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A Novel Strategy for the Asymmetric Synthesis of Chiral Cyclopropane Carboxaldehydes

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Representative procedure for the asymmetric aldol reaction

(4*S*,3'*R*,2'*S*,4'*E*)-4-Benzyl-3-[3'-hydroxy-2'-methyl-5'-(2''-nitro-phenyl)-pent-4'-enoyl]-5,5-dimethyl-oxazolidin-2-one **3d**:

To a stirred solution of (*S*)-4-benzyl-5,5-dimethyl-3-propionyl-oxazolidin-2-one **1** (500 mg, 1.91 mmol) in CH_2Cl_2 (20 ml) at 0°C was added 9BBN-OTf (4.21 ml, 2.10 mmol, 0.5M solution in hexane) dropwise. The reaction mixture was stirred for 30 minutes at 0°C before *N*,*N*'-diisopropylethylamine (0.40 ml, 2.30 mmol) was added dropwise. Stirring was continued for a further 30 minutes at 0°C before cooling the reaction to -78°C and 3-(2'-Nitro-phenyl)-propenal (373 mg, 2.10 mmol, 0.5M solution in CH_2Cl_2) was added dropwise. Stirring was maintained overnight as the reaction was allowed to warm to room temperature. The reaction was then quenched with pH7 phosphate buffer solution (10 ml) and stirred for 10 minutes, before a 2:1 mixture of 30% H_2O_2 and methanol (10 ml) was added and the reaction stirred for a further two hours. CH_2Cl_2 (10 ml) and sat. $NaHCO_3$ solution (10 ml) were added and the aqueous layer was separated and extracted with CH_2Cl_2 (3 × 10ml). The combined organic layers were washed with brine (10 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude diastereoisomeric excess was determined as >95% by inspection of the 300 MHz ^{1}H NMR spectrum of the crude reaction product. Purification by column chromatography eluting with CH_2Cl_2 gave the title compound **3d** (730 mg, 87%) as a yellow oil. **3d**: $[\alpha]_D^{24}$= -7.6 (*c* 0.8, CH_2Cl_2,); ^{1}H NMR (300 MHz, $CDCl_3$) : δH = 7.86 (1H, app. d, ^3J (H,H) = 7.9 Hz, C*H*CNO_2, Ar), 7.52 – 7.11 (8H, m, 8 × C*H*, Ar), 7.05 (1H, dd, ^3J (H,H) = 15.7 and 1.5 Hz, *o*-NO_2PhC*H*=CH), 6.10 (1H, dd, ^3J (H,H) = 15.7 and 5.7 Hz, *o*-NO_2PhCH=C*H*), 4.60 (1H, m, C*H*OH), 4.53 (1H, dd, ^3J (H,H) = 9.0 and 4.8 Hz, NC*H*), 3.99 (1H, dq, ^3J (H,H) = 3.8 and 7.1, CH_3C*H*), 3.01 (1H, dd, ^3J (H,H) = 14.2 and 4.5, PhC$H_A$$CH_B$), 2.90-2.80 (2H, m,

O*H* and PhCH$_A$C*H*$_B$), 1.33 (3H, s, C*H*$_3$(CH$_3$)C), 1.30 (3H, s, (CH$_3$(C*H*$_3$)C), 1.14 (3H, d, ^3J (H,H) = 7.1, CHC*H*$_3$); ^{13}C NMR (75 MHz, CDCl$_3$) : δC = 176.0 (CH*C*O), 158.0 (O*C*O), 148.2 (NO$_2$*C*, Ar), 136.9 (Ar), 134.3 (Ar), 133.5 (Ar), 133.0 (Ar), 129.5 (Ar), 129.3 (Ar), 129.1 (Ar), 128.5 (Ar), 127.4 (Ar), 127.3 (*o*-NO$_2$Ph*C*H=CH), 125.9 (*o*-NO$_2$PhCH=*C*H), 82.9 ((CH$_3$)$_2$*C*), 72.9 (*C*HOH), 63.7 (N*C*H), 43.1 (CH$_3$*C*H), 35.7 (Ph*C*H$_2$), 28.8 (*C*H$_3$(CH$_3$)C), 22.6 (CH$_3$(*C*H$_3$)C), 12.0 (*C*H$_3$CH); IR (film / cm^{-1}) ν = 3447 (OH), 1773 (OC=O), 1700 (NC=O), 1570 (C=C), 1552 (NO$_2$), 1351 (NO$_2$); HRMS : *m*/*z* (ES) 459.2123, C$_{24}$H$_{26}$N$_2$O$_6$ [M+NH$_4$]$^+$ requires 456.2129.

