HIGHLY ENANTIOSELECTIVE SYNTHESIS OF TETRAHYDRO- β -CARBOLINES AND TETRAHYDRO- γ -CARBOLINES VIA Pd-CATALYZED INTRAMOLECULAR ALLYLIC ALKYLATION.

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General.

CH₂Cl₂, toluene, THF, Et₂O and DMF were supplied by Fluka in Sureseal® bottles and used as received. All starting materials and reagents were obtained from Aldrich and Fluka and used without further purification. All the allylic carbonates were prepared following a procedure reported in the literature.¹ ¹H-NMR spectra were recorded on Varian 200 (200 MHz) or Varian 300 (300 MHz) spectrometers. Chemical shifts are reported in ppm from TMS with the solvent resonance as the internal standard (deuteriochloroform: δ 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz). ¹³C-NMR spectra were recorded on a Varian 200 (50 MHz) or Varian 300 (75 MHz) spectrometers with complete proton decoupling. Chemical shifts are reported in ppm from TMS with the solvent as the internal standard (deuteriochloroform: δ 77.0 ppm). GC-mass spectra were performed at an ionizing voltage of 70 eV. LC-electrospray ionization mass spectra were obtained with Agilent Technologies MSD1100 single-quadrupole mass spectrometer. Chromatographic purification was done with 70-230 mesh aluminium oxide 90 mesh alumina or with 240-400 mesh silica gel. IR analysis were performed with a FT-IR spectrophotometer. IR spectra are expressed by wavenumber (cm⁻¹). Elemental analyses were carried out by using a EACE 1110 CHNOS analyzer. Analytical high performance liquid chromatograph (HPLC) was performed on a liquid chromatograph equipped with a variable wave-length UV detector (deuterium lamp 190-600 nm), using a Daicel ChiralcelTM OD and AD column (0.46 cm I.D. x 25 cm) (Daicel Inc.). HPLC grade isopropanol and hexane were used as the eluting solvents. Optical rotations were determined in a 1 ml cell with a path length of 10 mm (Na_D line). LC-electrospray ionization mass spectra were obtained with Agilent Technologies MSD1100 single-quadrupole mass spectrometer. Melting points are uncorrected.

Preparation of benzyl-(1*H*-indol-2-yl-methyl)-amine

To a mixture of **4/5**¹ (5 mmol, 1.0 equiv), and MgSO₄ (5.0 equiv) in toluene (30 mL), benzylamine (1.5 equiv) was added. The reaction was kept under reflux for 48h (complete consumption of **4/5** as judged by GC-MS). The solvent was then evaporated under reduced pressure to give a dark viscous oil (¹H-NMR data of the crude were consistent with data of the benzylimine reported in the literature). The crude was dissolved in methanol (35 mL) and then NaBH₄ (1.5 equiv) was added portionwise at 0°C. The reaction mixture was stirred at rt for 6h and then quenched with water (10 mL). Methanol was removed under reduced pressure, the aqueous phase was extracted with AcOEt, the combined organics were dried over Na₂SO₄ and then concentrated to give a crude brown oil.

(c-Hex:AcOEt 8:2→1:1). Brown solid. Yield 79% (two steps). M.p. = 77-78°C. ¹H-NMR (200 MHz, CDCl₃): δ 3.75 (s, 2H), 3.79 (s, 3H), 3.89 (s, 2H), 6.23 (s, 1H), 6.74 (dd, *J* = 1.4, 8.8 Hz, 1H), 6.97 (s, 1H), 7.13-7.29 (m, 7H), 8.44 (br, 1H); ¹³C-NMR (50 MHz, CDCl₃): δ 45.8, 52.7, 55.8, 100.7, 102.2, 111.4, 111.6, 127.4, 128.3(2C), 128.6(2C), 128.7, 131.6, 137.2, 138.9, 154.1; GC-MS *m/z* 51(5), 65 (11), 77(9), 91(85), 106(56), 117(15), 165(100), 179(4), 191(44), 191, (2), 270(15); IR (nujol): ν 3304(m), 2917(s), 2716(w), 1441(s), 1372(s), 1204(m), 1166(m) cm⁻¹. Anal. calcd for (C₁₇H₁₈NO₂): C, 76.66; H, 6.81; N, 10.52; Found: C, 76.60; H, 6.88; N, 10.55.

[Imine intermediate, ¹H-NMR (200 MHz, CDCl₃): δ 3.86 (s, 3H), 4.87 (s, 2H), 6.74 (s, 1H), 6.95 (dd, *J* = 2.6, 9.2 Hz, 1H), 7.27-7.39 (m, 7H), 8.34 (s, 1H), 9.20 (br, 1H); IR (CH₂Cl₂): ν 3406, 2924, 2853, 1636, 1483, 1457, 697 cm⁻¹; GC-MS *m/z* 51(5), 65 (11), 77(9), 91(100), 117(15), 163(6), 191(44), 191, (49), 268(78)].

(c-Hex, washing). Yield 81% (two steps). Brown solid. M.p. = 113-116°C. ¹H-NMR (300 MHz, CDCl₃): δ 2.52 (br, 1H), 3.82, (s, 2H), 3.98 (s, 2H), 6.31 (s, 1H), 7.11 (dd, *J* = 2.1, 8.7 Hz, 1H), 7.21-7.35 (m, 6H), 7.52 (s, 1H), 8.88 (br, 1H); ¹³C-NMR (75 MHz, CDCl₃): δ 45.9, 53.1, 100.1, 111.6, 119.4, 121.6, 125.1, 127.3, 128.2, 128.5, 129.5, 134.2, 138.8, 139.4; LC-ESI-MS 271 (M+1), 293 (M+Na); IR (nujol): ν 3377, 2870,

1462, 1376, 721 cm^{-1} ; Anal. calcd for ($\text{C}_{16}\text{H}_{15}\text{ClN}_2$): C, 70.98; H, 5.58; N, 10.35; Found: C, 70.89; H, 5.53; N, 10.30.

[Imine intermediate, ^1H -NMR (200 MHz, CDCl_3): δ 4.79 (s, 2H), 6.93 (s, 1H), 7.12-7.40 (m, 7H), 7.57 (s, 1H), 8.32 (s, 1H), 9.22 (br, 1H); GC-MS m/z 51(6), 65(12), 91(100), 104(7), 117(11), 193(41), (195(43); IR (nujol): ν 3085, 2868, 1537, 1451, 1314, 731, 689 cm^{-1}].

(*c*-Hex:AcOEt 1:1). Yield 77% (two steps). Brown-red solid. Mp = 79-81°C.

^1H -NMR (200 MHz, CDCl_3): δ 1.93 (br, 1H), 2.45 (s, 3H), 3.82 (s, 2H), 3.97 (s, 2H), 6.29 (s, 1H), 6.95 (d, J = 8.2 Hz, 1H), 7.25-7.38 (m, 7H), 8.47 (br, 1H); ^{13}C -NMR (50 MHz, CDCl_3): δ 21.4, 46.1, 53.0, 99.9, 110.3, 119.8, 122.9, 127.1(2C), 128.1(2C), 128.5(2C), 128.7, 134.2, 137.5, 139.8; LC-ESI-MS 251 ($M+1$); IR (nujol): ν 3266(w), 3128(m), 2856(m), 1549(w), 1452(s), 1208(w) cm^{-1} ; Anal. calcd for ($\text{C}_{17}\text{H}_{18}\text{N}_2$): C, 81.56; H, 7.25; N, 11.19; Found: C, 81.50; H, 7.19; N, 11.17.

[Imine intermediate, ^1H -NMR (200 MHz, CDCl_3): δ 2.45 (s, 3H), 4.82 (s, 2H), 6.74 (s, 1H), 7.07-7.44 (m, 8 H), 8.35 (s, 1H), 9.14 (br, 1H); GC-MS m/z 51(5), 65(12), 77(9), 91(92), 103(12), 177(21), 132(19), 144(19), 171(100), 220(10), 248(98); IR (neat): ν 3404(s), 1635(s), 1451(m), 1318(m), 1024(w) cm^{-1}].

(no-purification). Yield 91% (two steps, purity >95% by ^1H -NMR). Brown viscous oil. ^1H -NMR (200 MHz, CDCl_3): δ 1.87 (s, 1H), 3.80 (s, 2H), 3.83 (s, 2H), 6.05 (s, 1H), 6.15 (q, J = 2.8 Hz, 1H), 6.75 (dd, J = 2.2, 4.0, Hz, 1H), 7.29-7.32 (m, 5H), 8.62 (br, 1H); ^{13}C -NMR (75 MHz, CDCl_3): δ 46.0, 53.3, 106.7, 108.3, 117.5, 127.4, 128.4(2C), 128.8(2C), 130.4, 140.1; LC-ESI-MS 187 ($M+1$); IR (nujol): ν 3190(s), 3061(m), 1494(w), 1098(m) cm^{-1} ; Anal. calcd for ($\text{C}_{12}\text{H}_{14}\text{N}_2$): C, 77.38 H, 7.58; N, 15.04; Found: C, 77.40; H, 7.55 N, 15.01.

