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Peptide-tethered monodentate and chelating histidylidene metal complexes: synthesis and application in catalytic hydrosilylation

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1. General comments

Compound **1**,[S1] **8**,[S2] **12**,[S3] **13**,[S3] **14**,[S2] (*S*)-Ph-binepine,[S4] Ag_2O,[S5] $[NEt_3Me]I$,[S6] $[Ir(Cp^*)Cl_2]_2$[S7] and $[Rh(cod)Cl]_2$[S8] were prepared according to literature procedures. All other reagents are commercially available and were used as received. Unless specified otherwise, NMR spectra were recorded at room temperature on Varian spectrometers at the frequencies indicated. Chemical shifts (δ in ppm, coupling constants J in Hz) were referenced to residual solvent resonances. Assignments are based on homo- and heteronuclear shift correlation spectroscopy and comparison with related compounds. Elemental analyses were performed by the Microanalytical Laboratory at University College Dublin (Ireland).

Circular Dichroism spectra were obtained at room temperature on a Jasco J-815 dichrograph. Data were collected from 260 to 190 nm, at 0.2 nm intervals with a 20 nm min^{-1} scan speed, a 2 nm bandwidth and a 16 s response. 1 cm path length quartz cells were used for the

measurements. CD intensities are expressed as mean residue ellipticities (deg cm^2 $dmol^{-1}$ res^{-1}), calculated by dividing the total molar ellipticities by the number of amino acids in the molecule. Stock solutions of the three samples at concentration in the range 25.0–30.0 mM were prepared in acetonitrile or in trifluoroethanol, and diluted to 25.0–30.0 μM for the CD analysis.

2. Synthesis of numbered compounds

Synthesis of 2

To a solution of **1** (7.49 g, 26.4 mmol) in MeOH (200 mL) was added a 3 M solution of HCl in MeOH (27.3 mL, 81.9 mmol) and the reaction mixture was stirred at reflux for 15 h. The volatiles were removed under reduced pressure in a well-ventilated fume hood. The residue was dissolve in a small volume of hot MeOH, precipitated with Et_2O, filtered and washed with Et_2O to give the product as a white solid (6.01 g, 89%).

^{1}H NMR (500 MHz, CD_3OD) δ 8.94 (s, 1H, $C_\varepsilon H$), 7.59 (s, 1H, $C_\delta H$), 4.49 (t, $^3J_{HH}$ = 6.9 Hz, 1H, $C_\alpha H$), 3.96 (s, 3H, NCH_3), 3.88 (s, 3H, $COOCH_3$), 3.49 (dd, $^2J_{HH}$ = 15.8 Hz, $^3J_{HH}$ = 6.9 Hz, 1H $C_\beta H_2$), 3.41 (dd, $^2J_{HH}$ = 15.8 Hz, $^3J_{HH}$ = 6.9 Hz, 1H $C_\beta H_2$), NH_2 not resolved; $^{13}C\{^1H\}$NMR (125 MHz, CD_3OD) δ 169.3 (C=O), 137.4 ($C_\varepsilon H$), 128.7 (C_γ), 123.8 ($C_\delta H$), 54.2 ($COOCH_3$), 53.0 ($C_\alpha H$), 36.5 (NCH_3), 26.5 ($C_\beta H_2$); Elem. anal. calcd. for $C_8H_{15}Cl_2N_3O_2$ (256.13): C 37.51, H 5.90, N 16.41; found: C 37.52, H 5.83, N 16.23; $[\alpha]_D^{20}$ = +10° (c = 1 in MeOH).

Synthesis of 3a

Following a procedure as described for Boc–Ala–His(Me)–OMe, **3a** was obtained from a mixture of Boc–Ala–OH (850 mg, 4.49 mmol), H–Ala–His(Me)–OMe·2HCl (1.47 mg, 4.49

mmol), HATU (1.71 g, 4.49 mmol) and DIEA (2.20 mL, 13.5 mmol) in dry THF (100 mL), after purification by flash chromatography (SiO_2, CH_2Cl_2/MeOH 92:8), as a white solid (1.64 g, 86%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, $^3J_{HH}$ = 7.6 Hz, 1H, $N_{His}H$), 7.31 (s, 1H, $C_\varepsilon H$), 7.19 (br, 1H, $N_{Ala}H$), 6.64 (s, 1H, $C_\delta H$), 5.45 (br d, $^3J_{HH}$ = 6.0 Hz, 1H, $N_{Ala}H$), 4.70–4.64 (m, 1H, $C_\alpha H$), 4.45 (quintet, $^3J_{HH}$ = 7.1 Hz, 1H, C*H*CH_3), 4.14 (br, 1H, C*H*CH_3), 3.60 (s, 3H, $COOCH_3$), 3.56 (NCH_3), 3.00 (dd, $^2J_{HH}$ = 15.0 Hz, $^3J_{HH}$ = 5.9 Hz, 1H, $C_\beta H_2$), 2.94 (dd, $^2J_{HH}$ = 15.0 Hz, $^3J_{HH}$ = 5.0 Hz, 1H, $C_\beta H_2$), 1.36 (s, 9H, $C(CH_3)_3$), 1.30 (d, $^3J_{HH}$ = 7.1 Hz, 3H, CHC*H*$_3$), 1.26 (d, $^3J_{HH}$ = 7.0 Hz, 3H, CHC*H*$_3$); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 172.5 (C=O), 172.1 (C=O), 171.6 (C=O), 155.4 (NHCOO), 137.5 ($C_\varepsilon H$), 137.0 (C_γ), 118.1 ($C_\delta H$), 79.8 (*C*$(CH_3)_3$), 52.4 ($C_\alpha H$), 52.3 ($COOCH_3$), 50.1 (*C*HCH_3), 48.8 (*C*HCH_3), 33.4 (NCH_3), 29.3 ($C_\beta H_2$), 28.3 (C(*C*H$_3$)$_3$), 18.6 (CH*C*H$_3$), 18.5 (CH*C*H$_3$); *m/z* (HRMS, ESI^-) found 424.2181 ($[M–H^+]^-$), $C_{19}H_{30}N_5O_6$ requires 424.2196.

Synthesis of 3b

Following a procedure as described for Boc–Ala–His(Me)–OMe, **3b** was obtained from a mixture of Boc–Ala–Ala–Ala–OH (200 mg, 0.60 mmol), **2** (155 mg, 0.60 mmol), HATU (229 mg, 0.60 mmol) and DIEA (0.30 mL, 1.81 mmol) in dry THF (20 mL), after purification by flash chromatography (SiO_2, CH_2Cl_2/MeOH 9:1), as a white solid (239 mg, 80%).

^{1}H NMR (400 MHz, CD_3OD) δ 7.70 (s, 1H, $C_\varepsilon H$), 6.99 (s, 1H, $C_\delta H$), 4.67–4.64 (m, 1H, $C_\alpha H$), 4.36–4.26 (m, 2H, 2 × C*H*CH_3), 4.04 (q, $^3J_{HH}$ = 7.2 Hz, 1H, C*H*CH_3), 3.70 (br, 6H, $COOCH_3$ + NCH_3), 3.14–2.98 (m, 2H, $C_\beta H_2$), 1.45 (s, 9H, $C(CH_3)_3$), 1.36 (d, $^3J_{HH}$ = 6.8 Hz, 3H, CHC*H*$_3$), 1.35 (d, $^3J_{HH}$ = 6.9 Hz, 3H, CHC*H*$_3$), 1.31 (d, $^3J_{HH}$ = 7.2 Hz, 3H, CHC*H*$_3$), NH's not resolved; ^{13}C{^{1}H}NMR (100 MHz, CD_3OD) δ 176.2 (C=O), 174.7 (C=O), 174.6 (C=O), 172.9 (C=O), 158.0 (NHCOO), 138.4 ($C_\varepsilon H$), 136.8 (C_γ), 120.4 ($C_\delta H$), 80.8 (*C*$(CH_3)_3$), 53.7

($C_\alpha H$), 52.8 ($COOCH_3$), 52.2 ($CHCH_3$), 50.7 ($CHCH_3$), 50.3 ($CHCH_3$), 34.1 (NCH_3), 30.4 ($C_\beta H_2$), 28.7 ($C(CH_3)_3$), 17.9 (2 × $CHCH_3$), 17.7 ($CHCH_3$); *m/z* (HRMS, ESI^+) found 497.2735 ($[M + H^+]^+$), $C_{22}H_{37}N_6O_7$ requires 497.2724.

Synthesis of 4a

To a solution of **3a** (1.60 g, 3.76 mmol) in acetonitrile (30 mL) was added MeI (0.47 mL, 7.51 mmol) and the reaction mixture was stirred at 40 °C for 14 h. The volatiles were removed under reduced pressure in a well-ventilated fume hood and the residue was purified by flash chromatography (SiO_2, CH_2Cl_2/MeOH 95:5) to give the desired product as a hygroscopic pale yellow solid (1.77 g, 83%).

