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# **Supporting Information**

# Direct Catalytic Enantioselective Amination of Ketones for the Formation of Tri- and Tetrasubstituted Stereocenters

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# **Table of Contents**

I.	General Information	S2
II.	Experimental Procedures and Compound Characterization	S3
III.	SI References	S34
IV.	Copies of NMR Spectra	S35

#### **I.** General Information

All reactions were carried out in oven- or flame-dried glassware under a nitrogen atmosphere. THF was distilled from a sodium-benzophenone still under argon, toluene and acetonitrile was stored under an atmosphere of air over 4 Å molecular sieves. All commercial reagents were used without further purification unless states otherwise. Flash chromatography was performed with 0.035-0.070 µm Silica Gel (Acros). <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy was performed at ambient temperature with CDCl<sub>3</sub> as the solvent on a Mercury NMR at 400 (<sup>1</sup>H) or 100 (<sup>13</sup>C) MHz, an Inova NMR at 500 (<sup>1</sup>H) or 125 (<sup>13</sup>C) MHz, and an Inova NMR at 600 (<sup>1</sup>H) MHz unless otherwise indicated. Chemical shifts are reported in ppm relative to tetramethylsilane or residual protonated solvent. All <sup>13</sup>C NMR spectra are proton decoupled. When high temperature NMR is utilized with epimerizable products, the *ee* values reported are those obtained before the material is subjected to the high temperature NMR. Infrared spectroscopy data was recorded on sodium chloride plates as thin films made from the indicated solvent on a Thermo Scientific Nicolet IR100 FT-IR spectrometer. Analytical thin layer chromatography was performed using silica gel 60-F<sub>254</sub> plates (Millipore) and visualized with a UV lamp (254 nm), or using a solution of KMnO<sub>4</sub>-K<sub>2</sub>CO<sub>3</sub> in water followed by heating. High-resolution mass spectra were obtained in the Vincent Coates Foundation Mass Spectrometry Laboratory, Stanford University Mass Spectrometry (http://massspec.stanford.edu).

#### **II. Experimental Procedures and Compound Characterization**

#### **ProPhenol Ligands:**



O Boc 16 mol% (S,S)-L2 O



(S,S)-L2 (24.8 mg, 0.0320 mmol), 2-methyl-1-indanone (29.2 mg, 0.200 mmol), and activated 3 Å molecular sieves (5 mg) were measured into a microwave vial equipped with stir bar. The flask was placed under a nitrogen atmosphere and PhMe (0.6 mL) was added. After stirring for 15 minutes, diethylzinc (1.0 M in hexanes,  $60\mu$ L, 0.060 mmol) was added and the reaction was allowed to stir for an additional 15 minutes. At this time, a premixed (15 min) PhMe (0.4 mL) solution of di-*tert*-butyl azodicarboxylate (69.1 mg, 0.300 mmol) and 3 Å molecular sieves (5 mg) was added. The reaction was allowed to stir at 40 °C for 16 h at which point the reaction mixture was filtered through a small plug of fluorosil. The residue was concentrated under reduced pressure using rotary evaporation. The resulting residue was purified via flash chromatography (SiO2; DCM to petroleum ether / EtOAc 6:1 to petroleum ether / EtOAc 5:1 to petroleum ether / EtOAc 4:1) to afford 73.8 mg (98 %) of a clear oil.

IR(CDCl<sub>3</sub>) 3316, 2979, 2933, 1730, 1611, 1478, 1368, 1302, 1251, 1160, 1119, 1057, 733 cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, 75 °C, Benzene- $d_6$ )  $\delta$  7.77 (d, J = 7.6 Hz, 1H), 7.17 (t, J = 7.6 Hz, 1H), 7.06 – 6.95 (m, 2H), 6.26 (s, 1H), 3.89 (d, J = 17.2 Hz, 1H), 2.97 (d, J = 17.1 Hz, 1H), 1.41 (s, 9H), 1.20 (2 S, 12H total). <sup>13</sup>C NMR (126 MHz, 75 °C, Benzene)  $\delta$  202.95, 156.39, 154.23, 150.90, 135.24, 134.45, 127.42, 126.53, 124.85, 81.92, 80.70, 68.30, 42.56, 28.40, 28.16, 23.09. HRMS (EI) calculated for C<sub>20</sub>H<sub>28</sub>N<sub>2</sub>O<sub>5</sub> (Na<sup>+</sup>) 399.1896, found: 399.1896. R<sub>f</sub> (petroleum ether / EtOAc 4:1) = 0.35. [ $\alpha$ ]<sub>D</sub><sup>23</sup> = -10.9 (c = 0.97, CHCl<sub>3</sub>). HPLC: (*Chiralpak*® *IA*, heptane-isopropanol 95:5, 0.8 mL/min, 254 nm): t<sub>R</sub>(minor) = 7.5 min, t<sub>R</sub>(major) = 21.5 min, 97% *ee*.





To determine the absolute stereochemistry of the tetrasubstituted ketone products, the optical rotation of the title compound was compared to that reported by Terada.  $[\alpha]_D^{25} = 12.6$  (c = 1.01, CHCl<sub>3</sub>). As the signs of the optical rotations are opposite, we assigned the stereochemistry of our products to be opposite of that reported by Terada.<sup>1</sup> All other tetrasubstituted ketone products are assigned by analogy to the title compound.

### Large-scale procedure:

(S,S)-L2 (85.2 mg, 0.110 mmol), 2-methyl-1-indanone (146 mg, 1.00 mmol), and activated 3 Å molecular sieves (25 mg) were measured into a microwave vial equipped with stir bar. The flask was placed under a nitrogen atmosphere and PhMe (3.0 mL) was added. After stirring for 15 minutes, diethylzinc (1.0 M in hexanes, 200 µL, 0.20 mmol) was added and the reaction was allowed to stir for an additional 15 minutes. At this time, a premixed (15 min) PhMe (2 mL) solution of di-*tert*-butyl azodicarboxylate (345 mg, 1.50 mmol) and 3 Å molecular sieves (25 mg) was added. The reaction was allowed to stir at 60 °C for 16 h at which point the reaction mixture was filtered through a small plug of fluorosil. The residue was concentrated under reduced pressure using rotary evaporation. The resulting residue was purified via flash chromatography (SiO2; petroleum ether / EtOAc 6:1) to afford 0.35 g (93 %) of a clear oil.

HPLC: (*Chiralpak*® *IA*, heptane-isopropanol 95:5, 0.8 mL/min, 254 nm):  $t_R(minor) = 7.1 min$ ,  $t_R(major) = 19.3 min$ , 92% *ee*.



di-tert-butyl 1-(2-butyl-1-oxo-2,3-dihydro-1H-inden-2-yl)hydrazine-1,2-dicarboxylate 2b



(S,S)-L2 (24.8 mg, 0.0320 mmol), 2-butyl-1-indanone (37.7 mg, 0.200 mmol), and activated 3 Å molecular sieves (5 mg) were measured into a microwave vial equipped with stir bar. The flask was placed under a nitrogen atmosphere and PhMe (0.6 mL) was added. After stirring for 15 minutes, diethylzinc (1.0 M in hexanes, 60µL, 0.060 mmol) was added and the reaction was allowed to stir for an additional 15 minutes. At this time, a premixed (15 min) PhMe (0.4 mL) solution of di-*tert*-butyl azodicarboxylate (69.1 mg, 0.300 mmol) and 3 Å molecular sieves (5 mg) was added. The reaction was allowed to stir at 40 °C for 16 h at which point the reaction mixture was filtered through a small plug of fluorosil. The residue was concentrated under reduced pressure using rotary evaporation. The resulting residue was purified via flash chromatography (SiO2; DCM to petroleum ether / EtOAc 6:1 to petroleum ether / EtOAc 5:1 to petroleum ether / EtOAc 4:1) to afford 64.1 mg (77 %) of a clear oil.

IR(CDCl<sub>3</sub>) 3348, 2929, 1726, 1613, 1466, 1368, 1251, 1159 cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, 75 °C, Benzened<sub>6</sub>)  $\delta$  7.77 (d, J = 7.6 Hz, 1H), 7.21 – 7.12 (obscured t, 1H), 7.05 (d, J = 7.7 Hz, 1H), 6.99 (t, J = 7.5 Hz, 1H), 6.32 – 6.16 (m, 1H), 3.92 (d, J = 17.4 Hz, 1H), 3.11 (d, J = 17.2 Hz, 1H), 1.96 – 1.84 (m, 1H), 1.74 – 1.60 (m, 1H), 1.43 (s, 9H), 1.38 – 1.28 (m, 2H), 1.22 (s, 9H), 1.12 – 1.05 (m, 2H), 0.68 (t, J = 6.8 Hz, 3H). <sup>13</sup>C NMR (126 MHz, 75 °C, Benzene)  $\delta$  202.41, 156.56, 154.56, 151.30, 136.85, 134.37, 127.36, 126.15, 124.35, 82.00, 80.81, 70.93, 41.35, 36.79, 28.43, 28.16, 26.13, 23.47, 13.60. HRMS (EI) calculated for C<sub>23</sub>H<sub>34</sub>N<sub>2</sub>O<sub>5</sub> (Na<sup>+</sup>) 441.2365, found: 441.2347. R<sub>f</sub> (petroleum ether / EtOAc 4:1) = 0.41. [ $\alpha$ ]<sub>D</sub><sup>23</sup> = 15.3 (c = 0.83, CHCl<sub>3</sub>). HPLC: (*Chiralpak*® *IA*, heptane-isopropanol 95:5, 0.8 mL/min, 254 nm): t<sub>R</sub>(minor) = 7.7 min, t<sub>R</sub>(major) = 16.2 min, 90% *ee*.







(S,S)-L2 (24.8 mg, 0.0320 mmol), 2-benzyl-1-indanone (44.5 mg, 0.200 mmol), and activated 3 Å molecular sieves (5 mg) were measured into a microwave vial equipped with a stir bar. The flask was placed under a nitrogen atmosphere and PhMe (0.6 mL) was added. After stirring for 15 minutes, diethylzinc (1.0 M in hexanes, 60µL, 0.060 mmol) was added and the reaction was allowed to stir for an additional 15 minutes. At this time, a premixed (15 min) PhMe (0.4 mL) solution of di-*tert*-butyl azodicarboxylate (69.1 mg, 0.300 mmol) and 3 Å molecular sieves (5 mg) was added. The reaction was allowed to stir at 40 °C for 15 h at which point the reaction mixture was filtered through a small plug of fluorosil. The residue was concentrated under reduced pressure using rotary evaporation. The resulting residue was purified via flash chromatography (SiO2; petroleum ether / EtOAc 7:1) to afford 86.7 mg (96 %) of a clear oil.

