Synthesis and Chromatography of [CpRu]$^+$-Complexed Bastadin Precursors

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Dedicated to Professor Burchard Franck on the occasion of his 75th birthday

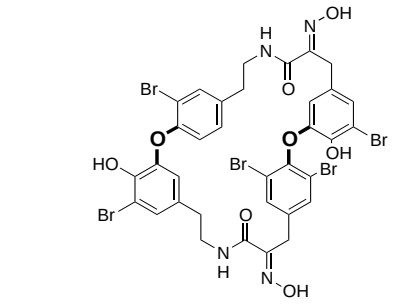
Abstract: The eastern and western diaryl ether portions of the macrocyclic bastadins, natural products from the marine sponge *Ianthella* sp., have been assembled as [CpRu]$^+$ complexes. In an HPLC study, aminopropyl-functionalised silica was found as a very suitable stationary phase for the chromatographic separation of the different cationic ruthenium sandwich complexes. It is now possible for the first time to effectively monitor and purify [CpRu]$^+$ complexes and to carry them through several synthetic steps.

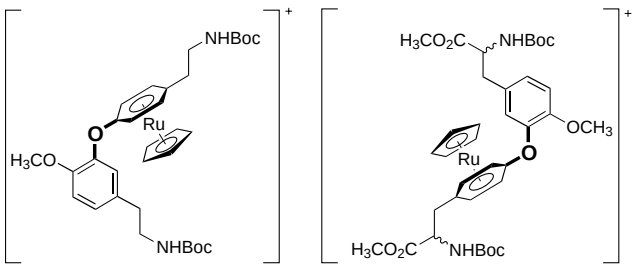
Keywords: aminopropyl silica · diaryl ether synthesis · ion chromatography · ruthenium · sandwich complexes

Introduction

Diaryl ethers constitute a very important structural element of biologically active natural products. Most prominently, the peptide antibiotic vancomycin is clinically used in cases of bacterial resistance against β-lactam antibiotics.[1] Other examples include K-13, a potent inhibitor of the angiotensin I converting enzyme[2] and the OF4949 series of aminopeptidase inhibitors.[3] The marine sponge *Ianthella* sp. is the source of unique macrocyclic tyrosine derivatives[4] which have been synthesised through low-yielding phenol oxidation,[5a,b] the iodonium salt method,[5c] and Ullmann-type coupling.[5d] Bastadin 5 (**1**, Figure 1) has the interesting biological activity of inhibiting the Ca^{2+} uptake into the sarcoplasmatic reticulum, being antagonised by the important immunosuppressant natural product FK506.[6]

Among the synthetic routes to diaryl ethers,[7] the nucleophilic attack of phenolates at [CpRu]$^+$-complexed chloroarenes, pioneered by Nesmeyanov[8a] and Segal,[8b] and utilised by Moriarty,[9a,b] Pearson,[9c,d] Rich,[9e] and Matassa,[9f] is unique. Ruthenium sandwich complexes are readily formed even from electron-poor arenes, are inert against arene exchange, and can be handled under non-anhydrous conditions. Therefore, the [CpRu]$^+$ fragment may be suitable for the stable metal-labelling of aromatic amino acids in peptides.





2 **3**

Figure 1. Bastadin 5 (**1**) from the marine sponge *Ianthella basta* and the ruthenium-complexes **2** and **3** (anion hexafluorophosphate) representing the western and eastern partial structures.

Results and Discussion

Surprisingly only very rarely chromatography was used to purify charged ruthenium complexes.[10] Their limited use in organic synthesis may be the result of their difficult purification and, if desired, demetalation. As a consequence, the analytical and preparative separation of the charged sandwich complexes *from each other* is of fundamental importance for the success of [CpRu]$^+$ complexes in both organic synthesis

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and bioinorganic chemistry.[11] Despite more than 20 papers on the application of $[(\eta^5\text{-Cp})\text{Ru}(\eta^6\text{-arene})]^+$ complexes to the synthesis of peptide-like diaryl ethers,[9] no general protocol yet exists for the purification of charged ruthenium sandwich complexes by chromatography.

The $[\text{CpRu}]^+$-complexed diaryl ethers **2** and **3** (Figure 1) represent the western and eastern halves of the bastarane skeleton. Figure 2 completes the series of sandwich complexes, ordered by increasing polarity, which have been synthesised and subjected to a detailed chromatographic study.

The synthesis of the $[\text{CpRu}]^+$-complexed diaryl ethers **2**–**6** is outlined schematically in Scheme 1. The appropriate phenolate, generated using KO*t*Bu/[18]crown-6 in THF, was added to the $[\text{CpRu}]^+$-complexed chloroarenes **7**,[9c] **8**, **10**,[12] and **13**. The new compounds **8**, **9**, and **13** were obtained by treatment with $[\text{CpRu}(\text{CH}_3\text{CN})_3]\text{PF}_6$[13] in dichloroethane. As concluded from the elemental analyses, the counteranion PF_6^- always remained associated with the ruthenium cation after chromatography on aminopropyl silica. The phenol complex **11**[14a] was obtained from *O*-trimethylsilylphenol and did not form a zwitterion.[14b]

The usual work-up of $[\text{CpRu}]^+$ complexes combines column filtration on alumina, followed by precipitation upon addition diethyl ether. Of course, mixtures of different sandwich complexes are hardly separated by that procedure. Instead, the separation and purification problem is circumvented by photochemical demetalation immediately following the diaryl ether coupling. The reasons of the frequently low yields obtained over these two steps remain to be resolved.

