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The Assembly of Macrocyclic Bis- and Tetra-β-lactams with Embedded Platinum or Palladium Square-Planar Centers

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Abstract: The synthesis, isolation, and full characterization of different types of stable, metal-assembled macrocyclic β-lactams are reported. By using adequately functionalized bis-β-lactams with defined stereochemistry as building blocks, a series of mono- and bimetallic Pd and Pt macrocycles has been prepared in good to quantitative yields. These novel structures combine the β-lactam moiety with transition-metal fragments with *cis*-square-planar geometry and constitute a new class of metal-assembled cavities involving molecules with biological relevance as building blocks. By combining the adequate ligands, metallic fragments, and tuning the reaction conditions, different mono- and bimetallic macrocyclic β-lactam cavities can be selectively obtained. Macrocycles with Pt–ethynyl groups are suitable to form host–silver triflate guest complexes in a tweezer fashion.

Keywords: lactams · heterometallic complexes · metallomacrocycles · platinum

Introduction

Methodologies and structural requirements to build di- and tetranuclear metallomacrocycles are well established. However, the repertoire of the building blocks used to prepare these compounds is rather limited.[1] Geometry and length are in fact the main requirements for the choice of the bridging ligands, with little attention given to the benefits that the incorporation of functionalized or flexible ligands could ascribe to the properties or applications of the final macrocycles.[1,2] Thus, the majority of the reported metallomacrocycles are based on bipyridines (**1**, **2**), conjugated diynyl- and polynyl chains (**3**), or combinations of both, with slight variations in the structure of the M–L ligands in the metal corners (Scheme 1).[3] Consequently, there are comparatively few reports on molecules of biological relevance as building blocks in the construction of metal-assembled cavities. Adenine derivatives with cationic $\{Cp^*M^{III}\}$ ($Cp^* = C_5Me_5$; M = Ru, Rh, Ir) **4**[4,5] or $\{PtMe_3\}$ **5**[6] as corners are the most studied compounds in this family. These cationic metallomacrocycles are trimeric structures in which the presence of the adenine fragments improves their properties as hosts and sensors for neutral molecules, cations, and anions.[1f,4,5]

Similar metallocyclic trimers **6** were obtained by using deprotonated amino acids as linkers, acting both as N,O-chelating and as carboxylate bridging ligands (Scheme 2).[7] More recently, the preparation of different metallomacrocycles based on non-natural amino acids and modified peptides has been reported.[8,9]

The pivotal role of β-lactam antibiotics in the treatment of bacterial diseases, together with the apparition of antibiotic-resistant bacteria[10] justify the tireless efforts devoted to the preparation of new 2-azetidinone-derived compounds and the study of their antibiotic properties.[11] Examples of the synthesis of β-lactam derivatives that bear an organometallic complex are scarce,[12] and among them, metallocene-derived 2-azetidinones are possibly the most abundant group.[13] We have recently reported the synthesis of new

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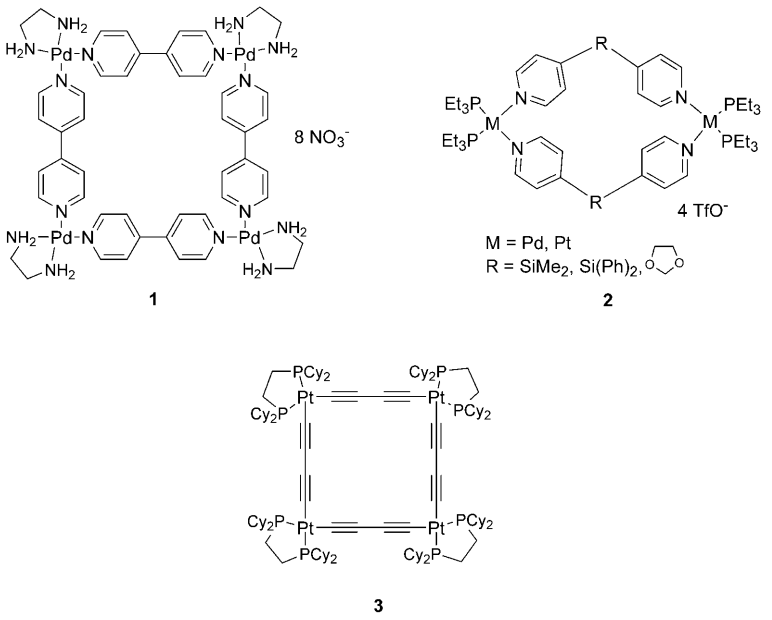


Scheme 1. Some examples of metallomacrocycles. Cy = cyclohexyl.

types of 2-azetidinone-derived compounds, either embedding the β-lactam rings in a macrocyclic structure[14] or with metallocene nuclei attached to the 2-azetidinone ring.[13a,b] In this context, the macrocyclic β-lactams that incorporate M–L (M = Pd, Pt) bonds within the macrocycle framework are yet unknown.[15] Furthermore, the synthesis of macrocyclic metallo-β-lactams by metal assembling has not been reported in the literature, and the combination in a macrocyclic structure of the rigid 2-azetidinone rings with one or two ligand-tunable metal centers with *cis*-square-planar geometry, makes this approach a respectable synthetic challenge.[14,16] Herein, we report the development of methodology for the straightforward assembly of a series of diastereomerically pure novel macrocyclic Pd- and Pt-bis- and -tetra-β-lactams, as well as the modification of the selectivity of the Pt assembling processes by tuning the reaction conditions.

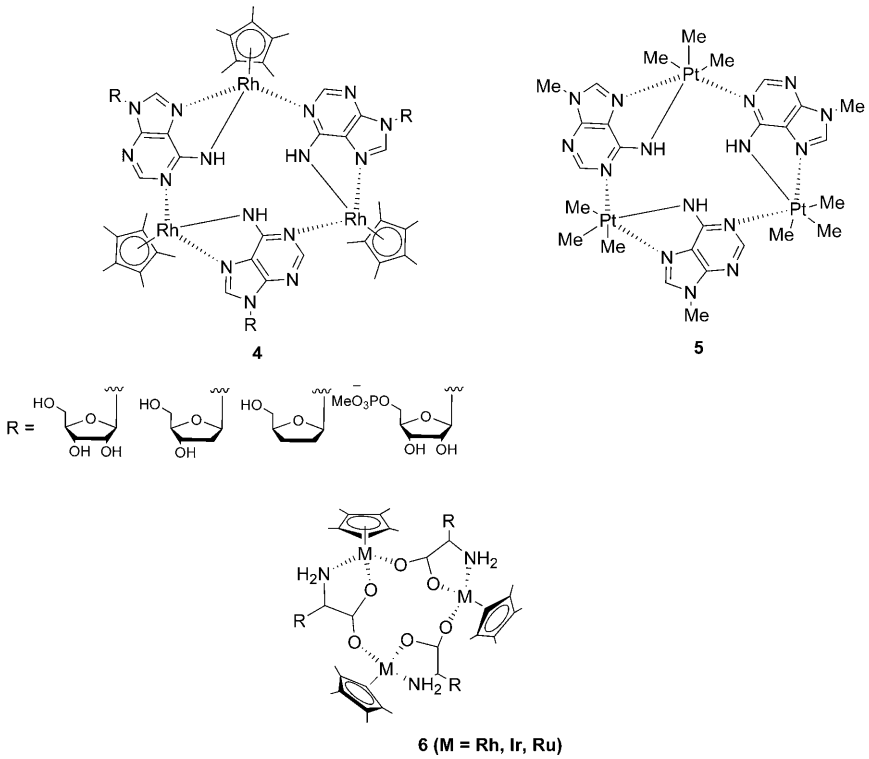
Abstract in Spanish: *El trabajo describe la síntesis, aislamiento y caracterización completa de una serie de Pd y Pt-metalo-β-lactamas. Estos compuestos se obtienen con excelente rendimiento a partir de bis-β-lactamas adecuadamente funcionalizadas y con estereoquímica definida, y los correspondientes complejos de Pd y Pt. Las bis y tetra-metalo-β-lactamas obtenidas constituyen un nuevo tipo de cavidades macrocíclicas, que combinan en su estructura los fragmentos β-lactámicos con complejos metálicos de geometría cis-plano cuadrada. Combinando adecuadamente los ligandos precursores (bis-β-lactama y complejo metálico) y las condiciones de reacción, es posible controlar de forma totalmente selectiva, el tamaño del macrociclo obtenido y preparar bis y tetra-β-lactamas mono o bimetálicas. La presencia de fragmentos Pt-etinilo en la estructura permite a las compuestos macrocíclicos obtenidos la formación de complejos pinzados con sales de plata.*

Results and Discussion

The synthesis of the bis-β-lactam building blocks that will be used as scaffolds for the macrocyclic structures is depicted in Scheme 3. Diimine **8** was prepared from aldehyde **7**[17] in quantitative yield and then reacted with phenoxyacetyl chloride and NEt_3 by standard Staudinger conditions[18] to form a 1:1 mixture of diastereomeric bis-β-lactams **9** and **10** in 75% yield. The isomers were separated by SiO_2 chromatography and treated independently with tetra-*n*-butylammonium fluoride (TBAF) to remove the TMS groups, affording pure ligands **11** and **12** in nearly quantitative yields. In both cases, the *cis*-stereochemistry of the β-lactam rings was confirmed by the coupling constants of H3–H4 and H3′–H4' protons ($J_{3,4}$ = 4.4 Hz for compounds **11** and **12**).[19] Additionally, bis-pyridine ligands **13** and **14** were prepared by Sonogashira[20] coupling from bis-ethynyl ligands **11** and **12** and 4-iodopyridine ([Pd(PPh_3)$_4$]/NEt_3/CuI/THF) in 82% and 76% yields, respectively (Scheme 3).

The *cis–anti*-stereochemistry of bis-β-lactam **11** was unequivocally assigned by X-ray diffraction as described below. Thus, by reaction of **11** and $AlCl_2H$,[14a] azetidine **15** was prepared in 95% yield (Scheme 4). A single crystal of the azetidine/$ZnCl_2$ complex **16** (prepared by reaction of **15** with $ZnCl_2$ in MeOH, followed by slow crystallization from MeOH/MeCN), was submitted to X-ray diffraction analysis, which unambiguously established the *cis–anti* arrangement of the β-lactam rings in the complex (Figure 1). Therefore, the *cis–anti* stereochemistry of bis-β-lactam **11**, and by comparison, the stereochemistry of **12** as well as that of the pyridine derivatives **13** and **14**, could be unequivocally assigned.

The preparation of Pd^{II}- and Pt^{II}-cornered complexes based on bis-pyridine dative donor groups was approached first. A chelating phosphine (diphenylphosphanylethane (dppe)) was used to enforce the required *cis* geometry at the Pd and Pt atoms of the final products. Thus, the reaction of equimolar amounts of *cis*-[Pd(dppe)(OTf)$_2$][21] (Tf = triflate) and either *anti*- or *syn*-bis-pyridine ligands **13** and **14**, in $CHCl_3$ at room temperature, afforded the complexes **17** and **18** in nearly quantitative yields as pale-yellow, air-stable solids (Scheme 5). The macrocyclic mononuclear structure of these triflate complexes was established by analytical and spectroscopic data (see the Experimental Section). The pres-



Scheme 2. Examples of bio-organometallic metallomacrocycles.

