A Practical Approach to the Resolution of Racemic N-Benzyl α-Amino Acids by Liquid-Liquid Extraction, Using a Lipophilic Chiral Cobalt(III) Salen Complex

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Experimental Section

General: Proton NMR spectra were recorded on 400, 300 or 200 MHz spectrometers. Proton chemical shifts are reported in ppm (δ) with the solvent reference relative to tetramethylsilane (TMS) employed as the internal standard (CDCl₃, δ 7.26 ppm). Carbon NMR spectra were recorded on a 400 (100 MHz) or 300 (75 MHz) spectrometer with complete proton decoupling. Carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard (CDCl₃, δ 77.0). Infrared spectra were recorded on a standard Infrared Spectrophotometer; peaks are reported in cm⁻¹. Optical rotation values were measured on an automatic polarimeter at the sodium D line. High resolution mass spectra (HRMS) were performed on a hybrid quadrupole time of flight mass spectrometer equipped with an ESI ion source.

Materials: All commercially available reagents were used as received. (R,R)-N,N'-Bis(3,5-di-tert-butylsalicylidene)-1,2-cyclo-hexanediaminocobalt(II) ([Co²⁺(3)]) was purchased from Strem. (R),(R)-trans-cyclohexane-1,2-diamine tartrate salt[¹] and (R,R)-N,N'-Bis-salicylidene-1,2-cyclohexanediamine[²] (1) were prepared as reported. Extractions were performed using HPLC grade water.

Typical Procedure for the Synthesis of N-Benzyl Amino Acids: These were prepared according to the method reported by Quitt et al. as follows:[³] Benzaldehyde (5.09 mL, 50.0 mmol) was added to a vigorously stirred solution of the amino acid (50.0 mmol) in aqueous NaOH (2 M, 25 mL). The emulsion was stirred for 30 min before the mixture was cooled in an ice bath and sodium borohydride (0.570 g, 15.0 mmol) was added in small portions over 15 min. The mixture was allowed to warm to room temperature then stirred for a further hour before a second equivalent of benzaldehyde (5.09 mL, 50.0 mmol) was added. The mixture was stirred vigorously for 30 min, cooled in an ice bath and sodium borohydride (0.570 g, 15.0 mmol) was added in small portions over 15 min. The mixture was stirred for a further 2 h then diluted with H₂O (30 mL) and washed with dichloromethane (2 x 30 mL). Hydrochloric acid (1 M) was added until neutral pH was obtained and the resulting white precipitate was collected by filtration, washed with water (2 x 10 mL) and then acetone (2 x 10 mL) to give the N-benzyl amino acid as a white powder.
(rac)-N-Benzylalanine: Yield = 71%. Analytical and spectroscopic data was consistent with that previously reported.\cite{4} $^1$H NMR (200 MHz, D$_2$O): δ = 7.29-7.25 (m, 5H), 4.00 (m, 2H), 3.47 (q, $J$ = 7.0 Hz, 1H), 1.27 ppm (d, $J$ = 7.0 Hz, 3H); HPLC conditions: Chirobiotic R (50 x 4.6 mm) column (9:1 H$_2$O:CH$_3$CN), 1.0 mL/min, (S) enantiomer $t_R$ = 1.141 min, (R) enantiomer $t_R$ = 2.754 min.

(rac)-N-Benzylthreonine: Yield = 56%. Analytical and spectroscopic data was consistent with that previously reported.\cite{5} $^1$H NMR (400 MHz, D$_2$O-NaOH): δ = 7.35-7.23 (m, 5H), 3.74-3.71 (overlapping m, 1H), 3.73 (overlapping AB, $J$ = 12.8 Hz, 1H), 2.76 (d, $J$ = 6.8 Hz, 1H), 1.06 ppm (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (100 MHz, D$_2$O-NaOH): δ = 180.0, 139.1, 128.7, 127.3, 69.5, 68.6, 51.4, 19.0 ppm; HPLC conditions: Chirobiotic R (50 x 4.6 mm) column (H$_2$O), 0.5 mL/min, (S) enantiomer $t_R$ = 3.331 min, (R) enantiomer $t_R$ = 4.008 min.

