

**Supporting Information**  
**Regio- and Enantioselective Nitronc Cycloaddition to Alkynones for the Synthesis of**  
**Optically Pure  $\Delta^4$ -Isoxazolines**

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**General Experimental Information:** Methylene chloride was distilled from calcium hydride prior to use. Powdered molecular sieves 4 A (MS 4A) was purchased from Aldrich Chemical and dried at 250-300 °C under vacuum before use. Flash chromatography was performed using EM Science silica gel 60 (230-400 mesh) or on an ISCO CombiFlash Companion with Analogix RS-4 columns. Thin layer chromatographic analyses were performed on silica gel Whatmann-60F glass plates and components were visualized by illumination with UV light. All glassware was oven dried, assembled hot and cooled under a stream of dry nitrogen before used. Reactions with air sensitive materials were carried out by standard syringe techniques.

Melting points were recorded on a Fisher-Johns melting point apparatus and are uncorrected. <sup>1</sup>H NMR was recorded on a Varian Unity/Inova-500 NB (500 MHz), Varian Unity/Inova-400 NB (400 MHz), or Varian Mercury-300 (300 MHz) spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from TMS, using residual CDCl<sub>3</sub> (7.27 ppm) as an internal standard. Data are reported as follows: Chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, dd = doublets of doublets, dt = doublet of triplets, dq = doublet of quartets, m = multiplet, br = broad, AB sys = AB system), coupling constant(s) and integration. <sup>13</sup>C NMR was recorded on a Varian Unity/Inova-500 NB (125 MHz) or a Varian/Inova-400 (100 MHz) spectrometers using broadband proton decoupling. Chemical shifts are reported in parts per million (ppm) down field from TMS, using the middle resonance of CDCl<sub>3</sub> (77.23) as an internal standard. HPLC analyses were carried out on Waters 515 HPLC pump and a 2487 dual λ absorbance detector connected to a PC with Empower Workstation. Optical rotations were measured on a JASCO-DIP-370 polarimeter. High-resolution mass spectra (HRMS) [ESI+] were obtained from the Mass Spectrometry Laboratory, North Dakota State University, Fargo, North Dakota.

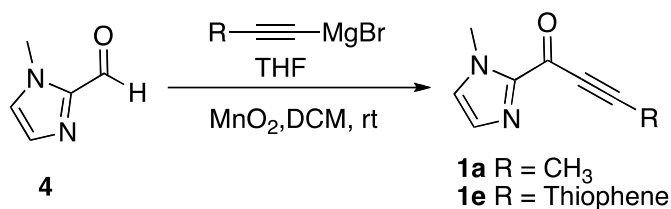
**Materials and Methods:** Zn(OTf)<sub>2</sub> was used as received from Aldrich. The nitrones were synthesized using *N*-methylhydroxylamine hydrochloride, *p*-methoxyphenylhydroxylamine or *N*-benzylhydroxylamine and condensed with the corresponding aldehyde according to literature.<sup>2</sup> The ligands were synthesized according to the method reported by our laboratory.<sup>3</sup>

**General procedure for the synthesis of N-methyl imidazole alkynones (1a-e):**

β-substituted alkynones **1a-e** were prepared starting from 1-methyl imidazole caboxaldehyde **4** according to modified literature methods.<sup>4</sup>

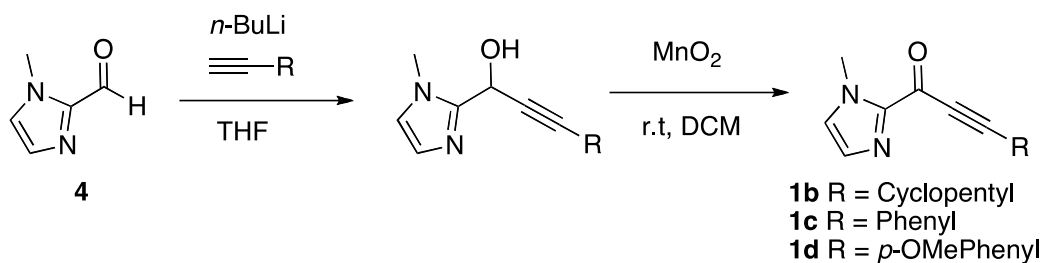
**Procedure A:** 1-Methylimidazole-2-carboxaldehyde **4** (1 equiv.) was stirred in THF (100 mL). The solution was cooled to -78 °C and stirred for 10 minutes. The corresponding Grignard was added dropwise (1.1 equiv., 0.5M soln in THF) and the solution was stirred for 15 minutes (Scheme 1). The solution was then warmed to room temperature and stirred for four hours. The reaction was then quenched with ammonia chloride and

solvent was removed under reduced pressure. The aqueous layer was extracted with ethyl acetate. Organic layer was dried with sodium sulfate. Solvent was removed under reduced pressure and crude product was used directly in oxidation step. The product was dissolved in dichloromethane and activated manganese dioxide (10 equiv.) was added and stirred for 30 minutes (Note: Activated manganese dioxide is essential as reactions conducted with reagent grade manganese dioxide gave poor conversions). The solution was filtered through celite to remove manganese dioxide. The product was purified by column chromatography (0.5:95.5 – 40:60 ethyl acetate/hexane). Following this procedure alkynones **1a** and **1e** were prepared in 0.5-2.0g scale.

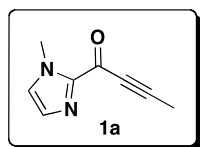


Scheme 1: Preparation of alkynones starting from Grignards reagent.

