Enantioselective Addition of Vinylzinc Reagents to Aldehydes Catalyzed by Modular Ligands Derived from Amino Acids

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General Methods. NMR spectra were recorded on a 300 MHz instrument using CDCl₃ as the solvent and TMS as the internal standard. Mass spectra were recorded using either electrospray or fast atom bombardment ionization methods. Enantiomeric excess was measured by HPLC using a Daicel Chiralcel OD-H column (0.46 cm i.d. × 25 cm) and UV detection at 219 nm, or by ¹⁹F NMR spectroscopic analysis of the Mosher's ester derivative. Racemic standards for all allylic alcohols were synthesized and analyzed by HPLC or by ¹⁹F NMR analysis in order to confirm the peak assignments of the two enantiomers. The absolute configurations of allylic alcohols **6a-i** are inferred based upon the supposition that the reactions catalyzed by the optimized ligand **3d** gave the same sense of stereochemical induction for formation of these products as for formation of the allylic alcohol products **5a-f**. Optical rotations were recorded on a polarimeter at ambient temperature and 589 nm (c = g/100 mL). Melting points are uncorrected. Solvents were of reagent grade and used as received except for CH₂Cl₂, which was purified by passage through a column of activated alumina. Solvents were removed by rotary evaporation at water aspirator pressure followed by further drying at approximately 1 torr. Benzaldehyde, cyclohexanecarboxaldehyde, and all alkynes were distilled prior to use. 4-Chlorobenzaldehyde and 4-bromobenzaldehyde were recrystallized from EtOAc prior to use. 4-Methoxybenzaldehyde, 2-naphthaldehyde, and 1-naphthaldehyde were purified by column chromatography. All reactions were conducted under a nitrogen atmosphere unless otherwise noted. Anhydrous procedures were conducted using oven dried or flame dried glassware and standard syringe and cannula transfer techniques. Reactions were monitored using TLC. TLC plates were visualized using an ethanol solution of phosphomolybdic acid (PMA) staining solution, UV at 254 nm, or a ninhydrin staining solution.

Conditions for determining enantiomeric excess:

(*R,E*)-4,4-Dimethyl-1-phenylpent-2-en-1-ol (5a)¹

89% ee (*R*) by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (99:1) at 1.0 mL/min and detected at 219 nm), $t_R = 16.2$ min for (*R*) and $t_R = 24.4$ min for (*S*).

(*R,E*)-3-Cyclohexyl-1-phenylprop-2-en-1-ol (5b)¹

73% ee (*R*) by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (99:1) at 1.0 mL/min and detected at 219 nm), $t_R = 21.3$ min for (*R*) and $t_R = 30.6$ min for (*S*).

(*R,E*)-1,5-Diphenylpent-2-en-1-ol (5c)²

67% ee (*R*) by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (99:1) at 1.0 mL/min and detected at 219 nm), $t_R = 65.8$ min for (*R*) and $t_R = 80.4$ min for (*S*).

(*R,E*)-1-Phenylnon-2-en-1-ol (5d)¹

65% ee (*R*) by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (99:1) at 1.0 mL/min and detected at 219 nm), $t_R = 19.1$ min for (*R*) and $t_R = 28.2$ min for (*S*).

(*R,E*)-1-Phenylhept-2-en-1-ol (5e)¹

60% ee (*R*) by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (99:1) at 1.0 mL/min and detected at 219 nm), $t_R = 20.7$ min for (*R*) and $t_R = 29.7$ min for (*S*).

(*R,E*)-3-Cyclopropyl-1-phenylprop-2-en-1-ol (5f)³

52% ee (*R*) by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (99:1) at 1.0 mL/min and detected at 219 nm), $t_R = 29.5$ min for (*R*) and $t_R = 40.1$ min for (*S*).

(*R,E*)-(4-Chlorophenyl)-4,4-dimethylpent-2-en-1-ol (6a)⁴

91% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes at 1.0 mL/min and detected at 219 nm), $t_R = 53.6$ min for (*R*) and $t_R = 63.6$ min for (*S*).

(*R,E*)-4,4-Dimethyl-1-(naphthalene-2-yl)pent-2-en-1-ol (6b)⁴

97% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (99.5:0.5) at 1.0 mL/min and detected at 219 nm), $t_R = 82.0$ min for (*R*) and $t_R = 91.5$ min for (*S*).

(*R,E*)-(4-Bromophenyl)-4,4-dimethylpent-2-en-1-ol (6c)⁴

89% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (99.5:0.5) at 1.0 mL/min and detected at 219 nm), $t_R = 28.0$ min for (*R*) and $t_R = 31.3$ min for (*S*).

(*R,E*)-Methyl 4-(1-hydroxy-4,4-dimethylpent-2-enyl)benzoate (6d)⁴

86% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (95:5) at 1.0 mL/min and detected at 219 nm), $t_R = 21.3$ min for (*S*) and $t_R = 24.4$ min for (*R*).

(*R,E*)-1-(4-Methoxyphenyl)-4,4-dimethylpent-2-en-1-ol (6e)⁴

81% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (99:1) at 1.0 mL/min and detected at 219 nm), $t_R = 25.3$ min for (*R*) and $t_R = 35.7$ min for (*S*).

(*R,E*)-4,4-Dimethyl-1-(naphthalene-1-yl)pent-2-en-1-ol (6f)⁴

70% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (90:10) at 1.0 mL/min and detected at 219 nm), $t_R = 7.5$ min for (*S*) and $t_R = 9.6$ min for (*R*).

(*S*,1*E*,4*E*)-6,6-Dimethyl-1-phenylhepta-1,4-dien-3-ol (6g)⁴

67% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (95:5) at 1.0 mL/min and detected at 219 nm), $t_R = 14.2$ min for (*S*) and $t_R = 31.5$ min for (*R*).

(*S*,*E*)-6,6-Dimethyl-1-phenylhept-4-en-3-ol (6h)⁴

67% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (99.5:0.5) at 1.0 mL/min and detected at 219 nm), $t_R = 40.4$ min for (*S*) and $t_R = 88.8$ min for (*R*).

Table S1. Structure of Amides **2a-r**^a

amide	R ¹	R ² = side chain of amino acid	amide	R ¹	R ² = side chain of amino acid
2a	-(CH ₂) ₂ O(CH ₂) ₂ -	Ile	2m	Et	Chg
2b	-(CH ₂) ₅ -	Ile	2n	Et	Ala
2c	-(CH ₂) ₄ -	Ile	2o	Et	Nle
2d	Et	Ile	2p	Et	Dph
2e	Me	Ile	2q	Et	D-2-Nal
2f	-(CH ₂) ₄ -	Phe	2r	Et	Met
2g	Et	Phe			
2h	-(CH ₂) ₄ -	Val			
2i	Et	Val			
2j	Et	Tle			
2k	Et	Leu			
2l	Et	Cha			

^a Abbreviations: Tle = *tert*-leucine, Cha = cyclohexylalanine, Chg = cyclohexylglycine, Nle = norleucine, Dph = diphenylalanine, D-2-Nal = D-3-(2-naphthyl)alanine.

Experimental Details.

General procedure for the synthesis of amides 2d-g and 2j-r. The Boc-protected amino acid (1 equiv) was suspended or dissolved in dry DMF. To this solution was added DIEA (2 equiv) and HBTU (1.5 equiv). After stirring at rt for 1 h, the appropriate secondary amine (1.1 equiv) was added and the reaction was allowed to stir for 1 h. The reaction was quenched by the addition of 1 N HCl. The mixture was extracted with EtOAc and the organic phase was washed with 1 N HCl, brine and dried (MgSO_4). The solvent was removed and purification was performed by flash column chromatography.

