Metal and Organic Templates Together Control the Size of Covalent Macrocycles and Cages

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Supporting Information

ABSTRACT: Covalent macrocycles and three-dimensional cages were prepared by the self-assembly of di- or tritopic anilines and 2,6-diformylpyridine subcomponents around palladium(II) templates. The resulting 2,6-bis(imino)pyridyl-PdII motif contains a tridentate ligand, leaving a free coordination site on the PdII centers, which points inward. The binding of ligands to the free coordination sites in these assemblies was found to alter the product stability, and multitopic ligands could be used to control product size. Multitopic ligands also bridged metallomacrocycles to form higher-order supramolecular assemblies, which were characterized via NMR spectroscopy, mass spectrometry, and X-ray crystallography. An efficient method was developed to reduce the imine bonds to secondary amines, leading to fully organic covalent macrocycles and cages that were inaccessible through other means.

INTRODUCTION

Covalent organic macrocycles and cages have found wide application. These structures serve as hosts for guest recognition, in molecular separations, as catalysts, for surface modification and to enable the generation of new mechanically interlocked molecular architectures. The preparation of these species is not trivial, however, as many covalent bonds need to be formed in the correct geometry to enable macrocycles and cage structures to come together. Where bonds are not formed reversibly, the formation of off-pathway kinetic products can limit the yield of a desired species, rendering product isolation challenging. Higher yields and cleaner products may be obtained through the use of templates and reversibly formed linkages such as imines, boronic esters, and alkenes (with appropriate catalysts). The use of such dynamic covalent bonds leads to the formation of thermodynamic products, but such products may show limited stability due to cleavage of the dynamic bonds, such as hydrolysis of imines.

Functional macrocycles and cages can also be prepared using metal–organic self-assembly. Palladium(II) is among the most frequently employed metals for metal–organic assemblies. PdII-based assemblies often incorporate two or four pyridine-based ligands coordinated to each palladium center. These assemblies benefit from the strong propensity of palladium(II) to adopt a square planar coordination geometry, allowing the 90° angles between ligands to translate into structural elements within larger assemblies, from two-dimensional macrocycles to three-dimensional cages. The use of PdII in subcomponent self-assembly, where intricate metal complexes are brought together at the same time as the multitopic ligands that compose them are templated, has provided access to small macrocycles, (pseudo)-rotaxanes, and a catenane. Here we report the use of this technique to generate a new class of macrocycles, as well as cages and larger assemblies. These macrocycles and cages were demetalated and reduced, yielding large, complex organic structures whose preparation would be otherwise difficult to envisage.

RESULTS AND DISCUSSION

Properties of the Bis(imino)pyridyl-PdII Building Block. In order to elucidate the design principles for this class of Pd-templated architectures, we carried out a careful analysis of the crystal structures of complexes bearing a 2,6-bis(imino)pyridyl-PdII moiety. The angle between the aniline residues ranged from 87° to 97° [see Figures 1 and S83 (Supporting Information, SI)]. This motif may thus be used to engender an angle close to 90° but displaying some flexibility. Moreover, the tridentate ligand leaves one free

Figure 1. The 2,6-bis(imino)pyridyl-PdII motif provides a 90° bend within higher-order structures.

Received: June 10, 2019
Published: July 9, 2019
Scheme 1. Synthesis and Crystal Structure of Pd₄[4 + 4] complex 3\(\text{(MeCN)}_4\)

\[
\begin{array}{c}
\text{Pd} \text{(MeCN)}_4(BF_4)_2 \\
\text{HC} \text{C} \\
\text{O} \text{O} \\
\text{N} \text{N} \\
\text{H} \text{N} \\
\end{array}
\]

MeCN, 60°C, 20 h

93%

"Anions and free solvent molecules are not shown for clarity."
addition for the subcomponents in this case. In contrast, the addition of template $T_2$ either before or after the formation of macrocycles $5\cdot(\text{MeCN})_3$ and $6\cdot(\text{MeCN})_4$ resulted in the exclusive formation of $6\cdot T_2$ after heating.

