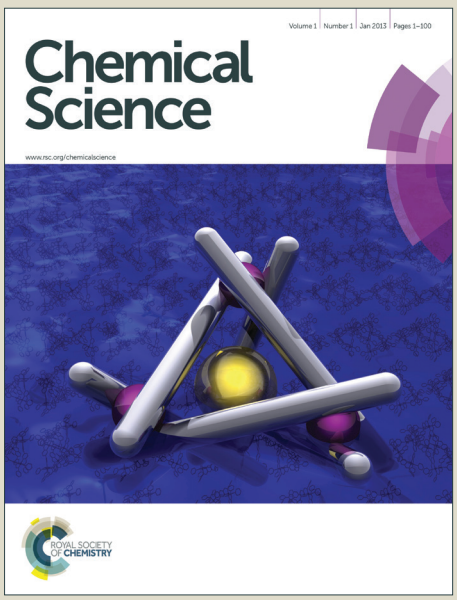
Chemical Science

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemicalscience

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

'Click' to Functionalise: Synthesis, Characterisation and Enhancement of the Physical Properties of a Series of *Exo*- and *Endo*-Functionalised Pd_2L_4 Nanocages

James E. M. Lewis,[a] Anastasia B. S. Elliott,[a,b] C. John McAdam,[a] Keith C. Gordon[a,b] and James D. Crowley.*[a]

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

The synthesis of self-assembled metallosupramolecular architectures has been of steadily growing interest in recent years due to their diverse applications. Appending additional functionality to the ligands of these architectures has been limited as this often involves incorporation of coordinating groups that can potentially disrupt formation of the desired structure. Herein we report the use of the facile, functional group tolerant and high yielding CuAAC 'click' reaction to attach a variety of functional moieties to a tripyridyl ligand system. Despite the presence of the potentially coordinating 1,2,3-triazole rings, self-assembly of quadruply-stranded dipalladium(II) cage architectures in the presence of Pd(II) ions was almost universally observed for the functionalised "click" ligands. The only system which did not assemble into the expected cage featured a 2-(1,2,3-triazole-4-yl)pyridine binding pocket which sequestered the Pd(II) ions. Blocking this chelating pocket with an inert $[Re(CO)_3Cl]$ moiety restores the ability of the ligand to self-assemble into the desired quadruply-stranded dipalladium(II) cage, generating a heterometallic cage architecture. All ligands and cage architectures have been characterised using ^1H, ^{13}C and DOSY NMR, IR and UV-Vis spectroscopies, mass spectrometry and in some cases by X-ray crystallography. Whilst the parent cage system is devoid of useful physical properties and displays a limited range of solubility, the CuAAC methodology provides a facile method to enhance the cage's properties. A variety of fluorescent, redox active and biologically relevant species have been appended to the external surface of these cages. These groups enabled the generation of a series of aqueous soluble, fluorescent and electrochemically active Pd_2L_4 cages in a modular fashion.

Introduction

Self-assembled coordination complexes of defined two- and three-dimensional geometries, or metallosupramolecular architectures, have become an increasingly active area of research over the past two decades.[1] Prudent ligand design and efficacious choice of metal ions generally allow the accurate prediction of the resultant architecture's geometry. Whilst initially interesting purely as a result of their structural features, a variety of applications for these systems are currently being realised.[2] The novel biological,[3] photophysical[4] and electronic[5a-k, 4j, 5l-o] properties of these species as well as their use as molecular reaction flasks,[6] catalysts[7] and hosts capable of recognising guest molecules,[6a, 8] have resulted in burgeoning activity in this field.

With this array of potential applications, the augmentation of chemical and physical properties through both *endo*- and *exo*-functionalisation has become a key target for developing tailored nano-assemblies. Of paramount importance in synthesising functionalised ligands for self-assembled architectures is the need to retain the self-assembly instructions inherent to the unfunctionalised ligand framework. Indeed, there are already several examples in the literature of ligands with appended functional moieties that upon addition of metal ions form self-assembled architectures isostructural to the 'naked' ligand framework.

Fujita and co-workers have reported peptide-[9] and DNA-[10]decorated dipyridyl species that form *exo*-functionalised $M_{12}L_{24}$ nano-spheres upon complexation with palladium(II). Furthermore a reported ubiquitin-appended ligand in the presence of palladium(II) ions, and 23 equivalents of a stabilising ligand, form a similar $M_{12}L_{24}$ coordination cage containing the *endo*-encapsulated protein.[11] A variety[12] of other functionalised architecture ligands,[13a-h, 5o, 13i, 13j] as well as the post-synthetic modifications[14] of inert coordination assemblies have been reported. However, thus far, the scope of functional substrates has been limited.

Metallosupramolecular architectures have emerged as a new class of nano-scale drug delivery vectors due to their host-guest capabilities and potential to exploit the enhanced permeability and retention (EPR)[15] effect. Therrien and co-workers have demonstrated the use of water-soluble, ruthenium-based multi-nuclear assemblies that encapsulate and effectively increase the solubility and cell permeability of drug-like molecules[16] and

photodynamic therapy (PDT) agents.[17]

Inspired by this 'Trojan-horse' approach,[16d] we have been interested in developing functional metallosupramolecular architectures for targeted cisplatin drug delivery. We previously reported the self-assembly of a stimuli-responsive Pd_2L_4-type[18] cage complex in which the interior cavity was *endo*-functionalised with non-coordinating pyridine units to facilitate cisplatin binding through classical and non-classical supramolecular hydrogen-bonding interactions (Figure 1a).[19] As part of these efforts towards metallosupramolecular drug delivery vectors, we have been interested in developing a single methodology for attaching a variety of functional groups to the exterior surface of this cisplatin-binding cage in order to augment the chemical and biological properties in a modular fashion. We recently reported a preliminary communication on the use of the copper(I)-catalysed azide-alkyne cycloaddition, or CuAAC 'click' reaction, to append phenyl-, ferrocenyl- and caffeine-substituents to a tripyridyl ligand framework through the 'click' 1,2,3-triazole unit.[20] Addition of half an equivalent of palladium(II) tetrafluoroborate resulted in formation of the desired dipalladium quadruply-stranded architecture, without interference from the potentially-coordinating[21] 1,2,3-triazole moieties.[22] Furthermore we have shown that this *exo*-functionalization does not affect the ability of the architecture to bind cisplatin within its interior cavity (Figure 1c).

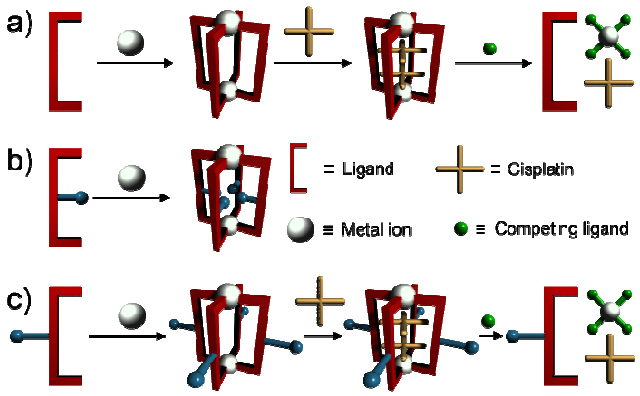


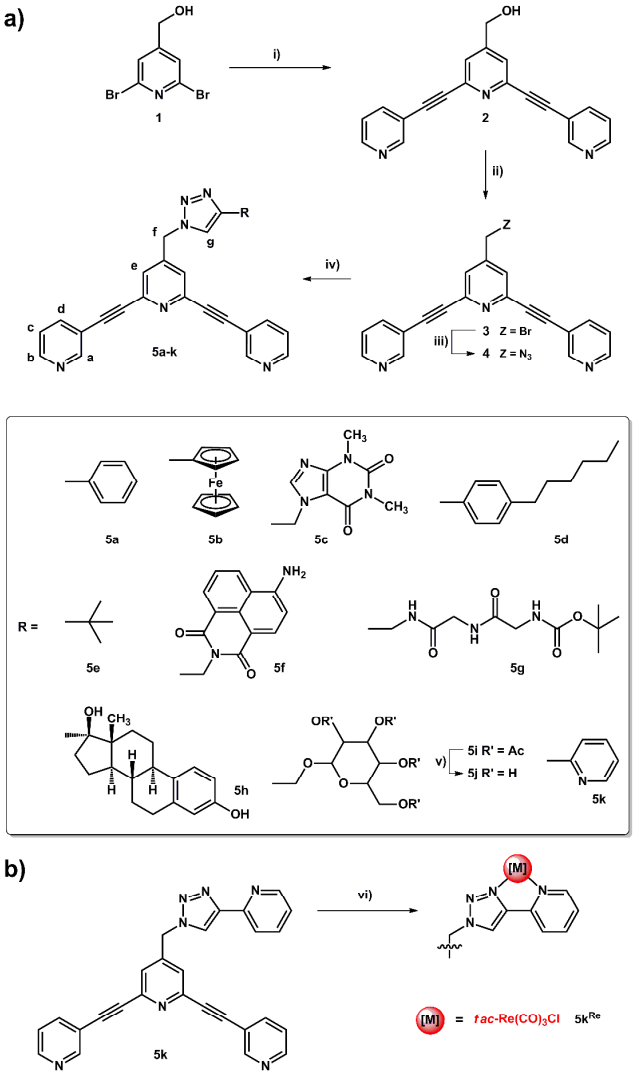
Fig. 1. Cartoon representations showing a) our previous work forming an unfunctionalised M_2L_4 metallosupramolecular system capable of encapsulating cisplatin and releasing upon addition of a competing ligand, b) *endo*-functionalised M_2L_4 system, and c) this work towards *endo*- and *exo*-functionalised cisplatin-binding systems.