[Imine intermediate, ^1H -NMR (200 MHz, CDCl_3): δ 4.72 (s, 2H), 6.26 (dd, J = 2.4, 3.6 Hz, 1H), 6.56 (dd, J = 1.4, 3.6 Hz, 1H), 6.92 (br, 1H), 7.31-7.36 (m, 5H), 8.14 (s, 1H); GC-MS m/z 51(5), 65(21), 79(22), 91(100), 106(15), 177(33), 156(10), 184(72); IR (neat): ν 1734(s), 1637(s), 1027 (m) cm^{-1}].

(washing with *c*-Hex). Yield 90% (two steps). Pale yellow solid. Mp = 89-90°C. ^1H -NMR (200 MHz, CDCl_3): δ 1.72 (br, 1H), 3.93 (s, 2H), 4.01 (s, 2H), 7.11 (s, 1H), 7.16-7.40 (m, 8H), 7.69 (d, J = 7.4 Hz, 1H), 8.39 (br, 1H); ^{13}C -NMR (75 MHz, CDCl_3): δ 44.1, 53.4, 111.2, 114.8, 118.8, 119.4, 122.0, 122.6, 126.9, 127.0, 128.2, 128.4, 136.3, 140.4; LC-

ESI-MS 237 (M+1); IR (nujol): ν 3317(w), 2952(s), 2854(s), 1456(m), 1379(m), 1247(w) cm^{-1} ; Anal. calcd for ($\text{C}_{16}\text{H}_{16}\text{N}_2$): C, 81.32; H, 6.82; N, 11.85; Found: C, 81.30; H, 6.78; N, 11.87.

[Imine intermediate, ^1H -NMR (300 MHz, CDCl_3): δ 4.86 (s, 2H), 7.23-7.45 (m, 10H), 8.37-8.40 (m, 1H), 8.61 (s, 1H); IR (nujol): ν 3023(m), 2931 (s), 1624(s), 1460 (m), 810 (w) cm^{-1}].

Yield 98% (two steps). Pale-yellow solid. Mp = 90-93°C. ^1H -NMR (200 MHz, CDCl_3): δ 1.64 (s, 1H), 2.48 (s, 3H), 3.91-4.00 (m, 4H), 7.05 (d, J = 8.0 Hz, 1H), 7.13 (s, 1H), 7.28-7.43 (m, 7H), 8.03 (br, 1H); ^{13}C -NMR (75 MHz, CDCl_3): δ 21.5, 43.9, 53.2, 110.8, 118.4, 122.8, 123.7, 126.9, 127.0, 128.3, 128.4, 128.5, 128.7, 134.6, 140.2; LC-ESI-MS 251 (M+1); IR (nujol): ν 2952(s), 2925(s), 2854(s), 1500(w), 1456(s), 1379(m), 1352(m), 1110(m) cm^{-1} ; Anal. calcd for ($\text{C}_{17}\text{H}_{18}\text{N}_2$): C, 81.56; H, 7.25; N, 11.19; Found: C, 81.53; H, 7.21; N, 11.18.

[Imine intermediate, ^1H -NMR (200 MHz, CDCl_3): δ 2.48 (s, 3H), 4.86 (s, 2H), 7.08 (dd, J = 1.6, 6.8 Hz, 1H), 7.22-7.45 (m, 8H), 8.17 (s, 1H), 8.58 (s, 1H); LC-ESI-MS: 250 (M+1); IR (nujol): ν 3025(m), 2929 (s), 1622(s), 1463 (m), 800 (w) cm^{-1}].

Preparation of carbonic acid (*E*)-4-[benzyl-(1*H*-indol-2-yl-methyl)-amino]-but-2-enyl ethyl esters.

To a solution of amine (2 mmol, 1.0 equiv) and Et_3N (1.2 equiv) in dry THF (25 mL), ethyl 4-bromocrotonate (2.0 equiv) was added at 0°C. The ice bath was removed and the reaction mixture was stirred at rt for 4h. Finally, the mixture was filtered and solid residue washed with Et_2O . Evaporation of the volatiles under reduced pressure and subsequent purification by flash-chromatography.

(*c*-Hex:AcOEt 85:15). Yield 72%. Pale yellow oil. (*E/Z* > 95:5). ^1H -NMR (300 MHz, CDCl_3): δ 1.30 (t, J = 7.2 Hz, 3H), 3.24 (d, J = 5.1 Hz, 2H), 3.65 (s, 2H), 3.73 (s, 2H), 3.80 (s, 3H), 4.20 (q, J = 7.2 Hz, 2H), 6.03 (d, J = 15.9 Hz, 1H), 6.32 (s, 1H), 6.82 (dd, J = 2.4, 8.7 Hz, 1H), 6.95-7.05 (m, 2H), 7.22-7.63 (m, 6H), 8.24 (br, 1H); ^{13}C -NMR (75 MHz, CDCl_3): δ 14.2, 51.3, 54.2, 55.8, 58.2, 60.5, 101.3, 111.6, 119.5, 121.9, 123.4, 125.3, 127.5, 128.5(2C), 128.8(2C), 129.5, 134.3, 137.6,

137.8, 145.6, 166.2; LC-ESI-MS: 379 (M+1); IR (neat): ν 3086(s), 2992(w), 2708(w), 1744(s), 1583(m), 1488(s), 1277(s) cm^{-1} ; Anal. calcd for ($\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_3$): C, 72.99; H, 6.92; N, 7.40; Found: C, 72.91; H, 6.89; N, 7.37.

(c-Hex:AcOEt 8:2). Yield 85%. Pale yellow oil. (*E/Z* > 95:5). ^1H -NMR (200 MHz, CDCl_3): δ 1.30 (t, $J = 7.2$ Hz, 3H), 3.26 (s, 2H), 3.62 (s, 2H), 3.74 (s, 2H), 4.19 (q, $J = 7.2$ Hz, 2H), 6.02 (d, $J = 15.8$ Hz, 1H), 5.32 (s, 1H), 6.95-7.09 (m, 1H), 7.11-7.13 (m, 1H), 7.22-7.35 (m, 6H), 7.50 (s, 1H), 8.19 (br, 1H); ^{13}C -NMR (75 MHz, CDCl_3): δ 14.2, 51.2, 54.3, 58.4, 60.5, 101.3, 111.6, 119.5, 121.9, 123.4, 125.3, 127.5, 128.5(2C), 128.8(2C), 129.5, 134.3, 137.6, 137.8, 145.3, 166.9; LC-ESI-MS: 383 (M+1), 406 (M+Na), 421 (M+K); IR (neat): ν 3646(w), 3367(s), 3188(m), 3026 (m), 2977(s), 2804(s), 2714(w), 1706(s), 1657(m), 1576(s), 1452(m) cm^{-1} ; Anal. calcd for ($\text{C}_{22}\text{H}_{23}\text{ClN}_2\text{O}_2$): C, 69.01; H, 6.05; N, 7.32; Found: C, 68.94; H, 6.00; N, 7.33.

(c-Hex:AcOEt 85:15). Yield 92%. Viscous pink oil. (*E/Z* > 95:5). ^1H -NMR (200 MHz, CDCl_3): δ 1.33 (t, $J = 7.4$ Hz, 3H), 2.43 (s, 3H), 3.24 (d, $J = 5.0$ Hz, 2H), 3.64 (s, 2H), 3.73 (s, 2H), 4.20 (q, $J = 7.4$ Hz, 2H), 6.05 (d, $J = 13.8$ Hz, 1H), 6.30 (s, 1H), 6.93-7.06 (m, 1H), 7.24-7.41 (m, 8H), 8.25 (br, 1H); ^{13}C -NMR (50 MHz, CDCl_3): δ 14.2, 21.4, 51.3, 54.1, 58.2, 60.5, 101.3, 110.4, 119.8, 122.0, 123.2, 125.0, 127.4, 128.5(2C), 128.9(2C), 132.8, 136.0, 138.4, 142.5, 145.7, 166.2; LC-ESI-MS: 363 (M+1), 385 (M+Na); IR (neat): ν 3399(s), 3085(w), 3052(m), 2981(s), 2805(s), 1709(s), 1659(m), 1599(m), 1455(s) cm^{-1} ; Anal. calcd for ($\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_2$): C, 76.21; H, 7.23; N, 7.73; Found: C, 76.25; H, 7.18; N, 7.71.