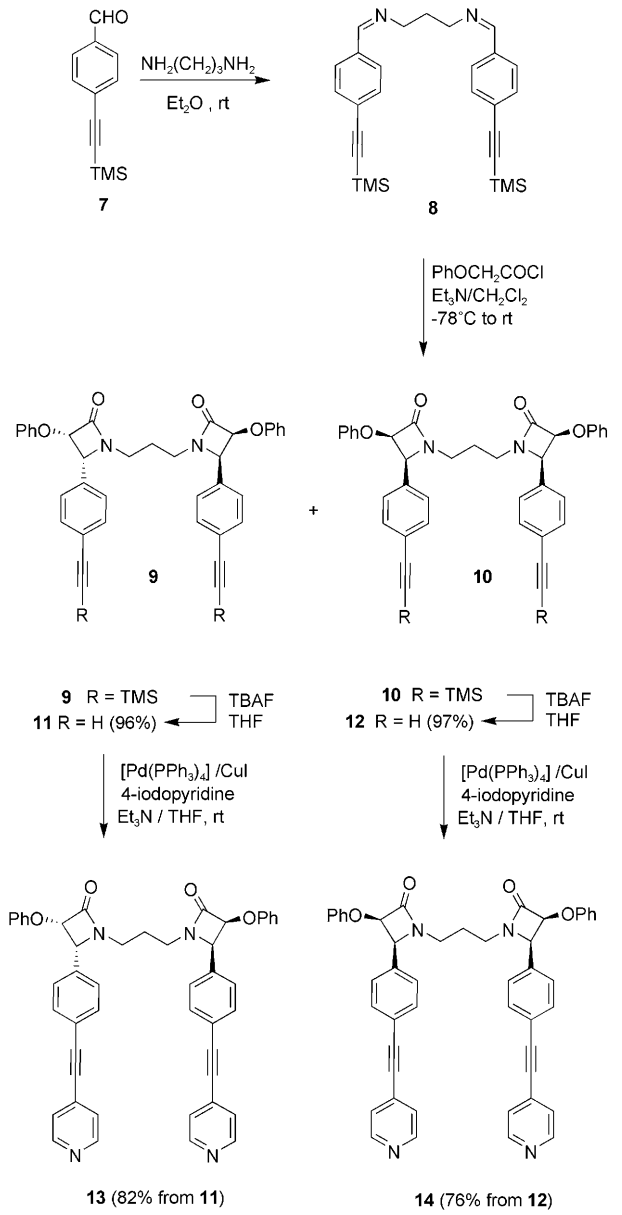
ence of the triflate counterion in all cases was indicated by the ^{19}F signal located at around $\delta = -78$ ppm, which is highly characteristic of ionic triflates.[3b] The ^{31}P spectra showed sharp singlets and, as expected, the ^{31}P signals for **17** ($\delta = 66.8$ ppm) and **18** ($\delta = 64.3$ ppm) are shielded $\delta = 5.3$ and 7.8 ppm, respectively, relative to the precursor metal triflate.[21] The ^{1}H and ^{13}C NMR spectra were particularly diagnostic for the macrocyclic mononuclear complexes **17** and **18**, respectively, in which the methylene signals of the chelating dppe unit are deshielded, as expected for the cationic species relative to the neutral *cis*-[Pd(dppe)(OTf)$_2$] precursor. Finally, the structural formulation of the proposed macrocycles **17** and **18** was firmly elucidated by ESI mass spectrometry.[22] The ESI-MS spectrum of **17** obtained from an acetone/CH_3CN solution resolved the peak centered at m/z 612.1 with an m/z peak spacing of 1/2, which corresponds to the $[M-2OTf]^{2+}$ charge state ion (Figure 2). In the case of **18**, the ESI-MS spectrum showed peaks at m/z 1523.8 $[M+H]^+$ and 1373.8 $[M-OTf]^+$. In both cases, the observed molecular isotope patterns are in excellent agreement with the theoretical pattern.[23]

The synthesis of the parent Pt macrocycles was attempted next under the same conditions (Scheme 5). The reaction of *cis*-[Pt(dppe)(OTf)$_2$][21] and *anti*-bis-pyridine ligand **13** yielded the expected mononuclear complex **19** as the main product.[24] However, the isomeric *syn*-bis-pyridine ligand **14** afforded a 1:1 mixture of Pt complex **20** and oligomeric material under the same reaction conditions (determined by the ^{31}P and ^{1}H NMR spectra of the crude reaction). The different behavior of *anti*- and *syn*-bis-pyridine ligands **13** and **14** towards *cis*-[Pt(dppe)(OTf)$_2$] could be explained by the combination of two factors, namely, the different topology of both isomers and the strength of the Pt–pyridine bonds. Thus, the kinetically inert nature of Pt^{II}–pyridine coordination bonds at room temperature generally favors the rapid formation of oligomers over the assembly of the macrocycle.[1d] The presence of the electron-donor phosphine ligands has proved to increase the lability of the Pt–N bonds, but even so, in our case, when starting from *syn*-ligand **14**, the formation of oligomeric material as a by-product could not be avoided.

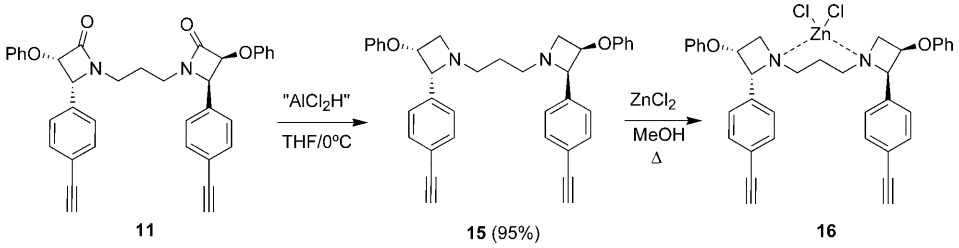
It is known that kinetically controlled processes frequently lead irreversibly to the kinetic and statistic distribution of products, including a collection of linear/cyclic oligomers and polymers of different chain length, which results inevitably in poor yields of the desired macrocyclic structures. In sharp contrast, reversible reactions can avoid these undesired effects that are introduced in kinetically controlled processes. This is clearly the case with Pd^{II}–pyridine macrocyclic structures **17** and **18**, as the Pd–pyridine bonds are much weaker than their Pt counterparts and kinetically labile at room temperature.[1d,25] The term dynamic covalent chemistry (DCC) is used to describe those reversible reactions conducted under equilibrium conditions that allow the preparation of the macrocyclic target molecule, overcoming the formation of undesired by-products.[26]

In an attempt to increase the lability of Pt^{II}–pyridine bonds and to shift the process to the quantitative assembly of the macrocycle, a solution of the crude 1:1 mixture of Pt complex **20** and oligomeric material was heated in acetone at 100 °C, in a sealed tube for a week.[3a,b,27] The ^{1}H NMR spectroscopic analysis, however, revealed that there was no improvement in the amount of macrocycle **20** present in the reaction mixture after the experiment.

Pt-cornered macrocyclic β-lactams incorporating ethynyl groups were prepared next, and the reaction turned out to be extremely dependent on the coupling reaction conditions that were employed. Direct coupling of *anti* bis-alkynyl ligand **11** with *cis*-[Pt(dppe)(OTf)$_2$] only resulted in rapid polymerization of the starting material. However, when the reaction was carried out in the presence of a weak base such as sodium acetate,[28] a single product **21** was obtained. The ^{31}P NMR spectrum of the crude reaction product showed a sharp signal at $\delta = 42.6$ ppm ($J_{P,Pt} = 2367$ Hz), which is consis-



Scheme 3. The synthesis of ligands **11**–**14**.



Scheme 4. The preparation of azetidine **15**.

tent with the presence of a single *cis*-phosphine center. The absence of any other signal in the spectrum confirmed that no Pt-containing oligomers were formed in the reaction. Compound **21** was air stable, and was isolated by chromatography on silica gel in 65% yield (Scheme 6). The structure of **21** was established by spectroscopic and analytical data. The IR spectrum contained a single ν(C≡C) absorption at 2110 cm^{-1} and the ^{13}C NMR spectrum showed signals that could be assigned to the two carbons of the alkynyl moiety at $\delta = 129.9$ ppm ($C_{\alpha-Pt}$, m) and $\delta = 113.0$ ppm ($C_{\beta-Pt}$ d, $J_{PC} = 33.9$ Hz) together with a signal at $\delta = 28.6$ ppm (CH_2, d, $J = 154.6$ Hz) appropriate for a single phosphine ligand. Final confirmation of the structure of *mono*-assembled *cis*-Pt(dppe)-bis-β-lactam **21** was obtained by fast-atom-bombardment mass spectrometric analysis (FABMS) that showed a $[M+H]^+$ peak at m/z 1158.5, with the expected Pt isotopic distribution pattern (Figure 3).[23] Similar results were obtained starting from the isomeric *syn*-bis-alkynyl-β-lactam **12**. Thus, *mono*-assembled *cis*-Pt(dppe)-bis-β-lactam **22** was obtained as the sole reaction product (61% isolated yield) by reaction of **12** with *cis*-[Pt(dppe)$(OTf)_2$] and sodium acetate. Macrocyclic Pt-bis-β-lactams **21** and **22** are diastereomerically pure metallic cavities.

When bis-β-lactam **11** was allowed to react with *cis*-[Pt(dppe)Cl_2][29] and NEt_3 in the presence of catalytic amounts of CuI (10%), a new product **23** was formed. The absence of *cis*-Pt(dppe)-bis-β-lactam **21** as a by-product was confirmed by the ^{31}P NMR spectrum of the crude reaction product. The reaction product was isolated by chromatography on silica gel (68% yield) and identified as an inseparable 1:1 mixture of the diastereomeric *syn*/*anti*-bimetallic tetra-β-lactams **23a**,**b** by NMR spectroscopy and FABMS (Scheme 7). Thus, the ^{31}P NMR spectrum showed two sharp signals at $\delta = 42.4$ and 42.3 ppm ($J_{P,Pt} = 2288$ Hz) and the ^{13}C NMR spectra contained signals assignable to the carbons of the alkynyl moiety at $\delta = 129.9$–129.7 ($C_{\alpha-Pt}$, m) and 111.6-111.1 ppm ($C_{\beta-Pt}$, m), together with a signal at $\delta = 30.5$–27.8 ppm (CH_2, m), which corresponds to the phosphine ligands. Final confirmation of the structures of bimetallic tetra-β-lactams **23a**,**b** came from the FABMS analysis, which showed the $[M+H]^+$ peak at m/z 2315.7, which was expected for the proposed structures.[23] In a similar way, bimetallic *cis*-Pt(dppe)-tetra-β-lactams **24a**,**b** (1:1 *syn*/*anti* diastereomeric mixture) were formed from **12** and *cis*-[Pt(dppe)Cl_2] under analogous Sonogashira-coupling conditions. Macrocycles **24a**,**b** were obtained in lower yields (23%) and accompanied by polymeric material (Scheme 8).