^{1}H NMR (400 MHz, CD_3OD) δ 8.85 ($C_\varepsilon H$), 7.39 ($C_\delta H$), 4.78 (dd, $^3J_{HH}$ = 9.8, 4.3 Hz, 1H, $C_\alpha H$), 4.24 (q, $^3J_{HH}$ = 7.2 Hz, 1H, $CHCH_3$), 4.03 (q, $^3J_{HH}$ = 7.2 Hz, 1H, $CHCH_3$), 3.91 (s, 3H, NCH_3), 3.88 (s, 3H, NCH_3), 3.78 (s, 3H, $COOCH_3$), 3.36 (dd, $^2J_{HH}$ = 16.0 Hz, $^3J_{HH}$ = 4.3 Hz, 1H, $C_\beta H_2$), 3.18 (dd, $^2J_{HH}$ = 16.0 Hz, $^3J_{HH}$ = 9.8 Hz, 1H, $C_\beta H_2$), 1.44 (s, 9H, $C(CH_3)_3$), 1.36 (d, $^3J_{HH}$ = 7.2 Hz, 3H, $CHCH_3$), 1.30 (d, $^3J_{HH}$ = 7.2 Hz, 3H, $CHCH_3$), NH's not resolved; $^{13}C\{^1H\}$NMR (100 MHz, CD_3OD) δ 175.6 (C=O), 175.2 (C=O), 171.7 ($COOCH_3$), 157.7 (NHCOO), 138.1 ($C_\varepsilon H$), 132.6 (C_γ), 123.5 ($C_\delta H$), 80.6 ($C(CH_3)_3$), 53.4 ($COOCH_3$), 51.6 ($C_\alpha H$), 51.5 ($CHCH_3$), 50.4 ($CHCH_3$), 36.7 (NCH_3), 34.4 (NCH_3), 28.7 ($C(CH_3)_3$), 26.2 ($C_\beta H_2$), 18.2 ($CHCH_3$), 17.6 ($CHCH_3$); *m/z* (HRMS, ESI^+) found 440.2513 ($[M–I^-]^+$), $C_{20}H_{34}N_5O_6$ requires 440.2509; $[\alpha]_D^{20}$ = −43° (c = 1 in MeOH).

Synthesis of 4b

Following a procedure as described for **4a**, **4b** was obtained from a mixture of **3b** (400 mg, 0.81 mmol) and MeI (0.10 mL, 1.61 mmol) in MeCN (8 mL), after purification by flash chromatography (SiO_2, CH_2Cl_2/MeOH 95:5), as a pale yellow solid (488 mg, 95%).

^{1}H NMR (500 MHz, CD_3OD) δ 8.85 (s, 1H, $C_\varepsilon H$), 7.39 (s, 1H, $C_\delta H$), 4.77–4.74 (m, 1H, $C_\alpha H$), 4.24 (q, $^{3}J_{HH}$ = 7.2 Hz, 2H, 2 × C*H*CH_3), 4.05–3.97 (m, 1H, C*H*CH_3), 3.91 (s, 3H, NCH_3), 3.88 (s, 3H, NCH_3), 3.78 (s, 3H, $COOCH_3$), 3.36 (dd, $^{2}J_{HH}$ = 16.0 Hz, $^{3}J_{HH}$ = 4.3 Hz, 1H, $C_\beta H_2$), 3.20 (dd, $^{2}J_{HH}$ = 16.0 Hz, $^{3}J_{HH}$ = 10.0 Hz, 1H, $C_\beta H_2$), 1.46 (s, 9H, $C(CH_3)_3$), 1.38 (d, $^{3}J_{HH}$ = 7.2 Hz, CHC*H*$_3$), 1.37 (d, $^{3}J_{HH}$ = 7.3 Hz, CHC*H*$_3$), 1.33 (d, $^{3}J_{HH}$ = 7.2 Hz, CHC*H*$_3$), NH's not resolved; ^{13}C{^{1}H}NMR (125 MHz, CD_3OD) δ 176.4 (C=O), 175.1 (C=O), 174.7 (C=O), 171.7 (C=O), 158.1 (NHCOO), 138.1 ($C_\varepsilon H$), 132.7 (C_γ), 123.5 ($C_\delta H$), 80.9 (*C*(CH_3)), 53.3 ($COOCH_3$), 52.4 (C*H*CH_3), 51.7 ($C_\alpha H$), 50.9 (C*H*CH_3), 5.6 (C*H*CH_3), 36.7 (NCH_3), 34.4 (NCH_3), 28.7 ($C(CH_3)_3$), 26.2 ($C_\beta H_2$), 17.9 (CH*C*H_3), 17.6 (2 × CH*C*H_3); *m/z* (HRMS, ESI^+) found 511.2874 ($[M–I^-]^+$), $C_{23}H_{39}N_6O_7$ requires 511.2880; $[\alpha]_D^{20}$ = −37° (c = 1 in MeOH).

Synthesis of 5a

4a (131 mg, 0.231 mmol) was dissolved in dry CH_2Cl_2 (5 mL) in a Schlenk tube under N_2. Ag_2O (28.0 mg, 0.120 mmol) was added and the mixture was stirred at rt for 1 h in the absence of light. $[Ir(Cp^*)Cl_2]_2$ (92.0 mg, 0.115 mmol) was added and the solution was stirred for a further 1 h. The formed precipitate was removed by centrifugation and the supernatant was concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, CH_2Cl_2/MeOH, 9:1), followed by precipitation (3 × CH_2Cl_2/pentane) to give the desired compound as a dark orange solid (157 mg, 81%).

NMR spectroscopy showed two sets of signals in a 2:1 integral ratio.

Major isomer: ^{1}H NMR (500 MHz, $CDCl_3$, 50 °C) δ 7.29 (d, $^{3}J_{HH}$ = 8.7 Hz, 1H, $N_{His}H$), 7.06 (d, $^{3}J_{HH}$ = 7.2 Hz, 1H, $N_{Ala}H$), 6.92 (s, 1H, $C_\delta H$), 5.19 (d, $^{3}J_{HH}$ = 6.6 Hz, 1H, $N_{Ala}H$), 4.73–4.70 (m, 1H, $C_\alpha H$), 4.42 (quintet, $^{3}J_{HH}$ = 7.2 Hz, 1H, C*H*CH_3), 4.01 (br, 1H, C*H*CH_3), 3.82 (br, 3H, NCH_3), 3.80 (br, 3H, NCH_3), 3.71 (br, 3H, $COOCH_3$), 3.11–3.05 (m, 1H, $C_\beta H_2$), 2.92–2.87 (m, 1H, $C_\beta H_2$), 1.57 (s, 15H, Cp–CH_3), 1.40 (s, 9H, $C(CH_3)_3$), 1.35–1.28 (m, 6H, 2 ×

CHC*H*$_3$); ^{13}C{^{1}H}NMR (125 MHz, $CDCl_3$, 50 °C) δ 172.9 (C=O), 172.6 (C=O), 171.0 (*C*OOCH$_3$), 156.9 (C_ε–Rh), 155.5 (NHCOO), 130.2 (C_γ), 122.6 (C_δH), 88.9 (C_{Cp*}), 80.0 (*C*(CH$_3$)$_3$), 52.7 (COO*C*H$_3$), 50.6 (*C*HCH$_3$), 50.3 (C_αH), 49.24 (*C*HCH$_3$), 38.4 (NCH$_3$), 35.6 (NCH$_3$), 28.5 (C(*C*H$_3$)$_3$), 27.2 ($C_\beta H_2$), 18.6 (CH*C*H$_3$), 18.0 (CH*C*H$_3$), 9.2 (Cp–*C*H$_3$).

Minor isomer: ^{1}H NMR (500 MHz, $CDCl_3$, 50 °C) δ 7.19 (br, 1H, N_{His}H), 6.99 (br d, $^3J_{HH}$ = 7.2 Hz, 1H, N_{Ala}H), 6.77 (s, 1H, C_δH), 5.19 (d, $^3J_{HH}$ = 6.6 Hz, 1H, N_{Ala}H), 4.60 (br, 1H, C_αH), 4.42 (quintet, $^3J_{HH}$ = 7.2 Hz, 1H, C*H*CH$_3$), 4.01 (br, 1H, C*H*CH$_3$), 3.82 (br, 3H, NCH$_3$), 3.80 (br, 3H, NCH$_3$), 3.71 (br, 3H, COOCH$_3$), 3.07 (br, 2H, $C_\beta H_2$), 1.57 (s, 15H, Cp–CH$_3$), 1.40 (s, 9H, C(CH$_3$)$_3$), 1.35–1.28 (m, 6H, 2 × CHC*H*$_3$); ^{13}C{^{1}H}NMR (125 MHz, $CDCl_3$, 50 °C) δ 173.1 (C=O), 172.6 (C=O), 170.9 (*C*OOCH$_3$), 157.2 (C_ε–Rh), 155.5 (NHCOO), 130.3 (C_γ), 122.0 (C_δH), 88.9 (C_{Cp*}), 80.0 (*C*(CH$_3$)$_3$), 52.6 (COO*C*H$_3$), 51.8 (C_αH), 50.6 (*C*HCH$_3$), 49.18 (*C*HCH$_3$), 38.5 (NCH$_3$), 35.8 (NCH$_3$), 28.5 (C(*C*H$_3$)$_3$), 26.6 ($C_\beta H_2$), 18.4 (CH*C*H$_3$), 17.7 (CH*C*H$_3$), 9.2 (Cp–*C*H$_3$).

m/z (HRMS, ESI$^+$) found 766.3185 ([M–2Cl$^-$–H$^+$]$^+$), $C_{30}H_{47}N_5O_6Ir$ requires 766.3156.