(rac)-N-Benzylvaline: Yield = 60%. Analytical and spectroscopic data was consistent with that previously reported.\cite{6} $^1$H NMR (400 MHz, D$_2$O-NaOH): δ = 7.33-7.22 (m, 5H), 3.67 (AB, $J$ = 12.8 Hz, 1H), 3.45 (AB, $J$ = 12.8 Hz, 1H), 2.76 (d, $J$ = 6.0 Hz, 1H), 1.75-1.68 (m, 1H), 0.82 (d, $J$ = 6.8 Hz, 3H), 0.78 ppm (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (100 MHz, D$_2$O-NaOH): δ = 181.7, 139.0, 128.7, 128.6, 127.3, 69.0, 51.6, 30.7, 18.8, 18.4 ppm; HPLC conditions: Chirobiotic R (50 x 4.6 mm) column (9:1 H$_2$O:CH$_3$CN), 1.0 mL/min, (S) enantiomer $t_R$ = 1.175 min, (R) enantiomer $t_R$ = 2.199 min.

(rac)-N-Benzylphenylalanine: Yield = 91%. Analytical and spectroscopic data was consistent with that previously reported.\cite{7} $^1$H NMR (400 MHz, D$_2$O-NaOH): δ = 7.30-7.12 (m, 10H), 3.65 (AB, $J$ = 12.4 Hz, 1H), 3.46 (AB, $J$ = 12.4 Hz, 2H), 3.28-3.23 (m, 1H), 2.86-2.74 ppm (m, 2H); $^{13}$C NMR (100 MHz, D$_2$O-NaOH): δ = 181.1, 138.8, 138.0, 129.3, 128.6, 128.5, 127.3, 126.6, 64.5, 51.0, 39.0 ppm; HPLC conditions: Chirobiotic R (50 x 4.6 mm) column (9:1 H$_2$O:CH$_3$CN), 1.0 mL/min, (S) enantiomer $t_R$ = 1.824 min, (R) enantiomer $t_R$ = 2.489 min.

(rac)-N-Benzyleucine: Yield = 65%. Analytical and spectroscopic data was consistent with that previously reported.\cite{6} $^1$H NMR (400 MHz, D$_2$O-NaOH): δ = 7.34-7.23 (m, 5H), 3.66 (AB, $J$ = 12.4 Hz, 1H), 3.47 (AB, $J$ = 12.4 Hz, 1H), 3.04-3.00 (m, 1H), 1.52-1.44 (m, 1H), 1.38-1.24 (m, 2H), 0.80 (d, $J$ = 6.4 Hz, 3H), 0.77 ppm (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (100 MHz, D$_2$O-NaOH): δ = 183.0, 138.9, 128.8, 128.6, 127.3, 91.9, 51.1, 42.6, 24.8, 22.5, 21.7 ppm; HPLC conditions: Chirobiotic R (50 x 4.6 mm) column (9:1 H$_2$O:CH$_3$CN), 1.0 mL/min, (S) enantiomer $t_R$ = 1.304 min, (R) enantiomer $t_R$ = 1.909 min.
**Synthesis of (R,R)-N,N'-Bis(3-methyl-salicylidene)-1,2-cyclohexanediamine (2):** Prepared according to the method reported by Jacobsen *et al.* [8] A 250 mL flask fitted with a reflux condenser was charged with (R),(R)-trans-cyclohexane-1,2-diamine tartrate salt (1.950 g, 7.35 mmol), K₂CO₃ (2.030 g, 14.68 mmol) and H₂O (15 mL). The mixture was stirred to dissolve the solids, then EtOH (70 mL) was added and the yellow suspension was heated to 70 °C for 20 min. A solution of 2-hydroxy-3-methyl-benzaldehyde (2.000 g, 14.68 mmol) in EtOH (20 mL) was added dropwise over 15 min. The mixture was stirred at 70 °C for 2 h, cooled in ice then H₂O (60 mL) was added. The resulting yellow precipitate was collected by filtration and washed with cold EtOH (2 x 10 mL). The solid was dissolved in dichloromethane (40 mL) and washed with H₂O (2 x 25 mL), aqueous NaCl (2 x 25 mL) then the organic phase was dried (Na₂SO₄) and volatiles removed under reduced pressure to give the product as a yellow oil, which solidified and was then recrystallised from acetone. Yield: 1.52 g (60%). [α]D = –468 (c = 0.103, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ = 13.61 (bs, 2H), 8.29 (s, 2H), 7.14 (d, J = 7.6 Hz, 2H), 7.03 (d, J = 7.6 Hz, 2H), 6.76-6.72 (m, 2H), 3.36-3.30 (m, 2H), 2.26 (s, 6H), 1.98-1.88 (m, 4H), 1.79-1.68 (m, 2H), 1.52-1.46 ppm (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ = 164.9, 159.3, 133.2, 129.1, 125.7, 118.1, 117.9, 72.6, 33.2, 24.2, 15.4 ppm; HRMS (ESI) calcd. for C₂₂H₂₆N₂O₂ 373.1887 [M]+; found: 373.1884.

