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Introduction

Macrocyclic compounds, such as cyclodextrins,¹ crown ethers,² calix[*n*]arenes,³ and cycloparaphenylenes,⁴ are expected to be applied in switchable systems,^{5a} drug delivery,^{5b} and chiral recognition^{5c} because of their unique ability to incorporate guest compounds into the cavities. Such properties of macrocycles are determined by the chemical structures of component units and linkers. Therefore, alteration of the components is a powerful strategy to gain novel macrocycles. For example, simple changes of calix[*n*]arene π -units produced different classes of macrocycles, including calix[*n*]pyrroles,⁶ pillar[*n*]arenes,⁷ prism[*n*]arenes,^{8a} pagoda[*n*]arenes,^{8b,c} and saucer[*n*]arenes.^{8d} However, the synthesis of oligomeric macrocycles often competes against the formation of linear polymers to some extent and even small alteration of the monomeric units or reaction conditions may lead to severe drops in the product yields or changes of preferred ring sizes.^{6–10} By contrast, post-functionalization of macrocycles is a reliable method to alter the properties. However, small effect by one substituent often requires amplification by multi-fold reactions in a highly

Pillar[5]arenes decorated with six-membered-ring aromatics at all the substitution positions†

Tomoya Kaneda,^a Kenichi Kato,^b Shunsuke Ohtani^b and Tomoki Ogoshi^{a,b}

Macrocyclic molecules have characteristic properties different from linear ones, such as high symmetry and guest-inclusion ability. To bring drastic changes to these properties, direct introduction of many substituents is a challenging but effective tool. Herein, we attain direct installation of ten six-membered-ring aromatic π -units into both rims of a pillar[5]arene. In contrast to previous pillar[*n*]arenes with less hindered five-membered-ring units, which showed conformational complexity and crushed crystal structures, the per-phenyl-substituted pillar[5]arene has a cylinder-shaped crystal structure with a dichloromethane inside the cavity and is obtained as a single pair of D_5 -symmetric enantiomers. The average dihedral angles between the core and peripheral benzene rings sharply increase from 38° to 66°. These differences indicate the importance of local steric repulsion on both rims for determining the structures and properties of macrocycles.

efficient and selective manner, which is rarely attained in most macrocycle platforms.¹¹

Pillar[*n*]arene is a highly symmetric cylinder-shaped macrocyclic oligomer of 1,4-dialkoxybenzene with methylene linkers

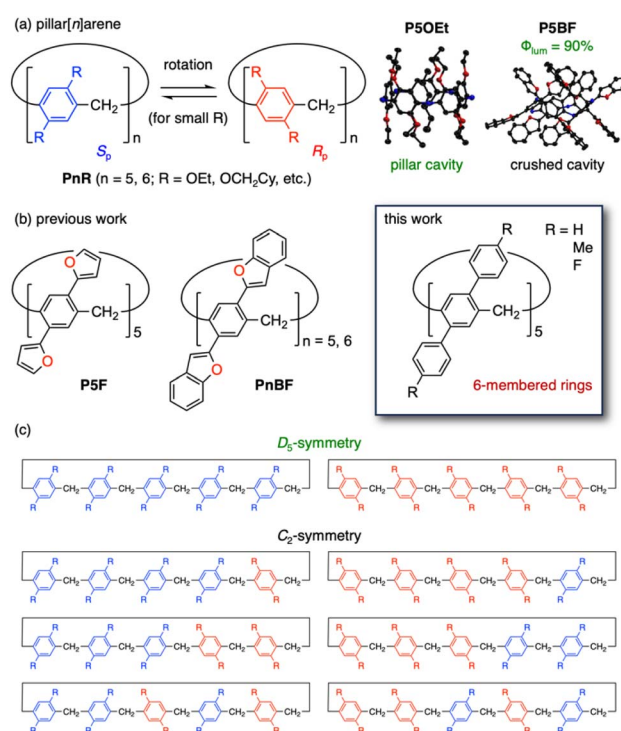


Fig. 1 (a) Chemical structure of pillar[*n*]arene PnR and major differences between per-alkoxy and per-aryl derivatives. (b) Chemical structures of per-aryl-substituted pillar[*n*]arenes. (c) Possible eight isomers of pillar[5]arene P5R.