(c-Hex:AcOEt 90:10). Yield 73%. Pale yellow oil. (*E/Z* > 95:5). ^1H -NMR (300 MHz, CDCl_3): δ 1.33 (t, $J = 7.2$ Hz, 3H), 3.23 (d, $J = 6.0$ Hz, 2H), 3.63 (s, 2H), 3.73 (s, 2H), 4.24 (q, $J = 7.2$ Hz, 2H), 6.01-6.07 (m, 2H), 6.16 (dd, $J = 3.3, 4.8$ Hz, 1H), 6.77-6.79 (m, 1H), 7.00 (dt, $J = 6.2, 13.8$ Hz, 1H), 7.30-7.35 (m, 5H), 8.41 (br, 1H); ^{13}C -NMR (75 MHz, CDCl_3): δ 14.2, 50.8, 54.1, 58.1, 60.4, 107.6, 108.1, 117.4, 123.1, 127.4, 128.1, 128.4(2C), 128.8(2C), 138.5, 145.9, 166.2; LC-ESI-MS: 299 (M+1); IR (neat): ν 3365(s), 3050(w), 2805(s), 1712(s), 1660(s), 1599(m), 1435(m) cm^{-1} ; Anal. calcd for ($\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_2$): C, 72.46; H, 7.43; N, 9.39; Found: C, 72.44; H, 7.40; N, 9.35.

(*E*)-Ethyl 4-bromo-3-methylcrotonate¹ was used for the synthesis. (*c*-Hex:AcOEt 90:10). Yield 45%. Pale yellow oil. (*E/Z* > 95:5). ¹H-NMR (200 MHz, CDCl₃): δ 1.30 (t, *J* = 7.2 Hz, 3H), 2.18 (s, 3H), 3.09 (s, 2H), 3.59 (s, 2H), 3.69 (s, 2H), 4.17 (q, *J* = 7.2 Hz, 2H), 6.03 (s, 1H), 6.39 (s, 1H), 7.08-7.17 (m, 1H), 7.19-7.35 (m, 7H), 7.53 (d, *J* = 5.8 Hz, 1H), 8.21 (br, 1H); ¹³C-NMR (50 MHz, CDCl₃): δ 14.3, 17.5, 51.2, 58.4, 59.7, 62.1, 101.9, 110.7, 117.3, 119.4, 119.7, 120.1, 121.3, 121.6, 127.3, 128.5(2C), 128.9(2C), 136.1, 138.3, 156.3, 166.5; LC-ESI-MS: 363 (M+1), 385 (M+Na); Anal. calcd for (C₂₃H₂₆N₂O₂): C, 76.21; H, 7.23; N, 7.73; Found: C, 76.15; H, 7.20; N, 7.70.

(*c*-Hex:AcOEt 8:2). Yield 85%. Yellow oil. (*E/Z* > 95:5). ¹H-NMR (300 MHz, CDCl₃): δ 1.29 (t, *J* = 8.1 Hz, 3H), 3.24 (d, *J* = 4.0 Hz, 2H), 3.67 (s, 2H), 3.81 (s, 2H), 4.19 (q, *J* = 4.0 Hz, 2H), 6.05 (dd, *J* = 1.8, 15.9 Hz, 1H), 7.00-7.11 (m, 1H), 7.15-7.41 (m, 9H), 7.74 (d, *J* = 7.5 Hz, 1H), 8.01 (br, 1H); ¹³C-NMR (75 MHz, CDCl₃): δ 14.3, 49.6, 54.2, 58.4, 60.3, 111.0, 113.3, 119.5, 119.7, 122.0, 122.6, 123.4, 126.9, 127.6(2C), 128.2(2C), 128.8, 136.4, 139.3, 147.0, 166.4; LC-ESI-MS: 363 (M+1); IR (neat): ν 3416(s), 3025(m), 2904(m), 2786(s), 1703(s), 1659(m), 1615(w), 1301(s), 1037(m) cm⁻¹; Anal. calcd for (C₂₂H₂₄N₂O₂): C, 75.83; H, 6.94; N, 8.04; Found: C, 75.80; H, 6.92; N, 8.03.

(*c*-Hex:AcOEt 8:2). Yield 88%. Brown viscous oil. (*E/Z* > 95:5). ¹H-NMR (300 MHz, CDCl₃): δ 1.30 (t, *J* = 7.2 Hz, 3H), 2.47 (s, 3H), 3.25 (dd, *J* = 1.5, 6.0 Hz, 2H), 3.66 (s, 2H), 3.78 (s, 2H), 4.20 (q, *J* = 7.2 Hz, 2H), 6.08 (dt, *J* = 1.5, 15.6 Hz, 1H), 7.01-7.08 (m, 2H), 7.11 (d, *J* = 2.1 Hz, 1H), 7.23-7.42 (m, 7H), 7.99 (br, 1H); ¹³C-NMR (75 MHz, CDCl₃): δ 14.2, 21.5, 49.3, 54.2, 58.3, 60.3, 110.6, 119.3, 122.6, 123.5, 123.6, 125.3, 126.9, 127.9(2C), 128.2(2C), 128.6, 128.8, 134.7, 139.4, 147.0, 166.4; LC-ESI-MS: 363 (M+1); IR (neat): ν 3389(s), 3024(m), 2983(m), 2799(m), 1711(s), 1653(m), 1451(m), 1367(m), 1176(m) cm⁻¹; Anal. calcd for (C₂₃H₂₆N₂O₂): C, 76.21; H, 7.23; N, 7.73; Found: C, 76.18; H, 7.16; N, 7.70.

Preparation of (*E*)-4-[benzyl-(1*H*-indol-2-yl-methyl)-amino]-but-2-enyl alcohol.

The ethyl ester (1.5 mmol, 1.0 equiv) was dissolved in dry toluene (20 mL) and then DIBALH (1.0 M in hexane, 2.5 equiv) was added dropwise at -78°C . The reaction was stirred at -78°C for 1h (complete consumption of the ester was judged by TLC) and then quenched with 0.5 mL of AcOH:H₂O (1:1) mixture. The organics were washed with H₂O concentrated under reduced pressure and purified by flash chromatography.

(CH₂Cl₂:MeOH 9:1). Yield 91%. Brown viscous oil. ¹H-NMR (200 MHz, CDCl₃): δ 2.50 (br, 1H), 3.14 (d, J = 3.4 Hz, 1H), 3.66 (s, 2H), 3.75 (s, 2H), 3.84 (s, 3H), 4.11-4.18 (m, 1H), 5.79 (s, 1H), 6.30 (s, 1H), 6.80 (dd, J = 3.4, 8.2 Hz, 1H), 7.03 (s, 3H), 7.23-7.37 (m, 7H), 8.56 (br, 1H); ¹³C-NMR (50 MHz, CDCl₃): δ 51.0, 55.1, 55.9, 58.0, 63.1, 101.5, 102.1, 111.4, 111.6, 127.3(2C), 128.4(2C), 127.9, 128.8, 129.1, 131.2, 133.1, 136.7, 137.9, 154.1; LC-ESI-MS: 336 (M+1); IR (nujol): ν 3605(w), 3453(m), 3318(m), 3048(s), 2983(m), 2837(s), 1614(m), 1587(s), 1479(s), 1263(s) cm⁻¹; Anal. calcd for (C₂₁H₂₄N₂O₂): C, 74.97; H, 7.19; N, 8.33; Found: C, 74.90; H, 7.12; N, 8.30.

(CH₂Cl₂:MeOH 9:1). Yield 98%. Brown viscous oil. ¹H-NMR (200 MHz, CDCl₃): δ 3.13 (s, 2H), 3.65 (s, 2H), 3.75 (s, 2H), 4.13 (s, 2H), 5.78-5.80 (m, 2H), 6.31 (s, 1H), 7.05-7.17 (m, 1H), 7.20-7.35 (m, 7H), 7.40 (s, 1H), 7.48 (br, 1H); ¹³C-NMR (75 MHz, CDCl₃): δ 50.7, 55.1, 57.9, 62.9, 101.3, 111.7, 119.4, 121.7, 125.1, 125.3, 127.4, 127.5, 128.2, 128.4, 129.0, 129.1, 129.4, 133.3, 134.4, 137.5; LC-ESI-MS: 341 (M+1), 363 (M+Na); IR (neat): ν 3556(m), 2415(s), 3026(m), 2918(s), 2815(s), 1717(m), 1576(s), 1490(s), 1144(w) cm⁻¹; Anal. calcd for (C₂₀H₂₁ClN₂O): C, 70.48; H, 6.21; N, 8.22; Found: C, 70.45; H, 6.15; N, 8.15.

(CH₂Cl₂:MeOH 9:1). Yield 94%. Brown viscous oil. ¹H-NMR (200 MHz, CDCl₃): δ 2.44 (s, 3H), 3.23 (s, 2H), 3.80 (s, 2H), 3.90 (s, 2H), 4.14 (s, 2H), 5.80-5.89 (m, 2H), 6.34 (s, 1H), 6.99 (d, J = 8.0 Hz, 1H), 7.25-7.40 (m, 8H), 9.45 (br, 1H); ¹³C-NMR (75 MHz, CDCl₃): δ 21.7, 49.7, 53.3, 55.9, 62.1, 105.6, 112.0, 118.9, 120.3, 124.9, 127.7(2C), 128.0(2C), 129.4, 129.7, 130.4, 131.2, 131.4, 136.1, 140.6; LC-ESI-MS: 321 (M+1); IR (neat): ν 3245(s), 3031(s), 1722(s), 1554(m), 1452(s), 1315, (w), 1009(m) cm⁻¹; Anal. calcd for (C₂₁H₂₄N₂O): C, 78.71; H, 7.55; N, 8.74; Found: C, 78.65; H, 7.49; N, 8.70.

