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (**16c**) using a procedure analogous to that described in General Tetrahydropyranyl Deprotection, Method A. ^1H NMR (400 MHz, CD₃OD) δ 8.63 - 8.71 (m, 2H), 7.79 - 7.83 (m, 1H), 7.69 - 7.79 (m, 2H), 6.92 (d, J = 1.66 Hz, 1H), 6.80 (dd, J = 2.10, 7.08 Hz, 1H), 4.32 (m, 1H), 3.98 (m, Hz, 1H), 3.12 (s, 3H), 2.62 (m, 1H), 2.39 (m, 1H), 1.72 (s, 3H). HRMS: *m/z* calc'd for C₁₆H₁₉N₃O₅S [M+H]⁺: 366.1118; found: 366.1121.

Preparation of (2*R*)-*N*-hydroxy-4-(6-methoxy-2'-oxo-3,4'-bipyridin-1'(2'H)-yl)-2-methyl-2-(methylsulfonyl)butanamide (17d).

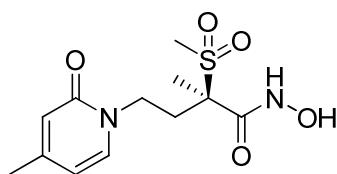


(2*R*)-4-(6-Methoxy-2'-oxo-3,4'-bipyridin-1'(2'H)-yl)-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (16d). The title compound (240.6 mg, 100%) was obtained as a yellow solid from (2*R*)-4-(4-iodo-2-oxopyridin-1(2*H*)-yl)-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (**15**) and 6-methoxy-3-pyridinylboronic acid using a procedure analogous to that described in the General Suzuki-Miyaura Coupling, Method A. LCMS: *m/z* 478.5 [M-H]⁻.

(2*R*)-*N*-Hydroxy-4-(6-methoxy-2'-oxo-3,4'-bipyridin-1'(2'H)-yl)-2-methyl-2-(methylsulfonyl)butanamide (17d). The title compound (50 mg, 25%) was obtained as a solid from (2*R*)-2-methyl-2-(methylsulfonyl)-4-(2-oxo-4,4'-bipyridin-1(2*H*)-yl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (**16f**) using a procedure analogous to that described in General Tetrahydropyranyl Deprotection, Method A. ^1H NMR (400 MHz, CD₃OD) δ 8.49 (d, J = 2.54 Hz, 1H), 8.09 (s, 1H), 8.00 (dd, J = 2.63, 8.68 Hz, 1H), 7.72 (d, J = 7.02 Hz, 1H), 6.90 (d, J =

8.78 Hz, 1H), 6.78 (d, J = 1.95 Hz, 1H), 6.75 (dd, J = 1.95, 7.02 Hz, 1H), 4.22 - 4.35 (m, 1H), 3.87 - 4.01 (m, 4H), 3.12 (s, 3H), 2.53 - 2.64 (m, 1H), 2.30 - 2.43 (m, 1H), 1.71 (s, 3H). HRMS: m/z calc'd for $C_{17}H_{21}N_3O_6S$ [M+H]⁺: 396.1231; found: 396.1224.

Preparation of (2*R*)-*N*-hydroxy-2-methyl-4-(4-methyl-2-oxopyridin-1(2*H*)-yl)-2-(methylsulfonyl)butanamide (17e).

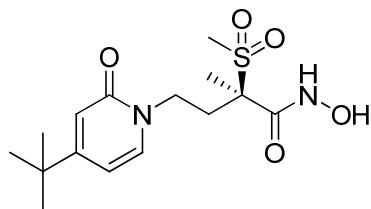


(2*R*)-2-Methyl-4-(4-methyl-2-oxopyridin-1(2*H*)-yl)-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (16e). Tetrakis(triphenylphosphine)palladium(0) (70.0 mg, 0.06 mmol) was added to a mixture of (2*R*)-4-(4-iodo-2-oxopyridin-1(2*H*)-yl)-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (**15**, 300 mg, 0.60 mmol), trimethylboroxin (79.3 mg, 0.63 mmol), and K_2CO_3 (250 mg, 1.81 mmol) in 1,4-dioxane (10 mL) and water (1 mL) under N_2 . The suspension was heated to 100 °C and was stirred at this temperature for 48 h. The reaction mixture was allowed to cool to rt and concentrated *in vacuo*. The crude material was purified via flash chromatography on silica and a gradient of 0-20% methanol in ethyl acetate to afford the title compound as a solid (233 mg, 61%). LCMS: m/z 385.1 [M-H]⁻.

(2*R*)-*N*-Hydroxy-2-methyl-4-(4-methyl-2-oxopyridin-1(2*H*)-yl)-2-(methylsulfonyl)butanamide (17e). The title compound (47 mg, 43%) was obtained as a solid from (2*R*)-2-methyl-4-(4-methyl-2-oxopyridin-1(2*H*)-yl)-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-

pyran-2-yloxy)butanamide (**16e**) using a procedure analogous to that described in the General Tetrahydropyranyl Deprotection, Method A. ^1H NMR (400 MHz, DMSO- d_6) δ 11.17 (br. s., 1H), 9.23 (s, 1H), 7.54 (d, J = 7.03 Hz, 1H), 6.22 (s, 1H), 6.13 (dd, J = 1.85, 6.93 Hz, 1H), 3.97 - 4.12 (m, 1H), 3.58 - 3.72 (m, 1H), 3.09 (s, 3H), 2.25 - 2.40 (m, 1H), 2.04 - 2.17 (m, 4H), 1.54 (s, 3H). HRMS: m/z calc'd for $\text{C}_{17}\text{H}_{21}\text{N}_3\text{O}_6\text{S} [\text{M}+\text{H}]^+$: 303.1014; found: 303.1014.

Preparation of (2*R*)-4-(4-*tert*-butyl-2-oxopyridin-1(2*H*)-yl)-2-methyl-2-(methylsulfonyl)butanamide (19).



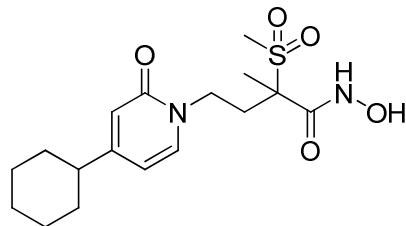
(2*R*)-4-(4-*tert*-Butyl-2-oxopyridin-1(2*H*)-yl)-2-methyl-2-(methylsulfonyl).⁶ A neat mixture of ethyl (2*R*)-4-bromo-2-methyl-2-(methylsulfonyl)butanoate (287 mg, 1.0 mmol) and 4-*tert*-butylpyridine (135 mg, 1.0 mmol) was heated to 100 °C and stirred at this temperature for 1 h. Potassium ferricyanide (III) (692 mg, 2.0 mmol) and aq 1 N NaOH (4 mL, 4 mmol) were added to the reaction and the mixture was stirred at 100 °C for 10 min. The reaction mixture was allowed to cool to rt and concentrated *in vacuo*. The crude material was purified using preparative HPLC to afford the title compound as a white solid (329 mg, 18%). ^1H NMR (400 MHz, CD_3OD) δ 7.53 (d, J = 7.22 Hz, 1H), 6.52 (dd, J = 2.05, 7.12 Hz, 1H), 6.47 (d, J = 2.15 Hz, 1H), 4.26 (m, 1H), 4.00 (m, 1H), 3.16 (s, 3H), 2.52 (m, 1H), 2.35 (m, 1H), 1.70 (s, 3H), 1.26 (s, 9H). LCMS: m/z 330.1 $[\text{M}+\text{H}]^+$.

(2*R*)-4-(4-*tert*-Butyl-2-oxopyridin-1(2*H*)-yl)-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-

pyran-2-yloxy)butanamide. The title compound (88 mg, 100%) was obtained as a solid from (2*R*)-4-(4-*tert*-butyl-2-oxopyridin-1(2*H*)-yl)-2-methyl-2-(methylsulfonyl)butanoic acid using a procedure analogous to that described in the General Amide Coupling, Method B. LCMS: m/z 429.1 [M+H]⁺.

(2*R*)-4-(4-*tert*-Butyl-2-oxopyridin-1(2*H*)-yl)-*N*-hydroxy-2-methyl-2-(methylsulfonyl)butanamide (19). Trifluoroacetic acid (1 mL) was added to a solution of (2*R*)-4-(4-*tert*-butyl-2-oxopyridin-1(2*H*)-yl)-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (88.3 mg, 0.21 mmol) in dimethylsulfoxide (2 mL). The reaction mixture was stirred at rt for 2 h. The reaction mixture was concentrated *in vacuo*. The crude material was purified via preparative HPLC to afford the title compound as a white solid (13.9 mg, 20%). ¹H NMR (400 MHz, DMSO-d₆) δ 11.18 (s, 1H), 8.13 (s, 1H), 7.56 (d, *J* = 7.22 Hz, 1H), 6.38 (dd, *J* = 2.15, 7.22 Hz, 1H), 6.27 (d, *J* = 1.95 Hz, 1H), 4.05 (m, 1H), 3.66 (m, 1H), 3.08 (s, 3H), 2.28 - 2.43 (m, 1H), 2.04 - 2.17 (m, 1H), 1.54 (s, 3H), 1.17 (s, 9H). HRMS: m/z calc'd for C₁₅H₂₄N₂O₆S [M+H]⁺: 345.1; found: 345.1.

Preparation of 4-(4-cyclohexyl-2-oxopyridin-1(2*H*)-yl)-*N*-hydroxy-2-methyl-2-(methylsulfonyl)butanamide (17f).



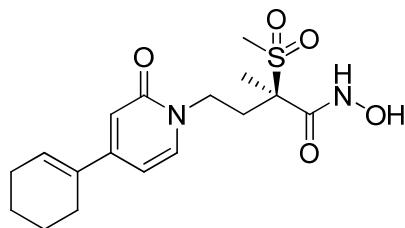
4-(4-Cyclohexyl-2-oxopyridin-1(2*H*)-yl)-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (16f). Cyclohexylmagnesium bromide (1 M in THF, 1.56 mL, 1.56 mmol) was added to a suspension of copper(I) bromide-dimethyl sulfide complex (160 mg, 0.78 mmol) in tetrahydrofuran (6 mL) at -78 °C under N₂. The mixture was warmed to rt, stirred for 15 minutes, and then cooled to -78 °C. (2*R*)-4-(4-Iodo-2-oxopyridin-1(2*H*)-yl)-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (**15**, 249 mg, 0.5 mmol) in tetrahydrofuran (6.5 mL) was added and the reaction mixture was stirred for 2 h at -78 °C. The

reaction mixture was allowed to warm to rt and then was quenched with saturated aq NH₄Cl (6 mL) and diluted with water (60 mL). The aqueous layer was extracted with ethyl acetate (2x60 mL). The organic layers were combined, washed with water (100 mL) and brine (100 mL), dried (Na₂SO₄), filtered, and concentrated *in vacuo*. The crude material was purified on silica using a gradient of 0-100% ethyl acetate in *n*-heptane to afford the title compound as a clear oil (220 mg), containing **15**. LCMS: m/z 453.9 [M-H]⁻. The title compound was used without further purification.

4-(4-Cyclohexyl-2-oxopyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-

(methylsulfonyl)butanamide (17f). The title compound (105 mg, 59%) was obtained as a white solid from 4-(4-cyclohexyl-2-oxopyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (**16f**) using a procedure analogous to that described in the General Tetrahydropyranyl Deprotection, Method A. ¹H NMR (400 MHz, CD₃OD) δ 7.49 - 7.59 (m, 1H), 6.39 (s, 1H), 6.36 - 6.38 (m, 1H), 4.16 - 4.31 (m, 1H), 3.79 - 3.91 (m, 1H), 3.10 (s, 3H), 2.37 - 2.56 (m, 2H), 2.26 - 2.37 (m, 1H), 1.79 - 1.93 (m, 4H), 1.71 - 1.79 (m, 1H), 1.68 (s, 3H), 1.34 - 1.50 (m, 4H), 1.20 - 1.34 (m, 1H). HRMS: *m/z* calc'd for C₁₇H₂₆N₂O₅S [M+H]⁺: 371.1635; found: 371.1634.

Preparation of (2*R*)-4-(4-cyclohex-1-en-1-yl-2-oxopyridin-1(2*H*)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide (17g).