Synthesis of 6a

4a (200 mg, 0.352 mmol) was dissolved in dry CH_2Cl_2 (7 mL) in a Schlenk tube under N_2. Ag_2O (42.0 mg, 0.183 mmol) was added and the mixture was stirred at rt for 1 h in the absence of light. [Rh(cod)Cl]$_2$ (87.0 mg, 0.176 mmol) was added and the solution was stirred for a further 1 h. The mixture was filtered through Celite® and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (SiO_2, CH_2Cl_2/MeOH, 92:8) to give the desired compound as a yellow solid (165 mg, 68%).

NMR spectroscopy showed two sets of signals in a 1:0.9 integral ratio.

Major isomer: ^{1}H NMR (500 MHz, $CDCl_3$, 50 °C) δ 7.10–6.81 (m, 2H, 2 × NH), 6.56 (s, 1H, C_δH), 5.14 (d, $^3J_{HH}$ = 7.0 Hz, 1H, NH), 4.95 (br, 2H, 2 × C_{cod}H), 4.69–4.62 (m, 1H, C_αH),

4.35 (q, $^{3}J_{HH}$ = 7.1 Hz, 1H, C*H*CH$_3$), 4.06 (q, $^{3}J_{HH}$ = 7.0 Hz, 1H, C*H*CH$_3$), 3.95 (s, 3H, NCH$_3$), 3.94 (s, 3H, NCH$_3$), 3.67 (s, 3H, COOCH$_3$), 3.31–3.23 (m, 2H, 2 × C$_{cod}$H), 3.05–3.01 (m, 1H, C$_\beta$H$_2$), 2.96 (dd, $^{2}J_{HH}$ = 15.8 Hz, $^{3}J_{HH}$ = 5.6 Hz, 1H, C$_\beta$H$_2$), 2.43–2.31 (m, 4H, 2 × C$_{cod}$H$_2$), 1.95–1.86 (m, 4H, 2 × C$_{cod}$H$_2$), 1.399 (s, 9H, C(CH$_3$)$_3$), 1.31 (d, $^{3}J_{HH}$ = 7.0 Hz, 3H, CHC*H*$_3$), 1.27 (d, $^{3}J_{HH}$ = 7.1 Hz, 3H, CHC*H*$_3$); ^{13}C{^{1}H}NMR (125 MHz, CDCl$_3$, 50 °C) δ 182.9 ($^{1}J_{RhC}$ = 51.0 Hz, C$_\varepsilon$–Rh), 172.9 (C=O), 172.3 (C=O), 171.03 (*C*OOCH$_3$), 155.7 (NHCOO), 129.0 (C$_\gamma$), 120.3 (C$_\delta$H), 98.7–98.4 (2 × C$_{cod}$H), 80.2 (*C*(CH$_3$)$_3$), 68.1–67.6 (2 × C$_{cod}$H), 52.7 (COO*C*H$_3$), 50.8 (C$_\alpha$H), 50.6 (*C*HCH$_3$), 49.0 (*C*HCH$_3$), 37.67 (NCH$_3$), 35.0 (NCH$_3$), 33.2–32.9 (2 × C$_{cod}$H$_2$), 29.0–28.8 (2 × C$_{cod}$H$_2$), 28.41 (C(*C*H$_3$)$_3$), 26.5 (C$_\beta$H$_2$), 18.2 (CH*C*H$_3$), 17.5 (CH*C*H$_3$).

Minor isomer: ^{1}H NMR (500 MHz, CDCl$_3$, 50 °C) δ 7.10–6.81 (m, 2H, 2 × NH), 6.60 (s, 1H, C$_\delta$H), 5.17 (d, $^{3}J_{HH}$ = 7.0 Hz, 1H, NH), 4.95 (br, 2H, 2 × C$_{cod}$H), 4.69–4.62 (m, 1H, C$_\alpha$H), 4.42 (q, $^{3}J_{HH}$ = 7.2 Hz, 1H, C*H*CH$_3$), 4.11 (q, $^{3}J_{HH}$ = 7.0 Hz, 1H, C*H*CH$_3$), 3.97 (s, 3H, NCH$_3$), 3.94 (s, 3H, NCH$_3$), 3.70 (s, 3H, COOCH$_3$), 3.31–3.23 (m, 2H, 2 × C$_{cod}$H), 3.08–3.04 (m, 1H, C$_\beta$H$_2$), 2.86 (dd, $^{2}J_{HH}$ = 15.9 Hz, $^{3}J_{HH}$ = 8.6 Hz, 1H, C$_\beta$H$_2$), 2.43–2.31 (m, 4H, 2 × C$_{cod}$H$_2$), 1.95–1.86 (m, 4H, 2 × C$_{cod}$H$_2$), 1.395 (s, 9H, C(CH$_3$)$_3$), 1.34 (d, $^{3}J_{HH}$ = 7.2 Hz, 3H, CHC*H*$_3$), 1.27 (d, $^{3}J_{HH}$ = 7.0 Hz, 3H, CHC*H*$_3$); ^{13}C{^{1}H}NMR (125 MHz, CDCl$_3$, 50 °C) δ 183.0 ($^{1}J_{RhC}$ = 51.0 Hz, C$_\varepsilon$–Rh), 173.1 (C=O), 172.3 (C=O), 170.96 (*C*OOCH$_3$), 155.5 (NHCOO), 129.1 (C$_\gamma$), 120.6 (C$_\delta$H), 98.7–98.4 (2 × C$_{cod}$H), 80.4 (*C*(CH$_3$)$_3$), 68.1–67.6 (2 × C$_{cod}$H), 52.8 (COO*C*H$_3$), 51.3 (C$_\alpha$H), 50.6 (*C*HCH$_3$), 49.1 (*C*HCH$_3$), 37.70 (NCH$_3$), 35.1 (NCH$_3$), 33.2–32.9 (2 × C$_{cod}$H$_2$), 29.0–28.8 (2 × C$_{cod}$H$_2$), 28.44 (C(*C*H$_3$)$_3$), 27.0 (C$_\beta$H$_2$), 18.5 (CH*C*H$_3$), 17.8 5 (CH*C*H$_3$).

m/z (HRMS, ESI$^+$) found 650.2446 ([M–Cl$^-$]$^+$), C$_{28}$H$_{45}$N$_5$O$_6$Rh requires 650.2425; $[\alpha]_D^{20}$ = −16° (c = 1 in CHCl$_3$).

Synthesis of 6b

Following a procedure as described for **6a**, **6b** was obtained from a mixture of **4b** (165 mg, 0.258 mmol), Ag_2O (31.0 mg, 0.134 mmol) and $[Rh(cod)Cl]_2$ (64.0 mg, 0.129 mmol) in dry CH_2Cl_2 (5 mL), after purification by flash chromatography (SiO_2, CH_2Cl_2/MeOH 92:8), as a yellow solid (137 mg, 70%).

NMR spectroscopy showed two sets of signals in a 1:0.9 integral ratio.

Major isomer: ^{1}H NMR (500 MHz, $CDCl_3$, 50 °C) δ 7.34–6.76 (m, 3H, 3 × NH), 6.62 (s, 1H, $C_\delta H$), 5.38 (br, 1H, NH), 4.91 (br, 2H, 2 × $C_{cod}H$), 4.65–4.60 (m, 1H, $C_\alpha H$), 4.44–4.38 (m, 1H, C*H*CH_3), 4.21–4.16 (m, 1H, C*H*CH_3), 3.97 (s, 3H, NCH_3), 3.88 (s, 3H, NCH_3), 3.68 (s, 3H, $COOCH_3$), 3.68–3.63 (m, 1H, C*H*CH_3), 3.27–3.19 (m, 2H, 2 × $C_{cod}H$), 3.06–2.93 (m, 2H, $C_\beta H_2$), 2.41–2.27 (m, 4H, 2 × $C_{cod}H_2$), 1.92–1.84 (m, 4H, 2 × $C_{cod}H_2$), 1.39 (s, 9H, $C(CH_3)_3$), 1.36–1.27 (m, 9H, 3 × CHC*H*$_3$); ^{13}C{^{1}H}NMR (125 MHz, $CDCl_3$, 50 °C) δ 182.3 ($^1J_{RhC}$ = 51.3 Hz, C_ε–Rh), 174.5 (C=O), 172.6 (C=O), 172.0 (C=O), 171.0 (*C*$OOCH_3$), 156.7 (NHCOO), 129.7 (C_γ), 120.4 ($C_\delta H$), 98.5–98.2 (2 × $C_{cod}H$), 80.8 (*C*$(CH_3)_3$), 68.0–67.7 (2 × $C_{cod}H$), 52.6 (COO*C*H_3), 52.2 (*C*HCH_3), 50.4 (*C*HCH_3), 50.3 ($C_\alpha H$), 49.0 (*C*HCH_3), 37.5 (NCH_3), 34.8 (NCH_3), 33.1–32.9 (2 × $C_{cod}H_2$), 28.9–28.8 (2 × $C_{cod}H_2$), 28.3 (C(*C*$H_3)_3$), 26.8 ($C_\beta H_2$), 17.8–17.2 (3 × CH*C*H_3).