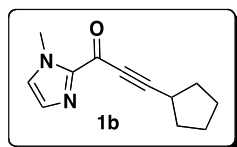
**Procedure B:** The corresponding alkyne (1 equiv.) in 50 mL of THF was cooled to -78 °C and stirred for 10 minutes. n-Butyl lithium (1.1 equiv., 2.5 M) was added dropwise to the solution. The solution was then warmed to room temperature for 15 minutes and was then cooled again to -78°C and stirred for 10 minutes. 1-Methyl-imidazole-2-carboxaldehyde **1a** (1 equiv.) was dissolved in THF (25 mL) and added dropwise to the solution of the alkyne (Scheme 2). The solution was then warmed to room temperature and stirred for four hours. The solution was then quenched with ammonia chloride and solvent was removed under reduced pressure. The aqueous layer was extracted with ethyl acetate. The organic layer was dried with sodium sulfate. The solvent was removed and the crude product was used directly in the oxidation step. The product was dissolved in dichloromethane and activated manganese dioxide (10 equiv.) was added and stirred for 30 minutes. The solution was filtered through celite to remove manganese dioxide. The product was purified by column chromatography (0.5:95.5 – 40:60 ethyl acetate/hexane). Following this procedure alkynones **1b-c** were prepared in 0.5-1.0g scale.



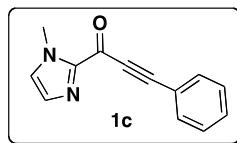
Scheme 2: Preparation of alkynones from terminal alkynes



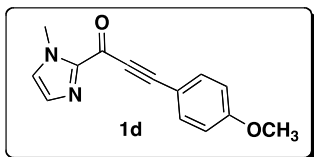
**(1-Methyl-1*H*-imidazole-2-yl)-but-2-yn-1-one (1a):** Yellow solid; yield: 89%; mp = 78-79°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 2.18 (s, 3H), 4.03 (s, 3H), 7.08 (s, 1H), 7.28 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 4.9, 36.2, 78.7, 92.9, 127.6, 131.0, 143.9, 168.3; IR (KBr) 3108, 2961, 2272, 2216, 1633, 1474, 1402, 1255, 1162, 1134, 882 cm<sup>-1</sup>; HRMS calcd. for C<sub>8</sub>H<sub>8</sub>N<sub>2</sub>ONa<sup>+</sup> 171.0534; found 171.0538.



**(1-Methyl-1*H*-imidazole-2-yl)-3-cyclopentylprop-2-yn-1-one (1b):** Bright yellow solid; yield: 80%; mp = 44-45°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 1.58 (m, 2H), 1.77 (m, 4H), 2.01 (m, 2H), 2.89 (m, 1H) 3.97 (s, 3H), 7.02 (d, *J* = 1.0 Hz, 1H), 7.20 (d, *J* = 1.0 Hz, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 25.6, 30.6, 33.5, 36.3, 80.1, 105.7, 127.5, 130.9, 144.1, 168.7; IR (KBr) 3106, 2960, 2208, 1628, 1461, 1402, 1250, 1161, 950, 910 cm<sup>-1</sup>; HRMS calcd. for C<sub>12</sub>H<sub>14</sub>N<sub>2</sub>ONa<sup>+</sup> 225.0998; found 225.0987.

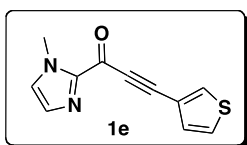


**(1-Methyl-1*H*-imidazole-2-yl)-3-phenylprop-2-yn-1-one (1c):** Off-white solid; yield: 30%; mp = 108-109°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 4.06 (s, 3H), 7.11 (s, 1H), 7.30 (m, 1H), 7.41 (m, 3H), 7.71 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 36.3, 87.8, 93.2, 120.5, 123.5, 127.9, 128.7, 130.9, 131.2, 133.5, 195.0; IR (KBr) 3107, 2958, 2203, 1623, 1489, 1399, 1276, 1157, 1030, 996, 916, 759, 689 cm<sup>-1</sup>; HRMS calcd. for C<sub>13</sub>H<sub>10</sub>N<sub>2</sub>ONa<sup>+</sup> 233.0685; found 233.0679.



**(1-Methyl-1*H*-imidazole-2-yl)-3-*p*-methoxyphenylprop-2-yn-1-one (1d):** Yellow solid; yield: 40%; mp = 103-105°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 3.80 (s, 3H), 4.01 (s, 3H), 6.87 (td, *J* = 6.9, 1.9 Hz, 2H), 7.08 (s, 1 H), 7.23 (d, *J* = 0.8 Hz, 1H), 7.64 (td, *J* = 6.9, 1.9 Hz, 2H);

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 36.4, 55.7, 87.9, 94.6, 112.3, 114.4, 127.6, 130.9, 135.6, 144.0, 161.9, 168.3; IR (KBr) 2961, 2838, 2191, 1623, 1600, 1511, 1403, 1254, 1173, 1027, 916, 834 cm<sup>-1</sup>; HRMS calcd. for C<sub>14</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub>Na<sup>+</sup> 263.0791; found 263.0801.



