SUPPORTING INFORMATION

A New Class of Modular Chiral Ligands with Fluxional Groups

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General Experimental. Methylene chloride and THF were dried using dry alumina on a Solvatek solvent purification system prior to use. Flash chromatography was performed using EM Science silica gel 60 (230-400 mesh). Melting points were determined using the Fisher-Johns melting point apparatus. All glassware was oven dried, assembled hot, and cooled under a stream of dry nitrogen before use. Reactions with air sensitive materials were carried out by standard syringe techniques.

¹H NMR were recorded on a Varian Unity/Inova-500 NB (500 MHz), a Varian Unity/Inova-400 NB (400 MHz), or a Varian Mercury-300 (300 MHz). Chemical shifts are reported in parts per million (ppm) down field from TMS, using residual CDCl₃ (7.27 ppm) as an internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublets of doublets, m = multiplet, b = broad), coupling constant(s) and integration. ¹³C NMR were recorded on a Varian Unity/Inova-500 NB (125 MHz), a Varian Unity/Inova-400 (100 MHz), or a Varian Mercury-300 (75 MHz) spectrometers using broad band proton decoupling. Chemical shifts are reported in parts per million (ppm) down field from TMS, using the middle resonance of CDCl₃ (77.0 ppm) as an internal standard. HPLC analyses were carried out on a Waters 515 HPLC pump and a 2487 dual λ absorbance detector connected to a PC with Millennium³² workstation. Optical rotations were recorded on a JASCO-DIP-370 instrument. High-resolution mass spectra (FAB-HRMS) [EI+] were obtained at the Mass spectrometry Laboratory, Ohio State University, Columbus, OH.

Experimental Procedures.

Dienophiles:

The dienophiles **14**, **17-20** were prepared using literature procedures.¹

Ligand Synthesis

Preparation of (*S*)-dimethyl-prolidin-2-yl-methanol²

L-Proline methyl ester hydrochloride (5.8 g, 35 mmol) was suspended in CH_2Cl_2 (40 mL). After the addition of Et_3N (11 mL, 84 mmol), a large amount of precipitates was produced in 5 min, which was filtered off. Benzyl bromide (5.0 g, 42 mmol) was mixed with the filtrate and stirred for 4h at room temperature. The reaction mixture was diluted with EtOAc and washed with water and brine, dried over Na_2SO_4 . After concentrating in vacuum, the residue was purified by flash chromatography to give N-benzyl L-proline methyl ester (6.14 g) in 80% yield. $[\alpha]_D^{23} = -65.3$ (c 3.6, CH_2Cl_2); ^1H NMR (CDCl_3 , 500 MHz) δ 7.40-7.15 (m, 5H), 3.88 (d, 1H, $J=12.5$ Hz), 3.63 (s, 3H), 3.56 (d, 1H, $J=12.5$ Hz), 3.24 (dd, 1H, $J=6.0$ Hz), 3.08-3.0 (m, 1H), 2.38 (dd, 1H, $J=17.0$ Hz, 9 Hz), 2.17-2.06 (m, 1H), 2.0-1.83 (m, 2H), 1.81-1.71 (m, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 174.8, 138.5, 129.5 (2xC), 128.4 (2xC), 127.3, 65.5, 59.0, 53.5, 51.9, 29.6, 23.2; IR (film, cm^{-1}): 2963, 2802, 1733, 1466, 1197, 1170, 745, 702; HRMS: calcd for $\text{C}_{13}\text{H}_{17}\text{NO}_2\text{Na}^+$ 242.1151, found 242.1150.

MeMgCl (36.5 mL, 110 mmol, 3.0M in THF) was slowly injected into a solution of N-benzyl L-proline methyl ester (6.0 g, 27.4 mmol) in dry THF (80 mL) at 0 °C, then stirred for 3.5 h at that

temperature. The reaction mixture was quenched with saturated NH_4Cl and extracted with EtOAc. The combined organic phase was washed with water and brine, dried over Na_2SO_4 . After removing the solvent under reduced pressure, the residue was purified by flash chromatography to afford 2-(1-benzyl-pyrrolidin-2-yl)-propan-2-ol (5.97 g) as a colorless oil in 95% yield. $[\alpha]_{\text{D}}^{23} = -40.2$ (*c* 2.45, CH_2Cl_2); ^1H NMR (CDCl_3 , 400 MHz) δ 7.40-7.10 (m, 5H), 4.13 (d, 1H, $J=13.6$ Hz), 3.58 (d, 1H, $J=14.0$ Hz), 2.89 (m, 1H), 2.74 (dd, 1H, $J=8.8$ Hz, 5.2 Hz), 2.63 (br, 1H), 2.41 (dt, 1H, $J=6.8$ Hz and 7.2 Hz), 1.95-1.83 (m, 1H), 1.83-1.63 (m, 3H), 1.24 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 140.8, 128.5 (2xC), 128.3 (2xC), 127.0, 73.1, 72.9, 63.4, 55.6, 28.8, 28.0, 25.4, 25.4; IR (film, cm^{-1}): 3447, 2968, 2791, 1451, 1374, 1119, 941, 732, 698; HRMS calcd for $\text{C}_{14}\text{H}_{21}\text{NONa}^+$ 242.1515, found 242.1516.

