Highly Stereoselective Intramolecular $\alpha$-Arylation of Self-Stabilized Non-Racemic Enolates: Synthesis of $\alpha$-Quaternary $\alpha$-Amino Acid Derivatives

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Materials and Methods.

All reactions were carried out in flame-dried glassware with magnetic stirring. Isolated yields refer to homogeneous materials (TLC, HPLC, NMR). Reagent-grade commercially available reagents and solvents were used; anhydrous solvents were used as purchased. TLC was performed using 0.25 mm silica-gel pre-coated plates and visualized by UV-254 light and CAM staining. Silica-gel (particle size 0.040–0.063 mm) was used for flash column chromatography (FCC) and medium pressure liquid chromatographic (MPLC). Melting points are corrected. Chiral HPLC analyses were performed using CHIRALPAK AD (250/4.6) or CHIRALCEL OD (250/4.6) columns. IR spectra are reported in frequency of absorption (cm\(^{-1}\)). \([\alpha]_D\)'s were measured at 589 nm, using a (10 cm \( \times \) 5 ml) cell and \( c \) is in g/100 ml. NMR spectra were recorded at: 300.13 MHz for \( ^1\)H and 75.00 MHz for \( ^{13}\)C; TMS was used as external reference; \( \delta \) are in ppm and \( J \) are in Hz.

Discussion of Migration Stereochemical Outcome

The stereochemical outcome of the aryl migration was determined by transforming the \( \alpha \)-quaternary alanine derivative \( 4c \) into the corresponding \( \alpha \)-amino acid \( R-7 \) (Scheme 1): \( 4c \) was N-deallylated and the resulting \( \alpha \)-amino \( t \)-butyl ester \( 6 \) was then reacted with trifluoroacetic acid to give \( R-7 \). The comparison with \( S-7 \) showed that 4-nitrophenyl group preferentially rearranges to give the retention product, notwithstanding this step occurs with inversion of absolute configuration.

![Scheme 1. Synthesis of \( \alpha \)-quaternary \( \alpha \)-amino acid \( R-7 \).]

Synthesis of Quaternary α-Amino Acid Derivatives

Synthesis of 2-(4-nitrophenylsulphonamido)carboxylic esters 1. General Procedure

To a suspension of the α-amino acid tert-butyl ester hydrochloride (10 mmol) in dry dichloromethane (40 mL), DIPEA (21 mmol) was added dropwise (10 min) at 25 °C. The reaction mixture was stirred for further 10 min, then cooled to 0 °C, and (4-nitrobenzene)sulphonyl chloride (10 mmol) was added dropwise (10 min). The resulting solution was stirred until completion (TLC control), then was diluted with dichloromethane (20 mL), washed with saturated NH4Cl solution (2×15 mL), saturated NaHCO3 solution (2×15 mL) and brine (20 mL), dried over MgSO4, and filtered. After evaporation of the solvent under vacuum (RV), the crude was purified by FCC to afford sulphonamides 1. Starting material, product, yield, chromatographic eluant, physical and analytical data are as follows.

(S)-tert-Butyl 2-(4-nitrophenylsulphonamido)-3-phenylpropanoate (1a)
L-Phenylalanine tert-butyl ester hydrochloride, 2.58 g; sulphonamide 1a (4.02 g, 99%, 2 h); FCC - AcOEt/hexane (1:6); white solid, mp 79-81°C, [α]D20 = +5.74 (c 1, CHCl3). 1H NMR (300 MHz, CDCl3) δ 8.21 (d, 2H, J = 8.7), 7.87 (d, 2H, J = 8.7), 7.22-7.20 (m, 3H), 7.11-7.08 (m, 2H), 5.35 (d, 1H, J = 9.4), 4.16-4.09 (m, 1H), 3.09-2.92 (m, 2H), 1.28 (s, 9H). 13C NMR (75 MHz, CDCl3) δ 169.7 (CO), 149.9 (C ArNO2), 145.7 (C ArSO2), 135.1 (C ArCH2), 129.5, 128.5, 128.3, 127.3, 124.1 (9 CHAr), 83.3 (CtBu), 57.4 (CHN), 39.4 (CH2Ph), 27.7 (3 CH3-tBu). IR (nujol) 3297, 1754, 1549, 1365, 1342, 1302, 1261, 1172, 1154, 1089, 1066, 949, 856, 835, 746 cm−1. Anal. Calcd. for C19H22N2O6S: C, 56.15; H, 5.46; N, 6.89. Found: C, 56.18; H, 5.49; N, 6.85.

(S)-tert-Butyl 2-(4-nitrophenylsulphonamido)-2-phenylacetate (1b)
L-Phenylglycine tert-butyl ester hydrochloride, 2.44 g; sulphonamide 1b (3.68 g, 94%, 2 h); FCC - AcOEt/hexane (1:8); white solid, mp 131-132°C, [α]D20 = -68.3 (c 1, CHCl3). 1H NMR (300 MHz, CDCl3) δ 8.14 (d, 2H, J = 8.7), 7.79 (d, 2H, J = 8.7), 7.25-7.14 (m, 5H), 5.91 (d, 1H, J = 7.3), 5.03 (d, 1H, J = 7.3), 1.28 (s, 9H). 13C NMR (75 MHz, CDCl3) δ 168.7 (CO), 149.8 (C ArNO2), 146.3 (C ArSO2), 135.2 (C ArCH2), 128.7, 128.6, 128.3, 127.1, 123.8 (9 CHAr), 83.3 (CtBu), 60.0 (CHN), 27.6 (3 CH3-tBu). IR (nujol) 3276, 1719, 1529, 1354, 1308, 1263, 1172, 1151, 1089, 1066, 931, 856, 835, 742 cm−1. Anal. Calcd. for C18H20N2O6S: C, 55.09; H, 5.17; N, 7.14. Found: C, 55.03; H, 5.14; N, 7.10.