Amide 2d. Amide **2d** was prepared as described above from Boc-Ile-OH (1.68 g, 7.0 mmol) and diethylamine (0.800 mL, 7.7 mmol). Purification (EtOAc:hexanes 1:3) gave a clear oil (1.70 g, 5.94 mmol, 78%). ^1H NMR (CDCl_3 , 300 MHz) δ 0.89 (t, $J = 7.4$ Hz, 3 H), 1.13 (t, $J = 7.1$ Hz, 3 H), 1.23 (t, $J = 7.1$ Hz, 3 H), 1.43 (s, 10 H), 3.17 (m, 1 H), 3.47 (m, 2 H), 3.62 (m, 1 H), 4.39 (dd, $J = 9.5, 7.5$ Hz, 1 H), 5.21 (d, $J = 9.5$ Hz, 1 H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 172.0, 156.0, 79.7, 54.7, 42.5, 40.7, 38.9, 28.7, 24.5, 16.1, 14.9, 13.3, 11.8; IR (neat) 3438, 3295, 2971, 2934, 2878, 1707, 1636, 1498, 1459, 1365, 1246, 1173, 1042, 1018, 758 cm^{-1} ; HRMS-ESI ($\text{M} + \text{H}^+$) calcd for $\text{C}_{15}\text{H}_{31}\text{N}_2\text{O}_3$: 287.2335, found: 287.2330; $[\alpha]_{\text{D}}^{25} = -3.51$ ($c = 5.52$, CHCl_3).

Amide 2e. Amide **2e** was prepared as described above from Boc-Ile-OH (0.101 g, 0.42 mmol) and dimethylamine (1 M in THF, 0.46 mL, 0.46 mmol). Purification (EtOAc:hexanes 2:5) gave a clear oil (0.826 g, 0.319 mmol, 76%). ^1H NMR (CDCl_3 , 300 MHz) δ 0.93 (m, 6 H), 1.07 (m, 1 H), 1.40 (s, 9 H), 1.51 (m, 1 H), 1.61-1.69 (m, 1 H), 2.95 (s, 3 H), 3.09 (s, 3 H), 4.46 (dd, $J = 9.3, 6.6$ Hz, 1 H), 5.27 (d, $J = 9.2$ Hz, 1 H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 172.8, 156.2, 79.7, 74.7, 38.5, 37.8, 35.9, 28.7, 24.3, 16.0, 11.7; IR (neat) 3432, 3299, 2966, 1701, 1650, 1503, 1397, 1366, 1250, 1172, 1044, 1019, 877, 754 cm^{-1} ; HRMS-FAB ($\text{M} + \text{Na}^+$) calcd for $\text{C}_{13}\text{H}_{36}\text{N}_2\text{O}_3\text{Na}$: 281.1841, found: 281.1851; $[\alpha]_{\text{D}}^{25} = +15.2$ ($c = 4.67$, CHCl_3).

Amide 2f. Amide **2f** was prepared as described above from Boc-Phe-OH (0.539 g, 2.0 mmol) and pyrrolidine (0.185 mL, 2.2 mmol). Purification (EtOAc:hexanes 2:3) gave a clear oil (0.511 g, 1.60

mmol, 80%). ¹H NMR (CDCl₃, 300 MHz) δ 1.43 (s, 9 H), 1.48-1.77 (m, 4 H), 2.56 (m, 1 H), 2.98 (m, 2 H), 3.27-3.46 (m, 3 H), 4.60 (dd, *J* = 14.8, 8.8 Hz, 1 H), 5.43 (d, *J* = 8.6 Hz, 1 H), 7.21-7.30 (m, 5 H); ¹³C NMR (CDCl₃, 75 MHz) δ 170.3, 155.5, 136.9, 129.8, 128.7, 127.2, 79.9, 53.9, 46.6, 46.6, 46.1, 40.6, 28.7, 26.1, 24.4; IR (neat) 3430, 3289, 2975, 2878, 1708, 1637, 1496, 1450, 1366, 1287, 1249, 1170, 1054, 1022, 869, 754, 702 cm⁻¹; HRMS-ESI (*M* + *H*⁺) calcd for C₁₈H₂₇N₂O₃: 319.2002, found: 319.2018; [α]_D²⁶ = +3.25 (*c* = 1.17, CHCl₃).

Amide 2g. Amide **2g** was prepared as described above from Boc-Phe-OH (0.525 g, 2.0 mmol) and diethylamine (0.230 mL, 2.2 mmol). Purification (EtOAc:hexanes 3:7) gave a clear oil (0.487 g, 1.52 mmol, 76%). ¹H NMR (CDCl₃, 300 MHz) δ 0.98 (t, *J* = 7.2 Hz, 3 H), 1.05 (t, *J* = 7.1 Hz, 3 H), 1.43 (s, 9 H), 2.91-3.12 (m, 5 H), 3.53 (m, 1 H), 4.75 (dd, *J* = 14.9, 8.4 Hz, 1 H), 5.37 (d, *J* = 8.9 Hz, 1 H), 7.25 (m, 5 H); ¹³C NMR (CDCl₃, 75 MHz) δ 171.2, 155.4, 137.0, 129.9, 128.8, 127.2, 79.7, 51.8, 42.0, 40.9, 40.8, 28.7, 14.6, 13.2; IR (neat) 3426, 3296, 2976, 2933, 1699, 1650, 1504, 1457, 1366, 1247, 1169, 1050, 864, 755, 702 cm⁻¹; HRMS-ESI (*M* + *H*⁺) calcd for C₁₈H₂₉N₂O₃: 321.2178, found: 321.2181; [α]_D²⁶ = +3.25 (*c* = 1.17, CHCl₃).

Amide 2j. Amide **2j** was prepared as described above from Boc-*tert*-Leu-OH (0.669 g, 2.9 mmol) and diethylamine (0.330 mL, 3.2 mmol). Purification (EtOAc:hexanes 1:3) gave a clear oil (0.592 g, 2.07 mmol, 71%). ¹H NMR (CDCl₃, 300 MHz) δ 0.97 (s, 9 H), 1.11 (t, *J* = 7.1 Hz, 3 H), 1.20 (t, *J* = 7.1 Hz, 3 H), 1.41 (s, 9 H), 3.00 (m, 1 H), 3.23 (m, 1 H), 3.58-3.79 (m, 2 H), 4.45 (d, *J* = 9.9 Hz, 1 H), 5.29 (d, *J* = 9.7 Hz, 1 H); ¹³C NMR (CDCl₃, 75 MHz) δ 171.3, 155.9, 79.6, 56.1, 43.2, 40.6, 36.1, 28.7, 26.8, 14.8; IR (neat) 3441, 3317, 2972, 2875, 1710, 1636, 1499, 1453, 1366, 1337, 1239, 1173, 1096, 1058, 1010, 904, 862, 834, 756 cm⁻¹; HRMS-ESI (*M* + *H*) calcd for C₁₅H₃₁N₂O₃: 287.2335, found: 287.2335; [α]_D²⁶ = -6.73 (*c* = 3.35, CHCl₃).

