SYNLETT-Supporting Information

Palladium Mediated Intramolecular Buchwald-Hartwig α-Arylation of β-Aminoesters: Synthesis of Functionalized Tetrahydroisoquinolines

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Data for all new compounds S2-S14
Experimental Section

General: IR spectra were recorded on a Bruker Tensor 37 (FTIR) spectrophotometer. $^1$H NMR spectra were recorded on Bruker Avance 200 and 400 (200 and 400 MHz) spectrometers at 295 K in CDCl$_3$; chemical shifts (δ ppm) and coupling constants (Hz) are reported in standard fashion with reference to either internal standard tetramethylsilane (TMS) (δH = 0.00 ppm) or CHCl$_3$ (δH = 7.25 ppm). $^{13}$C NMR spectra were recorded on 200 (50 MHz) and/or Bruker Avance 400 (100 MHz) spectrometers at RT in CDCl$_3$; chemical shifts (δ ppm) are reported relative to CHCl$_3$ [δC = 77.00 ppm (central line of triplet)]. In the $^{13}$C NMR, the nature of carbons(C, CH, CH$_2$ and CH$_3$) was determined by recording the DEPT-135 spectra, and is given in parentheses and noted as s = singlet (for C), d = doublet (for CH), t = triplet (for CH$_2$) and q = quartet (for CH$_3$). In the $^1$H-NMR, the following abbreviations were used throughout: s = singlet, d = doublet, t = triplet, q = quartet, qui =quintet, m = multiplet and br s. = broad singlet. The assignment of signals was confirmed by $^1$H, $^{13}$C CPD and DEPT spectra. High-resolution mass spectra (HRMS) were recorded using Micromass Q-TOF micro mass spectrometer using electron spray ionization mode. Microwave experiments were carried out with a CEM Discover Labmate™ instrument with 10 ml vials, closed vessel, Power: 250W, Temperature 80 °C, 110 °C and 120 °C for 60 minutes. All small scale dry reactions were carried out using standard syringe-septum technique. Reactions were monitored by TLC on silica gel using a combination of hexane and ethyl acetate as eluents. Reactions were generally run under argon or a nitrogen atmosphere. Solvents were distilled prior to use; petroleum ether with a boiling range of 40 to 60 °C was used. Acme’s silica gel (60–120 mesh) was used for column chromatography (approximately 20 g per one gram of crude material).

General Procedure 1 (for reductive amination): To a magnetically stirred solution of bromobenzaldehyde 1 (1 mol) and benzylamine (2 mol) in methanol (5 mL) in a round bottom flask was added acetic acid and the reaction mixture was stirred for 30 minutes at room temperature. Then to the reaction mixture was added sodium borohydride (1.5 mol) in 5 to 10 portions (in order to control effervescences) followed by refluxing mixture for 12 h at 65 °C. After complete conversion of starting material to the product monitored by TLC, methanol was evaporated in vacuo, washed with aqueous sodium bicarbonate solution and extracted with ethyl acetate. The combined organic layers were washed with saturated NaCl solution, dried over Na$_2$SO$_4$ and concentrated under reduced pressure. Purification of the residue on a silica gel column chromatography using petroleum ether/ethyl acetate as eluent furnished the reductive amination products 2.

General Procedure 2 (for aza-Michael addition): To the solution of N-(benzyl)-2-bromobenzylamine 2 (1 mmol) in methanol (~4 mL), was added ethylacrylate (2 mmol) and the reaction mixture was refluxed for 48 h. After complete conversion of starting material to the product monitored by TLC, methanol was evaporated in vacuo. Purification of the residue on a silica gel column using petroleum ether/ethyl acetate as eluent furnished pure aza-Michael addition products 3.

General Procedure 3 (for Buchwald-Hartwig cyclization): In a oven dried Schlenk tube under nitrogen atmosphere were taken Pd(OAc)$_2$ (10 mol%), PPh$_3$ (20 mol%) and Cs$_2$CO$_3$ (2 mmol) in toluene (~1.5 mL) stirred for 5 minutes. To this mixture was added boromoester 3 (1 mmol) in toluene (~3.0 mL) and the
reaction mixture was stirred for 24 h at 80 °C. Progress of the reaction was monitored by TLC, and after the reaction is complete, it was quenched by addition of aq. NH₄Cl and extracted with methylene chloride (3 × 10 mL). The organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. Purification of the residue on a silica gel column chromatography using petroleum ether/ethyl acetate as eluent furnished the cyclized products 4.

Secondary amines 2a, 2b and 2d were already reported in literature¹

![Chemical Structure](image)

**N-Benzyl-N-(2-bromo-3,4,5-triethoxybenzyl)amine (2c):** GP1 was carried out with 2-bromo-3,4,5-triethoxy benzaldehyde 1c (1.0 g, 3.634 mmol), benzylamine (779 mg, 7.27 mmol) and acetic acid (0.3 mL) in methanol (25 mL) and the reaction mixture was stirred for 30 minutes at room temperature. Then to the reaction mixture was added NaBH₄ (207 mg, 5.45 mmol) in 5 to 10 portions (in order to control effervescences) followed by refluxing for 12 h at 65 °C. After TLC control (petroleum ether/ethylacetate 7:3, \( R_f \) (1c) = 0.6, \( R_f \) (2c) = 0.3, UV detection) showed complete conversion, methanol was concentrated in vacuo, washed with aqueous NaHCO₃ and extracted with ethyl acetate (3 × 30 mL). The organic layer was washed with saturated NaCl solution, dried over Na₂SO₄ and concentrated under reduced pressure. Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 90:10 to 70:30) furnished the product secondary amine 2c (1.21 g, 91%) as brownish yellow viscous liquid. IR (MIR-ATR, 4000 – 600 cm⁻¹): \( \nu_{\text{max}} \) = 2935, 1567, 1478, 1452, 1394, 1327, 1161, 1104, 1007, 974, 923, 737, 698 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): \( \delta \) = 7.42-7.30 (m, 4H, Ar-H), 7.30-7.23 (m, 1H, Ar-H), 6.84 (s, 1H, 6'-H), 3.91 (s, 3H, Ar-OCH₃), 3.89 (s, 3H, Ar-OCH₃), 3.86 (s, 3H, Ar-OCH₃), 3.86 (s, 2H, CH₂-Bn), 3.83 (s, 2H, CH₂-Ar), 1.96 (b r. s, 1H, NH) ppm. ¹³C NMR (CDCl₃, 100 MHz): \( \delta \) = 152.62 (s, Ar-C=OCH₃), 150.91 (s, Ar-C=OCH₃), 142.06 (s, Ar-C=OCH₃), 140.10 (s, Ar-C), 134.86 (s, Ar-C), 128.45 (d, 2C, Ar-C), 128.22 (d, 2C, Ar-C), 127.07 (d, Ar-C), 109.95 (s, C-2’), 109.10 (d, 1C, C-6’), 61.11 (q, OCH₃), 61.00 (q, OCH₃), 56.13 (q, OCH₃), 53.37 (t, N-CH₂), 53.21 (t, N-CH₂) ppm. HR-MS (ESI+) m/z calculated for \([C_{17}H_{20}BrNNaO₃]^+ = [M+Na]^+ \): 388.0519; found 388.0528.

