

# Chemical Science

Accepted Manuscript



This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

*Accepted Manuscripts* are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this *Accepted Manuscript* with the edited and formatted *Advance Article* as soon as it is available.

You can find more information about *Accepted Manuscripts* in the [Information for Authors](#).

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard [Terms & Conditions](#) and the [Ethical guidelines](#) still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

## COMMUNICATION

# From Tc<sup>VII</sup> to Tc<sup>I</sup>; Facile Syntheses of Bis-arene Complexes [<sup>99(m)</sup>Tc(arene)<sub>2</sub>]<sup>+</sup> from Pertechnetate

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,  
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

Michael Benz, Henrik Braband, Paul Schmutz, Jonathan Halter and Roger Alberto\*<sup>a</sup>

Bis-arene complexes of technetium represent a fundamental class of organometallic compounds. **Due to intricate synthetic routes**, no detailed insights in their properties have been reported so far. Reacting [<sup>99</sup>TcO<sub>4</sub>]<sup>-</sup> with arenes in the exclusive presence of AlCl<sub>3</sub> gives highly stable [<sup>99</sup>Tc(arene)<sub>2</sub>]<sup>+</sup> in good yields. These complexes have extraordinarily high stabilities; where oxidation is found to occur at potentials higher than +1.3V and reduction below -2V vs. Fc/Fc<sup>+</sup>. The <sup>99m</sup>Tc analogues are equally synthesised by applying a novel ionic liquid extraction pathway. Complexes of <sup>99m</sup>Tc with suitably derivatised arenes will represent new building blocks for bioorganometallic pharmaceuticals in molecular imaging.

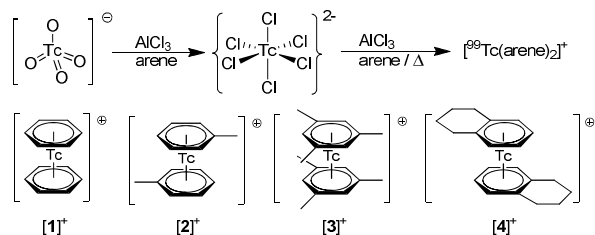
## Introduction

The realm of organometallic chemistry emerges from a comparably small number of basic ligand types, CO and cyclopentadienyl being two of them. Aromatic hydrocarbons constitute a further fundamental class of ligands, being isoelectronic with [C<sub>5</sub>H<sub>5</sub>]<sup>-</sup> (Cp<sup>-</sup>) but providing a different hapticity and coordinating properties. Whereas Cp<sup>-</sup> is an ubiquitous ligand in organometallic chemistry, complexes with aromatic hydrocarbons C<sub>6</sub>H<sub>n</sub>R<sub>6-n</sub> are much less explored, likely due to synthetic challenges and lower thermodynamic or kinetic stabilities. Since arene ligands are uncharged, vacancies at the metal center are more easily generated than with Cp<sup>-</sup> by haptotropic shifts. Binary arene complexes represent precursors for numerous reactions.<sup>1-3</sup> After their discovery by Fischer and Hafner in 1955, a multitude of synthetic approaches were reported. A recent, excellent review describes these synthetic strategies comprehensively and in detail.<sup>4</sup> Of particular interest are syntheses starting from metal halides, in the absence or presence of reducing agents such as aluminum or zinc. Where the metals such as Fe<sup>II</sup> or Ru<sup>II</sup> are already present in the desired oxidation state, no reducing agents are needed, higher starting oxidation state require reduction for coordination to the arenes.<sup>5,6</sup>

Bis-arene complexes [Re(η<sup>6</sup>-C<sub>6</sub>H<sub>n</sub>R<sub>6-n</sub>)<sub>2</sub>]<sup>+</sup> (n=1-6) are known but have been studied only occasionally and not in great detail. The first bis-arene complex of <sup>99</sup>Tc was prepared by a very uncommon method, namely by element transmutation from