The total selectivity observed in the assembling of mono- and bimetallic macrocyclic β-lactams **21**–**24** is appealing. What is typical in the coordination-metal assembling processes is that the size of the macrocycle formed in preference is predetermined by the angles and symmetry of the starting building blocks.[30] However, in our case, it should be noted that starting from the same precursors, with de-

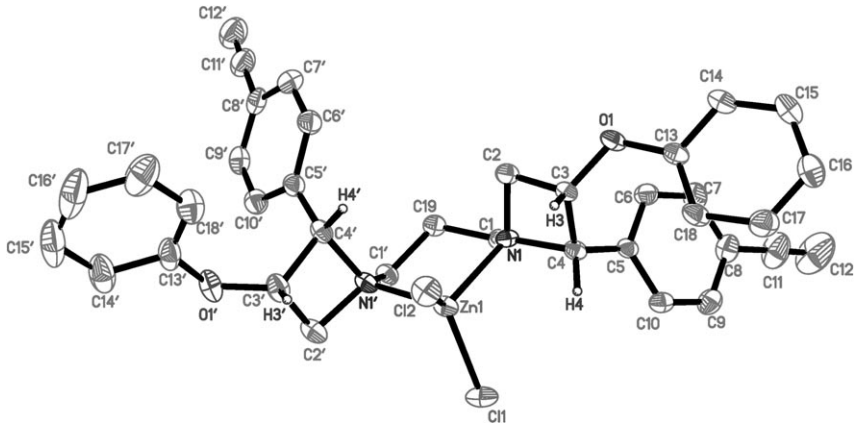
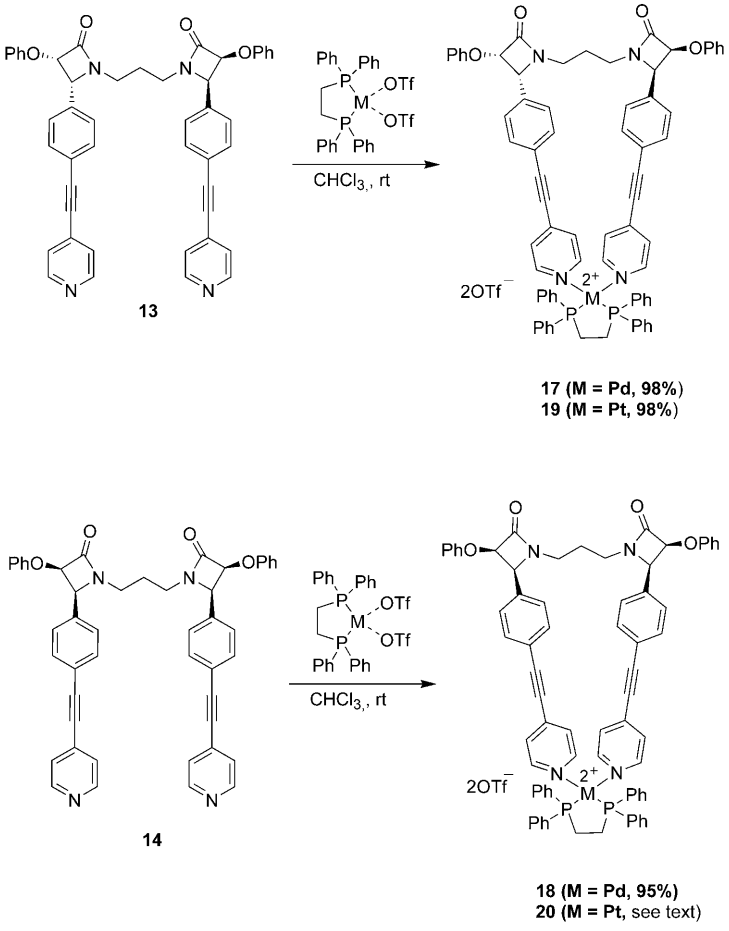


Figure 1. ORTEP plot with 25% probability of the Zn complex **16.** Hydrogen atoms are omitted for clarity exception made of H3, H4, H3', and H4' bonded to the chiral carbon atoms. The asymmetric unit is one half of the molecule.



Scheme 5. The preparation of Pd- and Pt-metallomacrocyclic β-lactams **17**–**20**.

fined geometries, we are only able to obtain *mono*- and *di-nuclear*-assembled products with a total selectivity by switching the reaction conditions That the reaction is driven by different mechanisms with *cis*-[Pt(dppe)$(OTf)_2$]/NaOAc and *cis*- [Pt(dppe)Cl_2]/NEt_3/CuI is evident, but the reasons why the formation of *mono*-assembled products **21** and **22** is preferred in the absence of Cu^I remain elusive to date and should await further data. However, it is likely that the Pt–C≡C coupling process leading to the ring closure is much faster under the Cu^I catalyst, which favors the rapid self-assembly of two molecules over the intramolecular coupling, and hence, the formation of the *bimetallic* tetra- β-lactams **23** and **24.**[26]

Macrocycles that incorporate ethynyl groups and transition metals provide binding sites for other metal atoms.[31] With the idea of incorporating new metals inside the bio-organometallic cavities, and the access to new compounds, we have taken advantage of the ability of the Pt–C≡C bond linkages to form silver complexes in a tweezer fashion. Thus, silver-binding studies have been carried out for compounds **21**–**24**. The addition of slightly more than the equimolar amount of AgOTf to solutions containing β-lactams **21** and **22**, respectively, resulted in the quantitative formation of silver triflate complexes **25** and **26** (Scheme 9). These complexes were also characterized by spectroscopic and analytical means. The incorporation of silver triflate resulted in the significant shift differences in the IR and ^{31}P spectra of the macrocycle. Thus, the sharp signal in the IR spectra at 2110 cm^{-1} in the starting macrocycles **21** and **22** is replaced by a broad signal at 2087–2056 cm^{-1} in silver triflates **25** and **26**. Furthermore, significant changes are observed in the ^{31}P NMR spectra of these complexes upon complexation. Thus, for example, compared with free macrocycle **21**, the ^{31}P signal of **25** is only slightly deshielded ([D_6]acetone, about $\delta = 1.6$ ppm) but the coupling constant $^1J_{P,Pt}$ increases by 277 Hz. These changes can be attributed to the modification of the angle between the two acetylene ligands upon complexation, thus affecting the angle of the phosphine.[32]

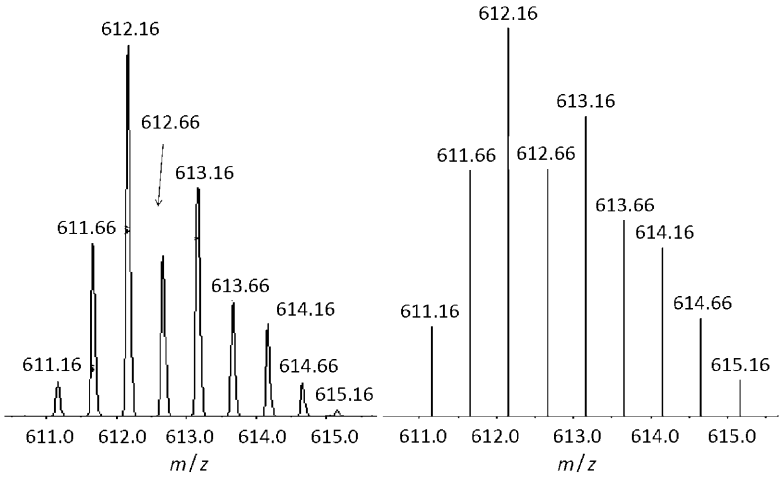
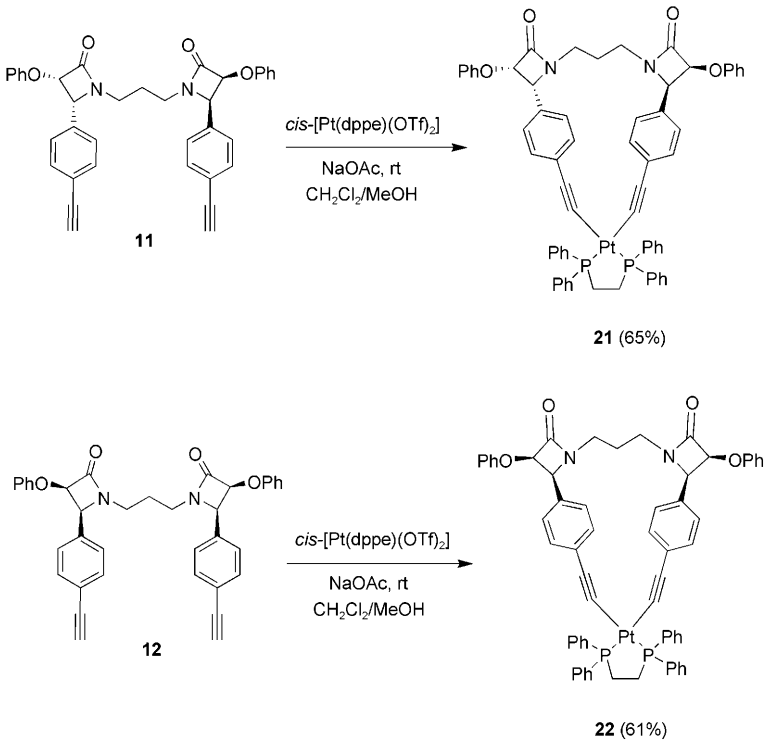


Figure 2. Experimental (left) and theoretical (right) isotopical distribution of $[M-2OTf]^{2+}$ peak of **17**. For the theoretical and experimental isotopical distribution of $[M+H]^{+}$ and $[M-OTf]^{+}$ peaks of **19**, see the Supporting Information.



Scheme 6. The synthesis of macrocyclic Pt-alkynyl-bis-β-lactams, **21** and **22**.

Similar changes in the chemical shift and coupling constant $^{1}J_{P,Pt}$ were observed in the double silver triflates **27** and **28** (Scheme 9). Final evidence for the coordination of AgOTf came from the MS spectra. Silver triflates **25** and **26** showed the $[M-OTf]^{+}$ peaks at *m/z* 1264.9 and 1264.2, respectively (Figure 4 and the Supporting Information), with isotopic distributions essentially equivalent to the calculated patterns, confirming the 1:1 stoichiometry of the complexes. On the other hand, the 1:2 stoichiometry for complexes **27** and **28** was evidenced by their $[M-OTf]^{+}$ peaks at *m/z* 2680.4 and 2680.6 respectively, with the expected 1 *m/z* separation corresponding to the +1 charge state, together with the $[M-2OTf]^{2+}$ peak at 1265.7 with the isotopic distribution pattern corresponding to a 0.5 *m/z* separation of the peaks (Figure 4 and the Supporting Information).

Conclusions

The synthesis, isolation, and full characterization of different types of stable-metal-assembled macrocyclic β-lactams is reported. By using adequately functionalized bis-β-lactams with defined stereochemistry as building blocks, a series of mono- and bimetallic Pd and Pt metallamacrocycles has been prepared in good to quantitative yields. These novel structures combine the β-lactam moiety with transition-metal fragments with a defined *cis*-square planar geometry and constitute a new class of metal-assembled cavities involving molecules with biological relevance as building blocks. By combining the adequate ligands, metallic fragments and tuning the reaction conditions, different mono- and bimetallic macrocyclic β-lactam cavities can be selectively obtained. The macrocycles bearing Pt–ethynyl groups can also incorporate other metal cations in their structures. Thus, owing to the π-tweezer effect between the Pt–ethylnyl moieties and the Ag^{+}, 1:1 or 1:2 host/silver triflate guest complexes are formed.

Experimental Section

General procedures: ^{1}H NMR and ^{13}C NMR spectra were recorded at 22 °C on a Bruker Avance 700 (700.1 and 176.0 MHz), 500 (500.1 and 125.7 MHz), 300 (300.1 and 75.54 MHz), or Bruker 200-AC (200.1 and

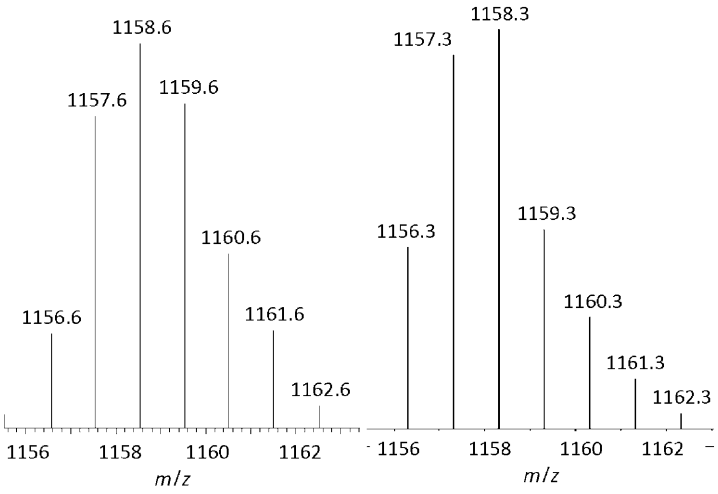
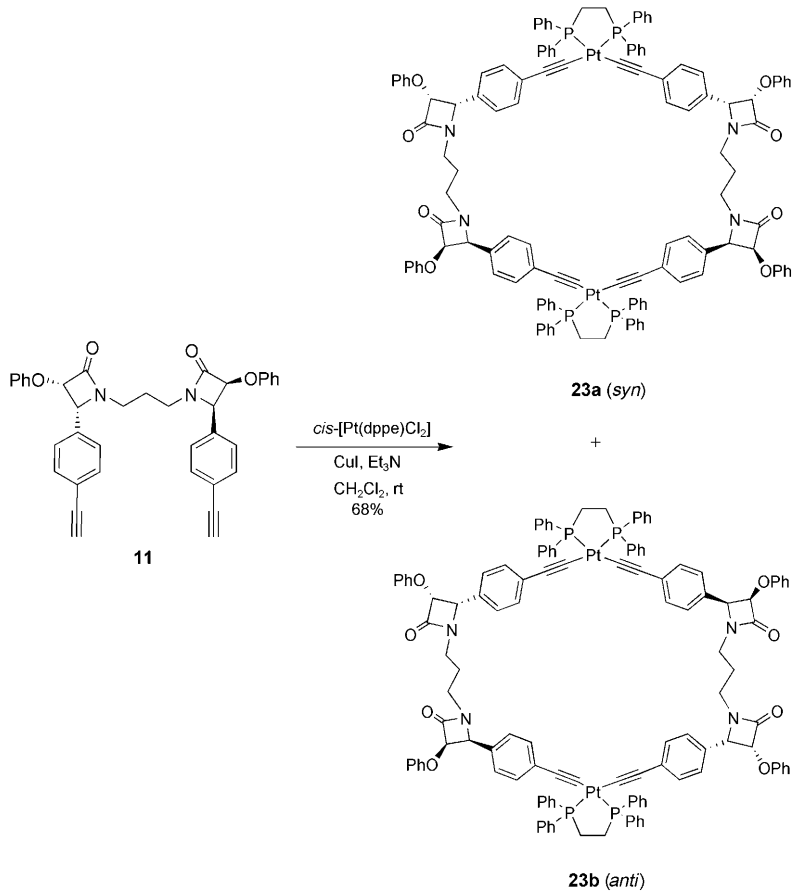


Figure 3. Experimental (left) and theoretical (right) isotopical distribution of $[M+H]^+$ peak of **21**.



