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Rhenium complexes of bidentate, bis-bidentate and tridentate N-heterocyclic carbene ligands†

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A series of eight Rhenium(I)-N-heterocyclic carbene (NHC) complexes of the general form [ReCl-(CO)$_3$(C^C)] (where C^C is a bis(NHC) bidentate ligand), [ReCl(CO)$_3$(C^C)]$_2$ (where C^C is a bis-bidentate tetra-NHC ligand) and [Re(CO)$_3$(C^N^C)]$^+$[X]$^-$ (where C^N^C is a bis(NHC)-amine ligand and the counter ion X is either the ReO_4^- or PF_6^-) have been synthesised using a Ag_2O transmetallation protocol. The novel precursor imidazolium salts and Re(I) complexes were characterized by elemental analysis, ^{1}H and ^{13}C NMR spectroscopy and the molecular structures for two imidazolium salt and six Re(I) complexes were determined by single crystal X-ray diffraction. These NHC ligand systems are of interest for possible applications in the development of Tc-99m or Re-186/188 radiopharmaceuticals and as such the stability of two complexes of the form [ReCl(CO)$_3$(C^C)] and [Re(CO)$_3$(C^N^C)][ReO_4] were evaluated in ligand challenge experiments using the metal binding amino acids L-histidine or L-cysteine. These studies showed that the former was unstable, with the chloride ligand being replaced by either cysteine or histidine, while no evidence for transchelation was observed for the latter suggesting that bis(NHC)-amine ligands of this type may be suitable for biological applications.

Introduction

Technetium-99m is a medically important isotope used for single photon emission computed tomography (SPECT) imaging of a variety of organ conditions and disease states. Technetium-99m offers optimal nuclear properties for imaging applications, including: intermediate half-life ($t_{1/2}$ = 6.02 h), almost pure gamma-emission (E_γ = 140 keV) and convenient availability from a ^{99}Mo/^{99m}Tc generator.[1,2] Sharing many similarities in chemical properties to technetium, the third row congener rhenium also offers significant potential for use in nuclear medicine, as the isotopes: Re-186 and Re-188 have properties suitable for radiotherapeutic applications. Rhenium-186 is a medium energy β-emitting isotope (max 1.08 MeV) with a long half-life of 3.7 days, while Re-188 is a high energy β-emitter (max 2.1 MeV) with a half-life of 17 h.[3] The similarity in the chemical properties displayed by Tc and Re offers the potential for these radiometals being used as a 'matched pair', where ^{99m}Tc and $^{186/188}$Re complexes of the same ligand may be used for both imaging and therapeutic applications respectively.

There has been much recent interest in the use of N-heterocyclic carbene (NHCs) ligands in medicinal inorganic chemistry applications.[4–6] For example, the anti-tumor properties of a variety of metals including Ag,[7–9] Au,[10,11] Pd[12] and Pt[13] have been evaluated and pioneering work by Youngs and co-workers has elucidated the remarkable antimicrobial properties of Ag(I)-NHC complexes.[14] Despite the favorable properties of metal complexes of NHC ligands for use in medicinal inorganic chemistry, there been relatively few reports of their potential applications in nuclear medicine. Early studies recognized the possibility of using pre-formed Ag(I)-NHC complexes for the delivery of NHC ligands to metallic radionuclides.[15–17] More recently, for the first time our group reported the labelling of an NHC ligand with ^{99m}Tc using a Ag_2O transmetalation protocol (**1**, Fig. 1).[18] In the same year an N-heterocyclic biscarbene ligand was labelled with ^{188}Re also *via* transmetalation from a preformed Ag(I) complex (**2**, Fig. 1).[19] Abram and co-workers have been particularly active in the synthesis of ^{99}Tc and Re complexes of NHC ligands,[20–22] indeed these workers reported the first example of a ^{99}Tc(V)-NHC complex.[23] More recently, a series of ^{99}Tc(V)-NHC complexes of the nitridotechnetium core[24] and the dioxotechnetium core were described.[25]

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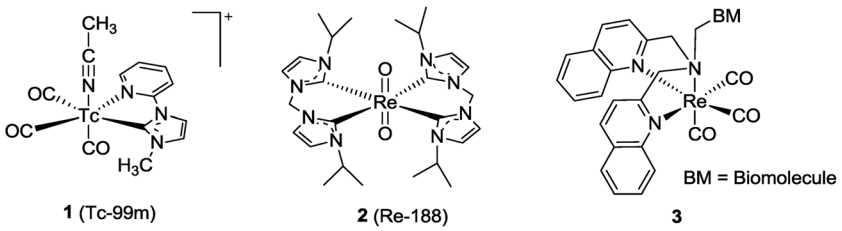
†Electronic supplementary information (ESI) available:Synthetic details for H-Gly-OBzl·TsO, **4**·Br_2 and **5**·Cl_2. Further X-ray crystallography details and refinement data. NMR spectra, ESI-MS and HPLC chromatograms for **8**·Cl_2, **9**·Cl_2, **10**, **11**·Cl_2, **12**·Cl_3 and **13**·Cl_2. HPLC Chromatograms for the reaction product obtained in the synthesis of **15** and **16**. ^{1}H NMR spectra of *trans*-**15** and *trans–trans*-**16** and *trans–cis*-**16**. Variable temperature ^{1}H NMR spectra for **15**. Additional details for the kinetc analysis of the reaction of of **14**Cl with CD_3CN. HPLC chromatograms obtained in the ligand challenge experiments for complexes **14** and **17**·ReO_4. CCDC 1419735–1419742. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5dt03295d



1 (Tc-99m) 2 (Re-188) 3

Fig. 1 Examples of N-heterocyclic carbene ligands labelled with (1) Tc-99m and (2) Re-188 and an example of a biomolecule labelled with a luminescent Re(I) complex *via* the 'single amino acid chelate' (SAAC) strategy.

First described by Alberto and co-workers, $[^{99m}Tc(H_2O)_3(CO)_3]^+$ (ref. 26 and 27) has garnered much attention in the development of potential SPECT imaging agents.[28] The popularity of this precursor compound results from its impressive synthetic versatility and convenient preparation from $^{99m}TcO_4^-$ using the commercially available Isolink labelling kit. The facially coordinated carbonyl ligands are strongly bound while the three water molecules are labile and easily displaced by other ligand systems.

A wide range of ligands have been investigated in combination with the ^{99m}Tc-tricarbonyl core and among these tridentates often form stable complexes that are suitable for *in vivo* applications.[28] The 'single amino acid chelates' (SAACs) are a class of tridentate ligands have shown significant promise for labelling small peptides with either the $^{99m}Tc(CO)_3$ or the $Re(CO)_3$ cores.[29,30] These systems involve the modification of natural or synthetic amino acids (*e.g.* lysine), yielding a tridentate terminus. A range of donor groups have been investigated, including pyridine and quinoline, with the latter generating luminescent complexes with the $Re(CO)_3$ core (**3**, Fig. 1) suitable for biodistribution studies in single cells.

We are interested in the synthesis and study of metal complexes of N-heterocyclic carbene ligands[31] for potential radiopharmaceutical applications[32] and as novel luminescent materials.[33–36] Herein we describe the synthesis of a series of bidentate, bis-bidentate and tridentate imidazolium salt, NHC pro-ligands and the corresponding Re(I)$(CO)_3$-NHC complexes. The stability of Re(I) complexes with either a bidentate NHC ligand or a bis(NHC)-amine (tridentate) NHC ligand were evaluated in ligand challenge experiments using the metal binding amino acids L-histidine or L-cysteine. These studies showed that the Re(I) complex with a [2 + 1] ligand combination were unstable with the chloride ligand replaced by the amino acids while the Re(I) complex of the bis(NHC)-amine ligand was stable and showed no evidence for transchelation.

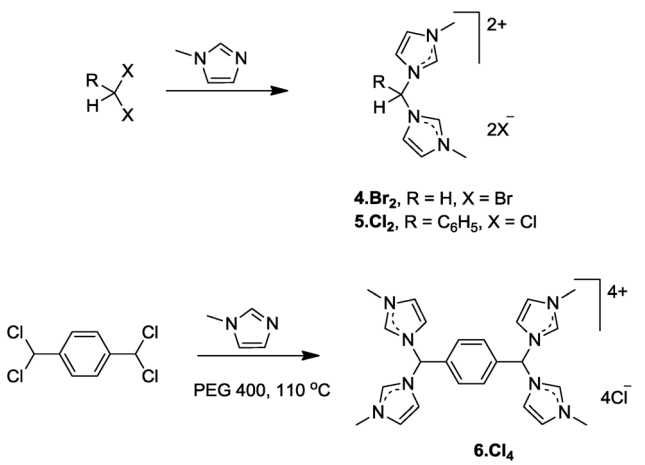
Results and discussion

Ligand synthesis

The known bidentate NHC pro-ligands: **4**·Br_2 and **5**·Cl_2 [37,38] and the novel bis-bidentate NHC pro-ligand (**6**·Cl_4) were prepared similarly by heating either dibromomethane or α,α-dichlorotoluene or α,α,α,α-tetrachloro-*p*-xylene with the appropriate molar ratios of 1-methylimidazole in acetonitrile (**4**·Br_2) or polyethylene glycol 400 (**5**·Cl_2 and **6**·Cl_4) (Scheme 1).

Previously, we showed that for Re(I) tricarbonyl complexes of the form [ReCl$(CO)_3$(C^N)] (where C^N is a bidentate NHC containing ligand) that the monodentate chloride group is labile and exchanges with acetonitrile and anionic carboxylate and sulfonate ligands.[18] As a labile monodentate ligand is expected to be unsuitable for potential diagnostic imaging applications using Tc-99m, we became interested in developing tridentate NHC ligand systems for use in combination with the tricarbonyl core of Tc and Re. Using a previously reported acyclic ligand as a template,[39,40] a series of new bis(NHC)-amine ligands, designed to bind to an octahedral metal centre in a facial array (thereby increasing the stability of potential Re and Tc complexes) were prepared (Scheme 2).

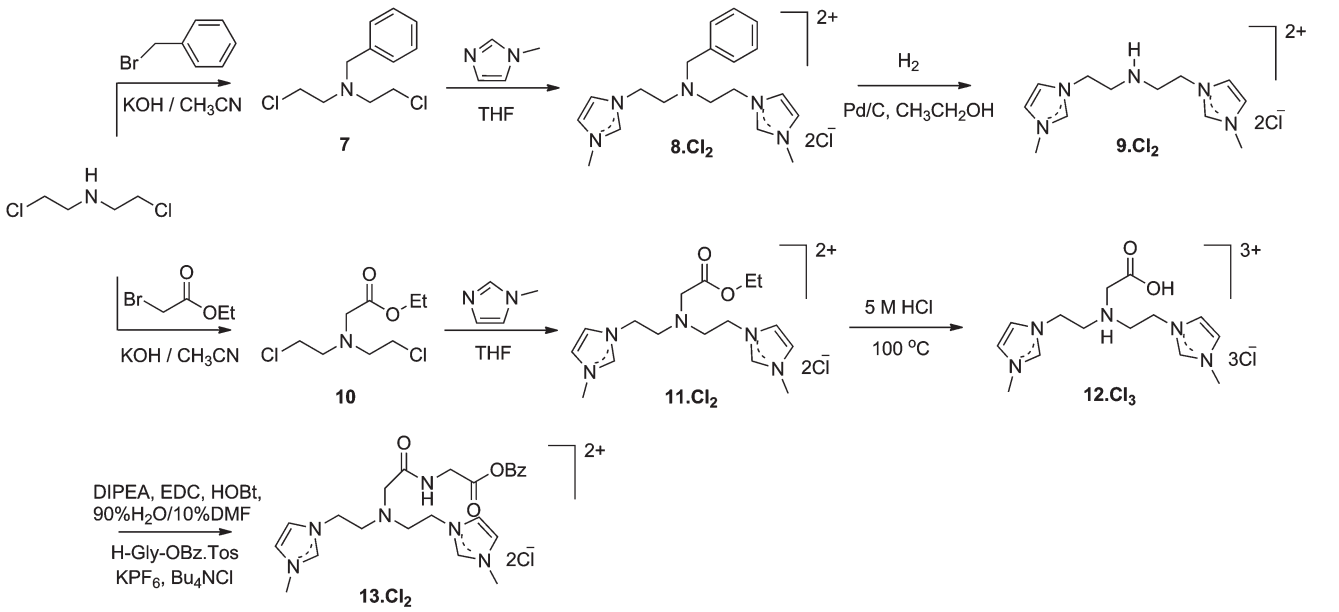
As was described previously for the synthesis of closely related imidazolium salts,[39,40] it was necessary to protect the amine of bis(2-chloroethyl)amine before introduction of the imidazolium units to avoid formation of polymerised by-products. Thus, reaction of **7** with two equivalents of 1-methylimidazole gave the diimidazolium salt **8**·Cl_2 and subsequent removal of the benzyl group by catalytic hydrogenation furnished the secondary amine containing diimidazolium salt **9**·Cl_2. To provide bifunctional ligands for potential conjugation



4.Br$_2$, R = H, X = Br
5.Cl$_2$, R = C_6H_5, X = Cl

6.Cl$_4$

Scheme 1 Synthesis of bis-imidazolium salts **4**·Br_2 and **5**·Cl_2 and *tetra*-imidazolium salt **6**·Cl_4.