[<sup>99</sup>Mo(arene)<sub>2</sub>] via β<sup>-</sup>-decay <sup>99</sup>Mo → <sup>99m</sup>Tc → <sup>99</sup>Tc, the later directly from weighable amounts of <sup>99</sup>TcCl<sub>4</sub> in the presence of Al<sup>0</sup> and AlCl<sub>3</sub>,<sup>7,8</sup> in low yields.<sup>9</sup> Only recently, Kudinov and coworkers reported an improved synthesis of [Re(arene)<sub>2</sub>]<sup>+</sup> directly from K[ReO<sub>4</sub>] with Zn<sup>0</sup> as the reductant, AlCl<sub>3</sub> as a Lewis acid and the arene as solvent in moderate yields.<sup>10</sup> For over 50 years, no progress was made in the study of [<sup>99</sup>Tc(η<sup>6</sup>-C<sub>6</sub>H<sub>n</sub>R<sub>6-n</sub>)<sub>2</sub>]<sup>+</sup> type compounds, not only due to the radioactivity of this element but also for synthetic difficulties. The preparation of binary halides such as <sup>99</sup>TcCl<sub>4</sub> as starting materials for accessing bis-arene complexes has made a significant impact over the past couple of years.<sup>11-13</sup> Their syntheses are well described but preparation and isolation are still not routine. A direct, high yield route to [<sup>99</sup>Tc(arene)<sub>2</sub>]<sup>+</sup> from [<sup>99</sup>TcO<sub>4</sub>]<sup>-</sup> salts would therefore be highly desirable since it would allow for the chemical exploration of these fundamental complexes and for setting their properties in relation to neighboring elements. In addition, arene complexes with metastable <sup>99m</sup>Tc are potential molecular imaging agents: Phenyl groups are frequent in pharmaceuticals and coordination of a <sup>99m</sup>Tc fragment to such arenes enables labeling without additional, pendent ligands,<sup>14</sup> a concept verified with the {Cr(CO)<sub>3</sub>} moiety bound to e.g. a phenyl ring in estradiol.<sup>15,16</sup> The importance of the {M(arene)}<sup>n+</sup> moiety is corroborated by the impact of the [Ru(cymantrene)]<sup>2+</sup> fragment in medicinal inorganic chemistry.<sup>17,18</sup> Along their endeavors for new

myocardial imaging agents, Wester *et al.* reported syntheses of  $[\text{}^{99\text{m}}\text{Tc}(\text{arene})_2]^+$  in the early nineties. Since yields were “variable”, the syntheses multi-step, and pharmacology not satisfying, the compounds were abandoned.<sup>19</sup> Enthusiastic about new  $^{99}\text{Tc}$  chemistry and convinced that opportunities of  $[\text{}^{99\text{m}}\text{Tc}(\text{arene})_2]^+$  will go beyond myocardial imaging, we developed practical, one step syntheses of  $[\text{}^{99(\text{m})}\text{Tc}(\text{arene})_2]^+$  in high yields and radiochemical purities, serving as an entry into a deeper understanding of the chemical and reactive properties of fundamental  $[\text{}^{99}\text{Tc}(\text{arene})_2]^+$  complexes.



**Scheme 1** Reaction sequence for the preparation of  $[\text{}^{99}\text{Tc}(\text{arene})_2]^+$  complexes.

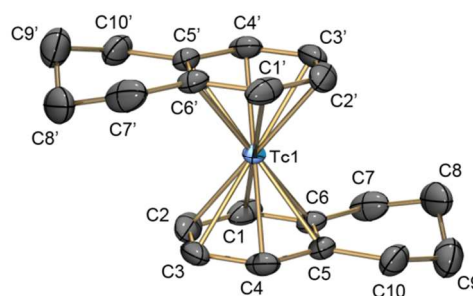
## Results and discussion

The reaction with  $\text{NH}_4[\text{}^{99}\text{TcO}_4]$ ,  $\text{Zn}^\circ$  and  $\text{AlCl}_3$  gave yields of <15% when applying conditions in analogy to those described for rhenium by Kudinov *et al.* The products were difficult to separate from a black, colloidal material (ESI, sect. 1). In contrast to classical Fischer-Hafner conditions, we carried out a reaction without  $\text{Zn}^\circ$ , assuming that  $\text{Zn}^\circ$  could over-reduce the starting material to metallic, colloidal  $\text{Tc}^\circ$ . Addition of toluene to solid  $\text{AlCl}_3$  and  $\text{K}[\text{}^{99}\text{TcO}_4]$  immediately produced a brown suspension. Heating the reaction mixture to  $85^\circ\text{C}$  for 4 h gave a dark colored suspension. After extraction with water and precipitation with  $\text{NH}_4\text{PF}_6$ , we obtained  $[\text{}^{99}\text{Tc}(\text{C}_6\text{H}_5\text{CH}_3)_2]^+$  as  $[\mathbf{2}][\text{PF}_6]$  in 75% isolated yield (scheme 1). Comparable yields were obtained with mesitylene ( $[\mathbf{3}][\text{PF}_6]$ ) and tetralin ( $[\mathbf{4}][\text{PF}_6]$ ) (ESI, sect. 1). Only the reaction with benzene to  $[\text{}^{99}\text{Tc}(\text{C}_6\text{H}_6)_2]^+$   $[\mathbf{1}][\text{PF}_6]$  required  $\text{Zn}^\circ$  (*vide infra*). With tetralin and  $\text{AlCl}_3$ , we found product  $[\mathbf{4}]^+$  but also a side product caused by Friedel-Crafts *trans*-alkylation reactions. Accordingly, the complex  $[\text{}^{99}\text{Tc}(\text{tetralin})(\text{OHPhen})]^+$  (OHPhen = 1,2,3,4,5,6,7,8-octahydrophenanthrene)  $[\mathbf{5}][\text{PF}_6]$  was isolated and structurally characterised as a major side product of  $[\mathbf{4}][\text{PF}_6]$  (ESI sect. 1 and 4).

