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Supporting Information

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The Direct Catalytic Enantioselective Synthesis of Protected Aryl β-Hydroxy-α-Amino Acids.

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General Information: Melting points were determined on a Büchi 535 melting point apparatus and are uncorrected. ^{1}H NMR spectra were obtained on a Bruker Avance 300 spectrometer operating at 300 MHz, unless otherwise noted, with tetramethylsilane as an internal standard. *J* values are given in Hz. ^{13}C NMR spectra were obtained on a Bruker Avance 300 spectrometer operating at 75 MHz, unless otherwise noted. Mass spectrometry measurements were performed at the EPSRC National Mass Spectrometry Service Centre, University of Wales Swansea; values are quoted as *m*/*z* with relative intensity in parentheses. High Pressure Liquid Chromatography was performed on SP Thermo Separation products spectra SERIES and Spectra Physics Systems using Chiralcel OD column obtained from Fisher Scientific supplies.

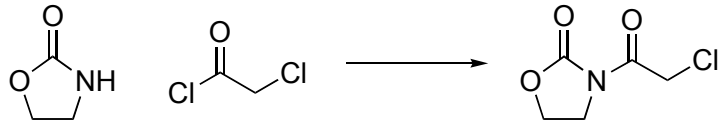
All dry solvents were freshly distilled under nitrogen prior to use. Methylene chloride was distilled from calcium hydride. Petroleum ether refers to that fraction obtained between 40-60 ºC. All glassware was dried in an oven and allowed to cool under nitrogen prior to use. All commercial reagents were used as obtained. (*R*)-Ph-PyBOX was purchased from Sigma-Aldrich Company Limited.

Thin layer chromatographic analyses were performed on plates coated with Kieselgel 60F_{254}. Visualisation was achieved with a 254 nm ultraviolet lamp, followed by staining with vanillin or potassium permanganate. Flash chromatography was conducted under medium pressure, using matrix 60 silica.

(*4S*,*5R*)-*5*-Phenyl-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester, (*4S*,*5R*)-5-(4-methoxy-phenyl)-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester and (*4S*,*5R*)-5-naphthalen-2-yl-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester (Table 2, entries 1, 2 and 10) gave data identical with that reported in the literature.[1]

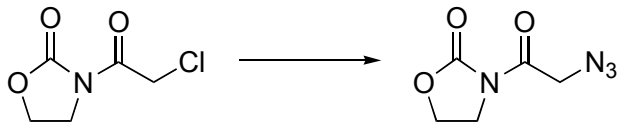
Preparation of oxazolidinone 3:

Preparation of 3-(2-chloroacetyl)-oxazolidin-2-one



A solution of BuLi (2.5 M in hexane, 8.0 mL, 20.0 mmol) was added dropwise to a solution of oxazolidine-2-one (1.74 g, 20.0 mmol) in dry THF (300 mL) at -78 °C and the reaction was stirred for an additional 15 min. The temperature was allowed to reach RT for 2.5 h and then the mixture was cooled to -78 °C for 15 min. Chloroacetyl chloride (1.75 mL, 22.0 mmol) was added slowly to the reaction mixture. After 15 min, the light yellow solution was warmed to RT for a further 30 min. The reaction was quenched with saturated aqueous ammonium chloride solution (10 mL). The mixture was concentrated under reduced pressure, taken up in water (10 mL) and extracted with DCM (3 × 40 mL). The organic portions were dried ($MgSO_4$) and concentrated under reduced pressure. The *chloroimide* (3.14 g, 96%) was obtained as a white solid. An analytical sample was prepared by recrystallization from DCM; mp 61 °C (DCM); R_f(SiO_2, DCM) 0.19; δ_H(400 MHz; $CDCl_3$) 4.74 (2H, s, CH_2Cl), 4.51 (2H, t, J = 8.0, CH_2), 4.09 (2H, t, J = 8.0, CH_2); δ_C(100 MHz; $CDCl_3$) 165.7, 152.9, 62.7, 43.3, 42.5; HRMS (ES+): $C_5H_6{}^{35}ClNO_3$, M^+ requires 163.0036. Found 163.0038.