The idea to investigate aminopropyl-functionalised silica as a stationary phase for a true chromatography of the inert, positively charged ruthenium sandwich complexes resulted from the consideration that ionic interactions should be minimal on basic stationary phases that cannot be deprotonated. It was expected that the free amino groups would not attack the $[\text{CpRu}]^+$ complexes, because of the clean Boc deprotection of chloroarene **8** to the equally stable, free amine.

Figure 3 gives retention volumes of the $[\text{CpRu}]^+$-complexed diaryl ethers **2**, **4**, **5**, **6**, of the chloroarenes **7**, **8**, **10**, **13**, and of $[\text{CpRu(benzene)}]\text{PF}_6$ (**12**) obtained by preparative HPLC. Compound **3** has been omitted, because it was obtained as a mixture of diastereomers showing a double-peaked band. In all cases the products were separable from the respective starting materials. The mobile phase *i*PrOH/CH_3CN (4:1) allowed the separation (resolution >1.5) of the less polar (**2**, **4**–**8**) from the more polar compounds (**9**–**13**), as indicated by the bold line in Figure 2. The less polar mobile phase *i*PrOH/CH_3CN (8:1) differentiated between the diaryl ethers (**2**, **4**–**6**) and the chloroarenes **7** and **8** (dotted lines in

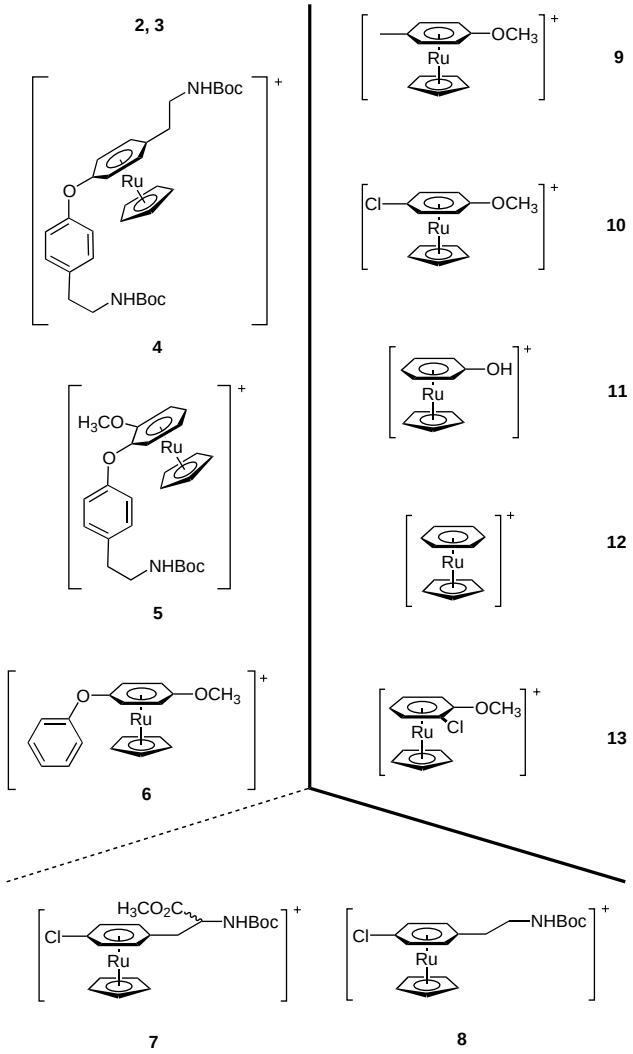
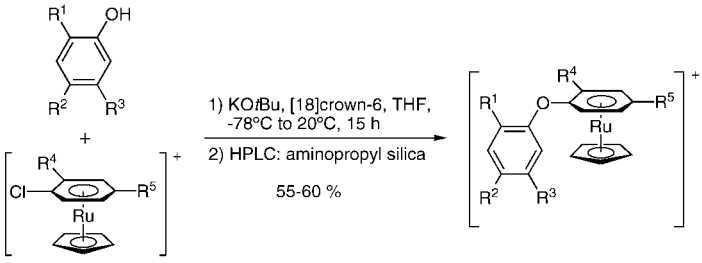


Figure 2. Ruthenium sandwich complexes **2**, **4**–**13** (anion hexafluorophosphate), grouped by increasing HPLC retention volumes on aminopropyl silica as stationary phase. The bold and dotted lines indicate separation using *i*PrOH/CH_3CN (4:1) and (8:1) as mobile phases, respectively. For details see Experimental Section.



Scheme 1. Outline of the synthesis of the $[\text{CpRu}]^+$-complexed diaryl ethers **2**–**6** via S_NAr reaction (Figure 2), followed by chromatographic purification on aminopropyl silica. Details see Experimental Section.

Abstract in Portuguese: *Os éteres de diarila correspondentes às porções oeste e leste das bastadinas cíclicas, produtos naturais da esponja marinha Ianthella sp., foram obtidos como complexos ciclopentadienila de rutênio. Através de um estudo com cromatografia líquida de alta eficiência (CLAE), foi descoberto que a sílica gel funcionalizada com propil amina é uma fase estacionária muito apropriada para a separação cromatográfica de complexos sanduíche catiônicos de rutênio. Pela primeira vez é possível o monitoramento de reações que envolvem complexos ciclopentadienila de rutênio, assim como a purificação dos mesmos, o que possibilita seu uso por várias etapas sintéticas.*