To confirm the authenticity of  $[\mathbf{1}][\text{PF}_6]$ ,  $[\mathbf{2}][\text{PF}_6]$ ,  $[\mathbf{3}][\text{PF}_6]$  and  $[\mathbf{4}][\text{PF}_6]$ , their structures were elucidated by single crystal X-ray diffraction (ESI, sect. 4). An ellipsoid representation of the tetralin complex is given in figure 1. This series completes the structures of bis-arene complexes of the neighboring group 6 and 8 elements and the straight forward preparation paves the way for exploring fundamental chemistry and physico-chemical properties of  $[\text{}^{99}\text{Tc}(\eta^6\text{-C}_6\text{H}_n\text{R}_{6-n})_2]^+$  type complexes.

We emphasise that no metallic reducing agent is present in these reactions. Whereas chloride does reduce  $[\text{}^{99}\text{Tc}^{\text{VII}}\text{O}_4]^-$  to  $\text{Tc}^{\text{V}}$  or  $\text{Tc}^{\text{IV}}$ , arenes may also act as reductants under Friedel-

Crafts conditions to achieve oxidation states lower than  $\text{Tc}^{\text{IV}}$ . Indeed, when the reaction was carried out in cyclohexane and  $\text{AlCl}_3$  with no arene present and with  $[\text{NBu}_4][\text{}^{99}\text{TcOCl}_4]$ , a yellow precipitate formed from a blue solution. Evaporation of the solvent and crystallization of the crude solid under  $\text{N}_2$  in dimethyl-formamide (dmf) gave large yellow crystals. X-ray analysis confirmed the intermediate as  $[\text{Al}(\text{dmf})_6][\text{}^{99}\text{TcCl}_6]\text{Cl}\cdot\text{dmf}$ . The presence of this  $\text{Tc}^{\text{IV}}$  complex supports  $\text{AlCl}_3$  as a reducing agent from  $\text{Tc}^{\text{VII}}$  or  $\text{Tc}^{\text{V}} \rightarrow \text{Tc}^{\text{IV}}$ . Consequently, the reaction to  $[\text{}^{99}\text{Tc}(\text{arene})_2]^+$  can also be performed from  $\text{K}_2[\text{}^{99}\text{TcCl}_6]$  with otherwise identical conditions as from  $\text{K}[\text{}^{99}\text{TcO}_4]$  (ESI, sect. 1). The complexes  $[\mathbf{2}][\text{PF}_6]$  and  $[\mathbf{4}][\text{PF}_6]$  were prepared by this route in good yields.



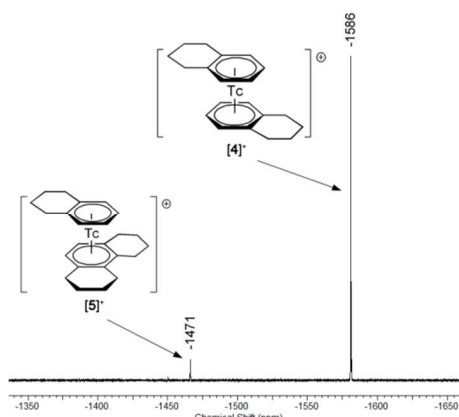
**Fig. 1** ORTEP representation<sup>20</sup> of the  $[\text{}^{99}\text{Tc}(\text{tetralin})_2]^+$   $[\mathbf{4}]^+$  cation of the  $[\mathbf{4}][\text{PF}_6]$  structure. Thermal ellipsoids represent 50% probability. Hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (°): Tc1-C1 2.219(2), Tc1-C2 2.228(2), Tc1-C3 2.231(2), Tc1-C4 2.227(2), Tc1-C5 2.250(2), Tc1-C6 2.250(2), C1-Tc1-C4 77.82(10), C2-Tc1-C5 78.34(9), C3-Tc1-C6 78.43(9).

These reactions represent a new procedure towards bis-arene complexes of group 7 elements. They combine the pure arene substitution with elements already present in the desired oxidation state, with concerted reduction-coordination but without additional reductants such as  $\text{Zn}^\circ$  or  $\text{Al}^\circ$ . Only one similar process has been reported for  $[\text{Fe}(\text{C}_6\text{H}_6)_2]^{2+}$  in the literature.<sup>21</sup>

The reaction of  $\text{K}[\text{}^{99}\text{TcO}_4]$  in benzene with  $\text{AlCl}_3$  did not lead to  $[\text{}^{99}\text{Tc}(\text{C}_6\text{H}_6)_2]^+$  ( $[\mathbf{1}]^+$ ). In this reaction, only unidentified products formed and  $^{99}\text{Tc}$  NMR spectra gave no evidence for  $\text{Tc}^{\text{I}}$  species. Significant amounts of  $[\text{}^{99}\text{TcO}_4]^-$  (~50%) could be recovered. We concluded that substituted alkenes with enhanced donating properties stabilised the intermediate oxidation states better than unsubstituted benzene. This interpretation is supported by the marked electrochemical differences found between the complexes (*vide infra*). Complex  $[\mathbf{1}][\text{PF}_6]$  could be synthesized from  $[\text{}^{99}\text{TcO}_4]^-$  along the Fischer-Hafner route in moderate yields with Zn dust as a reductant.

