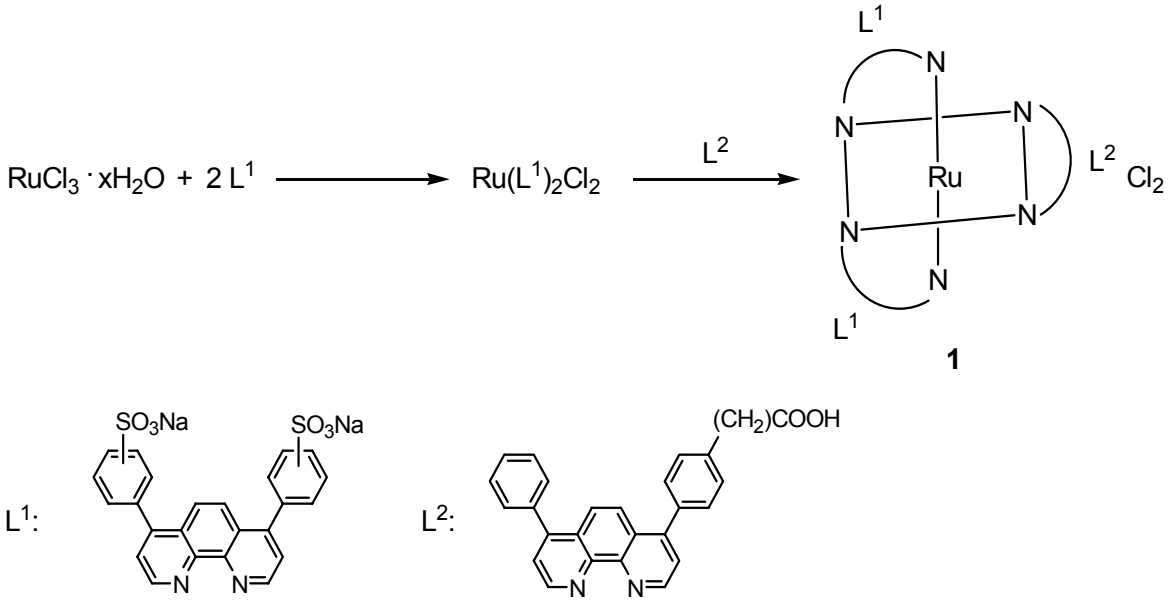
Electronic Supplementary Material for Chemical Communications


Synthesis of the Ru-bathophenanthroline-complex **1**

The synthesis was carried out according to Scheme 1:



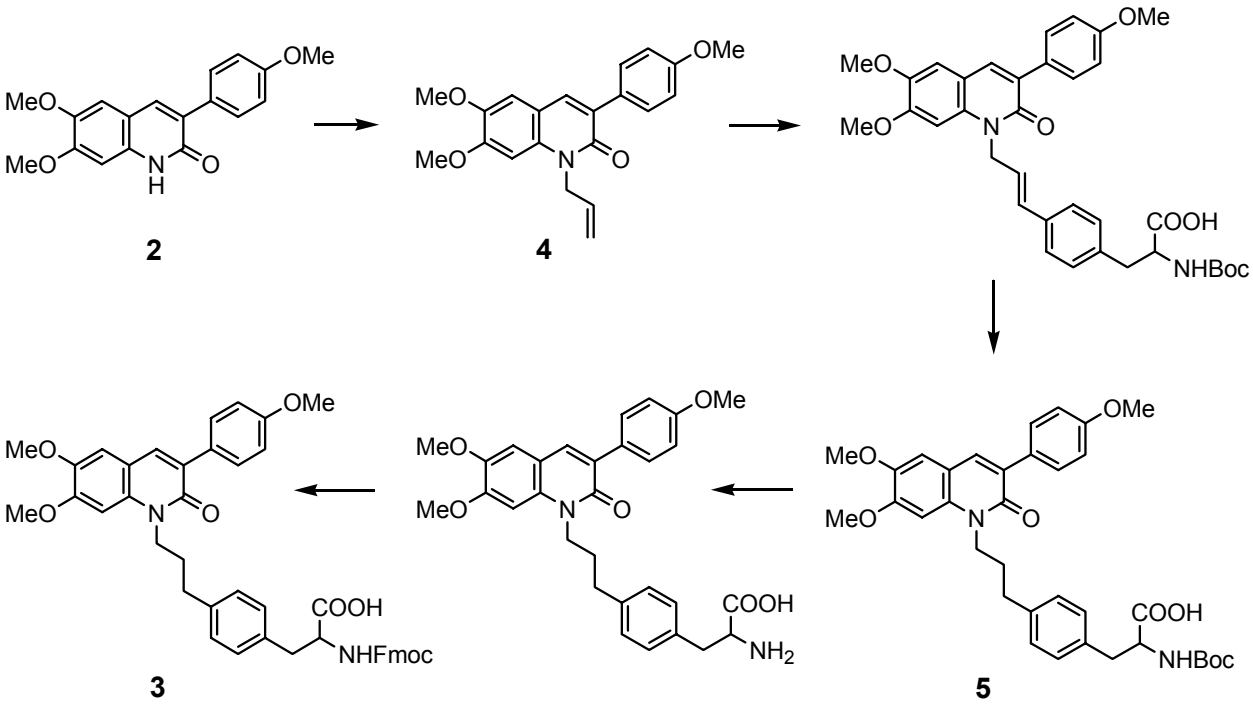

Scheme 1

Starting from commercially available disodium(1,10-phenanthroline-4,7-diyl)bis(benzenesulfonate) (Fluka) (460 mg, 0.78 mmol) and $RuCl_3 \cdot xH_2O$ (100 g, 0.38 mmol) we have synthesized $Ru(L^1)_2Cl_2$ according to [1] in quantitative yield. This (1.34 g, 1.07 mmol) was then reacted with $L^2$ according to [2] with modified work-up conditions, *i. e.*, instead of precipitation, the complex was purified by column chromatography over silica gel ($CH_2Cl_2$ / MeOH + TFA 75:25 + 0.05%) to yield the desired Ru-bathophenanthroline-complex **1** (1.44 g, 0.88 mmol, 80 %yield).

Activation of the Ru complex as O-succinimide ester with TSTU was also carried out according to [2] in 62% yield, and the progress of the reaction was monitored by LC-MS. The analytical data are in accordance with [1] and [2].

Synthesis of the donor Fmoc amino acid **3**

The synthesis was carried out according to Scheme 2.




Scheme 2

The starting compound **2** was synthesized from 2-chloro-6,7-dimethoxy-3-(4-methoxyphenyl) quinoline according to [3] and from 5 g of the starting material, we obtained 4.38 g (93 %) of **2**. The spectroscopic data were in accordance with the ones reported in [3].

Synthesis of **4**

To a suspension of **2** (883 mg, 2.84 mmol, 1.0 eq) in THF (10 ml) was added KHMDS (0.5M in toluene, 6.8 ml, 3.4 mmol, 1.2 eq) at –78°C. After stirring for 30 min, the mixture was allowed to reach room temperature. Allylbromide (0.75 ml, 8.5 mmol, 3.0 eq) was added and the white suspension was placed in a microwave oven (15 min, 120 °C, max. 15 bar, 200 W). The reaction mixture was quenched with $H_2O$ (70 ml) and $CHCl_3$ (70 ml) was added. The phases were separated and the aqueous layer was extracted with $CHCl_3$ (2 x 70 ml), the combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under

reduced pressure. Column chromatography of the crude product over silica (CH / EE 2:1) yielded **4** (828 mg, 2.36 mmol, 83%).

