Supplementary Material (ESI) for Chemical Communications

Supporting Information

Switching stereoselectivity in the rhodium-catalysed 1,4-addition: the asymmetric synthesis of 2-substituted pyrrolizidin-3-ones

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Experimental details for compound synthesis, characterisation and catalytic studies.

General Considerations

Commercially available solvents and reagents were obtained from Sigma-Aldrich Company Ltd, Lancaster Synthesis Ltd, Fisher Scientific Ltd and Strem Chemicals UK and were used without further purification. Solvents and reagents were deoxygenated where necessary by purging with nitrogen. Flash column chromatography was carried out using Merck kieselgel 60 H silica gel (particle size: 0.063–0.100 mm). Melting points were determined using a Büchi 535 melting point apparatus and are uncorrected. Infra red spectra (4000 to 600 cm^{-1}) were recorded on a Perkin Elmer (1600) FT spectrometer with internal calibration. Fast Atom Bombardment (FAB) and Electron Impact (EI) mass spectra were obtained using a Fisons VG Autospec Finnigan MAT 8340 instrument at the University of Bath. Additional mass spectra were run at the EPSRC National Mass Spectrometry Service Centre at Swansea University. High Performance Liquid Chromatography (HPLC) was performed on a Perkin Elmer HPLC-IPM using a Chiralpak OD–H column by Daicel Chemical Ind. Ltd. Elemental analyses were recorded on a Micromass Autospec Spectrometer at the University of Bath.

General experimental procedure for the rhodium-catalysed 1,4-addition of organotrialkoxysilanes.

To an oven dried pressure tube was charged $[Rh(cod)_2][BF_4]$ (5 mol%) and anhydrous dioxane (3 ml) under nitrogen. To the solution was added (S)-hexahydro-2-methylenepyrrolizin-3-one **1** (0.069 g, 0.5 mmol), aryl trialkoxysilane (1.5 mmol, 3 eq.) and water (0.3 ml). The resulting solution was refluxed for 24 hours at 110^{o}C and then allowed to cool to room temperature. The resulting gel was evaporated under reduced pressure, re-dissolved in ethyl acetate (20 ml) and washed with water (1 x 20 ml), saturated sodium bicarbonate solution (1x 20 ml) and brine (1 x 20 ml). The organic extract was dried over magnesium sulphate and concentrated *in vacuo* to afford the crude product, which was later purified by flash chromatography (ethyl acetate: petrol) to obtain the major diastereomer.

General experimental procedure for the rhodium-catalysed 1,4-addition of organozincs.

To an oven dried round bottom flask was charged $[Rh(cod)Cl]_2$ (5 mol%) and anhydrous THF (3 ml) under nitrogen. To the solution was added (S)-hexahydro-2-methylenepyrrolizin-3-one **1** (0.069g, 0.5 mmol), the appropriate aryl zinc chloride solution (0.75 mmol, 1.5 eq.) and trimethylsilyl chloride (95 µl, 0.75 mmol, 1.5 eq). The resulting solution was stirred at room temperature for 24 hours and then quenched with water (1 ml). The resulting solution was evaporated under reduced pressure, re-dissolved in ethyl acetate (20 ml) and washed with water (1 x 20 ml), saturated sodium bicarbonate solution (1x 20 ml) and brine (1 x 20 ml). The organic extract was dried over magnesium sulphate and concentrated *in vacuo* to afford the crude product, which was later purified by flash chromatography (ethyl acetate: petrol) to obtain the major diasteromer.

General experimental procedure for the rhodium-catalysed 1,4-addition of aryl boronic acids.

To an oven dried pressure tube was charged $[Rh(cod)Cl]_2$ (5 mol%) and anhydrous dioxane (3 ml) under nitrogen. To the solution was added (S)-hexahydro-2-methylenepyrrolizin-3-one **1** (0.069g, 0.5 mmol), aryl boronic acid (2 mmol, 4 eq.) and water (0.3 ml). The resulting solution was refluxed for 24 hours at 110^{o}C and then allowed to cool to room temperature. The solution was evaporated under reduced pressure, re-dissolved in ethyl acetate (20 ml) and washed with water (1 x 20 ml), saturated sodium bicarbonate solution (1x 20 ml) and brine (1 x 20 ml). The organic extract was dried over magnesium sulphate and concentrated *in vacuo* to afford the crude product, which was then purified by flash chromatography (ethyl acetate: petrol) to obtain the major diastereomer.