^aDepartment of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, Katsura, Nishikyo-ku, Kyoto, 615-8510, Japan. E-mail: katok@sbchem.kyoto-u.ac.jp; ogoshi@sbchem.kyoto-u.ac.jp

^bWPI Nano Life Science Institute, Kanazawa University, Kakuma-machi, Kanazawa, 920-1192, Japan

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(Fig. 1a).^{7,12} The pre-installed alkoxy groups are deprotected and resulting phenolic ones are widely used for re-alkylation,^{13b} acylation,^{13c} sulfonation,^{13d,14a} and so on.^{13a,e,f} These modifications have provided a variety of combinations with other functional segments whereas they have hardly perturbed the electronic properties of pillar[*n*]arene cores.

The alkoxy groups have also enabled *ortho*-functionalization¹⁵ and direct replacement with amino,^{16a,b} cyano,^{16c,d} and aryl substituents¹⁷ at a few positions.¹⁴ In addition, we recently found that per-arylation of triflates¹⁴ via Suzuki–Miyaura cross-coupling is possible at one and both rims of pillar[*n*]arenes, overcoming swing suppression and accompanying low reactivity caused by bulky groups on the other rim.^{17f,18} The first per-aryl-substituted pillar[*n*]arenes, **PnBF** (*n* = 5, 6) and **P5F** (Fig. 1b),¹⁸ were obtained by choosing benzofuran- and furan-2-boronic acids respectively, which have less hindered five-membered rings and lack hydrogen atoms on one of two adjoining positions.

Similar to most pillar[*n*]arene derivatives, **P5F** and **P6BF** gave dynamic mixtures of eight or more possible isomers (Fig. 1c) due to the π -unit rotation roughly on the ¹H NMR time scale at room temperature. On the other hand, **P5BF** was resolved into three pairs of enantiomers by chiral high-performance liquid chromatography (HPLC) because the benzofuran rings were large enough to suppress the rotation. This result made a sharp contrast to conventional pillar[*n*]arenes with bulky alkoxy substituents, which yield a single pair of chirality-aligned enantiomers regardless of synthetic routes.^{12,13e,19} Furthermore, the single crystals of **P5BF** and **P5F** showed crushed structures with larger average tilt angles of 29–30° (Table S5-2 in the ESI†) than the angle for a **P5OEt** crystal without guest inclusion (20°).²⁰ These results indicated that stable conformations of pillar[*n*]arenes are determined not only by steric repulsion between substituents on the benzene units but also by multipoint CH/O, CH/ π and other weak interactions between them.

In this study, we further optimize per-arylation reactions of pillar[5]arene to extend the scope to benzene analogues with versatile functionalities. Using a carbene-coordinating Pd-PEPPSI-*i*Pr catalyst,²¹ several benzene analogues can be fully attached to all the substitution positions owing to the excellent stability of the catalyst at elevated temperature. Different from **P5BF**, per-phenyl-substituted product **P5Ph** provides a single *D*₅-symmetric pair with slow conformational interconversion at room temperature and takes a symmetric pillar shape including a dichloromethane in the cavity.

Results and discussion

Full substitution with six-membered-ring aromatics

Initially, per-arylation of pillar[5]arene triflate **P5OTf** (ref. 14a) was attempted with 4-methylphenylboronic acid under the conditions used for the synthesis of per-benzofuranyl pillar[5]arene **P5BF** (ref. 18) (Table 1, entries 1 and 2). However, the reaction did not proceed completely even at higher temperature (entry 3). Mass spectrometry (MS) results included clear peaks for pillar[5]arenes with up to nine-fold substitution but showed only slight peaks for target **P5PhMe**. The ¹H NMR spectrum did not provide a *D*₅-symmetric set of sharp peaks expected for the **P5PhMe**. These results suggested that steric hindrance around the reaction sites was a highly important factor for the direct installation of π -units into pillar[5]arene rims. The installation of benzene derivatives would suffer from more severe steric repulsion due to the six-membered rings with hydrogen atoms at both 2,6-positions than that of furan ones due to the five-membered rings missing a hydrogen on each oxygen atom.