![Chemical Structure](image)

**N-Benzyl-N-[(6-bromo-1,3-benzodioxol-5-yl)methyl]amine (2e):** GP1 was carried out with 2-bromo-piperonal 1e (500 mg, 2.18 mmol), benzylamine (467 mg, 4.37 mmol) and acetic acid (0.2 mL) in methanol

(15 mL) and the reaction mixture was stirred for 30 minutes at room temperature. Then to the reaction mixture was added NaBH₄ (123 mg, 3.27 mmol) in 5 to 10 portions (in order to control effervescences) followed by refluxing for 12 h at 65 °C. After TLC control (petroleum ether/ethyl acetate 8:2, Rₜ (1e) = 0.6, Rₜ (2e) = 0.4, UV detection) showed complete conversion, methanol was concentrated in vacuo, washed with aqueous NaHCO₃ and extracted with ethyl acetate (3 × 20 mL). The organic layer was washed with saturated NaCl solution, dried over Na₂SO₄ and concentrated under reduced pressure. Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 95:5 to 75:25) furnished the product secondary amine 2e (597 mg, 85%) as colorless viscous liquid. IR (MIR -ATR, 4000 – 600 cm⁻¹): νₘₐₓ = 2892, 1471, 1234, 1109, 1035, 931, 862, 833, 736, 697 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ = 7.42-7.31 (m, 4H, Ar-H), 7.28 (dd, 1H, J = 6.8 Hz and 6.4 Hz, Ar-H), 7.02 (s, 1H, Ar-H), 6.95 (s, 1H, Ar-H), 5.98 (s, 2H, ArO-CH₂-OAr), 3.81 (s, 4H, CH₂-Bn), 1.95 (br. s, 1H, NH) ppm.¹³C NMR (CDCl₃, 100 MHz): δ = 147.38 (s, Ar-C-CH₂-OAr), 140.10 (s, Ar-C-CH₂-OAr), 132.50 (s, Ar-C), 128.45 (s, Ar-C), 128.21 (d, 2C, Ar-C), 127.05 (d, Ar-C), 114.17 (s, Ar-C), 112.78 (d, Ar-C), 110.23 (d, Ar-C), 101.69 (t, ArO-CH₂-OAr), 53.01 (t, 2C, N-CH₂) ppm. HR-MS (ESI+) m/z calculated for [C₁₅H₁₄BrNNaO₂]+ = [M+Na]+: 342.0100; found 342.0100.

**N-Benzyl-N-[5-(benzyloxy)-2-bromobenzyl]amine (2f):** GP1 was carried out with 2-bromo-5-benzyloxy benzaldehyde 1f (1.5g, 5.15 mmol), benzylamine (828 mg, 7.72 mmol) and acetic acid (0.3 mL) in methanol (10 mL) and the reaction mixture was stirred for 30 minutes at room temperature. Then to the reaction mixture was added NaBH₄ (300 mg, 7.72 mmol) in 5 to 10 portions (in order to control effervescences) followed by refluxing for 12 h at 65 °C. After TLC control (petroleum ether/ethyl acetate 9:1, Rₜ (1f) = 0.7, Rₜ (2f) = 0.15, UV detection) showed complete conversion, methanol was evaporated in vacuo, washed with aqueous NaHCO₃ and extracted with ethyl acetate (3 × 25 mL). The organic layer was washed with saturated NaCl solution, dried over Na₂SO₄ and concentrated under reduced pressure. Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 95:5 to 70:30) furnished the product, N-benzyl-N-[5-(benzyloxy)-2-bromobenzyl]amine 2f (1.46 g, 74%) as colorless viscous liquid. IR (LIQUID CELL, 4000 – 700 cm⁻¹): νₘₐₓ = 3030, 2868, 1580, 1463, 1376, 1289, 1236, 1166, 1015, 807 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ = 7.52-7.28 (m, 11H, Ar-H), 7.13 (d, 1H, J = 2.6, Ar-H), 6.80 (dd, 1H, J = 8.7 and 2.9 Hz, Ar-H), 5.09 (s, 2H, CH₂-Ar), 3.89 (s, 2H, CH₂-Bn), 3.84 (s, 2H, CH₂-Ar), 2.02 (br. s, 1H, NH) ppm.¹³C NMR (CDCl₃, 100 MHz): δ = 158.19 (s, 5'-C), 140.27 (s, Ar-C), 140.12 (s, Ar-C), 136.66 (s, Ar-C), 133.37 (d, Ar-C), 128.69 (d, 2C, Ar-C), 128.48 (d, 2C, Ar-C), 128.25 (d, 2C, Ar-C), 128.14 (d, Ar-C), 127.52 (d, 2C, Ar-C), 127.09 (d, Ar-C), 116.85 (d, Ar-C), 115.18 (d, Ar-C), 114.54 (s, Ar-C), 70.22 (t, O-C-Ar), 53.22 (t, N-CH₂), 53.09 (t, N-CH₂) ppm. HR-MS (ESI+) m/z calculated for [C₂₁H₂₁BrNNaO₂]⁺ = [M+Na]⁺: 404.0620; found 404.0621.
N-(2-bromobenzyl)-N(4-methylbenzyl)amine (2g): GP1 was carried out with 2-bromo benzaldehyde 1g (1.0 g, 5.40 mmol), 4-methylbenzylamine (983 mg, 8.10 mmol) and acetic acid (0.4 ml) in methanol (25 mL) and the reaction mixture was stirred for 30 minutes at room temperature. Then to the reaction mixture was added NaBH₄ (308.4 mg, 8.10 mmol) in 5 to 10 portions (in order to control effervescences) followed by refluxing for 12 h at 65 °C. After TLC control (petroleum ether/ethylacetate 8:2, Rf (1g) = 0.7, Rf (2g) = 0.25, UV detection) showed complete conversion, methanol was concentrated in vacuo, washed with aqueous NaHCO₃ and extracted with ethyl acetate (3 × 30 mL). The organic layer was washed with saturated NaCl solution, dried over Na₂SO₄ and concentrated under reduced pressure. Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 95:5 to 70:30) furnished the product secondary amine 2g (1.38 g, 87%) as colorless viscous liquid. IR (MIR-ATR, 4000 – 600 cm⁻¹): νmax = 3019, 2827, 1514, 1440, 1358, 1101, 1043, 1023, 802, 747, 656 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ = 7.57 (d, 1H, J = 7.9 Hz, Ar-H), 7.43 (d, 1H, J = 7.6 Hz, Ar-H), 7.29 (dd, 3H, 15.5 and 7.9 Hz, Ar-H), 7.15 (dd, 3H, J = 15.3 and 7.7 Hz, Ar-H), 3.90 (s, 2H, CH₂-Bn), 3.79 (s, 2H, CH₂-Ar), 2.37 (s, 3H, Ar-CH₃), 1.96 (br. s, 1H, NH) ppm. ¹³C NMR (CDCl₃, 100 MHz): δ = 139.23 (s, Ar-C), 137.05 (s, Ar-C), 136.62 (s, Ar-C), 132.84 (d, Ar-C), 130.41 (d, Ar-C), 129.14 (d, 2C, Ar-C), 128.62 (d, Ar-C), 128.21 (d, 2C, Ar-C), 127.43 (d, Ar-C), 124.06 (s, Ar-C), 53.13 (t, N-CH₂), 52.82 (t, N-CH₂), 21.16 (q, Ar-CH₃) ppm. HR-MS (ESI+) m/z calculated for [C₁₅H₁₇BrN]⁺ = [M+H]⁺: 290.0539; found 290.0553.