Control experiments elucidated the different behavior of the two templates toward Pd$^{II}$. When $T_1$ or $T_2$ was mixed with [Pd(MeCN)$_4$](BF$_4$)$_2$ (0.75 or 1.0 equiv, respectively) in acetonitrile at 60 °C, no discrete species were observed by $^1$H NMR. Whereas $T_2$ afforded a strongly colored solution, $T_1$ gave a precipitate and colorless solution, suggesting the removal of soluble Pd$^{II}$ species, which are usually colored. We thus infer that the one-step formation of $5\cdot T_1$ is prevented by the initial precipitation of a Pd$^{II}$-$T_1$ adduct. We note that $T_2$ has already been reported to form heteroleptic complexes with Pd$^{II}$ but that $5\cdot T_1$ is the first report of a Pd$^{II}$ complex involving $T_1$ as a ligand.

The $^1$H NMR spectra of $5\cdot T_1$ and $6\cdot T_2$ showed several sets of signals [Figures S9 (SI) and 2], which were attributed to different conformers having distinct orientations of the pyridyl moieties of the templates (i.e., either above or below the plane of the Pd$^{II}$ centers). DOSY analyses revealed the different sets of signals to correspond to species of similar sizes (Figures S14 and S22, SI). The $^1$H NMR spectrum of the major species observed for $5\cdot T_1$ is consistent with $C_s$ symmetry, which is expected from the conformer presenting one inverted pyridyl moiety, i.e., a partial cone; only traces of other conformers are observed.

Two conformers were observed for $6\cdot T_2$ [Figures 2 and S16 (SI)]; a $C_s$-symmetric (partial cone) conformer with a single inverted pyridyl unit and a $C_{2h}$ symmetric (1,2-alternate) conformer with two adjacent pyridyl units inverted. The conformers of $6\cdot T_2$ were observed in a $C_s/C_{2h}$ ratio of ca. 3:2 in CD$_3$CN at 25 °C. EXSY NMR experiments did not show exchange between the conformers, and variable-temperature (VT) $^1$H spectra showed only slight broadening of the peaks at 75 °C (Figure S23, SI), which indicates that conformational
exchange occurs slowly on the NMR chemical shift time scale. We infer the slow conformer exchange to be a consequence of the necessity of breaking a coordinative bond between the template pyridyl and PdII.

PM6 models22,23 of the four possible conformers suggested that the remaining cone and 1,3-alternate conformers25 would lead to high-energy distortion, clarifying why they were not observed (Tables S4–S7, SI). The presence of the pyridyl-based templates increased the stability of complexes 5’T1 and 6’T2 under ESI-MS conditions compared to their acetonitrile-bound counterparts, thus allowing their characterization by mass spectrometry (Figures S15 and S24, SI).

Reduction and Demetalation of PdII-Templated Macrocycles. Large, covalent macrocycles are challenging to produce in high yields, often requiring high-dilution conditions.26 We thus explored the reduction and demetalation of 5’T1 and 6’T2 to produce organic macrocycles of 48 or 64 atoms in circumference. Reducing conditions were screened for non-templated macrocycles 5'(MeCN)3 and 6'(MeCN)4 and showed that the reducing agent BH3·THF in acetonitrile at room temperature gave higher yields of the secondary-amine products than did NaBH4, LiAlH4 or NaH. Three changes to our initial experimental procedure were found to further optimize the yield of the reduced macrocycles. First, the BH3·THF was added in equal portions stepwise (0.25 equiv/imine) every 10 min, instead of all at once. Second, reduction was carried out in the presence of methanol as a cosolvent (MeCN/MeOH, 5:1, v/v) to quench excess BH3 after each addition, to avoid side reactions. Third, a stronger-field monodentate ligand than acetonitrile, such as a pyridine or chloride, served to protect the PdII center from reduction. Employing these optimized conditions were found to minimize the side reactions that produced undesired reduced products, such as palladium black and ring-opened macrocycles.

