CHEMISTRY
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Accepted Article

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To be cited as: *Chem. Eur. J.* 10.1002/chem.201801271

Link to VoR: http://dx.doi.org/10.1002/chem.201801271

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Multifunctional Cyclopentadiene as a Scaffold for Combinatorial Bioorganometallics in $[(\eta^5\text{-}C_5H_2R_1R_2R_3)M(CO)_3]$ (M = Re, ^{99m}Tc) Piano-stool Type Complexes

Angelo Frei*,[a] Bernhard Spingler[a] and Roger Alberto[a]

Abstract: Multifunctional cyclopentadiene ligands and their rhenium and ^{99m}Tc complexes were prepared along a versatile synthetic route. The properties of these Cp-ligands can be tuned on demand, either during their synthesis (variation of R_1) or through post-synthetic functionalization with two equal or different vectors (V_1 and V_2). Variation of these groups enables a combinatorial approach in the synthesis of bioorganometallic complexes. This is demonstrated by the preparation of Cp-ligands containing both electron-donating and withdrawing groups at the R_1 position and their subsequent homo- or hetero-functionalization with biovector models (benzylamine and phenylalanine) under standard amide bond formation conditions. All ligands can be coordinated to the *fac*-$[Re(CO)_3]^+$ and *fac*-$[^{99m}Tc(CO)_3]^+$ core, leading to tetra-functional complexes *via* straight-forward and functional-group tolerant procedures. Importantly, the ^{99m}Tc complexes were prepared in one-step, in 30 min and under aqueous conditions from generator eluted $[^{99m}TcO_4]^-$.

Introduction

The combination of organometallic complexes with biologically active, organic molecules or fragments has become an intensely researched field in medicinal inorganic chemistry. These bioorganometallic complexes play a distinct role and benefit from a series of properties different from coordination compounds.[1] They may form integrated substructures in pharmaceutically active lead compounds such as in the tamoxifen/ferrocifen couple,[2] exert cytotoxicity through metal-mediated interactions with proteins or nucleic acids as in the case of the $[(\eta^6\text{-arene})Ru]^{2+}$ fragment[3] or form *de novo* parts as e.g. in bioorganometallic kinase inhibitors.[4] Ferrocene (Fc) represents one of the main building blocks in this field and the cyclopentadienyl (Cp) ligand plays an important role in all Fc-based bioorganometallic concepts. The majority of Cp-based bioorganometallic complexes comprises one single additional functionality, a pendent targeting moiety, a cytotoxic or otherwise biologically active agent. Cp-ligands are not only found in ferrocene but also in Re/^{99m}Tc piano-stool type complexes. We recently reported two examples in which such Re/^{99m}Tc complexes were conjugated to carbonic anhydrase inhibitors or cytotoxic doxorubicin.[5] Since biological activities of group 7 piano-stool complexes are rather overall structure- than metal-based, a combination of rhenium and ^{99m}Tc complexes is a complementary strategy in theranostics; the rhenium complex for therapy and its ^{99m}Tc homologue for imaging. This combination is interesting since ^{99m}Tc is still core in Single Photon Emission Tomography (SPECT)[6] due to its half-life ($t_{1/2}$ = 6.02 h), decay characteristics and, of growing importance, its price.[7] Since 2001 only a limited number of new ^{99m}Tc imaging agents have been introduced into clinical routine.[8] This mirrors the challenges encountered when aiming at introducing a well-defined transition metal complex into a targeting molecule in quantitative yields and in one-step as required for routine clinical application.[9] The preparation of *fac*-$[^{99m}Tc(OH_2)_3(CO)_3]^+$ was a step in this direction and a wide variety of complexes based on the fac-$[^{99m}Tc(CO)_3]^+$ core have been explored ever since.[5a, 10] Recently, a PSMA targeting biovector coupled to the tricarbonyl core made it into phase III clinical trials.[11] The general concept of targeted radiotracers is the conjugation of a receptor-binding molecule with a ligand for coordination to the respective metal centre or complex fragment, also referred to as the bifunctional ligand or pendent approach.

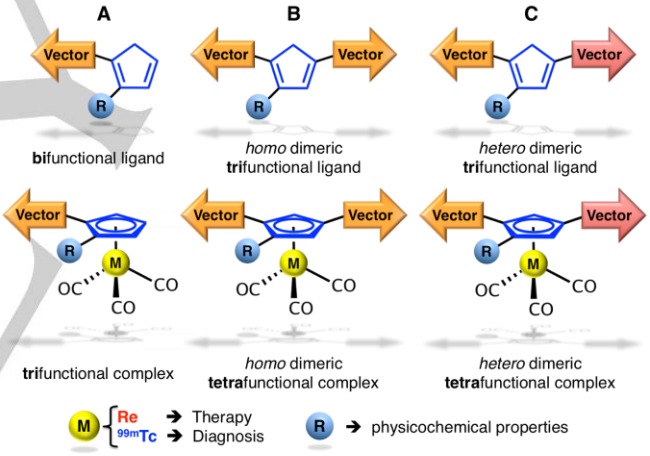

Figure 1. Overview of the different poly-modalities accessible with the new multifunctional cyclopentadienyl ligands.

Current pharmaceutical research aims at combining multiple modalities such as targeting and cytotoxicity, in one single molecule. This approach has not yet found the consideration it deserves in bioorganometallic chemistry, probably since the modalities are ideally conjugated to one single ligand. With respect to imaging, the concept is further affected by the fact that a multi-modality ^{99m}Tc complex must be synthesized in one single step from $[^{99m}TcO_4]^-$ and in water.
Cp-ligands represent a scaffold to which multiple functionalities can be bound according to elaborate organic synthetic strategies. In addition, Cp is a small and strongly binding ligand with a low molecular weight. After coordination to the *fac*-$[M(CO)_3]^+$ core, the complexes are highly inert and of zero charge. Our group reported a one-pot synthesis of singly functionalized $\{(\eta^5\text{-}C_5H_5)^{99m}Tc\}$ complexes in water under moderate heating.[12] By derivatizing di-cyclopentadiene "Thiele's acid" through amid bond formation, chemically stable and functionalized Cp-precursors and complexes of the type $[(\eta^5\text{-}C_5H_4R)^{99m}Tc(CO)_3]$ became accessible.[5a, 13]