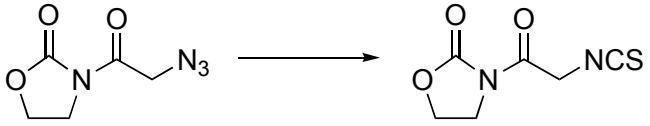
Preparation of 3-(2-azidoacetyl)-oxazolidin-2-one



A solution of sodium azide (6.50 g, 100 mmol) in water (20 mL) was added to a solution of the chloroimide (3.14 g, 19.2 mmol) in DCM (20 mL). This biphasic system was stirred vigorously and tetrabutylammonium hydrogen sulphate (0.68 g, 2.00 mmol) was

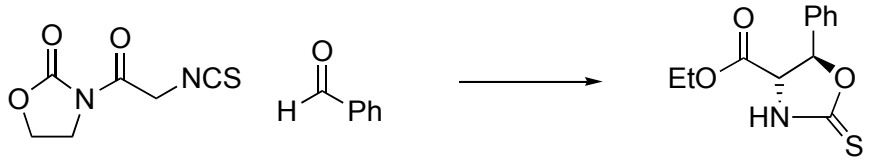
added. After 1.5 h at RT, the organic layer was separated and concentrated under reduced pressure. The residue was filtered through silica using DCM as the mobile phase. After concentration, the *azidoimide* (2.70 g, 83%) was obtained as a colourless oil; R_f(SiO_2, DCM) 0.18; δ_H (400 MHz; $CDCl_3$) 4.52 (2H, t, J = 8.1, CH_2), 4.51 (2H, s, CH_2N_3), 4.09 (2H, t, J = 8.1, CH_2); δ_C(100 MHz; $CDCl_3$) 167.5, 153.0, 62.9, 52.3, 42.1. Used without further purification.

Preparation of 3-(2-isothiocyanatoacetyl)-oxazolidin-2-one (3)



Triphenylphosphine (3.32 g, 12.7 mmol) was added to a solution of the azidoimide (1.96 g, 11.5 mmol) in THF (15 mL) and CS_2 (15 mL) in a 500 mL round bottom flask fitted with a condenser. After evolution of nitrogen, the solution gently self-refluxed and was left overnight. After concentration under reduced pressure, the residue was purified by flash chromatography (SiO_2, DCM) to yield the *isothiocyanatoimide* **3** (1.49 g, 69%), as a white solid which was recrystallized in DCM-hexane; mp 99 °C (DCM-hexane); R_f(SiO_2, DCM) 0.26; δ_H(400 MHz; $CDCl_3$) 4.85 (2H, s, CH_2NCS), 4.54 (2H, t, J = 8.1, CH_2), 4.11 (2H, t, J 8.1, CH_2); δ_C(100 MHz; $CDCl_3$) 165.7, 153.4, 140.0, 63.6, 49.6, 42.8; HRMS (ES+): $C_6H_6N_2O_3S$, M^+ requires 186.0099. Found 186.0099.

General procedure for the direct enantioselective addition of imide 3 to aryl aldehydes. Preparation of (*4S*,*5R*)-ethyl *5*-phenyl-2-thioxo-1,3-oxazolidine-4-carboxylate (Table 2, entry 1)



A mixture of $Mg(ClO_4)_2$ (15 mg, 0.07 mmol), 2,6-bis((*R*)-4,5-dihydro-4-phenyl-2-oxazolyl)pyridine (28 mg, 0.08 mmol) and 3-(2-isothiocyanatoacetyl)-oxazolidin-2-one (128 mg, 0.69 mmol) was stirred for 1 h in dry DCM (15 mL) with activated powdered 4 Å MS (200 mg) under nitrogen at RT. The temperature was then lowered to -78 °C. After

15 min, benzaldehyde (77 μL, 0.76 mmol) and diisopropylethylamine (24 μL, 0.14 mmol) were added and the mixture was stirred for a further 24 h at -78 °C. The reaction was quenched with saturated aqueous ammonium chloride (5 mL). The organic layer was separated and the aqueous layer was extracted with DCM (3 × 10 mL). The organic portions were combined, washed with brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was dissolved in dry THF (15 mL) and cooled to 0 °C. A solution of methyl magnesium bromide (3M in diethyl ether, 0.30 mL, 0.89 mmol) in ethanol (3.3 mL) at 0 °C was added *via* cannula transfer. After 3 min the reaction was quenched by addition of an aqueous pH 7 phosphate buffer (5 mL). The mixture was concentrated under reduced pressure, taken up in aqueous HCl (1M, 10 mL) and DCM (10 mL). The organic layer was separated and the aqueous layer was extracted with DCM (3 × 10 mL). The organic portions were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, DCM:EtOAc, 98:2) to provide the title compound as colourless crystals (119 mg, 69%).[1] HPLC using Chiracel OD column (80:20 hexane:isopropanol), 1.0 mL/min; t_r = 9.0 min and t_r = 10.8 min; ee = 90%; $[\alpha]_D^{21}$ = +44° (*c* = 1, DCM).

