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Post-assembly Functionalization of Organoplatinum(II) Metallacycles via Copper-free Click Chemistry

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Abstract

We describe the use of strain-promoted copper-free click reaction in the post-self-assembly functionalization of organoplatinum(II) metallacycles. The coordination-driven self-assembly of 120°-cyclooctyne tethered dipyrindyl donor with 60° and 120°-di-Pt(II) acceptors formed molecular rhomboids and hexagons bearing cyclooctynes. These species undergo post-self-assembly [3 + 2] Huisgen cycloaddition with a variety of azides to give functionalized ensembles under mild conditions.

The functionalization of supramolecular assemblies has been extensively investigated over the past few years with an aim to develop nanoscale ensembles that can find applications in diverse fields such biological systems, host-guest chemistry, cavity directed synthesis, catalysis, photonics, redox activity, magnetic behavior, self-organization, and sensing.¹ Although various functionalized nanoscopic systems have been developed through conventional covalent synthesis, the control of functional groups and structural precision, the ability to perform selective encapsulation, and synthetic ease and building-block versatility makes coordination-driven self-assembly a powerful tool to assemble functional supramolecules with relative simplicity. However, potential incompatibilities and interferences by various functional groups with the self-assembly process often limit the library and scope of the functionalized tectons. Thus post-self-assembly modification of supramolecular ensembles through transformation of the organic component of the assemblies may be a way to circumvent the problem. We have recently been able to achieve post-assembly functionalization of metallosupramolecular prisms via covalent modifications to incorporate new functionalities under mild conditions.² The free amino groups tethered on the edges of the prisms allowed facile reactions with isocyanate or maleic anhydride. Similarly, the free maleimide groups tethered on the edges of these prisms underwent Diels-Alders reaction with anthracenyl ferrocenoate. However, the range and scope of using amino group as a handle to introduce various functional groups is limited. The azide-alkyne based “click” reactions are attractive alternatives in this context since they usually involve weakly polarized reactants, minimizing undesired side reactions and thus could be an efficient method for expanding the range of chemical functionalities that can be tethered onto the metallosupramolecules. Post-synthetic modification of metal-organic frameworks³ have been achieved in recent years through copper(I) catalyzed azide-alkyne cycloaddition (CuAAC) reactions.⁴ However, the application of click chemistry to functionalize discrete assemblies has received much less attention. In a rare example, Zhou et al.⁵ described the functionalization of porous nanocages bearing free alkyne groups via the CuAAC reaction

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Supporting Information. Experimental procedures and characterizations data for all metallacyclic assemblies. This material is available free of charge via the Internet at <http://pubs.acs.org>.

with azide-terminated PEG to transform the nanocages into water-stable colloids, which showed controlled release of the anticancer drug 5-fluorouracil. However, use of CuAAC reactions in living systems is limited due to the cytotoxicity of the Cu(I) catalyst towards living cells. Copper free strain-promoted azide-alkyne cycloaddition (SPAAC) reactions⁶ recently developed between cyclooctynes and azides have found wide utility in chemical biology, such as labeling of biomolecules - glycans,⁷ proteins,⁸ lipids⁹ and nucleotides,¹⁰ modification of oligonucleotides¹¹ and enzymes¹², and cell and tissue surface engineering.¹³ In the field of material science, SPAAC reactions have been used for surface functionalization of dendrimers,¹⁴ polymers,¹⁵ nano-particles¹⁶ and nanowires,¹⁷ surface patterning,¹⁸ and cross-linking of polymers and hydrogels.¹⁹

Herein we report post-self-assembly functionalization of supramolecular ensembles through “copper-free click chemistry”. The 120°-cyclooctyne-tethered dipyriddy donor was synthesized via the amide coupling reaction of 3,5-bis(4-pyridylethynyl)aniline with 1-cyclooctyn-3-glycolic acid²⁰ in dichloromethane leading to the formation of the cyclooctyne-tethered donor **1** (Supporting Information, Scheme S1).