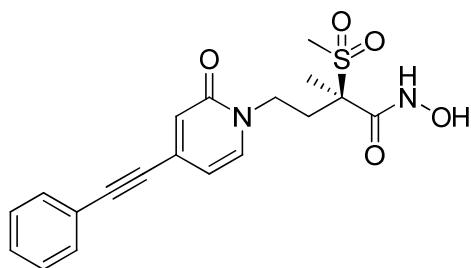


4-(4-Cyclohexyl-2-oxopyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (16g). SiliaCat[®] DPP-Pd (146 mg, 0.038 mmol, 0.27 mmol/g) was added to a suspension of (2*R*)-4-(4-iodo-2-oxopyridin-1(2*H*)-yl)-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (**15**, 250 mg, 0.50 mmol), 1-cyclohexenylboronic acid (95 mg, 0.75 mmol), and K₂CO₃ (140 mg, 1.0 mmol) in ethanol:water (9:1, 5 mL). The reaction

mixture was heated to 70 °C and stirred at this temperature for 1 h. The reaction mixture was allowed to cool to rt and filtered to remove the solids. The filter pad was washed with ethanol and the combined filtrates were concentrated *in vacuo*. The crude material was purified via flash chromatography using a SiliaSep™ 12g cartridge and a gradient of 20-100% ethyl acetate in hexanes to afford the title compound as a white solid (110 mg, 48%). LCMS: m/z 451.2 [M-H]⁻.

(2R)-4-(4-Cyclohex-1-en-1-yl-2-oxopyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide (17g). The title compound (50 mg, 56%) was obtained as a white solid from 4-(4-cyclohexyl-2-oxopyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)-N-(tetrahydro-2H-pyran-2-yloxy)butanamide (**16g**) using a procedure analogous to that described in the General Tetrahydropyranyl Deprotection, Method B. ¹H NMR (400 MHz, DMSO-d₆) δ 11.17 (br. s., 1H), 9.23 (br. s., 1H), 7.55 (d, *J* = 7.23 Hz, 1H), 6.39 - 6.52 (m, 2H), 6.29 (d, *J* = 1.95 Hz, 1H), 3.95 - 4.11 (m, 1H), 3.60 - 3.74 (m, 1H), 3.02 - 3.19 (m, 3H), 2.29 - 2.43 (m, 1H), 2.05 - 2.29 (m, 5H), 1.63 - 1.77 (m, 2H), 1.47 - 1.62 (m, 5H). HRMS: *m/z* calc'd for C₁₇H₂₄N₂O₅S [M+H]⁺: 369.1479; found: 369.1479.

Preparation of (2R)-2-methyl-2-(methylsulfonyl)-4-[2-oxo-4-(phenylethynyl)pyridin-1(2H)-yl]-N-(tetrahydro-2H-pyran-2-yloxy)butanamide (16h).

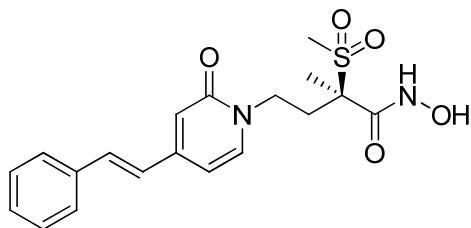


(2R)-2-Methyl-2-(methylsulfonyl)-4-[2-oxo-4-(phenylethynyl)pyridin-1(2H)-yl]-N-(tetrahydro-2H-pyran-2-yloxy)butanamide (16h). Copper iodide (9.70 mg, 10 mol%) and tetrakis(triphenylphosphine)palladium(0) (29.2 mg, 0.025 mmol) were added sequentially to a degassed solution of (2R)-4-(4-iodo-2-oxopyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)-N-

(tetrahydro-2*H*-pyran-2-yloxy)butanamide (**15**, 250 mg, 0.50 mmol), phenylacetylene (61.5 mg, 0.60 mmol) and diisopropylethylamine (3 mL) in tetrahydrofuran (5 mL). The reaction mixture was stirred at rt for 3 h. The reaction mixture was diluted with ethyl acetate (200 mL) and was washed with saturated aq NH₄Cl (100 mL) and brine. The organic layer was dried (Na₂SO₄), filtered, and concentrated *in vacuo*. The crude material was purified via flash chromatography using silica and a gradient of 50-100% ethyl acetate in hexanes to afford the title compound as a solid (197 mg, 83%). LCMS: m/z 471.4 [M-H]⁻.

(2*R*)-*N*-Hydroxy-2-methyl-2-(methylsulfonyl)-4-[2-oxo-4-(phenylethynyl)pyridin-1(2*H*)-yl]butanamide (17h**).** The title compound (142 mg, 88%) was obtained as an off-white solid from (2*R*)-2-methyl-2-(methylsulfonyl)-4-[2-oxo-4-(phenylethynyl)pyridin-1(2*H*)-yl]-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (**16h**) using a procedure analogous to that described in the General Tetrahydropyranyl Deprotection, Method A. ¹H NMR (400 MHz, DMSO-d₆) δ 11.08 (br. s., 1H), 9.20 (br. s., 1H), 7.72 (d, *J* = 7.02 Hz, 1H), 7.53 - 7.65 (m, 2H), 7.37 - 7.53 (m, 3H), 6.59 (d, *J* = 1.56 Hz, 1H), 6.38 (d, *J* = 7.03 Hz, 1H), 3.99 - 4.17 (m, 1H), 3.64 - 3.82 (m, 1H), 3.10 (s, 3H), 2.33 - 2.48 (m, 1H), 2.02 - 2.22 (m, 1H), 1.56 (s, 3H). HRMS: m/z calc'd for C₁₉H₂₀N₂O₅S [M+H]⁺: 389.1171; found: 389.1166.

Preparation of (2*R*)-*N*-hydroxy-2-methyl-2-(methylsulfonyl)-4-[2-oxo-4-[(*E*)-2-phenylvinyl]pyridin-1(2*H*)-yl]butanamide (17i**).**

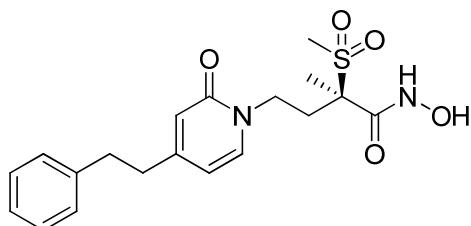


(2*R*)-2-Methyl-2-(methylsulfonyl)-4-{2-oxo-4-[(*E*)-2-phenylvinyl]pyridin-1(2*H*)-yl}-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (16i**).** The title compound (136 mg, 36%) was obtained as a clear residue from (2*R*)-4-(4-iodo-2-oxopyridin-1(2*H*)-yl)-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (**15**) and *trans*-2-

phenylvinylboronic acid using a procedure analogous to that described in the General Suzuki-Miyaura Coupling, Method A. LCMS: m/z 473.6 [M-H]⁻.

(2R)-N-Hydroxy-2-methyl-2-(methylsulfonyl)-4-{2-oxo-4-[(E)-2-phenylvinyl]pyridin-1(2H)-yl}butanamide (17i). The title compound (29.7 mg, 27%) was obtained as a solid from (2R)-2-methyl-2-(methylsulfonyl)-4-{2-oxo-4-[(E)-2-phenylvinyl]pyridin-1(2H)-yl}-N-(tetrahydro-2H-pyran-2-yloxy)butanamide (**16i**) using a method similar to that described in General Tetrahydropyranyl Deprotection, Method A. ¹H NMR (400 MHz, DMSO-d₆) δ 11.18 (br. s., 1H), 8.85 - 9.54 (m, 1H), 7.60 - 7.69 (m, 3H), 7.38 - 7.47 (m, 3H), 7.30 - 7.37 (m, 1H), 7.12 (d, *J* = 16.43 Hz, 1H), 6.68 (dd, *J* = 1.76, 7.24 Hz, 1H), 6.50 (d, *J* = 1.76 Hz, 1H), 3.98 - 4.13 (m, 1H), 3.63 - 3.78 (m, 1H), 3.08 (s, 3H), 2.34 - 2.46 (m, 1H), 2.06 - 2.22 (m, 1H), 1.51 - 1.61 (m, 3H). HRMS: *m/z* calc'd for C₁₉H₂₂N₂O₅S [M+H]⁺: 391.1322; found: 391.1324.

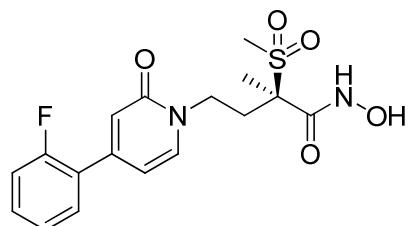
Preparation of (2R)-N-hydroxy-2-methyl-2-(methylsulfonyl)-4-{2-oxo-4-(2-phenylethyl)pyridin-1(2H)-yl}butanamide (20).



(2R)-2-Methyl-2-(methylsulfonyl)-4-{2-oxo-4-(2-phenylethyl)pyridin-1(2H)-yl}-N-(tetrahydro-2H-pyran-2-yloxy)butanamide (16h). Palladium on carbon (10 wt%, 20 mg) was added to a solution of (2R)-2-methyl-2-(methylsulfonyl)-4-{2-oxo-4-[(E)-2-phenylvinyl]pyridin-1(2H)-yl}-N-(tetrahydro-2H-pyran-2-yloxy)butanamide (**15**, 65 mg, 0.14 mmol) and 1,4-cyclohexadiene (0.3 mL, 3 mmol) in ethanol (25 mL). The reaction mixture was stirred at rt overnight. The suspension was filtered through a mixture of celite and silica, and the filter pad was washed with ethyl acetate. The filtrate was concentrated *in vacuo*. The crude material was resubmitted to the previous conditions and stirred for 4 h at rt. The reaction mixture was filtered, and the filtrate was concentrated *in vacuo* to afford the title compound as a clear residue (65 mg, 100%). LCMS: m/z 475.7 [M-H]⁻.

(2R)-N-hydroxy-2-methyl-2-(methylsulfonyl)-4-[2-oxo-4-(2-phenylethyl)pyridin-1(2H)-yl]butanamide (20). The title compound (25.9 mg, 49%) was obtained as a solid from (2R)-2-methyl-2-(methylsulfonyl)-4-[2-oxo-4-(2-phenylethyl)pyridin-1(2H)-yl]-N-(tetrahydro-2H-pyran-2-yloxy)butanamide (**16h**) using a method similar to that described in General Tetrahydropyranyl Deprotection, Method A. ^1H NMR (400 MHz, DMSO-d₆) δ 11.14 (br. s., 1H), 9.24 (br. s., 1H), 7.52 - 7.60 (m, 1H), 7.21 - 7.31 (m, 4H), 7.12 - 7.21 (m, 1H), 6.19 - 6.29 (m, 2H), 3.95 - 4.10 (m, 1H), 3.58 - 3.74 (m, 1H), 3.08 (s, 3H), 2.79 - 2.90 (m, 2H), 2.66 - 2.75 (m, 2H), 2.27 - 2.41 (m, 1H), 2.05 - 2.17 (m, 1H), 1.55 (s, 3H). HRMS: *m/z* calc'd for C₁₉H₂₄N₂O₅S [M+H]⁺: 393.1479; found: 393.148.

Preparation of (2R)-4-[4-(2-fluorophenyl)-2-oxopyridin-1(2H)-yl]-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide (17j).

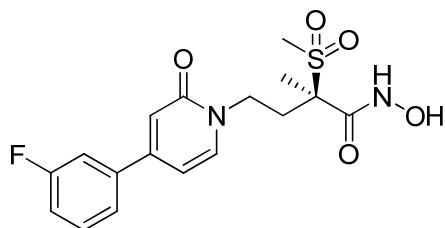


(2R)-4-[4-(2-Fluorophenyl)-2-oxopyridin-1(2H)-yl]-2-methyl-2-(methylsulfonyl)-N-(tetrahydro-2H-pyran-2-yloxy)butanamide (16j). The title compound (180 mg, 64%) was obtained as a colorless oil from (2R)-4-(4-iodo-2-oxopyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)-N-(tetrahydro-2H-pyran-2-yloxy)butanamide (**15**) and 2-fluorophenylboronic acid using a procedure analogous to that described in the General Suzuki-Miyaura Coupling. LCMS: *m/z* 465.7 [M-H]⁻.