Building on this initial investigation we herein report the synthesis of an extended family of 'click'-functionalised ligands, containing a variety of alkyl, aryl, luminescent, redox active and biologically relevant substituents. In nearly all cases, upon complexation with palladium(II) the desired discrete Pd_2L_4 cage architectures were formed, as determined by NMR spectroscopy and mass spectrometry. Additionally we have synthesised a ligand containing a chelating 2-(1,2,3-triazole-4-yl)pyridine moiety from which stable metallo-ligands can be prepared. Preparation of a suitably inert metallo-ligand, in this instance the $Re(CO)_3Cl$ complex, permits the formation of a heterometallic cage system. The CuAAC methodology has been exploited to tune the properties of the dipalladium(II) cage systems. A variety of biologically relevant species have been appended to the external surface of these cages, as well as groups that have imbued these systems with aqueous solubility along with photophysical and electrochemical activity.

Ligand Synthesis

Ligand Framework Synthesis

As we have previously reported, the azide 'click' ligand precursor, **4**, was prepared in three steps from 2,6-dibromo-4-(hydroxymethyl)pyridine **1** (Scheme 1a). The latter was synthesised in two steps from the commercially available citrazinic acid (2,6-dihydroxypyridine-4-carboxylic acid) according to the procedure described by Rasmussen and co-workers.[23]



Scheme 1. Reactants and reagents: a) i) TMS-acetylene, $Pd(PPh_3)_2Cl_2$, CuI, triethylamine, toluene, RT, N_2, 24 h; 3-iodopyridine, DBU, H_2O, RT, N_2, 24 h; ii) PPh_3, CBr_4, DCM, RT, N_2, 16 h; iii) NaN_3, DMF, RT, 3 h; iv) $CuSO_4{\cdot}5H_2O$, sodium ascorbate, R-alkyne, DMF, RT, 16 h; v) Amberlite IRA-400 (OH^-), MeOH, RT, 24 h; b) vi) $Re(CO)_5Cl$, MeOH, reflux, 7 h.

The ligand framework was subsequently assembled utilising a derivation of the one-pot Sonogashira-deprotection-Sonogashira strategy reported by Mio *et al.*[24] Following an initial Sonogashira coupling between the core unit, **1**, and ethynyltrimethylsilane, *in situ* deprotection of the alkyne units was achieved with DBU and water. Addition of 3-iodopyridine resulted in a second set of coupling reactions to give the tripyridyl alcohol precursor, **2** in modest 44% yield. Isolation and purification of the TMS-protected diethynyl intermediate, prior to deprotection and subsequent Sonogashira coupling with 3-iodopyridine, was found to improve the overall yield of **2** (56%). Conversion of the alcohol, **2**, to the bromide, **3** (60%), *via* the Appel reaction and subsequent substitution with sodium azide in DMF yielded the target azide, **4** (92%).

'Click' Ligand Synthesis

The "click" ligands **5a-5i, k** were synthesised in good to excellent yield (60% - 95%) using standard CuAAC conditions (Scheme 1a). Simply stirring the azide **4**, appropriate alkyne, $CuSO_4 \cdot 5H_2O$ and sodium ascorbate in DMF at room temperature for 16 h efficiently generated the ligands (Scheme 1a). The "click" ligands could also be generated directly from the bromide **3** using a standard one-pot *in situ* azide formation CuAAC 'click' reaction conditions.[22b, 25] However, it was found that the use of the pre-formed azide, **4**, lead to better isolated yields and "cleaner" products that required less rigorous purification techniques. Using the 'click' methodology we were able to successfully append a variety of functional groups to the ligand framework, including aryl (**5a**-**5c**), alkyl (both through an aromatic spacer, **5d**, and directly linked, **5e**), 4-amino-1,8-naphthalimide (**5f**), acetate protected-D-glucose (**5j**), estradiol (**5h**) and dipeptide (**5g**) moieties (Scheme 1a).

The ligands **5i** and **5k** were reacted further to provide the D-glucose substituted ligand **5j** and the metallo-ligand **5k^{Re}** respectively. The ligand **5j**, was generated from **5i** in 77% yield. The acetate protecting groups were removed by simply stirring **5i** and the hydroxide form of Amberlite IRA-400 exchange resin in methanol at room temperature. The metallo-ligand **5k^{Re}** was readily synthesised in 68% yield by refluxing a methanol solution of $[Re(CO)_5Cl]$ and **5k** (Scheme 1b).[26]

The identities of the "click" ligands **5a-5k^{Re}** were confirmed by ^1H, ^{13}C NMR and IR spectroscopies and HR-ESI-MS. IR spectra of the ligands display C-H stretching (3100-2900 cm^{-1}) and C-C stretching (2243–2208 cm^{-1}) bands of the ligand framework, along with characteristic peaks due to the presence of the triazole units functional group. The azide stretch (2110 cm^{-1}) observed for starting material **4** is absent in the "click" products. The spectrum of the metallo-ligand **5k^{Re}** displayed three carbonyl ν(CO) stretching bands (ν = 2021, 1927 and 1896 cm^{-1}) indicative of the presence of the *fac*-$[Re(CO)_3Cl]$ core.

The ^1H NMR spectra of **5a-5k^{Re}** display the expected five pyridyl resonances of the ligand framework along with resonances associated with the newly installed functional groups. Additionally, the appearance of a new one proton singlet in the aromatic region (δ 8.83-8.03 ppm) was indicative of formation of the 1,2,3-triazole moiety. A downfield shift was observed for the pyridyl-triazolyl proton signals of **5k^{Re}** while for the terminal pyridyl proton signals showed no significant change, indicating formation of the desired mononuclear *fac*-$[Re(CO)_3Cl]$ species binding through the bidentate pocket. High-resolution electrospray ionisation mass spectrometry (HR-ESMS) confirmed the formulation of the ligands, with isotopically resolved peaks due to the $[\mathbf{L} + Na]^+$ ion observed for each ligand, whilst the metallo-ligand **5k^{Re}** displayed an additional prominent peak due to the $[(\mathbf{5k})Re(CO)_3]^+$ ion.

Ultimately the solid-state structures of **5b, 5c,** and **5k^{Re}** (Figure 2 and ESI†) were confirmed by single-crystal X-ray diffraction. The structures are unremarkable, but confirm the presence of the 1,4-disubstituted-1,2,3-triazole units which are connected to the methylene carbon of the ligand framework through the N1 nitrogen atom. Consistent with the literature[26] and the IR data, the structure of the **5k^{Re}** metallo-ligand confirms that the carbonyl ligands of the rhenium(I) complex are in the facial orientation.

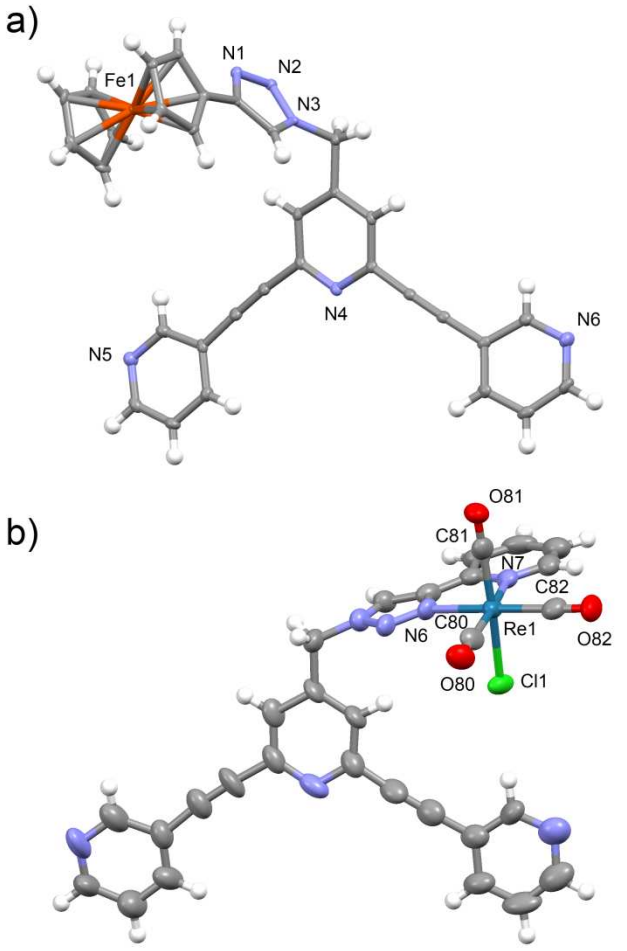
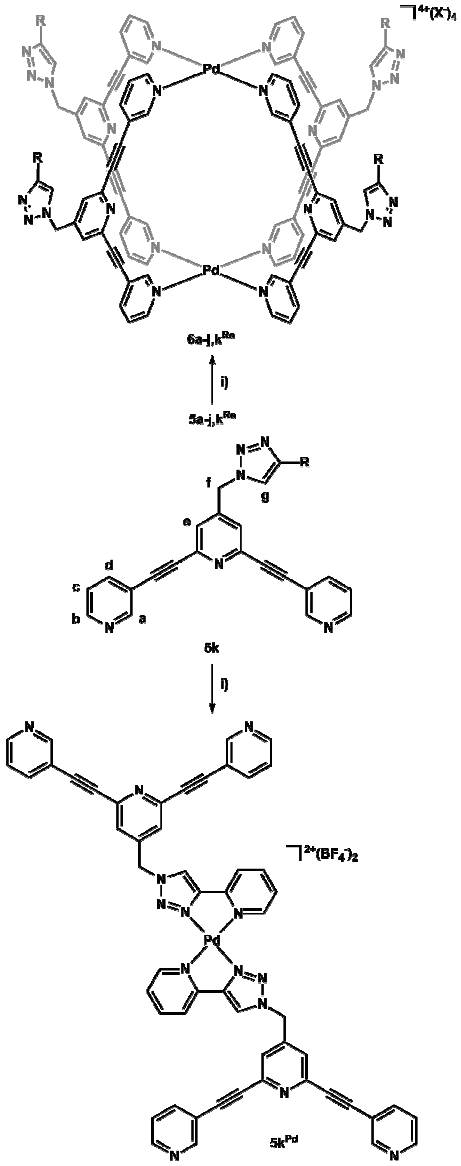