IR(C<sub>6</sub>D<sub>6</sub>) 3346, 3303, 2979, 2932, 1723, 1611, 1477, 1456, 1392, 1368, 1328, 1250, 1159, 1048, 755, 729, 702 cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, 75 °C, Benzene-*d*<sub>6</sub>)  $\delta$  7.58 (d, *J* = 7.6 Hz, 1H), 7.00 (d, *J* = 7.4 Hz, 2H), 6.92 (t, *J* = 7.6 Hz, 1H), 6.84 – 6.70 (m, 5H), 6.29 (s, 1H), 3.91 (s, 1H), 3.41 (d, *J* = 17.4 Hz, 1H), 3.23 (d, *J* = 12.7 Hz, 1H), 3.08 (d, *J* = 12.7 Hz, 1H), 1.42 (series of s, 9H), 1.22 (s, 9H). <sup>13</sup>C NMR (126 MHz, 75 °C, Benzene)  $\delta$  203.15, 156.50, 154.34, 151.29, 137.39, 134.94, 134.04, 130.95, 126.87, 125.63, 123.87, 82.13, 80.89, 71.34, 42.80, 39.78, 28.45, 28.14. Two aromatic carbon peaks are obscured in the spectrum. HRMS (EI) calculated for C<sub>26</sub>H<sub>32</sub>N<sub>2</sub>O<sub>5</sub> (Na<sup>+</sup>) 475.2203, found: 475.2203. [ $\alpha$ ]<sub>D</sub><sup>23</sup> = 50.8 (c = 1.76, CHCl<sub>3</sub>). R<sub>f</sub> (petroleum ether / EtOAc 6:1) = 0.27. HPLC: (*Chiralpak*® *IA*, heptane-isopropanol-triethylamine 95:5:0.5, 0.8 mL/min, 254 nm): t<sub>R</sub>(minor) = 7.9 min, t<sub>R</sub>(major) = 17.3 min, 95% *ee*.



di-tert-butyl 1-(2-allyl-1-oxo-2,3-dihydro-1H-inden-2-yl)hydrazine-1,2-dicarboxylate 2d



(S,S)-L2 (24.8 mg, 0.0320 mmol), 2-allyl-1-indanone (34.4 mg, 0.200 mmol), and activated 3 Å molecular sieves (5 mg) were measured into a microwave vial equipped with stir bar. The flask was placed under a nitrogen atmosphere and PhMe (0.6 mL) was added. After stirring for 15 minutes, diethylzinc (1.0 M in hexanes, 60µL, 0.060 mmol) was added and the reaction was allowed to stir for an additional 15 minutes. At this time, a premixed (15 min) PhMe (0.4 mL) solution of di*-tert*-butyl azodicarboxylate (69.1 mg, 0.300 mmol) and 3 Å molecular sieves (5 mg) was added. The reaction was allowed to stir at 40 °C for 16 h at which point the reaction mixture was filtered through a small plug of fluorosil. The residue was concentrated under reduced pressure using rotary evaporation. The resulting residue was purified via flash chromatography (SiO2; DCM to petroleum ether / EtOAc 6:1 to petroleum ether / EtOAc 5:1 to petroleum ether / EtOAc 4:1) to afford 67.8 mg (84 %) of a clear oil.

IR(CDCl<sub>3</sub>) 3379, 2982, 2937, 1723, 1611, 1477, 1368, 1249, 1158, 754 cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, 75 °C, Benzene- $d_6$ )  $\delta$  7.75 (d, J = 7.6 Hz, 1H), 7.15 (obscured t, J = 7.0 Hz, 1H), 7.02 (d, J = 7.6 Hz, 1H), 6.98 (t, J = 7.5 Hz, 1H), 6.27 (s, 1H), 5.62 (dq, J = 17.0, 7.8 Hz, 1H), 4.90 (d, J = 16.9 Hz, 1H), 4.76 (d, J = 10.2 Hz, 1H), 3.89 (d, J = 17.4 Hz, 1H), 3.17 (d, J = 17.3 Hz, 1H), 2.58 (dd, J = 14.0, 7.3 Hz, 1H), 2.44 (dd, J = 14.1, 6.8 Hz, 1H), 1.42 (s, 9H), 1.21 (s, 9H). <sup>13</sup>C NMR (126 MHz, 75 °C, Benzene)  $\delta$  202.03, 156.38, 154.46, 151.14, 136.57, 134.47, 132.71, 127.38, 126.17, 124.43, 118.59, 82.11, 80.86, 70.61, 41.29, 40.48, 28.43, 28.14. HRMS (EI) calculated for C<sub>22</sub>H<sub>30</sub>N<sub>2</sub>O<sub>5</sub> (Na<sup>+</sup>) 425.2052, found: 425.2050. R<sub>f</sub> (petroleum ether / EtOAc 4:1) = 0.38. [ $\alpha$ ]<sub>D</sub><sup>25</sup> = 17.5 (c = 1.16, CHCl<sub>3</sub>). HPLC: (*Chiralpak*® *IA*, heptane-isopropanol 95:5, 0.8 mL/min, 254 nm): t<sub>R</sub>(minor) = 7.6 min, t<sub>R</sub>(major) = 22.2 min, 95% *ee*.



di-tert-butyl 1-(2-propargyl-1-oxo-2,3-dihydro-1H-inden-2-yl)hydrazine-1,2-dicarboxylate 2e



(S,S)-L2 (24.8 mg, 0.0320 mmol), 2-propargyl-1-indanone (34.0 mg, 0.200 mmol), and activated 3 Å molecular sieves (5 mg) were measured into a microwave vial equipped with stir bar. The flask was placed under a nitrogen atmosphere and PhMe (0.6 mL) was added. After stirring for 15 minutes, diethylzinc (1.0 M in hexanes, 60µL, 0.060 mmol) was added and the reaction was allowed to stir for an additional 15 minutes. At this time, a premixed (15 min) PhMe (0.4 mL) solution of di*-tert*-butyl azodicarboxylate (69.1 mg, 0.300 mmol) and 3 Å molecular sieves (5 mg) was added. The reaction was allowed to stir at 40 °C for 16 h at which point the reaction mixture was filtered through a small plug of fluorosil. The residue was concentrated under reduced pressure using rotary evaporation. The resulting residue was purified via flash chromatography (SiO2; DCM to petroleum ether / EtOAc 6:1 to petroleum ether / EtOAc 4:1) to afford 75.0 mg (94 %) of a clear oil.

IR(C<sub>6</sub>D<sub>6</sub>) 3313, 2980, 2931, 1728, 1611, 1479, 1368, 1250, 1158, 757 cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, 75 °C, Benzene-*d*<sub>6</sub>)  $\delta$  7.76 (d, *J* = 7.7 Hz, 1H), 7.16 (obscured t, 1H), 7.03 (d, *J* = 7.7 Hz, 1H), 6.98 (t, *J* = 7.5 Hz, 1H), 6.19 (s, 1H), 3.89 (d, *J* = 17.6 Hz, 1H), 3.39 (d, *J* = 17.4 Hz, 1H), 2.70 – 2.48 (m, 2H), 1.53 – 1.46 (m, 1H), 1.41 (s, 9H), 1.20 (s, 9H). <sup>13</sup>C NMR (126 MHz, 75 °C, Benzene)  $\delta$  200.89, 156.25, 154.11, 151.53, 136.14, 134.54, 127.36, 126.10, 124.64, 82.30, 80.94, 79.16, 71.38, 69.67, 40.32, 28.40, 28.10, 26.76. HRMS (EI) calculated for C<sub>22</sub>H<sub>28</sub>N<sub>2</sub>O<sub>5</sub> (Na<sup>+</sup>) 423.1896, found: 423.1909. R<sub>f</sub> (petroleum ether / EtOAc 4:1) = 0.22. [ $\alpha$ ]<sub>D</sub><sup>24</sup> = 8.0 (c = 1.44, CHCl<sub>3</sub>). HPLC: (*Chiralpak*® *IA*, heptane-isopropanol 95:5, 0.8 mL/min, 254 nm): t<sub>R</sub>(minor) = 9.5 min, t<sub>R</sub>(major) = 35.3 min, 95% *ee*.



di-tert-butyl 1-(2-(2-methoxy-2-oxoethyl)-1-oxo-2,3-dihydro-1H-inden-2-yl)hydrazine-1,2-dicarboxylate



(S,S)-L2 (24.8 mg, 0.0320 mmol), methyl 2-(1-oxo-2,3-dihydro-1H-inden-2-yl)acetate (40.8 mg, 0.200 mmol), and activated 3 Å molecular sieves (5 mg) were measured into a microwave vial equipped with stir bar. The flask was placed under a nitrogen atmosphere and PhMe (0.6 mL) was added. After stirring for 15 minutes, diethylzinc (1.0 M in hexanes, 60µL, 0.060 mmol) was added and the reaction was allowed to stir for an additional 15 minutes. At this time, a premixed (15 min) PhMe (0.4 mL) solution of di-*tert*-butyl azodicarboxylate (69.1 mg, 0.300 mmol) and 3 Å molecular sieves (5 mg) was added. The reaction was allowed to stir at 40 °C for 16 h at which point the reaction mixture was filtered through a small plug of fluorosil. The residue was concentrated under reduced pressure using rotary evaporation. The resulting residue was purified via flash chromatography (SiO2; DCM to petroleum ether / EtOAc 5:1 to petroleum ether / EtOAc 3:1) to afford 79.0 mg (91 %) of a clear oil.

IR(C<sub>6</sub>D<sub>6</sub>) 3310, 2979, 1730, 1611, 1467, 1437, 1368, 12248, 1171, 1063, 1013, 853, 776, 739 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, 75 °C, Benzene-*d*<sub>6</sub>) spectrum complicated due to rotomers  $\delta$  7.76 (d, *J* = 7.6 Hz, 1H), 7.12 (d, *J* = 7.7 Hz, 1H), 7.08 – 6.98 (m, 1H), 6.95 (t, *J* = 7.4 Hz, 1H), 6.41 (2S, 1H total), 4.28 – 3.44 (broad m, 2H total), 3.25 (s, 3H), 2.57 (s, 2H), 1.32 (series of s, 18H total). <sup>13</sup>C NMR (101 MHz, 75 °C, Benzene-*d*<sub>6</sub>) spectrum complicated due to rotomers  $\delta$  200.42, 169.80, 155.83, 154.19, 150.99, 135.39, 134.61, 127.40, 126.44, 124.81, 82.08, 80.90, 69.97, 51.24, 40.36, 39.79, 28.40, 28.11. R<sub>f</sub> (petroleum ether / EtOAc 3:1) = 0.37. HRMS (EI) calculated for C<sub>22</sub>H<sub>30</sub>N<sub>2</sub>O<sub>7</sub> (Na<sup>+</sup>) 457.1951, found: 457.1939. [ $\alpha$ ]<sub>D</sub><sup>23</sup> = 6.7 (c = 1.27, CHCl<sub>3</sub>). HPLC: (*Chiralpak*® *IA*, heptane-isopropanol 90:10, 0.8 mL/min, 254 nm): t<sub>R</sub>(minor) = 8.4 min, t<sub>R</sub>(major) = 23.6 min, 94% *ee*.



di-tert-butyl (S)-1-(2-isopropyl-1-oxo-2,3-dihydro-1H-inden-2-yl)hydrazine-1,2-dicarboxylate 2g



(S,S)-L2 (24.8 mg, 0.0320 mmol), 2-isopropyl-1-indanone (34.8 mg, 0.200 mmol), and activated 3 Å molecular sieves (5 mg) were measured into a microwave vial equipped with a stir bar. The flask was placed under a nitrogen atmosphere and PhMe (0.6 mL) was added. After stirring for 15 minutes, diethylzinc (1.0 M in hexanes, 60µL, 0.060 mmol) was added and the reaction was allowed to stir for an additional 15 minutes. At this time, a premixed (15 min) PhMe (0.4 mL) solution of di*-tert*-butyl azodicarboxylate (69.1 mg, 0.300 mmol) and 3 Å molecular sieves (5 mg) was added. The reaction was allowed to stir at 40 °C for 17 h at which point the reaction mixture was filtered through a small plug of fluorosil. The residue was concentrated under reduced pressure using rotary evaporation. The resulting residue was purified via flash chromatography (SiO2; petroleum ether / EtOAc 7:1) to afford 31.2 mg (39 %) of a clear oil.