Then, we changed the XPhos Pd G3 catalyst to Pd-PEPPSI-*i*Pr,²¹ which is extremely air- and water-stable, in hopes of remaining active for sufficient duration without forming de-complexed palladium. As expected, the reaction proceeded sufficiently at 60 °C for 24 h (entry 4), giving a MS peak of **P5PhMe** at *m/z* = 1351.7093 (calcd for [C₁₀₅H₉₁]⁺: 1351.7115 [M

Table 1 Suzuki–Miyaura cross coupling of pillar[5]arene triflate^a

Entry	Boronic acid	Pd catalyst	Conditions	Product	Yield
1 (ref. 18)	Benzofuran-2-boronic acid	XPhos Pd G3	1,4-Dioxane/H ₂ O, 100 °C, 21 h	P5BF	50%
2	4-Methylphenylboronic acid	XPhos Pd G3	1,4-Dioxane/H ₂ O, 100 °C, 21 h	P5PhMe	Not detected
3 ^b	4-Methylphenylboronic acid	XPhos Pd G3	1,4-Dioxane/mesitylene/H ₂ O, 120 °C, 20 h	P5PhMe	Trace
4 ^c	4-Methylphenylboronic acid	Pd-PEPPSI- <i>i</i> Pr	1,4-Dioxane, 60 °C, 24 h	P5PhMe	Trace
5 ^c	Phenylboronic acid	Pd-PEPPSI- <i>i</i> Pr	1,4-Dioxane, 100 °C, 24 h	P5Ph	8.3%
6 ^d	Phenylboronic acid	Pd-PEPPSI- <i>i</i> Pr	1,4-Dioxane, 100 °C, 48 h	P5Ph	4.4%

^a Solvent (4.0 mL, 1,4-dioxane/H₂O = 4/1). ^b Solvent (8.2 mL, 1,4-dioxane/mesitylene/H₂O = 4/4/1). ^c 1,4-Dioxane (2.0 mL). ^d Boronic acid (60 equiv.), Pd catalyst (200 mol%), K₂CO₃ (40 equiv.), and 1,4-dioxane (2.0 mL).



+ H⁺). However, the yield was too low to isolate the target. Introduction of sterically demanding substituents into pillar[*n*]arenes was reported to be largely affected by bulkiness not only near the reaction sites but also on the other rim because of limited unit-swing motions. For example, the yield for introduction of five phenyl rings into a methoxy pillar[5]arene was quantitative (1),^{17c} whereas that into a cyclohexylmethoxy one was 26% (2).^{17f} Further drop to 12% was observed when five 4-methoxyphenyl rings were attached (3). Accordingly, we replaced 4-methylphenylboronic acid with phenylboronic acid to minimize the steric repulsion and raised the reaction temperature to 100 °C (entry 5). This entry afforded a *D*₅-symmetric set of ¹H NMR signals, enabling isolation of the target **P5Ph** in 8.3% yield after column chromatography on silica gel and recrystallization from CH₂Cl₂/*n*-hexane (Fig. S3-1 and S4-1†). Finally, the boronic acid, catalyst, and base were doubled in anticipation of increasing yield, which did not lead to further improvement (entry 6).

Characterization of pristine per-phenyl-substituted pillar[5]arene

Crystallography and guest-inclusion behaviour. A single crystal of **P5Ph** was obtained as a racemate with the *Pbcn* space group by vapor diffusion of *n*-hexane into a dichloromethane solution of **P5Ph** (Fig. 2). The crystal structure revealed that one CH₂Cl₂ molecule was included in the cavity of **P5Ph**, and another CH₂Cl₂ was located above the cavity and stuck between two **P5Ph**. Such guest inclusion was observed for typical alkoxy pillar[*n*]arene crystals.^{7a-c} In the packing structure, **P5Ph** molecules formed one-dimensional (1D) channels²² consisting of two layers, which overlapped with a rotation angle of 36° (Fig. S5-2†). The pillar shape of **P5Ph** was characterized by an average tilt angle of 3°, which was much smaller than the values for **P5BF** and **P5F** (29–30°) including CHCl₃ molecules outside the cavities (Table S5-2†). The average dihedral angle between the core and peripheral benzene rings was 66° for **P5Ph**, being slightly above the typical range (50–65°) for partially aryl-substituted compounds (Table S5-3†).¹⁷ The highly unit-twisted conformation was induced probably to avoid locally congested structures around the core benzene, rim-*ortho*, and methylene hydrogens. Such steric hindrance was a reason for taking the pillar shape

different from the crushed shapes of **P5BF** and **P5F** with some inter-unit CH/π and π/π interactions. In fact, the ¹H NMR signals of the *D*₅-symmetric **P5BF** isomer were severely broadened below –40 °C, owing to the exchange between (quasi) stable *C*₁-symmetric conformations. By contrast, those of **P5Ph** were almost unchanged in CD₂Cl₂ at –80 °C, except for suppressed rotation of the phenyl substituents (Fig. S3-5†), indicating the most stable symmetrical pillar shapes in solution.