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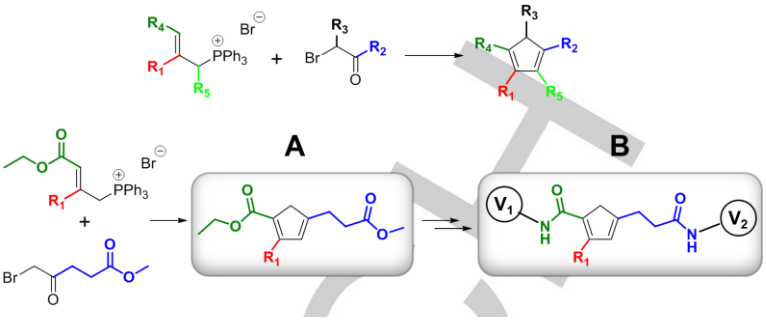
The bifunctional ligand approach, with or without Cp, does not immediately comprise the option of combining multiple, different or equal, targeting vectors. Multimeric molecular imaging agents would offer many new opportunities such as targeting of different sites, enhancing binding affinities and/or addition of a cytotoxic payload. Only a few multimeric molecular ^{99m}Tc imaging agents have been reported thus far, mainly by Liu *et al.* on integrin $\alpha_v\beta_3$ targeting multimeric cyclic-RGD peptide oligomers.[14] For Cp, all approaches described above are synthetically incompatible with multi-functionalization as required for multimeric targeting agents. We reported recently the synthesis of water soluble Re/^{99m}Tc complexes with a Cp-ligand for coordination to the $\{^{99m}Tc(CO)_3\}^+$ core and two carboxylato groups in 1,2-position for potential conjugation to two biomolecules.[15] In this study, we extend the flexibility of the multi-functional Cp-approach to a $C_5H_3R^1R^2R^3$-type scaffold, which can be mono- (Figure 1A) or homo (Figure 1B) and hetero (Figure 1B) bi-functionalized with respect to targeting molecules or other biovectors. The choice of biovectors or molecular functionalities attached to the central Cp-core is highly flexible which allows for a systematic exploration of new imaging compounds. The ligands as such do not undergo Diels-Alder dimerization and are water and air-stable at room temperature and up to 220 °C. Mono-, homo- and hetero-functionalization of the ligand is shown with model vectors on both the free ligand and the "cold" rhenium complexes. The corresponding ^{99m}Tc complexes were prepared in a one-pot reaction from $[^{99m}TcO_4]^-$ and in high radiochemical yields. Altogether, we present a ligand platform that allows for the synthesis of tetra-functional Re/^{99m}Tc complexes but also for other elements. Combinatorial variation of all pendent groups will lead to a wide variety of structurally different but functionally identical matched-pair complexes.



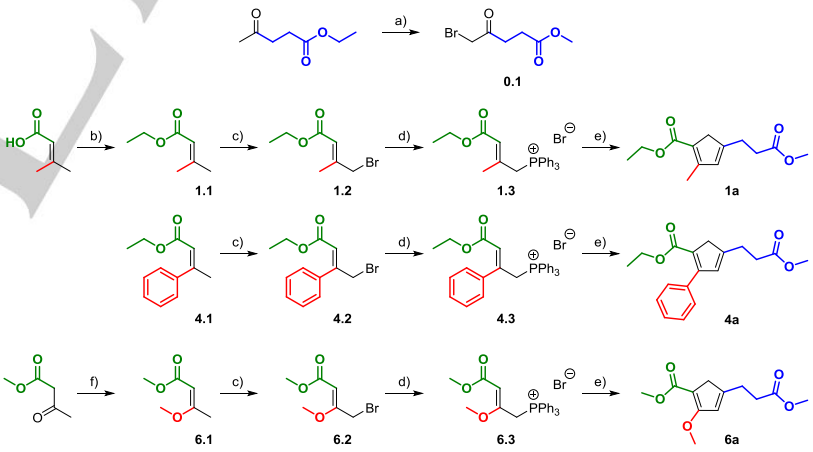
Scheme 1. General synthesis of multifunctional Cp-ligands (top) and the synthetic strategy pursued in this study (bottom): A) variation of R_1 to modify the chemical properties of the Cp. B) variation of the conjugated vectors (V_1, V_2) to modify biological properties of the Cp.

Results and Discussion

Design of Cp-Ligands. The syntheses of the multi-functional cyclopentadiene ligands in this study as shown in Figure 1 are based on a procedure by Hatanaka *et al.*[16]. A variety of triphenyl-phosphonium salts with different substituents R_1 react with α-bromo-ketones under mild conditions to form triply substituted Cp's in good yields. The most general concept towards such multi-functionalized Cp's is shown in Scheme 1 (top). The carboxylate group directly attached to the Cp-ring (R_4, green in Scheme 1) and the terminal carboxylate in R_2 (blue) allow for later conjugation of two equal or different biological functions V_1 and V_2. This synthetic approach thus enables a versatile alteration of three functionalities; R_1 for guiding the chemical properties and the two carboxylate groups for conjugation of bioactive functionalities (Scheme 1, A and B). The original literature also highlights the possibility to vary R_2 and to introduce further functionalities at R_3, while modifications of R_4 and R_5 are also conceivable.

We did not alter all these positions on the central cyclopentadiene scaffold but choose ethyl 5-bromo-4-oxopentanoate (**0.1** Scheme 2) as the standard α-bromo-ketone for the bi-functionalization, keeping R_2 thereby constant with the option of conjugating a vector V_2 to this position.

The $(CH_2)_2$-spacer in R_2 was introduced in this building block design to reduce interference of the terminal ester group with the reactivity of the α-ketone. Furthermore, this spacer suppresses the undesired rearrangement of the Cp-double bond in the final ligand, as previously observed in our group in mono-functional Cp's with one CH_2 group between Cp and the ester group. The ester group on the phosphonium building block (R_4, green in Scheme 1) was also kept constant and will enable the conjugation of a 2nd bioactive moiety V_1 to the Cp-scaffold after cyclization. In its essence, the approach towards multi-functionalized Cp derivatives focuses on the building block A in Scheme 1, prepared from ethyl 5-bromo-4-oxopentanoate and phosphonium salts with a methyl (**1a**), a phenyl (**4a**) and a methoxy (**6a**) group as R_1, red in Scheme 1 to show that both electron donating and withdrawing groups can equally be bound to the Cp-ring. Introduction of V_1 and V_2 will lead to the trifunctional Cp derivatives as shown with B in Scheme 1. Since metal complexes with Cp-ligands of type A have already been reported for iron[17], ruthenium[18], cobalt[19] and rhodium[17a, 20], we suggest that Cp derivatives of type B can equally be applied to other metal centres.



Scheme 2. Synthetic route to the Cp-ligands **1a**, **4a**, **6a**. Reaction conditions: a) Br_2, MeOH, 0 °C, 24 h, 23%. b) cat. H_2SO_4, EtOH, reflux, overnight, 87%. c) NBS, cat. AIBN, MeOAc, MW; 110 °C, 15 min (**1.2**, 83%); 110 °C 12 min (**4.2**, 97%); 85 °C, 30 s (**6.2**, 73%). d) PPh_3, dry toluene, 25 °C, 24 h (**1.3**, 84%; **4.3**, 65%; **6.3**, 54%). e) **0.1**, DCM/sat. $NaHCO_3$, 25 °C, 48 h (**1a**, 66%; **4a**, 27%; **6a**, 23%). f) Trimethoxymethane, H_2SO_4, 25 °C, 25 h, 82%.