IR(C<sub>6</sub>D<sub>6</sub>) 3323, 2978, 2935, 1724, 1611, 1469, 1393, 1368, 1249, 1157, 1053, 1020, 997, 867, 771, 735 cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, 75 °C, Benzene- $d_6$ )  $\delta$  7.82 – 7.65 (m, 1H), 7.29 – 7.18 (m, 1H), 7.10 – 6.90 (m, 2H), 6.31 (s, 1H), 3.93 (d, *J* = 17.7 Hz, 1H), 3.22 – 3.05 (m, 1H), 2.43 – 2.20 (m, 1H), 1.49 – 1.39 (m, 9H), 1.27 – 1.12 (m, 9H), 0.98 – 0.89 (m, 3H), 0.69 (dd, *J* = 12.4, 6.9 Hz, 3H). <sup>13</sup>C NMR (126 MHz, 75 °C, Benzene)  $\delta$  201.62, 156.65, 155.22, 151.85, 137.89, 134.25, 127.22, 125.64, 123.92, 82.17, 80.97, 73.70, 40.03, 33.90, 28.46, 28.15, 18.08, 17.75. HRMS (EI) calculated for C<sub>22</sub>H<sub>32</sub>N<sub>2</sub>O<sub>5</sub> (Na<sup>+</sup>) 427.2203, found: 427.2203. [ $\alpha$ ]<sub>D</sub><sup>24</sup> = 25.5 (c = 1.53, CHCl<sub>3</sub>). R<sub>f</sub> (petroleum ether / EtOAc 7:1) = 0.26. HPLC: (*Chiralpak*® *IB*, heptane-isopropanol 99:1, 0.8 mL/min, 254 nm): t<sub>R</sub>(minor) = 12.2 min, t<sub>R</sub>(major) = 9.7 min, 88% *ee*.



di-tert-butyl 1-(3-methyl-4-oxochroman-3-yl)hydrazine-1,2-dicarboxylate 2h



(S,S)-L2 (24.8 mg, 0.0320 mmol), 2-methyl-1-chromanone (32.4 mg, 0.200 mmol), and activated 3 Å molecular sieves (5 mg) were measured into a microwave vial equipped with stir bar. The flask was placed under a nitrogen atmosphere and PhMe (0.6 mL) was added. After stirring for 15 minutes, diethylzinc (1.0 M in hexanes, 60µL, 0.060 mmol) was added and the reaction was allowed to stir for an additional 15 minutes. At this time, a premixed (15 min) PhMe (0.4 mL) solution of di*-tert*-butyl azodicarboxylate (69.1 mg, 0.300 mmol) and 3 Å molecular sieves (5 mg) was added. The reaction was allowed to stir at 60 °C for 16 h at which point the reaction mixture was filtered through a small plug of fluorosil. The residue was concentrated under reduced pressure using rotary evaporation. The resulting residue was purified via flash chromatography (SiO2; DCM to petroleum ether / EtOAc 7:1 to petroleum ether / EtOAc 6:1) to afford 47.8 mg (61 %) of a clear oil.

IR(C<sub>6</sub>D<sub>6</sub>) 3326, 2982, 2933, 1703, 1608, 1480, 1368, 1281, 1250, 1152, 1016, 761 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, 75 °C, Benzene-*d*<sub>6</sub>)  $\delta$  8.10 (d, *J* = 7.8 Hz, 1H), 7.10 – 6.98 (m, 1H), 6.81 (d, *J* = 8.3 Hz, 1H), 6.76 – 6.65 (m, 1H), 6.13 (s, 1H), 5.23 (d, *J* = 11.1 Hz, 1H), 4.47 (s, 1H), 1.37 (s, 3H), 1.34 (s, 9H), 1.31 (s, 9H). <sup>13</sup>C NMR (101 MHz, 75 °C, Benzene-*d*<sub>6</sub>)  $\delta$  191.10, 161.19, 156.37, 154.14, 135.40, 128.59, 121.89, 121.16, 118.14, 82.16, 80.89, 73.53, 65.45, 28.27, 28.22, 19.14. HRMS (EI) calculated for C<sub>20</sub>H<sub>28</sub>N<sub>2</sub>O<sub>6</sub> (Na<sup>+</sup>) 415.1840, found: 415.1837. R<sub>f</sub> (petroleum ether / EtOAc 6:1) = 0.24. [ $\alpha$ ]<sub>D</sub><sup>24</sup> = 5.0 (c = 1.56, CHCl<sub>3</sub>). HPLC: (*Chiralpak*® *IA*, heptane-isopropanol 90:10, 0.8 mL/min, 254 nm): t<sub>R</sub>(minor) = 5.5 min, t<sub>R</sub>(major) = 9.0 min, 92% *ee*.



di-tert-butyl (E)-1-(3-benzylidene-1-methyl-2-oxocyclohexyl)hydrazine-1,2-dicarboxylate 2i



(S,S)-L2 (24.8 mg, 0.0320 mmol), (E)-2-benzylidene-6-methylcyclohexan-1-one (40.0 mg, 0.200 mmol), and activated 3 Å molecular sieves (5 mg) were measured into a microwave vial equipped with stir bar. The flask was placed under a nitrogen atmosphere and PhMe (0.6 mL) was added. After stirring for 15 minutes, diethylzinc (1.0 M in hexanes, 60µL, 0.060 mmol) was added and the reaction was allowed to stir for an additional 15 minutes. At this time, a premixed (15 min) PhMe (0.4 mL) solution of di*-tert*-butyl azodicarboxylate (69.1 mg, 0.300 mmol) and 3 Å molecular sieves (5 mg) was added. The reaction was allowed to stir at 40 °C for 16 h at which point the reaction mixture was filtered through a small plug of fluorosil. The residue was concentrated under reduced pressure using rotary evaporation. The resulting residue was purified via flash chromatography (SiO2; DCM to petroleum ether / EtOAc 7:1 to petroleum ether / EtOAc 6:1) to afford 62.9 mg (73 %) of a clear oil.

IR(C<sub>6</sub>D<sub>6</sub>) 3339, 2980, 2938, 1698, 1598, 1450, 1367, 1246, 1157, 1121, 1079, 1121, 1079, 1010 cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, 75 °C, Benzene- $d_6$ )  $\delta$  7.77 (s, 1H), 7.20 – 7.13 (obscured m, 2H), 7.09 (t, J = 8.1, 3H), 7.07 – 6.98 (m, 1H), 6.18 (s, 1H), 2.85 (d, J = 14.5 Hz, 2H), 2.63 (m, 1H), 2.05 (s, 1H), 1.75 – 1.59 (m, 1H), 1.42 (2 S, 18H total), 1.39 – 1.37 (m, 1H), 1.33 – 1.26 (broad s, 3H). <sup>13</sup>C NMR (126 MHz, 75 °C, Benzene)  $\delta$  199.22, 156.17, 154.74, 137.10, 136.91, 136.23, 130.40, 128.46, 128.46 (identified via HSQC), 81.49, 80.39, 68.39, 36.94, 28.61, 28.48, 28.44, 23.38, 21.70. HRMS (EI) calculated for C<sub>24</sub>H-<sub>34</sub>N<sub>2</sub>O<sub>5</sub> (Na<sup>+</sup>) 453.2360, found: 453.2357. [ $\alpha$ ]<sub>D</sub><sup>23</sup> = 161.4 (c = 1.57, CHCl<sub>3</sub>). HPLC: (*Chiralpak*® *IA*, heptane-isopropanol 90:10, 0.8 mL/min, 254 nm): t<sub>R</sub>(minor) = 6.5 min, t<sub>R</sub>(major) = 9.6 min, 91% *ee*.



di-tert-butyl (R)-1-(1-((benzyloxy)carbonyl)-3-methyl-2-oxoindolin-3-yl)hydrazine-1,2-dicarboxylate 2j



(S,S)-L2 (8.6 mg, 0.0110 mmol), N-Cbz-3-methyl-2-oxinodle (56.3 mg, 0.200 mmol), and activated 3 Å molecular sieves (5 mg) were measured into a microwave vial equipped with a stir bar. The flask was placed under a nitrogen atmosphere and PhMe (0.6 mL) was added. After stirring for 15 minutes, diethylzinc (1.0 M in hexanes, 20µL, 0.020 mmol) was added and the reaction was allowed to stir for an additional 15 minutes. At this time, a premixed (15 min) PhMe (0.4 mL) solution of di*-tert*-butyl azodicarboxylate (50.7 mg, 0.220 mmol) and 3 Å molecular sieves (5 mg) was added. The reaction was allowed to stir at rt for 15 min at which point the reaction mixture was filtered through a small plug of fluorosil. The residue was concentrated under reduced pressure using rotary evaporation. The resulting residue was purified via flash chromatography (SiO2; petroleum ether / EtOAc 6:1) to afford 97.0 mg (95 %) of a clear oil.

IR(C<sub>6</sub>D<sub>6</sub>) 3323, 2981, 2933, 1783, 1730, 1609, 1481, 1456, 1370, 1345, 1290, 1229, 1154, 1107, 1074, 1051, 1017, 772, 755, 698 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, 75 °C, Benzene-*d*<sub>6</sub>)  $\delta$  8.20 (s, 1H), 8.15 (d, *J* = 8.3 Hz, 1H), 7.40 (dd, *J* = 7.8, 4.1 Hz, 2H), 7.16 – 7.03 (m, 4H), 7.02 – 6.94 (m, 1H), 6.58 (s, 1H), 5.23 (s, 2H), 1.41 (s, 9H), 1.36 (s, 3H), 1.08 (s, 9H). <sup>13</sup>C NMR (101 MHz, 75 °C, c<sub>6</sub>d6)  $\delta$  175.59, 156.66, 153.24, 151.54, 138.83, 136.02, 133.17, 128.80, 128.73, 128.40, 125.18, 124.27, 115.21, 82.57, 80.97, 68.50, 66.31, 28.35, 27.88, 24.28. HRMS (EI) calculated for C<sub>27</sub>H<sub>33</sub>N<sub>3</sub>O<sub>7</sub> (H<sup>+</sup>) 512.2391, found: 512.2393. [ $\alpha$ ]<sub>D</sub><sup>24</sup> = -14.0 (c = 1.41, CHCl<sub>3</sub>). R<sub>f</sub> (petroleum ether / EtOAc 6:1) = 0.22. HPLC: (*Chiralpak*® *IA*, heptane-isopropanol 90:10, 0.8 mL/min, 254 nm): t<sub>R</sub>(minor) = 7.9 min, t<sub>R</sub>(major) = 35.2 min, 95% *ee*.



Large-scale procedure:

*S*,*S*)-**L2** (35.8 mg, 0.0462 mmol), N-Cbz-3-methyl-2-oxinodle (591 mg, 2.11 mmol), and activated 3 Å molecular sieves (55 mg) were measured into a round-bottom flask equipped with a stir bar. The flask was placed under a nitrogen atmosphere and PhMe (6.3 mL) was added. After stirring for 15 minutes, diethylzinc (1.0 M in hexanes, 0.84 mL, 0.84 mmol) was added and the reaction was allowed to stir for an additional 15 minutes. At this time, a premixed (15 min) PhMe (4.2 mL) solution of di-*tert*-butyl azodicarboxylate (531.9 mg, 2.31 mmol) and 3 Å molecular sieves (55 mg) was added. The reaction was allowed to stir at rt for 4 h at which point the reaction mixture was filtered through a small plug of fluorosil. The residue was concentrated under reduced pressure using rotary evaporation. The resulting residue was purified via flash chromatography (SiO2; petroleum ether / EtOAc 6:1) to afford 950 mg (89 %) of a white foam.

HPLC: (*Chiralpak*® *IA*, heptane-isopropanol 90:10, 0.8 mL/min, 254 nm):  $t_R(minor) = 7.8 min$ ,  $t_R(major) = 35.3 min$ , 92% *ee*.



<u>di-tert-butyl (R)-1-(1-((benzyloxy)carbonyl)-3-(2-((tert-butyldimethylsilyl)oxy)ethyl)-2-oxoindolin-3-</u> yl)hydrazine-1,2-dicarboxylate **2k** 



(S,S)-L2 (8.6 mg, 0.0110 mmol), 3-alkyl-2-oxinodle (85.1 mg, 0.200 mmol), and activated 3 Å molecular sieves (5 mg) were measured into a microwave vial equipped with a stir bar. The flask was placed under a nitrogen atmosphere and PhMe (0.6 mL) was added. After stirring for 15 minutes, diethylzinc (1.0 M in hexanes, 20µL, 0.020 mmol) was added and the reaction was allowed to stir for an additional 15 minutes. At this time, a premixed (15 min) PhMe (0.4 mL) solution of di-*tert*-butyl azodicarboxylate (50.7 mg, 0.220 mmol) and 3 Å molecular sieves (5 mg) was added. The reaction was allowed to stir at rt for 1 h at which point the reaction mixture was filtered through a small plug of fluorosil. The residue was concentrated under reduced pressure using rotary evaporation. The resulting residue was purified via flash chromatography (SiO2; petroleum ether / EtOAc 7:1) to afford 113.3 mg (86 %) of a clear oil.