Scheme 7. The synthesis of of macrocyclic bis-Pt-alkynyl-tetra-β-lactams, **23**.

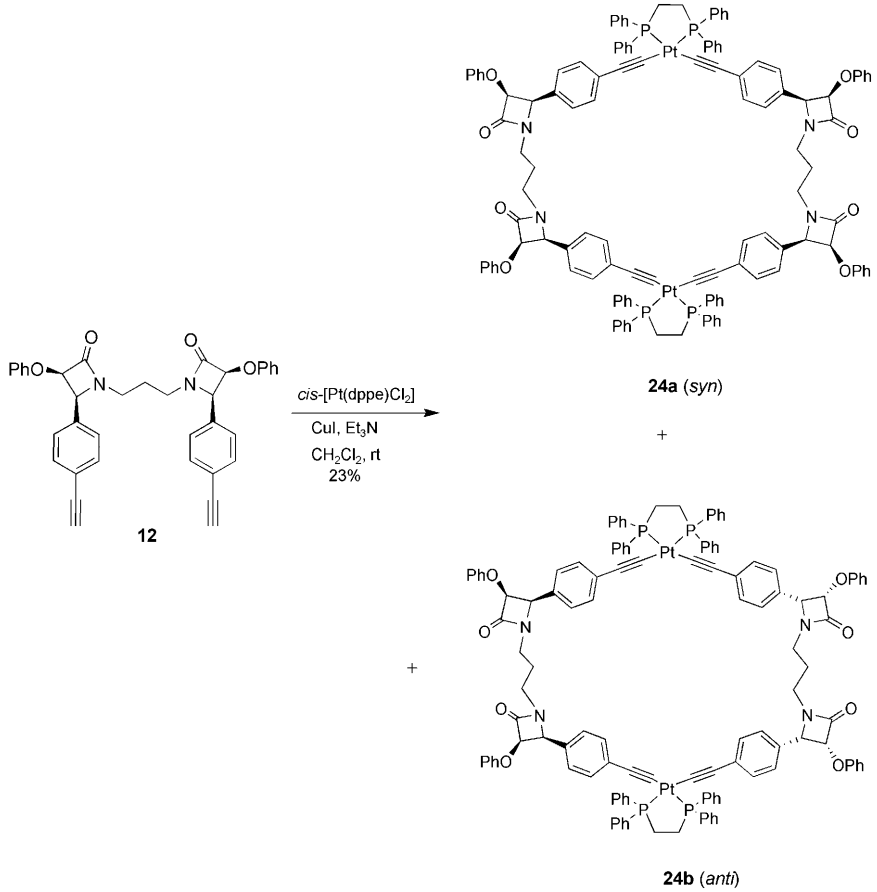
50 MHz) spectrometers. Chemical shifts are given in ppm relative to $CDCl_3$ (^{1}H, 7.27 ppm), $CDCl_3$ (^{13}C, 77.0 ppm), [D_6]acetone (^{1}H, 2.0 ppm), and [D_6]acetone (^{13}C, 206.0 ppm). ^{31}P NMR spectra were recorded at 121.4 MHz, and all chemical shifts are reported in ppm relative to external 85% H_3PO_4 at 0.00 ppm. ^{19}F NMR spectra were recorded at 282.4 MHz, and all chemical shifts are reported relative to external $CFCl_3$ at 0.00 ppm. IR spectra were taken on a Bruker Tensor 27 (MIR 8000–400 cm^{-1}) spectrometer. Mass spectra were recorded on a QSTAR pulsar I, (hybrid analyzed QTOF, applied biosystems), (ESI), or a MAT 95 XP ThermoFinnigan (FAB) apparatus. CH_2Cl_2 was distilled from calcium hydride and THF, and Et_2O from sodium-benzophenone. Flame-dried glassware and standard Schlenk techniques were used for moisture-sensitive reactions. Merck silica-gel (230–400 Mesh) was used as the stationary phase for purification of crude reaction mixtures by flash column chromatography. Identification of the products was made by TLC (kiesegel 60F-254). UV light ($\lambda = 254$ nm) was used to develop the plates.

Imine 8: Imine **8** was obtained in quantitative yields (2.2 g, yellow oil), by reaction of aldehyde **7** (2.0 g, 10.0 mmol)[17] and 1,3-diaminopropane (366.0 mg, 5.0 mmol) in Et_2O (40 mL) and in the presence of $MgSO_4$ at room temperature for 3 h. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 8.27$ (s, 2H, CH=N), 7.66 (d, $J = 8.2$ Hz, 4H, ArH), 7.50 (d, $J = 8.2$ Hz, 4H, ArH), 3.72 (t, $J = 6.6$ Hz, 4H, CH_2-N), 2.12 (qt, $J = 6.6$ Hz, 2H, CH_2), 0.26 ppm (s, 18H, CH_3); ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 160.5$ (C=N), 136.0, 132.1, 127.7, 125.1, (ArC), 104.6 (C), 96.1 (C), 59.2 (CH_2-N), 31.8 (CH_2), −0.1 ppm (CH_3); IR (film): $\tilde{\nu} = 2958$, 2839, 2157, (C≡C) 1643 (C=N), 1603, 1249 (C−O), 1221 (C−O), 864, 840 cm^{-1}; $C_{27}H_{37}N_2Si_2$: calcd: C 73.25, H 7.74, N 6.33; found: C 73.40, H 7.85, N 6.46.

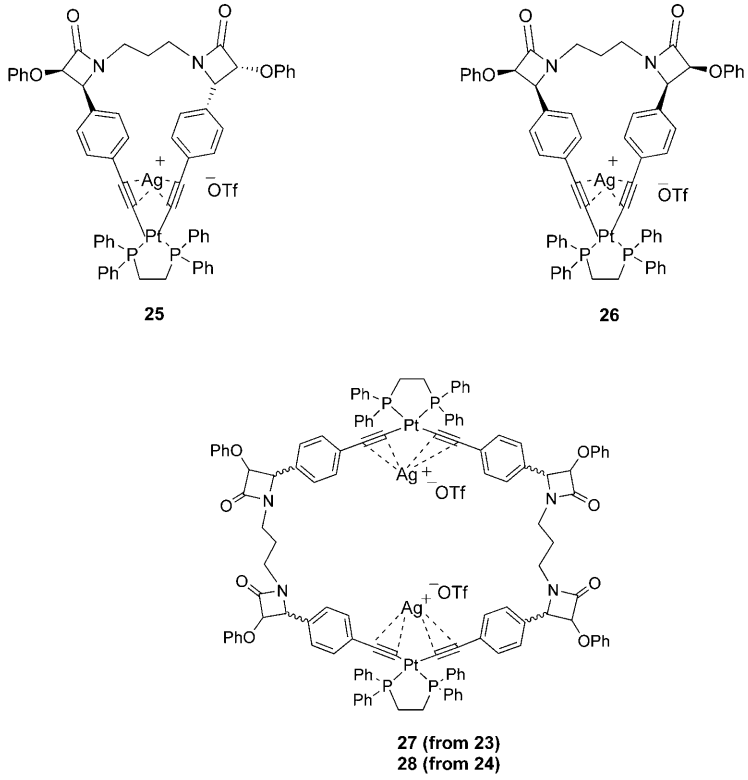
Synthesis of bis-β-lactams 9 and 10: A solution of phenoxyacetyl chloride (2.6 g, 15.0 mmol) in dry CH_2Cl_2 (50 mL) was purged with argon and cooled at −78 °C. Then, a solution of triethylamine (3.1 g, 30.0 mmol) in dry CH_2Cl_2 (15 mL) was added dropwise. The mixture was stirred for 30 min at −78 °C, and a solution of imine **8** (2.1 g, 5.0 mmol) in dry CH_2Cl_2 (30 mL) was added dropwise by a syringe pump for 3 h, maintaining the temperature at −78 °C. The reaction was stirred at room temperature overnight and then quenched with water/ice mixture (25 mL). The organic layer was washed with HCl 0.5 M (to remove the excess of triethylamine) and brine, and then dried over $MgSO_4$. The desiccant was removed by filtration and the solvent evaporated at reduced pressure. The crude solid was suspended in Et_2O, filtered, and dried with cold Et_2O to yield 2.6 g (75%) of a 1:1 mixture of *anti*- and *syn*-bis-β-lactams **9** and **10** that was separated by chromatography on silica gel (hexane/AcOEt 7:3).

***anti*-Bis-β-lactam 9**: It was obtained as a crystalline solid (1.1 g, 32%). ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.40$ (d, $J = 8.1$ Hz, 4H, ArH), 7.24 (d, $J = 8.1$ Hz, 4H, ArH), 7.13 (t, $J = 8.0$ Hz, 4H, ArH), 6.89 (t, $J = 7.3$ Hz, 2H, ArH), 6.70 (d, $J = 8.0$ Hz, 4H, ArH), 5.42 (d, $J = 4.4$ Hz, 2H, CH-O), 4.89 (d, $J = 4.4$ Hz, 2H, CH-N), 3.39 (dt, $J_1 = 13.8$ Hz, $J_2 = 7.0$ Hz, 2H, CH_2-N), 3.05 (dt, $J_1 = 13.8$ Hz, $J_2 = 7.0$ Hz, 2H, CH_2-N), 1.71 (qt, $J = 7.0$ Hz, 2H, CH_2), 0.24 ppm (s, 18H, CH_3); ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta =$ 165.9 (C=O), 156.5, 133.3, 131.8, 129.2, 128.4, 123.5, 122.0, 115.2 (ArC), 104.3 (C), 95.3 (C), 81.7 (CH−O), 62.3 (CH−N), 38.5 (CH_2−N), 25.2 (CH_2), −0.1 ppm (CH_3); IR (film): $\tilde{\nu} = 3042$, 2958, 2158 (C≡C), 1762 (C=O), 1598, 1494, 1235 (C−O), 863, 842 cm^{-1}; m. p. 199–202 °C ($CHCl_3$); $C_{43}H_{46}N_2O_4Si_2$: calcd: C 72.64, H 6.52, N 3.94; found: C 72.75, H 6.61, N 3.84.

***syn*-Bis-β-lactam 10**: It was obtained as a crystalline solid (1.0 g, 30%). ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.40$ (d, $J = 8.2$ Hz, 4H, ArH), 7.25 (d,



Scheme 8. The synthesis of of macrocyclic bis-Pt-alkynyl-tetra-β-lactams, **24**.