**(R,R)-N,N'-Bis-salicylidene)-1,2-cyclohexanediaminocobalt(II) ([CoII(1)]):** Prepared from (R,R)-N,N'-Bis-salicylidene-1,2-cyclohexanediamine (1) and cobalt(II) acetate as previously reported [9]. Yield: 83%. [α]D = –1398 (c = 0.049, CHCl₃). Lit. value [9] [α]D = 1420 (c = 0.050, CHCl₃); HRMS (ESI) calcd. for C₂₀H₂₀N₂O₂Co 379.0857 [M]+; found: 379.0855.

**(R,R)-N,N'-Bis(3-methyl-salicylidene)-1,2-cyclohexanediaminocobalt(II) ([CoII(2)]):** Prepared from (R,R)-N,N'-Bis(3-methyl-salicylidene)-1,2-cyclohexanediamine (2) and cobalt(II) acetate according to the method reported by Belokon *et al.* [9] Yield: 81%. [α]D = –745 (c = 0.050, CHCl₃); FT-IR (Nujol): ν = 2959, 2725, 2672, 1608, 1525, 1507, 1354, 1201, 1175 cm⁻¹; HRMS (ESI) calcd. for C₂₂H₂₄N₂O₂Co 407.1164 [M]+; found: 407.1155.

**General Procedure for the Preparation of Cobalt(III) Acetate Complexes [CoIII(1-3)(OAc)]:** Complexes [CoIII(1-3)(OAc)] were prepared following a slightly modified literature procedure [10]. Glacial acetic acid (0.35 mL, 6.0 mmol) was added to a stirred solution of the (salen)cobalt(II) complex (0.300 mmol) in toluene (20 mL) under air. An immediate colour change from bright red to brown was observed. The solution was stirred for a further 30 min before volatiles were removed.
under reduced pressure to leave the (salen)cobalt (III) acetates [Co$^{\text{III}}$(1-3)(OAc)] as brown powders, which were used directly in subsequent extractions without further purification.

[Co$^{\text{III}}$(1)(OAc)]: $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 8.42$ (s, 2H), 7.43-7.25 (m, 4H), 7.12 (d, $J = 8.3$ Hz, 2H), 6.97 (m, 2H), 3.52-3.45 (m, 2H), 2.09-1.75 (m, 5H), 1.65-1.51 ppm (m, 3H).

[Co$^{\text{III}}$(2)(OAc)]: $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.54$ (bs, 2H), 7.39-7.15 (m, 4H), 6.57 (bs 2H), 6.97 (m, 2H), 4.03 (bs, 2H), 2.12-1.90 (m, 3H), 1.87 (s, 6H), 1.66-1.50 ppm (m, 3H).

[Co$^{\text{III}}$(3)(OAc)]: Spectroscopic data was consistent with that previously reported.$^{[11]}$

(R,R)-N,N'-Bis(3,5-di-tert-butylsalicylidene)-1,2-cyclo-hexanediaminocobalt(III) trifluoromethanesulfonate ([Co$^{\text{III}}$(3)(OTf))]: Prepared according to a reported method:$^{[12]}$ To a stirred solution of complex [Co$^{\text{II}}$(3)] (0.181 g, 0.300 mmol) in toluene (20 mL), in a 50 mL flask wrapped in foil, was added silver trifluoromethanesulfonate (0.076 g, 0.300 mmol) and the mixture was stirred for 1 h. After removal of silver by filtration, the filtrate was concentrated to a green powder which was used immediately in an extraction without further purification. Yield: 0.206 g (99%).

(R,R)-N,N'-Bis(3,5-di-tert-butylsalicylidene)-1,2-cyclo-hexanediaminocobalt(III) hexafluorophosphate ([Co$^{\text{III}}$(3)(PF$_6$)]): Prepared according to a reported method:$^{[12]}$ To a stirred solution of complex [Co$^{\text{II}}$(3)] (0.181 g, 0.300 mmol) in MeCN (20 mL), was added ferrocenium hexafluorophosphate (0.099 g, 0.300 mmol) with an immediate colour change from red to dark green observed. The mixture was stirred for 30 min before volatiles were removed under reduced pressure and the brown residue washed with hexane (3 x 10 mL) to remove ferrocene. The resulting green powder was used immediately in an extraction without further purification. Yield: 0.222 g (99%).