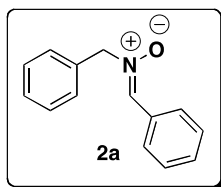
**(1-Methyl-1*H*-imidazole-2-yl)-3-thiopheneprop-2-yn-1-one**

**(1e):** Yellow solid; yield: 79%; mp = 70-71°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 4.07 (s, 3H), 7.13 (s, 1H), 7.31 (s, 1H), 7.34 (dd, *J* =

5.0, 2.9 Hz, 1H), 7.37 (dd, *J* = 5.0, 1.4 Hz, 1H), 7.90 (dd, *J* = 2.9, 1.4 Hz, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 36.3, 88.2, 88.8, 119.7, 126.1, 127.9, 130.8, 131.1, 134.5, 144.0, 168.3; IR (KBr) 3107, 2196, 1624, 1517, 1462, 1395, 1263, 1156, 1028, 910, 825, 789, 684 cm<sup>-1</sup>; HRMS calcd. for C<sub>11</sub>H<sub>8</sub>N<sub>2</sub>OSNa<sup>+</sup> 239.0250; found 239.0256.

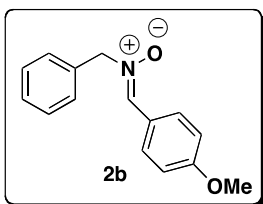
### Synthesis of Nitrones (2a-h):

The nitrones were synthesized using *N*-methylhydroxylamine hydrochloride, *p*-methoxyphenylhydroxylamine or *N*-benzylhydroxylamine and condensed with the corresponding aldehyde according to literature procedures.<sup>5</sup>



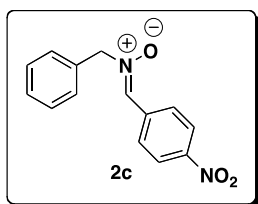
**(Z)-*N*-benzylidene-1-phenylmethanamine oxide (2a):** White solid; yield: 96%; mp = 123-124 °C; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ 8.19-8.23 (m, 2H), 7.47-7.51 (m, 2H), 7.38-7.43 (m, 7H), 5.08 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) 71.2, 128.5 (2 carbons), 128.8 (2

carbons), 129.1, 129.4, 130.6, 133.5, 134.4.



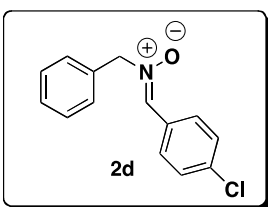
**(Z)-*N*-(4-methoxybenzylidene)-1-phenylmethanamine oxide (2b):** Off-white solid; yield: 94%; mp = 120-121 °C; <sup>1</sup>H NMR

(CDCl<sub>3</sub>, 500 MHz)  $\delta$  3.81(s, 3H), 5.00 (s, 2H), 6.89 (m, 2 H), 7.28 (s, 1H), 7.38 (m, 3H), 7.44 (m, 2H); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) 55.5, 70.9, 114.0, 123.6, 129.0, 129.1, 129.4, 130.8, 133.7, 134.0, 161.2.



**(Z)-N-(4-nitrobenzylidene)-1-phenylmethanamine oxide (2c):**

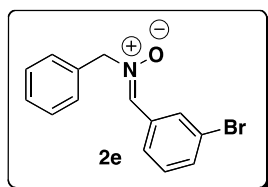
White solid, yield: 95%; mp = 121-122 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  5.09 (s, 2H), 7.41-7.49 (m, 6H), 8.22 (dt,  $J$  = 9.0, 2.2Hz, 2H), 8.34 (dt,  $J$  = 9.0, 2.6 Hz, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  72.3, 124.0, 129.1, 129.4, 129.6, 129.7, 132.4, 132.8, 136.2, 148.1; IR (KBr) 3070, 1565, 1516, 1348, 1151, 862, 714, 688 cm<sup>-1</sup>; HRMS calcd. for C<sub>14</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub>Na<sup>+</sup> 279.0740; found 279.0731.



**(Z)-N-(4-chlorobenzylidene)-1-phenylmethanamine oxide**

**(2d):** White solid; yield: 92%; mp = 198-199 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>,

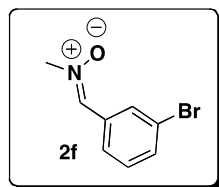
500 MHz)  $\delta$  5.03 (s, 2H), 7.37 (m, 8H), 8.14 (td,  $J$  = 8.5, 2.4 Hz, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  71.5, 128.9, 129.1, 129.2 (2 carbon), 129.3, 129.5, 129.9, 133.3, 136.0.



**(Z)-N-(3-bromobenzylidene)-1-phenylmethanamine oxide**

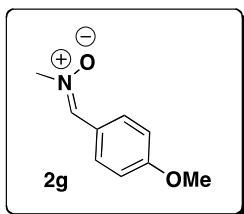
**(2e):** White crystalline solid; yield: 87%; mp = 213-214 °C; <sup>1</sup>H

NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  5.07 (s, 1H), 7.37 (s, 1H), 7.44 (m, 3H), 7.48 (m, 2H), 7.54 (dt,  $J$  = 9.0, 2.4 Hz, 2H), 8.11 (dt,  $J$  = 9.0, 2.4Hz, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  71.7, 122.8, 127.2, 129.3, 129.4, 129.5, 130.1, 131.2, 132.5, 132.9, 133.2, 133.4; IR (KBr) 3065, 1577, 1457, 1427, 1271, 1150, 887, 710, 682, 466 cm<sup>-1</sup>; HRMS calcd. for C<sub>14</sub>H<sub>12</sub>BrNONa<sup>+</sup> 311.9994; found 311.9985.