The 2-(1-benzyl-pyrrolidin-2-yl)-propan-2-ol (5.85 g, 27.4 mmol) was stirred in the presence of 20% Pd/C (1.0 g) and acetic acid (3mL) in MeOH (200 mL) under H_2 (balloon) for 24h at room temperature. The mix was then filtered through a pad of celite using MeOH as rinse. The solvent was evaporated and the residue was dissolved in 2N NaOH (100mL) and Et_2O (100mL). After extraction of the aqueous phase with Et_2O , the combined organic layer was dried over Na_2SO_4 , and evaporated. The residue was purified by flash chromatography to give dimethyl-pyrrolidin-2-yl-methanol (1.75 g) as an orange solid in 50% yield. $[\alpha]_{\text{D}}^{23} = -16.6$ (*c* 0.57, CH_2Cl_2); ^1H NMR (CDCl_3 , 400 MHz) δ 3.0-2.8 (m, 3H), 1.80-1.50 (m, 4H), 1.12 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 59.2, 55.6, 35.8, 17.5, 15.3, 14.9, 13.9; IR (film, cm^{-1}): 3254, 2972, 2872, 1548, 1382, 1164, 953; HRMS: calcd for $\text{C}_7\text{H}_{16}\text{NO}^+$ $[\text{M}+\text{H}]^+$, 130.1226, found 130.1222.

Preparation of Bromomethyl mesityloxide 4³

Trimethylsilyl enol ether of mesityloxide was prepared using the procedure described in the literature^{3a} in 75% yield as a colorless oil. ¹H NMR (CDCl₃, 300 MHz) δ 5.58 (s, 1H), 4.26 (s, 1H), 4.16 (s, 1H), 1.90 (s, 3H), 1.76 (s, 3H), 0.22 (s, 9H).

The enol ether (8.0 g, 47mmol) was dissolved in CCl₄ (15 mL) and cooled to -20 °C. A solution of bromine (2.4 mL, 47 mmol) in CCl₄ (10 mL) was slowly added dropwise into the above solution. After addition, the reaction mix was warmed to 0 °C, then the solvent was removed under reduced pressure.^{3b} The residue was purified by flash chromatography on silica gel (1% ethyl ether in pentane) to give **4** (6.4 g) in 76% yield. ^{3c} ¹H NMR (CDCl₃, 400 MHz) δ 6.26 (s, 1H), 3.85 (s, 2H), 2.19 (s, 3H), 1.95 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 179.9, 149.2, 109.2, 24.5, 16.8, 9.9.

General procedure for syntheses of the ligands:

A solution of **4** (1 equiv.) in CH₂Cl₂ was added to the mixture of chiral amine (1 equiv.) and Et₃N (1 equiv.) in CH₃CN/CH₂Cl₂ (1:1, v/v). The reaction mixture was stirred for 2-3 h at room

temperature, diluted with EtOAc, then washed with H₂O and brine. After drying over Na₂SO₄, the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel to give the tertiary amine in 50%-75% yield.

The tertiary amine (1 equiv.) and hydrazine hydrate (1.5 equiv.) were dissolved in EtOH and refluxed for 2h to construct the dihydropyrazole ring. After cooling to rt, the solvent was removed under reduced pressure and the water in the residue was removed through azeotropic distillation with benzene. The crude product was directly used in the next step.

The crude product (1 equiv.) and K₂CO₃ (1 equiv.) were mixed in CH₃CN, followed by addition of halide (1 equiv.). The reaction mixture was stirred overnight at room temperature, then quenched with H₂O. After extraction with EtOAc, the combined organic layer was washed with H₂O and brine, then dried over Na₂SO₄. After removing the solvent under reduced pressure, the residue was purified by flash chromatography to afford the ligand.

1-[2-(1-Hydroxy-1-methyl-ethyl)-pyrrolidin-1-yl]-4-methyl-pent-3-en-2-one

Alkylation of dimethyl-pyrrolidin-2-yl-methanol was prepared using the general procedure described above in 51% yield. $[\alpha]_D^{23} = -9.5$ (c 0.99, CH₂Cl₂); ¹H NMR (CDCl₃, 300 MHz) δ 6.13 (s, 1H), 3.72 (d, 1H, J=13.2 Hz), 3.47 (d, 1H, J=13.2 Hz), 3.37-3.17 (m, 1H), 2.75-2.67 (m, 1H), 2.55-2.45 (m, 1H), 2.15 (s, 3H), 1.88 (s, 3H), 1.97-1.85 (m, 1H), 1.70-1.60 (m, 3H), 1.13 (s, 6H); ¹³C NMR (CDCl₃, 75 MHz) δ 201.3, 157.4, 121.4, 74.1, 73.1, 69.1, 56.6, 28.4, 28.1, 28.1, 25.7, 24.9, 21.2; IR (film, cm⁻¹): 3336, 2978, 1683, 1617, 1444, 1378, 1146, 961, 866.