IR(C<sub>6</sub>D<sub>6</sub>) 3328, 2957 2931, 2885, 2857, 1786, 1727, 1481, 1468, 1369, 1348, 1291, 1251, 1223, 1164, 1112, 1075, 1045, 1022, 837, 772, 756, 698 cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, 75 °C, Benzene- $d_6$ )  $\delta$  8.15 (dt, J = 8.1, 0.8 Hz, 1H), 8.06 (s, 1H), 7.41 (dm, J = 7.5 Hz, 2H), 7.15 – 7.11 (m, 2H), 7.12 – 7.02 (m, 2H), 6.98 (td, J = 7.5, 1.1 Hz, 1H), 6.32 (s, 1H), 5.29 (d, J = 12.6 Hz, 1H), 5.20 (d, J = 12.6 Hz, 1H), 3.45 – 3.34 (m, 2H), 2.49 (dt, J = 13.4, 7.5 Hz, 1H), 2.19 (dt, J = 13.4, 5.3 Hz, 1H), 1.42 (s, 9H), 1.09 (s, 9H), 0.83 (s,

9H), -0.09 (s, 3H), -0.11 (s, 3H). <sup>13</sup>C NMR (126 MHz, 75 °C, Benzene)  $\delta$  174.55, 156.69, 153.42, 151.54, 140.29, 136.15, 130.92, 129.05, 128.69, 128.36, 128.31, 124.95, 124.74, 115.16, 82.70, 81.11, 68.36, 68.13, 58.89, 40.76, 28.39, 27.92, 26.14, 18.48, -5.42, -5.43. HRMS (EI) calculated for C<sub>34</sub>H<sub>49</sub>N<sub>3</sub>O<sub>8</sub>Si (Na<sup>+</sup>) 678.3181, found: 678.3179. [ $\alpha$ ]<sub>D</sub><sup>24</sup> = -11.3 (c = 1.61, CHCl<sub>3</sub>). R<sub>f</sub> (petroleum ether / EtOAc 7:1) = 0.22. HPLC: (*Chiralpak*® *IA*, heptane-isopropanol 97:3, 0.8 mL/min, 254 nm): t<sub>R</sub>(minor) = 49.4 min, t<sub>R</sub>(major) = 66.0 min, 95% *ee*.



<u>di-tert-butyl (R)-1-(1-(tert-butoxycarbonyl)-3-methyl-2-oxoindolin-3-yl)hydrazine-1,2-dicarboxylate</u> **SI** For determination of absolute stereochemistry of oxindole products:



(S,S)-L2 (8.3 mg, 0.011 mmol), N-Boc-3-methyl-2-oxinodle (22 mg, 0.089 mmol), and activated 3 Å molecular sieves (5 mg) were measured into a microwave vial equipped with a stir bar. The flask was placed under a nitrogen atmosphere and PhMe (0.3 mL) was added. After stirring for 15 minutes, diethylzinc (1.0 M in hexanes, 20µL, 0.020 mmol) was added and the reaction was allowed to stir for an additional 15 minutes. At this time, a premixed (15 min) PhMe (0.2 mL) solution of di*-tert*-butyl azodicarboxylate (69 mg, 0.30 mmol) and 3 Å molecular sieves (5 mg) was added. The reaction was allowed to stir at rt for 15 min at which point the reaction mixture was filtered through a small plug of fluorosil. The residue was concentrated under reduced pressure using rotary evaporation. The resulting residue was purified via flash chromatography (SiO2; petroleum ether / EtOAc 8:1) to afford 32.6 mg (77 %) of a white solid.

<sup>1</sup>H NMR (400 MHz, Chloroform-*d*)  $\delta$  7.89 (d, *J* = 7.4 Hz, 1H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.33 – 7.27 (m, 1H), 7.19 (t, *J* = 7.5 Hz, 1H), 6.59 (s, 1H), 1.64 (s, 9H), 1.53 (s, 9H), 1.52 (s, 3H), 1.13 (s, 9H). <sup>13</sup>C NMR

(101 MHz, CDCl<sub>3</sub>)  $\delta$  176.38, 156.37, 152.98, 149.38, 138.07, 128.59, 125.13, 123.82, 114.79, 84.48, 83.13, 81.68, 65.92, 28.35, 28.24, 27.79, 24.53. [ $\alpha$ ]<sub>D</sub><sup>23</sup> = -11.0 (c = 1.75, CHCl<sub>3</sub>). HPLC: (*Chiralpak*® *IA*, heptane-isopropanol 90:10, 0.8 mL/min, 254 nm): t<sub>R</sub>(minor) = 5.3 min, t<sub>R</sub>(major) = 11.4 min, 70% *ee*.



For the same compound, Shibasaki reports  $[\alpha]_D^{22.7} = -21.0$  (c = 1.34, CHCl<sub>3</sub>) for a compound with 99% *ee*. As the same sign was obtained, the absolute chirality was assigned as that reported by Shibasaki. The N-Cbz substrates were assigned by analogy.<sup>2</sup>

#### methyl (R)-2-(3-((tert-butoxycarbonyl)amino)-3-methyl-2-oxoindolin-1-yl)acetate 6



A vial containing a magnetic stir bar was charged with the hydrazine oxindole (76.7 mg, 0.150 mmol), placed under a nitrogen atmosphere, and brought into the glovebox. In the glovebox, freshly ground  $Cs_2CO_3$  (147 mg, 0.451 mmol) was added to the vial. The vial was sealed and removed from the glovebox and dry acetonitrile (1.0 mL) was added followed by methyl bromoacetate (35.5  $\mu$ L, 0.375 mmol). The reaction was allowed to stir in a 50 °C oil bath for 15 h at which point the reaction mixture was filtered through a small plug of celite using ethyl acetate as the eluting solvent. The filtrate was concentrated under reduced pressure using rotary evaporation and the resulting residue was purified via flash chromatography (SiO2; petroleum ether / EtOAc 4:1 to 3:1). R<sub>f</sub> (petroleum ether / EtOAc 3:1) = 0.29.

The purified material from above was utilized directly in the next step without full characterization due to the presence of significant rotomers. A vial containing a magnetic stir bar was charged with the purified alkylation product, placed under a nitrogen atmosphere, and brought into the glovebox. In the glovebox, freshly ground  $Cs_2CO_3$  (147 mg, 0.451 mmol) was added to the vial. The vial was removed from the glovebox and dry acetonitrile (1.0 mL) was added. The reaction was allowed to stir in an 80 °C oil bath for 20 h. At this point, the reaction was quenched with a saturated aqueous solution of ammonium chloride (15 ml) and diluted with 2 mL H<sub>2</sub>O and ethyl acetate (25 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 25 mL). The combined organic layers were washed with brine (20 mL), dried (MgSO4), filtered, and concentrated under reduced pressure using rotary evaporation. The resulting residue was purified via flash chromatography (SiO2; petroleum ether / EtOAc 2:1 to 1.5:1) to afford 34 mg (68% over 2 steps) of a white solid (mp 169-170 °C).

IR(CDCl<sub>3</sub>) 3355, 3332, 2982, 2918, 1728, 1616, 1493, 1469, 1367, 1217, 1168, 1065, 754, 665 cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, 55 °C, Chloroform-*d*)  $\delta$  7.30 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.25 (td, *J* = 7.7, 1.4 Hz, 1H), 7.07 (td, *J* = 7.5, 1.0 Hz, 1H), 6.72 (d, *J* = 7.8 Hz, 1H), 5.06 (s, 1H), 4.83 (d, *J* = 17.4 Hz, 1H), 4.14 (d, *J* = 17.4 Hz, 1H), 3.76 (s, 3H), 1.54 (s, 3H), 1.26 (s, 9H). <sup>13</sup>C NMR (126 MHz, 55 °C, CDCl<sub>3</sub>)  $\delta$  177.35, 168.32, 153.92, 141.80, 132.43, 128.77, 123.24, 122.46, 108.37, 80.61, 58.71, 52.50, 41.75, 28.30, 25.09. HRMS (EI) calculated for C<sub>17</sub>H<sub>22</sub>N<sub>2</sub>O<sub>5</sub> (Na<sup>+</sup>) 357.1421, found: 357.1421. [ $\alpha$ ]<sub>D</sub><sup>23</sup> = 23.8 (c = 0.68, CHCl<sub>3</sub>).

# <u>di-tert-butyl 1-((5S,6S)-5-hydroxy-6,7,8,9-tetrahydro-5H-benzo[7]annulen-6-yl)hydrazine-1,2-</u> <u>dicarboxylate</u> **SII**

The procedure used was based upon the work of Gmeiner and Bollinger, as recently used by Ma.<sup>3,4</sup>



A round-bottom flask equipped with a magnetic stir bar was charged with the ketone (145.2 mg, 0.372 mmol) and placed under an atmosphere of nitrogen. THF (10 mL) was added and the reaction was cooled to -78 °C. LiAlH<sub>4</sub> (1.0M in Et<sub>2</sub>O, 0.37 mL, 0.37 mmol) was added dropwise and the reaction was allowed to stir at -78 °C for 1.5 h. At this time, the reaction mixture was quenched via addition to 15 mL of 10% aqueous ammonium chloride solution. The reaction mixture was diluted with DCM (25 mL) and the organic layer was separated. The aqueous layer was extracted with DCM (2 x 25 mL). The organic layers were combined, washed with brine (15 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated under reduced pressure via rotary evaporation. The resulting residue was purified via careful flash chromatography (SiO2; petroleum ether / EtOAc 7:1) to afford 138 mg (94%) of a clear oil.

IR(CH<sub>2</sub>Cl<sub>2</sub>) 3394, 3302, 2979, 2932, 2857, 1712, 1482, 1456, 1393, 1368, 1326, 1290, 1254, 1157, 1110, 1061, 942, 857, 751 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, 75 °C, Benzene- $d_6$ )  $\delta$  8.21 (s, 1H), 7.22 (t, *J* = 7.7 Hz, 1H), 7.07 (td, *J* = 7.4, 1.4 Hz, 1H), 6.92 (dd, *J* = 7.3, 1.4 Hz, 1H), 5.95 (s, 1H), 4.80 (d, *J* = 9.3 Hz, 1H), 4.10 (s, 1H), 2.49 – 2.35 (m, 2H), 1.79 – 1.53 (m, 3H), 1.43 (s, 9H), 1.40 (s, 9H), 1.26 – 1.10 (m, 1H). <sup>13</sup>C NMR (101 MHz, 75 °C, c<sub>6</sub>d<sub>6</sub>)  $\delta$  158.61 (broad), 155.43, 142.13, 140.10, 128.59, 127.07, 126.96, 126.05, 82.14, 81.44, 72.14, 63.07 (broad), 35.27, 33.48, 28.37, 28.30, 26.94. HRMS (EI) calculated for C<sub>21</sub>H<sub>32</sub>N<sub>2</sub>O<sub>5</sub> (Na<sup>+</sup>) 415.2203, found: 415.2202. [ $\alpha$ ]<sub>D</sub><sup>22</sup> = 89.4 (c = 1.47, CHCl<sub>3</sub>). R<sub>f</sub> (petroleum ether /

EtOAc 7:1) = 0.23. HPLC: (*Chiralpak*® *IC*, heptane-isopropanol 95:5, 0.8 mL/min, 220 nm):  $t_R(minor) = 10.8 \text{ min}, t_R(major) = 17.3 \text{ min}, 98\%$  *ee*.



