Catalytic and Enantioselective C-C Bond Forming Conjugate Additions with Vinyl Sulfones

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Supporting Information

General Information. ^1H and ^{13}C NMR spectra were recorded on a Varian instrument (400 MHz and 100 MHz, respectively) and internally referenced to tetramethylsilane signal or residual protio solvent signals. Data for ^1H NMR are recorded as follows: chemical shift (δ , ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), integration, coupling constant (Hz). Data for ^{13}C NMR are reported in terms of chemical shift (δ , ppm). Infrared spectra were recorded on a Perkin Elmer FT-IR Spectrometer and are reported in frequency of absorption. Low resolution mass spectra for all the new compounds were performed by 70SE CI+, and were recorded and exact mass spectra on a 70-VSE-B high resolution mass spectrometer. Specific rotations were measured on a Jasco Digital Polarimeter.

High performance liquid chromatography (HPLC) analysis was performed on a Hewlett-Packard 1100 Series instrument equipped with a quaternary pump, using a Daicel Chiralcel OJ, OD Column (250 x 4.6 mm) or Chiralpak AD, AS Column (250 x 4.6 mm). UV absorption was monitored at 220 nm or at 280 nm.

Figure 1. The Structure of Cinchona Alkaloids

Materials: (For structure of cyanoesters **2**, sulfones **3**, see Table1, for structure of catalyst, see figure 1) Anhydrous toluene, vinyl phenyl sulfone **3a** was purchased from Aldrich Inc. Ethyl α -phenyl α -cyanoacetate **2A** were purchased from Alfa Aesar, ethyl α -methyl α -cyanoacetate **2K** was purchased from TCI America. They were used without further purifications. Other cyanoacetate **2B-2I**,¹ **2J**,² sulfone **3b**³ were prepared according to literature procedures. And 6'-OH catalysts **Q-1** and **QD-1** were prepared as described before⁴. β -ICD was prepared

according to literature procedures⁵. Other catalysts were purchased from Aldrich Inc. and used without further purification.

General procedure for enantioselective Michael addition of α -aryl or alkyl α -cyanoacetate **2** to vinyl sulfones **3**:

Table 1 Enantioselective Conjugate Addition of α -Substituted α -Cyanoacetate **2** to Vinyl Sulfone **3** Catalyzed by Q-1c and QD-1c (in brackets).

Entry	R	3	T / °C	Time / h	yield / %	ee / %	
1	2A	Ph-	3a	-25	72 (72)	89 (80)	95 (91)
2	2B	4-Me-Ph-	3a	0	48	96	93
3	2C	4-MeO-Ph-	3a	0	70	92	93
4	2D	4-F-Ph-	3a	-25	72	90	94
5	2E	4-Cl-Ph-	3a	-25	69 (72)	95 (94)	94 (89)
6	2F	4-Br-Ph-	3a	-25	66 (72)	95 (95)	94 (88)
7	2G	3-Cl-Ph-	3a	-25	60 (60)	96	93
8	2H	2-Naphthyl-	3a	-25	60 (60)	96 (95)	97 (90)
9	2I	2-Thienyl-	3a	-25	48 (48)	95 (91)	93 (88)
10	2J	Allyl-	3b	0	96	76	94
11	2k	Me	3b	0	96 (96)	85 (83)	92 (88)

At -25°C or 0 °C, to a solution of α -cyanoacetate **2** (for **2A**, **2B**, **2C**, entry 1-3, using 0.6 mmol, for **2D-2I**, entry 4-9, using 0.5mmol, for **2J**, **2K**, entry 10-11, using 0.2 mmol) in toluene (0.4 mL) was added the chiral catalyst (20 mol%.) and vinyl phenyl sulfone **3** (0.2 mmol). The resulting mixture was kept at the indicated temperature until sulfone is completely consumed. The reaction mixture was directly subjected to silica gel flash chromatography using the eluent specified below to afford the 1,4-adduct in the yields and enantiomeric excess summarized above. Finally, the column was washed with MeOH and the catalyst was recovered in greater than 95% yield. The recovered catalyst was shown to be identical to that before the reaction by NMR analysis.