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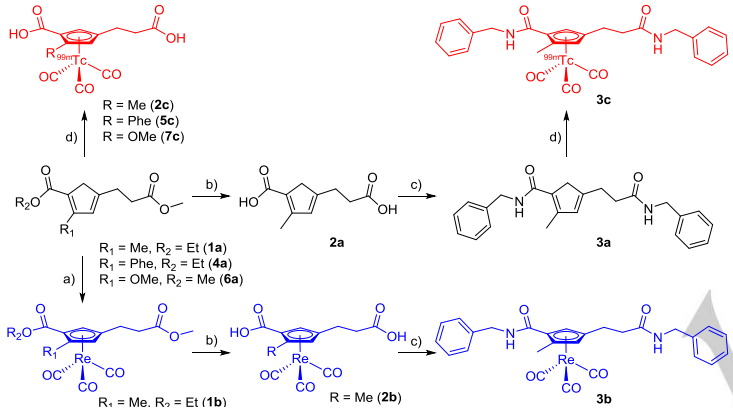
Synthesis and Characterization. The ligands **1a**, **4a** and **6a** represent the cores of the later trifunctional Cp-systems. These precursors were synthesized following the reported procedure with minor changes to improve yields and isolations (see Supplementary Information for details).[16] Notably, the radical brominations of **1.1**, **4.1**, and **6.1** (Scheme 2) to yield **1.2**, **4.2** and **6.2** were carried out under microwave conditions in less than 15 min (30 s at 85 °C for **6.1**). The harmful solvent CCl_4 could be replaced by methylacetate without loss of performance. Subsequent reactions with triphenyl-phosphine and cyclizations with 5-bromo-4-oxopentanoate lead straight to the Cp-ligands **1a**, **4a** and **6a** in moderate to good yields and in up to gram quantities after purification by silica column chromatography.



Scheme 3. Synthetic route towards bis-homo functionalized Re and ^{99m}Tc complexes. Reaction conditions: a) Re_2CO_{10}, *o*-xylene, MW, 220 °C, 15 min (**1b**, 76%; **4b**, 83%; **6b**, 44%). b) NaOH, MeOH, MW, 120 °C, 15 min (**2b**, 68%; **5b**, 92%; **7b**, 48%). c) benzylamine, HOBt, EDC, DMF, 25 °C, 24 h, (**3a**, 38%; **3b,** 16%). d) $[TcO_4]^-$, sodium boranocarbonate, sodium tartrate, sodium tetraborate, H_2O, MW, 120 °C, 30 min.

The rhenium complexes **1b**, **4b** and **6b** with all three Cp-derivatives were obtained by refluxing the respective ligand **1a**, **4a** and **6a** with Re_2CO_{10} for multiple days in *o*-xylene (Scheme 3). Under microwave conditions, the reaction solutions were heated to 220 °C and the reaction time reduced to 15 min (as described in the supplementary information) without loss of yields. For **1b**, UPLC analysis indicated complete consumption of starting material and sufficiently pure complex could be obtained without further purification. Complexes **4b** and **6b** were purified by column chromatography on silica. Ester hydrolysis to **2b**, **5b** and **7b** was achieved under basic conditions by either refluxing overnight under basic conditions or by microwave heating at 120 °C for 15 min. To demonstrate the possibility of bis-homo functionalization, ligand **2a** and complex **2b** were reacted with two equivalents of a model biovector, benzylamine, yielding the respective bis-amide compounds **3a** and **3b** after purification by preparative HPLC. Single crystals suitable for X-ray analysis were obtained for **2b** and **3b** (Figure 2).

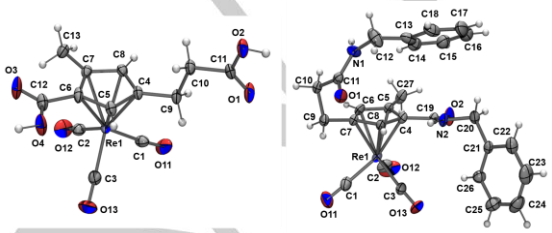
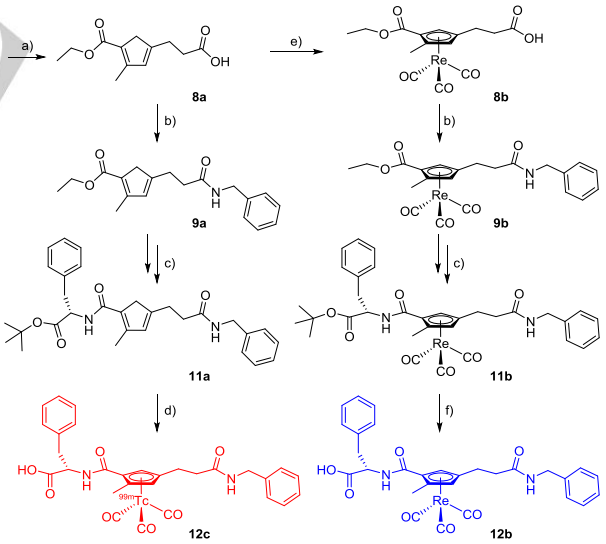


Figure 2. Crystal structures of **2b** and **3b**. Displacement ellipsoid representation. Ellipsoids are drawn at 50% probability. Important bond lengths (Å): **2b** Re-centroid of Cp: 1.950(2), **3b** Re-centroid of Cp: 1.945(3).

Bis-hetero functionalization of the Cp-ligand 1a: To assess the full potential of this approach and to open a scope towards two different functions V_1 and V_2, i.e. bis-hetero functionalized Cp-ligands and complexes, the individual carboxylato groups must be conjugated stepwise to biovectors. We exemplify this strategy with the Cp ligand **1a**, which comprises the methyl group at the R_1 position. The first mono-functionalization was achieved by hydrolysis of **1a** with slightly less than one equivalent of NaOH, yielding exclusively **8a** (Scheme 4). One could expect a statistical distribution of hydrolysis at both ester functions but the one at the R_2 position is obviously more susceptible, leaving R_4 untouched. Subsequent amide bond formation under the previously mentioned conditions gave **9a** in good yields. By further and carefully tuning the reaction conditions, **9a** could selectively be hydrolyzed to **10a**. Reaction times longer than 5 min and pressures over 5 bar usually resulted in decomposition of the compound. For subsequent bis-hetero-functionalization, we chose O-^{t}butyl-L-phenylalanine to demonstrate that our approach is substrate tolerant with the option of extension to e.g. peptides. Along a standard peptide bond formation strategy (see ESI), **10a** was converted into **11a**, containing two different functionalities on the cyclopentadiene ring.