Analytical data:

$^{1}$H-NMR ($CDCl_3$, 400 MHz): δ = 3.84 (3H, s, -OC*H*$_3$), 3.94 (3H, s, -OC*H*$_3$), 3.96 (3H, s, -OC*H*$_3$), 5.02 (2H, dt, $^{3}J$ = 4.8 Hz, $^{4}J$ = 1.5 Hz, -C*H*$_2$-), 5.20 (1H, dd, $^{3}J_{trans}$ = 17.2 Hz, $^{2}J$ = 1.1 Hz, =C*H*$_2$), 5.26 (1H, dd, $^{3}J_{cis}$ = 10.4 Hz, $^{2}J$ = 1.1 Hz, =C*H*$_2$), 6.00 (1H, ddt, $^{3}J_{trans}$ = 17.3 Hz, $^{3}J_{cis}$ = 10.4 Hz, $^{3}J$ = 5.2 Hz, -C*H*=CH$_2$), 6.80 (1H, s, 5-*H*), 6.95 (2H, m$_c$, AA'XX', 3'-*H*, 5'-*H*), 6.99 (1H, s, 8-*H*), 7.70 (2H, m$_c$, AA'XX', 2'-*H*, 6'-*H*), 7.71 (1H, s, 4-*H*).

$^{13}$C-NMR ($CDCl_3$, 100 MHz): δ = 45.66, 55.40, 56.15, 56.28, 97.98, 109.36, 113.62, 114.43, 117.23, 129.27, 129.54, 130.17, 132.35, 134.47, 135.60, 145.23, 151.68, 159.40, 161.18.

MS (70 eV, EI 198°C); *m/z* (%): 351 (95) [$M^+$], 336 (100) [$(M-CH_3)^+$].

HRMS (ESI): *m/z* = 352.15442, calculated for $C_{21}H_{22}O_4N_1^+$: 352.15434.

Synthesis of **5**

A mixture consisting of **4** (5.00 g, 14.2 mmol, 1.0 eq), Boc-*D,L-p*-bromophenylalanine-OMe [4] (7.63 g, 21.3 mmol, 1.5 eq), $Pd(OAc)_2$ (0.48 g, 2.15 mmol, 0.15 eq), $PPh_3$ (1.12 g, 4.25 mmol, 0.3 eq) and $K_2CO_3$ (5.89 g, 42.6 mmol, 3.0 eq) was suspended in DMF (100ml) / $H_2O$ (50 ml) under argon. After heating at 115°C for 13 h, a saturated NaCl solution (750 ml) was added and the pH of the mixture adjusted to 2 with 2N HCl. The aqueous phase was extracted with $CH_2Cl_2$ (3 x 750 ml), the combined organic layers were washed with $H_2O$ (500 ml) and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the crude product was purified by column chromatography over silica ($CH_2Cl_2$ / MeOH 97:3, then 80:20) in four portions. Under the reaction conditions, cleavage of the methyl ester took place and the unsaturated carboxylic acid intermediate was obtained as a light yellow powder (3.66 g, 5.95 mmol, 42%).

Analytical data:

$^1$H-NMR ($CDCl_3$, 300 MHz): δ = 1.39 (9H, s, C(C*H*$_3$)$_3$), 2.94-3.17 (2H, m, Ph-C*H*$_2$-CH-), 3.84 (3H, s, -OC*H*$_3$), 3.94 (3H, s, -OC*H*$_3$), 3.95 (3H, s, -OC*H*$_3$), 4.47-4.56 (1H, m, NH-C*H*-COOH), 4.96 (1H, d, br, $^3J$ = 7.0 Hz, N*H*), 5.17 (2H, d, $^3J$ = 5.3 Hz, N-C*H*$_2$-), 6.30 (1H, dt, $^3J_{trans}$ = 16.1 Hz, $^3J$ = 5.8 Hz, -CH$_2$-C*H*=), 6.57 (1H, d, $^3J_{trans}$ = 16.0 Hz, =C*H*-Ph), 6.90 (1H, s, 5-*H*), 6.95 (2H, m$_d$, AA'XX', $^3J_{app.}$ = 8.8 Hz, 3'-*H*, 5'-*H*), 7.01 (1H, s, 8-*H*), 7.07 (2H, m$_d$, AA'BB', $^3J_{app.}$ = 8.1 Hz, arom. Ph), 7.22 (2H, m$_d$, AA'BB', $^3J_{app.}$ = 8.1 Hz, arom. Ph), 7.69 (2H, m$_d$, AA'XX', $^3J_{app.}$ = 8.8 Hz, 2'-*H*, 6'-*H*), 7.74 (1H, s, 4-*H*).

