JACS JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
Cite This: J. Am. Chem. Soc. 2018, 140, 74−77
pubs.acs.org/JACS

Rim-Differentiated C_5-Symmetric Tiara-Pillar[5]arenes

Minjie Guo,[†,#] Xuemei Wang,[†,#] Caihong Zhan,[†] Paul Demay-Drouhard,[†] Wenjiao Li,[†] Ke Du,[†] Mark A. Olson,[†] Han Zuilhof,[*,†,‡,§] and Andrew C.-H. Sue[*,†]

[†]Institute for Molecular Design and Synthesis, School of Pharmaceutical Science & Technology, Health Science Platform, Tianjin University, 92 Weijin Road, Nankai District, Tianjin 300072, People's Republic of China

[‡]Laboratory of Organic Chemistry, Wageningen University, Stippeneng 4, 6703 WE Wageningen, The Netherlands

[§]Department of Chemical and Materials Engineering, King Abdulaziz University, Jeddah 21589, Saudi Arabia

Supporting Information

ABSTRACT: The synthesis of "rim-differentiated" C_5-symmetric pillar[5]arenes, whose two rims are decorated with different chemical functionalities, has remained a challenging task. This is due to the inherent statistical nature of the cyclization of 1,4-disubstituted alkoxybenzenes with different substituents, which leads to four constitutional isomers with only 1/16th being rim-differentiated. Herein, we report a "preoriented" synthetic protocol based on $FeCl_3$-catalyzed cyclization of asymmetrically substituted 2,5-dialkoxybenzyl alcohols. This yields an unprecedented 55% selectivity of the C_5-symmetric tiara-like pillar[5]arene isomer among four constitutional isomers. Based on this new method, a series of functionalizable tiara-pillar[5]arene derivatives with C_5-symmetry was successfully synthesized, isolated, and fully characterized in the solid state.

Since being introduced[1] almost a decade ago, pillararenes,[2] in particular the cyclopentameric pillar[5]arenes (P[5]s), have received rapidly growing attention of the macrocyclic,[3] supramolecular,[4] and mechanostereochemistry[5] communities. In addition to their straightforward syntheses[6] and promiscuous host−guest properties,[7] another reason for the popularity of P[5]s is their versatility in functionalization[8] compared to other seminal macrocycles, such as cyclodextrins,[9] crown ethers,[10] cucurbiturils,[11] and calixarenes.[12] The five hydroquinone rings in the P[5] scaffold offer 10 phenolic sites for further derivatization, either before the P[5] macrocycle formation or through postsynthetic modification approaches.

Among all synthetically accessible functionalization patterns, the most symmetric per-functionalized[13] P[5]s, are the easiest synthetic targets. The syntheses of P[5]s with lower symmetry, such as mono-[14] and (A1/A2)-disubstituted[15] ones, can be still relatively easily achieved through cocyclization of different types of 1,4-dialkoxybenzene monomers, or partial demethylation of the 1,4-dimethoxybenzene moieties in the P[5] scaffold. In contrast, selective syntheses of oligo-substituted P[5]s, in particular the so-called "rim-differentiated" C_5-symmetric pillar[5]arenes,[16] or briefly tiara-pillar[5]arenes (T-P[5]s), in which the two rims of the P[5] macrocycles are decorated differently, have remained elusive. This is due to the statistical nature of the cyclization process of 1,4-dialkoxybenzenes with different alkoxy groups, which yields the four constitutional isomers in a ratio of 5:5:5:1, with only the latter being the T-P[5]. As a result, this process typically gives rise to both low selectivity (∼1/16th, thus maximally only ∼6% of all P[5]s) and concomitantly even lower isolated yields.

This situation needs to be improved significantly, as indicated by both Ogoshi (ref 2b) and Stoddart (ref 8), in that novel strategies toward T-P[5]s are not only highly desirable but also required to take full advantage of the potential of this class of compounds. T-P[5]s are, for example, very appealing molecular design platforms on account of their high C_5-symmetry and their differing functionalities on either side of the macrocycles. By exploiting this unique symmetry, self-assembled micellar, vesicular, and tubular superstructures of several T-P[5]-based amphiphiles modified with hydrophilic and hydrophobic groups on opposite sides have been developed[17] for potential applications, e.g. artificial ion channels.[18] In addition, on account of their rim-differentiation, T-P[5]s, like many calixarenes, are ideal targets to be multivalently grafted onto various surfaces,[19] such as silicon[20] or graphene oxide,[21] for interface applications. However, the low-yielding synthesis is still the bottleneck for further investigation and application of this C_5-isomer. The results in this paper overcome that bottleneck.

