Supporting Information

Palladium-Catalyzed, Enantioselective Heine Reaction

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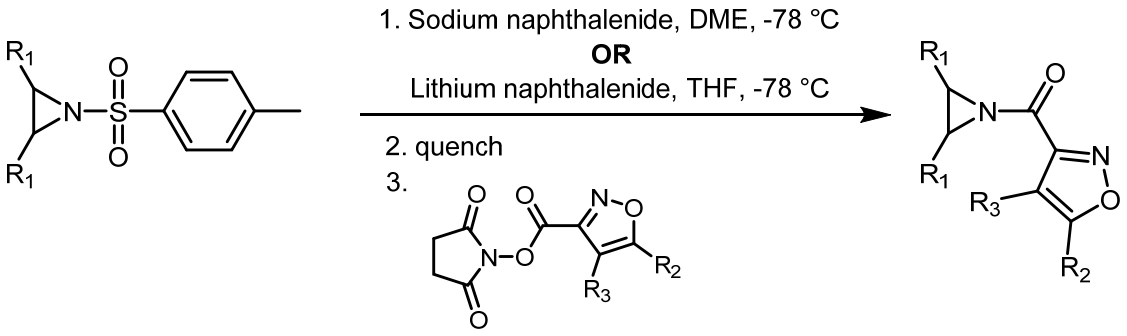
EXPERIMENTAL

General. ^{1}H NMR spectra were recorded on a Bruker DRX (400 MHz) or Bruker Avance (600 MHz). Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz) and integration. ^{13}C NMR spectra were recorded on a Bruker DRX 400 (100 MHz) or Bruker Avance 600 (151 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard ($CDCl_3$: 77.2 ppm). High resolution mass spectrometry was acquired with a Bruker MicrOTOF-Q II with electron spray ionization (ESI) at the University of North Carolina Wilmington.

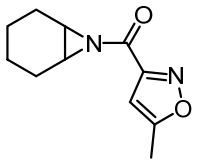
Liquid chromatography was performed using forced flow (flash chromatography) on silica gel (SiO_2, 32 to 63μm) purchased from Dynamic Adsorbents or Silacycle. Thin layer chromatography (TLC) was performed on EMD Chemicals 0.25 mm silica gel 60 plates. Visualization was achieved UV light (254 nm) or basic potassium permanganate in water followed by heating. High pressure liquid chromatography (HPLC) was performed on an HP instrument equipped with an autosampler and a UV detector set to 250 nm. A Daicel CHIRALPAK or CHIRALCEL (0.46 cm x 25 cm) column with a mixed solvent (hexane/isopropanol) at a flow rate of 1 mL/minute was used for data pertaining to enantiomeric excess calculations.

All reactions were conducted in oven or flame-dried glassware under an inert atmosphere of argon. All solvents were EMD Chemicals anhydrous solvents sold by VWR International. Dichloro(bisacetonitrile)palladium(II), (*R*)-(-)-5,5′-Bis[di(3,5-di-tert-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole, silver trifluoromethanesulfonate and all other metal salts were purchased from Strem Chemical Company. 5-Isopropylisoxazole-3-carboxylic acid was purchased from Chem-Impex International, Inc. 5-Cyclopropylisoxazole-3-carboxylic acid was purchased from Combi-Blocks. 4,5,6,7-Tetrahydrobenzo[d]isoxazole-3-carboxylic acid was purchased from Enamine. All other chemicals were purchased from Alfa Aesar, Acros Chemical Company, or Oakwood Products, and were used as received. Isoxazole-3-carboxylic acid was provided as a gift from A1-BioChem Labs.

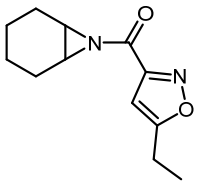
Aziridine synthesis from succinimide esters:[1]



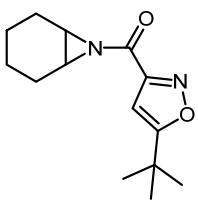
A flame-dried round bottom flask containing a Teflon®-coated stir bar was charged with *N*-tosylaziridine (between 1–1.2 equivalents) and anhydrous tetrahydrofuran (0.33 M based on aziridine) under argon. The reaction solution was cooled to -78 °C. Lithium naphthalenide solution (~1M in tetrahydrofuran) or sodium naphthalenide solution (~1M in DME) was added dropwise until the solution was consistently dark green in color (typically 2.5 equivalents relative to the starting aziridine).[2] After 5 additional minutes of continuous stirring -78 °C, the reaction was quenched with of pH = 7 buffer (2 mL per 1 mmol of limiting reagent) was added all at once. The suspension become colorless and was warmed to 0 °C. The succinimide reagent (1–1.2 equivalent) was added all at once, and the reaction was stirred for three hours at room temperature. *The following general work-up is written for a 3 mmol scale, so volumes should be adjusted appropriately*. The reaction mixture was diluted with 30 mL of ethyl acetate and 6 mL of H_2O. The organic layer was taken, and the aqueous layer was extracted with 20 mL of ethyl acetate. The combined organic layer was washed with 10 mL H_2O and 15 mL saturated brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. The product was purified the same day as synthesis or frozen in benzene until purification could be performed by silica gel column chromatography.



7-azabicyclo[4.1.0]heptan-7-yl(5-methylisoxazol-3-yl)methanone (**5,** *Table 2, entry 2*)**.** Synthesized from 7-tosyl-7-azabicyclo[4.1.0]heptane[3] (4.524 g, 18 mmol) and 2,5-dioxopyrrolidin-1-yl 5-methylisoxazole-3-carboxylate (3.362 g, 15 mmol) using lithium naphthalenide. The product was purified by silica gel column chromatography using 5:1 hexanes/ethyl acetate to afford a white solid (1.868 g, 60% yield). HRMS: calculated for $C_{11}H_{14}N_2NaO_2^+$: 229.0948 ($M+Na^+$), found 229.0942 ($M+Na^+$). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 6.38 (q, *J* = 0.8 Hz, 1H), 2.96 – 2.91 (m, 2H), 2.48 (d, *J* = 0.9 Hz, 3H), 2.19 – 2.06 (m, 2H), 1.94 – 1.85 (m, 2H), 1.57 – 1.49 (m, 2H), 1.38 – 1.27 (m, 2H). ^{13}C NMR: (151 MHz, $CDCl_3$) δ 171.1, 170.8, 159.3, 102.0, 37.6, 23.9, 20.1, 12.5.

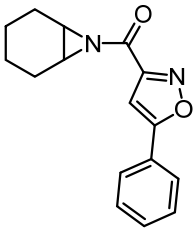


(7-azabicyclo[4.1.0]heptan-7-yl)(5-ethylisoxazol-3-yl)methanone (**SI-1,** *Table 2, entry 3*). Synthesized from 7-tosyl-7-azabicyclo[4.1.0]heptane[3] (1.26 g, 5 mmol) and 2,5-dioxopyrrolidin-1-yl 5-ethylisoxazole-3-carboxylate (1.31 g, 5.5 mmol) using lithium naphthalenide. The product was purified by silica gel chromatography using 9:1 hexanes/ethyl acetate to afford a clear oil (0.596 g, 54% yield). HRMS: calculated for $C_{12}H_{16}N_2NaO_2^+$: 243.1104 ($M+Na^+$), found 243.1107 ($M+Na^+$). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ 6.39 (t, *J* = 0.9 Hz, 1H), 2.97 – 2.92 (m, 2H), 2.79 (qd, *J* = 7.6 Hz, 0.9 Hz, 2H), 2.17 – 2.10 (m, 2H), 1.94 – 1.86 (m, 2H), 1.55 – 1.47 (m, 2H), 1.37 – 1.29 (m, 2H), 1.32 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR: (151 MHz, $CDCl_3$) δ 176.3, 171.1, 159.1, 100.6, 37.6, 23.9, 20.4, 20.1, 11.8.

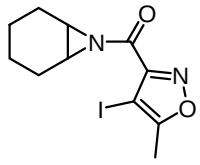


(7-azabicyclo[4.1.0]heptan-7-yl)(5-(tert-butyl)isoxazol-3-yl)methanone (**14,** *Table 2, entry 6*)**.** Synthesized from 7-tosyl-7-azabicyclo[4.1.0]heptane[3] (3.02 g, 12 mmol) and 2,5-dioxopyrrolidin-1-yl 5-(*tert*-butyl)isoxazole-3-carboxylate (2.66 g, 10 mmol) using lithium naphthalenide. The product was purified by silica gel chromatography using 7:1 hexanes/MTBE to afford a white solid. (1.96 g, 79% yield). HRMS:

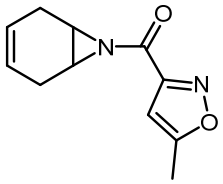
calculated for $C_{14}H_{20}N_2NaO_2^+$: 271.1417 ($M+Na^+$), found 271.1415 ($M+Na^+$). ^1H NMR: (600 MHz, $CDCl_3$) δ 6.37 (s, 1H), 2.94 – 2.98 (m, 2H), 2.18 – 2.11 (m, 2H), 1.94 – 1.87 (m, 2H), 1.55 – 1.48 (m, 2H), 1.37 (s, 9H), 1.36 – 1.29 (m, 2H). ^{13}C NMR: (151 MHz, $CDCl_3$) δ 182.7, 171.2, 158.9, 98.9, 37.6, 33.1, 29.0, 23.9, 20.1.



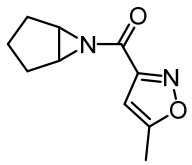
(7-azabicyclo[4.1.0]heptan-7-yl)(5-phenylisoxazol-3-yl)methanone (**SI-2,** *Table 2, entry 7*). Synthesized from 7-tosyl-7-azabicyclo[4.1.0]heptane[3] (2.11 g, 8.4 mmol) and 2,5-dioxopyrrolidin-1-yl 5-phenylisoxazole-3-carboxylate (2.00 g, 7 mmol) using sodium naphthalenide. The product was purified by silica gel chromatography using 7:1 hexanes/ethyl acetate to afford a white solid (0.75 g, 56% yield). HRMS: calculated for $C_{16}H_{16}N_2NaO_2^+$: 291.1104 ($M+Na^+$), found 291.1101 ($M+Na^+$). ^1H NMR: (600 MHz, $CDCl_3$) δ 7.78 – 7.84 (m, 2H), 7.52 – 7.45 (m, 3H), 6.93 (s, 1H), 3.03 – 2.99 (m, 2H), 2.22 – 2.15 (m, 2H), 1.98 – 1.89 (m, 2H), 1.59 – 1.51 (m, 2H), 1.40 – 1.32 (m, 2H). ^{13}C NMR: (151 MHz, $CDCl_3$) δ 171.3, 170.8, 159.7, 130.1, 129.3, 127.3, 126.1, 99.7, 37.7, 23.9, 20.1.



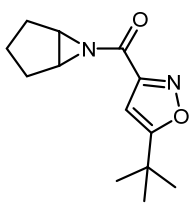
(7-azabicyclo[4.1.0]heptan-7-yl)(4-iodo-5-methylisoxazol-3-yl)methanone (**SI-3,** *Table 2, entry 8*). Synthesized from 7-tosyl-7-azabicyclo[4.1.0]heptane[3] (3.500 g, 13.9 mmol) and 2,5-dioxopyrrolidin-1-yl 4-iodo-5-methylisoxazole-3-carboxylate (3.501 g, 10 mmol) using sodium naphthalenide. The product was purified by silica gel chromatography using 6:1 hexanes/ethyl acetate to afford a pale yellow solid (1.06 g, 32% yield). HRMS: calculated for $C_{11}H_{13}IN_2NaO_2^+$: 354.9914 ($M+Na^+$), found 354.9912 ($M+Na^+$). ^1H NMR: (600 MHz, $CDCl_3$) δ 3.00 – 2.94 (m, 2H), 2.54 (s, 3H), 2.17 – 2.05 (m, 2H), 1.93 – 1.81 (m, 2H), 1.56 – 1.44 (m, 2H), 1.39 – 1.23 (m, 2H). ^{13}C NMR: (151 MHz, $CDCl_3$) δ 172.8, 170.0, 157.0, 56.3, 37.9, 23.7, 20.0, 12.7.



(7-azabicyclo[4.1.0]hept-3-en-7-yl)(5-methylisoxazol-3-yl)methanone (**SI-4,** *Table 3, entry 1).* Synthesized from 7-tosyl-7-azabicyclo[4.1.0]hept-3-ene[4] (1.25 g, 5 mmol) and 2,5-dioxopyrrolidin-1-yl 5-methylisoxazole-3-carboxylate (1.23 g, 5.5 mmol) using sodium naphthalenide. The product was purified using silica gel column using 5:1 hexane/ethyl acetate to afford a white solid (0.571 g, 56% yield). HRMS: calculated for $C_{11}H_{12}N_2NaO_2^+$: 227.0791 ($M+Na^+$) found 227.0795 ($M+Na^+$). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 6.39 (q, *J* = 0.9 Hz, 1H), 5.55 – 5.50 (m, 2H), 3.09 (s, 2H), 2.84 – 2.74 (m, 2H), 2.53 – 2.43 (m, 2H), 2.48 (s, 3H). ^{13}C NMR: (151 MHz, $CDCl_3$) δ 170.8, 170.6, 159.2, 122.4, 102.0, 36.8, 24.0, 12.5.

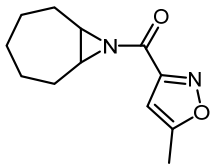


(6-azabicyclo[3.1.0]hexan-6-yl)(5-methylisoxazol-3-yl)methanone (**SI-5,** *Table 3, entry 3).* Synthesized from 6-tosyl-6-azabicyclo[3.1.0]hexane[5] (0.854 g, 3.6 mmol) and 2,5-dioxopyrrolidin-1-yl 5-methylisoxazole-3-carboxylate (0.673 g, 3 mmol) using lithium naphthalenide. The product was purified by silica gel column chromatography using 4:1 hexanes/ethyl acetate to afford a pale yellow oil (0.537 g, 56% yield). HRMS: calculated for $C_{10}H_{12}N_2NaO_2^+$: 215.0791 ($M+Na^+$) found 215.0801 ($M+Na^+$). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 6.39 (q, *J* = 0.8 Hz, 1H), 3.34 (s, 2H), 2.48 (d, *J* = 0.8 Hz, 3H), 2.25 – 2.16 (m, 2H), 1.75 – 1.61 (m, 3H), 1.32 – 1.16 (m, 1H). ^{13}C NMR: (151 MHz, $CDCl_3$) δ 170.8, 168.9, 159.2, 102.0, 44.0, 27.0, 19.3, 12.5.

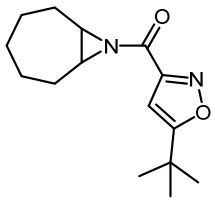


(6-azabicyclo[3.1.0]hexan-6-yl)(5-(tert-butyl)isoxazol-3-yl)methanone (**SI-6,** *Table 3, entry 4).* Synthesized from 6-tosyl-6-azabicyclo[3.1.0]hexane[5] (1.42 g, 6 mmol) and 2,5-dioxopyrrolidin-1-yl 5-(*tert*-butyl)isoxazole-3-carboxylate (1.33 g, 5 mmol) using lithium naphthalenide. The product was purified by silica gel column chromatography using 8:1 hexanes/ethyl acetate to afford a pale yellow oil (1.17 g, 86% yield).

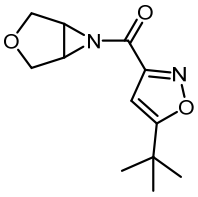
HRMS: calculated for $C_{13}H_{18}N_2NaO_2^+$: 257.1260 ($M+Na^+$) found 257.1273 ($M+Na^+$). ^1H NMR: (600 MHz, $CDCl_3$) δ 6.36 (s, 1H), 3.39 – 3.31 (m, 2H), 2.25 – 2.17 (m, 2H), 1.73 – 1.64 (m, 3H), 1.36 (s, 9H), 1.33 – 1.22 (m, 1H). ^{13}C NMR: (151 MHz, $CDCl_3$) δ 182.7, 169.1, 158.83, 98.8, 44.0, 33.0, 28.9, 27.0, 19.3.



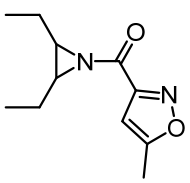
(8-azabicyclo[5.1.0]octan-8-yl)(5-methylisoxazol-3-yl)methanone (**SI-7,** *Table 3, entry 5)*. Synthesized from 8-tosyl-8-azabicyclo[5.1.0]octane[6] (1.33 g, 5 mmol) and 2,5-dioxopyrrolidin-1-yl 5-methylisoxazole-3-carboxylate (1.23 g, 5.5 mmol) using sodium naphthalenide. The product was purified by silica gel column chromatography in a gradient of 5:1 hexanes/ethyl acetate to 3:1 hexanes/ethyl acetate to afford a white solid (0.525 g, 48% yield). HRMS: calculated for $C_{12}H_{17}N_2O_2^+$: 221.1284 ($M+H^+$) found 221.1293 ($M+H^+$). ^1H NMR: (400 MHz, $CDCl_3$) δ 6.38 (q, J = 0.9 Hz, 1H), 2.94 – 2.87 (m, 2H), 2.48 (d, J = 0.9 Hz, 3H), 2.21 – 2.09 (m, 2H), 1.99 – 1.88 (m, 2H), 1.72 – 1.46 (m, 5H), 1.29 – 1.14 (m, 1H). ^{13}C NMR: (151 MHz, $CDCl_3$) δ 171.4, 170.8, 159.2, 101.9, 42.4, 31.4, 29.0, 25.4, 12.5.



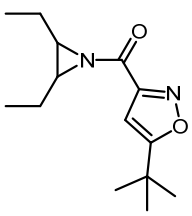
(8-azabicyclo[5.1.0]octan-8-yl)(5-(*tert*-butyl)isoxazol-3-yl)methanone (**SI-8,** *Table 3, entry 6)*. Synthesized from 8-tosyl-8-azabicyclo[5.1.0]octane[6] (0.955 g, 3.6 mmol) and 2,5-dioxopyrrolidin-1-yl 5-(*tert*-butyl)isoxazole-3-carboxylate (0.799 g, 3 mmol) using lithium naphthalenide. The product was purified by silica gel column chromatography using 30:1 hexanes/ethyl acetate to afford a white solid (0.691 g, 88% yield). HRMS: calculated for $C_{15}H_{22}N_2NaO_2^+$: 285.1574 ($M+Na^+$) found 285.1586 ($M+Na^+$). ^1H NMR: (600 MHz, $CDCl_3$) δ 6.36 (s, 1H), 2.93 – 2.89 (m, 2H), 2.23 – 2.12 (m, 2H), 1.96 – 1.88 (m, 2H), 1.70 – 1.63 (m, 1H), 1.62 – 1.48 (m, 4H), 1.36 (s, 9H), 1.21 – 1.13 (m, 1H). ^{13}C NMR: (151 MHz, $CDCl_3$) 182.7, 171.5, 158.8, 98.9, 42.4, 33.0, 31.4, 28.97, 28.95, 25.4.