(2R)-4-[4-(2-Fluorophenyl)-2-oxopyridin-1(2H)-yl]-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide (17j). The title compound (71 mg, 48%) was obtained as an off-white solid from (2R)-4-[4-(2-fluorophenyl)-2-oxopyridin-1(2H)-yl]-2-methyl-2-(methylsulfonyl)-N-(tetrahydro-2H-pyran-2-yloxy)butanamide (**16j**) using a procedure

analogous to that described in the General Tetrahydropyranyl Deprotection, Method A. ^1H NMR (400 MHz, DMSO-d₆) δ 11.13 (br. s., 1H), 9.25 (br. s., 1H), 7.76 (d, J = 7.02 Hz, 1H), 7.59 (td, J = 1.56, 7.90 Hz, 1H), 7.46 - 7.55 (m, 1H), 7.33 (none, 0H), 7.29 - 7.38 (m, 2H), 4.07 - 4.18 (m, 1H), 3.69 - 3.81 (m, 1H), 3.11 (s, 3H), 2.39 - 2.48 (m, 1H), 2.12 - 2.24 (m, 1H), 1.58 (s, 3H). HRMS (ESI) m/z calc'd for C₁₇H₁₉N₂O₅S [M+H]⁺: 383.1071; found: 383.1071.

Preparation of (2*R*)-4-[4-(3-fluorophenyl)-2-oxopyridin-1(2*H*)-yl]-*N*-hydroxy-2-methyl-2-(methylsulfonyl)butanamide (17k).

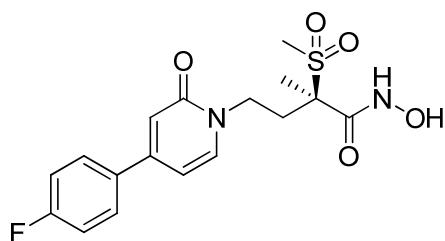


(2*R*)-4-[4-(3-Fluorophenyl)-2-oxopyridin-1(2*H*)-yl]-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (16k). The title compound (125 mg, 45%) was obtained as a colorless oil from (2*R*)-4-(4-iodo-2-oxopyridin-1(2*H*)-yl)-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (**15**) and 3-fluorophenylboronic acid using a procedure analogous to that described in the General Suzuki-Miyaura Coupling, Method A. LCMS: m/z 465.7 [M-H]⁻.

(2*R*)-4-[4-(3-Fluorophenyl)-2-oxopyridin-1(2*H*)-yl]-*N*-hydroxy-2-methyl-2-(methylsulfonyl)butanamide (17k). The title compound (55 mg, 54%) was obtained as an off-white solid from (2*R*)-4-[4-(3-fluorophenyl)-2-oxopyridin-1(2*H*)-yl]-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (**16k**) using a procedure

analogous to that described in the General Tetrahydropyranyl Deprotection, Method A. ^1H NMR (400 MHz, DMSO- d_6) δ 11.14 (d, J = 1.56 Hz, 1H), 9.24 (d, J = 1.56 Hz, 1H), 7.77 (d, J = 7.42 Hz, 1H), 7.49 - 7.63 (m, 3H), 7.26 - 7.35 (m, 1H), 6.77 (d, J = 1.95 Hz, 1H), 6.68 (dd, J = 1.95, 7.02 Hz, 1H), 4.07 - 4.17 (m, 1H), 3.76 (m, 1H), 3.11 (s, 3H), 2.37 - 2.48 (m, 1H), 2.17 (m, 1H), 1.58 (s, 3H). HRMS: m/z calc'd for $\text{C}_{17}\text{H}_{19}\text{N}_2\text{O}_5\text{S}$ [M+H] $^+$: 383.1071; found: 383.1055.

Preparation of (2*R*)-4-[4-(4-fluorophenyl)-2-oxopyridin-1(2*H*)-yl]-*N*-hydroxy-2-methyl-2-(methylsulfonyl)butanamide (17l).

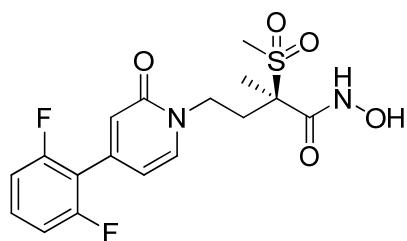


(2*R*)-4-[4-(4-Fluorophenyl)-2-oxopyridin-1(2*H*)-yl]-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (16l). The title compound (159 mg, 68%) was obtained as a solid from (2*R*)-4-(4-iodo-2-oxopyridin-1(2*H*)-yl)-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (**15**) and 4-fluorophenylboronic acid using a procedure analogous to that described in the General Suzuki-Miyaura Coupling, Method A. LCMS: m/z 465.4 [M-H] $^-$.

(2*R*)-4-[4-(4-Fluorophenyl)-2-oxopyridin-1(2*H*)-yl]-*N*-hydroxy-2-methyl-2-(methylsulfonyl)butanamide (17l). The title compound (27.6 mg, 21%) was obtained as an off-white solid from (2*R*)-4-[4-(4-fluorophenyl)-2-oxopyridin-1(2*H*)-yl]-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (**16l**) using a method similar to

that described in General Tetrahydropyranyl Deprotection, Method A. ^1H NMR (400 MHz, DMSO- d_6) δ 11.15 (br. s., 1H), 8.34 (br. s., 1H), 7.71 - 7.86 (m, 3H), 7.26 - 7.37 (m, 2H), 6.70 (d, J = 1.95 Hz, 1H), 6.65 (dd, J = 2.05, 7.12 Hz, 1H), 4.12 (m, 1H), 3.75 (m, 1H), 3.11 (s, 3H), 2.36 - 2.48 (m, 1H), 2.07 - 2.26 (m, 1H), 1.58 (s, 3H). HRMS: m/z calc'd for $\text{C}_{17}\text{H}_{19}\text{N}_2\text{O}_5\text{S}$ $[\text{M}+\text{H}]^+$: 383.1071; found: 383.1073.

Preparation of (2R)-4-[4-(2,6-difluorophenyl)-2-oxopyridin-1(2H)-yl]-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide (17m).

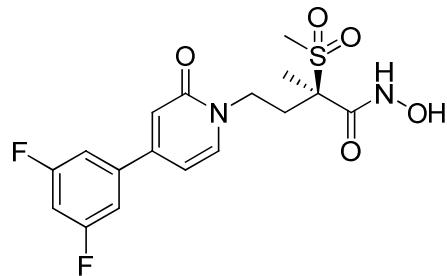


(2R)-4-[4-(2,6-Difluorophenyl)-2-oxopyridin-1(2H)-yl]-2-methyl-2-(methylsulfonyl)-N-(tetrahydro-2H-pyran-2-yloxy)butanamide (16m). Aqueous potassium carbonate (2 M, 1.5 mL, 3.0 mmol) was added to a suspension of 2,6-difluorophenylboronic acid (475 mg, 3.01 mmol), (2R)-4-(4-iodo-2-oxopyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2H-pyran-2-yloxy)butanamide (**15**, 500 mg, 1.0 mmol), and Pd(dppf)Cl₂ (232 mg, 0.3 mmol) in 1,4-dioxane (10 mL). The reaction mixture was heated to 80 °C and stirred at this temperature overnight. The reaction mixture was filtered and concentrated *in vacuo*. The crude material was purified via flash chromatography using silica (40g) and a gradient of 0-100% ethyl acetate in *n*-heptane to afford the title compound (90 mg, 19%). LCMS: m/z 483.1 $[\text{M}-\text{H}]^+$.

(2R)-4-[4-(2,6-Difluorophenyl)-2-oxopyridin-1(2H)-yl]-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide (17m). The title compound (40 mg, 54%) was obtained as a solid

(40 mg, 54%) from (2*R*)-4-[4-(2,6-difluorophenyl)-2-oxopyridin-1(2*H*)-yl]-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (**16m**) using a procedure analogous to that described in the General Tetrahydropyranyl Deprotection, Method A. ¹H NMR (400 MHz, DMSO-d₆) δ 11.11 (s, 1H), 9.25 (br. s., 1H), 7.77 (d, *J* = 7.02 Hz, 1H), 7.46 - 7.60 (m, 1H), 7.17 - 7.35 (m, 2H), 6.52 (s, 1H), 6.37 (d, *J* = 7.02 Hz, 1H), 4.13 (td, *J* = 4.88, 12.00 Hz, 1H), 3.76 (td, *J* = 4.68, 12.10 Hz, 1H), 3.11 (s, 3H), 2.39 - 2.48 (m, 1H), 2.10 - 2.23 (m, 1H), 1.58 (s, 3H). HRMS: *m/z* calc'd for C₁₇H₁₈F₂N₂O₅S [M+H]⁺: 401.0977; found: 401.0979.

Preparation of (2*R*)-4-[4-(3,5-difluorophenyl)-2-oxopyridin-1(2*H*)-yl]-*N*-hydroxy-2-methyl-2-(methylsulfonyl)butanamide (17n).

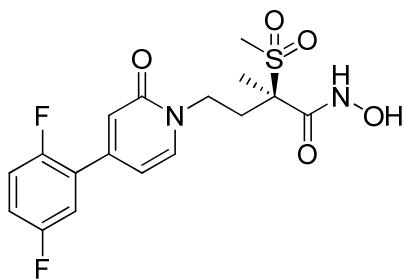


(2*R*)-4-[4-(3,5-Difluorophenyl)-2-oxopyridin-1(2*H*)-yl]-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (16n). The title compound (230 mg, 79%) was obtained from (2*R*)-4-(4-iodo-2-oxopyridin-1(2*H*)-yl)-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (**15**) and 3,5-difluorophenylboronic acid using a procedure analogous to that described in the General Suzuki-Miyaura Coupling, Method A. LCMS: *m/z* 483.1 [M-H]⁻.

(2*R*)-4-[4-(3,5-Difluorophenyl)-2-oxopyridin-1(2*H*)-yl]-*N*-hydroxy-2-methyl-2-(methylsulfonyl)butanamide (17n). The title compound (150 mg, 79%) was obtained from (2*R*)-4-[4-(3,5-difluorophenyl)-2-oxopyridin-1(2*H*)-yl]-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (**16n**) using a procedure analogous to that described

in the General Tetrahydropyranyl Deprotection, Method A. ^1H NMR (400 MHz, DMSO-d₆) δ 11.12 (s, 1H), 9.24 (s, 1H), 7.79 (d, J = 7.02 Hz, 1H), 7.44 - 7.61 (m, 2H), 7.35 (m, 1H), 6.83 (d, J = 2.15 Hz, 1H), 6.71 (dd, J = 2.05, 7.12 Hz, 1H), 4.12 (m, 1H), 3.76 (m, 1H), 3.11 (s, 3H), 2.39 - 2.48 (m, 1H), 2.11 - 2.21 (m, 1H), 1.58 (s, 3H). HRMS: *m/z* calc'd for C₁₇H₁₈F₂N₂O₅S [M+H]⁺: 401.0977; found: 401.0979.

Preparation of (2*R*)-4-[4-(2,5-difluorophenyl)-2-oxopyridin-1(2*H*)-yl]-*N*-hydroxy-2-methyl-2-(methylsulfonyl)butanamide (17o).

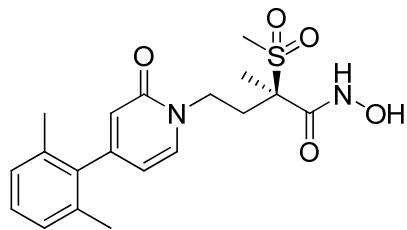


(2*R*)-4-[4-(2,5-Difluorophenyl)-2-oxopyridin-1(2*H*)-yl]-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (16o). The title compound (203 mg, 84%) was obtained as a solid from (2*R*)-4-(4-iodo-2-oxopyridin-1(2*H*)-yl)-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (**15**) and 2,5-difluorophenylboronic acid using a procedure analogous to that described in the General Suzuki-Miyaura Coupling, Method A. LCMS: *m/z* 483.4 [M-H]⁺.

(2*R*)-4-[4-(2,5-Difluorophenyl)-2-oxopyridin-1(2*H*)-yl]-*N*-hydroxy-2-methyl-2-(methylsulfonyl)butanamide (17o). The title compound (40.0 mg, 24%) was obtained as a solid from (2*R*)-4-[4-(2,5-difluorophenyl)-2-oxopyridin-1(2*H*)-yl]-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (**16o**) using a procedure analogous to that described

in the General Tetrahydropyranyl Deprotection, Method A. ^1H NMR (400 MHz, DMSO-d₆) δ 11.16 (br. s., 1H), 7.79 (d, J = 7.02 Hz, 1H), 7.45 - 7.53 (m, 1H), 7.30 - 7.45 (m, 2H), 6.62 (s, 1H), 6.50 (m, 1H), 4.13 (m, 1H), 3.77 (m, 1H), 3.11 (s, 3H), 2.39 - 2.47 (m, 1H), 2.10 - 2.23 (m, 1H), 1.58 (s, 3H). HRMS: m/z calc'd for C₁₇H₁₈F₂N₂O₅S [M+H]⁺: 401.0977; found: 401.0979.