(CH₂Cl₂:MeOH 95:5). Yield 41%. Pale brown oil. ¹H-NMR (300 MHz, CDCl₃): δ 2.20 (br, 1H), 3.11 (d, *J* = 4.8 Hz, 2H), 3.63 (s, 4H), 4.13 (s, 2H), 5.76 (d, *J* = 3.3, Hz, 2H), 6.04 (s, 1H), 6.12 (s, 1H), 6.47-6.76 (m, 1H), 7.26-7.34 (m, 5H), 8.70 (br, 1H); ¹³C-NMR (50 MHz, CDCl₃): δ 50.5, 54.7, 57.8, 62.9, 108.0, 108.3, 118.0, 126.9, 127.6, 128.5(2C), 128.6, 129.4(2C), 133.9, 136.9; LC-ESI-MS: 257 (M+1); IR (neat): ν 3404(s), 2922 (s), 2852(m), 1639(m), 1455(m) cm⁻¹; Anal. calcd for (C₁₆H₂₀N₂O): C, 74.97; H, 7.86; N, 10.93; Found: C, 74.95; H, 7.85; N, 10.90.

(*c*-Hex:AcOEt 70:30). Yield 37%. Viscous yellow oil. (*E/Z* > 95:5). ¹H-NMR (200 MHz, CDCl₃): δ 1.74 (s, 3H), 3.02 (s, 2H), 3.60 (s, 2H), 3.69 (s, 2H), 4.18 (d, *J* = 7.8 Hz, 2H), 5.67 (t, *J* = 5.8 Hz, 1H), 6.37 (s, 1H), 7.05-7.19 (m, 2H), 7.22-7.37 (m, 6H), 7.56 (d, *J* = 7.2 Hz, 1H), 8.35 (br, 1H); ¹³C-NMR (50 MHz, CDCl₃): δ 15.2, 51.1, 58.3, 59.2, 62.2, 101.7, 110.7, 119.6, 120.1, 121.5, 127.2, 128.4(2C), 128.5(2C), 129.0, 132.8, 136.0, 136.7, 138.5; LC-ESI-MS: 321 (M+1); Anal. calcd for (C₂₁H₂₄N₂O): C, 78.71; H, 7.55; N, 8.74; Found: C, 78.62; H, 7.51; N, 8.71.

(CH₂Cl₂:EtOAc 95:5). Yield 65%. Viscous yellow oil. ¹H-NMR (200 MHz, CDCl₃): δ 1.82 (br, 1H), 3.13 (d, *J* = 3.0 Hz, 2H), 3.64 (s, 2H), 3.80 (s, 2H), 4.01 (s, 2H), 5.79 (s, 2H), 7.17-7.37 (m, 9H), 7.75 (d, *J* = 7.0 Hz, 1H), 8.08 (br, 1H); ¹³C-NMR (50 MHz, CDCl₃): δ 49.4, 55.2, 58.1, 63.4, 111.0, 113.6, 119.4, 119.8, 122.0, 123.4, 126.8, 127.8(2C), 128.1(2C), 128.9, 130.1, 131.6, 136.4, 139.7; LC-ESI-MS: 307 (M+1); IR (nujol): ν 3423(s), 2926(s), 1653(s), 1380(m), 985(m), 572(m) cm⁻¹; Anal. calcd for (C₂₀H₂₂N₂O): C, 78.40; H, 7.24; N, 9.14; Found: C, 78.35; H, 7.21; N, 9.13

(CH₂Cl₂:EtOAc 95:5). Yield 55%. Viscous yellow oil. ¹H-NMR (200 MHz, CDCl₃): δ 2.45 (s, 3H), 3.28 (d, *J* = 4.4 Hz, 2H), 3.85 (s, 2H), 4.01 (s, 2H), 4.12 (s, 2H), 5.80-5.8 (m, 2H), 7.04 (d, *J* = 8.4 Hz, 1H), 7.30-7.43 (m, 8H), 8.54 (br, 1H); ¹³C-NMR (75 MHz, CDCl₃): δ 21.8, 22.6, 48.6, 54.2, 57.3, 63.0, 108.7, 111.4, 118.8, 119.0, 124.1, 128.2, 128.5(2C), 128.8(2C), 129.3, 129.8, 130.1, 134.8, 135.3; LC-ESI-MS: 321 (M+1); IR (neat): ν 3302(s), 3044(m), 2908(m), 1576(s), 1436(m), 1263(w), 1093(w), 1008(w) cm⁻¹; Anal. calcd for (C₂₁H₂₄N₂O): C, 78.71; H, 7.55; N, 8.74; Found: C, 78.65; H, 7.50; N, 7.73.

Preparation of the indolylacetate **1b**.

To a solution of alcohol (206 mg, 0.67 mmol) in dry CH₂Cl₂ (8 mL) were added 113 μ L (0.81 mmol) of TEA and 9 mg (10 mol%) of DMAP. The solution was cooled to 0°C, stirred for 10 min then 76 μ L (0.81 mmol) of acetic anhydride were added. The reaction mixture was allowed to stir at rt for 24h then quenched with water (5 mL), extracted with AcOEt (3 x 7 mL) and the collected organic phases washed with diluted HCl. After evaporation under reduced pressure, **1b** was purified by flash chromatography by using *c*-Hex:AcOEt 8:2 as the eluent mixture.

Pale yellow oil. Yield 75%. ¹H-NMR (200 MHz, CDCl₃): δ 2.08 (s, 3H), 3.15 (d, *J* = 5.6 Hz, 2H), 3.67 (s, 2H), 3.78 (s, 2H), 4.56 (d, *J* = 5.0 Hz, 2H), 5.80-5.85 (m, 2H), 6.38 (s, 1H), 7.08-7.17 (m, 1H), 7.17-7.40 (m, 7H), 7.57 (d, *J* = 8.8 Hz, 1H), 9.62 (br, 1H); ¹³C-NMR (50 MHz, CDCl₃): δ 21.0, 50.8, 54.9, 57.9, 64.5, 101.4, 110.6, 119.5, 120.0, 121.4, 127.1, 127.4, 128.3, 128.4, 128.9, 132.1, 135.9, 136.5, 138.5, 170.8; LC-ESI-MS: 349 (M+1), 371 (M+Na); IR (neat): ν 3391(s), 3031(m), 2907(m), 2799(m), 1734(s), 1456(m), 1238(s), 1026(w) cm⁻¹. Anal. calcd for (C₂₂H₂₄N₂O₂): C, 75.83; H, 6.94; N, 8.04; Found: C, 75.80; H, 6.92; N, 8.01.

Preparation of indolylcarbonates **1c-e/6a,b**.

To a solution of alcohol (1.0 mmol, 1.0 equiv) and pyridine (2.0 equiv) in dry Et₂O: CH₂Cl₂ mixture (1:1, 10 mL), a solution of methyl chloroformate (1.5 equiv) dissolved in dry Et₂O (1.0 mL) was added dropwise at 0°C. The reaction mixture was stirred for 24h at rt then quenched with water (5 mL), extracted with AcOEt (3 x 5 mL), dried over Na₂SO₄, concentrated under reduced pressure and purified by flash chromatography.

1c. (CH₂Cl₂:AcOEt 8:2). Yield 71%. Yellow oil. ¹H-NMR (200 MHz, CDCl₃): δ 3.16 (d, *J* = 5.6 Hz, 2H), 3.67 (s, 2H), 3.76 (s, 2H), 3.84 (s, 3H), 3.89 (s, 3H), 4.66 (d, *J* = 5.6 Hz, 2H), 5.83-5.92 (m, 2H), 6.35 (s, 1H), 6.85 (dd, *J* = 2.2, 8.8 Hz, 1H), 7.07 (d, *J* = 2.6 Hz, 1H), 7.27-7.40 (m, 6H), 8.37 (br, 1H); ¹³C-NMR (75 MHz, CDCl₃): δ 50.9, 54.8, 55.9, 58.0, 62.2, 67.8, 109.7, 111.6, 118.5, 121.4, 127.4, 128.0, 128.4, 128.6, 129.1, 133.4, 133.9, 134.4,

137.7, 139.6, 154.1; LC-ESI-MS: 365 (M+1), 387 (M+Na), 400 (M+K); IR (neat): ν 3693(w), 3389(s), 3085(w), 3058(w), 3025(m), 2927(s), 1710(s), 1655(m), 1590(m), 1476(s), 1367(m) cm^{-1} .
 Anal. calcd for ($\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_4$): C, 70.03; H, 6.64; N, 7.10; Found: C, 70.00; H, 6.69; N, 7.11.