$^{99}\text{Tc}$  NMR spectroscopy provides valuable insights into the symmetry and electronic properties of technetium complexes.<sup>17,22</sup>  $\text{Tc}^{\text{I}}$  signals are typically found between -3000 and -1000 ppm relative to  $[\text{}^{99}\text{TcO}_4]^-$  at 0 ppm.<sup>23</sup> Due to a scalar coupling of the nuclear spin ( $I = 9/2$ ) to the quadrupole moment of the  $^{99}\text{Tc}$  nucleus, decreasing symmetry of the complexes is

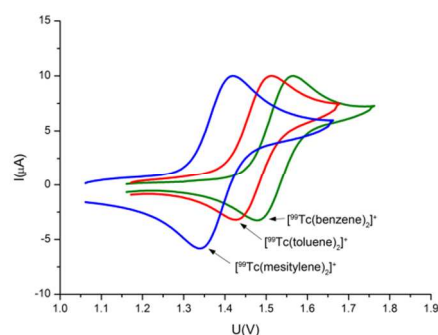
accompanied by a strong line broadening. However, the presented  $[\text{Tc}(\text{arene})_2]^+$  complexes have highly symmetrical first coordination spheres, reflected in their small half line widths (8 - 26 Hz). The observed  $^{99}\text{Tc}$  NMR signals,  $[\text{Tc}(\text{benzene})_2]^+$  -1860 ppm ( $\nu_{1/2}=8$  Hz),  $[\text{Tc}(\text{toluene})_2]^+$  -1744 ppm ( $\nu_{1/2}=26$  Hz),  $[\text{Tc}(\text{tetralin})_2]^+$  at -1586 ppm ( $\nu_{1/2}=11$  Hz), and  $[\text{Tc}(\text{mesitylene})_2]^+$  at -1532 ppm ( $\nu_{1/2}=14$  Hz), suggest that a higher substitution pattern at the aromatic backbone leads to a shift of the  $^{99}\text{Tc}$  resonances to lower field. The  $^{99}\text{Tc}$  NMR spectrum of the  $[\mathbf{4}][\text{PF}_6]$  (including the side product  $[\mathbf{5}][\text{PF}_6]$ ) is shown in figure 2. All  $^{99}\text{Tc}$  NMR spectra are given in section 3 of the electronic supplementary information.  $^1\text{H}$  NMR spectra show the strong influence of the metal center on the shift of the aromatic protons, appearing in the region around 5.5 ppm. Comparable features are found for isoelectronic complexes of the benzene complexes of  $\text{Ru}^{\text{II}}$  and  $\text{Cr}^{\text{0}}$  for which the arene signals are found at around 6.90<sup>24</sup> and 4.21 ppm<sup>25</sup> respectively.



**Fig. 2**  $^{99}\text{Tc}$  NMR spectrum of  $[\text{Tc}(\text{tetralin})_2]^+$  (-1586 ppm,  $[\mathbf{4}]^+$ ) and the side product  $[\text{Tc}(\text{tetralin})(\text{OHPhen})]^+$  (-1471 ppm,  $[\mathbf{5}]^+$ ).

The small but significant chemical shift differences of the complexes in the  $^{99}\text{Tc}$  NMR spectra are caused by different numbers of groups with negative Hammett constants. Increased electron donation to the  $^{99}\text{Tc}$  center should be paralleled by the corresponding electrochemical properties. Cyclic voltammetry (CV) investigations are in agreement with this prediction and reversible oxidation waves for the  $\text{Tc}^{\text{I/II}}$  couple were found at surprisingly high values, generally  $E^{\circ}_{1/2} > +1.4$  V vs.  $\text{Fc}/\text{Fc}^+$  in acetonitrile (figure 3 and ESI, sect. 5). Along the series  $[\mathbf{1}]^+ \rightarrow [\mathbf{4}]^+$ , the oxidation potentials become less positive with increasing number of donors on the arenes. Irreversible and essentially arene independent reductions assigned to the  $^{99}\text{Tc}^{\text{I/0}}$  couple appear below -2V. As expected from general trends in the triads of the d-elements, the rhenium homologues of  $[\mathbf{1}]^+ \rightarrow [\mathbf{4}]^+$  showed the  $\text{Re}^{\text{I/II}}$  couples shifted by about 0.19 - 0.15 V towards more negative potentials if compared to the  $^{99}\text{Tc}$  compounds (see ESI, Table ESI5.1.1), i.e. they are more easily oxidised than the  $^{99}\text{Tc}$  homologues, albeit still at a considerably positive potential. Comparing the herein reported  $^{99}\text{Tc}$  potentials with those of the neighbouring elements, as far as