(3-oxa-6-azabicyclo[3.1.0]hexan-6-yl)(5-(*tert*-butyl)isoxazol-3-yl)methanone (**SI-9,** *Table 3, entry 8).* Synthesized from 6-tosyl-3-oxa-6-azabicyclo[3.1.0]hexane[7] (0.718 g, 3 mmol) and 2,5-dioxopyrrolidin-1-yl 5-(*tert*-butyl)isoxazole-3-caroxylate (0.799 g, 3 mmol) using lithium naphthalenide. The product was purified by silica gel column chromatography using 3:1 hexanes/ethyl acetate to afford a white solid (0.442 g, 62% yield). HRMS: calculated for $C_{12}H_{16}N_2NaO_3^+$: 259.1053 ($M+Na^+$), found 259.1062 ($M+Na^+$). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 6.41 (s, 1H), 4.19 (d, *J* = 10.2 Hz, 2H), 3.63 (d, *J* = 10.2 Hz, 2H), 3.53 (s, 2H), 1.37 (s, 9H). ^{13}C NMR: (151 MHz, $CDCl_3$) δ 182.8, 168.1, 158.6, 99.0, 66.2, 41.4, 33.1, 28.9.



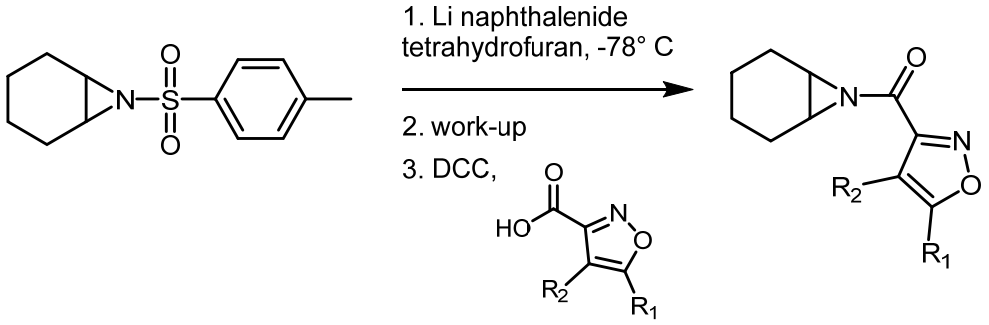
(2,3-diethylaziridin-1-yl)(5-methylisoxazol-3-yl)methanone (**SI-10,** *Table 3, entry 9).* Synthesized from *cis*-2,3-diethyl-1-tosylaziridine[8] (1.52 g, 6 mmol) and 2,5-dioxopyrrolidin-1-yl 5-methylisoxazole-3-carboxylate (0.97 g, 4.3 mmol) using sodium naphthalenide. The product was purified by silica gel column chromatography using 4:1 hexanes/ethyl acetate to afford a white solid (0.31 g, 35% yield). HRMS: calculated for $C_{11}H_{16}N_2NaO_2^+$: 231.1104 ($M+Na^+$) found 231.1108 ($M+Na^+$). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 6.38 (q, *J* = 0.9 Hz, 1H), 2.72 – 2.65 (m, 1H), 2.48 (d, *J* = 0.9 Hz, 3H), 1.94 – 1.81 (m, 2H), 1.64 – 1.52 (m, 2H), 1.10 (t, *J* = 7.5 Hz, 6H). ^{13}C NMR: (151 MHz, $CDCl_3$) δ 171.5, 170.7, 159.2, 102.0, 44.3, 21.1, 12.4, 11.7.



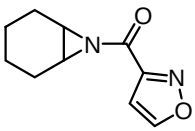
(5-(*tert*-butyl)isoxazol-3-yl)(2,3-diethylaziridin-1-yl)methanone (**SI-11,** *Table 3, entry 10).* Synthesized from *cis*-2,3-diethyl-1-tosylaziridine[8] (0.760 g, 3 mmol) and 2,5-dioxopyrrolidin-1-yl 5-(*tert*-butyl)isoxazole-3-carboxylate (0.799 g, 3 mmol) using lithium naphthalenide. The product was purified using silica gel column chromatography using 20:1 hexanes/ethyl acetate to afford a clear oil (0.545 g, 73% yield).

HRMS: calculated for $C_{12}H_{16}N_2NaO_3^+$: 259.1053 ($M+Na^+$) found 259.1062 ($M+Na^+$). ^1H NMR: (600 MHz, $CDCl_3$) δ 6.36 (s, 1H), 2.71 (t, J = 4.7 Hz, 2H), 1.93 – 1.84 (m, 2H), 1.63 – 1.52 (m, 2H), 1.37 (s, 9H), 1.11 (t, J = 7.5 Hz, 6H). ^{13}C NMR: (151 MHz, $CDCl_3$) δ 182.6, 171.5, 158.7, 99.0, 44.3, 33.1, 29.0, 21.1, 11.7.

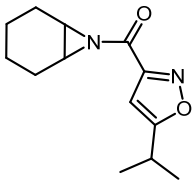
Aziridine synthesis from carboxylic acids by DCC coupling:



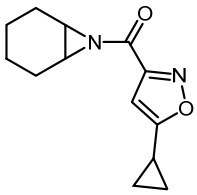
A flame-dried round bottom flask containing a Teflon®-coated stir bar was charged with 7-tosyl-7-azabicyclo[4.1.0]heptane[3] (0.905 g, 3.6 mmol) and anhydrous tetrahydrofuran (11 mL, 0.33 M based on the starting aziridine) under argon. The reaction mixture was cooled to -78 °C and lithium naphthalenide solution (~1M in tetrahydrofuran) was added dropwise until the solution was consistently dark green in color (typically 2.5 equivalents relative to the starting aziridine). After 5 additional minutes of stirring, the solution was quenched with 6 mL of H_2O and warmed to room temperature. The mixture was extracted two times with 20 mL of diethyl ether. The combined organic layers were washed with 10 mL of saturated brine and dried over $MgSO_4$. The suspension was filtered and concentrated to approximately half volume by rotary evaporation. The corresponding carboxylic acid (3.0 mmol) and *N*,*N*'-dicyclohexylcarbodiimide (0.681 g, 3.3 mmol) were added and the solution was stirred for two hours. The crude reaction mixture was concentrated in vacuo. The product residue was brought up in 20 mL acetonitrile and filtered. The filtrate was concentrated in vacuo and then purified using silica gel column chromatography.



(7-azabicyclo[4.1.0]heptan-7-yl)(isoxazol-3-yl)methanone (**SI-12,** *Table 2, entry 1)*. Synthesized from isoxazole-3-carboxylic acid (0.339 g, 3 mmol). The product was purified by silica gel column chromatography using 5:1 hexanes/ethyl acetate to afford a white solid (0.577 g, 63% yield). HRMS: calculated for $C_{10}H_{12}N_2NaO_2^+$: 215.0791 ($M+Na^+$), found 215.0798 ($M+Na^+$). ^1H NMR: (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 1.6 Hz, 1H), 6.79 (d, *J* = 1.6 Hz, 1H), 2.98 – 2.94 (m, 2H), 2.17 – 2.09 (m, 2H), 1.94 – 1.85 (m, 2H), 1.55 – 1.45 (m, 2H), 1.37 – 1.28 (m, 2H). ^{13}C NMR: (151 MHz, $CDCl_3$) δ 170.4, 159.5, 158.2, 104.9, 37.7, 23.8, 20.0.

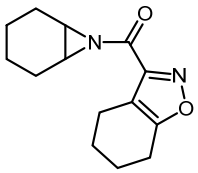


(7-azabicyclo[4.1.0]heptan-7-yl)(5-isopropylisoxazol-3-yl)methanone (**SI-13,** *Table 2, entry 4)*. Synthesized from 5-isopropylisoxazole-3-carboxylic acid (0.465 g, 3 mmol). The product was purified using silica gel column chromatography using a solvent system of 7:1 hexanes/ethyl acetate to afford a colorless oil (0.389 g, 55% yield). HRMS: calculated for $C_{13}H_{18}N_2NaO_2^+$: 257.1260 ($M+Na^+$) found 257.1273 ($M+Na^+$). ^1H NMR: (400 MHz, $CDCl_3$) δ 6.38 (s, 1H), 3.11 (septet, *J* = 7.0 Hz, 1H), 2.98 – 2.93 (m, 2H), 2.19 – 2.10 (m, 2H), 1.96 – 1.85 (m, 2H), 1.56 – 1.46 (m, 2H), 1.39 – 1.24 (m, 2H), 1.34 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR: (151 MHz, $CDCl_3$) δ 180.2, 171.2, 159.0, 99.5, 37.6, 27.4, 23.9, 21.0, 20.1.



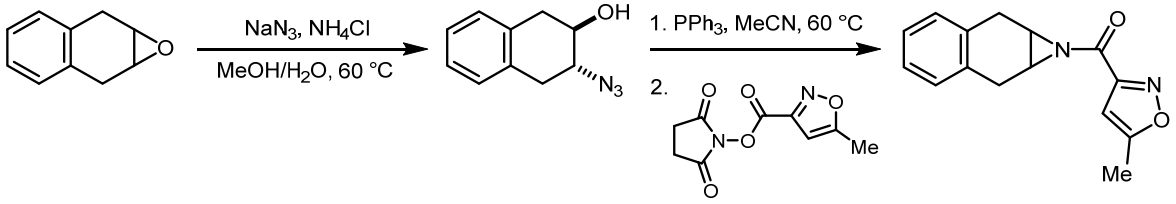
(7-azabicyclo[4.1.0]heptan-7-yl)(5-cyclopropylisoxazol-3-yl)methanone (**SI-14,** *Table 2, entry 5)*. Synthesized from 5-cyclopropylisoxazole-3-carboxylic acid (0.459 g, 3 mmol). The product was purified using silica gel column chromatography using a solvent system of 5:1 hexanes/ethyl acetate to afford a white solid (0.372 g, 53% yield). HRMS: calculated for $C_{13}H_{16}N_2NaO_2^+$: 255.1104 ($M+Na^+$) found 255.1104 ($M+Na^+$). ^1H NMR: (600 MHz, $CDCl_3$) δ 6.30 (s, 1H), 2.96 – 2.90 (m, 2H), 2.19 – 2.03 (m, 3H),

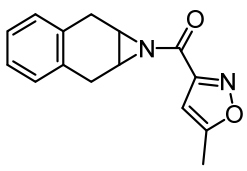
1.97 – 1.83 (m, 2H), 1.57 – 1.45 (m, 2H), 1.40 – 1.24 (m, 2H), 1.15 – 1.06 (m, 2H), 1.06 – 0.97 (m, 2H). ^{13}C NMR: (151 MHz, $CDCl_3$) δ 176.2, 171.0, 159.2, 99.1, 37.5, 23.8, 20.0, 8.9, 8.3.



(7-azabicyclo[4.1.0]heptan-7-yl)(4,5,6,7-tetrahydrobenzo [d]isoxazol-3-yl)methanone (**SI-15,** *Table 2, entry 9).* Synthesized from 4,5,6,7-tetrahydrobenzo[d]isoxazole-3-carboxylic acid (0.502 g, 3 mmol). The product was purified by silica gel column chromatography using 7:1 hexanes/ethyl acetate to afford a white solid (0.896 g, 71% yield). HRMS: calculated for $C_{14}H_{18}N_2NaO_2^+$: 269.1260 ($M+Na^+$), found 269.1255 ($M+Na^+$). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 2.98 – 2.91 (m, 2H), 2.73 (tt, *J* = 6.3 Hz, 1.5 Hz, 2H), 2.67 (tt, *J* = 6.1 Hz, 1.5 Hz, 2H), 2.19 – 2.09 (m, 2H), 1.95 – 1.81 (m, 4H), 1.79 – 1.71 (m, 2H), 1.57 – 1.45 (m, 2H), 1.39 – 1.24 (m, 2H). ^{13}C NMR: (151 MHz, $CDCl_3$) δ 172.1, 170.0, 156.0, 114.1, 37.4, 23.9, 22.8, 22.4, 22.1, 20.2, 20.1.

Aziridine synthesis from an epoxide:

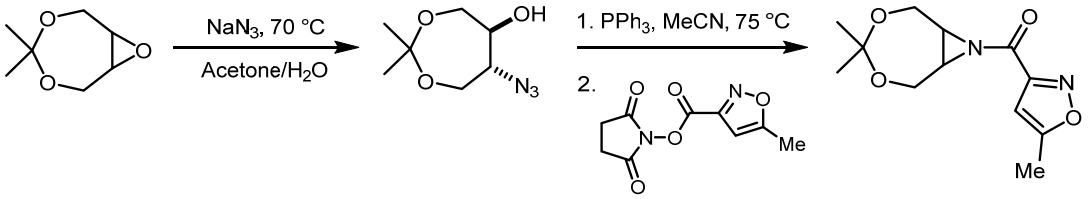


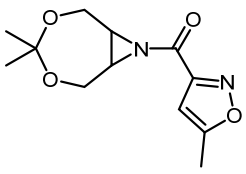


(5-methylisoxazol-3-yl)(1a,2,7,7a-tetrahydro-1H-naphtho[2,3-b]azirin-1-yl)methanone (**SI-16,** *Table 3, entry 2).* A round bottom flask containing a Teflon-coated stir bar was charged with 1a,2,7,7a-tetrahydronaptho[2,3-b]oxirene[9] (3.41 g, 18 mmol) and 28 mL of 3:1 methanol/water. Sodium azide (2.34 g, 36 mmol) and ammonium chloride (1.44 g, 27 mmol) were added sequentially, and the solution was stirred and heated to 60 °C for 6 hours under argon. After this time, the reaction was cooled to room temperature, and methanol was removed by rotary evaporation. The aqueous layer was extracted

two times with 50 mL of dichloromethane. The combined organic layers were washed with 25 mL of H_2O and 25 mL saturated brine. The organic layer was dried over magnesium sulfate and filtered. Concentration by rotary evaporation gave a clear oil that was used without further purification.

The 1,2-azidoalcohol was dissolved in 18 mL of dry acetonitrile in a round bottom containing a Teflon-coated stir bar. Triphenylphosphine (4.73 g, 18 mmol) was added in two portions with stirring at room temperature. After 1 hour, the solution was heated to 60 °C for 22 hours. After this time, the mixture was cooled to 0 °C and 2,5-dioxopyrrolidin-1-yl 5-methylisoxazole-3-carboxylate (4.44 g, 19.8 mmol) was added. The reaction was stirred for 3 hours at room temperature and then volatiles were removed by rotary evaporation. The crude mixture was dry loaded onto silica gel and eluted with 3:1 hexane/EtOAc to produce a white solid (2.36 g, 52% yield). HRMS: calculated for $C_{15}H_{14}N_2NaO_2^+$: 277.0948 ($M+Na^+$), found 277.0949 $M+Na^+$. ^1H NMR: (400 MHz, $CDCl_3$) δ 7.18 – 7.12 (m, 2H), 7.10 – 7.04 (m, 2H), 6.28 (q, J = 0.9 Hz, 1H), 3.50 (d, J = 16.7 Hz, 2H), 3.34 (m, 2H), 3.20 (d, J = 16.7 Hz, 2H), 2.46 (d, J = 0.9 Hz, 3H). ^{13}C NMR: (151 MHz, $CDCl_3$) δ 170.7, 170.3, 159.1, 132.2, 129.5, 126.9, 101.8, 37.7, 29.4, 12.4.



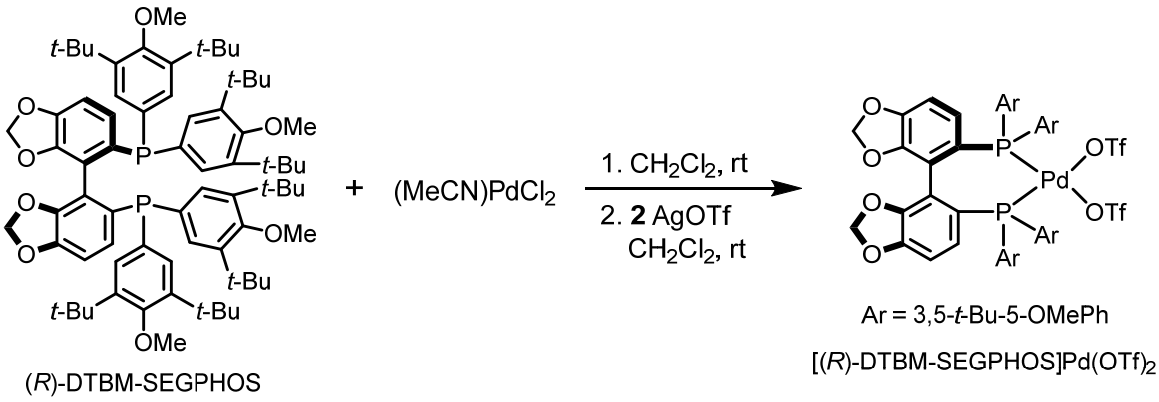


(4,4-dimethyl-3,5-dioxa-8-azabicyclo[5.1.0]octan-8-yl)(5-methylisoxazol-3-yl)methanone (**SI-17,** *Table 3, entry 7).* A round bottom flask containing a Teflon-coated stir bar was charged with 4,4-dimethyl-

3,5,8-trioxabicyclo[5.1.0]octane (2.16 g, 15 mmol) and 45 mL of 1:1 acetone/water. Sodium azide (1.95 g, 30 mmol) was added, and the solution was stirred and heated to 70 °C for 18 hours under argon. After this time, the reaction was cooled to room temperature, and acetone was removed by rotary evaporation. The aqueous layer was extracted two times with 50 mL of dichloromethane. The combined organic layers were washed with 25 mL of H_2O and 25 mL saturated brine. The organic layer was dried over magnesium sulfate and filtered. Concentration by rotary evaporation gave a yellow oil that was used without further purification.

The 1,2-azidoalcohol was dissolved in 50 mL of dry acetonitrile in a round bottom containing a Teflon-coated stir bar. Triphenylphosphine (4.13 g, 15.75 mmol) was added in two portions with stirring at room temperature. After 1 hour, the solution was heated to 75 °C for 22 hours. After this time, the mixture was cooled to 0 °C and 2,5-dioxopyrrolidin-1-yl 5-methylisoxazole-3-carboxylate (3.36 g, 15 mmol) was added. The reaction was stirred for 2 hours at room temperature and then volatiles were removed by rotary evaporation. The crude mixture was dry loaded onto silica gel and eluted with 3:1 hexane/EtOAc to produce a white solid (2.47g, 65% yield). A crystalline form of the product can be generated by recrystallization using 1:1 hexanes/MTBE. HRMS: calculated for $C_{12}H_{16}KN_2O_4^+$: 291.0742 ($M+K^+$) found 291.0748 ($M+K^+$). ^{1}H NMR: (600 MHz, $CDCl_3$) δ 6.38 (s, 1H), 4.16 (d, J = 29.0 Hz, 2H), 4.14 (d, J = 29.0 Hz, 2H), 3.04 (s, 2H), 2.46 (s, 3H), 1.37 (s, 3H), 1.31 (s, 3H). ^{13}C NMR: (151 MHz, $CDCl_3$) δ 171.0, 170.2, 158.9, 102.8, 101.9, 59.6, 42.0, 24.8, 23.7, 12.4.