Fig. 2 X-ray structures of a) **5b** and b) **5k^{Re}**; selected bond lengths (Å) and angles (°): Re1-N6 2.140(8), Re1-N7 2.201(9), Re-Cl1 2.471(3), Re1-C80 1.931(12), Re1-C81 1.894(12), Re1-C82 1.908(12), N6-Re1-N7 74.6(3), N6-Re1-C82 173.4(4), N7-Re1-C80 172.2(4). Solvent molecules have been omitted for clarity. Ellipsoids are shown at the 50% probability level.

Synthesis of the Cage Architectures

Titration of a solution containing one of the click-functionalised ligands, **5a-j**, in either d_6-DMSO or CD_3CN with

$[Pd(CH_3CN)_4](BF_4)_2$ resulted in quantitative formation of the Pd_2L_4 architectures (**6a-j**) once a 2:1 stoichiometry of ligand to metal ion was reached (Scheme 2). The proton resonances for the terminal pyridine rings (H_a – H_d) undergo significant downfield shifts until the 2:1 ligand to metal ratio was reached indicating that coordination was occurring through the terminal pyridine rings, consistent with cage formation (Figure 3 and ESI†). The chemical shifts for the remaining proton signals of the ligands were not greatly affected. Importantly, the signals due to the triazole protons of the ligands (H_g) are either unshifted or move slightly upfield relative to the "free" ligands suggesting that 1,2,3-triazole moieties within the ligand frameworks are not involved in coordination to the Pd(II) ions.



Scheme 2. Reactants and reagents: a) i) $[Pd(CH_3CN)_4](BF_4)_2$ or $Pd(NO_3)_2$, CH_3CN, DMF or DMSO, RT, 1 h.

Titration of $[Pd(CH_3CN)_4](BF_4)_2$ into a solution of ligand **5k,** featuring the bidentate functional 4-(2-pyridyl)-1,2,3-triazolyl moiety, did not yield the corresponding dinuclear, quadruply-stranded cage. Instead, the ^{1}H NMR spectra revealed downfield shifts in the proton signals associated with the 4-(2-pyridyl)-1,2,3-triazolyl moiety (H_g-H_k) until half an equivalent of palladium(II) salt was added, whilst those associated with the terminal pyridine rings (H_a-H_d) remained unaffected (Figure 3). This suggested formation of a mononuclear bis-bidenate palladium(II) species,[27] coordinated exclusively through the bidentate pyridyl-triazole moiety (**5k**^{Pd}, Scheme 2). This conclusion was further supported by evidence from HR-ESMS. No signals due to the dinuclear cage species could be identified, the major ion observed in the spectrum was found at m/z = 492.1066 consistent with the formulation $[Pd(\mathbf{5k})_2]^{2+}$. Additionally, the diffusion coefficient (D), obtained using ^{1}H DOSY NMR for this complex was 1.39 x 10^{-10} m^2 s^{-1}, quite different to those observed for the other cages (*vide infra*).

Addition of further equivalents of the palladium(II) salt to the **5k**^{Pd} complex resulted in a broad, ill-defined ^{1}H NMR spectrum, likely the result of forming a polymeric species made up of palladium linked Pd_2L_4 cages (ESI†). Thus in order to utilise ligand **5k** in the synthesis of discrete Pd_2L_4 cage architectures, it was necessary to "cap" this bidentate binding pocket with a suitable metallo-species. The *fac*-$Re(CO)_3Cl$ fragment was chosen as a robust, kinetically inert capping agent and was incorporated into the metallo-ligand **5k**^{Re}.

As with, **5a-j**, titration of a d_6-DMSO solution of the metallo-ligand **5k**^{Re} with $[Pd(CH_3CN)_4](BF_4)_2$ resulted in downfield shifts of the terminal pyridyl proton signals (H_a-H_d) and a slight upfield shift of the remaining signals until a 2:1 stoichiometry was reached (Figure 3), indicating formation of the mixed metal cage architecture, **6k**^{Re}.

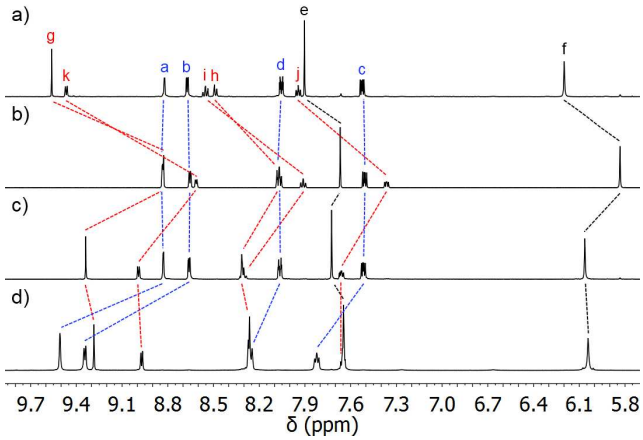


Fig. 3 Partial ^{1}H NMR (500 MHz, d_6-DMSO, 298 K) spectra of a) **5k**^{Pd}, b) **5k**, c) **5k**^{Re} and d) the palladium cage **6k**^{Re}.

The cages were subsequently prepared on a preparative scale, generally by stirring the appropriate ligand (2 equiv.) and palladium(II) salt (1 equiv.) in DMF for 1 hour at room temperature. Vapour diffusion of diethyl ether into the reaction mixtures led to the isolation of the cages, in good to excellent yields (56-95%), as colourless to orange solids. All the cages were prepared as the tetrafluoroborate (BF_4^-) salts. Additionally, the cage **6i** was synthesised as the nitrate (NO_3^-) salt, chosen as a pharmaceutically acceptable[28] counter-anion likely to assist in generating an aqueous soluble system.

The identities of the palladium(II) cage complexes were

confirmed by ^{1}H and ^{13}C NMR and IR spectroscopies and HR-ESMS as the expected Pd_2L_4 species.

Diffusion-ordered ^{1}H NMR spectroscopy (DOSY) provided strong support for the selective formation of the cages in solution. ^{1}H DOSY spectra (DMSO, 298K) were obtained for ligands **5a-5k^{Re}** and cages **6a-6k^{Re}** (Table 1). Each of the proton signals in the individual spectra show the same diffusion coefficient (*D*), indicating that there is only one species present in solution (ESI†). The $D_{complex}/D_{ligand}$ ratios of ~0.50:1 are similar to those observed for related literature compounds and suggests that the larger palladium cage species are stable in solution (ESI†).

Mass spectrometry experiments were consistent with the ^{1}H and DOSY NMR data and provided further evidence for the presence of the $[Pd_2L_4](X)_4$ architectures in solution. The HR-ESMS spectra (DMF/CH_3CN) of **6a-6k^{Re}** show isotopically resolved peaks due to $[Pd_2L_4]^{4+}$ and $[Pd_2L_4Cl]^{3+}$ ions along with peaks due to fragmentation of the cage structure (ESI†).

The collected NMR and MS data suggested the ligands **5a-5k^{Re}** cleanly and quantitatively assemble into the cages **6a-6k^{Re}** when treated with palladium(II) salts and the structure of one of the $[Pd_2L_4](X)_4$ cage architectures, **6b,** was finally proven unambiguously by X-ray crystallography (*vide infra*).

It is presumed that formation of the $[Pd_2L_4](X)_4$ cage architectures, solely through coordination of the terminal pyridine rings, is thermodynamically favoured despite the potential of the central *endo* pyridyl and *exo* 1,2,3-triazole rings to act as additional or alternative N-donors. Support for this idea was gained by reaction of the phenyl ligand **5a** with $AgSbF_6$ in CH_3CN. Vapour diffusion of diethyl ether into the reaction mixture resulted in the formation of X-ray quality crystals of the silver(I) complex **5a^{Ag}**. The structure was found to be an interesting coordination polymer, in which all of the N-donors, both central and terminal pyridines, as well as the *exo*-triazole of the ligand, are coordinated to the Ag(I) ions (ESI†).[29] The structure contains an unprecedented example of a 1,4-disubstituted-1,2,3-triazole unit acting as a monodentate donor ligand where the coordination to the metal ion is through the less electron rich N2 of the triazole. The structure confirms that all the heterocycles of the ligands are capable of metal coordination, suggesting that the $[Pd_2L_4](X)_4$ cages are indeed the thermodynamic products of the assembly reaction.