(*4S*,*5R*)-5-(4-Methoxy-phenyl)-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester (Table 2, entry 2)

109 mg, 56%. HPLC using Chiracel OD column (80:20 hexane:isopropanol), 1.0 mL/min; t_r = 12.0 min and t_r = 13.3 min; ee = 86%; $[\alpha]_D^{21}$ = +49° (*c* = 1, DCM).

(4*S*,5*R*)-5-(4-Ethoxy-phenyl)-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester (Table 2, entry 3)

144 mg, 71% as a pale yellow solid; mp 66 °C (DCM:EtOAc, 98:2); R_f(SiO_2, DCM:EtOAc, 98:2) 0.28; δ_H(300 MHz; $CDCl_3$) 7.65 (1H, s, N*H*), 7.32 (2H, d, *J* = 9.0, Ar*H*), 6.93 (2H, d, *J* = 9.0, Ar*H*), 5.90 (1H, d, *J* = 6.2, EtO(C=O)C*H*), 4.48 (1H, d, *J* = 6.0, ArC*H*), 4.25-4.40 (2H, m, (C=O)OCH_2CH$_3$), 4.05 (2H, q, *J* = 6.9, OCH_2CH$_3$), 1.43 (3H, t, *J* = 6.9, OCH$_2$CH_3), 1.34 (3H, t, *J* = 7.2, (C=O)OCH$_2$CH_3); δ_C(100 MHz; $CDCl_3$) 189.0, 168.0, 160.0, 128.4, 127.5, 115.0, 86.9, 64.5, 63.6, 62.9, 14.7, 14.1; HRMS (ES+): $C_{14}H_{18}NO_4S$, $[M+H]^+$ requires 296.0951. Found 296.0956. HPLC using Chiracel OD

column (80:20 hexane:isopropanol), 1.0 mL/min; t_r = 20.0 min and t_r = 21.6 min; ee = 93%; $[\alpha]_D^{21}$ = +46° (*c* = 1, DCM).

(4*S*,5*R*)-5-(4-Methylsulfanyl-phenyl)-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester (Table 2, entry 4)

122 mg, 60% as a yellow solid; mp 75 °C (DCM:EtOAc, 98:2); R_f(SiO_2, DCM:EtOAc, 98:2) 0.33; δ_H(300 MHz; $CDCl_3$) 7.56 (1H, s, N*H*), 7.27-7.35 (4H, m, Ar*H*), 5.92 (1H, d, *J* = 6.3, EtO(C=O)C*H*), 4.45 (1H, d, *J* = 6.3, ArC*H*), 4.25-4.40 (2H, m, C$H_2$$CH_3$), 2.50 (3H, s, SC$H_3$), 1.35 (3H, t, *J* = 7.2, CH_2CH_3); δ_C(100 MHz; $CDCl_3$) 188.4, 167.3, 140.4, 132.7, 126.2, 125.7, 85.0, 64.0, 62.5, 15.0, 13.6; HRMS (ES+): $C_{13}H_{16}NO_3S_2$, $[M+H]^+$ requires 298.0566. Found 298.0564. HPLC using Chiracel OD column (80:20 hexane:isopropanol), 1.0 mL/min; t_r = 13.1 min and t_r = 14.5 min; ee = 94%; $[\alpha]_D^{21}$ = +40° (*c* = 1, DCM).