Scheme 9. The synthesis of silver complexes **25**–**28**.

$J=8.2$ Hz, 4H, ArH), 7.13 (t, $J=8.0$ Hz, 4H, ArH), 6.89 (t, $J=7.5$ Hz, 2H, ArH), 6.69 (d, $J=8.0$ Hz, 4H, ArH), 5.39 (d, $J=4.4$ Hz, 2H, CH-O), 4.85 (d, $J=4.4$ Hz, 2H, CH-N), 3.46 (dt, $J_1=14.4$ Hz, $J_2=7.1$ Hz, 2H, CH_2-N), 2.98 (dt, $J_1=14.4$ Hz, $J_2=7.1$ Hz, 2H, CH_2-N), 1.90–1.81 (m, 1H, CH_2), 1.69–1.59 (m, 1H, CH_2), 0.23 ppm (s, 18H, CH_3); ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta=165.9$ (C=O), 156.5, 133.2, 131.9, 129.2, 128.4, 123.6, 122.1, 115.3 (ArC), 104.3 (C), 95.3 (C), 81.8 (CH-0), 62.3 (CH-N), 38.1 (CH_2-N), 25.5 (CH_2), −0.1 ppm (CH_3); IR (film): $\tilde{\nu}=$ 2961, 2162 (C≡C) 1751 (C=O), 1599, 1496, 1241 (C−O), 871, 843 cm^{-1}; m. p. 196–199 °C ($CHCl_3$); $C_{43}H_{46}N_2O_4Si_2$: calcd: C 72.65, H 6.52, N 3.94; found: C 72.58, H 6.45, N 4.03.

General procedure for the removal of the TMS group: To a stirred solution of the β-lactam in THF (30 mL), TBAF·3H_2O was added in one portion. The mixture was stirred at room temperature until total disappearance of the starting material (monitored by TLC; about 1 h). The crude reaction was diluted with water (25 mL), extracted with CH_2Cl_2 (3×30 mL), and the organic extracts dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude solid was purified by chromatography on silica gel (CH_2Cl_2/AcOEt 9:1).

Compound 11: Following the general procedure, *anti*-bis-β-lactam **9** (250 mg, 0.3 mmol) and TBAF·3H_2O (277 mg, 0.8 mmol). After 1.5 h of reaction and purification, compound **11** (191 mg, 96%) was obtained as a crystalline solid. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=7.42$ (d, $J=8.1$ Hz, 4H, ArH), 7.26 (d, $J=8.1$ Hz, 4H, ArH), 7.13 (t, $J=7.9$ Hz, 4H, ArH), 6.89 (t, $J=7.3$ Hz, 2H, ArH), 6.71 (d, $J=7.9$ Hz, 4H, ArH), 5.44 (d, $J=4.4$ Hz, 2H, CH-O), 4.91 (d, $J=4.4$ Hz, 2H, CH−N), 3.40 (dt, $J_1=14.2$ Hz, $J_2=7.7$ Hz, 2H, CH_2-N), 3.10 (s, 2H, C≡H), 3.07 (dt, $J_1=14.2$ Hz, $J_2=7.7$ Hz, 2H, CH_2-N), 1.74 ppm (q, $J=7.7$ Hz, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta=166.0$ (C=O), 156.5, 133.7, 132.0, 129.2, 128.5, 122.6, 122.1, 115.3 (ArC), 82.9 (C), 81.8 (CH−O), 78.1 (C), 62.3 (CH−N), 38.7 (CH_2−N), 25.3 ppm (CH_2); IR (film): $\tilde{\nu}=$ 3287 (C≡C−H), 2927, 2106 (C≡C) 1757 (C=O), 1597, 1493, 1233 (C−O), 840, 754 cm^{-1}; m.p. 152–154 °C ($CHCl_3$); $C_{37}H_{30}N_2O_4$: calcd: C 78.43, H 5.34, N 4.94; found C 78.51, H 5.22, N 4.79.

Compound 12: Following the general procedure, *syn*-bis-β-lactam **10** (150 mg, 0.2 mmol) and TBAF·3H_2O

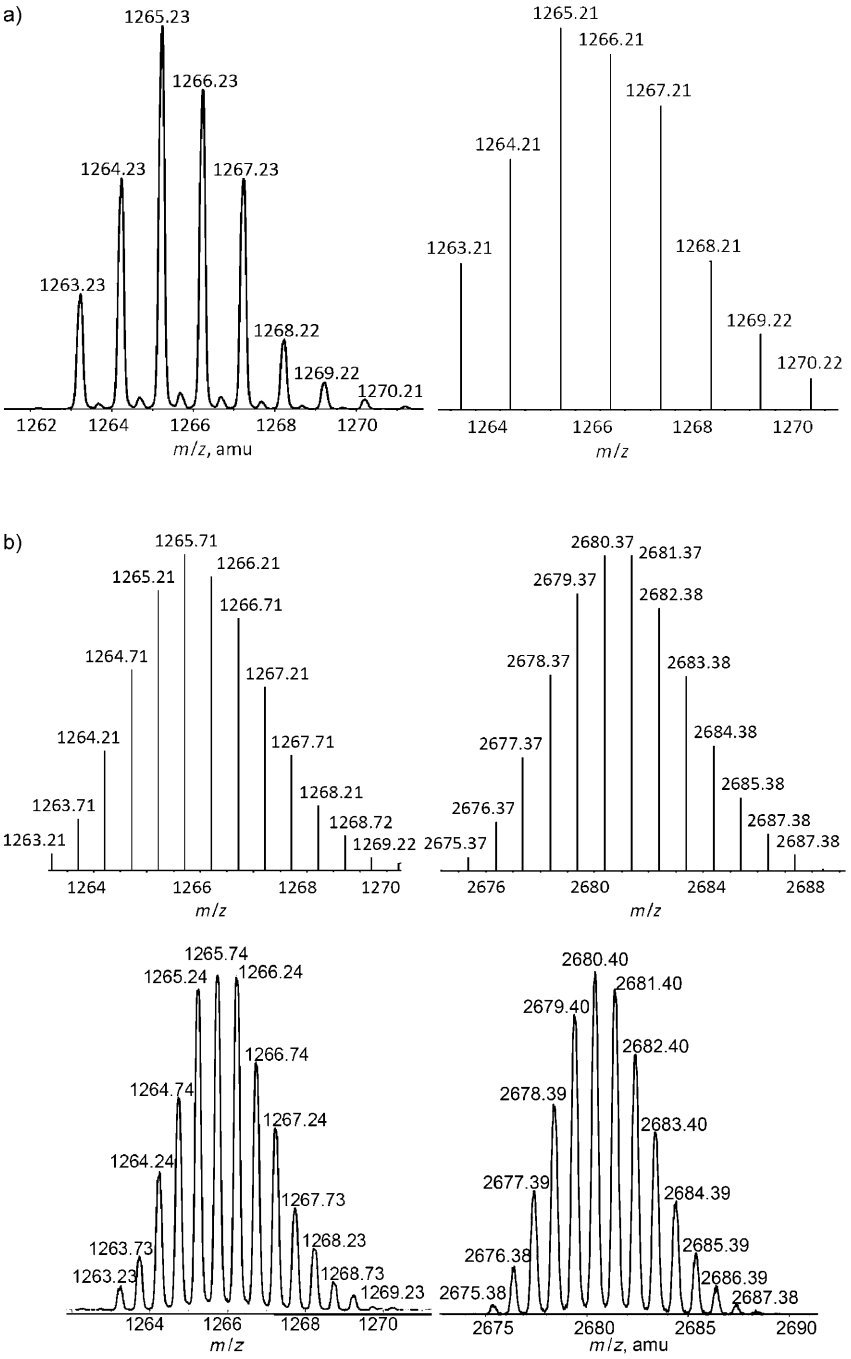


Figure 4. a) Experimental (left) and theoretical (right) isotopical distribution of 1264.2 $[M-OTf]^+$ peak of 1:1 silver triflate complex **25**. b) Theorethical (above) and experimental (below) isotopical distribution of 1264.7 $[M-2OTf]^{2+}$ (left) and 2680.3 $[M-OTf]^+$ (right) peaks of 1:2 silver triflate complex **27.**

(166 mg, 0.5 mmol). After 1.5 h reaction and purification, compound **12** (116 mg, 97%) was obtained as a crystalline solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=7.43 (d, J=8.1 Hz 4H, ArH), 7.27 (d, J=8.1 Hz 4H, ArH), 7.14 (t, J=7.7 Hz, 4H, ArH), 6.89 (t, J=7.2 Hz, 2H, ArH), 6.70 (d, J=8.2 Hz, 4H, ArH), 5.41 (d, J=4.4 Hz, 2H, CH-O), 4.89 (d, J= 4.4 Hz, 2H, CH-N), 3.49 (dt, J_1=14.1 Hz, J_2=7.0 Hz, 2H, CH_2-N), 3.11 (s, 2H, C≡H), 2.99 (dt, J_1=14.1 Hz, J_2=7.0 Hz, 2H, CH_2-N), 1.92–1.83 (m, 1H, CH_2), 1.73–1.62 ppm (m, 1H, CH_2); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ=165.9 (C=O), 156.5, 133.6, 132.0, 129.2, 128.5, 122.6, 122.1, 115.3 (ArC), 82.9 (C), 81.8 (CH−O), 78.1 (C), 62.2 (CH−N), 38.1 (CH_2−N), 25.5 ppm (CH_2); IR (film): $\tilde{\nu}$=3287 (C≡C−H), 3059, 2925, 2107 (C≡C) 1757 (C=O), 1596, 1493, 1234 (C−O), 833, 754 cm^{-1}; m. p. 156–158°C ($CHCl_3$); $C_{37}H_{30}N_2O_4$: calcd: C 78.43, H 5.34, N 4.94; found: C 78.57, H 5.19, N 4.83.

Synthesis of pyridine ligands: [Pd-(PPh_3)$_4$] (10 mol%) and CuI (5 mol%) were added under Ar to a stirred solution of 4-iodopyridine in a 4:1 mixture of dry THF and freshly distilled triethylamine. Then, a solution of the β-lactam was added dropwise. The β-lactam/4-iodopyridine ratio was 1:8 and the percentage of the catalyst was related to the amount of β-lactam used. The reaction mixture was stirred at room temperature and its progress monitored by TLC until disappearance of the reagents. The crude product was filtered though celite 545, the solvent removed under reduced pressure, the residue dissolved in CH_2Cl_2 (20 mL), and then washed with water (2× 10 mL) and brine (1×10 mL). The organic layer was dried over $MgSO_4$, the solvent remover under reduced pressure, and the crude product purified by chromatography on silica gel (CH_2Cl_2/AcOEt/MeOH).

Compound 13: β-Lactam **11** (150 g, 0.26 mmol), 4-iodopyridine (127 mg, 0.66 mmol), [Pd(PPh_3)$_4$] (24 mg, 0.02 mmol), and CuI (2 mg, 0.01 mmol) were added together in a 4:1 THF/Et_3N mixture (60 mL). After 5 h at room temperature and further purification, **13** (150 mg, 82%) was obtained as a pale-yellow crystalline solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=8.60 (brs, 4H, ArH), 7.63 (d, J= 7.9 Hz, 4H, ArH), 7.39–7.29 (m, 8H, ArH), 7.14 (t, J=7.9 Hz, 4H, ArH), 6.89 (t, J=7.3 Hz, 2H, ArH), 6.72 (d, J=7.9 Hz, 4H, ArH), 5.47 (d, J= 4.4 Hz, 2H, CH-O), 4.97 (d, J= 4.4 Hz, 2H, CH−N), 3.44 (dt, J_1= 14.4 Hz, J_2=6.7 Hz, 2H, CH_2−N), 3.12 (dt, J_1=14.4 Hz, J_2=6.7 Hz, 2H, CH_2−N), 1.80 ppm (quint, J=6.7 Hz, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ=166.0 (C=O), 156.5, 149.6, 134.3, 131.8, 131.1, 129.2, 128.7, 125.5, 122.6, 122.2, 115.3 (ArC), 93.3 (C), 87.4 (C), 81.9 (CH-O), 62.4 (CH−N), 38.8 (CH_2−N), 25.4 ppm (CH_2); IR (film): $\tilde{\nu}$=3040, 2924, 2885, 2222 (C≡C), 1760 (C=O), 1591, 1540, 1493, 1438, 1234 (C−O), 821, 753 cm^{-1}; m. p. 147–149°C ($CHCl_3$); ESI-MS: m/z: 721.5 $[M+H]^+$. $C_{47}H_{36}N_4O_4$: calcd: C 78.31, H 5.03, N 7.77; found: C 78.47, H 5.16, N 7.62.