$^{13}$C-NMR ($CDCl_3$, 75 MHz): δ = 28.49, 37.77, 45.62, 54.63, 55.54, 56.38, 56.45, 80.19, 98.11, 109.60, 113.81, 114.78, 123.64, 126.64, 128.60, 129.40, 129.64, 129.91, 130.35, 132.72, 134.60, 135.03, 136.10, 145.56, 152.02, 155.80, 159.57, 161.52, 176.33.

MS (LC/ESI, 400 µl/min); *m/z* (%): 637 (8), 615 (100) $[M+H]^+$.

HRMS (ESI): *m/z* = 615.27002, calculated for $C_{35}H_{39}O_8N_2^+$: 615.27009.

This intermediate (2.11 g, 3.4 mmol) was dissolved in MeOH (60 ml) under argon and Pd/C (10% Pd on charcoal, 318 mg, 15% m/m) was added to the solution. Then, $H_2$ (1 bar) was bubbled through the mixture for 16 h. The catalyst was removed by filtration over kieselguhr and the solvent distilled at reduced pressure. Column chromatography of the crude mixture over silica ($CH_2Cl_2$ / MeOH 100:1, then 80:20) yielded **5** (1.96 g, 3.1 mmol, 92%).

Analytical data:

$^1$H-NMR ($CDCl_3$, 300 MHz): δ = 1.40 (9H, s, C(C*H*$_3$)$_3$), 2.10 (2H, tt, $^3J_{1,2}$ = 7.5 Hz, -CH$_2$-C*H*$_2$-CH$_2$-), 2.78 (2H, t, $^3J$ = 7.3 Hz, -CH$_2$-C*H*$_2$-Ph), 3.03-3.17 (2H, m, Ph-C*H*$_2$-CH-), 3.79 (3H, s, -OC*H*$_3$), 3.84 (3H, s, -OC*H*$_3$), 3.91 (3H, s, -OC*H*$_3$), 4.31 (2H, t, $^3J$ = 7.9 Hz, N-C*H*$_2$-), 4.49-4.60 (1H, m, NH-C*H*-COOH), 5.02 (1H, d, br, $^3J$ = 4.8 Hz, N*H*), 6.53 (1H, s, 5-*H*), 6.92-6.96 (3H, m, 3'-*H*, 5'-*H,* 8-*H*), 7.12 (2H, m$_d$, AA'BB', $^3J_{app.}$ = 8.1 Hz, arom. Ph), 7.18 (2H, m$_d$, AA'BB', $^3J_{app.}$ = 8.1 Hz, arom. Ph), 7.66 (2H, m$_c$, AA'XX', 2'-*H*, 6'-*H*), 7.67 (1H, s, 4-*H*).

$^{13}$C-NMR ($CDCl_3$, 100 MHz): δ = 28.38, 28.58, 32.98, 37.58, 42.87, 54.47, 55.42, 56.19, 56.32, 80.28, 97.28, 109.63, 113.70, 114.75, 128.75, 129.30, 129.52, 129.69, 130.21, 134.04, 134.08, 135.67, 140.02, 145.37, 151.96, 155.51, 159.47, 161.42, 174.33.

MS (LC/ESI, 400 µl/min); *m/z* (%): 639 (10), 617 (100) $[M+H]^+$, 561 (13), 517 (10), 275 (10).

HRMS (ESI): *m/z* = 617.28575, calculated for $C_{35}H_{41}O_8N_2^+$: 617.28574.

Synthesis of **3**

Compound **5** (0.70 g, 1.14 mmol) was dissolved in $CH_2Cl_2$ (10 ml), TFA (10 ml) and triisopropylsilane (0.5 ml) were added, and the solution stirred for 2 h at room temperature. TLC-control ($CH_2Cl_2$ / MeOH 4:1) showed complete conversion. The mixture was concentrated to dryness under reduced pressure after addition of $CH_3CN$ (3 x 30 ml) and the solid residue suspended in $H_2O$ (30 ml). After washing of the aqueous phase with $Et_2O$ (5 x 20 ml) and re-extraction of the $Et_2O$ phase with water (20 ml), the combined aqueous layers were evaporated to dryness by azeotropic destillation with $CH_3CN$ under reduced pressure. The crude intermediate was used without further purification.