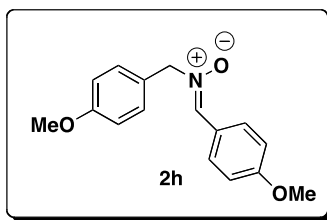
**(Z)-N-(3-bromobenzylidene)methanamine oxide (2f):** White solid;

yield: 70%; mp = 129-130 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  3.92 (s, 3H), 7.31 (t,  $J$  = 9.0 Hz, 1H), 7.36 (s, 1H), 7.56 (d,  $J$  = 9.0 Hz, 1H), 8.10 (d,  $J$  = 9.0 Hz, 1H), 8.49 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  54.8, 127.0, 130.2, 131.0, 132.4, 133.5.



130.6, 135.1, 161.3.

**(Z)-N-(4-methoxybenzylidene)methanamine oxide (2g):** White solid; yield: 80%; mp = 69-70 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 3.81 (s, 6H), 6.90 (d, *J* = 9.0 Hz, 2H), 7.26 (s, 1H), 8.17 (d, *J* = 9.0 Hz, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 54.1, 55.5, 114.1, 123.7,



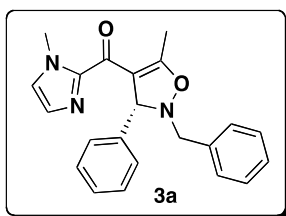
**(Z)-N-(4-methoxybenzylidene)-1-(4-methoxyphenyl)methanamine oxide (2h):** White solid; yield: 95%; mp = 99-100 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 2.79 (s, 3H), 3.80 (s, 3H), 4.98 (s, 2H), 6.94 (m, 4H), 7.29 (s, 1H), 7.42 (td, *J* = 9.0, 4.8 Hz, 2H), 8.21 (td, *J* = 9.0, 4.8 Hz, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 55.3 (2 carbons), 70.1, 113.7, 114.3, 123.5, 125.5, 130.5, 130.8, 133.3, 160.0, 160.9 IR (KBr) 3051, 2974, 2839, 1603, 1507, 1457, 1256, 1172, 1027, 940 cm<sup>-1</sup>; HRMS calcd. for C<sub>16</sub>H<sub>17</sub>NO<sub>3</sub>Na<sup>+</sup> 294.1101; found 294.1089.

#### General Procedure for the preparation of racemic samples:

An oven-dried vial was charged with Zn(OTf)<sub>2</sub> (0.03 mmol), freshly dried 4Å molecular sieves (150 mg), and substrate (0.15 mmol), and dry CH<sub>2</sub>Cl<sub>2</sub> (2 mL) were added. The mixture was then stirred at room temperature for 30 min before nitron (0.15 mmol) was added. The solution was then stirred at room temperature and monitored by TLC for completion. The reaction mixture was quenched with silica gel. The solvent was removed under reduced pressure to give the crude product, which was purified by flash chromatography (silica gel, hexane/ethyl acetate 95:5-70:30), to yield racemic cycloadducts.

#### General procedure for enantioselective nitron cycloadditions with β-substituted alkynes (3a-l):

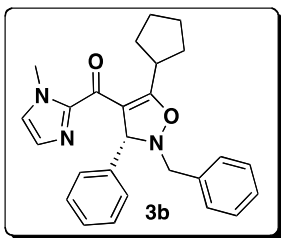
An oven-dried vial was charged with Zn(OTf)<sub>2</sub> (0.03 mmol) and the corresponding ligand (0.03 mmol) and 150 mg of freshly dried 4Å molecular sieves were added. Dry CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was added and the mixture was stirred for 45 minutes at room temperature. To the solution, alkyne substrate (0.15 mmol) in 0.5 mL dry CH<sub>2</sub>Cl<sub>2</sub> was added via syringe. After the mixture was stirred at room temperature for 30 min, nitron (0.15 mmol) was added. The reaction mixture was cooled and stirred at -40 °C. Reaction progress was monitored by TLC for starting material consumption. The reaction mixture was quenched with silica gel. The solvent was removed under reduced pressure to give the crude product, which was separated by FC (silica gel, hexane/ethyl acetate 95:5-70:30). The enantiomeric excess of the product was determined by chiral HPLC .



**(2-Benzyl-5-methyl-3-phenyl-2,3-dihydroisoxazol-4-yl)(1-methyl-1H-imidazol-2-yl)methanone (3a):**

Oil;  $[\alpha]_D^{25} = -208.8$  (*c* 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 2.41 (s, 3H), 3.84 (s, 3H), 4.23 (d, *J* = 13.0 Hz, 1H), 4.44 (d, *J* = 13.0 Hz, 1H), 6.27 (s, 1H), 6.88 (s, 1H), 7.07 (s, 1H), 7.20 (m, 5H), 7.35 (m, 3H), 7.46 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 13.8, 35.9, 64.0, 73.8, 113.2, 125.9, 127.6, 127.8, 127.9, 128.3, 128.4, 128.6, 129.8, 136.2, 142.5, 144.0, 166.9, 180.3; IR (KBr) 3030, 2922, 2850, 1644, 1576, 1409, 1286, 1225, 881, 736, 699 cm<sup>-1</sup>; HRMS calcd. for C<sub>22</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub>Na<sup>+</sup> 382.1526; found 382.1519.

**Table 3, Entry 1:** The enantiomeric purity for **3a** was determined by HPLC (254 nm, 25 °C) *t<sub>R</sub>* 8.6 min (minor), 9.5 min (major) [Chiralpak AD-3 (from Diacel Chemical Ltd.) hexane/*i*-PrOH, 90:10, 1mL/ min] as 86% ee for the cycloadduct.