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Figure 2). Using pure *i*PrOH as eluent the diaryl ethers **2** and **4** were separated from **5** and **6**. Even compounds **4**, **8**, and **13** were separated completely by preparative HPLC in one injection employing *i*PrOH/CH_3CN (12:1) as mobile phase (flow rate 15 mL min^{-1}, column diameter 25 mm, length 250 mm, 10 mg of each compound). Aminopropyl silica appears to act in the normal-phase mode[15] when using *i*PrOH/CH_3CN mixtures as mobile phases. While elution of the investigated $[CpRu]^+$ complexes shows considerable heading, [Cp*Ru(η^6-anisole)]PF_6 is eluted with tailing.[16]

As a spin-off, the new separation protocol solves earlier reported problems concerning the removal of [18]crown-6,[17] which accelerates the formation of **2** – **6** using KO*t*Bu as base.[18] On aminopropyl-functionalised silica, [18]crown-6 elutes later than the diaryl ethers **2** – **6** when toluene/CH_3CN (3:1) or *i*PrOH/CH_3CN (18:1) are used as mobile phases. Furthermore, the frequently observed impurity[19] [CpRu(benzene]PF_6 (**12**, transparent circles in Figure 3), is effectively removed on the diaryl ether level employing aminopropyl silica.

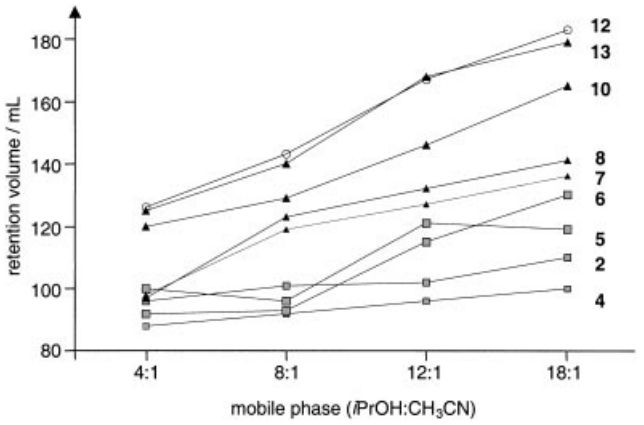

Figure 3. Preparative HPLC separation of the $[CpRu]^+$-complexed diaryl ethers (grey squares) from the corresponding chloroarenes (black triangles). Retention volumes (HPLC) are given for different *i*PrOH/CH_3CN mixtures as mobile phases (stationary phase aminopropyl silica, column length 25 cm, column diameter 2.5 cm, particle size 25 – 40 μm, flow rate 15 mL min^{-1}).

The HPLC results are directly reflected in the behaviour of the sandwich complexes on aminopropyl silica TLC plates. The kinetic stability of the complexes can be estimated by the fact that the characteristic, reddish staining of compounds **2** – **13** on the TLC treated with 1,10-phenanthroline in ethanol only occurs after intense heating.

In summary, one of the central obstacles of ruthenium-mediated diaryl ether synthesis and work-up has been overcome for the first time. Ruthenium-complexed synthetic intermediates can now be conveniently analysed by TLC and be carried through several synthetic steps. Aminopropyl silica may be generally recommended for the separation of cationic metal complexes. Double amide formation of deprotected analogues of the ruthenium-complexed diaryl ethers **2** and **3**, aiming at the regioselective synthesis of the bastarane skeleton is currently investigated.

Experimental Section

General: All reactions were carried out under an argon atmosphere with distilled, non-anhydrous solvents. Yields refer to purified compounds. Reagents were purchased from Aldrich, Acros, Alfa, and Fluka at high commercial quality and were used without further purification. Reactions were controlled by thin-layer chromatography (0.25 mm E. Merck alumina plates NH_2 $F_{254}S$). TLCs were analysed under UV light ($\lambda = 254$ nm), followed by heating after treatment with 1,10-phenanthroline (2 M dipping solution in EtOH). E. Merck Al_2O_3 90 standardised (activity grade II – III, particle size 63 – 200 μm) and E. Merck aminopropyl silica LiChroprep NH_2 (particle size 40 – 63 μm) were used for preparative column chromatography. The HPLC experiments were performed at 25 °C using a Merck-Hitachi L6200A Intelligent Pump System. The column was a preparative E. Merck Hibar Pre-Packed Column RT 250 – 25, customised packing LiChroprep NH_2 (length 25 cm, diameter 2.5 cm, particle size 25 – 40 μm). CH_3CN and *i*PrOH were HPLC grade. The detector used was a KONTRON ultraviolet spectrophotometer Uvitron 730S LC and the integrator was a Merck-Hitachi D-2500 Chromato-Integrator. The peaks were detected at $\lambda = 254$ nm, the flow rate was 15 mL min^{-1}, each injection contained 10 mg of sample. NMR spectra were recorded on Bruker WM 250, AM 360, and AM 500 spectrometers. The NMR shifts were calibrated using TMS as internal reference and assigned on the basis of HSQC and HMBC experiments. The multiplicities are: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad. All infrared spectra were recorded on a Perkin – Elmer 1600 series FT-IR spectrometer. The UV/Vis spectra were recorded using a Hewlett-Packard UV-spectrophotometer HP 8452 diode array system. Fast atom bombardment (FAB) mass spectra were recorded on a JEOL JMS-700 mass spectrometer. Only the three predominant isotopes are listed. Melting points were determined with a Reichert melting point microscope and are uncorrected. Elemental analyses were performed at the automatic microanalysator Foss-Heraeus Vario EL.