These optimized conditions on the mixture of 5’Cl4 and 6’Cl4 afforded a mixture of purely organic covalent macrocycles 9 and 10, which proved inseparable by chromatography. However, applying these conditions to 5’T1 and 6’T2 followed by demetalation afforded isolated macrocycles 9 and 10, respectively. Reduced macrocycles 7’T1 and 8’T2 (Scheme 2) could withstand higher cone voltage and temperatures under ESI-MS conditions than the parent imine-based macrocycles 5’T1 and 6’T2. We infer that this greater stability in the absence of imine functionality results from the impossibility of hydrolysis of the reduced macrocycles under ESI-MS conditions. We note that the ESI-MS spectra of 7’T1 and 8’T2 were consistent with a +2 oxidation state for all Pd centers, despite the reducing conditions, as was observed for all metal—organic complexes reported herein (see the SI). Compounds 7’T1 and 8’T2 displayed complex 1H NMR spectra, which we infer to be a result of the large number of stereoisomers originating from the new NH stereocenters coordinated to the PdII cations (see Figures S25, S26, 2B, and S30). Thus, we could not assess product purity at this stage and proceeded with the demetalation of 7’T1 and 8’T2 after their precipitation by addition of Et2O to MeCN solutions.

The demetalated trimeric (9) and tetrameric (10) macrocycles were obtained by treating 7’T1 and 8’T2, respectively, with ethylenediamine (2 equiv/Pd) as a competing ligand (Scheme 2). 1H NMR analysis of the crude products showed the desired species 9 or 10 with the corresponding free templates T1 or T2 and traces of side products (Figures S38 and 2C). Separation of the final products from the templates and side products was achieved by preparative-layer

Figure 2. Top left: PM6 model of 6’T2 partial cone. Right: 1H NMR spectra (500 MHz, 25 °C) of (A) 6’T2 in CD3CN, (B) 8’T2 in CD3CN (vertical scaling ×5), (C) 10 in CDCl3 (crude material after demetalation), and (D) isolated 10 in CDCl3. *Residual solvent peaks.
chromatography to isolate either 9 (40% yield) or 10 (83% yield). The isolated yield of 10 corresponds to a yield of at least 98% per imine reduction from 6T2 to 8T2 if the other steps proceeded quantitatively. The isolated yield of 9 is lower despite the ca. 68% yield by 1H NMR analysis of the crude product (Figure S38, SI) because lengthy purification was necessary to remove traces of impurities with similar polarity and solubility to the desired product 9. The purification process allowed for the clean recovery of the free templates T1 and T2 for future use. When the one-pot syntheses of 9 or 10 starting from 4 were attempted, the final separation proved extremely challenging, lowering the isolated yields. Thus, the precipitation of 7T1 and 8T2 after reduction was a crucial step to remove side products. The final covalent organic macrocycles 9 and 10 were stable over weeks when stored in the solid state but slowly degraded in chlorinated solvents. Despite the fast and efficient reduction of imine bonds reported herein with only limited equivalents of borane (2.0–2.5 equiv of BH3/imine), only rare examples of imine reduction with this inexpensive and easy-to-handle reducing agent have been reported.27