General Method for the Extraction of N-Benzylalanine Using Cobalt Complexes [Co$^{\text{II}}$(1-2)] and [Co$^{\text{III}}$(3)(X)] (X = OAc, OTf, PF$_6$): To a solution of the cobalt complex (0.3 mmol) in dichloromethane (40 mL) at 10 °C in a 100 mL round-bottom flask, was added a precooled (10 °C) solution of racemic N-benzylalanine (0.108 g, 2 eq, 0.600 mmol) in H$_2$O (30 mL). The biphasic mixture was stirred vigorously for 24 h at 10 °C, then transferred to a separating funnel, the organic phase removed and the aqueous phase washed once with dichloromethane (10 mL). The combined dichloromethane extracts were washed once with H$_2$O (10 mL) before volatiles were removed under reduced pressure to leave the complexes [Co$^{\text{III}}$(1-3)(N-Bn-Ala)] as green powders. The aqueous phases were combined and an aliquot removed which was filtered on micropore filters.
before the ee was determined by chiral HPLC as described above. The aqueous phase was evaporated to leave $N$-benzylalanine as a white powder.

**[Co\textsuperscript{III}(1)(N-Bn-Ala)]:** Spectroscopic data was consistent with that previously reported.\textsuperscript{[13]} Yield: 0.162 g (92%). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): $\delta$ = 7.93 (s, 1H), 7.68 (s, 1H), 7.46 (d, $J$ = 8.0 Hz, 1H), 7.32-7.22 (m, 7H), 7.12 (dd, $^1J$ = 8.4 Hz, $^2J$ = 2.8 Hz, 1H), 6.60 (d, $J$ = 8.0 Hz, 1H), 6.60-6.54 (m, 2H), 4.36 (dd, $^1J$ = 14.0 Hz, $^2J$ = 12.0 Hz, 1H), 4.32-4.21 (m, 1H), 4.20-4.12 (m, 2H), 3.39-3.32 (m, 1H), 3.29-3.18 (m, 1H), 2.84 (d, $J$ = 9.5 Hz, 1H), 2.43-2.38 (m, 1H), 2.04-1.81 (m, 4H), 1.62-1.39 (m, 3H), 0.78 ppm (d, $J$ = 7.6 Hz, 3H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): $\delta$ = 183.2, 166.1, 165.9, 164.0, 160.6, 136.3, 135.1, 134.7, 129.1, 129.0, 128.3, 123.3, 123.2, 118.1, 116.7, 114.3, 75.3, 71.1, 60.3, 54.5, 30.7, 29.3, 24.6, 23.9, 20.7 ppm; FT-IR (Nujol): $\nu$ = 2921, 2726, 2360, 2333, 1623, 1598, 1197, 1148, 1123, 1092, 1026, 964, 904 cm\textsuperscript{-1}; HRMS (ESI): calcd. for C\textsubscript{30}H\textsubscript{32}N\textsubscript{3}O\textsubscript{4}CoNa 580.1623 [M+Na]\textsuperscript{+}; found: 580.1625.

**[Co\textsuperscript{III}(2)(N-Bn-Ala)]:** Yield: 0.175 g (99%). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): $\delta$ = 7.94 (s, 1H), 7.66 (s, 1H), 7.36-7.15 (m, 7H), 6.78-6.75 (m, 1H), 6.61-6.49 (m, 2H), 4.41-4.38 (m, 1H), 4.39 (dd, $^1J$ = 8.5 Hz, $^2J$ = 14.1 Hz, 1H), 4.21-4.19 (m, 1H), 3.92 (d, $J$ = 9.5 Hz, 1H), 2.43 (s, 3H), 2.43-2.40 (m, 1H), 2.05 (s, 3H), 2.04-1.84 (m, 3H), 1.61-1.40 (m, 3H), 0.81 ppm (d, $J$ = 7.3 Hz, 3H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): $\delta$ = 183.2, 164.8, 164.7, 164.2, 160.6, 136.3, 135.2, 134.5, 134.0, 132.8, 131.0, 130.2, 129.2, 129.0, 128.3, 122.6, 116.9, 116.1, 113.6, 75.3, 71.4, 60.3, 54.7, 30.6, 29.2, 24.7, 23.9, 20.7, 18.6, 16.9 ppm; FT-IR (Nujol): $\nu$ = 2902, 2725, 1632, 1596, 1546, 1225, 1156, 1089, 1040, 966, 897 cm\textsuperscript{-1}; HRMS (ESI): calcd. for C\textsubscript{32}H\textsubscript{36}N\textsubscript{3}O\textsubscript{4}CoNa 608.1936 [M+Na]\textsuperscript{+}; found: 608.1933. Elemental analysis calcd (%) for C\textsubscript{32}H\textsubscript{36}N\textsubscript{3}O\textsubscript{4}Co (M\textsubscript{w} = 585.59): C 65.64, H 6.20, N 7.18; found: C 65.37, H 6.29, N 7.03.

