

Structural Diversification of Pillar[*n*]arene Macrocycles

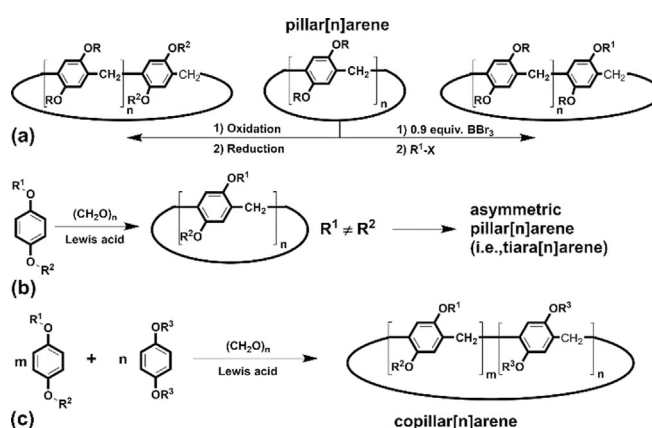
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**Keywords:** pillar[*n*]arene · sensors · separation of isomers · structural diversification · supramolecular chemistry

**Abstract:** Despite the fact that pillar[*n*]arenes receive major interest as building blocks for supramolecular chemistry and advanced materials, their functionalization is generally limited to the modification of the hydroxy or alkoxy units present on the rims. This limited structural freedom restricts further developments and has very recently been overcome. In this article, we highlight three very recent studies demonstrating further structural diversification of pillar[*n*]arenes by partial removal of the alkoxy substituents on the rims, which can be considered as the next generation of pillar[*n*]arenes.

Supramolecular chemistry has been defined as the “chemistry beyond the covalent bond” and has played a major role in various fields spanning from biology, catalysis, and advanced materials to molecular machines.<sup>[1]</sup> The concept of supramolecular chemistry was introduced by Lehn more than 40 years ago and has led to the development of host–guest chemistry based on concise and well-defined macrocyclic host molecules<sup>[2]</sup> such as cyclodextrins, calix[*n*]arenes, and cucurbit[*n*]urils. Paracyclophane macrocycles were first reported in 1985 by Gribble,<sup>[3]</sup> but the lack of functional groups on the phenyl units limited their solubility and processability, restricting their further development and use. 25 years later, Ogoshi and co-workers developed a new class of [1<sub>*n*</sub>]paracyclophane-like macrocycles, namely pillar[*n*]arenes (PA[*n*]s) based on a straightforward and versatile condensation of 1,4-dialkoxybenzenes with paraformaldehyde.<sup>[4]</sup> The versatile functionalization of the aromatic units, the unique pillar-shaped cavity, and the excellent host–guest properties have led to a rapidly increasing popularity of these PA[*n*]s.<sup>[5]</sup> However, the functionalization of PA[*n*]s is mostly limited to the alkoxy groups present on the rims.

More sophisticated PA[*n*]s with different alkoxy substituents have been obtained by hydrolysis of a certain number of methoxy groups or oxidation of one or more dialkoxybenzene rings to quinone structures, followed by reduction and alkoxylation (Scheme 1a).<sup>[6]</sup> Alternatively, different alkoxy



**Scheme 1.** Overview of selected synthetic routes to obtain more sophisticated, partially functionalized pillar[*n*]arenes. Synthesis of: a) mono/di-hydroxylated pillar[*n*]arenes by hydrolysis utilizing BBr<sub>3</sub>, or oxidation followed by reduction and an alkoxylation approach, b) asymmetric pillar[*n*]arenes using asymmetrically modified dialkoxybenzene precursors, and c) copillar[*n*]arene using two different dialkoxybenzenes.

substituents have been introduced by using asymmetrically modified dialkoxybenzene precursors for the PA[*n*] synthesis, leading to rim-differentiated PA[*n*]s (RD-PA[*n*]s), also referred to as tiara[*n*]arenes (Scheme 1b).<sup>[7]</sup> A final route towards mono- and bifunctional PA[*n*]s has been developed based on statistical co-condensation of two different dialkoxybenzenes, providing straightforward access to PA[*n*]s having different alkoxy substituents on different rings (Scheme 1c).<sup>[8]</sup> Even though these methods provide synthetic handles for making functionalized PA[*n*]s, they remain limited to macrocyclic structures that have two alkoxy substituents on all benzene rings.