Amide 2k. Amide **2k** was prepared as described above from Boc-Leu-OH (0.565 g, 2.3 mmol) and diethylamine (0.260 mL, 2.5 mmol). Purification (EtOAc:hexanes 1:3) gave a clear oil (0.502 g, 1.75 mmol, 76%). ¹H NMR (CDCl₃, 300 MHz) δ 0.95 (d, *J* = 6.7 Hz, 3 H), 1.01 (d, *J* = 6.7 Hz, 3 H), 1.13 (t,

$J = 7.1$ Hz, 3 H), 1.26 (t, $J = 7.2$ Hz, 3 H), 1.44 (s, 9 H), 1.46-1.59 (m, 2 H), 1.72 (m, 1 H), 3.18-3.30 (m, 1 H), 3.47-3.57 (m, 1 H) 4.38 (m, 2 H), 4.62 (td, $J = 9.9, 3.6$ Hz, 1 H), 5.23 (d, $J = 9.2$ Hz, 1 H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 172.7, 155.9, 79.7, 48.9, 43.7, 42.1, 40.7, 28.8, 25.0, 23.9, 22.2, 14.9, 13.3; IR (neat) 3420, 3308, 2970, 1702, 1649, 1504, 1458, 1365, 1249, 1173, 1048, 1023, 873, 756 cm^{-1} ; HRMS-ESI ($\text{M} + \text{H}$) calcd for $\text{C}_{15}\text{H}_{31}\text{N}_2\text{O}_3$: 287.2335, found: 287.2330; $[\alpha]_{\text{D}}^{26} = -15.7$ ($c = 0.42$, CHCl_3).

Amide 2l. Amide **2l** was prepared as described above from Boc-cyclohexylalanine (0.587 g, 2.2 mmol) and diethylamine (0.330 mL, 2.4 mmol). Purification (EtOAc:hexanes 1:4) gave a clear oil (0.475 g, 1.45 mmol, 66%). ^1H NMR (CDCl_3 , 300 MHz) δ 0.83-0.91 (m, 4 H), 1.11 (t, $J = 7.1$ Hz, 3 H), 1.24 (t, $J = 7.1$ Hz, 3 H), 1.49 (m, 15 H), 1.96 (m, 1 H), 3.24 (m, 1 H), 3.36 (m, 2 H), 3.49 (m, 1 H), 4.63 (td, $J = 9.7, 2.7$ Hz, 1 H), 5.20 (d, $J = 9.2$ Hz, 1 H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 172.8, 155.9, 79.7, 48.2, 42.2, 40.7, 34.6, 34.3, 32.8, 28.7, 26.8, 26.7, 26.5, 14.7, 13.3; IR (neat) 3432, 3303, 2977, 2926, 2852, 1708, 1639, 1499, 1450, 1366, 1246, 1173, 1047, 1023, 756 cm^{-1} ; HRMS-ESI ($\text{M} + \text{H}$) calcd for $\text{C}_{18}\text{H}_{35}\text{N}_2\text{O}_3$: 327.2648, found: 327.2658; $[\alpha]_{\text{D}}^{26} = -7.63$ ($c = 2.33$, CHCl_3).

Amide 2m. Amide **2m** was prepared as described above from Boc-cyclohexylglycine (0.645 g, 2.7 mmol) and diethylamine (0.310 mL, 3.0 mmol). Purification (EtOAc:hexanes 5:28) gave a clear oil (0.513 g, 1.64 mmol, 63%). ^1H NMR (CDCl_3 , 300 MHz) δ 0.99-1.29 (m, 10 H), 1.43 (s, 9 H), 1.54-1.77 (m, 7 H), 3.17 (m, 1 H), 3.30-3.51 (m, 2 H), 3.59 (m, 1 H), 4.37 (dd, $J = 9.4, 7.0$ Hz, 1 H), 5.22 (d, $J = 9.4$ Hz, 1 H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 171.8, 156.1, 79.7, 54.9, 42.5, 42.0, 40.6, 30.3, 28.7, 28.5, 26.6, 26.4, 15.0, 13.4; IR (neat) 3439, 3298, 2976, 2929, 2853, 1705, 1636, 1500, 1453, 1366, 1246, 1172, 1078, 1058, 755 cm^{-1} ; HRMS-ESI ($\text{M} + \text{H}$) calcd for $\text{C}_{17}\text{H}_{33}\text{N}_2\text{O}_3$: 313.2491, found: 313.2498; $[\alpha]_{\text{D}}^{26} = +0.326$ ($c = 1.94$, CHCl_3).

Amide 2n. Amide **2n** was prepared as described above from Boc-Ala-OH (0.775 g, 4.1 mmol) and diethylamine (0.470 mL, 4.5 mmol). Purification (EtOAc:hexanes 5:28) gave a clear oil (0.839 g, 3.43 mmol, 84%). ^1H NMR (CDCl_3 , 300 MHz) δ 1.11 (t, $J = 7.2$ Hz, 3 H), 1.22 (t, $J = 7.2$ Hz, 3 H), 1.29 (d, $J = 6.8$ Hz, 3 H), 1.42 (s, 9H), 3.19-3.38 (m, 3 H), 3.42 (m, 1 H), 5.47 (d, $J = 7.7$ Hz, 1 H); ^{13}C NMR

(CDCl₃, 75 MHz) δ 172.4, 155.5, 79.8, 46.5, 42.1, 40.6, 28.8, 20.1, 14.9, 13.3; IR (neat) 3425, 3303, 2977, 2935, 1702, 1647, 1456, 1366, 1248, 1171, 1056, 860, 755 cm⁻¹; HRMS-ESI (M + H) calcd for C₁₂H₂₅N₂O₃: 245.1865, found: 245.1860; $[\alpha]_D^{23} = -10.3$ ($c = 3.38$, CHCl₃).

Amide 2o. Amide **2o** was prepared as described above from Boc-norleucine (0.447 g, 2.0 mmol) and diethylamine (0.230 mL, 2.2 mmol). Purification (EtOAc:hexanes 5:28) gave a clear oil (0.400 g, 1.40 mmol, 70%). ¹H NMR (CDCl₃, 300 MHz) δ 0.89 (m, 3 H), 1.12 (t, $J = 7.1$ Hz, 3 H), 1.23 (t, $J = 7.1$ Hz, 3 H), 1.32 (m, 3 H), 1.38 (s, 10 H), 1.57 (m, 2 H), 3.25 (m, 1 H), 3.36 (m, 2 H), 3.52 (m, 1 H), 4.52 (m, 1 H), 5.34 (d, $J = 8.8$ Hz, 1 H); ¹³C NMR (CDCl₃, 75 MHz) δ 172.2, 155.9, 79.7, 50.4, 42.2, 40.6, 34.1, 28.7, 27.9, 22.9, 15.0, 14.4, 13.3; IR (neat) 3428, 3303, 2971, 2933, 2872, 1708, 1640, 1501, 1458, 1366, 1248, 1173, 1048, 1022, 756 cm⁻¹; HRMS-ESI (M + H) calcd for C₁₅H₃₁N₂O₃: 287.2335, found: 287.2336; $[\alpha]_D^{26} = -2.75$ ($c = 2.00$, CHCl₃).

Amide 2p. Amide **2p** was prepared as described above from Boc-diphenylalanine (0.636 g, 1.9 mmol) and diethylamine (0.220 mL, 2.1 mmol). Purification (EtOAc:hexanes 1:4) gave a clear oil (0.468 g, 1.18 mmol, 62%). ¹H NMR (CDCl₃, 300 MHz) δ 0.85 (t, $J = 7.1$ Hz, 3 H), 0.99 (t, $J = 7.1$ Hz, 3 H), 1.32 (s, 9 H), 2.85-2.99 (m, 2 H), 3.17 (m, 1 H), 3.55 (m, 1 H), 4.46 (d, $J = 11.1$ Hz, 1 H), 5.14 (d, $J = 10.1$ Hz, 1 H), 5.35 (t, $J = 10.4$ Hz, 1 H), 7.12-7.42 (m, 10 H); ¹³C NMR (CDCl₃, 75 MHz) δ 171.3, 155.4, 141.0, 140.7, 129.2, 128.8, 127.3, 127.0, 80.0, 55.6, 52.7, 42.2, 40.7, 28.6, 14.4, 12.8; IR (neat) 3437, 3295, 2977, 2933, 1698, 1634, 1499, 1454, 1248, 1171, 1018, 754, 701 cm⁻¹; HRMS-ESI (M + H) calcd for C₂₄H₃₃N₂O₃: 397.2491, found: 397.2490; $[\alpha]_D^{26} = +78.2$ ($c = 1.43$, CHCl₃).

