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A facile "click" approach to functionalised metallosupramolecular architectures†

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James E. M. Lewis,[a] C. John McAdam,[a] Michael G. Gardiner[b] and James D. Crowley*[a]

Herein we describe a CuAAC "click" methodology for *exo*-functionalisation of Pd_2L_4 metallosupramolecular architectures. The potentially coordinating 1,2,3-triazole does not affect formation of the desired discrete complexes, nor does this external functional decoration affect the cisplatin-binding ability of the interior cavity of the assembly.

The synthetic principles for the generation of self-assembled nanoscale coordination (metallosupramolecular) architectures are now well established. With judicious choice of the metal ions and ligands, architectures of the desired shape and size can almost be generated at will.[1] These metallosupramolecular architectures have been shown to possess a variety of interesting physical and chemical properties,[2] and have been extensively exploited as host molecules for the molecular recognition of a vast array of organic and inorganic guest molecules.[3] Building on these studies other metallo-cage systems have been used as nanoscale reaction flasks[4] and catalysts.[5] While the supramolecular host–guest properties of these systems dominate the area they are certainly not the only potential applications of these architectures. Metallosupramolecular systems have also been shown to display interesting biological,[6] electronic[7] and photophysical[8] properties. However, for the most part the ligands employed for the generation of these systems have been kept relatively simple and free of additional functionality in order to ensure assembly of the desired molecular architectures without interference from other (potentially) coordinating groups. In order to further enhance the properties and applications of these metallosupramolecular architectures efforts are now focusing on the incorporation of additional functionality into the ligand scaffolds. Cage architectures featuring both *endo*- and *exo*-functionalisation[9] (Fig. 1) have been realised and a range of biological molecules[10] and other functional groups[11] have been incorporated into the ligands with no observed interference towards subsequent formation of the intended metallosupramolecular architecture. Despite this interest, to date there have been no reports of a single mild method for appending a variety of functional moieties on a single "proto-ligand" enabling diverse functionalisation and rapid tuning of the resulting architectures' properties.

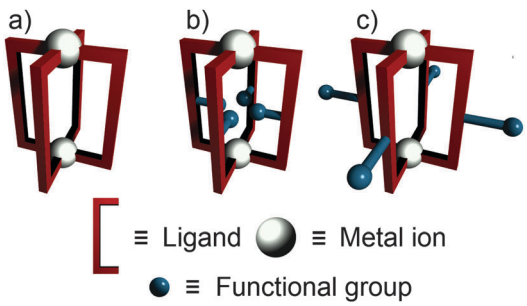

Fig. 1 Cartoon representations of (a) unfunctionalised (b) *endo*- and (c) *exo*-functionalised M_2L_4 metallosupramolecular assemblies.

We have previously reported[12] the synthesis of a $Pd^{II}{}_2L_4$ self-assembling cage architecture capable of encapsulating two cisplatin molecules. As part of our work towards exploiting these cages as stimuli-responsive metallosupramolecular cisplatin drug delivery agents we required a mild, selective, functional group tolerant synthetic method for decorating the ligands of these cages to enhance their physical properties. The Cu(I)-catalysed 1,3-cycloaddition of organic azides with terminal alkynes[13] (the CuAAC reaction), which has been extensively exploited in the synthesis of functional molecules during the past decade, seemed ideal for this propose due to its reliability, mild reaction conditions and wide substrate scope. Somewhat surprisingly, the CuAAC reaction has not been extensively examined as a method to functionalise metallosupramolecular ligand systems. This is presumably because the 1,4-disubstituted-1,2,3-triazoles created in the reaction have the potential to act as N donor ligands[14] and interfere with the

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

[b] *School of Chemistry, University of Tasmania, Hobart, Australia*

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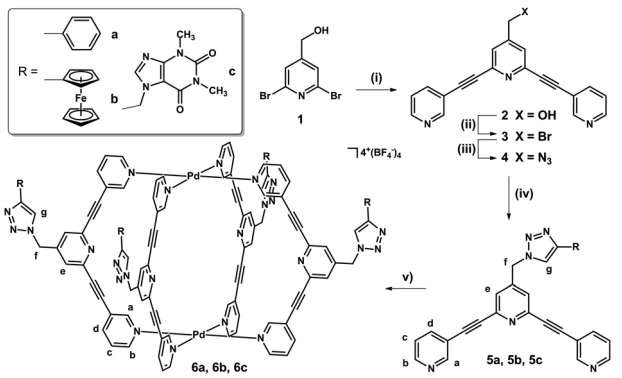
self-assembly process. In fact 1,4-disubstituted-1,2,3-triazole containing ligands have even been used in the construction of metallosupramolecular architectures.[15] Azide–alkyne ''click'' methods[16] were exploited to post-synthetically modify discrete kinetically robust metallosupramolecular metallocycles and cages, but to date have not been used to functionalise metallosupramolecular ligand systems before the assembly is formed.