(S)-tert-Butyl 2-(4-nitrophenylsulphonamido)propanoate (1c)
L-Alanine tert-butyl ester hydrochloride, 1.81 g; sulphonamide 1c (3.26 g, 99%, 2 h); FCC - AcOEt/hexane (1:8); white solid, mp 75-76°C, [α]D20 = +26.8 (c 1, CHCl3). 1H NMR (300 MHz, CDCl3) δ 8.33 (d, 2H, J = 8.7), 8.03 (d, 2H, J = 8.7), 5.37 (d, 1H, J = 8.6), 3.98-3.89 (m, 1H), 1.38 (d, 3H, J = 7.1), 1.30 (s, 9H). 13C NMR (75 MHz, CDCl3) δ 171.3 (CO), 150.5 (C ArNO2), 146.6 (C ArSO2), 128.9,
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124.7 (4 CH₃), 83.4 (C₆H₅), 28.1 (3 CH₃CH₂), 20.3 (CH₂CH₃). IR (nujol) 3264, 1722, 1523, 1350, 1309, 1226, 1180, 1160, 1130, 1089, 859, 739 cm⁻¹. Anal. Calcd. for C₁₃H₁₈N₂O₆S: C, 47.23; H, 5.49; N, 8.48. Found: C, 47.26; H, 5.49; N, 8.52.

(S)-tert-Butyl 3-methyl-2-(4-nitrophenylsulphonamido)butanoate (1d).

L-Valine tert-butyl ester hydrochloride, 2.10 g; sulphonamide 1d (3.44 g, 96%, 2 h); FCC - AcOEt/hexane (1:8); white solid, mp 94-95°C, [α]D⁰ = +54.1 (c 1, CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ 8.30 (d, 2H, J = 9.0), 8.03 (d, 2H, J = 9.0), 5.38 (d, 1H, J = 9.9), 3.68 (dd, 1H, J = 9.9, 4.4), 2.13-2.02 (m, 1H), 1.22 (s, 9H), 0.98 (d, 3H, J = 6.8), 0.83 (d, 3H, J = 6.8). ¹³C NMR (75 MHz, CDCl₃) δ 169.9 (CO), 150.0 (C₆H₅NO₂), 145.9 (C₆H₅SO₂), 128.6, 124.1 (4 CH₆H₅), 82.7 (C₆H₅), 61.5 (CH₃), 31.5 (CH₃N), 27.6 (3 CH₃CH₂), 18.9, 17.0 (2 CH₃CH₂). IR (nujol) 3301, 1721, 1698, 1524, 1363, 1347, 1310, 1248, 1182, 1158, 1081, 913, 856, 790, 739, 684 cm⁻¹. Anal. Calcd. for C₁₅H₂₂N₂O₆S: C, 50.27; H, 6.19; N, 7.82. Found: C, 50.31; H, 6.23; N, 7.79.

(2S,3S)-tert-Butyl 3-methyl-2-(4-nitrophenylsulphonamido)pentanoate (1e).

L-Isoleucine tert-butyl ester hydrochloride, 2.24 g; sulphonamide 1e (3.39 g, 91%, 2 h); FCC - AcOEt/hexane (1:9); white solid, mp 71-73°C, [α]D⁰ = +51.0 (c 1, CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ 8.31 (d, 2H, J = 8.7), 8.02 (d, 2H, J = 8.7), 5.37 (d, 1H, J = 9.8), 3.73 (dd, 1H, J = 9.8, 4.9), 1.84-1.76 (m, 1H), 1.40-1.27 (m, 1H), 1.23 (s, 9H), 1.13-1.08 (m, 1H), 0.94 (d, 3H, J = 6.8), 0.88 (t, 3H, J = 7.4). ¹³C NMR (75 MHz, CDCl₃) δ 169.9 (CO), 150.1 (C₆H₅NO₂), 145.9 (C₆H₅SO₂), 128.6, 124.2 (4 CH₆H₅), 82.9 (C₆H₅), 60.9 (CH₃), 38.6 (CH₃CH₂), 27.7 (3 CH₃CH₂), 24.6 (CH₃CH₃), 15.5 (CH₃CH₃), 11.5 (CH₃CH₂). IR (nujol) 3285, 2970, 2935, 2878, 1729, 1607, 1531, 1457, 1350, 1309, 1253, 1164, 1138, 1092, 915, 855, 789, 736, 686 cm⁻¹. Anal. Calcd. for C₁₆H₂₄N₂O₆S: C, 51.60; H, 6.50; N, 7.52. Found: C, 51.64; H, 6.52; N, 7.49.
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Synthesis of (S)-tert-butyl 2-(N-allyl-4-nitrophenylsulphonamido)-3-phenylpropanoate (3a) under SL-PTC conditions