Stirring a mixture of 120° cyclooctyne-tethered donor **3** and the 60° organoplatinum(II) acceptor, 3,6-Bis-*[trans-Pt(PET₃)₂(NO₃)₂]*phenanthrene (**4**) in a 1:1 ratio in CD₂Cl₂ for 8 h led to the formation of self-assembled [2 + 2] metallacyclic rhomboid **6**. Similarly, self-assembled [3 + 3] hexagon **7** was prepared by mixing the 120° donor ligand **3** with organoplatinum(II) acceptor, 4,4'-*[trans-Pt(PET₃)₂(NO₃)₂]*diphenylketone (**5**) in a 1:1 ratio in CD₃OD for 8 h. (Scheme 1). Multinuclear NMR (³¹P and ¹H) of the reaction products revealed the formation of discrete, highly symmetric assemblies. These metallacycles contain a pendant cyclooctyne moiety at their vertices. The ³¹P {¹H} NMR spectrum of **6** and **7** displayed sharp singlets at 12.7 and 14.1 ppm with concomitant ¹⁹⁵Pt satellites corresponding to a single phosphorus environment (Figure 1). The peaks were shifted upfield from their respective platinum acceptors **4** and **5** by approximately 6.4 and 5.1 ppm. The up-field shift as well as the decrease in coupling constant (ΔJ) for the ¹⁹⁵Pt satellites is consistent with back donation from the platinum atoms. In the ¹H NMR spectrum of **6**, signals due to the α - and β -protons of the pyridine rings showed the expected downfield shifts relative to **3** due to the loss of electron density that occurs upon coordination of the pyridyl-N atom to the Pt(II) metal center. As shown in Figure 2, the α - and β -protons on the pyridine rings are split into two sets of two doublets upon coordination that is consistent with previous observations of similar Pt-based rhomboids.²¹ The α -pyridyl protons of cyclooctyne-tethered donor **3**, which appears as a doublet at 8.62 ppm is split into two doublets at 9.34 and 8.68 ppm. Similarly, β -pyridyl protons ($\delta = 7.42$ ppm) are split into two doublets at 7.96 and 7.81 ppm. The signal at $\delta = 9.18$ ppm was assigned to the amide proton. In the ¹H NMR spectrum of **7**, sharp signals corresponding to coordinated α - and β -pyridyl protons were identified at 8.89 and 7.87 ppm with downfield shifts relative to **3** (Figure 2).

Electrospray ionization-mass spectroscopic (ESI-MS) studies further confirmed the formation of discrete supramolecular assemblies. The ESI mass spectrum for rhomboid **6** (Supporting Information) showed a peak at $m/z = 1560.5$, corresponding to $[M - 2NO_3]^{2+}$ and $m/z = 1019.02$ attributable to $[M - 3NO_3]^{3+}$. All the peaks were isotopically resolved, and agree very well with the calculated theoretical distribution. In the ESI-MS of **7**, no parent ion peak was observed due to fragmentation. However, unique fragments were observed that support the formation of the hexagonal structure when analyzed in conjunction with the NMR spectra (Supporting information).

In order to gain structural information about the metallacycles, single-point DFT energy minimization were performed using the Gaussian09 package.²² All calculations were performed using the B3LYP hybrid DFT functional,^{23,24} and a split basis set wherein the

6-31G** basis set²⁵ were used for C, H, N, O and P atoms, while the LANL2DZ basis set²⁶ and pseudo potential were used for Pt. To minimize the computational cost, PET_3 ligands were modeled as PH_3 . In rhomboid **6**, the two cyclooctyne moieties at the vertices lie above and below the plane of the central metallacyclic core. The cyclooctyne groups adopt a more stable boat conformation.²⁷ The alkyne bonds in the cyclooctynes are bent from linearity. Previous studies²⁸ using DFT-based models for the 1,3-dipolar cycloaddition of cyclooctynes with azides have shown that such deviation from linearity distorts the cyclooctynes towards the transition state geometry, thus requiring less distortion energy to reach their preferred transition state geometry relative to a linear alkyne.

The metallacyclic rhomboid **6** was tested for post-assembly functionalization via “copper free click chemistry”. The rhomboid **6** undergoes efficient [3 + 2] Huisgen-type SPAAC reactions with a variety of functionalized azides to give functionalized metallacycles under mild conditions (Scheme 2). Molecular rhomboids **8a-c** were obtained upon treatment of **6** with azidomethyl benzene, 1-(azidomethyl)pyrene and 2-(azidoethyl)biotinamide, respectively, in 1:5 ratio in CD_2Cl_2 for 2 h at room temperature. In all cases, the only product observed were the two regioisomeric 1, 4, 5-trisubstituted-1, 2, 3-triazoles in varying ratios as identified from ^1H NMR spectra of **8a-c**. The ^{31}P { ^1H } NMR spectra for all the assemblies remained unchanged with the peak appearing at about the same position relative to their unfunctionalized counterpart. The ^{31}P { ^1H } NMR spectrum of the functionalized rhomboids **8a-c** appear as sharp singlets at 12.7 ppm identical to that of its unfunctionalized rhomboid **7**. The ^1H NMR spectra of the ensembles showed additional peaks attributable to benzyl, pyrenyl, and biotinyl protons (Supporting information). In the ^1H NMR spectrum of **8a**, the phenyl protons originating from the benzyl azide appear as a multiplet 7.38 ppm while the benzyl protons appear at 5.60 ppm and are consistent with previous observations.²⁹ The pyrenyl protons in **8b** appear as a multiplet at 8.27-8.11 ppm with the benzyl proton appearing at 6.38 ppm.