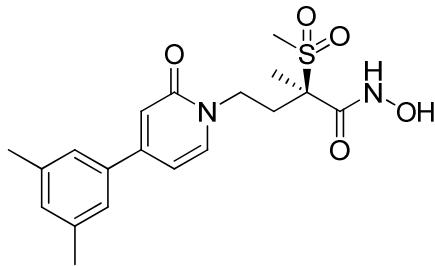
Preparation of (2*R*)-4-[4-(2,6-dimethylphenyl)-2-oxopyridin-1(2*H*)-yl]-*N*-hydroxy-2-methyl-2-(methylsulfonyl)butanamide (17p).



(2*R*)-4-[4-(2,6-Dimethylphenyl)-2-oxopyridin-1(2*H*)-yl]-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (16p). The title compound (180 mg, 47%) was obtained from (2*R*)-4-(4-iodo-2-oxopyridin-1(2*H*)-yl)-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (**15**) and 2,6-dimethylphenyl boronic acid using a procedure analogous to that described in the General Suzuki-Miyaura Coupling, Method B. LCMS: m/z 475.4 [M-H]⁺.

(2*R*)-4-[4-(2,6-Dimethylphenyl)-2-oxopyridin-1(2*H*)-yl]-*N*-hydroxy-2-methyl-2-(methylsulfonyl)butanamide (17p). The title compound (70 mg, 60%) was obtained as a solid from (2*R*)-4-[4-(2,6-dimethylphenyl)-2-oxopyridin-1(2*H*)-yl]-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (**16p**) using a method similar to that described in General Tetrahydropyranyl Deprotection, Method B. ^1H NMR (400 MHz, CD₃OD) δ 7.74 (d, J = 6.85 Hz, 1H), 7.13 - 7.23 (m, 1H), 7.03 - 7.14 (m, 2H), 6.34 (d, J = 1.17 Hz, 1H), 6.25 (dd, J = 1.76, 6.85 Hz, 1H), 4.24 - 4.47 (m, 1H), 3.87 - 4.05 (m, 1H), 3.14 (s, 3H), 2.57 - 2.70 (m, 1H), 2.35 - 2.49 (m, 1H), 2.11 (s, 6H), 1.72 (s, 3H). HRMS: m/z calc'd for C₁₉H₂₄N₂O₅S [M+H]⁺: 393.1479; found: 393.148.

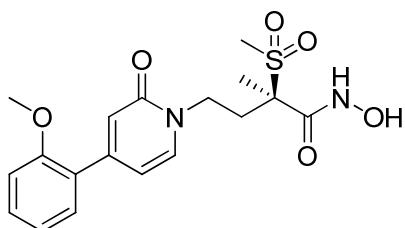
Preparation of (2*R*)-4-[4-(3,5-dimethylphenyl)-2-oxopyridin-1(2*H*)-yl]-*N*-hydroxy-2-methyl-2-(methylsulfonyl)butanamide (17q).



(2R)-4-[4-(3,5-Dimethylphenyl)-2-oxopyridin-1(2H)-yl]-2-methyl-2-(methylsulfonyl)-N-(tetrahydro-2H-pyran-2-yloxy)butanamide (16q). The title compound (140 mg, 59%) was obtained as a white solid from (2R)-4-(4-iodo-2-oxopyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)-N-(tetrahydro-2H-pyran-2-yloxy)butanamide (**15**) and 3,5-dimethylphenyl boronic acid using a procedure analogous to that described in the General Suzuki-Miyaura Coupling, Method B. LCMS: m/z 475.1 [M-H]⁻.

(2R)-4-[4-(3,5-dimethylphenyl)-2-oxopyridin-1(2H)-yl]-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide (17q). The title compound (66.4 mg, 58%) was obtained as a solid from (2R)-4-[4-(3,5-dimethylphenyl)-2-oxopyridin-1(2H)-yl]-2-methyl-2-(methylsulfonyl)-N-(tetrahydro-2H-pyran-2-yloxy)butanamide (**16q**) using a procedure analogous to that described in General Tetrahydropyranyl Deprotection, Method A. ¹H NMR (400 MHz, DMSO-d₆) δ 11.17 (br. s., 1H), 9.25 (br. s., 1H), 7.73 (d, J = 7.04 Hz, 1H), 7.32 (s, 2H), 7.10 (s, 1H), 6.66 (d, J = 1.76 Hz, 1H), 6.62 (dd, J = 2.05, 7.14 Hz, 1H), 4.01 - 4.18 (m, 1H), 3.66 - 3.81 (m, 1H), 3.11 (s, 3H), 2.37 - 2.48 (m, 1H), 2.33 (s, 6H), 2.10 - 2.22 (m, 1H), 1.53 - 1.62 (m, 3H). HRMS: m/z calc'd for C₁₉H₂₄N₂O₅S [M+H]⁺: 393.1479; found: 393.148.

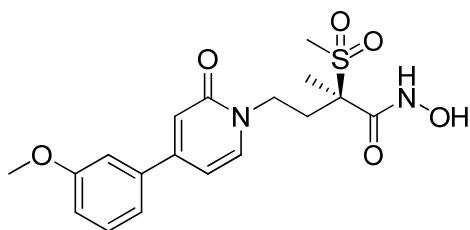
Preparation of (2R)-N-hydroxy-4-[4-(2-methoxyphenyl)-2-oxopyridin-1(2H)-yl]-2-methyl-2-(methylsulfonyl)butanamide (17r).



(2R)-4-[4-(2-Methoxyphenyl)-2-oxopyridin-1(2H)-yl]-2-methyl-2-(methylsulfonyl)-N-(tetrahydro-2H-pyran-2-yloxy)butanamide (16r). The title compound (182 mg, 76%) was obtained as a solid from (2R)-4-(4-iodo-2-oxopyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)-N-(tetrahydro-2H-pyran-2-yloxy)butanamide (**15**) and 2-methoxyphenyl boronic acid using a procedure analogous to that described in the General Suzuki-Miyaura Coupling, Method A. LCMS: m/z 477.4 [M-H]⁺.

(2R)-N-Hydroxy-4-[4-(2-methoxyphenyl)-2-oxopyridin-1(2H)-yl]-2-methyl-2-(methylsulfonyl)butanamide (17r). The title compound (116 mg, 77%) was obtained as a white solid from (2R)-4-[4-(2-methoxyphenyl)-2-oxopyridin-1(2H)-yl]-2-methyl-2-(methylsulfonyl)-N-(tetrahydro-2H-pyran-2-yloxy)butanamide (**16r**) using a method similar to that described in the General Tetrahydropyranyl Deprotection, Method A. ¹H NMR (400 MHz, DMSO-d₆) δ 10.89 (br. s., 1H), 7.68 (d, *J* = 7.02 Hz, 1H), 7.37 - 7.45 (m, 1H), 7.34 (dd, *J* = 1.66, 7.51 Hz, 1H), 7.13 (d, *J* = 7.81 Hz, 1H), 7.03 (td, *J* = 0.88, 7.46 Hz, 1H), 6.51 (d, *J* = 1.95 Hz, 1H), 6.46 (dd, *J* = 1.95, 7.02 Hz, 1H), 4.12 (m, 1H), 3.80 (s, 3H), 3.68 - 3.79 (m, 1H), 3.10 (s, 3H), 2.43 (m, 1H), 2.17 (m, 1H), 1.60 (s, 3H). HRMS: m/z calc'd for C₁₈H₂₂N₂O₆S [M+H]⁺: 395.1271; found: 383.1279.

Preparation of (2R)-N-hydroxy-4-[4-(3-methoxyphenyl)-2-oxopyridin-1(2H)-yl]-2-methyl-2-(methylsulfonyl)butanamide (17s).

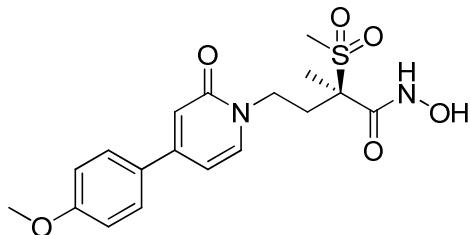


(2R)-4-[4-(3-Methoxyphenyl)-2-oxopyridin-1(2H)-yl]-2-methyl-2-(methylsulfonyl)-N-(tetrahydro-2H-pyran-2-yloxy)butanamide (16s). The title compound (243 mg, 100%) was obtained as a solid from (2R)-4-(4-iodo-2-oxopyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)-N-(tetrahydro-2H-pyran-2-yloxy)butanamide (**15**) and 2-methoxyphenyl boronic acid using a

procedure analogous to that described in the General Suzuki-Miyaura Coupling, Method A. LCMS: m/z 477.4 [M-H]⁺.

(2R)-N-Hydroxy-4-[4-(3-methoxyphenyl)-2-oxopyridin-1(2H)-yl]-2-methyl-2-(methylsulfonyl)butanamide (17s). The title compound (39.50 mg, 20%) was obtained as a white solid from (2R)-4-[4-(3-methoxyphenyl)-2-oxopyridin-1(2H)-yl]-2-methyl-2-(methylsulfonyl)-N-(tetrahydro-2H-pyran-2-yloxy)butanamide (16s) using a procedure analogous to that described in the General Tetrahydropyranyl Deprotection, Method A. ¹H NMR (400 MHz, DMSO-d₆) δ 11.16 (br. s., 1H), 7.76 (d, *J* = 7.22 Hz, 1H), 7.34 - 7.47 (m, 1H), 7.27 (d, *J* = 7.81 Hz, 1H), 7.20 - 7.24 (m, 1H), 7.00 - 7.06 (m, 1H), 6.72 (d, *J* = 1.95 Hz, 1H), 6.66 (dd, *J* = 2.05, 7.12 Hz, 1H), 4.12 (m, 1H), 3.82 (s, 3H), 3.69 - 3.81 (m, 1H), 3.10 (s, 3H), 2.37 - 2.48 (m, 1H), 2.11 - 2.23 (m, 1H), 1.58 (s, 3H). HRMS: *m/z* calc'd for C₁₈H₂₂N₂O₆S [M+H]⁺: 395.1271; found: 395.1275.

Preparation of (2R)-N-hydroxy-4-[4-(4-methoxyphenyl)-2-oxopyridin-1(2H)-yl]-2-methyl-2-(methylsulfonyl)butanamide (17t).

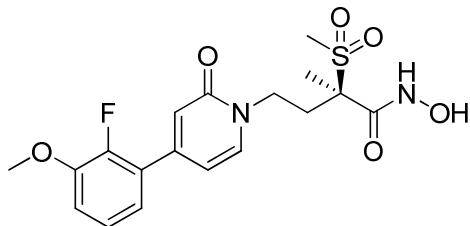


(2R)-4-[4-(4-Methoxyphenyl)-2-oxopyridin-1(2H)-yl]-2-methyl-2-(methylsulfonyl)-N-(tetrahydro-2H-pyran-2-yloxy)butanamide (16t). The title compound (175 mg, 73%) was obtained as a solid from (2R)-4-(4-iodo-2-oxopyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)-N-(tetrahydro-2H-pyran-2-yloxy)butanamide (15) and 4-methoxyphenyl boronic acid using a procedure analogous to that described in the General Suzuki-Miyaura Coupling, Method A. LCMS: m/z 477.4 [M-H]⁺.

(2R)-N-Hydroxy-4-[4-(4-methoxyphenyl)-2-oxopyridin-1(2H)-yl]-2-methyl-2-(methylsulfonyl)butanamide (17t). The title compound (62.6 mg, 43%) was obtained as a

white solid from $(2R)$ -4-[4-(4-methoxyphenyl)-2-oxopyridin-1(2*H*)-yl]-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (**16t**) using a procedure analogous to that described in the General Tetrahydropyranyl Deprotection, Method A. ^1H NMR (400 MHz, DMSO- d_6) δ 11.18 (br. s., 1H), 8.57 (br. s., 1H), 7.64 - 7.78 (m, 3H), 6.99 - 7.07 (m, 2H), 6.66 (s, 1H), 6.64 (d, J = 2.15 Hz, 1H), 4.11 (m, 1H), 3.81 (s, 3H), 3.74 (m, 1H), 3.11 (s, 3H), 2.35 - 2.47 (m, 1H), 2.09 - 2.24 (m, 1H), 1.57 (s, 3H). HRMS: m/z calc'd for $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_6\text{S}$ $[\text{M}+\text{H}]^+$: 395.1271; found: 395.1274.