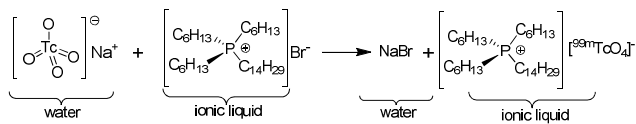
available, confirms general trends for d-elements in the periodic system. For instance,  $E^{\circ}_{1/2}$  for  $[\text{Cr}(\text{C}_6\text{H}_6)_2]^{2+/+}$  is reported at +0.82 V vs  $\text{Ag}/\text{AgCl}$ , hence, although not reported to our knowledge, the corresponding molybdenum complex should have an even more negatively shifted potential. For  $[\text{Ru}(\text{C}_6\text{H}_6)_2]^{2+/3+}$  no  $\text{Ru}^{\text{II}}/\text{Ru}^{\text{III}}$  potential are reported, probably because observation of oxidation in common solvents is not possible. On the other hand  $E^{\circ}_{1/2}$  for the  $\text{Ru}^{\text{III/II}}$  couple is found at -1.02 V, almost 1 V more positive than the potential of its  $^{99}\text{Tc}$  analogue (Table ESI5.1.1).<sup>26-28</sup> Spectro-electrochemistry in an OTTLE cell supported the reversibility of the  $[\text{Re}(\text{arene})_2]^+ / [\text{Re}(\text{arene})_2]^{2+}$  couple. The  $\text{Re}^{\text{I}}$  complex is oxidised to  $\text{Re}^{\text{II}}$  and reduced back to  $\text{Re}^{\text{I}}$  as is evident from the isosbestic points detected in the electrochemical experiment (Figure ESI5.10.1). In agreement with these electrochemical potentials, the  $[\text{Tc}(\text{arene})_2]^+$  complexes are difficult to chemically oxidise and are very stable under ambient conditions. They are also not sensitive to pH changes and do not decompose over the whole pH range even at elevated temperature, a substantial feature for their application as potential molecular imaging agents.



**Fig. 3** Cyclic voltammograms of  $[\text{Tc}(\text{benzene})_2][\text{PF}_6]$  (green line,  $E^{\circ}_{1/2} = 1.52$  V),  $[\text{Tc}(\text{toluene})_2][\text{PF}_6]$  (red line,  $E^{\circ}_{1/2} = 1.47$  V), and  $[\text{Tc}(\text{mesitylene})_2][\text{PF}_6]$  (blue line,  $E^{\circ}_{1/2} = 1.38$  V) in acetonitrile vs.  $\text{Fc}/\text{Fc}^+$ .

The high yield and one step synthesis to  $[\text{Tc}(\text{arene})_2]^+$  is the incentive for translating the conditions to short-lived  $^{99\text{m}}\text{Tc}$ . Apart from fundamental interests, conjugation of biologically active groups to the arene ring will open a path to novel, functionalised and targeting SPECT imaging agents. In the original preparation of  $[\text{Tc}(\text{arene})_2]^+$ ,<sup>19</sup> the multiple steps required for transferring  $[\text{TcO}_4]^-$  from the generator saline eluate into an organic solvent were difficult and time consuming, ultimately prohibitive for any application. To facilitate this step, we coated a glass vial with a thin layer of ionic liquid (IL) by evaporating a dilute solution of  $[\text{P}(\text{C}_6\text{H}_{13})_3(\text{C}_{14}\text{H}_{29})]\text{Br}$  in MTBE. Addition of the generator eluate to this vial extracted within 10 min 80 - 97 % of  $[\text{TcO}_4]^-$  into the IL layer by an anion exchange process (Scheme 2). The saline was removed, the IL dissolved in the corresponding arene and added to a vial charged with  $\text{AlCl}_3$  under  $\text{N}_2$ . The vial was heated for 10 min at 100°C in a microwave reactor. Upon addition of water, the

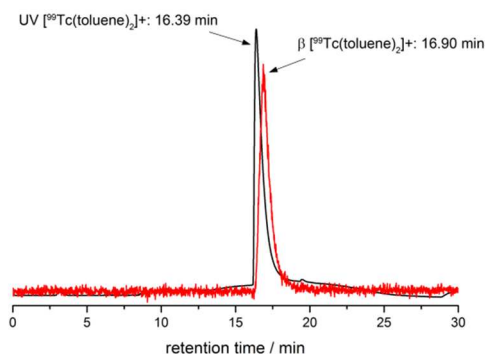
$[\text{}^{99\text{m}}\text{Tc}(\text{arene})_2]^+$  complexes were extracted in yields of 35 - 87% and in radiochemical purities >93%. Loading the aqueous solution on a SepPak column and rinsing with water removed hydrolyzed  $\text{AlCl}_3$ . The product was then eluted with an aqueous EtOH solution with >96% radiochemical purity (ESI, section 1.2).



**Scheme 2** Extraction of  $\text{Na}[\text{}^{99\text{m}}\text{TcO}_4]$  from saline (0.9%  $\text{NaCl}$  in  $\text{H}_2\text{O}$ ) into an ionic liquid.