Minor isomer: ^{1}H NMR (500 MHz, $CDCl_3$, 50 °C) δ 7.34–6.76 (m, 3H, 3 × NH), 6.64 (s, 1H, $C_\delta H$), 5.35 (br, 1H, NH), 4.91 (br, 2H, 2 × $C_{cod}H$), 4.60–4.55 (m, 1H, $C_\alpha H$), 4.44–4.38 (m, 1H, C*H*CH_3), 4.21–4.16 (m, 1H, C*H*CH_3), 3.94 (s, 3H, NCH_3), 3.93 (s, 3H, NCH_3), 3.91–3.83 (m, 1H, C*H*CH_3), 3.64 (s, 3H, $COOCH_3$), 3.27–3.19 (m, 2H, 2 × $C_{cod}H$), 3.06–2.93 (m, 2H, $C_\beta H_2$), 2.41–2.27 (m, 4H, 2 × $C_{cod}H_2$), 1.92–1.84 (m, 4H, 2 × $C_{cod}H_2$), 1.38 (s, 9H, $C(CH_3)_3$), 1.36–1.27 (m, 9H, 3 × CHC*H*$_3$); ^{13}C{^{1}H}NMR (125 MHz, $CDCl_3$, 50 °C) δ 182.3 ($^1J_{RhC}$ = 51.3 Hz, C_ε–Rh), 173.9 (C=O), 172.6 (C=O), 172.3 (C=O), 170.9 (*C*$OOCH_3$), 156.2 (NHCOO), 129.4 (C_γ), 120.5 ($C_\delta H$), 98.5–98.2 (2 × $C_{cod}H$), 80.5 (*C*$(CH_3)_3$), 68.0–67.7 (2 × $C_{cod}H$), 52.5

($COOCH_3$), 51.5 ($CHCH_3$), 51.2 ($C_\alpha H$), 50.4 ($CHCH_3$), 49.2 ($CHCH_3$), 37.6 (NCH_3), 35.0 (NCH_3), 33.1–32.9 (2 × $C_{cod}H_2$), 28.9–28.8 (2 × $C_{cod}H_2$), 28.3 ($C(CH_3)_3$), 26.3 ($C_\beta H_2$), 17.8–17.2 (3 × $CHCH_3$).

m/z (HRMS, ESI^+) found 779.2417 ($[M + Na^+]^+$), $C_{31}H_{50}N_6O_7NaClRh$ requires 779.2382.

Synthesis of 7

6a (15.0 mg, 21.8 μmol) was dissolved in CH_2Cl_2 (4 mL). (*S*)-Ph-binepine (9.3 mg, 23.9 μmol) was added, followed by a solution of KPF_6 (40.0 mg, 218 μmol) in H_2O (3 mL). The biphasic mixture was vigorously shaken, the organic layer was removed and the aqueous layer was further extracted with CH_2Cl_2 until colourless. The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by precipitation (3 × CH_2Cl_2/pentane) and the resulting yellow solid was dried under high vacuum (23 mg, 89% yield).

NMR spectroscopy showed two sets of signals in a 1:0.9 integral ratio.

Major isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12–7.07 (m, 18H, 17 × $C_{Ar}H$ + $N_{His}H$), 6.76 (br, 1H, $N_{Ala}H$), 6.63 (s, 1H, $C_\delta H$), 5.19 (br, 1H, $N_{Ala}H$), 4.97–4.58 (m, 3H, 3 × $C_{cod}H$), 4.75–4.67 (m, 1H, $C_\alpha H$), 4.38–4.25 (m, 1H, $CHCH_3$), 4.11–3.98 (m, 1H, $CHCH_3$), 4.05 (s, 3H, NCH_3), 4.05–3.63 (m, 1H, $C_{cod}H$), 3.71 (s, 1H, $COOCH_3$), 3.39, (d, $^2J_{HH}$ = 12.1 Hz, 1H, PCH_2), 3.16–3.05 (m, 1H, PCH_2), 3.09–2.87 (m, 2H, $C_\beta H_2$), 3.03–2.95 (m, 1H, PCH_2), 2.98 (s, 3H, NCH_3), 2.63–2.40 (m, 1H, PCH_2), 2.42–2.13 (m, 8H, 4 × $C_{cod}H_2$), 1.40 (s, 9H, $C(CH_3)_3$), 1.29 (d, $^3J_{HH}$ = 7.0 Hz, 3H, $CHCH_3$), 1.21 (d, $^3J_{HH}$ = 7.3 Hz, 3H, $CHCH_3$); ^{31}P NMR (121 MHz, $CDCl_3$) δ 40.22 (d, $^1J_{RhP}$ = 153 Hz, (*S*)-Ph-binepine), −144.25 (septet, $^1J_{PF}$ = 712 Hz, PF_6).

Minor isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12–7.07 (m, 18H, 17 × $C_{Ar}H$ + $N_{His}H$), 7.02 (s, 1H, $C_\delta H$), 6.66 (br, 1H, $N_{Ala}H$), 5.11 (br, 1H, $N_{Ala}H$), 4.97–4.58 (m, 3H, 3 × $C_{cod}H$), 4.45–

4.38 (m, 1H, $C_{\alpha}H$), 4.38–4.25 (m, 1H, C*H*CH_3), 4.11 (s, 3H, NCH_3), 4.11–3.98 (m, 1H, C*H*CH_3), 4.05–3.63 (m, 1H, $C_{cod}H$), 3.67 (s, 1H, $COOCH_3$), 3.39, (d, $^2J_{HH}$ = 12.1 Hz, 1H, PCH_2), 3.16–3.05 (m, 1H, PCH_2), 3.03–2.95 (m, 1H, PCH_2), 2.80 (s, 3H, NCH_3), 2.63–2.40 (m, 1H, PCH_2), 2.59–2.51 (m, 2H, $C_{\beta}H_2$), 2.42–2.13 (m, 8H, 4 × $C_{cod}H_2$), 1.43 (s, 9H, $C(CH_3)_3$), 1.38 (d, $^3J_{HH}$ = 7.3 Hz, 3H, CHC*H*$_3$), 1.16 (d, $^3J_{HH}$ = 7.0 Hz, 3H, CHC*H*$_3$); ^{31}P NMR (121 MHz, $CDCl_3$) δ 40.01 (d, $^1J_{RhP}$ = 153 Hz, (*S*)-Ph-binepine), −144.25 (septet, $^1J_{PF}$ = 712 Hz, PF_6).

^{19}F NMR (282 MHz, $CDCl_3$, 30 °C) δ −71.88 (d, $^1J_{PF}$ = 712 Hz); *m/z* (HRMS, ESI$^+$) found 1038.3856 ([M–PF_6^-]$^+$), $C_{56}H_{66}N_5O_6PRh$ requires 1038.3806.

Synthesis of 9

A 4 M solution of HCl 1,4-dioxane (23 mL, 92 mmol) was added to **8** (2.33 g, 5.47 mmol) at 0 °C and the reaction mixture was vigorously stirred at rt for 30 h. The volatiles were removed under reduced pressure in a well-ventilated fume hood. The residue was dissolved in a small volume of MeOH and precipitated with Et_2O. After centrifugation, the supernatant was discarded. The brown oil was then dissolved in MeOH and passed through a small pad of ion-exchange resin (Dowex® 1x4-200 ion-exchange resin) and eluted with MeOH. The solvent was removed under reduced pressure and the resulting colourless oil was purified three times by precipitation (MeOH/Et_2O). Finally the product was dried under high vacuum to give a hygroscopic white solid (1.378 g, 93% yield).

^{1}H NMR (500 MHz, CD_3OD) δ 9.01 (s, 1H, $C_{\varepsilon}H$), 7.65 (s, 1H, $C_{\delta}H$), 4.57–4.54 (m, 1H, $C_{\alpha}H$), 3.953 (s, 3H, NCH_3), 3.947 (s, 3H, NCH_3), 3.56 (dd, $^2J_{HH}$ = 16.2 Hz, $^3J_{HH}$ = 6.3 Hz, 1H, $C_{\beta}H_2$), 3.46 (dd, $^2J_{HH}$ = 16.2 Hz, $^3J_{HH}$ = 7.5 Hz, 1H, $C_{\beta}H_2$), NH_2 not resolved; ^{13}C{^{1}H}NMR (125 MHz, CD_3OD) δ 169.3 (C=O), 139.2 ($C_{\varepsilon}H$), 130.4 (C_{γ}), 124.5 ($C_{\delta}H$), 54.3 (COO*C*H_3), 52.3 ($C_{\alpha}H$), 36.7 (NCH_3), 34.5 (NCH_3), 25.1 ($C_{\beta}H_2$); Elem. anal. calcd. for $C_9H_{17}Cl_2N_3O_2$

(270.16): C 40.01, H 6.34, N 15.55; found: C 39.84, H 6.28, N 15.33; $[\alpha]_D^{20}$ = +7° (c = 1 in MeOH).