Ethyl N-benzyl-N-(2-bromobenzyl)-β-alaninate (3a): GP2 was carried out with secondary amine 2a (1.1 g, 3.98 mmol), ethylacrylate (1.1 g, 7.97 mmol) in methanol (25 mL) and the reaction mixture was refluxed for 2 days. After TLC control (petroleum ether/ethyl acetate 9:1, Rf (2a) = 0.25, Rf (3a) = 0.55, UV detection) showed complete conversion, methanol was concentrated in vacuo. Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 99:1 to 96:4) furnished the product ester 3a (1.32 g, 88%) as colorless liquid. IR (MIR-ATR, 4000 – 600 cm⁻¹): νmax = 2980, 2805, 1731, 1444, 1368, 1244, 1182, 1129, 1024, 749, 698 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ = 7.57 (d, 1H, J = 7.6 Hz, Ar-H), 7.51 (d, 1H, J = 8.0 Hz, Ar-H), 7.40-7.20 (m, 6H, Ar-H), 7.09 (dd, 1H, J = 7.8 and 7.6 Hz, Ar-H), 4.09 (q, 2H, J = 7.2 Hz, O-CH₂CH₃), 3.71 (s, 2H, CH₂-Ar), 3.64 (s, 2H, CH₂-Bn), 2.86 (t, 2H, J = 7.2 Hz, N-CH₂-
CH₂COOEt), 2.53 (t, 2H, J = 7.2 Hz, CH₂-COOEt), 1.21 (t, 3H, J = 7.1 Hz, O-CH₂CH₃) ppm. ¹³C NMR (CDCl₃, 100 MHz): δ = 172.54 (s, O-C=O), 139.09 (s, Ar-C), 138.53 (s, Ar-C), 132.61 (d, Ar-C), 130.61 (d, Ar-C), 128.77 (d, 2C, Ar-C), 128.32 (d, Ar-C), 128.25 (d, 2C, Ar-C), 127.28 (d, Ar-C), 127.03 (d, Ar-C), 124.27 (s, C-2'), 60.38 (t, O-C₆H₄-CH₃), 58.26 (t, N-CH₂), 57.54 (t, N-CH₂), 49.45 (t, N-C₆H₄CH₂COOEt), 32.70 (t, C₆H₄-COOEt), 14.17 (q, O-CH₂C₆H₃) ppm. HR-MS (ESI+) m/z calculated for [C₁₉H₂₂BrNNaO₂]⁺ = [M+Na]⁺: 398.0726; found 398.0729.

Ethyl N-benzyl-N-(2-bromo-4,5-dimethoxybenzyl)-β-alaninate (3b): GP2 was carried out with secondary amine 2b (510 mg, 1.52 mmol), ethylacrylate (304 mg, 3.03 mmol) in methanol (15 mL) and the reaction mixture was refluxed for 2 days. After TLC control (petroleum ether/ethyl acetate 7:3, Rᶠ(2b) = 0.2, Rᶠ(3b) = 0.5, UV detection) showed complete conversion, methanol was concentrated in vacuo. Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 95:5 to 80:20) furnished the product, bromoester 3b (629 mg, 95%) as a light brownish viscous liquid. IR (MIR-ATR, 4000 – 600 cm⁻¹): ν_max = 2977, 2838, 1730, 1502, 1443, 1374, 1252, 1184, 1157, 1032, 799, 739, 699 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ = 7.38-7.26 (m, 4H, Ar-H), 7.25-7.20 (m, 1H, Ar-H), 7.13 (s, 1H, Ar-H), 6.97 (s, 1H, Ar-H), 4.07 (q, 2H, J = 7.1 Hz, O-C₆H₄-CH₃), 3.89 (s, 3H, OCH₃), 3.86 (s, 3H, OCH₃), 3.65 (s, 2H, N-CH₂-Ar), 3.62 (s, 2H, N-CH₂-Bn), 2.87 (t, 2H, J = 7.1 Hz, N-C₆H₄CH₂COOEt), 2.52 (t, 2H, J = 7.1 Hz, CH₂-COOEt), 1.19 (t, 3H, J = 7.1 Hz, -OCH₂CH₃) ppm. ¹³C NMR (CDCl₃, 100 MHz): δ = 172.52 (s, O-C=O), 148.39 (s, Ar-C-OCH₃), 148.33 (s, Ar-C-OCH₃), 139.22 (s, Ar-C), 130.59 (s, Ar-C), 128.73 (d, 2C, Ar-C), 128.24 (d, 2C, Ar-C), 127.04 (d, Ar-C), 115.03 (d, Ar-C), 113.77 (s, Ar-C), 113.12 (d, Ar-C), 60.34 (t, O-C₆H₄CH₃), 58.18 (t, N-CH₂), 56.97 (t, N-CH₂), 56.14 (q, Ar-C-OCH₃), 55.97 (q, Ar-C-OCH₃), 49.52 (t, N-C₆H₄CH₂COOEt), 32.83 (t, CH₂-COOEt), 14.15 (q, O-CH₂CH₃) ppm. HR-MS (ESI+) m/z calculated for [C₂₁H₂₆BrNNaO₄]⁺ = [M+Na]⁺: 458.0937; found 458.0937.

Ethyl N-benzyl-N-(2-bromo-3,4,5-trimethoxybenzyl)-β-alaninate (3c): GP2 was carried out with secondary amine 2c (1.1 g, 3.27 mmol), ethylacrylate (656 mg, 6.55mmol) in methanol (15 mL) and the reaction mixture was refluxed for 2 days. After TLC control (petroleum ether/ethyl acetate 7:3, Rᶠ(2c) = 0.3, Rᶠ(3c) = 0.6, UV detection) showed complete conversion, methanol was concentrated in vacuo. Purification
of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 97:3 to 85:15) gave the product, bromoester 3c (1.29 g, 92%) as a yellowish viscous liquid. IR (MIR-ATR, 4000 – 600 cm⁻¹): νmax = 2938, 1731, 1570, 1388, 1330, 1241, 1185, 1105, 1011, 740, 698 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ = 7.37-7.26 (m, 4H, Ar-H), 7.26-7.21 (m, 1H, Ar-H), 7.06 (s, 1H, Ar-H), 4.09 (q, 2H, J = 7.1 Hz, O-CH₂CH₃), 3.89 (s, 3H, Ar-C-OC₆H₄), 3.88 (s, 6H, 2 Ar-C-OC₆H₄), 3.69 (s, 2H, N-CH₂-Ar), 2.89 (t, 2H, J = 7.1 Hz, N-C₄H₉CH₂COOEt), 2.54 (t, 2H, J = 7.1 Hz, CH₂COOEt), 1.20 (t, 3H, J = 7.1 Hz, O-CH₂C₆H₃) ppm. ¹³C NMR (CDCl₃, 100 MHz): δ = 172.49 (s, O-C=O), 152.62 (s, Ar-C), 150.50 (s, Ar-C), 141.81 (s, Ar-C), 139.13 (s, Ar-C), 128.64 (d, 2C, Ar-C), 128.26 (d, 2C, Ar-C), 127.06 (s, Ar-C), 109.98 (s, Ar-C), 108.93 (d, Ar-C), 61.08 (q, Ar-C-O₆H₄), 58.36 (t, O-C₄H₉-CH₃), 56.06 (q, Ar-C-O₆H₄), 49.74 (t, N-C₄H₉CH₂COOEt), 32.82 (t, N-C₄H₉COOEt), 14.17 (q, O-CH₂C₆H₃) ppm. HR-MS (ESI+) m/z calculated for [C₂₂H₂₈BrNNaO₅]+ = [M+Na]+: 488.1043; found 488.1045.