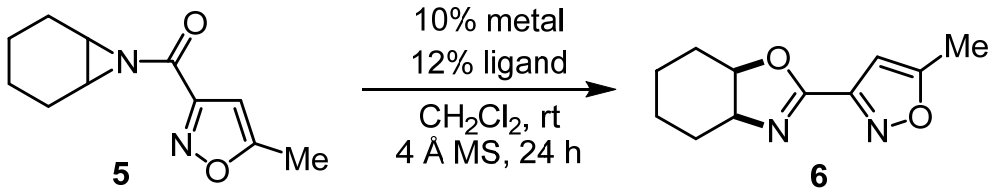
Synthesis of [(*R*)-DTBM·SEGPHOS]Pd(OTf)$_2$:



An oven-dried 20 mL vial containing a Teflon-coated stir bar was charged with dichloro(bisacetonitrile)palladium(II) (0.259 g, 1.0 mmol) and (*R*)-(-)-5,5′-Bis[di(3,5-di-tert-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole (1.18 g, 1.0 mmol) in a glove box. Dry dichloromethane (10 mL) was added, and the mixture stirred under argon for 20 hours. After this time, the orange solution was passed through a pad of Celite, followed by 10 mL of reagent grade dichloromethane. The combined solution was concentrated by a rotary evaporator and low pressure vacuum to dryness. The orange solid was taken into the glove box in a round bottom flask and charged with silver trifluoromethanesulfonate (0.514 g, 2.0 mmol) and a Teflon-coated stir bar. Dry dichloromethane (10 mL) was added, and the mixture stirred under argon for 4 hours in the dark. After this time, the bright yellow suspension was passed through a pad of Celite, followed by 10 mL of reagent grade dichloromethane. The combined solution was concentrated by a rotary evaporator and low pressure vacuum to dryness. The catalyst was purified by adding 10 mL of hot 1:1 dichloromethane/MTBE. After cooling to room temperature, the suspension was filtered in air to produce [(*R*)-DTBM·SEGPHOS]Pd(OTf)$_2$ as a bright yellow solid (1.33 g, 84% yield). The ^{1}H NMR and ^{31}P NMR matched published data.[10] Catalyst produced by this method was stable for over a year stored under argon, but used in open air. Slow evaporation in air of a sample from 1:1

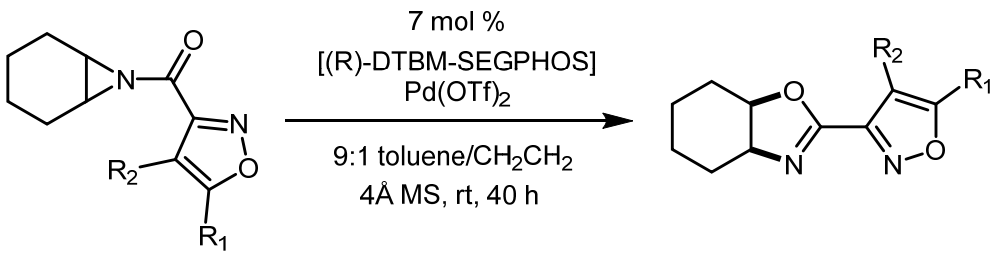
dichloromethane/MTBE gave yellow-orange needles that confirmed the anhydrous structure by X-ray analysis, which matches a published structure.[11]

Catalyst survey for the enantioselective Heine reaction (Table 1):

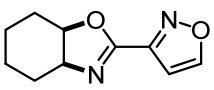


An oven-dried 2 dram vial containing a Teflon-coated stir bar was charged with metal triflate salt (0.01 mmol) and enantiopure ligand (0.012 mmol) under argon. Dichloromethane (0.5 mL) was added, and solution was stirred at room temperature for 1 hour. For palladium catalysts, the corresponding $LPdCl_2$ was first generated, followed by the addition of silver triflate (0.02 mmol). After ligand metal complexation, powdered 4 Å molecular sieves (50 mg) were added, followed by aziridine **5** (0.1 mmol). The reaction was stirred for 24 hours at room temperature. The crude mixture was loaded directly onto a silica gel plug and eluted with 2:1 hexanes/EtOAc collecting a single metal-free solution containing **5** and **6**. Direct injection of this solution into the HPLC equipped with a CHIRALPAK OJ column (97:3 hexanes/isopropanol and UV detection at 250 nm) allowed for the determination of % conversion and % ee.

Palladium-catalyzed, enantioselective Heine reaction with varying isoxazoles (Table 2):

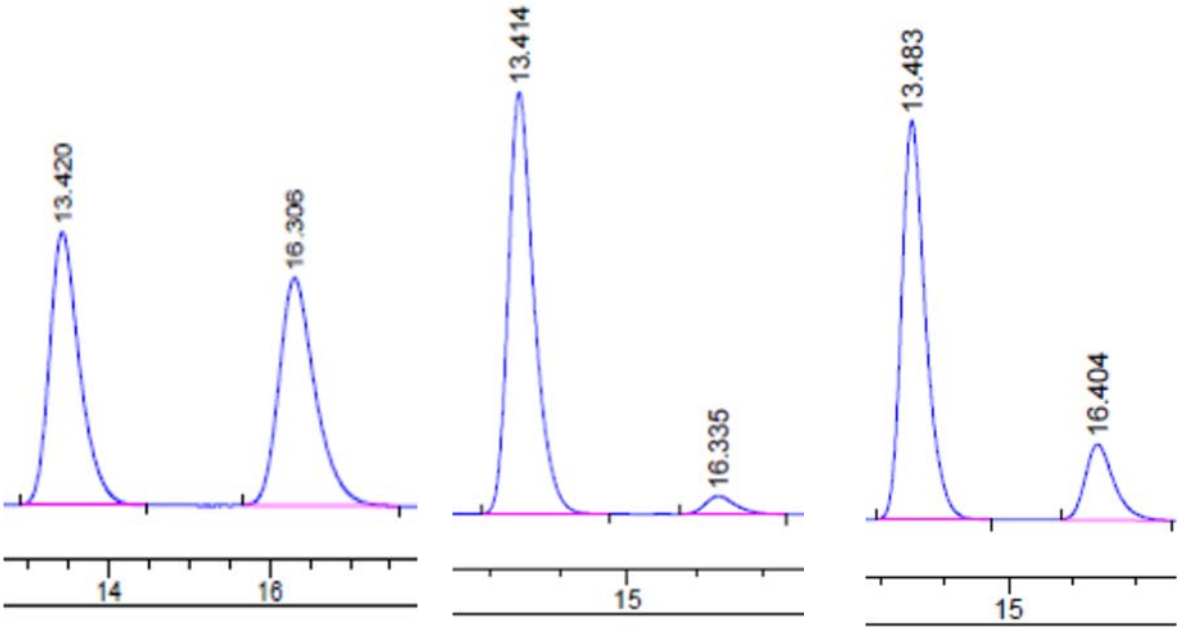


An oven-dried 2 dram vial containing a Teflon-coated stir bar was charged with [(*R*)-DTBM·SEGPHOS]Pd(OTf)$_2$ (22.2 mg, 0.014 mmol) under argon. Toluene (0.9 mL) and dichloromethane (0.1 mL) were added and the reaction stirred at room temperature. Then, powdered 4 Å molecular sieves (100 mg) were added, and reaction mixture was stirred. The corresponding aziridine (0.2 mmol) was added, and the yellow reaction mixture was stirred for 40 hours at room temperature. The crude mixture was loaded directly onto a silica gel column and eluted with the appropriate solvent system. Racemic mixtures were prepared from the corresponding aziridines by rearrangement in the presence of 10 mol % of indium(III) triflate OR 5 mol % of triflic acid in dichloromethane. HPLC data was acquired at 250 nm with a UV-Vis detector at a flow rate of 1 mL/min.

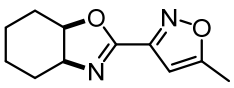


2-(isoxazol-3-yl)-3a,4,5,6,7,7a-hexahydrobenzo[d]oxazole (**SI-18,** *Table 2, entry 1)*. Synthesized from **SI-12** (38.4 mg, 0.2 mmol). The product was eluted from a silica gel column with 1:1 hexanes/ethyl acetate to afford a white solid (23.5 mg, 61% yield, 90% ee). HRMS: calculated for $C_{10}H_{12}N_2NaO_2^+$: 215.0791 ($M+Na^+$) found: 215.0797 ($M+Na^+$). ^1H NMR: (600 MHz, $CDCl_3$) δ 8.49 (d, J = 1.6 Hz, 1H), 6.82 (d, J = 1.6 Hz, 1H), 4.77 (dt, J = 8.2 Hz, 5.1 Hz, 1H), 4.20 (q, J = 6.7 Hz, 1H), 2.04 – 1.93 (m, 2H), 1.92 – 1.83 (m, 1H), 1.66 – 1.54 (m, 3H), 1.52 – 1.36 (m, 2H). ^{13}C NMR: (151 MHz, $CDCl_3$) δ 159.4, 157.2, 153.6, 104.8, 80.2, 63.8, 27.6, 26.0, 19.8, 19.0.

HPLC analysis: CHIRALCEL OD column, 96:4 hexanes/isopropanol

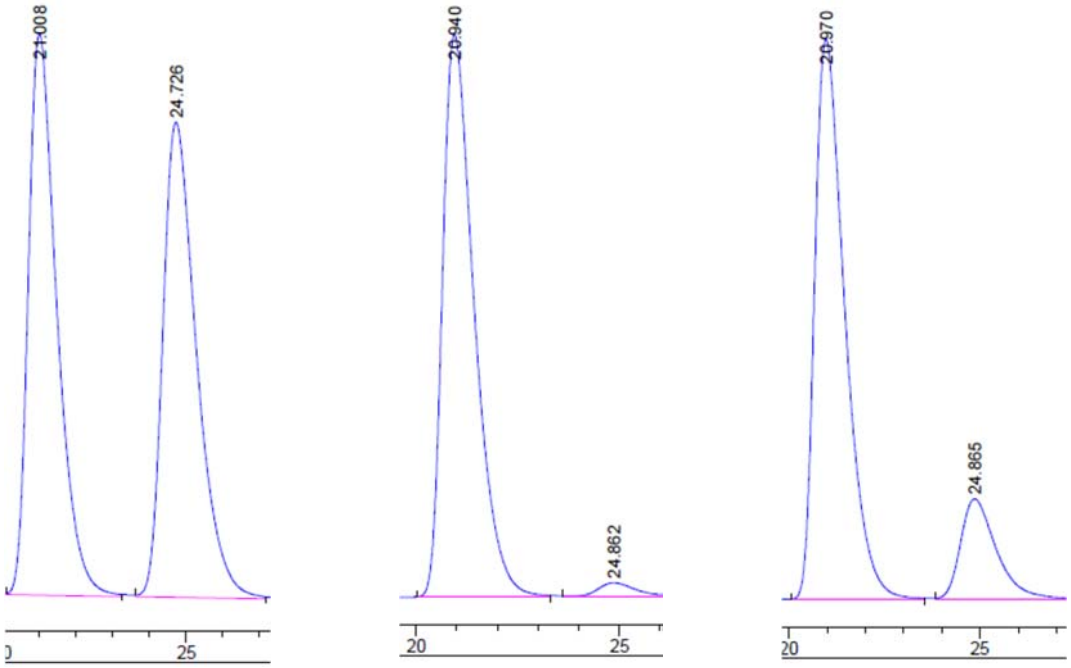


Racemic Enantioselective Spike

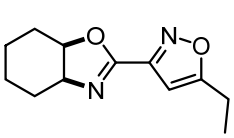


2-(5-methylisoxazol-3-yl)-3a,4,5,6,7,7a- hexahydrobenzo[d]oxazole (**6,** *Table 2, entry 2).* Synthesized from **7** (41.2 mg, 0.2 mmol). The product was eluted from a silica gel column with 2:1 hexanes/ethyl acetate to afford a white solid (32.4 mg, 79% yield, 92% ee). HRMS: calculated for $C_{11}H_{14}N_2NaO_2^+$: 229.0948 ($M+Na^+$) found: 229.0957 ($M+Na^+$). ^1H NMR: (400 MHz, $CDCl_3$) δ 6.44 (q, *J* = 0.9 Hz, 1H), 4.74 (dt, *J* = 8.3 Hz, 5.1 Hz, 1H), 4.13 (dt, *J* = 8.2 Hz, 6.4 Hz, 1H), 2.49 (d, *J* = 0.9 Hz, 3H), 2.05 – 1.80 (m, 3H), 1.66 – 1.51 (m, 3H), 1.50 – 1.34 (m, 2H). ^{13}C NMR: (151 MHz, $CDCl_3$) δ 170.7, 157.5, 154.5, 101.8, 80.0, 63.8, 27.6, 26.0, 19.8, 19.0, 12.4.

HPLC analysis: CHIRALCEL OJ column, 96:4 hexanes/isopropanol

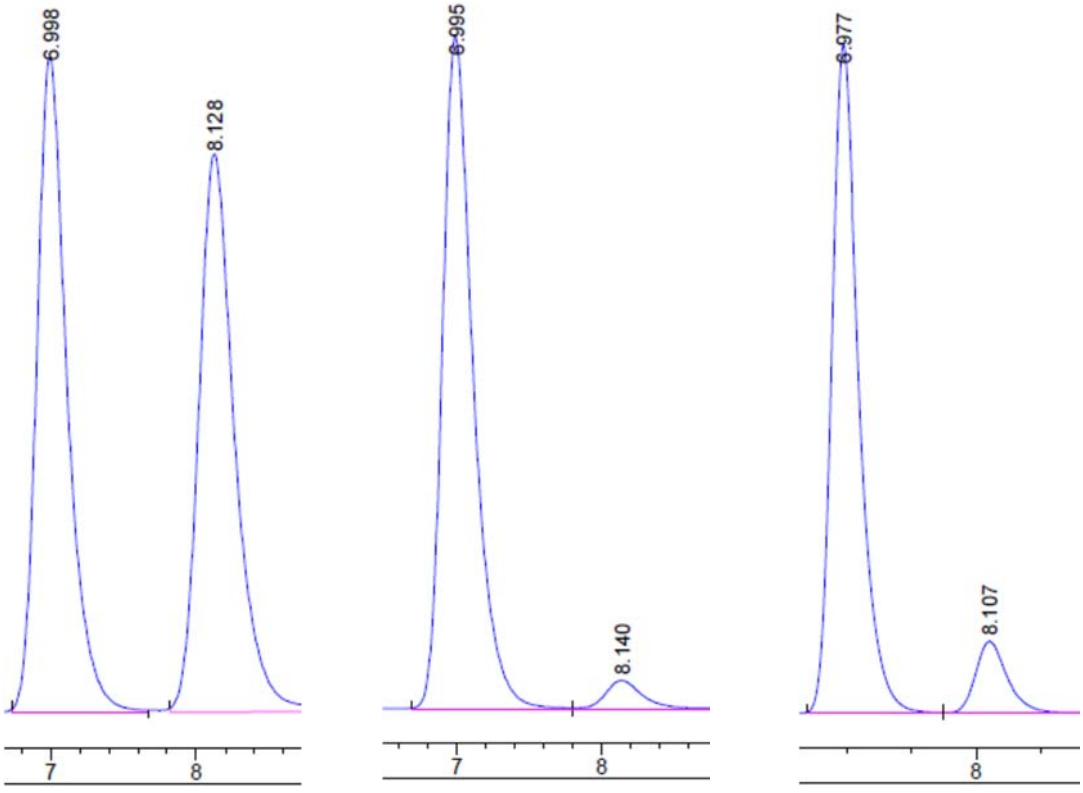


Racemic Enantioselective Spike

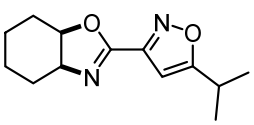


2-(5-ethylisoxazol-3-yl)-3a,4,5,6,7,7a-hexahydrobenzo[d]oxazole (**SI-19,** *Table 2, entry 3).* Synthesized from **SI-1** (44.1 mg, 0.2 mmol). The product was eluted from a silica gel column with 3:1 hexanes/ethyl acetate to afford a white solid (37.1 mg, 84% yield, 91% ee). HRMS: calculated for $C_{12}H_{16}N_2NaO_2^+$: 243.1104 ($M+Na^+$) found 243.1109 ($M+Na^+$). ^1H NMR: (600 MHz, $CDCl_3$) δ 6.45 (t, *J* = 0.9 Hz, 1H), 4.76 (dt, *J* = 8.3 Hz, 5.1 Hz, 1H), 4.16 (dt, *J* = 8.2 Hz, 6.3 Hz, 1H), 2.82 (qt, *J* = 7.6 Hz, 0.9 Hz, 2H), 2.05 – 1.80 (m, 3H), 1.68 – 1.51 (m, 3H), 1.51 – 1.36 (m, 2H), 1.33 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR: (151 MHz, $CDCl_3$) δ 176.2, 157.3, 154.3, 100.4, 80.0, 63.7, 27.6, 26.0, 20.3, 19.8, 19.0, 11.7.