Preparation of $(2R)$ -4-[4-(2-fluoro-3-methoxyphenyl)-2-oxopyridin-1(2*H*)-yl]-*N*-hydroxy-2-methyl-2-(methylsulfonyl)butanamide (17u**).**

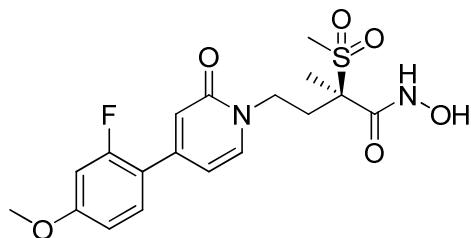


$(2R)$ -4-[4-(2-Fluoro-3-methoxyphenyl)-2-oxopyridin-1(2*H*)-yl]-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (16u**).** The title compound (210 mg, 84%) was obtained as a white solid from $(2R)$ -4-(4-iodo-2-oxopyridin-1(2*H*)-yl)-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (**15**) and 2-fluoro-3-methoxyphenyl boronic acid using a procedure analogous to that described in the General Suzuki-Miyaura Coupling, Method A. LCMS: m/z 495.1 $[\text{M}-\text{H}]^+$.

$(2R)$ -4-[4-(2-Fluoro-3-methoxyphenyl)-2-oxopyridin-1(2*H*)-yl]-*N*-hydroxy-2-methyl-2-(methylsulfonyl)butanamide (17u**).** The title compound (150 mg, 86%) was obtained as a white solid from $(2R)$ -4-[4-(2-fluoro-3-methoxyphenyl)-2-oxopyridin-1(2*H*)-yl]-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (**16u**) using a procedure analogous to that described in the General Tetrahydropyranyl Deprotection, Method B. ^1H

¹H NMR (400 MHz, DMSO-d₆) δ 11.13 (d, *J* = 1.76 Hz, 1H), 9.25 (d, *J* = 1.76 Hz, 1H), 7.75 (d, *J* = 7.02 Hz, 1H), 7.19 - 7.32 (m, 2H), 7.03 - 7.13 (m, 1H), 6.54 (s, 1H), 6.46 (m, 1H), 4.12 (m, 1H), 3.88 (s, 3H), 3.75 (m, 1H), 3.11 (s, 3H), 2.39 - 2.48 (m, 1H), 2.12 - 2.22 (m, 1H), 1.58 (s, 3H). HRMS *m/z* calc'd for C₁₈H₂₁N₂O₆S [M+H]⁺: 413.1177; found: 413.1179.

Preparation of (2*R*)-4-[4-(2-fluoro-4-methoxyphenyl)-2-oxopyridin-1(2*H*)-yl]-*N*-hydroxy-2-methyl-2-(methylsulfonyl)butanamide (17v).

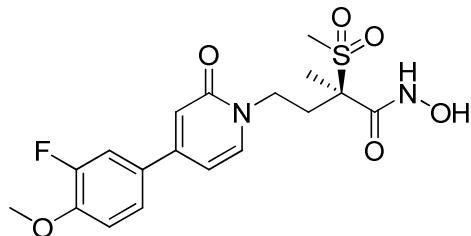


(2*R*)-4-[4-(2-Fluoro-4-methoxyphenyl)-2-oxopyridin-1(2*H*)-yl]-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (16v). The title compound (540 mg, 77%) was obtained as a yellow solid from (2*R*)-4-(4-iodo-2-oxopyridin-1(2*H*)-yl)-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (15) and 2-fluoro-4-methoxyphenyl boronic acid using a procedure analogous to that described in the General Suzuki-Miyaura Coupling, Method A. LCMS: *m/z* 495.7 [M-H]⁻.

(2*R*)-4-[4-(2-Fluoro-4-methoxyphenyl)-2-oxopyridin-1(2*H*)-yl]-*N*-hydroxy-2-methyl-2-(methylsulfonyl)butanamide (17v). The title compound (408 mg, 91%) was obtained as a white solid from (2*R*)-4-[4-(2-fluoro-4-methoxyphenyl)-2-oxopyridin-1(2*H*)-yl]-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (16v) using a procedure analogous to that described in the General Tetrahydropyranyl Deprotection, Method A. ¹H NMR (400 MHz, CD₃OD) δ 7.68 (d, *J* = 6.64 Hz, 2H), 7.50 (t, 1H), 6.86 - 6.91 (m, 1H), 6.80 -

6.86 (m, 1H), 6.72 (br. s., 1H), 6.63 - 6.68 (m, 1H), 3.88 - 3.98 (m, 1H), 3.86 (s, 3H), 3.12 (s, 3H), 2.52 - 2.66 (m, 1H), 2.30 - 2.45 (m, 1H), 1.71 (s, 3H). HRMS: *m/z* calc'd for C₁₈H₂₁FN₂O₆S [M+H]⁺: 413.1177; found: 413.1179.

Preparation of (2*R*)-4-[4-(3-fluoro-4-methoxyphenyl)-2-oxopyridin-1(2*H*)-yl]-*N*-hydroxy-2-methyl-2-(methylsulfonyl)butanamide (17w).

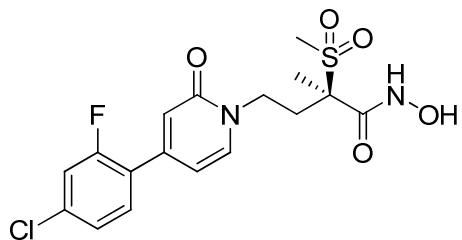


(2*R*)-4-[4-(3-Fluoro-4-methoxyphenyl)-2-oxopyridin-1(2*H*)-yl]-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (16w). The title compound (130 mg, 52%) was obtained as a solid from (2*R*)-4-(4-iodo-2-oxopyridin-1(2*H*)-yl)-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (**15**) and 3-fluoro-4-methoxyphenyl boronic acid using a procedure analogous to that described in the General Suzuki-Miyaura Coupling, Method A. LCMS: *m/z* 495.4 [M-H]⁻.

(2*R*)-4-[4-(3-Fluoro-4-methoxyphenyl)-2-oxopyridin-1(2*H*)-yl]-*N*-hydroxy-2-methyl-2-(methylsulfonyl)butanamide (17w). The title compound (52.3 mg, 48%) was obtained as a white solid from (2*R*)-4-[4-(3-fluoro-4-methoxyphenyl)-2-oxopyridin-1(2*H*)-yl]-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (**16w**) using a procedure analogous to that described in the General Tetrahydropyranyl Deprotection, Method A. ¹H NMR (400 MHz, DMSO-d₆) δ 11.16 (s, 1H), 9.24 (s, 1H), 7.72 (d, *J* = 7.03 Hz, 1H), 7.67 (dd, *J* = 2.34, 12.88 Hz, 1H), 7.58 (d, *J* = 8.59 Hz, 1H), 7.25 (t, *J* = 8.78 Hz, 1H), 6.72 (d, *J* = 1.95 Hz,

1H), 6.67 (dd, J = 1.95, 7.02 Hz, 1H), 4.10 (m, 1H), 3.89 (s, 3H), 3.73 (m, 1H), 3.10 (s, 3H), 2.41 (m, 1H), 2.16 (m, 1H), 1.57 (s, 3H). HRMS: m/z calc'd for $C_{18}H_{21}FN_2O_6S$ [M+H]⁺: 413.1177; found: 413.1182.

Preparation of (2*R*)-4-[4-(4-chloro-2-fluorophenyl)-2-oxopyridin-1(2*H*)-yl]-*N*-hydroxy-2-methyl-2-(methylsulfonyl)butanamide (17x).

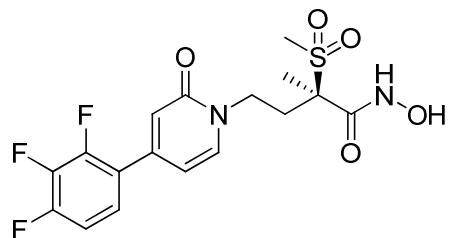


(2*R*)-4-[4-(4-Chloro-2-fluorophenyl)-2-oxopyridin-1(2*H*)-yl]-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (16x). The title compound (808.5 mg, 54%) was obtained as a solid from (2*R*)-4-(4-iodo-2-oxopyridin-1(2*H*)-yl)-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (**15**) and 4-chloro-2-fluorophenyl boronic acid using a procedure analogous to that described in the General Suzuki-Miyaura Coupling, Method A. LCMS: m/z 499.6 [M-H]⁻.

(2*R*)-4-[4-(4-Chloro-2-fluorophenyl)-2-oxopyridin-1(2*H*)-yl]-*N*-hydroxy-2-methyl-2-(methylsulfonyl)butanamide (17x). The title compound (514 mg, 77%) was obtained as a white solid from (2*R*)-4-[4-(4-chloro-2-fluorophenyl)-2-oxopyridin-1(2*H*)-yl]-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (**16x**) using a procedure analogous to that described in the General Tetrahydropyranyl Deprotection, Method A. ¹H NMR (400 MHz, CD₃OD) δ 7.72 (d, J = 7.03 Hz, 1H), 7.56 (t, 1H), 7.32 - 7.40 (m, 2H), 6.74 (s, 1H), 6.63 (m, 1H), 4.25 - 4.38 (m, 1H), 3.87 - 4.01 (m, 1H), 3.12 (s, 3H), 2.54 - 2.67 (m, 1H),

2.32 - 2.46 (m, 1H), 1.71 (s, 3H). HRMS: *m/z* calc'd for C₁₇H₁₈ClFN₂O₅S [M+H]⁺: 417.0682; found: 417.0685. (96.7247% - HPLC).

Preparation of (2*R*)-*N*-Hydroxy-2-methyl-2-(methylsulfonyl)-4-[2-oxo-4-(2,3,4-trifluorophenyl)pyridin-1(2*H*)-yl]butanamide (17y).

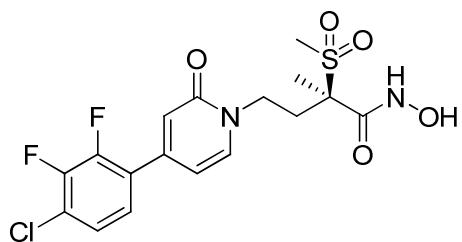


(2*R*)-2-Methyl-2-(methylsulfonyl)-4-[2-oxo-4-(2,3,4-trifluorophenyl)pyridin-1(2*H*)-yl]-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (16y). The title compound (258 mg, 51%) was obtained as a solid from (2*R*)-4-(4-iodo-2-oxopyridin-1(2*H*)-yl)-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (**15**) and 4-2,3,4-trifluorophenyl boronic acid using a procedure analogous to that described in the General Suzuki-Miyaura Coupling, Method A. LCMS: *m/z* 501.1 [M-H]⁻.

(2*R*)-*N*-Hydroxy-2-methyl-2-(methylsulfonyl)-4-[2-oxo-4-(2,3,4-trifluorophenyl)pyridin-1(2*H*)-yl]butanamide (17y). The title compound (103 mg, 48%) was obtained as an off-white solid from (2*R*)-2-methyl-2-(methylsulfonyl)-4-[2-oxo-4-(2,3,4-trifluorophenyl)pyridin-1(2*H*)-yl]-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (**16y**) using a procedure analogous to that described in the General Tetrahydropyranyl Deprotection, Method B. ¹H NMR (400 MHz, CD₃OD) δ 7.74 (d, *J* = 6.83 Hz, 1H), 7.34 - 7.43 (m, 1H), 7.19 - 7.30 (m, *J* = 2.15, 7.18, 9.40, 9.40 Hz, 1H), 6.73 (s, 1H), 6.62 (m, 1H), 4.25 - 4.37 (m, 1H), 3.88 - 4.02 (m, 1H), 3.12 (s, 3H),

2.52 - 2.66 (m, 1H), 2.32 - 2.45 (m, 1H), 1.71 (s, 3H). HRMS: *m/z* calc'd for C₁₇H₁₇F₃N₂O₅S [M+H]⁺: 419.0883; found: 419.0883.

Preparation of (2*R*)-4-[4-(4-Chloro-2,3-difluorophenyl)-2-oxopyridin-1(2*H*)-yl]-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide (17z).