Ethyl N-benzyl-N-(2-bromo-5-methoxybenzyl)-β-alaninate (3d): GP2 was carried out with secondary amine 2d (4.0 g, 13.07mmol), ethylacrylate (3.92 g, 39.22 mmol) in methanol (40 mL) and the reaction mixture was refluxed for 2 days. After TLC control (petroleum ether/ethyl acetate 6:4, Rf (2d) = 0.45, Rf (3d) = 0.7, UV detection) showed complete conversion, methanol was concentrated in vacuo. Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 95:5 to 80:20) yielded bromoester 3d (5.2 g, 98%) as a viscous liquid. IR (LIQUID CELL, 4000 – 700 cm⁻¹): νmax = 2935, 2836, 1733, 1595, 1468, 1370, 1272, 1186, 1048, 1021, 809 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ = 7.45-7.18 (m, 7H, Ar-H), 6.68 (dd, 1H, J = 8.7 and 3.0 Hz, Ar-H), 4.11 (q, 2H, J = 7.2 Hz, O-CH₂CH₃), 3.68 (s, 3H, Ar-C-OC₆H₄), 3.66 (s, 2H, N-CH₂-Bn), 2.89 (t, 2H, J = 7.2 Hz, N-C₄H₉CH₂COOEt), 2.54 (t, 2H, J = 7.2 Hz, N-CH₂CH₂CH₂COOEt), 1.22 (t, 3H, J = 7.1 Hz, O-CH₂CH₃) ppm. ¹³C NMR (CDCl₃, 100 MHz): δ = 172.51 (s, O-C=O), 159.01 (s, Ar-C), 139.63 (s, Ar-C), 139.06 (s, Ar-C), 133.02 (d, Ar-C), 128.73 (d, 2C, Ar-C), 128.27 (d, 2C, Ar-C), 127.05 (d, Ar-C), 115.79 (d, Ar-C), 114.38 (d, Ar-C), 60.39 (t, O-CH₂CH₃), 58.33 (t, N-CH₂), 57.54(t, N-CH₂), 55.41 (q, Ar-C-O₆H₄), 49.59 (t, N-CH₂CH₂CH₂COOEt), 32.77 (t, N-CH₂CH₂COOEt), 14.17 (q, O-CH₂CH₃) ppm. HR-MS (ESI+) m/z calculated for [C₂₀H₂₆BrNNaO₅]+ = [M+Na]+: 428.0832; found 428.0833.
Ethyl N-benzyl-N-[(6-bromo-1,3-benzodioxol-5-yl)methyl]-β-alaninate (3e): GP2 was carried out with the secondaryamine 2e (500 mg, 1.56 mmol), ethylacrylate (312 mg, 3.13 mmol) in methanol (20 mL) and the reaction mixture was refluxed for 2 days. After TLC control (petroleum ether/ethyl acetate 7:3, \( R_f (2e) = 0.3 \), \( R_f (3e) = 0.55 \), UV detection) showed complete conversion, methanol was concentrated in vacuo. Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 95:5 to 80:20) furnished the product ester 3e (613 mg, 93%) as a viscous liquid. IR (LIQUID CELL, 4000 – 700 cm\(^{-1}\)): \( \nu_{\text{max}} = 2978, 2903, 1732, 1473, 1236, 1185, 1115, 1038, 934, 838 \) cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \( \delta = 7.37-7.27 \) (m, 4H, Ar-H), 7.25 (dd, 1H, \( J = 6.9 \) and 6.9 Hz, Ar-H), 7.10 (s, 1H, Ar-H), 6.97 (s, 1H, Ar-H), 5.96 (s, 2H, Ar-O-C\(_2\)H\(_2\)-O-Ar), 4.13 (q, 2H, \( J = 7.1 \) Hz, O-C\(_2\)H\(_3\)-CH\(_3\)), 3.64 (s, 2H, N-C\(_2\)H\(_2\)-Bn), 3.62 (s, 2H, N-C\(_2\)H\(_2\)-Ar), 2.85 (t, 2H, \( J = 7.1 \) Hz, N-CH\(_2\)-CH\(_2\)COOEt), 2.53 (t, 2H, \( J = 7.1 \) Hz, N-CH\(_2\)-CH\(_2\)COOEt), 1.24 (t, 3H, \( J = 7.1 \) Hz, O-CH\(_2\)-CH\(_3\)) ppm. \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \( \delta = 172.52 \) (s, O-C=O), 147.44 (s, Ar-C), 147.18 (s, Ar-C), 139.07 (s, Ar-C), 131.83 (s, Ar-C), 128.80 (d, 2C, Ar-C), 128.28 (d, 2C, Ar-C), 127.06 (d, Ar-C), 114.18 (s, Ar-C), 112.36 (d, Ar-C), 110.19 (d, Ar-C), 101.59 (t, Ar-O-CH\(_2\)-O-Ar), 60.43 (t, O-CH\(_2\)-CH\(_3\)), 58.17 (t, N-CH\(_3\)), 57.20 (t, N-CH\(_3\)), 49.40 (t, N-CH\(_2\)-CH\(_2\)COOEt), 32.75 (t, N-CH\(_2\)-CH\(_2\)COOEt), 14.20 (q, O-CH\(_2\)-CH\(_3\)) ppm. HR-MS (ESI+) m/z calculated for [C\(_{20}\)H\(_{22}\)BrNNaO\(_4\)]\(^+\) = [M+Na\(^+\)]: 442.0624; found 442.0638.

Ethyl N-benzyl-N-[5-(benzyloxy)-2-bromobenzyl]-β-alaninate (3f): GP2 was carried out with secondary amine 2f (1.4 g, 3.66 mmol), ethylacrylate (733 mg, 7.3 mmol) in methanol (10 mL) and the reaction mixture was refluxed for 2 days. After TLC control (petroleum ether/ethyl acetate 8:2, \( R_f (2f) = 0.2 \), \( R_f (3f) = 0.55 \), UV detection) showed complete conversion, methanol was concentrated in vacuo. Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 98:2 to 85:15) furnished the product ester 3f (1.6 g, 90%) as a liquid. IR (LIQUID CELL, 4000 – 700 cm\(^{-1}\)): \( \nu_{\text{max}} = 2980, 2933, 2815, 1732, 1591, 1463, 1373, 1275, 1237, 1183, 1018, 808 \) cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \( \delta = 7.50-7.23 \) (m, 12H, Ar-H), 6.75 (dd, 1H, \( J = 8.7 \) and 2.8 Hz, Ar-H), 5.08 (s, 2H, Ar-O-C\(_2\)H\(_2\)-Bn), 4.12 (q, 2H, \( J = 7.1 \) Hz, O-C\(_2\)H\(_3\)-CH\(_3\)), 3.68 (s, 2H, N-C\(_2\)H\(_2\)-Bn), 3.67 (s, 2H, N-C\(_2\)H\(_2\)-Ar), 2.88 (t, 2H, \( J = 7.2 \) Hz, N-CH\(_2\)-CH\(_2\)COOEt), 2.53 (t, 2H, \( J = 7.1 \) Hz, O-CH\(_2\)-CH\(_2\)COOEt), 1.23 (t, 3H, \( J = 7.1 \) Hz, O-CH\(_2\)-CH\(_3\)) ppm. \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \( \delta = 172.53 \) (s, O-C=O), 158.19 (s, Ar-C), 139.66 (s, Ar-C), 139.06 (s, Ar-C), 136.81 (s, Ar-C), 133.09 (d, Ar-C), 128.74 (d, 2C, Ar-C), 128.64 (d, 2C, Ar-C), 128.30 (d, 2C, Ar-C), 128.06 (d, Ar-C), 127.49 (d, 2C, Ar-C), 127.06 (d, Ar-C), 116.61 (d, Ar-C), 115.35 (d, Ar-C), 114.66 (s, Ar-C), 70.15 (t, Ar-O-CH\(_2\)-Bn), 60.42 (t, O-CH\(_2\)-CH\(_3\)), 58.33 (t, N-CH\(_2\)), 57.54 (t, N-CH\(_2\)), 49.40 (t, N-CH\(_2\)-CH\(_2\)COOEt), 32.72 (t, N-CH\(_2\)-CH\(_2\)COOEt), 14.20 (q, O-CH\(_2\)-CH\(_3\)) ppm. HR-MS (ESI+) m/z calculated for [C\(_{26}\)H\(_{28}\)BrNNaO\(_3\)]\(^+\) = [M+Na\(^+\)]: 504.1145; found 504.1150.
Ethyl \( N \)-\( (2\)-bromobenzyl\)-\( N \)-\( (4\)-methylbenzyl\)-\( \beta \)-alaninate (3g): GP2 was carried out with secondary amine 2g (600 mg, 2.07 mmol), ethylacrylate (414 mg, 4.13 mmol) in methanol (15 mL) and the reaction mixture was refluxed for 2 days. After TLC control (petroleum ether/ethyl acetate 8:2, \( R_f \) (2g) = 0.25, \( R_f \) (3g) = 0.6, UV detection) showed complete conversion, methanol was concentrated \( in \ vacuo \). Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 99:1 to 95:5) furnished the product ester 3g (679 mg, 84%) as colorless liquid. IR (MIR-ATR, 4000 – 600 cm\(^{-1}\)): \( \nu_{\text{max}} \) = 2980, 2814, 1732, 1513, 1440, 1367, 1242, 1181, 1130, 1042, 1023, 797, 749, 662 cm\(^{-1}\). \( ^1 \)H NMR (CDCl\(_3\), 400 MHz): \( \delta \) = 7.60 (d, 1H, \( J \) = 7.0 Hz, Ar-H), 7.50 (dd, 1H, \( J \) = 7.8 and 0.4 Hz, Ar-H), 7.27 (dd, 3H, \( J \) = 14.5 and 7.5 Hz, Ar-H), 7.08 (dd, 3H, \( J \) = 17.0 & 8.0 Hz, Ar-H), 4.14 (q, 2H, \( J \) = 7.1 Hz, O-CH\(_2\)CH\(_3\)), 3.71 (s, 2H, CH\(_2\)-Ar), 3.62 (s, 2H, CH\(_2\)-Bn), 2.87 (t, 2H, \( J \) = 7.2 Hz, N-CH\(_2\)-COOEt), 2.54 (t, 2H, \( J \) = 7.2 Hz, CH\(_2\)-COOEt), 2.34 (s, 3H, Ar-CH\(_3\)), 1.19 (t, 3H, \( J \) = 7.1 Hz, O-CH\(_2\)CH\(_3\)) ppm. \( ^{13} \)C NMR (CDCl\(_3\), 100 MHz): \( \delta \) = 172.58 (s, O-C=O), 138.65 (s, Ar-C), 136.57 (s, Ar-C), 135.95 (d, Ar-C), 132.60 (d, Ar-C), 130.60 (d, Ar-C), 128.96 (d, 2C, Ar-C), 128.76 (d, 2C, Ar-C), 128.29 (d, Ar-C), 127.29 (d, Ar-C), 124.25 (s, Ar-C), 60.38 (t, O-CH\(_2\)CH\(_3\)), 57.96 (t, N-CH\(_2\)), 57.44 (t, N-CH\(_2\)), 49.37 (t, N-CH\(_2\)CH\(_2\)COOEt), 32.72 (t, CH\(_2\)-COOEt), 21.15 (q, Ar-CH\(_3\)), 14.19 (q, O-CH\(_2\)CH\(_3\)) ppm. HR-MS (ESI+) m/z calculated for [C\(_{20}\)H\(_{24}\)BrNNaO\(_2\)]\(^+\) = [M+Na]\(^+\): 412.0883; found 412.0875.