(S)-tert-butyl-2(2-(methoxycarbonyl)allyl)pyrrolidine-1-carboxylate (5)

A solution of tert-butyl (S)-*tert*-butyl 2-((2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)methyl)pyrrolidine-1-carboxylate **4** (1.4 g, 4.28 mmol) and N,N-dimethylmethylene ammonium iodide (1.98 g, 10.7 mmol, 2.5 equiv.) in anhydrous methanol (50 ml) was heated at 65^{o}C for 16 hours. The reaction mixture was then evaporated to dryness, re-dissolved in ether and washed with $NaHCO_3$ (50 ml), $KHSO_4$ (50 ml) and brine (2 x 50 ml). The organic extract was dried over magnesium sulphate and concentrated *in vacuo* to afford the crude product, which was purified by flash chromatography (ethyl acetate: petrol, 1:4 by volume) to afford the product **5** as a colourless oil (0.8 g, 70 %); R_f (petrol: ethyl

acetate, 1:1) 0.52, δ_H (300 MHz, $CDCl_3$) 6.15 (1H, app.s, C*H*$_2$), 5.5 (1H, br. s, C*H*$_2$), 3.9 (1H, m, C*H*), 3.69 (3H, s, OC*H*$_3$), 3.25 (2H, m, C*H*$_2$), 2.5-2.7 (1H, m, C*H*$_2$), 2.2-2.4 (1H, m, CH_2), 1.7-1.85 (3H, m, CH_2), 1.6-1.85 (1H, m, C*H*), 1.38 (9H, s, (C*H*$_3$)$_3$); δ_C (75.5 MHz; $CDCl_3$) 167.8, 154.9, 138.1, 127.8, 79.6, 57.1, 52.2, 46.8, 37.0, 29.6, 28.8, 23.0; IR (film, cm^{-1}) ν 2974, 2880, 1723, 1693, 1630, 1440, 1396, 1168, 949, 772; *m/z* (EI+); Accurate mass (HRMS); 270.1700, found 270.1700 (M^++H).

(S)-hexahydro-2-methylenepyrrolizin-3-one (1)

To a solution of *tert*-butyl 2-(2-(methoxycarbonyl)allyl) pyrrolidine-1-carboxylate **5** (0.4 g, 1.48 mmol) in DCM at room temperature (10 ml) was added trifluoroacetic acid (3 ml). After 5 hours, or following completion by TLC, the resulting solution was evaporated under reduced pressure and re-dissolved in methanol (10 ml). Potassium carbonate (1.02g, 7.4 mmol) was then added to the solution and the reaction mixture was stirred for a further 12 hours at room temperature. The corresponding solution was evaporated to dryness, re-dissolved in ether (20 ml) and washed with water (1 x 25 ml). The aqueous layer was then back extracted with ether (2 x 10 ml) and the combined organics dried over $MgSO_4$. The solution was evaporated to dryness to generate the desired compound as a colourless oil which was purified by silica chromatography (ethyl acetate: petrol, 1:1 by volume) to afford the product **1** as a colourless oil (0.125 g, 62%), R_f (petrol: ethyl acetate, 1:1) 0.23; δ_H (300 MHz, $CDCl_3$) 5.85 (1H, t, J = 2.71 Hz, C*H*), 5.21 (1H, t, J = 2.31 Hz, C*H*), 3.55-3.75 (2H, m, C*H*$_2$), 3.1-3.2 (1H, m, C*H*), 2.93 (1H, ddt, J = 17.0, 7.3, 2.1 Hz, C*H*$_2$), 2.4 (1H, ddt, J = 17.0, 4.5, 3.0 Hz, C*H*$_2$), 1.81-2.15 (3H, m, CH_2), 1.15-1.2 (1H, m, CH_2); δ_C (75.5 MHz; $CDCl_3$) 167.3, 142.1, 114.2, 57.5, 40.5, 31.0, 30.5, 25.2; IR (film, cm^{-1}) ν 2971, 2890, 1682, 1656, 1421, 1329, 1294, 1210, 1093, 1016, 914, 805, 731; *m/z* (EI+) 155.1 (100%, M+NH_4)$^+$. Accurate mass (HRMS); 137.0835, found 137.0834 (M^++H).