Bis-hetero functionalization of the rhenium complex 2b: Unlike the Cp-ligand **1a** itself, selective mono-hydrolysis of **1b** (Scheme 3) was not possible. Addition of 1 eq. of NaOH and subsequent heating gave a statistical mixture of ester-hydrolyzed products. Thus, to accomplish the rhenium complex **8b**, a direct reaction between the mono-acid ligand **8a** and Re_2CO_{10} in DMF under microwave irradiation was performed. The obtained crude mixture was directly reacted under standard peptide coupling conditions to give **9b** after purification by preparative HPLC (Figure 4). Complex **9b** was



Scheme 4. Synthetic route towards hetero-functionalized Re and ^{99m}Tc complexes. Reaction conditions: a) NaOH, MeOH, MW, 120 °C, 15 min. b) benzylamine, HOBt, EDC, DMF, 25 °C, 48 h, 69%. c) i) NaOH, MeOH, MW, 120 °C, 15 min. ii) O-tertbutyl-L-Phenylalanine, HOBt, EDC, DMF, 25 °C, 24 h, (**11a**, 26%; **11b**, 46%). d) $[TcO_4]^-$, sodium boranocarbonate, sodium tartrate, sodium tetraborate, H_2O, MW, 140 °C, 30 min. e) Re_2CO_{10}, DMF, MW, 220 °C, 15 min. f) TFA, DCM, MW, 80 °C, 15 min, 80%

then easily further hydrolyzed and functionalized with O-^{t}butyl-L-phenylalanine, yielding **11b** after preparative HPLC in 26% yield. The

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tert-butyl protecting group of **11b** could be cleaved by treatment with TFA in DCM at 80 °C, yielding **12b** as a model for the later ^{99m}Tc complexes.

The chiral centre in the attached amino acid together with the chiral planarity of the asymmetric Cp-ligand leads to the formation of two diastereomers (see Figure SI88). This was confirmed by the observation of two sets of NMR signals in both ^{1}H and ^{13}C NMR spectra of **11b** and **12b** (Figures SI83-84). All compounds were fully characterized by NMR, HPLC and HR ESI-MS. These synthetic results clearly imply that more complex biomolecules can be conjugated to both, the free ligand and to the rhenium complexes themselves. For rhenium, ligand **8a** and complex **8b** are key since they will allow the consecutive introduction of two different functionalities on the ligand (**8a**) for later labelling with ^{99m}Tc (vide infra) or on the rhenium complex (**8b**) for biological evaluation and comparison with the ^{99m}Tc complex.

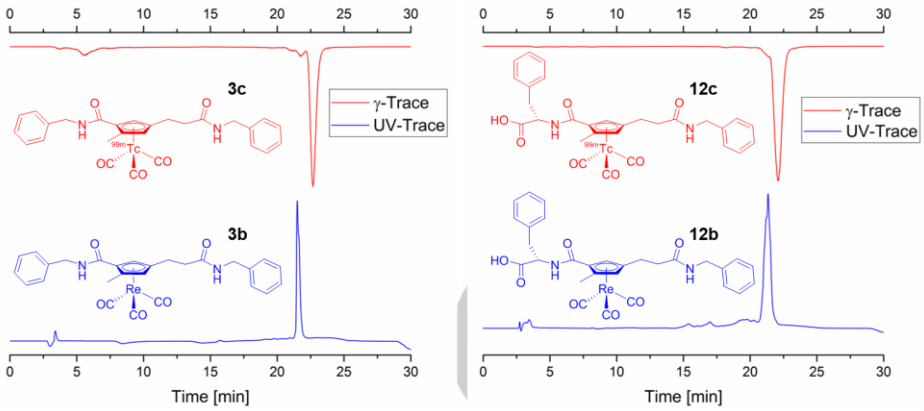

Figure 4. UV/vis- and γ-traces of the co-injection of the rhenium compounds **3b** and **12b** with the ^{99m}Tc compounds **3c** and **12c** respectively. Time differences are due to detector separation.

Radiolabelling with ^{99m}Tc: It is the common notion that Cp-systems, capable of binding in aqueous solution to the $[^{99m}Tc(CO)_3]^+$ fragment, have to comprise electron withdrawing groups directly on the cyclopentadiene scaffold. This will sufficiently acidify the ring to have at least small amounts of the ligand deprotonated and therefore prone to coordination. Accordingly, most of the approaches towards $[(\eta^5\text{-}C_5H_4\text{-}R)^{99m}Tc(CO)_3]$ type complexes comprise a carbonyl function directly on the Cp ring.[5a, 10c, 13a, 21] First, we radiolabelled the underivatized ligands **1a**, **4a** and **6a** which follow this concept of acidification and should therefore readily react with the $[^{99m}Tc(OH_2)_3(CO)_3]^+$ precursor. In a two-step approach, *fac*-$[^{99m}Tc(OH_2)_3(CO)_3]^+$ was prepared and then reacted with ligands **1a**, **4a** and **6a** at millimolar concentrations. Along this path, the ^{99m}Tc complexes **2c**, **5c** and **7c** (Scheme 3) could all be obtained in high radiochemical yields under alkaline conditions and microwave heating at 120 °C for 30 min (see experimental part). Having shown that radiolabelling of these ligands with *fac*-$[^{99m}Tc(OH_2)_3(CO)_3]^+$ was straight-forward, we attempted the direct synthesis of the ^{99m}Tc complexes (**2c**, **5c** and **7c**) directly from $[TcO_4]^-$ in a "one-pot" approach. By mixing all components in a single vial and adding directly the $[^{99m}TcO_4]^-$ generator eluate, complexes **2c**, **5c** and **7c** formed quantitatively by an improved procedure under microwave conditions in 30 min at 120 °C (Figure 3). We emphasize that these are conditions compatible with routine applications in clinics.

As typical ^{99m}Tc concentrations are too low for standard chemical characterizations of the formed complexes by e.g. NMR, the accepted procedure for their characterizations is HPLC co-injection with the "cold" rhenium homologue and comparison of retention times (γ-trace for ^{99m}Tc, UV-trace for Re). Figure 3 shows the HPLC traces of the respective ^{99m}Tc complexes as obtained after direct preparations in quantitative yields with all three ligands from $[^{99m}TcO_4]^-$. Further purification was not required. Due to the basic conditions, the ester groups hydrolysed during the labelling process, wherefore co-injections were performed with the di-acid rhenium homologues (**2b**, **5b** and **7b**). The retention times match, corroborating the identity of the two homologous complexes with Re and ^{99m}Tc.