(+)-4Aa This product was obtained as a colorless oil in 89 % yield after flash chromatography (elution gradient: ethyl acetate/hexane=1/8 to 6/1) and 95 % ee as determined by HPLC analysis [Daicel chiralcel OD, hexanes:IPA, 90:10, 1.0 ml/min, λ 220 nm, t (major) = 16.48 min, t (minor) = 14.93 min] from a reaction catalyzed by **Q-1c** (20 mol%) at -25 °C for 72 hours. $[\alpha]_D^{25} = +31.6$ (c 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.89 (d, J = 8.0 Hz, 2H), 7.69 (t, J = 7.2 Hz, 1H), 7.59 (t, J = 8.0 Hz, 2H), 7.45-7.39 (m, 5H), 4.28-4.15 (m, 2H), 3.27 (dt, J = 4.4 Hz, 12.8 Hz, 1H), 3.04 (dt, J = 4.4 Hz, 12.8 Hz, 1H), 2.75-2.59 (m, 2H), 1.21 (t, J = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 166.2, 138.3, 134.1, 132.6, 129.54, 129.48, 128.0, 125.8, 117.0, 63.7, 52.3, 52.1, 30.8, 13.7; HRMS (CI) m/z calcd. for (C₁₉H₁₉NO₄S+H⁺): 358.1113, found: 358.1108; IR (CHCl₃) ν 3064, 2984, 2939, 1745, 1448, 1321, 1237, 1087 cm⁻¹.

(-)-4Ab This product was obtained as a colorless oil in 80 % yield and 91 % ee from a reaction catalyzed by **QD-1c** (20 mol %) at -25 °C for 72 hours.

(+)-4Ba This product was obtained as a colorless oil in 96 % yield after flash chromatography (ethyl acetate/hexane=1/7) and 93 % ee as determined by HPLC analysis [Daicel Chiralpak AD, hexanes:IPA, 85:15, 1.0 ml/min, λ 220 nm, t (major) = 13.33 min, t (minor) = 22.06 min] from a reaction catalyzed by **Q-1c** (20 mol%) at 0 °C for 48 hours. $[\alpha]_D^{25} = +31.4$ (c 1.02, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.89 (d, J = 8.0 Hz, 2H), 7.69 (t, J = 7.2 Hz, 1H), 7.58 (t, J = 8.0 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H), 4.27-4.11 (m, 2H), 3.25 (dt, J = 5.6 Hz, 12.8 Hz, 1H), 3.03 (dt, J = 4.4 Hz, 12.8 Hz, 1H), 2.72-2.58 (m, 2H), 2.35 (s, 3H), 1.21 (t, J = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 166.3, 139.5, 138.3, 134.0, 130.1, 129.5, 129.4, 127.9, 125.6, 117.2, 63.6, 52.06, 51.98, 30.7, 20.9, 13.6; HRMS (CI) m/z calcd. for (C₂₀H₂₁NO₄S+H⁺): 372.1270, found: 372.1276; IR (CHCl₃) ν 2983, 1744, 1447, 1321, 1235, 1148, 1087 cm⁻¹.

(+)-4Ca This product was obtained as a colorless oil in 92 % yield after flash chromatography (ethyl acetate/hexane=1/6) and 93 % ee as determined by HPLC analysis [Daicel Chiralpak AD, hexanes:IPA, 85:15, 0.9 ml/min, λ 220 nm, t (major) = 28.93 min, t (minor) = 33.20 min] from a reaction catalyzed by **Q-1c** (20 mol%) at 0 °C for 70 hours. $[\alpha]_D^{25} = +31.0$ (c 1.10, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.89 (d, J = 7.2 Hz, 2H), 7.69 (t, J = 7.2 Hz, 1H), 7.58 (t, 7.2 Hz, 2H), 7.34 (td, J = 2.4 Hz, 9.2 Hz, 2H), 6.90 (td, J = 2.4 Hz, 9.2 Hz, 2H), 4.27-4.14 (m, 2H), 3.81 (s, 3H), 3.25 (dt, J = 5.2 Hz, 12.0 Hz, 1H), 3.04 (dt, J = 4.0 Hz, 12.0 Hz, 1H), 2.72-2.57 (m, 2H), 1.21 (t, J = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 166.4, 160.2, 138.3, 134.1, 129.4, 128.0, 127.1, 124.2, 117.2, 114.8, 63.6, 55.3, 52.1, 51.6, 30.7, 13.7; HRMS (CI) m/z calcd. for (C₂₀H₂₁NO₅S+H⁺): 388.1219, found: 388.1210; IR (CHCl₃) ν 2982, 1743, 1512, 1307, 1257, 1236, 1147 cm⁻¹.