1d. (*c*-Hex:AcOEt 1:1). Yield 68%. Yellow oil. ^1H -NMR (200 MHz, CDCl_3): δ 3.06 (d, J = 5.7 Hz, 2H), 3.56 (s, 2H), 3.66 (s, 2H), 3.73 (s, 3H), 4.56 (d, J = 5.4 Hz, 2H), 5.76-5.82 (m, 2H), 6.25 (s, 1H), 7.06 (dd, J = 2.2, 8.8 Hz, 1H), 7.19-7.29 (m, 6H), 7.44 (s, 1H), 8.39 (br, 1H); ^{13}C -NMR (75 MHz, CDCl_3): δ 50.7, 54.8, 58.0, 60.4, 67.8, 101.0, 111.6, 119.4, 121.6, 125.1, 126.9, 127.3, 128.4, 128.9, 129.5, 132.6, 134.2, 138.1, 138.3, 155.6. LC-ESI-MS: 399 (M+1), 421 (M+Na), 437 (M+K); IR (neat): ν 3432(s), 3031(m), 2874(s), 1744(s), 1457(m) cm^{-1} . Anal. calcd for ($\text{C}_{22}\text{H}_{23}\text{ClN}_2\text{O}_3$): C, 66.24; H, 5.81; N, 7.02; Found: C, 66.29; H, 5.80; N, 6.98.

1e. (CH_2Cl_2 :EtOAc 95:5). Yield 61%. Pale yellow oil. ^1H -NMR (300 MHz, CDCl_3): δ 2.42 (s, 3H), 3.09 (d, J = 6.0 Hz, 2H), 3.60 (s, 2H), 3.70 (s, 2H), 3.80 (s, 3H), 4.61 (d, J = 5.4 Hz, 2H), 5.70-5.90 (m, 2H), 6.28 (s, 1H), 6.97 (dd, J = 1.2, 8.1 Hz, 1H), 7.14-7.34 (m, 7H), 8.29 (br, 1H); ^{13}C -NMR (50 MHz, CDCl_3): δ 21.4, 50.8, 54.8(2C), 57.9, 67.8, 101.0, 110.3, 119.7, 123.0, 126.6, 127.1, 128.3(2C), 128.7(2C), 128.9(2C), 132.9, 134.3, 136.5, 138.6, 155.6. LC-ESI-MS: 379 (M+1); IR (neat): ν 3395(s), 3030(m), 2878(s), 2807(s), 1734(s), 1582(w), 1495(m), 1250(s) cm^{-1} . Anal. calcd for ($\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_3$): C, 72.99; H, 6.92; N, 7.40; Found: C, 72.95; H, 6.87; N, 7.40.

1f. (*c*-Hex:EtOAc 70:30). Yield 45%. Pale yellow oil. ^1H -NMR (300 MHz, CDCl_3): δ 3.09 (d, J = 5.7 Hz, 2H), 3.56 (d, J = 3.0 Hz, 4H), 3.79 (s, 3H), 4.61 (d, J = 5.7 Hz, 2H), 5.74-5.81 (m, 1H), 5.84-5.91 (m, 1H), 6.03 (s, 1H), 6.12 (dd, J = 2.7, 5.4 Hz, 1H), 6.74 (s, 1H), 7.27-7.33 (m, 5H), 8.42 (br, 1H); ^{13}C -NMR (75 MHz, CDCl_3): δ 50.5, 54.7, 57.8, 62.3, 67.9, 107.5, 108.0, 117.2, 127.1, 128.3(2C), 129.0(2C), 129.9, 138.9, 155.7; LC-ESI-MS: 315 (M+1); Anal. calcd for ($\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_3$): C, 68.77; H, 7.05; N, 8.91; Found: C, 68.71; H, 7.00; N, 8.93.

(*c*-Hex:AcOEt 95:5→90:10). Yield 93%. Viscous yellow oil. (*E/Z* > 95:5). ¹H-NMR (200 MHz, CDCl₃): δ 1.80 (s, 3H), 3.01 (s, 2H), 3.58 (s, 2H), 3.67 (s, 2H), 3.78 (s, 3H), 4.72 (d, *J* = 7.0 Hz, 2H), 5.72 (t, *J* = 7.2 Hz, 1H), 6.38 (s, 1H), 7.05-7.20 (m, 2H), 7.23-7.37 (m, 6H), 7.57 (d, *J* = 7.4 Hz, 1H), 8.32 (br, 1H); ¹³C-NMR (50 MHz, CDCl₃): δ 15.4, 50.9, 54.8, 58.2, 61.8, 64.4, 101.6, 110.6, 119.6, 120.1, 121.5, 121.6, 126.1, 127.4, 128.4(2C), 128.9(2C), 129.2, 130.7, 140.4, 155.7; LC-ESI-MS: 379 (M+1), 401 (M+Na); IR (neat): ν 3401, 3055, 3016, 2956, 2825, 1752, 1455, 1268, 1140 cm⁻¹; Anal. calcd for (C₂₃H₂₆N₂O₃): C, 72.99; H, 6.92; N, 7.40; Found: C, 72.95; H, 6.89; N, 7.38.

6a. (CH₂Cl₂:MeOH 95:5). Yield 84%. Yellow viscous oil. ¹H-NMR (200 MHz, CDCl₃): δ 3.13 (d, *J* = 5.4 Hz, 2H), 3.62 (s, 2H), 3.69 (s, 2H), 3.78 (s, 3H), 4.62 (d, *J* = 6.4 Hz, 2H), 5.74-5.84 (m, 1H), 5.89-5.99 (m, 1H), 7.09-7.39 (m, 9H), 7.73 (d, *J* = 7.2 Hz, 1H), 8.07 (br, 1H); ¹³C-NMR (50 MHz, CDCl₃): δ 49.1, 54.7, 57.9, 60.3, 68.1, 110.9, 113.2, 119.2, 119.7, 121.8, 123.4, 125.7, 126.7, 127.6(2C), 128.1(2C), 128.8, 134.2, 136.3, 139.6, 155.5. LC-ESI-MS: 365 (M+1), 387 (M+Na); IR (neat): ν 3419(s), 3023(w), 2950(m), 2729(m), 1734(s), 1491(m), 1456(s), 1259(s), 1096(m), 736(s) cm⁻¹. Anal. calcd for (C₂₂H₂₄N₂O₃): C, 72.50; H, 6.64; N, 7.69; Found: C, 72.46; H, 6.56; N, 7.60.

6b. (CH₂Cl₂:MeOH 95:5). Yield 86%. Brown viscous oil. ¹H-NMR (200 MHz, CDCl₃): δ 2.47 (s, 3H), 3.13 (d, *J* = 5.4 Hz, 2H), 3.62 (s, 2H), 3.75 (s, 2H), 3.79 (s, 3H), 4.62 (d, *J* = 6.0 Hz, 2H), 5.70-6.01 (m, 2H), 7.04 (d, *J* = 8.4 Hz, 1H), 7.10 (s, 1H), 7.23-7.45 (m, 7H), 7.94 (br, 1H); ¹³C-NMR (50 MHz, CDCl₃): δ 21.5, 49.0, 54.8, 57.9, 64.7, 68.1, 110.6, 112.9, 119.4, 123.6, 125.8, 126.5, 126.8, 128.0(2C), 128.1(2C), 128.5, 129.0, 134.2, 134.7, 139.8, 155.6. LC-ESI-MS: 379 (M+1); IR (neat): ν 3419(s), 3023(m), 2950(m), 2792(s), 1734(s), 1616(w), 1491(m), 1456(s), 1259(s), 736(m) cm⁻¹. Anal. calcd for (C₂₃H₂₆N₂O₃): C, 72.99; H, 6.92; N, 7.40; Found: C, 72.95; H, 6.90; N, 7.41.

Preparation of indolylcarbonate 1h.