**Higher-Order Supramolecular Assembly of Macrocycles.** When 1, 4, and PdII reacted in the presence of naphthalene diimide (NDI)-based template T3, a triply bridged dimer of trimeric macrocycles $5_2T3_3$ was observed to form (Scheme 3). When less T3 was employed, free 5(CD$_3$CN)$_3$ and $5_2T3_3$ were observed as the principal products (see 1H NMR spectra in Figure S53, SI). This observation suggests the presence of positive cooperativity in the binding of T3 by 5.28 Crystals of $5_2T3_3$ were grown by slow diffusion of benzene into an MeCN solution in the presence of KsBF$_6$ (10 equiv/Pd). The single-crystal X-ray structure (Scheme 3) shows that the macrocycles adopt a cone conformation, similar to the crystal structure of 5(MeCN)$_3$17 with the concave face pointing outward. The three bridging T3 ligands twist around the central C$_3$ axis, lending helicity to the complex in the solid state. Both right-handed and left-handed helices were present in the crystal, related by inversion symmetry. The three NDI units enclose a tubular 98 Å³ cavity that contains a BF$_4^-$ anion despite crystallization in the presence of excess SbF$_6^-$.29 The angles between phenylene rings around PdII centers are in the range $\alpha = 85°$–91°, which shows that the bis(imino)pyridyl-PdII moiety again adopts an angle close to 90°. The 1H NMR spectrum of $5_2T3_3$ in CD$_3$CN at 25 °C corresponds to a $D_3h$ structure, which does not reflect the helicity observed in the solid state. VT NMR (Figure S51, SI) showed desymmetrization at $\sim 40$ °C, with a 1H NMR spectrum corresponding to the $D_3$-symmetric species observed in the solid state. Conversion between enantiomers thus occurred in solution with an activation barrier $\Delta G^\ddagger = 52 \pm 2$ kJ mol$^{-1}$ at 0 °C (Figure S51, SI). VT 19F NMR showed that the inclusion and release of BF$_4^-$ is rapid on the chemical shift time scale at 25 °C but slow at $\sim 40$ °C, as indicated by the appearance of a peak for the included BF$_4^-$ at low temperature (Figure S52, SI).

**Three-Dimensional Covalent Cages.** Considering the bis(imino)pyridyl-PdII motif as a 90° 2-fold connector, a corresponding 3-fold connector with $\sim 117°$ angles30 could generate two distinct three-dimensional high-symmetry cages: a Pd$_4$ structure with $T_d$ symmetry and a larger Pd$_{12}$ architecture with $O_h$ symmetry (Figure 3).27

Considering that the ideal angle$^{30}$ of 117° is close to the 120° of planar tris-anilines, we tested four planar tris-anilines and a pyramidal one [Figures 4 and S73 (SI)]. The more rigid tris-anilines gave only traces of discrete species along with oligomeric products, as suggested by the presence of small sharp 1H NMR signals along with more intense broad signals (Figure S73, SI). This result is not surprising, as a fully planar tris-aniline, with an angle $\beta$ of 120°, would require an angle $\alpha$ of either 71° or 109° to form the small or large cage structures proposed in Figure 3, respectively.30 Such $\alpha$ values are outside the range of angles adopted by the bis(imino)pyridyl-PdII building block studied herein.

The product mixture formed from the more flexible tris(4-aminophenyl)amine 11 had two sets of sharp peaks in the 1H NMR spectrum, suggesting that the nitrogen atom in the ligand core can rehybridize in order to adopt the geometry required to form stable cages (Figure 4). DOSY analysis indicated that the two sets of peaks correspond to structures having different sizes (Figure S61, SI). As with their smaller...
congeners, the products having MeCN bound to the internally facing PdII coordination site were unstable under ESI-MS conditions. Replacement of MeCN with chloride increased the stability, which allowed successful analysis by ESI-MS (Figure S62, SI).

We initially expected these products to correspond to the Pd6 and Pd12 cages shown in Figure 3. The 1H NMR and ESI-MS analyses indicated that the major species corresponded to the expected highly symmetrical (Td) Pd6 cage 12, but the minor species corresponded instead to an intermediate Pd9 cage 13 with D3h symmetry (Figure 4), having two sets of 1H NMR peaks in a 2:1 ratio.

Crystals of 12·Cl6 were grown from the mixture of 12·Cl6 and 13·Cl6 by slow diffusion of benzene into an MeCN solution in the presence of KAsF6 (10 equiv/Pd) (Figure 4). The single-crystal X-ray data were of lower quality than for the other complexes reported herein, which we attributed partly to disorder around the phenylene rings. The three phenylene rings around each central nitrogen adopt a propeller shape with disorder observed between the right-handed and left-handed propellers. This propeller geometry has been observed for other self-assembled cages incorporating tris-anilines 11.32 The X-ray data did not allow us to differentiate whether the crystal of 12·Cl6 contained pure enantiomers (i.e., entirely right-handed and left-handed cages) randomly scattered or if each cage within the crystal contained a random mixture of right- and left-handed propellers. For clarity, the crystal structure in Figure 4 is shown with only right-handed propeller units. The 1H NMR spectra of cages 12 and 13 in acetonitrile at 25 °C (400 and 500 MHz) were consistent with fast rotation of the phenylene moieties on the NMR chemical shift time scale in solution.

