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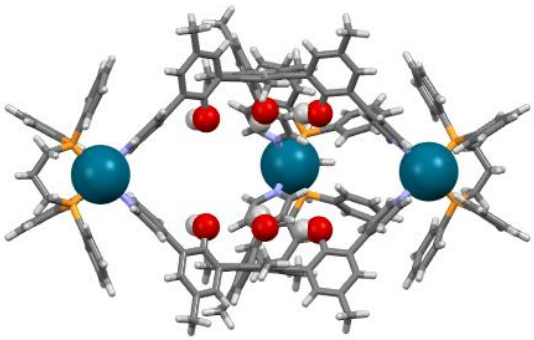
Hexaphenolic Rigid Cages Prepared by Self-Organization of C_{3v} Tridentates

Hajime Abe,[†]* Daisuke Hashikawa,[†] Takaya Minami,[‡] Kohei Ohtani,[†] Kentaro Masuda,[†] Shinya Matsumoto,[‡] and Masahiko Inouye[†]*

[†]Graduate School of Pharmaceutical Sciences, University of Toyama, Toyama 930-0194

[‡]Graduate School of Environment and Information Sciences, Yokohama National University, Yokohama, Kanagawa 240-8501

e-mail: abeh@pha.u-toyama.ac.jp



Abstract

Coordination cages were composed by self-organization of rigid C_{3v}-symmetric heptaarene tridentates and Pd(II) precursors. The heptaarene framework involves one mesitylene, three phenol, and three pyridine moieties which were connected by Suzuki coupling reactions. The treatment of the tridentates with Pd(dppp)$(OTf)_2$ or Pd(en)$(NO_3)_2$ in a 2:3 molar ratio furnished coordination cages, which was ascertained by crystallography, ^{1}H NMR and DOSY measurements, and ESI-TOFMS and UV-vis spectra. The cages have six phenolic hydroxy groups inside and were expected to incorporate hydrogen-bonding guest molecules such as saccharides. CD and DOSY measurements showed that octyl hexoside guests could be incorporated into the cage.

Introduction

Construction of cage-type structures has been one of most important projects in the field of supramolecular chemistry. For this purpose, chemists occasionally utilize self-organization of appropriate combinations of multidentate ligands with metal center precursors.[1–4] The multidentate

ligands are usually designed to have rigidity by the use of sp^2 and *sp*-type atoms. Thus, the resulting cage-type complexes have provided interesting host spaces to recognize, stabilize, and manipulate guest species.

Meanwhile, our group has so far developed host molecules for saccharide recognition from the standpoint of host-guest chemistry. Among the host molecules, we have reported a C_{3v}-symmetric triphenolic compound **1**,[5] which showed satisfactory affinity for glycosides. The three hydroxy groups of **1** are forced to direct to one side of the molecule because the rotation of the biaryl bonds is inhibited by the methyl groups of the mesitylene center. Furthermore, Beletskiy and coworkers revealed that **1** is effective as a multivalent acidic catalyst.[6] Thus the fundamental framework of the host **1** was found to be suitable for the structure of host molecules, and it is due to the rigidity and C_{3v}-symmetry to lower the entropic loss caused by host-guest association. We considered that this framework can also be favorable as parts of self-organizing cage-type complexes.[7] Tridental heptaarene **2** was designed (Figure 1), in which three 4-pyridyl groups were introduced as a coordinating group preserving the original rigidity and symmetry of **1**. The *ortho*-positions of the three phenol groups were considered to be suitable for electrophilic iodination followed by Suzuki-Miyaura coupling. The tridentate **2** was expected to form a M_3L_2-cage-type complex **3** by the addition of a metal center (M) precursor. Herein we describe the preparation of tridentate **2** and construction of cage complex **3**. The resulting cages were expected to have D_{3h} or twisting D_3 symmetry.[2,3] Saccharide recognition by **3** was also studied to make use of the inwardly directed phenolic hydroxy groups.

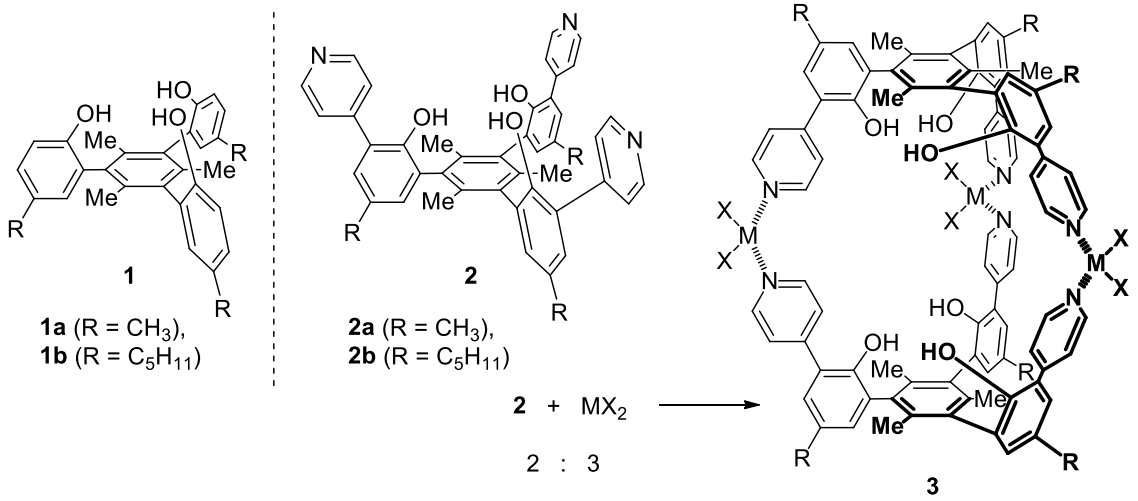


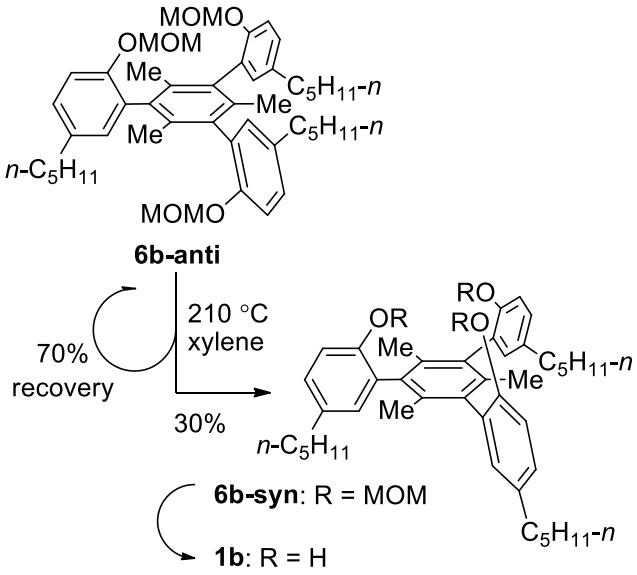
Figure 1. (left) Host molecules **1**, (center) tridentates **2** and (right) formation of cage-type M_3L_2 complexes **3** by self-organization.

Results and Discussion

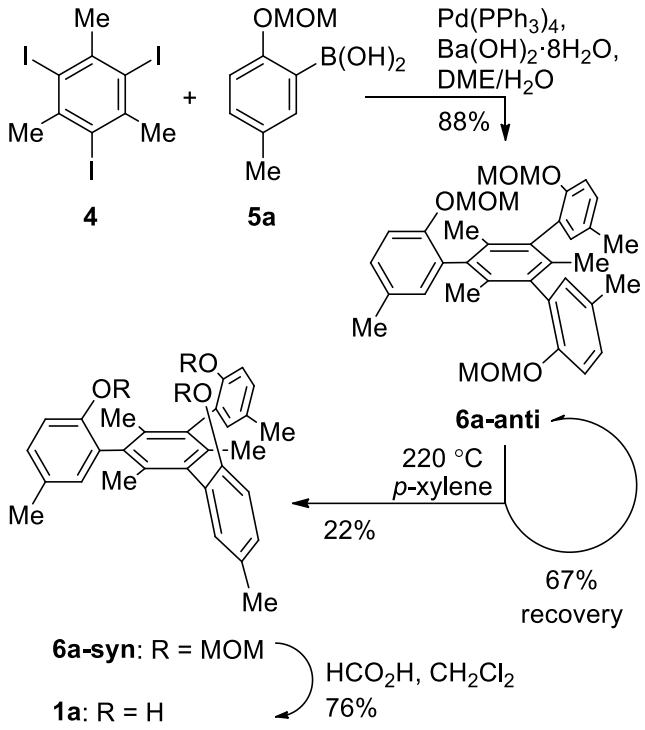
The tridentate **2** has three alkyl groups R to tune solubility, and here we synthesized methyl (**2a**) and pentyl (**2b**) derivatives. The former was used to prepare crystals suitable for X-ray structure analyses, and the latter was used to study properties in a solution phase.