The synthesis of the indolyl-aldehyde was performed analogously to the previously described procedure for the synthesis of indolyl-esters. In this case, a slight excess of (*E*)-4-bromo-2-methylcrotonaldehyde³ (1.55 mmol, 253 mg) respect to 1.50 of indolyl-amine was used and all the reaction was carried out at 0°C. After completion of the reaction judged by ¹H-NMR (32h), the reaction was quenched with H₂O and the volatiles were removed under reduced pressure using a cooled rotavapor bath. The remaining aqueous phase was extracted with CH₂Cl₂ and washed with brine. After evaporation, the crude compound (viscous brown oil) was stirred in 5 mL of *c*-Hex until a red solid was obtained and isolated by filtration. The crude aldehyde (≈10% of starting indole-amine was still detected by ¹H-NMR) was directly employed in the next step without further purifications. ¹H-NMR (300 MHz, CDCl₃): δ 1.68 (d, *J* = 1.2 Hz, 3H), 3.40 (d, *J* = 6.0 Hz, 2H), 3.69 (s, 2H), 3.80 (s, 2H), 6.40 (s, 1H), 6.58 (dt, *J* = 1.5, 6.3 Hz, 1H), 7.06-7.15 (m, 1H), 7.17-7.21 (m, 1H), 7.30-7.39 (m, 5H), 7.42-7.48 (m, 1H), 7.55 (d, *J* = 7.2 Hz, 1H), 8.41 (br, 1H), 9.39 (s, 1H). LC-ESI-MS: 319 (M+1). The crude aldehyde (1 mmol) was dissolved in anhydrous toluene (10 mL) and the solution was cooled to -78°C. After 5 min. stirring at this temperature, a solution of DIBAL in *n*-Hex (1.1 mmol, 1 M) was added dropwise. The reaction mixture was stirred at -78°C for 2.5h, then 5 mL of H₂O were added and allowing the temperature to worm up to rt. Then, the two phases were separated and the aqueous extracted with CH₂Cl₂ (3 x 5 mL). The collected organic phases were washed with brine (5 mL) and dried under Na₂SO₄. After removal of the volatiles, the crude was purified by flash chromatography (*c*-Hex:AcOEt 60:40) to leave the desired alcohol as a pale yellow oil in 35% yield (two steps). ¹H-NMR (200 MHz, CDCl₃): δ 1.61 (s, 3H); 3.13 (d, *J* = 5.4 Hz, 2H); 3.63 (s, 2H); 3.74 (s, 2H); 3.98 (s, 2H); 5.77 (t, *J* = 6.6 Hz, 1H); 6.36 (s, 1H); 7.01-7.10 (m, 2H); 7.14-7.37 (m, 6H); 7.52 (d, *J* = 7.2 Hz, 1H); 8.54 (br, 1H). ¹³C-NMR (50

MHz, CDCl₃): δ 14.0, 50.2, 51.2, 57.7, 67.7, 102.9, 111.2, 119.8, 120.2, 122.0, 127.8, 128.0, 128.3, 128.7(2C), 129.1, 129.6(2C), 129.7, 136.4. LC-ESI-MS: 321 (M+1).

The final synthesis of the carbonate **1h** was performed analogously to the previously described for the synthesis of indolyl-carbonates **1**. (*c*-Hex:AcOEt 90:10) to leave the desired carbonate as a pale yellow solid in 38% yield. ¹H-NMR (200 MHz, CDCl₃): δ 1.60 (s, 3H), 3.62 (s, 2H), 3.73 (s, 2H), 3.79 (s, 3H), 4.54 (s, 2H), 5.70 (t, *J* = 6.0 Hz, 1H), 3.37 (s, 1H), 7.07-7.25 (m, 2H), 7.29-7.35 (m, 6H), 7.54 (d, *J* = 9.6 Hz, 1H), 8.62 (br, 1H). IR (neat): ν 3409, 3050, 3022, 2815, 1749, 1450, 1281 cm⁻¹. ¹³C-NMR (75 MHz, CDCl₃): δ 14.2, 50.4, 51.0, 54.8, 58.0, 72.9, 101.7, 110.8, 119.6, 120.1, 121.2, 121.6, 126.0, 127.3, 128.4(2C), 128.7, 129.1(2C), 130.6, 136.1, 155.7. LC-ESI-MS: 379 (M+1), 401 (M+Na). Anal. calcd for (C₂₃H₂₆N₂O₃): C, 72.99; H, 6.92; N, 7.40; Found: C, 72.96; H, 6.86; N, 7.42.

Preparation of 4-vinyl-THBCs (**2**) and 1-vinyl-THGCs (**7**).

The reaction was carried out at rt under nitrogen atmosphere. A solution of [Pd₂dba₃].CHCl₃ (3.6 mmol, 5 mol%) and the desired chiral ligand (11 mol%) in anhydrous CH₂Cl₂ (1.0 mL) was stirred until the solution colour turned from deep red to orange (about 30 min). Then, the carbonate **1/6** (0.07 mmol, 1 equiv) dissolved in 0.5 mL of CH₂Cl₂ and Li₂CO₃ (2 equiv) were added. The resulting reaction mixture slowly turned from yellow. The reaction was stirred overnight (complete consumption of **1/6** as judged by TLC) and then quenched with water (4 mL) and extracted with AcOEt. The combined organics were dried over Na₂SO₄ and concentrated under reduced pressure. The crude was purified by passage through a pad of silica gel and the enantiomeric excess determined through HPLC analysis with chiral column. The *C/N* regiochemistry of the cyclization was determined on the reaction crude by HPLC and confirmed after flash chromatography.

(*R*)-**2a**. Pale yellow oil. (CH₂Cl₂:AcOEt 8:2). Yield 95% (*C/N* > 50:1). Ee = 92%. $[\alpha]_D^{25}$ = +55.6 (*c* 0.4, CHCl₃). HPLC analysis: OD column (225m), method: *n*-Hex:IPA 90:10, flow 0.5 mL/min, *t*_S = 28.7 min, *t*_R = 30.2 min.¹

(R)-2c. Yellow solid. (CH₂Cl₂:AcOEt 8:2). Mp = 138-141°C. Yield 98% (*C/N* > 50:1). Ee = 90%, (yield = 50%, ee = 94% at 0°C). [α]^D = 45.2 (*c* 0.9, CHCl₃).

HPLC analysis: AD column (225 nm), method: *n*-Hex:IPA 90:10 flow 0.6 mL/min, *t*_S = 19.9 min, *t*_R = 27.5 min. ¹H-NMR (200 MHz, CDCl₃): δ 2.66 (dd, *J* = 7.0, 11.8 Hz, 1H), 2.97 (dd, *J* = 2.6, 11.8 Hz, 1H), 3.63 (s, 3H), 3.77 (d, *J* = 3.0 Hz, 2H), 3.83 (s, 3H), 5.14-5.31 (m, 2H), 5.85-6.08 (m, 1H), 6.77 (dd, *J* = 2.2, 8.8 Hz, 1H), 7.01 (d, *J* = 1.8 Hz, 1H), 7.17 (d, *J* = 8.8 Hz, 1H), 7.27-7.38 (m, 5H), 7.60 (br, 1H); ¹³C-NMR (75 MHz, CDCl₃): δ 38.8, 50.5, 56.1, 57.5, 62.2, 101.9, 110.0, 110.9, 111.5, 115.7, 127.5, 127.8(2C), 128.6(2C), 129.3, 131.4, 133.3, 138.6, 140.5, 154.0; LC-ESI-MS: 319 (M+1); IR (nujol): ν 3395(w), 3188(m), 2726(s), 1731(m), 1460(s), 1373(s) cm⁻¹. Anal. calcd for (C₂₁H₂₂N₂O): C, 79.21; H, 6.69; N, 8.80; Found: C, 79.05; H, 6.60; N, 8.77.

(R)-2d. Yellow solid. (CH₂Cl₂:AcOEt 95:5). Mp = 140-142°C. Yield 82% (*C/N* > 50:1). Ee = 82%. [α]^D = +48.7 (*c* 0.2, CHCl₃). HPLC analysis: OD column

(225/280 nm), method: *n*-Hex:IPA 93:7 flow 0.5 mL/min, *t*_R = 39.6 min, *t*_S = 45.2 min. ¹H-NMR (200 MHz, CDCl₃): δ 2.67 (dd, *J* = 7.0, 11.8 Hz, 1H), 3.02 (dd, *J* = 5.2, 11.8 Hz, 1H), 3.64 (s, 2H), 3.66-3.69 (m, 1H), 3.77 (d, *J* = 2.6 Hz, 2H), 5.21 (t, *J* = 8.4 Hz, 1H), 5.33 (s, 1H), 5.83-6.01 (m, 1H), 7.10 (dd, *J* = 2.2, 8.8 Hz, 1H), 7.19-7.51 (m, 7H), 7.85 (br, 1H); ¹³C-NMR (50 MHz, CDCl₃): δ 30.9, 37.6, 49.7, 60.4, 109.0, 111.9, 116.9, 118.5, 121.8, 125.1, 127.6(2C), 128.1(2C), 128.6, 129.6, 134.6, 136.6, 138.8, 155.1. ESI-MS: 322 (M+1); IR (neat): ν 3399(s), 2999(m), 2950(s), 2826(s), 1749(s), 1528(m), 1490(w), 1257(s) cm⁻¹. Anal. calcd for (C₂₀H₁₉ClN₂): C, 74.41; H, 5.93; N, 8.68; Found: C, 74.37; H, 5.89; N, 8.65.