(2S,7S)-2-benzyl-hexahydropyrrolizin-3-one (2a)

R_f (petrol: ethyl acetate, 1:1) 0.27; δ_H (300 MHz, $CDCl_3$) 7.1-7.25 (5H, m, *Ar*), 3.6-3.7 (1H, m, C*H*), 3.41-3.52 (1H, m, C*H*$_2$), 3.24 (1H, dd, J = 13.8, 3.9 Hz, C*H*$_2$), 2.9-3.08 (2H, m, C*H*$_2$), 2.49 (1H, dd, J = 13.8, 10.3 Hz, C*H*$_2$), 2.22 (1H, ddd, J = 12.05, 7.53, 6.02 Hz, C*H*$_2$), 1.84-2.06 (3H, m, C*H*$_2$), 1.31 (1H, dt, J = 11.9, 8.55 Hz, C*H*$_2$), 1.05-1.2 (1H, m, C*H*$_2$); δ_C (75.5 MHz; $CDCl_3$) 175.2, 140.3, 129.2, 128.8, 126.5, 59.8, 48.8, 41.4, 37.4, 35.4, 32.6, 27.2; IR (film, cm^{-1}) ν 2968, 2880, 1680, 1453, 1422, 1331; *m/z* (EI+) 234.2 (5%, M+NH_4)$^+$. Accurate mass (HRMS); 216.1383, found 216.1380 (M^++H).

(2R,7S)-2-benzyl-hexahydropyrrolizin-3-one (*epi*-2a)

R_f (petrol: ethyl acetate, 1:1) 0.2; δ_H (300 MHz, $CDCl_3$) 7.1-7.25 (5H, m, *Ar*), 3.4-3.6 (2H, m, C*H*$_2$), 3.05 (1H, dd, J = 13.1, 3.7 Hz, C*H*$_2$), 2.97 (1H, ddd, J = 12.4, 9.2, 3.7 Hz, C*H*$_2$), 2.8-2.9 (1H, m, C*H*$_2$), 2.73 (1H, dd, J = 12.9, 9.4 Hz, C*H*$_2$), 1.9-2.1 (2H, m, C*H*$_2$), 1.82-1.92 (2H, m, C*H*$_2$), 1.71 (1H, ddd, J = 13.2, 9.0, 6.9 Hz, C*H*$_2$), 1.06-1.22 (1H, m, C*H*$_2$); δ_C (75.5 MHz; $CDCl_3$) 176.9, 139.6, 129.5, 128.8, 126.7, 60.6, 49.1, 41.4, 37.8, 32.4, 31.2, 27.1. Accurate mass (HRMS); 216.1383, found 216.1380 (M^++H).

(2S,7S)-2-(naphthalen-1-ylmethyl)-hexahydropyrrolizin-3-one (2b)

R_f (petrol: ethyl acetate, 1:1) 0.09; δ_H (300 MHz, $CDCl_3$); 8.01 (1H, d, J = 7.5 Hz, *Ar*), 7.74-7.78 (1H, m, *Ar*) 7.63 (1H, d, J = 7.9, Ar), 7.35-7.45 (2H, m, Ar), 7.17-7.32 (2H, m, Ar), 3.92 (1H, dd, J = 14.3, 3.3 Hz, NC*H*), 3.45-3.6 (2H, m, C*H*$_2$), 3.07-3.2 (1H, m, C*H*$_2$), 2.95-3.05 (1H, m, C*H*$_2$), 2.69 (1H, dd, J = 14.3, 10.9 Hz, C*H*$_2$), 1.8-2.16 (4H, m, C*H*$_2$), 1.33 (1H, dt, J = 12.0, 8.6 Hz, C*H*$_2$), 1.13-1.23 (1H, m, C*H*$_2$); δ_C (75.5 MHz; $CDCl_3$) 175.9, 134.4, 132.9, 130.8, 127.7, 126.2, 125.8, 125.1, 124.6, 124.2, 122.8, 59.3, 46.8, 40.2, 33.6, 30.9, 30.2, 25.7. ; IR (film, cm^{-1}) ν 3448, 2968, 2878, 1681, 1596, 1510, 1453, 1425, 1331, 1286, 912, 793, 730; *m/z* (ES); Accurate mass (HRMS); 266.1539, found 266.1538 (M^++H).