Scheme 2 Synthesis of functionalised bis-imidazolium salts.

to biomolecules, bis(2-chloroethyl)amine was initially alkylated with ethyl bromoactate yielding **10**, which was reacted with 1-methylimidazole giving the diimidazolium salt **11**·Cl_2. To investigate the potential for coupling this imidazolium salt pro-ligand to biomolecules, the amino acid compound **12**·Cl_3 was prepared from **11**·Cl_2 by hydrolysis of the ester group using 5 M HCl. Compound **12**·Cl_3 was then conjugated to benzyl ester protected glycine yielding **13**·Cl_2 using the peptide coupling reagent: 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) in combination with hydroxybenzotriazole (HOBt) (Scheme 2).

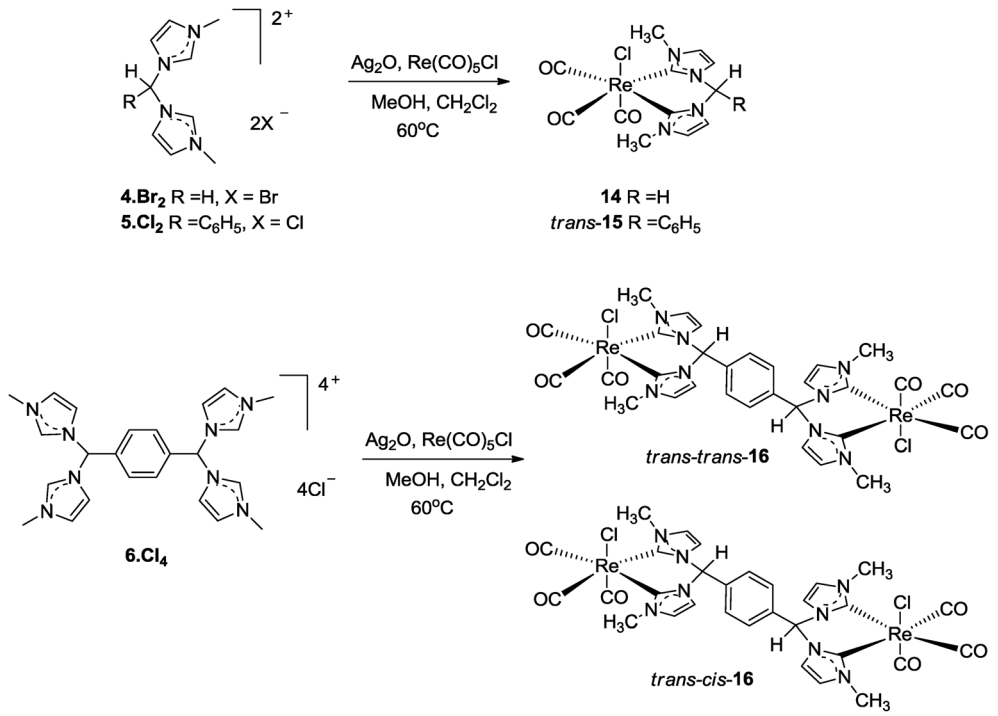
In all cases, the synthesized symmetrical imidazolium salts (**4–6**, **8**, **9**, **11–13**) gave relatively simple ^{1}H NMR spectra, with a characteristic downfield signal for the strongly deshielded imidazolium NC*H*N (pro-carbenic) proton, which resonated within the range 9.13–9.96 ppm. The formation of glycine coupled product **13**·Cl_2 was accompanied by the appearance of a broad triplet resonance (9.32 ppm) corresponding to the amide group N–H proton.

Rhenium complex synthesis and studies

Two mononuclear Re(I) tricarbonyl complexes of the form [ReCl(CO)$_3$(C^C)] (where C^C is a bidentate NHC ligand) (**14** and **15**, Scheme 3) were prepared by the heating imidazolium salts **4**·Br_2 or **5**·Cl_2 respectively with $Re(CO)_5Cl$ in the presence of Ag_2O. The bimetallic complex **16** was prepared similarly from the bis-bidentate NHC pro-ligand **6**·Cl_4 (Scheme 3). Complexes **14–16** were crystallographically characterized (see Structural studies section) and in all cases the Re(I) centres adopt octahedral coordination geometries, with three facially arrayed carbonyl ligands, the chelating bis-NHC unit, and a monodentate chloride ligand.

The structure of complex **14** is closely related to previously reported Re(I) complexes of this ligand where the halide ligand was either bromide[41] or iodide.[42] These previous studies showed that two conformational isomers (*endo* or *exo*) were possible, due to a 'flapping wing' type motion of the imidazole rings. Variable temperature ^{1}H NMR analysis (X = Br^-) showed a fast equilibrium between the isomers at RT with coalescence occurring at 220 K, with signals apparent for both isomers at 183 K.[41] High pressure liquid chromatography mass spectrometric (HPLC-MS) analysis of the crude reaction mixture for complex **14** shows only one Re(I) containing species and the ^{1}H NMR spectrum for the purified complex shows a broadened AX pattern for the methylene groups protons. A variable temperature (VT) ^{1}H NMR study was conducted for **14** in d_6-acetone (Fig. 2) and as expected this compound displayed similar properties to those reported previously for the Br^- and I^- analogues. In the case of **14**, coalescence was evident at 253 K and signals for both isomers were apparent at 213 K.

High pressure liquid chromatography in combination with ^{1}H NMR analysis (Fig. S10, ESI†) of the crude reaction product for **15** (before purification) shows the formation of only one Re(I)-NHC complex. Due to the phenyl substituent on the methylene linker group between the imidazole rings, there are two possible geometric isomers for this complex, these being *trans*-**15** where the chloride ligand is *trans* with respect to phenyl group and *cis*-**15** where the chloride ligand *cis* with respect to phenyl group (Fig. 3). X-ray structural analysis of the only Re(I)-NHC complex formed in the synthesis of **15** showed that only *trans*-**15** was formed. The preference for the formation of the *trans*-geometric isomer, may be due to hydrogen bonding interactions between the methyl NHC wingtip groups and the chloride ligand, which are evident in the crystal structure for this compound (see Structural studies section). As was



Scheme 3 Synthesis of Re(I) complexes **14**–**16**.

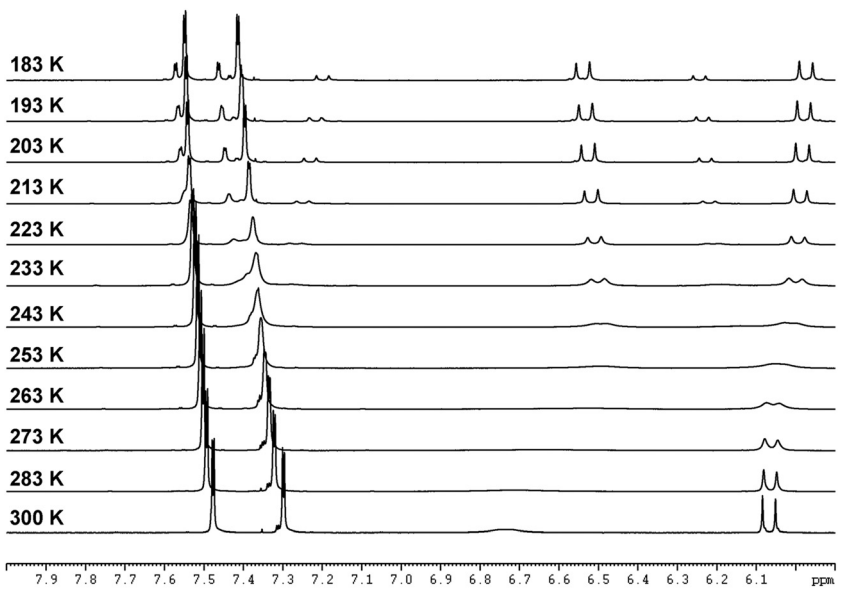


Fig. 2 Variable temperature (300 K–183 K) ^{1}H NMR spectra (400 MHz, d_6-acetone) for complex **14**.

the case for **14**, it is also possible that at RT *trans*-**15** exist in equilibrium with its ring-flip conformational isomer, where the 'flapping wing' motion of the imidazole rings would interconvert the position of the phenyl ring from axial (Fig. 3) to equatorial. To determine if this is the case, a VT ^{1}H NMR study (300 K–183 K) was performed on *trans*-**15** in d_6-acetone. The results of this study (Fig. S15, ESI†) showed no evidence that *trans*-**15** is in equilibrium with the ring-flip conformer. The barrier associated with the generation of the ring-flip form may result from an unfavourable steric interaction between the phenyl substituent and the imidazolylidene units when the phenyl group is brought into the equatorial position.

The bimetallic complex **16** was synthesised from the tetra-imidazolium salt **6**·Cl_4 and semi-preparative HPLC was used to

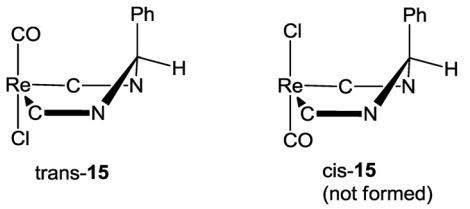


Fig. 3 The possible geometric isomeric forms of complex **15**: *trans*-**15**, chloride ligand *trans* with respect to phenyl group and *cis*-**15**, chloride ligand *cis* with respect to phenyl group (for clarity only the metallacycle is shown).

isolate the geometric isomeric forms of the complex generated in the synthetic reaction. Two geometric isomeric forms of **16** (*trans–trans*-**16** and *trans–cis*-**16**, (Fig. S11, ESI†) were isolated and these species gave identical ESI-MS results. The ^{1}H NMR spectrum obtained for *trans–trans*-**16** was consistent with a highly symmetrical molecule, while that obtained for *trans–cis*-**16** was more complicated, suggesting a lower level of molecular symmetry (Fig. S14, ESI†). A crystal structure (see Structural studies section) was obtained for *trans–trans*-**16** and this showed that the phenyl linker group is in the axial position of the metallacycles incorporating each Re(I) centre (as was the case for *trans*-**15**) and is *trans* with respect to the orientation of the chloride ligands. The second geometric isomer was assigned as *trans–cis*-**16** (Scheme 3) on the basis of the ^{1}H NMR spectrum and ESI-MS result (Fig. S14, ESI†). Interestingly, the third possible geometric isomer *cis–cis*-**16** was not observed.