Ligand 6

Compound **6** was prepared using the general procedure described above in 55% yield for 2 steps. $[\alpha]_D^{23} = +5.7$ (c 1.04, CH_2Cl_2); ^1H NMR (CDCl_3 , 500 MHz) δ 7.50-7.17 (m, 5H), 4.05 (d, 1H, J=14.5 Hz), 3.45 (d, 1H, J=13.5 Hz), 2.93-2.87 (m, 1H), 2.72 (d, 1H, J=16.0 Hz), 2.70-2.55 (m, 2H), 2.51 (d, 1H, J=16.0 Hz), 1.90-1.80 (m, 1H), 1.75-1.65 (m, 3H), 1.23 (s, 3H), 1.18 (s, 3H), 1.17 (s, 3H), 1.11 (s, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 152.6, 140.3, 128.6 (2xC), 128.4 (2xC), 127.0, 73.5, 72.6, 66.3, 58.6, 55.0, 52.2, 49.1, 28.9, 28.0, 25.3, 25.1, 24.5, 23.3; IR (film, cm^{-1}): 3447, 2968, 1455, 1366, 1127, 942, 733; HRMS: calcd for $\text{C}_{20}\text{H}_{32}\text{N}_3\text{O}^+$ $[\text{M}+\text{H}]^+$, 330.2540, found 330.2543.

1-[2-(1-Hydroxy-1-diphenyl-methyl)-pyrrolidin-1-yl]-4-methyl-pent-3-en-2-one

Diphenyl-pyrrolidin-2-yl-methanol was alkylated using the general procedure described above in 52% yield. $[\alpha]_D^{23} = +48.6$ (c 0.73, CH_2Cl_2); ^1H NMR (CDCl_3 , 500 MHz) δ 7.63-7.47 (m, 4H), 7.35-7.20 (m, 4H), 7.20-7.05 (m, 2H), 5.60 (s, 1H), 4.17-4.07 (m, 1H), 3.23-3.17 (m, 1H), 2.91 (d, 1H, J=17.0 Hz), 2.81(d, 1H, J=17.0 Hz), 2.70-2.55 (m, 1H), 2.09 (s, 3H), 2.03-1.87 (m, 1H), 1.82 (s, 3H), 1.80-1.67 (m, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 198.9, 156.0, 148.1, 146.5,

128.4 (2XC), 128.2 (2XC), 126.5, 126.4, 125.8 (4XC), 121.4, 77.9, 69.8, 65.0, 56.3, 29.8, 27.9, 24.8, 21.0; HRMS calcd for $C_{23}H_{27}NO_2Na^+$ 372.1934, found 372.1933.

Ligand 7

After condensation with hydrazine hydrate, the crude product (1.54 mmol) was dissolved in CH_3CN (3 mL) and CH_2Cl_2 (2 mL), then Et_3N (0.21 mL, 1 equiv.) was added, followed by addition of EtI (0.12 mL, 1 equiv.). The mixture was refluxed 2 h, then cooled to room temperature. After removing the solvent, the residue was purified by flash chromatography to yield **7** (158 mg) in 26% yield for 2 steps as a pale yellow solid. $[\alpha]_D^{23} = +80.0$ (c 0.85, CH_2Cl_2); 1H NMR ($CDCl_3$, 400 MHz) δ 7.58 (d, 2H, $J=8.4$ Hz), 7.52 (d, 2H, $J=8.0$ Hz), 7.35-7.17 (m, 4H), 7.17-7.0 (m, 2H), 4.69 (m, 1H), 3.93-3.85 (m, 1H), 3.07-2.97 (m, 1H), 2.96 (d, 1H, $J=14.0$ Hz), 2.80-2.63 (m, 2H), 2.55 (d, 1H, $J=13.2$ Hz), 2.53-2.45 (m, 1H), 2.42 (d, 1H, $J=16.0$ Hz), 2.02 (d, 1H, $J=16.0$ Hz), 2.0-1.87 (m, 1H), 1.77-1.60 (m, 3H), 1.22 (t, 3H, $J=7.2$ Hz), 1.10 (s, 3H), 1.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.2, 147.9, 146.4, 128.31 (2xC), 128.26 (2xC), 126.6, 126.5, 125.8 (4xC), 77.98, 71.2, 65.7, 56.1, 55.8, 48.5, 41.9, 29.9, 24.6, 24.1, 22.8, 15.3; IR (film, cm^{-1}): 3327, 2968, 1447, 1378, 1146, 1034, 749, 702; HRMS calcd for $C_{25}H_{33}N_3O[Na]^+$ 414.2516, found 414.2531.

Ligand 8

Ligand **8** was prepared using the general procedure described above as a pale-yellow solid in 63% yield for 2 steps. $[\alpha]_D^{23} = +73.9$ (*c* 2.04, CH_2Cl_2); ^1H NMR (CDCl_3 , 500 MHz) δ 7.63-7.56 (m, 2H), 7.55-7.49 (m, 2H), 7.39-7.32 (m, 2H), 7.31-7.05 (m, 9H), 4.69 (s, 1H), 3.97 (d, 1H, *J*=14.0 Hz), 3.92 (d, 1H, *J*=14.0 Hz), 3.90-3.85 (m, 1H), 3.20-3.0 (m, 1H), 2.96 (d, 1H, *J*=13.2 Hz), 2.54 (d, 1H, *J*=13.2 Hz), 2.57-2.47 (m, 1H), 2.46 (d, 1H, *J*=16.0 Hz), 2.07 (d, 1H, *J*=16.0 Hz), 1.97-1.83 (m, 1H), 1.77-1.60 (m, 3H), 1.13 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 152.0, 148.0, 146.4, 140.2, 128.6 (2xC), 128.4 (2xC), 128.3 (2xC), 128.2 (2xC), 127.0, 126.6, 126.5, 125.8 (2xC), 125.8 (2xC), 78.0, 71.1, 66.0, 55.9, 55.7, 52.2, 48.6, 29.9, 24.6, 24.5, 23.2; IR (film, cm^{-1}): 3327, 2968, 1602, 1451, 1360, 1034, 733, 702; HRMS calcd for $\text{C}_{30}\text{H}_{35}\text{N}_3\text{O}$ 454.2853, found 454.2849.