<u>di-tert-butyl 1-((5S,6S)-5-((tert-butyldimethylsilyl)oxy)-6,7,8,9-tetrahydro-5H-benzo[7]annulen-6-yl)hydrazine-1,2-dicarboxylate</u> **SIII** 



A round-bottom flask equipped with a magnetic stir bar was charged with the alcohol (127 mg, 0.324 mmol) and placed under an atmosphere of nitrogen. DCM (3.3 mL) was added followed by 2,6-lutidine (0.15 mL, 1.3 mmol). The reaction flask was cooled to -78 °C and *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) (84  $\mu$ L, 0.36 mmol) was added dropwise. After stirring for 1 h at -78 °C, the dry ice acetone bath was removed and the reaction was stirred at rt for 1 h. Incomplete reactivity was observed, so the reaction mixture was cooled once again to -78 °C and additional TBSOTf (84  $\mu$ L, 0.36 mmol) was added dropwise. After stirring for 20 min at -78 °C, the cold bath was removed and the reaction was allowed to stir at rt for 1.5 h. Once again, incomplete conversion was observed, and the reaction mixture was cooled to -78 °C for 20 minutes at which point the cold bath was once again removed and the reaction was allowed to stir at -78 °C for 20 minutes at which point the cold bath was once again removed and the reaction was allowed to stir 1 h at rt. At this point, saturated aqueous sodium bicarbonate (20 mL) was added to the reaction mixture, which was subsequently diluted with DCM (25 mL). The organic layer was separated and the aqueous layer was extracted with DCM (2 x 25 mL). The organic layers were combined, washed with brine (15 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated

under reduced pressure via rotary evaporation. The resulting residue was purified via careful flash chromatography (SiO2; petroleum ether / EtOAc 20:1) to afford 116 mg (71%) of a clear oil. The product contained very significant rotomers, even at 70 °C, and was used immediately in the next step without full characterization. The unassigned/unprocessed <sup>1</sup>H NMR spectra at rt and at 70 °C in  $C_6D_6$  are included below for reference.

<u>tert-butyl ((5S,6S)-5-((tert-butyldimethylsilyl)oxy)-6,7,8,9-tetrahydro-5H-benzo[7]annulen-6-</u> yl)carbamate **7** 



A vial containing a magnetic stir bar was charge with the protected alcohol (55.8 mg, 0.110 mmol). NBu<sub>4</sub>I (40.6 mg, 0.110 mmol) was added and the vial was placed under a nitrogen atmosphere and brought into the glovebox. In the glovebox, freshly ground  $Cs_2CO_3$  (127 mg, 0.390 mmol) was added. The vial was brought out of the glovebox and dry acetonitrile (0.7 mL) was added followed by methyl bromoacetate (11.4 µL, 0.120 mmol). The reaction mixture was allowed to stir in a 50 °C oil bath for 18 h at which point the oil bath temperature was raised to 80 °C and the reaction mixture was allowed to stir for an additional 48 h. At this point, the reaction was quenched with a saturated aqueous solution of ammonium chloride (15 ml) and diluted with 2 mL H<sub>2</sub>O and ethyl acetate (25 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 25 mL). The combined organic layers were washed with brine (20 mL), dried (MgSO4), filtered, and concentrated under reduced pressure using rotary evaporation. The resulting residue was purified via flash chromatography (SiO2; petroleum ether / EtOAc 30:1) to afford 21.7 mg (51%) of a clear oil.

IR(CH<sub>2</sub>Cl<sub>2</sub>) 3441, 3337, 2954, 2930, 2857, 1719, 1494, 1390, 1365, 1251, 1170, 1061, 993, 941, 881, 859, 837, 777, 750, 666 cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, Benzene- $d_6$ )  $\delta$  7.05 (dd, J = 7.2, 1.6 Hz, 1H), 6.99 – 6.90 (m, 2H), 6.88 (dd, J = 7.3, 1.5 Hz, 1H), 4.89 (d, J = 6.2 Hz, 1H), 4.49 – 4.37 (m, 1H), 4.26 (d, J = 9.1 Hz, 1H), 2.48 – 2.38 (m, 1H), 2.33 (ddt, J = 13.9, 6.9, 1.5 Hz, 1H), 1.81 (d, J = 14.2 Hz, 1H), 1.59 – 1.45 (m, 1H), 1.40 (s, 9H), 1.25 – 1.13 (m, 1H), 0.89 (s, 9H), 0.04 (s, 3H), -0.22 (s, 3H). <sup>13</sup>C NMR (126 MHz, Benzene)  $\delta$  155.21, 143.70, 139.28, 130.97, 130.60, 128.51, 126.03, 78.86, 78.43, 51.88, 35.29, 30.21, 28.48, 26.00, 23.45, 18.27, -4.74, -5.07. HRMS (EI) calculated for C<sub>22</sub>H<sub>37</sub>NO<sub>3</sub>Si (Na<sup>+</sup>) 414.2435, found: 414.2435. [ $\alpha$ ]<sub>D</sub><sup>22</sup> = 12.6 (c = 0.54, CHCl<sub>3</sub>). R<sub>f</sub> (petroleum ether / EtOAc 25:1) = 0.34.

## tert-butyl ((3aS,10bR)-2-oxo-4,5,6,10b-tetrahydro-2H-benzo[3,4]cyclohepta[1,2-d]oxazol-3(3aH)yl)carbamate **SIV**

The procedure used was based upon the work of Gmeiner and Bollinger:<sup>3</sup>



A flask equipped with a magnetic stir bar was charged with the ketone (66.2 mg, 0.170 mmol) and placed under nitrogen. THF (10 mL) was added and the flask was cooled to -78 °C. L-selectride (1.0 M in THF, 0.19 mL, 0.19 mmol) was added dropwise and the reaction was allowed to slowly warm up to rt overnight. In the morning, the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride and diluted with 20 mL CHCl<sub>3</sub>. The organic layer was separated and the aqueous layer was extracted with CHCl<sub>3</sub> (2 x 20 mL). The organic layers were combined, washed with brine (15 mL), dried (MgSO<sub>4</sub>), filtered, and concentrated under reduced pressure via rotary evaporation. The resulting residue was purified via flash chromatography (SiO2; petroleum ether / EtOAc 3.5:1) to afford 50.6 mg (94%) of a clear oil that was 90-95% pure.

IR(CDCl<sub>3</sub>) 3251, 2947, 1780, 1729, 1457, 1370, 1257, 1160, 1029, 912, 734 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, Chloroform-*d*)  $\delta$  7.45 (dd, *J* = 5.3, 3.7 Hz, 1H), 7.33 – 7.22 (m, 2H), 7.13 – 7.07 (m, 1H), 6.58 (s, 1H), 5.82 (d, *J* = 9.6 Hz, 1H), 4.21 (s, 1H), 2.76 (dd, *J* = 14.6, 7.5, 2.1 Hz, 1H), 2.50 (ddd, *J* = 14.0, 11.3, 7.4 Hz, 1H), 1.88 – 1.61 (m, 3H), 1.47 (s, 9H), 1.21 – 1.10 (m, 1H) some "grease" is visible in the nmr spectrum. <sup>13</sup>C NMR (101 MHz, cdcl<sub>3</sub>)  $\delta$  156.57, 154.48, 135.79, 134.40, 128.76, 128.64, 127.10, 124.24, 82.62, 76.09, 57.30, 30.31, 28.27, 25.24, 21.31. HRMS (EI) calculated for C<sub>17</sub>H<sub>22</sub>N<sub>2</sub>O<sub>4</sub> (Na<sup>+</sup>) 341.1472, found: 341.1472. R<sub>f</sub> (petroleum ether / EtOAc 4:1) = 0.15. HPLC: (*Chiralpak*® *IB*, heptane-isopropanol 90:10, 0.8 mL/min, 220 nm): t<sub>R</sub>(minor) = 9.5 min, t<sub>R</sub>(major) = 12.2 min, 97% *ee*.



One pot reduction/elimination:



A vial containing a magnetic stir bar was charge with the cyclic carbamate (34 mg, 0.11 mmol). NBu<sub>4</sub>I (39.6 mg, 0.107 mmol) was added and the vial was placed under a nitrogen atmosphere and brought into the glovebox. In the glovebox, freshly ground  $Cs_2CO_3$  (122 mg, 0.375 mmol) was added. The vial was brought out of the glovebox and dry acetonitrile (0.7 mL) was added followed by methyl bromoacetate (11.1 µL, 0.117 mmol). The reaction mixture was allowed to stir in a 50 °C oil bath for 18 h at which point the oil bath temperature was raised to 80 °C and the reaction mixture was allowed to stir for an additional 24 h. At this point, the reaction was quenched with a saturated aqueous solution of ammonium chloride (15 ml) and diluted with 2 mL H<sub>2</sub>O and ethyl acetate (25 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 25 mL). The combined organic layers were washed with brine (20 mL), dried (MgSO4), filtered, and concentrated under reduced pressure using rotary evaporation. The resulting residue was purified via flash chromatography (SiO2; petroleum ether / EtOAc 1:1) to afford 12.8 mg (59%) of a clear oil.

Two pot alkylation/elimination:



A vial equipped with a magnetic stir bar was charged with the cyclic carbamate (59.7 mg, 0.188 mmol), placed under a nitrogen atmosphere, and brought into the glovebox. In the glovebox, freshly ground  $Cs_2CO_3$  (184 mg, 0.564 mmol) was added to the vial and the vial was removed from the glovebox. Dry acetonitrile (1.2 mL) and dry CDCl<sub>3</sub> (for solubility, 0.5 mL) was added followed by methyl bromoacetate (44.5  $\mu$ L, 0.470 mmol). The reaction mixture was allowed to stir in a 50 °C oil bath for 17 h. At this point, the reaction was quenched with a saturated aqueous solution of ammonium chloride (15 ml) and diluted with 2 mL H<sub>2</sub>O and ethyl acetate (25 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 25 mL). The combined organic layers were washed with brine (20 mL), dried (MgSO4), filtered, and concentrated under reduced pressure using rotary evaporation. The resulting residue was purified via a short silica plug (SiO2; petroleum ether / EtOAc 3:1). The purified material was utilized immediately in the following step without characterization due to the presence of significant rotomers.

A vial equipped with a magnetic stir bar was charged with the purified alkylation product, placed under an atmosphere of nitrogen, and brought into the glovebox. In the glovebox, freshly ground  $Cs_2CO_3$  (184 mg, 0.564 mmol) was added to the vial. The vial was removed from the glovebox and dry acetonitrile (1.0 mL) was added. The reaction was allowed to stir in an 80 °C oil bath for 20 h. At this point, the reaction was quenched with a saturated aqueous solution of ammonium chloride (15 ml) and diluted with 2 mL H<sub>2</sub>O and ethyl acetate (25 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 25 mL). The combined organic layers were washed with brine (15 mL), dried (MgSO4), filtered, and concentrated under reduced pressure using rotary evaporation. The resulting residue was purified via careful flash chromatography (SiO2; petroleum ether / EtOAc 1:1) to afford 23 mg (64% over 2 steps) of a white solid (mp 167-169 °C).