In addition to the desired complexes (**15**, **16**) significant amounts of a common by-product were formed in the Ag_2O transmetallation reaction between $Re(CO)_5Cl$ and the imidazolium salts: **5**·Cl_2 and **6**·Cl_4. The by-product was identified and purified using semi-preparative HPLC and a poor quality crystals structure was obtained (Fig. S3, ESI†). The complex (Fig. 4) is bimetallic, with a pair of Re(I) tricarbonyl centres bridged by two μ^2-methoxide ligands, with a methylimidazole ligand occupying sixth coordination site for each of the Re(I) centres. Related Re(I) complexes have been reported previously.[43]

The formation of this bimetallic Re(I) by-product appears to result from *C–N* bond cleavage of the imidazolium salts **5**·Cl_2 and **6**·Cl_4, yielding 1-methylimidazole which coordinates to the Re(I) centre. A second decomposition product was identified in the separation of the geometric isomers of the bimetallic complex **16** using semi-preparative HPLC. This species gave an identical ^{1}H NMR spectrum to that of *trans*-**15**, suggesting *C–C* bond cleavage of the methylene group to phenyl group bond and formation of the mononuclear complex. Previously, Cu_2O was shown to promote unusual *C–N* bond cleavage and *C–C* bond formation reactions, when utilized as a metal source in the synthesis of Cu(I)-NHC complexes of the pro-ligands **4**·Br_2 and **5**·Cl_2.[37] As Ag_2O was used in the synthesis of the Re(I)-NHC complexes prepared in this work, it is possible that this compound was involved in the *C–N* and *C–C* bond cleavage reactions observed here.

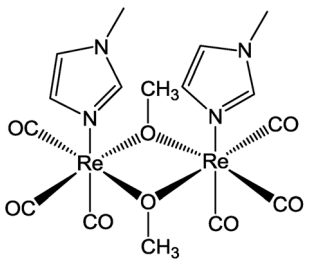
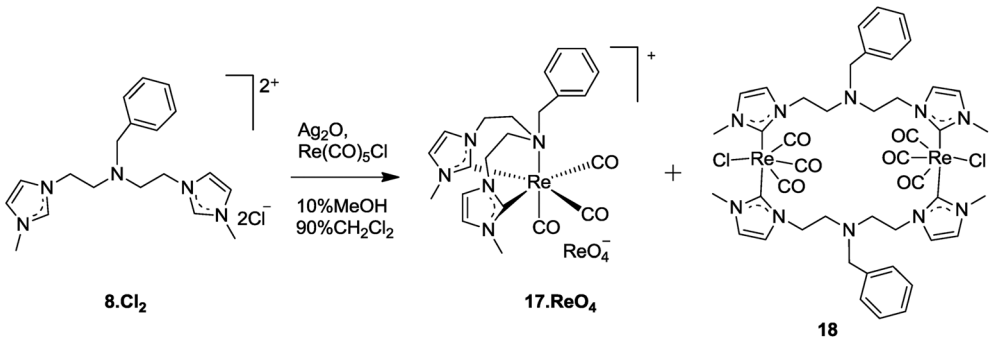


Fig. 4 Structure of common by-product formed in the synthesis of complexes **15** and **16**.

Poor solution stability has been previously noted for complexes of the ^{99m}Tc-tricarbonyl core in combination with monodentate and bidentate ligands.[44] As a result of the chelate effect, facial tridentate ligands offer the greatest potential for highly stable complexes and the tridentate single amino acid chelate ligand systems (SAACs) form ^{99m}Tc and Re complexes with high kinetic stability.[30] With this in mind the tridentate imidazolium salt pro-ligands (**8**·Cl_2, **9**·Cl_2, **11**·Cl_2 and **13**·Cl_2), were used to prepare a series of cationic rhenium(I) tricarbonyl complexes of the form $[Re(CO)_3(C\hat{}N\hat{}C)]^+[X]^-$ (where C^N^C is a bis(NHC)-amine ligand and the counter ion X is either the ReO_4^- or PF_6^-). Initial attempts to synthesise Re(I) complexes of the tridentate pro-ligands were carried out using the same one-pot reaction conditions as were employed for the preparation of complexes **14–16**. The crude product obtained from the reaction of imidazolium salt **8**·Cl_2 with Ag_2O and $Re(CO)_5Cl$ in the same pot gave a complex ^{1}H NMR spectrum, suggestive of more than one Re(I)-NHC complex in addition to unidentified decomposition products. In an effort to separate the cationic and neutral complexes formed in this reaction, the crude product was recrystallised using two different conditions; the first being the diffusion of vapours between diethyl ether and a solution of the crude product in methanol and the second the diffusion of vapours between diethyl ether and a solution of the crude product in acetonitrile. Each crystallisation method produced crystals suitable for XRD and the crystal structures were obtained (see Structural studies section). Vapour diffusion using methanol and ether produced a mononuclear cationic complex **17**, while vapour diffusion using acetonitrile and ether produced a bimetallic neutral complex **18** (Scheme 4). The mononuclear product, **17** showed the expected coordination mode, where the ligand was bound to the Re(I)$(CO)_3$ core as a facial bis(NHC)-amine ligand *via* the two NHC units and the amine donor group, yielding a cationic complex. The counterion for the cationic Re(I) complex was unexpectedly found to be the perrhenate anion (ReO_4^-). The oxidative process responsible for the oxidation of the Re(I) source to ReO_4^- in this reaction is unknown. However, the unexpected generation of ReO_4^- has been noted in a number of previous studies including those involving NHC ligands, and is proposed to result from oxidation and hydrolysis in the

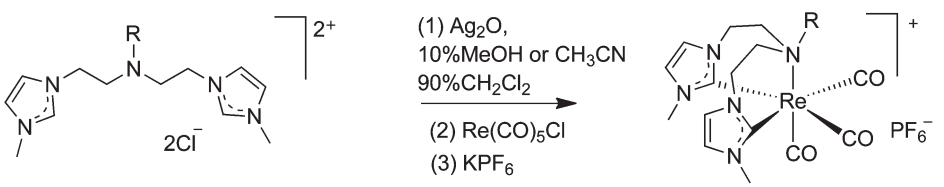


Scheme 4 Synthesis of Re(I) complexes **17**·ReO_4 and **18**.

presence of water.[23,45–47] For the neutral bimetallic complex **18**, two Re(I)$(CO)_3$Cl units were bridged by two ligands, which were bound to the metal centres by the NHC units with the amine groups remaining uncoordinated. The bimetallic complex could not be isolated in sufficient quantities for further analysis and appears to be a minor reaction product associated with the presence of the coordinating chloride counter ion in the synthetic reaction mixture. A ^{1}H NMR experiment was conducted to evaluate if the cationic mononuclear complex **17** exists in a chloride ion dependent equilibrium in solution with the neutral bimetallic complex **18**. In acetonitrile-d_3, **17**·ReO_4 was treated with 10 molar equivalents of TBACl and no changes were observed in the ^{1}H NMR spectra over a period of 5 days (Fig. S16, ESI†) suggesting that once formed, **17** is stable with respect to conversion to **18** in the presence of chloride ions.

To optimise the yield of the desired cationic mononuclear complex, a second synthetic method was adopted (Scheme 5). Here the chosen imidazolium salt was initially reacted with Ag_2O and the insoluble AgCl formed in the reaction was removed by filtration. The residual Ag(I)-NHC complex was then treated with $Re(CO)_5Cl$ and the final cationic Re(I) complex was isolated as a hexafluorophosphate salt with the addition of KPF_6. This method yielded the mononuclear cationic complexes **17–21** in moderate to good yield. The use of preformed Ag(I)-NHC complexes for use as ligand transfer agents to Pd(II) has been previously described for closely related ligand systems.[40]

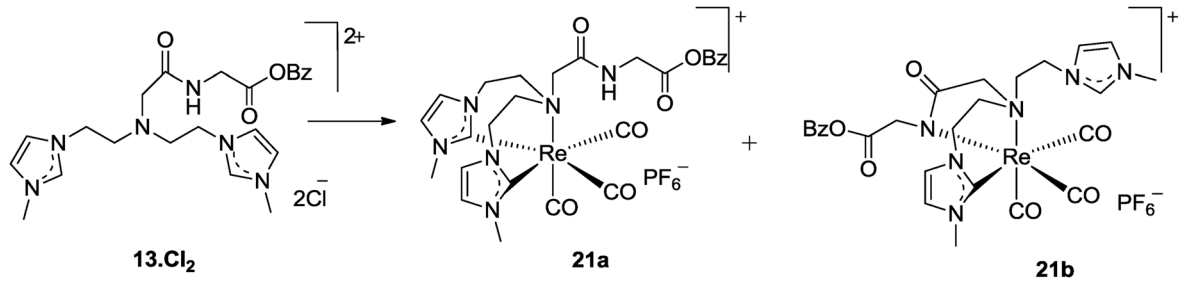
The number of signals observed in the ^{1}H and ^{13}C NMR spectra for the cationic complexes **17–20** are consistent with an internal mirror symmetry plane. Upon coordination of the NHC group, the signal for the imidazolium salt, pro-carbenic proton was lost from the ^{1}H NMR spectra, while a characteristic downfield chemical shift was observed for the carbenic carbon atom in the ^{13}C NMR spectra. Synthesis of the Re(I) complex of the imidazolium salt pro-ligand coupled to glycine (**13**·Cl_2) yielded two linkage isomeric products **21a** and **21b** (Scheme 6). Here the tridentate ligand was either coordinated to the metal centre in the expected manner (**21a**), *via* the two NHC units and the tertiary amine group. The alternative linkage isomer involved deprotonation and coordination of the amide group of the coupled protected glycine fragment, as an amidate donor group in combination with one NHC unit, with the second imidazolium group was unbound. As expected each of these linkage isomers gave distinctive ^{1}H and ^{13}C NMR spectra. As complex **21a** possesses an internal mirror symmetry plane a relatively simple ^{1}H NMR spectrum was obtained with a broad triplet signal (9.08 ppm, DMSO-d_6) corresponding to the amide N–H proton. In contrast, the linkage isomer **21b** has no molecular symmetry and displays a correspondingly more complicated ^{1}H NMR spectrum with a set of signals corresponding to the unbound imidazolium group (Fig. S17, ESI†).



8.Cl_2 R = $CH_2C_6H_5$
9.Cl_2 R = H
11.Cl_2 R = $CH_2CO_2CH_2CH_3$
13.Cl_2 R = $CH_2CONHCH_2CO_2Bz$

17.PF_6 R = $CH_2C_6H_5$
19 R = H
20 R = $CH_2CO_2CH_2CH_3$
21 R = $CH_2CONHCH_2CO_2Bz$

Scheme 5 Synthesis of Re(I) complexes **17–21**.



Scheme 6 Formation of the two linkage isomeric forms of complexes **21** with bis(NHC) (**21a**) and NHC/amidate (**21b**) coordination modes.

Structural studies

Crystallographic refinement data for the imidazolium salts **6**·Cl_4 and **12**·Cl_3 and the Re(I) complexes **14**, *trans*-**15**, *trans*–*trans*-**16**, **17**·ReO_4, **18**, **20** are given in Table S1 (ESI†). The crystal structures of the tetracationic imidazolium salt: **6**·Cl_4 and the tricationic amino acid substituted bis-imidazolium compound: **12**·Cl_3 (Fig. S1 and S2 respectively, ESI†) confirm the structures of these molecules. In both cases, extensive hydrogen bonded networks are present, with interactions between the imidazolium group hydrogens, anions and in the case of **6**·Cl_4 methanol and water molecules of crystallisation.