(+)-4Da This product was obtained as a colorless oil in 90 % yield after flash chromatography (ethyl acetate/hexane = 1/5) and 94 % ee as determined by HPLC analysis [Daicel chiralcel OD, hexane:IPA, 90:10, 1.0 mL/min, λ 220 nm, $t(\text{major}) = 21.42$ min, $t(\text{minor}) = 17.98$ min] from a reaction catalyzed by **Q-1c** (20 mol%) at -25°C for 72 hours. $[\alpha]_{\text{D}}^{25} = +27.2$ (c 1.13, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.90-7.88 (m, 2H), 7.70 (tt, $J = 1.2$ Hz, 7.6 Hz, 1H), 7.59 (t, $J = 7.2$ Hz, 2H), 7.45-7.41 (m, 2H), 7.11 (tt, $J = 1.6$ Hz, 8.0 Hz, 2H), 4.29-4.16 (m, 2H), 3.26 (dt, $J = 4.8$ Hz, 13.6 Hz, 1H), 3.03 (dt, $J = 3.6$ Hz, 12.8 Hz, 1H), 2.72 (dt, $J = 4.4$ Hz, 14.0 Hz, 1H), 2.61 (dt, $J = 4.4$ Hz, 14.0 Hz, 1H), 1.22 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.0, 163.0 (d, $^1J_{\text{C,F}} = 249.0$ Hz), 138.3, 134.1, 129.5, 128.4 (d, $^4J_{\text{C,F}} = 3.0$ Hz), 128.0, 127.8 (d, $^3J_{\text{C,F}} = 8.3$ Hz), 116.9, 116.6 (d, $^2J_{\text{C,F}} = 22.1$ Hz), 63.9, 52.0, 51.7, 30.8, 13.6; HRMS (CI) m/z calcd for $(\text{C}_{19}\text{H}_{18}\text{FNO}_4\text{S}+\text{H}^+)$: 376.1019, found: 376.1015; IR (CHCl_3) ν 3070, 2985, 2940, 1745, 1604, 1510, 1447, 1307, 1237, 1087 cm^{-1} .

(+)-4Ea This product was obtained as a colorless oil in 95 % yield after flash chromatograph (ethyl acetate/hexane=1/6) and 94 % ee as determined by HPLC analysis [Daicel chiralcel OD, Hexane:IPA, 85:15, 1.0 mL/min, λ 220 nm, $t(\text{major}) = 16.75$ min, $t(\text{minor}) = 13.57$ min] from a reaction catalyzed by **Q-1c** (20 mol%) at -25°C for 69 hours. $[\alpha]_{\text{D}}^{25} = +31.9$ (c 1.10, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.85 (d, $J = 8.8$ Hz, 2H), 7.65 (t, $J = 7.2$ Hz, 1H), 7.55 (t, $J = 6.4$ Hz, 2H), 7.34 (s, 4H), 4.22-4.14 (m, 2H), 3.23 (dt, $J = 4.4$ Hz, 12.8 Hz, 1H), 2.99 (dt, $J = 4.4$ Hz, 12.8 Hz, 1H), 2.69 (dt, $J = 4.4$ Hz, 12.8 Hz, 1H), 2.56 (dt, $J = 4.4$ Hz, 12.8 Hz, 1H), 1.17 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 165.8, 138.2, 135.6, 134.1, 131.1, 129.6, 129.4, 127.9, 127.2, 116.6, 63.9, 51.9, 51.8, 30.6, 13.6; HRMS (CI) m/z calcd for $(\text{C}_{19}\text{H}_{18}\text{ClNO}_4\text{S}+\text{H}^+)$: 392.0723, found: 392.0728; IR (CHCl_3) ν 3066, 2984, 1745, 1493, 1447, 1322, 1236, 1148 cm^{-1} .

(-)-4Ea This product was obtained as a colorless oil in 94 % yield and 89 % ee from a reaction catalyzed by **QD-1c** (20 mol %) at -25°C for 72 hours.

(+)-4Fa This product was obtained as a colorless oil in 95 % yield after flash chromatography (ethyl acetate/hexane=1/6) and 94 % ee as determined by HPLC analysis [Daicel chiralpak AD, Hexane:IPA, 85:15, 1.0 mL/min, λ 220 nm, $t(\text{major}) = 22.51$ min, $t(\text{minor}) = 26.82$ min] from a reaction catalyzed by **Q-1c** (20 mol%) at -25°C for 66 hours. $[\alpha]_{\text{D}}^{25} = +28.8$ (c 1.10, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.89 (d, $J = 8.0$ Hz, 2H), 7.70 (t, $J = 8.0$ Hz, 1H), 7.60 (t, $J = 8.0$ Hz, 2H), 7.54 (d, $J = 8.8$ Hz, 2H), 7.32 (d, $J = 8.8$ Hz, 2H), 4.29-4.16 (m, 2H), 3.25 (dt, $J = 4.4$ Hz, 13.2 Hz, 1H), 3.01 (dt, $J = 4.0$ Hz, 13.2 Hz, 1H), 2.71 (dt, $J = 4.4$ Hz, 13.2 Hz, 1H), 2.60 (dt, $J = 4.0$ Hz, 13.2 Hz, 1H), 1.23 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 165.8, 138.2, 134.2, 132.7, 131.6, 129.5, 128.0, 127.5, 123.9, 116.6, 64.0, 52.01, 51.96, 30.7, 13.7; HRMS (CI) m/z calcd for $(\text{C}_{19}\text{H}_{18}\text{BrNO}_4\text{S}+\text{H}^+)$: 436.0218, found: 436.0208; IR (CHCl_3) ν 2983, 1745, 1489, 1447, 1322, 1236, 1148 cm^{-1} .