In a screw cap vial, a heterogeneous mixture of starting sulphonamido ester 1a (4.06 g, 10 mmol), TEBA (0.23 g, 1 mmol), and allyl bromide (3.63 g, 30 mmol) solution in anhydrous acetonitrile (30 mL) and anhydrous potassium carbonate (2.21 g, 16 mmol) was vigorously stirred at 25 °C until completion (13 h, TLC analysis). The crude was then diluted with AcOEt (30 mL) and filtered through a celite pad. After evaporation of the solvent under reduced pressure (RV), purification of the crude by FCC - AcOEt/hexane (1:10) - on silica gel gave the $N$-alkyl sulphonamido ester 3a (4.11 g, 92%); $[\alpha]_D^{20} = -11.3$ (c 0.4, CHCl$_3$). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.16 (d, 2H, $J = 9.0$), 7.74 (d, 2H, $J = 8.7$), 7.28-7.20 (m, 5H), 5.73-5.64 (m, 1H), 5.23 (dd, 1H, $J = 17.1, 1.2$), 5.11 (dd, 1H, $J = 10.2, 1.2$), 4.81 (dd, 1H, $J = 8.7, 6.9$), 4.02 (ddt, 1H, $J = 16.5, 6.3, 1.5$), 3.87 (ddt, 1H, $J = 16.5, 6.9, 1.5$), 3.32 (dd, 1H, $J = 14.1, 6.6$), 2.97 (dd, 1H, $J = 14.4, 8.7$), 1.33 (s, 9H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 168.9 (CO), 149.6 (C$_{Ar}$NO$_2$), 146.2 (C$_{Ar}$SO$_2$), 135.2 (C$_{Ar}$CH$_2$), 134.0 (CH$_{All}$), 129.1, 128.5, 128.4, 126.8, 123.7 (9 CH$_{Ar}$), 118.6 (CH$_2$-All), 82.5 (C$_{tBu}$), 62.2 (CHN), 48.3 (CH$_2$-Ph), 36.6 (CH$_3$-Ph), 27.6 (3 CH$_3$-Ar). IR (neat) 3299, 3030, 1731, 1530, 1349, 1164, 930 cm$^{-1}$. Anal. Calcd. for C$_{22}$H$_{26}$N$_2$O$_6$S: C, 59.18; H, 5.87; N, 6.27. Found: C, 59.22; H, 5.89; N, 6.23.

Rearrangement of N-allyl-4-nitrophenylsulphonamido ester 3a

In a flame-dried round bottomed flask, 60% sodium hydride (120 mg, 3 mmol) was rinsed with anhydrous n-pentane and, after cooling at 0°C, a solution of $N$-alkyl-sulphonamido ester 3a (447 mg, 1 mmol) in anhydrous N,N-dimethylacetamide (7 mL) was added under nitrogen atmosphere. The reaction mixture was stirred at 0 °C until completion (2 h, TLC analysis), then was quenched with saturated NH$_4$Cl solution (1 mL). After extraction with AcOEt (2 X 10 mL) and evaporation of the solvent under reduced pressure (RV), the crude was purified by FCC - AcOEt/hexane (1:15) - on silica gel. Product 2a (333 mg, 87%) was isolated as yellow oil, $[\alpha]_D^{20} = +6.0$ (c 1, CHCl$_3$), ee 62% [CHIRALPAK AD, hexane/iPrOH (95:5), flow rate 1 mL/min, P l8 bar, t$_1$ 5.08, t$_2$ 6.19]. For physical and spectroscopic data see the corresponding section in ‘One-pot’ alkylation/rearrangement.
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‘One-pot’ alkylation/rearrangement of 4-nitrophenylsulphonamido esters 1: General Procedure

In a flame-dried round bottomed flask, 60% sodium hydride (120 mg, 3 mmol) was rinsed with anhydrous n-pentane, under nitrogen. After cooling at 0 °C, a solution of sulphonamido ester 1 (1 mmol) in anhydrous DMA (3 mL) was added dropwise. The reaction mixture was stirred until hydrogen evolution ended (ca. 30 min), then a solution of the alkylating agent RX (3 mmol) in anhydrous DMA (1 mL) was added by syringe. The resulting solution was stirred at 0 °C until completion (TLC analysis), then it was quenched with saturated NH₄Cl solution (1 mL). After dilution with AcOEt (20 mL) and water (20 mL), the organic phase was separated, dried on MgSO₄, evaporated under reduced pressure (RV), and the crude was purified by FCC on silica gel.

(R)-tert-Butyl 2-(allylamino)-2-(4-nitrophenyl)-3-phenylpropanoate (2a). Sulphonamide 1a, 406 mg; allyl bromide, 363 mg; 2a (333 mg, 87%, 5 h); FCC - AcOEt/hexane (1:15); yellow oil, [α]D²⁰ = +13.5 (c 0.3, CHCl₃), ee 62% [CHIRALPAK AD, hexane/iPrOH (95:5), flow rate 1 mL/min, P 18 bar, t₁ 5.08, t₂ 6.19]. ¹H NMR (300 MHz, CDCl₃) δ 8.14 (d, 2H, J = 8.7), 7.56 (d, 2H, J = 8.7), 7.21-7.18 (m, 3H), 6.97-6.93 (m, 2H), 6.03-5.92 (m, 1H), 5.30 (dd, 1H, J = 16.9, 1.2), 5.17 (d, 1H, J = 10.3), 3.38 (s, 2H), 3.28 (dd, 1H, J = 13.7, 5.4), 3.16 (dd, 1H, J = 13.7, 5.7), 1.97 (br, 1H), 1.48 (s, 9H). ¹³C NMR (75 MHz, CDCl₃) δ 172.1 (CO), 148.8 (C Ar), 147.0 (C Ar NO₂), 136.1 (CH All), 135.5 (C Ar), 130.4, 128.0, 127.9, 126.7, 122.9 (9 CH Ar), 115.9 (CH₂All), 82.4 (C₃No), 69.7 (C Ar), 46.2 (CH₂N₃), 42.6 (CH₂Ph), 27.9 (3 CH₃All). IR (neat) 3348, 3084, 3065, 3031, 1725, 1496, 1249, 842, 749 cm⁻¹. Anal. Calcd. for C₂₂H₂₆N₂O₄: C, 69.09, H, 6.85; N, 7.32. Found: C, 69.07, H, 6.83; N, 7.30.