The coordination spheres for the octahedral Re(I) complexes: **14**, *trans*-**15** and *trans*–*trans*-**16** (Fig. 5) are composed of three facially arrayed carbonyl ligands, a chloride ligand and the bis-carbene units. In all three cases, hydrogen bonding interactions are evident between the axial chloride ligand and the hydrogen atoms of the NHC-methyl wing-tip groups, with the C_{methyl}–Cl distances being within the range 3.4707(1) Å–3.7292(1) Å. A structure closely related to that of **14** with a bromide rather than chloride ligand has been reported previously.[41] As discussed in the Synthesis section, the phenyl substituent of *trans*-**15** and *trans*–*trans*-**16** adopts an axial position on the metallacycle and is *trans* with respect to the Re(I)

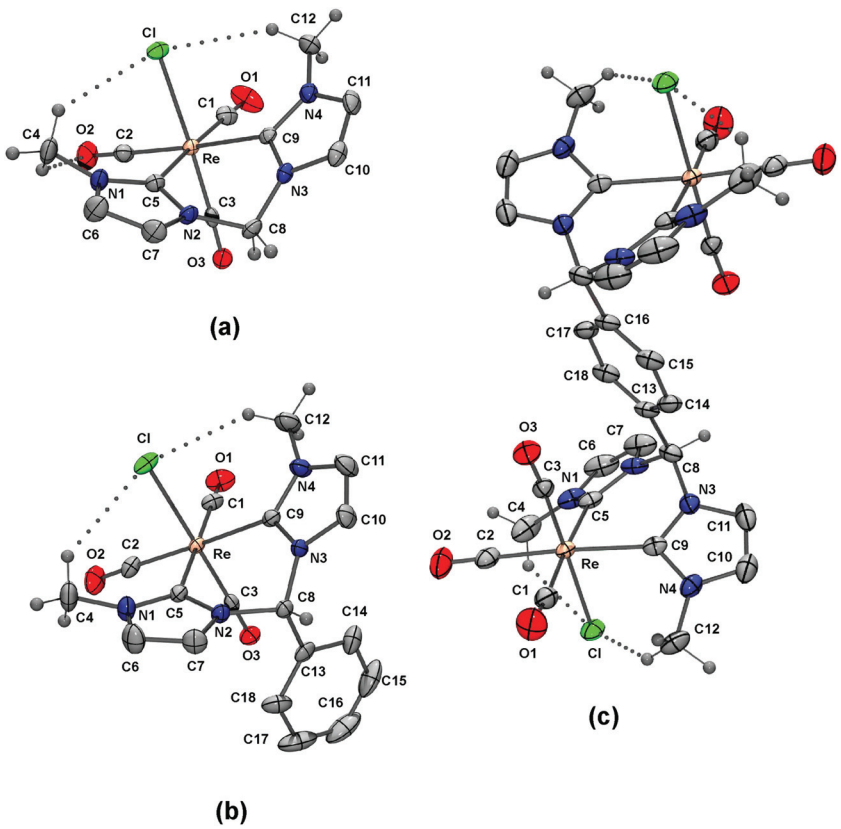


Fig. 5 ORTEP[49] structures of (a) **14**, (b) *trans*-**15** (co-crystallized chloroform molecule omitted for clarity) and (c) *trans*–*trans*-**16** (co-crystallized molecules of acetone and methanol omitted for clarity). Hydrogen atoms (except those of the methyl groups) omitted for clarity. Thermal ellipsoids are shown at 50% probability.

chloride ligand. The ring flip isomer, where the phenyl group would move into an equatorial position is not observed crystallographically (or in solution studies for *trans*-**15**) possibly as a result of unfavourable steric interactions. Previously the crystal structure of a tetrahedral Fe(II) complex of the NHC ligand used to prepare *trans*-**15** was reported,[38] while attempts to prepare a Cu(I) complex of this ligand were unsuccessful.[37] To the best of our knowledge there have been no previous crystallographic studies of bimetallic Re(I)-NHC complexes similar to *trans–trans*-**16**. Canella and co-workers detected the formation of bimetallic complexes by NMR and mass spectroscopy as by-products formed in the synthesis of $[ReCl(CO)_3(C\hat{}C)]$ complexes (where C^C was a propylene or butylene bridged bis-carbene ligand).[48]

The structures of the mononuclear complexes: **17**·ReO_4 and **20** (Fig. 6a and b) of bis(NHC)-amine ligands are similar, with the amino groups of the bis(NHC)-amine ligands bearing benzyl or ethyl acetate substituents respectively. In each case the coordination sphere of the Re(I) centre is composed of three facially arrayed carbonyl ligands with the bis(NHC)-amine ligand bound to the metal centre *via* the two NHC moieties and the tertiary amine group. The $Re–C_{carbene}$ bond lengths are similar for each complex with the average of these being: 2.177 Å for **17**·ReO_4 and 2.180 Å for **20**. Very similar $Re–N_{amine}$ bond lengths are also observed, with these values being 2.337(7) Å and 2.361(6) Å for **17**·ReO_4 and **20** respectively. These structures represent the first examples of tridentate bis-(NHC)-amine ligands bound in a facial manner to an octahedral metal centre. The structure of the bimetallic complex **18** (Fig. 6c) is composed of two $Re(I)(CO)_3Cl$ units bridged by two benzyl substituted ligands, which are bound to the metal

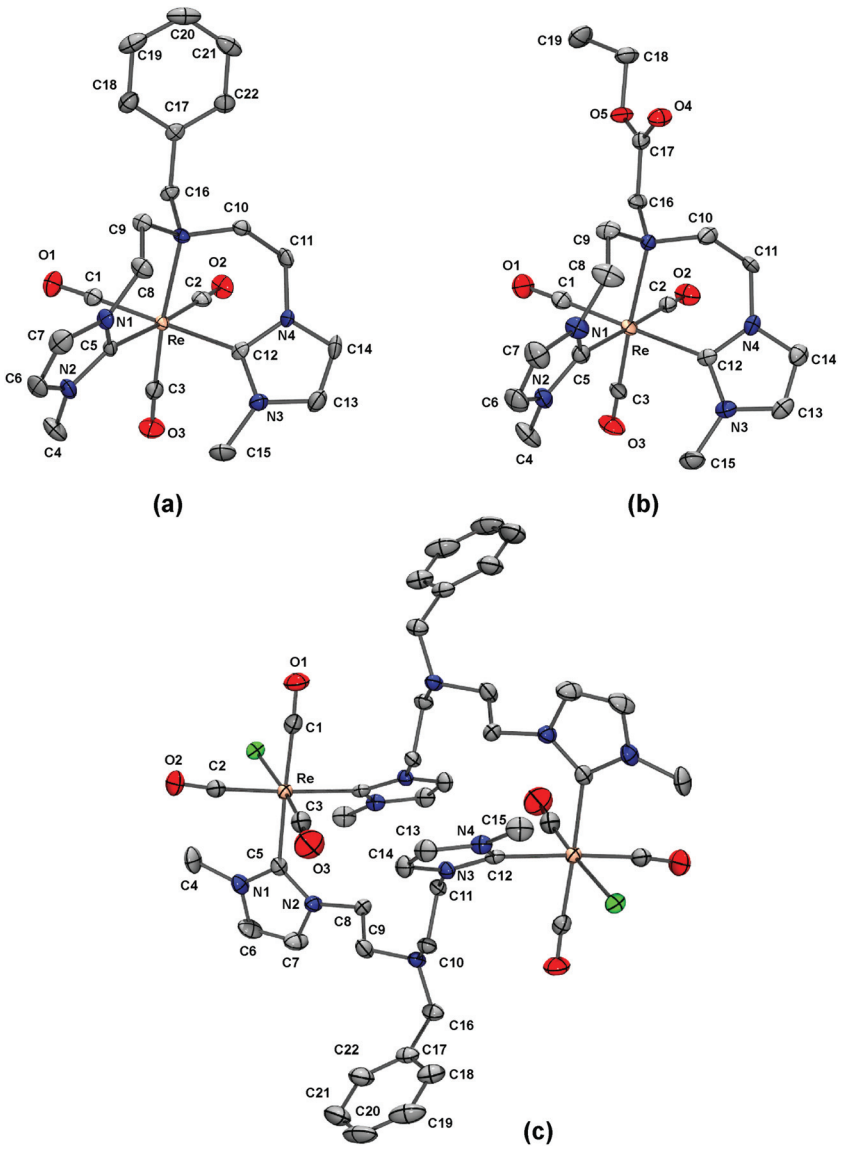


Fig. 6 ORTEP[49] structures of (a) **17**·ReO_4 (ReO_4^- counterion omitted for clarity) (b) **20** (PF_6^- counterion omitted for clarity) and (c) **18** (co-crystallized acetonitrile molecule omitted for clarity). Hydrogen atoms omitted for clarity. Thermal ellipsoids are shown at 50% probability.

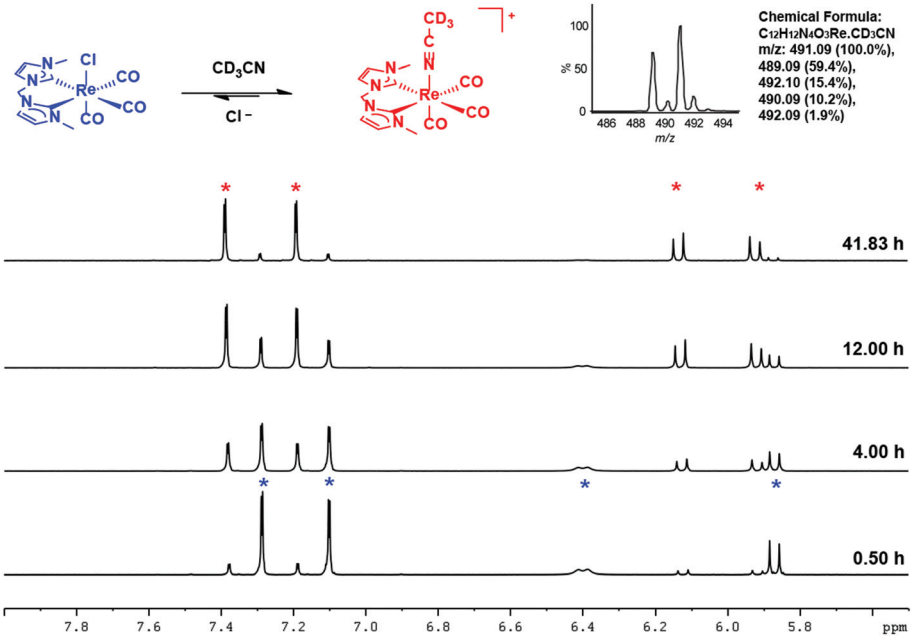


Fig. 7 ^{1}H NMR spectra (500.13 MHz) recorded for a solution of **14**Cl in CD_3CN over a period of 41.83 h at 25.0 ± 0.1 °C showing the exchange of the chloride ligand for a molecule of CD_3CN. Inset spectrum: expansion of main signal from the positive-ion ESI-mass spectrum for **14**CD_3CN.

centres by the NHC units with the amine groups remaining uncoordinated. Mononuclear, square planar Pd(II) complexes of similar bis(NHC)-amine ligands have been previously reported, where the NHC groups were bound to the metal in a *trans* configuration and examples were given where the amine was either coordinated or uncoordinated.[39,40] Using a range of imidazole- and benzimidazole-based bis(NHC)-amine ligands with different length alkyl linker groups, bridged Rh(I) and Ir(I)[50] and tetrahedral Fe(II) complexes were prepared and structurally characterised.[51]

Chloride ligand exchange for complex 14

Previously we reported that the dissolution of the complex: [ReCl(CO)$_3$(1-(2-pyridyl)-3-methylimidazolylidene)] in acetonitrile, resulted in a slow ligand exchange reaction, where the anionic chloride ligand was replaced by a molecule of acetonitrile yielding a cationic complex.[18] A similar reaction is seen for complex **14** and the changes observed in the aromatic region of the ^{1}H NMR spectrum for a solution of **14** in CD_3CN are shown in Fig. 7. During the course of the exchange reaction a new set of signals for the bis-carbene unit associated with the cationic complex with CD_3CN coordinated are evident at ~30 min and reaction is near to completion at ~41 h.