(-)-4Fa This product was obtained as a colorless oil in 95 % yield and 88 % ee from a reaction catalyzed by QD-1c (20 mol %) at -25 °C for 72 hours.

(+)-4Ga This product was obtained as a colorless oil in 96 % yield after flash chromatography (ethyl acetate/hexane = 1/7) and 93 % ee as determined by HPLC analysis [Daicel chiralpak AD, Hexane:IPA, 85:15, 1.0 mL/min, λ 220 nm, t (major) = 15.00 min, t (minor) = 12.58 min] from a reaction catalyzed by Q-1c (20 mol%) at -25 °C for 60 hours. $[\alpha]_D^{25} = +29.5$ (c 1.00, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.91-7.88 (m, 2H), 7.73-7.68 (m, 1H), 7.60 (t, J = 7.2 Hz, 2H), 7.42-7.33 (m, 4H), 4.31-4.17 (m, 2H), 3.27 (dt, J = 4.4 Hz, 13.6 Hz, 1H), 3.04 (dt, J = 3.6 Hz, 12.8 Hz, 1H), 2.73 (dt, J = 4.8 Hz, 12.8 Hz, 1H), 2.58 (dt, J = 4.4 Hz, 12.8 Hz, 1H), 1.23 (t, J = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 165.7, 138.2, 135.6, 134.5, 134.2, 130.8, 129.8, 129.5, 128.0, 126.1, 124.0, 116.5, 64.1, 52.0, 30.9, 13.7; HRMS (CI) m/z calcd for (C₁₉H₁₈ClNO₄S+H⁺): 392.0723, found: 392.0721; IR (CHCl₃) ν 2984, 1746, 1478, 1447, 1309, 1322, 1237, 1148 cm⁻¹.

(+)-4Ha This product was obtained as a colorless oil in 96 % yield after flash chromatography (elution gradient: Ethyl Acetate / Hexane = 1/6) and 98 % ee as determined by HPLC analysis [Daicel chiralcel OD, Hexane:IPA, 90:10, 1.0 mL/min, λ 220 nm, t(major) = 23.90 min, t(minor) = 27.21 min] from a reaction catalyzed by Q-1c (20 mol%) at -25 °C for 60 hours. $[\alpha]_D^{25} = +46.7$ (c 1.00, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.97 (d, J = 1.6 Hz, 1H), 7.88-7.84 (m, 5H), 7.68-7.64 (m, 1H), 7.57 (m, 4H), 7.44 (dd, J = 2.4 Hz, 8.4 Hz, 1H), 4.29-4.15 (m, 2H), 3.32 (dt, J = 4.8 Hz, 13.6 Hz, 1H), 3.04 (dt, J = 4.4 Hz, 12.4 Hz, 1H), 2.87-2.71 (m, 2H), 1.20 (t, J = 7.6 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 166.2, 138.3, 134.0, 133.1, 132.9, 129.7, 129.6, 129.4, 128.2, 127.9, 127.6, 127.4, 127.2, 125.9, 122.0, 117.1, 63.8, 52.5, 52.1, 30.6, 13.6; HRMS (CI) m/z calcd for (C₂₃H₂₁NO₄S+H⁺): 408.1270, found: 408.1266; IR (CHCl₃) ν 3061, 2983, 1744, 1321, 1234, 1151, 1087 cm⁻¹.

(-)-4Ha This product was obtained as a colorless oil in 95 % yield and 90 % ee from a reaction catalyzed by QD-1c (20 mol %) at -25 °C for 60 hours.