IR(CDCl<sub>3</sub>) 3283, 3244, 3220, 2925, 2844, 1744, 1705, 1447, 1273, 1241, 1108, 1027, 954, 899, 757, 726, 662 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, Chloroform-*d*)  $\delta$  7.53 – 7.46 (m, 1H), 7.32 – 7.26 (m, 2H), 7.17 – 7.07 (m, 1H), 5.93 (s, 1H), 5.85 (d, *J* = 9.5 Hz, 1H), 4.22 – 4.09 (m, 1H), 2.78 (ddd, *J* = 14.4, 7.4, 2.6 Hz, 1H), 2.52 (ddd, *J* = 14.4, 11.2, 7.7 Hz, 1H), 1.84 – 1.58 (m, 3H), 1.38 – 1.17 (m, 1H). <sup>13</sup>C NMR (101 MHz, cdcl<sub>3</sub>)  $\delta$  158.67, 135.78, 134.80, 128.77, 128.67, 127.08, 124.86, 79.05, 53.62, 30.24, 27.99, 21.66. HRMS (EI) calculated for C<sub>12</sub>H<sub>13</sub>NO<sub>2</sub> (Na<sup>+</sup>) 226.0839, found: 226.0839. [ $\alpha$ ]<sub>D</sub><sup>23</sup> = -65.8 (c = 0.69, CHCl<sub>3</sub>). R<sub>f</sub> (petroleum ether / EtOAc 1:1) = 0.22.

### di-tert-butyl 1-(1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)hydrazine-1,2-dicarboxylate 21



(*R*,*R*)-ProPhenol L1 (13.7 mg, 0.0214 mmol),  $\alpha$ -tetralone (30.0 mg, 0.205 mmol), and activated 3 Å molecular sieves (5 mg) were measured into a microwave vial equipped with stir bar. The flask was placed under a nitrogen atmosphere and THF (0.5 mL) was added. After stirring for 15 minutes, diethylzinc (1.0 M in hexanes, 40µL, 0.040 mmol) was added and the reaction was allowed to stir for an additional 15 minutes. At this time, a premixed (15 min) THF (0.3 mL) solution of di-*tert*-butyl azodicarboxylate (50.0 mg, 0.217 mmol) and 3 Å molecular sieves (5 mg) was added. The reaction was allowed to stir at rt for 14 hours at which point the reaction mixture was filtered through a small plug of fluorosil. The residue was concentrated under reduced pressure using rotary evaporation. The resulting residue was purified via flash chromatography (SiO2; DCM to petroleum ether / EtOAc 5:1 to petroleum ether / EtOAc 4:1) to afford 67.1 mg (86%) of a pale-yellow oil.

IR(C<sub>6</sub>D<sub>6</sub>) 3270, 2940, 2890, 1670, 1580, 1440, 1370, 1350, 1300, 1220, 1140, 1040, 950, 920, 880, 840, 750 cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, 75 °C, Benzene-*d*<sub>6</sub>)  $\delta$  8.13 – 7.99 (m, 1H), 7.10 – 7.00 (m, 1H), 6.94 (t, *J* = 7.6 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 6.49 (s, 1H), 5.08 (s, 1H), 2.67 – 2.53 (m, 1H), 2.49 – 2.29 (m, 2H), 2.26 – 1.93 (m, 1H), 1.46 (s, 9H), 1.39 (d, *J* = 4.0 Hz, 9H). <sup>13</sup>C NMR (126 MHz, 75 °C, Benzene-*d*<sub>6</sub>)  $\delta$  194.39, 155.78, 144.10, 133.42, 133.03, 128.77, 126.73, 81.36, 80.32, 64.65, 29.08, 28.41, 28.38, 28.21. HRMS (EI) calculated for C<sub>20</sub>H<sub>28</sub>N<sub>2</sub>O<sub>5</sub> (Na<sup>+</sup>) 399.1890, found: 399.1892. R<sub>f</sub> (petroleum ether / EtOAc 4:1) = 0.27. [ $\alpha$ ]<sub>D</sub><sup>23</sup> = 7.7 (c = 0.37, CHCl<sub>3</sub>). HPLC: (*Chiralpak*® *IA*, heptane-isopropanol 95:5, 0.8 mL/min, 254 nm): t<sub>R</sub>(minor) = 20.9 min, t<sub>R</sub>(major) = 15.9 min, 94% *ee*.





The title compound was also run on an HPLC under the following conditions: HPLC: (*Chiralpak*® *IB*, heptane-isopropanol 95:5, 0.8 mL/min, 254 nm):  $t_R(minor) = 6.6 \text{ min}$ ,  $t_R(major) = 7.9 \text{ min}$ , 93% *ee*. Under these conditions, the major enantiomer was the second enantiomer to elute, in line with the results obtained by Ma and co-workers for the same compound under the same HPLC conditions. As such, the absolute stereochemistry was assigned to be the same as that reported by Ma. All other trisubstituted products were assigned by analogy.<sup>4</sup>



di-tert-butyl 1-(7-bromo-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)hydrazine-1,2-dicarboxylate 2m



(*R*,*R*)-ProPhenol **L1** (13.7 mg, 0.0214 mmol), 7-bromo-1-tetralone (45.0 mg, 0.200 mmol), and activated 3 Å molecular sieves (5 mg) were measured into a microwave vial equipped with stir bar. The flask was placed under a nitrogen atmosphere and THF (0.5 mL) was added. After stirring for 15 minutes, diethylzinc (1.0 M in hexanes,  $40\mu$ L, 0.040 mmol) was added and the reaction was allowed to stir for an additional 15 minutes. At this time, a premixed (15 min) THF (0.3 mL) solution of di*-tert*-butyl azodicarboxylate (50.7 mg, 0.220 mmol) and 3 Å molecular sieves (5 mg) was added. The reaction was allowed to stir at rt for 3.5 h at which point the reaction mixture was filtered through a small plug of fluorosil. The residue was concentrated under reduced pressure using rotary evaporation. The resulting residue was purified rapidly via flash chromatography (SiO2; DCM to petroleum ether / EtOAc 6:1 to petroleum ether / EtOAc 5:1 to petroleum ether / EtOAc 4:1) to afford 89.7 mg (98%) of a white foam (m.p. 56-57 °C).

IR(CDCl<sub>3</sub>) 3346, 2977, 2931, 1747, 1695, 1477, 1393, 1368, 1313, 1241, 1216, 1156, 733 cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, 75 °C, Benzene-*d*<sub>6</sub>)  $\delta$  8.18 (d, *J* = 2.2 Hz, 1H), 6.40 (d, *J* = 9.2 Hz, 2H), 4.97 (s, 1H), 2.52 – 2.22 (series of m, 3H total), 2.10 (m, 1H), 1.46 (s, 9H), 1.40 (s, 9H). <sup>13</sup>C NMR (126 MHz, 75 °C, Benzene)  $\delta$  193.12, 155.83 (broad), 155.63, 142.63, 136.23, 134.45, 130.86, 130.53, 121.02, 81.58, 80.50, 64.72 (broad), 28.48, 28.40, 28.36, 27.87. HRMS (EI) calculated for C<sub>20</sub>H<sub>27</sub>BrN<sub>2</sub>O<sub>5</sub> (Na<sup>+</sup>) 477.0996, found: 477.0995. R<sub>f</sub> (petroleum ether / EtOAc 5:1) = 0.35. [ $\alpha$ ]<sub>D</sub><sup>23</sup> = 17.4 (c = 0.80, CHCl<sub>3</sub>). HPLC: (*Chiralpak*® *IA*, heptane-isopropanol 95:5, 0.8 mL/min, 254 nm): t<sub>R</sub>(minor) = 13.6 min, t<sub>R</sub>(major) = 19.0 min, 90% *ee*.



di-tert-butyl 1-(5-bromo-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)hydrazine-1,2-dicarboxylate 2n



(R,R)-ProPhenol **L1** (13.7 mg, 0.0214 mmol), 5-bromo-1-tetralone (45.0 mg, 0.200 mmol), and activated 3 Å molecular sieves (5 mg) were measured into a microwave vial equipped with stir bar. The flask was placed under a nitrogen atmosphere and THF (0.5 mL) was added. After stirring for 15 minutes, diethylzinc (1.0 M in hexanes, 40µL, 0.040 mmol) was added and the reaction was allowed to stir for an additional 15 minutes. At this time, a premixed (15 min) THF (0.3 mL) solution of di-*tert*-butyl azodicarboxylate (50.7 mg, 0.220 mmol) and 3 Å molecular sieves (5 mg) was added. The reaction was allowed to stir at rt for 3 h at which point the reaction mixture was filtered through a small plug of fluorosil. The residue was concentrated under reduced pressure using rotary evaporation. The resulting residue was purified rapidly via flash chromatography (SiO2; DCM to petroleum ether / EtOAc 7:1 to petroleum ether / EtOAc 6:1) to afford 83.2 mg (91 %) of a clear viscous oil.

IR(CDCl<sub>3</sub>) 3370, 2978, 2932, 1747, 1697, 1588, 1479, 1393, 1367, 1318, 1254, 1155, 1050, 757 cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, 75 °C, Benzene- $d_6$ )  $\delta$  7.89 (dd, J = 7.7, 1.3 Hz, 1H), 7.34 (dd, J = 7.8, 1.3 Hz, 1H), 6.65

(t, J = 7.8 Hz, 1H), 6.43 (s, 1H), 4.98 (s, 1H), 2.85 (d, J = 18.2 Hz, 1H), 2.48 – 2.28 (two obscured m, 2H total), 2.04 (qd, J = 12.9, 4.6 Hz, 1H), 1.45 (s, 9H), 1.41 (s, 9H). <sup>13</sup>C NMR (126 MHz, 75 °C, Benzene)  $\delta$  193.56, 155.81, 155.65, 143.14, 137.42, 134.80, 127.22, 124.88, 81.50, 80.47, 63.93 (broad), 29.68, 28.42, 28.37, 26.75, 1 aromatic carbon peak obscured. HRMS (EI) calculated for C<sub>20</sub>H<sub>27</sub>BrN<sub>2</sub>O<sub>5</sub> (Na<sup>+</sup>) 477.0996, found: 477.0997. [ $\alpha$ ]<sub>D</sub><sup>23</sup> = -5.9 (c = 1.29, CHCl<sub>3</sub>). HPLC: (*Chiralpak*® *IA*, heptane-isopropanol 95:5, 0.8 mL/min, 254 nm): t<sub>R</sub>(minor) = 21.7 min, t<sub>R</sub>(major) = 16.7 min, 95% *ee*.



di-tert-butyl 1-(7-fluoro-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)hydrazine-1,2-dicarboxylate 20



(R,R)-ProPhenol **L1** (13.7 mg, 0.0214 mmol), 7-fluoro-1-tetralone (32.8 mg, 0.200 mmol), and activated 3 Å molecular sieves (5 mg) were measured into a microwave vial equipped with stir bar. The flask was placed under a nitrogen atmosphere and THF (0.5 mL) was added. After stirring for 15 minutes, diethylzinc (1.0 M in hexanes, 40µL, 0.040 mmol) was added and the reaction was allowed to stir for an additional 15 minutes. At this time, a premixed (15 min) THF (0.3 mL) solution of di-*tert*-butyl azodicarboxylate (50.7 mg, 0.220 mmol) and 3 Å molecular sieves (5 mg) was added. The reaction was allowed to stir at rt for 1.3 h at which point the reaction mixture was filtered through a small plug of fluorosil. The residue was concentrated under reduced pressure using rotary evaporation. The resulting residue was purified rapidly via flash chromatography (SiO2; DCM to petroleum ether / EtOAc 6:1 to petroleum ether / EtOAc 4:1) to afford 63.8 mg (81 %) of a clear oil.