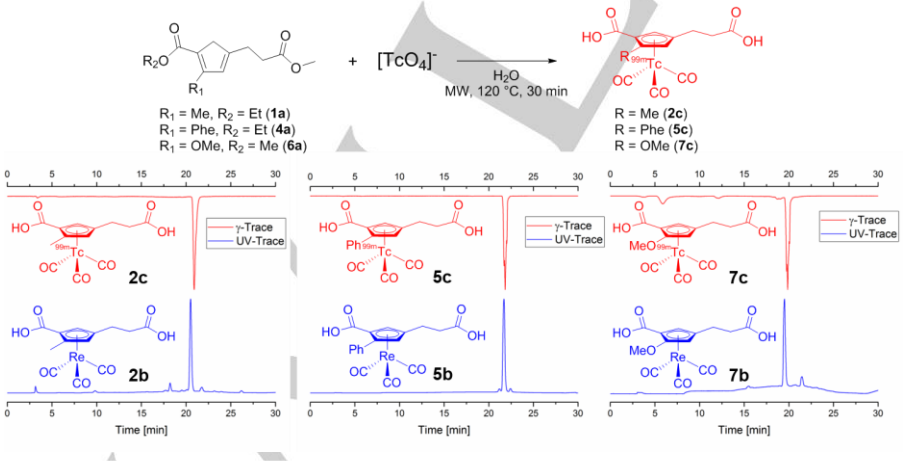

Figure 3. General reaction scheme for the "one-pot" synthesis of ^{99m}Tc compounds (top). UV- and γ-traces of the co-injection of the rhenium compounds **2b**, **5b** and **7b** with the ^{99m}Tc compounds **2c**, **5c** and **6c** respectively (bottom). Differences in retention times are due to detector separation.

The Cp compounds **3a** (homo-difunctionalized) and **11a** (hetero-difunctionalized) bear two model functionalities V_1 and V_2 at positions R_2 and R_4 in the basic cyclopentadiene structure, conjugated via an amide to the cyclopentadiene ring. These ligands represent the basic structure for a combinatorial approach since essentially any two amine-bearing biovectors can be added. The labeling of such more complex systems in general and **3a** and **11a** in particular is an exemplary step in the preparation of multi-functional molecular imaging agents. Accordingly, by following the preparations as described above, ligands **3a** and **11a** could be labelled along the one-pot procedure directly from $[^{99m}TcO_4]^-$, giving the corresponding ^{99m}Tc complexes **3c** and **12c** in good yields (Figure 4). Slightly higher temperatures and reaction times were

required. As a convenient "side effect", the *tert*-butyl protective group was concertedly cleaved during the reaction in case of **11a**. Taken together, these results demonstrate the possibility to synthesize ^{99m}Tc piano-stool type molecular imaging agents with structurally complex and multifunctional Cp ligands in one step directly from $[^{99m}TcO_4]^-$ in a straight-forward and efficient way. The option of altering V_1 and V_2 (phenyl-alanine and benzyl-amine in our case) opens a path towards further combinations of biologically active moieties.

Conclusions

We present versatile synthetic routes towards multiply substituted cyclopentadiene, which are the basis for the subsequent preparation of multifunctional ligands. Both, the physico-chemical (group R_1) as well as the biological (V_1 and V_2) properties can be tuned individually in the same ligand. We have furthermore shown that these cyclopentadiene scaffolds serve as a ligand platform in bioorganometallic ^{99m}Tc chemistry that allows the introduction of multiple modalities in a straightforward way. The ligands as such can be prepared separately with functionalities V_1 and V_2 according to the target requirements. The "innocent" group R_1 on the Cp scaffold influences the physico-chemical properties such as lipo/hydrophilicity while leaving the targeting properties untouched. Three representative ligands (**1a**, **3a**, **5a**) with different R_1 groups have been synthesized, fully characterized and coordinated to the *fac*-$[Re(CO)_3]$ moiety. As a further proof-of-concept, **1a** was both bis-homo - and bis-hetero functionalized with two simple biovector-models. Established amide bond formation chemistry for the vector conjugation, ensures its applicability to a wide variety of modalities. The combination of these ligands with the theranostic pair Re and ^{99m}Tc leads to tetra-functional complexes. Their synthesis is both straightforward, highly tolerant to different functionalities and, most importantly, the ^{99m}Tc homologues are prepared in one step directly from generator eluted $[^{99m}TcO_4]^-$. We envision that this ligand platform will enable a combinatorial approach towards targeted and multimodal bioorganometallic complexes.

Experimental Section

Materials. All chemicals were of reagent-grade quality or higher and were obtained from commercial suppliers. Solvents were used as received or dried over molecular sieves. Sodium boranocarbonate was a gift from Mallinckrodt Medical B.V. (The Netherlands). $Na[^{99m}TcO_4]$ in 0.9% saline was eluted from a ^{99}Mo/^{99m}Tc UTK FM generator purchased from Mallinckrodt Medical B.V.

Instrumentation and methods. ^{1}H and ^{13}C-NMR spectra were recorded in deuterated solvents on a Bruker DRX 400 (^{1}H: 400 MHz, ^{13}C: 100.6 MHz) or DRX 500 (^{1}H: 500 MHz ^{13}C: 125.8 MHz) MHz spectrometer at 300 K. The chemical shifts, δ, are reported in ppm (parts per million) relative to residual solvent peaks. IR spectra were obtained with a PerkinElmer Spectrum Two spectrometer. UPLC-ESI-MS was performed on a Waters Acquity UPLC System coupled to a Bruker HCT^{TM}, using an Acquity UPLC BEH C18 1.7µm (2.1 x 50 mm) column. UPLC solvents were formic acid (0.1% in millipore water) (solvent A) and acetonitrile UPLC grade (solvent B). The temperature was regulated with a Peltier thermostatic system to the specified temperatures. High-resolution mass spectrometry (HR-MS) was performed on a Thermo DFS double-focusing system (ThermoFisher Scientific, Germany).
Preparative HPLC was performed on a Varian ProStar 320 system, using a Dr. Maisch Reprosil C18 100-7 (40 x 250 mm) column (flow rate: 40.0 ml/min) or a LiChroCART RP-18e (10 x 250 mm) column. HPLC solvents were 0.1% trifluoroacetic acid (solvent A) and acetonitrile (solvent B), HPLC grade. Microwave reactions were performed using a Biotage Initiator+ Robot Eight or Anton Paar (AP) Monowave 200 instrument. Analytical HPLC was performed on a Merck Hitachi L7000 system, equipped with a L-7400 UV-detector and an in-line radio-detector Berthold FlowStar LB513, using an analytical Macherey-Nagel Nucleosil C18 5 μm (4.6 × 250 mm) column. HPLC solvents were 0.1% trifluoroacetic acid (solvent A) and acetonitrile, HPLC grade (solvent B). Analytical UPLC was performed on a VWR Hitachi Chrommaster Ultra, using an Acquity UPLC BEH C18 1.7µm (2.1 x 50 mm) column. UPLC solvents were trifluoroacetic acid (0.1% in millipore water) (solvent A) and acetonitrile UPLC grade (solvent B). HPLC and UPLC gradients are given in the Supporting Information.