HPLC analysis: CHIRALCEL OD column, 90:10 hexanes/isopropanol

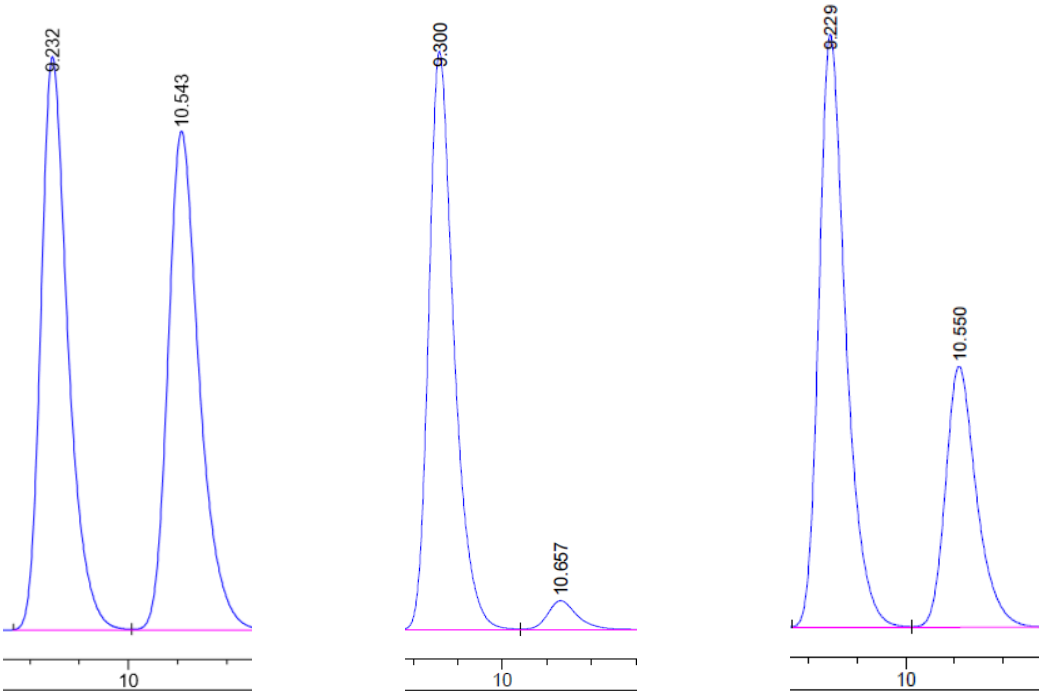


Racemic Enantioselective Spike

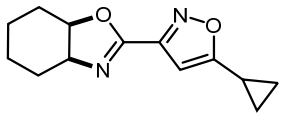


2-(5-isopropylisoxazol-3-yl)-3a,4,5,6,7,7a-hexahydrobenzo[d]oxazole (**SI-20,** *Table 2, entry 4)*. Synthesized from **SI-13** (46.8 mg, 0.2 mmol). The product was eluted from a silica gel column with 3:1 hexanes/ethyl acetate to afford a white solid (36.4 mg, 74% yield, 89% ee). HRMS: calculated for $C_{13}H_{18}N_2NaO_2^+$: 257.1260 ($M+Na^+$) found 257.1274 ($M+Na^+$). ^1H NMR: (400 MHz, $CDCl_3$) δ 6.43 (s, 1H), 4.76 (dt, J = 8.2 Hz, 5.2 Hz, 1H), 4.15 (q, J = 6.4 Hz, 1H), 3.12 (septet, J = 7.0 Hz, 1H), 2.02 – 1.90 (m, 2H), 1.90 – 1.82 (m, 1H), 1.65 – 1.52 (m, 3H), 1.49 – 1.36 (m, 2H), 1.34 (d, J = 7.0 Hz, 3H), 1.33 (d, J = 7.0 Hz, 3H). ^{13}C NMR: (151 MHz, $CDCl_3$) δ 180.1, 157.7, 154.1, 99.4, 80.0, 63.7, 27.6, 27.3, 26.0, 20.9, 19.8, 19.0.

HPLC analysis: CHIRALCEL OD column, 97:3 hexanes/isopropanol

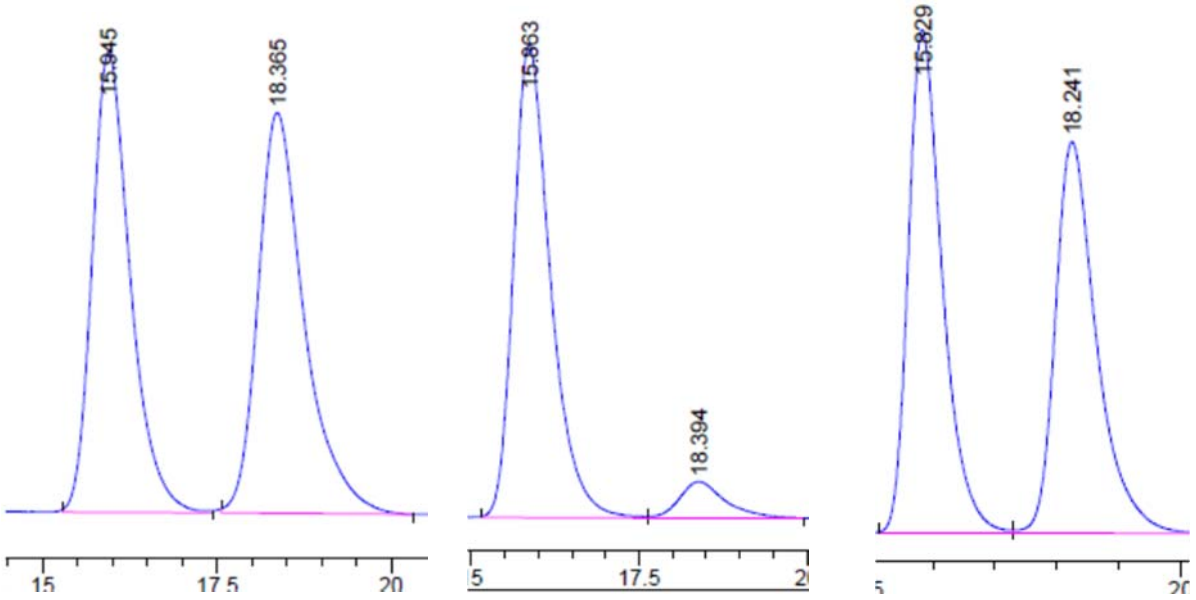


Racemic Enantioselective Spike

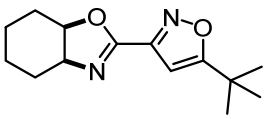


2-(5-cyclopropylisoxazol-3-yl)-3a,4,5,6,7,7a-hexahydrobenzo[*d*]oxazole (**SI-21,** *Table 2, entry 5)*. Synthesized from **SI-14** (30.6 mg, 0.2 mmol). The product was eluted from a silica gel column with 2:1 hexanes/ethyl acetate to afford a white solid (21.2 mg, 69% yield, 83% ee). HRMS: calculated for $C_{13}H_{16}N_2NaO_2^+$: 255.1104 ($M+Na^+$) found 255.1110 ($M+Na^+$). ^1H NMR: (600 MHz, $CDCl_3$) δ 6.33 (s, 1H), 4.76 (dt, *J* = 8.2 Hz, 5.1 Hz, 1H), 4.15 (q, *J* = 7.0 Hz, 1H), 2.08 (tt, *J* = 8.5, 5.0 Hz, 1H), 2.02 – 1.90 (m, 2H), 1.89 – 1.81 (m, 1H), 1.64 – 1.52 (m, 3H), 1.49 – 1.35 (m, 2H), 1.14 – 1.08 (m, 2H), 1.02 – 0.96 (m, 2H). ^{13}C NMR: (151 MHz, $CDCl_3$) δ 176.3, 157.6, 154.4, 98.7, 80.0, 63.7, 27.6, 26.0, 19.8, 19.0, 8.9, 8.2.

HPLC analysis: CHIRALCEL OD column, 96:4 hexanes/isopropanol

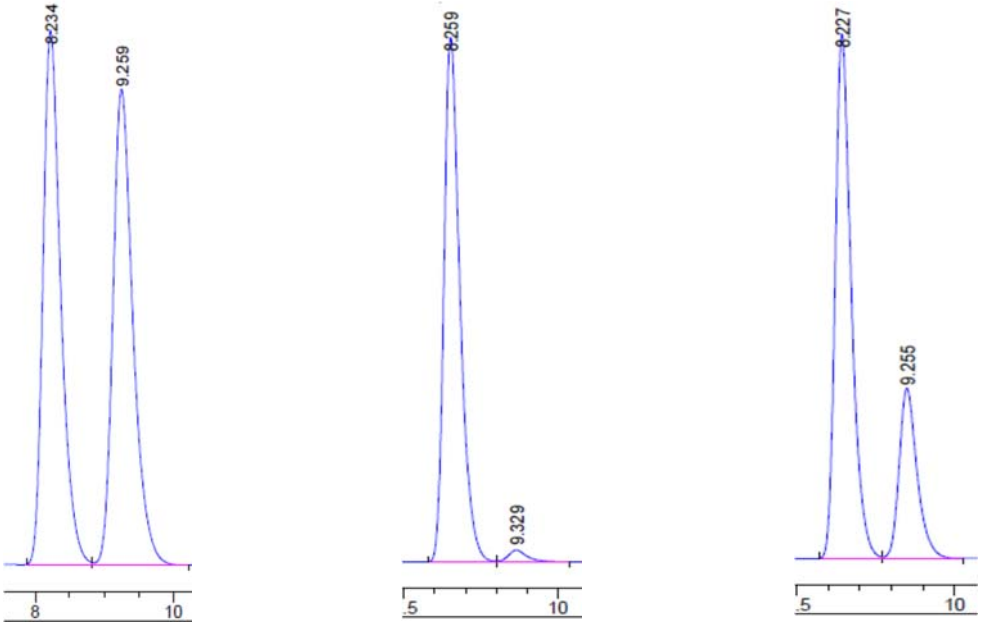


Racemic Enantioselective Spike

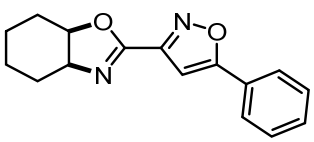


2-(5-(tert-butyl)isoxazol-3-yl)-3a,4,5,6,7,7a-hexahydrobenzo[d]oxazole (**12,** *Table 2, entry 6).* Synthesized from **14** (49.7 mg, 0.2 mmol). The product was eluted from a silica gel column with 3:1 hexanes/ethyl acetate to afford an off white solid (36.5 mg, 73% yield, 95% ee). HRMS: calculated for $C_{14}H_{21}N_2O_2^+$: 249.1598 ($M+H^+$) found 249.1594 ($M+H^+$). ^{1}H NMR: (600 MHz, $CDCl_3$) δ 6.42 (s, 1H), 4.75 (dt, *J* = 8.3 Hz, 5.2Hz, 1H), 4.15 (dt, *J* = 8.2 Hz, 6.4 Hz, 1H), 2.01 – 1.90 (m, 2H), 1.89 – 1.82 (m, 1H), 1.66 – 1.53 (m, 3H), 1.49 – 1.35 (m, 2H), 1.37 (s, 9H). ^{13}C NMR: (151 MHz, $CDCl_3$) δ 182.5, 157.7, 154.0, 98.8, 80.0, 63.7, 33.0, 28.9, 27.5, 26.1, 19.8, 19.0.

HPLC analysis: CHIRALCEL OD column, 98:2 hexanes/isopropanol

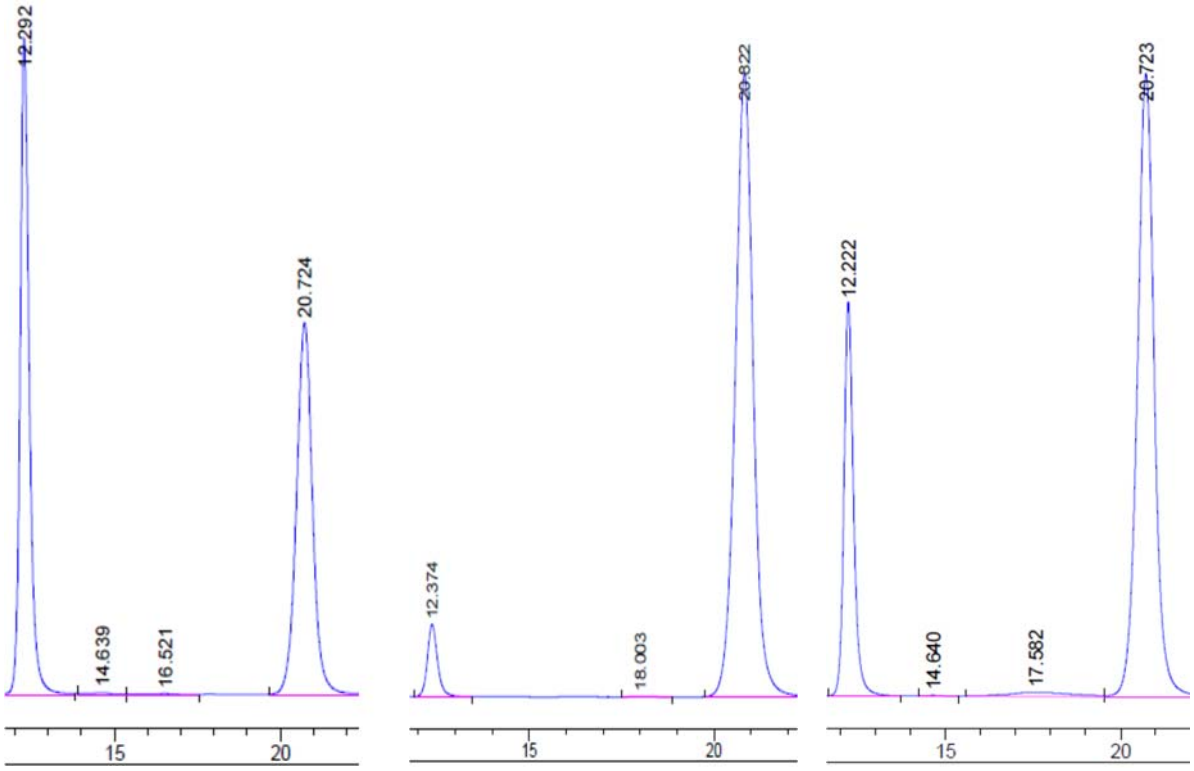


Racemic Enantioselective Spike

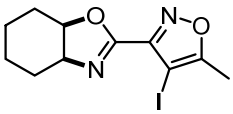


2-(5-phenylisoxazol-3-yl)-3a,4,5,6,7,7a-hexahydrobenzo[d]oxazole (**SI-22,** *Table 2, entry 7*). Synthesized from **SI-2** (53.7 mg, 0.2 mmol). The product was eluted from a silica gel column with 2:1 hexanes/ethyl acetate to afford a white solid (35.1 mg, 65% yield, 91% ee) HRMS: calculated for $C_{16}H_{17}N_2O_2$: 269.1284 (M^+) found 269.1291 (M^+). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.83 – 7.80 (m, 2H), 7.52 – 7.45 (m, 3H), 6.98 (s, 1H), 4.82 (dt, *J* = 8.3 Hz, 5.2 Hz, 1H), 4.20 (dt, *J* = 8.2 Hz, 6.5 Hz, 1H), 2.06 – 1.94 (m, 2H), 1.93 – 1.86 (m, 1H), 1.69 – 1.55 (m, 3H), 1.52 – 1.38 (m, 2H). ^{13}C NMR: (100 MHz, $CDCl_3$) δ 171.2, 157.4, 154.9, 130.8, 129.3, 127.0, 126.1, 99.6, 80.2, 63.8, 27.6, 26.0, 19.8, 19.0.

HPLC analysis: CHIRALPAK IB column, 90:10 hexanes/isopropanol

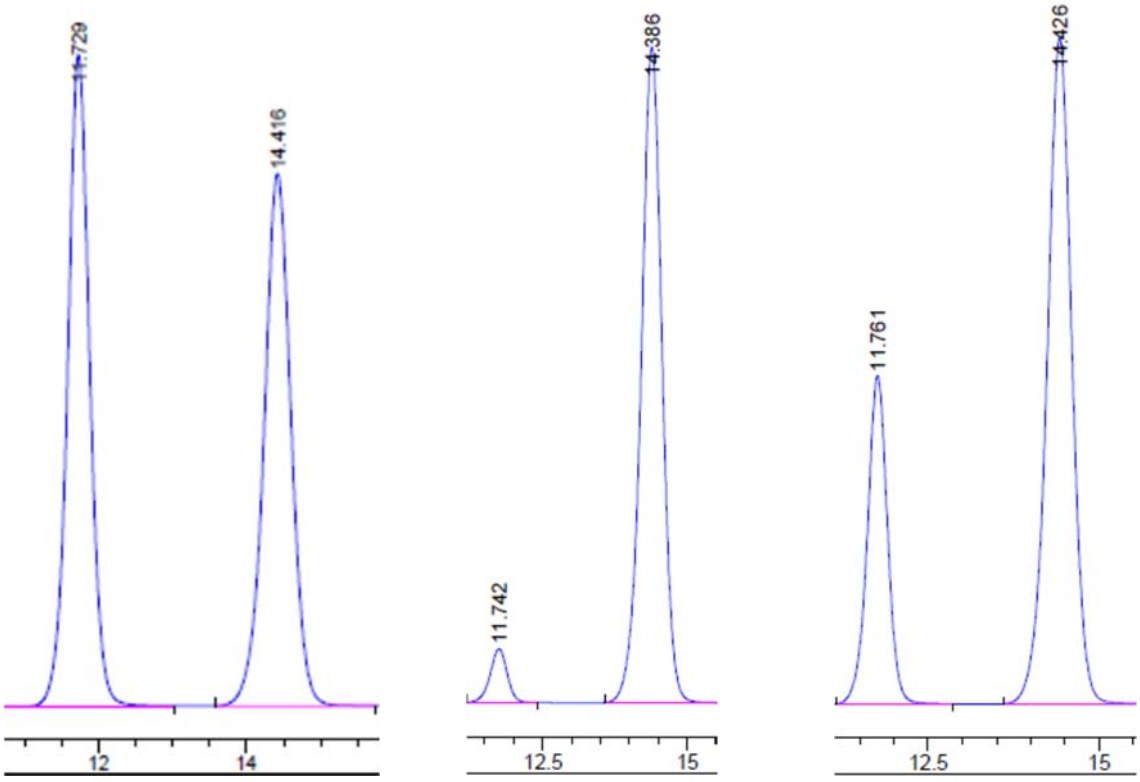


Racemic Enantioselective Spike

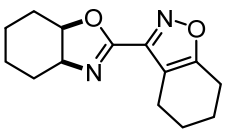


2-(4-iodo-5-methylisoxazol-3-yl)-3a,4,5,6,7,7a-hexahydrobenzo[d]oxazole (**SI-23,** *Table 2, entry 8*). Synthesized from **SI-3** (64.4 mg, 0.2 mmol). The product was eluted from a silica gel column with 3:1 hexanes/MTBE to afford a white solid (48.3 mg, 75% yield, 87% ee). HRMS: calculated for $C_{11}H_{13}IN_2NaO_2^+$: 354.9914 ($M+Na^+$) found 354.9917 ($M+Na^+$). ^1H NMR: (600 MHz, $CDCl_3$) δ 4.75 – 4.72 (m, 1H), 4.23 (q, *J* = 7.2 Hz, 1H), 2.55 (s, 3H), 2.10 – 2.03 (m, 1H), 2.02 – 1.95 (m, 1H), 1.88 – 1.80 (m, 1H), 1.65 – 1.52 (m, 3H), 1.52 – 1.45 (m, 1H), 1.43 – 1.34 (m, 1H). ^{13}C NMR: (151 MHz, $CDCl_3$) δ 172.8, 156.1, 154.3, 79.7, 64.2, 56.8, 27.8, 25.8, 19.9, 18.9, 12.9.