The framework of 12 can be viewed as a truncated tetrahedron bearing four trigonal aromatic panels and four empty panels, with PdII centers describing the vertices of an octahedron. These features recall the Pd12(tris(4-pyridyl)-1,3,5-triazine)4 coordination cages first reported by Fujita et al. in 1995 and intensively studied since then.33 In comparison, 12·Cl6 shows shorter Pd–Pd distances than the purely coordination cage studied by Fujita (15.0–16.0 Å between antipodal Pd centers and 10.9–11.5 Å for adjacent pairs of Pd ions in 12·Cl6 vs 18.1–18.8 and 12.7–13.4 Å for Pd4(tris(4-pyridyl)-1,3,5-triazine)4 with various bidentate peripheral ligands33). In addition to the smaller size of 12, it differs from the Fujita cage in having a covalent framework, trans-coordinated imines around each PdII, and an extra single binding site per PdII center, all oriented toward the central cavity of 12. The angles between phenylene rings around PdII centers are in the range α = 90°–95°, in common with the other structures that incorporate this motif. We could not obtain single crystals of the larger 13·Cl6 cage, but a PM3 model minimized to a structure having α = 89°–95° (Figure 4, and Table S8 (SI)).23

In addition to chloride, the anions bromide, iodide, and thiocyanate were also tested as prospective inner ligands. Solutions of 12·(MeCN)6 and 13·(MeCN)6 were treated with these anions as nBu4N+ salts (Figure S72, SI). Bromide provided 12·Br6 and 13·Br6, which had sharp 1H NMR spectra at similar chemical shifts to 12·Cl6 and 13·Cl6, but the bromide adducts were not stable enough for ESI-MS analyses. Both the chloride and bromide adducts of 12 and 13 remained stable in solution in MeCN over weeks at 25 °C and overnight at 60 °C; heating for longer was not tested. In contrast, iodide and thiocyanate led to broadened 1H NMR signals and precipitation over a period of hours. We infer that the larger sizes of these two anions may lead to steric clashes with the proximate phenyl groups, thus destabilizing the structures.

We were not able to separate cages 12 and 13 using a size-exclusion column due to their poor solubility in the solvents used as eluents. The mixture of 12·(MeCN)6 and 13·(MeCN)6 with BF4− as counteranions could be isolated in the solid state and subsequently dissolved in MeCN, but the mixture of 12·Cl6 and 13·Cl6 did not redissolve after drying. This lack of solubility was surprising considering that the complexes were not observed to precipitate from MeCN over 1 month at 25 °C, suggesting slow kinetics of dissolution for the dry material rather than low solubility. We therefore replaced the BF4− counteranions with bulkier NTf2− to accelerate dissolution. Intriguingly, the triflimide salt of 12·Cl6 dissolved more rapidly than 13·Cl6, which allowed sample enrichment through multiple washes with fresh MeCN (see Figure 4C,D and Supporting Information, section 1.11). Although 12·(MeCN)6 and 13·(MeCN)6 exhibited dynamic imine exchange (see below), no conversion was observed between 12·Cl6 and 13·Cl6 at 25 °C in MeCN over 1 month.