Ligand 9

Ligand **9** was prepared using the general procedure described above as a yellow solid in 41% yield for 2 steps. $[\alpha]_D^{23} = +114.5$ (*c* 0.38, CH_2Cl_2); ^1H NMR (CDCl_3 , 500 MHz) δ 8.21 (d, 1H, *J*=8.0 Hz), 7.83 (d, 1H, *J*=8.0 Hz), 7.74 (d, 1H, *J*=8.5 Hz), 7.60 (d, 2H, *J*=7.5 Hz), 7.57-7.51 (m,

3H), 7.51-7.38 (m, 3H), 7.32-7.19 (m, 4H), 7.15 (t, 1H, J=7.5 Hz), 7.11 (t, 1H, J=7.5 Hz), 4.72 (s, 1H, OH), 4.46 (d, 1H, J=14.5 Hz), 4.43 (d, 1H, J=14.5 Hz), 3.97-3.83 (m, 1H), 3.17-3.03 (m, 1H), 2.97 (d, 1H, J=14.0 Hz), 2.65-2.50 (m, 2H), 2.48 (d, 1H, J=16.0 Hz), 2.09 (d, 1H, J=16.0 Hz), 2.0-1.85 (m, 1H), 1.77-1.60 (m, 3H), 1.20 (s, 3H), 1.19 (s, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 151.8, 148.0, 146.5, 135.3, 134.0, 132.3, 128.7, 128.3 (2xC), 128.2 (2xC), 127.8, 127.1, 126.6, 126.51, 125.8, 125.7 (4xC), 125.6 (2xC), 124.4, 77.9, 71.0, 66.4, 55.9, 55.7, 50.3, 48.9, 29.9, 24.6, 24.5, 23.1; IR (film, cm^{-1}): 3327, 2968, 1598, 1447, 1363, 1170, 1034, 783, 737, 706; HRMS: calcd for $\text{C}_{34}\text{H}_{37}\text{N}_3\text{ONa}^+$, 526.2829, found 526.2816.

Precursor for Ligand **10**

Alkylation of (1S,2S)-(+)-pseudoephedrine was carried out using the general procedure described above in 75% yield. $[\alpha]_{\text{D}}^{23} = +91.8$ (*c* 0.49, CH_2Cl_2); ^1H NMR (CDCl_3 , 500 MHz) δ 7.43-7.20 (m, 5H), 6.22 (q, 1H, J=1.5 Hz), 4.24 (d, 1H, J=9.5 Hz), 3.35 (d, 1H, J=16.5 Hz), 3.20 (d, 1H, J=16.5 Hz), 2.67-2.57 (m, 1H), 2.33 (s, 3H), 2.21 (s, 3H), 1.94 (s, 3H), 0.74 (d, 3H, J=6.5 Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 198.2, 157.7, 142.1, 128.4 (2xC), 127.9, 127.6 (2xC), 121.5, 75.3, 66.0, 64.3, 37.4, 28.1, 21.3, 8.3; IR (film, cm^{-1}): 3260, 2970, 1660, 1451, 1378, 1073, 756, 702; HRMS: calcd for $\text{C}_{16}\text{H}_{23}\text{NO}_2\text{Na}^+$ 284.1621, found 284.1620.

Ligand **10**

Ligand **10** was prepared using similar procedure as for **7** in 52% yield for 2 steps as a pale-yellow oil. $[\alpha]_D^{23} = +128.6$ (*c* 0.73, CH₂Cl₂); ¹H NMR (CDCl₃, 500 MHz) δ 7.40-7.20 (m, 5H), 5.17-4.85 (br, 1H), 4.62 (d, 1H, *J*=9.5 Hz), 3.34 (d, 1H, *J*=14.0 Hz), 3.24 (d, 1H, *J*=14.0 Hz), 2.83 (q, 2H, *J*= 7.5 Hz), 2.73-2.65 (m, 1H), 2.64 (d, 1H, *J*=16.0 Hz), 2.56 (d, 1H, *J*=16.0 Hz), 2.28 (s, 3H), 1.30 (t, 3H, *J*=7.0 Hz), 1.21 (s, 3H), 1.20 (s, 3H), 0.76 (d, 3H, *J*=7.0 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 150.7, 141.9, 128.4 (2xC), 127.9, 127.5 (2xC), 75.0, 66.1, 65.1, 53.8, 48.7, 41.9, 36.3, 23.9, 23.5, 15.3, 7.5; IR (film, cm⁻¹): 3368, 2968, 2856, 1451, 1324, 1150, 1038, 957, 756, 702; HRMS: calcd for C₁₈H₂₉N₃ONa⁺ 326.2203, found 326.2211.