Herein, we will highlight three inspiring recent studies that further expand the structural diversification of PA[*n*]s towards macrocycles that do not have two alkoxy substituents on all benzene rings as well as the exploitation of these newly developed PA[*n*] derivatives for the selective separation of

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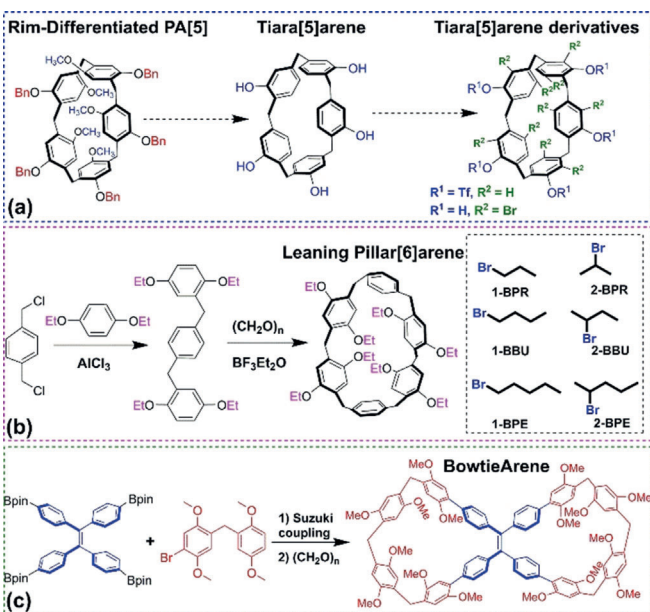
isomers and multiple stimuli-responsive fluorescent materials.<sup>[9]</sup> In the following, we will discuss the advances as well as the limitations of these recent works and their future application potential.

In the first highlighted article, Sue et al. reported the synthesis of tiara[5]arenes (T[5]s) in which every benzene ring only bears one alkoxy substituent.<sup>[9a]</sup> These structures cannot be prepared by direct condensation of mono-alkoxybenzenes as this will lead to the formation of branched or even cross-linked structures. Therefore, they developed a methodology starting from a dialkoxy rim-differentiated PA[5] (RD-PA[5]; Scheme 2a). At first, methoxy-benzyloxy RD-PA[5] was

flexibility enabling multifaceted conformations in the solid state. Consequently, their binding affinity for cationic guests is lower in comparison with PA[5]s. It was, however, demonstrated that T[5]s could be used for selective fractionation of aromatic/aliphatic mixtures. Even though the T[5]s showed a rather low binding capability for guest molecules, especially for flexible alkyl molecules (for example, 1,6-dicyanohexane), this limitation may be overcome in the future by attaching more electron-rich molecular substituents.

The potential and power of structural diversification of PA[*n*]s were also demonstrated in another recent study on a leaning PA[6] that was used for the separation of bromoalkane isomers.<sup>[9b]</sup> The leaning PA[6]s were defined as PA[6]s in which the hydroxy or alkoxy substituents are selectively removed from two opposing phenyl rings. The reported synthetic protocol involves two steps: first, the formation of 1,4-bis(2,5-diethoxybenzyl)benzene through the reaction between 1,4-bis(chloromethyl)benzene and 1,4-diethoxybenzene in the presence of AlCl<sub>3</sub>, followed by macrocyclization with paraformaldehyde in the presence of BF<sub>3</sub>·O(Et)<sub>2</sub>, yielding the perethoxylated leaning PA[6] (EtLPA[6]) in 36% yield (Scheme 2b).<sup>[10]</sup> Interestingly, this EtLPA[6] could not only enhance the binding properties of PA[6], but it could also selectively separate 1-bromoalkane isomers from mixtures of 1/2-positional isomers through simple solid–vapor adsorption. More specifically, the EtLPA[6] could efficiently and selectively adsorb 1-bromopropane, 1-bromobutane, and 1-bromopentane over their corresponding 2-bromoalkane isomers with a selectivity of 89.6%, 93.8%, and 96.3%, respectively. This efficient selectivity was demonstrated to result from different solid-state host–guest binding modes and the relative stability of EtLPA[6] crystals with the 1- and 2-positional bromoalkanes. Single-crystal structures of EtLPA[6] loaded with the 1-bromoalkanes suggested that each 1-bromoalkane molecule is intriguingly located outside the cavity and sandwiched in between two adjacent EtLPA[6] rings through multiple C–H···π interactions. In contrast, single structures of EtLPA[6] loaded with 2-bromopropane showed that the 2-bromopropane is inside the cavity, stabilized by C–H···π and C–H···O interactions, leading to a distorted hexagonal structure. The removal of the trapped guest molecules could be achieved by heating under reduced pressure, allowing the EtLPA[6] to be re-used many times without any decay in performance. Although the synthesis of EtLPA[6] is not very laborious, the low reaction yield may limit future applications of leaning PA[6]s. Nonetheless, the effect of removal of specific alkoxy substituents of the PA[6] on the flexibility and guest uptake is intriguing and may find further applications.