**[Co\textsuperscript{III}(3)(N-Bn-Ala)]:** Yield: 0.233 g (99%). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): $\delta$ = 7.94 (s, 1H), 7.59 (s, 1H), 7.43 (d, $J$ = 2.6 Hz, 1H), 7.35-7.25 (m, 5H), 7.14 (d, $J$ = 2.6 Hz, 1H), 6.64 (s, 1H), 6.62 (s, 1H), 4.65 (dd, $^1J$ = 13.4 Hz, $^2J$ = 11.8Hz, 1H), 4.38-4.35 (m, 1H), 4.25-4.20 (m, 1H), 4.15 (d, $J$ = 13.4 Hz, 1H), 3.46-3.39 (m, 1H), 2.92 (d, $J$ = 9.7 Hz, 1H), 2.42 (d, $J$ = 9.7 Hz, 1H), 2.06-1.88 (m, 3H), 1.59-1.52 (m, 4H), 1.55 (s, 9H), 1.43 (s, 9H), 1.37 (s, 9H), 1.21 (s, 9H), 0.78 ppm (d, $J$ = 7.3 Hz, 3H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): $\delta$ = 183.9, 165.3, 164.2, 163.8, 160.9, 145.7, 141.8, 138.4, 137.5, 135.7, 130.8, 130.5, 129.8, 129.8, 129.0, 126.1, 122.6, 118.3, 76.2, 71.3, 60.9, 56.5, 36.5, 36.4, 34.8, 34.5, 32.2, 31.6, 30.5, 30.3, 29.9, 25.3, 24.6, 21.9 ppm; FT-IR (Nujol): $\nu$ = 3252, 2928,
**Extraction of N-Benzylthreonine Using Cobalt Complex [Co^{III}(3)(OAc)] (Method A):** To a solution of the cobalt complex (0.150 mmol) in dichloromethane (20 mL) at 10 °C in a 50 mL round-bottom flask, was added a precooled (10 °C) solution of racemic N-benzylthreonine (0.067 g, 2 eq, 0.600 mmol) in H$_2$O (15 mL). The biphasic mixture was stirred vigorously for 24 h at 10 °C, then transferred to a separating funnel, the organic phase removed and the aqueous phase washed once with dichloromethane (10 mL). The combined dichloromethane extracts were washed once with H$_2$O (10 mL) before volatiles were removed under reduced pressure to leave the complex [Co^{III}(3)(N-Bn-Thr)] as a green powder. Yield: 0.121 g (94%). The aqueous phases were combined and an aliquot removed which was filtered on micropore filters before the ee was determined by chiral HPLC as described above.

[Co^{III}(3)(N-Bn-Thr)]: $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.91$ (s, 1H), 7.53 (s, 1H), 7.46 (s, 1H), 7.32-7.16 (m, 5H), 7.14 (s, 1H), 6.60 (s, 1H), 6.58 (s, 1H), 4.81-4.60 (m, 2H), 4.33-4.18 (m, 2H), 3.40-3.34 (m, 2H), 3.15-3.03 (m, 2H), 2.86 (d, $J = 8.4$ Hz, 1H), 2.45-2.35 (m, 1H), 2.00-1.81 (m, 3H), 1.60-1.52 (m, 3H), 1.55 (s, 9H), 1.42 (s, 9H), 1.37 (s, 9H), 1.19 (s, 9H), 0.72 ppm (d, $J = 4.4$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 182.7, 165.4, 163.7, 163.6, 161.0, 145.4, 141.7, 138.5, 137.3, 135.6, 130.9, 130.4, 130.2, 129.8, 129.2, 126.1, 122.9, 118.0, 76.0, 71.3, 68.8, 67.8, 57.1, 36.5, 36.4, 32.1, 31.5, 30.5, 30.3, 29.8, 25.3, 24.5, 20.0 ppm; FT-IR (Nujol): $\nu = 3367, 2918, 2723, 1655, 1631, 1574, 1544, 1526, 1406, 1270, 1256, 1208, 1168, 1128, 1098, 1056, 1024, 987, 932, 915$ cm$^{-1}$; HRMS (ESI): calcd. for C$_{46}$H$_{64}$N$_3$O$_4$CoNa 834.4227 [$M^+Na]^+$; found: 834.4259.

Elemental analysis calcd (%) for C$_{46}$H$_{64}$N$_3$O$_4$Co (M$_W$ = 811.99): C 69.52, H 8.19, N 5.17; found: C 69.21, H 8.21, N 4.87.