Among the hundreds of publications on pillararenes that have appeared in the past decade, only a handful of them have addressed[16,17,20,21] the syntheses and applications of the T-P[5]s. Generally, penta-functionalized P[5]s can be prepared (Figure 1a) from the Lewis acid-catalyzed cyclization of asymmetrically functionalized 1,4-dialkyoxybenzenes ($\mathbf{M}_1$) with paraformaldehyde[16b] or 1,4-dialkoxy-2,5-bis(ethoxymethyl)benzenes ($\mathbf{M}_2$),[16a] forming two key intermediates ($\mathbf{M}_A$/$\mathbf{M}_B$) via Friedel−Crafts alkylation/dealkylation. The subsequent oligomerization processes involving $\mathbf{M}_A$ and $\mathbf{M}_B$ lead to two types of isomeric dimers $\mathbf{D}_{syn}$ and $\mathbf{D}_{anti}$, depending on how the two 1,4-alkoxylated benzene rings and the methylene bridges are positioned relative to each other. The reaction pathways differentiate (see Supporting Information Scheme S5) even more after three following alkylation steps, leading to 32 different linear pentamers, which eventually form (see Supporting Information Scheme S6) four distinct P[5] macrocyclic isomers (Figure 1b) after the final cyclization steps. The theoretical ratio of these four isomers (based on permutations with $p = 0.5$) is 5:5:5:1, which is in very good agreement with experimental results in literature.[16a]

Received: October 11, 2017
Published: December 8, 2017

DOI: 10.1021/jacs.7b10767
J. Am. Chem. Soc. 2018, 140, 74−77

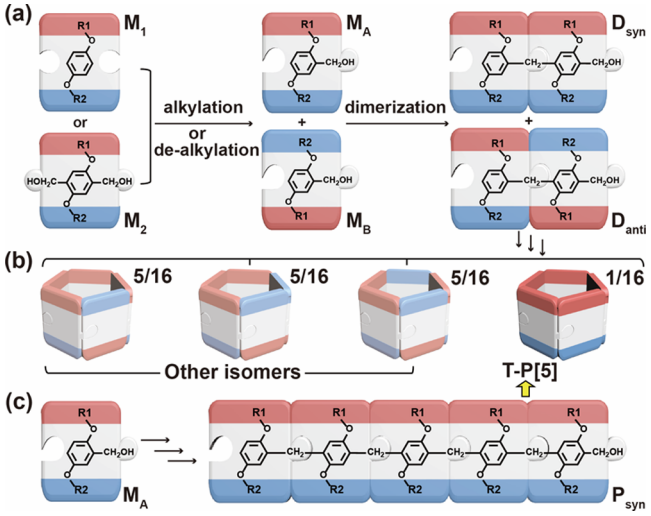


Figure 1. (a) In the Lewis acid-catalyzed oligocyclization, the reaction of asymmetrically functionalized monomer ($\mathbf{M}_1$ or $\mathbf{M}_2$) with formaldehyde can form two key monomeric intermediates $\mathbf{M}_A$ and $\mathbf{M}_B$, which undergo further oligomerization. The alkoxy substituents (OR1 and OR2) can be oriented in both *syn* and *anti* fashions when two adjacent phenylene rings are connected by the CH_2 bridge. This process, after ring closure of the linear pentamers, eventually leads to the formation of four P[5] constitutional isomers (see panel b). The nearly statistical nature of this oligomerization/cyclization makes the desired tiara-P[5] (T-P[5]) with C_5 symmetry the least abundant product (~1/16th). To circumvent this, (see panel c) our "preoriented" strategy employs monomer $\mathbf{M}_A$ with a hydroxymethylene handle. This handle directs the reaction to formation of all-*syn* linear pentamer ($\mathbf{P}_{syn}$) in the presence of a weak Lewis acid, resulting in T-P[5] with high selectivity and yield.