General procedure for the preparation of the ruthenium sandwich complexes: At 70 °C, $[CpRu(CH_3CN)_3]PF_6$[13] (concentrated from a CH_3CN solution immediately prior to use) was added to a solution of the respective chlorobenzene derivative (1 equiv) in 1,2-dichloroethane (20 mL) and the reaction mixture was heated under reflux for 4 h. After concentration, the residue was dissolved in CH_3CN and pre-purified by column filtration (alumina, CH_3CN). The product was purified by column chromatography (aminopropyl silica, *i*PrOH).

[η^6-4-Chloro-1-[2-*N*-[(*tert*-butoxy)carbonyl]aminoethyl]benzene](η^5-cyclopentadienyl)ruthenium hexafluorophosphate (8): Prepared from [2-(4-chloro-phenyl)-ethyl]-carbamic acid *tert*-butyl ester (1.1 g, 2.4 mmol). Colourless needles (*i*PrOH; 910 mg, 65 %). M.p. 127 °C (decomp); TLC: $R_f = 0.46$ (*i*PrOH); HPLC retention volumes: 103 mL (CH_3CN), 95 mL (*i*PrOH/CH_3CN 1:1), 95 mL (*i*PrOH/CH_3CN 2:1), 97 mL (*i*PrOH/CH_3CN 4:1), 123 mL (*i*PrOH/CH_3CN 8:1), 132 mL (*i*PrOH/CH_3CN 12:1), 141 mL (*i*PrOH/CH_3CN 18:1), 230 mL (*i*PrOH); ^{1}H NMR (360 MHz, $CDCl_3$): $\delta =$ 6.47 (d, $J = 6.1$ Hz, 2H; η-CH_{ar}), 6.31 (d, $J = 6.3$ Hz, 2H; η-CH_{ar}), 5.47 (s, 5H; Cp), 5.20 (br t, 1H; CH_2NH), 3.37 (dt, $J = 6.7$, 6.7 Hz, 2H; CH_2NH), 2.73 (t, $J = 6.7$ Hz, 2H; CH_2CH$_2$NH), 1.39 (s, 9H; OC(CH_3)$_3$); ^{13}C NMR (90.6 MHz, $CDCl_3$): $\delta = 156.10$ (*C*=O), 104.83 (η-C_{ar}Cl), 103.86 (η-C_{ar}CH$_2$), 86.85 (η-C_{ar}H), 86.66 (η-C_{ar}H), 82.74 (Cp), 79.60 (O*C*(CH$_3$)$_3$), 40.80 (*C*H$_2$NH), 33.90 (*C*H$_2$CH$_2$NH), 28.32 (OC(*C*H$_3$)$_3$); IR (KBr): $\tilde{\nu} =$ 3369, 3125, 3096, 2987, 2937, 1684, 1524, 1453, 1369, 1281, 1251, 1176, 1094, 839 cm^{-1}; UV/Vis (CH_3CN): λ_{max} (ε) = 224 (11000), 200 nm (46000 mol^{-1} dm^3 cm^{-1}); MS (FAB+, NBA): *m*/*z* (%) 421/422/424 (61/100/78) $[M]^+$; HRMS (FAB): calcd for $C_{18}H_{23}{}^{35}ClNO_2{}^{102}Ru$ $[M]^+$: 422.0463, found 422.0449; elemental analysis calcd (%) for $C_{18}H_{23}ClF_6NO_2PRu$ (566.87): C 38.14, H 4.09, N 2.47; found C 37.86, H 4.30, N 2.27.

[η^6-(1-Methoxy-4-methyl)benzene](η^5-cyclopentadienyl)ruthenium hexafluorophosphate (9): Prepared from 4-methylanisol (69.0 mg, 0.07 mL, 0.565 mmol). Colourless powder (197 mg, 80 %). M.p. 147 – 148 °C (decomp); TLC: $R_f = 0.26$ (*i*PrOH); HPLC retention volumes: 108 mL (CH_3CN), 104 mL (*i*PrOH/CH_3CN 1:1), 107 mL (*i*PrOH/CH_3CN 2:1), 116 mL (*i*PrOH/CH_3CN 4:1), 126 mL (*i*PrOH/CH_3CN 8:1), 138 mL (*i*PrOH/CH_3CN 12:1), 150 mL (*i*PrOH/CH_3CN 18:1); ^{1}H NMR (360 MHz, [D$_6$]acetone): $\delta = 6.34$ (d, $J = 6.7$ Hz, 2H; η-CH_{ar}), 6.26 (d, $J = 6.7$ Hz, 2H; η-CH_{ar}), 5.48 (s, 5H; Cp), 3.84 (s, 3H; OCH_3), 2.35 (s, 3H;

CH_3); ^{13}C NMR (90.6 MHz, [D$_6$]acetone): $\delta = 134.73$ (η-$C_{ar}OCH_3$), 100.46 (η-$C_{ar}CH_3$), 86.27 (η-$C_{ar}H$), 81.13 (Cp), 74.67 (η-$C_{ar}H$), 57.71 (OCH_3), 19.69 (η-$C_{ar}CH_3$); IR (KBr): $\tilde{\nu} = 3118, 1549, 1491, 1446, 1264, 1011, 840\ cm^{-1}$; UV/Vis ($CH_3CN$): λ_{max} (ε) = 280 (10800), 226 (15600), 200 nm (61600 mol^{-1} dm^3 cm^{-1}); MS (FAB+, NBA): *m*/*z* (%): 288/289/291 (61/100/60) [*M*]$^+$; HRMS (FAB): calcd for $C_{13}H_{15}O^{102}Ru$ [*M*]$^+$: 289.0170, found 289.0159; elemental analysis calcd (%) for $C_{13}H_{15}F_6OPRu$ (433.30): C 36.04, H 3.49; found C 35.64, H 3.50.