The methyl derivative **2a** was prepared via the syn conformer of 2,4,6-tris(2-hydroxy-5-methylphenyl)mesitylene (**1a**) as an intermediate. The preparation of **1a** could be carried out in a similar way to the case of the pentyl analogue **1b** we previously developed.[5] In the route to **1b**, the key steps were Suzuki-Miyaura coupling to construct the 2,4,6-tris(2-hydroxyphenyl)mesitylene structure and the thermal atropisomerization of the anti conformer **6b-anti** to a mixture with the syn isomer **6b-syn** (Scheme 1).

Scheme 1. Key atropisomerization to prepare 1b (ref 5)

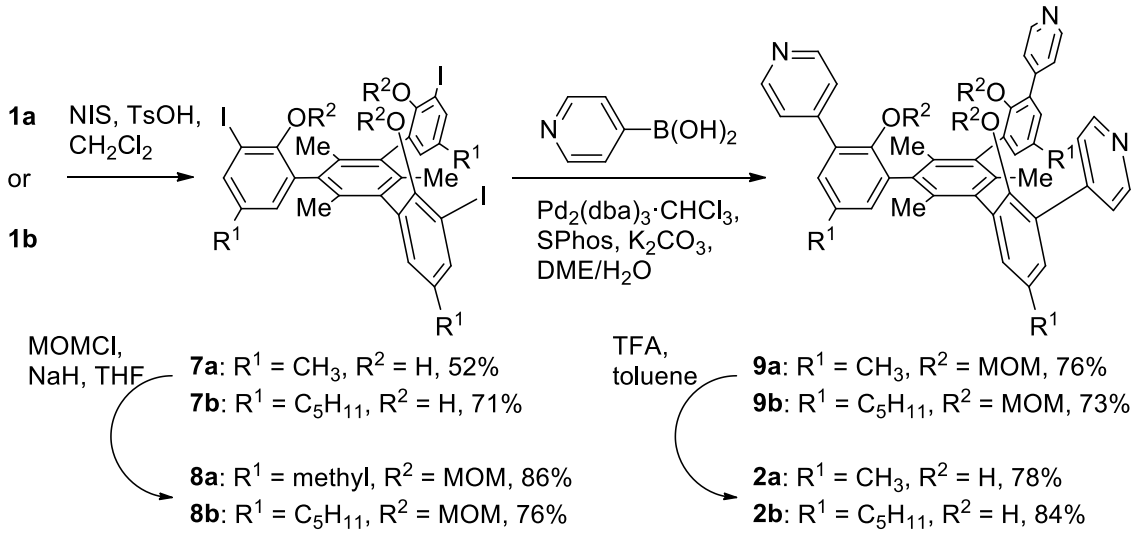


Scheme 2. Preparation of 1a[a]



[a]DME = 1,2-dimethoxyethane.

Scheme 3. Preparation of tridentates 2a and 2b from 1a and 1b[a]



[a]NIS = *N*-iodosuccinimide, dba = dibenzylideneacetone, SPhos = 2-(dicyclohexylphosphino)-2',6'-dimethoxybiphenyl, TFA = trifluoroacetic acid.

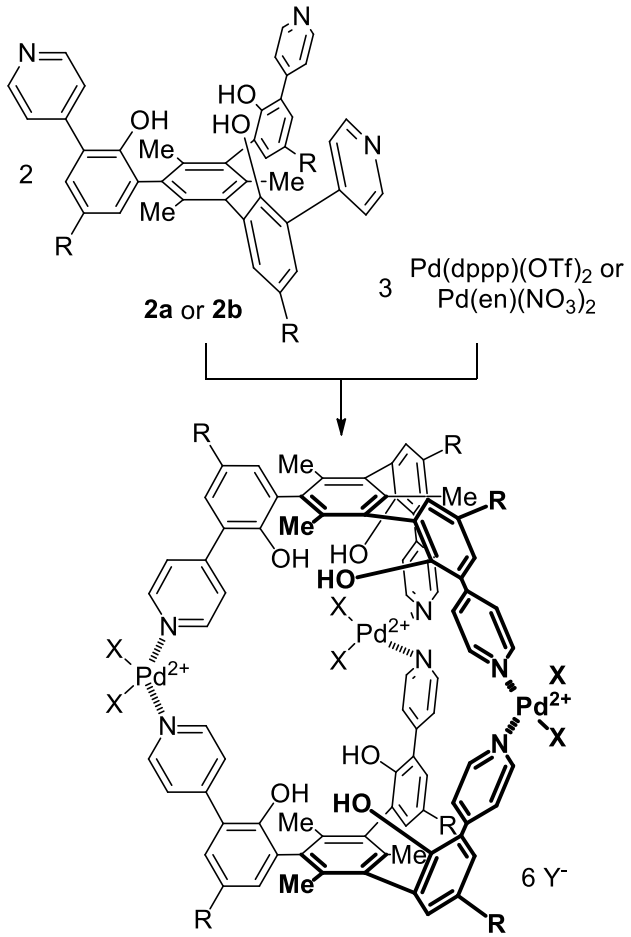
The preparation route to **2a** was shown in Schemes 2 and 3. The Suzuki-Miyaura coupling of 2,4,6-triiodomesitylene[5,8] (**4**) and 2-(methoxymethoxy)-5-methylbenzeneboronic acid[9,10] (**5a**) gave tetraarene product **6a-anti**, conformational isomer of the required intermediate **6a-syn**. When a solution of **6a-anti** in *o*-xylene was heated at 220 °C for 12 h, atropisomerization occurred and the mixture reached the equilibrium mixture involving **6a-anti** and **6a-syn** in yields of 67% and 22%, respectively. The conformers can be separated and purified easily by silica gel column chromatography because the R_f value of **6a-syn** is much smaller than that of **6a-anti**. The MOM groups of **6a-anti** were detached by HCO_2H, and once the product **1a** was isolated as a solid, long preservation at room temperature caused no isomerization to the anti conformer (checked by ^{1}H NMR) at least for a year.

Triiodide **7a** could be obtained by triple iodination of **1a** with *N*-iodosuccinimide (NIS) at the *ortho*-positions of the three phenol units. Then the three hydroxy groups of **7a** were protected again with MOM groups to give **8a**, and the Suzuki-Miyaura coupling of **8a** with pyridine-4-boronic acid gave MOM-protected tridentate **9a**. Finally, the treatment of **9a** with trifluoroacetic acid (TFA) afforded the target tridentate **2a** (Scheme 3).

The target **2b** with pentyl groups was prepared from 4-pentylphenol through **1b**.[5] The synthetic route from **1b** to the target **2b** could be carried out similarly to that from **1a** to **2a** as shown in Scheme 3.

With the target C_{3v}-symmetric tridentates **2a** and **2b** in hands, we studied the construction of cage-type M_3L_2 complexes such as **3a**,**b** by the treatment with Pd(II) precursors (Scheme 4). Mixtures of the tridentates and Pd(II) precursors were subjected to ^{1}H NMR, DOSY, and ESI-TOF-MS analyses in organic solutions, and X-ray crystallography of a single crystal.

Scheme 4. Formation of 3a, 3b, and 3c from 2a and 2b[a]



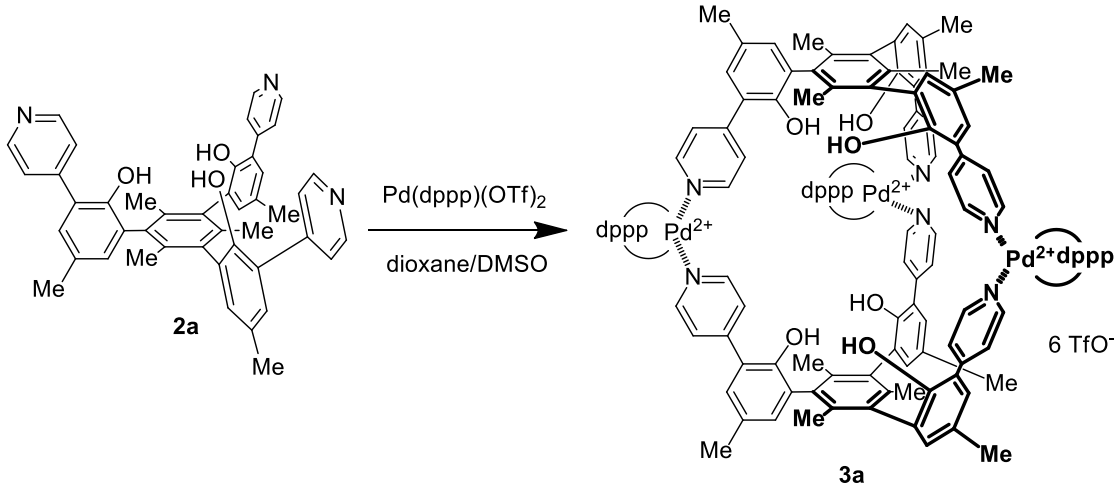
3a: R = methyl, 2X = dppp, Y^- = TfO^-
3b: R = pentyl, 2X = dppp, Y^- = TfO^-
3c: R = pentyl, 2X = en, Y^- = NO_3^-

[a]dppp = 1,3-bis(diphenylphosphino)propane, en = ethylenediamine.