Kinetic analysis of the ^{1}H NMR data was performed by fitting speciation plots (Fig. S18 and S19, ESI†) to the pseudo-first-order (CD_3CN in large excess) kinetic model depicted in eqn (1). Using a single concentration, estimated forward and reverse rate constants were k_f = 0.12 M^{-1} h^{-1} and k_r = 0.02 M^{-1} h^{-1}, respectively. These values are similar in magnitude to those reported previously for [ReCl(CO)$_3$(1-(2-pyridyl)-3-methylimidazolylidene)][18] and indicate that [ReCl(CO)$_3$(bidentate)] complexes are unlikely to be suitable for biological applications as a result of the lability of the Cl^- ligand. In contrast, complexes **17–21** show no evidence for instability in acetonitrile solutions, demonstrating that the use of a facial tridentate NHC ligand as opposed to a monodentate/bidentate ligand combination improves the solution stability. A range of complexes of the form: $[Re^{I}(CO)_3bis(NHC)(CH_3CN)]^+$ with weakly coordinating anions have been previously reported.[52]

$$\mathbf{14}\mathrm{Cl} + \mathrm{CD_3CN} \underset{k_r}{\overset{k_f}{\rightleftharpoons}} [\mathbf{14}\mathrm{CD_3CN}]^+ + \mathrm{Cl}^- \quad (\mathrm{CD_3CN\ in\ large\ excess}) \tag{1}$$

Stability studies

As the NHC ligands reported here are of interest for potential radiopharmaceutical applications, the stability of the Re(I) complexes **14** and **17**·ReO_4 were evaluated in ligand challenge experiments using the well-known metal binding amino acids: L-histidine and L-cysteine. Compounds **14** and **17**·ReO_4 were chosen for these studies as they represent examples of complexes bearing either bidentate (**14**) or tridentate (**17**·ReO_4) NHC ligand systems. Solutions of each complex in phosphate buffered saline (PBS, pH = 7), were incubated at 37 °C for 51 h (**14**) or 91 h (**17**·ReO_4) with either: no addition (control) or L-cysteine (100 mM) or L-histidine (100 mM). Complex stability was evaluated by monitoring the reactions using HPLC over the course of the incubation period. HPLC chromatograms obtained for complex **14** are given in Fig. S20 (control – no addition), S21 (L-cysteine) and S22 (L-histidine) (ESI†). In the control experiment, one major HPLC peak (R_T = 8.32 min) eluted and this species remained unchanged over the time

course of the experiment. The peak eluting at 8.32 min was collected and subjected to ESI-MS analysis and the main signal (m/z = 447.0) corresponded to a cationic fragmentation product of the original complex, where the chloride ligand had been lost. In contrast, significant levels of transchelation were observed for complex **14** in the presence of L-histidine or L-cysteine over the course of these experiments. The transchelation products were identified using ESI-MS. The mass spectral results showed that the monodentate chloride ligand of the complex **14** had been replaced by either a cysteine (HPLC: R_T = 8.04 min, ESI-MS: m/z = 568.0, Fig. S21†) or a histidine (HPLC: R_T = 7.86 min, ESI-MS: m/z = 602.0, Fig. S22†), generating cationic complexes. These results confirm, that the labile nature of the chloride ligand for complex **14**, causes ligand exchange and formation of $[Re(CO)_3(C\hat{}C)(\text{amino acid})]^+$ complexes with histidine and cysteine.

In order to obtain acceptable peak shape in the HPLC analysis of complex **17**, 0.1% trifluoroacetic acid (TFA) was added to the eluent as an organic modifier. Under these conditions, two peaks containing the cationic complex **17** eluted (Fig. S23, ESI†) and these corresponded to ion pairs composed of **17**·CF_3COO (R_T = 9.50 min) and **17**·ReO_4 (R_T = 10.36 min). Ion pair formation in reverse phase HPLC is well known and the use of ion pair reagents is a standard tool to aid in the separation of ionic compounds.[53] HPLC analysis complex **17**·ReO_4 showed good stability in PBS alone (Fig. S24, ESI†) and no evidence for *trans*-chelation was seen in the presence of L-histidine and L-cysteine (Fig. S25–S26, ESI†). The stability studies for complex **17**·ReO_4 were conducted over a relatively long incubation period (91 h) and the results show that the cationic complex $\mathbf{17}^+$ was highly stable in the presence of large excesses of these competing ligands. It can therefore be concluded that bis(NHC)-amine ligands may be suitable of for imaging (Tc-99m) or therapeutic (Re-186/188) applications.

Conclusion

There has been much recent interest in the use of NHC ligands in medicinal inorganic chemistry,[4,5,54,55] including their potential application in radiopharmaceutical development. In an earlier study, we described the first example of labelling an NHC with the medically important metallic radionuclide: ^{99m}Tc[32] and Wagner and co-workers reported a ^{188}Re complex of a bis(NHC) ligand.[19] It has been previously noted that monodentate/bidentate or [2 + 1] ligand combinations with the M(I)$(CO)_3$ core (M = Tc or Re) can be unsuitable for biological applications due to poor complex stability,[44] and that complexes with tridentate ligands display improved kinetic stability, due to the capacity of the tridentate ligand to shield the organometallic metal centre.[56] To further explore the chemistry of chelating NHC ligands in combination with the Re(I)$(CO)_3$ core, in the present study a series of known and novel bidentate, bis-bidentate and tridentate NHC pro-ligands, and their corresponding Re(I) complexes have been prepared. To demonstrate the potential for the conjugation of biologically active molecules, the bis-imidazolium amine pro-ligand **12**·Cl_3 was functionalised with a carboxylic acid group and linked to benzyl ester protected glycine *via* amide bond formation using the peptide coupling reagent: EDC.

The stability of two complexes **14** and **17**·ReO_4 were evaluated using ligand challenge experiments with the metal binding amino acids L-histidine or L-cysteine. These compounds were chosen because they represent examples of complexes with either a [2 + 1] monodentate/bidentate ligand set or a tridentate ligand respectively. Complex **14**, with the [2 + 1] ligand combination, displayed low stability in these assays, with the labile chloride ligand being replaced by the metal binding amino acids. In addition, ^1H NMR studies of complex **14** in acetonitrile solution showed that the chloride ligand is labile and was replaced by an acetonitrile solvent molecule to give a cationic complex. In contrast, complex **17**·ReO_4 was stable in the presence of the metal binding amino acids and showed no evidence for displacement of the tridentate NHC ligand.

These results indicate that bidentate bis-NHC ligands in combination with the M(I)$(CO)_3$ core (M = Tc or Re) are unlikely to be suitable for biological applications due to the labile nature of the monodentate ligand. Whereas tridentate, bis(NHC)-amine ligands, bind to the Re(I)$(CO)_3$ core as a facial tridentate and form kinetically stable complexes. Currently the radiochemistry associated with labelling bis(NHC)-amine ligands with ^{99m}Tc is being developed in addition to the conjugation of these ligands to biologically active molecules (BAMS) for *in vivo* applications.

Experimental details

General procedures

All reagents were purchased from Sigma-Aldrich or Alfa Aesar and were of analytical grade or higher and were used without further purification unless otherwise stated. All compounds were prepared in air unless otherwise stated. Experimental details for the synthesis of the bis-imidazolium salts: **4**·Br_2 and **5**·Cl_2 are given in the ESI;† these compounds were prepared using similar procedures to those published previously.[37,38,41] NMR spectra were recorded on either a Bruker Avance ARX-300 (300.14 MHz for ^1H, 75.48 MHz for ^{13}C) or a Bruker Avance ARX-400 (400.13 MHz for ^1H, 100.61 MHz for ^{13}C) or a Bruker Avance ARX-500 (500.13 MHz for ^1H, 125.77 MHz for ^{13}C) spectrometer and were internally referenced to solvent resonances. In all cases proton-decoupled ^{13}C NMR spectra were collected. Mass spectra were obtained using a Bruker Esquire6000 mass spectrometer fitted with an Agilent electrospray (ESI) ion source. Microanalyses were performed by the Microanalytical Laboratory at the ANU Research School of Chemistry, Canberra, Australia or the Campbell Microanalytical Laboratory, Department of Chemistry, University of Otago, New Zealand.

High pressure liquid chromatography

Reverse Phase-HPLC (RP-HPLC) analyses and purifications were performed using a Shimadzu HPLC fitted with two Shimadzu LC-20AD pumps, a SIL-20AHT autosampler, a SPD-M20A photodiode array detector and a FRC-10A fraction collector. For all HPLC methods chromatograms were obtained by monitoring absorbance at 258 nm. Elution was carried out as follows: ***Method 1***: Atlantis T3 DC_{18} analytical column (4.6 × 150 mm), flow rate of 1 mL min^{-1}, mobile phase: (A) water and (B) methanol. Gradient elution: 30% (B) 0–1 min, 30–90% (B) 1–4 min, 90% (B) 4–8 min, 90–30% (B) 8–11 min, stop at 14 min. ***Method 2***: Atlantis T3 DC_{18} analytical column (4.6 × 150 mm), flow rate of 1 mL min^{-1}, mobile phase: (A) water and (B) methanol. Gradient elution: 30% (B) 0–1 min, 30–70% (B) 1–3 min, 70–90% (B) 3–6 min 90% (B) 6–11 min, 90–30% (B) 11–16 min, stop at 18 min. ***Method 3***: Atlantis T3 DC_{18} analytical column (4.6 × 150 mm), flow rate of 1 mL min^{-1}, mobile phase: (A) 0.1% trifluoroacetic acid (TFA) in water and (B) 0.1% TFA in methanol. Gradient elution: 30% (B) 0–1 min, 30–90% (B) 1–5 min, 90% (B) 5–10 min, 90–30% (B) 10–13 min, stop at 17 min. ***Method 4***: Alltima C_{18} semi-preparative column (22 × 250 mm), flow rate of 3 mL min^{-1}, mobile phase: (A) water and (B) methanol. Gradient elution: 30% (B) 0–1 min, 30–80% (B) 1–5 min, 80–90% (B) 5–10 min, 90–30% (B) 10–12 min, stop at 16 min.

Stability studies

Stock solutions of either **14** or **17**·ReO_4 (10 mM in DMSO) were reconstituted in phosphate buffered saline (pH = 7) (final complex concentration = 5.0 mM) containing either: no addition (control), L-cysteine (100 mM) or L-histidine (100 mM). These solutions were incubated in the dark at 37 °C ± 1 °C for 51 h (**14**) or 91 h (**17**·ReO_4). The complex stability was monitored by recording HPLC chromatograms at set time points (see ESI†) over the course of the incubation period. To identify the transchelation reaction products, the HPLC peaks were collected and the positive ion mass spectra recorded. For complex **14**, HPLC ***Method 1*** was used, while for complex **17**·ReO_4 HPLC ***Method 3*** was used.