Compound 14: β-Lactam **12** (100 mg, 0.17 mmol), 4-iodopyridine (288 mg, 1.41 mmol), [Pd(PPh_3)$_4$] (19 mg, 0.02 mmol), and CuI (2 mg, 0.01 mmol) were combined in a 4:1 THF/Et_3N mixture (50 mL). After 5 h at room temperature and further purification, **14** (95 mg, 76%) was obtained as a pale-yellow crystalline solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=8.60 (brs, 4H, ArH), 7.49 (d, J=8.0 Hz, 4H, ArH), 7.39–7.31 (m, 8H, ArH), 7.13 (t, J=7.8 Hz, 4H, ArH), 6.89 (t, J=7.3 Hz, 2H, ArH), 6.71 (d, J=8.0 Hz, 4H, ArH), 5.44 (d, J=4.3 Hz, 2H, CH-O), 4.95 (d, J=

4.3 Hz, 2H, CH-N), 3.57–3.47 (m, 2H, CH_2-N), 3.07–2.98 (m, 2H, CH_2-N), 1.94–1.89 (m, 1H, CH_2), 1.76–1.69 ppm (m, 1H, CH_2); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 165.9 (C=O), 156.5, 149.6, 134.1, 131.7, 131.1, 129.2, 128.7, 125.4, 122.5, 122.1, 115.3 (ArC), 93.2 (C), 87.4 (C), 81.8 (CH−O), 62.2 (CH−N), 38.2 (CH_2−N), 25.5 ppm (CH_2); IR (film): $\tilde{\nu}$ = 3041, 2928, 2224 (C≡C), 1762 (C=O), 1593, 1542, 1495, 1236 (C−O), 823, 755 cm^{-1}; m. p. 145–148 °C ($CHCl_3$); ESI-MS: *m/z*: 721.5 $[M+H]^+$; $C_{47}H_{36}N_4O_4$: calcd: C 78.31, H 5.03, N 7.77; found: C 78.55, H 5.18, N 7.83.

Synthesis of bis-azetidine 15: A solution of $AlCl_3$ (292 mg, 2.12 mmol) in dry THF (35 mL) was added via cannula to a stirred suspension of $LiAlH_4$ (80 mg, 2.12 mmol) in dry THF (10 mL) at 0 °C and under argon. The mixture was stirred for 30 min at room temperature and then cooled to 0 °C before the addition (via cannula) of a solution of bis-β-lactam **11** (200 mg, 0.35 mmol) in dry THF (29 mL). After 20 min at room temperature, the reaction was quenched with ice and extracted with Et_2O (3× 25 mL). The organic phases were washed with brine and water and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel (CH_2Cl_2/AcOEt 9:1). Bis-azetidine **15** (180 mg, 95%) was obtained as a pale-yellow viscous oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.43 (d, *J* = 8.3 Hz, 4H, ArH), 7.38 (d, *J* = 8.3 Hz, 4H, ArH), 7.12 (t, *J* = 7.8 Hz, 4H, ArH), 6.84 (t, *J* = 7.4 Hz, 2H, ArH), 6.56 (d, *J* = 8.2 Hz, 4H, ArH), 4.88 (t, *J* = 5.5 Hz, 2H, CH−O), 4.13 (d, *J* = 5.5 Hz, 2H, CH-N), 3.59 (d, *J* = 8.7 Hz, 2H, CH_2-N), 3.19 (dd, J_1 = 8.7 Hz, J_2 = 5.5 Hz, 2H, CH_2-N), 3.09 (s, 2H, −CH), 2.63–2.49 (m, 4H, CH_2-N), 1.30–1.24 ppm (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 157.1, 138.4, 131.4, 129.0, 128.4, 120.8, 120.7, 114.9 (ArC), 83.7 (C), 77.0 (C≡CH), 72.4 (CH−O), 71.0 (CH−N), 57.6 (CH_2−N), 56.5 (CH_2−N), 26.3 ppm (CH_2); IR (film): $\tilde{\nu}$ = 3287 (C≡C−H), 3057, 2937, 2830, 2106 (C≡C), 1599, 1587, 1494, 1237 (C−O), 814, 752 cm^{-1}; $C_{37}H_{34}N_2O_2$: calcd: C 82.50, H 6.36, N 5.20; found: C 82.73, H 6.12, N 5.39.

Synthesis of Zn complex 16: $ZnCl_2$ (38 mg, 0.28 mmol) was added to a stirred solution of bis-azetidine **15** (150 mg, 0.28 mmol) in anhydrous MeOH. The mixture was refluxed for 5 h under constant stirring and then left to reach room temperature before the addition of Et_2O (30 mL). The Zn complex **16** precipitated in the medium and was removed by filtration. Slow crystallization in MeOH/MeCN 1:1 yielded suitable crystals for X-ray diffraction.

General procedure for the synthesis of Pd– and Pt–pyridine complexes 17–20: A solution of the pyridine–bis-β-lactam was stirred in $CHCl_3$ or acetone (HPLC), and under an argon atmosphere, and the corresponding *cis*-[M(dppe)$(OTf)_2$] (M = Pd, Pt)[21] was added as a single portion (molar ratio β-lactam/*cis*-[M(dppe)$(OTf)_2$], 1:1). After 15 min at room temperature, the solvent was removed under reduced pressure and the macrocycles were obtained as pale-yellow crystalline solids that decompose before melting at temperatures of around 180 °C.

Compound 17: Compound **13** (20 mg, 0.03 mmol) and *cis*-[Pd(dppe)$(OTf)_2$] (22 mg, 0.03 mmol) in $CHCl_3$ (10 mL) were mixed together to obtain macrocycle **17** (41 mg, 98%). ^{1}H NMR ([D_6]acetone, 300 MHz): δ = 8.85 (brs, 4H, ArH), 7.99–7.85 (m, 8H, ArH), 7.66–7.59 (m, 12H, ArH), 7.41–7.20 (m, 12H, ArH), 7.05 (t, *J* = 7.4 Hz, 4H, ArH), 6.78–6.69 (m, 6H, ArH), 5.53 (d, *J* = 4.0 Hz, 2H, CH−O), 5.15 (brs, 2H, CH−N), 3.49–3.24 (m, 6H, CH_2−N + CH_2−P), 3.21–3.04 (m, 2H, CH_2−N), 1.78–1.61 ppm (m, 2H, CH_2); ^{13}C NMR ([D_6]acetone, 75.5 MHz): δ = 166.1 (C=O), 157.8, 151.5, 138.0, 135.7, 134.6–134.2 (m, dppe), 134.1, 132.7, 131.4–130.7 (m, dppe), 130.1, 130.0, 128.7, 126.8, 126.1, 122.6, 122.4 (q, *J* = 322.0 Hz, CF_3), 121.7, 116.0 (ArC), 98.9 (C), 86.4 (C), 82.8 (CH-O), 62.6 (CH−N), 39.5 (CH_2−N), 29.8–28.3 (m, CH_2−P), 26.4 ppm (CH_2); ^{31}P NMR ([D_6]acetone, 121.4 MHz): δ = 66.8 ppm; ^{19}F NMR ([D_6]acetone, 282.4 MHz): δ = −78.8 ppm; IR (film): $\tilde{\nu}$ = 3058, 2925, 2222 (C≡C), 1760 (C=O), 1610, 1514, 1494, 1407, 1276, 1256, 1225 (C−O), 1157, 1029, 838, 723, cm^{-1}; ESI-MS: *m/z*: 612.1 $[M-2OTf]^{2+}$; $C_{75}H_{60}F_6N_4O_{10}P_2PdS_2$: calcd: C 59.12, H 3.97, N 3.68; found: C 58.86, H 3.79, N 3.46.

Compound 18: Compound **14** (20 mg, 0.03 mmol) and *cis*-[Pd(dppe)$(OTf)_2$] (22 mg, 0.03 mmol) in $CHCl_3$ (10 mL) were mixed together to obtained macrocycle **18** (40 mg, 95%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.86 (brs, 4H, ArH), 7.81–7.68 (m, 8H, ArH), 7.53 (brs, 12H, ArH), 7.41–7.28 (m, 8H, ArH), 7.19–7.04 (m, 8H, ArH), 6.89–6.80 (m, 2H, ArH), 6.71–6.63 (m, 4H, ArH), 5.43 (d, *J* = 3.9 Hz, 2H, CH−O), 4.98 (brs, 2H, CH−N), 3.57–3.43 (m, 2H, CH_2−N), 3.32–2.92 (m, 6H, CH_2−N + CH_2−P), 1.98–1.83 (m, 1H, CH_2), 1.78–1.67 ppm (m, 1H, CH_2); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 165.9 (C=O), 156.4, 150.5, 135.1, 134.5, 133.4–133.0 (m, dppe), 132.0, 130.3–1329.7 (m, dppe), 129.2, 128.8, 127.9, 125.6, 124.8, 122.1, 121.5, 120.8 (q, *J* = 318.7 Hz, CF_3), 115.2 (ArC), 97.8 (C), 85.8 (C), 81.8 (CH−O), 62.1 (CH−N), 38.3 (CH_2−N), 29.4–28.0 (m, CH_2−P), 25.5 ppm (CH_2); ^{31}P NMR ($CDCl_3$, 121.4 MHz): δ = 64.3 ppm; ^{19}F NMR ($CDCl_3$, 282.4 MHz): δ = −78.3 ppm; IR (film): $\tilde{\nu}$ = 3058, 2924, 2853, 2221 (C≡C), 1761 (C=O), 1610, 1514, 1494, 1405, 1276, 1254, 1225 (C−O), 1029, 838, 725 cm^{-1}; ESI-MS: *m/z*: 1523.8 $[M+H]^+$, 1373.8 $[M-OTf]^+$; $C_{75}H_{60}F_6N_4O_{10}P_2PdS_2$: calcd: C 59.12, H 3.97, N 3.68; found: C 58.79, H 3.82, N 3.49.

Compound 19: Compound **13** (20 mg, 0.03 mmol) and *cis*-[Pt(dppe)$(OTf)_2$] (22 mg, 0.03 mmol) in acetone (10 mL) (HPLC) were mixed together to obtain **19** (41 mg, 98%) accompanied by trace amounts of oligomeric material (5%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.86 (brs 4H, ArH), 7.81–7.66 (m, 8H, ArH), 7.65–7.45 (m, 12H, ArH), 7.41–7.27 (m, 8H, ArH), 7.20–7.02 (m, 8H, ArH), 6.93–6.80 (m, 2H, ArH), 6.68 (brs, 4H, ArH), 5.43 (brs, 2H, CH−O), 4.98 (brs, 2H, CH−N), 3.58–3.41 (m, 2H, CH_2−N), 3.23–2.89 (m, 6H, CH_2−N + CH_2−P), 1.96–1.79 ppm (m, 2H, CH_2); ^{13}C NMR ([D_6]acetone, 75.5 MHz): δ = 165.9 (C=O), 157.4, 151.2, 137.8, 136.1, 134.6–133.9 (m, dppe), 132.5, 130.7, 130.5, 129.8, 129.1, 125.5, 124.6, 122.2, 122.2 (q, *J* = 321.6 Hz, CF_3), 121.4, 115.8 (ArC), 99.5 (C), 86.1 (C), 82.6 (CH-O), 62.3 (CH-N), 39.3 (CH_2−N), 28.9–27.7 (m, CH_2−P), 26.0 ppm (CH_2); ^{31}P NMR ([D_6]acetone, 121.4 MHz): δ = 38.4 ppm (s, J_{P-Pt} = 3230.5 Hz); ^{19}F NMR ([D_6]acetone, 282.4 MHz): δ = −78.8 ppm; IR (film): $\tilde{\nu}$ = 3058, 2925, 2221 (C≡C), 1761 (C=O), 1610, 1514, 1491, 1409, 1255, 1156, 1108, 1030, 840, 754, cm^{-1}; ESI-MS: *m/z*: 1612.9 $[M+H]^+$, 1462.9 $[M-OTf]^+$.