Ethyl 2-benzyl-1,2,3,4-tetrahydroisoquinolidine-4-carboxylate (4a): GP3 was carried out with Pd(OAc)_2 (6 mg, 10 mol%), PPh\(_3\) (15 mg, 20 mol%) and Cs\(_2\)CO\(_3\) (182 mg, 0.56 mmol) in toluene (0.5 mL) and stirred for 5 minutes. To the reaction mixture was added bromoester 3a (100 mg, 0.28 mmol) in toluene (1 mL) and then the reaction mixture stirred for 24 h at 80 °C. After TLC control (petroleum ether/ethyl acetate 9:1, \( R_f \) (3a) = 0.55, \( R_f \) (4a) = 0.45, UV detection) showed complete conversion, quenched with aq. NH\(_4\)Cl solution and extracted with methylene chloride (3 \( \times \) 10 mL). The organic layer was washed with saturated NaCl solution, dried over Na\(_2\)SO\(_4\) and concentrated under reduced pressure. Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 98:2 to 95:5) furnished the cyclic ester 4a (64.4
mg, 82%) as a colorless viscous liquid. IR (MIR-ATR, 4000 – 600 cm⁻¹): ν_max = 2926, 2806, 1732, 1452, 1369, 1242, 1166, 1034, 741, 699 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ = 7.36-7.10 (m, 8H, Ar-H), 7.06-6.98 (m, 1H, Ar-H), 4.20-4.10 (m, 2H, O-CH₂CH₃), 3.85 (dd, 1H, J = 14.9 Hz, N-CH₂(a,b)), 3.74 [d, 1H, J = 13.2 Hz, N-CH₂(a’,b’)], 3.65 [d, 1H, J = 13.2 Hz, N-CH₂(a’,b’)], 3.59 [d, 1H, J = 14.9 Hz, N-CH₂(a,b)], 3.18 (dd, 1H, J = 11.5 and 5.6 Hz, N-C₆H₃CH₂OCH₂), 2.85 (dd, 1H, J = 11.5 and 4.8 Hz, N-CH₂CHCOOEt), 1.23 (t, 3H, J = 7.2 Hz, OCH₂CH₃) ppm. ¹³C NMR (CDCl₃, 50 MHz): δ = 173.25 (s, O-C=O), 138.13 (s, Ar-C), 135.19 (s, Ar-C), 131.58 (s, Ar-C), 129.31 (d, Ar-C), 129.05 (d, 2C, Ar-C), 128.32 (d, 2C, Ar-C), 127.25 (d, Ar-C), 126.92 (d, Ar-C), 126.75 (d, Ar-C), 126.31 (d, Ar-C), 62.31 (t, N-CH₂), 56.11 (t, O-CH₂CH₃), 52.95 (t, C-3’), 45.46 (d, C-4’), 14.22 (q, OCH₂CH₃) ppm. HR-MS (ESI+) m/z calculated for [C₁₉H₂₂NO₂]+ = [M+H]+: 296.1645; found 296.1656.