**Extraction of N-Benzylvaline and N-Benzyleucine Using Cobalt Complex [Co^{III}(3)(OAc)] (Method A):** To a solution of [Co^{III}(3)(OAc)] (0.091 g, 0.150 mmol) in dichloromethane (20 mL) at 10 °C in a 50 mL round-bottom flask, was added H$_2$O (15 mL) and racemic N-Bn-amino acid (2 eq, 0.300 mmol). The biphasic mixture was stirred vigorously for 24 h at 10 °C, then transferred to a separating funnel, the organic phase removed and the aqueous phase washed once with dichloromethane (10 mL). The combined dichloromethane extracts were washed once with H$_2$O (10
mL) before volatiles were removed under reduced pressure to leave the ternary complexes [Co\(^{III}\)(3)(N-Bn-AA)] as green powders. The aqueous phases were combined and an aliquot removed which was filtered on micropore filters before the ee was determined by chiral HPLC as described above. The aqueous phase was evaporated to leave the N-Bn-amino acid as a white powder.

\[\text{[Co}^{III}\text{(3)(N-Bn-Val)]:} \text{ Yield: 0.120 g (98%).} \]

\( \text{\textsuperscript{1}H NMR (400 MHz, CDCl}_3\text{):} \delta = 7.92 \text{ (s, 1H), 7.58 (s, 1H), 7.44 (d, } J = 2.5 \text{ Hz, 1H), 7.35-7.25 (m, 5H), 7.12 (d, } J = 2.5 \text{ Hz, 1H), 6.62 (s, 1H), 6.60 (s, 1H), 4.67 (dd, } J_1 = 11.7 \text{ Hz, } J_2 = 13.6 \text{ Hz, 1H), 4.34-4.25 (m, 2H), 4.25 (d, } J = 13.6 \text{ Hz, 1H), 3.23-3.20 (m, 1H), 3.16-3.11 (m, 1H), 2.90 (d, } J = 9.5 \text{ Hz, 1H), 2.43-2.38 (m, 1H), 2.06-1.88 (m, 3H), 1.61-1.52 (m, 3H), 1.54 (s, 9H), 1.43 (s, 9H), 1.36 (s, 9H), 1.19 (s, 9H), 1.13-1.04 (m, 1H), 0.66 (d, } J = 6.9 \text{ Hz, 3H), 0.59 ppm (d, } J = 6.9 \text{ Hz, 3H);} \text{ \textsuperscript{13}C NMR (100 MHz, CDCl}_3\text{):} \delta = 181.3, 164.7, 163.5, 163.0, 160.0, 144.9, 141.0, 137.7, 137.0, 134.8, 130.2, 129.8, 129.7, 129.6, 129.0, 128.3, 125.2, 121.8, 117.5, 75.4, 70.7, 69.4, 56.7, 35.9, 35.7, 34.1, 33.8, 31.5, 30.9, 29.9, 29.6, 29.1, 24.7, 24.1, 20.0, 17.3 ppm; FT-IR (Nujol): \nu = 2923, 2853, 1655, 1635, 1617, 1545, 1525, 1407, 1319, 1257, 1201, 1169, 1096, 1025, 988, 933, 913 \text{ cm}^{-1}; \text{ HRMS (ESI): calcd. for C}_{48}H_{68}N_3O_4CoNa 832.4434 \text{ [M+Na]}^+; \text{ found: 832.4419. Elemental analysis calcd (%) for C}_{48}H_{68}N_3O_4Co (M}_W = 810.02): C 71.17, H 8.46, N 5.18; found: C 70.85, H 8.53, N 4.97.}

\[\text{[Co}^{III}\text{(3)(N-Bn-Leu)]:} \text{ Yield: 0.122 g (99%).} \]