(2S,7S)-2-(4-phenyl) benzyl)-hexahydropyrrolizin-3-one (2c)

R_f (petrol: ethyl acetate, 1:1) 0.27; δ_H (300 MHz, $CDCl_3$) 7.42-7.52 (4H, m, *Ar*), 7.32-7.38 (2H, m, *Ar*), 7.22-7.28 (1H, m, *Ar*), 7.16-7.2 (2H, m, *Ar*), 3.6-3.7 (1H, m, C*H*), 3.41-3.52 (1H, m, C*H*$_2$), 3.27 (1H, dd, J = 13.9, 3.7 Hz, C*H*$_2$), 2.95-3.08 (2H, m, C*H*$_2$), 2.52 (1H, dd, J = 13.9, 10.5 Hz, C*H*$_2$), 2.27 (1H, ddd, J = 12.4, 7.5, 6.4 Hz, CH_2), 1.84-2.08 (3H, m, C*H*$_2$), 1.34 (1H, dt, J = 12.0, 8.6 Hz, C*H*$_2$), 1.05-1.22 (1H, m, C*H*$_2$); δ_C (75.5 MHz; $CDCl_3$) 175.2, 141.3, 139.5, 129.7, 129.1, 127.5, 127.5, 127.3, 59.8, 48.8, 41.4, 37.0, 35.5, 32.6 27.2; IR ($CDCl_3$, cm^{-1}) ν 2971, 2881, 2225, 1682, 1600, 1520, 1488, 1451, 1410, 1331, 1313, 1284; *m/z* (ES); Accurate mass (HRMS); 292.1696, found 292.1694 (M^++H).

(2S,7S)-2-(4-(trifluoromethyl)benzyl)-hexahydropyrrolizin-3-one (2d)

R_f (petrol: ethyl acetate, 1:1) 0.27; Isolated with approx. 5% starting material; δ_H (300 MHz, $CDCl_3$) 7.46 (2H, d, J = 7.9 Hz, *Ar*), 7.24 (2H, d, J = 7.9 Hz, *Ar*), 3.60-3.75 (1H, m, NC*H*), 3.41-3.58 (1H, m, CH_2), 3.26 (1H, dd, J = 13.9, 4.1 Hz, CH_2), 2.94-3.10 (2H, m, CH_2), 2.56 (1H, dd, J = 13.9, 9.7 Hz, CH_2), 2.23 (1H, ddd, J = 12.4, 7.9, 6.4 Hz, CH_2), 1.88-2.08 (3H, m, CH_2), 1.29 (1H, dt, J = 12.0, 8.6 Hz, CH_2), 1.09-1.22 (1H, m, CH_2); δ_C (75.5 MHz; $CDCl_3$) 176.5, 144.5, 129.1, 128.7, 128.2, 125.7, 60.5, 48.4, 41.6, 37.6, 35.4, 32.5, 27.1; IR ($CDCl_3$, cm^{-1}) ν 2971, 2883, 1690, 1618, 1454, 1418, 1326, 1162, 1116, 1067; *m/z* (ES); Accurate mass (HRMS); 284.1257, found 284.1257 (M^++H).

(2S,7S)-2-(4-methoxybenzyl)-hexahydropyrrolizin-3-one (2e)

R_f (petrol: ethyl acetate, 1:1) 0.1; δ_H (300 MHz, $CDCl_3$); 7.02 (2H, d, J = 8.63 Hz, *Ar*), 6.74 (2H, d, J = 8.65 Hz, *Ar*) 3.71 (3H, s, OCH_3), 3.60-3.68 (1H, m, NC*H*), 3.41-3.5 (1H, m, NCH_2), 3.15 (1H, dd, J = 13.9, 4.0 Hz, CH_2), 2.88-3.05 (2H, m, CH_2), 2.44 (1H, dd, J = 13.9, 10.0 Hz, CH_2), 2.22 (1H, ddd, J = 12.4, 7.9, 6.4 Hz, CH_2), 1.88-2.08 (3H, m, CH_2), 1.33 (1H, dt, J = 11.6, 8.6 Hz, CH_2), 1.1-1.2 (1H, m, CH_2); δ_C (75.5 MHz; $CDCl_3$) 173.8, 156.9, 130.8, 130.0, 128.7, 113.0, 112.7, 58.4, 54.1, 47.5, 39.9, 34.9, 33.8, 31.2, 28.6, 25.7; IR (film, cm^{-1}) ν 2927, 1689, 1611, 1513, 1454, 1417, 1300, 1247, 1178, 1112, 1033; *m/z* (ES); Accurate mass (HRMS); 246.1489, found 246.1489 (M^++H).