Compound 20: Compound **14** (20 mg, 0.03 mmol) and *cis*-[Pt(dppe)$(OTf)_2$] (22 mg, 0.03 mmol) in acetone (10 mL) (HPLC) were mixed together to obtain a 1:1 mixture of **20** and oligomeric material (40 mg) that could not be separated. ^{1}H NMR ([D_6]acetone, 300 MHz): δ = 8.87 (brs 4H, ArH), 8.00–7.87 (m, 8H, ArH), 7.74–7.56 (m, 12H, ArH), 7.49–7.33 (m, 12H, ArH), 7.14–7.01 (m, 4H, ArH), 6.79–6.68 (m, 6H, ArH), 5.55 (brs, 2H, CH−O), 5.20 (brs, 2H, CH−N), 3.54–3.00 (m, 8H, CH_2−N + CH_2−P) 1.85–1.96 ppm (m, 2H, CH_2). Signals at δ = 8.56, 5.51, 5.07, and 1.67–1.58 ppm correspond to oligomeric material. The ^{31}P NMR spectrum ($CDCl_3$, 121.4 MHz) showed a signal assignable to **20** at δ = 38.4 ppm (s, J_{P-Pt} = 3225.7 Hz), (oligomer δ = 38.5), and the ^{19}F NMR ($CDCl_3$, 282.4 MHz) shows a signal at δ = −78.7 ppm. The presence of **20** was also demonstrated by ESI-MS: *m/z*: 1612.9 $[M+H]^+$, 1462.9 $[M-OTf]^+$.

General procedure for the synthesis of Pt–C complexes 21 and 22: To a stirred solution of the bis-β-lactam **11** or **12** in CH_2Cl_2 (100 mL), under argon, was added a solution of NaOAc·3H_2O in MeOH (5 mL). Then, a solution of *cis*-[Pt(dppe)$(OTf)_2$][21] in CH_2Cl_2 (10 mL) was subsequently added dropwise The reaction mixture was stirred at room temperature for 12 h, quenched by addition of water (20 mL) and extracted. The organic layer was dried over $MgSO_4$, the solvent was removed under reduced pressure, and the products were purified by chromatography on silica gel (CH_2Cl_2/AcOEt/MeOH).

Compound 21: Following the general procedure, bis-β-lactam **11** (40 mg, 0.07 mmol), *cis*-[Pt(dppe)$(OTf)_2$] (62 mg, 0.07 mmol), and NaOAc (53 mg, 0.28 mmol) were added together. After 12 h at room temperature and further purification, **21** (52 mg, 65%) was obtained as a pale yellow crystalline solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.03–7.93 (m, 8H, ArH), 7.46–7.37 (m, 12H, ArH), 7.23 (d, *J* = 8.1 Hz, 4H, ArH), 7.09 (t, *J* = 8.0 Hz, 4H, ArH), 7.03 (d, *J* = 8.1 Hz, 4H, ArH), 6.84 (t, *J* = 7.3 Hz, 2H, ArH), 6.70 (d, *J* = 7.8 Hz, 4H, ArH), 5.35 (d, *J* = 4.4 Hz, 2H, CH−O), 4.80 (d, *J* = 4.4 Hz, 2H, CH−N), 3.48 (dt, J_1 = 14.3 Hz, J_2 = 8.0 Hz, 2H, CH_2−N), 3.01 (dt, J_1 = 14.3 Hz, J_2 = 8.0 Hz, 2H, CH_2−N), 2.58–2.21 (m, 4H, CH_2−P), 1.76 ppm (quint, *J* = 8.0 Hz, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 166.3 (C=O), 156.8, 133.5–133.1 (m, dppe), 131.3, 131.1, 129.9 (m, C_α C≡C), 129.7, 129.1, 128.9–128.6 (m, dppe), 127.8,

121.8, 115.5 (ArC), 113.0 (d, $J=33.9$ Hz, C_β C≡C), 81.8 (CH-O), 64.2 (CH–N), 41.2 (CH_2–N), 28.6 (d, $J=154.6$ Hz, CH_2–P), 28.4 ppm (CH_2); ^{31}P NMR ($CHCl_3$, 121.4 MHz): $\delta=42.6$ ppm ($J_{Pt-P}=2367.5$ Hz); ^{31}P NMR ([D$_6$]acetone, 121.4 MHz): $\delta=43.3$ ppm ($J_{Pt-P}=2344.8$ Hz); IR (film): $\tilde{\nu}=$ 3054, 2922, 2110 (C≡C), 1755 (C=O), 1597, 1493, 1234 (C–O), 1104, 825, 750 cm^{-1}; m.p. 235 °C; FABMS: 1158.5 $[M+H]^+$; $C_{63}H_{53}N_2O_4P_2Pt$: calcd: C 65.34, H 4.53, N 2.42; found: C 65.39, H 4.65, N 2.35.

Compound 22: Following the general procedure, bis-β-lactam **12** (50 mg, 0.09 mmol), *cis*-[Pt(dppe)(OTf)$_2$] (78 mg, 0.09 mmol), and NaOAc (47 mg, 0.35 mmol) were combined. After 12 h at room temperature and further purification, **22** (62 mg, 61 %) was obtained as a pale yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=8.03$–7.93 (m, 8H, ArH), 7.43 (m, 12H, ArH), 7.33 (d, $J=8.1$ Hz, 4H, ArH), 7.13–7.05 (m, 8H, ArH), 6.85 (t, $J=$ 7.3 Hz, 2H, ArH), 6.74 (d, $J=7.8$ Hz, 4H, ArH), 5.33 (d, $J=4.4$ Hz, 2H, CH-O), 4.73 (d, $J=4.4$ Hz, 2H, CH–N), 3.42–3.32 (m, 2H, CH_2–N), 2.89–2.79 (m, 2H, CH_2–N), 2.51–2.31 (m, 4H, CH_2–P), 2.03–1.91 ppm (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta=165.8$ (C=O), 157.0, 133.7–133.1 (m, dppe), 132.0, 131.3, 131.1, 129.9 (dd, $J_1=54.7$ Hz, $J_2=$ 21.3 Hz, C_α C≡C), 129.6, 129.1, 129.0–128.6 (m, dppe), 127.7, 121.8, 115.6 (ArC), 113.1 (d, $J=33.9$ Hz, C_β C≡C), 82.0 (CH–O), 63.9 (CH–N), 40.0 (CH_2–N), 29.7 (CH_2–P), 27.4 ppm (CH_2); ^{31}P NMR ($CHCl_3$, 121.4 MHz): $\delta=42.6$ ppm ($J_{Pt-P}=2359.3$ Hz); IR (film): $\tilde{\nu}=2923$, 2853, 2110 (C≡C), 1759 (C=O), 1598, 1493, 1234 (C–O), 1105, 840, 754 cm^{-1}; m.p. 243 °C (decomp); FABMS: 1158.8 $[M+H]^+$; $C_{63}H_{53}N_2O_4P_2Pt$: calcd: C 65.34, H 4.53, N 2.42; found: C 65.61, H 4.40, N 2.38.

General procedure for the synthesis of Pt–C complexes 23 and 24: To a stirred solution of the bis-β-lactams **11** and **12** and *cis*-[Pt(dppe)Cl$_2$][29] in CH_2Cl_2/Et_3N (9:1; 100 mL), under an argon atmosphere, CuI (10 %) was added in a single portion. The reaction mixture was stirred at room temperature for 12 h, quenched by addition of water (20 mL) and extracted. The organic layer was dried over $MgSO_4$, the solvent was removed under reduced pressure, and the products were purified by chromatography on silica gel (CH_2Cl_2/AcOEt/MeOH 6:3:1).

Compounds 23a,b: Following the general procedure, bis-β-lactam **11** (40 mg, 0.07 mmol), *cis*-[Pt(dppe)Cl$_2$] (44 mg, 0.07 mmol), and CuI (1.3 mg, 0.01 mmol) were added together. After 12 h at room temperature and further purification, a 1:1 *syn/anti* diastereomeric mixture of doubly assembled compounds **23a** and **23b** (55 mg; 68 %) was obtained as a pale yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=7.96$–7.79 (m, 16H, ArH), 7.47–7.29 (m, 24H, ArH), 7.18–7.10 (m, 8H, ArH), 7.06–6.96 (m, 16H, ArH), 6.86–6.78 (m, 4H, ArH), 6.68–6.63 (m, 8H, ArH), 5.27–5.25 (m, 4H, CH–O), 4.58–4.56 (m, 4H, CH–N), 3.37–3.30 (m, 4H, CH_2–N), 3.00–2.91 (m, 4H, CH_2–N), 2.51–2.29 (m, 8H, CH_2–P), 1.59–1.50 ppm (m, 4H, CH_2); ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta=166.0$ (C=O), 156.6, 156.5 133.7–133.1 (m, dppe), 132.0, 131.5–131.1 (m), 129.9–129.7 (m, C_α C≡C), 129.3, 129.2, 128.8–128.5 (m, dppe), 127.8, 121.8, 115.5, 115.4 (ArC), 111.6–111.1 (m, C_β C≡C), 81.6, (CH–O), 62.0, 61.9 (CH–N), 37.6 (CH_2–N), 30.5–27.8 (m, CH_2–P), 24.5, 24.4 ppm (CH_2); ^{31}P NMR ($CHCl_3$, 121.4 MHz): $\delta=42.4$, 42.3 ppm ($J_{Pt-P}=2288.8$ Hz); IR (KBr): $\tilde{\nu}=$ 3056, 2923, 2853, 2114 (C≡C), 1760 (C=O), 1597, 1493, 1235 (C–O), 1105, 828, 750 cm^{-1}; FABMS: 2315.7 $[M+H]^+$; m.p. 240 °C (decomp); $C_{126}H_{106}N_4O_8P_4Pt_2$: calcd: C 65.34, H 4.53, N 2.42; found: C 65.49, H 4.34, N 2.31.

Compounds 24a,b: Following the general procedure, of bis-β-lactam **12** (70 mg, 0.12 mmol), *cis*-[Pt(dppe)Cl$_2$] (78 mg, 0.12 mmol), and CuI (2.6 mg, 0.02 mmol) were added together. After 12 h at room temperature and further purification, a 1:1 *syn/anti* diastereomeric mixture of doubly assembled compounds **24a** and **24b** (27 mg, (23 %) was obtained as a pale yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=7.99$–7.79 (m, 16H, ArH), 7.45–7.31 (m, 24H, ArH), 7.15–6.97 (m, 24H, ArH), 6.82–6.72 (m, 4H, ArH), 6.70–6.62 (m, 8H, ArH), 5.29–5.29 (m, 4H, CH–O), 4.65–4.62 (m, 4H, CH–N), 3.40–3.23 (m, 4H, CH_2–N), 3.03–2.89 (m, 4H, CH_2–N), 2.55–2.28 (m, 8H, CH_2–P), 2.09–1.95 (m, 2H, CH_2), 1.75–1.60 ppm (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta=166.0$ (C=O), 156.7, 156.6 133.7–133.1 (m, dppe), 131.2, 131.1, 129.9, 129.7, 129.4, 129.3, 129.2, 129.1, 128.8–128.4 (m, dppe), 127.8, 127.7, 121.8, 115.6, 115.5 (ArC + C≡C), 81.8, 81.7 (CH–O), 62.5 (CH–N), 38.3 (CH_2–N), 29.8–28.3 (m, CH_2–P), 26.1 ppm (CH_2); ^{31}P NMR ($CHCl_3$, 121.4 MHz): $\delta=42.3$ ppm ($J_{Pt-P}=2279.1$ Hz); IR (film): $\tilde{\nu}=$ 3055, 2923, 2853, 2114 (C≡C), 1755 (C=O), 1597, 1493, 1235 (C–O), 1105, 822, 751 cm^{-1}; FABMS: 2316.4 $[M+H]^+$; m.p. 245 °C (decomp); $C_{126}H_{106}N_4O_8P_4Pt_2$: calcd: C 65.34, H 4.53, N 2.42; found: C 65.43, H 4.60, N 2.30.