X-ray crystallography

Single crystals suitable for X-ray diffraction were obtained as follows: **6**·Cl_4: diffusion of vapors between a solution of the title compound in methanol and diethyl ether; **12**·Cl_3: slow evaporation of a solution of the title compound in methanol and acetone; **14**, *trans*-**15** and *trans–trans*-**16**: slow evaporation of methanol, chloroform and acetone solutions of these compound respectively; **17**·ReO_4, **18** and **20** diffusion of vapors between a solution of the title compounds in methanol or acetonitrile or methanol with small amount of acetone and diethyl ether. Crystallographic data for all structures determined are given in Tables S1 (ESI†). For all samples, crystals were removed from the crystallization vial and immediately coated with paratone oil on a glass slide. A suitable crystal was mounted in Paratone oil on a glass fiber and cooled rapidly to 173 K in a stream of cold N_2 using an Oxford low temperature device. Diffraction data were measured using an Oxford Gemini diffractometer mounted with Mo-Kα λ = 0.71073 Å and Cu-Kα λ = 1.54184 Å. Data were reduced and corrected for absorption using the CrysAlis Pro program.[57] The SHELXL2013-2[58] program was used to solve the structures with Direct Methods, with refinement by the Full-Matrix Least-Squares refinement techniques on F^2. The non-hydrogen atoms were refined anisotropically and hydrogen atoms were placed geometrically and refined using the riding model. Co-ordinates and anisotropic thermal parameters of all non-hydrogen atoms were refined. All calculations were carried out using the program Olex^2.[59] Images were generated by using ORTEP-3.[49] Further XRD details are provided in the ESI.† CCDC 1419735–1419742 contains the supplementary crystallographic data for this paper.

Synthesis

6·Cl_4. A solution of α,α,α,α-tetrachloro-*p*-xylene (2.00 g, 8.26 mmol) and 1-methylimidazole (2.71 g, 33.00 mmol) in PEG 400 (5 mL) was heated at 110 °C for 48 h. After cooling to RT, acetone (10 mL) was added and a sticky solid formed. After carefully decanting the solvent, the solid was redissolved in methanol and re-precipitated by the addition of ether. The product was obtained as brown hygroscopic solid. (Yield: 3.00 g, 64%). ^{1}H NMR (500 MHz) (DMSO-d_6): δ (ppm) 9.96 (s, 4H, $4H_{imi}$ (NC*H*N)), 9.00 (s, 2H, 2ArC*H*) 8.27 (dd, $^3J_{HH}$ = 1.50 Hz, $^4J_{HH}$ = 1.50 Hz, 4H, $4H_{imi}$), 7.93 (dd, $^3J_{HH}$ = 1.50 Hz, $^4J_{HH}$ = 1.50 Hz, 4H, $4H_{imi}$), 7.62 (s, 4H, $4H_{Ar}$), 3.92 (s, 12H, $4CH_3$). ^{13}C NMR (DMSO-d_6): δ (ppm) 138.3 $4C_{imi}$ (N*C*HN), 133.7 $2C_q$, 128.9 $4C_{imi}$, 125.0 $4C_{imi}$, 121.3 $4C_{Ar}$, 70.6 2Ar*C*H, 36.2 $4CH_3$. Anal. Calcd for $C_{24}H_{30}Cl_4N_8{\cdot}2H_2O$: C, 47.38. H, 5.63. N, 18.42%. Found: C, 47.65. H, 5.72. N, 18.57%.

7. A modified literature procedure was used to prepare this compound.[39] An aqueous solution of bis(2-dichloroethyl) amine hydrochloride (20 mL, 1.40 M) was added to an aqueous NaOH solution (15 mL, 2.07 M) and after stirring for 5 min, two layers separated and the organic phase was extracted into dichloromethane. After the removal of solvent from the organic extracts, the residual oil was dissolved in acetonitrile (30 mL) and this solution was added to a suspension of K_2CO_3 (11.68 g, 84.51 mmol) in acetonitrile (30 mL) and finally a solution of benzyl bromide (5.30 g, 30.99 mmol) in acetonitrile (30 mL) was added. The mixture was stirred for 24 h, filtered, and the solvent removed under reduced pressure, yielding a cream colored crystalline solid. To the solid was added a solution of triethylamine (1.09 g, 10.77 mmol) in hexane (50 mL) and the precipitate of benzyltriethylammonium bromide which formed was removed by filtration and the filtrate was concentrated under reduced pressure to give a yellow liquid (10 mL). After purification on silica, with dichloromethane (10%) and hexane (90%) as eluent, the product was obtained as a colorless oil. (Yield: 5.50 g, 85%). ^{1}H NMR (300 MHz) (DMSO-d_6): δ (ppm) 7.35–7.23 (m, 5H, H_{Ar}), 3.72 (s, 2H, ArCH_2), 3.60 (t, $^3J_{HH}$ = 6.90 Hz, 4H, 2CH_2CH$_2$), 2.84 (t, $^3J_{HH}$ = 6.90 Hz, 4H, 2CH$_2$CH_2). ^{13}C

NMR (DMSO-d_6): δ (ppm) 139.2 C_q, 128.5 2C_{Ar}, 128.1 2C_{Ar}, 126.9 C_{Ar}, 57.5 ArCH_2, 55.1 2CH_2CH_2, 42.1 2CH_2CH_2.

8·Cl$_2$. A solution of **7** (0.87 g, 3.74 mmol) and 1-methylimidazole (0.61 g, 7.50 mmol) in tetrahydrofuran (10 mL) was heated at 120 °C for 24 h. After cooling to RT, a yellow/brown oil was formed and triturated with acetone (5 × 20 mL). The product was obtained as yellow/brown oil. (Yield: 0.34 g, 23%). ^{1}H NMR (300 MHz) (DMSO-d_6): δ (ppm) 9.13 (s, 2H, 2H_{imi} (NCHN)), 7.64 (d, $^3J_{HH}$ = 1.20 Hz, 4H, 4H_{imi}), 7.25–7.23 (m, 3H, H_{Ar}), 7.01–6.98 (m, 2H, H_{Ar}), 4.30 (t, $^3J_{HH}$ = 6.00 Hz, 4H, 2CH_2CH$_2$), 3.85 (s, 6H, 2CH_3), 3.63 (s, 2H, ArCH_2), 2.86 (t, $^3J_{HH}$ = 6.00 Hz, 4H, 2CH$_2$CH_2). ^{13}C NMR (DMSO-d_6): δ (ppm) 137.9 C_q, 136.6 2C_{imi} (NCHN), 128.5 2C_{Ar}, 128.1 2C_{Ar}, 127.0 C_{Ar}, 123.1 2C_{imi}, 122.5 2C_{imi}, 56.9 CH$_2$, 52.4 2CH$_2$$CH_2$, 46.4 2CH$_2CH_2$, 35.7 2$CH_3$. This compound was obtained as a hygroscopic oil and was characterised by HPLC, ESI-MS and ^{1}H and ^{13}C NMR spectroscopy. The NMR spectra, ESI-MS and HPLC chromatogram are provided in the ESI (Fig. S4†) as evidence of purity.

9·Cl$_2$. To a mixture of **8**·Cl$_2$ (0.50 g, 1.26 mmol) in ethanol (30 mL) was added 5% Pd/C (34 mg) and resulting suspension was stirred at 65 °C under one atmosphere of hydrogen for 24 h. The mixture was filtered and the volatiles removed from the filtrate under reduced pressure to give **9**·Cl$_2$ as an as yellow oil. (Yield: 0.35 g, 91%). ^{1}H NMR (500 MHz) (DMSO-d_6): δ (ppm) 9.13 (s, 2H, 2H_{imi} (NCHN)), 7.70 (dd, $^3J_{HH}$ = 1.50 Hz, $^4J_{HH}$ = 1.50 Hz, 2H, 2H_{imi}), 7.68 (dd, $^3J_{HH}$ = 1.50 Hz, $^4J_{HH}$ = 1.50 Hz, 2H, 2H_{imi}), 4.19 (t, $^3J_{HH}$ = 5.50 Hz, 4H, 2CH_2CH$_2$), 3.86 (s, 6H, 2CH_3), 2.89 (t, $^3J_{HH}$ = 6.00 Hz, 4H, 2CH$_2$CH_2). ^{13}C NMR (DMSO-d_6): δ (ppm) 137.2 2C_{imi} (NCHN), 123.6 2C_{imi}, 123.0 2C_{imi}, 49.0 2CH$_2$$CH_2$, 47.8 2$CH_2CH_2$, 36.1 2$CH_3$. This compound was obtained as a hygroscopic oil and was characterised by HPLC, ESI-MS and ^{1}H and ^{13}C NMR spectroscopy. The NMR spectra, ESI-MS and HPLC chromatogram are provided in the ESI (Fig. S5†) as evidence of purity.

10. This compound was prepared as described for **7** from ethyl bromoacetate (8.94 g, 53.53 mmol) and was obtained as a colourless oil after purification on silica, with ethyl acetate (20%) and hexane (80%) as eluent. (Yield: 8.64 g, 78%). ^{1}H NMR (300 MHz) ($CDCl_3$): δ (ppm) 4.07 (q, $^3J_{HH}$ = 7.08 Hz, 2H, OCH_2), 3.58 (t, $^3J_{HH}$ = 6.90 Hz, 4H, 2CH_2CH$_2$), 3.54 (s, 2H, CH_2CO), 2.97 (t, $^3J_{HH}$ = 6.90 Hz, 4H, 2CH$_2$CH_2), 1.18 (t, $^3J_{HH}$ = 7.08 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ (ppm) 171.1 CO, 59.8 CH$_3$$CH_2$, 55.7 2CH$_2$$CH_2$, 54.4 CH$_2$CO, 42.6 2CH$_2CH_2$, 14.0 CH$_3$. This compound was obtained as a hygroscopic oil and was characterised by HPLC, ESI-MS and ^{1}H and ^{13}C NMR spectroscopy. The NMR spectra, ESI-MS and HPLC chromatogram are provided in the ESI (Fig. S6†) as evidence of purity.

11·Cl$_2$. This compound was prepared as described for **8**·Cl$_2$ from **10** (3.08 g, 13.50 mmol). The isolated crude oil was triturated with acetone (5 × 20 mL). The product was obtained as brown oil. (Yield: 2.96 g, 56%). ^{1}H NMR (400 MHz) (DMSO-d_6): δ (ppm) 9.20 (s, 2H, H_{imi} (NCHN)), 7.69 (dd, $^3J_{HH}$ = 1.60 Hz, $^4J_{HH}$ = 1.60 Hz, 2H, H_{imi}), 7.66 (dd, $^3J_{HH}$ = 1.60 Hz, $^4J_{HH}$ = 1.60 Hz, 2H, H_{imi}), 4.20 (t, $^3J_{HH}$ = 6.40 Hz, 4H, 2CH_2CH$_2$), 4.08 (q, $^3J_{HH}$ = 7.20 Hz, 2H, OCH_2), 3.85 (s, 6H, imi-CH_3), 3.54 (s, 2H, CH_2CO), 3.06 (t, $^3J_{HH}$ = 6.40 Hz, 4H, 2CH$_2$CH_2), 1.19 (t, $^3J_{HH}$ = 7.20 Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ (ppm) 170.8 CO, 136.7 2C_{imi} (NCHN), 122.9 2C_{imi}, 122.4 2C_{imi}, 60.0 CH$_3$$CH_2$, 52.7 2CH$_2$$CH_2$ and CH$_2$CO 46.5 2CH$_2$CH$_2$, 35.7 2imi-CH$_3$, 14.0 CH$_3$. This compound was obtained as a hygroscopic oil and was characterised by HPLC, ESI-MS and ^{1}H and ^{13}C NMR spectroscopy. The NMR spectra, ESI-MS and HPLC chromatogram are provided in the ESI (Fig. S7†) as evidence of purity.