Table 1 Diffusion coefficients (D, $\times 10^{-10}$ m^2 s^{-1}) of ligands and cage architectures as determined by ^{1}H DOSY NMR spectroscopy (500 MHz, d_6-DMSO).

Compound	Ligand (L)	Cage (C)	Ratio
5a	2.00	0.89	2.25
5b	1.95	0.85	2.29
5c	2.54	0.80	3.18
5d	1.78	0.83	2.14
5e	2.08	0.93	2.24
5f	1.53	0.71	2.15
5g	1.51	1.00	1.51
5h	1.54	0.75	2.05
5i	1.57	0.68	2.31
5j	1.63	0.74	2.20
5k^{Re}	1.73	0.84	2.06

Host-Guest Chemistry

Having demonstrated that the aforementioned "click" approach can be used to rapidly generate a series of *exo*-functionalised cages it was important to confirm that the surface functionalisation had not interfered with the ability of the *endo*-functionalised cavity to bind cisplatin. The cisplatin binding ability of the cages that were soluble in CD_3CN was examined via ^{1}H NMR spectroscopy. Cisplatin was added to a CD_3CN solution of one of the cages (**6a, b, d, e** and **i)** in CD_3CN and the resulting suspension was sonicated for a brief period (1-2 minutes). This led to the dissolution of the insoluble cisplatin and a significant downfield shift ($\Delta\delta$ = 0.06-0.10 ppm) and broadening of the internally directed H_a proton signal of the cages (Figure 4 and ESI†). This is consistent with what we have previously observed for the parent unfunctionalised cage system upon encapsulation of cisplatin,[19] indicating that surface functionalisation does not retard guest binding within the cage cavity. For the ferrocene substituted cage **6b** the host-guest interaction was proven using X-ray crystallography.

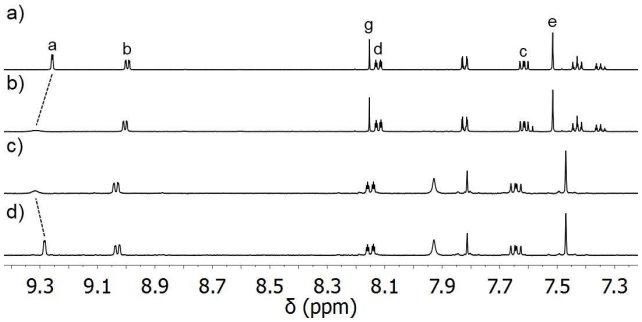


Fig. 4. ^{1}H NMR spectra (400 MHz, CD_3CN) of a) **6a**, b) [**6a**⊃(cisplatin)$_2$], and c) [**6i**⊃(cisplatin)$_2$] and d) **6i**.

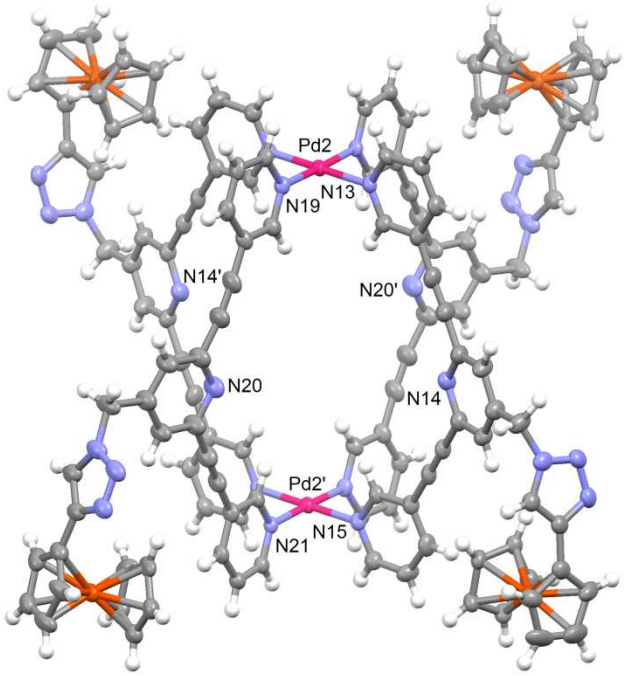


Fig. 5. X-ray structure of the empty cage architecture **6b**. Solvent molecules have been omitted for clarity. Ellipsoids are shown at 30% probability. Selected bond lengths (Å) and angles (°): Pd2'-N13 2.008(5), Pd2-N15 2.010(5), Pd2'-N19 2.013(6), Pd2-N21 2.024(5), N13-Pd2'-N19

89.4(2), N15-Pd2-N21 88.9(2), N14···N14' 10.926(8), N20···N20' 10.73(1), Pd2···Pd2' 11.588(4).

Red X-ray quality crystals were grown by vapour diffusion of diethyl ether into a DMF solution of cage complex $[Pd_2(\mathbf{5b})_4](BF_4)_4$ and cisplatin that had been briefly sonicated. The structure was solved in the triclinic space group P-1, and revealed the expected Pd_2L_4 cage assembly, with coordination to the palladium(II) ions solely through the terminal pyridine rings, with the *endo*-pyridine and *exo*-triazole moieties remaining uncoordinated. The structure was found to be a co-crystal of both the empty cage complex, **6b** and the intended 1:2 host/guest species **6b**⊃(cisplatin)$_2$, with the crystal lattice containing alternating chains of these two species (ESI†). The dimensions of the empty and host-guest assemblies were very similar, as judged by the distance between opposing endohedral pyridyl nitrogen atoms (10.5 – 10.9 Å) and the distance between palladium(II) ions (approximately 11.6 Å for both). Furthermore, these distances are consistent with those we have previously observed for the unfunctionalised tripyridyl system (Ltpy = 2,6-bis(pyridin-3-ylethynyl)pyridine) as both the host-guest adduct,[19] as well as the empty assembly with various different counter-anions[30] (Table 2). Finally the distances representative of interactions between the guest cisplatin molecules themselves and with the host architecture - namely the distance between platinum(II) ions and the nitrogen atoms of the amine ligands with the endohedral pyridyl nitrogen atoms - were very similar to those reported for the parent host-guest system.

Table 2 Cavity dimensions from the solid state structures of the parent system and the new ferrocene-substituted structure.

	$[Pd_2(Ltpy)_4{}^a]^{4+}(X^-)_4$		$[Pd_2(\mathbf{5b})_4]^{4+}(BF_4^-)_4$	
	Cage[b]	Host-Guest[c]	Cage	Host-Guest
Pd···Pd (Å)	11.498(3)	11.669(2)	11.588(4)	11.595(3)
$N_{Py}\cdots N_{Py}$ (Å)	11.00(1)	10.71(1)	10.73(1)	10.780(9)
$N_{Py}\cdots N_{Py}$ (Å)	11.06(2)	10.97(1)	10.926(9)	10.91(1)
Pt···Pt (Å)		3.3211(7)		3.327(1)

[a] Ltpy = 2,6-bis(pyridin-3-ylethynyl)pyridine, [b] X = SbF_6^-, [c] X = BF_4^-

Tuning Physical Properties

Whist the unfunctionalised tripyridyl cage system ($[Pd_2(Ltpy)_4](X)_4$) displays excellent molecular recognition properties and is able to efficiently encapsulate two molecules of cisplatin,[19] it is devoid of any other useful physical properties and has a relatively limited range of solubility (CH_3CN, DMF, DMSO). The powerful CuAAC methodology provides a facile way to tune both the physical and solubility properties of the cage without interfering with the molecular recognition of the system.

Aqueous Solubility

Of paramount importance towards the utilisation of these systems as drug delivery vectors would be the endowment of aqueous solubility. We have previously attempted to prepare water soluble versions of the parent unfunctionalised cage system ($[Pd_2(Ltpy)_4](X)_4$) by varying the counter-anion employed.[30] Unfortunately none of the anions tested were found to imbue the parent cage with aqueous solubility. It was hypothesised, based on literature precedent,[31] that the number of free hydroxyl moieties in the glucose-functionalised ligand **5j** would be sufficient to achieve this end.

Pleasingly, both the ligand **5j** and the cage **6j** (X = NO_3^-) were found to be soluble in water (Figure 6 and ESI†). The ^{1}H NMR spectrum of the cage **6j** clearly demonstrated that the glucose-functionalised system is soluble and stable in D_2O, while the DOSY NMR spectra, obtained for **5j** ($D = 3.06 \times 10^{-10}$ m^2 s^{-1}) and **6j** ($D = 1.66 \times 10^{-10}$ m^2 s^{-1}) were consistent with cage formation (ESI†).