**Ethyl 2-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (4b):** GP3 was carried out with Pd(OAc)₂ (5.2 mg, 10 mol%), PPh₃ (12.1 mg, 20 mol%) and Cs₂CO₃ (150 mg, 0.46 mmol) in toluene (0.5 mL) and stirred for 5 minutes. To the reaction mixture was added bromoester 3b (100 mg, 0.23 mmol) in toluene (1 mL) and reaction mixture was stirred for 24 h at 80 °C. After TLC control (petroleum ether/ethyl acetate 7:3, Rf(3b) = 0.5, Rf(4b) = 0.4, UV detection) showed complete conversion, quenched with aq. NH₄Cl solution and extracted with methylene chloride (3 × 10 mL). The organic layer was washed with saturated NaCl solution, dried over Na₂SO₄ and concentrated under reduced pressure. Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 98:2 to 80:20) furnished the product cyclic ester 4b (64.5 mg, 79%) as a viscous liquid. IR (MIR-ATR, 4000 – 600 cm⁻¹): ν_max = 2931, 1729, 1514, 1455, 1366, 1252, 1134, 1032, 741, 697 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ = 7.41-7.24 (m, 5H, Ar-H), 6.74 (s, 1H, Ar-H), 6.52 (s, 1H, Ar-H), 4.26-4.06 (m, 2H, OCH₂CH₃), 3.85 (s, 3H, Ar-OCH₃), 3.83 (s, 3H, Ar-OCH₃), 3.78 (dd, 1H, J = 5.0 and 5.0 Hz, 4’-H), 3.74 [d, 1H, J = 13.1 Hz, N-CH₂(a’,b’)], 3.67 [d, 1H, J = 14.5 Hz, N-CH₂(a,b)], 3.65 [d, 1H, J = 13.1 Hz, N-CH₂(a’,b’)], 3.52 [d, 1H, J = 14.5 Hz, N-CH₂(a,b)], 3.17 (dd, 1H, J = 11.4 and 5.5 Hz, N-CH₂CHCOOEt), 2.85 (dd, 1H, J = 11.4 and 4.8 Hz, N-CH₂CHCOOEt), 1.22 (t, 3H, J = 7.1 Hz, OCH₂CH₃) ppm. ¹³C NMR (CDCl₃, 100 MHz): δ = 173.30 (s, O=C=O), 148.10 (s, Ar-C), 147.48 (s, Ar-C), 135.19 (s, Ar-C), 129.05 (d, 2C, Ar-C), 128.09 (d, 2C, Ar-C), 127.36 (s, Ar-C), 127.22 (d, Ar-C), 123.27 (s, Ar-C), 111.82 (d, Ar-C), 109.22 (d, Ar-C), 62.23 (t, N-CH₂), 60.87 (t, OCH₂CH₃), 55.92 (q, Ar-OCH₃), 55.83 (q, Ar-OCH₃), 55.66 (t, N-CH₂), 52.98 (t, C-3’), 44.91 (d, C-4’), 14.22 (q, OCH₂CH₃) ppm. HR-MS (ESI+) m/z calculated for [C₂₁H₂₅NNaO₄]+ = [M+Na]+: 378.1676; found 378.1685.
Ethyl 2-benzyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinolinidine-4-carboxylate (4c): GP3 was carried out with Pd(OAc)\(_2\) (5 mg, 10 mol%), PPh\(_3\) (11.3 mg, 20 mol%) and Cs\(_2\)CO\(_3\) (140 mg, 0.43 mmol) in toluene (0.5 mL) and stirred for 5 minutes. To this mixture was added bromoester 3c (100 mg, 0.22 mmol) in toluene (1 mL) and reaction mixture was stirred for 24 h at 80 °C. After TLC control (petroleum ether/ethyl acetate 7:3, \(R_f\) (3c) = 0.55, \(R_f\) (4c) = 0.45, UV detection) showed around 90% conversion, quenched with aq. NH\(_4\)Cl solution and extracted with methylene chloride (3 × 10 mL). The organic layer was washed with saturated NaCl solution, dried over Na\(_2\)SO\(_4\) and concentrated under reduced pressure. Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 95:5 to 85:15) furnished the cyclic ester 4c (56.9 mg, 85%) as a viscous liquid based on the recovery of starting material 3c (19 mg, 19%) of starting material. IR (MIR-ATR, 4000 – 600 cm\(^{-1}\)): \(\nu_{\text{max}}\) = 2937, 1732, 1598, 1458, 1357, 1238, 1171, 1118, 1020, 741, 698 cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) = 7.42-7.20 (m, 5H, Ar-H), 6.35 (s, 1H, Ar-H), 4.25-4.00 (m, 2H, OCH\(_2\)CH\(_3\)), 3.87 (s, 3H, Ar-OCH\(_3\)), 3.83 (s, 3H, Ar-OCH\(_3\)), 3.81 (s, 3H, Ar-OCH\(_3\)), 3.80-3.67 (m, 1H, 4’-H), 3.74 [d, 1H, \(J = 14.8\) Hz, N-CH\(_2\)(a,b)], 3.72 [d, 1H, \(J = 13.2\) Hz, N-CH\(_2\)(a’,b’)], 3.70 [d, 1H, \(J = 14.8\) Hz, N-CH\(_2\)(a,b)], 3.60 [d, 1H, \(J = 13.2\) Hz, N-CH\(_2\)(a’,b’)], 3.08 (dd, 1H, \(J = 11.5\) and 5.1 Hz, N-CH\(_2\)C\(_{\text{HCOOEt}}\)), 2.81 (dd, 1H, \(J = 11.5\) and 5.1 Hz, N-CH\(_{\text{26}}\)CH-COOEt), 1.20 (t, 3H, \(J = 7.2\) Hz, OCH\(_2\)CH\(_3\)) ppm. \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) = 173.86 (s, O-C=O), 152.79 (s, Ar-C), 151.54 (s, Ar-C), 140.05 (s, Ar-C), 138.05 (s, Ar-C), 130.75 (s, Ar-C), 128.94 (d, 2C, Ar-C), 128.30 (d, 2C, Ar-C), 127.22 (d, Ar-C), 118.36 (s, Ar-C), 104.82 (d, Ar-C), 61.98 (t, OCH\(_2\)CH\(_3\)), 60.71 (q, Ar-O-CH\(_3\)), 60.69 (t, N-CH\(_2\)), 60.33 (q, Ar-O-CH\(_3\)), 55.90 (t, 2C, N-CH\(_2\)& OCH\(_3\)), 53.48 (t, N-CH\(_2\)CHCOOEt), 41.27 (d, N-CH\(_2\)CHCOOEt), 14.23 (q, O-CH\(_2\)CH\(_3\)) ppm. HR-MS (ESI+) m/z calculated for [C\(_{22}\)H\(_{27}\)NNaO\(_5\)]\(^+\) = [M+Na]\(^+\): 408.1781; found 408.1781.

Ethyl 2-benzyl-7-methoxy-1,2,3,4-tetrahydroisoquinolinidine-4-carboxylate (4d): GP3 was carried out with Pd(OAc)\(_2\) (6 mg, 10 mol%), PPh\(_3\) (14 mg, 20 mol%) and Cs\(_2\)CO\(_3\) (174 mg, 0.54 mmol) in toluene (0.5 mL) and stirred for 5 minutes. To this mixture was added bromoester 3d (109 mg, 0.27 mmol) in toluene (1 mL) and then reaction mixture was stirred for 24 h at 80 °C. After TLC control (Petroleum ether/ethyl acetate 8:2, \(R_f\) (3d) = 0.55, \(R_f\) (4d) = 0.45, UV detection) showed complete conversion, quenched with aq. NH\(_4\)Cl solution and extracted with methylene chloride (3 × 10 mL). The organic layer was washed with saturated NaCl solution, dried over Na\(_2\)SO\(_4\) and concentrated under reduced pressure. Purification of the
residue on a silica gel column chromatography (petroleum ether/ethyl acetate 95:5 to 80:20) furnished the cyclic ester 4d (76 mg, 87%) as a viscous liquid. IR (LIQUID CELL, 4000 – 700 cm⁻¹): ν_max = 2931, 2802, 1732, 1613, 1503, 1458, 1324, 1250, 1168, 1035, 854 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ = 7.4-7.25 (m, 5H, Ar-H), 7.16 (d, 1H, J = 8.5 Hz, Ar-H), 6.79 (dd, 1H, J = 8.4 and 2.2 Hz, Ar-H), 6.58 (d, 1H, J = 1.6 Hz, Ar-H), 4.24-4.10 (m, 2H, O-CH₂CH₃), 3.83-3.79 (m, 1H, 4’-H), 3.78 (s, 3H, Ar-C-OCH₃), 3.77 [d, 1H, J = 15.0 Hz, N-CH₂(a’,b’)], 3.74 [d, 1H, J = 13.2 Hz, N-CH₂(a,b)], 3.68 [d, 1H, J = 13.2 Hz, N-CH₂(a,b)], 3.60 [d, 1H, J = 15.0 Hz, N-CH₂(a’,b’)], 3.19 (dd, 1H, J = 11.4, 5.7 Hz, N-CH₂CHCOOEt), 2.87 (dd, 1H, J = 11.5, 4.8 Hz, N-CH₂CHCOOEt), 1.23 (t, 3H, J = 7.1 Hz, OCH₂CH₃) ppm. ¹³C NMR (CDCl₃, 100 MHz): δ 173.48 (s, O-C=O), 158.40 (s, Ar-C=O), 158.10 (s, Ar-C), 156.32 (s, Ar-C), 130.33 (d, Ar-C), 129.04 (d, 2C, Ar-C), 128.31 (d, 2C, Ar-C), 127.23 (d, Ar-C), 123.74 (s, Ar-C), 112.84 (d, Ar-C), 111.18 (d, Ar-C), 62.16 (t, O-CH₂CH₂), 60.88 (t, N-CH₂), 56.19 (t, N-CH₂CHCOOEt), 55.25 (q, Ar-C-OCH₃), 53.13 (t, N-CH₂), 44.62 (d, N-CH₂CHCOOEt), 14.22 (q, O-CH₂CH₂) ppm. HR-MS (ESI+) m/z calculated for [C₂₀H₂₃NNaO₃]^+ = [M+Na]^+; 348.1570; found 348.1575.