12·Cl$_3$. A solution of **11**·Cl$_2$ (1.00 g, 2.55 mmol) in 5 M HCl (20 mL) was heated at 110 °C for 2 h. After cooling to RT, the solvent was removed under reduced pressure and the crude product was recrystallised from methanol with the addition of acetone. The product was obtained as a hygroscopic white crystalline solid. (Yield: 0.68 g, 67%). ^{1}H NMR (500 MHz) (DMSO-d_6): δ (ppm) 9.31 (s, 2H, 2H_{imi} (NCHN)), 7.76 (dd, $^3J_{HH}$ = 1.50 Hz, $^4J_{HH}$ = 1.50 Hz, 2H, H_{imi}), 7.68 (dd, $^3J_{HH}$ = 1.50 Hz, $^4J_{HH}$ = 1.50 Hz, 2H, H_{imi}), 4.26 (t, $^3J_{HH}$ = 6.00 Hz, 4H, 2CH_2CH$_2$), 3.85 (s, 6H, 2imi-CH_3), 3.51 (s, 2H, CH_2CO), 3.13 (t, $^3J_{HH}$ = 6.00 Hz, 4H, 2CH$_2$CH_2). ^{13}C NMR (DMSO-d_6): δ (ppm) 172.0 CO, 136.9 2C_{imi} (NCHN), 122.9 2C_{imi}, 122.4 2C_{imi}, 53.2 CH$_2$CO, 52.7 2CH$_2$CH$_2$, 46.3 2CH$_2$$CH_2$, 35.7 2$CH_3$. This compound was obtained as a hygroscopic solid and was characterised by HPLC, ESI-MS and ^{1}H and ^{13}C NMR spectroscopy. NMR spectra, ESI-MS and HPLC chromatogram are provided in the ESI (Fig. S8†) as evidence of purity.

13·Cl$_2$. A mixture of H-Gly-OBzl·TsO (0.18 g, 0.52 mmol) and DIPEA (0.07 g, 0.52 mmol) in dimethylformamide was stirred for 35 min and a solution of **12**·Cl$_3$ (0.21 g, 0.52 mmol) and DIPEA (0.14 g, 1.04 mmol) and HOBt (0.01 g, 0.08 mmol) in water were added. The mixture was cooled to 10 °C and EDC (0.15 g, 0.78 mmol) was added. After stirring for 24 h, the solvent and other volatiles were removed under reduced pressure and the residue was dissolved in water (10 mL) and a solution of KPF_6 (0.39 g, 2.09 mmol) in water (5 mL) was added. After stirring for 1 h a colourless oil separated, which was collected by centrifugation. The oil was dissolved in acetone (5 mL) and a solution of Bu_4NCl (0.58 g, 2.09 mmol) in acetone (5 mL) was then added. After 1 h a second colourless oil formed, which was isolated by centrifugation and washed with acetone (10 mL). The product was obtained as colourless oil. (Yield: 0.17 g, 64%). ^{1}H NMR (400 MHz) ($CDCl_3$): δ (ppm) 9.87 (s, 2H, 2H_{imi} (NCHN)), 9.32 (t, $^3J_{HH}$ = 6.00 Hz, 1H, NH), 7.96 (s, 2H, 2H_{imi}), 7.34–7.23 (m, 5H, 5H_{Ar}), 7.24 (s, 2H, 2H_{imi}), 5.08 (s, 2H, ArCH_2), 4.55 (t, $^3J_{HH}$ = 6.40 Hz, 4H, 2CH_2CH$_2$), 4.04 (d, $^3J_{HH}$ = 6.00 Hz, 2H, NHCH_2), 3.88 (s, 6H, 2imi-CH_3), 3.47 (s, 2H, CH_2CO), 3.25 (t, $^3J_{HH}$ = 6.40 Hz, 4H, 2CH$_2$CH_2). ^{13}C NMR ($CDCl_3$): δ (ppm) 171.5 CO, 170.8 CO, 137.8 2C_{imi} (NCHN), 135.7 C_q, 128.9 2C_{Ar}, 128.6 C_{Ar}, 128.1 2C_{Ar}, 123.9 2C_{imi}, 122.7 2C_{imi}, 67.0 ArCH_2, 59.3 COCH_2, 54.9 2CH_2CH$_2$, 47.7 2CH$_2$$CH_2$, 41.2 NH$CH_2$, 36.6 2imi-$CH_3$. This compound was obtained as a hygroscopic oil and was characterised by HPLC, ESI-MS and ^{1}H and ^{13}C NMR spectroscopy. The NMR spectra, ESI-MS and HPLC chromatogram are provided in the ESI (Fig. S9†) as evidence of purity.

14. A solution of **4**·Br$_2$ (75 mg, 0.22 mmol), Re(CO)$_5$Cl (80 mg, 0.22 mmol) and Ag_2O (51 mg, 0.22 mmol) in a

1 : 9 mixture of methanol and dichloromethane (30 mL) was heated at 60 °C for 24 h. After cooling to RT, the mixture was filtered through celite and the filtrate was concentrated to ~5 mL under reduced pressure and a small amount of ether was added resulting in the precipitation of an off-white solid. The crude product was collected and recrystallised from methanol with the addition of ether. The product was obtained as a white solid (Yield: 55 mg, 52%). ^{1}H NMR (500 MHz) (DMSO-d_6): δ (ppm) 7.51 (d, $^3J_{HH}$ = 2.00 Hz, 2H, 2H_{imi}), 7.39 (d, $^3J_{HH}$ = 2.00 Hz, 2H, 2H_{imi}), 6.55 (d, $^3J_{HH}$ = 13.00 Hz, 1H, CH_2), 5.87 (d, $^3J_{HH}$ = 13.00 Hz, 1H, CH_2), 3.89 (s, 6H, 2CH_3). ^{13}C NMR (DMSO-d_6): δ (ppm) 197.8 C_q, 177.1 2C_{imi} (N*C*N), 123.0 2C_{imi}, 121.5 2C_{imi}, 63.2 *C*H$_2$, 38.2 2*C*H$_3$. Anal. Calcd for $C_{12}H_{12}ClN_4O_3Re$: C, 29.97. H, 2.24. N, 11.63%. Found: C, 29.91. H, 2.51. N, 11.63%. HPLC: R_T = 8.32 min (HPLC ***Method 1***).

trans*-15.** This compound was prepared as described for **14** from **5**·Cl_2 (90 mg, 0.28 mmol). The crude residue was washed with chilled methanol (5 mL) and the undissolved solid was collected and recrystallised from a minimum volume of chloroform with addition of small amount of ether. The product was obtained as a colourless crystalline solid. (Yield: 46 mg, 30%). ^{1}H NMR (500 MHz) (DMSO-d_6): δ (ppm) 7.90 (s, 1H, ArC*H*), 7.76 (d, $^3J_{HH}$ = 2.00 Hz, 2H, 2H_{imi}), 7.59 (d, $^3J_{HH}$ = 2.00 Hz, 2H, 2H_{imi}), 7.35–7.27 (m, 3H, H_{Ar}), 6.65 (d, $^3J_{HH}$ = 8.00 Hz, 2H, H_{Ar}), 3.98 (s, 6H, 2CH_3). ^{13}C NMR (DMSO-d_6): δ (ppm) 176.9 2C_{imi} (N*C*N), 138.3 C_q, 129.0 2C_{Ar}, 128.6 C_{Ar}, 124.9 2C_{Ar}, 123.1 2C_{imi}, 122.4 2C_{imi}, 74.5 Ar*C*H, 38.3 2*C*H$_3$. ESI-MS: *m*/*z* = 523.1 $[C_{18}H_{16}N_4O_3Re]^+$. Anal. Calcd for $C_{18}H_{16}ClN_4O_3Re$: C, 38.74. H, 2.89. N, 10.04%. Found: C, 39.07. H, 2.91. N, 10.00%. HPLC: R_T = 9.05 min (HPLC ***Method 1).

trans–trans*-16 and *trans–cis*-16.** These compounds were prepared as described for **14** from **6**·Cl_4 (50 mg, 0.09 mmol). Upon completion of the reaction, the solvent was removed under reduced pressure and the crude product was dissolved in a minimum volume of methanol. The geometric isomeric forms of the complex were separated using semi-preparative HPLC (HPLC ***Method 4, Experimental section). *trans–trans*-**16** (HPLC: R_T = 9.60 min) and *trans–cis*-**16** (HPLC: R_T = 10.63 min) were obtained as off-white solids after HPLC purification. Both compounds were further purified by the diffusion of vapours between diethyl ether and solutions of each compound in acetone. Compound *trans–trans*-**16** was obtained as colourless crystalline solid (Total yield: 10 mg, 11%), and *trans–cis*-**16** was obtained as colourless solid. Only a very small amount of this isomer was isolated after HPLC purification and recrystallization and characterisation was only possible by ^{1}H NMR and mass spectrometry. *trans–trans*-**16**: ^{1}H NMR (400 MHz) (DMSO-d_6): δ (ppm) 7.94 (s, 2H, 2ArC*H*), 7.54 (d, $^3J_{HH}$ = 2.00 Hz, 4H, 4H_{imi}), 7.49 (d, $^3J_{HH}$ = 2.00 Hz, 4H, 4H_{imi}), 6.83 (s, 4H, 4H_{Ar}), 3.95 (s, 12H, 4CH_3). ^{13}C NMR (DMSO-d_6): δ (ppm) 197.1 4*C*O, 190.3 2*C*O, 176.9 4C_{imi} (N*C*N), 126.9 4C_{Ar}, 123.0 4C_{imi}, 121.9 4C_{imi}, 74.0 2Ar*C*H, 38.4 2*C*H$_3$. ESI-MS: *m*/*z* = 1001.1 $[C_{30}H_{26}N_8O_6Re_2Cl]^+$. Anal. Calcd for $C_{30}H_{26}Cl_2N_8O_6Re_2$: C, 34.72. H, 2.52. N, 10.80%. Found: C, 34.85. H, 2.59. N, 10.75%.

***trans–cis*-16.** ^{1}H NMR (500 MHz) (CD_3CN): δ (ppm) 7.67 (d, $^3J_{HH}$ = 8.50 Hz, 2H, H_{Ar}), 7.59 (s, 1H, ArC*H*), 7.56 (d, $^3J_{HH}$ = 2.00 Hz, 2H, 2H_{imi}), 7.31 (d, $^3J_{HH}$ = 2.00 Hz, 2H, 2H_{imi}), 7.03 (d, $^3J_{HH}$ = 8.50 Hz, 2H, H_{Ar}), 7.01 (s, 1H, ArC*H*), 6.99 (d, $^3J_{HH}$ = 2.00 Hz, 2H, 2H_{imi}), 6.56 (d, $^3J_{HH}$ = 2.00 Hz, 2H, 2H_{imi}), 4.08 (s, 6H, 2CH_3), 4.04 (s, 6H, 2CH_3). ESI-MS: *m*/*z* = 1001.1 $[C_{30}H_{26}N_8O_6Re_2Cl]^+$.