Representative procedure for the stereoselective cyclopropanation reaction (4*S*,3'*R*,2'*S*,2''*S*,1''*S*)–4-Benzyl-3-{3'-hydroxy-2'-methyl-3'-[2''-(2'''-nitro-phenyl)-cyclopropyl] -propionyl}-5,5-dimethyl-oxazolidin-2-one **4d** :

To a stirred solution of (4*S*,3'*R*,2'*S*,4'*E*)-4-benzyl-3-[3'-hydroxy-2'-methyl-5'-(2''-nitro-phenyl)-pent-4'-enoyl]-5,5-dimethyl-oxazolidin-2-one **3d** (700 mg, 1.60 mmol) in CH_2Cl_2 (10 ml) at -10°C was added diethyl zinc (7.98 ml, 7.98 mmol, 1.0 M solution in hexane) in one portion, before the addition of diiodomethane (0.64 ml, 7.98 mmol) in one portion. The reaction was stirred for 2 hours and allowed to warm to 0 °C. The reaction was then quenched with sat. sodium sulfite solution (5 ml). CH_2Cl_2 (5 ml) and 2M $HCl_{(aq)}$ solution (5 ml) were added and the aqueous layer was separated and extracted with CH_2Cl_2 (3 $\times$ 10 ml). The combined organic layers were washed with brine (10 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The diastereomeric excess was determined as >95% by inspection of the 300 MHz NMR spectrum of the crude reaction product. Purification by column chromatography eluting with CH_2Cl_2 gave the title compound **4d** (650mg, 90%) as a white solid. **4d**: m.p. 101-104°C; $[\alpha]_D^{24}$= +57.3 (*c* 0.9, CH_2Cl_2,); ^{1}H NMR (300 MHz, CDCl$_3$) : δH = 7.75 (1H, app. d, ^3J (H,H) = 7.9 Hz, C*H*CNO$_2$, Ar), 7.47 – 7.06 (8H, m, 8 $\times$ C*H*, Ar), 4.47 (1H, dd, ^3J (H,H) = 9.4 and 4.5, NC*H*), 3.97 (1H, dq, ^3J (H,H) = 3.4 and 7.2, CH$_3$C*H*), 3.68 (1H, m, C*H*OH), 3.01 (1H, dd, ^3J (H,H) = 14.3 and 4.5, PhC*H*$_A$CH$_B$), 2.83 (1H, dd, ^3J (H,H) = 14.3 and 9.0, PhCH$_A$C*H*$_B$), 2.71 (1H, app. s, O*H*), 2.36 (1H, app. dt, ^3J (H,H) = 8.7 and 5.3, *o*-NO$_2$PhC*H*), 1.32 (3H, s, C*H*$_3$(CH$_3$)C), 1.26 (3H, s, (CH$_3$(C*H*$_3$)C), 1.20 (3H, d, ^3J (H,H) = 7.2, CHC*H*$_3$), 1.16 (2H, obscured m, cyclopropyl-C*H* and cyclopropyl-C*H*$_A$CH$_B$), 0.90