Herein we report the synthesis of three 'click'-functionalised tripyridyl ligands and show that the presence of the potentially coordinating 1,2,3-triazole units does not interfere with ability of the ligands to self-assemble into the desired M_2L_4 palladium(II) cage architectures. Furthermore, the presence of the additional *exo*-functionality does not interfere with the cages' ability to bind guest molecules within the interior cavity of the architectures.

The azide **4** was selected as our target ''click'' ligand precursor and was synthesised from 2,6-dibromo-4-(hydroxymethyl)-pyridine **1**[17] in 3 steps with an overall yield of 24% (Scheme 1). Reaction of the azide **4** under standard copper-catalysed ''click'' conditions[18] gave the phenyl- (**5a**), ferrocenyl- (**5b**) and caffeine-substituted (**5c**) ligands in good isolated yields (64–88%). The identity of the ligands was confirmed by IR, ^{1}H and ^{13}C NMR spectroscopy as well as electrospray-mass spectrometry (ESMS) (ESI†).

The quantitative formation, in less than 5 minutes, of the desired cage complexes (**6a–c**) was observed using *in situ* ^{1}H NMR spectroscopy (Scheme 1).‡ Simply mixing stoichiometric amounts of one of the ligands (**5a–c**) and $[Pd(CH_3CN)_4](BF_4)_2$ salt in a 2 : 1 ratio in d_6-DMSO, resulted in a significant downfield shift in the proton signals corresponding to the terminal pyridyl moieties (H_a–H_d, Fig. 2 and ESI†). The chemical shifts for the remaining proton signals were not greatly affected, and importantly the H_g signal of the triazole proton was actually observed to shift upfield. This evidence suggested that despite the presence of the potentially coordinating 1,2,3-triazole moiety within the ligand framework, coordination was only occurring through the terminal pyridine rings. Further solution phase evidence for the formation of the desired discrete cage architectures was obtained from ^{1}H DOSY NMR. Each of the proton signals in the individual spectra show the same diffusion coefficients (D), indicating that



Scheme 1 Reactants and reagents: (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, 44%; (ii) PPh_3, CBr_4, DCM, RT, N_2, 16 h, 60%; (iii) NaN_3, DMF, RT, 3 h, 92%; (iv) $CuSO_4{\cdot}5H_2O$, sodium ascorbate, R-alkyne, H_2O–DMF, RT, 16 h; (v) $[Pd(CH_3CN)_4](BF_4)_2$, d_6-DMSO.

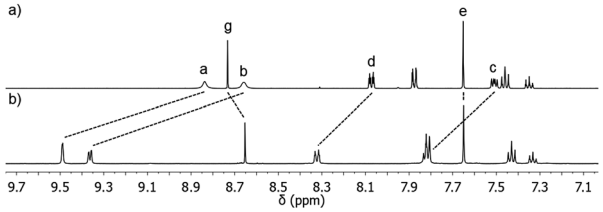


Fig. 2 ^{1}H NMR (500 MHz, d_6-DMSO) spectra of the aromatic regions of (a) **5a**, (b) **6a**. For signal labelling refer to Scheme 1.

there is only one species present in solution (ESI†) and the ratio of the diffusion coefficients of the ligands and palladium complexes in d_6-DMSO were approximately 2 : 1 (ESI†), consistent with the presence of the larger molecular cage species in solution.

HR-ESMS experiments provided additional evidence for the formation of the $[Pd_2L_4](X)_4$ architectures. The ESMS spectra (CH_3CN–DMSO) of **6a–c** show isotopically resolved peaks consistent with the formulation $[Pd_2(\mathbf{L})_4(X)_n(\text{solvent})_y]^{(4-n)+}$ (n = 0–2, y = 3–6) along with peaks due to fragmentation of the cage structure (ESI†). The precise molecular structure of the cage architecture was ultimately proved by single-crystal X-ray diffraction studies (*vide infra* §).

Having demonstrated that the 1,2,3-triazole units do not interfere with the cage formation, it was next examined if the cages retained the guest bind ability of the parent system. Addition of cisplatin to a solution of either **6a** or **6b** in CD_3CN, followed by brief sonication, in both instances resulted in a broadened and downfield shifted H_a proton signal in the ^{1}H NMR spectrum (ESI†), as we have previously reported for the parent system,[12] indicating that the cisplatin-binding functionality of the interior cavity had been retained.

The exact nature of the host–guest adduct $[\mathbf{6b}\supset(\text{cisplatin})_2]^{4+}$ was determined by X-ray crystallography (Fig. 3 and ESI†). Small X-ray quality crystals were grown by vapour diffusion of diethyl ether into a sonicated DMF solution of **6b** and cisplatin. The use of synchrotron radiation enabled the molecular structure of the host–guest adduct to be determined. As previously observed,[12] two cisplatin molecules were found encapsulated within the cavity of the dipalladium(II) quadruply-stranded cage structure. As suggested by the aforementioned sporting methods, the presence of the potentially coordinating 1,2,3-triazole moieties did not disrupt formation of the thermodynamically favourable, discrete cage architectures. Intriguingly the crystal lattice consists of intercalating alternating 1D chains of $[\mathbf{6b}]^{4+}$ and the host–guest adduct $[\mathbf{6b}\supset(\text{cisplatin})_2]^{4+}$ (ESI†). As observed for the unfunctionalised parent system[12] the host–guest adduct contains two molecules of cisplatin within the cavity of the cage, rotated 180° with respect to each other; hydrogen bonds between the cisplatin and cage ($N{-}H\cdots N_{Py}$ and $Cl\cdots H{-}C_{Py}$) as well as a metal–metal interaction[19] between the platinum atoms of the guests were observed (Fig. 3).