The coordination structure in a solid phase could be investigated by using the methyl-tridentate **2a**. Single crystals could be prepared from **2a** and $Pd(dppp)(OTf)_2$ (2:3) in a mixed solvent 1,4-dioxane/DMSO (Scheme 5). These colorless crystals were subjected to X-ray structure analyses and the locations of Pd(II) centers and almost all atoms of **2a** and dppp ligands could be determined (Figure 2),[11] whereas positions of solvent molecules and triflate anions were so ambiguous to specify that the PLATON-SQUEEZE method was applied.[12] The targeted cage framework could be assured in the crystal phase by this analysis. The plane involving three Pd(II) centers was found to be the symmetry plane of the crystal structure of the cage. The distances between oxygen atoms facing each

other were 0.594, 0.639, and 0.641 nm.

Scheme 5. Preparation of 3a from 2a and Pd(dppp)(OTf)$_2$ in mixed solvent of 1,4-dioxane/DMSO



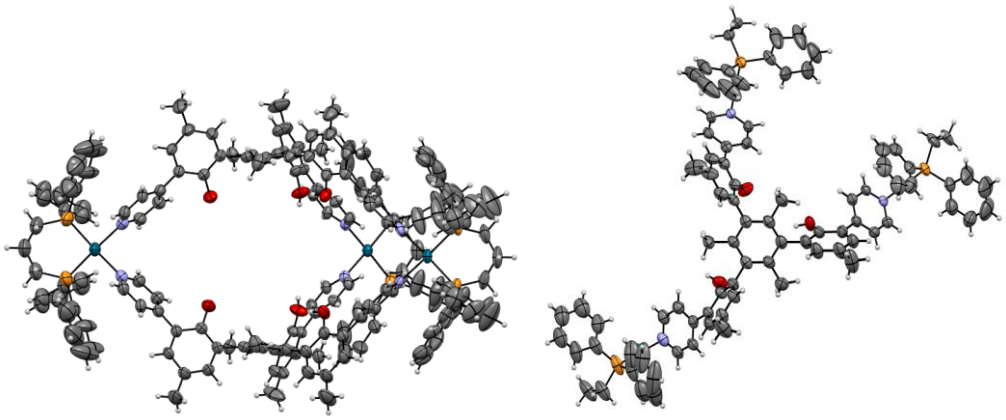


Figure 2. ORTEP diagrams for the crystal structure of **3a**.[a] (left) Side view and (right) top view. Details for conditions and parameters were described in Experimental and Supporting Information. [a]ORTEP plot shown with Gaussian ellipsoids at 50% probability level. Enlarged drawings are shown in Figure S12.

Through the crystallography of **3a**, the validity of the cage structure **3** could be demonstrated. Now the coordination structure in a solution phase was studied by using the pentyl derivative **2b**. A solution of **2b** (2.0×10^{-3} M) and Pd(dppp)(OTf)$_2$ (dppp = 1,3-bis(diphenylphosphino)propane, 3.0

× 10^{-3} M) in a mixed solvent $CDCl_3/CD_3OD$ (9:1 *v*/*v*) was subjected to ^1H NMR measurements. The solubility of **2b** in only $CDCl_3$ was not enough for NMR measurements, so that the mixed solvent of $CDCl_3/CD_3OD$ was applied here. As mentioned below, the coordinated species of **2b** with $Pd(dppp)(OTf)_2$ showed good solubility in $CDCl_3$. The spectrum of the solution was broadened but very simple to suggest high symmetry of the resulting species (Figure 3). The signal of protons H_a (marked as ●) at the 2-positions of the pyridine rings shifted downfield probably because of the coordination of the neighbor nitrogen atoms with Pd(II). On the other hand, the coordination caused upfield shift to the signal of protons H_b (○) at the 3-positions most likely by the change of the dihedral angle between the phenol and the pyridine rings. At the same time, anisotropic upfield shift was also observed for the signal of protons H_c (▼) at the 5-positions of the phenol rings. ^{31}P NMR measurement of the **2b**/$Pd(dppp)(OTf)_2$ mixture showed a single signal at δ −5.87 ppm. The chemical shift of the ^{31}P NMR signal of $Pd(dppp)(OTf)_2$ was δ 17.59 ppm, so it was supported that the cage **3b** formed here, in which all the six P atoms are equivalent as a result of the ligand exchange from triflate to pyridine.

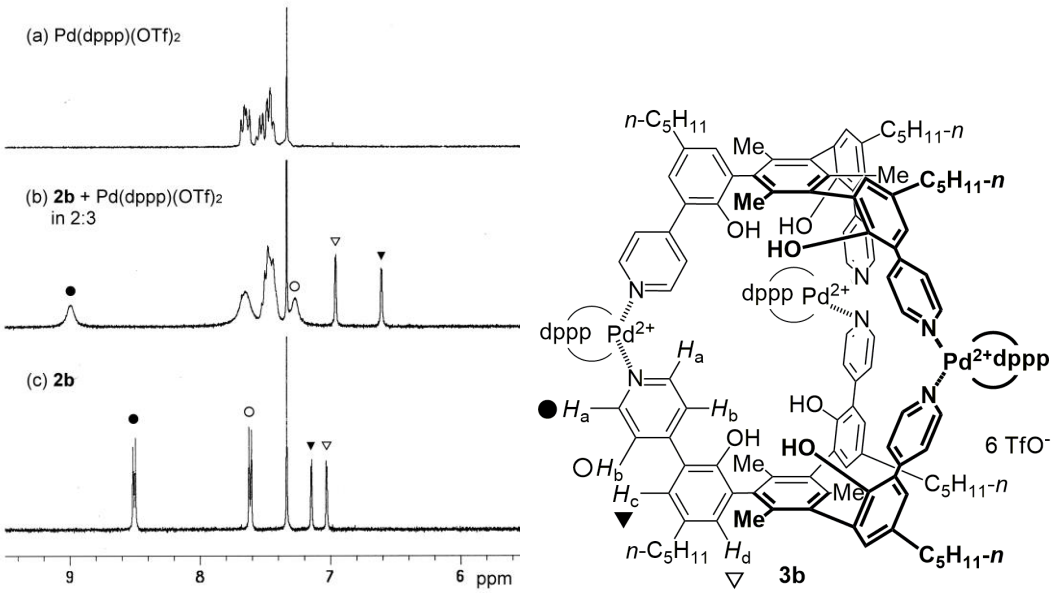


Figure 3. ^1H NMR spectra in $CDCl_3/CD_3OD$ (9:1 *v*/*v*) of (a) $Pd(dppp)(OTf)_2$, (b) a mixture of **2b** + $Pd(dppp)(OTf)_2$ in a 2:3 molar ratio, and (c) **2b**. The signals for pyridine (H_a (●) and H_b (○) in the structure) and phenol units (H_c (▼) and H_d (▽)) are marked with open and filled circles and triangles. Conditions: [**2b**] = 2.0 × 10^{-3} M, [$Pd(dppp)(OTf)_2$] = 3.0 × 10^{-3} M, $CDCl_3/CD_3OD$ (9:1 *v*/*v*), 23 °C, 300 MHz.

Figure S1 in Supporting Information shows the ^{1}H NMR spectra of **2b**/Pd(dppp)(OTf)$_2$ mixtures in different ratios of 2:3, 2:2, and 2:1 in $CDCl_3$ ([**2b**] = 2.0×10^{-3} M). Although **2b** by itself hardly dissolved in chloroform, the addition of the Pd precursor made the solubility much better. The ^{1}H NMR spectra of 2:2 and 2:1 mixtures involve the signal sets of both **2b** and the M_3L_2 complex **3b** independently on the ^{1}H NMR time scale, and the 2:3 mixture showed only one set of the signals of **3b**.