(R)-tert-Butyl 2-(methylamino)-2-(4-nitrophenyl)-3-phenylpropanoate (2b). Sulphonamide 1a, 406 mg; methyl iodide, 426 mg; 2b (342 mg, 96%, 7 h); FCC - AcOEt/hexane (1:6); yellow oil, [α]D²⁰ = +21.4 (c 1.5, CHCl₃), ee 80% [CHIRALPAK AD, hexane/iPrOH (8:2), flow rate 0.7 mL/min, P 15 bar, t₁ 7.89, t₂ 10.18]. ¹H NMR (300 MHz, CDCl₃) δ 8.15 (d, 2H, J = 9.0 Hz), 7.49 (CO₂tBu), 7.31 (CO₂tBu), 2.43 (s, 3H), 2.20 (br, 1H), 1.48 (s, 9H). ¹³C NMR (75 MHz, CDCl₃) δ 172.1 (CO), 148.7 (C Ar), 147.0 (C Ar NO₂), 135.5 (C Ar), 130.4, 128.0, 127.8, 126.7, 122.9 (9 CH Ar), 115.9 (CH₂All), 82.4 (C₃No), 69.7 (C Ar), 46.2 (CH₂N₃), 42.6 (CH₂Ph), 27.9 (3 CH₃All). IR (neat) 3354, 2803, 1943, 1726, 1603, 1520, 1347, 1031, 800 cm⁻¹. Anal. Calcd. for C₂₀H₂₄N₂O₄: C, 67.40; H, 6.79; N, 7.86. Found: C, 67.37; H, 6.77; N, 7.82.

(R)-tert-Butyl 2-(ethylamino)-2-(4-nitrophenyl)-3-phenylpropanoate (2c). Sulphonamide 1a, 406 mg; ethyl iodide, 468 mg; 2c (367 mg, 99%, 5 h); FCC - AcOEt/hexane (1:6); yellow oil, [α]D²⁰ = +12.1 (c 0.87, CHCl₃), ee 56% [CHIRALPAK AD, hexane/iPrOH (95:5), flow rate 0.7 mL/min, P 12 bar, t₁ 7.16, t₂ 8.45]. ¹H NMR (300 MHz, CDCl₃) δ 8.08 (d, 2H, J = 9.0 Hz), 7.49
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(d, 2H, J = 9.0 Hz), 7.15-7.12 (m, 3H), 6.90-6.87 (m, 2H), 3.31 (s, 2H), 2.65-2.50 (m, 2H), 1.77 (br, 1H), 1.42 (s, 9H), 1.15 (t, 3H, J = 7.0 Hz). 13C NMR (75 MHz, CDCl3) δ 172.3 (CO), 149.1 (CAr), 147.0 (CArNO2), 135.7 (CAr), 130.4, 128.0, 127.8, 126.7, 122.9 (9 CHAr), 82.3 (CtBu), 70.0 (Cα), 42.0 (CH2Ph), 37.9 (CH2N), 27.9 (3 CH3-), 15.5 (CH3). IR (neat) 3348, 3076, 3029, 2927, 1730, 1597, 851 cm⁻¹. Anal. Calcd. for C21H26N2O4: C, 68.09; H, 7.07; N, 7.56. Found: C, 68.13; H, 7.10; N, 7.52.

(R)-tert-Butyl 2-(4-nitrophenyl)-3-phenyl-2-(propylamino)propanoate (2d).

Sulphonamide 1a, 406 mg; propyl iodide, 510 mg; 2d (308 mg, 80%, 5 h); FCC - AcOEt/hexane (1:6); yellow oil, [α]D²⁰ = +13.3 (c 0.91, CHCl₃), ee 56% [CHIRALPAK AD, hexane/i-PrOH (95:5), flow rate 0.7 mL/min, P 12 bar, t₁ 7.20, t₂ 8.49]. 1H NMR (300 MHz, CDCl3) δ 8.08 (d, 2H, J = 9.0 Hz), 7.48 (d, 2H, J = 9.0 Hz), 7.15-7.13 (m, 3H), 6.90-6.88 (m, 2H), 3.31 (s, 2H), 2.60-2.41 (m, 2H), 1.80 (br, 1H), 1.63-1.52 (m, 2H), 1.42 (s, 9H), 0.96 (t, 3H, J = 7.4 Hz). 13C NMR (75 MHz, CDCl3) δ 172.4 (CO), 149.2 (CAr), 146.9 (CArNO2), 135.7 (CAr), 130.5, 128.0, 127.8, 126.7, 122.9 (9 CHAr), 82.1 (CtBu), 69.8 (Cα), 45.4 (CH2Ph), 42.1 (CH2N), 27.9 (3 CH3-), 23.6 (CH2CH3), 11.8 (CH2CH3). IR (neat) 3354, 3093, 3033, 2931, 1726, 1574, 843, 715 cm⁻¹. Anal. Calcd. for C22H28N2O4: C, 68.73; H, 7.34; N, 7.29. Found: C, 68.76; H, 7.36; N, 7.25.

(R)-tert-Butyl 2-(butylamino)-2-(4-nitrophenyl)-3-phenylpropanoate (2e).