(4*S*,5*R*)-2-Thioxo-5-*p*-tolyl-oxazolidine-4-carboxylic acid ethyl ester (Table 2, entry 5)

142 mg, 76% as a colourless oil; R_f(SiO_2, DCM:EtOAc, 98:2) 0.43; δ_H(300 MHz; $CDCl_3$) 7.83 (1H, s, N*H*), 7.22-7.31 (4H, m, Ar*H*), 5.93 (1H, d, *J* = 6.0, EtO(C=O)C*H*), 4.47 (1H, d, *J* = 6.0, ArC*H*), 4.25-4.40 (2H, m, C$H_2$$CH_3$), 2.38 (3H, s, C$H_3$), 1.35 (3H, t, *J* = 7.2, CH_2CH_3); δ_C(100 MHz; $CDCl_3$) 188.5, 167.5, 139.2, 133.3, 129.3, 125.2, 85.3, 64.1, 62.5, 20.8, 13.6; HRMS (ES+): $C_{13}H_{16}NO_3S$, $[M+H]^+$ requires 266.0845. Found 266.0842.HPLC using Chiracel OD column (80:20 hexane:isopropanol), 1.0 mL/min; t_r = 9.0 min and t_r = 9.9 min; ee = 92%; $[\alpha]_D^{21}$ = +32° (*c* = 1, DCM).

(4*S*,5*R*)-5-(4-Ethyl-phenyl)-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester ester (Table 2, entry 6)

156 mg, 81% as a white solid; mp 74 °C (DCM:EtOAc, 98:2); R_f(SiO_2, DCM:EtOAc, 98:2) 0.39; δ_H(300 MHz; $CDCl_3$) 7.46 (1H, s, N*H*), 7.32 (2H, d, *J* = 8.4, Ar*H*), 7.26 (2H, d, *J* = 8.4, Ar*H*), 5.94 (1H, d, *J* = 6.0, EtO(C=O)C*H*), 4.47 (1H, d, *J* = 6.0, ArC*H*), 4.25-4.40 (2H, m, (C=O)OC$H_2$$CH_3$), 2.67 (2H, q, *J* = 7.8, C$H_2$$CH_3$), 1.35 (3H, t, *J* = 7.2, (C=O)OCH$_2$CH_3), 1.24 (3H, t, *J* = 7.8, CH_2CH_3); δ_C(100 MHz; $CDCl_3$) 189.0, 168.0,

146.0, 134.0, 128.7, 125.8, 85.8, 64.5, 63.0, 28.6, 15.5, 14.1; HRMS (ES+): $C_{14}H_{18}NO_3S$, $[M+H]^+$ requires 280.1002. Found 280.0999. HPLC using Chiracel OD column (80:20 hexane:isopropanol), 1.0 mL/min; t_r = 7.4 min and t_r = 9.6 min; ee = 91%; $[\alpha]_D^{21}$ = +34° (*c* = 1, DCM).

(4*S*,5*R*)-5-Biphenyl-4-yl-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester (Table 2, entry 7)

119 mg, 53% as a pale yellow solid; mp 145 °C (DCM:EtOAc, 98:2); R_f(SiO_2, DCM:EtOAc, 98:2) 0.37; δ_H(300 MHz; $CDCl_3$) 7.75 (1H, s, N*H*), 7.65 (2H, m, Ar*H*), 7.58 (2H, m, Ar*H*), 7.37-7.50 (5H, m, Ar*H*), 6.02 (1H, d, *J* = 6.2, EtO(C=O)C*H*), 4.53 (1H, d, *J* = 6.2, ArC*H*), 4.30-4.40 (2H, m, CH_2CH$_3$), 1.37 (3H, t, *J* = 7.2, CH$_2$CH_3); δ_C(100 MHz; $CDCl_3$) 188.5, 167.5, 142.1, 139.6, 135.2, 128.4, 127.3, 126.7, 125.7, 85.0, 64.1, 62.6, 13.7; HRMS (ES+): $C_{18}H_{18}NO_3S$, $[M+H]^+$ requires 328.1002. Found 328.0998. HPLC using Chiracel OD column (80:20 hexane:isopropanol), 1.0 mL/min; t_r = 14.7 min and t_r = 16.5 min; ee = 87%; $[\alpha]_D^{21}$ = +26° (*c* = 1, DCM).