IR(CDCl<sub>3</sub>) 3314, 2979, 2932, 1747, 1694, 1614, 1493, 1457, 1426, 1394, 1368, 1307, 1262, 1241, 1158, 1052, 891, 850, 812 cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, 75 °C, Benzene- $d_6$ )  $\delta$  7.71 (dd, J = 9.0, 2.9 Hz, 1H), 6.73 (td, J = 8.3, 2.8 Hz, 1H), 6.54 (dd, J = 8.5, 5.1 Hz, 1H), 6.43 (s, 1H), 4.99 (s, 1H), 2.55 – 2.42 (m, 1H), 2.42 – 2.29 (m, 2H), 2.20 – 2.05 (m, 1H), 1.46 (s, 9H), 1.40 (s, 9H). <sup>13</sup>C NMR (126 MHz, 75 °C,

Benzene- $d_6$ )  $\delta$  193.42, 162.11 (d,  $J_{C-F} = 246.2$  Hz), 155.84, 155.65, 139.74, 134.55, 130.60 (d,  $J_{C-F} = 6.1$  Hz), 120.73 (d,  $J_{C-F} = 22.3$  Hz), 113.74 (d,  $J_{C-F} = 22.0$  Hz), 81.54 , 80.48 , 64.89 (broad), 28.40, 28.36, 28.32, 28.15. HRMS (EI) calculated for C<sub>20</sub>H<sub>27</sub>FN<sub>2</sub>O<sub>5</sub> (Na<sup>+</sup>) 417.1796, found: 417.1793. R<sub>f</sub> (petroleum ether / EtOAc 6:1) = 0.20. [ $\alpha$ ]<sub>D</sub><sup>22</sup> = -2.4 (c = 0.33, CHCl<sub>3</sub>). HPLC: (*Chiralpak*® *IA*, heptane-isopropanol 98:2, 0.8 mL/min, 254 nm): t<sub>R</sub>(minor) = 24.5 min, t<sub>R</sub>(major) = 29.8 min, 96% *ee*.



### Large-scale procedure:

(*R*,*R*)-ProPhenol **L1** (21.1 mg, 0.0330 mmol), 7-fluoro-1-tetralone (164 mg, 1.00 mmol), and activated 3 Å molecular sieves (25 mg) were measured into a microwave vial equipped with stir bar. The flask was placed under a nitrogen atmosphere and THF (2.5 mL) was added. After stirring for 15 minutes, diethylzinc (1.0 M in hexanes,  $60\mu$ L, 0.060 mmol) was added and the reaction was allowed to stir for an additional 15 minutes. At this time, a premixed (15 min) THF (1.5 mL) solution of di-*tert*-butyl azodicarboxylate (253 mg, 1.10 mmol) and 3 Å molecular sieves (25 mg) was added. The reaction was allowed to stir at rt for 5 h at which point the reaction mixture was filtered through a small plug of fluorosil. The residue was concentrated under reduced pressure using rotary evaporation. The resulting residue was purified rapidly via flash chromatography (SiO2; petroleum ether / EtOAc 6:1) to afford 305 mg (77 %) of a clear oil.

HPLC: (*Chiralpak*® *IA*, heptane-isopropanol 98:2, 0.8 mL/min, 254 nm):  $t_R(minor) = 21.1 \text{ min}$ ,  $t_R(major) = 25.1 \text{ min}$ , 96% *ee*. Note: The difference in retention time between the large-scale and the standard-scale retention times is due to normal column drift, as the large-scale reaction was performed and run on the HPLC 1 year after the standard-scale reaction. The same racemic sample was utilized for both HPLC runs.



di-tert-butyl 1-(7-nitro-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)hydrazine-1,2-dicarboxylate 2p



(*R*,*R*)-ProPhenol **L1** (13.7 mg, 0.0214 mmol), 7-nitro-1-tetralone (38.2 mg, 0.200 mmol), and activated 3 Å molecular sieves (5 mg) were measured into a microwave vial equipped with stir bar. The flask was placed under a nitrogen atmosphere and THF (0.5 mL) was added. After stirring for 15 minutes, diethylzinc (1.0 M in hexanes,  $40\mu$ L, 0.040 mmol) was added and the reaction was allowed to stir for an additional 15 minutes. At this time, a premixed (15 min) THF (0.3 mL) solution of di*-tert*-butyl azodicarboxylate (50.7 mg, 0.220 mmol) and 3 Å molecular sieves (5 mg) was added. The reaction was allowed to stir at rt for 25 min at which point the reaction mixture was filtered through a small plug of fluorosil. The residue was concentrated under reduced pressure using rotary evaporation. The resulting residue was purified rapidly via preparatory TLC (SiO2; petroleum ether / EtOAc 1:1) to afford 65.7 mg (83 %) of a clear viscous oil.

IR(CDCl<sub>3</sub>) 3348, 2977, 1700, 1612, 1529, 1479, 1394, 1347, 1311, 1242, 1155, 760 cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, 75 °C, Benzene-*d*<sub>6</sub>)  $\delta$  8.70 (d, *J* = 2.5 Hz, 1H), 7.74 (dd, *J* = 8.4, 2.5 Hz, 1H), 6.43 (d, *J* = 8.4 Hz, 1H), 6.39 (s, 1H), 4.95 (s, 1H), 2.45 – 2.21 (m, 3H), 2.07 (tt, *J* = 15.3, 8.4 Hz, 1H), 1.47 (s, 9H), 1.41 (s, 9H). <sup>13</sup>C NMR (126 MHz, 75 °C, Benzene)  $\delta$  192.47, 149.64, 147.81, 133.42, 129.78, 127.02, 123.03, 81.85, 80.71, 64.47 (broad), 28.86, 28.38, 28.34, 27.40. HRMS (EI) calculated for C<sub>20</sub>H<sub>27</sub>N<sub>3</sub>O<sub>7</sub> (Na<sup>+</sup>) 444.1741, found: 444.1741. R<sub>f</sub> (petroleum ether / EtOAc 1:1) = 0.68. [ $\alpha$ ]<sub>D</sub><sup>24</sup> = 23.9 (c = 0.86, CHCl<sub>3</sub>). HPLC: (*Chiralpak*® *IA*, heptane-isopropanol 90:10, 0.8 mL/min, 254 nm): t<sub>R</sub>(minor) = 13.7 min, t<sub>R</sub>(major) = 21.6 min, 94% *ee*.



di-tert-butyl 1-(6-cyano-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)hydrazine-1,2-dicarboxylate 2q



(*R*,*R*)-ProPhenol **L1** (13.7 mg, 0.0214 mmol), 6-cyano-1-tetralone (34.2 mg, 0.200 mmol), and activated 3 Å molecular sieves (5 mg) were measured into a microwave vial equipped with stir bar. The flask was placed under a nitrogen atmosphere and THF (0.5 mL) was added. After stirring for 15 minutes, diethylzinc (1.0 M in hexanes, 40µL, 0.040 mmol) was added and the reaction was allowed to stir for an additional 15 minutes. At this time, a premixed (15 min) THF (0.3 mL) solution of di*-tert*-butyl azodicarboxylate (50.7 mg, 0.220 mmol) and 3 Å molecular sieves (5 mg) was added. The reaction was allowed to stir at rt for 30 min at which point the reaction mixture was filtered through a small plug of fluorosil. The residue was concentrated under reduced pressure using rotary evaporation. The resulting residue was purified rapidly via preparatory TLC (SiO2; petroleum ether / EtOAc 1.5:1) to afford 69.1 mg (86 %) of a clear viscous oil.

IR(CDCl<sub>3</sub>) 3340, 3134, 2980, 2932, 1697, 1480, 1458, 1394, 1368, 1315, 1243, 1155, 757 cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, 75 °C, Benzene-*d*<sub>6</sub>)  $\delta$  7.73 (d, *J* = 8.1 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 6.70 (s, 1H), 6.37 (s, 1H), 4.92 (s, 1H), 2.41 – 2.25 (m, 2H), 2.25 – 2.15 (m, 1H), 2.05 (qd, *J* = 13.3, 12.9, 4.6 Hz, 1H), 1.45 (s, 9H), 1.40 (s, 9H). <sup>13</sup>C NMR (126 MHz, 75 °C, Benzene)  $\delta$  193.40, 155.84, 155.49, 144.34, 135.10, 132.63, 129.74, 128.29, 117.82, 117.37, 81.76, 80.69, 64.96 (broad), 28.45, 28.37, 28.33, 27.56. HRMS (EI) calculated for C<sub>21</sub>H<sub>27</sub>N<sub>3</sub>O<sub>5</sub> (Na<sup>+</sup>) 424.1843, found: 424.1842. R<sub>f</sub> (petroleum ether / EtOAc 2:1) = 0.63. [ $\alpha$ ]<sub>D</sub><sup>23</sup> = -6.6 (c = 1.12, CHCl<sub>3</sub>). HPLC: (*Chiralpak*® *IA*, heptane-isopropanol 90:10, 0.8 mL/min, 254 nm): t<sub>R</sub>(minor) = 22.6 min, t<sub>R</sub>(major) = 17.2 min, 93% *ee*.



di-tert-butyl (S)-1-(4-oxochroman-3-yl)hydrazine-1,2-dicarboxylate 2r



(R,R)-ProPhenol L1 (13.7 mg, 0.0214 mmol), 4-chromanone (29.6 mg, 0.200 mmol), and activated 3 Å molecular sieves (5 mg) were measured into a microwave vial equipped with stir bar. The flask was placed under a nitrogen atmosphere and THF (0.5 mL) was added. After stirring for 15 minutes, diethylzinc (1.0 M in hexanes, 40µL, 0.040 mmol) was added and the reaction was allowed to stir for an additional 15 minutes at 4 °C. At this time, a premixed (15 min) THF (0.3 mL) solution of di*-tert*-butyl azodicarboxylate (50.7 mg, 0.220 mmol) and 3 Å molecular sieves (5 mg) at 4 °C was added. The reaction was allowed to stir at 4°C for 9 h at which point the reaction mixture was filtered through a small plug of fluorosil. The residue was concentrated under reduced pressure using rotary evaporation. The resulting residue was purified rapidly via flash chromatography (SiO2; petroleum ether / CHCl<sub>3</sub> 2:1 to DCM to to petroleum ether / EtOAc 4:1 to 3:1) to afford 39.4 mg (52 %) of a clear viscous oil.

IR(CHCl<sub>3</sub>) 3317, 2978, 2926, 1699, 1608, 1479, 1395, 1369, 1326, 1298, 1248, 1216, 1154, 1116, 1037, 1013, 867, 762 cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, 75 °C, Benzene-*d*<sub>6</sub>)  $\delta$  7.90 (d, *J* = 7.8 Hz, 1H), 7.03 – 6.92 (m, 1H), 6.72 (d, *J* = 8.4 Hz, 1H), 6.63 (t, *J* = 7.6 Hz, 1H), 6.45 (s, 1H), 5.32 (s, 1H), 4.76 (s, 1H), 4.42 (t, *J* = 12.2 Hz, 1H), 1.39 (d, *J* = 6.0 Hz, 9H), 1.33 (s, 9H). <sup>13</sup>C NMR (126 MHz, 75°C, Benzene)  $\delta$  189.22, 162.28, 155.94 (broad), 155.05, 135.92, 121.65, 121.47, 118.13, 82.09, 80.92, 69.07, 61.29 (broad), 28.20. One aromatic carbon peak is obscured. LRMS (EI) calculated for C<sub>19</sub>H<sub>26</sub>N<sub>2</sub>O<sub>6</sub> (Na<sup>+</sup>) 401.2, found: 401.2. [ $\alpha$ ]<sub>D</sub><sup>26</sup> = -13.9 (c = 1.20, CHCl<sub>3</sub>). HPLC: (*Chiralpak*® *IA*, heptane-isopropanol 95:10, 0.8 mL/min, 254 nm): t<sub>R</sub>(minor) = 15.8 min, t<sub>R</sub>(major) = 13.7 min, 75% *ee*.



di-tert-butyl 1-(1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)hydrazine-1,2-dicarboxylate 2s



(R,R)-ProPhenol **L1** (20.6 mg, 0.0322 mmol), 1-benzosuberone (32.0mg, 0.200 mmol), and activated 3 Å molecular sieves (5 mg) were measured into a microwave vial equipped with stir bar. The flask was placed under a nitrogen atmosphere and THF (0.3 mL) was added. After stirring for 15 minutes, diethylzinc (1.0 M in hexanes,  $60\mu$ L, 0.060 mmol) was added and the reaction was allowed to stir for an additional 15 minutes. At this time, a premixed (15 min) THF (0.2 mL) solution of di*-tert*-butyl azodicarboxylate (50.0 mg, 0.217 mmol) and 3 Å molecular sieves (5 mg) was added. The reaction was allowed to stir at rt for 14 hours at which point the reaction mixture was filtered through a small plug of fluorosil. The residue was concentrated under reduced pressure using rotary evaporation. The resulting residue was purified via flash chromatography (SiO2; DCM to petroleum ether / EtOAc 5:1 to petroleum ether / EtOAc 4:1) to afford 66.2 mg (85%) of a pale-yellow oil.