HPLC analysis: CHIRALPAK AD column, 97:3 hexanes/isopropanol

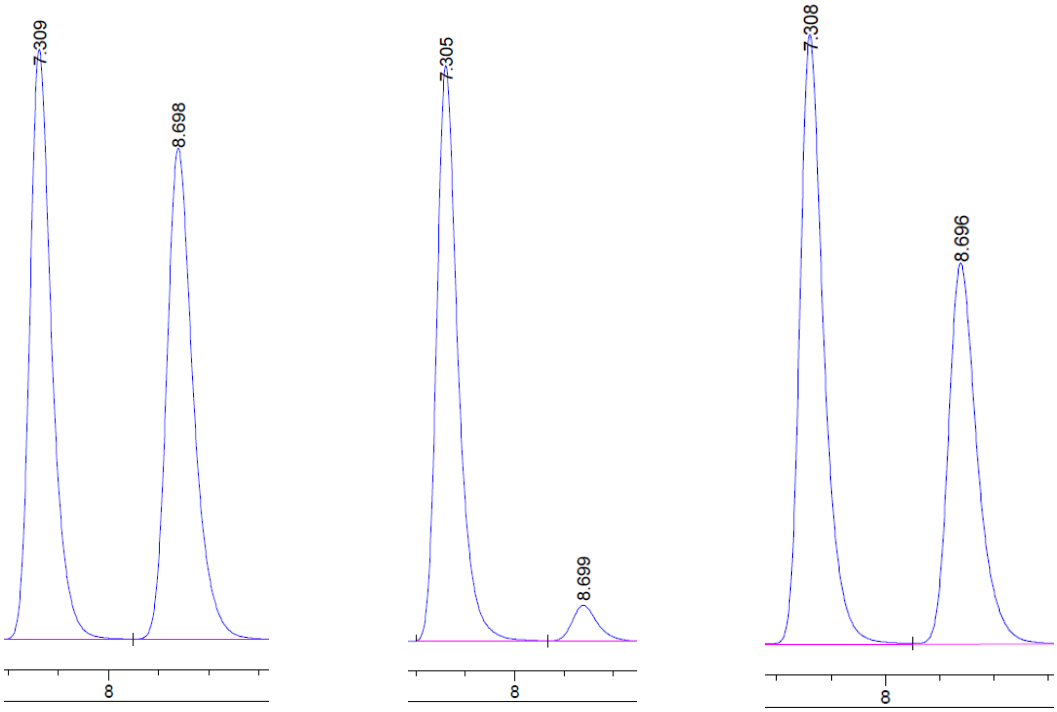


Racemic Enantioselective Spike



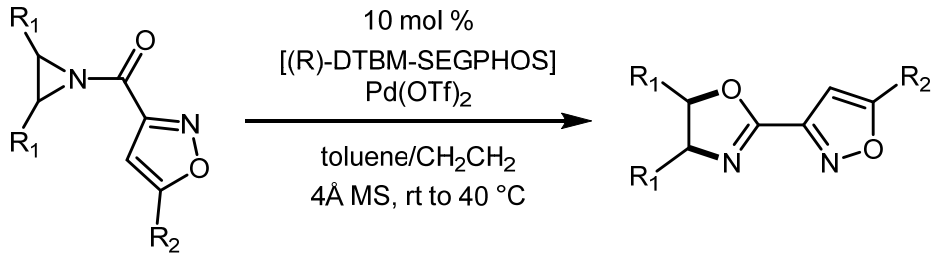
3-(3a,4,5,6,7,7a-hexahydrobenzo[d]oxazol-2-yl)-4,5,6,7-tetrahydrobenzo[d]isoxazole (**SI-24,** *Table 2, entry 9).* Synthesized from **SI-15** (49.3 mg, 0.2 mmol). The product was eluted from a silica gel column with 1:1 hexanes/ethyl acetate to afford a white solid (37.7 mg, 76% yield, 86% ee). HRMS: calculated for $C_{14}H_{18}N_2NaO_2^+$: 269.1260 ($M+Na^+$) found: 269.1273 ($M+Na^+$). ^1H NMR: (600 MHz, $CDCl_3$) δ 4.68 (dt, J = 8.2 Hz, 4.8 Hz, 1H), 4.14, (q, J = 6.5 Hz, 1H), 2.78 – 2.71 (m, 2H), 2.71 – 2.60 (m, 2H), 2.10 – 1.71 (m, 7H), 1.67 – 1.31 (m, 5H). ^{13}C NMR: (151 MHz, $CDCl_3$) δ 169.7, 157.7, 152.0, 113.4, 79.3, 63.9, 27.9, 25.9, 22.8, 22.4, 22.2, 20.8, 20.0, 19.0.

HPLC analysis: CHIRALCEL OD column, 90:10 hexanes/isopropanol

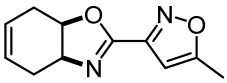


Racemic Enantioselective Spike

Palladium-catalyzed, enantioselective Heine reaction with varying aziridine backbone (Table 3):

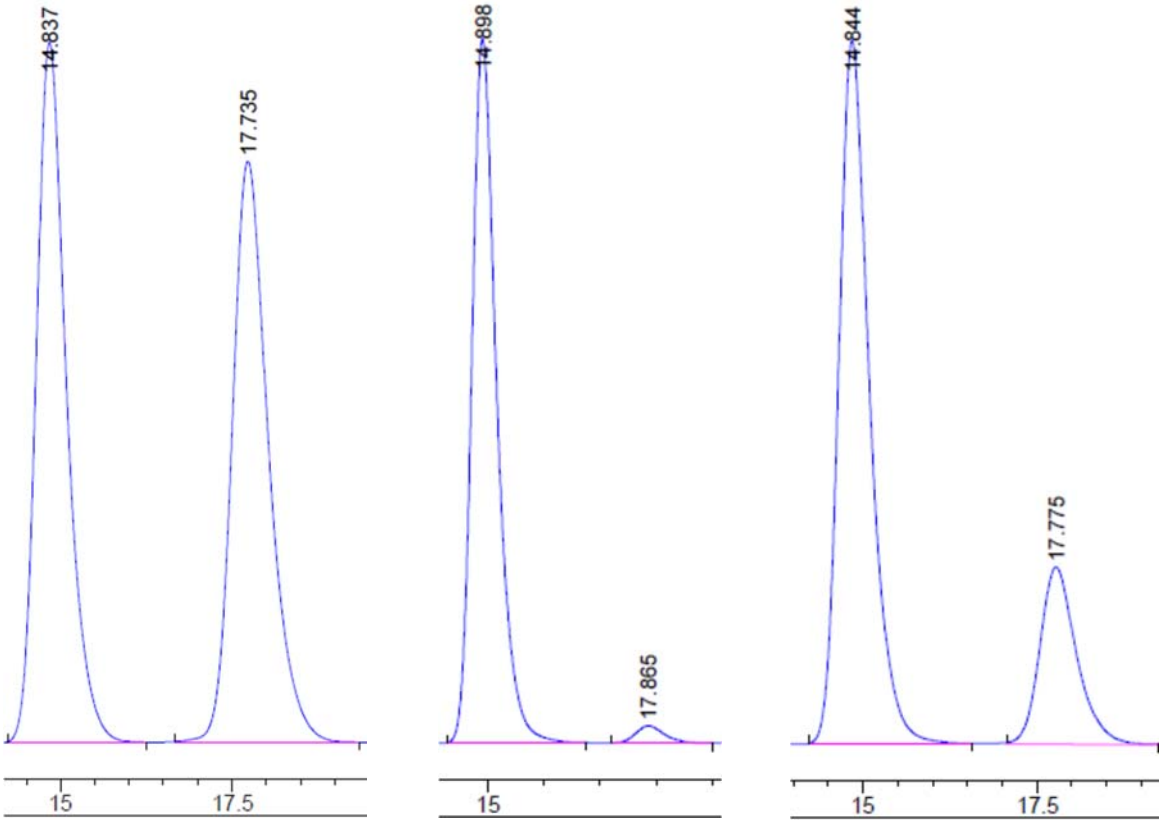


An oven-dried 2 dram vial containing a Teflon-coated stir bar was charged with [(*R*)-DTBM·SEGPHOS]Pd(OTf)$_2$ (31.7 mg, 0.02 mmol) under argon. Toluene (0.66 mL) and dichloromethane (0.34 mL) were added and the reaction stirred at room temperature. Then, powdered 4 Å molecular sieves (100 mg) were added, and reaction mixture was stirred. The corresponding aziridine (0.2 mmol) was added, and the yellow reaction mixture was stirred for the designated time at an optimized temperature. The crude mixture was loaded directly onto a silica gel column and eluted with the appropriate solvent system. Racemic mixtures were prepared from the corresponding aziridines by rearrangement in the presence of 10 mol% of In(OTf)$_3$ in dichloromethane.

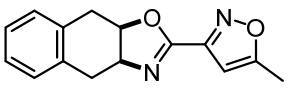


2-(5-methylisoxazol-3-yl)-3a,4,7,7a-tetrahydrobenzo [d]oxazole (**SI-25,** *Table 3, entry 1).* Synthesized from **SI-4** (40.8 mg, 0.2 mmol) at 40 °C for 24 hours. The reaction solvent was altered to 0.5 mL of toluene and 0.5 mL of dichloromethane. The product was eluted from a silica gel column with 2:1 hexanes/EtOAc to afford a white solid (31.4 mg, 77% yield, 94% ee). HRMS: calculated for $C_{11}H_{12}N_2NaO_2^+$: 227.0791 ($M+Na^+$) found 227.0795 ($M+Na^+$). ^1H NMR: (400 MHz, $CDCl_3$) δ 6.40 (q, J = 0.9 Hz, 1H), 5.97 – 5.84 (m, 2H), 5.14 – 5.07 (m, 1H), 4.62 (ddd, J = 9.7 Hz, 6.3 Hz, 3.4 Hz, 1H), 2.68 – 2.58 (m, 1H), 2.53 – 2.43 (m, 1H), 2.47 (d, J = 0.9 Hz, 3H), 2.36 – 2.23 (m, 2H). ^{13}C NMR: (151 MHz, $CDCl_3$) δ 170.6, 157.3, 154.0, 128.3, 126.2, 101.9, 79.7, 65.4, 27.75, 27.73, 12.4.

HPLC analysis: CHIRALCEL OD column, 93:7 hexanes/isopropanol

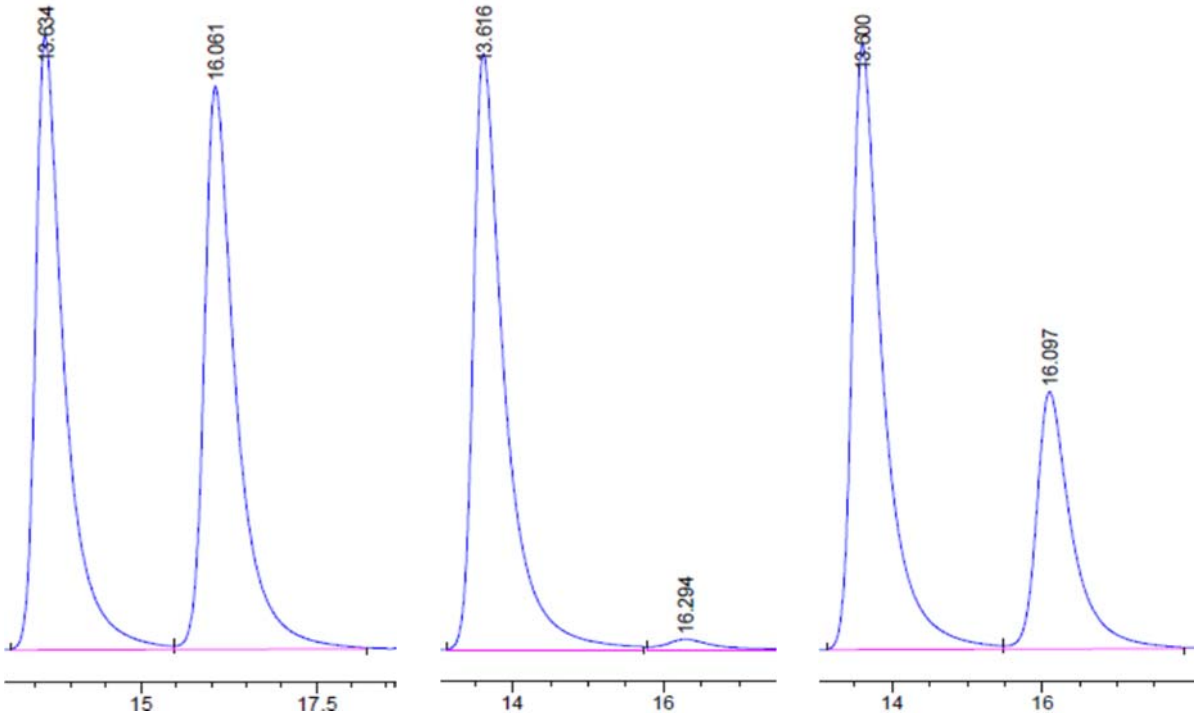


Racemic Enantioselective Spike

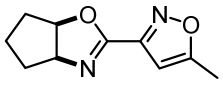


2-(5-methylisoxazol-3-yl)-3a,4,9,9a-tetrahydronaphtho [2,3-d]oxazole (**SI-26,** *Table 3, entry 2).* Synthesized from **SI-16** (50.9 mg, 0.2 mmol) at 40 °C for 24 hours. The reaction solvent was altered to 0.5 mL of toluene and 0.5 mL of dichloromethane. The product was eluted from a silica gel column with 1:1 hexanes/ethyl acetate to afford a white solid (40.9 mg, 80% yield, 95% ee). HRMS: calculated for $C_{15}H_{14}N_2NaO_2^+$: 277.0948 ($M+Na^+$), found 277.0943 ($M+Na^+$). ^1H NMR: (400 MHz, $CDCl_3$) δ 7.21 – 7.15 (m, 4H), 6.28 (q, *J* = 0.9 Hz, 1H), 5.25 (dt, *J* = 10 Hz, 4.4 Hz, 1H), 4.80 (dt, *J* = 10.0 Hz, 5.2 Hz, 1H), 3.15 (dd, *J* = 15.2 Hz, 4.4 Hz, 1H), 3.01 (d, *J* = 5.2 Hz, 2H), 2.97 (dd, *J* = 15.2 Hz, 4.4 Hz, 1H), 2.41 (d, *J* = 0.9 Hz, 3H). ^{13}C NMR: (151 MHz, $CDCl_3$) δ 170.6, 157.0, 153.8, 135.8, 134.1, 128.7, 128.5, 127.2, 127.1, 101.8, 79.7, 66.0, 33.62, 33.59, 12.4.

HPLC analysis: CHIRALPAK IB column, 87:13 hexanes/isopropanol

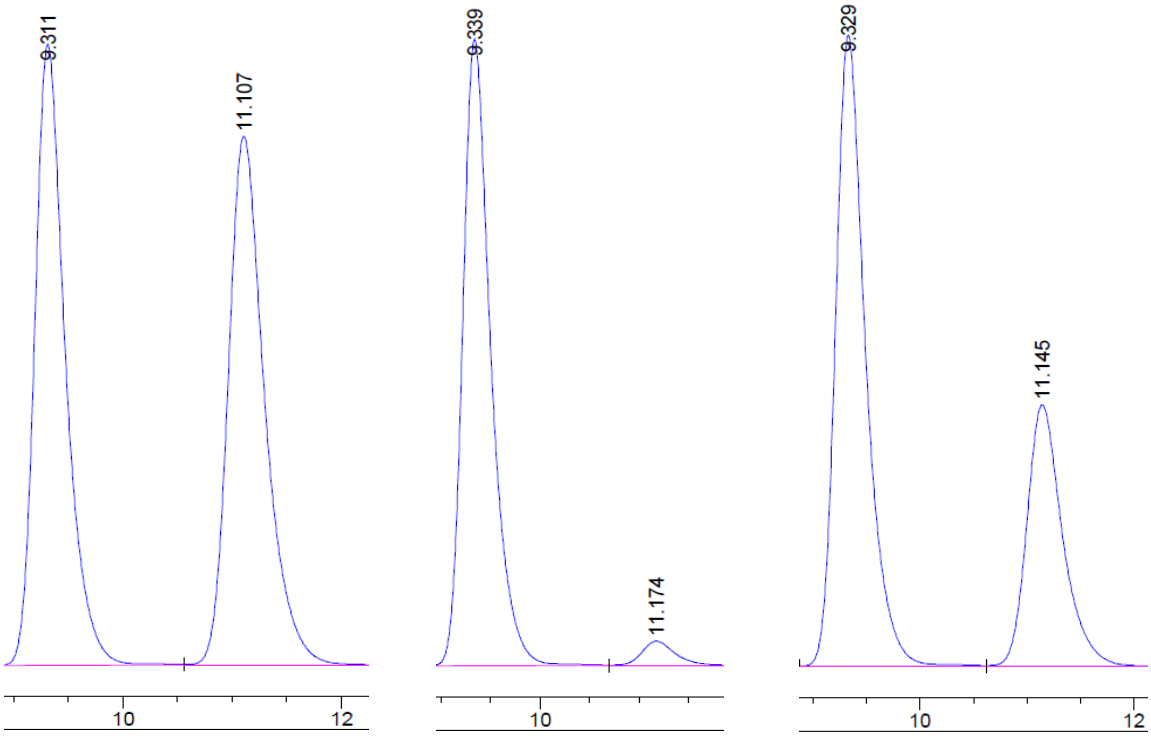


Racemic Enantioselective Spike

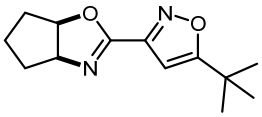


2-(5-methylisoxazol-3-yl)-3a,5,6,6a-tetrahydro-4H-cyclopenta[d]oxazole (**SI-27,** *Table 3, entry 3).* Synthesized from **SI-5** (36.5 mg, 0.2 mmol) at 40 °C for 24 hours. The product was eluted from a silica gel column with 1:1 hexanes/ethyl acetate to afford a yellow solid (32.5 mg, 89% yield, 91% ee). HRMS: calculated for $C_{10}H_{12}N_2NaO_2^+$: 215.0791 ($M+Na^+$) found 215.0797 ($M+Na^+$). ^1H NMR: (400 MHz, $CDCl_3$) δ 6.40 (q, J = 0.9 Hz, 1H), 5.18 (m, 1H), 4.74 (t, J = 7.3 Hz, 1H), 2.48 (d, J = 0.9 Hz, 3H), 2.21 – 2.14 (m, 1H), 2.04 – 1.97 (m, 1H), 1.83 – 1.64 (m, 3H), 1.56 – 1.44 (m, 1H). ^{13}C NMR: (151 MHz, $CDCl_3$) δ 170.7, 156.9, 154.0, 101.9, 86.0, 72.0, 34.6, 33.8, 22.4, 12.4.