[η^6-(1-Chloro-2-methoxy)benzene](η^5-cyclopentadienyl)ruthenium hexafluorophosphate (13): Prepared from 2-chloroanisol (116 mg, 0.10 mL, 0.825 mmol). Colourless needles (*i*PrOH; 300 mg, 80%). M.p. 147–149 °C (decomp); TLC: $R_f = 0.24$ (*i*PrOH); HPLC retention volumes: 109 mL (CH_3CN), 100 mL (*i*PrOH/CH_3CN 1:1), 114 mL (*i*PrOH/CH_3CN 2:1), 126 mL (*i*PrOH/CH_3CN 4:1), 143 mL (*i*PrOH/CH_3CN 8:1), 167 mL (*i*PrOH/CH_3CN 12:1), 183 mL (*i*PrOH/CH_3CN 18:1); ^1H NMR (360 MHz, [D$_6$]acetone): $\delta = 6.78$ (d, $J = 5.7$ Hz, 1H; η-CH_{ar}), 6.69 (d, $J = 6.0$ Hz, 1H; η-CH_{ar}), 6.25 (t, $J = 5.5$ Hz, 1H; η-CH_{ar}), 6.21 (t, $J = 5.4$ Hz, 1H; η-CH_{ar}), 5.58 (s, 5H; Cp), 4.06 (s, 3H; OCH_3); ^{13}C NMR (91 MHz, [D$_6$]acetone): $\delta = 132.30$ (η-$C_{ar}OCH_3$), 96.46 (η-$C_{ar}Cl$), 86.81 (η-$C_{ar}H$), 84.52 (η-$C_{ar}H$), 83.90 (η-$C_{ar}H$), 81.50 (Cp), 72.71 (η-$C_{ar}H$), 58.13 (OCH_3); IR (KBr): $\tilde{\nu} = 3109, 1521, 1465, 1435, 1276, 1011, 841, 823, 557\ cm^{-1}$; UV/Vis ($CH_3CN$): λ_{max} (ε) = 232 (4000), 204 nm (26500 mol^{-1} dm^3 cm^{-1}); MS (FAB+, NBA): *m*/*z* (%): 308/309/311 (61/100/78) [*M*]$^+$; HRMS (FAB): calcd for $C_{12}H_{12}{}^{35}ClO^{102}Ru$ [*M*]$^+$: 308.9620, found 308.9642; elemental analysis calcd (%) for $C_{12}H_{12}ClF_6OPRu$ (453.71): C 31.77, H 2.67; found C 31.85, H 2.81.

General procedure for the preparation of the diaryl ether ruthenium sandwich complexes: The respective phenol (1.0 equiv) was added to a solution of KO*t*Bu (1.0 equiv) and [18]crown-6 (0.1 equiv) in THF (15 mL). After 30 min the mixture was cooled to 0 °C and transferred to a pre-cooled (−78 °C) solution of the respective ruthenium aryl complex (1.0 equiv) in THF (20 mL). After 1 h the reaction was slowly brought to 20 °C. After 16 h, the reaction mixture was filtered and concentrated. The residue was purified by chromatography (aminopropyl silica, toluene/CH_3CN 3:1).

[η^6-1-[[5-[2-*N*-[(*tert*-butoxy)carbonyl]aminoethyl]-2-methoxy]phenoxy]-4-[2-*N*-[(*tert*-butoxy)carbonyl]aminoethyl]benzene](η^5-cyclopentadienyl)ruthenium hexafluorophosphate (2): Prepared from **8** (100 mg, 0.17 mmol) and from *N*-Boc-4′-*O*-methyldopamine[20] (45.0 mg, 0.17 mmol). After column chromatography the product was dissolved in *i*PrOH at 60 °C, followed by slow precipitation after addition of trace amounts of diethyl ether at RT to yield the title compound (81 mg, 60%). M.p. 80–81 °C (decomp); TLC: $R_f = 0.49$ (*i*PrOH); HPLC retention volumes: 109 mL (CH_3CN), 95 mL (*i*PrOH/CH_3CN 1:1), 95 mL (*i*PrOH/CH_3CN 2:1), 96 mL (*i*PrOH/CH_3CN 4:1), 101 mL (*i*PrOH/CH_3CN 8:1), 102 mL (*i*PrOH/CH_3CN 12:1), 110 mL (*i*PrOH/CH_3CN 18:1), 172 mL (*i*PrOH); ^1H NMR (360 MHz, $CDCl_3$): $\delta = 7.13$ (d, $J = 8.7$ Hz, 1H; CH_{ar}), 7.00 (d, $J = 8.4$ Hz, 1H; CH_{ar}), 6.88 (s, 1H; η-CH_{ar}), 6.12 (d, $J = 6.0$ Hz, 2H; η-CH_{ar}), 6.01 (d, $J = 5.7$ Hz, 2H; η-CH_{ar}), 5.34 (s, 5H; Cp), 4.95 (m, 1H; CH$_2$N*H*), 4.36 (t, $J = 7.1$ Hz, 1H; CH$_2$N*H*), 3.81 (s, 3H; OCH_3), 3.34 (br d, 4H; CH_2NH), 2.77 (br t, $J = 6.7$ Hz, 2H; CH_2CH$_2$NH), 2.67 (br t, 2H; CH_2CH$_2$NH), 1.40 (s, 18H; OC(CH_3)$_3$); ^{13}C NMR (90.6 MHz, $CDCl_3$): $\delta =$ 156.15 (*C*=O), 155.99 (*C*=O), 149.59 ($C_{ar}OCH_3$), 140.33 (C_{ar}O(η-Ph)), 133.12 (CH$_2$$C_{ar}$), 132.76 ($\eta$-$C_{ar}$OPh), 128.46 ($C_{ar}H$), 122.37 ($C_{ar}H$), 113.41 ($C_{ar}H$), 101.18 ($\eta$-$C_{ar}CH_2$), 84.81 ($\eta$-$C_{ar}H$), 82.74 (Cp), 79.43 (O$C$(CH$_3$)$_3$), 79.19 (O$C$(CH$_3$)$_3$), 74.77 ($\eta$-$C_{ar}H$), 55.98 (O$CH_3$), 41.80 (*C*H$_2$NH), 41.00 (*C*H$_2$NH), 35.38 (*C*H$_2CH_2$NH), 33.70 (*C*H$_2CH_2$NH), 28.37 (OC(*C*H$_3$)$_3$), 28.33 (OC(*C*H$_3$)$_3$); IR (KBr): $\tilde{\nu} = 3440, 3354, 2979, 1700, 1512, 1477, 1367, 1274, 1233, 1171, 1122, 841\ cm^{-1}$; UV/Vis ($CH_3CN$): λ_{max} (ε) = 282 (30400), 222 (43500), 196 nm (120900 mol^{-1} dm^3 cm^{-1}); MS (FAB+, NBA): *m*/*z* (%): 652/653/655 (62/100/56) [*M*]$^+$, 596/597/599 (5/7/4) [*M* − C_4H_8]$^+$; HRMS (FAB): calcd for $C_{32}H_{43}O_6N_2{}^{102}Ru$ [*M*]$^+$: 653.2174, found 653.2144; elemental analysis calcd (%) for $C_{32}H_{43}F_6N_2O_6PRu$ (797.74): C 48.18, H 5.43, N 3.51; found C 47.46, H 5.68, N 3.20.