In the DOSY analysis of **3b** by using a mixture of **2b** (1.0×10^{-2} M) and Pd(dppp)(OTf)$_2$ (1.5×10^{-2} M) in $CDCl_3$, all of the C-*H* signals of **2b** and dppp moieties could be assigned to one diffusion constant $D = 2.8 \times 10^{-10}$ m^{2}s^{-1} (Figure 4a). This finding indicated that **2b** and dppp moieties were involved in one species, and its Stokes radius was calculated as r_s = 1.5 nm from a Stokes-Einstein equation $D = K_B T / 6\pi \eta r_s$. The DOSY analyses of **2b** was also carried out in DMSO-d_6 and gave $D = 1.3 \times 10^{-10}$ m^{2}s^{-1} corresponding to r_s = 1.7 nm.

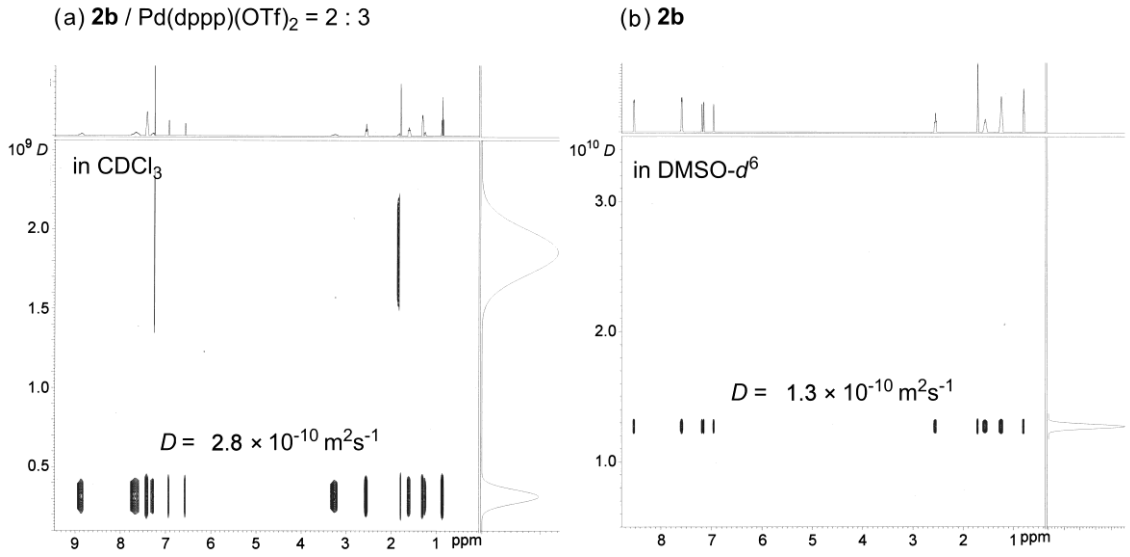


Figure 4. DOSY spectra of (a) **3b** (**2b**/Pd(dppp)(OTf)$_2$ (2:3) mixture) in $CDCl_3$, (b) **2b** in DMSO-d_6. Conditions: [**2b**] = 1.0×10^{-2} M, [Pd(dppp)(OTf)$_2$] = 1.5×10^{-2} M, 25 °C, 400 MHz.

ESI-TOF-MS measurements of **3b** were carried out by using a 2:3 molar mixture of **2b** and Pd(dppp)(OTf)$_2$ in $CDCl_3$/MeOH (*ca.* 1:1). As shown in Figure 5, two kinds of molecular ions corresponding to the Pd_3L_2 species, $[(\mathbf{2b})_2(Pd(dppp))_3(TfO)_4]^{2+}$ (= **3b** − 2TfO$^-$) and

$[(\mathbf{2b})_2(\text{Pd(dppp)})_3(\text{TfO})_5]^+$ (= **3b** − TfO^-), were observed.

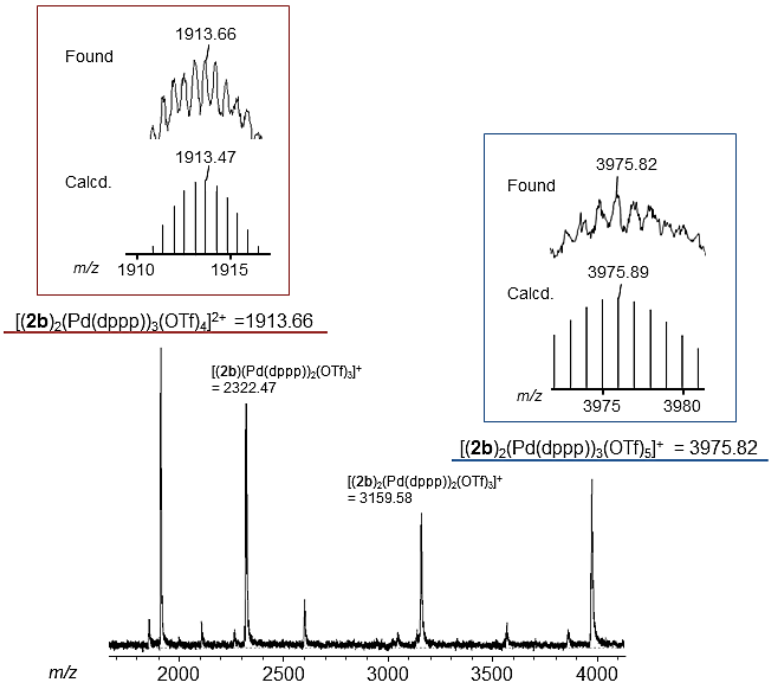


Figure 5. ESI-TOF-MS spectrum of a 2:3 molar mixture of **2b** and Pd(dppp)(OTf)_2. Sample: **2b** (*ca.* 1×10^{-2} M) and Pd(dppp)(OTf)_2 in CDCl_3/MeOH (*ca.* 1:1).

UV-vis spectra were measured for solutions of **2b** (1.6×10^{-4} M), Pd(dppp)(OTf)_2 (2.3×10^{-3} M), and **3b** (a mixture of **2b** (1.6×10^{-4} M) and Pd(dppp)(OTf)_2 (2.3×10^{-4} M)) in CH_2Cl_2 (Figure 6). The spectrum of **3b** was much different from the sum spectrum of the spectra of **2b** and the Pd(dppp)(OTf)_2 because of coordination.

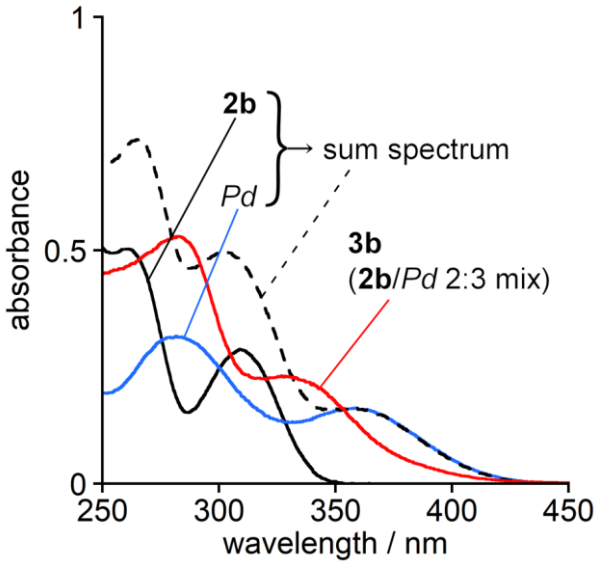


Figure 6. UV-vis spectra in CH_2Cl_2 of (black solid) **2b** (1.6×10^{-4} M), (blue) Pd(dppp)$(OTf)_2$ (2.3×10^{-4} M), (black broken) the sum spectrum of these two spectra, and (red) **3b**, a mixture of **2b** (1.6×10^{-4} M) and Pd(dppp)$(OTf)_2$ (2.3×10^{-4} M). Conditions: CH_2Cl_2, 23 °C, path length = 1 mm.

The concentration dependence was studied for the UV-vis spectrum of **3b** generated from a mixture **2b**/Pd(dppp)$(OTf)_2$ (2:3) in CH_2Cl_2 at a concentration range of [**3b**] = 6.3×10^{-4} to 3.9×10^{-5} M (Figure S2). The plots for the absorbance at 283 and 327 nm obeyed linear laws, and no meaningful concentration dependence was observed for molar absorptivity. Thus, the coordinative organization of **2b** and Pd(II) was strong enough, and no decomposition of the cage framework of **3b** occurred in that concentration range for the study of guest recognition abilities of the cage as mentioned below.