HPLC analysis: CHIRALCEL OD column, 90:10 hexanes/isopropanol

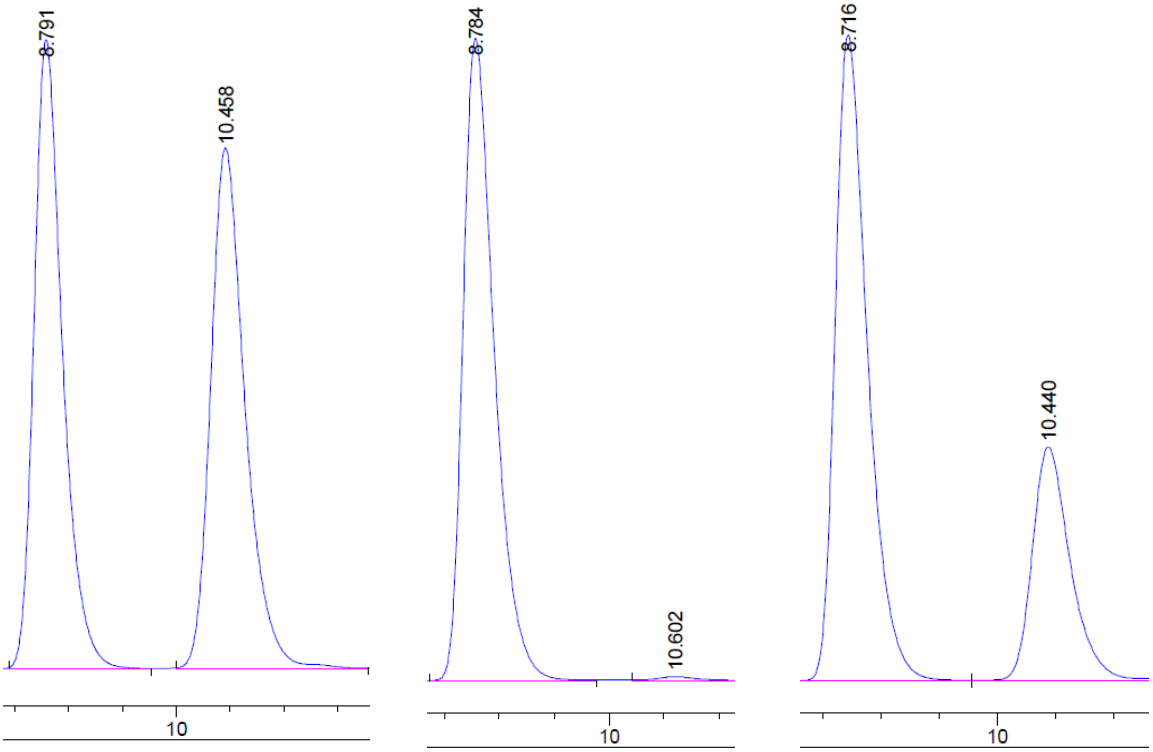


Racemic Enantioselective Spike

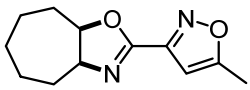


2-(5-(*tert*-butyl)isoxazol-3-yl)-3a,5,6,6a-tetrahydro-4*H*-cyclopenta[*d*]oxazole (**SI-28,** *Table 3, entry 4)*. Synthesized from **SI-6** (46.8 mg, 0.2 mmol) at 40 °C for 24 hours. The product was eluted from a silica gel column with 3:1 hexanes/ethyl acetate to afford a clear oil (35.5 mg, 77% yield, 98% ee). HRMS: calculated for $C_{13}H_{18}N_2NaO_2^+$: 257.1260 ($M+Na^+$) found 257.1273 ($M+Na^+$). ^{1}H NMR: (600 MHz, $CDCl_3$) δ 6.37 (s, 1H), 5.19 – 5.15 (m, 1H), 4.72 (t, J = 7.5 Hz, 1H), 2.19 – 2.12 (m, 1H), 2.02 – 1.96 (m, 1H), 1.82 – 1.64 (m, 3H), 1.56 – 1.44 (m, 1H), 1.35 (s, 9H). ^{13}C NMR: (151 MHz, $CDCl_3$) δ 182.5, 157.2, 153.5, 98.9, 86.0, 72.0, 34.6, 33.8, 33.0, 28.9, 22.4.

HPLC analysis: CHIRALCEL OD column, 98:2 hexanes/isopropanol

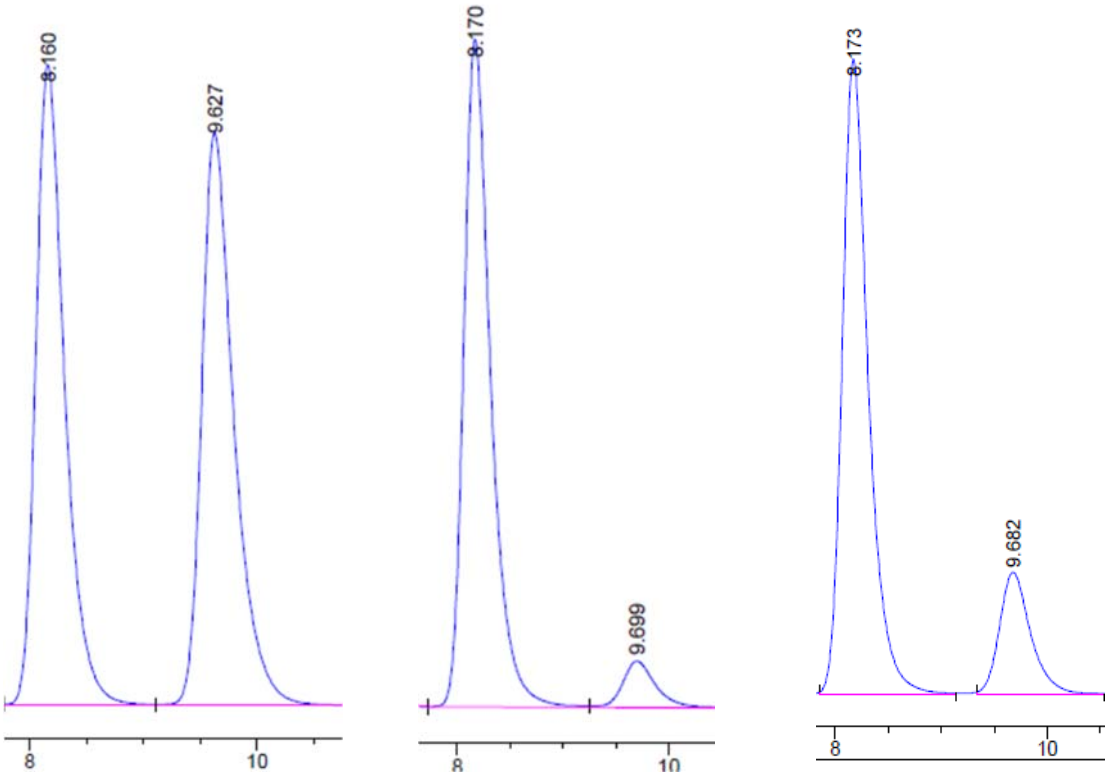


Racemic Enantioselective Spike

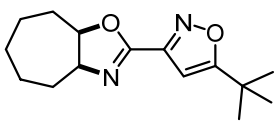


2-(5-methylisoxazol-3-yl)-3a,5,6,7,8,8a-hexahydro-4H-cyclohepta[d]oxazole (**SI-29,** *Table 3, entry 5)*. Synthesized from **SI-7** (44.0 mg, 0.2 mmol) at 30 °C for 24 hours. The product was eluted from a silica gel column with 3:1 hexanes/ethyl acetate to afford a white solid (17.6 mg, 40% yield, 84% ee). Recovery of 21.1 mg of **SI-7** gave an 88% yield based on recovered starting material (brsm). HRMS: calculated for $C_{12}H_{16}N_2NaO_2^+$: 243.1104 ($M+Na^+$) found 243.1111 ($M+Na^+$). ^1H NMR: (600 MHz, $CDCl_3$) δ 6.41 (q, J = 0.9 Hz, 1H), 4.96 – 4.87 (m, 1H), 4.43 (td, J = 10.0 Hz, 3.6 Hz, 1H), 2.46 (d, J = 0.9 Hz, 3H), 2.07 – 1.85 (m, 3H), 1.83 – 1.54 (m, 4H), 1.52 – 1.28 (m, 3H). ^{13}C NMR: (151 MHz, $CDCl_3$) δ 170.6, 155.6, 154.2, 101.9, 84.2, 70.0, 31.4, 31.0, 30.8, 26.3, 24.4, 12.4.

HPLC analysis: CHIRALCEL OD column, 90:10 hexanes/isopropanol

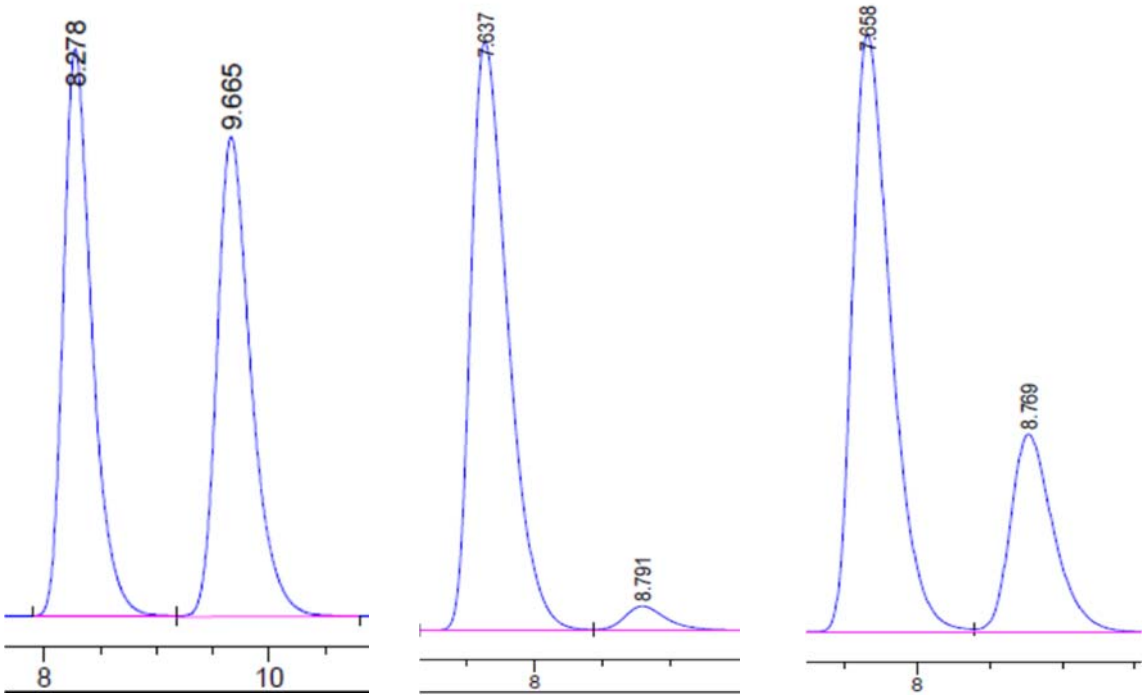


Racemic Enantioselective Spike

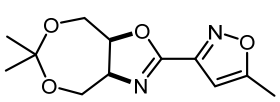


2-(5-(*tert*-butyl)isoxazol-3-yl)-3a,5,6,7,8,8a-hexahydro-4*H*-cyclohepta[*d*]oxazole (**SI-30,** *Table 3, entry 6)*. Synthesized from **SI-8** (59.7 mg, 0.2 mmol) at 30 °C for 168 hours. The product was eluted from a silica gel column with 5:1 hexane/ethyl acetate to 4:1 hexanes/ethyl acetate to afford a colorless oil (28.7 mg, 48% yield, 91% ee). Recovery of 25.6 mg of **SI-8** gave a 91% yield based on recovered starting material (brsm). HRMS: calculated for $C_{15}H_{23}N_2NaO_2^+$: 263.1754 ($M+H^+$) found 263.1764 ($M+H^+$). ^1H NMR: (600 MHz, $CDCl_3$) δ 6.40 (s, 1H), 4.95 – 4.89 (m, 1H), 4.43 (td, J = 10.0 Hz, 3.6 Hz, 1H), 2.05 – 1.84 (m, 4H), 1.84 – 1.66 (m, 4H), 1.53 – 1.43 (m, 2H), 1.43 – 1.32 (m, 2H), 1.37 (s, 9 H). ^{13}C NMR: (151 MHz, $CDCl_3$) δ 182.5, 155.8, 153.7, 98.9, 84.3, 69.9, 33.0, 31.4, 31.0, 30.8, 28.9, 26.3, 24.4.

HPLC analysis: CHIRALCEL OD column, 98:2 hexanes/isopropanol

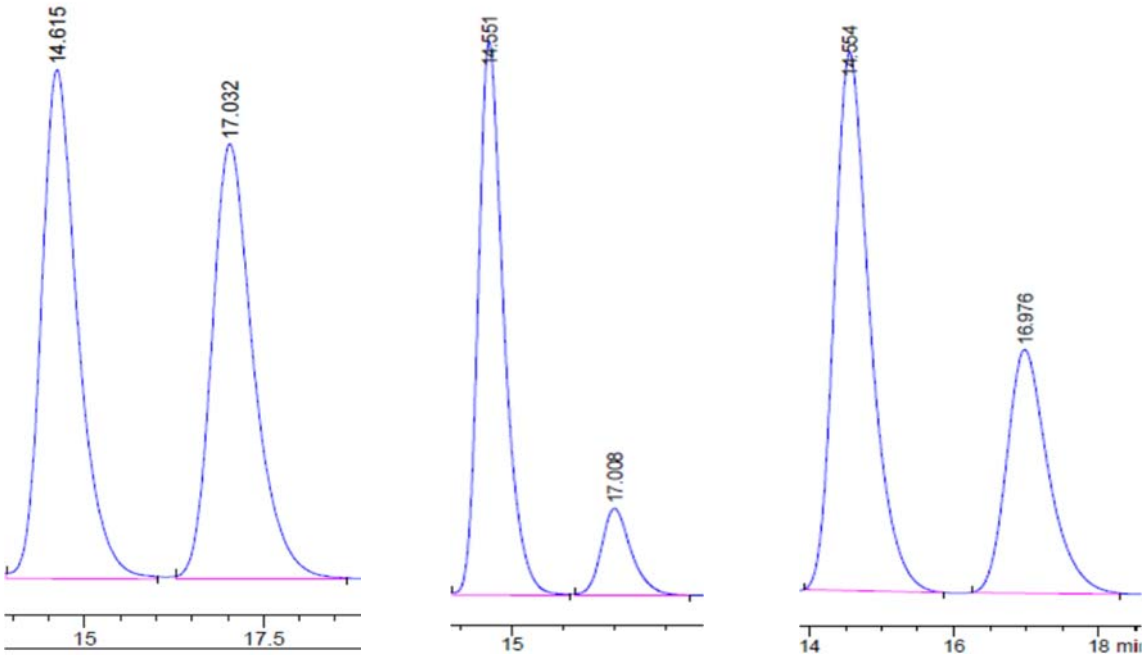


Racemic Enantioselective Spike

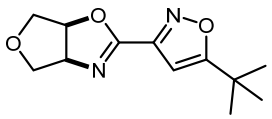


6,6-dimethyl-2-(5-methylisoxazol-3-yl)-3a,4,8,8a-tetrahydro-[1,3]dioxepino[5,6-*d*]oxazole (**SI-31,** *Table 3, entry 7).* Synthesized from **SI-17** (50.5 mg, 0.2 mmol) at room temperature for 168 hours. The reaction solvent was altered to 1.0 mL of dichloromethane. The product was eluted from a silica gel column with 3:1 hexanes/acetone to afford a white solid (30.1 mg, 59% yield, 63% ee). HRMS: calculated $C_{12}H_{17}N_2O_4^+$: 253.1183 ($M+H^+$) found 253.1186 ($M+H^+$). ^{1}H NMR: (600 MHz, $CDCl_3$) δ 6.43 (s, 1H), 4.79 – 4.74 (m, 1H), 4.34 (td, *J* = 8.1 Hz, 4.8 Hz, 1H), 4.10 (dd, *J* = 13.8 Hz, 4.9 Hz, 1H), 4.02 (dd, *J* = 13.8 Hz, 3.5 Hz, 1H), 3.95 (dd, *J* = 12.8 Hz, 4.8 Hz, 1H), 3.85 (dd, *J* = 12.8 Hz, 7.5 Hz, 1H), 2.49 (s, 3H), 1.40 (s, 3H), 1.35 (s, 3H). ^{13}C NMR: (151 MHz, $CDCl_3$) δ 170.9, 158.9, 154.0, 103.0, 102.0, 81.7, 67.8, 61.1, 59.2, 24.8, 23.9, 12.4.