We then investigated the effects of multivalent templates coordinating to the inward-facing PdII sites of these three-dimensional cage structures. Mixtures of 12·(MeCN)6 and 13·(MeCN)6 were treated with T1 and T2 to see if they would selectively template Pd6 cage 12, Pd9 cage 13, or the larger Pd12 cage of Figure 3, which contain faces consisting of trimeric and tetrameric macrocycles. Numerous attempts using different amounts of template did not induce selectivity, leading instead to highly complex NMR and ESI-MS spectra (see Table S1, SI). As the 5′T1 and 6′T2 macrocycles described above adopted non-cone conformers, we infer that the analogous macrocyclic subunits of the structures formed from 11 with templates T1 and T2 would also form non-cone conformers, which are not configured for cage formation.

We then tested the ability of NDI-based bis(pyridine) T3 to selectively template cage 13·T3 (Scheme 4), because cage 13...
contains a pair of Pd₃ rings that are held in a similar configuration as in the bridged macrocycles of 5·T₃₃. Our initial attempts at mixing 1, 11, [Pd(MeCN)₄]BF₄₂ and T₃ in a 9:6:6:3 ratio were unsuccessful (see Table S1), but addition of nBu₄N⁺Cl⁻ (0.33 equiv/Pd) provided 13·T₃₃·Cl₃ in ca. 10% yield according to NMR and ESI-MS analyses [Scheme 4 and Figures S64 and S65 (SI)]. PM3 models of 13·T₃₃·Cl₃ and 13·T₃₃·Cl⁻ suggested that the internal MeCN ligands in the former would clash with the three central T₃, whereas chloride in the latter complex would not [Scheme 4 and Table S9 (SI)]. We infer that this lack of clash in 13·T₃₃·Cl₃ underpins the importance of chloride for the formation of this cage.

The ¹H NMR spectrum of crude 13·T₃₃·Cl₃ clearly shows the 17 signals expected for the D₃h-symmetric product, along with a set of broad signals that could correspond to oligomeric byproducts. Comparison between the integrals of the 13·T₃₃·Cl₃ product and nBu₄N⁺ signals was used to gauge the yield, which was never observed to increase beyond 11%. Different attempted optimizations included running the reaction at 150 °C in a microwave reactor and changing the order of addition of the starting materials (Table S1, SI). Isolation of 13·Cl₃ from the putative oligomer coproducts by size-exclusion column was prevented by the lack of product solubility in the solvents used as eluents. The templated formation of a single discrete species nonetheless shows the potential for templation involving the bis(imino)pyridyl-Pd⁻⁻ building block.
for the construction of covalent metalallocages. Careful optimization of template geometry may enable the yields of specific cage products to be further improved.

The mixture of 12-Cl₆ and 13-Cl₉ was subjected to the optimized imine reduction conditions used for macrocycles 5-T₁ and 6-T₂ (Figures S66–S68, SI). ESI-MS monitoring of the reaction showed effective reduction of all imine bonds, but NMR spectra of the crude product were indecipherable, as expected considering the numerous stereoisomers originating from the NH stereocenters of the reduced cages, as was observed in the cases of 7-T₁ and 8-T₂. Treatment with ethylenediamine in DMSO led to species with broad ¹H NMR signals in the anticipated chemical shift regions for the demetalated and reduced cages (Figure S68, SI). We infer the broadness to be a consequence of slow interconversion between different hydrogen-bonded conformers. Precipitation of the demetalated cages by adding water afforded a solid that only dissolved in highly acidic aqueous solutions [i.e. > 4 M HCl(aq)]. Degradation appeared to accompany dissolution, as no trace of the product was observed by ¹H NMR in DCl/D₂O. The product was also suspended in 17 organic solvents, including chlorinated, aromatic, aliphatic, polar, apolar, protic, and aprotic solvents, with no evidence of dissolution (see Supporting Information, section 1.13). This lack of solubility prevented further characterization, purity, and yield determination. Building blocks that incorporate solubilizing moieties may allow for soluble covalent organic cages to be prepared.