\( \text{\textsuperscript{1}H NMR (400 MHz, CDCl}_3\text{):} \delta = 7.96 \text{ (s, 1H), 7.56 (s, 1H), 7.45 (d, } J = 2.4 \text{ Hz, 1H), 7.35 (d, } J = 2.8 \text{ Hz, 1H), 7.33-7.19 (m, 4H), 7.14 (d, } J = 2.4 \text{ Hz, 1H), 6.62 (s, 1H), 6.60 (s, 1H), 4.67-4.61 (m, 2H), 4.34-4.29 (m, 1H), 4.29-4.19 (m, 1H), 3.31-3.27 (m, 1H), 3.18-3.12 (m, 1H), 2.92 (d, } J = 10.4 \text{ Hz, 1H), 2.44-2.39 (m, 1H), 2.06-1.70 (m, 5H), 1.65-1.52 (m, 3H), 1.54 (s, 9H), 1.43 (s, 9H), 1.35 (s, 9H), 1.19 (s, 9H), 1.03-0.97 (m, 1H), 0.63 (d, } J = 6.4 \text{ Hz, 3H), 0.31 ppm (d, } J = 6.4 \text{ Hz, 3H);} \text{ \textsuperscript{13}C NMR (100 MHz, CDCl}_3\text{):} \delta = 183.7, 165.5, 163.9, 163.8, 160.7, 145.7, 141.8, 138.4, 137.2, 135.5, 130.8, 130.4, 130.2, 129.7, 128.9, 125.7, 122.7, 118.2, 75.9, 71.4, 62.8, 57.0, 44.0, 36.5, 36.4, 32.1, 31.6, 30.5, 30.3, 29.8, 25.3, 24.9, 24.6, 22.9, 22.7 ppm; FT-IR (Nujol): \nu = 3253, 2924, 2726, 1660, 1640, 1544, 1523, 1406, 1269, 1256, 1203, 1168, 1095, 1028, 983, 953, 931 \text{ cm}^{-1}; \text{ HRMS (ESI): calcd. for C}_{49}H_{70}N_3O_4CoNa 846.4591 \text{ [M+Na]}^+; \text{ found: 846.4592. Elemental analysis calcd (%) for C}_{49}H_{70}N_3O_4Co (M}_W = 824.06): C 71.42, H 8.56, N 5.10; found: C 71.10, H 8.43, N 4.91.}

**Extraction of N-Benzylphenylalanine Using Cobalt Complex [Co\(^{III}\)(3)(OAc)] (Method B):** To a solution of [Co\(^{III}\)(3)(OAc)] (0.090 g, 0.150 mmol) in dichloromethane (20 mL) at 10 °C in a 50
mL round-bottom flask, was added H₂O (15 mL) and racemic N-benzylphenylalanine (0.076 g, 2 eq, 0.300 mmol). The mixture was stirred vigorously for 24 h at 10 °C, then transferred to a separating funnel, the organic phase removed and the aqueous phase washed once with dichloromethane (10 mL). The combined dichloromethane extracts were washed once with H₂O (10 mL) before volatiles were removed under reduced pressure to leave the ternary complex [Co(III)(3)(N-Bn-Phe)]. Yield: 0.127 g (99%). The aqueous phase was filtered to recover N-benzylphenylalanine as a white powder which was washed with dichloromethane (5 mL), water (5 mL) and acetone (5 mL) then dried in vacuo. Yield: 0.037 g (99%). The ee was determined by chiral HPLC analysis as described above.

[Co(III)(3)(N-Bn-Phe)]: ¹H NMR (400 MHz, CDCl₃): δ = 7.82 (s, 1H), 7.44-7.25 (m, 8H), 7.10 (s, 1H), 7.06 (s, 1H), 6.84 (d, J = 7.2 Hz, 2H), 6.73 (d, J = 6.0 Hz, 2H), 6.34 (s, 1H), 4.83-4.75 (m, 1H), 4.40-4.37 (m, 1H), 4.04 (d, J = 14.0 Hz, 1H), 3.80 (s, 2H), 3.21 (d, J = 13.6 Hz, 1H), 2.87-2.79 (m, 2H), 2.06-1.88 (m, 6H), 1.63-1.52 (m, 3H), 1.53 (s, 9H), 1.47 (s, 9H), 1.36 (s, 9H), 1.15 ppm (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ = 182.7, 165.0, 163.8, 163.6, 159.5, 145.3, 141.6, 137.9, 137.1, 135.5, 132.6, 131.6, 130.7, 130.7, 130.5, 129.9, 129.7, 129.4, 128.9, 127.8, 126.6, 124.4, 122.3, 118.3, 76.0, 70.7, 56.9, 38.1, 36.4, 34.7, 34.4, 32.3, 32.2, 31.4, 30.6, 30.3, 29.8, 25.4, 24.7 ppm; FT-IR (Nujol): ν = 2923, 2853, 1658, 1644, 1621, 1574, 1567, 1546, 1523, 1406, 1406, 1256, 1200, 1168, 1124, 1096, 1017, 978, 913 cm⁻¹; HRMS (ESI): calcd. for C₅₂H₆₈N₃O₄CoNa 880.4434 [M+Na]⁺; found: 880.4411. Elemental analysis calcd (%) for C₅₂H₆₈N₃O₄Co (Mₚ = 858.06): C 72.79, H 7.99, N 4.90; found: C 72.40, H 7.80, N 4.61.