IR(CDCl<sub>3</sub>) 3270, 2940, 2890, 1670, 1580, 1440, 1370, 1350, 1300, 1220, 1140, 1040, 950, 920, 880, 840, 750 cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, 75 °C, Benzene-*d*<sub>6</sub>)  $\delta$  7.93 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.04 (td, *J* = 7.4, 1.6 Hz, 1H), 6.97 (t, *J* = 7.3 Hz, 1H), 6.78 (d, *J* = 7.5 Hz, 1H), 6.67 (s, 1H), 5.22 (s, 1H), 2.57 (ddd, *J* = 15.5, 11.5, 3.9 Hz, 1H), 2.45 – 2.35 (m, 1H), 2.35 – 2.28 (m, 1H), 1.96 – 1.83 (m, 1H), 1.71 – 1.60 (m, 1H), 1.43 (s, 18H). <sup>13</sup>C NMR (126 MHz, 75 °C, Benzene-*d*<sub>6</sub>)  $\delta$  201.83, 155.99, 155.01, 142.37, 137.49, 132.34, 130.17, 129.88, 126.83, 81.36, 80.28, 66.41, 33.96, 28.46, 28.36, 26.72, 24.38. HRMS (EI) calculated for C<sub>21</sub>H<sub>30</sub>N<sub>2</sub>O<sub>5</sub> (Na<sup>+</sup>) 413.2047, found: 413.2044. R<sub>f</sub> (petroleum ether / EtOAc 4:1) = 0.40. [ $\alpha$ ]<sub>D</sub><sup>23</sup> = 40.3 (c =



0.66, CHCl<sub>3</sub>). HPLC: (*Chiralpak*® *IB*, heptane-isopropanol 98:2, 0.8 mL/min, 254 nm):  $t_R(minor) = 7.5$  min,  $t_R(major) = 9.3$  min, 98% *ee*.

Large-scale and recovery of ligand:

(R,R)-ProPhenol **L1** (61.8 mg, 0.0967 mmol), 1-benzosuberone (96.0 mg, 0.600 mmol), and activated 3 Å molecular sieves (15 mg) were measured into a microwave vial equipped with stir bar. The flask was placed under a nitrogen atmosphere and THF (0.9 mL) was added. After stirring for 15 minutes, diethylzinc (1.0 M in hexanes, 180µL, 0.180 mmol) was added and the reaction was allowed to stir for an additional 15 minutes. At this time, a premixed (15 min) THF (0.6 mL) solution of di-*tert*-butyl azodicarboxylate (150 mg, 0.651 mmol) and 3 Å molecular sieves (15 mg) was added. The reaction was allowed to stir at rt for 16 hours at which point silica gel was added to the reaction mixture. The reaction miture was concentrated under reduced pressure using rotary evaporation and the resulting silica gel was loaded directly onto a flash chromatography column (SiO2; petroleum ether / EtOAc 7.5:1 to 1.5:1 to 1:1) to afford 208 mg (89%) of a pale-yellow oil, and, separately, impure ligand. The impure ligand was dissolved in DCM (30 mL) and extracted with 10 mL of 0.5 M HSO<sub>4</sub>Na (aqueous). The organic layer was disposed of and the aqueous layer was neutralized with 7.4 pH phosphate buffer. The neutral aqueous phase was extracted with DCM (3 x 30 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated to yield 51.1 mg (83%) of the (*R*,*R*)-ProPhenol **L1** ligand as a white foamy solid.

HPLC: (*Chiralpak*® *IB*, heptane-isopropanol 98:2, 0.8 mL/min, 254 nm):  $t_R(minor) = 7.2 min$ ,  $t_R(major) = 8.8 min$ , 96% *ee*.

	VWD1 A, Wavelength=254 nm (JAKE\DEF_LC_CORRECT 2017-11-16 12-10-23/091-0201.D)	Pea)	RetTime	в Туре	Width	Area	Height	Area
mAU		+	[min]		[min]	mAU *s	[mAU ]	8
160			7.20	-   7 VV	0.2213	79.39741	5.39215	2.1061
140		2	8.80	5 VB	0.3098	3690.54614	179.43520	97.8939
120								
100								
80								
60								
40								
20	507							
0								
	5 6 7 8 9 10 11 12 13 14 mi							

The recovered ligand (20.6 mg, 0.0322 mmol), 1-benzosuberone (32.0mg, 0.200 mmol), and activated 3 Å molecular sieves (5 mg) were measured into a microwave vial equipped with stir bar. The flask was placed under a nitrogen atmosphere and THF (0.3 mL) was added. After stirring for 15 minutes, diethylzinc (1.0 M in hexanes,  $60\mu$ L, 0.060 mmol) was added and the reaction was allowed to stir for an additional 15 minutes. At this time, a premixed (15 min) THF (0.2 mL) solution of di*-tert*-butyl azodicarboxylate (50.0 mg, 0.217 mmol) and 3 Å molecular sieves (5 mg) was added. The reaction was allowed to stir at rt for 13 hours at which point the reaction mixture was filtered through a small plug of fluorosil. The residue was concentrated under reduced pressure using rotary evaporation. The resulting residue was purified via flash chromatography (SiO2; petroleum ether / EtOAc 6:1) to afford 65.5 mg (84%) of a pale-yellow oil.

HPLC: (*Chiralpak*® *IB*, heptane-isopropanol 98:2, 0.8 mL/min, 254 nm):  $t_R(minor) = 7.2 min$ ,  $t_R(major) = 8.8 min$ , 97% *ee*.



di-tert-butyl 1-(4-methoxy-1-oxo-2,3-dihydro-1H-inden-2-yl)hydrazine-1,2-dicarboxylate 2t



(*R*,*R*)-ProPhenol L1 (13.7 mg, 0.0214 mmol), 4-methoxy-1-indanone (32.4 mg, 0.200 mmol), and activated 3 Å molecular sieves (5 mg) were measured into a microwave vial equipped with stir bar. The flask was placed under a nitrogen atmosphere and THF (0.5 mL) was added. After stirring for 15 minutes, diethylzinc (1.0 M in hexanes,  $40\mu$ L, 0.040 mmol) was added and the reaction was allowed to stir for an additional 15 minutes. At this time, a premixed (15 min) THF (0.3 mL) solution of di-*tert*-butyl azodicarboxylate (50.7 mg, 0.220 mmol) and 3 Å molecular sieves (5 mg) was added. The reaction was allowed to stir at rt for 2 h at which point the reaction mixture was filtered through a small plug of fluorosil. The residue was concentrated under reduced pressure using rotary evaporation. The resulting

residue was purified rapidly via flash chromatography (SiO2; DCM to petroleum ether / EtOAc 5:1 to petroleum ether / EtOAc 3:1) to afford 40.9 mg (52%) of a white solid (m.p. 76-78 °C) as well as 12.0 mg of the starting indanone (37%).

IR(CDCl<sub>3</sub>) 3303, 2978, 2934, 2280, 1730, 1603, 1490, 1393, 1368, 1262, 1155, 1078, 1013, 936, 895, 845, 814, 768 cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, 75 °C, Benzene-*d*<sub>6</sub>)  $\delta$  7.36 (d, *J* = 7.6 Hz, 1H), 6.96 (t, *J* = 7.8 Hz, 1H), 6.55 (d, *J* = 8.0 Hz, 1H), 6.37 (s, 1H), 4.69 (s, 1H), 3.47 – 3.39 (m, 2H), 3.31 (s, 3H), 1.36 – 1.34 (m, 9H), 1.33 (s, 9H). <sup>13</sup>C NMR (126 MHz, 75 °C, Benzene)  $\delta$  200.92, 157.56, 155.90, 154.90, 141.21, 137.44, 128.97, 116.11, 115.78, 81.71, 80.78, 65.89, 55.19, 28.30, 28.27. HRMS (EI) calculated for C<sub>20</sub>H-<sub>28</sub>N<sub>2</sub>O<sub>6</sub> (Na<sup>+</sup>) 415.1840, found: 415.1839. R<sub>f</sub> (petroleum ether / EtOAc 4:1) = 0.27. [ $\alpha$ ]<sub>D</sub><sup>23</sup> = 4.8 (c = 0.28, CHCl<sub>3</sub>). HPLC: (*Chiralpak*® *IA*, heptane-isopropanol 95:5, 0.8 mL/min, 254 nm): t<sub>R</sub>(minor) = 35.0 min, t<sub>R</sub>(major) = 24.2 min, 89% *ee*.



di-tert-butyl 1-(1-oxo-2,3-dihydro-1H-inden-2-yl)hydrazine-1,2-dicarboxylate 2u



(S,S)-L2 (8.5 mg, 0.011 mmol), 1-indanone (26.4 mg, 0.200 mmol), and activated 3 Å molecular sieves (5 mg) were measured into a microwave vial equipped with stir bar. The flask was placed under a nitrogen atmosphere and THF (0.5 mL) was added. After stirring for 15 minutes, diethylzinc (1.0 M in hexanes, 20µL, 0.020 mmol) was added and the reaction was allowed to stir for an additional 15 minutes. At this time, a premixed (15 min) THF (0.3 mL) solution of di-*tert*-butyl azodicarboxylate (50.7 mg, 0.220 mmol) and 3 Å molecular sieves (5 mg) was added. The reaction was allowed to stir at rt for 2.5 h at which point the reaction mixture was filtered through a small plug of fluorosil. The residue was concentrated under reduced pressure using rotary evaporation. The resulting residue was purified rapidly via flash chromatography (SiO2; DCM to petroleum ether / EtOAc 6:1 to petroleum ether / EtOAc 5:1 to

petroleum ether / EtOAc 4:1) to afford 49.7 mg (69 %) of a clear oil as well as 6.3 mg (24%) of the staring indanone.

IR(CDCl<sub>3</sub>) 3297, 2978, 2930, 1729, 1612, 1475, 1394, 1368, 1301, 1247, 1155, 760 cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, 75 °C, Benzene- $d_6$ )  $\delta$  7.63 (s, 1H), 7.10 (t, J = 7.5 Hz, 1H), 6.97 – 6.87 (m, 2H), 6.34 (s, 1H), 4.70 (s, 1H), 3.41 (dd, J = 17.1, 5.6 Hz, 1H), 3.19 (dd, J = 17.0, 8.4 Hz, 1H), 1.37 (s, 9H), 1.34 (s, 9H). <sup>13</sup>C NMR (126 MHz, 75 °C, Benzene)  $\delta$  200.75, 155.95, 154.92, 151.99, 135.96, 134.80, 127.53, 126.73, 124.25, 81.76, 80.80, 65.87 (broad), 31.61, 28.30, 28.27. HRMS (EI) calculated for C<sub>19</sub>H<sub>26</sub>N<sub>2</sub>O<sub>5</sub> (Na<sup>+</sup>) 385.1734, found: 385.1734. R<sub>f</sub> (petroleum ether / EtOAc 4:1) = 0.26. [ $\alpha$ ]<sub>D</sub><sup>23</sup> = 28.6 (c = 1.25, CHCl<sub>3</sub>). HPLC: (*Chiralpak*® *IA*, heptane-isopropanol 90:10, 0.8 mL/min, 254 nm): t<sub>R</sub>(minor) = 9.2 min, t<sub>R</sub>(major) = 14.8 min, 86% *ee*.



#### **III. References**

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