The procedure was successfully applied for toluene and mesitylene. As described for  $[\text{}^{99\text{m}}\text{Tc}(\text{tetralin})_2]^+$ , the yield of the  $[\text{}^{99\text{m}}\text{Tc}(\text{tetralin})_2]^+$  was reduced due to formation of the trans-alkylated side product in a 1 : 0.8 ratio ( $[\text{}^{99\text{m}}\text{Tc}(\text{tetralin})_2]^+ : [\text{}^{99\text{m}}\text{Tc}(\text{tetralin})(\text{OHPhen})]^+$ ). As for the reactions with  $^{99}\text{Tc}$ , no additional reducing agent was required (except for the synthesis of  $[\text{}^{99\text{m}}\text{Tc}(\text{benzene})_2]^+$ ). We emphasise that the  $^{99\text{m}}\text{Tc}$  bis-arene complexes are extraordinarily stable. Heating an aqueous solution at  $180^\circ\text{C}$  in a microwave oven in the presence of air does not decompose the complex to a measurable extent. This stability against oxidation (and hydrolysis) is in agreement with the observed redox potentials and makes the complexes resistant to oxidation in air.

The assessment of identities of  $^{99\text{m}}\text{Tc}$  complexes by HPLC coinjection with fully characterised rhenium homologues and comparison of retention times, is an FDA accepted procedure. Due to a serial arrangement of the UV- and radiodetector, the respective  $\gamma$ -signal ( $^{99\text{m}}\text{Tc}$ ) is separated by a constant time delay (here 0.5 min) from the UV signal (Re). This delay time was quantified with  $[\text{}^{99\text{m}}\text{Tc}(\text{toluene})_2]^+$  (UV- and  $\beta^-$ - detection for the same compound, figure 4).



**Fig. 4** HPLC traces (UV- /  $\beta^-$ -detection) of  $[\text{}^{99\text{m}}\text{Tc}(\text{toluene})_2]^+$  (UV-detection: 16.39 min, black line;  $\beta^-$ -detection: 16.90 min, red line).

Despite their isostructural nature and comparable physico-chemical properties, slightly different retention times ( $R_t$ ) ( $\Delta R_t$

different from the 0.5 min) are sometimes observed for homologous  $^{99\text{m}}\text{Tc}$  and Re complexes. This makes their identification by  $R_t$  comparison somewhat ambiguous. The reported  $[\text{}^{99\text{m}}\text{Tc}(\text{arene})_2]^+$  complexes are good examples for this ambiguity, where the  $R_t$  for  $[\text{}^{99\text{m}}\text{Tc}(\text{benzene})_2]^+$  is 0.58 min shorter than the one of the corresponding Re complex. This effect diminishes with the increasing number of arene substituents; ( $[\text{}^{99\text{m}}\text{Tc}(\text{toluene})_2]^+$ : 0.45 min,  $[\text{}^{99\text{m}}\text{Tc}(\text{mesitylene})_2]^+$ : 0.42 min,  $[\text{}^{99\text{m}}\text{Tc}(\text{tetralin})_2]^+$ : 0.39 min). These small but non-negligible uncertainties for the assessment of the identity of  $^{99\text{m}}\text{Tc}$  complexes can only be ruled out by HPLC coinjection with fully characterised  $^{99}\text{Tc}$  analogues;  $\Delta R_t$  must be approximately 0.5 min (for our instrumental arrangement). This has been additionally verified by coinjection of  $[\text{}^{99\text{m}}\text{Tc}(\text{tetralin})_2]^+$  and  $[\text{}^{99}\text{Tc}(\text{tetralin})_2]^+$ ; the separation of the UV signal ( $^{99}\text{Tc}$  complex) and the  $\gamma$ -signal ( $^{99\text{m}}\text{Tc}$ ) showed the expected separation ( $\Delta t = 0.51$  min, ESI, sect. 2). We emphasise that such direct comparisons between  $^{99\text{m}}\text{Tc}$  and  $^{99}\text{Tc}$  complexes are very rarely reported, if ever, but ultimately the only way for truly assessing the authenticity of a  $^{99\text{m}}\text{Tc}$  complex.

## Conclusions

Mono- and bis-arene complexes of d-elements are fundamental in organometallic chemistry. The difficult of, for technetium essentially non-existent, access to  $[\text{}^{99\text{m}}\text{Tc}(\text{arene})_2]^+$  type complexes impeded their detailed chemical studies and their application for molecular imaging. We now present a new, high yielding synthetic procedure to these fundamental organometallic complexes of the group 7 elements. In our procedure, no additional reducing agents are required with the exception of  $[\text{}^{99\text{m}}\text{Tc}(\text{benzene})_2]^+$ .  $\text{AlCl}_3$  serves as oxygen abstracting Lewis acid and as a source of chloride reducing agent in the high valency regime at the same time. The reaction principle can be fully applied to  $^{99\text{m}}\text{Tc}$ , enabling the introduction of novel organometallic complexes in the area of molecular imaging. Studies with arene substituents different from alkyl groups are currently ongoing.