Ligand 11

Ligand **11** was prepared using the general procedure described above as a white solid in 51% yield for 2 steps. $[\alpha]_D^{23} = +66.3$ (*c* 0.74, CH₂Cl₂); ¹H NMR (CDCl₃, 400 MHz) δ 7.55-7.07 (m, 10H), 5.15-4.70 (br, 1H), 4.27 (d, 1H, *J*=9.6 Hz), 4.08 (s, 2H), 3.34 (d, 1H, *J*=12.8 Hz), 3.24 (d, 1H, *J*=12.8 Hz), 2.80-2.55 (m, 3H), 2.28 (s, 3H), 1.25 (s, 6H), 0.75 (d, 3H, *J*=6.4 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ 150.6, 142.0, 140.2, 128.6 (2xC), 128.5 (4xC), 128.0, 127.6 (2xC), 127.0, 75.0, 66.4, 64.9, 53.7, 52.1, 48.8, 36.3, 24.3, 23.9, 7.5; IR (film, cm⁻¹): 3354, 2968, 2876, 1600, 1455, 1366, 1127, 1031, 938, 733, 698; HRMS: calcd for C₂₃H₃₁N₃ONa⁺ 388.2359, found 388.2368.

Ligand 12

Ligand **14** was prepared using the general procedure described above as a yellow oil in 42% yield for 2 steps. $[\alpha]_D^{23} = +56.2$ (c 0.49, CH_2Cl_2); ^1H NMR (CDCl_3 , 500 MHz) δ 8.26 (d, 1H, $J=8.0$ Hz), 7.85 (d, 1H, $J=8.5$ Hz), 7.77 (d, 1H, $J=8.5$ Hz), 7.61 (d, 1H, $J=7.0$ Hz), 7.55-7.40 (m, 3H), 7.40-7.20 (m, 5H), 5.15-4.83 (br, 1H), 4.56 (s, 2H), 4.28 (d, 1H, $J=10.0$ Hz), 3.34 (d, 1H, $J=13.5$ Hz), 3.25 (d, 1H, $J=13.5$ Hz), 2.80-2.65 (m, 2H), 2.63 (d, 1H, $J=16.0$ Hz), 2.29 (s, 3H), 1.30 (s, 3H), 1.28 (s, 3H), 0.76 (d, 3H, $J=6.5$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ 150.5, 142.0, 135.2, 134.1, 132.3, 128.8, 128.5 (2xC), 128.0, 127.9, 127.6 (2xC), 127.0, 125.9, 125.6 (2XC), 124.3, 75.0, 66.7, 64.8, 53.7, 50.4, 49.1, 36.4, 24.1, 23.8, 7.5; IR (film, cm^{-1}): 3364, 2968, 1598, 1455, 1328, 1127, 1038, 942, 779, 702; HRMS: calcd for $\text{C}_{27}\text{H}_{33}\text{N}_3\text{ONa}^+$ 438.2516, found 438.2507.

4-Methyl-1-[methyl-(1-phenyl-ethyl)-amino]-pent-3-en-2-one

Compound **4** (1.1 g, 6.2 mmol) was injected into the solution of (R)-(+)-N, β -dimethylbenzylamine (560 mg, 4.1 mmol) and K_2CO_3 (566 mg, 4.1 mmol) in DMF (7 mL) and stirred overnight at room temperature. The reaction mixture was diluted with EtOAc, then washed with water and brine, dried over Na_2SO_4 . After removing the solvent in vacuum, the

residue was purified by flash chromatography on silica gel to give the tertiary amine (481 mg) in 51% yield. $[\alpha]_D^{23} = +16.0$ (*c* 1.16, CH₂Cl₂); ¹H NMR (CDCl₃, 500 MHz) δ 7.43-7.17 (m, 5H), 6.30 (s, 1H), 3.75-3.65 (m, 1H), 3.19 (d, 1H, *J*=16.5 Hz), 3.01 (d, 1H, *J*=16.0 Hz), 2.25 (s, 3H), 2.16 (s, 3H), 1.90 (s, 3H), 1.38 (d, 3H, *J*=6.5 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ 200.3, 156.3, 143.8, 128.5 (2xC), 127.9 (2xC), 127.2, 121.7, 65.6, 63.6, 40.1, 28.1, 21.1, 19.0; HRMS: calcd for C₁₅H₂₂NO⁺ [M+H]⁺, 232.1696, found 232.1697.

Ligand 13

Ligand **13** was prepared using the general procedure described above in 51% yield for 2 steps. $[\alpha]_D^{23} = +28.4$ (*c* 0.82, CH₂Cl₂); ¹H NMR (CDCl₃, 500 MHz) δ 7.57-7.15 (m, 10H), 4.07 (s, 2H), 3.70-3.57 (m, 1H), 3.19 (d, 1H, *J*=13.5 Hz), 3.06 (d, 1H, *J*=14.0 Hz), 2.63 (d, 1H, *J*=16.0 Hz), 2.54 (d, 1H, *J*=16.0 Hz), 2.20 (s, 3H), 1.39 (d, 3H, *J*=7.0 Hz), 1.22 (s, 3H), 1.20 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 152.6, 144.0, 140.4, 128.6 (2xC), 128.4 (2xC), 128.3 (2xC), 127.9 (2xC), 127.0, 126.9, 66.0, 63.2, 54.3, 52.2, 49.2, 38.7, 24.1, 24.0, 18.3; HRMS: calcd for C₂₂H₂₉N₃Na⁺, 358.2254, found 358.2248.