Therefore, the yield for the C_5-symmetric T-P[5] isomer is the lowest, accounting for only 1/16th of the total P[5] isomers formed. So far, all literature examples[16,17,20,21] involving T-P[5]s have relied on this type of statistical synthetic protocol to obtain the desired C_5-symmetric products in barely 5−7% yield in the reaction mixtures. Isolation is then often aggravated even further by the nontrivial purification of this minor product by chromatography or HPLC.[16a,b]

Considering that it is the presence of both monomeric intermediates $\mathbf{M}_A$ and $\mathbf{M}_B$ that leads to the complicated reaction pathways and results in the isomeric mixtures, we reasoned that the exclusive use of one of the two monomers (Figure 1c), in the presence of a suitable Lewis acid, would direct toward the formation of the all-*syn* pentamer ($\mathbf{P}_{syn}$) and allow the selective synthesis of T-P[5]. On the basis of this idea, herein we propose a "preoriented" synthetic strategy, which employs a monomer equipped with one hydroxymethylene handle installed at a specific position on the dialkoxylated benzene ring[22] to orient the oligomerization process.

In our initial study, (propargyl)$_5$(methyl)$_5$-tiara-P[5] (or (propargyl)$_5$-T-P[5], the five methyl groups on the other rim are from now on omitted for clarity) **2a** (Figure 2a) was chosen as the model compound. Following the statistical synthetic protocol, the mixture of (propargyl)$_5$-P[5] isomers was synthesized (see Supporting Information) from the condensation reaction of 1-methoxy-4-(prop-2-yn-1-yloxy)-benzene with paraformaldehyde catalyzed by trifluoroacetic acid in 1,2-dichloroethane (DCE). Although the total cyclization yield of all four constitutional isomers combined reaches 78%, which is higher than the 51% reported in literature,[16c] only 7% of the resulting P-[5] mixture is the desired (propargyl)$_5$-T-P[5] **2a**

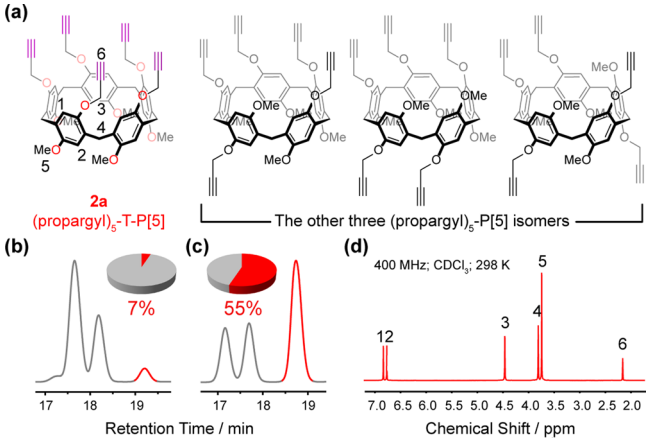
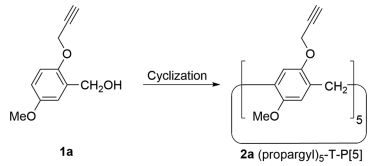


Figure 2. (a) Rim-differentiated (propargyl)$_5$-T-P[5] **2a** and the other three constitutional isomers of (propargyl)$_5$-P[5] isomers. HPLC chromatograms of mixtures of (propargyl)$_5$-P[5]isomers obtained from (b) conventional statistical and (c) our "preoriented" synthesis. (d) ^{1}H NMR spectrum of **2a**.

isomer, as determined by analytical HPLC (Figure 2b, also see Supporting Information).