Disappointingly, efforts to generate a cisplatin containing host-guest adduct in D_2O were unsuccessful. Sonication of **6j** (X = NO_3^-) and cisplatin in D_2O generated a pale yellow coloured solution, but no complexation-induced chemical shifts were observed for any of the cage's protons signals. This was consistent with previous findings that suggested addition of H_2O to an acetonitrile solution of the $[\text{cage} \supset (\text{cisplatin})_2]^{4+}$ host-guest adduct caused decomplexation of the guest from the cage cavity.[19]

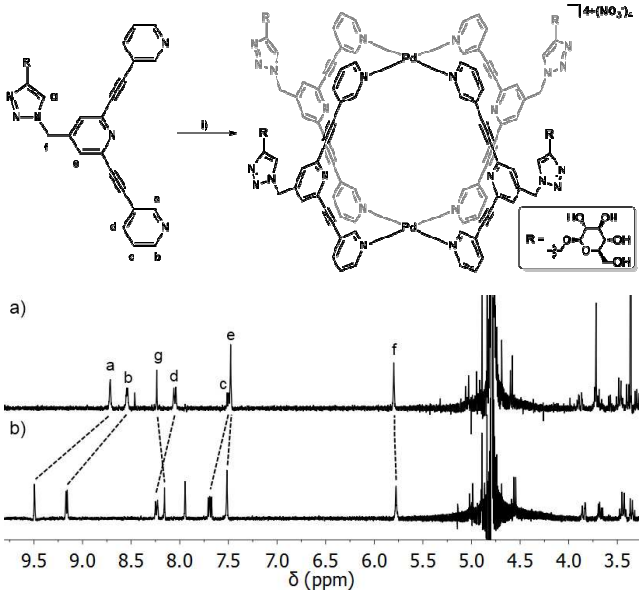


Fig. 6. Stacked ^{1}H NMR spectra (400 MHz, D_2O, 298 K) of a) **5j** and b) **6j**. Reagents and conditions: i) $Pd(NO_3)_2(H_2O)_2$, DMF, RT, 1 h, 93%.

Electronic Properties

There has recently been a surge of interest in the generation of metallosupramolecular cages that display photophysical[4] or electrochemical[5a-i, 5k, 4j, 5l-o] properties. These compounds have been generated through two different synthetic strategies; 1) a metal ion with the desired physical properties is used as the assembly unit or 2) an organic building block with the required photophysical or electrochemical features is incorporated into the ligand framework. Whilst both these approaches have been successfully exploited to generate functionalised systems there are limitations. Many of the metal ions that display desirable photophysical properties are quite kinetically inert making their use in self-assembly processes problematic. The incorporation of new functional organic units into the ligand framework can interfere with either the self-assembly process or the molecular recognition properties of the parent system. The CuAAC methodology described here offers a new, alternative approach

which can potentially avoid these issues.

Palladium(II)-based self-assembled architectures[32] do not normally show extensive photophysical or electrochemical properties and the parent cage is no exception.[30, 19, 33] The modularity of the CuAAC methodology, described here, allows the ready tuning of the absorption, emission and electrochemical properties of the ligands and the corresponding palladium(II) "click" cages.

Absorption

The parent cage compound **6a** (R = Ph) and majority of the other cages (**6c-e**, **6g-k**) were isolated as colourless solids. Similar to related literature compounds,[34, 19-20, 33] the UV-Vis spectra (DMSO) of these materials are dominated by π-π* transitions (λ_{max} = 313-319 nm) in the UV with weak MLCT bands that tail off near the visible. However, the optical absorption properties of the cages can be readily tuned by the addition of suitable chromophores. The complexes, **6b** (R = ferrocene), **6f** (R = 4-amino-1,8-naphthalimide) and **6k^{Re}** are orange-red (λ_{max} = 426), bright yellow (λ_{max} = 439 nm) and yellow (λ_{max} = 357 (sh)) respectively (Figure 7 and ESI†), showing that the visible absorption properties of the cages can be easily modified.

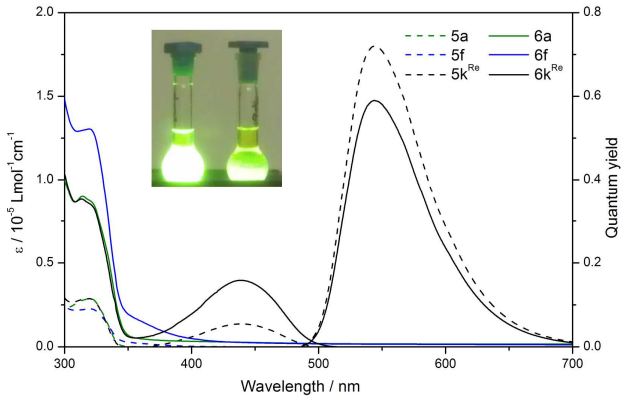


Fig. 7 UV-Vis spectra (DMSO) of **5a**, **6a**, **5k^{Re}**. **6k^{Re}**, **5f** and **6f**, and emission spectra (DMF, λ_{ex} = 448 nm) of **5f** and **6f**. Inset: photograph of fluorescing DMSO (10^{-3} M) solutions of **5f** (left) and **6f** (right) (λ_{ex} = 365 nm).

Emission

The emissive properties of the cages (and ligands) were examined using excited state spectroscopy in DMF solution. Table 3 summarises the emission data of the systems studied. The compounds **5a, 6a, 5k^{Re}** and **6k^{Re}** were excited at 337 nm due to poor absorption at wavelengths longer than this, whilst **5f** and **6f** were excited at 448 nm. Unsurprisingly, no (or extremely weak) emission was observed for the parent compounds **5a** and **6a**. Decoration of the ligands and cages with the known organic (R = 4-amino-1,8-naphthalimide,[35] **5f** and **6f**) and inorganic (R = *fac*-[(2-(1-R-1*H*-1,2,3-triazol-4-yl)pyridine)Re(CO)$_3$Cl],[26] **5k^{Re}** and **6k^{Re}**), fluorophores led to the generation of emissive compounds. Emission maxima were observed at 525 nm for **5f** and **6f** and at around 540 nm for **5k^{Re}** and **6k^{Re}** (Figure 7 and ESI†). The quantum yields calculated for the fluorescent **5f** and **6f** samples were 0.72 and 0.59 respectively whilst those for **5k^{Re}** and **6k^{Re}** were 0.007. A decrease in quantum yield upon forming the cage architecture is consistent with the presence of the Pd(II) centers increasing spin-orbit coupling, leading to an increase in non-radiative decay pathways. Presumably, the presence of the saturated methylene linking units between the coordinating portion of the ligand framework and the fluorescent moiety, decouples the two fragments. As such the presence of the palladium(II) ions does not result in complete quenching of the ligand fluorescence, as has previously been observed for dipalladium(II) complexes in which the fluorescent moieties are conjugated to the coordinating heterocycles.[36, 4g-i]

Table 3 Emission maxima, lifetimes and quantum yields obtained in DMF with 448 nm excitation for **5f** and **6f** and 337 nm excitation for **5a**, **6a**, **5k^{Re}** and **6k^{Re}**.

Compound	λ_{em} / nm	τ_{em}[a] / ns	Φ[b]	k_r x 10^5 /s^{-1}	k_{nr} x 10^7 /s^{-1}
5a	-	-	<0.001	-	-
6a	-	-	<0.001	-	-
5f	525	13	0.72	549	2.14
6f	525	12	0.59	480	3.27
5k^{Re}	534	43	0.007	7.78	11.0
6k^{Re}	542	43	0.007	2.80	3.97

[a] ± 5 ns, lifetimes were convoluted with the laser pulse, [b] ± 5%

Electrochemistry

The redox properties of selected ligands (**5a-c, f** and **5k^{Re}**) and cage (**6a-c, f** and **6k^{Re}**) compounds in DMF solution were examined with cyclic voltammetry using Bu_4NPF_6 as supporting electrolyte. An internal decamethylferrocene $(Fc^*)^{+/0}$ reference standard was used, under which conditions $E°([FcH]^{+/0}) = 0.55$ V. Data are presented in Table 9 and the selected voltammograms for the compounds are displayed in Figure 8 and the supporting information (ESI†).

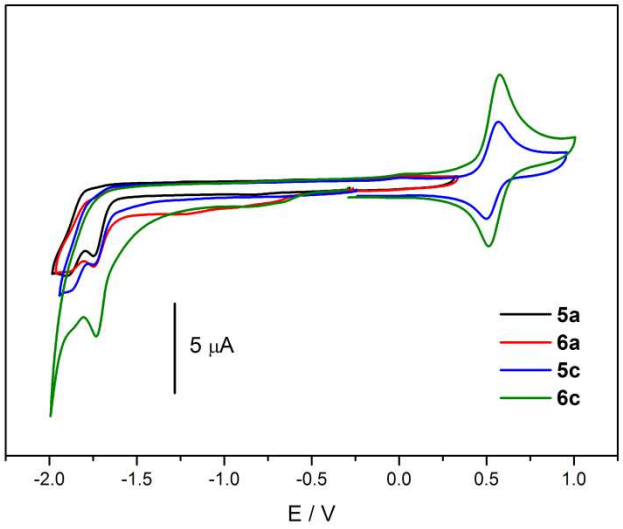


Fig. 8. Cyclic voltammograms of compounds **5a**, **6a**, **5c** and **6c**.

All the compounds studied displayed irreversible reductions at negative potentials (approx. -1.7 and -1.9 V), which are presumed to be associated with the 2,6-bis(ethynyl)pyridine ligand framework. For the parent phenyl-substituted ligand and cage, **5a** and **6a**, these reductions are the only process observed within the solvent accessible redox window. The ligands (**5b**, **c**, **f**, **5k^{Re}**) and

cages (**6b**, **c**, **f**, **6k^{Re}**) with redox active substituents displayed additional redox processes associated with the appended functional groups. Thus the caffeine,[37] **5c** and **6c**, and *fac*-[(2-(1-R-1H-1,2,3-triazol-4-yl)pyridine)Re(CO)$_3$Cl][26] **5k^{Re}** and **6k^{Re}** substituted compounds showed irreversible oxidation processes at E_{pa} 1.5-1.6 V, values consistent with previous literature. The 4-amino-1,8-naphthalimides[38] **5f** and **6f**, display both irreversible amine oxidation (Epa = 1.1-1.2 V) and a reversible one-electron reduction process (E° -1.5 V) as expected for compounds of this type. The ferrocenyl-substituted species, **5c** and **6c**, displayed the expected reversible oxidation of the ferrocenyl moiety at 0.5 V.[27] Interestingly, the complexation of the ligands with palladium(II) ions to generate the cages does not affect the potential or reversibility of any of the redox processes (within experimental error). Additionally, no electronic communication was observed between the four redox active units of the cages. Presumably, the large distance between the palladium(II) ions of the cages and the triazole functional groups along with the saturated methylene linker disrupting conjugation between the coordinating ligand framework and triazole substituent means that the redox active groups do not "feel" the presence of each other or the palladium ions when the cages form.