(+)-4Ia This product was obtained as a brown oil in 95 % yield after flash chromatography (ethyl acetate/hexane = 1/6) and 93% ee as determined by HPLC analysis [Daicel chiralcel OD, hexane:IPA, 90:10, 1.0 mL/min, λ 220 nm, t (major) = 20.54 min, t (minor) = 18.50 min] from a reaction catalyzed by Q-1c (20 mol%) at -25 °C for 48 hours. $[\alpha]_D^{25} = +20.2$ (c 1.00, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.91-7.88 (m, 2H), 7.72-7.68 (m, 1H), 7.59 (t, J = 8.0 Hz, 2H), 7.36 (dd, J = 1.2 Hz, 4.8 Hz, 2H), 7.20 (dd, J = 1.2 Hz, 4.0 Hz, 1H), 6.99 (dd, J = 3.6 Hz, 4.8 Hz, 1H), 4.29-4.23 (m, 2H), 3.27 (dt, J = 4.8 Hz, 12.8 Hz, 1H), 3.14 (dt, J = 4.4 Hz, 12.4 Hz, 1H), 2.78-2.61 (m, 2H), 1.27 (t, J = 7.6 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 165.5, 138.2,

134.9, 134.1, 129.4, 127.9, 127.5, 127.4, 127.1, 116.3, 64.0, 52.0, 49.3, 32.1, 13.6; HRMS (CI) m/z calcd for ($C_{17}H_{17}NO_4S_2+H^+$): 364.0677, found: 364.0669; IR ($CHCl_3$) ν cm^{-1} ;

(-)-4Ia This product was obtained as a brown oil in 91 % yield and 88 % ee from a reaction catalyzed by QD-1c (20 mol %) at -25 °C for 48 hours.

(+)-4Jb This product was obtained as a white solid in 76 % yield after flash chromatography (ethyl acetate: hexane= 1:10) and in 93% ee as determined by HPLC analysis [Daicel Chiralcel OD, hexane: IPA, 90:10, 1.0 ml/min, λ =220 nm, t (major) = 9.78 min, t (minor) = 13.73 min] from the reaction catalyzed by Q-1c (20 mol%) at 0 °C for 96 hours. $[\alpha]_D^{25} = +1.6$ (c 1.5, $CHCl_3$); 1H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 2H), 8.18 (s, 1H), 5.66-5.78 (m, 2H) 5.20-5.30 (m, 1H), 4.18-4.32 (m, 2H), 3.36 (dt, $J = 12.8$ Hz, $J = 4.4$ Hz, 1H), 3.32 (dt, $J = 12.8$ Hz, $J = 4.4$ Hz, 1H), 2.68 (dd, $J=13.6$ Hz, $J=6.8$ Hz, 1H), 2.65 (dd, $J=13.6$ Hz, $J=6.8$ Hz, 1H), 2.40 (dt, $J = 12.4$ Hz, $J = 4.4$ Hz, 1H), 2.24 (dt, $J = 12.4$ Hz, $J = 4.4$ Hz, 1H), 1.29 (t, $J=6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 141.4, 133.5 (q, $J = 34$ Hz) 129.2, 128.5, 127.9, 122.3 (q, $J = 273.0$ Hz), 122.2, 117.2, 63.6, 52.3, 47.4, 41.3, 28.0, 13.9; IR ($CHCl_3$) ν 3088, 2987, 1739, 1360, 1279, 1185, 1147 cm^{-1} ; HRMS (CI) m/z calcd for ($C_{18}H_{17}F_6NO_4S + H^+$): 458.0861, found 458.0862.

(-)-4Kb This product was obtained as a white solid in 85 % yield after flash chromatography (ethyl ether: hexane=1:5) and in 92% ee as determined by HPLC analysis [Daicel Chiralcel OD, hexane: IPA, 90:10, 1.0 ml/min, λ =220 nm, t (major) = 10.88 min, t (minor) = 17.64 min] from the reaction catalyzed by Q-1c (20 mol%) at 0 °C for 96 hours. $[\alpha]_D^{25} = -1.0$ (c 2.0, $CHCl_3$); 1H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 2H), 8.21 (s, 1H), 4.28 (dq, $J = 1.6$ Hz, $J = 7.2$ Hz, 2H), 3.38 (dt, $J = 13.6$ Hz, $J = 4.4$ Hz, 1H), 3.31 (dt, $J = 12.8$ Hz, $J = 4.4$ Hz, 1H), 2.45 (dt, $J = 12.8$ Hz, $J = 4.4$ Hz, 1H), 2.27 (dt, $J = 12.8$ Hz, $J = 4.4$ Hz, 1H), 1.67 (s, 3H), 1.32 (t, $J=6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 141.4, 133.5 (q, $J = 30$ Hz) 128.5, 128.0, 127.9, 122.1 (q, $J = 272.4$ Hz), 118.2, 63.1, 52.4, 42.4, 29.8, 23.7, 13.9; IR ($CHCl_3$) ν 3088, 2990, 1745, 1281, 1186, 1147 cm^{-1} ; HRMS (CI) m/z calcd for ($C_{16}H_{15}F_6NO_4S + H^+$): 432.0708, found 432.0712.

(+)-4Kb This product was obtained as a white solid in 83% yield and 88% ee from a reaction catalyzed by QD-1c (20 mol %) at 0 °C for 96 hours.