17·ReO_4. This compound was prepared as described for **14** from **8**·Cl_2 (20 mg, 0.05 mmol). The crude product was recrystallised from dichloromethane by the addition of ether. The product was obtained as pale yellow crystalline solid. (Yield: 15 mg, 35%). ^{1}H NMR (500 MHz) (DMSO-d_6): δ (ppm) 7.63–7.61 (m, 2H, 2H_{Ar}), 7.46 (s, 4H, 4H_{imi}), 7.44–7.43 (m, 3H, H_{Ar}), 4.63 (s, 2H, ArCH_2), 4.21–4.17 (m, 2H, 2CH_2CH$_2$), 3.69–3.65 (m, 2H, 2CH_2CH$_2$), 3.63 (s, 6H, 2CH_3), 3.27–3.22 (m, 2H, 2CH$_2$CH_2), 2.65–2.60 (m, 2H, 2CH$_2$CH_2). ^{13}C NMR (DMSO-d_6): δ (ppm) 195.7 C_q, 195.5 2C_q, 173.9 2C_{imi} (N*C*N), 133.3 2C_{Ar}, 132.2 C_q, 129.1 C_{Ar}, 128.3 2C_{Ar}, 123.5 2C_{imi}, 122.4 2C_{imi}, 73.9 Ar*C*H$_2$, 56.6 2CH$_2$*C*H$_2$, 48.3 2*C*H$_2$CH$_2$, 38.1 2*C*H$_3$. ESI-MS: *m*/*z* = 594.1 $[C_{22}H_{25}N_5O_3Re]^+$. Anal. Calcd for $C_{22}H_{25}N_5O_3Re$·ReO_4: C, 31.33. H, 2.99. N, 8.30%. Found: C, 31.63. H, 2.88. N, 8.46%. HPLC: R_T = 10.3 min (HPLC ***Method 3***).

17·PF_6. A solution of **8**·Cl_2 (80 mg, 0.20 mmol) and Ag_2O (47 mg, 0.20 mmol) in a 1 : 9 mixture of methanol and dichloromethane (30 mL) was stirred for 24 h and then filtered through celite and the solvent removed under reduced pressure. The residual solid was dissolved in dichloromethane and $Re(CO)_5Cl$ (73 mg, 0.20 mmol) was added in one portion. The reaction mixture was heated to 60 °C for 24 h and after cooling to RT, the mixture was filtered through celite and the solvent removed under reduced pressure. The residual solid was dissolved in a mixture of 2 : 8 methanol and water (10 mL) and a solution of KPF_6 (0.31 g, 1.68 mmol) in water (5 mL) was added. A pale pink precipitate formed, which was collected *via* centrifugation and then recrystallised from a minimum volume of a 1 : 1 mixture of acetonitrile and methanol with addition of ether. The product was obtained as white crystalline solid. (Yield: 77 mg, 52%). ^{1}H NMR (400 MHz) (DMSO-d_6): δ (ppm) 7.63–7.61 (m, 2H, 2H_{Ar}), 7.45 (s, 4H, 4H_{imi}), 7.44–7.42 (m, 3H, H_{Ar}), 4.63 (s, 2H, ArCH_2), 4.22–4.16 (m, 2H, 2CH_2CH$_2$), 3.70–3.62 (m, 2H, 2CH_2CH$_2$), 3.63 (s, 6H, 2CH_3), 3.24–3.22 (m, 2H, 2CH$_2$CH_2), 2.65–2.60 (m, 2H, 2CH$_2$CH_2). ^{13}C NMR (DMSO-d_6): δ (ppm) 195.7 C_q, 195.5 2C_q, 173.9 2C_{imi} (N*C*N), 133.3 2C_{Ar}, 132.2 C_q, 128.9 C_{Ar}, 128.3 2C_{Ar}, 123.5 2C_{imi}, 122.4 2C_{imi}, 73.8 Ar*C*H$_2$, 56.6 2CH$_2$*C*H$_2$, 48.3 2*C*H$_2$CH$_2$, 38.0 2*C*H$_3$. ESI-MS: *m*/*z* = 594.1 $[C_{22}H_{25}N_5O_3Re]^+$. Anal. Calcd for $C_{22}H_{25}F_6N_5O_3PRe$·0.5 CH_3CN: C, 36.39. H, 3.52. N, 10.15%. Found: C, 36.62. H, 3.78. N, 10.14%.

19. This compound was prepared as described for **17**·PF_6 from **9**·Cl_2 (20 mg, 0.07 mmol). (Yield: 16 mg, 38%). ^{1}H NMR (500 MHz) (DMSO-d_6): δ (ppm) 7.40 (d, $^3J_{HH}$ = 2.30 Hz, 2H, 2H_{imi}), 7.39 (d, $^3J_{HH}$ = 2.30 Hz, 2H, 2H_{imi}), 7.02 (m, 1H, N*H*), 3.97–3.68 (m, 4H, 2CH$_2$CH_2), 3.62 (s, 6H, 2CH_3), 2.98–2.92 (m, 2H, CH_2CH$_2$), 3.69–3.65 (m, 2H, CH_2CH$_2$). ^{13}C NMR (DMSO-d_6): δ (ppm) 195.2 *C*O, 194.3 2*C*O, 172.0 2C_{imi} (N*C*N), 123.1 2C_{imi}, 122.6 2C_{imi}, 50.6 2*C*H$_2$CH$_2$, 48.4 2CH$_2$*C*H$_2$, 38.2 2*C*H$_3$.

ESI-MS: m/z = 504.1 $[C_{15}H_{19}N_5O_3Re]^+$. Anal. Calcd for $C_{15}H_{19}N_5O_3RePF_6$: C, 27.95. H, 2.99. N, 10.60%. Found: C, 27.78. H, 2.95. N, 10.80%.

20. This compound was prepared as described for **17**·PF_6 from **11**·Cl_2 (0.12 g, 0.31 mmol) in a 1 : 9 mixture of acetonitrile and dichloromethane (20 mL). (Yield: 0.12 g, 53%). ^{1}H NMR (500 MHz) (DMSO-d_6): δ (ppm) 7.44 (d, $^3J_{HH}$ = 4.00 Hz, 4H, 4H_{imi}), 4.29 (s, 2H, CH_2CO), 4.22–4.14 (m, 2H, OCH_2 and 4H, 2CH_2CH_2), 3.56–3.54 (m, 2H, 2CH_2CH_2), 3.53 (s, 6H, 2CH_3), 3.26–3.22 (m, 2H, CH_2CH_2), 1.28 (t, $^3J_{HH}$ = 8.90 Hz, 3H, CH$_2$CH3). ^{13}C NMR (DMSO-d_6): δ (ppm) 195.2 *C*O, 195.1 2*C*O, 174.1 2C_{imi} (N*C*N), 168.2 COO, 123.4 2C_{imi}, 122.3 2C_{imi}, 70.1 *C*H$_2$CO, 60.9 *C*H$_2$CH$_3$, 60.3 2CH$_2$*C*H$_2$, 49.2 2*C*H$_2$CH$_2$, 37.7 2*C*H$_3$, 13.8 CH$_2$*C*H$_3$. ESI-MS: m/z = 590.1 $[C_{19}H_{25}N_5O_5Re]^+$. Anal. Calcd for $C_{19}H_{25}F_6N_5O_5PRe$: C, 31.06. H, 3.43. N, 9.53%. Found: C, 31.35. H, 3.69. N, 9.66%.

21a and 21b. These compounds were prepared as described for **17**·PF_6 from **13**·Cl_2 (40 mg, 0.08 mmol) in a 1 : 9 mixture of acetonitrile and dichloromethane. After the metathesis reaction using KPF_6, the crude solid was collected and dissolved methanol. The linkage isomeric forms of **21** were then separated using RP-HPLC (***Method 2***, Experimental section). After HPLC purification **21a** (HPLC: R_T = 8.6 min) was recrystallised from in a minimum volume of a 1 : 9 mixture of acetone and methanol with addition of ether, and obtained as off-white solid, (Yield: 8 mg, 12%), whereas **21b** (HPLC: R_T = 7.3 min) was recrystallised from a minimum volume of a 1 : 9 mixture of acetone and dichloromethane with addition of ether, and obtained as off-white solid, (Yield: 7 mg, 11%). **21a**: ^{1}H NMR (400 MHz) (CD_3CN): δ (ppm) 7.39–7.27 (m, 6H, 5H_{Ar} and N*H*), 7.14 (d, $^3J_{HH}$ = 2.00 Hz, 2H, 2H_{imi}), 7.11 (d, $^3J_{HH}$ = 2.00 Hz, 2H, 2H_{imi}), 5.14 (s, 2H, N-CH_2), 4.22–4.09 (m, 4H, Ar-CH_2 and CH_2CH$_2$), 3.99 (d, $^3J_{HH}$ = 5.60 Hz, 2H, NHCH_2), 3.58 (s, 6H, 2imi-CH_3), 3.51–3.41 (m, 2H, CH_2CH$_2$), 3.32–3.16 (m, 4H, 2CH$_2$CH_2). ^{13}C NMR (CD_3CN): δ (ppm) 196.3 C_q, 176.5 2C_{imi} (N*C*N), 129.6 2C_{Ar}, 129.4 C_{Ar}, 129.3 2C_{Ar}, 124.4 2C_{imi}, 123.2 2C_{imi}, 72.5 Ar-*C*H$_2$, 67.7 N-*C*H$_2$, 61.0 2*C*H$_2$CH$_2$, 50.7 2CH$_2$*C*H$_2$, 42.2 NH*C*H$_2$, 39.2 2*C*H$_3$. ESI-MS: m/z = 709.1 $[C_{26}H_{30}N_6O_6Re]^+$. Anal. Calcd for $C_{26}H_{30}F_6N_6O_6PRe$·2H_2O: C, 35.10. H, 3.85. N, 9.45%. Found: C, 34.95. H, 3.51. N, 9.59%.

21b. ^{1}H NMR (400 MHz) (CD_3CN): δ (ppm) 8.49 (s, 1H, H_{imi} (NC*H*N)), 7.47 (t, d, $^3J_{HH}$ = 2.00 Hz, 1H, H_{imi}), 7.40–7.30 (m, 6H, 5H_{Ar} and H_{imi}), 7.16 (d, $^3J_{HH}$ = 2.00 Hz, 1H, H_{imi}), 7.11 (d, $^3J_{HH}$ = 2.00 Hz, 1H, H_{imi}), 5.09 (dd, $^2J_{HH}$ = 12.40 Hz, $^2J_{HH}$ = 12.40 Hz, 2H, Ar-CH_2), 4.58–4.51 (m, 1H, CH_2CH$_2$), 4.46–4.38 (m, 1H, CH_2CH$_2$), 4.24–3.98 (m, 6H, CH_2-CON, CH_2COO and CH$_2$CH_2), 3.95–3.85 (m, 5H, CH_2CH$_2$ and imi-CH_3), 3.86 (s, 3H, imi-CH_3), 3.40–3.34 (m, 1H, CH$_2$CH_2), 2.97–2.92 (m, 1H, CH$_2$CH_2). ^{13}C NMR (CD_3CN): δ (ppm) 196.2 C_q, 195.6 C_q, 180.8 C_q, 168.5 C_{imi} (N*C*N), 137.8 C_q, 136.6 C_q, 129.6 2C_{Ar}, 129.5 C_{Ar}, 129.1 2C_{Ar}, 125.2 C_{imi}, 124.4 C_{imi}, 123.7 C_{imi}, 123.6 C_{imi}, 68.1 Ar-*C*H$_2$, 65.9 *C*H$_2$CH$_2$, 63.7 *C*H$_2$-COO or *C*H$_2$-CON, 59.4 CH$_2$*C*H$_2$, 48.0 CH$_2$*C*H$_2$, 45.1 *C*H$_2$CH$_2$, 43.2 *C*H$_2$-COO or *C*H$_2$-CON, 39.7 imi-*C*H$_3$, 37.1 imi-*C*H$_3$. ESI-MS: m/z = 855.1 $[C_{26}H_{30}N_6O_6RePF_6]H^+$. Anal. Calcd for $C_{26}H_{30}F_6N_6O_6PRe$·2CH_2Cl_2: C, 32.85. H, 3.35. N, 8.21%. Found: C, 32.57. H, 3.64. N, 8.48%.

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