General procedure for the asymmetric Diels-Alder reaction: A mixture of ligand (0.03 mmol) and Lewis acid (0.026 mmol) in dichloromethane (1.5 mL) was stirred at rt for 40min to give a clear solution. The solution of dienophile (0.2 mmol) in dichloromethane (1.0 mL) was added at room temperature, which was stirred for another 30 min. This was followed by the

addition of freshly distilled diene (10 equiv) at the temperature given in the tables. The progress of the reaction was monitored by TLC. After completion, the reaction was quenched with water (2 mL) and warmed to rt. The reaction mixture was diluted with EtOAc (30 mL) and washed with water and brine, dried over Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified by flash chromatography to give pure product and recover the ligand. The endo/exo ratio was determined by ¹HNMR spectrum. The enantiomeric purity was evaluated on the basis of HPLC.

Diels-Alder adducts of N-acryloyl-2-oxazolidinone **14 and cyclopentadiene **15** (Table 1)**

The reaction was performed using the general procedure. The *endo/exo* ratio was determined by integration of the olefinic protons of the *exo* diastereomer [δ 6.18 (m, 2H)]. HPLC analysis of **16** was carried out using a Chiralcel OD-H with hexanes/2-propanol (95:5) as eluant (0.6mL/min). The average retention times (*exo* diastereomers (2-*S*) t_R =42 min, (2-*R*) t_R =44 min; *endo* diastereomers (2-*S*) t_R = 46 min, (2-*R*) t_R = 52 min).^{1a, 4} Yields are based on isolated products, which had been purified by chromatography on silica gel. Absolute stereochemistry was assigned according to elution order of the isomers on HPLC. The major isomer is the (2*S*) isomer based on retention times.

Diels-Alder adducts of imides (17-20**) and cyclopentadiene **15** (Table 2)**

Cycloadduct **21.**

The racemic cycloadduct **21** was prepared in the presence of Mg(ClO₄)₂ (1 equiv) as Lewis acid, CH₂Cl₂/THF(1:1, v/v) as solvent at room temperature (yield, 79%).

The general procedure was used to generate the chiral cycloadduct **21**. The endo/exo ratio was measured by ¹HNMR (16.7/1). The HPLC analysis was performed on Chiralcel OD with

hexanes/2-propanol (96:4) as eluant (1mL/min), only the *exo* isomers was separated (*exo*_{minor} *t*_R= 20.6 min, *exo*_{major} *t*_R= 21.7 min, *endo* isomers *t*_R= 24.9 min).^{4a} The two *endo* isomers was separated with hexanes/ethylacetate/2-propanol (94:4:2) as eluant (1.1mL/min) (*exo* isomers *t*_R=14.6 min; *endo*_{major} *t*_R=15.6 min, *endo*_{minor} *t*_R=16.7 min). Enantiomeric excess was determined to be 90% for the major *endo*-2(S) enantiomer. Absolute configuration of the *endo* cycloadduct was assigned to be 2(S)(by comparing the reported retention time of 2(S)-isomer as well as from the sign of measured optical rotation).^{5a} Spectral data corresponded exactly to that previously reported in the literature.^{5b}

Cycloadduct 22.

The racemic cycloadduct **22** was prepared in the presence of Mg(ClO₄)₂ (1 equiv) as Lewis acid, CH₂Cl₂/THF(1:1, v/v) as solvent at room temperature (yield, 93%).

The general procedure was used to generate the chiral cycloadduct **22**. The *endo*/*exo* ratio was measured by ¹HNMR (5.8/1). HPLC analysis (Chiralcel OD, 96:4 hexanes/2-propanol, 1mL/min) *exo*_{minor} *t*_R=34.8 min, *exo*_{major} *t*_R=42.2 min, *endo*_{major} *t*_R=49.3 min, *endo*_{minor} *t*_R=62 min. $[\alpha]_D^{20} = -174.9$ (*c* 1.86, CH₂Cl₂); Lit. $[\alpha]_D^{20} = -113.0$ (*c* 1.1, CH₂Cl₂). ¹H NMR (CDCl₃, 500 MHz) δ 6.26 (dd, 1H, J=5.0 Hz, 3.0 Hz), 5.93 (dd, 1H, J=5.5 Hz, 2.5 Hz), 4.5-4.37(m, 2H), 4.26(m, 1H), 4.16(m, 1H), 4.10-3.90 (m, 2H), 3.42 (s, 1H), 3.09 (s, 1H), 2.13 (d, 1H, J=9.5 Hz), 1.75 (dd, 1H, J=9.0 Hz, 2.0 Hz).

Cycloadduct 23.

The racemic cycloadduct **23** was prepared in the presence of Mg(ClO₄)₂ (1equiv) as Lewis acid, CH₂Cl₂/THF(1:1, v/v) as solvent at room temperature (yield, 81%).