Amide 2q. Amide **2q** was prepared as described above from Boc-D-2-naphthylalanine (0.315 g, 1.9 mmol) and diethylamine (0.220 mL, 2.1 mmol). Purification (EtOAc:hexanes 5:28) gave a clear oil (0.566 g, 1.52 mmol, 80%). ¹H NMR (CDCl₃, 300 MHz) δ 0.64 (t, $J = 7.1$ Hz, 3 H), 0.87 (t, $J = 7.1$ Hz, 3 H), 1.47 (s, 9 H), 2.41 (m, 1 H), 2.57 (m, 1 H), 2.91 (m, 1 H), 3.33-3.50 (m, 2 H), 3.66 (dd, $J = 13.2$, 4.8, 1 H), 4.99 (m, 1 H), 5.54 (d, $J = 8.7$ Hz, 1 H), 7.37 (m, 2 H), 7.50 (t, $J = 7.4$ Hz, 1 H), 7.61 (t, $J = 7.2$, 1 H), 7.75 (m, 1 H), 7.84 (d, $J = 8.0$ Hz, 1 H), 8.30 (d, $J = 8.4$ Hz, 1 H); ¹³C NMR (CDCl₃, 75 MHz)

δ 171.2, 155.5, 134.0, 133.1, 132.7, 129.0, 128.4, 128.0, 126.1, 125.7, 124.1, 80.0, 50.8, 41.6, 40.5, 38.4, 28.8, 14.1, 12.9; IR (neat) 3429, 3299, 2978, 2933, 1704, 1635, 1492, 1457, 1365, 1246, 1169, 1058, 1019, 756 cm^{-1} ; HRMS-ESI ($M + H$) calcd for $\text{C}_{22}\text{H}_{31}\text{N}_2\text{O}_3$: 371.2335, found: 371.2330; $[\alpha]_{\text{D}}^{26} = -26.8$ ($c = 1.72$, CHCl_3).

Amide 2r. Amide **2r** was prepared as described above from Boc-Met-OH (0.603 g, 2.4 mmol) and diethylamine (0.270 mL, 2.6 mmol). Purification (EtOAc:hexanes 1:3) gave a clear oil (0.625 g, 2.05 mmol, 86%). ^1H NMR (CDCl_3 , 300 MHz) δ 1.09 (t, $J = 7.1$ Hz, 3 H), 1.22 (t, $J = 7.1$ Hz, 3 H), 1.41 (s, 9 H), 1.76-1.90 (m, 2 H), 2.08 (s, 3 H), 2.51 (t, $J = 7.0$ Hz, 2 H), 3.14-3.28 (m, 3 H), 3.31-3.54 (m, 3 H), 4.67 (m, 1 H), 5.38 (d, $J = 8.7$ Hz, 1 H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 171.4, 155.8, 79.9, 49.6, 42.2, 40.7, 34.1, 30.6, 28.7, 16.0, 15.0, 13.3; IR (neat) 3420, 3292, 2977, 2931, 1708, 1637, 1499, 1456, 1366, 1248, 1171, 1050, 1024, 755 cm^{-1} ; HRMS-ESI ($M + H$) calcd for $\text{C}_{14}\text{H}_{29}\text{N}_2\text{O}_3\text{S}$: 305.1899, found: 305.1901; $[\alpha]_{\text{D}}^{26} = -3.84$ ($c = 4.11$, CHCl_3).

General procedure for the synthesis of ligands 3d-g and 3j-r. To a solution of the amide (1 equiv) dissolved in anhydrous THF was slowly added 1.8 M BH_3 in THF (4 equiv). The reaction was stirred at rt for 18 h, then cooled to 0 $^\circ\text{C}$ and carefully quenched (evolution of H_2 gas!) with methanol. The solvent was removed and the residue was redissolved in methanol. To this solution was added ethylenediamine (4 equiv) and the solution was heated by microwave irradiation for 120 s at 100 $^\circ\text{C}$. The methanol was removed and the residue was dissolved in water and extracted with CH_2Cl_2 . The organic phase was washed with water, dried (Na_2CO_3) and concentrated. The crude product was purified by flash column chromatography.

Ligand 3d. Amide **2d** (1.67 g, 5.8 mmol) was reduced as described above with 1.8 M BH_3 (13.0 mL, 23.3 mmol) followed by boron exchange with ethylenediamine (1.50 mL, 23.3 mmol). Purification (gradient of 0.1:0.9:49 to 0.1:0.9:11.5 30% aqueous $\text{NH}_4\text{OH}:\text{CH}_3\text{OH}:\text{CH}_2\text{Cl}_2$) gave a yellow oil (0.250 g, 0.925 mmol, 51%). ^1H NMR (CDCl_3 , 300 MHz) δ 0.82-1.12 (m, 13 H), 1.44 (s, 10 H), 2.30-2.60 (m, 6 H), 3.57 (s, 1 H), 4.72 (s, 1 H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 156.2, 79.1, 53.3, 52.9, 47.3, 37.1, 28.8,

25.2, 15.3, 12.5, 12.0; IR (neat) 3360, 2968, 2876, 2806, 1704, 1497, 1459, 1385, 1367, 1244, 1175, 1065 cm^{-1} ; HRMS-FAB ($\text{M} + \text{Na}^+$) calcd for $\text{C}_{15}\text{H}_{32}\text{N}_2\text{O}_2\text{Na}$: 295.2361, found: 295.2359; $[\alpha]_{\text{D}}^{26} = +13.8$ ($c = 1.36$, CHCl_3).

Ligand 3e. Amide **3e** (0.473 g, 1.8 mmol) was reduced as described above with 1.8 M BH_3 (4.0 mL, 7.3 mmol) followed by boron exchange with ethylenediamine (0.490 mL, 7.3 mmol). Purification (gradient of 0.1:0.9:49 to 0.1:0.9:11.5 30% aqueous $\text{NH}_4\text{OH}:\text{CH}_3\text{OH}:\text{CH}_2\text{Cl}_2$) gave a white solid (0.163 g, 0.666 mmol, 37%): mp 55-56 $^{\circ}\text{C}$; ^1H NMR (CDCl_3 , 300 MHz) δ 0.92 (m, 6 H), 1.08 (m, 1 H), 1.45 (s, 9 H), 1.75 (s, 1 H), 2.24 (m, 9 H), 3.63 (s, 1 H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 156.5, 79.3, 59.8, 52.7, 46.1, 37.3, 28.9, 25.4, 15.1, 12.5; IR (neat) 3326, 2964, 2803, 1704, 1520, 1461, 1364, 1333, 1244, 1165, 1077 cm^{-1} ; HRMS-FAB ($\text{M} + \text{Na}^+$) calcd for $\text{C}_{15}\text{H}_{28}\text{N}_2\text{O}_2\text{Na}$: 267.2048, found: 267.2055; $[\alpha]_{\text{D}}^{25} = +26.7$ ($c = 0.45$, CHCl_3).