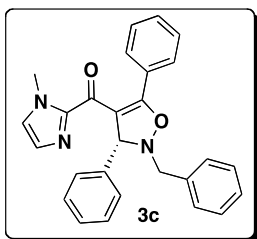
**(2-Benzyl-5-cyclopentyl-3-phenyl-2,3-dihydroisoxazol-4-yl)(1-methyl-1H-imidazol-2-yl)methanone (3b):**

Oil;  $[\alpha]_D^{25} = -111.4$  (*c* 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 1.55 – 1.82 (m, 6H), 1.85 – 1.95 (m, 2H), 2.05 – 2.15 (m, 1H), 3.79 (s, 3H), 4.15 (d, *J* = 13.0 Hz, 1H), 4.34 (d, *J* = 13.0 Hz, 1 H), 6.30 (s, 1H), 6.82 (s, 1H), 7.00 (m, 2H), 7.13 (m, 3H), 7.28 (m, 3H), 7.42 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 26.4, 26.5, 31.0, 31.4, 35.9, 37.4, 63.9, 73.4, 111.9, 125.8,



127.4, 127.6, 127.8, 128.2, 128.4, 128.5, 129.9, 136.2, 142.7, 144.3, 173.5, 180.3; IR (KBr) 2956, 2870, 1634, 1537, 1455, 1409, 1287, 862, 737, 698  $\text{cm}^{-1}$ ; HRMS calcd. for  $\text{C}_{26}\text{H}_{27}\text{N}_3\text{O}_2\text{Na}^+$  436.1995; found 436.1982.

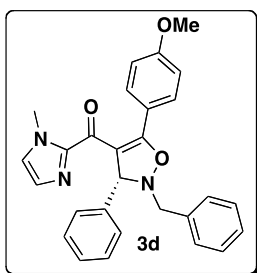
**Table 3, Entry 2:** The enantiomeric purity for **3b** was determined by HPLC (254 nm, 25  $^{\circ}\text{C}$ )  $t_{\text{R}}$  8.0 min (minor), 10.6 min (major) [Chiralpak AD-3 (from Diacel Chemical Ltd.) hexane/ *i*-PrOH, 95:05, 1mL/ min] as 47% ee for the cycloadduct.



**(2-Benzyl-3,5-diphenyl-2,3-dihydroisoxazol-4-yl)(1-methyl-1H-imidazol-2-yl)methanone (3c):**

Foamy solid;  $[\alpha]_{\text{D}}^{25} = -169.7$  (*c* 1.0,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  3.77 (s, 3H), 4.36 (d,  $J = 13.0$  Hz, 1H), 4.59 (d,  $J = 13.0$  Hz, 1H), 6.31 (s, 1H), 6.83 (s, 1H), 6.95 (s, 1H), 7.23 (m, 5H), 7.39 (m, 6H), 7.51 (m, 2H), 7.66 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  35.6, 63.4, 71.5, 75.3, 113.1, 125.6, 127.8, 127.9, 128.2, 128.4, 128.5, 128.6, 128.7, 129.6, 129.9, 131.1, 136.1, 141.7, 163.9, 188.0, 190.7; IR (KBr) 3029, 2924, 1637, 1567, 1490, 1402, 860, 755, 697  $\text{cm}^{-1}$ ; HRMS calcd. for  $\text{C}_{27}\text{H}_{23}\text{N}_3\text{O}_2\text{Na}^+$  444.1682; found 444.1703.

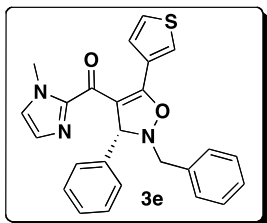
**Table 3, Entry 3:** The enantiomeric purity for **3c** was determined by HPLC (254 nm, 25  $^{\circ}\text{C}$ )  $t_{\text{R}}$  29.3 min (minor), 47.5 min (major) [Chiralpak AD-3 (from Diacel Chemical Ltd.) hexane/ *i*-PrOH, 95:05, 1mL/ min] as 77% ee for the cycloadduct.



**(2-Benzyl-5-(4-methoxyphenyl)-3-phenyl-2,3-dihydroisoxazol-4-yl)(1-methyl-1H-imidazol-2-yl)methanone (3d):**

Foamy solid;  $[\alpha]_{\text{D}}^{25} = -94.0$  (*c* 1.0,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  3.77 (s, 3H), 3.86 (s, 3H), 4.34 (d,  $J = 13.0$  Hz, 1H), 4.57 (d,  $J = 13.0$  Hz, 1H), 6.36 (s, 1H), 6.84 (s, 1H), 6.98 (s, 1H), 7.23 (m, 4H), 7.44 (m, 5H), 7.52 (m, 3H), 7.77 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  35.6, 55.6, 63.3, 71.5, 75.1, 113.7, 114.5, 125.5, 127.7, 127.9, 128.4, 128.5, 128.6, 128.7, 128.9, 129.3, 129.5, 129.9, 130.7, 131.7, 135.7, 190.7; IR (NaCl) 2960, 1602, 1564, 1507, 1456, 1255, 1148, 754, 703, 665  $\text{cm}^{-1}$ ; HRMS calcd. for  $\text{C}_{28}\text{H}_{25}\text{N}_3\text{O}_3\text{Na}^+$  474.1788; found 474.1786.