Sulphonamide 1a, 406 mg; butyl iodide, 552 mg; 2e (343 mg, 86%, 4 h); FCC - AcOEt/hexane (1:15); yellow oil, [α]D²⁰ = +12.7 (c 1, CHCl₃), ee 62% [CHIRALPAK AD, hexane/i-PrOH (95:5), flow rate 0.6 mL/min, P 10 bar, t₁ 7.41, t₂ 8.76]. 1H NMR (300 MHz, CDCl3) δ 8.13 (d, 2H, J = 9.0), 7.53 (d, 2H, J = 9.0), 7.19-7.17 (m, 3H), 6.94-6.93 (m, 2H), 3.35 (s, 2H), 2.66-2.51 (m, 2H), 1.87 (br, 1H), 1.60-1.30 (m, 4H), 1.47 (s, 9H), 0.96 (t, 3H, J = 7.2). 13C NMR (75 MHz, CDCl3) δ 172.4 (CO), 149.1 (CAr), 146.8 (CArNO2), 135.8 (CAr), 130.4, 127.9, 127.7, 126.6, 122.7 (9 CHAr), 82.1 (CtBu), 69.8 (Cα), 43.1 (CH2Ph), 42.1, 32.6 (2 CH3), 27.8 (3 CH3-), 20.4 (CH2CH3), 13.9 (CH2CH3). IR (neat) 3341, 3087, 3031, 2930, 1725, 1604, 843, 735 cm⁻¹. Anal. Calcd. for C23H30N2O4: C, 69.32; H, 7.59; N, 7.03. Found: C, 69.29; H, 7.57; N, 7.06.

(R)-tert-Butyl 2-(octylamino)-2-(4-nitrophenyl)-3-phenylpropanoate (2f).

Sulphonamide 1a, 406 mg; octyl iodide, 720 mg; 2f (332 mg, 73%, 6 h); FCC - AcOEt/hexane (1:15); yellow oil, [α]D²⁰ = +9.7 (c 0.3, CHCl₃), ee 61% [CHIRALPAK AD, hexane/i-PrOH (98:2), flow rate 0.7 mL/min, P 11 bar, t₁ 6.44, t₂ 8.15]. 1H NMR (300 MHz, CDCl3) δ 8.08 (d, 2H, J = 8.8 Hz), 7.47 (d, 2H, J = 8.8 Hz), 7.14-7.12 (m, 3H), 6.88-6.86 (m, 2H), 3.29 (s, 2H), 2.62-2.42 (m, 2H), 1.79 (br, 1H), 1.52-1.27 (m, 21H), 0.88 (t, 3H, J = 10.3). 13C NMR (75 MHz, CDCl3) δ 173.1 (CO), 149.7 (CAr), 147.3 (CArNO2), 136.1 (CAr), 130.8, 128.3, 128.1, 127.0, 123.2 (9 CHAr), 82.3 (CtBu), 68.1 (Cα), 43.3 (CH2Ph), 41.8, 31.5, 30.2, 29.2, 28.9 (5 CH3), 27.6 (3 CH3-), 27.0, 22.3 (2 CH3), 13.7 (CH2CH3). IR (neat) 3368, 3063, 3031, 2928, 1726, 1521, 842, 737, 702 cm⁻¹. Anal. Calcd. for C27H38N2O4: C, 69.32; H, 7.59; N, 7.03. Found: C, 69.29; H, 7.57; N, 7.06.
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**(R)-tert-Butyl 2-(benzylamino)-2-(4-nitrophenyl)-3-phenylpropanoate (2g).**

Sulphonamide 1a, 406 mg; benzyl bromide, 513 mg; 2g (324 mg, 75%, 5 h); FCC - AcOEt/hexane (1:15); yellow oil, \([\alpha]_D^{20} = +6.7 (c 1.2, CHCl_3), ee 51\% [CHIRALPAK AD, hexane/iPrOH (95:5), flow rate 0.7 mL/min, P 12 bar, t₁ 9.26, t₂ 10.24].\)

\(^{1}H\) NMR (300 MHz, CDCl₃) δ 8.11 (d, 2H, \(J = 8.9\) Hz), 7.56 (d, 2H, \(J = 8.9\) Hz), 7.38-7.29 (m, 5H), 7.18-7.13 (m, 3H), 6.95-6.92 (m, 2H), 3.83 (d, 1H, \(J = 12.3\) Hz), 3.66 (d, 1H, \(J = 12.3\) Hz), 3.45 (d, 1H, \(J = 13.8\) Hz), 3.37 (d, 1H, \(J = 13.8\) Hz), 2.24 (br, 1H), 1.47 (s, 9H).

\(^{13}C\) NMR (75 MHz, CDCl₃) δ 171.4 (CO), 147.7 (C₉ArO₂), 147.0, 135.0 (2 C₉Ar), 130.3, 127.9, 127.8, 126.8, 123.0 (9 C₉Ar), 82.8 (C₉propargyl), 81.3 (C₉(C₉)), 71.5 (C₉(propargyl)), 69.6 (C₉), 42.8 (CH₂Ph), 33.2 (CH₂N), 27.8 (3 C₃(CH₃)). IR (neat) 3343, 3030, 1725, 1604, 1369, 843, 734 cm⁻¹. Anal. Calcd. for C₂₆H₂₈N₂O₄: C, 72.20; H, 6.53; N, 6.48. Found: C, 72.23; H, 6.53; N, 6.45.

**(R)-tert-Butyl 2-(4-nitrophenyl)-3-phenyl-2-(prop-2-ynylamino)propanoate (2h).**

Sulphonamide 1a, 406 mg; propargyl bromide, 357 mg; 2h (335 mg, 88%, 8 h); FCC - AcOEt/hexane (1:15); yellow oil, \([\alpha]_D^{20} = +3.7 (c 0.2, CHCl₃), ee 80\% [CHIRALPAK AD, hexane/iPrOH (95:5), flow rate 0.8 mL/min, P 14 bar, t₁ 10.48, t₂ 12.26].\)

\(^{1}H\) NMR (300 MHz, CDCl₃) δ 8.17 (d, 2H, \(J = 9.0\) Hz), 7.62 (d, 2H, \(J = 9.0\) Hz), 7.24-7.22 (m, 3H), 7.05-7.01 (m, 2H), 3.50-3.29 (m, 4H), 2.28 (t, 1H, \(J = 2.7\) Hz), 1.48 (s, 9H).