[η^6-D,L-1-[[5-D,L-[2-[*N*-[(*tert*-butoxy)carbonyl]amino]-3-oxo-3-methoxypropyl]-2-methoxy]phenoxy]-4-[2-[*N*-[(*tert*-butoxy)carbonyl]amino]-3-oxo-3-methoxypropyl]benzene](η^5-cyclopentadienyl)ruthenium hexafluorophosphate (3): Prepared from **7**[9c] (100 mg, 0.16 mmol) and *N*-Boc-4′-*O*-methyl-D,L-dopa methyl ester[21] (52 mg, 0.16 mmol). After column chromatography the product was recrystallised yielding colourless needles (*i*PrOH; 87 mg, 60%). M.p. 98–100 °C (decomp); TLC: $R_f = 0.51$ (*i*PrOH); ^1H NMR (360 MHz, $CDCl_3$): $\delta = 7.09$ (dd, $J = 8.4$, 2.3 Hz, 1H; CH_{ar}), 7.00 (d, $J = 8.4$ Hz, 1H; CH_{ar}), 6.83 (d, $J = 2.3$ Hz, 1H; CH_{ar}), 6.17 (t, $J = 8.7$ Hz, 1H; η-CH_{ar}), 6.05 (m, 2H; η-CH_{ar}), 5.97 (t, $J = 6.7$ Hz, 1H; η-CH_{ar}), 5.43 (m, 1H; CHN*H*), 5.35 (s, 5H; Cp), 5.09 (m, 1H; CHN*H*), 4.51 (m, 1H; CH$_2$C*H*(NH)CO), 4.42 (m, 1H; CH$_2$C*H*(NH)CO), 3.83 (s, 3H; COOCH_3), 3.81 (s, 3H; COOCH_3), 3.74 (s, 3H; PhOCH_3), 3.12 (br dd, 1H; PhC*H*HCH), 3.00–2.93 (m, 2H; PhC*H*HCH), 2.82 (dd, $J = 13.4$, 8.7 Hz, 1H; PhCH*H*CH), 1.41 (s, 9H; OC(CH_3)$_3$), 1.40 (s, 9H; OC(CH_3)$_3$); ^{13}C NMR (90.6 MHz, $CDCl_3$): $\delta = 172.06$ (*C*=O), 170.89 (*C*=O), 155.46 (*C*=O), 155.43 (*C*=O), 150.21 ($C_{ar}OCH_3$), 140.21 (C_{ar}O(η-Ph)), 132.93 (CH$_2$$C_{ar}$), 130.21 ($\eta$-$C_{ar}$OPh), 129.23 ($C_{ar}H$), 122.96 ($C_{ar}H$), 113.44 ($C_{ar}H$), 98.95 ($\eta$-$C_{ar}CH_2$), 85.72 ($\eta$-$C_{ar}H$), 85.58 ($\eta$-$C_{ar}H$), 81.13 (Cp), 80.46 (O$C$(CH$_3$)$_3$), 80.41 (O$C$(CH$_3$)$_3$), 74.86 ($\eta$-$C_{ar}H$), 74.76 ($\eta$-$C_{ar}H$), 56.04 (PhO$CH_3$), 54.60 (CH$_2$*C*H(NH)CO), 53.06 (COO$CH_3$), 52.55 (COO$CH_3$), 37.83 (*C*H$_2$CH(NH)CO), 36.69 (*C*H$_2$CH(NH)CO), 28.30 (OC(*C*H$_3$)$_3$), 28.26 (OC(*C*H$_3$)$_3$); IR (KBr): $\tilde{\nu} = 3419, 2979, 1743, 1717, 1710, 1700, 1513, 1477, 1368, 1275, 1235, 1166, 1023, 843, 558\ cm^{-1}$; UV/Vis ($CH_3CN$): λ_{max} (ε) = 278 (11400), 224 (23100), 196 nm (66600 mol^{-1} dm^3 cm^{-1}); MS (FAB+, NBA): *m*/*z* (%): 768/769/771 (61/100/56) [*M*]$^+$; HRMS (FAB): calcd for $C_{36}H_{47}O_{10}N_2{}^{102}Ru$ [*M*]$^+$: 769.2274, found 769.2299.