The N-deprotected amino acid (1.14 mmol, 1.0 eq) was suspended in an aqueous $Na_2CO_3$ solution (9%, 20 ml) and cooled in an ice-bath. To this mixture, a suspension of Fmoc-OSu (0.58 g, 1.70 mmol, 1.5 eq) in acetone (10 ml) was added dropwise. After 1 h of stirring the ice-bath was removed, more acetone (20 ml) was added and the suspension stirred for a further 3 h. Then, conc. HCl was used to neutralise the mixture and the solvent was removed under reduced pressure. The residue was resuspended in a NaCl solution spiked with 2N HCl(60 ml) and extracted with $CH_2Cl_2$ (5 x 40 ml). The combined organic layers were re-extracted with a saturated NaCl solution (40 ml), dried over $Na_2SO_4$, warmed to 40°C and filtered. Column chromatography of the crude mixture over silica ($CH_2Cl_2$ / MeOH 100:1, then 90:10) yielded the desired carbostyril-derivative **3** (0.82 g, 0.11 mmol, 97%).

Analytical data:

$^{1}$H-NMR ($CDCl_3$, 300 MHz): δ = 2.08 (2H, tt, $^{3}J_1$ = 7.5 Hz, $^{3}J_2$ = 7.3 Hz, -$CH_2$-C$H_2$-$CH_2$-), 2.78 (2H, t, $^{3}J$ = 7.0 Hz, -$CH_2$-C$H_2$-Ph), 3.13, (2H, $m_c$, Ph-C$H_2$-CH-), 3.79 (3H, s, -OC$H_3$), 3.83 (3H, s, -OC$H_3$), 3.90 (3H, s, -OC$H_3$), 4.15 (1H, dd, $^{3}J_{1,2}$ = 6.7 Hz, Fmoc-C*H*-), 4.24-4.33 (3H, m, Fmoc-C$H_2$-, N-C$H_2$-), 4.44 (1H, dd, $^{2}J$ = 10.3 Hz, $^{3}J$ = 7.0 Hz, Fmoc-C$H_2$-), 4.66 (1H, $m_c$, NH-C*H*-COOH), 5.34 (1H, d, $^{3}J$ = 8.1 Hz, N*H*), 6.51 (1H, s, 5-*H*), 6.93-6.96 (3H, m, 3'-*H*, 5'-*H*, 8-*H*), 7.10 (2H, $m_d$, AA'BB', $^{3}J_{app.}$ = 7.5 Hz, arom. Ph), 7.17 (2H, $m_d$, AA'BB', $^{3}J_{app.}$ = 7.5 Hz, arom. Ph), 7.24-7.29 (2H, m, arom. Fmoc), 7.36 (2H, $m_t$, ABCD, $^{3}J_{app.}$ = 7.4 Hz, arom. Fmoc), 7.51-7.54 (2H, m, arom. Fmoc), 7.63-7.66 (3H, m, 2'-*H*, 6'-*H,* 4-*H*), 7.71 (2H, $m_d$, ABCD, $^{3}J_{app.}$ = 7.5 Hz, arom. Fmoc).

$^{13}$C-NMR ($CDCl_3$, 126 MHz): δ = 28.41, 32.89, 37.54, 42.89, 47.13, 54.76, 55.33, 56.02, 56.16, 67.03, 97.01, 109.32, 113.64, 114.68, 119.93, 125.03, 127.02, 127.68, 128.70, 129.41, 129.52, 129.68, 130.17, 133.86, 133.88, 135.84, 139.91, 141.25, 143.72, 145.29, 151.88, 155.80, 159.38, 161.39, 174.10.

MS (LC/ESI, 400 µl/min); *m/z* (%): 739 (100) $[M+H]^+$.

HRMS (ESI): *m/z* = 739.30139, calculated for $C_{45}H_{43}O_8N_2^+$: 739.30139.

References:

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