Ferrocene has been appended onto a number of metallosupramolecular architectures with the goal of generating electrochemically active systems.[11] As such we examined the electrochemistry of the ligands (**5a–b**) and cages (**6a–b**) in DMF solution (ESI†). For **5a** and **5b** a cathodic sweep to −2.0 V

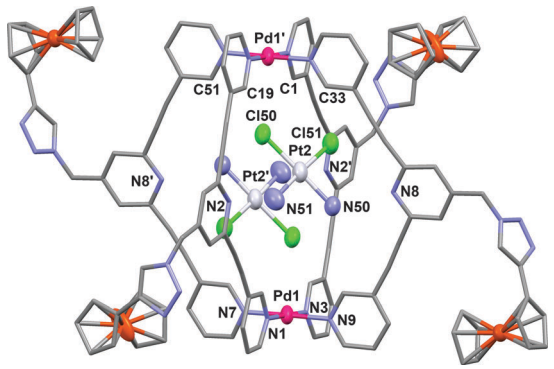


Fig. 3 Labeled Mercury diagram of the X-ray crystal structure of $[Pd_2(\mathbf{6b})_4 \supset (cisplatin)_2]^{4+}$. Empty cage, solvent molecules and hydrogen atoms have been omitted for clarity. Selected bond lengths (Å) and angles (°): Pd1–N1 2.024(7), Pd1–N3 2.023(7), Pd1–N7 2.039(6), Pd1–N9 2.028(6), Pd1···Pd1′ 11.595(3), N50···N8 2.88(1), N51···N2 3.10(1), Cl51···C33 3.627(9), Cl51···C1 3.396(8), Cl50···C19 3.347(8), Cl50···C51 3.497(7), Pt2···Pt2′ 3.327(1), N1–Pd1–N7 90.9(2), N7–Pd1–N3 88.4(3), N3–Pd1–N9 90.0(3), N9–Pd1–N1 90.7(3). Metal and cisplatin guest atom ellipsoids are shown at the 50% probability level.

showed two irreversible reductions at *ca.* −1.7 and −1.9 V, which are attributed to the 2,6-bis(ethynyl)pyridine structural element. In the cage complexes **6a** and **6b**, coordination of the pyridine termini to palladium had little effect on the position of the reduction processes. An anodic sweep on a DMF solution of **5b** displayed the predicted one-electron reversible oxidation at E° 0.53 V, a value comparable with other reported 4-ferrocenyl triazoles.[18] As expected, complexation of the ligand with palladium did not affect the potential or reversibility of this process (within experimental error) due to the saturated methylene linker between the coordinating ligand framework and triazole substituent. No electronic communication between the four ferrocene units of the cage **6b** was observed.

In conclusion we have developed a methodology for facile "click" modification of tripyridyl ligands which, despite the potentially coordinating 1,2,3-triazolyl moiety, still assemble into discrete Pd_2L_4 metallosupramolecular cage architectures in the presence of Pd(II) ions. Having demonstrated that this facile CuAAC "click" functionalisation does not interfere with formation of the desired cage complexes, this methodology could easily be applied to other discrete metallosupramolecular systems, allowing simple and diverse augmentation of various chemical and physical properties of the architectures. It is foreseeable that this methodology could be easily applied to a variety of ligand frameworks that have been previously shown to form nanoscale architectures, and ready access to these functionalised metallosupramolecular systems could open up new applications for these species. Additionally, in view of our work towards functional drug delivery vectors,[12] we are currently synthesising a more exhaustive collection of functionalised "click" ligands and their palladium cage complexes.

Data for the structure of complex **6b** was obtained on the MX2 beamline at the Australian Synchrotron, Victoria, Australia.

Notes and references

‡ Subsequently the cage architectures **6a–c** were synthesised on a preparative scale and isolated in good yields (68–76%, ESI†).
§ Crystal data for **6b**: $C_{64}H_{52.50}ClFe_2N_{13}O_{2.75}PdPt_{0.50}$, M = 1398.79, triclinic, space group $P\bar{1}$, cell parameters a = 14.809(3), b = 21.668(4), c = 24.158(5) Å, α = 105.56(3), β = 94.22(3), γ = 90.62(3)°, V = 7444(3) Å^3, T = 173(2) K, Z = 4, D_c = 1.248 mg m^{-3}, λ (synchrotron) = 0.71073 Å, 158 104 reflections measured, 41 676 unique (R_{int} = 0.0724, completeness = 87.2. R_1 = 0.0945 and wR_2 = 0.2832 ($I > 2\sigma(I)$), GOF = 1.020; max/min residual density 4.104/−3.383 eÅ^{-3}. CCDC 924182.

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