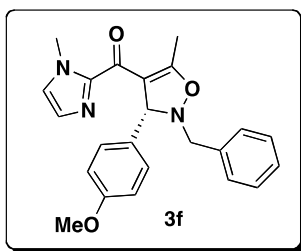
**Table 3, Entry 4:** The enantiomeric purity for **3d** was determined by HPLC (254 nm, 25 °C)  $t_R$  29.2 min (minor), 33.2 min (major) [Chiralpak AD-3 (from Diacel Chemical Ltd.) hexane/ *i*-PrOH, 90:10, 1mL/ min] as 70% ee for the cycloadduct.



**(2-Benzyl-3-phenyl-5-(thiophen-3-yl)-2,3-dihydroisoxazol-4-yl)(1-methyl-1H-imidazol-2-yl)methanone (3e):**

Oil;  $[\alpha]_D^{25} = -48.5$  ( $c$  1.0,  $\text{CHCl}_3$ );  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  3.77 (s, 3H), 4.28 (d,  $J = 13.0$  Hz, 1H), 4.51 (d,  $J = 13.0$  Hz, 1 H), 6.55 (s, 1H), 6.85 (s, 1H), 7.02 (s, 1H), 7.14 (m, 5H), 7.31 (m, 5 H), 7.48 (m, 2H), 7.54 (m, 1H);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  35.9, 58.5, 62.4, 63.5, 74.7, 74.8, 105.7, 125.2, 125.9, 127.4, 127.6, 127.7, 127.9, 128.4, 128.5, 128.6, 130.0, 131.6, 133.4, 136.3, 179.6, 190.6; IR (KBr) 2922, 1635, 1558, 1455, 1399, 1284, 847, 737, 697  $\text{cm}^{-1}$ ; HRMS calcd. for  $\text{C}_{25}\text{H}_{21}\text{N}_3\text{O}_2\text{SNa}^+$  450.1247; found 450.1220.

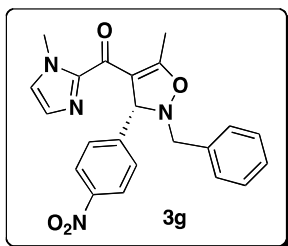
**Table 3, Entry 5:** The enantiomeric purity for **3e** was determined by HPLC (254 nm, 25 °C)  $t_R$  20.5 min (minor), 29.0 min (major) [Chiralpak AD-3 (from Diacel Chemical Ltd.) hexane/ *i*-PrOH, 90:10, 1mL/ min] as 72% ee for the cycloadduct.



**(2-Benzyl-3-(4-methoxyphenyl)-5-methyl-2,3-dihydroisoxazol-4-yl)(1-methyl-1H-imidazol-2-yl)methanone (3f):**

Foamy solid;  $[\alpha]_D^{25} = -158.4$  ( $c$  1.0,  $\text{CHCl}_3$ );  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  2.33 (s, 3H), 3.70 (s, 3H), 3.81 (s, 3H), 4.15 (d,  $J = 13.0$  Hz, 1H), 4.36 (d,  $J = 13.0$  Hz, 1 H), 6.14 (s, 1H), 6.70 (td,  $J = 8.8, 2.9$  Hz, 2H), 6.84 (s, 1H), 7.01 (d,  $J = 1.0$  Hz, 1H), 7.04 (td,  $J = 8.8, 2.9$  Hz, 2H), 7.30 (m, 3H), 7.40 (m, 2H);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  13.8, 35.9, 55.4, 63.8, 73.3, 113.3, 113.8, 125.8, 127.8, 128.3, 128.5, 129.0, 129.7, 134.6, 136.3, 144.0, 159.0, 166.7, 180.4; IR (KBr) 3061, 2924, 1640, 1590, 1407, 1285, 1226, 879, 737, 700  $\text{cm}^{-1}$ ; HRMS calcd. for  $\text{C}_{23}\text{H}_{23}\text{N}_3\text{O}_2\text{Na}^+$  412.1632; found 412.1624.

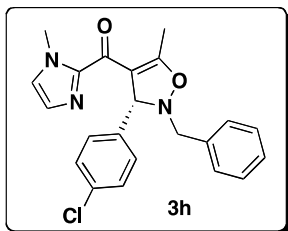
**Table 4, Entry 2:** The enantiomeric purity for **3f** was determined by HPLC (254 nm, 25 °C)  $t_R$  18.2 min (minor), 20.1 min (major) [Chiralpak AD-3 (from Diacel Chemical Ltd.) hexane/ *i*-PrOH, 95:05, 1mL/ min] as 73% ee for the cycloadduct.



**(2-Benzyl-5-methyl-3-(4-nitrophenyl)-2,3-dihydroisoxazol-4-yl)(1-methyl-1H-imidazol-2-yl)methanone (**3g**):**

Foamy solid;  $[\alpha]_D^{25} = -94.9$  (*c* 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  2.39 (d, *J* = 1 Hz, 3H), 3.86 (s, 3H), 4.15 (d, *J* = 13.0 Hz, 1H), 4.42 (d, *J* = 13 Hz, 1H), 6.35 (s, 1H), 6.98 (d, *J* = 1.0 Hz, 1H), 6.99 (d, *J* = 1.0 Hz, 1H), 7.31 (m, 7H), 7.99 (dt, *J* = 8.9, 2.0 Hz, 2 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  13.9, 36.3, 64.0, 72.8, 112.1, 123.6, 124.0, 126.5, 128.3, 128.5, 128.8, 129.8, 135.4, 143.5, 147.3, 150.1, 167.9, 179.4; IR (KBr) 3029, 2926, 1642, 1582, 1521, 1409, 1347, 1265, 1220, 881, 738, 702 cm<sup>-1</sup>; HRMS calcd. for C<sub>22</sub>H<sub>20</sub>N<sub>4</sub>O<sub>4</sub>Na<sup>+</sup> 427.1377; found 427.1383.