HPLC spectrum for adducts 4:

HPLC Conditions: Daicel chiralcel OD, Hexane:IPA, 90:10, 1.0 mL/min, λ 220 nm

Racemic **4-Aa**

(+)- **4-Aa** 95% ee
QD-1c catalyzed product

(-)- **4-Aa** 91% ee
QD-1c catalyzed product

HPLC Conditions: Chiralpak AD, Hexane:IPA, 85:15, 1.0 mL/min, λ 220 nm

(+)- **4-Ba** 93% ee
Q-1c catalyzed product

HPLC Conditions: Chiralpak AD, Hexane:IPA, 85:15, 0.9 mL/min, λ 220 nm

(+)- **4-Ca** 93% ee
Q-1c catalyzed product

HPLC Conditions: Daicel chiralcel OD, Hexane:IPA, 90:10, 1.0 mL/min, λ 220 nm

racemic 4Da

(+)- 4-Da 94% ee
Q-1c catalyzed product

HPLC Conditions: Daicel chiralcel OD, Hexane:IPA, 85:15, 1.0 mL/min, λ 220 nm

racemic **4-Ea**

(+)- **4-Ea** 94% ee
Q-1c catalyzed product

(-)- **4-Ea** 89% ee
QD-1c catalyzed product

HPLC Conditions: Chiralpak AD, Hexane:IPA, 85:15, 1.0 mL/min, λ 220 nm

(+)- **4-Fa** 94% ee
Q-**1c** catalyzed product

(-)- **4-Fa** 88% ee
QD-**1c** catalyzed product

HPLC Conditions: Chiralpak AD, Hexane:IPA, 85:15, 1.0 mL/min, λ 220 nm

(+)- **4-Ga** 93% ee
Q-1c catalyzed product

HPLC Conditions: Daicel chiralcel OD, Hexane:IPA, 90:10, 1.0 mL/min, λ 280 nm

racemic **4Ha**

(+)- **4-Ha** 97% ee
Q-1c catalyzed product

Error storing signal to M:SIGNAL .BNA
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Storing processed peaks to M:SIGNAL .PRA

PEAK	RT	AREA	TYPE	WIDTH	AREA%
23.905	75943424	SBB	1.060	98.41821	
27.213	1220574	BB	.832	1.58179	

TOTAL AREA=7.7164E+07
MUL FACTOR=1.0000E+00

(-)- **4-Ha** 90% ee
QD-1c catalyzed product

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DIRECTORY FULL
Storing processed peaks to M:SIGNAL .PRA

PEAK	RT	AREA	TYPE	WIDTH	AREA%
23.725	2747461	PU	.958	5.16422	
26.380	50454400	UB	1.255	94.83578	

TOTAL AREA=5.3202E+07
MUL FACTOR=1.0000E+00

Error storing signal to M:SIGNAL .BNA
DIRECTORY FULL
Storing processed peaks to M:SIGNAL .PRA

PEAK	RT	AREA	TYPE	WIDTH	AREA%
24.262	9710970	BU	1.079	50.13682	
27.265	9657978	UB	1.265	49.86320	

TOTAL AREA=1.9369E+07
MUL FACTOR=1.0000E+00

HPLC Conditions: Daicel chiralcel OD, Hexane:IPA, 90:10, 1.0 mL/min, λ 220 nm

racemic **4-la**

(+)- **4-la** 93% ee
QD-1c catalyzed product

(-)- **4-la** 88% ee
QD-1c catalyzed product

HPLC Condition: Daicel Chiralcel OD Hexane:IPA, 90:10, 1.0ml min⁻¹, 220nm

(+)- **4-Jb** 93% ee
Q-1c catalyzed product

HPLC Condition: Daicel Chiralcel OD, Hexane:IPA, 90:10, 1.0ml·min⁻¹, 220nm

(-)- **4-Kb** 92% ee
Q-1c catalyzed product

(+)- **4-Kb** 88% ee
QD-1c catalyzed product

Synthesis of optically active α,α -disubstituted amino acid **6**:

Preparation of amide **7** from adduct **4Aa**:⁶

At room temperature, to a solution of **4Aa** (357 mg, 1.0 mmol) in DMSO (3.0 ml) was added $\text{K}_2\text{CO}_3 \cdot 1.5\text{H}_2\text{O}$ (70 mg, 0.5 eq.), after which H_2O_2 (0.15 mL, 30%, 4eq.) was added. After 1 h another portion of H_2O_2 was added, then another 3 portions was added Portion/2 h. The mixture was then stirred for another 1h, after which the reaction mixture was diluted with brine (20 mL), the resulting mixture was subjected to extraction with ethyl acetate (2 x 30 mL). The combined organic phase was washed with brine (2 x 20 mL), dried over Na_2SO_4 , concentrated in vacuo, and the residue was subjected to flash chromatography (eluent: hexanes/ EtOAc = 4/1 to 1/1) to give amide **7** (240 mg, 62% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.86 (d, J = 7.2 Hz, 2H), 7.64 (t, J = 7.2 Hz, 1H), 7.54 (t, J = 7.2 Hz, 2H), 7.34-7.30 (m, 3H), 7.19-7.17 (m, 2H), 6.83 (br, 1H), 6.14 (br, 1H), 4.23 (q, J = 7.2 Hz, 2H), 3.28-3.21 (m, 1H), 3.10-3.03 (m, 1H), 2.64-2.56 (m, 2H), 1.24 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.4, 170.8, 138.7, 137.8, 133.6, 129.2, 129.0, 128.2, 128.0, 126.7, 62.5, 62.0, 52.7, 29.2, 13.8; IR (CHCl_3) ν 3456 (br), 3342 (br), 3063, 2982, 2934, 1729, 1684, 1585, 1447, 1300, 1237, 1143, 1087, 725 cm^{-1} ; HRMS (ESI) m/z calcd. for ($\text{C}_{19}\text{H}_{21}\text{NO}_5\text{S}+\text{H}^+$): 376.1219, found: 376.1213.

Preparation of amino-acid **5** form amide **7**:⁷

To a solution of **7** (124mg, 0.33 mmol) in CH_3CN (1.6 mL) and H_2O (0.8 mL) was added $\text{PhI(OCOCF}_3)_2$ (214mg, 1.5 eq.). The resulting mixture was stirred overnight and then was diluted with ether (20 mL) and washed with HCl (2.0 N, 3 x 4.0 mL), the combined aqueous phase was basified with Na_2CO_3 (5%, aq.) until the pH = 12-13. Then the mixture was extracted with ethyl acetate (2 x 30 mL), and the combined organic phase was washed with brine (2 x 20 mL), dried over Na_2SO_4 , concentrated in vacuo. The residue was dissolved in anhydrous CH_2Cl_2 (2 mL). To the resulting solution was added Et_3N (0.14 mL, 3eq.) and PhCOCl (0.046 mL, 1.2 eq.). The solution was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate (60 mL), and

washed with Na₂CO₃ (5% aq., 10mL), brine (2 x 20mL), dried over anhydrous Na₂SO₄, concentrated in vacuo and the residue was subjected to flash chromatography (eluent: ethyl acetate/hexane = 1/2) to give amino acid **5** (120 mg, 79% yield) in 95 % ee as determined by HPLC analysis [Daicel chiralpak AD, Hexane:IPA, 80:20, 1.0 mL/min, λ 220 nm, t (major) = 29.3 min, t (minor) = 21.2 min]. $[\alpha]_D^{25} = +8.3$ (c 1.1, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.87 (d, J = 7.2 Hz, 2H), 7.75 (d, J = 7.2 Hz, 2H), 7.62 (t, J = 7.2 Hz, 1H), 7.57 (br, 1H), 7.53-7.50 (m, 3H), 7.45-7.39 (m, 4H), 7.35-7.26 (m, 3H), 4.21-4.08 (m, 2H), 3.35-3.20 (m, 2H), 3.08-2.93 (m, 2H), 1.15 (t, J = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 171.6, 165.7, 138.4, 138.0, 133.7, 133.6, 131.9, 129.3, 128.8, 128.6, 128.3, 127.9, 127.0, 125.5, 64.5, 62.8, 52.1, 27.2, 13.7; IR (CHCl₃) ν 3403 (br), 3063, 3027, 2983, 1732, 1667, 1581, 1513, 1480, 1447, 1307, 1245, 1204, 1149, 1086, 752 cm⁻¹; HRMS (ESI) m/z calcd. for (C₂₅H₂₅NO₅S+H⁺): 452.1532, found: 452.1533.