![Chemical Structure](image)

**Ethyl 6-benzyl-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-g]isoquinolinedine-8-carboxylate (4e):** GP3 was carried out with Pd(OAc)₂ (7.9 mg, 10 mol%), PPh₃ (18.4 mg, 20 mol%) and Cs₂CO₃ (229 mg, 0.71 mmol) in toluene (0.5 mL) and stirred for 5 minutes. To this mixture was added bromoester 3e (148 mg, 0.35 mmol) in toluene (1 mL) and reaction mixture was stirred for 24 h at 80 °C. After TLC control (petroleum ether/ethyl acetate 8:2, R_f (3e) = 0.5, R_f (4e) = 0.4, UV detection) showed complete conversion, quenched with aq. NH₄Cl solution and extracted with methylene chloride (3 × 10 mL). The organic layer was washed with saturated NaCl solution, dried over Na₂SO₄ and concentrated under reduced pressure. Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 95:5 to 80:20) furnished the cyclic ester 4e (83 mg, 70%) as a viscous liquid. IR (MIR-ATR, 4000 – 600 cm⁻¹): ν_max = 2918, 1728, 1488, 1454, 1238, 1213, 1179, 1119, 1029, 925, 730, 693 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ = 7.39-7.26 (m, 5H, Ar-H), 6.70 (s, 1H, Ar-H), 6.50 (s, 1H, Ar-H), 5.91 (d, 2H, J = 5.04 Hz, O-CH₂O), 4.18-4.15 (m, 2H, O-CH₂CH₃), 3.76-3.65 (m, 1H), 3.75 [d, 1H, J = 13.0 Hz, N-CH₂(a,b)], 3.73 [d, 1H, J = 14.6 Hz, N-CH₂(a’,b’)], 3.65 [d, 1H, J = 13.0 Hz, N-CH₂(a,b)], 3.51 [d, 1H, J = 14.6 Hz, N-CH₂(a’,b’)], 3.16 (dd, 1H, J = 11.32, 5.32 Hz, N-CH₂CHCOOEt), 2.82 (dd, 1H, J = 11.0, 4.08 Hz, N-CH₂CHCOOEt), 1.23 (t, J = 6.88 Hz, 3H) ppm. ¹³C NMR (CDCl₃, 100 MHz): δ = 173.28 (s, O-C=O), 146.69 (s, Ar-C), 146.16 (s, Ar-C), 138.07 (s, Ar-C), 129.01 (d, 2C, Ar-C), 128.57 (s, Ar-C), 128.30 (d, 2C, Ar-C), 127.23 (d, Ar-C), 124.43 (s, Ar-C), 109.02 (d, Ar-C), 106.47 (d, Ar-C), 100.87 (t, O-CH₂O), 62.11 (t, O-CH₂CH₃), 60.96 (t, N-CH₂), 56.12 (t, N-CH₂CHCOOEt), 52.85 (t, N-CH₂), 45.29 (d, N-CH₂CHCOOEt), 14.21 (q, O-CH₂CH₃) ppm. HR-MS (ESI+) m/z calculated for [C₂₀H₂₁NNaO₄]^+ = [M+Na]^+; 362.1363; found 362.1367.
Ethyl 2-benzyl-7-(benzyloxy)-1,2,3,4-tetrahydroisoquinolidine-4-carboxylate (4f): GP3 was carried out with Pd(OAc)$_2$ (7.2 mg, 10 mol%), PPh$_3$ (16.9 mg, 20 mol%) and Cs$_2$CO$_3$ (210 mg, 0.65 mmol) in toluene (0.5 mL) and stirred for 5 minutes. To reaction mixture was then added bromoester 3f (156 mg, 0.33 mmol) in toluene (1 mL) and the reaction mixture was stirred for 24 h at 80 °C. After TLC control (petroleum ether/ethyl acetate 8:2, $R_f$ (3f) = 0.6, $R_f$ (4f) = 0.4, UV detection) showed complete conversion, quenched with aq. NH$_4$Cl solution and extracted with methylene chloride (3 × 10 mL). The organic layer was washed with saturated NaCl solution, dried over Na$_2$SO$_4$ and concentrated under reduced pressure. Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 95:5 to 85:15) furnished the cyclic ester 4f (105 mg, 80%) as colorless solid. IR (MIR-ATR, 4000 – 600 cm$^{-1}$): $\nu_{\text{max}}$ = 3060, 2983, 1732, 1612, 1504, 1454, 1265, 1173, 1096, 1027, 736, 700 cm$^{-1}$. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ = 7.50-7.25 (m, 10H, Ar-H), 7.18 (d, 1H, $J = 8.0$ Hz, Ar-H), 6.87 (dd, 1H, $J = 8.0$ and 0.0 Hz, Ar-H), 6.68 (d, 1H, $J = 4$ Hz, Ar-H), 5.05 (s, 2H, O-C$_2$H$_2$-Ar), 5.05 (s, 2H, O-C$_2$H$_2$-Ar), 4.22-4.13 (m, 2H, O-C$_2$H$_2$-CH$_3$), 3.88-3.53 (m, 1H), 3.83 [d, 1H, $J = 16.0$ Hz, N-CH$_2$ (a,b)], 3.79 [d, 1H, $J = 16.0$ Hz, N-CH$_2$ (a,b)], 3.79 [d, 1H, $J = 16.0$ Hz, N-CH$_2$ (a,b)], 3.79 [d, 1H, $J = 16.0$ Hz, N-CH$_2$ (a,b)], 3.79 [d, 1H, $J = 16.0$ Hz, N-CH$_2$ (a,b)], 3.79 [d, 1H, $J = 16.0$ Hz, N-CH$_2$ (a,b)], 3.79 [d, 1H, $J = 16.0$ Hz, N-CH$_2$ (a,b)], 3.79 [d, 1H, $J = 16.0$ Hz, N-CH$_2$ (a,b)], 3.79 [d, 1H, $J = 16.0$ Hz, N-CH$_2$ (a,b)], 3.79 ppm. $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ = 173.47 (s, O-C=O), 157.66 (s, Ar-C-O-Bn), 138.15 (s, Ar-C), 137.07 (s, Ar-C), 136.43 (s, Ar-C), 130.38 (d, Ar-C), 129.03 (d, 2C, Ar-C), 128.61 (d, 2C, Ar-C), 128.32 (d, 2C, Ar-C), 127.96 (d, Ar-C), 127.46 (d, 2C, Ar-C) 127.23 (d, Ar-C), 124.07 (s, Ar-C), 113.64 (d, Ar-C), 112.24 (d, Ar-C), 69.98 (t, O-CH$_2$-Ar), 62.19 (t, O-CH$_2$CH$_3$), 60.90 (t, N-CH$_2$), 56.25 (t, N-CH$_2$), 53.12 (t, N-CH$_2$CHCOOEt), 44.68 (d, N-CH$_2$CHCOOEt), 14.24 (q, O-CH$_2$-CH$_3$) ppm. HR-MS (ESI+) m/z calculated for[C$_{26}$H$_{27}$NNaO$_3$]$^+ = [M+Na]^+$: 424.1883; found 424.1887. Melting Point: 102-105 °C