(2S,7S)-2-(4-methylbenzyl)-hexahydropyrrolizin-3-one (2f)

R_f (petrol: ethyl acetate, 1:1) 0.18; δ_H (300 MHz, $CDCl_3$) 6.99-7.04 (4H, m, *Ar*), 3.60-3.68 (1H, m, NC*H*), 3.42-3.52 (1H, m, CH_2), 3.20 (1H, dd, J = 13.9, 3.7 Hz, CH_2), 2.90-3.05 (2H, m, CH_2), 2.44 (1H, dd, J = 13.5, 10.1 Hz, CH_2), 2.24 (3H, s, CH_3), 1.85-2.04 (4H, m, CH_2), 1.30 (1H, dt, J = 12.0, 8.6 Hz, CH_2), 1.08-1.22 (1H, m, CH_2); δ_C (75.5 MHz; $CDCl_3$) 173.9, 135.7, 134.8, 128.5, 128.0, 58.4, 47.4, 40.0, 35.0, 34.0, 31.2, 25.7, 19.9; IR ($CDCl_3$, cm^{-1}) ν 2968, 2923, 2879, 1689, 1514, 1417, 1330, 1285, 1022, 806; *m/z* (ES); Accurate mass (HRMS); 230.1539, found 230.1538 (M^++H).

(2S,7S)-2-(4-bromobenzyl)-hexahydropyrrolizin-3-one (2g)

R_f (petrol: ethyl acetate, 1:1); 0.09; δ_H (300 MHz, $CDCl_3$); 7.32 (2H, d, J = 8.2 Hz, *Ar*), 6.99 (2H, d, J = 8.6 Hz, *Ar*), 3.6-3.71 (1H, m, C*H*$_2$), 3.4-3.51 (1H, m, C*H*), 3.15 (1H, dd, J= 13.9, 4.1 Hz, C*H*$_2$), 2.9-3.06 (2H, m, C*H*$_2$), 2.44-2.52 (1H, dd, J = 13.9, 9.7 Hz, C*H*$_2$), 2.22 (1H, ddd, J = 12.0, 7.5, 6.4 Hz, CH_2), 1.84-2.08 (3H, m, CH_2), 1.27 (1H, dt, J = 12.05, 8.6 Hz, C*H*$_2$), 1.05-1.2 (1H, m, C*H*$_2$); δ_C (75.5 MHz; $CDCl_3$) 174.8, 139.2, 131.8, 131.09, 120.3, 59.8, 48.5, 41.4, 36.6, 35.3, 32.6, 27.1; IR (film, cm^{-1}); 2967, 2878, 1686, 1487, 1414, 1330, 1283, 1070, 1011; *m/z* (ES); Accurate mass (HRMS); 294.0488, found 294.0485 (M^++H).

4-(((2S,7S)-hexahydro-3-oxo-1H-pyrrolizin-2-yl)methyl) benzaldehyde (2h)

R_f (petrol: ethyl acetate, 1:1); 0.06; δ_H (300 MHz, $CDCl_3$); 9.9 (1H, s, C*H*O), 7.74 (2H, d, J = 8.2 Hz, *Ar*), 7.3 (2H, d, J = 7.9 Hz, *Ar*) 3.62-3.72 (1H, m, C*H*), 3.42-3.52 (1H, m, C*H*$_2$), 3.29 (1H, dd, J= 13.9, 4.1 Hz, C*H*$_2$), 2.95-3.08 (2H, m, C*H*$_2$), 2.61 (1H, dd, J= 13.8, 9.7 Hz, C*H*$_2$), 2.23 (1H, ddd, J = 12.0, 7.5, 6.0 Hz, CH_2), 1.9-2.04 (3H, m, CH_2), 1.3 (1H, dt, J = 12.0, 8.6 Hz, C*H*$_2$), 1.08-1.2 (1H, m, C*H*$_2$); δ_C (75.5 MHz; $CDCl_3$); 190.9, 173.1, 146.4, 133.8, 128.8, 128.2, 58.4, 47.2, 40.0, 36.1, 34.0, 31.2, 25.7; IR (film, cm^{-1}); 2969.1, 2881.7, 2238.5, 1693.7, 1605.8, 1575.2, 1453.3, 1421.7, 1331.7, 1306.5, 1214.1; *m/z* (ES); Accurate mass (HRMS); 244.1332, found 244.1332 (M^++H).