[η^6-1-[4-[2-*N*-[(*tert*-butoxy)carbonyl]aminoethyl]phenoxy]-4-[2-*N*-[(*tert*-butoxy)carbonyl]aminoethyl]benzene](η^5-cyclopentadienyl)ruthenium hexafluorophosphate (4): Prepared from **8** (87 mg, 0.15 mmol) and from *N*-Boc-tyramine (35 mg, 0.15 mmol). After column chromatography the product was recrystallised yielding colourless needles (*i*PrOH; 70 mg, 60%). M.p. 117–118 °C (decomp); TLC: $R_f = 0.70$ (*i*PrOH); HPLC retention volumes: 97 mL (CH_3CN), 89 mL (*i*PrOH/CH_3CN 1:1), 90 mL (*i*PrOH/CH_3CN 2:1), 88 mL (*i*PrOH/CH_3CN 4:1), 92 mL (*i*PrOH/CH_3CN 8:1), 96 mL (*i*PrOH/CH_3CN 12:1), 100 mL (*i*PrOH/CH_3CN 18:1), 149 mL (*i*PrOH); ^1H NMR (360 MHz, $CDCl_3$): $\delta = 7.32$ (d, $J = 8.5$ Hz, 2H; CH_{ar}), 6.95 (d, $J = 8.4$ Hz, 2H; CH_{ar}), 6.16 (d, $J = 6.5$ Hz, 2H; η-CH_{ar}), 6.01 (d, $J = 6.4$ Hz, 2H; η-CH_{ar}), 5.35 (s, 5H; Cp), 5.16 (m, 1H; CH$_2$N*H*), 4.79 (m, 1H; CH$_2$N*H*), 3.39 (m, 4H; C*H*$_2$NH), 2.84 (t, $J = 7.0$ Hz, 2H; C*H*$_2$CH$_2$NH), 2.70 (t, $J = 7.1$ Hz, 2H; C*H*$_2$CH$_2$NH), 1.45 (s, 9H; OC(CH_3)$_3$), 1.41 (s, 9H; OC(CH_3)$_3$); ^{13}C NMR (90.6 MHz, $CDCl_3$): $\delta = 156.13$ (*C*=O), 155.79 (*C*=O), 150.68 (C_{ar}O(η-Ph)), 138.32 (CH$_2$$C_{ar}$), 132.93 ($\eta$-$C_{ar}$OPh), 131.06 ($C_{ar}H$), 120.21 ($C_{ar}H$), 101.60 ($\eta$-$C_{ar}CH_2$), 85.12 ($\eta$-$C_{ar}H$), 80.79 (Cp), 79.48 (O$C$(CH$_3$)$_3$), 79.27 (O$C$(CH$_3$)$_3$), 75.14 ($\eta$-$C_{ar}H$), 41.60 (*C*H$_2$NH), 40.87 (*C*H$_2$NH), 35.64 (*C*H$_2CH_2$NH), 33.66 (*C*H$_2CH_2$NH), 28.29 (OC(*C*H$_3$)$_3$), 28.25 (OC(*C*H$_3$)$_3$); IR (KBr): $\tilde{\nu} = 3373, 1687, 1366, 1249, 843\ cm^{-1}$; UV/Vis ($CH_3CN$): λ_{max} (ε) = 266 (8800), 204 (65800), 192 nm (87700 mol^{-1} dm^3 cm^{-1}); MS (FAB+, NBA): *m*/*z* (%): 622/623/625 (60/100/54) [*M*]$^+$, 566/567/569 (4/7/4) [*M* − C_4H_8]$^+$; HRMS (FAB): calcd for $C_{31}H_{41}O_5N_2{}^{102}Ru$ [*M*]$^+$: 623.2044, found 623.2057; elemental analysis calcd (%) for $C_{31}H_{41}F_6N_2O_5PRu$ (797.74): C 48.50, H 5.38, N 3.65; found C 48.22, H 5.59, N 3.45.