Synthesis of Cp-ligands and Re-complexes.

General Procedure for the synthesis of complexes 1b, 4b and 6b
A solution of the complex (1 equiv.) and $Re_2(CO)_{10}$ (0.52 equiv) in *o*-Xylene (2 ml) in a Anton Paar microwave vial (10 ml) equipped with a stirring bar was heated to 220 °C for 15 min (Careful, toxic CO gas is released during the reaction, take appropriate precautions). The solvent was evaporated *in vacuo*, yielding pure complex after column chromatography on silica gel (no further purification was necessary for complex **1b**).

General procedure for the synthesis of complexes 2b, 5b and 7b
A solution of the complex (1 equiv) in MeOH (1 ml) and 1 M NaOH (0.5 ml) in a Anton Paar microwave vial (10 ml) was heated by microwave to 120 °C for 15 min. The crude was diluted with 1 M HCl (20 ml) and washed with DCM twice (2 x 20 ml). The combined organic phase was washed once with water (20 ml) dried over $MgSO_4$ and the solvent removed *in vacuo* yielding pure complex.

2a. 1a (31 mg, 0.13 mmol) was dissolved in MeOH (1 ml) in a Anton Paar microwave vial (10 ml) equipped with a stirring bar. 1 M NaOH was added (0.4 ml) and the solution was heated by microwave to 120 °C for 15 min. UPLC measurement showed complete consumption of the starting material. The reaction solution was diluted with H_2O (5 ml) and neutralized to pH = 3 by dropwise addition of 1 M HCl. **2a** was obtained by evaporating the solvent *in vacuo* and was used without further purification. UPLC (gradient U1): RT = 1.91 min.

3a. **2a** (48 mg, 0.21 mmol) was dissolved in DMF (2 ml). Benzylamine (0.53 ml, 0.49 mmol) and HOBt (66 mg, 0.49 mmol) were added under stirring. After 5 min, EDC (93 mg, 0.49 mmol) and DIPEA (0.170 ml, 0.98 mmol) were added and the solution was stirred at room temperature for 48 h. The solvent was removed *in vacuo* and the crude was purified by preparative HPLC (Method A) and **3a** was obtained as a yellowish powder (30 mg, 0.08 mm, 38 %). UPLC (gradient U1): RT = 2.65 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.25 (m, 3H), 2.49 (m, 2H), 2.72 – 2.75 (m, 2H), 3.25 – 3.26 (m, 2H), 4.34 (s, 2H), 4.46 (s, 2H), 6.11 (s, 1H), 7.19 – 7.30 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 15.39, 27.54, 36.51, 43.78, 44.05, 44.69, 127.99, 128.18, 128.40, 128.48, 129.45, 129.52, 130.64, 133.87,

139.95, 140.68, 152.27, 152.95, 168.03, 174.92. HR-ESI mass spectrum (MeOH): found 375.20669; calcd. for $[C_{24}H_{27}O_2N_2]$ 375.20670.

3b. 2b (47 mg, 0.1 mmol) was dissolved in DMF (5 ml). Benzylamine (0.023 ml, 0.21 mmol) and HOBt (29 mg, 0.21 mmol) were added under stirring. After 5 min, EDC (41 mg, 0.21 mmol) and DIPEA (0.073 ml, 0.42 mmol) were added and the solution was stirred for 24 h. The solvent was removed *in vacuo* and the crude was purified by preparative HPLC (Method A) and **3a** was obtained as a pale yellow powder (10 mg, 0.016 mmol, 16 %). Single crystals were obtained by slow evaporation of a MeOH solution. UPLC (gradient U1): RT = 3.20 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.45 (t, ^{3}J = 7.2 Hz, 2H), 2.48 (s, 3H), 2.64 – 2.78 (m, 2H), 4.32 – 4.51 (m, 4H), 5.40 (d, J^3 = 2.0 Hz, 1H), 5.97 (d, J^3 = 2.0 Hz, 1H) 7.21 – 7.30 (m, 10H) 8.40 – 8.44 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 14.17, 25.30, 38.73, 43.98, 44.12, 49.00, 84.82, 86.78, 90.93, 108.57, 111.42, 128.14, 128.26, 128.38, 128.56, 129.50, 129.57, 139.85, 139.99, 166.28, 173.85, 195.29. IR bands (Golden Gate, cm^{-1}): 2017, 1906. HR-ESI mass spectrum (MeOH): found 645.13941; calcd. for $[C_{27}H_{26}O_5N_2Re+H^+]$ 645.13937.

8a. 1a (38 mg, 0.16 mmol) was dissolved in MeOH (1 ml) in a Anton Paar microwave vial (10 ml) equipped with a stirring bar. 1 M NaOH was added (0.150 ml, 0.150 mmol) and the solution was heated to 120 °C for 15 min. UPLC measurement showed complete consumption of the starting material. The reaction solution was diluted with H_2O (5 ml) and neutralized to pH = 3 by dropwise addition of 1 M HCl. **8a** was obtained by evaporating the solvent *in vacuo* and was used without further purification. UPLC (gradient U1): RT = 2.49 min.

9a. 8a (59 mg, 0.26 mmol) was dissolved in DMF (4 ml). Benzylamine (0.031 ml, 0.29 mmol) and HOBt (39 mg, 0.29 mmol) were added under stirring. After 5 min, EDC (55 mg, 0.29 mmol) and DIPEA (0.100 ml, 0.57 mmol) were added and the solution was stirred for 48 h. The solvent was removed *in vacuo* and the crude was purified by preparative HPLC (Method A) and **9a** was obtained as a yellow oil (57 mg, 0.18 mmol, 69 %). UPLC (gradient U1): RT = 2.76 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 1.29 (t, J^3 = 7.1 Hz, 3H), 2.27 (t, J^3 = 2.3 Hz, 3H), 2.48 (t, J^3 = 7.5 Hz, 2H), 2.76 (t, J^3 = 7.5 Hz, 2H), 3.21 (m, 2H), 4.18 (q, J^3 = 7.1 Hz, 2H), 4.42 (d, J = 5.7 Hz, 2H), 6.08 (s, 1H), 6.13 (t, J = 5.3 Hz, 1H), 7.20 – 7.33 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm): 14.57, 15.59, 26.73, 35.89, 43.93, 44.42, 59.63, 127.20, 127.79, 127.89, 128.88, 133.07, 137.86, 153.11, 155.85. 165.26, 172.61. HR-ESI mass spectrum (MeOH): found 314.17497; calcd. for $[C_{19}H_{23}NO_3+H^+]$ 314.17507.