\(^{13}C\) NMR (75 MHz, CDCl₃) δ 171.4 (CO), 147.7 (C₉ArO₂), 147.0, 135.0 (2 C₉Ar), 130.3, 127.9, 127.8, 126.8, 123.0 (9 C₉Ar), 82.8 (C₉propargyl), 81.3 (C₉(C₉)), 71.5 (C₉(propargyl)), 69.6 (C₉), 42.8 (CH₂Ph), 33.2 (CH₂N), 27.8 (3 C₃(CH₃)). IR (neat) 3342, 3296, 2130, 1723, 1604, 1523, 856, 735 cm⁻¹. Anal. Calcd. for C₂₁H₂₄N₂O₄: C, 69.46; H, 6.36; N, 7.36. Found: C, 69.44; H, 6.32; N, 7.40.

**(R)-tert-Butyl 2-(allylamino)-2-(4-nitrophenyl)-2-phenylacetate (4b).**

Sulphonamide 1b, 392 mg; allyl bromide, 363 mg; 4b (339 mg, 92%, 26 h); FCC - AcOEt/hexane (1:12); yellow oil, \([\alpha]_D^{20} = +12.5 (c 1, CHCl₃), ee 50\% [CHIRALCEL OD, hexane/iPrOH (99:1), flow rate 0.7 mL/min, P 11 bar, t₁ 11.96, t₂ 12.88].\)

\(^{1}H\) NMR (300 MHz, CDCl₃) δ 8.15 (d, 2H, \(J = 9.0\) Hz), 7.75 (d, 2H, \(J = 9.0\) Hz), 7.37-7.25 (m, 5H), 5.99-5.86 (m, 1H), 5.23 (dd, 1H, \(J = 17.1, 1.5\) Hz), 5.09 (dd, 1H, \(J = 10.2, 1.5\) Hz), 2.90-2.87 (m, 2H), 2.43 (br, 1H), 1.40 (s, 9H).

\(^{13}C\) NMR (75 MHz, CDCl₃) δ 171.8 (CO), 149.5 (C₉ArO₂), 147.3, 141.4 (2 C₉Ar), 136.6 (CH₃N), 130.0, 128.7, 128.2, 128.1, 123.3 (9 C₉Ar), 116.2 (CH₂All), 83.3 (C₃(CH₃)), 73.1 (C₉), 47.1 (CH₂N), 28.2 (3 C₃(CH₃)). IR (neat) 3331, 2979, 2932, 1726, 1644, 1604, 1520, 1368, 1348, 1246, 1153, 991, 918, 852, 733, 703 cm⁻¹. Anal. Calcd. for C₂₃H₂₅N₂O₄: C, 68.46; H, 6.57; N, 7.60. Found: C, 68.41; H, 6.55; N, 7.63.

**(R)-tert-Butyl 2-(allylamino)-2-(4-nitrophenyl)propanoate (4c).**

Sulphonamide 1c, 330 mg; allyl bromide, 363 mg; 4c (273 mg, 89%, 6 h); FCC - AcOEt/hexane (1:7); yellow oil, \([\alpha]_D^{20} = -2.0 (c 1, CHCl₃), ee 59\% [CHIRALPAK AD, hexane/iPrOH (95:5), flow rate 1 mL/min, P 17 bar, t₁ 5.49, t₂ 6.18].\)

\(^{1}H\) NMR (300 MHz, CDCl₃) δ 8.23 (d, 2H, \(J = 8.7\) Hz), 7.73 (d, 2H, \(J = 8.7\) Hz), 6.04-5.93 (m, 1H), 5.28 (dd, 1H, \(J = 17.1, 1.5\) Hz), 5.16 (dd, 1H, \(J = 10.2, 1.2\) Hz), 3.23-3.11 (m, 2H), 2.05 (br, 1H), 1.70 (s, 3H), 1.48 (s, 9H).

\(^{13}C\) NMR (75 MHz, CDCl₃) δ 173.0 (CO), 151.1 (C₉Ar), 147.0 (C₉ArO₂), 136.4 (CH₃N), 126.9, 123.3 (4 CH₉Ar), 115.8 (CH₂All), 82.0 (C₃(CH₃)), 65.6 (C₉), 46.5 (CH₂N), 27.7 (3 C₃(CH₃)).
Synthesis of Quaternary α-Amino Acid Derivatives


(R)-tert-Butyl 2-(allylamino)-3-methyl-2-(4-nitrophenyl)butanoate (4d).

Sulphonamide 1d, 358 mg; allyl bromide, 363 mg (331 mg, 99%, 24 h); FCC - AcOEt/hexane (1:12); yellow oil, [α]D²⁰ = -60.1 (c 1.1, CHCl₃), ee 95% [CHIRALPAK AD, hexane/iPrOH (9:1), flow rate 0.8 mL/min, P 14 bar, t₁ 5.04, t₂ 6.61]. ¹H NMR (300 MHz, CDCl₃) δ 8.21 (d, 2H, J = 9.0), 7.78 (d, 2H, J = 9.0), 6.03-5.91 (m, 1H), 5.29 (d, 1H, J = 17.4), 5.16 (dd, 1H, J = 10.2, 1.5), 3.12 (dd, 1H, J = 13.5, 5.4), 2.98 (dd, 1H, J = 14.0, 4.2), 2.43-2.40 (m, 1H), 1.70 (br, 1H), 1.56 (s, 9H), 0.90 (d, 3H, J = 5.7), 0.80 (d, 3H, J = 6.9). ¹³C NMR (75 MHz, CDCl₃) δ 172.0 (CO), 146.8 (Cas), 145.1 (C₄NO₂), 136.4 (CH₂All), 130.2, 121.9 (4 CH₃), 115.3 (CH₂All), 81.8 (C₄B), 72.6 (C₃), 46.5 (CH₂N), 28.0 (3 CH₃(tBu)), 18.4, 16.7 (2 CH₃-CH₂). IR (neat) 3341, 2974, 2934, 1723, 1644, 1520, 1349, 1244, 1160, 885 cm⁻¹. Anal. Calcd. for C₁₈H₂₆N₂O₄: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.69; H, 7.86; N, 8.35.