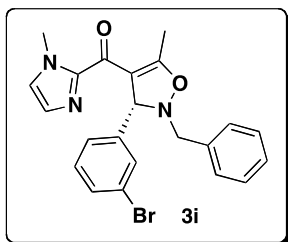
**Table 4, Entry 3:** The enantiomeric purity for **3g** was determined by HPLC (254 nm, 25 °C)  $t_R$  24.7 min (major), 38.5 min (minor) [Chiralpak AD-3 (from Diacel Chemical Ltd.) hexane/ *i*-PrOH, 95:05, 1mL/ min] as 51% ee for the cycloadduct.



**(2-Benzyl-3-(4-chlorophenyl)-5-methyl-2,3-dihydroisoxazol-4-yl)(1-methyl-1H-imidazol-2-yl)methanone (**3h**):**

Foamy solid;  $[\alpha]_D^{25} = -6.7$  (*c* 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  2.39 (s, 3H), 3.87 (s, 3H), 4.19 (d, *J* = 13.0 Hz, 1H), 4.43 (d, *J* = 13.0 Hz, 1H), 6.24 (s, 1H), 6.90 (s, 1H), 7.05 (s, 1H), 7.09-7.10 (m, 2H), 7.15-7.17 (d, 2H), 7.35 (m, 3H), 7.41-7.43 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  13.8, 36.1, 63.9, 73.1, 112.8, 126.2, 128.1, 128.4, 128.5, 128.7, 129.3, 129.8, 133.2, 135.9, 141.1, 143.8, 167.2, 179.2; IR (KBr) 2925, 1642, 1581, 1410, 1372, 1265, 1223, 1089, 1015, 881, 738, 701, 663 cm<sup>-1</sup>; HRMS calcd. for C<sub>22</sub>H<sub>20</sub>ClN<sub>3</sub>O<sub>2</sub>Na<sup>+</sup> 416.1121; found 416.1136.

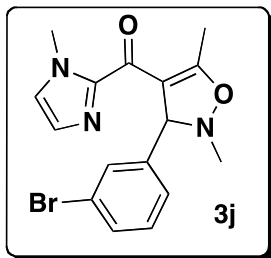
**Table 4, Entry 4:** The enantiomeric purity for **3h** was determined by HPLC (254 nm, 25 °C)  $t_R$  14.6 min (minor), 15.6 min (major) [Chiralpak AD-3 (from Diacel Chemical Ltd.) hexane/ *i*-PrOH, 95:05, 1mL/ min] as 56% ee for the cycloadduct.



**(2-Benzyl-3-(3-bromophenyl)-5-methyl-2,3-dihydroisoxazol-4-yl)(1-methyl-1H-imidazol-2-yl)methanone (**3i**):**

Foamy solid;  $[\alpha]_D^{25} = -78.4$  (*c* 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  2.38 (s, 3H), 3.86 (s, 3H), 4.16 (d, *J* = 13.0 Hz, 1H), 4.40 (d, *J* = 13.0 Hz, 1H), 6.23 (d, *J* = 1.0 Hz, 1H), 6.89 (d, *J* = 1.0 Hz, 1H), 7.04 (m, 3H), 7.34 (m, 7H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  13.8, 36.0, 63.9, 73.1, 112.5, 122.5, 126.1, 126.5, 128.0, 128.4, 128.6, 129.7, 129.9, 130.6, 130.9, 135.8, 143.8, 144.9, 167.5, 179.9; IR (KBr) 3013, 1641, 1579, 1473, 1409, 1287, 1217, 1071, 879, 757, 700, 666 cm<sup>-1</sup>; HRMS calcd. for C<sub>22</sub>H<sub>20</sub>BrN<sub>3</sub>O<sub>2</sub>Na<sup>+</sup> 460.0631; found 460.0628.

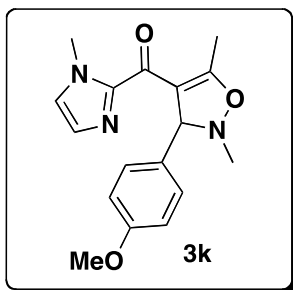
**Table 4, Entry 5:** The enantiomeric purity for **3i** was determined by HPLC (254 nm, 25 °C)  $t_R$  7.5 min (major), 11.2 min (minor) [Chiralpak AD-3 (from Diacel Chemical Ltd.) hexane/ *i*-PrOH, 90:10, 1mL/ min] as 67% ee for the cycloadduct.



**(3-(4-Bromophenyl)-2,5-dimethyl-2,3-dihydroisoxazol-4-yl)(1-methyl-1H-imidazol-2-yl)methanone (**3j**):**

Foamy solid;  $[\alpha]_D^{25} = -76.9$  (*c* 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  2.37 (s, 3H), 2.97 (s, 3H), 3.82 (s, 3H), 5.95 (s, 1H), 6.86 (s, 1H), 7.02 (s, 1H), 7.06 (s, 1H), 7.16 (dt, *J* = 7.8, 1.2 Hz, 1H), 7.27 (dt, *J* = 7.9, 1.2 Hz, 1H), 7.37 (m, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  13.9, 36.1, 47.7, 76.1, 112.4, 122.6, 126.2, 126.5, 128.3, 130.1, 130.8, 130.9, 143.8, 144.9, 167.2, 179.8; IR (KBr) 2961, 1641, 1581, 1409, 1372, 1409, 1287, 1226, 1071, 880, 758 cm<sup>-1</sup>; HRMS calcd. for C<sub>16</sub>H<sub>16</sub>BrN<sub>3</sub>O<sub>2</sub>Na<sup>+</sup> 384.0318; found 384.0307.