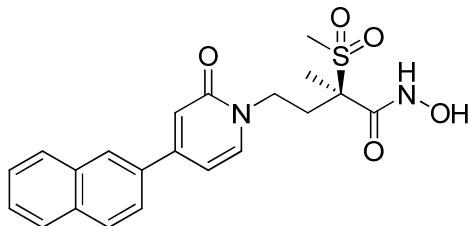
(2*R*)-4-[4-(4-Chloro-2,3-difluorophenyl)-2-oxopyridin-1(2*H*)-yl]-2-methyl-2-(methylsulfonyl)butanoic acid. Isopropylmagnesium chloride (2.0 M in THF, 247 mL, 494 mmol) was added drop-wise to a solution of 1-bromo-4-chloro-2,3-difluorobenzene (102 g, 449 mmol) in 2-methyltetrahydrofuran (1.6 L) at 0 °C. The mixture was stirred at 0 °C for 1 h. 2-Isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (92 g, 102 mL, 250 mmol) was added to the reaction drop-wise over a period of 45 min. The reaction mixture was stirred for 15 min at 0 °C and then allowed to warm to rt. Aqueous K₃PO₄ (1.0 M, 1.12 L, 1120 mmol) was added to the mixture and the reaction mixture was stirred at rt for 5 min. Ethyl-(2*R*)-4-(4-iodo-2-oxopyridin-1(2*H*)-yl)-2-methyl-2-(methylsulfonyl)butanoate (**13a, R₄ = I**, 160 g, 374 mmol) was added and the mixture was stirred and degassed with N₂ for 10 min. [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (14.4 g, 18.7 mmol, 5 mol%) was added to the mixture and the mixture was degassed for 5 min. The reaction was heated to 50 °C, was stirred at this temperature for 0.5 h, and was allowed to cool to rt. The reaction mixture was stirred at rt for 15 h. The aqueous layer was separated and extracted with 2-methyltetrahydrofuran (400 mL). The organic layer was added to a solution of

LiOH (27 g, 1120 mmol) in water (500 mL) and the resulting mixture was heated to 55 °C. The reaction was stirred at this temperature for 2 h. The reaction mixture was allowed to cool to rt and the aqueous layer was separated. The organic layer was extracted with aq 1 N NaOH (350 mL). The aqueous layers were combined, washed with ethyl acetate (3x400 mL), treated with celite (100 g), and filtered. The aqueous layer was heated to 80 °C and acidified to a pH of ~4 using aq 6 N HCl and then adjusted to a pH of ~2 using aq 1 N HCl to afford a milky aqueous layer. Ethanol (100 mL) was added to the aqueous material and concentration was done *in vacuo* to promote solid formation. The solid was collected via filtration, washed with ethanol:ethyl acetate (1:1, 200 mL), and dried *in vacuo* to afford an off-white solid (122 g, 78%). ¹H NMR (400 MHz, DMSO-d₆) δ 13.90 (br. s., 1H), 7.81 (d, *J* = 7.22 Hz, 1H), 7.52 - 7.60 (m, 1H), 7.41 - 7.50 (m, 1H), 6.60 (s, 1H), 6.47 (m, 1H), 4.05 - 4.17 (m, 1H), 3.88 - 4.01 (m, 1H), 3.17 (s, 3H), 2.39 - 2.48 (m, 1H), 2.13 - 2.27 (m, 1H), 1.58 (s, 3H). LCMS: m/z 420.0 [M+H]⁺.

(2*R*)-4-[4-(4-Chloro-2,3-difluorophenyl)-2-oxopyridin-1(2*H*)-yl]-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (16z). The title compound (138 g) was obtained as a white solid from (2*R*)-4-[4-(4-chloro-2,3-difluorophenyl)-2-oxopyridin-1(2*H*)-yl]-2-methyl-2-(methylsulfonyl)butanoic acid using a procedure analogous to that described in the General Amide Coupling. The title compound was used without further purification. Method B. LCMS: m/z 517.5 [M-H]⁻.

(2*R*)-4-[4-(4-Chloro-2,3-difluorophenyl)-2-oxopyridin-1(2*H*)-yl]-*N*-hydroxy-2-methyl-2-(methylsulfonyl)butanamide (17z). The title compound (94 g, 67%) was obtained as a solid from (2*R*)-4-[4-(4-chloro-2,3-difluorophenyl)-2-oxopyridin-1(2*H*)-yl]-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (16z) using a procedure analogous to that described in the General Tetrahydropyranyl Deprotection, Method B. ¹H NMR (400 MHz, CD₃OD) δ 7.75 (d, *J* = 6.64 Hz, 1H), 7.34 - 7.47 (m, 2H), 6.75 (s, 1H), 6.63 (m, 1H), 4.26 - 4.40 (m, 1H), 3.89 - 4.02 (m, 1H), 3.13 (s, 3H), 2.54 - 2.67 (m, 1H), 2.29 - 2.45 (m, 1H), 1.71 (s, 3H). HRMS: m/z calc'd for C₁₇H₁₇ClF₂N₂O₅S [M+H]⁺: 435.0588; found: 435.0589.

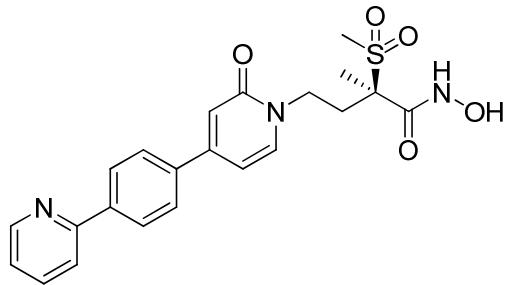
Preparation of (2*R*)-*N*-hydroxy-2-methyl-2-(methylsulfonyl)-4-[4-(2-naphthyl)-2-oxopyridin-1(2*H*)-yl]butanamide (17aa).



(2*R*)-2-Methyl-2-(methylsulfonyl)-4-[4-(2-naphthyl)-2-oxopyridin-1(2*H*)-yl]-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (16aa). The title compound (240 mg, 95%) was obtained as a tan gum from (2*R*)-4-(4-iodo-2-oxopyridin-1(2*H*)-yl)-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (**15**) and 2-naphthaleneboronic acid using a procedure analogous to that described in the General Suzuki-Miyaura Coupling, Method A. LCMS: m/z 497.1 [M-H]⁻.

(2*R*)-*N*-Hydroxy-2-methyl-2-(methylsulfonyl)-4-[4-(2-naphthyl)-2-oxopyridin-1(2*H*)-yl]butanamide (17aa). The title compound (90 g, 45%) was obtained as a white solid from (2*R*)-2-methyl-2-(methylsulfonyl)-4-[4-(2-naphthyl)-2-oxopyridin-1(2*H*)-yl]-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (**16aa**) using a procedure analogous to that described in the General Tetrahydropyranyl Deprotection, Method B. ¹H NMR (400 MHz, DMSO-d₆) δ 11.17 (br. s., 1H), 9.27 (br. s., 1H), 8.36 (d, *J* = 1.37 Hz, 1H), 8.00 - 8.08 (m, 2H), 7.94 - 8.00 (m, 1H), 7.87 (dd, *J* = 1.96, 8.61 Hz, 1H), 7.81 (d, *J* = 7.04 Hz, 1H), 7.53 - 7.62 (m, 2H), 6.87 (d, *J* = 2.15 Hz, 1H), 6.83 (dd, *J* = 2.15, 7.04 Hz, 1H), 4.05 - 4.22 (m, 1H), 3.71 - 3.84 (m, 1H), 3.12 (s, 3H), 2.38 - 2.48 (m, 1H), 2.12 - 2.27 (m, 1H), 1.61 (s, 3H). HRMS: *m/z* calc'd for C₂₁H₂₂N₂O₅S [M+H]⁺: 415.1322; found: 415.1317.

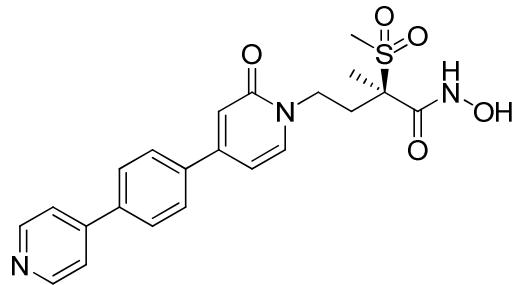
Preparation of (2*R*)-*N*-hydroxy-2-methyl-2-(methylsulfonyl)-4-[2-oxo-4-(4-pyridin-2-ylphenyl)pyridin-1(2*H*)-yl]butanamide (17bb).



(2R)-2-Methyl-2-(methylsulfonyl)-4-[2-oxo-4-(4-pyridin-2-ylphenyl)pyridin-1(2H)-yl]-N-(tetrahydro-2H-pyran-2-yloxy)butanamide (16bb). The title compound (190 mg, 72%) was obtained as an off-white solid from (2R)-4-(4-iodo-2-oxopyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)-N-(tetrahydro-2H-pyran-2-yloxy)butanamide (15) and 2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyridine using a procedure analogous to that described in the General Suzuki-Miyaura Coupling, Method A. LCMS: m/z 524.8 [M-H]⁻.

(2R)-N-Hydroxy-2-methyl-2-(methylsulfonyl)-4-[2-oxo-4-(4-pyridin-2-ylphenyl)pyridin-1(2H)-yl]butanamide (17bb). The title compound (58.1 mg, 46%) was obtained as an off-white solid from (2R)-2-methyl-2-(methylsulfonyl)-4-[2-oxo-4-(4-pyridin-2-ylphenyl)pyridin-1(2H)-yl]-N-(tetrahydro-2H-pyran-2-yloxy)butanamide (16bb) using a procedure analogous to that described in the General Tetrahydropyranyl Deprotection, Method B. ¹H NMR (400 MHz, DMSO-d₆) δ 11.16 (s, 1H), 9.25 (s, 1H), 8.60 - 8.76 (m, 1H), 8.14 - 8.30 (m, 1H), 8.01 - 8.10 (m, 1H), 7.92 (m, 1H), 7.84 - 7.89 (m, 1H), 7.79 (d, *J* = 7.02 Hz, 1H), 7.30 - 7.45 (m, 1H), 6.79 (d, *J* = 2.15 Hz, 1H), 6.74 (dd, *J* = 1.95, 7.02 Hz, 1H), 4.08 - 4.19 (m, 2H), 3.72 - 3.82 (m, 2H), 3.12 (s, 3H), 2.40 - 2.48 (m, 1H), 2.13 - 2.25 (m, 1H), 1.59 (s, 3H). HRMS: m/z calc'd for C₂₂H₂₃N₃O₅S [M+H]⁺: 442.1431; found: 442.1438.

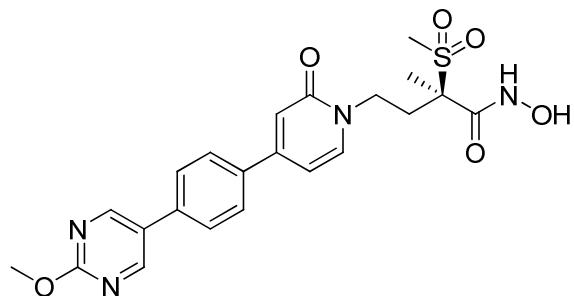
Preparation of (2R)-N-hydroxy-2-methyl-2-(methylsulfonyl)-4-[2-oxo-4-(4-pyridin-4-ylphenyl)pyridin-1(2H)-yl]butanamide (17cc).



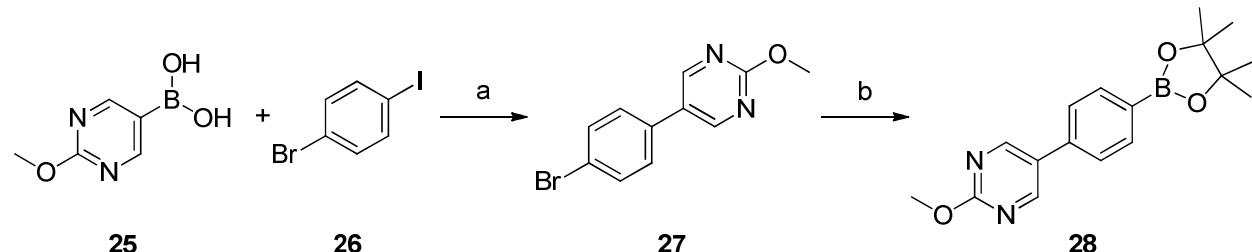
(2R)-2-Methyl-2-(methylsulfonyl)-4-[2-oxo-4-(4-pyridin-4-ylphenyl)pyridin-1(2H)-yl]-N-(tetrahydro-2H-pyran-2-yloxy)butanamide (16cc). The title compound (290 mg, 91%) was obtained as an off-white solid from (2R)-4-(4-iodo-2-oxopyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)-N-(tetrahydro-2H-pyran-2-yloxy)butanamide (15) and 4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyridine using a method analogous to that described in General Suzuki-Miyaura Coupling, Method A. LCMS: m/z 526.7 [M+H]⁺.