(2R,3S)-tert-Butyl 2-(allylamino)-3-methyl-2-(4-nitrophenyl)pentanoate (4e).

Sulphonamide 1e, 372 mg; allyl bromide, 363 mg; 4e (345 mg, 99%, 26h); FCC - AcOEt/hexane (1:8); yellow oil, [α]D²⁰ = -53.2 (c 1.2, CHCl₃), ee 96% [CHIRALCEL OD, hexane/iPrOH (98:2), flow rate 0.8 mL/min, P 13 bar, t₁ 5.04, t₂ 5.63]. ¹H NMR (300 MHz, CDCl₃) δ 8.14 (d, 2H, J = 8.7), 7.74 (d, 2H, J = 9.0), 5.97-5.86 (m, 1H), 5.25 (d, 1H, J = 17.1), 5.09 (d, 1H, J = 10.2), 3.05 (dd, 1H, J = 13.8, 5.7), 2.94 (dd, 1H, J = 13.8, 4.5), 2.06-2.02 (m, 1H), 1.88-1.81 (m, 1H), 1.71 (br, 1H), 1.52 (s, 9H), 0.87-0.80 (m, 6H), 0.46-0.32 (m, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 172.1 (CO), 146.8 (CAr), 145.5 (C₄NO₂), 136.4 (CH₂All), 130.0, 122.0 (4 CH₃), 115.4 (CH₂All), 81.8 (C₄B), 72.6 (C₃), 46.5 (CH₂N), 43.0 (CH₃(tBu)), 28.0 (3 CH₃(tBu)), 23.5 (CH₂CH₂), 14.8 (CH₂CH₂), 12.2 (CH₃CH₂). IR (neat) 3338, 1743, 1639, 1525, 1298, 1217, 1106, 889, 899 cm⁻¹. Anal. Calcd. for C₁₉H₂₈N₂O₄: C, 65.49; H, 8.10; N, 8.04. Found: C, 65.53; H, 8.14; N, 8.00.

(R)-tert-Butyl 2-(4-nitrophenyl)-2-(prop-2-ynylamino)propanoate (5c).

Sulphonamide 1c, 330 mg; propargyl bromide, 357 mg; 5c (283 mg, 93%, 5h); FCC - AcOEt/hexane (1:7); yellow oil, [α]D²⁰ = -15.2 (c 1, CHCl₃), ee 68% [CHIRALPAK AD, hexane/iPrOH (9:1), flow rate 0.8 mL/min, P 14 bar, t₁ 8.31, t₂ 13.53]. ¹H NMR (300 MHz, CDCl₃) δ 8.23 (d, 2H, J = 9.0), 7.73 (d, 2H, J = 9.0), 3.46 (dd, 1H, J = 16.5, 2.4), 3.35 (dd, 1H, J = 16.2, 2.4), 2.26 (t, 1H, J = 2.4), 1.72 (s, 3H), 1.48 (s, 9H); NH signal is not visible. ¹³C NMR (75 MHz, CDCl₃) δ 172.6 (CO), 150.4 (C₄NO₂), 147.1 (CAr), 126.9, 123.4 (4 CH₃), 82.4 (Cpropargyl), 81.8 (C₃), 71.6 (CHpropargyl), 65.4 (C₃), 33.1 (CH₂-propargyl), 27.7 (3 CH₃-tBu), 23.8 (CH₃). IR (neat) 3299, 2980, 2935, 1724, 1605, 1520, 1477, 1457, 1369, 1348, 1253, 1164, 1128, 1087, 1014, 856, 845, 739, 700 cm⁻¹. Anal. Calcd. for C₁₉H₂₉NO₃: C, 63.14; H, 6.62; N, 9.20. Found: C, 63.18; H, 6.65; N, 9.17.
Synthesis of Quaternary $\alpha$-Amino Acid Derivatives

(R)-tert-Butyl 3-methyl-2-(4-nitrophenyl)-2-(prop-2-ynylamino)butanoate (5d).