As well as Pd(dppp)$(OTf)_2$, another kind of precursor Pd(en)$(NO_3)_2$ (en = ethylenediamine) was applied.[1d] The construction of Pd_3L_2-type cage complex **3c** (Scheme 4) was assured in DMSO-d_6 on the basis of ^{1}H NMR and DOSY analyses in a manner similar to the case of **3b** (Figures S3 and S4). Solubility of **3c** in apolar solvents such as chloroform and dichloromethane was not enough to carried out further studies.

A DFT calculation was carried out to study the structure of Pd_3L_2 cage after the coordination of **2b** and Pd(II) (2:3), and an optimized structure could be obtained as shown in Figure S5 in the Supporting Information. The distances between opposite pairs of terminal carbons of pentyl groups were in the range of 2.96−2.82 nm from the structure, which is approximately twice of the Stokes radius r_s calculated from the DOSY analysis mentioned above (Figure 4). In this structure the

distances between oxygen atoms facing each other were 0.559, 0.559, and 0.555 nm, slightly short but not so different from those measured in the X-ray structure of **3a** in Figure 2.

Molecular recognition targeting glycosides has been one of the important topics in host-guest chemistry.[13–16] The triphenolic compound **1** was originally developed as a host device for saccharide recognition. Here host ability by the cage complex **3b** was also studied by the use of a series of octyl hexosides, octyl α- and β-D-glucopyranoside (**α-Glc** and **β-Glc**), octyl α- and β-D-mannopyranoside (**α-Man** and **β-Man**), octyl β-D-galactopyranoside (**β-Gal**), and octyl β-D-fructopyranoside (**β-Fru**) (Figure S6).

First, solutions of the cage **3b**, generated from a mixtures of **2b** (2.0×10^{-3} M) and Pd(dppp)$(OTf)_2$ (3.0×10^{-3} M) in $CDCl_3$ with and without **β-Glc** (1.0×10^{-3} M) were prepared and their ^{1}H NMR spectra were compared with the ^{1}H NMR spectrum of **β-Glc** (1.0×10^{-3} M) in $CDCl_3$ (Figure 7).

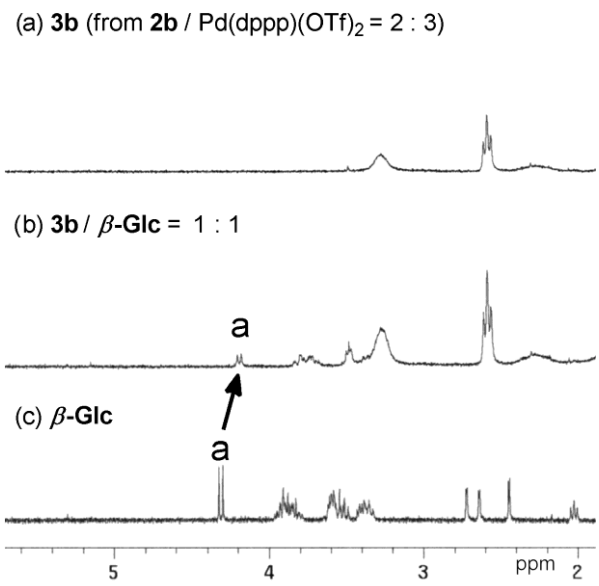


Figure 7. Change of chemical shifts of ^{1}H NMR signals of β-glucoside guest. ^{1}H NMR spectra of (a) **3b**, (b) **3b** + **β-Glc**, and (c) **β-Glc**. Host **3b** was prepared from **2b** and Pd/(dppp)$(OTf)_2$ (2:3). Mark "a" indicate the signals of anomeric proton of **β-Glc**. Conditions: **2b** (2.0×10^{-3} M), Pd(dppp)$(OTf)_2$ (3.0×10^{-3} M), **β-Glc** (1.0×10^{-3} M), $CDCl_3$, 300 MHz, 23˚C

The signals of C-*H* protons of **β-Glc** broadened and moved upfield in the presence of **3b**. These changes would be rationalized as anisotropic effects receiving from the cage framework of **3b**. Also other kinds of hexosides received broadening and anisotropic effects from **3b** (Figure S7 in the

Supporting Information). A similar type of upfield shifts for C-*H* signals of the saccharide guests have been observed for our tetraarene host molecules triphenolic **1b**[5] and triresorcinolic one.[17] The addition order of the substrates was irrelevant to the product, for example, when two ^{1}H NMR samples were prepared in different addition orders, **2b** → Pd(dppp)(OTf)$_2$ → ***β*-Glc** and ***β*-Glc** → Pd(dppp)(OTf)$_2$ → **2b**, the spectra were observed to be identical (Figure S8). ^{1}H NMR spectra of mixtures of **3b** and ***β*-Glc** in various ratios showed averaged broad signals, and signals of caged and free guests did not separate (Figure S9). These findings indicated that the guest can easily go in and out of the cage at room temperature. During the titration experiment (see below), no meaningful time-dependence was observed in CD measurements.

DOSY analyses of the cage **3b**, generated from a mixture of **2b** (1.0×10^{-2} M) and Pd(dppp)(OTf)$_2$ (1.5×10^{-2} M), were carried out again in the presence of ***β*-Glc** (5.0×10^{-3} M). The signals of all the C-*H* protons not only **3b** but also ***β*-Glc** could be attributed to a single diffusion constant $D = 2.8 \times 10^{-10}$ m^{2}s^{-1} (Figure 8a). This D value was same as that of **3b** in the absence of ***β*-Glc** ($D = 2.8 \times 10^{-10}$ m^{2}s^{-1}, Figure 4a), so the cage framework was hardly deformed by the addition of the guest. On the other hand, a solution of solely ***β*-Glc** (5.0×10^{-3} M) in CDCl$_3$ showed a much bigger diffusion constant $D = 7.0 \times 10^{-10}$ m^{2}s^{-1} (Figure 8b), indicating that the guest ***β*-Glc** molecules were incorporated in the cage framework of **3b**.

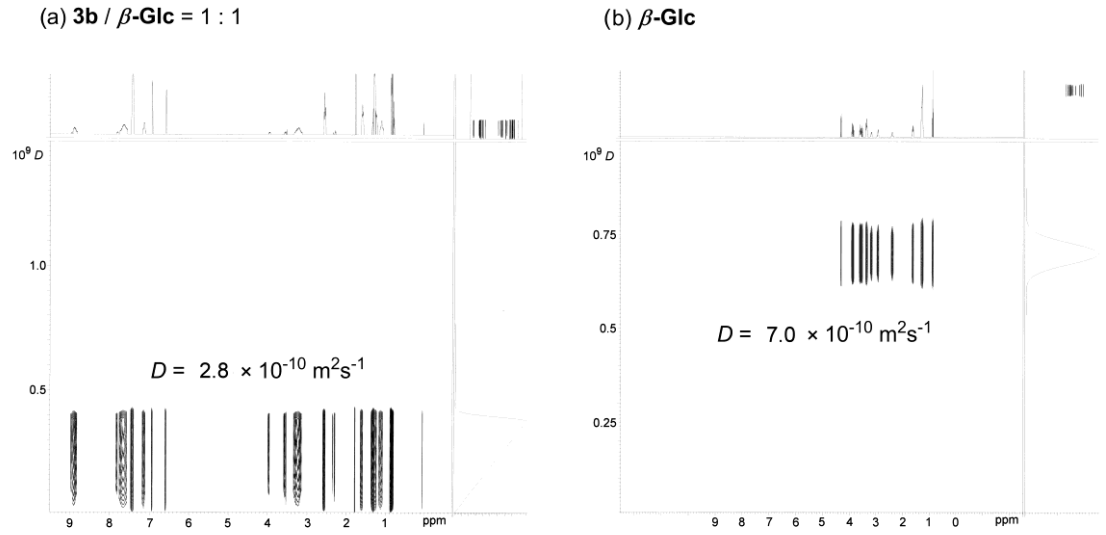


Figure 8. DOSY spectra of (a) **3b** (**2b**/Pd(dppp)(OTf)$_2$ (2:3) mixture) in CDCl$_3$ in the presence of ***β*-Glc**, and (b) ***β*-Glc** in CDCl$_3$. Conditions: **2b** (1.0×10^{-2} M), Pd(dppp)(OTf)$_2$ (1.5×10^{-2} M), ***β*-Glc** (5.0×10^{-3} M), 25 °C, 400 MHz.