Synthesis of 10

Boc–Tyr–Ala–Ala–OH (564 mg, 1.33 mmol), **9** (360 mg, 1.33 mmol) and HATU (506 mg, 1.33 mmol) were placed in a dry Schlenk tube under N_2. Dry THF (50 mL) was added at 0 °C and stirring was maintained at 0 °C for 20 min. DIEA (0.66 mL, 4.0 mmol) was added and the reaction mixture was stirred at rt overnight. The volatiles were removed under reduced pressure. The crude product was dissolved in a small volume of MeOH, precipitated with Et_2O and separated by centrifugation (5 ×). The residue was then dissolved in MeOH and passed through a small pad of ion-exchange resin (Dowex 1×4-200 ion-exchange resin) and eluted with MeOH. The product was finally purified by gradient column chromatography (SiO_2, CH_2Cl_2/MeOH 9:1 then 8:2) followed by precipitation (8 × MeOH/Et_2O), thus yielding the title product as a very hygroscopic yellow solid (638 mg, 75%).

^{1}H NMR (500 MHz, CD_3OD) δ 8.79 (s, 1H, $C_\varepsilon H$), 7.37 (s, 1H, $C_\delta H$), 7.06 (d, $^3J_{HH}$ = 8.3 Hz, 2H, 2 × $C_{Ar}H$), 6.72 (d, $^3J_{HH}$ = 8.3 Hz, 2H, 2 × $C_{Ar}H$), 4.80–4.75 (m, 1H, $C_\alpha H$), 4.26–4.16 (m, 3H, 2 × C*H*CH_3 + C*H*CH_2), 3.86 (NCH_3), 3.84 (NCH_3), 3.77 ($COOCH_3$), 3.35–3.31 (m, 1H, $C_\beta H_2$), 3.16 (dd, $^2J_{HH}$ = 16.0 Hz, $^3J_{HH}$ = 10.0 Hz, 1H, $C_\beta H_2$), 3.00 (dd, $^2J_{HH}$ = 13.7 Hz, $^3J_{HH}$ = 5.7 Hz, 1H, CHCH_2), 2.79 (dd, $^2J_{HH}$ = 13.7 Hz, $^3J_{HH}$ = 8.9 Hz, 1H, CHCH_2), 1.39 (s, 9H, $C(CH_3)_3$), 1.37 (d, $^3J_{HH}$ = 7.3 Hz, 3H, CHCH_3), 1.35 (d, $^3J_{HH}$ = 7.4 Hz, 3H, CHCH_3); ^{13}C{^{1}H}NMR (125 MHz, CD_3OD) δ 175.2 (C=O), 174.7 (C=O), 174.5 (C=O), 171.7 (C=O), 157.9 (C_{Ar}), 157.3 (NHCOO), 183.1 ($C_\varepsilon H$), 132.7 (C_γ), 131.3 (2 × $C_{Ar}H$), 128.9 (C_{Ar}), 123.5 ($C_\delta H$), 116.2 (2 × $C_{Ar}H$), 80.9 (*C*$(CH_3)_3$), 58.1 (C*H*CH_2), 53.3 ($COOCH_3$), 51.7 ($C_\alpha H$), 50.7 (*C*HCH_3), 50.6 (*C*HCH_3), 38.1 (CHCH_2), 36.5 (NCH_3), 34.1 (NCH_3), 28.7 ($C(CH_3)_3$), 26.1

($C_\beta H_2$), 17.7 ($CHCH_3$), 17.6 ($CHCH_3$); *m/z* (HRMS, ESI^+) found 603.3135 ($[M–Cl^-]^+$), $C_{29}H_{43}N_6O_8$ requires 603.3142; $[\alpha]_D^{20}$ = −25° (c = 1 in MeOH).

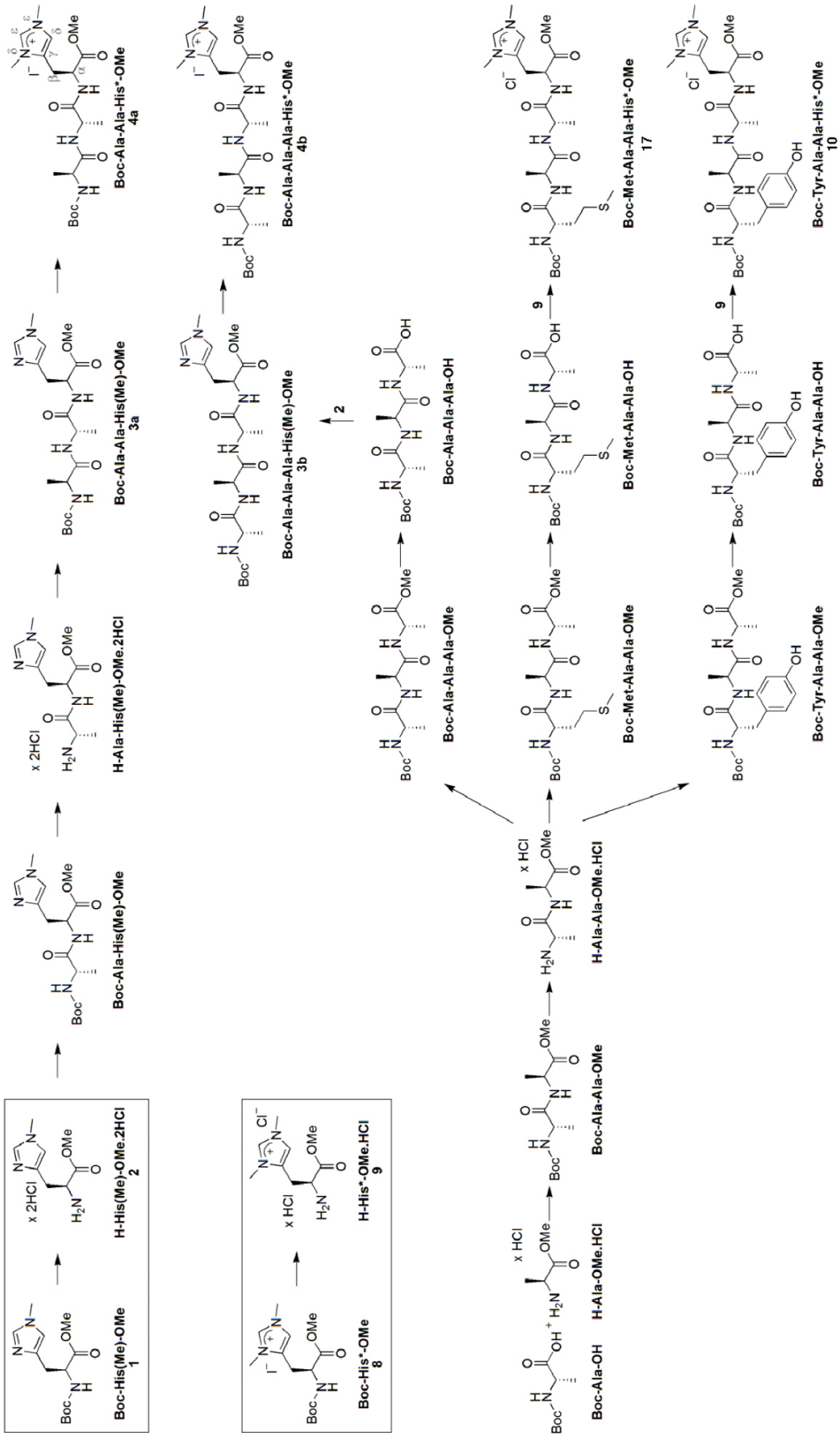
Synthesis of 11

A solution of **10** (246 mg, 385 μmol) dissolved in dry CH_2Cl_2 (10 mL) was placed in a Schlenk tube under N_2. Then [NEt_3Me]I (94 mg, 0.39 mmol) was added, followed by freshly prepared Ag_2O (46 mg, 0.20 mmol) and the mixture was stirred at rt in the absence of light. After 1 h, $[Rh(cod)Cl]_2$ (95 mg, 0.19 mmol) was added and stirring was continued for 1 h. The crude reaction mixture was directly purified by gradient column chromatography (SiO_2, CH_2Cl_2, then CH_2Cl_2/MeOH 9:1). Evaporation of the second fraction to dryness afforded complex **12** as a yellow solid (207 mg, 63%). Two sets of signals were observed in the NMR spectra in a 1:0.2 integral ratio.