Ligand 3f. Amide **2f** (0.489 g, 1.5 mmol) was reduced as described above with 1.8 M BH_3 (6.0 mL, 3.3 mmol) followed by boron exchange with ethylenediamine (0.400 mL, 3.3 mmol). Purification (gradient of 0.1:0.9:49 to 0.1:0.9:11.5 30% aqueous $\text{NH}_4\text{OH}:\text{CH}_3\text{OH}:\text{CH}_2\text{Cl}_2$) gave a white solid (0.179 g, 0.587 mmol, 39%): mp 80-83 $^{\circ}\text{C}$; ^1H NMR (CDCl_3 , 300 MHz) δ 1.44 (s, 9 H), 1.81 (s, 4 H), 2.34-2.56 (m, 6 H), 2.81-2.93 (m, 2 H), 3.89 (s, 1 H), 4.76 (s, 1 H), 7.19-7.32 (m, 5 H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 156.1, 138.5, 130.1, 126.6, 79.5, 77.9, 77.7, 77.0, 58.9, 54.6, 51.1, 39.6, 28.8, 24.0; IR (film) 3380, 2957, 2877, 2787, 1683, 1516, 1446, 1364, 1250, 1169 cm^{-1} ; HRMS-FAB ($\text{M} + \text{Na}^+$) calcd for $\text{C}_{18}\text{H}_{28}\text{N}_2\text{O}_2\text{Na}$: 327.2048, found: 327.2042; $[\alpha]_{\text{D}}^{26} = +17.3$ ($c = 1.35$, CHCl_3).

Ligand 3g. Amide **2g** (0.506 g, 1.6 mmol) was reduced as described above with 1.8 M BH_3 (3.5 mL, 6.4 mmol) followed by boron exchange with ethylenediamine (0.430 mL, 6.4 mmol). Purification (gradient of 0.1:0.9:49 to 0.1:0.9:11.5 30% aqueous $\text{NH}_4\text{OH}:\text{CH}_3\text{OH}:\text{CH}_2\text{Cl}_2$) gave a yellow oil (0.239 g, 0.779 mmol, 49%). ^1H NMR (CDCl_3 , 300 MHz) δ 0.98 (t, $J = 7.1$ Hz, 6 H), 1.44 (s, 9 H), 2.31-2.44 (m, 2 H), 2.46-2.53 (m, 4 H), 2.85 (m, 2 H), 3.83 (s, 1 H), 4.75 (s, 1 H), 7.19-7.32 (m, 5 H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 156.3, 138.8, 129.9, 128.6, 126.6, 124.2, 79.4, 56.3, 50.4, 47.5, 39.7, 28.8, 12.1; IR

(neat) 3363, 2971, 2932, 2813, 1705, 1496, 1367, 1245, 1171, 1050 cm^{-1} ; HRMS-ESI ($\text{M} + \text{H}^+$) calcd for $\text{C}_{18}\text{H}_{31}\text{N}_2\text{O}_2$: 307.2386, found: 307.2382; $[\alpha]_{\text{D}}^{26} = +10.0$ ($c = 1.02$, CHCl_3).

Ligand 3j. Amide **2j** (0.531 g, 1.9 mmol) was reduced as described above with 1.8 M BH_3 (4.1 mL, 7.4 mmol) followed by boron exchange with ethylenediamine (0.500 mL, 7.4 mmol). Purification (gradient of 0.1:0.9:49 to 0.1:0.9:11.5 30% aqueous $\text{NH}_4\text{OH}:\text{CH}_3\text{OH}:\text{CH}_2\text{Cl}_2$) gave a yellow oil (0.103 g, 0.377 mmol, 49%). ^1H NMR (CDCl_3 , 300 MHz) δ 0.89 (s, 9 H), 0.98 (t, $J = 7.1$, 6 H), 1.44 (s, 9 H), 2.25 (t, $J = 11$ Hz, 1 H), 2.36-2.47 (m, 2 H), 2.52-2.64 (m, 3 H), 3.45 (m, 1 H), 4.37 (s, 1 H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 156.9, 78.9, 56.6, 53.6, 47.1, 34.8, 28.8, 26.9, 12.3; IR (neat) 3362, 3271, 3144, 2968, 2872, 2803, 1705, 1450, 1387, 1243, 1175, 1052, 759 cm^{-1} ; HRMS-ESI ($\text{M} + \text{H}^+$) calcd for $\text{C}_{15}\text{H}_{33}\text{N}_2\text{O}_2$: 273.2542, found: 273.2537; $[\alpha]_{\text{D}}^{26} = +28.9$ ($c = 0.920$, CHCl_3).

Ligand 3k. Amide **2k** (0.488 g, 1.9 mmol) was reduced as described above with 1.8 M BH_3 (4.2 mL, 7.6 mmol) followed by boron exchange with ethylenediamine (0.510 mL, 7.6 mmol). Purification (gradient of 0.1:0.9:49 to 0.1:0.9:11.5 30% aqueous $\text{NH}_4\text{OH}:\text{CH}_3\text{OH}:\text{CH}_2\text{Cl}_2$) gave an amorphous white solid (0.056 g, 0.204 mmol, 11%). ^1H NMR (CDCl_3 , 300 MHz) δ 0.90-1.01 (m, 12 H), 1.39 (m, 1 H), 1.68 (m, 1 H), 2.34 (d, $J = 6.7$ Hz, 2 H), 2.48 (q, $J = 7.1$ Hz, 4 H), 3.62 (s, 1 H), 4.51 (s, 1 H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 156.3, 79.2, 58.2, 47.9, 43.6, 28.8, 25.2, 23.7, 22.7, 12.2; IR (film) 3552, 2967, 2871, 2809, 1702, 1502, 1468, 1387, 1369, 1248, 1174, 1063, 757 cm^{-1} ; HRMS-ESI ($\text{M} + \text{H}^+$) calcd for $\text{C}_{15}\text{H}_{33}\text{N}_2\text{O}_2$: 273.2542, found: 273.2593; $[\alpha]_{\text{D}}^{24} = -24.5$ ($c = 1.07$, CHCl_3).

Ligand 3l. Amide **2l** (0.474 g, 1.5 mmol) was reduced as described above with 1.8 M BH_3 (3.2 mL, 5.8 mmol) followed by boron exchange with ethylenediamine (0.400 mL, 5.8 mmol). Purification (gradient of 0.1:0.9:49 to 0.1:0.9:11.5 30% aqueous $\text{NH}_4\text{OH}:\text{CH}_3\text{OH}:\text{CH}_2\text{Cl}_2$) gave a white solid (0.063 g, 0.202 mmol, 14%); mp 69-72 $^{\circ}\text{C}$; ^1H NMR (CDCl_3 , 300 MHz) δ 0.87-1.02 (m, 8 H), 1.15-1.26 (m, 4 H), 1.42 (m, 11 H), 1.64-1.71 (m, 4 H), 1.81 (m, 1 H), 2.36 (m, 2 H), 2.53 (m, 4 H), 3.68 (d, $J = 4.9$ Hz, 1 H), 4.51 (s, 1 H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 156.3, 79.2, 58.2, 47.9, 47.2, 42.2, 34.7, 34.4, 33.4, 28.8, 27.0, 26.8, 26.7, 12.2; IR (film) 3349, 2961, 2920, 1683, 1530, 1363, 1176, 1049 cm^{-1} ; HRMS-

ESI ($M + H^+$) calcd for $C_{18}H_{37}N_2O_2$: 313.2855, found: 313.2845; $[\alpha]_D^{26} = -21.9$ ($c = 0.53$, $CHCl_3$).

Ligand 3m. Amide **2m** (0.513 g, 1.7 mmol) was reduced as described above with 1.8 M BH_3 (3.8 mL, 6.8 mmol) followed by boron exchange with ethylenediamine (0.455 mL, 6.8 mmol). Purification (gradient of 0.1:0.9:49 to 0.1:0.9:11.5 30% aqueous $NH_4OH:CH_3OH:CH_2Cl_2$) gave a white solid (0.094 g, 0.313 mmol, 18%): mp 39-42 °C; 1H NMR ($CDCl_3$, 300 MHz) δ 0.94-1.09 (m, 6 H), 1.13-1.26 (m, 3 H), 1.43 (s, 9 H), 1.53 (m, 1 H), 1.65 (m, 5 H), 2.39-2.61 (m, 6 H), 3.51 (s, 1 H), 4.65 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.6, 79.2, 54.3, 53.2, 47.4, 40.7, 30.1, 28.8, 28.2, 26.9, 26.7, 11.9; IR (film) 3365, 2970, 2926, 2853, 1700, 1503, 1453, 1365, 1244, 1172, 1066 cm^{-1} ; HRMS-ESI ($M + H^+$) calcd for $C_{17}H_{33}N_2O_2$: 299.2699, found: 299.2702; $[\alpha]_D^{26} = +8.89$ ($c = 1.08$, $CHCl_3$).