Sulphonamide 1d, 358 mg; propargyl bromide, 357 mg; 5d (326 mg, 98%, 20 h); FCC - AcOEt/hexane (1:9); yellow oil, [\(\alpha\)]\(_{D}\)\(^{20} = -77.0\) (c 1, CHCl\(_3\)), ee 96% [CHIRALPAK AD, hexane/PrOH (9:1), flow rate 0.8 mL/min, P 14 bar, t\(_1\) 5.649, t\(_2\) 6.288]. 1H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.23 (d, 2H, \(J\) = 9.0), 7.81 (d, 2H, \(J\) = 9.0), 3.32 (dd, 1H, \(J\) = 16.2, 2.4), 3.17 (dd, 1H, \(J\) = 16.2, 2.4), 2.49-2.40 (m, 1H), 2.28 (t, 1H, \(J\) = 2.4), 1.58 (s, 9H), 0.93 (d, 3H, \(J\) = 6.8), 0.82 (d, 3H, \(J\) = 6.9); NH signal is not visible. 13C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 171.5 (CO), 147.0 (C\(_{Ar}\)), 144.5 (C\(_{Ar}\)NO\(_2\)), 130.1, 122.3 (4 C\(_{Ar}\)), 82.4 (C\(_{propargyl}\)), 81.7 (C\(_{tBu}\)), 72.8 (CH\(_{propargyl}\)), 71.3 (C\(_{\alpha}\)), 36.0 (CH\(_{iPr}\)), 33.8 (CH\(_2\)-propargyl), 28.0 (3 CH\(_3\)-tBu), 18.2, 16.9 (CH\(_2\)-pr). IR (neat) 3303, 2974, 2934, 1720, 1604, 1525, 1451, 1369, 1355, 1237, 1164, 1010, 851, 828, 731 cm\(^{-1}\). Anal. Calcd. for C\(_{18}\)H\(_{24}\)N\(_2\)O\(_4\): C, 65.04; H, 7.28; N, 8.43. Found: C, 65.00; H, 7.26; N, 8.47.

(2R,3S)-tert-butyl 3-methyl-2-(4-nitrophenyl)-2-(prop-2-ynylamino)pentanoate (5e).

Sulphonamide 1e, 372 mg; propargyl bromide, 357 mg; 5e (336 g, 97%, 26 h); FCC - AcOEt/hexane (1:10); yellow oil, [\(\alpha\)]\(_{D}\)\(^{20} = -61.7\) (c 1, CHCl\(_3\)) de 98% [CHIRALCEL OD, hexane/iPrOH (98:2), flow rate 0.8 mL/min, P 13 bar, t\(_1\) 7.156, t\(_2\) 7.613]. 1H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.12-8.09 (m, 2H), 7.71-7.68 (m, 2H), 3.19 (dd, 1H, \(J\) = 16.1, 2.4), 3.03 (dd, 1H, \(J\) = 16.1, 2.5), 2.19 (t, 1H, \(J\) = 2.2), 1.98 (br, 1H), 1.97-1.92 (m, 1H), 1.65-1.75 (m, 1H), 1.46 (s, 9H), 0.81-0.74 (m, 6H), 0.45-0.34 (m, 1H). 13C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 172.0 (CO), 147.4 (C\(_{Ar}\)), 145.3 (C\(_{Ar}\)NO\(_2\)), 130.4, 122.7 (4 C\(_{Ar}\)), 82.8 (C\(_{propargyl}\)), 82.2 (C\(_{tBu}\)), 73.5 (CH\(_{propargyl}\)), 71.7 (C\(_{\alpha}\)), 43.7 (CH\(_{tBu}\)), 34.2 (CH\(_2\)-propargyl), 28.4 (3 CH\(_3\)-tBu), 24.1 (CH\(_2\)CH\(_3\)), 15.0 (CH\(_3\)), 12.7 (CH\(_3\)CH\(_3\)). IR (neat) 3336, 2971, 2944, 1715, 1612, 1525, 1451, 1369, 1355, 1237, 1164, 1131, 1111, 1010, 851, 828, 731 cm\(^{-1}\). Anal. Calcd. for C\(_{19}\)H\(_{26}\)N\(_2\)O\(_4\): C, 65.87; H, 7.56; N, 8.09. Found: C, 65.90; H, 7.59; N, 8.05.

Synthesis of (R)-2-amino-2-(4-nitrophenyl)propanoic acid (R-7)

Tetrakis(triphenylphosphine)palladium(0) (81 mg, 0.07 mmol) was added to a solution of (R)-tert-butyl 2-(allylamino)-2-(4-nitrophenyl)propanoate (4c) (306 mg, 1 mmol) and dimedone (178 mg, 1.2 mmol) in THF (5 mL) previously purged with nitrogen through three freeze-pump-thaw cycles. The reaction mixture was stirred at 25 °C overnight; the crude, after solvent evaporation, was purified by FCC - AcOEt/hexane on silica gel. The isolated product 6 (229 mg, 0.86 mmol, 86%) was dissolved in CHCl\(_3\) (6 mL), TFA (1.96 g, 17.2 mmol,) was added, and this solution was stirred at 62 °C for 2 h. After evaporation under reduced pressure (RV), the crude was diluted with 10% HCl aq (20 mL) and extracted with Et\(_2\)O (2 X 20 ml). The aqueous layer was evaporated (RV) and the product R-7 (187 mg, 88%) was isolated as a white solid, mp 148-149 °C (lit.\(^{[1]}\) 152-153 °C). [\(\alpha\)]\(_{D}\)\(^{20} = -38.0\) (c 0.44, 1 N HCl) ee 53% [lit.\(^{[1]}\)].

1H NMR (300 MHz, D\(_2\)O) \(\delta\) 8.37 (d, 2H, \(J\) = 8.7), 7.81 (d, 2H, \(J\) = 8.7), 2.07 (s, 3H). 13C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 175.3 (CO), 148.3 (C\(_{Ar}\)NO\(_2\)), 145.3 (C\(_{\alpha}\)), 127.9, 124.8 (4 CH\(_3\)), 63.3 (C\(_{\alpha}\)), 22.1 (CH\(_3\)).


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[Spectrum images showing NMR data]
Synthesis of Quaternary \( \alpha \)-Amino Acid Derivatives

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Synthesis of Quaternary α-Amino Acid Derivatives
Synthesis of Quaternary $\alpha$-Amino Acid Derivatives

[Diagram of molecular structures and spectra]

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Synthesis of Quaternary α-Amino Acid Derivatives

![Chemical Structures]

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