Table 9 Electrochemical data for selected compounds.

Compound	E_{pc} (ligand) / V	Other reductions / V	Other oxidations / V
5a	-1.9, -1.7		
6a	-1.9, -1.7		
5b	-1.9, -1.7		*E*° 0.5[a] (Fc)
6b	-1.9, -1.8		*E*° 0.5[a] (Fc)
5c	-1.9, -1.7		E_{pa} 1.6 (caffeine)
6c	-1.9, -1.8, -1.6		E_{pa} 1.6 (caffeine)
5f	-1.7[b]	*E*° -1.5 (Naphth.)	E_{pa} 1.2 (amine)
6f	-1.8[b]	*E*° -1.5 (Naphth.)	E_{pa} 1.1 (amine)
5k^{Re}	-1.9, -1.6		E_{pa} 1.5 (Re)
6k^{Re}	-1.9, -1.6		E_{pa} 1.6 (Re)

[a] In CH_2Cl_2 E° = 0.59 V (vs. $[Fc^*]^{+/0}$ = 0.00 V, $[FcH]^{+/0}$ = 0.55 V), [b] The second reduction not resolved, [c] Caffeine in DMF exhibits an irreversible oxidation process E_{pa} 1.6 V.

Conclusions

We have developed a methodology for facile 'click' modification of tripyridyl ligands which, despite incorporating the potentially coordinating 1,2,3-triazolyl moiety, still quantitatively form Pd_2L_4 metallosupramolecular architectures in the presence of Pd(II) ions. A wide variety of functional groups which were of interest for their electrochemical, fluorescent, solubility and potential bio-targeting properties were readily incorporated into both the ligands and cages. Nearly all the "click" functionalised ligands readily assembled into corresponding functionalised Pd(II) cages, the exception was the system that contained the (2-(1-R-1*H*-1,2,3-triazol-4-yl)pyridine chelating group. In this case the chelating pocket sequesters the Pd(II) disrupting the self-assembly of the cage. Simply blocking this chelating unit with the inert $Re(CO)_3Cl$ moiety restores the ability of the ligand to assemble into the Pd(II) cage, generating a heterometallic system. The functionalised ligands and cages were characterised using ^{1}H, ^{13}C and DOSY NMR spectroscopy, electronic absorption, emission, IR spectroscopy and HR-ESMS. In addition the X-ray crystal structures of three of the ligands and one cage, the [**6b** ⊃(cisplatin)$_2$] co-crystal, were obtained.

^{1}H NMR and ESMS studies confirm that the presence of the functional groups on the surface of the cage architectures does not interfere with the ability of the system to form host-guest adducts with cisplatin in acetonitrile solutions.

The unfunctionalised tripyridyl cage system was devoid of any useful physical properties and has a relatively limited range of solubility. The CuAAC methodology provides ready access to cages with enhanced solubility, electrochemical and photophysical properties in a modular fashion without interfering with the molecular recognition properties of the system.

Having demonstrated that this facile method of functionalisation does not interfere with formation of the desired complexes, this methodology could easily be applied to other metallosupramolecular systems, allowing simple and diverse augmentation of various chemical and physical properties whilst retaining the general structure and molecular recognition properties of the parent architectures. Additionally, the described "click" methodology also provides a facile synthetic route to heterometallic cage systems. These functionalised cage systems have potential applications in a variety of areas including biology and catalysis and efforts in these directions are underway.

Acknowledgement

We thank Dr. Michael G. Gardiner for collecting the data for the structure of **6c** on the MX2 beamline at the Australian Synchrotron, Victoria, Australia. JDC (Laurenson Award), JEML (PhD scholarship), ABSE (PhD scholarship) and CJM (Grant No. UOO-X0808) thank the Otago Medical Research Foundation, the University of Otago and New Economy Research Fund respectively for financial support.

Notes and references

[a] *Department of Chemistry, University of Otago, PO Box 56, Dunedin, New Zealand. Fax: +64 3 479 7906; Tel: +64 3 479 7731; E-mail: jcrowley@chemistry.otago.ac.nz*

[b] *MacDiarmid Institute for Advanced Materials and Nanotechnology, New Zealand*

†Electronic Supplementary Information (ESI) available: the supplementary information contains the experimental procedures, ^{1}H, ^{13}C and DOSY NMR, ESMS, UV-vis, CV, emission and crystallographic data. CCDC reference numbers 985678-985681 and 924182. See DOI: 10.1039/b000000x/

1. a) For some selected recent reviews see; b) J. E. Beves, B. A. Blight, C. J. Campbell, D. A. Leigh and R. T. McBurney, *Angew. Chem. Int. Ed.*, 2011, **50**, 9260-9327; c) R. Chakrabarty, P. S. Mukherjee and P. J. Stang, *Chem. Rev.*, 2011, **111**, 6810-6918; d) S. De, K. Mahata and M. Schmittel, *Chem. Soc. Rev.*, 2010, **39**, 1555-1575; e) M. Fujita, M. Tominaga, A. Hori and B. Therrien, *Acc. Chem. Res.*, 2005, **38**, 369-378; f) C. R. K. Glasson, L. F. Lindoy and G. V. Meehan, *Coord. Chem. Rev.*, 2008, **252**, 940-963; g) Y.-F. Han, H. Li and G.-X. Jin, *Chem. Commun.*, 2010, **46**, 6879-6890; h) K. Harris, Q.-F. Sun, S. Sato and M. Fujita, *J. Am. Chem. Soc.*, 2013, **135**, 12497-12499; i) T. Nakamura, H. Ube and M. Shionoya, *Chem. Lett.*, 2013, **42**, 328-334; j) T. K. Ronson, S. Zarra, S. P. Black and J. R. Nitschke, *Chem. Commun.*, 2013, **49**, 2476-2490; k) M. M. J. Smulders, I. A. Riddell, C. Browne and J. R. Nitschke, *Chem. Soc. Rev.*, 2013, **42**, 1728-1754; l) M. D. Ward, *Chem. Commun.*, 2009, 4487-4499; m) N. J. Young and B. P. Hay, *Chem. Commun.*, 2013, **49**, 1354-1379.
2. M. D. Ward and P. R. Raithby, *Chem. Soc. Rev.*, 2013, **42**, 1619-1636.

3. a) D. R. Boer, J. M. C. A. Kerckhoffs, Y. Parajo, M. Pascu, I. Uson, P. Lincoln, M. J. Hannon and M. Coll, *Angew. Chem. Int. Ed.*, 2010, **49**, 2336-2339; b) V. Brabec, S. E. Howson, R. A. Kaner, R. M. Lord, J. Malina, R. M. Phillips, Q. M. A. Abdallah, P. C. McGowan, A. Rodger and P. Scott, *Chem. Sci.*, 2013, **4**, 4407-4416; c) L. Cardo, V. Sadovnikova, S. Phongtongpasuk, N. J. Hodges and M. J. Hannon, *Chem. Commun.*, 2011, **47**, 6575-6577; d) T. R. Cook, V. Vajpayee, M. H. Lee, P. J. Stang and K.-W. Chi, *Acc. Chem. Res.*, 2013, **46**, 2464-2474; e) A. Dubey, J. W. Min, H. J. Koo, H. Kim, T. R. Cook, S. C. Kang, P. J. Stang and K.-W. Chi, *Chem. Eur. J.*, 2013, **19**, 11622-11628; f) A. C. G. Hotze, N. J. Hodges, R. E. Hayden, C. Sanchez-Cano, C. Paines, N. Male, M.-K. Tse, C. M. Bunce, J. K. Chipman and M. J. Hannon, *Chem. Biol.*, 2008, **15**, 1258-1267; g) S. E. Howson, A. Bolhuis, V. Brabec, G. J. Clarkson, J. Malina, A. Rodger and P. Scott, *Nat. Chem.*, 2012, **4**, 31-36; h) I. Meistermann, V. Moreno, M. J. Prieto, E. Moldrheim, E. Sletten, S. Khalid, P. M. Rodger, J. C. Peberdy, C. J. Isaac, A. Rodger and M. J. Hannon, *Proc. Natl. Acad. Sci. U. S. A.*, 2002, **99**, 5069-5074; i) A. Mishra, H. Jung, J. W. Park, H. K. Kim, H. Kim, P. J. Stang and K.-W. Chi, *Organometallics*, 2012, **31**, 3519-3526; j) A. Mishra, S. Ravikumar, S. H. Hong, H. Kim, V. Vajpayee, H. W. Lee, B. C. Ahn, M. Wang, P. J. Stang and K.-W. Chi, *Organometallics*, 2011, **30**, 6343-6346; k) A. D. Richards, A. Rodger, M. J. Hannon and A. Bolhuis, *Int. J. Antimicrob. Agents*, 2009, **33**, 469-472; l) A. Terenzi, C. Ducani, V. Blanco, L. Zerzankova, A. F. Westendorf, C. Peinador, J. M. Quintela, P. J. Bednarski, G. Barone and M. J. Hannon, *Chem. Eur. J.*, 2012, **18**, 10983-10990; m) B. Therrien, *Top. Curr. Chem.*, 2012, **319**, 35-56; n) B. Therrien, *Chem. Eur. J.*, 2013, **19**, 8378-8386.