Aniline Exchange. Dynamic covalent imines can exchange aniline residues with free anilines.³⁵ The side of the equilibrium favored depends upon the stoichiometry and relative nucleophilicities of the anilines. Aniline exchange was previously used to modify the periphery of self-assembled structures³⁶ but, to the best of our knowledge, has not yet been applied to the construction of assemblies whose cores consist of multitopic aniline residues displacing monoanilines, as reported herein. For the previously reported peripheral modifications, excess aniline could be added to ensure complete exchange. In the present case, however, such an excess would be impractical as it would result in a mixture of...
products that incorporated multiotopic anilines that had not fully reacted.

We thus screened several electron-poor monoanilines 14a–14g (Figure S5) for the formation of the corresponding bis(imino)pyridyl-PdII complexes 15a–15f. We then evaluated the efficiency of the displacement of these different electron-poor aniline residues by the more electron-rich bis-aniline 2 to form macrocycle 3. Aniline 14e (Figure S5) was observed to give the best result; full details are provided in Figures S74–S77 and the accompanying text (SI).

The electron densities of the monoanilines were assessed on the basis of the Hammett σ parameters of their substituents.34 Monoanilines 14a–14f formed the corresponding bis(imino)pyridyl-PdII complexes 15a–15f cleanly, as gauged by 1H NMR (Figure S74, SI). The most electron-deficient aniline, 14g, failed to generate the imine complex, however.

The displacement of the aniline residues 14a–14f by benzidine 2 occurred in better yield as the electron-deficiency of the leaving aniline increased (Figure S77, SI). The monoanilines that yielded macrocycle 3 the most efficiently were thus 3,5-dichloroaniline 14e and 4-nitroaniline 14f, which possess a similar degree of electron-deficiency according to their Hammett σ parameters (σ14e = 0.74 vs σ14f = 0.78).

The corresponding mononuclear complexes 15e and 15f were treated with tris-aniline 11 to evaluate the formation of cages 12 and 13 through aniline exchange. Both reactions afforded the desired cages (Figures S78 and S79, SI), but 15f also led to an extra set of unidentified 1H NMR peaks. Aniline 14e was therefore selected as the best aniline leaving group for aniline exchange. Templated cage 13-T3,Cl3 was also successfully prepared through aniline exchange, albeit in low yield, similarly to the direct synthesis (Figure S80, SI).

## CONCLUSIONS

The bis(imino)pyridyl-PdII motif thus serves as a 90° building block to generate a wide variety of dynamic covalent metal-containing macrocycles and cages. This motif provides some flexibility, adopting angles that range from 85° to 97°. The free coordination site on the PdII center oriented to the inside of the assemblies allows the stability and shape of the covalent assemblies to be tuned, as well as permitting covalent assemblies to be bridged by multiotopic ligands in order to form more complex supramolecular assemblies. Efficient imine reduction conditions were developed to afford covalent organic macrocycles in good yields from these multi-imino PdII complexes. Future work will focus upon the extension of these methods to generate larger structures and the use of other metal cations with similar tridentate building blocks,37 which could lead to different angles and more free coordination sites. The imine-containing macrocycles and cages reported herein could also be good candidates to undergo oxidation to amides, as recently reported by Mastalerz et al. in the context of another imine-based covalent cage.38 Furthermore, we will explore the potential of the new reduced and demetalated macrocycles and cages for guest recognition, including anionic guests via hydrogen bonding and metal cations via coordination to the tridentate sites.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b06182.

Experimental section, NMR spectra, mass spectra, geometry-optimized models, and crystallographic details (PDF)

- Single-crystal XRD structures of 3[MeCN]4 (CCDC 1903235) (CIF)
- Single-crystal XRD structures of 5,7-T3 (CCDC 1903237) (CIF)
- Single-crystal XRD structures of 12-Cl6 (CCDC 1903236) (CIF)

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Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

This study was supported by the European Research Council (695009) and the UK Engineering and Physical Sciences Research Council (EPSRC, EP/P027067/1). R.L. was funded by the Fondation Wiener-Anspach postdoctoral fellowship. We thank Diamond Light Source for time on Beamline I19 (MT15768). We thank the National Mass Spectrometry Facility at the University of Swansea for high-resolution mass spectrometry analyses of 7-T1, 8-T2, 9, and 10.

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