Ligand 3n. Amide **2n** (0.485 g, 2.0 mmol) was reduced as described above with 1.8 M BH_3 (4.4 mL, 7.9 mmol) followed by boron exchange with ethylenediamine (0.528 mL, 7.9 mmol). Purification (gradient of 0.1:0.9:49 to 0.1:0.9:11.5 30% aqueous $NH_4OH:CH_3OH:CH_2Cl_2$) gave a yellow oil (0.299 g, 1.30 mmol, 65%). 1H NMR ($CDCl_3$, 300 MHz) δ 0.98 (t, $J = 7.1$ Hz, 6 H), 1.14 (d, $J = 6.4$ Hz, 3 H), 1.43 (s, 9 H), 2.32 (m, 2 H), 2.44-2.57 (m, 4 H), 3.60 (m, 1 H), 4.80 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.3, 79.2, 58.9, 47.6, 45.3, 28.8, 19.9, 12.1; IR (neat) 3366, 2971, 2933, 2874, 2812, 1699, 1506, 1457, 1366, 1245, 1174, 1057 cm^{-1} ; HRMS-ESI ($M + H^+$) calcd for $C_{12}H_{27}N_2O_2$: 231.2073, found: 231.2070; $[\alpha]_D^{22} = +8.9$ ($c = 0.56$, $CHCl_3$).

Ligand 3o. Amide **2o** (0.365 g, 1.3 mmol) was reduced as described above with 1.8 M BH_3 (2.8 mL, 5.1 mmol) followed by boron exchange with ethylenediamine (0.340 mL, 5.1 mmol). Purification (gradient of 0.1:0.9:49 to 0.1:0.9:11.5 30% aqueous $NH_4OH:CH_3OH:CH_2Cl_2$) gave a white solid (0.106 g, 0.387 mmol, 30%): mp 42-44 °C; 1H NMR ($CDCl_3$, 300 MHz) δ 0.86 (s, 4 H), 0.97 (t, $J = 7.1$ Hz, 6 H), 1.28 (s, 1 H), 1.41 (s, 9 H), 1.54 (m, 1 H), 2.35 (d, $J = 5.4$ Hz, 2 H), 2.50 (q, $J = 6.9$ Hz, 4 H), 3.50 (s, 1 H), 4.64 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.4, 79.2, 57.5, 49.5, 47.7, 33.8, 28.8, 28.3, 23.1, 14.1, 12.0; IR (film) 3352, 2967, 2931, 2869, 2808, 1700, 1520, 1458, 1366, 1246, 1174, 1069 cm^{-1} ; HRMS-ESI ($M + H^+$) calcd for $C_{15}H_{33}N_2O_2$: 273.2542, found: 273.2547; $[\alpha]_D^{25} = -6.84$ ($c = 0.91$,

CHCl₃).

Ligand 3p. Amide **2p** (0.445 g, 1.1 mmol) was reduced as described above with 1.8 M BH₃ (2.4 mL, 4.4 mmol) followed by boron exchange with ethylenediamine (0.295 mL, 4.4 mmol). Purification (gradient of 0.1:0.9:49 to 0.1:0.9:11.5 30% aqueous NH₄OH:CH₃OH:CH₂Cl₂) gave an amorphous yellow solid (0.154 g, 0.403 mmol, 36%). ¹H NMR (CDCl₃, 300 MHz) δ 0.97 (t, *J* = 7.1 Hz, 6 H), 1.38 (s, 9 H), 2.43 (d, *J* = 5.4 Hz, 2 H), 2.49-2.62 (m, 4 H), 4.27 (d, *J* = 7.1 Hz, 1 H), 4.49 (m, 1 H), 7.28 (m, 10 H); ¹³C NMR (CDCl₃, 75 MHz) δ 155.9, 143.4, 142.2, 129.5, 128.9, 126.8, 79.4, 58.7, 56.1, 53.5, 51.7, 47.6, 28.8, 12.1; IR (film) 3389, 2969, 1686, 1523, 1450, 1366, 1241, 1170, 1054 cm⁻¹; HRMS-ESI (M + H⁺) calcd for C₂₄H₃₅N₂O₂: 383.2699, found: 383.2695; [α]_D²⁶ = -6.73 (*c* = 0.49, CHCl₃).

Ligand 3q. Amide **2q** (0.529 g, 1.4 mmol) was reduced as described above with 1.8 M BH₃ (3.2 mL, 5.7 mmol) followed by boron exchange with ethylenediamine (0.380 mL, 5.7 mmol). Purification (gradient of 0.1:0.9:49 to 0.1:0.9:11.5 30% aqueous NH₄OH:CH₃OH:CH₂Cl₂) gave a yellow oil (0.120 g, 0.338 mmol, 24%). ¹H NMR (CDCl₃, 300 MHz) δ 0.99 (t, *J* = 7.1 Hz, 6 H), 1.41 (s, 9 H), 2.38-2.57 (m, 6 H), 3.38 (m, 2 H), 3.98 (m, 1 H), 4.91 (s, 1 H), 7.38 (m, 2 H), 7.52 (m, 2 H), 7.75 (d, *J* = 8.0 Hz, 1 H), 7.86 (d, *J* = 8.2 Hz, 1 H), 8.30 (s, 1 H); ¹³C NMR (CDCl₃, 75 MHz) δ 156.4, 135.3, 134.3, 132.8, 128.9, 127.9, 127.5, 126.4, 125.9, 124.8, 79.5, 56.9, 50.1, 47.8, 37.4, 28.8, 12.2; IR (neat) 3366, 3045, 2971, 2932, 2813, 1703, 1504, 1389, 1367, 1245, 1170, 1150, 776, 756 cm⁻¹; HRMS-ESI (M + H⁺) calcd for C₂₂H₃₃N₂O₂: 357.2542, found: 357.2532; [α]_D²⁴ = +27.9 (*c* = 1.45, CHCl₃).

Ligand 3r. Amide **2r** (0.553 g, 1.8 mmol) was reduced as described above with 1.8 M BH₃ (4.2 mL, 7.6 mmol) followed by boron exchange with ethylenediamine (0.500 mL, 7.6 mmol). Purification (gradient of 0.1:0.9:49 to 0.1:0.9:11.5 30% aqueous NH₄OH:CH₃OH:CH₂Cl₂) gave a white solid (0.104 g, 0.358 mmol, 20%); mp 42-45 °C; ¹H NMR (CDCl₃, 300 MHz) δ 0.99 (m, 6 H), 1.44 (s, 9 H), 1.66 (m, 1 H), 1.89 (m, 1 H), 2.10 (s, 3 H), 2.36 (m, 2 H), 2.43-2.61 (m, 6 H), 3.68 (m, 1 H), 4.69 (s, 1 H); ¹³C NMR (CDCl₃, 75 MHz) δ 156.3, 79.5, 57.4, 49.2, 47.7, 33.7, 31.1, 28.8, 15.9, 12.2; IR (film) 3344, 2966, 2792, 1686, 1529, 1451, 1388, 1352, 1295, 1249, 1170, 1047, 1021 cm⁻¹; HRMS-ESI (M + H⁺)

calcd for $C_{14}H_{31}N_2O_2$: 291.2106, found: 291.2110; $[\alpha]_D^{25} = -7.92$ ($c = 0.52$, $CHCl_3$).