## Experiment section

### General preparation of $[\text{}^{99\text{m}}\text{Tc}(\text{arene})_2]^+$ complexes

**Caution:**  $^{99\text{m}}\text{Tc}$  is a weak  $\beta^-$  emitter ( $E_{\text{max}}=0.292$  MeV, half life time =  $2.12 \cdot 10^5$  y. It should be handled only in appropriately equipped laboratories.

**Method a)**  $(\text{NH}_4)[\text{}^{99\text{m}}\text{TcO}_4]$  (18 mg, 0.10 mmol), Zn-dust (22 mg, 0.34 mmol),  $\text{AlCl}_3$  (134 mg, 1.00 mmol) and the corresponding arene (6 ml) were heated to  $85^\circ\text{C}$ . After 8 h, the solvent of the resulting dark brown suspension was removed with a stream of  $\text{N}_2$ . The residue was washed with  $\text{Et}_2\text{O}$  ( $3 \times 2$  ml). The remaining solid was extracted with  $\text{H}_2\text{O}$  ( $3 \times 2$  ml) and the aqueous solution filtered.  $\text{NH}_4\text{PF}_6$  (150 mg, 0.92 mmol) in  $\text{H}_2\text{O}$  (1 ml) was added to the red-brown filtrate. The colorless

precipitate was filtered off, washed with H<sub>2</sub>O (2 × 0.5 ml) and Et<sub>2</sub>O (2 × 0.5 ml) and dried *in vacuo* to give [<sup>99</sup>Tc(arene)<sub>2</sub>](PF<sub>6</sub>) as a pale yellow powder. Alternatively, the precipitate can be extracted by CH<sub>2</sub>Cl<sub>2</sub> from the aqueous suspension.

Method b) K<sub>2</sub>[<sup>99</sup>TcO<sub>4</sub>] (20 mg, 0.10 mmol), AlCl<sub>3</sub> (200 mg, 1.50 mmol) and the corresponding arene (8 ml) were heated at 85°C. After 4 h, H<sub>2</sub>O (6 ml) was added to the hot dark brown solution and the aqueous phase was separated and filtered. The process was repeated with additional H<sub>2</sub>O (2 × 2 ml). To the combined aqueous solutions was added a solution of NH<sub>4</sub>PF<sub>6</sub> (150 mg, 0.92 mmol) in H<sub>2</sub>O (1 ml). The formed colorless precipitate was filtered, washed with H<sub>2</sub>O (2 × 0.5 ml) and dried *in vacuo* to give [Tc(arene)<sub>2</sub>](PF<sub>6</sub>).

Method c) K<sub>2</sub>[<sup>99</sup>TcCl<sub>6</sub>] (37 mg, 0.10 mmol), AlCl<sub>3</sub> (134 mg, 1.00 mmol) and the corresponding arene (8 ml) were heated on 85°C for 4 h. H<sub>2</sub>O (4 ml) was added to the dark brown hot solution and the aqueous phase was separated and filtered. The process was repeated with additional H<sub>2</sub>O (2 × 2 ml) and to the combined aqueous solution was added a solution of NH<sub>4</sub>PF<sub>6</sub> (150 mg, 0.92 mmol) in H<sub>2</sub>O (1 ml). The colorless precipitate was filtered, washed with H<sub>2</sub>O (2 × 0.5 ml) and dried *in vacuo* to give [Tc(arene)<sub>2</sub>](PF<sub>6</sub>) as a pale yellow powder.

#### General preparation of [<sup>99m</sup>Tc(arene)<sub>2</sub>]<sup>+</sup> complexes

The ionic liquid [P(C<sub>6</sub>H<sub>13</sub>)<sub>3</sub>(C<sub>14</sub>H<sub>29</sub>)]Br (2 mg) dissolved in 0.1 ml methyl tert-butyl ether (MTBE), was added to a capped vial. Under constant rotation of the vial, the solvent was evaporated by a N<sub>2</sub> stream. The [<sup>99m</sup>TcO<sub>4</sub>]<sup>-</sup> eluate (1 -2 ml) was added and the vial gently shaken for 10 min. The aqueous solution was removed and the vial purged with N<sub>2</sub> for 30 min. 80 - 97% of the starting activity remain in the vial. The ionic liquid was dissolved in the corresponding arene (1 ml). This solution was added to a vial, charged with AlCl<sub>3</sub> (100 mg) under N<sub>2</sub>. The reaction mixture was heated for 10 min at 100°C in a microwave oven. 1 ml of saline solution was added to the yellow reaction mixture and the vial vortexed for 20 sec. and centrifuged for 6 min. The aqueous phase was separated with a syringe and contained > 90% of the final product. Extraction can be repeated a second time the workup procedure was repeated for a second time. Standard SepPack procedure removes salts and the product was eluted with ethanol.