4. a) J.-S. Chen, G.-J. Zhao, T. R. Cook, K.-L. Han and P. J. Stang, *J. Am. Chem. Soc.*, 2013, **135**, 6694-6702; b) O. Chepelin, J. Ujma, X. Wu, A. M. Z. Slawin, M. B. Pitak, S. J. Coles, J. Michel, A. C. Jones, P. E. Barran and P. J. Lusby, *J. Am. Chem. Soc.*, 2012, **134**, 19334-19337; c) M. W. Cooke, D. Chartrand and G. S. Hanan, *Coord. Chem. Rev.*, 2008, **252**, 903-921; d) M. W. Cooke and G. S. Hanan, *Chem. Soc. Rev.*, 2007, **36**, 1466-1476; e) S. Goeb, V. Prusakova, X. Wang, A. Vezinat, M. Salle and F. N. Castellano, *Chem. Commun.*, 2011, **47**, 4397-4399; f) M. Han, R. Michel, B. He, Y.-S. Chen, D. Stalke, M. John and G. H. Clever, *Angew. Chem. Int. Ed.*, 2013, **52**, 1319-1323; g) N. Kishi, Z. Li, K. Yoza, M. Akita and M. Yoshizawa, *J. Am. Chem. Soc.*, 2011, **133**, 11438-11441; h) Z. Li, N. Kishi, K. Hasegawa, M. Akita and M. Yoshizawa, *Chem. Commun.*, 2011, **47**, 8605-8607; i) Z. Li, N. Kishi, K. Yoza, M. Akita and M. Yoshizawa, *Chem. Eur. J.*, 2012, **18**, 8358-8365; j) K. Mahata, P. D. Frischmann and F. Würthner, *J. Am. Chem. Soc.*, 2013, **135**, 15656-15661; k) P. P. Neelakandan, A. Jimenez and J. R. Nitschke, *Chem. Sci.*, 2014; l) P. P. Neelakandan, A. Jimenez and J. R. Nitschke, *Chem. Sci.*, 2014, **5**, 908-915; m) J. B. Pollock, T. R. Cook, G. L. Schneider, D. A. Lutterman, A. S. Davies and P. J. Stang, *Inorg. Chem.*, 2013, **52**, 9254-9265; n) J. B. Pollock, T. R. Cook and P. J. Stang, *J. Am. Chem. Soc.*, 2012, **134**, 10607-10620; o) J. B. Pollock, G. L. Schneider, T. R. Cook, A. S. Davies and P. J. Stang, *J. Am. Chem. Soc.*, 2013, **135**, 13676-13679.

5. a) R. J. Archer, C. S. Hawes, G. N. L. Jameson, V. McKee, B. Moubaraki, N. F. Chilton, K. S. Murray, W. Schmitt and P. E. Kruger, *Dalton Trans.*, 2011, **40**, 12368-12373; b) J.-Y. Balandier, M. Chas, S. Goeb, P. I. Dron, D. Rondeau, A. Belyasmine, N. Gallego and M. Salle, *New J. Chem.*, 2011, **35**, 165-168; c) R. A. Bilbeisi, S. Zarra, H. L. C. Feltham, G. N. L. Jameson, J. K. Clegg, S. Brooker and J. R. Nitschke, *Chem. Eur. J.*, 2013, **19**, 8058-8062; d) S. Bivaud, J.-Y. Balandier, M. Chas, M. Allain, S. Goeb and M. Salle, *J. Am. Chem. Soc.*, 2012, **134**, 11968-11970; e) S. Bivaud, S. Goeb, V. Croue, P. I. Dron, M. Allain and M. Salle, *J. Am. Chem. Soc.*, 2013, **135**, 10018-10021; f) A. Ferguson, M. A. Squire, D. Siretanu, D. Mitcov, C. Mathoniere, R. Clerac and P. E. Kruger, *Chem. Commun.*, 2013, **49**, 1597-1599; g) M. Frank, J. Hey, I. Balcioglu, Y.-S. Chen, D. Stalke, T. Suenobu, S. Fukuzumi, H. Frauendorf and G. H. Clever, *Angew. Chem. Int. Ed.*, 2013, **52**, 10102-10106; h) K. Ghosh, Y. Zhao, H.-B. Yang, B. H. Northrop, H. S. White and P. J. Stang, *J. Org. Chem.*, 2008, **73**, 8553-8557; i) S. Goeb, S. Bivaud, P. I. Dron, J.-Y. Balandier, M. Chas and M. Salle, *Chem. Commun.*, 2012, **48**, 3106-3108; j) J. G. Hardy, *Chem. Soc. Rev.*, 2013, **42**, 7881-7899; k) F. Jiang, N. Wang, Z. Du, J. Wang, Z. Lan and R. Yang, *Chem. Asian J.*, 2012, **7**, 2230-2234; l) D. Pelleteret, R. Clerac, C. Mathoniere, E. Harte, W. Schmitt and P. E. Kruger, *Chem. Commun.*, 2009, 221-223; m) M. Ruben, J. Rojo, F. J. Romero-Salguero, L. H. Uppadine and J.-M. Lehn, *Angew. Chem. Int. Ed.*, 2004, **43**, 3644-3662; n) H.-B. Yang, K. Ghosh, Y. Zhao, B. H. Northrop, M. M. Lyndon, D. C. Muddiman, H. S. White and P. J. Stang, *J. Am. Chem. Soc.*, 2008, **130**, 839-841; o) G.-Z. Zhao, L.-J. Chen, C.-H. Wang, H.-B. Yang, K. Ghosh, Y.-R. Zheng, M. M. Lyndon, D. C. Muddiman and P. J. Stang, *Organometallics*, 2010, **29**, 6137-6140.

6. a) H. Amouri, C. Desmarets and J. Moussa, *Chem. Rev.*, 2012, **112**, 2015-2041; b) M. J. Wiester, P. A. Ulmann and C. A. Mirkin, *Angew. Chem. Int. Ed.*, 2011, **50**, 114-137; c) M. Yoshizawa and M. Fujita, *Bull. Chem. Soc. Jpn.*, 2010, **83**, 609-618; d) M. Yoshizawa, J. K. Klosterman and M. Fujita, *Angew. Chem. Int. Ed.*, 2009, **48**, 3418-3438.

7. M. D. Pluth, R. G. Bergman and K. N. Raymond, *Acc. Chem. Res.*, 2009, **42**, 1650-1659.

8. a) B. Breiner, J. K. Clegg and J. R. Nitschke, *Chem. Sci.*, 2011, **2**, 51-56; b) M. Hardouin-Lerouge, P. Hudhomme and M. Salle, *Chem. Soc. Rev.*, 2011, **40**, 30-43; c) M. D. Pluth and K. N. Raymond, *Chem. Soc. Rev.*, 2007, **36**, 161-171.

9. M. Ikemi, T. Kikuchi, S. Matsumura, K. Shiba, S. Sato and M. Fujita, *Chem. Sci.*, 2010, **1**, 68-71.

10. T. Kikuchi, S. Sato and M. Fujita, *J. Am. Chem. Soc.*, 2010, **132**, 15930-15932.

11. D. Fujita, K. Suzuki, S. Sato, M. Yagi-Utsumi, Y. Yamaguchi, N. Mizuno, T. Kumasaka, M. Takata, M. Noda, S. Uchiyama, K. Kato and M. Fujita, *Nat. Commun.*, 2012, **3**, 2093/2091-2093/2097.

12. a) For a review of the area see; b) B. H. Northrop, H.-B. Yang and P. J. Stang, *Chem. Commun.*, 2008, 5896-5908.

13. a) For other selected examples see; b) K. Ghosh, J. Hu, H.-B. Yang, B. H. Northrop, H. S. White and P. J. Stang, *J. Org. Chem.*, 2009, **74**, 4828-4833; c) N. Kamiya, M. Tominaga, S. Sato and M. Fujita, *J. Am. Chem. Soc.*, 2007, **129**, 3816-3817; d) T. Murase, S. Sato and M. Fujita, *Angew. Chem. Int. Ed.*, 2007, **46**, 1083-1085; e) T. Murase, S. Sato and M. Fujita, *Angew. Chem. Int. Ed.*, 2007, **46**, 5133-5136; f) S. Sato, J. Iida, K. Suzuki, M. Kawano, T. Ozeki and M. Fujita, *Science*, 2006, **313**, 1273-1276; g) M. Tominaga, K. Suzuki, T. Murase and M. Fujita, *J. Am. Chem. Soc.*, 2005, **127**, 11950-11951; h) N.-W. Wu, J. Zhang, D. Ciren, Q. Han, L.-J. Chen, L. Xu and H.-B. Yang, *Organometallics*, 2013, **32**, 2536-2545; i) L. Zhao, K. Ghosh, Y.-R. Zheng and P. J. Stang, *J. Org. Chem.*, 2009, **74**, 8516-8521; j) Z. Zhao, Y.-R. Zheng, M. Wang, J. B. Pollock and P. J. Stang, *Inorg. Chem.*, 2010, **49**, 8653-8655.