The UV-vis spectrum of **3b** scarcely changed in the presence of ***β*-Glc** as a guest (Figure S10). When the M_3L_2 cage **3** is incorporating the guest hexoside, chirality can be induced on its framework by twisting or distortion of the cage. The CD measurements were carried out for **3b** (1.5×10^{-4} M), generated from the mixture of **2b** (3.0×10^{-4} M) and Pd(dppp)$(OTf)_2$ (4.5×10^{-4} M), in the presence of octyl hexosides (1.5×10^{-4} M). The spectra were summarized in Figure 9A and it was found that three kinds of guest ***β*-Glc**, ***β*-Gal**, and ***β*-Man** induced Cotton effects at the absorptive range of the cage.

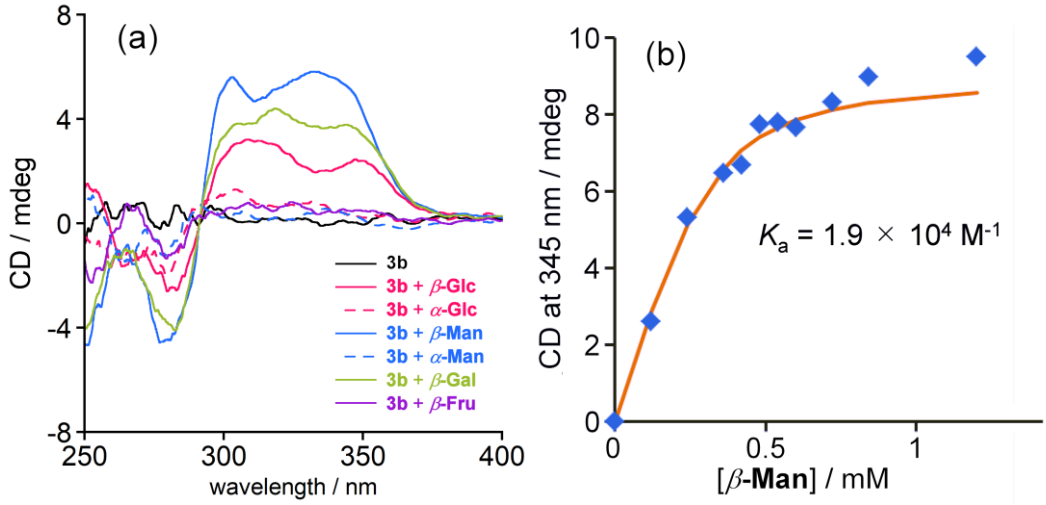


Figure 9. (a) CD spectra of mixtures of **3b** with octyl hexosides. Conditions: **2b** (3.0×10^{-4} M), Pd(dppp)$(OTf)_2$ (4.5×10^{-4} M), octyl hexoside (1.5×10^{-4} M), CH_2Cl_2, 25 °C, path length = 1 mm. (b) The titration curve from CD spectrum of **3b** at 345 nm by the addition of ***β*-Man**. The line is the fitted curve assuming 1:1 binding. The corresponding CD spectra were shown in Figure S11. Conditions: **2b** (6.0×10^{-4} M), Pd(dppp)$(OTf)_2$ (9.0×10^{-4} M), ***β*-Man** (0 to 1.2×10^{-3} M), CH_2Cl_2, 25 °C, path length = 1 mm.

Among the hexoside guests, ***β*-Man** induced the strongest Cotton effect around 300 − 350 nm (Figure 9A, blue solid line). A titration experiment was carried out by using ***β*-Man** as a titrant in CH_2Cl_2. The spectral changes were shown in Figure S11, and the association constant assuming 1:1 binding was obtained as $K_a = 1.9 \times 10^4$ mol L^{-1} from the titration curve plotting the CD change at 345 nm (Figure 9B). This K_a value was slightly stronger than that between **1b** and ***β*-Man** we reported previously ($K_a = 1.5 \times 10^4$ mol L^{-1}).[5] Allosteric effect seemed to be limited among the six

hydroxy groups of **3b** and those of the hexoside guest.

In conclusion, L_2M_3-type cage complexes **3a-c** could be constructed by the use of rigid C_{3v}-symmetric tridentates **2** with Pd(II) precursors. The formation of the cage structures could be ascertained on the basis of ^{1}H NMR, DOSY, ESI-TOF-MS analyses, and X-ray crystallography. The cage **3b** was found to incorporate octyl glycosides as guests with displaying Cotton effects. The CD titration showed that association between **3b** and octyl β-mannoside was slightly stronger than that using the triphenolic parent **1b**. We are now looking for guests incorporated tightly within cages **3** much efficiently to utilize the cage as a host molecule and a solubilizing agent.

Experimental Section

General.

^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on a Varian Gemini 300, a JEOL ECX-400P, and a JEOL ECA500II spectrometers using tetramethylsilane (TMS) and H_3PO_4 as internal references. ESI-HRMS analyses were carried out on a JEOL JMS-T100LC mass spectrometer. IR spectra were measured with a JASCO FT/IR-460plus spectrometer. Melting points were determined with a Yanako MP-500D and not corrected. THF was distilled from sodium benzophenone ketyl before use. Other commercially available reagents and solvents were used without further purification. *anti*-1,3,5-Tris(2-hydroxy-5-pentylphenyl)-2,4,6-trimethylbenzene (**1b**)[5] and 2,4,6-triiodomesitylene (**4**)[5,8] were prepared according to the procedures in the literature.

2-(Methoxymethoxy)-5-methylbenzeneboronic acid (5a).

To a solution of 4-(methoxymethoxy)toluene (17.5 g, 115 mmol) in THF (320 mL) was added *n*-BuLi (2.6 M in hexane, 49 mL, 127 mmol) at 0 °C. The mixture was stirred at that temperature for 2 h, then B(O*i*-Pr)$_3$ (32 g, 172 mmol) was added in one portion to the mixture, which was additionally stirred for 1 h, being allowed to room temperature. The reaction mixture was quenched with a saturated aqueous NH_4Cl solution and stirred for 1 h at room temperature. The resulting mixture was extracted with AcOEt (50 mL × 3), and the combined organic layer was washed with brine and dried over $MgSO_4$, and concentrated by a rotary evaporator. The resulting residue was washed with hexane (50 mL × 3) to give **5a** (14 g, 62%) as a colorless solid. ^{1}H and ^{13}C NMR spectra of this product matched with those reported by Naruta and coworkers.[10] Mp 80 − 83 °C; IR (KBr) ν_{max} 3349, 3008, 2958, 2927, 2911, 2826, 1491 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.31 (3 H, s), 3.50 (3 H, s), 5.26 (2 H, s), 6.78 (2 H, s), 7.02 (1 H, d, J = 8.4 Hz), 7.21 (1 H, d, J = 8.4 Hz), 7.67

(1 H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.1, 56.4, 94.6, 113.2, 131.3, 133.1, 137.0, 160.1; HRMS (ESI-TOF) *m/z*: $[M + 2MeOH - 2H_2O + Na]^+$ Calcd for $C_{11}H_{17}BNaO_4$ 247.1118; Found 247.1126.

***anti*-1,3,5-Tris(2-(methoxymethoxy)-5-methylphenyl)-2,4,6-trimethylbenzene (6a-anti).** A mixture of **5** (8.0 g, 41 mmol), 2,4,6-triiodomesitylene[5,8] (**4**, 4.06 g, 8.2 mmol), $Pd(PPh_3)_4$ (565 mg, 0.49 mmol), and $Ba(OH)_2 \cdot 8H_2O$ (23.3 g, 82 mmol), 1,2-dimethoxyethane (200 mL), and water (30 mL) was stirred under reflux for 24 h. The resulting mixture was concentrated and subjected to silica gel column chromatography (eluent: hexane/CH_2Cl_2 = 4:1) to afford **6a-anti** (4.1 g, 88%) as a colorless solid. Mp 178−179 °C; IR (KBr) ν_{max} 2952, 2924, 2824, 1497 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.73 (9 H, s), 2.31 (9 H, s), 3.30 (6 H, s), 3.35 (3 H, s), 4.98 (4 H, s), 5.06 (2 H, s), 6.90 (1 H, s), 6.97 (2 H, s), 7.06−7.10 (6 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.8, 18.9, 20.7, 55.7, 94.8, 95.2, 115.5, 116.1, 128.4, 131.2, 131.5, 131.65, 131.70, 131.8, 132.2, 133.6, 135.4, 135.5, 152.0, 152.2; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{36}H_{42}NaO_6$ 593.2879; Found 593.2897.