(R)-2e. Pale yellow solid. (CH₂Cl₂:AcOEt 95:5). Mp = 152-153°C. Yield 95% (*C/N* > 50:1). Ee = 97%. [α]^D = +63.0 (*c* 0.3, CHCl₃). HPLC analysis: OD column

(225 nm), method: *n*-Hex:IPA 92:8 flow 0.5 mL/min, *t*_S = 30.8 min, *t*_R = 32.1 min. ¹H-NMR (300 MHz, CDCl₃): δ 2.42 (s, 3H), 2.67 (dd, *J* = 6.9, 11.4, 1H), 2.97 (dd, *J* = 4.8, 11.4 Hz, 1H), 3.63 (d, *J* = 11.7 Hz, 2H), 3.70-3.74 (m, 1H), 3.77 (d, *J* = 11.7 Hz, 2H), 5.16 (dd, *J* = 1.5, 9.9 Hz, 1H), 5.30 (d, *J* = 16.2 Hz, 1H), 5.92-6.03 (m, 1H), 6.94 (d, *J* = 8.1 Hz, 1H), 7.16 (d, *J* = 9.0 Hz, 1H), 7.29-7.41 (m, 6H), 7.59 (br, 1H). ¹³C-NMR (75 MHz, CDCl₃): δ 21.5, 38.4, 50.2, 57.3, 61.9, 109.5, 110.3, 115.3, 118.8, 122.7, 127.2, 127.3(2C), 128.3(2C), 128.5, 129.0, 132.2, 134.4, 138.4, 140.5. ESI-MS: 303 (M+1); IR (nujol): ν 3386(s), 2925(s), 2854(s), 1450(s), 1346(m) cm⁻¹. Anal. calcd for (C₂₁H₂₂N₂): C, 83.40; H, 7.33; N, 9.26; Found: C, 83.35; H, 7.27; N, 9.25.

2f. Viscous brown oil. (*c*-Hex:AcOEt 90:10). Yield 85% (*C/N* > 50:1). Ee = 95%.

$[\alpha]_D^{25} = -23.6$ (*c* 0.36, CHCl₃). HPLC analysis: OD column (214 nm), method: *n*-Hex:IPA 90:10 flow 0.5 mL/min, *t*(+) = 12.3 min, *t*(-) = 13.2 min. ¹H-NMR (200 MHz, CDCl₃): δ 2.47 (dd, *J* = 8.4, 12.4 Hz, 1H), 3.01 (dd, *J* = 6.0 Hz, 1H), 3.42-3.62 (m, 2H), 5.13 (dd, *J* = 1.4, 9.8 Hz, 1H), 5.18-5.27 (m, 1H), 5.71-5.88 (m, 1H), 5.96 (t, *J* = 2.6 Hz, 1H), 6.56 (t, *J* = 3.0 Hz, 1H), 7.30-7.41 (m, 5H), 7.82 (br, 1H). ¹³C-NMR (50 MHz, CDCl₃): δ 39.6, 51.1, 56.3, 62.0, 105.7, 117.1, 119.2, 121.2, 127.2, 127.4, 128.4(2C), 129.3(2C), 132.0, 138.4. ESI-MS: 239 (*M*+1); IR (nujol): ν 3392(s), 2932(s), 2860(s), 1459(s), 1357(m) cm⁻¹. Anal. calcd for (C₁₆H₁₈N₂): C, 80.63; H, 7.61; N, 11.75; Found: C, 80.60; H, 7.58; N, 11.72.

2g. Viscous brown oil. (*c*-Hex:AcOEt 90:10). Yield 45% (*C/N* > 50:1). Ee = 90%.

$[\alpha]_D^{25} = -15.2$ (*c* 0.5, CHCl₃). HPLC analysis: OD column (214 nm), method: *n*-Hex:IPA 97:3 flow 0.5 mL/min, *t*(-) = 38.9 min, *t*(+) = 41.9 min. ¹H-NMR (200 MHz, CDCl₃): δ 1.60 (s, 3H), 2.55 (d, *J* = 11.6 Hz, 1H), 2.68 (d, *J* = 11.6 Hz, 1H), 3.64 (s, 2H), 3.77 (s, 2H), 5.01 (s, 1H), 5.14 (d, *J* = 6.0 Hz, 1H), 6.09 (dd, *J* = 10.6, 16.4 Hz, 1H), 7.03-7.16 (m, 2H), 7.35-7.46 (m, 6H), 7.56 (d, *J* = 5.2 Hz, 1H), 7.69 (br, 1H). ¹³C-NMR (50 MHz, CDCl₃): δ 26.9, 39.0, 51.0, 62.5, 64.1, 110.8, 112.6, 119.1, 119.8, 121.1, 121.7, 125.7, 128.3(2C), 128.8(2C), 132.2, 133.9, 145.2. ESI-MS: 303 (*M*+1); IR (nujol): ν 3380(s), 2926(s), 2856(s), 1451(s), 1351(m) cm⁻¹. Anal. calcd for (C₂₁H₂₂N₂): C, 83.40; H, 7.33; N, 9.26; Found: C, 83.35; H, 7.30; N, 9.22.

2h. Viscous brown oil. (*c*-Hex:AcOEt 90:10). Yield 49% (*C/N* > 50:1). Ee = 94%.

$[\alpha]_D^{25} = -18.9$ (*c* 0.1, CHCl₃). HPLC analysis: OD column (214 nm), method: *n*-Hex:IPA 87:13 flow 0.5 mL/min, *t*(-) = 18.6 min, *t*(+) = 21.4 min. ¹H-NMR (200 MHz, CDCl₃): δ 1.64 (s, 3H), 2.72 (dd, *J* = 3.6, 10.4 Hz, 1H), 3.03 (dd, *J* = 5.8, 10.4, 1H), 3.11 (d, *J* = 6.2 Hz, 1H), 3.66 (s, 2H), 3.85 (s, 2H), 4.96 (d, *J* = 5.6 Hz, 2H), 7.02-7.16 (m, 2H), 7.32-7.45 (m, 6H), 7.55 (d, *J* = 7.2 Hz, 1H), 8.44 (br, 1H). ¹³C-NMR (50 MHz, CDCl₃): δ 19.9, 41.8, 50.1, 56.7, 61.9, 109.9, 110.6, 112.8, 119.1, 119.3, 120.0, 121.2, 127.2, 128.3(2C), 129.0(2C), 132.7, 136.0, 138.4, 146.6. ESI-MS: 303 (*M*+1); IR (nujol): ν 3375(s), 2930(s), 2875(s), 1450(s), 1328(m) cm⁻¹. Anal. calcd for (C₂₁H₂₂N₂): C, 83.40; H, 7.33; N, 9.26; Found: C, 83.35; H, 7.29; N, 9.20.

7a. Yellow solid. (*c*-Hex:AcOEt 7:3). Yield 93% (*C/N* > 50:1). Ee = 93%.

$[\alpha]_D^{25} = +22.5$ (*c* 0.7, CHCl₃). Mp = 109-113°C. HPLC analysis: OD column (225

nm), method: *n*-Hex:IPA 90:10 flow 0.5 mL/min, *t*(+) = 26.5 min, *t*(-) = 27.9 min. ¹H-NMR (300 MHz, CDCl₃): δ 2.70 (dd, *J* = 6.6, 11.4 Hz, 1H), 3.03 (dd, *J* = 5.2, 11.4 Hz, 1H), 3.69-3.71 (m, 2H), 3.72-3.74 (m, 1H), 3.80 (d, *J* = 2.8 Hz, 2H), 5.17 (dd, *J* = 1.5, 9.9, 1H), 5.29 (dd, *J* = 1.5, 17.1 Hz, 1H), 5.91-6.03 (m, 1H), 7.05-7.16 (m, 2H), 7.29-7.43 (m, 6H), 7.55 (d, *J* = 7.0, 1H), 7.72 (br, 1H); ¹³C-NMR (75 MHz, CDCl₃): δ 38.7, 50.2, 57.3, 62.0, 110.1, 111.0, 115.9, 119.4, 119.6, 121.6, 117.6, 128.2(2C), 128.7(2C), 129.4, 132.0, 136.3, 138.1, 140.4; LC-ESI-MS: 289 (M+1); IR (neat): ν 3399(m), 3256(s), 3058(s), 2920(s), 2810(m), 1615(w), 1494(m), 1455(s), 1257(s), 1098(m) cm⁻¹. Anal. calcd for (C₂₀H₂₀N₂): C, 83.30; H, 6.99; N, 9.71; Found: C, 83.22; H, 6.94; N, 9.70.

7b. Yellow solid. (*c*-Hex:AcOEt 7:3). Yield 82% (*C/N* > 50:1). *Ee* = 92%. [α]_D²⁰ = +36.2 (*c* 0.3, CHCl₃). Mp = 134-136°C. HPLC analysis: OD column (225 nm), method: *n*-Hex:IPA 92:8 flow 0.5 mL/min, *t*(-) = 31.3 min, *t*(+) = 32.8 min.