Typical per-alkoxy pillar[5]arenes show excellent guest-inclusion abilities with linear alkyl segments bearing electron-withdrawing or cationic groups in solution.^{7a-c,23} In contrast, previous per-aryl pillar[5]arene **P5BF** did not show such behaviour because its cavity was crushed in a major conformation and the core benzene units were no longer electron-rich without alkoxy substituents. The host ability of **P5Ph** was also investigated by ¹H NMR spectroscopy. Upon addition of neutral and cationic guests (1,2-dicyanoethane, 1,4-dicyanobutane, and *n*-octyltrimethylammonium hexafluorophosphate), no peak shift or peak appearance/disappearance was detected in CDCl₃ solution (Fig. S3-6 to S3-8†). These results revealed that **P5Ph** did not form complexes with these guest molecules in solution, despite the cavity in the crystal structure like those for per-alkoxy pillar[5]arenes. The poor host ability of **P5Ph** was probably because the cavity was less electron-rich, and the rims were more hindered than those of per-alkoxy compounds (Fig. S5-3†).

Stereoisomers and optical properties. The optical resolution of **P5Ph** was measured by HPLC using a chiral column (Fig. 3a), affording only two major fractions (**f1** and **f2**). These fractions were revealed to be a pair of *D*₅-symmetric enantiomers on the basis of ¹H NMR spectra containing sharp singlet peaks at 6.3 and 4.0 ppm (Fig. 3b). These results were parallel to those of a pillar[5]arene with ten bulky cyclohexylmethoxy groups^{19a} and made a sharp contrast to the previous per-aryl-substituted pillar[5]arenes.¹⁸

The separated isomers, **f1** and **f2**, were then evaluated by ultraviolet/visible (UV/vis) absorption, fluorescence (FL), and circular dichroism (CD) spectroscopy in CHCl₃ (Fig. 4a and b). The **P5Ph** isomers showed broad absorption at around 270 nm and fluorescence at around 360 nm with a quantum yield (Φ_{lum}) of 0.18. In comparison with *p*-terphenyl, which corresponds to the π-unit structure, **P5Ph** showed blue-shifted absorption

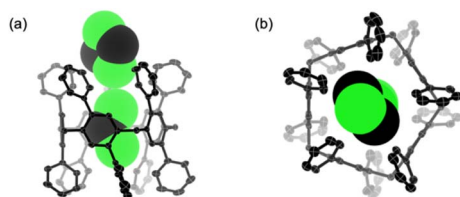


Fig. 2 X-ray crystal structure of **P5Ph**. (a) Side view and (b) top view. The molecule was obtained as a half structure in the asymmetric unit. Two dichloromethane molecules located at the special points were assigned without hydrogen atoms and are displayed with a space-filling model. Thermal ellipsoids are scaled to 50% probability and all hydrogen atoms are omitted for clarity. Element colours: black, carbon; light green, chlorine.

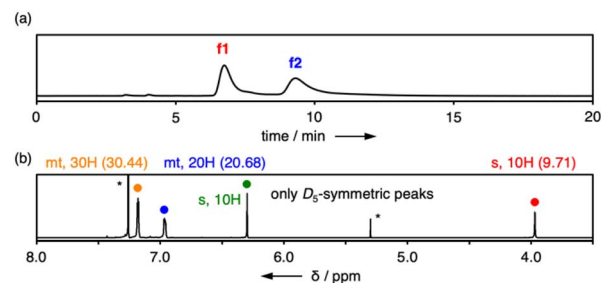


Fig. 3 (a) HPLC chart of *rac*-**P5Ph** recorded as absorption of 250 nm light. Conditions: CHIRALPAK IA ($\phi = 4.6$ mm, $l = 250$ mm) column; room temperature; flow rate = 1.0 mL min⁻¹; eluent = CH₂Cl₂/*n*-hexane (1/10). (b) ¹H NMR (600 MHz) spectrum of an isolated fraction of **P5Ph** in CDCl₃ at 25 °C.