ESI-MS data provided further evidence for the formation of the discrete functionalized species. The ESI mass spectrum for **8a** showed isotopically resolved peaks at $m/z = 1693.6$, corresponding to $[\text{M} - 2\text{NO}_3]^{2+}$ and $m/z = 1108.1$ attributable to $[\text{M} - 3\text{NO}_3]^{3+}$ (Supporting information). Similarly, isotopically resolved peaks due to $[\text{M} - 2\text{NO}_3]^{2+}$ and $[\text{M} - 3\text{NO}_3]^{3+}$ were observed at $m/z = 1817.6$ and 1190.8 in the ESI-MS spectrum of **8b**. The ESI-MS spectrum of biotin functionalized species **9c** also showed isotopically resolved peak at $m/z = 1228.1$, corresponding to $[\text{M} - 3\text{NO}_3]^{3+}$.

In conclusion, we have demonstrated that copper-free strain-promoted azide-alkyne cycloaddition (SPAAC) reactions can be effectively used to functionalize metallacycles having pendant cyclooctyne groups. In contrast to other methodologies for construction of functionalized supramolecules where a pre-functionalized unit is used, this method provides a facile way to incorporate a wide range of chemical functionalities on appropriate supramolecular assemblies with relative synthetic ease. The ready access to a multi-biotin scaffold permits the formation of a biotin multimeric structure for potential enhancement of avidin-biotin assays. Since a multivalent biotin scaffold allows many biotin binding proteins to dock simultaneously and form larger complexes.³⁰ These conjugates may recruit more detection molecules to bind at the site of an analyte that can have a direct effect on the sensitivity of immuno-assays, fluorescent detection, enzyme linked immune-adsorbent assays and western blotting procedures. Functionalization of three-dimensional supramolecular cages via this methodology, having large cavities, with biologically relevant homing devices may lead to better drug delivery devices. Investigation along these lines is currently underway in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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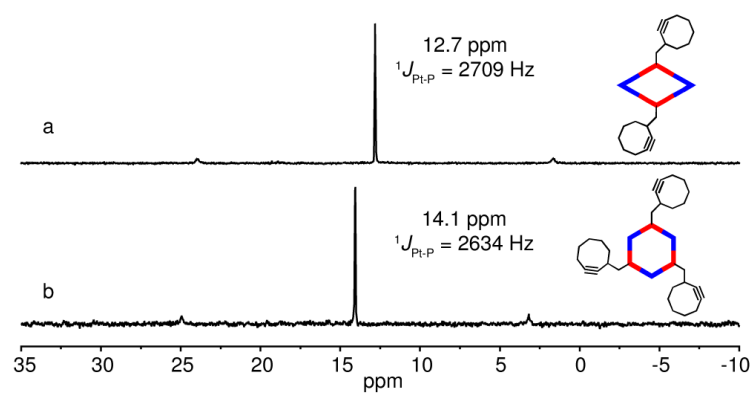


Figure 1.
 $^{31}\text{P}\{^1\text{H}\}$ NMR spectra of a) rhomboid **6** and b) hexagon **7**.

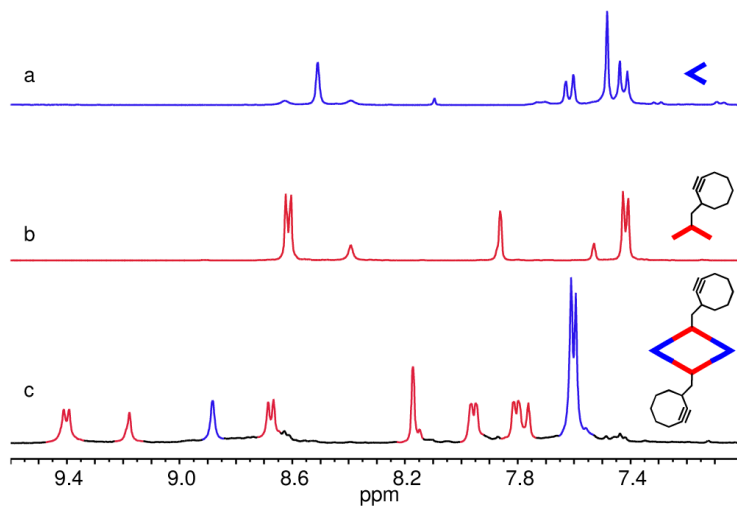


Figure 2. Partial ^1H NMR spectra (in CD_2Cl_2) of a) Pt(II) acceptor **4**, b) cyclooctyne tethered donor **3**, and c) rhomboid **6**.