***syn*-1,3,5-Tris(2-(methoxymethoxy)-5-methylphenyl)-2,4,6-trimethylbenzene (6a-syn). Thermal atropisomerization of 6a-anti.** A solution of **6a-anti** (4.7 g, 8.3 mmol) in *o*-xylene (20 mL) was set in an autoclave reactor and stirred at 220 °C for 12 h. The resulting solution was concentrated by a rotary evaporator and subjected to silica gel column chromatography (eluent: CH_2Cl_2) to collect recovered **6a-anti** (3.18 g, 67%) and **6a-syn** (1.05 g, 22%) as a colorless solid. Mp 151−154 °C; IR (KBr) ν_{max} 2923, 2822, 1497 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.75 (9 H, s), 2.32 (9 H, s), 3.27 (9 H, s), 4.91 (6 H, s), 6.98 (3 H, s), 7.02−7.11 (6 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.9, 20.8, 55.7, 95.3, 116.3, 128.4, 131.7, 132.3, 133.8, 135.6, 151.9; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{36}H_{42}NaO_6$ 593.2879; Found 593.2895.

***syn*-1,3,5-Tris(2-hydroxy-5-methylphenyl)-2,4,6-trimethylbenzene (1a).**

A mixture of **6a-syn** (107 mg, 0.19 mmol), HCO_2H (3 mL), and CH_2Cl_2 (5 mL) was stirred for 20 h at room temperature. The resulting mixture was concentrated by a rotary evaporator and subjected to silica gel column chromatography (eluent: CH_2Cl_2/MeOH = 100:1) to give **1a** (62 mg, 76%) as a colorless solid. Mp 302 °C (dec); IR (KBr) ν_{max} 3419 (br), 3018, 2922, 2863, 1496 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.72 (9 H, s), 2.29 (9 H, s), 6.19 (3 H, br s), 6.72 (3 H, d, *J* = 8.1 Hz), 6.89 (3 H, s), 6.99 (3 H, d, *J* = 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.3, 20.7, 115.3, 127.5, 129.0, 129.9, 130.4, 134.9, 136.7, 150.1; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{30}H_{30}NaO_3$ 461.2093; Found 461.2082.

***syn*-1,3,5-Tris(2-hydroxy-3-iodo-5-methylphenyl)-2,4,6-trimethylbenzene (7a).**

To a mixture of **1a** (400 mg, 0.91 mmol) and *p*-toluenesulfonic acid (52 mg, 0.27 mmol) in MeOH (5 mL) was added *N*-iodosuccinimide (NIS) (677 mg, 3.0 mmol) and the mixture was stirred for 1 h at room temperature. After that a 10% aqueous solution of $Na_2S_2O_3$ (5 mL) was added to the reaction mixture, which was stirred until that the color of iodine faded. The resulting mixture was extracted with CH_2Cl_2 (10 mL × 2), and the combined organic layer was dried over $MgSO_4$, concentrated by a rotary evaporator, and subjected to silica gel column chromatography (eluent: CH_2Cl_2) to give **7a** (390 mg, 52%) as a colorless solid. Mp 282 °C (dec); IR (KBr) ν_{max} 3368 (br), 3013, 2918, 2859, 1458 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.74 (9 H, s), 2.28 (9 H, s), 6.29 (3 H, br s), 6.86 (3 H, s), 7.53 (3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.5, 20.1, 84.6, 126.8, 130.7, 131.8, 134.9, 136.6, 138.2, 149.7; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{30}H_{27}I_3NaO_3$ 838.8992; Found 838.8965.

***syn*-1,3,5-Tris(2-hydroxy-3-iodo-5-pentylphenyl)-2,4,6-trimethylbenzene** (**7b**).

To a mixture of **1b**[5] (230 mg, 0.38 mmol) and *p*-toluenesulfonic acid (5.7 mg, 0.03 mmol) in CH_2Cl_2 (20 ml) was added *N*-iodosuccinimide (NIS) (22 mg, 0.11 mmol) and the mixture was stirred for 1 h at room temperature. After that a 10% aqueous solution of $Na_2S_2O_3$ (10 mL) was added to the reaction mixture, which was stirred until that the color of iodine faded. The resulting mixture was extracted with CH_2Cl_2 (10 mL × 2), and the combined organic layer was dried over $MgSO_4$, concentrated by a rotary evaporator, and subjected to silica gel column chromatography (eluent: CH_2Cl_2) to give **7b** (240 mg, 59%) as a colorless solid. Mp 154−157 °C; IR (KBr) ν_{max} 3570, 3468, 3360, 2953, 2927, 2855, 1460 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (9 H, t, J = 6.9 Hz), 1.26−1.31 (12 H, m), 1.55−1.61 (6 H, m), 1.75 (9 H, s), 2.52 (6 H, t, J = 7.8 Hz), 6.24 (3 H, br s), 6.88 (3 H, s), 7.52 (3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 18.4, 22.5, 31.2, 31.3, 34.5, 84.8, 126.7, 135.0, 136.6, 135.0, 137.0, 137.5, 149.8; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{42}H_{51}I_3NaO_3$ ($[M + Na]^+$) 1007.0870; Found 1007.0909.

***syn*-1,3,5-Tris(2-(methoxymethoxy)-3-iodo-5-methylphenyl)-2,4,6-trimethylbenzene** (**8a**). To a suspension of NaH (47 mg, 1.2 mmol; commercial 55% dispersion was washed thoroughly with hexane before use) in THF (7 mL) were subsequently added a solution of **7a** (247 mg, 0.3 mmol) in THF (5 mL) and chloromethyl methyl ether (0.11 mg, 1.36 mmol) at 0 °C. After the mixture was stirred at 0 °C for 3 h, to the mixture were added a saturated aqueous $NaHCO_3$ solution (5 mL) and AcOEt (10 mL), and the organic layer was separated and concentrated by a rotary evaporator. Water (10 mL) was added to the resulting residue and extracted with AcOEt (5 mL × 2), and the combined

AcOEt extract was washed with water (5 mL) and a saturated aqueous $NaHCO_3$ solution (5 mL) subsequently, dried over Na_2SO_4, and concentrated by a rotary evaporator. The resulting residue was subjected to silica gel column chromatography (eluent: hexane/CH_2Cl_2 = 1:1) to give **8a** (246 mg, 86%) as a colorless solid. Mp 234−236 °C; IR (KBr) ν_{max} 2991, 2921, 2825, 1450, 1436 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.79 (9 H, s), 2.28 (9 H, s), 3.51 (9 H, s), 4.60 (6 H, s), 6.88 (3 H, s), 7.64 (3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 20.3, 58.3, 93.0, 98.2, 132.4, 134.2, 134.3, 135.4, 136.2, 139.0, 151.4; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{36}H_{39}I_3NaO_6$ 970.9778; Found 970.9813.

***syn*-1,3,5-Tris(2-(methoxymethoxy)-3-iodo-5-pentylphenyl)-2,4,6-trimethylbenzene (8b)**. To a suspension of NaH (49 mg, 1.2 mmol; commercial 55% dispersion was washed thoroughly with hexane before use) in THF (5 mL) were subsequently added a solution of **7b** (300 mg, 0.31 mmol) in THF (5 mL) and chloromethyl methyl ether (110 mg, 1.4 mmol) at 0 °C. After the mixture was stirred at 0 °C for 5 h, to the mixture were added a saturated aqueous $NaHCO_3$ solution (10 mL) and AcOEt (15 mL), and the organic layer was separated and concentrated by a rotary evaporator. Water (30 mL) was added to the resulting residue and extracted with AcOEt (15 mL × 2), and the combined AcOEt extract was washed with water (15 mL) and a saturated aqueous $NaHCO_3$ solution (15 mL) subsequently, dried over Na_2SO_4, and concentrated by a rotary evaporator. The resulting residue was subjected to silica gel column chromatography (eluent: hexane/CH_2Cl_2 = 1:1) to give **8b** (261 mg, 76%) as a dilute yellow oil. IR (NaCl) ν_{max} 2955, 2927, 2856, 1454 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (9 H, t, J = 6.6 Hz), 1.25−1.30 (12 H, m), 1.55−1.61 (6 H, m), 1.80 (9 H, s), 2.53 (6 H, t, J = 7.5 Hz), 3.52 (9 H, s), 4.60 (6 H, s), 6.89 (3 H, s), 7.63 (3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 19.1, 22.5, 31.0, 31.3, 34.7, 58.3, 93.1, 98.3, 131.8, 134.1, 134.4, 136.3, 138.4, 140.5, 151.5; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{48}H_{63}I_3NaO_6$ 1139.1656; Found 1139.1666.