The final highlighted study demonstrates the combination of a tetraphenylethylene (TPE) fluorophore with two PA[5]s leading to the so-called BowtieArene macrocyclic structure with multi-stimuli-responsive fluorescence, vapor absorption, as well as host–guest properties.<sup>[9c]</sup> Even though PA[*n*]s are very popular in supramolecular chemistry, they exhibit only slight fluorescence due to the absence of fluorophore units. Therefore, various functionalities have been introduced in PA[*n*]s, mostly as alkoxy substituents, to impart fluorescent properties.<sup>[11]</sup> In the highlighted study, the authors developed



**Scheme 2.** Schematic representation of the structural diversification of pillar[*n*]arenes. Synthesis of: a) sophisticated tiara[5]arenes which cannot be prepared by condensation of phenol with formaldehyde, but can be obtained from rim-differentiated pillar[5]arenes, b) perethoxylated leaning pillar[6]arene (EtLPA[6]) and 1/2-bromoalkanes structures used in the separation process, and c) BowtieArene with emissive properties.

prepared, followed by removal of the benzyl groups yielding methoxy-hydroxy RD-PA[5]. Subsequent activation of the hydroxyl groups with triflate groups allowed their complete removal, yielding the monomethoxy RD-PA[5]. The methoxy groups were then converted into hydroxyl groups, allowing the preparation of mono-hydroxy RD-PA[5], which consists of phenol units linked by methylene bridges in *ortho*-position with respect to the OH groups. This T[5] parent molecule could be further functionalized either by alkylation or esterification of the hydroxyl groups or by regioselective electrophilic substitutions of the aromatic ring. Even though the synthesis could be performed on the gram scale, the industrialization of this process might be tedious and time-consuming due to the many steps involved and the purification processes by column chromatography. Interestingly, these mono-substituted T[5]s do not exhibit the typical pillar-like structure of PA[*n*]s due to the increased structural

an innovative strategy based on Suzuki–Miyaura cross-coupling between an arylbromide and a tetraboronate-ester-functionalized TPE derivative, followed by a Lewis-acid-promoted condensation with paraformaldehyde to obtain the BowtieArene consisting of two integrated PA[5]s with two unsubstituted benzene rings per PA[5] resulting from the TPE (Scheme 2c). The molecular solid-state packing of the BowtieArene was found to change from ordered to disordered by various stimuli, such as solvent, vapor, or mechanic force, which led to an associated change in fluorescence-emission wavelength over 100 nm going from blue to yellow emission. In particular, increasing the amount of water content over 50% in a THF/water solution of the BowtieArene or direct exposure to *p*-xylene vapors could trigger the molecular packing of the BowtieArene, leading to a significant blue-shift of the emission. This fluorochromism was found to be reversible upon application of mechanical force or vapor treatment with xylene isomers. The main advantages of this new PA[*n*]-like macrocycle are the multi-stimuli-responsive fluorescence, excellent reversibility, and high stability resulting from the stimuli-induced changes in the molecular packing. The potential of these BowtieArenes for supramolecular chemistry are, however, yet to be explored, for example, the scope of guest molecules and their corresponding binding constants.

In conclusion, these three recent reports on PA[*n*] derivatives with incomplete alkoxy-substitution patterns are believed to pave the way towards the development of new PA[*n*]-based structures with different substitution patterns. The highlighted studies open new directions for the use of PA[*n*]s for sensing materials and isomer separation, indicating a breakthrough for the development of more advanced derivatives and applications of PA[*n*]s. The current large interest in this area is believed to take this field of diverse PA[*n*] structures closer towards real-life applications, such as molecular sensors, imaging, data-security, separation and purification, and responsive hydrogels.

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### Conflict of interest

The authors declare no conflict of interest.

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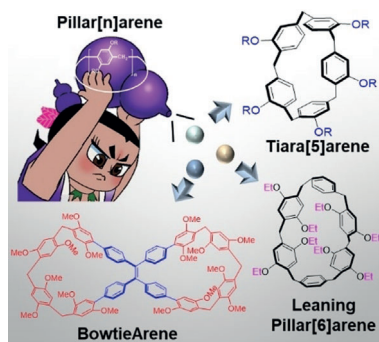
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## Highlights

### Supramolecular Chemistry

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Structural Diversification of Pillar[*n*]arene  
Macrocycles



**The next generation:** Recent developments made in the field of pillar[*n*]arene-based macrocyclic molecules to go beyond single macrocyclic structures with two alkoxy-substituents on every benzene ring are highlighted. The recently introduced tiara[*n*]arenes, leaning pillar[*n*]arenes, and BowtieArenes with incomplete alkoxy substitution may be regarded as a next step in the structural diversification of pillar[*n*]arenes.