General procedure for the synthesis of AgOTf complexes: To a solution of the corresponding macrocycle in $CDCl_3$ and under argon, AgOTf was added in one portion. The ratios macrocycle/AgOTf used were 1:1 for the monometallic macrocycles **21** and **22** and 1:2 for the bimetallic macrocycles **23** and **24**. The mixture was stirred for 3 h in the dark (a brown precipitate was formed). The products were obtained by centrifugation (3000 rpm, 30 min–1 h), followed by washing with $CDCl_3$ and drying. The AgOTf complexes were light-sensitive products.

AgOTf complex 25: Complex **21** (20 mg, 17 μmol) and AgOTf (4.5 mg, 17 μmol) in $CDCl_3$ (5 mL) were mixed together. After 3 h, silver triflate complex **25** (20 mg, 82 %) was obtained as a light brown solid. ^{1}H NMR ([D$_6$]acetone, 300 MHz): $\delta=8.01$–6.95 (m, 34H, ArH), 6.94–6.76 (m, 4H, ArH), 5.60–5.53 (br s, 2H, CH–O), 5.31–5.22 (br s, 2H, CH–N), 3.64–3.43 (m, 2H, CH_2–N), 3.22–3.02 (m, 2H, CH_2–N), 2.92–2.64 (m, 4H, CH_2–P), 1.69–1.48 ppm (m, 2H, CH_2); ^{13}C NMR ([D$_6$]acetone, 176.0 MHz $CDCl_3$): $\delta=165.3$ (C=O), 157.0, 134.0–131.5 (m, dppe + ArC), 129.5, 128.9, 124.9, 120.5, 115.0 (ArC), 81.9 (CH-O), 63.3 (CH–N), 40.4 (CH_2–N), 30.7–28.0 (m, CH_2–P), 26.9 ppm (CH_2); ^{31}P NMR ([D$_6$]acetone, 121.4 MHz): $\delta=$ 42.9 ppm (s, $J_{Pt-P}=2621.9$ Hz); ^{19}F NMR ([D$_6$]acetone, 282 MHz): $\delta=$ −78.9 ppm; IR (film): $\tilde{\nu}=3057$, 2923, 2087 (C≡C), 1756 (C=O), 1596, 1493, 1277, 1259, 1233 (C–O), 1159, 1105, 1030, 825, 753 cm^{-1}; FABMS: 1264.9 $[M-OTf]^+$.

AgOTf complex 26: Complex **22** (15 mg, 12 μmol) and AgOTf (3.3 mg, 12 μmol) were added together in $CDCl_3$ (4 mL). After 3 h, AgOTf complex **26** (12 mg, 65 %) was obtained as a light brown solid. ^{1}H NMR ([D$_6$]acetone, 300 MHz): $\delta=7.94$–7.81 (m, 4H, ArH), 7.74–7.58 (m, 12H, ArH), 7.32–7.02 (m, 16H, ArH), 6.94–6.84 (m, 6H, ArH), 5.57 (d, $J=$ 4.3 Hz, 2H, CH–O), 5.23 (br s, 2H, CH–N), 3.64–3.55 (m, 2H, CH_2–N), 2.97–2.68 (m, 6H, CH_2–N + CH_2–P), 1.63–1.55 ppm (m, 2H, CH_2); ^{13}C NMR ([D$_6$]acetone, 176.0 MHz): $\delta=165.2$ (C=O), 157.0, 133.9–133.6 (m, dppe), 132.9–132.5 (m, dppe), 131.7, 130.4–130.2 (m, dppe), 129.5, 129.4–129.3 (m, dppe), 122.2, 115.3, (ArC), 82.6 (CH–O), 63.4 (CH–N), 41.7 (CH_2–N), 29.6.7–28.5 (m, CH_2–P), 29.4 ppm (CH_2); ^{31}P NMR ([D$_6$]acetone, 121.4 MHz): $\delta=42.4$ ppm ($J_{Pt-P}=2577.9$ Hz); ^{19}F NMR ([D$_6$]acetone, 282 MHz): $\delta=-79.1$ ppm; IR (film): $\tilde{\nu}=3061$, 2960, 2919, 2056 (C≡C), 1761 (C=O), 1594, 1491, 1261, 1233 (C–O), 1159, 1102, 1030, 801, 754 cm^{-1}; ESI-MS: 1264.23 $[M-OTf]^+$.

AgOTf complexes 27: The mixture of diastereoisomers **23a**,**b** (20 mg, 8 μmol) and AgOTf (4.5 mg, 17 μmol) were mixed together in $CDCl_3$ (5 mL). After 3 h, AgOTf complexes **27** (18 mg, 75 %; mixture of diastereoisomers) were obtained as a light brown solid. ^{1}H NMR ([D$_6$]acetone, 300 MHz): $\delta=8.07$–7.73 (m, 16H, ArH), 7.72–7.30 (m, 24H, ArH), 7.23–7.02 (m, 16H, ArH), 6.97–6.60 (m, 20H, ArH), 5.56–5.52 (m, 4H, CH-O), 5.13–5.08 (m, 4H, CH-N), 3.44–3.26 (m, 4H, CH_2-N), 3.15–2.83 (m, 12H, CH_2-N + CH_2-P), 1.41–1.26 ppm (m, 4H, CH_2); ^{13}C NMR ([D$_6$]acetone, 75.5 MHz): $\delta=165.5$, 165.4 (C=O), 157.8, 156.7, 135.5, 135.4, 133.9–133.8 (m, dppe), 133.5–133.4 (m, dppe), 132.8–132.7 (m, dppe), 132.4, 132.1, 132.09, 132.03, 131.3, 131.2, 129.4–129.1 (m, dppe), 128.8, 128.5, 122.4, 122.3, 121.8, 121.7, 115.1, 114.9 (ArC), 81.9, 81.6 (CH–O), 62.8, 62.7 (CH–N), 40.1, 40.0 (CH_2–N), 29.8–28.8 (m, CH_2–P), 28.0, 27.8 ppm (CH_2); ^{31}P NMR ([D$_6$]acetone, 121.4 MHz): $\delta=44.0$ ($J_{Pt-P}=2516.1$ Hz), 43.9 ppm ($J_{Pt-P}=2510.8$ Hz); ^{19}F NMR ([D$_6$]acetone, 282 MHz): $\delta=-78.9$ ppm; IR (film): $\tilde{\nu}=3064$, 2926, 2854, 1759 (C=O), 1597, 1494, 1284, 1237 (C–O), 1168, 1108, 1031, 826, 756 cm^{-1}; ESI-MS: 2680.40 $[M-OTf]^+$, 2421.57 $[M-Ag-2OTf]^+$, 1264.74 $[M-2OTf]^{2+}$.

AgOTf complexes 28: The mixture of diastereoisomers **24a**,**b** (15 mg, 6 μmol) and AgOTf (3.3 mg, 12 μmol) were added together in $CDCl_3$ (4 mL). After 3 h, AgOTf complexes **28** (11 mg, 60 %; mixture of diastereoisomers) were obtained as a light-brown solid. ^{1}H NMR ([D$_6$]acetone, 300 MHz): $\delta=8.10$–7.86 (m, 16H, ArH), 7.75–7.29 (m, 24H, ArH), 7.20–6.89 (m, 24H, ArH), 6.77–6.64 (m, 12H, ArH), 5.51–5.43 (m, 4H, CH–O), 5.02–4.93 (m, 4H, CH–N), 3.54–2.75 (m, 16H, CH_2–N), 1.44–1.20 ppm (m, 4H, CH_2); ^{13}C NMR ([D$_6$]acetone, 176.0 MHz): $\delta=165.1$, 164.9 (C=O), 156.9, 135.8, 135.5, 134.1–133.9 (m, dppe), 133.6–133.4 (m,

dppe), 132.7–132.6 (m, dppe), 132.5, 132.3, 132.2, 131.9, 131.3, 129.6–129.4 (m, dppe), 129.3, 129.2, 129.17, 129.10, 128.6, 128.5, 128.0, 122.6, 122.5, 121.9, 121.8, 120.3, 115.3, 115.2 (ArC), 82.2, 82.0 (CH–O), 62.3, 62.2 (CH–N), 39.5, 39.4 (CH_2–N), 31.7–28.1 (m, CH_2–P), 26.9, 26.8 ppm (CH_2); ^{31}P NMR ([D$_6$]acetone, 121.4 MHz): $\delta = 44.2$ (s, $J_{Pt-P} = 2504.2$ Hz), 43.4 ppm (s, $J_{Pt-P} = 2522.9$ Hz); ^{19}F NMR ([D$_6$]acetone, 282 MHz): $\delta = -79.0$ ppm; IR (film): $\tilde{\nu} = 3058$, 2959, 2920, 2853, 1760 (C=O), 1594, 1491, 1260, 1235 (C-O), 1162, 1101, 1031, 801, 754 cm^{-1}; FABMS: 2680.6 [M–OTf]$^+$ 2424.0 [M–Ag–2OTf]$^+$.

X-ray data collection and structure refinement for compound 16: A suitable crystal for X-ray-diffraction experiments was obtained by crystallization of **16** from MeOH/Et_2O. Data collection was carried out at room temperature on a Bruker Smart CCD diffractometer by using graphite-monochromated $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å) operating at 50 kV and 30 mA. Data were collected over a hemisphere of the reciprocal space by combination of three exposure sets. Each exposure of 30 s covered 0.3 in ω. The first 100 frames were recollected at the end of the data collection to monitor crystal decay, and no appreciable decay was observed.

A summary of the fundamental crystal and refinement data is given in Table 1. The structure was solved by direct methods and refined by full-matrix least-square procedures on F^2 (SHELXL-97).[33] All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included in the calculated positions and refined riding on the respective carbon atoms with some exceptions. Thus, the hydrogen atoms H3, H4, H3', and H4' bonded to C3, C4, C3', and C4' atoms, respectively, were located in a Fourier synthesis and refined riding on the respective carbon bonded atoms. CCDC-718551 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table 1. Crystal data and structure refinement for $C_{37}H_{34}Cl_2N_2O_2Zn$.

empirical formula	$C_{37}H_{34}Cl_2N_2O_2Zn$
formula weight	674.93
temperature [K]	296(2)
wavelength [Å]	0.71073
crystal system	triclinic
space group	$P\bar{1}$
unit cell dimensions	
a [Å], α [°]	8.5548(7), 84.009(2)
b [Å], β [°]	12.4210(10), 82.206(2)
c [Å], γ [°]	16.7526(14), 76.382(2)
volume [Å^3]	1709.2(2)
z	2
ρ_{calcd}	1.311 Mg m^{-3}
μ [mm^{-1}]	0.909
F(000)	700
θ range for data collection	1.23 to 25.00°
index ranges	$-10 \le h \le 10$, $-14 \le k \le 13$, $-19 \le l \le 18$
reflections collected	12135
independent reflections	5496 [R(int) = 0.0857]
completeness to $\theta = 25.00°$	91.3 %
refinement method	full-matrix least-squares on F^2
data/restraints/parameters	5496/0/401
strength of fit on F^2	0.844
final R indices [$I > 2\sigma(I)$]	$R1 = 0.0449$,[a] $wR2 = 0.0845$[b]
R indices (all data)	$R1 = 0.1318$,[a] $wR2 = 0.1070$[b]
largest diff. peak and hole	0.295 and −0.326 e Å^{-3}

[a] $\Sigma[|F_o|-|F_c|]/\Sigma|F_o|$. [b] $\{\Sigma[w(F_o^2-F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$.

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