¹H-NMR (200 MHz, CDCl₃): δ 2.37 (s, 3H), 2.65 (dd, *J* = 2.8, 6.8 Hz, 1H), 2.91-3.00 (m, 1H), 3.58-3.62 (m, 2H), 3.65-3.68 (m, 1H), 3.70-3.72 (m, 2H), 5.08 (d, *J* = 9.8 Hz, 1H), 5.21 (d, *J* = 16.6 Hz, 1H), 5.82-6.08 (m, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 7.11-7.18 (m, 1H), 7.21-7.34 (m, 6H), 7.57 (br, 1H); ¹³C-NMR (50 MHz, CDCl₃): δ 21.5, 38.4, 50.2, 57.3, 61.9, 110.3, 115.3, 118.8, 122.7, 127.2, 128.0(2C), 128.3(2C), 129.0, 129.4, 132.5, 134.4, 136.4, 138.8, 140.6; LC-ESI-MS: 303 (M+1); IR (neat): ν 3396(s), 2962(m), 2907(m), 1653(s), 1451(w), 1263(m), 1073(m) cm⁻¹. Anal. calcd for (C₂₁H₂₂N₂): C, 83.40; H, 7.33; N, 9.26; Found: C, 83.35; H, 7.29; N, 9.25.

Preparation of the (Z)-3-indolyl-methyl carbonate.

To a cooled solution (0°C) of 3-indolyl-amine (0.3 mmol, 70 mg) and Et₃N (50 μL, 0.6 mmol) in dry CH₂Cl₂ (5 mL), (Z)-(4-bromobut-2-en-1-yl) methyl carbonate⁴ (85 mg, 0.33 mmol) dissolved in 3 mL of CH₂Cl₂ was added. The ice bath was removed and the reaction mixture was stirred at rt overnight. Then the reaction was quenched with water (5 mL) and the organic phases washed with HCl (1N, 5 mL). After evaporation of the volatiles under reduced pressure the desired carbonate was purified by flash chromatography with *c*-Hex:AcOEt 8:2 as the eluent mixture.

Viscous yellow oil. Yield 81% (88 mg). ¹H-NMR (200 MHz, CDCl₃): δ 3.15 (d, *J* = 6.6 Hz, 2H), 3.62 (s, 2H), 3.78 (s, 5H), 4.63 (d, *J* = 6.6 Hz, 2H), 5.64-5.78 (m, 1H), 5.84-5.95 (m, 1H), 7.16-7.24 (m, 3H), 7.31-7.42 (m, 6H), 7.74 (d, *J* = 6.8 Hz, 1H), 8.03 (br, 1H); ¹³C-NMR (75 MHz, CDCl₃): δ 50.0, 50.9, 54.9, 58.2, 63.4, 101.7, 110.8, 119.5, 120.0, 121.4, 126.5, 127.2, 128.4(2C), 129.0(2C), 132.3, 136.1, 138.4, 155.8; LC-ESI-MS: 365 (M+1); IR (nujol): ν 3414(s), 2960(m), 2924 (s), 1750(s), 1456 (m),

1375(w), 1264(m), 739(w), 418(s) cm^{-1} . Anal. calcd for ($\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_3$): C, 72.50; H, 6.64; N, 7.69; Found: C, 72.39; H, 6.62; N, 7.63.

Determination of the absolute configuration.

1) X-Ray analysis

Cleavage of the benzyl group. The tetrahydro- β -carboline (*S*)-**2a** (ee: 65%, 60 mg, 0.21 mmol) was added to a suspension of $\text{Pd}(\text{OH})_2$ (20 mol%) in anhydrous MeOH (4 mL). The apparatus was connected to a balloon filled with hydrogen in order to maintain a reducing atmosphere (≈ 1 atm). The dark mixture was stirred at room temperature overnight. Then the insoluble black powder was filtered off (CAUTION!) with celite, washed with Et_2O (5 mL) and the organics evaporated under reduced pressure. The crude **8** was finally purified by flash chromatography (CH_2Cl_2 :MeOH 92:8) to give a brown solid. Yield = 95% (40 mg), ee = 65%. $[\alpha]_D^{25} = +45.7$ (c 0.7, CHCl_3). Mp = 119–121°C. HPLC analysis: OD column (225 nm), method: *n*-Hex:IPA 85:15 flow 0.5 mL/min, $t_S = 33.3$ min, $t_R = 35.2$ min. ^1H -NMR (200 MHz, CDCl_3): δ 1.03 (t, $J = 7.4$ Hz, 3H), 1.58–1.69 (m, 2H), 1.97–2.05 (m, 2H), 3.07 (dq, $J = 4.8, 14.2$ Hz, 2H), 4.00 (s, 2H), 7.09–7.15 (m, 2H), 7.27–7.32 (m, 1H), 7.53–7.60 (m, 1H), 8.05 (br, 1H); ^{13}C -NMR (75 MHz, CDCl_3): δ 11.8, 26.3, 34.2, 42.7, 47.5, 110.9, 112.2, 118.7, 119.2, 121.2, 127.0, 131.8, 135.8; LC-ESI-MS: 201 ($\text{M}+1$).

Synthesis of the THBC-camphorsulfonamide derivative (**9**).

To a solution of enantiomerically enriched (*R*)-4-ethyl-THBC (10 mg, 0.05 mmol, ee = 65%) in 2 mL of dry CH_2Cl_2 were added 6 mg (0.056 mmol) of DMAP. The solution was cooled to 0°C, stirred 10 min then 13 mg (0.055 mmol) of (1*R*)-(-)-10-camphorsulfonyl chloride were added. The reaction mixture was allowed to stir at rt for 10h then quenched with water (5 mL), extracted with CH_2Cl_2 and the collected organic phases washed with diluted HCl. After evaporation under reduced pressure, the diastereoisomeric sulfonamide mixture (**9**) was purified by flash chromatography by using CH_2Cl_2 : Et_2O 7:3 as the eluent mixture.

9. White solid. Yield 55% (11 mg, 82:18 diastereoisomeric mixture). LC-ESI-MS: $\text{Rt}_{(R,R)} = 14.6$ min, 415 ($\text{M}+1$), 437 ($\text{M}+\text{Na}$), 453 ($\text{M}+\text{K}$), see HPLC spectra. $\text{Rt}_{(S,R)} = 14.9$ min, 415 ($\text{M}+1$), 437 ($\text{M}+\text{Na}$), 453 ($\text{M}+\text{K}$).

Crystals of (*S,R*)-**9** (minor diastereoisomer) were obtained by slow diffusion of petroleum ether into a solution of **9** in acetone. Some crystals of (*S,R*)-**9** were then injected in LC-MS in order to assign the absolute C(4) configuration of both diastereoisomers (Figure S1).

Crystal data for (*S,R*)-**9** collected on a Bruker APEX II CCD diffractometer (Mo-K α radiation, $\lambda = 0.71073$ Å) Empirical absorption correction was applied, initial structure model by direct methods. Anisotropic full-matrix least-squares refinement on F^2 . C₂₃H₃₀N₂O₃S, M_r = 414.55, Orthorhombic, P2₁2₁2₁, $a = 8.7131(15)$, $b = 10.2665(17)$, $c = 24.621(4)$ Å, $V = 2202.4(6)$ Å³, $Z = 4$, $D_x = 1.250$ Mg/m³, $\mu = 0.173$ mm⁻¹, $F(000) = 888$, $T = 293(2)$ K, theta max 28.66°, 18802 reflections collected, 3717 reflections $I > 2\sigma(I)$. Final agreement indices $R_1 = 0.0413$ and $wR_2 = 0.1051$. Goodness-of-fit = 0.98, absolute structure parameter = -0.09(7), CCDC 275640 contains the supplementary crystallographic data for this crystal structure.

Figure S1

¹ The 2-indolylcarboxyaldehydes can be easily synthesized following a known procedure, see: Bandini, M.; Melloni, A. Umani-Ronchi, A. *Org. Lett.* **2004**, 6, 3199. **4f**, **5a,b** are commercially available (Aldrich and co.)

² (*E*)-Ethyl 4-bromo-3-methylcrotonate was obtained by In particular, (*E*)-4-bromo-3-methyl-2-butenoyl chloride was synthesized from the corresponding carboxylic acid with (COCl)₂/DMF_{cat} in CH₂Cl₂ (rt, 1.5h). The crude ester was obtained through a modification of the known procedure, see: Jeon, H.-S.; Yeo, J.E.; Jeong, Y.C.; Koo, S. *Synthesis*, **2004**, 2913, (EtOLi at -78°C). ¹H-NMR (200 MHz, CDCl₃): δ 1.30 (t, *J* = 7.4 Hz, 3H), 2.28 (s, 3H), 3.95 (s, 2H), 4.18 (q, *J* = 7.4 Hz, 2H), 5.96 (s, 1H).

³ Gray, G.M. *Synlett* **1983**, 488.

⁴ Oppolzer, W.; Fürstner, A. *Helv. Chim. Acta* **1993**, 76, 2329.