10a. 9a (50 mg, 0.16 mmol) was dissolved in MeOH (2 ml) in a Anton Paar microwave vial (10 ml) equipped with a stirring bar. 1 M NaOH (1 ml) was added and the solution was heated to 120 °C for 5 min. UPLC measurement showed complete consumption of the starting material. The reaction solution was diluted with H_2O (5 ml) and neutralized to pH = 3 by dropwise addition of 1 M HCl. **10a** was obtained by evaporating the solvent *in vacuo* and was used without further purification. UPLC (gradient U1): RT = 2.33 min.

11a. The crude of **10a** obtained from **9a** (36 mg, 0.115 mmol) was dissolved in DMF (3 ml). O-tertbutyl-L-Phenylalanine (33 mg, 0.13 mmol) and HOBt (17 mg, 0.13 mmol) were added under stirring. After 5 min, EDC (24 mg, 0.13 mmol) and DIPEA (0.044 ml, 0.25 mmol) were added and the solution was stirred for 24 h. The solvent was removed *in vacuo* and the crude was purified by preparative HPLC (Method A) and **11a** was obtained as a yellow oil (15 mg, 0.03 mmol, 26 % from **9a**). UPLC (gradient U1): RT = 3.19 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 1.41 (s, 9H), 2.22 (t, J^3 = 2.2 Hz, 3H), 2.43 (t, J^3 = 7.6 Hz, 3H), 2.75 (t, J^3 = 7.6 Hz, 2H), 3.12 – 3.16 (m, 4H), 4.44 (d, J^3 = 5.7 Hz, 2H), 4.86 (m, 1H), 5.80 (m, 1H), 5.98 (d, J^3 = 7.5 Hz, 1H), 6.04 (s, 1H), 7.15 – 7.33 (m, 10H). ^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm): 15.37, 26.50, 28.13, 35.98, 38.35, 43.83, 53.40, 76.90, 77.16, 77.41, 82.48, 127.05, 127.73, 127.94, 128.46, 128.60, 128.89, 129.57, 129.74, 133.12, 136.54, 138.26, 150.68, 151.24, 164.70, 171.23, 171.79. HR-ESI mass spectrum (MeOH): found 489.27518; calcd. for $[C_{30}H_{35}N_2O_4+H^+]$ 489.27478.

8b. 8a (80 mg, 0.34 mmol) was dissolved in DMF (4 ml) in an Anton Paar microwave vial (10 ml). $Re_2(CO)_{10}$ (110 mg, 0.17 mmol) was added and the mixture was heated by microwave to 220 °C for 15 min (Careful, toxic CO gas is released during the reaction, take appropriate precautions). UPLC showed complete consumption of the starting material. The crude solution was dried in vacuo and used without further purification in the next step. UPLC (gradient UMS1): RT = 2.88 min.

9b. 8b (154 mg, 0.31 mmol) was dissolved in DMF (5 ml). Benzylamine (0.037 ml, 0.34 mmol) and HOBt (46 mg, 0.34 mmol) were added under stirring. After 5 min, EDCI (66 mg, 0.34 mmol) and DIPEA (0.120 ml, 0.69 mmol) were added and the solution was stirred for 24 h. The solvent was removed *in vacuo* and the crude was purified by preparative HPLC (Method A) and **9b** was obtained as an orange oil (45 mg, 0.08 mmol, 26%). UPLC (gradient U1): RT = 3.23 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 1.31 (t, J^3 = 7.1 Hz, 3H), 2.40 (m, J = 3.3 Hz, 2H), 2.48 (s, 3H) 2.68 – 2.88 (m, 2H), 4.17 – 4.34 (m, 2H), 4.45 (d, J = 5.7, 2 H), 5.20 (d, J = 2.1 Hz, 1H), 5.77 (d, J = 2.2 Hz, 1H), 5.85 (t, 1 H), 7.25 – 7.36 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm): 13.87, 14.28, 23.75, 38.07, 44.10, 61.13, 84.61, 85.73, 86.06, 107.58, 110.76, 127.95, 128.04, 128.99, 137.78, 164.92, 171.19, 193.56. IR bands (Golden Gate, cm^{-1}): 2021, 1918. HR-ESI mass spectrum (MeOH): found 584.10780; calcd. for $[C_{22}H_{23}O_6NRe+H^+]$ 584.10774.

10b. A solution of **9b** (43 mg, 0.074 mmol) in MeOH (2 ml) and 1 M NaOH (0.15 ml) in a Anton Paar microwave vial (10 ml) was heated by microwave to 110 °C for 15 min. The crude was diluted with 1 M HCl (10 ml) and washed with DCM twice (2 x 10 ml). The combined organic phase was washed once with water (10 ml) dried over $MgSO_4$ and the solvent removed *in vacuo* yielding **10b** as an orange solid (32 mg, 0.058 mmol, 78 %). The product was used in the next step without further purification. UPLC (gradient U1): RT = 2.81 min. ^{1}H NMR (400 MHz, CD_3OD): δ (ppm): 2.45 (s, 3H), 2.45 (m, 2H), 2.61 – 2.68 (m, 1H), 2.75 – 2.82 (m, 1H), 4.37 (m, 2H), 5.42 (d, J^3 = 2.1 Hz, 1H), 5.89 (d, J^3 = 2.2 Hz, 1H), 7.21 – 7.32 (m, 5H). ^{13}C NMR (101 MHz, CD_3OD): δ (ppm): 12.63, 23.71, 37.17, 42.77, 84.60, 86.65, 107.46, 110.82, 126.87, 127.26, 128.18, 138.49, 166.58, 172.44, 193.60. IR bands (Golden Gate, cm^{-1}): 2021, 1917. HR-ESI mass spectrum (MeOH): found 554.06196; calcd. for $[C_{20}H_{18}O_6NRe-H^+]$ 554.06189.

11b. 10b (181 mg, 0.326 mmol) was dissolved in DMF (2 ml). O-tertbutyl-L-Phenylalanine (93 mg, 0.36 mmol) and HOBt (49 mg, 0.36 mmol) were added under stirring. After 5 min, EDCI (69 mg, 0.36 mmol) and DIPEA (0.125 ml, 0.72 mmol) were added and the solution was stirred for 24 h. The solvent was removed *in vacuo* and the crude was purified by preparative HPLC (Method A) and **11b** was obtained

as a pale red solid and directly used for the next step (112.8 mg, 0.149 mmol, 46%). UPLC (gradient U1): RT = 3.68 min.