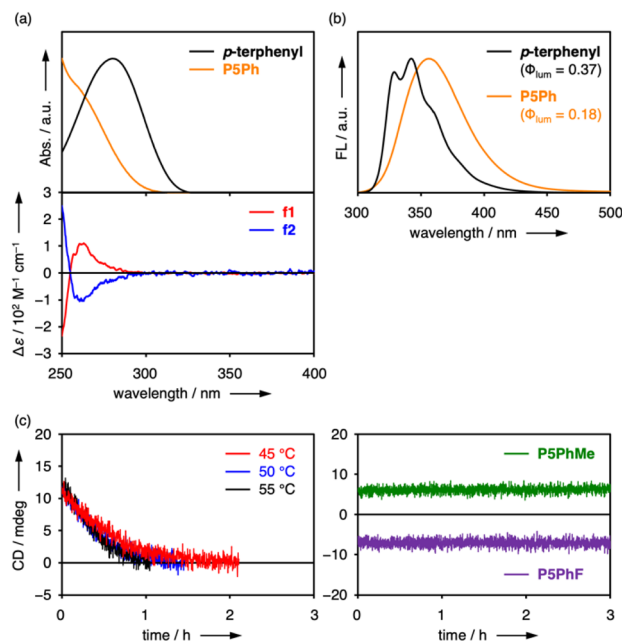


Fig. 4 (a) UV/vis absorption (top) and CD (bottom) spectra of P5Ph isomers (f1, f2) in CHCl_3 . (b) FL spectra of P5Ph ($\lambda_{\text{ex}} = 255 \text{ nm}$) and *p*-terphenyl ($\lambda_{\text{ex}} = 280 \text{ nm}$) in CHCl_3 . (c) Decay profiles of CD intensities at 260 nm for P5Ph at 45–55 °C in CHCl_3 (left), and P5PhMe and P5PhF at 80 °C in 1,2-dichloroethane (right).

because the *p*-terphenyl backbones of P5Ph had more twisted structures with smaller conjugative effect than the *p*-terphenyl structure. In fact, the average dihedral angle of P5Ph was 66° in the single crystal while that of *p*-terphenyl had been reported to be 14–26°.²⁴ By contrast, the fluorescence band showed the opposite trend to the absorption despite weak conjugation at the ground state. The red-shifted fluorescence implies that the *p*-terphenyl units in P5Ph had small dihedral angles enabling conjugation within the units and through-space interactions between the units became operative at the excited states. In the CD spectra, positive and negative peaks appeared around 260 nm as a symmetrical pair for f1 and f2, which were assigned to R_p and S_p isomers, respectively, by using a theoretically calculated spectrum of the (R_p)-structure (Fig. S8-5†). The dissymmetry factor was *ca.* 2×10^{-3} , being comparable to that of P5BF (1×10^{-3}).

Substituent-dependent panel-rotation barriers

CD intensity decay in P5Ph. The CD intensities of enantiopure P5Ph fractions decreased gradually over time at room temperature. To estimate the rotation behaviour,^{9b,12,25} racemization of f1 was characterized by time-dependent circular dichroism. From the decay profile in Fig. 4c, activation energy for the unit rotation ($\Delta G_{25^\circ\text{C}}^\ddagger$) was determined to be 95.3 kJ mol^{-1} at 25 °C (Fig. S7-5 and S7-6†). After complete racemization by heating at 100 °C, no C_2 -symmetric isomers were produced from a solution of f1 (Fig. S7-1†). These results suggested that the D_5 -structures should be considerably stable than the others due to minimum steric repulsion between the six-membered-ring substituents. In the previous study on per-

arylated pillar[5]arenes, 2-furyl pillar[5]arene P5F showed averaged ^1H NMR signals due to fast unit rotation, whereas 2-benzofuranyl compound P5BF gave an isolable mixture of stereoisomers because of prohibited rotation.¹⁸ Therefore, the energetic differences for P5Ph isomers were larger than those for P5BF ones owing to the increased local steric hindrance. Furthermore, even if the C_2 -isomers were produced during the cross-coupling reaction, they should be converted to the D_5 -isomers by unit rotation because the activation energy of unit rotation was sufficiently small for the reaction temperature ($\Delta G_{100^\circ\text{C}}^\ddagger = 107 \text{ kJ mol}^{-1}$).