(2R)-N-Hydroxy-2-methyl-2-(methylsulfonyl)-4-[2-oxo-4-(4-pyridin-4-ylphenyl)pyridin-1(2H)-yl]butanamide (17cc). The title compound (20 mg, 8%) was obtained as a white solid from (2R)-2-methyl-2-(methylsulfonyl)-4-[2-oxo-4-(4-pyridin-4-ylphenyl)pyridin-1(2H)-yl]-N-(tetrahydro-2H-pyran-2-yloxy)butanamide (16cc) using a procedure analogous to that described in the General Tetrahydropyranyl Deprotection, Method B. ¹H NMR (400 MHz, CD₃OD) δ 8.56 - 8.66 (m, 2H), 7.83 - 7.96 (m, 4H), 7.73 - 7.82 (m, 3H), 6.88 (d, *J* = 1.76 Hz, 1H), 6.83 (dd, *J* = 2.05, 7.14 Hz, 1H), 4.26 - 4.39 (m, 1H), 3.89 - 4.03 (m, 1H), 3.12 (s, 3H), 2.55 - 2.64 (m, 1H), 2.32 - 2.47 (m, 1H), 1.72 (s, 3H). HRMS (ESI) *m/z* calc'd for C₂₂H₂₃N₃O₅S [M+H]⁺: 442.1431; found: 442.1431.

Preparation of (2R)-N-hydroxy-4-[4-(2-methoxypyrimidin-5-yl)phenyl]-2-oxopyridin-1(2H)-yl}-2-methyl-2-(methylsulfonyl)butanamide (17dd).



Scheme 4. Synthesis of 2-methoxy-5-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrimidine (**28**).^a



^aReagents and conditions. (a) Siliacat™ DPP-Pd, K_2CO_3 , EtOH, H_2O , 60°C . (b) $\text{Pd}(\text{dppf})\text{Cl}_2$ - CH_2Cl_2 complex, bis(pinacolato)diborane, KOAc , 1,4-dioxane, 100°C .

5-(4-Bromophenyl)-2-methoxypyrimidine (27). Siliacat™ DPP-Pd (500 mg, 0.013 mmol, 0.27 mmol/g) was added to a mixture of (2-methoxypyrimidin-5-yl)boronic acid (**25**, 571 mg, 3.71 mmol) 1-bromo-4-iodobenzene (**26**, 750 mg, 2.65 mmol) and K_2CO_3 (733 mg, 5.3 mmol) in ethanol (4.5 mL) and water (4.0 mL). The reaction mixture was heated to 60°C and stirred at this temperature overnight. The reaction mixture was allowed to cool to rt, filtered, and the filter pad was washed with methanol. The combined filtrates were concentrated *in vacuo*. The crude material was purified via flash chromatography using a SiliCycle SiliaSep™ cartridge and a gradient of 20-100% ethyl acetate in hexanes to afford the title compound as a white solid (200 mg, 28%). ^1H NMR (400 MHz, CD_3OD) δ 8.83 (s, 2H), 7.64 - 7.69 (m, 2H), 7.55 - 7.60 (m, 2H), 4.06 (s, 3H). LCMS: m/z 266.1 [$\text{M}+\text{H}$]⁺.

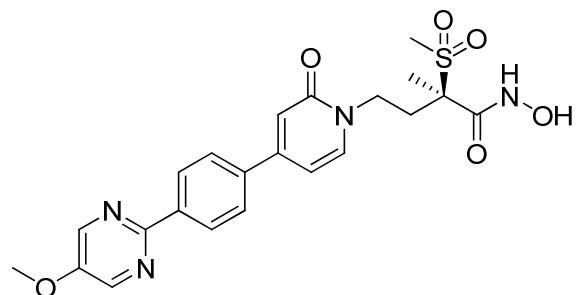
2-Methoxy-5-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrimidine (27). [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (62 mg, 0.075) was added to a suspension of 5-(4-bromophenyl)-2-methoxypyrimidine (**26**, 200 mg, 0.754 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (270 mg, 1.06 mmol), and potassium acetate (300 mg, 3.02 mmol) in 1,4-dioxane (10 mL). The reaction mixture was heated to reflux and stirred at this temperature for 16 hours. The reaction mixture was allowed to cool, filtered through celite, and the filter pad was washed with methanol (50 mL). The filtrates were combined and concentrated *in vacuo*. The crude material was purified via flash chromatography using a SiliCycle SiliaSep™ 25g Cartridge and a gradient of 20-100% ethyl

acetate in hexanes to afford the title compound as a tan solid (220 mg, 93%). ^1H NMR (400 MHz, CD₃OD) δ 8.86 (s, 2H), 7.86 (d, 2H), 7.66 (d, 2H), 4.06 (s, 3H), 1.24 (s, 12H). LCMS: m/z 313.1 [M+H]⁺.

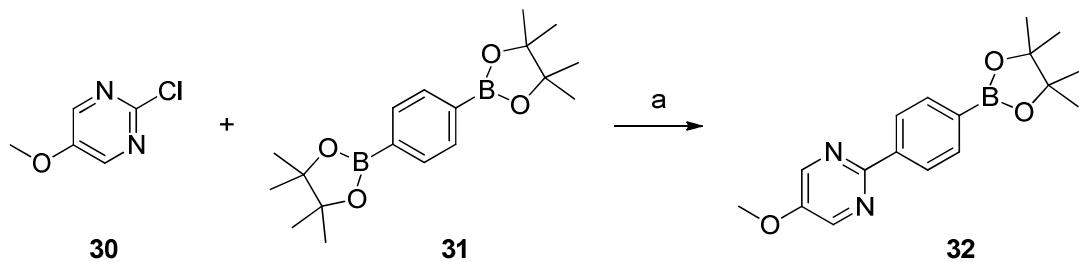
(2*R*)-4-{4-[4-(2-Methoxypyrimidin-5-yl)phenyl]-2-oxopyridin-1(2*H*)-yl}-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide(16dd). The title compound (200 mg, 85%) was obtained as a tan gum from (2*R*)-4-(4-iodo-2-oxopyridin-1(2*H*)-yl)-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (**15**) and 2-methoxy-5-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrimidine using a procedure analogous to that described in the General Suzuki-Miyaura Coupling, Method A. LCMS: m/z 555.2 [M-H]⁻

(2*R*)-*N*-Hydroxy-4-{4-[4-(2-methoxypyrimidin-5-yl)phenyl]-2-oxopyridin-1(2*H*)-yl}-2-methyl-2-(methylsulfonyl)butanamide (17dd). The title compound (50 mg, 29%) was obtained as a white solid was obtained from (2*R*)-4-{4-[4-(2-methoxypyrimidin-5-yl)phenyl]-2-oxopyridin-1(2*H*)-yl}-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide(**16dd**) using a procedure analogous to that described in the General Tetrahydropyranyl Deprotection, Method B. ^1H NMR (400 MHz, DMSO-d₆) δ 11.17 (s, 1H), 9.25 (s, 1H), 9.01 (s, 2H), 7.86 (s, 4H), 7.78 (d, *J* = 7.24 Hz, 1H), 6.79 (d, *J* = 1.96 Hz, 1H), 6.72 (dd, *J* = 2.15, 7.24 Hz, 1H), 4.07 - 4.21 (m, 1H), 3.98 (s, 3H), 3.70 - 3.85 (m, 1H), 3.10 (s, 3H), 2.38 - 2.48 (m, 1H), 2.11 - 2.25 (m, 1H), 1.59 (s, 3H). HRMS: *m/z* calc'd for C₂₂H₂₄N₄O₆S [M+H]⁺: 473.1489; found: 473.1495.

Preparation of (2*R*)-*N*-hydroxy-4-{4-[4-(5-methoxypyrimidin-2-yl)phenyl]-2-oxopyridin-1(2*H*)-yl}-2-methyl-2-(methylsulfonyl)butanamide (17ee).



Scheme 5. Synthesis of 5-methoxy-2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrimidine (**32**).^a



^aReagents and conditions. (a) $\text{Pd}(\text{PPh}_3)_4$, K_2CO_3 , $\text{THF}:\text{H}_2\text{O}$ (2:1).

5-Methoxy-2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrimidine (32).

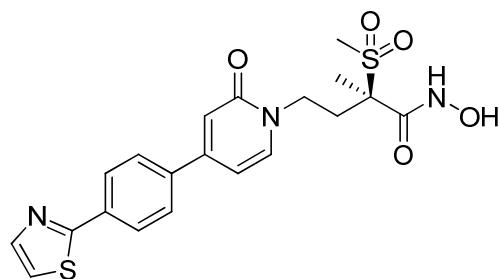
Tetrakis(triphenylphosphine)palladium(0) (53 mg, 0.045 mmol) was added to a mixture of 2-chloro-5-methoxypyrimidine (**30**, 280 mg, 1.94 mmol), 2,2'-(1,4-phenylene)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (**31**, 1.48 g, 4.48 mmol) and K_2CO_3 (638 mg, 4.48 mmol) in tetrahydrofuran:water (2:1, 30 mL). The reaction was heated at 60 °C for 2 h under N_2 . The reaction was allowed to cool to rt. The organic layer was separated and concentrated *in vacuo*. The crude material was purified via flash chromatography using silica and a gradient of 0-40% ethyl acetate in hexanes to afford the title compound as a white solid (105 mg, 17%). LCMS: m/z 313.1 [M+H]⁺.

(2*R*)-4-{4-[4-(5-Methoxypyrimidin-2-yl)phenyl]-2-oxopyridin-1(2*H*)-yl}-2-methyl-2-(methylsulfonyl)-N-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (16ee).

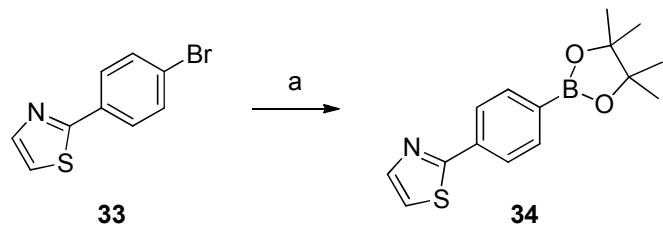
Tetrakis(triphenylphosphine)palladium(0) (40 mg, .034 mmol) was added to a mixture of (2*R*)-4-(4-iodo-2-oxopyridin-1(2*H*)-yl)-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (167 mg, 0.34 mmol), 5-methoxy-2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrimidine (105 mg, 0.34 mmol), and K_2CO_3 (139 mg, 1.01 mmol) in 1,4-dioxane:water (10:1, 11 mL). The suspension was heated to 83 °C and stirred at this temperature for 2 h. The reaction mixture was allowed to cool and concentrated *in vacuo*. The crude material was purified via flash chromatography using silica and a gradient of 0-10% methanol in ethyl acetate to afford the title compound as a yellow solid (143 mg, 77%). LCMS: m/z 555.2 [M-H]⁻.

(2*R*)-*N*-Hydroxy-4-{4-[4-(5-methoxypyrimidin-2-yl)phenyl]-2-oxopyridin-1(2*H*)-yl}-2-methyl-2-(methylsulfonyl)butanamide (17ee). The title compound (38 mg, 31%) was obtained as a white solid from (2*R*)-4-{4-[4-(5-methoxypyrimidin-2-yl)phenyl]-2-oxopyridin-1(2*H*)-yl}-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (16ee) using a procedure analogous to that described in the General Tetrahydropyranyl Deprotection, Method A. ^1H NMR (400 MHz, DMSO- d_6) δ 11.16 (d, J = 1.56 Hz, 1H), 9.25 (d, J = 1.76 Hz, 1H), 8.71 (s, 2H), 8.40 (d, J = 8.59 Hz, 2H), 7.84 - 7.92 (m, 2H), 7.79 (d, J = 7.22 Hz, 1H), 6.79 (d, J = 2.15 Hz, 1H), 6.73 (dd, J = 2.05, 7.12 Hz, 1H), 4.08 - 4.19 (m, 1H), 3.98 (s, 3H), 3.71 - 3.84 (m, 1H), 3.12 (s, 3H), 2.38 - 2.47 (m, 1H), 2.11 - 2.25 (m, 1H), 1.58 (s, 3H). HRMS: m/z calc'd for $\text{C}_{22}\text{H}_{24}\text{N}_4\text{O}_6\text{S} [\text{M}+\text{H}]^+$: 473.1417; found: 473.1485.

Preparation of (2*R*)-*N*-hydroxy-2-methyl-2-(methylsulfonyl)-4-{2-oxo-4-[4-(1,3-thiazol-2-yl)phenyl]pyridin-1(2*H*)-yl}butanamide (17ff).