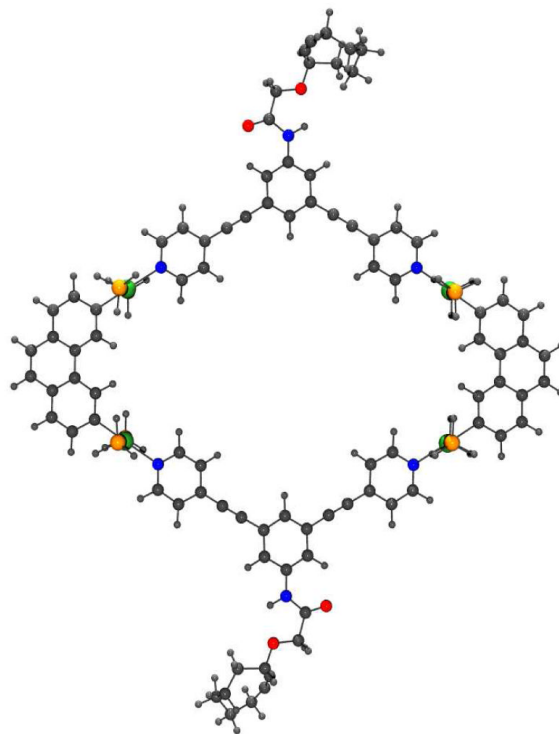
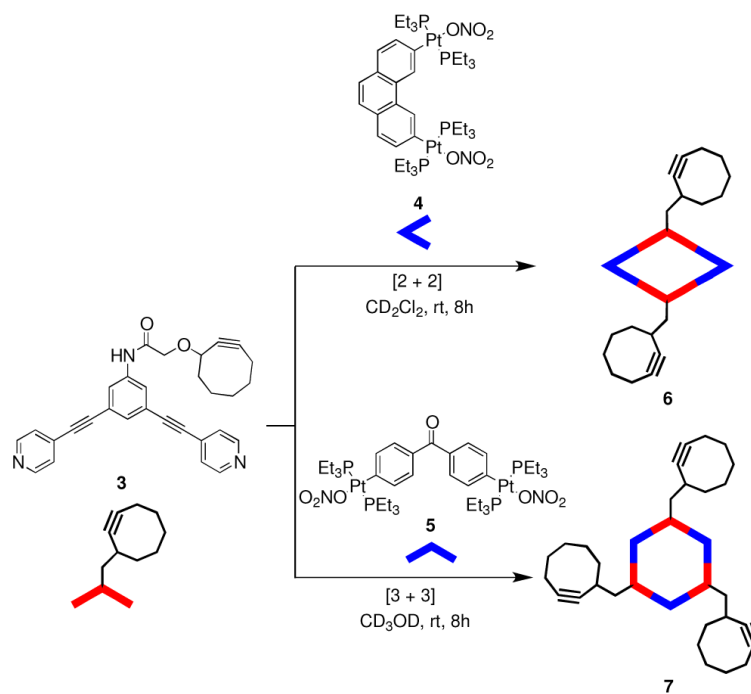
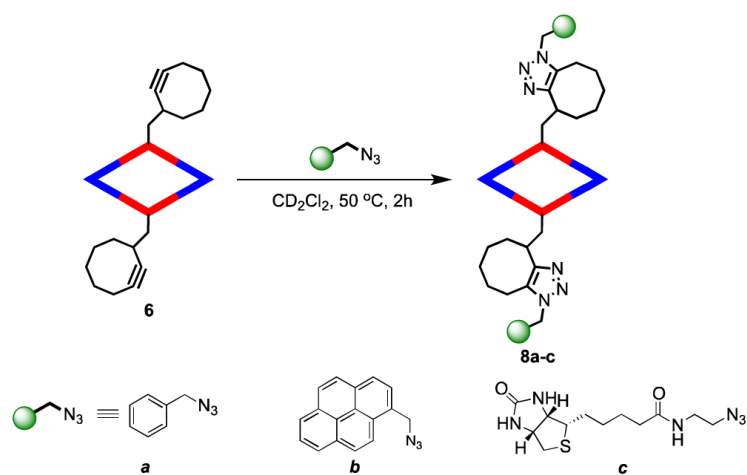


Figure 3. Density Functional Theory (DFT) optimized structure of metallacyclic rhomboid **6**. Color code: gray, C; light gray, H; Blue, N; red, O; orange, P; green, Pt.



Scheme 1.
Self-assembly of Discrete Metallacyclic Rhomboids and Hexagons bearing cyclooctyne functionality.

**Scheme 2.**

Post-assembly modification of discrete metallacyclic rhomboids with different azides via copper-free click chemistry.