Preparation of amino acid **8** from **5**:⁸

Under argon at -65°C to a solution of **5** (90 mg, 0.2 mmol) in anhydrous THF (1.5 mL) was added LDA (2.0 M in heptane/tetrahydrofuran/ethylbenzene, 0.3 ml, 3eq.). The resulting mixture was gradually warmed to -40°C over 30 min, after which PhCHO (0.024ml, 1.2 eq.) was added in one portion. Then the reaction mixture was gradually warmed to room temperature over 1 h. The reaction was then quenched with NH₄Cl (sat. aq.) and diluted with ethyl acetate (30 mL). The organic phase was washed with brine (2 x 10 mL), dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was dissolved in anhydrous CH₂Cl₂ (1.5 mL). To the resulting solution, Et₃N (0.084 ml, 3eq.) and PhCOCl (0.028mL, 1.2 eq.) were added sequentially. The mixture was stirred at room temperature for 3 hours and was then diluted with ethyl acetate (40 mL), washed with Na₂CO₃ (5% aq. 10 mL), brine (2 x 10 mL), dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue was dissolved in anhydrous EtOH (2.0 mL). To the resulting solution HgCl₂ (11 mg, 0.2 eq.) and Mg (15 mg, 3 eq. -50 mesh) was added sequentially. The resulting reaction mixture was stirred for 2 hours, then was poured into NH₄Cl (sat. aq. 5 mL). The mixture was subjected to extraction with ethyl acetate (50 mL). The organic phase was washed with brine (2 x 20 ml), dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The residue was subjected to flash chromatography (eluent: ethyl acetate/hexane = 1/9) to give olefin **8** (32 mg, 40 % yield, E/Z = 3/1) Data for *E* isomer: ¹H NMR (400 MHz, CDCl₃) δ 7.81 (d, J = 7.2 Hz, 2H), 7.76 (br, 1H), 7.53 (d, J = 7.2 Hz, 2H), 7.50-7.47 (m, 1H), 7.43 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 6.8 Hz, 1H), 7.36 (d, J = 7.6 Hz, 2H), 7.34-7.28 (m, 1H), 7.26-7.24 (m, 3H), 7.23-7.17 (m, 1H), 6.53 (d, J = 16.0 Hz, 1H), 6.08 (dt, J = 16.0 Hz, 8.0 Hz, 1H), 4.32-4.24 (m, 1H), 4.21-4.10 (m, 1H), 3.97 (dd, J = 8.0 Hz, 13.6 Hz, 1H), 3.46 (dd, J = 8.0 Hz, 13.6 Hz, 1H), 1.22 (t, J = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 172.6, 165.8, 139.2, 137.1, 134.7, 134.6, 131.6, 128.61, 128.57, 128.46, 127.9, 127.4, 126.70, 126.2, 125.9, 123.7, 66.0, 62.6, 36.3, 14.0; IR (CHCl₃) ν 3413 (br), 3060, 3027, 2981, 2933, 1728, 1673, 1506, 1480, 1447,

1307, 1216 cm^{-1} ; HRMS (ESI) m/z calcd. for $(\text{C}_{26}\text{H}_{25}\text{NO}_3 + \text{H}^+)$: 400.1913 found: 400.1929.

Preparation of amino acid **6** from **8**:

The suspension formed by the addition of Pd/C (10%, 4 mg) to the solution of **8** (13 mg) in ethyl acetate (1.0 mL) was stirred under H_2 (1 atmosphere) for 2 hours. The reaction mixture was passed through a short pad of silica gel to remove Pd/C (using ethyl acetate as eluent), and concentrated in vacuo to give **6** (13 mg, 99% yield) in 92 % ee as determined by HPLC analysis [Daicel chiralpak AD, Hexane:IPA, 90:10, 1.0 mL/min, λ 220 nm, t (major) = 14.6 min, t (minor) = 20.7 min]. $[\alpha]_{\text{D}}^{25} = -3.7$ (c 0.3, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.84-7.82 (m, 3H), 7.53-7.42(m, 5H), 7.34-7.24 (m, 5H), 7.19-7.14 (m, 3H), 4.23-4.14 (m, 1H), 4.13-4.03 (m, 1H), 3.12 (dt, $J = 4.8$ Hz, 12.8 Hz, 1H), 2.80-2.72 (m, 1H), 2.67-2.57(m, 2H), 1.85-1.73 (m, 1H), 1.47-1.36 (m, 1H), 1.12 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 173.2, 165.3, 141.2, 139.8, 134.5, 131.6, 128.6, 128.5, 128.33, 128.32, 127.7, 127.0, 125.8, 65.9, 62.4, 35.7, 32.1, 26.5, 13.8; IR (CHCl_3) ν 3414, 3061, 3026, 2979, 2943, 1724, 1672, 1510, 1480, 1292, 1243, 1094 cm^{-1} ; HRMS (ESI) m/z calcd. for $(\text{C}_{26}\text{H}_{27}\text{NO}_3 + \text{H}^+)$: 402.2069, found: 402.2077.

HPLC spectrum for transformation products:

HPLC Conditions: chiralpak AD, Hexane:IPA, 80:20, 1.0 mL/min, λ 220 nm

HPLC Conditions: chiralpak AD, Hexane:IPA, 90:10, 1.0 mL/min, λ 220 nm

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