Major isomer: ^{1}H NMR (500 MHz, CD_3OD) δ 7.05 (d, $^3J_{HH}$ = 8.4 Hz, 2H, 2 × $C_{Ar}H$), 6.87 (s, 1H, $C_\delta H$), 6.71 (d, $^3J_{HH}$ = 8.4 Hz, 2H, 2 × $C_{Ar}H$), 4.87–4.83 (m, 2H, 2 × $C_{cod}H$), 4.66–4.64 (m, 1H, $C_\alpha H$), 4.31–4.22 (m, 2H, 2 × $CHCH_3$), 4.20–4.16 (m, 1H, $CHCH_2$), 4.02 (s, 3H, NCH_3), 3.96 (s, 3H, NCH_3), 3.72 (s, 3H, $COOCH_3$), 3.37–3.33 (m, 2H, 2 × $C_{cod}H$), 3.15–3.07 (m, 1H, $C_\beta H_2$), 3.06–2.98 (m, 1H, $CHCH_2$), 2.96–2.88 (m, 1H, $C_\beta H_2$), 2.80–2.74 (m, 1H, $CHCH_2$), 2.49–2.35 (m, 4H, 2 × $C_{cod}H_2$), 1.98–1.93 (m, 4H, 2 × $C_{cod}H_2$), 1.39 (s, 9H, $C(CH_3)_3$), 1.36–1.27 (m, 6H, 2 × $CHCH_3$); $^{13}C\{^1H\}$NMR (125 MHz, CD_3OD) δ 182.0 ($^1J_{RhC}$ = 50.5 Hz, C_ε–Rh), 174.9–174.2 (3 × C=O), 172.4 ($COOCH_3$), 157.9 (C_{Ar}), 157.3 (NHCOO), 131.3 (2 × $C_{Ar}H$), 130.9 (C_γ), 129.0 (C_{Ar}), 122.4 ($C_\delta H$), 116.2 (2 × $C_{Ar}H$), 99.2–99.0 (2 × $C_{cod}H$), 80.9 ($C(CH_3)_3$), 69.8–69.5 (2 × $C_{cod}H$), 58.0 ($CHCH_2$), 53.1 ($COOCH_3$), 52.4 ($C_\alpha H$), 50.6–50.3 (2 × $CHCH_3$), 38.16 ($CHCH_2$), 37.92 (NCH_3), 35.3 (NCH_3), 33.9–33.8 (2 × $C_{cod}H_2$), 29.8–29.7 (2 × $C_{cod}H_2$), 28.7 ($C(CH_3)_3$), 27.1 ($C_\beta H_2$), 17.9–17.8 (2 × $CHCH_3$).

Minor isomer: ^{1}H NMR (500 MHz, CD_3OD) δ 7.01 (d, $^{3}J_{HH}$ = 8.4 Hz, 2H, 2 × $C_{Ar}H$), 6.80 (s, 1H, $C_{\delta}H$), 6.67 (d, $^{3}J_{HH}$ = 8.4 Hz, 2H, 2 × $C_{Ar}H$), 4.87–4.83 (m, 2H, 2 × $C_{cod}H$), 4.66–4.64 (m, 1H, $C_{\alpha}H$), 4.31–4.22 (m, 2H, 2 × C*H*CH_3), 4.20–4.16 (m, 1H, C*H*CH_2), 4.00 (s, 3H, NCH_3), 3.97 (s, 3H, NCH_3), 3.69 (s, 3H, $COOCH_3$), 3.44–3.41 (m, 2H, 2 × $C_{cod}H$), 3.15–3.07 (m, 1H, $C_{\beta}H_2$), 3.06–2.98 (m, 1H, CHC*H*$_2$), 2.96–2.88 (m, 1H, $C_{\beta}H_2$), 2.80–2.74 (m, 1H, CHC*H*$_2$), 2.49–2.35 (m, 4H, 2 × $C_{cod}H_2$), 1.98–1.93 (m, 4H, 2 × $C_{cod}H_2$), 1.40 (s, 9H, $C(CH_3)_3$), 1.36–1.27 (m, 6H, 2 × CHC*H*$_3$); ^{13}C{^{1}H}NMR (125 MHz, CD_3OD) δ 181.8 ($^{1}J_{RhC}$ = 50.8 Hz, C_{ε}–Rh), 174.9–174.2 (3 × C=O), 172.3 (*C*$OOCH_3$), 157.8 (C_{Ar}), 157.3 (NHCOO), 131.3 (2 × $C_{Ar}H$), 130.7 (C_{γ}), 128.9 (C_{Ar}), 121.9 ($C_{\delta}H$), 116.2 (2 × $C_{Ar}H$), 99.2–99.0 (2 × $C_{cod}H$), 80.8 (*C*$(CH_3)_3$), 69.8–69.5 (2 × $C_{cod}H$), 57.9 (*C*HCH_2), 53.0 ($COOCH_3$), 52.0 ($C_{\alpha}H$), 50.6–50.3 (2 × *C*HCH_3), 38.18 (CH*C*H_2), 37.94 (NCH_3), 35.5 (NCH_3), 33.9–33.8 (2 × $C_{cod}H_2$), 29.8–29.7 (2 × $C_{cod}H_2$), 28.7 ($C(CH_3)_3$), 26.9 ($C_{\beta}H_2$), 17.9–17.8 (2 × CH*C*H_3). *m/z* (HRMS, ESI^{+}) found 813.3075 ($[M–Cl^{-}]^{+}$), $C_{37}H_{54}N_6O_8Rh$ requires 813.3058; $[\alpha]_D^{20}$ = −3° (c = 1 in $CHCl_3$).

3. Synthesis of unnumbered intermediates



Scheme S1 Complete reaction scheme for the synthesis of the ligand precursors **4a**, **4b**, **10** and **17**, the precursor of **12**.

Synthesis of Boc–Ala–His(Me)–OMe

Boc–Ala–OH (148 mg, 0.78 mmol), **2** (200 mg, 0.78 mmol) and HATU (297 mg, 0.78 mmol) were placed in a dry Schlenk tube under N_2. Dry THF (30 mL) was added at 0 °C and stirring was maintained at 0 °C for 20 min. DIEA (0.39 mL, 2.34 mmol) was added and the reaction mixture was stirred at rt overnight. The volatiles were removed under reduced pressure. The resulting yellow oil was dissolved in CH_2Cl_2 and washed with aqueous $NaHCO_3$ (1 M) once, then with aqueous citric acid (10%) twice and finally with water once. A saturated aqueous solution of Na_2CO_3 was then slowly added to the aqueous phase until pH ~ 8–9 and this resulting solution was extracted several times with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, CH_2Cl_2/MeOH 95:5) gave the pure product as an off-white solid (224 mg, 81%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (br, 1H, $N_{His}H$), 7.41 (s, 1H, $C_\varepsilon H$), 6.69 (s, 1H, $C_\delta H$), 5.26 (br, 1H, $N_{Ala}H$), 4.76 (ddd, $^3J_{HH}$ = 7.6, 5.4, 4.7 Hz, 1H, $C_\alpha H$), 4.21 (br, 1H, C*H*CH_3), 3.68 (s, 3H, $COOCH_3$), 3.64 (s, 3H, NCH_3), 3.09 (dd, $^2J_{HH}$ = 14.9 Hz, $^3J_{HH}$ = 5.4 Hz, 1H, $C_\beta H_2$), 3.02 (dd, $^2J_{HH}$ = 14.9 Hz, $^3J_{HH}$ = 4.7 Hz, 1H, $C_\beta H_2$), 1.43 (s, 9H, $C(CH_3)_3$), 1.36 (d, $^3J_{HH}$ = 7.1 Hz, 3H, CHC*H*$_3$); ^{13}C{^{1}H}NMR (125 MHz, $CDCl_3$) δ 172.9 (C_{Ala}=O), 171.5 (*C*$OOCH_3$), 155.3 (NHCOO), 137.3 ($C_\varepsilon H$), 136.3 (C_γ), 118.4 ($C_\delta H$), 79.7 (*C*$(CH_3)_3$), 52.3 (COO*C*H_3 + $C_\alpha H$), 50.2 (*C*HCH_3), 33.6 (NCH_3), 29.2 ($C_\beta H_2$), 28.3 (C(*C*$H_3)_3$), 18.6 (CH*C*H_3); *m/z* (HRMS, ESI^-) found 353.1838 ($[M–H^+]^-$), $C_{16}H_{25}N_4O_5$ requires 353.1825.

Synthesis of H–Ala–His(Me)–OMe·2HCl

A 4 M solution of HCl in 1,4-dioxane (24 mL, 96 mmol) was added to Boc–Ala–His(Me)–OMe (2.04 g, 5.77 mmol) at 0 °C and the mixture was stirred at rt for 6 h. The volatiles were removed under reduced pressure in a well-ventilated fume hood. The resulting residue was dissolved in a small volume of MeOH and precipitated with Et_2O. The white solid was

separated by centrifugation and this purification step was repeated three times. Finally the product was dried under high vacuum (1.45 g, 77%).

^{1}H NMR (400 MHz, CD_3OD) δ 8.82 (s, 1H, $C_\varepsilon H$), 7.47 (s, 1H, $C_\delta H$), 4.87 (dd, $^{3}J_{HH}$ = 8.8, 4.9 Hz, 1H, $C_\alpha H$), 4.09 (q, $^{3}J_{HH}$ = 7.1 Hz, 1H, $CHCH_3$), 3.94 (s, 3H, NCH_3), 3.77 (s, 3H, $COOCH_3$), 3.35 (dd, $^{2}J_{HH}$ = 15.5 Hz, $^{3}J_{HH}$ = 4.9 Hz, 1H, $C_\beta H_2$), 3.21 (dd, $^{2}J_{HH}$ = 15.5 Hz, $^{3}J_{HH}$ = 8.8 Hz, 1H, $C_\beta H_2$), 1.55 (d, $^{3}J_{HH}$ = 7.1 Hz, 3H, $CHCH_3$), NH and NH_2 not resolved; $^{13}C\{^{1}H\}$NMR (100 MHz, CD_3OD) δ 171.6 ($COOCH_3$), 171.2 (C=O), 136.5 ($C_\varepsilon H$), 130.8 (C_γ), 122.7 ($C_\delta H$), 53.4 ($COOCH_3$), 52.7 ($C_\alpha H$), 50.1 ($CHCH_3$), 36.4 (NCH_3), 27.4 ($C_\beta H_2$), 17.5 ($CHCH_3$); *m/z* (HRMS, ESI^+) found 255.1469 ($[M–HCl–Cl^-]^+$), $C_{11}H_{19}N_4O_3$ requires 255.1457.