#### Acknowledgements

The authors acknowledge financial support from the University of Zürich, the Staatssekretariat für Bildung, Forschung und Innovation (SBFI) C13.0080 and the Swiss National Science Foundation (200021\_140665).

#### Notes and references

<sup>a</sup> Department of Chemistry, University of Zürich, Winterthurerstr. 190, CH-8057 Zürich, Switzerland. E-mail: ariel@chem.uzh.ch  
The first two authors contributed equally to this work.

† Electronic Supplementary Information (ESI) available: Additional synthetic and characterization details (including HPLC, NMR, CV), and crystallographic details (CCDC 1017765, 1017766, 1017767, 1017768, 1017769). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c000000x/

- 1 E. L. Muetterties, *Chem. Soc. Rev.*, 1982, **11**, 283.
- 2 H. Lebozec, D. Touchard, P. H. Dixneuf, *Adv. Organomet. Chem.*, 1989, **29**, 163.
- 3 P. W. Jolly, *Acc. Chem. Res.*, 1996, **29**, 544.
- 4 G. Pampaloni, *Coord. Chem. Rev.*, 2010, **254**, 402.
- 5 J. F. Helling, D. M. Braitsch, *J. Am. Chem. Soc.*, 1970, **92**, 7207.
- 6 F. Calderazzo, G. Pampaloni, *J. Organomet. Chem.*, 1995, **500**, 47.
- 7 F. Baumgartner, E. O. Fischer, U. Zahn, *Chem. Ber. Recl.*, 1961, **94**, 2198.
- 8 C. Palm, E. O. Fischer, *Tetrahedron Lett.*, 1962, **6**, 253.
- 9 E. O. Fischer, A. Wirzmueller, *Chem. Ber.*, 1957, **90**, 1725.
- 10 E. A. Trifonova, D. S. Perekalin, K. A. Lyssenko, A. R. Kudinov, *J. Organomet. Chem.*, 2013, **727**, 60.
- 11 E. V. Johnstone, F. Poineau, P. M. Forster, L. Z. Ma, T. Hartmann, A. Cornelius, D. Antonio, A. P. Sattelberger, K. R. Czerwinski, *Inorg. Chem.*, 2012, **51**, 8462.
- 12 F. Poineau, E. V. Johnstone, K. R. Czerwinski, A. P. Sattelberger, *Acc. Chem. Res.*, 2014, **47**, 624.
- 13 C. D. Malliakas, F. Poineau, E. V. Johnstone, P. F. Weck, E. Kim, B. L. Scott, P. M. Forster, M. G. Kanatzidis, K. R. Czerwinski, A. P. Sattelberger, *J. Am. Chem. Soc.*, 2013, **135**, 15955.
- 14 D. Can, B. Spingler, P. Schmutz, F. Mendes, P. Raposinho, C. Fernandes, F. Carta, A. Innocenti, I. Santos, C. T. Supuran, R. Alberto, *Angew. Chem. Int. Ed.*, 2012, **51**, 3354.
- 15 C. Sergheraert, A. Tartar, *J. Organomet. Chem.*, 1982, **240**, 163.
- 16 C. Baldoli, S. Maiorana, E. Licandro, G. Zinzalla, D. Perdicchia, *Org. Lett.*, 2002, **4**, 4341.
- 17 C. G. Hartinger, N. Metzler-Nolte, P. J. Dyson, *Organometallics*, 2012, **31**, 5677.
- 18 Y. K. Yan, M. Melchart, A. Habtemariam, P. J. Sadler, *Chem. Commun.*, 2005, **38**, 4764.
- 19 D. W. Wester, J. R. Coveney, D. L. Nosco, M. S. Robbins, R. T. Dean, *J. Med. Chem.*, 1991, **34**, 3284.
- 20 L. J. Farrugia, ORTEP-3 for Windows - a version of ORTEP-III with a Graphical User Interface (GUI), 1997.
- 21 Q. Dabirmanesh, R. M. G. Roberts, *J. Organomet. Chem.*, 1993, **460**, C28.
- 22 A. Davison, J. F. Kronauge, A. G. Jones, R. M. Pearlstein, J. R. Thorback, *Inorg. Chem.*, 1988, **27**, 3245.
- 23 V. A. Mikhalev, *Radiochemistry*, 2005, **47**, 319.
- 24 E. O. Fischer, C. Elschenbroich, *Chem. Ber.*, 1970, **103**, 162.
- 25 L. Phillips, G. R. Dennis, M. J. Aroney, *New J. Chem.*, 2000, **24**, 27.
- 26 T. Satou, K. Takehara, M. Hirakida, Y. Sakamoto, H. Takemura, H. Miura, M. Tomonou, T. Shinmyozu, *J. Organomet. Chem.*, 1999, **577**, 58.
- 27 D. T. Pierce, W. E. Geiger, *J. Am. Chem. Soc.*, 1989, **111**, 7636.
- 28 R. L. Lord, C. K. Schauer, F. A. Schultz, M. H. Baik, *J. Am. Chem. Soc.*, 2011, **133**, 18234.