HPLC analysis: CHIRALCEL OD column, 90:10 hexanes/isopropanol

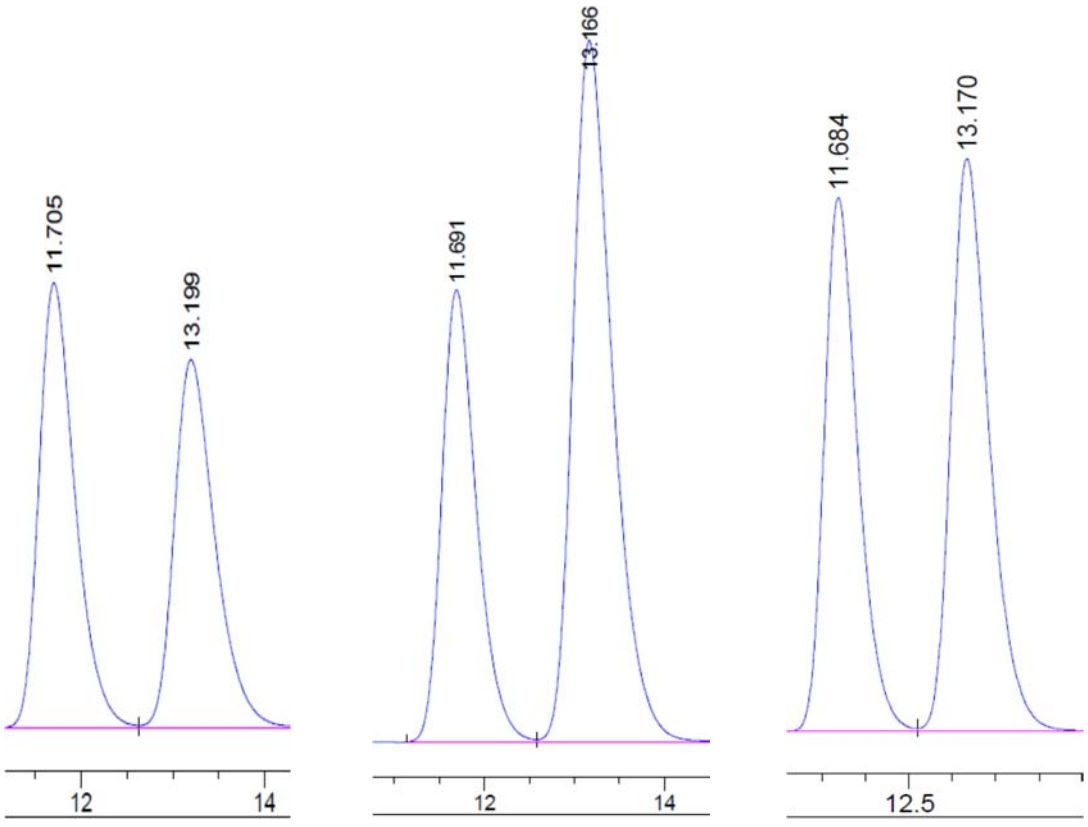


Racemic Enantioselective Spike

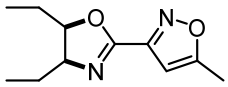


2-(5-(*tert*-butyl)isoxazol-3-yl)-3a,4,6,6a-tetrahydrofuro[3,4-*d*]oxazole (SI-32, *Table 3, entry 8)*. Synthesized from **SI-9** (52.0 mg, 0.2 mmol) 40 °C for 72 hours. The product was eluted from a silica gel column with 1:1 hexanes/ethyl acetate to afford a pale yellow solid (29.6 mg, 57% yield, 28% ee). Recovery of 21.4 mg of **SI-9** gave a 98% yield based on recovered starting material (brsm). HRMS: calculated for $C_{12}H_{16}N_2NaO_2^+$: 259.1053 ($M+Na^+$) found 259.1066 ($M+Na^+$). ^1H NMR: (400 MHz, $CDCl_3$) δ 6.38 (s, 1H), 5.27 (dd, J = 7.7 Hz, 3.9 Hz, 1H), 4.91 – 4.86 (m, 1H), 4.30 (d, J = 11.3 Hz, 1H), 4.14 (d, J = 10.0 Hz, 1H), 3.71 (dd, J = 10.0 Hz, 5.5 Hz, 1H), 3.65 (dd, J = 11.3 Hz, 3.9 Hz, 1H), 1.37 (s, 9H). ^{13}C NMR: (151 MHz, $CDCl_3$) δ 182.8, 157.9, 153.1, 99.0, 84.2, 74.6, 74.0, 72.6, 33.0, 28.9.

HPLC analysis: CHIRALCEL OD column, 90:10 hexanes/isopropanol

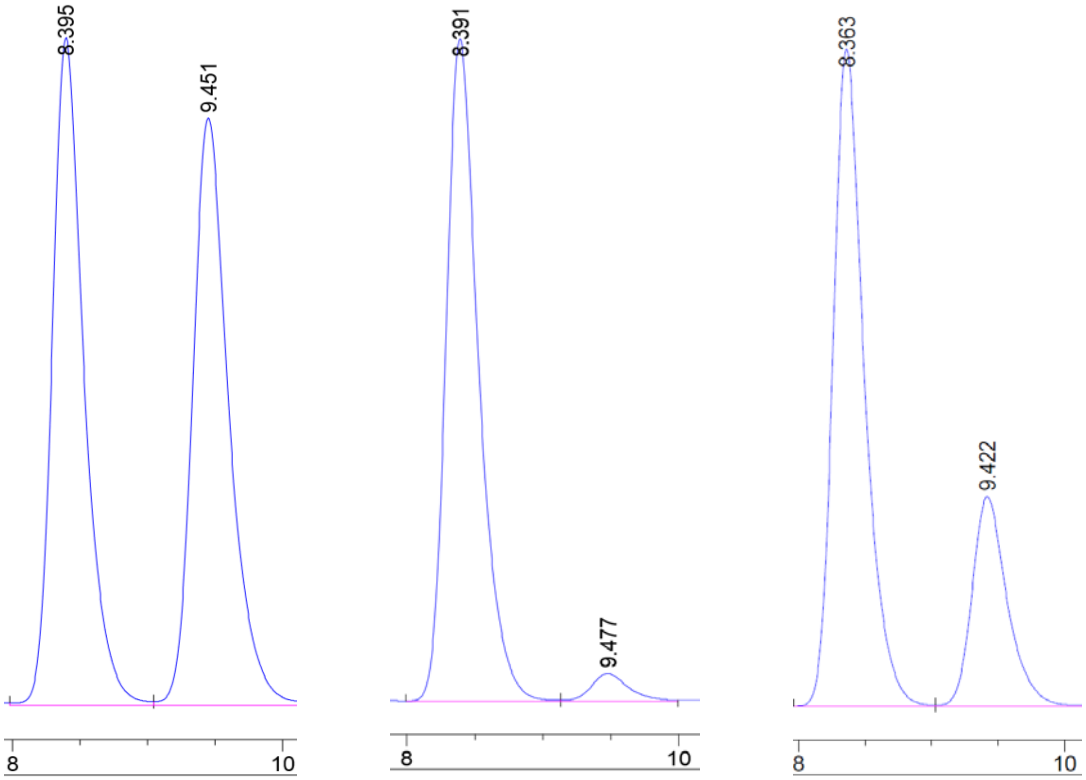


Racemic Enantioselective Spike

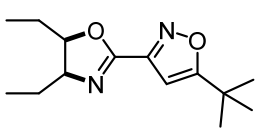


3-(4,5-diethyl-4,5-dihydrooxazol-2-yl)-5-methylisoxazole (**SI-33,** *Table 3, entry 9).* Synthesized from **SI-10** (41.6 mg, 0.2 mmol) at room temperature for 24 hours. The product was eluted from a silica gel column with 2:1 hexanes/ethyl acetate to afford a pale yellow oil (26.9 mg, 65% yield, 91% ee). Recovery of 6.9 mg of **SI-10** gave a 77% yield based on recovered starting material (brsm). HRMS: calculated for $C_{11}H_{16}N_2NaO_2^+$: 231.1104 ($M+Na^+$) found 231.1116 ($M+Na^+$). ^1H NMR: (400 MHz, $CDCl_3$) δ 6.42 (q, J = 0.9 Hz, 1H), 4.62 (td, J = 9.3 Hz, 4.3 Hz, 1H), 4.10 (td, J = 9.4 Hz, 5.0 Hz, 1H), 2.48 (d, J = 0.9 Hz, 3H), 1.79 – 1.60 (m, 3H), 1.60 – 1.48 (m, 1H), 1.11 (t, J = 7.3 Hz, 3H), 1.10 (t, J = 7.3 Hz, 3H). ^{13}C NMR: (151 MHz, $CDCl_3$) δ 170.6, 156.2, 154.5, 101.9, 85.6, 69.9, 23.4, 22.6, 12.4, 12.0, 11.4.

HPLC analysis: CHIRALCEL OD column, 93:7 hexanes/isopropanol

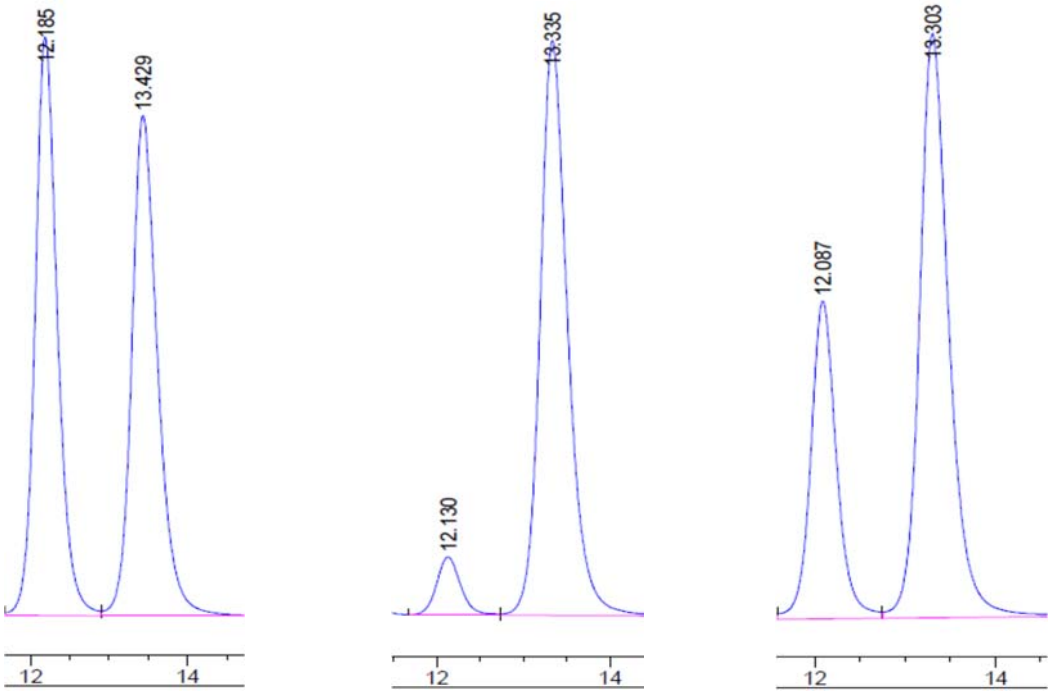


Racemic Enantioselective Spike



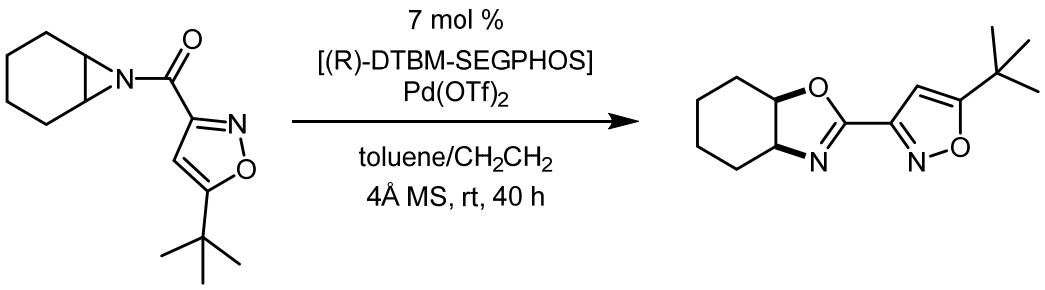
5-(*tert*-butyl)-3-(4,5-diethyl-4,5-dihydrooxazol-2-yl)isoxazole (**SI-34,** *Table 3, entry 10)*. Synthesized from **SI-11** (50.0 mg, 0.2 mmol) at 25 °C for 48 hours. The product was eluted from a silica gel column with 6:1 hexanes/ethyl acetate to afford a pale yellow solid (33.3 mg, 61% yield, 84% ee). Recovery of 10.8 mg of **SI-11** gave 88% yield based on recovered starting material (brsm). **SI-34** was hydrolyzed with 1M HCl in ethyl acetate (0.1 M) to achieve enantiomer separation via HPLC. HRMS: calculated for $C_{14}H_{23}N_2O_2^+$: 251.1754 ($M+H^+$) found 251.1766 ($M+H^+$). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 6.41 (s, 1H), 4.66 (td, *J* = 9.4 Hz, 4.3 Hz, 1H), 4.10 (td, *J* = 9.4 Hz, 5.0 Hz, 1H), 1.79 – 1.50 (m, 4H), 1.37 (s, 9H), 1.11 (t, *J* = 7.3 Hz, 3H), 1.10 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR: (151 MHz, $CDCl_3$) δ 182.4, 156.5, 154.0, 98.9, 85.6, 69.9, 33.0, 28.9, 23.4, 22.6, 12.0, 11.4.

HPLC analysis: CHIRALPAK IA column, 95:5 hexanes/isopropanol after hydrolysis with 1M HCl



Racemic Enantioselective Spike

Palladium-catalyzed, enantioselective Heine reaction scale-up:

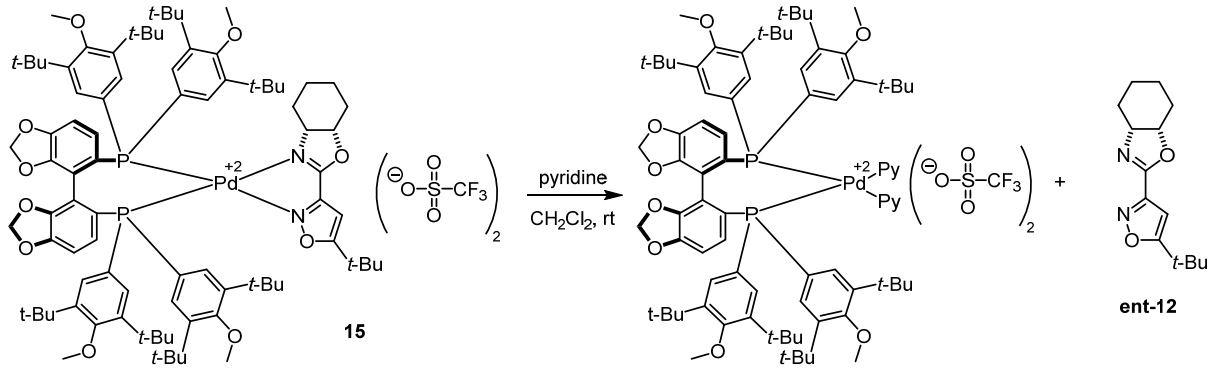


An oven-dried 20 mL vial containing a Teflon-coated stir bar was charged with [(*R*)-DTBM·SEGPHOS]$Pd(OTf)_2$ (111 mg, 0.07 mmol) under argon. Toluene (4.5 mL) and dichloromethane (0.5 mL) were added and the reaction stirred at room temperature. Then, powdered 4 Å molecular sieves (500 mg) were added, and reaction mixture was stirred. Aziridine **14** (248 mg, 1.0 mmol) was added, and the yellow reaction mixture was stirred for 40 hours at room temperature. After this time, 10 mL of hexanes was added, and the mixture was filtered. The yellow solid was washed with 10 mL of 1:1 toluene/hexanes and collected after air drying for further analysis. The filtrate was concentrated and purified by silica gel chromatography with 3:1 hexanes/ethyl acetate to afford **12** as a clear oil (133 mg, 54% yield, 99.1% ee). Recovery of 94.6 mg of **14** gave an 87% yield based on recovered starting material (brsm).

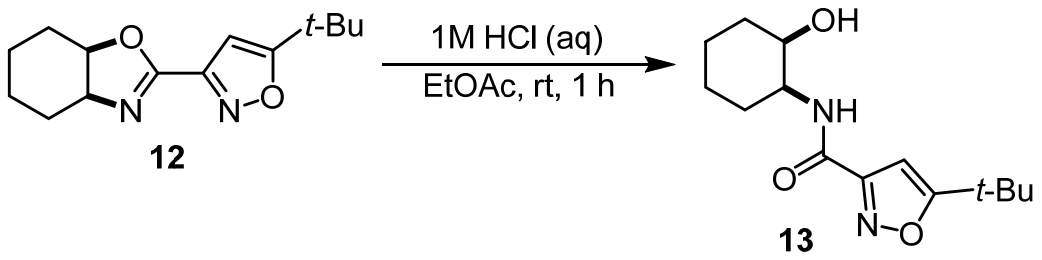
The recovered yellow solid was suspended in 5 mL of dichloromethane. The bright yellow mixture was passed through a pad of Celite with an additional 5 mL of dichloromethane wash. Concentration of the solution provided 100 mg of recovered palladium catalyst **15** as a yellow powder. HRMS: calculated for $C_{88}H_{120}N_2O_{10}P_2Pd^{2+}$: 766.3726 ($M^{2+}$) found 766.3770 ($M^{2+}$). ^1H NMR: (600 MHz, $CDCl_3$ @ 290 K) δ 8.26 (d, *J* = 18.0 Hz, 1H), 8.07 (br d, *J* = 12.6 Hz, 1H), 7.97 (d, *J* = 17.1 Hz, 1H), 7.18 – 7.11 (m, 3H), 7.04 (dd, *J* = 11.6 Hz, 1.7 Hz, 1H), 6.71 (dd, *J* = 8.3 Hz, 1.5 Hz, 1H), 6.67 (d, *J* = 11.3, 1H), 6.62 (dd, *J* = 8.3 Hz, 1.5 Hz, 1H), 6.12 (dd, *J* = 14.2 Hz, 8.2

Hz, 1H), 6.01 (s, 1H), 6.00 (s, 1H), 5.92 (s, 1H), 5.89 (s, 1H), 4.68 (br s, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 3.74 (s, 3H), 3.69 (s, 3H), 2.38 (br d, J = 14.2 Hz, 1H), 1.90 – 1.78 (m, 3H), 1.76 – 1.69 (m, 1H), 1.31 (m, 78H), 0.95 (s, 9H).

Spectroscopic data suggested a structure consistent with that shown below, which was a single diastereomer by ^{1}H-NMR. Treatment of recovered palladium catalyst with pyridine released oxazoline **ent-12**, as determined by HPLC analysis (CHIRALCEL OD, 98:2 hexane/isopropanol).



Oxazoline hydrolysis:

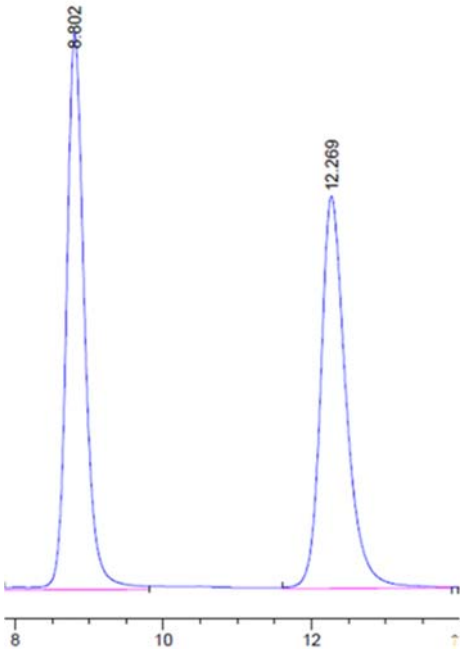


12 **13**

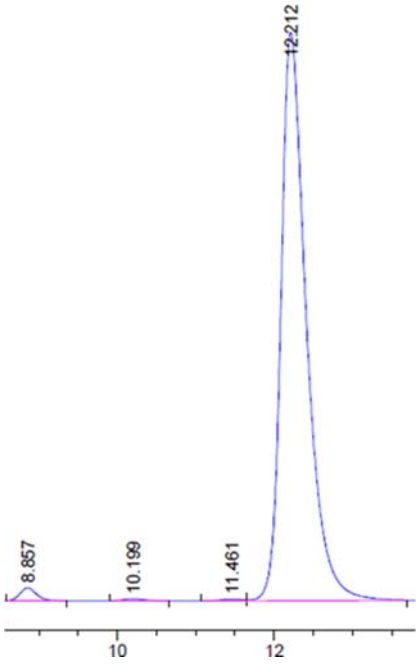
A 2 dram vial containing a Teflon-coated stir bar was charged with oxazoline **12** (24.8 mg, 0.1 mmol) under argon. Ethyl acetate (1 mL) and 1 M HCl (0.2 mL, 0.4 mmol) were added sequentially. The reaction stirred at room temperature for 1 hour. After this time, 0.6 mL of saturated sodium bicarbonate was added. The mixture was stirred for 30 minutes before the layers were separated. The aqueous layer was extracted two times with 2 mL of ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated in vacuo. The crude mixture was purified by silica gel chromatography with 3:1 hexanes/ethyl acetate to afford **13** as a white solid (22.6 mg, 85% yield). CHIRALPAK IA chiral column under 90:10 hexane/isopropyl alcohol. HRMS: calculated for $C_{14}H_{22}N_2NaO_3^+$: 289.1528 ($M+Na^+$) found 289.1523 ($M+Na^+$). ^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.15 (br d, J = 7.8 Hz, 1H), 6.41 (s, 1H), 4.13 – 4.06 (m, 1H), 4.06 – 4.01 (m, 1H), 2.14 (br s, 1H), 1.85 – 1.77 (m, 1H), 1.77 – 1.55 (m, 5H), 1.49 – 1.37 (m, 2H), 1.36 (s, 9H). ^{13}C NMR: (151 MHz, $CDCl_3$) δ 183.2, 159.1, 158.6, 98.5, 69.0, 51.2, 33.1, 32.0, 28.9, 27.1, 23.9, 19.8.