Synthesis of Boc–Ala–Ala–OMe

Boc–Ala–OH (2.00 g, 10.6 mmol), H–Ala–OMe·HCl (1.48 g, 10.6 mmol) and HATU (4.02 g, 10.6 mmol) were placed placed in a dry Schlenk tube under N_2. Dry THF (200 mL) was added at 0 °C and stirring was maintained at 0 °C for 20 min. DIEA (5.24 mL, 31.7 mmol) was added and the reaction mixture was stirred at rt for 22 h. The volatiles were removed under reduced pressure. The resulting yellow oil was dissolved in CH_2Cl_2 and washed with aqueous $NaHCO_3$ (1 M) once, then with aqueous citric acid (10%) twice and finally with water once. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, cyclohexane/EtOAc 7:3) gave the pure product as a white solid (2.54 g, 88%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.58 (br, 1H, NH), 4.94 (br, 1H, NH), 4.57 (quintet, $^{3}J_{HH}$ = 7.2 Hz, 1H, $CHCH_3$), 4.20–4.11 (m, 1H, $CHCH_3$), 3.75 (s, 3H, $COOCH_3$), 1.45 (s, 9H, $C(CH_3)_3$), 1.41 (d, $^{3}J_{HH}$ = 7.2 Hz, 3H, $CHCH_3$), 1.36 (d, $^{3}J_{HH}$ = 7.1 Hz, 3H, $CHCH_3$); $^{13}C\{^{1}H\}$NMR (75 MHz, $CDCl_3$) δ 173.3 (C=O), 172.4 (C=O), 155.5 (NHCOO), 80.1 ($C(CH_3)_3$), 52.5

($COOCH_3$), 50.1 ($CHCH_3$), 48.1 ($CHCH_3$), 28.4 ($C(CH_3)_3$), 18.4 ($CHCH_3$), 18.3 ($CHCH_3$); *m/z* (HRMS, ESI^-) found 273.1438 ($[M–H^+]^-$), $C_{12}H_{21}N_2O_5$ requires 273.1450.

Synthesis of H–Ala–Ala–OMe·HCl

A 4 M solution of HCl 1,4-dioxane (33 mL, 132 mmol) was added to Boc–Ala–Ala–OMe (2.19 g, 7.99 mmol) at 0 °C and the mixture was stirred at rt for 2.5 h. The volatiles were removed under reduced pressure in a well-ventilated fume hood. The resulting residue was dissolved in a small volume of MeOH and precipitated with Et_2O. The white solid was separated by centrifugation and this purification step was repeated five times. Finally the product was dried under high vacuum (1.60 g, 95%).

^1H NMR (500 MHz, CD_3OD) δ 4.46 (q, $^3J_{HH}$ = 7.4 Hz, 1H, $CHCH_3$), 4.08 (q, $^3J_{HH}$ = 7.1 Hz, 1H, $CHCH_3$), 3.72 (s, 3H, $COOCH_3$), 1.57 (d, $^3J_{HH}$ = 7.1 Hz, 3H, $CHCH_3$), 1.43 (d, $^3J_{HH}$ = 7.4 Hz, 3H, $CHCH_3$) ; $^{13}C\{^1H\}$NMR (125 MHz, CD_3OD) δ 174.1 (C=O), 170.9 (C=O), 52.9 ($COOCH_3$), 50.1 ($CHCH_3$), 49.5 ($CHCH_3$), 17.7 ($CHCH_3$), 17.3 ($CHCH_3$); *m/z* (HRMS, ESI^+) found 175.1079 ($[M–Cl^-]^+$), $C_7H_{15}N_2O_3$ requires 175.1083; Elem. anal. calcd. for $C_7H_{15}ClN_2O_3$ (210.66): C 39.91, H 7.18, N 13.30; found: C 39.46, H 7.43, N 13.16.

Synthesis of Boc–Ala–Ala–Ala–OMe

Following a procedure as described for Boc–Ala–Ala–OMe, the title product was obtained from a mixture of Boc–Ala–OH (867 mg, 4.58 mmol), H–Ala–Ala–OMe·HCl (965 mg, 4.58 mmol), HATU (1.742 g, 4.58 mmol) and DIEA (2.27 mL, 13.7 mmol) in dry THF (100 mL), after purification by flash chromatography (SiO_2, CH_2Cl_2/MeOH 97:3), as a white solid (1.04 g, 66%).

^1H NMR (500 MHz, $CDCl_3$) δ 7.19 (d, $^3J_{HH}$ = 7.2 Hz, 1H, NH), 7.10 (br, 1H, NH), 5.36 (d, $^3J_{HH}$ = 7.3 Hz, 1H, NH), 4.59–4.48 (m, 2H, 2 × $CHCH_3$), 4.20 (br, 1H, $CHCH_3$), 3.70 (s, 3H,

$COOCH_3$), 1.40 (s, 9H, $C(CH_3)_3$), 1.36 (d, $^3J_{HH}$ = 7.1 Hz, 3H, $CHCH_3$) , 1.35 (d, $^3J_{HH}$ = 6.7 Hz, 3H, $CHCH_3$), 1.32 (d, $^3J_{HH}$ = 7.0 Hz, 3H, $CHCH_3$); $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$) δ 173.2 (C=O), 172.9 (C=O), 172.0 (C=O), 155.6 (NHCOO), 80.0 ($C(CH_3)_3$), 52.5 ($COOCH_3$), 50.2 ($CHCH_3$), 48.8 ($CHCH_3$), 48.2 ($CHCH_3$), 28.4 ($C(CH_3)_3$), 18.7 ($CHCH_3$), 18.5($CHCH_3$), 18.1($CHCH_3$); *m/z* (HRMS, ESI^+) found 368.1780 ($[M + Na^+]^+$), $C_{15}H_{27}N_3O_6Na$ requires 368.1798.

Synthesis of Boc–Ala–Ala–Ala–OH

To a solution of Boc–Ala–Ala–Ala–OMe (1.028 g, 2.98 mmol) in a mixture of THF, MeOH and H_2O (3:1:1, 7.4 mL) was added LiOH (214 mg, 8.93 mmol) and the reaction mixture was stirred at rt for 30 h. Water (5 mL) was added and the solution was washed with EtOAc once. A 10% aqueous solution of HCl was slowly added to the aqueous phase until pH ~ 4 and the resulting solution was extracted six times with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The resulting white solid was dried under high vacuum and used without further purification.

^1H NMR (400 MHz, CD_3OD) δ 4.44–4.34 (m, 2H, 2 × $CHCH_3$), 4.09–4.01 (m, 1H, $CHCH_3$), 1.43 (s, 9H, $C(CH_3)_3$), 1.40 (d, $^3J_{HH}$ = 7.3 Hz, 3H, $CHCH_3$), 1.36 (d, $^3J_{HH}$ = 7.1 Hz, 3H, $CHCH_3$), 1.31 (d, $^3J_{HH}$ = 7.2 Hz, 3H, $CHCH_3$), NH's and OH not resolved; $^{13}C\{^1H\}$NMR (100 MHz, CD_3OD) δ 175.6 (C=O), 175.5 (C=O), 174.4 (C=O), 157.6 (NHCOO), 80.6 ($C(CH_3)_3$), 51.4 (2 × $CHCH_3$), 50.0 ($CHCH_3$), 28.7 ($C(CH_3)_3$), 18.3 ($CHCH_3$), 18.2 ($CHCH_3$), 17.7 ($CHCH_3$); *m/z* (HRMS, ESI^-) found 330.1662 ($[M–H^+]^-$), $C_{14}H_{24}N_3O_6$ requires 330.1665.