***syn*-1,3,5-Tris(2-(methoxymethoxy)-3-(4-pyridyl)-5-methylphenyl)-2,4,6-trimethylbenzene (9a).** A mixture of triiodide **8a** (86 mg, 0.091 mmol), 4-pyridineboronic acid (56 mg, 0.45 mmol), K_2CO_3 (125 mg, 0.91 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (11 mg, 0.009 mmol), and 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (17 mg, 0.036 mmol), 1,2-dimethoxyethane (8 mL), and water (1.5 mL) was stirred under reflux for 20 h. The resulting mixture was concentrated and subjected to silica gel column chromatography (eluent: CH_2Cl_2/MeOH = 40:1 to 20:1) to give **9a** (55 mg, 76%) as a colorless solid. Mp 133−136 °C; IR (KBr) ν_{max} 3022, 2925, 2836, 1598 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.98 (9 H, s), 2.41 (9 H, s), 2.76 (9 H, s), 4.33 (6 H, s), 7.05 (3 H, s),

7.16 (3 H, s), 7.52 (6 H, d, J = 5.7 Hz), 8.64 (6 H, d, J = 4.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4, 20.9, 56.7, 98.3, 124.6, 130.0, 132.6, 133.5, 134.0, 134.3, 135.1, 136.3, 147.1, 149.1, 149.2; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{51}H_{52}N_3O_6$ 802.3856; Found 802.3864.

***syn*-1,3,5-Tris(2-(methoxymethoxy)-3-(4-pyridyl)-5-pentyllphenyl)-2,4,6-trimethylbenzene (9b).** A mixture of triiodide **8b** (224 mg, 0.21 mmol), 4-pyridineboronic acid (154 mg, 1.25 mmol), K_2CO_3 (288 mg, 2.1 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (11 mg, 0.011 mmol), and 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (17 mg, 0.042 mmol), 1,2-dimethoxyethane (6 mL), and water (1 mL) was stirred under reflux for 20 h. The resulting mixture was concentrated by a rotary evaporator and subjected to silica gel column chromatography (eluent: CH_2Cl_2/MeOH = 80:1 to 20:1) to give **9b** (148 mg, 73%) as a colorless viscous oil. IR (KBr) ν_{max} 2954, 2926, 2855, 1598, 1455 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (9 H, t, J = 6.6 Hz), 1.30−1.37 (12 H, m), 1.64−1.69 (6 H, m), 1.99 (9 H, s), 2.66 (6 H, t, J = 7.5 Hz), 2.77 (9 H, s), 4.34 (6 H, s), 7.08 (3 H, s), 7.16 (3 H, s), 7.53 (6 H, br s), 8.65 (6 H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 19.3, 22.6, 31.2, 31.4, 35.2, 56.7, 98.3, 124.6, 129.3, 132.0, 133.5, 134.4, 135.0, 136.1, 139.1, 147.1, 149.2; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{63}H_{76}N_3O_6$ 970.5734; Found 970.5761.

***syn*-1,3,5-Tris(2-hydroxy-3-(4-pyridyl)-5-methylphenyl)-2,4,6-trimethylbenzene (2a).** A mixture of trifluoroacetic acid (3 mL) and **9b** (300 mg, 0.37 mmol) in toluene (5 mL) was stirred at 90 °C for 2 h . The resulting mixture was concentrated by a rotary evaporator and treated with a saturated aqueous $NaHCO_3$ solution (20 mL). The mixture was extracted with CH_2Cl_2/MeOH = 10 : 1 (20 mL × 2), and the combined organic layer was dried over $MgSO_4$, and concentrated by a rotary evaporator, and subjected to silica gel column chromatography (eluent: CH_2Cl_2/MeOH = 20:1 → 15:1) to give **2a** (195 mg, 78%) as a colorless solid. Mp 275 °C (dec); IR (KBr) ν_{max} 3362 (br), 3023, 2923, 2863, 1604 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$/CD_3OD = 9 : 1) δ 1.85 (9 H, s), 2.39 (9 H, s), 7.03 (3 H, s), 7.16 (3 H, s), 7.62 (6 H, d, J = 6.0 Hz), 8.46 (6 H, d, J = 5.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$/CD_3OD = 9 : 1) δ 18.2, 20.3, 124.3, 125.3, 129.0, 129.7, 130.0, 131.0, 134.8, 136.6, 147.5, 147.8, 148.2; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{45}H_{40}N_3O_3$ 670.3070; Found 670.3075.

***syn*-1,3,5-Tris(2-hydroxy-3-(4-pyridyl)-5-pentylphenyl)-2,4,6-trimethylbenzene (2b)**. A mixture of trifluoroacetic acid (2 mL) and **9b** (148 mg, 0.15 mmol) in toluene (3 mL) was stirred at 90 °C for 2 h . The resulting mixture was concentrated by a rotary evaporator and treated with a saturated aqueous $NaHCO_3$ solution (10 mL). The mixture was extracted with CH_2Cl_2 / MeOH = 10 : 1 (10 mL × 2), and the combined organic layer was dried over $MgSO_4$, and concentrated by a rotary

evaporator, and subjected to silica gel column chromatography (eluent: CH_2Cl_2/MeOH = 20:1 to 15:1) to give **2b** (107 mg, 84%) as a colorless solid. Mp 242−245°C; IR (KBr) ν_{max} 3384 (br), 2955, 2927, 2856, 1604 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 0.84 (9 H, t, J = 6.6 Hz), 1.27−1.31 (12 H, m), 1.57−1.62 (6 H, m), 1.75 (9 H, s), 2.60 (6 H, t, J = 7.8 Hz), 6.99 (3 H, s), 7.23 (3 H, s), 7.25 (3 H, s), 7.64 (6 H, d, J = 5.7 Hz), 8.57 (6 H, br s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.0, 18.3, 22.0, 30.80, 30.84, 34.2, 123.9, 124.7, 127.9, 129.1, 130.0, 134.2, 134.5, 136.3, 146.0, 148.5, 149.0; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{57}H_{64}N_3O_3$ 838.4948; Found 838.4952.

Cage Complex 3b; $\{2(2b)\cdot3[Pd(dppp)]\}^{6+}\cdot6(TfO^-)$. Typical Procedure to prepare a ^1H NMR sample.

To a $CDCl_3$ (1.0 mL) solution of Pd(dppp)$(OTf)_2$ (2.45 mg, 0.0030 mmol) was added tridentate ligand **2b** (1.68 mg, 0.0020 mmol) and the mixture was stirred for 15 min at room temperature. ^1H NMR spectrum of this $CDCl_3$ solution suggested that L_2M_3-type coordination cage formed quantitatively. ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (9 H, t, J = 6.9 Hz), 1.23−1.37 (24 H, m), 1.59−1.64 (12 H, m), 1.80 (18 H, s), 2.25 (6 H, br s), 2.57 (6 H, t, J = 7.5 Hz), 3.26 (12 H, br s), 6.58 (6 H, s), 6.94 (6 H, s), 7.54−7.10 (60 H, br s), 7.72 (12H, br s), 8.87 (12H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0 17.7, 18.4, 22.5, 31.05, 31.17, 34.9, 68.0, 123.9, 126.4, 128.8, 129.3, 130.6, 131.19, 131.44, 132.9, 133.9, 134.9, 136.6, 149.1, 149.8; ^{31}P NMR (400 MHz, $CDCl_3$) δ −5.87 (s). HRMS (ESI-TOF): *m/z* $[(\mathbf{2b})_2\cdot(Pd(dppp)_3(OTf)_5]^+$ Calcd for 3977.9058; Found 3977.8846.

X-ray Crystallography of 3a.

To a suspension of **2a** and Pd(dppp)$(OTf)_2$ (2:3 molar ratio) in 1,4-dioxane was slowly added DMSO until the mixture became homogeneous. Single crystals of **3a** appeared as blocks according to slow vaporization of dioxane during standing at room temperature.

The diffraction data for the single crystal of **3a** were collected at 123 K under a nitrogen atmosphere on a Rigaku XtaLAB P200 diffractometer using graphite-monochromated Cu-$K\alpha$ radiation (λ= 1.54187 Å) and data reduction was performed using CrysAlisPro.[18] The structure of **3a** was solved by direct methods using SHELXT[19] and refined by full-matrix least-squares methods based on F^2 using SHELXL.[20] There were found residual peaks based on solvent molecules and triflate anions inside the cage structure. However, residual peaks could not be assigned to any molecules due to heavy disorder including triflate anions. We then refined these peaks using the SQUEEZE procedure[12] implemented into PLATON software and the analysis was converged. All non-hydrogen atoms were anisotropically refined and the hydrogen atoms were refined with the riding model.

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Supporting Information.

Figures S1−S12, crystallographic data for **3a**, and ^{1}H and ^{13}C NMR data for **5a** and new compounds. X-ray data in CIF format for **3a**. These materials are available free of charge via the Internet at http://pubs.acs.org.

References and Notes

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