The general procedure was used to generate the chiral cycloadduct **23**. The *endo*/*exo* ratio was evaluated on the basis of the ¹HNMR spectrum (1.5/1). The enantiomeric purity was determined

by HPLC (Daicel Chiralpak AD, 95:5 hexanes/2-propanol, 1mL/min, *exo*_{minor} *t*_R=15.6 min, *exo*_{major} *t*_R=25.1 min, *endo*_{minor} *t*_R=17.8 min, *endo*_{major} *t*_R=39.4 min).⁶ Absolute configuration of the *endo* cycloadduct was assigned to be 2(*R*) by comparing the reported retention time of 2(*R*)-isomer. ¹H NMR (CDCl₃, 500 MHz) δ 7.37-7.10 (m, 5H), 6.53 (dd, 1H, *J*=5.4 Hz, 3.0 Hz), 5.93 (dd, 1H, *J*=5.7 Hz, 2.7 Hz), 4.50-4.30 (m, 2H), 4.20 (dd, 1H, *J*=5.4 Hz, 3.3Hz), 4.10-3.90 (m, 2H), 3.47 (m, 1H), 3.36 (dd, 1H, *J*=5.1 Hz, 1.5 Hz), 3.0 (m, 1H), 1.96 (d, 1H, *J*=8.7 Hz), 1.59 (dd, 1H, *J*=9.0, 1.5 Hz).

Cycloadduct 24.

The general procedure was used to generate the chiral cycloadduct **24**. The *endo*/*exo* ratio was evaluated on the basis of the ¹HNMR spectrum (1.3/1). The enantiomeric excess of *endo* cycloadduct **24** was calculated from the known optical rotation of the iodolactone derived from **24**. The cycloadduct **24** (mixture of *endo* and *exo*) was converted to iodolactone using a procedure in the literature.⁷ Yield of iodolactone is 66%. [α]_D²³ = +39.0 (*c* 3.48, CHCl₃), 96% ee (2*R*-isomer); Lit^{1a, 7} 94% ee [α]_D²³ = +38.1 (*c* 0.84, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 5.09 (d, 1H, *J*=4.8 Hz), 4.20-4.0 (m, 2H), 3.85 (d, 1H, *J*=2.0 Hz), 3.2-3.15 (m, 1H), 3.06 (d, 1H, *J*=3.6 Hz), 2.98 (br s, 1H), 2.79 (br s, 1H), 2.28 (d, 1H, *J*=12.0 Hz), 1.92 (d, 1H, *J*=12.0 Hz), 1.24 (t, 3H, *J*=6.8 Hz); ¹³CNMR (100MHz, CDCl₃) δ 177.5, 170.3, 88.6, 62.1, 50.7, 50.6, 46.4, 41.1, 35.2, 28.2, 14.4.

Diels-Alder adducts of acryloyl-N-oxazolidinone **14** and diene (**25-28**) (Table 3)

Cycloadduct **29**.

The racemic cycloadduct **29** was prepared in the presence of $\text{Mg}(\text{ClO}_4)_2$ (1equiv) as Lewis acid, $\text{CH}_2\text{Cl}_2/\text{THF}$ (1:1, v/v) as solvent at room temperature.

The general procedure was used to generate the chiral cycloadduct **29**. The endo/exo ratio was evaluated on the basis of the ^1H NMR spectrum (40/1). HPLC analysis (Chiralpak AD, 95:5 hexanes/2-propanol, 1mL/min) exo_{minor} t_R =16.6 min, exo_{major} t_R =18.4 min, $endo_{\text{major}}$ t_R =20.6 min, $endo_{\text{minor}}$ t_R =23.2 min. Absolute configuration of the *endo* cycloadduct was assigned to be 2(*R*) by comparing the reported retention time of 2(*R*)-isomer.^{4a} ^1H NMR (300 MHz, CDCl_3) δ 6.35 (t, 1H, J =6.9 Hz), 6.16 (t, 1H, J =6.6 Hz), 4.47-4.30 (m, 2H), 3.97 (t, 2H, J =8.4 Hz), 3.80-3.70 (m, 1H), 2.83 (br, s, 1H), 2.62 (t, 1H, J =3.3 Hz), 1.95-1.20 (m, 6H).

Cycloadduct **30**.

The racemic cycloadduct **30** was prepared in the presence of $\text{Mg}(\text{ClO}_4)_2$ (1equiv) as Lewis acid, $\text{CH}_2\text{Cl}_2/\text{THF}$ (1:1, v/v) as solvent at room temperature.

The general procedure was used to generate the chiral cycloadduct **30**. The enantiomeric excess was evaluated on Chiralcel OJ (97:3 hexanes/2-propanol, 1mL/min). The average retention time is (major enantiomer (*R*) t_R =51 min, minor enantiomer (*S*) t_R =47 min). Stereochemical assignment is based upon comparison of the optical rotation to the literature value. $[\alpha]_D^{23} = -34.6$ (c 0.8, CHCl_3), 89%ee. Lit.^{4a} 93% ee $[\alpha]_D^{23} = -36.9$ (c 1.96, CHCl_3). ^1H NMR (CDCl_3 , 500 MHz) δ 5.37 (br s, 1H), 4.38 (t, 2H, J =8.0 Hz), 3.98 (t, 2H, J =8.4 Hz), 3.73-3.57(m, 1H), 2.30-1.90 (m, 6H), 1.64 (s, 3H).

Cycloadduct 31.

The racemic cycloadduct **31** was prepared in the presence of $\text{Mg}(\text{ClO}_4)_2$ (1equiv) as Lewis acid, $\text{CH}_2\text{Cl}_2/\text{THF}(1:1, \text{v/v})$ as solvent at room temperature.