14. a) R. Chakrabarty and P. J. Stang, *J. Am. Chem. Soc.*, 2012, **134**, 14738-14741; b) D. Zhao, S. Tan, D. Yuan, W. Lu, Y. H. Rezenom, H. Jiang, L.-Q. Wang and H.-C. Zhou, *Adv. Mater.*, 2011, **23**, 90-93.

15. a) H. Maeda, J. Wu, T. Sawa, Y. Matsumura and K. Hori, *J. Control. Release*, 2000, **65**, 271-284; b) Y. Matsumura and H. Maeda, *Cancer Res.*, 1986, **46**, 6387-6392.

16. a) N. P. E. Barry, O. Zava, W. Wu, J. Zhao and B. Therrien, *Inorg. Chem. Commun.*, 2012, **18**, 25-28; b) M. A. Furrer, F. Schmitt, M. Wiederkehr, L. Juillerat-Jeanneret and B. Therrien, *Dalton Trans.*, 2012, **41**, 7201-7211; c) A. Pitto-Barry, O. Zava, P. J. Dyson, R. Deschenaux and B. Therrien, *Inorg. Chem.*, 2012, **51**, 7119-7124; d) B. Therrien, G. Suess-Fink, P. Govindaswamy, A. K. Renfrew and P. J. Dyson, *Angew. Chem. Int. Ed.*, 2008, **47**, 3773-3776; e) J. W. Yi, N. P. E. Barry, M. A. Furrer, O. Zava, P. J. Dyson, B. Therrien and B. H. Kim, *Bioconjugate Chem.*, 2012, **23**, 461-471; f) O. Zava, J. Mattsson, B. Therrien and P. J. Dyson, *Chem. Eur. J.*, 2010, **16**, 1428-1431.

17. a) J. Freudenreich, C. Dalvit, G. Suss-Fink and B. Therrien, *Organometallics*, 2013, **32**, 3018-3033; b) F. Schmitt, N. P. E. Barry, L. Juillerat-Jeanneret and B. Therrien, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 178-180; c) F. Schmitt, J. Freudenreich, N. P. E. Barry, L. Juillerat-Jeanneret, G. Suss-Fink and B. Therrien, *J. Am. Chem. Soc.*, 2012, **134**, 754-757.

18. a) Pd_2L_4 cages have become the "workhorse" of metallosupramolecular architectures with many groups investigating the properties of these systems. For a recent review see; b) M. Han, D. M. Engelhard and G. H. Clever, *Chem. Soc. Rev.*, 2014, DOI: 10.1039/C1033CS60473J.

19. J. E. M. Lewis, E. L. Gavey, S. A. Cameron and J. D. Crowley, *Chem. Sci.*, 2012, **3**, 778-784.
20. J. E. M. Lewis, C. J. McAdam, M. G. Gardiner and J. D. Crowley, *Chem. Commun.*, 2013, **49**, 3398-3400.
21. a) There has been an explosion of interest in the coordination chemistry of CuAAC derived 1,4-disubstituted 1,2,3-triazole ligands, for recent reviews see; b) J. D. Crowley and D. A. McMorran, *Top. Heterocycl. Chem.*, 2012, **28**, 31-83; c) D. Schweinfurth, N. Deibel, F. Weisser and B. Sarkar, *Nachr. Chem.*, 2011, **59**, 937-941; d) H. Struthers, T. L. Mindt and R. Schibli, *Dalton Trans.*, 2010, **39**, 675-696.
22. a) CuAAC "click" derived 1,2,3-triazole ligands have been used to generate metallosupramolecular architectures, see ; b) J. D. Crowley and P. H. Bandeen, *Dalton Trans.*, 2010, **39**, 612-623; c) J. D. Crowley and E. L. Gavey, *Dalton Trans.*, 2010, **39**, 4035-4037; d) L. Garcia, S. p. Maisonneuve, J. Xie, R. g. Guillot, P. Dorlet, E. Rivière, M. Desmadril, F. o. Lambert and C. Policar, *Inorg. Chem.*, 2010, **49**, 7282-7288; e) M. L. Gower and J. D. Crowley, *Dalton Trans.*, 2010, **39**, 2371-2378; f) B. Happ, G. M. Pavlov, E. Altuntas, C. Friebe, M. D. Hager, A. Winter, H. Görls, W. Günther and U. S. Schubert, *Chem. Asian J.*, 2011, **6**, 873-880; g) K. J. Kilpin, U. S. D. Paul, A.-L. Lee and J. D. Crowley, *Chem. Commun.*, 2011, **47**, 328-330; h) U. R. Pokharel, F. R. Fronczek and A. W. Maverick, *Dalton. Trans.*, 2013, **42**, 14064-14067; i) B. Schulze, D. Escudero, C. Friebe, R. Siebert, H. Görls, U. Köhn, E. Altuntas, A. Baumgaertel, M. D. Hager, A. Winter, B. Dietzek, J. Popp, L. González and U. S. Schubert, *Chem. Eur. J.*, 2011, **17**, 5494-5498; j) S. O. Scott, E. L. Gavey, S. J. Lind, K. C. Gordon and J. D. Crowley, *Dalton Trans.*, 2011, **40**, 12117-12124; k) K. A. Stevenson, C. F. C. Melan, O. Fleischel, R. Wang and A. Petitjean, *Cryst. Growth Des.*, 2012, **12**, 5169-5173; l) S. K. Vellas, J. E. M. Lewis, M. Shankar, A. Sagatova, J. D. A. Tyndall, B. C. Monk, C. M. Fitchett, L. R. Hanton and J. D. Crowley, *Molecules*, 2013, **18**, 6383-6407; m) N. G. White and P. D. Beer, *Supramolecular Chemistry*, 2012, **24**, 473-480; n) H. Zhao, X. Li, J. Wang, L. Li and R. Wang, *ChemPlusChem*, 2013, **78**, 1491-1502.
23. C. M. Amb and S. C. Rasmussen, *J. Org. Chem.*, 2006, **71**, 4696-4699.
24. M. J. Mio, L. C. Kopel, J. B. G. Braun, Tendai L., K. L. Hull, R. G. Brisbois, C. J. Markworth and P. A. Grieco, *Org. Lett.*, 2002, **4**, 3199-3202.
25. a) J. D. Crowley, P. H. Bandeen and L. R. Hanton, *Polyhedron*, 2010, **29**, 70-83; b) A. K. Feldman, B. Colasson and V. V. Fokin, *Org. Lett.*, 2004, **6**, 3897-3899.
26. T. Y. Kim, A. B. S. Elliott, K. J. Shaffer, M. C. John, K. C. Gordon and J. D. Crowley, *Polyhedron*, 2013, **52**, 1391-1398.
27. K. J. Kilpin, E. L. Gavey, C. J. McAdam, C. B. Anderson, S. J. Lind, C. C. Keep, K. C. Gordon and J. D. Crowley, *Inorg. Chem.*, 2011, **50**, 6334-6346.
28. D. A. Haynes, W. Jones and W. D. S. Motherwell, *J. Pharm. Sci.*, 2005, **94**, 2111-2120.
29. K. J. Kilpin, M. L. Gower, S. G. Telfer, G. B. Jameson and J. D. Crowley, *Inorg. Chem.*, 2011, **50**, 1123-1134.
30. J. E. M. Lewis and J. D. Crowley, *Supramol. Chem.*, 2013, DOI: 10.1080/10610278.10612013.10842644.
31. D. A. Ryan and J. Rebek, *J. Am. Chem. Soc.*, 2011, **133**, 19653-19655.
32. N. B. Debata, D. Tripathy and D. K. Chand, *Coord. Chem. Rev.*, 2012, **256**, 1831-1945.
33. P. Liao, B. W. Langloss, A. M. Johnson, E. R. Knudsen, F. S. Tham, R. R. Julian and R. J. Hooley, *Chem. Commun.*, 2010, **46**, 4932-4934.
34. a) A. M. Johnson and R. J. Hooley, *Inorg. Chem.*, 2011, **50**, 4671-4673; b) A. M. Johnson, O. Moshe, A. S. Gamboa, B. W. Langloss, J. F. K. Limtiaco, C. K. Larive and R. J. Hooley, *Inorg. Chem.*, 2011, **50**, 9430-9442.
35. R. M. Duke, E. B. Veale, F. M. Pfeffer, P. E. Kruger and T. Gunnlaugsson, *Chem. Soc. Rev.*, 2010, **39**, 3936-3953.
36. N. Kishi, Z. Li, Y. Sei, M. Akita, K. Yoza, J. S. Siegel and M. Yoshizawa, *Chem. Eur. J.*, 2013, **19**, 6313-6320.
37. L. Svorc, *Int. J. Electrochem. Sci.*, 2013, **8**, 5755-5773.
38. a) A. Altieri, F. G. Gatti, E. R. Kay, D. A. Leigh, D. Martel, F. Paolucci, A. M. Z. Slawin and J. K. Y. Wong, *J. Am. Chem. Soc.*, 2003, **125**, 8644-8654; b) F. Cecchet, P. Rudolf, S. Rapino, M. Margotti, F. Paolucci, J. Baggerman, A. M. Brouwer, E. R. Kay, J. K. Y. Wong and D. A. Leigh, *J. Phys. Chem. B*, 2004, **108**, 15192-15199; c) C. J. McAdam, B. H. Robinson and J. Simpson, *Organometallics*, 2000, **19**, 3644-3653; d) C. J. McAdam, B. H. Robinson, J. Simpson and T. Tagg, *Organometallics*, 2010, **29**, 2474-2483.