General procedure for the synthesis of ligands 4b-c and 4j-k. To the Boc-protected precursor (1 mmol) was added trifluoroacetic acid (1 mL) at rt and the reaction was stirred for 1 h. The TFA was removed by rotary evaporation and the residue was diluted with water and the pH was adjusted to pH 10 with 10% aqueous KOH. The aqueous solution was extracted with CH_2Cl_2 (3 x 10 mL) and the organic layers were combined, dried (Na_2CO_3) and the solvent was removed by rotary evaporation. The residue was redissolved in anhydrous CH_2Cl_2 (3 mL) and DIEA (1.5 mmol) was added. The reaction was cooled to 0°C, the appropriate fluoroformate, chloroformate or acid chloride (1.1 mmol) was added and the solution was warmed to rt and stirred for 1 h. The reaction was diluted with CH_2Cl_2 , washed with water (2 x 10 mL), brine (1 x 10 mL) and dried (Na_2CO_3). The solvent was removed by rotary evaporation and the crude product was purified by flash column chromatography.

Ligand 4b. Compound **2a**⁵ (0.128 g, 0.45 mmol) was deprotected and transformed to **4b** as described above using DIEA (0.156 mL, 0.90 mmol) and (*S*)-(+)-menthyl chloroformate (0.096 mL, 0.45 mmol). Purification (0.1:0.9:32 30% aqueous $NH_4OH:CH_3OH:CH_2Cl_2$) gave a white solid (0.103 g, 0.281 mmol, 62%): mp 128-131 °C; 1H NMR ($CDCl_3$, 300 MHz) δ 0.80 (d, $J = 6.9$ Hz, 2 H), 0.91 (m, 14 H), 1.09 (m, 2 H), 1.46 (m, 3 H), 1.66 (m, 3 H), 1.92 (m, 2 H), 2.34 (m, 4 H), 2.52 (m, 4 H), 2.52 (s, 2 H), 3.70 (m, 5 H), 4.56 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.0, 74.7, 67.4, 59.8, 54.2, 52.1, 47.9, 42.0, 37.6, 34.7, 31.8, 26.8, 25.3, 24.0, 22.5, 21.2, 16.9, 15.4, 12.3; IR (film) 3327, 2955, 2857, 1688, 1533, 1254, 1238, 1118, 1036 cm^{-1} ; HRMS-ESI ($M + H^+$) calcd for $C_{21}H_{41}N_2O_3$: 369.3117, found: 369.3117; $[\alpha]_D^{24} = +40.2$ ($c = 0.98$, $CHCl_3$).

Ligand 4c. Compound **2a**⁵ (0.132 g, 0.65 mmol) was deprotected and similarly transformed to **4c** as described above using DIEA (0.080 mL, 0.46 mmol) and (*R*)-(-)-menthyl chloroformate (0.100 mL, 0.46 mmol). Purification (0.1:0.9:32 30% aqueous $NH_4OH:CH_3OH:CH_2Cl_2$) gave a white solid (0.136 g, 0.369 mmol, 80%): mp 43-46 °C; 1H NMR ($CDCl_3$, 300 MHz) δ 0.80 (d, $J = 6.9$ Hz, 3 H), 0.92 (m, 14 H), 1.09 (m, 2 H), 1.31 (m, 1 H), 1.44 (m, 2 H), 1.66 (m, 3 H), 1.92 (m, 1 H), 2.03 (d, $J = 11.4$ Hz, 2

H), 2.32 (d, $J = 7.3$ Hz, 2 H), 2.52 (m, 2 H), 3.68 (m, 5 H), 4.55 (td, $J = 10.8, 4.2$ Hz, 1 H), 4.72 (s, 1 H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 157.1, 74.5, 67.4, 59.4, 54.1, 51.9, 47.9, 41.9, 38.0, 34.7, 31.8, 26.8, 25.5, 24.1, 22.5, 21.2, 17.1, 15.3, 12.4; IR (film) 3279, 2955, 2868, 2807, 1682, 1542, 1454, 1369, 1299, 1267, 1244, 1118, 1039 cm^{-1} ; HRMS-ESI ($\text{M} + \text{H}^+$) calcd for $\text{C}_{21}\text{H}_{41}\text{N}_2\text{O}_3$: 369.3117, found: 369.3121; $[\alpha]_{\text{D}}^{24} = -23.8$ ($c = 1.20$, CHCl_3).

Ligand 4j. Compound **3c** (0.093 g, 0.34 mmol) was deprotected and transformed to **4j** as described above using DIEA (0.065 mL, 0.37 mmol) and adamantyl fluoroformate (0.074 mL, 0.37 mmol). Purification (0.1:0.9:11.5 30% aqueous $\text{NH}_4\text{OH}:\text{CH}_3\text{OH}:\text{CH}_2\text{Cl}_2$) gave a clear oil (0.072 g, 0.206 mmol, 61%); ^1H NMR (CDCl_3 , 300 MHz) δ 0.89 (m, 6 H), 1.12 (m, 1 H), 1.43 (s, 1 H), 1.64 (s, 7 H), 1.78 (s, 4 H), 2.13 (s, 9 H), 2.38 (m, 1 H), 2.57 (m, 1 H), 3.20 (s, 1 H), 3.66 (s, 1 H), 4.84 (s, 1 H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 156.1, 79.3, 56.6, 54.7, 53.8, 42.1, 37.8, 36.7, 31.2, 25.5, 23.9, 15.3, 12.4; IR (neat) 3363, 3044, 2971, 2932, 2813, 1703, 1504, 1456, 1388, 1366, 1245, 1170, 1049, 1024, 777, 756 cm^{-1} ; HRMS-ESI ($\text{M} + \text{H}^+$) calcd for $\text{C}_{21}\text{H}_{37}\text{N}_2\text{O}_2$: 349.2855, found: 349.2847; $[\alpha]_{\text{D}}^{24} = +9.5$ ($c = 1.06$, CHCl_3).

Ligand 4k. Compound **3d** (0.220 g, 0.81 mmol) was deprotected and transformed to **4k** as described above using DIEA (0.210 mL, 1.2 mmol) and adamantyl fluoroformate (0.177 g, 0.89 mmol). Purification (0.1:0.9:9 30% aqueous $\text{NH}_4\text{OH}:\text{CH}_3\text{OH}:\text{CH}_2\text{Cl}_2$) gave a clear oil (0.260 g, 0.704 mmol, 91%); ^1H NMR (CDCl_3 , 300 MHz) δ 0.92 (m, 6 H), 1.00-1.12 (m, 6 H), 1.43 (m, 1 H), 1.65 (s, 1 H), 1.71 (s, 1 H), 2.12 (s, 9 H), 2.37-2.46 (m, 2 H), 3.57 (s, 1 H), 4.79 (s, 1 H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 156.3, 79.1, 53.2, 52.7, 47.3, 45.7, 42.1, 41.9, 37.9, 36.5, 31.2, 25.3, 15.3, 12.5, 11.9; IR (neat) 3350, 2964, 2913, 2854, 1699, 1497, 1458, 1378, 1350, 1295, 1234, 1058, 756 cm^{-1} ; HRMS-ESI ($\text{M} + \text{H}^+$) calcd for $\text{C}_{21}\text{H}_{39}\text{N}_2\text{O}_2$: 351.3012, found: 351.3002; $[\alpha]_{\text{D}}^{24} = +4.69$ ($c = 2.13$ CHCl_3).

Figure S1. ¹H NMR of Amide 2c.

Figure S3. ¹H NMR of Amide 2d.