Resolution of N-Benzyl Amino Acids Using Cobalt Complex [Co(III)(3)(OAc)] (Method C): To a stirred, cooled (10 °C) solution of [Co(III)(3)(OAc)] (0.045 g, 0.075 mmol) in dichloromethane (10 mL) was added the powdered racemic N-Bn-amino acid (2 eq, 0.150 mmol). The mixture was stirred at 10 °C for 24 h, then filtered to recover uncomplexed N-Bn-amino acid. After washing with dichloromethane (5 mL), the ee of this material was determined by chiral HPLC as described above. The filtrate was concentrated under reduced pressure to leave the complexes [Co(III)(3)(N-Bn-AA)] as dark green powders.

General Procedure for the Reductive Counter-Extraction of Complexes [Co(III)(3)(N-Bn-AA)]: The following procedure for the reductive counter-extraction of complex [Co(III)(3)(N-Bn-Ala)] is typical: To a solution of [Co(III)(3)(N-Bn-Ala)] (0.050 g, 0.064 mmol) in dichloromethane (20 mL) was added a solution of sodium dithionite (0.110 g, 0.640 mmol, 10 equiv) in H₂O (10 mL). The
mixture was stirred vigorously for 5 h (or until the dichloromethane phase became bright red). The organic phase was separated, washed with H$_2$O (5 mL) and then volatiles were removed under reduced pressure. The resulting residue was suspended in MeOH (5 mL) and filtered to collect cobalt(II) complex [Co$^{II}$(3)] as a red powder. Yield: 0.029 g (78%). HRMS (ESI): calcd. for C$_{36}$H$_{52}$N$_2$O$_2$Co 603.3360 [M$^+$]; found: 603.3332. Elemental analysis calcd (%) for C$_{36}$H$_{52}$N$_2$O$_2$Co (M$_W$ = 603.76): C 71.62, H 8.68, N 4.64; found: C 71.41, H 8.71, N 4.61. An aliquot was removed from the aqueous phase, filtered on micropore filters and the ee of the counter-extracted N-benzylalanine was determined by chiral HPLC as described above (ee 93.5 %).
Determination of Enantiomeric Excesses by HPLC: N-Bn-Ala

HPLC conditions: Chirobiotic R (50 x 4.6 mm) column (9:1 H₂O:CH₃CN), 1.0 mL/min, (S) enantiomer $t_R = 1.141$ min, (R) enantiomer $t_R = 2.754$ min.

![HPLC trace of the aqueous phase following extraction of N-Bn-Ala with [Co^{III}(3)(OAc)] (93.0% ee).](image1.png)
Determination of Enantiomeric Excesses by HPLC: N-Bn-Thr

HPLC conditions: Chirobiotic R (50 x 4.6 mm) column (H₂O), 0.5 mL/min, (S) enantiomer tᵣ = 3.331 min, (R) enantiomer tᵣ = 4.008 min.

Figure 2a. HPLC trace of the aqueous phase following extraction of N-Bn-Thr with [Co³⁺(3)(OAc)]: 0.94 equiv extracted into the organic phase; >90% ee N-Bn-Thr remained in the aqueous phase.

Figure 2b. HPLC trace of the aqueous phase following counter-extraction of [Co³⁺(3)(N-Bn-Thr)] with sodium dithionite (96.3% ee).
**Determination of Enantiomeric Excesses by HPLC: N-Bn-Val**

HPLC conditions: Chirobiotic R (50 x 4.6 mm) column (9:1 H₂O:CH₃CN), 1.0 mL/min, (S) enantiomer $t_R = 1.175$ min, (R) enantiomer $t_R = 2.199$ min.

**Figure 3.** HPLC trace of the aqueous phase following extraction of N-Bn-Val with [Co$^{III}$(3)(OAc)] (90.1% ee).
**Determination of Enantiomeric Excesses by HPLC: N-Bn-Phe**

HPLC conditions: Chirobiotic R (50 x 4.6 mm) column (9:1 H₂O:CH₃CN), 1.0 mL/min, (S) enantiomer $t_R = 1.824$ min, (R) enantiomer $t_R = 2.489$ min.

**Figure 4.** HPLC trace of the aqueous phase following extraction of N-Bn-Phe with [Co<sup>III</sup>(3)(OAc)] (93.3% ee).
Determination of Enantiomeric Excesses by HPLC: N-Bn-Leu

HPLC conditions: Chirobiotic R (50 x 4.6 mm) column (9:1 H2O:CH3CN), 1.0 mL/min, (S) enantiomer t_R = 1.304 min, (R) enantiomer t_R = 1.909 min.

Figure 5. HPLC trace of the aqueous phase following extraction of N-Bn-Leu with [Co^{III}(3)(OAc)] (99.0% ee).