Synthesis of Boc–Met–Ala–Ala–OMe

Following a procedure as described for Boc–Ala–Ala–OMe, the title product was obtained from a mixture of Boc–Met–OH (662 mg, 2.65 mmol), H–Ala–Ala–OMe·HCl (559 mg, 2.65

mmol), HATU (1.009 g, 2.65 mmol) and DIEA (1.32 mL, 7.96 mmol) in dry THF (100 mL), after purification by flash chromatography (SiO_2, CH_2Cl_2/MeOH 97:3), as a white solid (988 mg, 92%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (br, 2H, 2 × NH), 5.53 (d, $^3J_{HH}$ = 7.8 Hz, 1H, NH), 4.56 (q, $^3J_{HH}$ = 7.2 Hz, 1H, C*H*CH$_3$), 4.52 (q, $^3J_{HH}$ = 7.3 Hz, 1H, C*H*CH$_3$), 4.29 (br, 1H, C*H*CH$_2$), 3.70 (s, 3H, COOCH$_3$), 2.52 (t, $^3J_{HH}$ = 7.4 Hz, 2H, C*H*$_2$S), 2.05 (s, 3H, SCH$_3$), 2.07–2.00 (m, 1H, CHC*H*$_2$), 1.89 (dt, $^3J_{HH}$ = 14.5, 7.4 Hz, 1H, CHC*H*$_2$), 1.40 (s, 9H, C(CH$_3$)$_3$), 1.37–1.34 (m, 6H, 2 × CHC*H*$_3$); ^{13}C{^{1}H}NMR (125 MHz, $CDCl_3$) δ 173.2 (C=O), 171.8 (C=O), 171.7 (C=O), 155.7 (NHCOO), 80.1 (*C*(CH$_3$)$_3$), 53.6 (*C*HCH$_2$), 52.5 (COO*C*H$_3$), 48.9 (*C*HCH$_3$), 48.2 (*C*HCH$_3$), 32.1 (CH*C*H$_2$), 30.2 (CH$_2$S), 28.4 (C(*C*H$_3$)$_3$), 18.5 (CH*C*H$_3$), 18.1 (CH*C*H$_3$), 15.4 (SCH$_3$); *m/z* (HRMS, ESI$^+$) found 406.2012 ([M + H$^+$]$^+$), $C_{17}H_{32}N_3O_6S$ requires 406.2012.

Synthesis of Boc–Met–Ala–Ala–OH

Following a procedure as described for Boc–Ala–Ala–Ala–OH, the title product was obtained from the reaction of Boc–Met–Ala–Ala–OMe (885 mg, 2.18 mmol) and LiOH (157 mg, 6.55 mmol) in a mixture of THF, MeOH and H_2O (3:1:1, 5.5 mL), after purification by flash chromatography (SiO_2, CH_2Cl_2/MeOH, 95:5), as a white solid (685 mg, 80%).

^{1}H NMR (400 MHz, CD_3OD) δ 4.46–4.32 (m, 2H, 2 × C*H*CH$_3$), 4.19–4.12 (m, 1H, C*H*CH$_2$), 2.61–2.46 (m, 2H, CH$_2$S), 2.09 (s, 3H, SCH$_3$), 2.07–1.98 (m, 1H, CHC*H*$_2$), 1.91–1.82 (m, 1H, CHC*H*$_2$), 1.44 (s, 9H, C(CH$_3$)$_3$), 1.39 (d, $^3J_{HH}$ = 7.3 Hz, 3H, CHC*H*$_3$), 1.37 (d, $^3J_{HH}$ = 7.3 Hz, 3H, CHC*H*$_3$), NH's and OH not resolved; ^{13}C{^{1}H}NMR (100 MHz, CD_3OD) δ 176.6 (C=O), 174.4 (C=O), 174.3 (C=O), 157.8 (NHCOO), 80.7 (*C*(CH$_3$)$_3$), 55.0 (*C*HCH$_2$), 50.1 (*C*HCH$_3$), 49.6 (*C*HCH$_3$), 32.9 (CH*C*H$_2$), 31.1 (CH$_2$S), 28.7 (C(*C*H$_3$)$_3$), 18.1 (CH*C*H$_3$), 17.9 (CH*C*H$_3$), 15.3 (SCH$_3$); *m/z* (HRMS, ESI$^-$) found 390.1681 ([M–H$^+$]$^-$), $C_{16}H_{28}N_3O_6S$ requires 390.1699.

Synthesis of Boc–Tyr–Ala–Ala–OMe

Following a procedure as described for Boc–Ala–Ala–OMe, the title product was obtained from a mixture of Boc–Tyr–OH (796 mg, 2.83 mmol), H–Ala–Ala–OMe·HCl (596 mg, 2.83 mmol), HATU (1.076 g, 2.83 mmol) and DIEA (1.40 mL, 8.49 mmol) in dry THF (100 mL), after purification by flash chromatography (SiO_2, CH_2Cl_2/MeOH 97:3), as a white solid (670 mg, 54%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (OH), 7.37 (d, $^3J_{HH}$ = 7.2 Hz, 1H, $N_{Ala}H$), 7.19 (br, 1H, $N_{Ala}H$), 6.94 (d, $^3J_{HH}$ = 8.4 Hz, 2H, 2 × $C_{Ar}H$), 6.69 (d, $^3J_{HH}$ = 8.4 Hz, 2H, 2 × $C_{Ar}H$), 5.43 (d, $^3J_{HH}$ = 7.0 Hz, 1H, $N_{Tyr}H$), 4.52–4.43 (m, 2H, 2 × C*H*CH_3), 4.37 (br, 1H, C*H*CH_2), 3.68 (s, 3H, $COOCH_3$), 2.97–2.90 (m, 2H, CHC*H*$_2$), 1.35 (s, 9H, $C(CH_3)_3$), 1.34 (d, $^3J_{HH}$ = 8.2 Hz, 3H, CHC*H*$_3$), 1.29 (d, $^3J_{HH}$ = 6.8 Hz, 3H, CHC*H*$_3$); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 173.3 (C=O), 172.2 (C=O), 171.9 (C=O), 155.8 (NHCOO), 155.6 (C_{Ar}), 130.4 (2 × $C_{Ar}H$), 127.4 (C_{Ar}), 115.7 (2 × $C_{Ar}H$), 80.4 (*C*$(CH_3)_3$), 55.9 (*C*HCH_2), 52.5 ($COOCH_3$), 48.9 (*C*HCH_3), 48.3 (*C*HCH_3), 37.7(CH*C*H$_2$), 28.3 ($C(CH_3)_3$), 18.3 (CH*C*H$_3$), 17.7 (CH*C*H$_3$); *m/z* (HRMS, ESI$^+$) found 460.2052 ([M + Na$^+$]$^+$), $C_{21}H_{31}N_3O_7Na$ requires 260.2060.

Synthesis of Boc–Tyr–Ala–Ala–OH

Following a procedure as described for Boc–Ala–Ala–Ala–OH, the title product was obtained from the reaction of Boc–Tyr–Ala–Ala–OMe (814 mg, 1.86 mmol) and LiOH (134 mg, 5.58 mmol) in a mixture of THF, MeOH and H_2O (3:1:1, 4.7 mL), after purification by flash chromatography (SiO_2, CH_2Cl_2/MeOH, 95:5), as a white solid (481 mg, 61%).

^{1}H NMR (400 MHz, CD_3OD) δ 7.05 (d, $^3J_{HH}$ = 8.4 Hz, 2H, 2 × $C_{Ar}H$), 6.70 (d, $^3J_{HH}$ = 8.4 Hz, 2H, 2 × $C_{Ar}H$), 4.41–4.34 (m, 2H, 2 × C*H*CH_3), 4.25 (dd, $^3J_{HH}$ = 9.0 Hz, 5.0 Hz, 1H, C*H*CH_2), 3.02 (dd, $^2J_{HH}$ = 13.9 Hz, $^3J_{HH}$ = 5.0 Hz, 1H, CHC*H*$_2$), 2.73 (dd, $^2J_{HH}$ = 13.9 Hz, $^3J_{HH}$ = 9.0 Hz,

1H, CHC*H*$_2$), 1.40 (d, $^3J_{HH}$ = 7.2 Hz, 3H, CHC*H*$_3$), 1.37 (s, 9H, C(CH$_3$)$_3$), 1.35 (d, $^3J_{HH}$ = 7.4 Hz, 3H, CHC*H*$_3$), NH's and OH's not resolved; $^{13}C\{^1H\}$NMR (100 MHz, CD$_3$OD) δ 174.2 (3 × C=O), 157.7 (NHCOO), 157.2 (C_{Ar}), 131.4 (2 × C_{Ar}H), 129.2 (C_{Ar}), 116.2 (2 × C_{Ar}H), 80.7 (*C*(CH$_3$)$_3$), 57.5 (*C*HCH$_2$), 50.1 (2 × *C*HCH$_3$), 38.3 (CH*C*H$_2$), 28.6 (C(*C*H$_3$)$_3$), 18.2 (CH*C*H$_3$), 17.8 (CH*C*H$_3$); *m/z* (HRMS, ESI$^-$) found 422.1914 ([M–H$^+$]$^-$), $C_{20}H_{28}N_3O_7$ requires 422.1927.

4. General procedure for the catalytic hydrosilylation

The catalyst (10 μmol) and 4'-fluoroacetophenone (0.12 mL, 1.0 mmol) were dissolved in CD_2Cl_2 (1 mL). Diphenylsilane (0.37 mL, 2.0 mmol) was added and the mixture was placed in an NMR tube. Conversions were determined by ^1H and/or ^{19}F NMR spectroscopy. Hydrolysis was performed by addition of a 1% solution of TFA in MeOH (0.5 mL). The solution was stirred for 10 min and then filtered through a small pad of SiO_2, eluting with pentane/Et_2O (3:1). The volatiles were removed under reduced pressure and the enantiomeric excess was determined by chiral HPLC (IA or OBH column, heptane/EtOH 99:1, 1 mL/min).

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