Figure S4. ¹³C NMR of Amide 2d.

Figure S5. ¹H NMR of Amide **2e**.

Figure S6 ¹³C NMR of Amide **2e**.

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Figure S13. ¹H NMR of Amide **2k**.

Figure S14. ¹³C NMR of Amide **2k**.

Figure S15. ¹H NMR of Amide 2l.

Figure S17. ¹H NMR of Amide 2m.

Figure S18. ¹³C NMR of Amide 2m.

Figure S21. ¹H NMR of Amide 2o.

Figure S22. ¹³C NMR of Amide 2o.

Figure S27. ¹H NMR of Amide 2r.

Figure S28. ¹³C NMR of Amide 2r.

Chemical shifts (ppm): 165.00, 164.98, 164.96, 164.94, 164.92, 164.90, 164.88, 164.86, 164.84, 164.82, 164.80, 164.78, 164.76, 164.74, 164.72, 164.70, 164.68, 164.66, 164.64, 164.62, 164.60, 164.58, 164.56, 164.54, 164.52, 164.50, 164.48, 164.46, 164.44, 164.42, 164.40, 164.38, 164.36, 164.34, 164.32, 164.30, 164.28, 164.26, 164.24, 164.22, 164.20, 164.18, 164.16, 164.14, 164.12, 164.10, 164.08, 164.06, 164.04, 164.02, 164.00, 163.98, 163.96, 163.94, 163.92, 163.90, 163.88, 163.86, 163.84, 163.82, 163.80, 163.78, 163.76, 163.74, 163.72, 163.70, 163.68, 163.66, 163.64, 163.62, 163.60, 163.58, 163.56, 163.54, 163.52, 163.50, 163.48, 163.46, 163.44, 163.42, 163.40, 163.38, 163.36, 163.34, 163.32, 163.30, 163.28, 163.26, 163.24, 163.22, 163.20, 163.18, 163.16, 163.14, 163.12, 163.10, 163.08, 163.06, 163.04, 163.02, 163.00, 162.98, 162.96, 162.94, 162.92, 162.90, 162.88, 162.86, 162.84, 162.82, 162.80, 162.78, 162.76, 162.74, 162.72, 162.70, 162.68, 162.66, 162.64, 162.62, 162.60, 162.58, 162.56, 162.54, 162.52, 162.50, 162.48, 162.46, 162.44, 162.42, 162.40, 162.38, 162.36, 162.34, 162.32, 162.30, 162.28, 162.26, 162.24, 162.22, 162.20, 162.18, 162.16, 162.14, 162.12, 162.10, 162.08, 162.06, 162.04, 162.02, 162.00, 161.98, 161.96, 161.94, 161.92, 161.90, 161.88, 161.86, 161.84, 161.82, 161.80, 161.78, 161.76, 161.74, 161.72, 161.70, 161.68, 161.66, 161.64, 161.62, 161.60, 161.58, 161.56, 161.54, 161.52, 161.50, 161.48, 161.46, 161.44, 161.42, 161.40, 161.38, 161.36, 161.34, 161.32, 161.30, 161.28, 161.26, 161.24, 161.22, 161.20, 161.18, 161.16, 161.14, 161.12, 161.10, 161.08, 161.06, 161.04, 161.02, 161.00, 160.98, 160.96, 160.94, 160.92, 160.90, 160.88, 160.86, 160.84, 160.82, 160.80, 160.78, 160.76, 160.74, 160.72, 160.70, 160.68, 160.66, 160.64, 160.62, 160.60, 160.58, 160.56, 160.54, 160.52, 160.50, 160.48, 160.46, 160.44, 160.42, 160.40, 160.38, 160.36, 160.34, 160.32, 160.30, 160.28, 160.26, 160.24, 160.22, 160.20, 160.18, 160.16, 160.14, 160.12, 160.10, 160.08, 160.06, 160.04, 160.02, 160.00, 159.98, 159.96, 159.94, 159.92, 159.90, 159.88, 159.86, 159.84, 159.82, 159.80, 159.78, 159.76, 159.74, 159.72, 159.70, 159.68, 159.66, 159.64, 159.62, 159.60, 159.58, 159.56, 159.54, 159.52, 159.50, 159.48, 159.46, 159.44, 159.42, 159.40, 159.38, 159.36, 159.34, 159.32, 159.30, 159.28, 159.26, 159.24, 159.22, 159.20, 159.18, 159.16, 159.14, 159.12, 159.10, 159.08, 159.06, 159.04, 159.02, 159.00, 158.98, 158.96, 158.94, 158.92, 158.90, 158.88, 158.86, 158.84, 158.82, 158.80, 158.78, 158.76, 158.74, 158.72, 158.70, 158.68, 158.66, 158.64, 158.62, 158.60, 158.58, 158.56, 158.54, 158.52, 158.50, 158.48, 158.46, 158.44, 158.42, 158.40, 158.38, 158.36, 158.34, 158.32, 158.30, 158.28, 158.26, 158.24, 158.22, 158.20, 158.18, 158.16, 158.14, 158.12, 158.10, 158.08, 158.06, 158.04, 158.02, 158.00, 157.98, 157.96, 157.94, 157.92, 157.90, 157.88, 157.86, 157.84, 157.82, 157.80, 157.78, 157.76, 157.74, 157.72, 157.70, 157.68, 157.66, 157.64, 157.62, 157.60, 157.58, 157.56, 157.54, 157.52, 157.50, 157.48, 157.46, 157.44, 157.42, 157.40, 157.38, 157.36, 157.34, 157.32, 157.30, 157.28, 157.26, 157.24, 157.22, 157.20, 157.18, 157.16, 157.14, 157.12, 157.10, 157.08, 157.06, 157.04, 157.02, 157.00, 156.98, 156.96, 156.94, 156.92, 156.90, 156.88, 156.86, 156.84, 156.82, 156.80, 156.78, 156.76, 156.74, 156.72, 156.70, 156.68, 156.66, 156.64, 156.62, 156.60, 156.58, 156.56, 156.54, 156.52, 156.50, 156.48, 156.46, 156.44, 156.42, 156.40, 156.38, 156.36, 156.34, 156.32, 156.30, 156.28, 156.26, 156.24, 156.22, 156.20, 156.18, 156.16, 156.14, 156.12, 156.10, 156.08, 156.06, 156.04, 156.02, 156.00, 155.98, 155.96, 155.94, 155.92, 155.90, 155.88, 155.86, 155.84, 155.82, 155.80, 155.78, 155.76, 155.74, 155.72, 155.70, 155.68, 155.66, 155.64, 155.62, 155.60, 155.58, 155.56, 155.54, 155.52, 155.50, 155.48, 155.46, 155.44, 155.42, 155.40, 155.38, 155.36, 155.34, 155.32, 155.30, 155.28, 155.26, 155.24, 155.22, 155.20, 155.18, 155.16, 155.14, 155.12, 155.10, 155.08,

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Figure S32. ^{13}C NMR of Ligand **3d**.

Figure S33. ¹H NMR of Ligand 3e.

Figure S35. ¹H NMR of Ligand **3f**.

Figure S36. ¹³C NMR of Ligand **3f**.

[illegible]

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Figure S41. ¹H NMR of Ligand **3k**.

Figure S42. ¹³C NMR of Ligand **3k**.

Figure S43. ^1H NMR of Ligand **3l**.

Figure S44. ^{13}C NMR of Ligand **3l**.

Figure S47. ¹H NMR of Ligand **3n**.

Figure S48. ¹³C NMR of Ligand **3n**.

Figure S49. ¹H NMR of Ligand 3o.

Figure S50. ¹³C NMR of Ligand 3o.

Figure S55. ¹H NMR of Ligand 3r.

Figure S56. ¹³C NMR of Ligand 3r.

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