(1H, app. dt, ^3J (H,H) = 8.7 and 5.3, cyclopropyl-CH_ACH_B); ^{13}C NMR (75 MHz, $CDCl_3$) : δC = 177.2 (CHCO), 152.8 (OCO), 151.1 (NO_2C, Ar), 137.2 (Ar), 137.0 (Ar), 133.2 (Ar), 129.5 (Ar), 129.1 (Ar), 128.2 (Ar), 127.3 (Ar), 127.0 (Ar), 124.6 (Ar), 82.7 ($(CH_3)_2C$), 73.7 (CHOH), 63.7 (NCH), 43.4 (CH_3CH), 35.8 ($PhCH_2$), 28.8 ($CH_3(CH_3)C$), 25.5 ($CH_3(CH_3)C$), 22.6 (Cyclopropyl-CHPhNO_2), 17.3 (cyclopropyl-CH), 12.7 (CH_3CH), 12.3 (cyclopropyl-CH_2); IR (KBr / cm^{-1}) ν = 3431 (OH), 1769 (OC=O), 1694 (NC=O),1528 (NO_2), 1367 (NO_2); HRMS : *m/z* (ES) 470.2287, $C_{25}H_{28}N_2O_6$ [M+NH_4] requires 470.2286.

Representative procedure for the base catalysed *retro*-aldol reaction

(1*S*, 2*S*)-2-(2'-Nitro-phenyl)-cyclopropane-carboxaldehyde **5d**

To a stirred solution of (4*S*,3'*R*,2'*S*,2''*S*,1''*S*)–4-benzyl-3-{3'-hydroxy-2'-methyl-3'-[2''-(2'''-nitro-phenyl)-cyclopropyl]-propionyl}-5,5-dimethyl-oxazolidin-2-one **4d** (500 mg, 1.10 mmol) in toluene (10 ml) at 5°C was added LHMDS (1.22 ml, 1.22 mmol, 1M solution in toluene) dropwise and stirred for 4 hours. The reaction was quenched with sat. $NaHCO_3$ solution (5 ml) and the aqueous layer was separated and extracted with CH_2Cl_2 (3 × 10ml). The combined organic layers were washed with brine (10 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The diastereomeric excess was determined as >95% d.e. by inspection of the 300 MHz NMR spectrum of the crude reaction product. Purification by passing the crude product through a plug of silica eluting with CH_2Cl_2:ether (95:5) and extraction *via* the bisulphite salt gave the title compound **5d** (116 mg, 55 %) as a clear oil. **5d**: $[\alpha]_D^{24}$= +109.6 (*c* 0.7, CH_2Cl_2,); ^{1}H NMR (300 MHz, $CDCl_3$) : δH = 9.32 (1H, d, ^3J (H,H) = 4.5 Hz, CHO), 7.90 (1H, dd, ^3J (H,H) = 8.2 and 1.3 Hz, NO_2CCH, Ar), 7.50 (1H, app. dt, ^3J (H,H) = 1.5 and 7.5 Hz, *m*-CH, Ar), 7.36 (1H, app. dt, ^3J (H,H) = 1.5 and 8.7 Hz, *p*-CH, Ar), 7.21(1H, app. d, ^3J (H,H) = 7.9 Hz, *o*-CH, Ar), 3.04 (1H, ddd, ^3J (H,H) = 8.7, 7.4 and 4.5 Hz, *o*-NO_2PhCH), 2.04 (1H, m, CHOCH) 1.71 (1H, app. dt, ^3J (H,H) = 9.0 and 5.3 Hz, cyclopropyl-CH_ACH_B), 1.44 (1H, ddd, ^3J (H,H) = 8.7, 7.2 and 5.3 Hz, cyclopropyl-CH_ACH_B); ^{13}C NMR (75 MHz, $CDCl_3$) : δC = 199.4 (CHO), 150.8 (NO_2CH) 134.2 (Ar), 133.6 (Ar), 129.5 (Ar), 128.5 (Ar), 125.3 (Ar) 32.0 (CHOCH), 24.0 (*o*-NO_2PhCH), 16.9 (cyclopropyl-CH_2); IR (film / cm^{-1}) ν = 1708 (CHO), 1519 (NO_2), 1344 (NO_2); HRMS : *m/z* (EI) 191.0572, $C_{10}H_9NO_3$ requires 191.0577.