An authentic sample of **13** was produced in 80% yield by the reaction of commercially available (1*R*,2*S*)-2-aminocyclohexanol hydrochloride, 2,5-dioxopyrrolidin-1-yl 5-(*tert*-butyl)isoxazole-3-carboxylate (**SI-38**), and triethylamine in dichloromethane. The product was identical to **13** by ^{1}H-NMR and matched the major enantiomer by HPLC.

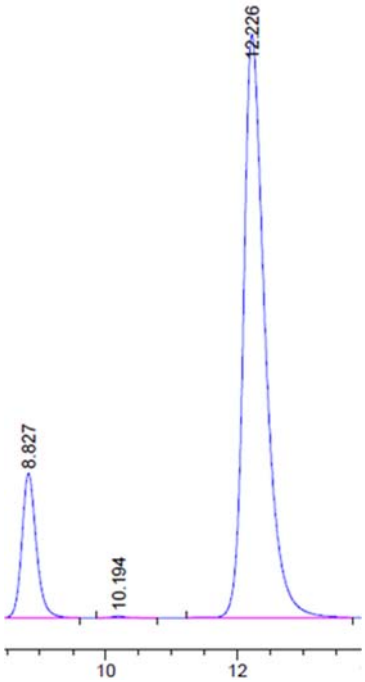
HPLC analysis: CHIRALPAK IA column, 90:10 hexanes/isopropanol



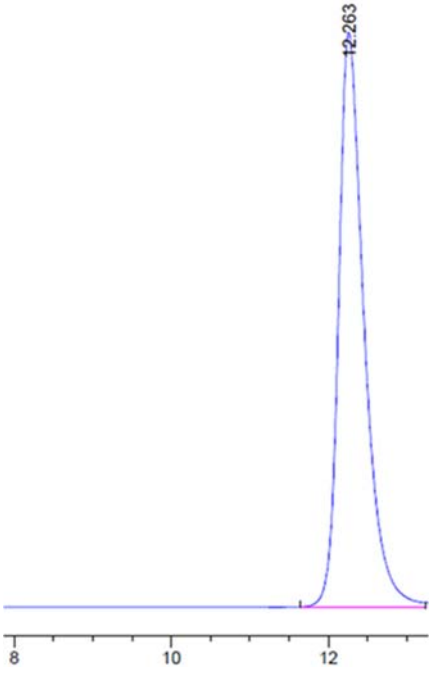
Racemic



Enantioenriched

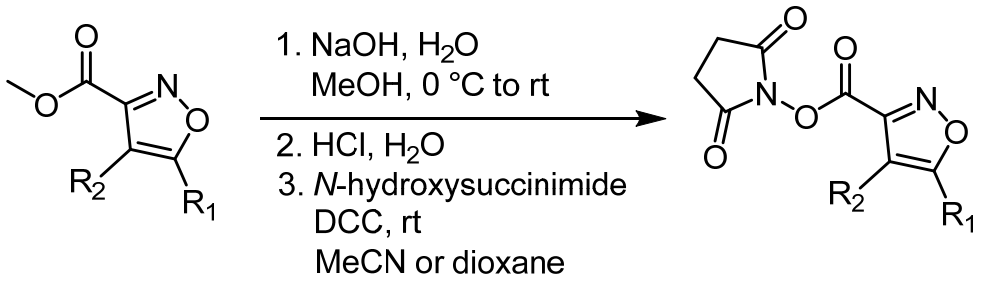


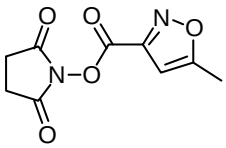
Spike



Authentic

Synthesis of succinimide esters:

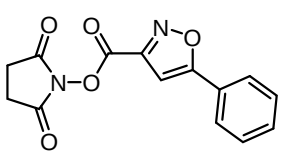




2,5-dioxopyrrolidin-1-yl 5-methylisoxazole-3-carboxylate (SI-35). A round bottom flask containing a Teflon®-coated stir bar was charged with methyl 5-methylisoxazole-3-carboxylate (21.17 g, 150 mmol) and 300 mL of methanol. The solution was cooled to 0 °C, and 45 mL of 4 M aqueous NaOH was added dropwise. The reaction mixture was then warmed to room temperature and stirred under argon overnight. After this time, the suspension was acidified with 45 mL of 6 M HCl. The methanol was removed by a rotary evaporator under reduced pressure. The remaining aqueous layer was extracted two times with 200 mL of ethyl acetate (400 mL total). The combined organic layers were washed with 50 mL of saturated brine and dried over magnesium sulfate. The mixture was filtered and concentrated in vacuo.

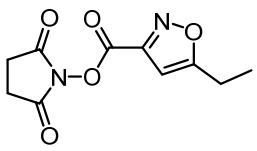
The unpurified carboxylic acid was combined with *N*-hydroxysuccinimide (17.26 g, 150 mmol) in a round bottom flask containing a Teflon-coated stir bar. Dry acetonitrile (450 mL) was added under argon. *N*, *N*'-Dicyclohexylcarbodiimide (32.5 g, 157.5 mmol) was added as a solid in three portions to the stirred reaction solution at room temperature. After stirring for 3 hours, the thick suspension was filtered. The solid was re-suspended in 200 mL of reagent grade acetonitrile and filtered. The combined filtrates were concentrated in vacuo. The solid was suspended in 80 mL of hot 3:1 dichloromethane/hexanes and filtered. The solid was washed with 50 mL of 3:1 dichloromethane/hexanes and dried in vacuo to produce a white solid (32.66 g, 97% yield). HRMS:

calculated for $C_9H_8N_2NaO_5^+$: 247.0325 ($M+Na^+$) found 247.0333 ($M+Na^+$). ^1H NMR: (600 MHz, $CDCl_3$) δ 6.56 (s, 1H), 2.93 (s, 4H), 2.56 (s, 3H). ^{13}C NMR: (151 MHz, $CDCl_3$) 172.6, 168.6, 155.7, 152.7, 102.9, 25.8, 12.5.



2,5-dioxopyrrolidin-1-yl 5-methylisoxazole-3-carboxylate (SI-36). A round bottom flask containing a Teflon®-coated stir bar was charged with methyl 5-phenylisoxazole-3-carboxylate (3.05 g, 15 mmol) and 60 mL of methanol. The solution was cooled to 0 °C, and 4.5 mL of 4 M aqueous NaOH was added dropwise. The reaction mixture was then warmed to room temperature and stirred under argon overnight. After this time, the suspension was acidified with 5 mL of 6 M HCl. The methanol was removed by a rotary evaporator under reduced pressure. The remaining aqueous layer was extracted two times with 100 mL of ethyl acetate (200 mL total). The combined organic layers were washed with 25 mL of saturated brine and dried over magnesium sulfate. The mixture was filtered and concentrated in vacuo.

The unpurified carboxylic acid was combined with *N*-hydroxysuccinimide (1.73 g, 15 mmol) in a round bottom flask containing a Teflon-coated stir bar. Dry dioxane (60 mL) was added under argon. *N*, *N*'-Dicyclohexylcarbodiimide (3.09 g, 15 mmol) was added as a solid in on portion to the stirred reaction solution at room temperature. After stirring for 4 hours, the thick suspension was filtered. The solid was washed with 30 mL of reagent grade dioxane, and the filtrate was concentrated in vacuo. The solid was purified by suspension in dichloromethane/hexanes and filtration to produce a white solid (3.81 g, 89% yield). HRMS: calculated for $C_{14}H_{10}N_2NaO_5^+$: 309.0494 ($M+Na^+$) found 309.0482 ($M+Na^+$). ^1H NMR: (400 MHz, $CDCl_3$) δ 7.86 – 7.82 (m, 2H), 7.56 – 7.50 (m, 3H), 7.05 (s, 1H), 2.95 (s, 4H). ^{13}C NMR: (100 MHz, $CDCl_3$) δ 172.9, 168.5, 155.7, 153.0, 131.5, 129.5, 126.25, 126.20, 100.4, 25.6.



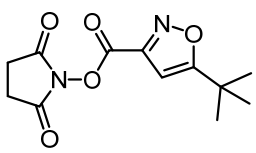
2,5-dioxopyrrolidin-1-yl 5-ethylisoxazole-3-carboxylate (SI-37). A round bottom flask containing a Teflon®-coated stir bar was charged with 2-butanone (4.5 mL, 50 mmol), dimethyl oxalate (5.9 g, 50 mmol), and 50 mL of dry diethyl ether under argon.[12] The suspension was cooled to 0 °C, and 9.8 mL of 30 % w/w sodium methoxide in methanol was added dropwise. The reaction mixture was warmed to room temperature after 30 minutes and stirred under argon overnight. After this time, the suspension was acidified with 75 mL of 1 M HCl. The mixture was extracted two times with 50 mL of MTBE (100 mL total). The combined organic layers were washed with 25 mL of saturated brine and dried over magnesium sulfate. The mixture was filtered and concentrated in vacuo.

The unpurified diketone was combined with hydroxylamine hydrochloride (3.82 g, 55 mmol) in a round bottom flask containing a Teflon-coated stir bar. Methanol (50 mL) was added under argon. The reaction mixture was heated to 70 °C for 3 hours. After this time, the solution was cooled to room temperature and 25 mL of saturated $NaHCO_3$ was added slowly (CAUTION: gas evolution). The methanol was removed by a rotary evaporator under reduced pressure. The remaining aqueous layer was extracted three times with 50 mL of MTBE (150 mL total). The combined organic layers were washed with 25 mL of saturated brine and dried over magnesium sulfate. The mixture was filtered and concentrated in vacuo to give 5.39 g (34.7 mmol) of a clear oil. ^{1}H-NMR of the crude reaction mixture was consistent with methyl 5-ethylisoxazole-3-carboxylate.

The unpurified ester was dissolved in 69 mL of methanol. The solution was cooled to 0 °C, and 10.4 mL of 4 M aqueous NaOH was added dropwise. The reaction mixture was then warmed to room temperature and stirred under argon overnight. After this time, the suspension was acidified with 11 mL of 6 M HCl. The methanol was removed by a rotary evaporator under reduced

pressure. The remaining aqueous layer was extracted two times with 200 mL of ethyl acetate (400 mL total). The combined organic layers were washed with 50 mL of saturated brine and dried over magnesium sulfate. The mixture was filtered and concentrated in vacuo.

The unpurified carboxylic acid was combined with *N*-hydroxysuccinimide (4.0 g, 34.7 mmol) in a round bottom flask containing a Teflon-coated stir bar. Dry dioxane (140 mL) was added under argon. *N*, *N*'-Dicyclohexylcarbodiimide (7.16 g, 34.7 mmol) was added as a solid in on portion to the stirred reaction solution at room temperature. After stirring for 4 hours, the thick suspension was filtered. The solid was washed with 60 mL of reagent grade dioxane, and the filtrate was concentrated in vacuo. The solid was purified by suspension in dichloromethane/hexanes and filtration to produce a white solid (5.47 g, 66% yield). HRMS: calculated for $C_{12}H_{13}N_3NaO_5^+$: 302.0747 ($M+Na^+$) found 302.0750 ($M+Na^+$). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 6.56 (s, 1H), 2.98 – 2.79 (m, 6H), 1.35 (t, J = 7.6 Hz, 3H). ^{13}C NMR: (151 MHz, $CDCl_3$) δ 178.0, 168.5, 155.8, 152.3, 101.6, 25.8, 20.5, 11.7.



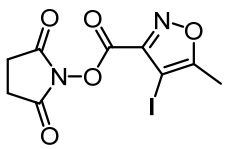
2,5-dioxopyrrolidin-1-yl 5-(tert-butyl)isoxazole-3-carboxylate (SI-38). A round bottom flask containing a Teflon®-coated stir bar was charged with pinacolone (6.3 mL, 50 mmol), dimethyl oxalate (5.9 g, 50 mmol), and 50 mL of dry diethyl ether under argon.[12] The suspension was cooled to 0 °C, and 9.8 mL of 30 % w/w sodium methoxide in methanol was added dropwise. The reaction mixture was warmed to room temperature after 30 minutes and stirred under argon overnight. After this time, the suspension was acidified with 75 mL of 1 M HCl. The mixture was extracted two times with 50 mL of MTBE (100 mL total). The combined organic layers were washed with 25 mL of saturated brine and dried over magnesium sulfate. The mixture was filtered and concentrated in vacuo.

The unpurified diketone was combined with hydroxylamine hydrochloride (3.82 g, 55 mmol) in a round bottom flask containing a Teflon-coated stir bar. Methanol (50 mL) was added under argon. The reaction mixture was heated to 70 °C for 3 hours. After this time, the solution was cooled to room temperature and 25 mL of saturated $NaHCO_3$ was added slowly (CAUTION: gas evolution). The methanol was removed by a rotary evaporator under reduced pressure. The remaining aqueous layer was extracted three times with 50 mL of MTBE (150 mL total). The combined organic layers were washed with 25 mL of saturated brine and dried over magnesium sulfate. The mixture was filtered and concentrated in vacuo to give a clear oil. ^{1}H-NMR of the crude reaction mixture was consistent with methyl 5-*tert*-butylisoxazole-3-carboxylate.

The unpurified ester was dissolved in 100 mL of methanol. The solution was cooled to 0 °C, and 15 mL of 4 M aqueous NaOH was added dropwise. The reaction mixture was then warmed to room temperature and stirred under argon overnight. After this time, the suspension was acidified with 15 mL of 6 M HCl. The methanol was removed by a rotary evaporator under reduced pressure. The remaining aqueous layer was extracted two times with 200 mL of ethyl acetate (400 mL total). The combined organic layers were washed with 50 mL of saturated brine and dried over magnesium sulfate. The mixture was filtered and concentrated in vacuo.

The unpurified carboxylic acid was combined with *N*-hydroxysuccinimide (5.75 g, 50 mmol) in a round bottom flask containing a Teflon-coated stir bar. Dry dioxane (150 mL) was added under argon. *N*, *N*'-Dicyclohexylcarbodiimide (10.3 g, 50 mmol) was added as a solid in on portion to the stirred reaction solution at room temperature. After stirring for 4 hours, the thick suspension was filtered. The solid was washed with 60 mL of reagent grade dioxane, and the filtrate was concentrated in vacuo. The solid was crystalized from 1:1 MTBE/hexanes to produce a white crystalline solid (8.71 g, 65% yield). HRMS: calculated for $C_{12}H_{14}N_2NaO_5^+$: 289.0795

(M+Na$^+$) found 289.0804 (M+Na$^+$). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 6.52 (s, 1H), 2.92 (s, 4H), 1.39 (s, 9H). ^{13}C NMR: (100 MHz, $CDCl_3$) δ 184.4, 168.6, 155.8, 152.0, 99.9, 33.3, 28.8, 25.8.



2,5-dioxopyrrolidin-1-yl 4-iodo-5-methylisoxazole-3-carboxylate (SI-39). A round bottom flask containing a Teflon®-coated stir bar was charged with methyl 5-methylisoxazole-3-carboxylate (2.82 g, 20 mmol), *N*-iodosuccinimide (5.40 g, 24 mmol), and 33 mL of trifluoroacetic acid under argon.[13] The mixture was heated to 65 °C for 4 hours. After this time, the trifluoroacetic acid was removed by rotary evaporation. The residue was dissolved in 200 mL of ethyl acetate and washed with 100 mL of saturated $NaHCO_3$ and 200 mL of 10% sodium thiosulfate. The organic layer was dried with 100 mL of saturated brine, followed by solid magnesium sulfate. The mixture was filtered and concentrated in vacuo. ^{1}H-NMR of the crude reaction mixture was consistent with methyl 4-iodo-5-methylisoxazole-3-carboxylate.

The unpurified ester was dissolved in 33 mL of methanol. The solution was cooled to 0 °C, and 4.5 mL of 4 M aqueous NaOH was added dropwise. The reaction mixture was then warmed to room temperature and stirred under argon for 4 hours. After this time, the suspension was acidified with 5 mL of 6 M HCl. The mixture was extracted two times with 50 mL of ethyl acetate (100 mL total). The combined organic layers were washed with 25 mL of saturated brine and dried over magnesium sulfate. The mixture was filtered and concentrated in vacuo.

The unpurified carboxylic acid was combined with *N*-hydroxysuccinimide (1.81 g, 15.75 mmol) in a round bottom flask containing a Teflon-coated stir bar. Dry dioxane (60 mL) was added under argon. *N*, *N*'-Dicyclohexylcarbodiimide (3.25 g, 15.75 mmol) was added as a solid in on portion to the stirred reaction solution at room temperature. After stirring for 4 hours, the thick suspension was filtered. The solid was washed with 20 mL of reagent grade dioxane, and the

filtrate was concentrated in vacuo. The solid was purified by recrystallization from MTBE/dichloromethane to produce a white crystalline solid (3.64 g, 69% yield). HRMS: calculated for $C_9H_7IN_2NaO_5^+$: 372.9292 ($M+Na^+$) found: 372.9299 ($M+Na^+$). ^1H NMR: (600 MHz, $CDCl_3$) δ 2.61 (s, 3H), 2.93 (s, 4H). ^{13}C NMR: (151 MHz, $CDCl_3$) δ 174.7, 168.4, 155.2, 152.4, 57.4, 25.4, 12.9.

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