Ethyl 2-(4-methylbenzyl)-1,2,3,4-tetrahydroisoquinolidine-4-carboxylate (4g): GP3 was carried out with Pd(OAc)$_2$ (5.7 mg, 10 mol%), PPh$_3$ (13.4 mg, 20 mol%) and Cs$_2$CO$_3$ (167 mg, 0.52 mmol) in toluene (0.5 mL), stirred for 5 minutes. To this mixture was added bromoester 3g (100 mg, 0.26 mmol) in toluene (1 mL) and the reaction mixture was stirred for 24 h at 80 °C. After TLC control (petroleum ether/ethyl acetate 9:1, $R_f$ (3g) = 0.55, $R_f$ (4g) = 0.45, UV detection) showed complete conversion, quenched with aq. NH$_4$Cl solution and extracted with methylene chloride (3 × 10 mL). The organic layer was washed with saturated NaCl solution, dried over Na$_2$SO$_4$ and concentrated under reduced pressure. Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 98:2 to 95:5) furnished the cyclic ester 4g (58.6 mg, 74%) as a colorless viscous liquid. IR (MIR-ATR, 4000 – 600 cm$^{-1}$): $\nu_{\text{max}}$ = 2979, 2798, 1731,
1514, 1453, 1366, 1238, 1092, 803, 745, 725 cm$^{-1}$. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta = 7.34$-
7.10 (m, 7H, Ar-H), 7.06 (dd, 1H, $J = 8.6$ and 3.8 Hz, Ar-H), 4.30-4.05 (m, 2H, O-CH$_2$CH$_3$), 3.88 (dd, 1H, $J = 5.2$ Hz, CHCOOEt), 3.78 [d, 1H, $J = 15.0$, N-CH$_2$(a,b)], 3.71 [d, 1H, $J = 13.0$, N-CH$_2$(a’,b’)], 3.65 [d, 1H, $J = 13.0$, N-CH$_2$(a’,b’)], 3.60 [d, 1H, $J = 15.0$, N-CH$_2$(a,b)], 3.18 (dd, 1H, $J = 11.4$ and 5.8 Hz, N-CH$_2$CH$_3$), 2.88 (dd, 1H, $J = 11.5$ and 4.9 Hz, N-CH$_2$CHCOOEt), 2.37 (s, 3H, Ar-CH$_3$), 1.24 (t, 3H, $J = 7.1$ Hz, OCH$_2$C$_3$H$_3$) ppm. $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta = 173.25$ (s, O-C=O), 136.78 (s, Ar-C), 135.24 (s, Ar-C), 135.01 (s, Ar-C), 131.61 (s, Ar-C), 129.24 (d, Ar-C), 128.99 (d, Ar-C), 126.88 (d, Ar-C), 126.74 (d, Ar-C), 126.27 (d, Ar-C), 126.01 (t, OCH$_2$CH$_3$), 60.92 (t, N-CH$_2$), 56.06 (t, N-CH$_2$), 52.89 (t, N-CH$_2$CHCOOEt), 45.47 (d, CHCOOEt), 21.17 ppm. HR-MS (ESI+) m/z calculated for [C$_{20}$H$_{23}$NNaO$_2$]$^+ = [M+Na]^+$: 332.1621; found 332.1628.

![Ethyl 3-[benzyl(2-bromobenzyl)amino]-2-methylpropanoate (5)](image)

Ethyl 3-[benzyl(2-bromobenzyl)amino]-2-methylpropanoate (5): To a cold (–78 °C) magnetically stirred solution of diisopropylethylamine (0.09 mL, 0.64 mmol) in dry THF (1 mL) was slowly added a solution of nBuLi (2.5 M in hexane, 0.24 mL, 0.58 mmol) and the reaction mixture was stirred for 5 min. To the LDA thus formed was added dropwise, a solution of ester 3a (200 mg, 0.53 mmol) in dry THF (2 mL) and the reaction mixture was stirred for 30 min at the same temperature. The enolate was treated with methyl iodide (0.05 ml, 0.64 mmol) and stirred for 5 h at RT. After TLC control (petroleum ether/ethyl acetate 9.5:0.5, $R_f$(3a) = 0.45, $R_f$(4a) = 0.44, UV detection) showed complete conversion, quenched with aq. NH$_4$Cl solution and extracted with diethyl ether (3 × 10 mL). The organic layer was washed with saturated NaCl solution, dried over Na$_2$SO$_4$ and concentrated under reduced pressure. Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate 98:2 to 95:5) furnished the methylated ester 5 (181 mg, 87%) as a colorless viscous liquid. IR (MIR-ATR, 4000 – 600 cm$^{-1}$): $\nu_{\text{max}}$ = 2977, 2800, 1730, 1453, 1440, 1370, 1237, 1183, 1153, 1024, 974, 749, 698, 663 cm$^{-1}$. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta = 7.58$ (d, 1H, $J = 7.5$ Hz, Ar-H), 7.51 (d, 1H, $J = 7.9$ Hz, Ar-H), 7.38-7.10 (m, 6H, Ar-H), 7.10 (dd, 1H, $J = 7.8$ & 7.8 Hz, Ar-H), 4.20-4.03 (m, 2H, O-CH$_2$CH$_3$), 3.71 [d, 1H, $J = 14.8$, N-CH$_2$(a,b)], 3.70 [d, 1H, $J = 13.0$, N-CH$_2$(a’,b’)], 3.69 [d, 1H, $J = 14.8$, N-CH$_2$(a,b)], 3.58 [d, 1H, $J = 13.0$, N-CH$_2$(a’,b’)], 2.82 (m, 2H, N-CH$_2$CHCOOEt and CHCOOEt), 2.48 (dd, 1H, $J = 12.3$ and 6.0 Hz, N-CH$_2$CHCOOEt), 1.22 (t, 3H, O-CH$_2$CH$_3$), 1.19 (d, 3H, $J = 7.1$ Hz, N-CH$_2$CH$_3$) ppm. $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta = 175.82$ (s, O-C=O), 138.94 (s, Ar-C), 138.53 (s, Ar-C), 132.55 (d, Ar-C), 130.72 (d, Ar-C), 128.97 (d, 2C, Ar-C), 128.29 (d, Ar-C), 128.19 (d, 2C, Ar-C), 127.25 (d, Ar-C), 127.02 (d, Ar-C), 124.27 (s, Ar-C), 60.31 (t, O-CH$_2$CH$_3$), 58.80 (t, N-CH$_2$), 57.89 (t, N-CH$_2$), 57.69 (t, N-CH$_2$), 38.66 (t, CH-CH$_3$), 15.52 (q, CH$_2$CH$_3$), 14.18 (q, O-CH$_2$CH$_3$) ppm. HR-MS (ESI+) m/z calculated for [C$_{20}$H$_{24}$BrNaO$_2$]$^+ = [M+Na]^+$: 412.0883; found 412.0888.
**SYNLETT-Supporting Information**

**Palladium Mediated Intramolecular Buchwald-Hartwig α-Arylation of β-Aminoesters: Synthesis of Functionalized Tetrahydroisoquinolines**

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$^1$H- and $^{13}$C-NMR spectra of all new compounds
GS-GK-2-44 (CDCl3, 18.12.10, 400 MHz)

2C (400 MHz)
2e (400 MHz)
2e (100 MHz)
$^{13}C$ NMR spectrum of compound 2f (100 MHz) in CDCl$_3$. The spectrum shows the chemical shifts of various carbon atoms in the molecule.
GS-GK-2-130 (CDCl3, 26.3.11, 400 MHz)

2g (400 MHz)
3a (100 MHz)
3b (400 MHz)
$3b$ (100 MHz)
3c (400 MHz)
$3c$ (100 MHz)
GS-JK-2-100 A (CDCl3, 17.12.10, 400 MHz)

3d (400 MHz)
68-JK-2-115 A (CDCl$_3$, 171210, 100 MHz)

3e (100 MHz)
GS-GK-2-134 [CDCl₃, 26.3.11, 400 MHz]

3g (400 MHz)
$3g$ (100 MHz)
GG-JK-2-127 (CDCl3, 17.12.10, 400 MHz)
4f (400 MHz)