The general procedure was used to generate the chiral cycloadduct **31**. The enantiomeric excess was evaluated on Chiralpak AD (97:3 hexanes/2-prapanol, 0.5mL/min). The average retention time is (major enantiomer (*R*) $t_R=38.7$ min, minor enantiomer (*S*) $t_R=48$ min). Stereochemical assignment is based upon comparison of the reported retention time of *R*-isomer as well as from the sign of measured optical rotation. $[\alpha]_D^{23} = -53.4$ (c 1.25, CHCl_3), 90% ee. Lit.^{1b, 4a} 92% ee, $[\alpha]_D^{23} = -55.7$ (c 1.96, CHCl_3). ^1H NMR (CDCl_3 , 500 MHz) δ 4.41 (t, 2H, $J=7.8$ Hz), 4.02 (t, 2H, $J=8.4$ Hz), 3.77-3.60 (m, 1H), 2.33-1.87 (m, 6H), 1.62 (s, 6H). ^{13}C NMR (CDCl_3 , 125 MHz) δ 176.9, 153.4, 125.5, 123.9, 62.1, 43.0, 39.3, 33.6, 31.3, 26.4, 19.2, 19.0.

Cycloadduct 32.

The racemic cycloadduct **32** was prepared in the presence of $\text{Mg}(\text{ClO}_4)_2$ (1equiv) as Lewis acid, $\text{CH}_2\text{Cl}_2/\text{THF}(1:1, \text{v/v})$ as solvent at room temperature.

The general procedure was used to generate the chiral cycloadduct **32**. The title compound was obtained as an inseparable mixture of diastereomers and regioisomers. The ratio of the diastereomers (6.9:2.6:1.0) was determined by integration of the protons of the 2-methyl groups [major *endo* δ 1.02 (d, 3H, $J=7.0$ Hz), isomer 2 δ 1.12 (d, 3H, $J=7.0$ Hz), isomer 3 δ 0.91 (d, 3H, $J=7.0$ Hz)].^{4a} The enantiomeric excess was evaluated on Chiralcel OD (96:4 hexanes/2-prapanol, 0.5mL/min, major *endo* $t_R=53.5$ min, minor *endo* $t_R=59.1$ min, others isomers 41.9 min, 46 min, 65.8 min). The absolute configuration has not been determined. The following is the ^1H NMR spectra of the major isomer. ^1H NMR (CDCl_3 , 500MHz): 5.39 (d, 1H, $J=2.0$ Hz), 4.40 (t, 2H, $J=8.0$ Hz), 4.02 (t, 2H, $J=8.0$ Hz), 3.76-3.60 (m, 1H), 2.34-2.22 (m, 3H), 2.08-1.98 (m, 1H),

1.90-1.77 (m, 1H), 1.65 (s, 3H), 1.02 (d, 3H, J=7.0 Hz); ^{13}C (CDCl₃, 125MHz): 176.8, 153.4, 138.0, 120.2, 62.1, 43.0, 39.1, 35.9, 34.2, 28.1, 21.1, 19.6. HRMS: calcd for C₁₂H₁₇NO₃Na⁺, 246.1101, found 246.1117.

References:

1. a) Evans, D. A.; Miller, S. J.; Lectka, T.; Matt, P. von *J. Am. Chem. Soc.* **1999**, *121*, 7559-7573. b) Evans, D. A.; Barnes, D. M.; Johnson, J. S.; Lectka, T.; Matt, P. von; Miller, S. J.; Murry, J. A.; Norcross, R. D.; Shaughnessy, E. A.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 7582-7594.
2. a) Bhaskar Kanth, J. V.; Periasamy M. *Tetrahedron*, **1993**, *49*, 5127-5132. b) Trost, B. M.; Yeh, Vince S. C.; Ito, H.; Bremeyer, N. *Org. Lett.* **2002**, *4*, 2621-2623.
3. a) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead H. D. *J. Org. Chem.* **1969**, *34*, 2324-2336. b) Blanco, L.; Amice, P.; Conia, J. M. *Synthesis* **1976**, 194-196. c) Calo, V.; Lopez, L.; Pesce, G.; Todesco, P. E. *Tetrahedron* **1973**, *29*, 1625-1628.
4. a) Owens, T. D.; Souers, A. J.; Ellman, J. A. *J. Org. Chem.* **2003**, *68*, 3-10. b) Desimoni, G.; Faita, G.; Guala, M.; Pratelli, C. *Tetrahedron* **2002**, *58*, 2929-2935.
5. a) Ghosh, A. K.; Matsuda, H. *Org. Lett.* **1999**, *1*, 2157-2159. b) Sibi, M. P.; Venkatraman, L.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **2001**, *123*, 8444-8445.
6. a) Gothelf, K. V.; Jorgensen, K. A. *J. Org. Chem.* **1995**, *60*, 6847-6851. b) Kanemasa, S.; Oderaotoshi, Y.; Sakaguchi, S.; Yamamoto, H.; Tanaka, J.; Wada, E.; Curran, D. P. *J. Am. Chem. Soc.* **1998**, *120*, 3074-3088.
7. Ghosh, A. K.; Cho, H.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 3687-3691.