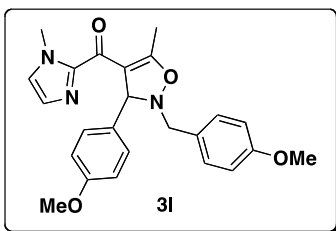
**Table 4, Entry 6:** The enantiomeric purity for **3j** was determined by HPLC (254 nm, 25 °C)  $t_R$  6.9 min (minor), 8.7 min (major) [Chiralpak AD-3 (from Diacel Chemical Ltd.) hexane/ *i*-PrOH, 90:10, 1mL/ min] as 58% ee for the cycloadduct.



**(3-(4-Methoxyphenyl)-2,5-dimethyl-2,3-dihydroisoxazol-4-yl)(1-methyl-1H-imidazol-2-yl)methanone (3k):**

Foamy solid;  $[\alpha]_D^{25} = -68.9$  ( $c$  1.0,  $\text{CHCl}_3$ );  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  2.35 (s, 3H), 2.96 (s, 3H), 3.71 (s, 3H), 3.79 (s, 3H), 5.87 (s, 1H), 6.73 (dt,  $J = 8.6, 2.9$  Hz, 2H), 6.83 (s, 1H), 7.02 (s, 1H), 7.15 (dt,  $J = 8.7, 2.8$  Hz, 2H);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  13.8, 35.9, 47.5, 55.4, 76.3, 113.2, 113.9, 125.8, 128.2, 128.9, 134.5, 144.0, 159.2, 166.6, 180.4; IR (KBr) 2917, 2848, 1652, 1558, 1540, 1521, 1506, 1472, 1456, 1247  $\text{cm}^{-1}$ ; HRMS calcd. for  $\text{C}_{17}\text{H}_{19}\text{N}_3\text{O}_3\text{Na}^+$  336.1319; found 336.1299.

**Table 4, Entry 7:** The enantiomeric purity for **3k** was determined by HPLC (254 nm, 25 °C)  $t_R$  10.6 min (minor), 16.3 min (major) [Chiralpak AD-3 (from Diacel Chemical Ltd.) hexane/*i*-PrOH, 90:10, 1mL/ min] as 74% ee for the cycloadduct.



**(2-(4-Methoxybenzyl)-3-(4-methoxyphenyl)-5-methyl-2,3-dihydroisoxazol-4-yl)(1-methyl-1H-imidazol-2-yl)methanone (3l):**

Foamy solid;  $[\alpha]_D^{25} = -157.9$  ( $c$  1.0,  $\text{CHCl}_3$ );  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  2.38 (s, 3H), 3.73 (s, 3H), 3.82 (s, 3H), 3.84 (s, 3H), 4.13 (d,  $J = 13.0$  Hz, 1H), 4.34 (d,  $J = 13.0$  Hz, 1H), 6.18 (s, 1H), 6.73 (dt,  $J = 8.8, 2.0$  Hz, 2H), 6.87 (s, 1H), 6.89 (dt,  $J = 8.7, 2.9$  Hz, 2H), 7.03 (s, 1H), 7.07 (dt,  $J = 10.2, 2.9$  Hz, 2H), 7.36 (dt,  $J = 10.2, 2.8$  Hz, 2H);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  13.8, 35.9, 55.4, 55.5, 63.2, 73.0, 113.2, 113.8, 114.0, 125.9, 128.3, 128.4, 129.0, 131.1, 134.7, 144.0, 159.0, 159.4, 166.8, 180.4; IR (KBr) 3001, 2956, 2836, 1641, 1584, 1512, 1462, 1408, 1247, 1175, 1033, 881, 828, 665  $\text{cm}^{-1}$ ; HRMS:  $m/z$  calcd. for  $\text{C}_{24}\text{H}_{25}\text{N}_3\text{O}_4\text{Na}^+$  442.1737; found 442.1744.

**Table 4, Entry 8:** The enantiomeric purity for **3l** was determined by HPLC (254 nm, 25 °C)  $t_R$  19.0 min (minor), 24.6 min (major) [Chiralpak AD-3 (from Diacel Chemical Ltd.) hexane/ *i*-PrOH, 90:10, 1mL/ min] as 76% ee for the cycloadduct.

**Assignment of Absolute Stereochemistry:**

The absolute stereochemistry for cycloadduct **3k** has been assigned as (*R*) based on the crystal structure for cycloadduct **3k**.

## Reference:

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- (1) Present address: Department of Medicinal Chemistry, University of Kansas, Lawrence, Kansas 66047, USA
- (2) (a) M. P. Sibi, Z. Ma, and C. P. Jasperse, *J. Am. Chem. Soc.*, 2005, **127**, 5764. (b) K. S. Chan, M. L. Yeung, W.-K. Chan, R.-J. Wang, and T. C. W. Mak, *J. Org. Chem.*, 1995, **60**, 1741. (c) M. P. Sibi, Z. Ma, and C. P. Jasperse, *J. Am. Chem. Soc.*, 2004, **126**, 718. (d) Ref. 1a
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- (4) M. C. Myers, A. R. Bharadwaj, B. C. Milgram, and K. A. Scheidt, *J. Am. Chem. Soc.*, 2005, **127**, 14675.
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