12b. 11b (15 mg, 0.02 mmol**)** was dissolved in DCM (2 ml) in an Anton Paar microwave vial (10 ml). TFA (0.5 ml) was added and the solution was heated to 80 °C by microwave for 15 min. The solvent was evaporated and the crude was purified by preparative HPLC (Method A) and **12b** was obtained as an orange oil (15 mg, .0.16 mmol, 80 %). UPLC (gradient U1): RT = 3.08 min, 3.13 min. ^{1}H NMR (500 MHz, CD_3OD): δ (ppm): 2.31 (s, 3 H), 2.37 (s, 3H), 2.42 – 2.45 (m, 4H), 2.61 – 2.67 (m, 2H), 2.72 – 2.79 (m, 2H), 3.04 – 3.09 (m, 2H), 3.25 – 3.29 (m, 2H), 4.34 – 4.35 (m, 4H), 4.71 – 4.75 (m, 2H), 5.35 (d, J^3 = 2.0 Hz, 1H), 5.38 (d, J^3 = 2.0 Hz, 1H), 5.95 (d, J^3 = 2.0 Hz, 1H), 5.96 (d, J^3 = 2.0 Hz, 1H), 7.16 – 7.32 (m, 20H). ^{13}C NMR (101 MHz, CD_3OD): 13.98, 25.21, 25.25, 37.90, 38.07, 38.62, 38.78, 44.17, 44.19, 55.16, 55.23, 85.50, 85.65, 86.61, 87.26, 90.94, 91.47, 107.56, 108.37, 110.41, 110.74, 127.81, 128.27, 128.36, 128.65, 128.67, 129.53, 129.59, 130.15. 130.25, 138.46, 138.49, 139.84, 165.84, 166.12, 173.85, 173.88, 174.37, 174.56, 195.12. IR bands (Golden Gate, cm^{-1}): 2021, 1921. HR-ESI mass spectrum (MeOH): found 725.12675; calcd. for $[C_{29}H_{27}N_2O_7Re+Na^+]$ 725.12680.

^{99m}Tc experiments. Caution! ^{99m}Tc is a *γ*-emitter (E= 140 keV, $t_{1/2}$= 6.02 h) which should only be handled in a licensed and appropriately shielded facility. Sodium boranocarbonate releases CO gas, which is highly toxic, it is recommended to be handled only in ventilated hoods.

$[^{99m}Tc(OH_2)_3(CO)_3]^+$

A Biotage microwave vial (2 – 5 ml) was charged with sodium boranocarbonate (4 mg, 38.5 *μ*mol), sodium tartrate dihydrate (7 mg, 30.4 *μ*mol) and sodium tetraborate decahydrate (7 mg, 18.5 *μ*mol). The vial was sealed and flushed with N_2 for 5 min before adding $[^{99m}TcO_4]^-$ eluate (1-2 ml) from a commercial generator. The solution was heated by microwave to 110 °C for 7 min. In order to normalize the overpressure, evolving gases were released with a 1 ml disposable syringe. Excess sodium boranocarbonate was quenched *via* dropwise addition of 1 M HCl to pH = 2 and the solution was subsequently basified by addition of 1 M NaOH to pH = 8.

General procedure for the labelling of Cp-Ligands 1a, 4a, 6a, 3a and 12a.

Generally, 0.5 ml of a 5 mM stock solution of the respective ligand in MeOH was added to a Biotage microwave vial (2 – 5 ml). The vial was sealed, and the solvent was removed by passing a stream of N_2 through the vial *via* two syringe needles for 30 min.

Method A (**1a**, **4a**, **6a**). $[^{99m}Tc(OH_2)_3(CO)_3]^+$ (0.5 ml, pH = 8) was added to the dried ligand and the pH adjusted to 12 by addition of 1 M NaOH. The solution was heated by microwave to 120 °C for 30 min. In order to normalize the overpressure, evolving gases were released with a 1 ml disposable syringe-needle.

Method B "one pot" (**1a**, **4a**, **6a**, **3a**, **12a**). The vial with the dried ligand was opened and sodium boranocarbonate (4 mg, 38.5 *μ*mol), sodium tartrate dihydrate (7 mg, 30.4 *μ*mol) and sodium tetraborate decahydrate (7 mg, 18.5 *μ*mol). The vial was sealed again and flushed with N_2 for 5 min before adding $[^{99m}TcO_4]^-$ eluate (1-2 ml) from a commercial generator. The solution was heated by microwave to 120 °C for 30 min (**1a**, **4a**, **6a**) or 140 °C for 30 min (**3a**) or 2 x 30 min (**12a**). Complexes **2c**, **5c**, **7c** and **3c** were obtained in radiochemical puritiy > 95%. For **12c**, some $[^{99m}TcO_4]^-$ and $[^{99m}Tc(OH_2)_3(CO)_3]^+$ was observed (< 20 %, c.f. Figure SI89). **12c** was purified by loading the reaction mixture onto a Chromafix C18 cartridge and washing it with H_2O (2 ml). Pure **12c** could be eluted by washing the cartridge with MeOH (2 ml).

X-ray Crystallography. Crystallographic data were collected at 183(2) K with Mo K_α radiation (λ = 0.7107 Å) that was graphite-monochromated on an Oxford Diffraction CCD Xcalibur system with a Ruby detector. Suitable crystals were covered with oil (Infineum V8512, formerly known as Paratone N), placed on a nylon loop that is mounted in a CrystalCap Magnetic™ (Hampton Research) and immediately transferred to the diffractometer. The program suite CrysAlis^{Pro} was used for data collection, multi-scan absorption correction and data reduction.[22] The structures were solved with direct methods using SIR97[23] and were refined by full-matrix least-squares methods on F^2 with SHELXL-2014.[24] (CCDC numbers 1828105-1828106)

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Acknowledgements

Financial assistance from the University of Zurich. We thank Giuseppe Meola for help with the crystal structures. We thank the Swiss National Science Foundation (SNF Project IZLSZ2_149029/1 within the SSAJRP program) and the South African National Research Foundation for financial support.

Keywords: Technetium • Rhenium • Cyclopentadiene • Bioorganometallic • Theranostics

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10.1002/chem.201801271

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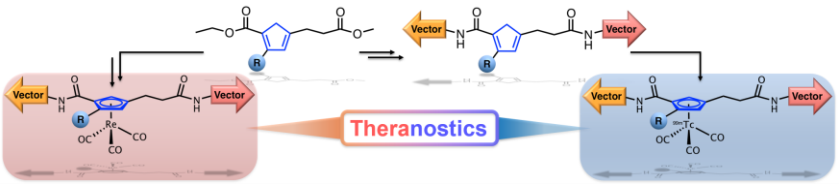

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Title

Multifunctional cyclopentadiene ligands with tuneable properties and their rhenium and ^{99m}Tc complexes were prepared following a versatile synthetic route.