Synthesis and conformational stability of P5PhMe and P5PhF. To investigate the utility of the present reaction, per-arylation of P5OTf was attempted for arylboronic acids with several functional groups. First, we aimed to improve the yield of P5PhMe, which had been synthesized above in very low yields. By applying the optimum conditions of Table 1, isolation of P5PhMe was enabled in 3.1% yield (Table S2-1,† entry 1). Use of 4-methoxy- and 4-fluorophenylboronic acids produced P5PhOMe and P5PhF respectively, though P5PhOMe failed to be isolated because of low solubility (entries 2 and 3, Fig. S10-4†). On the other hand, 4-dimethylamino-, 4-ethoxycarbonyl-, and 3,4-dimethoxyphenylboronic acids did not provide per-arylated compounds (entries 4–6). Anthracene-2-boronic acid could not afford the target product (entry 7). It is obvious that the per-arylation includes ten-fold cross-coupling reactions and therefore only very good combinations of substrates can lead to the final products. Furthermore, MS results of the crude products mostly included peaks for compounds with nine aryl substituents, which suggested that the cross coupling became more difficult as the intermediates gained more aryl groups. As a result, only small changes in electronic nature and steric bulkiness at the *para*-positions of boronic acids were allowed in this reaction.

The obtained products, P5PhMe and P5PhF, were separated into two fractions by chiral HPLC (Fig. S7-2 and S7-3†). These fractions were revealed to be pairs of D_5 -symmetric enantiomers by ^1H NMR spectra (Fig. S3-2 and S3-3†). The UV/vis absorption, FL, and CD spectra of P5PhMe and P5PhF were almost the same with only slight peak shifts as those of P5Ph (Fig. S6-1 and S6-2†). On the other hand, CD peaks of these fractions did not diminish even after heating at 80 °C (Fig. 4c). These compounds have slightly larger atoms or groups at *para*-positions than P5Ph, and these small differences made the unit rotation suppressed efficiently. These phenomena were consistent with the fact that the efficiency of cross-coupling reactions was highly sensitive to the aryl groups of boronic acids. In per-alkoxy pillar[5]arenes, even per-dodecyloxy^{9b} and per-(2-cyclohexylethoxy)^{19a} derivatives showed conformational interconversion due to the flexibility of alkyl chains. Therefore, the sharp increase of the rotational barrier in the present series was ascribed to the unique rigidity of directly per-arylated pillar[5]arenes.

Conclusions

In this work, we accomplished the direct installation of six-membered-ring aromatic π -units at all the substitution



positions of a pillar[5]arene. In the Suzuki–Miyaura cross coupling, use of a carbene-coordinating Pd complex was a key to success due to the high stability at elevated temperature. Although six-membered-ring reagents were expected to offer a large number of options and expand the possibilities of pillar [5]arenes, the scope of reaction was rather limited because small drops in reaction efficiency led to a large decrease in overall yields and increasing steric hindrance during the reaction disturbed the progress of further cross coupling.

Each of the obtained compounds provided a pair of D_5 -symmetric enantiomers by the locally hindered substituents suppressing the unit rotation. Variable-temperature CD intensity monitoring of **P5Ph** revealed that the activation energy at 25 °C ($\Delta G^\ddagger_{25^\circ\text{C}}$) was 95.3 kJ mol⁻¹. After optical resolution by chiral HPLC, heating an enantiopure fraction caused racemization but did not produce any C_2 -symmetric isomers. These results indicated that the D_5 -symmetric isomer was selectively obtained, which was different from **P5BF** obtained as a mixture of six isomers. On the other hand, heating at 80 °C could not cause any unit rotation for **P5PhMe** and **P5PhF** because of slight differences in the steric bulkiness at substituent *para*-positions. Although **P5Ph** did not serve as a host for neutral and cationic linear molecules in solution, a single-crystal structure revealed that pillar-shaped **P5Ph** could incorporate a dichloromethane in its cavity. Overall, the structures and properties of macrocycles were largely changed by the increase of steric hindrance in **P5Ph** from **P5F** and **P5BF**, which had less hindered five-membered-ring segments and resulting crushed crystal structures. Non-alkoxy pillar[*n*]arenes are an emerging class of functional macrocycles and are pursued by all the synthetic means in our group.

Data availability

The data that support the findings of this study are available in the ESI† of this article.

Author contributions

T. O. supervised and administrated this project. T. K. and K. K. performed conceptualization. T. K. conducted the experiments. T. K. and K. K. prepared the draft and initial version of ESI. All authors reviewed and edited the draft and ESI.

Conflicts of interest

There are no conflicts to declare.

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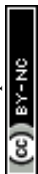
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