Scheme 6. Synthesis of 5-methoxy-2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrimidine (34).^a



^aReagents and conditions. (a) Pd(dppf)Cl₂-CH₂Cl₂, bis(pinacolato)diborane, K₂CO₃, 1,4-dioxane, 80 °C.

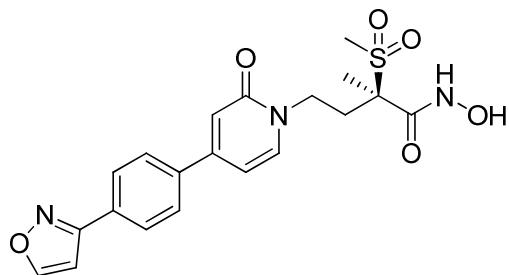
2-[4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,3-thiazole (34).

[1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (206 mg, 0.27 mmol) was added to a mixture of 2-(4-bromophenyl)-1,3-thiazole (610 mg, 2.54 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (406 mg, 1.60 mmol), and K_2CO_3 (540 mg, 5.33 mmol) in 1,4-dioxane (10 mL). The reaction mixture was heated to 80 °C and was stirred at this temperature overnight. The reaction mixture was diluted with water (5 mL) and was extracted with ethyl acetate (4x10 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified via flash chromatography using silica and a gradient of 0-40% ethyl acetate in *n*-heptane to afford the title compound (620 mg, 84.9%). 1H NMR (400 MHz, $CDCl_3$) δ 7.94 - 8.01 (m, 2H), 7.85 - 7.93 (m, 3H), 7.36 (d, J = 3.32 Hz, 1H), 1.37 (s, 12H). LCMS: m/z 288.2 [M+H]⁺.

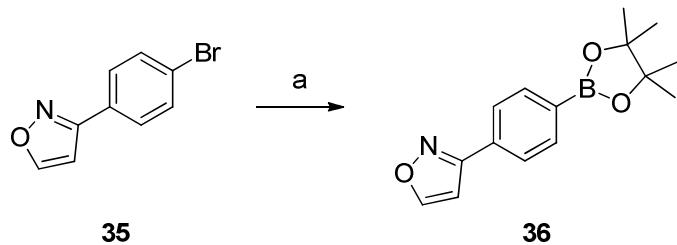
(2*R*)-2-Methyl-2-(methylsulfonyl)-4-{2-oxo-4-[4-(1,3-thiazol-2-yl)phenyl]pyridin-1(2*H*)-yl}-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (16ff). The title compound (250 mg, 78%) was obtained as a solid from (2*R*)-4-(4-iodo-2-oxopyridin-1(2*H*)-yl)-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (15) and 2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,3-thiazole using a procedure analogous to that described in the General Suzuki-Miyaura Coupling, Method A. LCMS: m/z 530.1 [M-H]⁻.

(2*R*)-*N*-Hydroxy-2-methyl-2-(methylsulfonyl)-4-{2-oxo-4-[4-(1,3-thiazol-2-yl)phenyl]pyridin-1(2*H*)-yl}butanamide (17ff). The title compound (85 mg, 40%) was obtained as a solid from (2*R*)-2-methyl-2-(methylsulfonyl)-4-{2-oxo-4-[4-(1,3-thiazol-2-yl)phenyl]pyridin-1(2*H*)-yl}-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (16ff) using a procedure analogous to that described in the General Tetrahydrofuran Deprotection, Method A. 1H NMR (400 MHz, $DMSO-d_6$) δ 11.15 (s, 1H), 9.25 (s, 1H), 8.03 - 8.08 (m, 2H), 7.98 (d, J = 3.32 Hz, 1H), 7.84 - 7.91 (m, 3H), 7.79 (d, J = 7.22 Hz, 1H), 6.79 (d, J = 1.95 Hz, 1H), 6.71 (dd, J = 2.15, 7.22 Hz, 1H), 4.06 - 4.20 (m, 1H), 3.69 - 3.85 (m, 1H), 3.12 (s, 3H), 2.38 - 2.48 (m, 1H), 2.10 - 2.25 (m, 1H), 1.58 (s, 3H). HRMS: m/z calc'd for $C_{20}H_{21}N_3O_5S_2$ [M+H]⁺: 448.0995; found: 448.0998.

Preparation of (2*R*)-*N*-hydroxy-4-[4-(4-isoxazol-3-ylphenyl)-2-oxopyridin-1(2*H*)-yl]-2-methyl-2-(methylsulfonyl)butanamide (17gg).



Scheme 7. Synthesis of 2-methoxy-5-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrimidine (**36**).^a



^aReagents and conditions. (a) Pd(dppf)Cl₂-CH₂Cl₂ complex, bis(pinacolato)diborane, KOAc, 1,4-dioxane, 80 °C.

3-[4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]isoxazole (36**).**

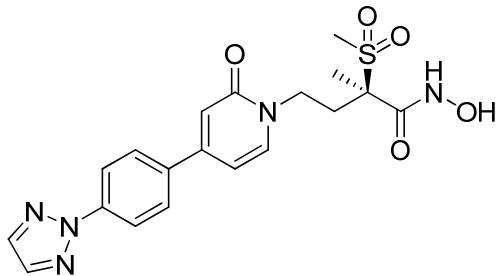
[1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (340 mg, 0.42 mmol) was added to a solution of 3-(4-bromophenyl)isoxazole (**35**, 930 mg, 4.15 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (1.58 g, 6.22 mmol), and potassium acetate (1.26 g, 4.15 mmol) in 1,4-dioxane (30 ml). The reaction mixture was heated to 80 °C and stirred at this temperature overnight. The reaction mixture was allowed to cool to rt and filtered through celite (~1 inch). The filter pad was washed with ethyl acetate (2x30 ml) and the combined filtrates were concentrated *in vacuo*. The crude material was purified via flash

chromatography using a Biotage SNAP Cartridge (KP-Sil 25g) and a gradient of 0-50% ethyl acetate in *n*-heptane to afford the title compound as an orange solid (1.35 g). The title compound was taken forward without further purification. ^1H NMR (400 MHz, CDCl_3) δ 8.48 (d, J = 1.76 Hz, 1H), 7.79 - 7.97 (m, 4H), 6.70 (d, J = 1.66 Hz, 1H), 1.37 (s, 12H). LCMS: m/z 272.1 [M+H] $^+$.

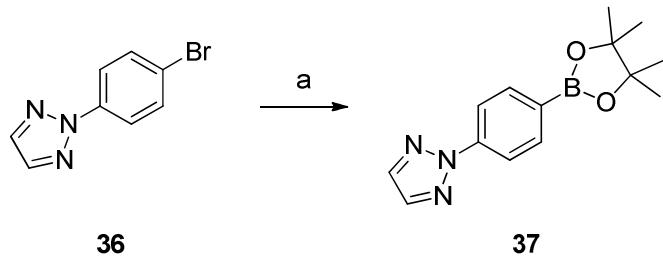
(2*R*)-4-[4-(4-Isoxazol-3-ylphenyl)-2-oxopyridin-1(2*H*)-yl]-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (16gg). The title compound (110 mg, 43%) was obtained as an off-white solid from (2*R*)-4-(4-iodo-2-oxopyridin-1(2*H*)-yl)-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (15) and 3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]isoxazole using a procedure analogous to that described in the General Suzuki-Miyaura Coupling, Method A. LCMS: m/z 514.1 [M-H] $^-$.

(2*R*)-*N*-Hydroxy-4-[4-(4-isoxazol-3-ylphenyl)-2-oxopyridin-1(2*H*)-yl]-2-methyl-2-(methylsulfonyl)butanamide (17gg). The title compound (68 mg, 46.4%) was obtained as a white solid from (2*R*)-4-[4-(4-isoxazol-3-ylphenyl)-2-oxopyridin-1(2*H*)-yl]-2-methyl-2-(methylsulfonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)butanamide (16gg) using a procedure analogous to that described in General Tetrahydropyranyl Deprotection, Method B. (68 mg, 46%), ^1H NMR (400 MHz, DMSO-d_6) δ 11.15 (s, 1H), 9.25 (s, 1H), 9.05 (d, J = 1.76 Hz, 1H), 7.84 - 8.07 (m, 3H), 7.80 (d, J = 7.02 Hz, 1H), 6.80 (d, J = 2.15 Hz, 1H), 6.72 (dd, J = 2.05, 7.12 Hz, 1H), 4.05 - 4.20 (m, 1H), 3.69 - 3.85 (m, 1H), 3.11 (s, 3H), 2.38 - 2.48 (m, 1H), 2.12 - 2.24 (m, 1H), 1.58 (s, 3H). (HRMS (ESI) m/z calc'd for $\text{C}_{20}\text{H}_{21}\text{N}_3\text{O}_6\text{S}$ [M-H] $^+$: 430.1151; found: 430.1079.

Preparation of (2*R*)-*N*-hydroxy-2-methyl-2-(methylsulfonyl)-4-[2-oxo-4-[4-(2*H*-1,2,3-triazol-2-yl)phenyl]pyridin-1(2*H*)-yl]butanamide (17hh).



Scheme 8. Synthesis of 2-methoxy-5-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrimidine (**37**).^a



^aReagents and conditions. (a) Pd(dppf)Cl₂-CH₂Cl₂ complex, bis(pinacolato)diborane, KOAc, 1,4-dioxane, 80 °C.

2-[4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2H-1,2,3-triazole (37**).**

[1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (280 mg, 0.34 mmol) was added to a mixture of 2-(4-bromophenyl)-2H-1,2,3-triazole (**36**, 255 mg, 1.14 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (350 mg, 1.38 mmol), and potassium acetate (340 mg, 3.46 mmol) in 1,4-dioxane (10 ml). The reaction mixture was heated to 80 °C and stirred at this temperature overnight. The reaction mixture was allowed to cool to rt and diluted with ethyl acetate (30 mL) and brine (30 mL). The mixture was filtered through celite (~1 inch). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2x30 mL). The organic layers were combined, dried (MgSO₄), filtered, and concentrated *in vacuo*. The crude material was purified via flash chromatography using an Analogix SF15-12g column and a gradient of 0-10% ethyl acetate in *n*-heptane to afford an orange solid (240.6 mg, 78%). ¹H NMR (400 MHz, CDCl₃) δ 8.10 (d, *J* = 8.59 Hz, 2H), 7.94 (d, *J* = 8.59 Hz, 2H), 7.83 (s, 2H), 1.36 (s, 12H). LCMS: m/z 272.4 [M+H]⁺.

(2R)-2-Methyl-2-(methylsulfonyl)-4-{2-oxo-4-[4-(2H-1,2,3-triazol-2-yl)phenyl]pyridin-1(2H)-yl}-N-(tetrahydro-2H-pyran-2-yloxy)butanamide (16hh). The title compound (101 mg, 49%) was obtained as a white solid from (2R)-4-(4-iodo-2-oxopyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)-N-(tetrahydro-2H-pyran-2-yloxy)butanamide (15) and 2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2H-1,2,3-triazole using a procedure analogous to that described in the General Suzuki-Miyaura Coupling, Method A. LCMS: m/z 514.7 [M-H]⁻.

(2R)-N-Hydroxy-2-methyl-2-(methylsulfonyl)-4-{2-oxo-4-[4-(2H-1,2,3-triazol-2-yl)phenyl]pyridin-1(2H)-yl}butanamide (17hh). The title compound (63.7 mg, 74%) was obtained as a white solid from (2R)-2-methyl-2-(methylsulfonyl)-4-{2-oxo-4-[4-(2H-1,2,3-triazol-2-yl)phenyl]pyridin-1(2H)-yl}-N-(tetrahydro-2H-pyran-2-yloxy)butanamide (16hh) using a procedure analogous to that described in the General Tetrahydropyranyl Deprotection, Method A. ¹H NMR (400 MHz, CD₃OD) δ 8.17 - 8.26 (m, 2H), 7.96 (s, 2H), 7.84 - 7.91 (m, 2H), 7.75 (d, *J* = 7.23 Hz, 1H), 6.87 (d, *J* = 1.76 Hz, 1H), 6.82 (dd, *J* = 2.15, 7.03 Hz, 1H), 4.25 - 4.44 (m, 1H), 3.88 - 4.03 (m, 1H), 3.13 (s, 3H), 2.54 - 2.67 (m, 1H), 2.29 - 2.46 (m, 1H), 1.72 (s, 3H). HRMS: *m/z* calc'd for C₁₉H₂₁N₅O₅S [M+H]⁺: 432.1336; found: 432.1334.

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