(4*S*,5*R*)-2-Thioxo-5-*m*-tolyl-oxazolidine-4-carboxylic acid ethyl ester (Table 2, entry 8)

112 mg, 61% as a colourless oil; R_f(SiO_2, DCM:EtOAc, 98:2) 0.45; δ_H(300 MHz; $CDCl_3$) 7.39 (1H, s, N*H*), 7.18-7.35 (4H, m, Ar*H*), 5.94 (1H, d, *J* = 6.0, EtO(C=O)C*H*), 4.46 (1H, d, *J* = 6.0, ArC*H*), 4.25-4.40 (2H, m, CH_2CH$_3$), 2.38 (3H, s, CH_3), 1.35 (3H, t, *J* = 7.2, CH$_2$CH_3); δ_C(100 MHz; $CDCl_3$) 188.5, 167.5, 138.6, 136.3, 129.8, 128.6, 125.7, 122.3, 85.3, 64.1, 62.5, 20.9, 13.6; HRMS (ES+): $C_{13}H_{16}NO_3S$, $[M+H]^+$ requires 266.0845. Found 266.0847. HPLC using Chiracel OD column (80:20 hexane:isopropanol), 1.0 mL/min; t_r = 8.2 min and t_r = 9.7 min; ee = 86%; $[\alpha]_D^{21}$ = +25° (*c* = 1, DCM).

(4*S*,5*R*)-2-Thioxo-5-*o*-tolyl-oxazolidine-4-carboxylic acid ethyl ester (Table 2, entry 9)

90 mg, 49% as a colourless oil; R_f(SiO_2, DCM:EtOAc, 98:2) 0.23; δ_H(400 MHz; $CDCl_3$) 7.69 (1H, s, N*H*), 7.21-7.34 (4H, m, Ar*H*), 6.23 (1H, d, *J* = 4.0, EtO(C=O)C*H*), 4.44 (1H,

d, J = 4.0, ArC*H*), 4.25-4.40 (2H, m, (C=O)OCH_2CH$_3$), 2.42 (3H, s, CH_3), 1.35 (3H, t, J = 8.0, (C=O)OCH$_2$CH_3); δ_C(100 MHz; CDCl$_3$) 189.2, 168.1, 135.1, 134.7, 131.2, 129.5, 126.9, 125.7, 83.5, 64.0, 63.0, 19.1, 14.1; HRMS (ES+): $C_{13}H_{16}NO_3S$, $[M+H]^+$ requires 266.0845. Found 266.0844. HPLC using Chiracel OD column (80:20 hexane:isopropanol), 1.0 mL/min; t_r = 9.7 min and t_r = 11.7 min; ee = 89%, 62%; $[\alpha]_D^{21}$ = +12.5° (c = 3, DCM).

(*4S*,*5R*)-5-Naphthalen-2-yl-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester (Table 2, entry 10)

96 mg, 46%. HPLC using Chiracel OD column (80:20 hexane:isopropanol), 1.0 mL/min; t_r = 11.8 min and t_r = 14.0 min; ee = 87%; $[\alpha]_D^{21}$ = +46° (c = 1, DCM).

(4*S*,5*R*)-5-[3-Chloro-4-(methoxy-benzyloxy)-phenyl]-2-thioxo-oxazolidine-4-carboxylic acid ethyl ester (Table 2, entry 11)

186 mg, 65% as a white foam; R_f(SiO$_2$, DCM:EtOAc, 98:2) 0.37; δ_H(300 MHz; CDCl$_3$) 7.55 (1H, s, N*H*), 7.43 (1H, m, Ar*H*), 7.37 (2H, m, Ar*H*), 7.24 (1H, m, Ar*H*), 7.00 (1H, m, Ar*H*), 6.92 (2H, m, Ar*H*), 5.87 (1H, d, J = 6.5, EtO(C=O)C*H*), 5.11 (2H, s, ArCH_2OAr), 4.43 (1H, d, J = 6.5, ArC*H*), 4.27-4.38 (2H, m, (C=O)OCH_2CH$_3$), 3.82 (3H, s, OCH_3), 1.35 (3H, t, J = 7.2, (C=O)OCH$_2$CH_3); δ_C(75 MHz; CDCl$_3$) 188.7, 167.7, 159.6, 155.1, 129.8, 128.9, 127.9 × 2, 125.4, 124.0, 114.3, 114.1, 84.8, 70.8, 64.4, 63.1, 55.3, 14.1; HRMS (ES+): $C_{20}H_{21}{}^{35}ClNO_5S$, $[M+H]^+$ requires 422.0823. Found 422.0827. HPLC using Chiracel OD column (80:20 hexane:isopropanol), 1.0 mL/min; t_r = 29.6 min and t_r = 32.2 min; ee = 95%; $[\alpha]_D^{21}$ = +24° (c = 1, DCM).

References

1. M. C. Willis, V. J.-D. Piccio, *Synlett* **2002**, 1625.