[η^6-1-[4-[2-*N*-[(*tert*-butoxy)carbonyl]aminoethyl]phenoxy]-2-methoxybenzene](η^5-cyclopentadienyl)ruthenium hexafluorophosphate (5): Prepared from **13** (110 mg, 0.242 mmol) and from *N*-Boc-tyramine (57 mg, 0.242 mmol). After column chromatography the product was dissolved in *i*PrOH at 60 °C, followed by slow precipitation after addition of trace amounts of diethyl ether at rt; (86 mg, 55%). M.p. 70 °C (decomp); TLC: $R_f = 0.36$ (*i*PrOH); HPLC retention volumes: 112 mL (CH_3CN), 93 mL (*i*PrOH/CH_3CN 1:1), 90 mL (*i*PrOH/CH_3CN 2:1), 92 mL (*i*PrOH/CH_3CN 4:1), 93 mL (*i*PrOH/CH_3CN 8:1), 115 mL (*i*PrOH/CH_3CN 12:1), 130 mL (*i*PrOH/CH_3CN 18:1), 273 mL (*i*PrOH); ^1H NMR (360 MHz, $CDCl_3$): $\delta =$ 7.29 (d, $J = 8.4$ Hz, 2H; CH_{ar}), 6.99 (d, $J = 8.7$ Hz, 2H; CH_{ar}), 6.48 (d, $J =$ 6.4 Hz, 1H; η-CH_{ar}), 5.95 (t, $J = 6.1$ Hz, 1H; η-CH_{ar}), 5.89 (d, $J = 6.0$ Hz, 1H; η-CH_{ar}), 5.82 (d, $J = 6.0$ Hz, 1H; η-CH_{ar}), 5.36 (s, 5H; Cp), 4.68 (br m, 1H; CH$_2$N*H*), 3.95 (s, 3H; OCH_3), 3.38 (br q, $J = 6.7$ Hz, 2H; C*H*$_2$NH), 2.83 (t, $J = 7.0$ Hz, 2H; C*H*$_2$CH$_2$NH), 1.44 (s, 9H; OC(CH_3)$_3$); ^{13}C NMR (90.6 MHz, $CDCl_3$): $\delta = 155.91$ (*C*=O), 152.26 ((η-Ph)OC_{ar}), 137.54 (CH$_2$$C_{ar}$), 130.94 ($C_{ar}H$), 127.01 ($\eta$-$C_{ar}OCH_3$), 123.75 ($\eta$-$C_{ar}$OPh), 119.65 ($C_{ar}H$), 81.69 ($\eta$-$C_{ar}H$), 80.70 ($\eta$-$C_{ar}H$), 80.61 (Cp), 79.65 (O$C$(CH$_3$)$_3$), 75.79 ($\eta$-$C_{ar}H$), 72.30 ($\eta$-$C_{ar}H$), 57.87 (O$CH_3$), 41.75 (*C*H$_2$NH), 35.71 (*C*H$_2CH_2$NH), 28.42 (OC(*C*H$_3$)$_3$); IR (KBr): $\tilde{\nu} = 3438, 2878, 1700, 1528, 1501, 1477, 1277, 1258, 1221, 840\ cm^{-1}$; UV/Vis ($CH_3CN$): λ_{max} (ε) = 260 (6900), 220 (21600), 196 nm (62200 mol^{-1} dm^3 cm^{-1}); MS (FAB+, NBA): *m*/*z* (%): 509/510/512 (58/100/54) [*M*]$^+$, 452/453/455 (5/10/5) [*M* − C_4H_8]$^+$, 406/407/409 (3/4/5) [*M* − $C_5H_8O_2$]$^+$; HRMS (FAB): calcd for $C_{25}H_{30}O_4N^{102}Ru$ [*M*]$^+$: 510.1226, found 510.1221.

[η^6-(1-Methoxy-4-phenoxy)benzene](η^5-cyclopentadienyl)ruthenium hexafluorophosphate (6): Prepared from **10** (108 mg, 0.24 mmol) and phenol

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(23 mg, 0.24 mmol). After column chromatography the product was recrystallised (*i*PrOH/EtOH) to yield a colourless powder (70 mg, 57 %). M.p. 152 – 153 °C (decomp); TLC: $R_f = 0.40$ (*i*PrOH); HPLC retention volumes: 107 mL (CH_3CN), 98 mL (*i*PrOH/CH_3CN 1:1), 100 mL (*i*PrOH/CH_3CN 2:1), 96 mL (*i*PrOH/CH_3CN 4:1), 101 mL (*i*PrOH/CH_3CN 8:1), 121 mL (*i*PrOH/CH_3CN 12:1), 119 mL (*i*PrOH/CH_3CN 18:1), 220 mL (*i*PrOH); ^{1}H NMR (360 MHz, [D$_6$]acetone): $\delta = 7.58$ (t, $J = 8.2$ Hz, 2H; CH_{ar}), 7.40 (t, $J = 7.5$ Hz, 2H; CH_{ar}), 7.27 (d, $J = 7.7$ Hz, 1H; CH_{ar}), 6.37 (d, $J = 6.6$ Hz, 2H; η-CH_{ar}), 6.23 (d, $J = 6.6$ Hz, 2H; η-CH_{ar}), 5.59 (s, 5H; Cp), 3.85 (s, 3H; OCH_3); ^{13}C NMR (91 MHz, [D$_6$]acetone): $\delta = 154.38$ (C_{ar}O(η-Ph)), 133.49 (η-C_{ar}OCH$_3$), 131.85 (C_{ar}H), 131.70 (η-C_{ar}OPh), 127.64 (C_{ar}H), 121.73 (C_{ar}H), 81.63 (Cp), 75.26 (η-C_{ar}H), 73.41 (η-C_{ar}H), 58.17 (OCH_3); IR (KBr): $\tilde{\nu} = 3447$, 3118, 1482, 1238, 1008, 839, 779, 693 cm^{-1}; UV/Vis (CH_3CN): λ_{max} (ε) = 264 (5700), 222 (14600), 198 nm (56700 mol^{-1} dm^3 cm^{-1}); MS (FAB +, NBA): *m*/*z* (%): 366/367/369 (56/100/56) $[M]^+$; HRMS (FAB): calcd for $C_{18}H_{17}O_2{}^{102}Ru$ $[M]^+$: 367.0263, found 367.0237; elemental analysis calcd (%) for $C_{18}H_{17}F_6O_2PRu$ (511.37): C 42.28, H 3.35, found C 42.03, H 3.48.

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