For the "preoriented" synthesis, our initial studies were focused on optimizing the reaction parameters (see Table 1) for monomer **1a** (see Supporting Information for synthesis). The popular $BF_3{\cdot}Et_2O$-catalyzed cyclization conditions for P[5] (Table 1, Entry 1) resulted in a 22% yield for all four constitutional isomers combined, in which the ratio of the T-P[5] isomer **2a** accounted for 17% (see Supporting Information). Although the overall calculated yield of T-P[5] **2a** was merely 3.7%, this 17% selectivity showed an encouraging

Table 1. Optimization of the Preoriented Synthetic Protocol of (propargyl)$_5$-Tiara-Pillar[5]arene 2a[a]



Entry	Catalyst[b] (10%)	Solvent[c]	Time (hr)	Yield[d] of P[5]s (%)	Fraction[e] of 2a (%)	Yield[f] of 2a (%)
1	$BF_3{\cdot}Et_2O$	DCE	1	22	17	4
2	$AlCl_3$	DCE	1	16	20	3
3	$FeCl_3$	DCE	1	26	55	14
4	$FeBr_3$	DCE	1	24	54	13
5	FeF_3	DCE	1	—	—	—
6	$FeCl_3$	CH_2Cl_2	1	30	48	14
7	$FeCl_3$	$CHCl_3$	1	23	56	13
8	$FeCl_3$	DCE	4	33	54	18
9	$FeCl_3$	DCE	8	35	55	19

[a]The reactions were performed by combining **1a** (2.0 mmol) and catalyst (0.2 mmol, 10%) in solvent (10.0 mL) at room temperature. [b]Several other Lewis acids ($AuCl_3$, $InCl_3$, $Sc(OTf)_3$, $ZnCl_2$, AgOTf, CuOTf, $CuCl_2$, $RuCl_3$) were tested, but no P[5] product was identified. [c]No P[5] product was isolated in reactions employing CH_3CN and THF as solvents. [d]Isolated yield of four constitutional isomers combined. The yields in entries 6 to 9 were obtained from the average of at least three independent reactions. [e]As determined by HPLC analysis. [f]Based on the isolated yield of all P[5] isomers and the fraction of T-P[5] determined by HPLC analysis.

DOI: 10.1021/jacs.7b10767
J. Am. Chem. Soc. 2018, 140, 74−77

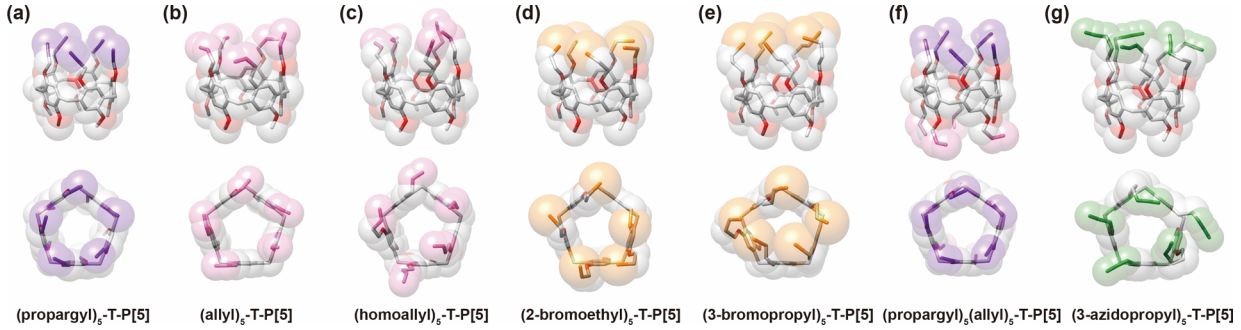


Figure 3. Side and top views of X-ray solid-state structures of different tiara-pillar[5]arenes obtained by preoriented synthetic protocol, illustrated in a blend of tubular stick and space-filling representations: (a) $(propargyl)_5$-T-P[5] (**2a**), (b) $(allyl)_5$-T-P[5] (**2b**), (c) $(homoallyl)_5$-T-P[5] (**2c**), (d) $(2\text{-}bromoethyl)_5$-T-P[5] (**2d**), (e) $(3\text{-}bromopropyl)_5$-T-P[5] (**2e**), (f) $(propargyl)_5(allyl)_5$-T-P[5] (**2f**), and (g) $(3\text{-}azidopropyl)_5$-T-P[5] (**3**) [all T-[P5]s, apart from **2f**, have five OCH_3 groups on the other rim]. Only one of the two enantiomeric coconformations in the solid state is shown for each compound. All hydrogens and guest molecules are omitted for clarity. Color code: alkyne, purple; allyl, magenta; azido, green; bromine, orange; carbon, gray; oxygen, red.

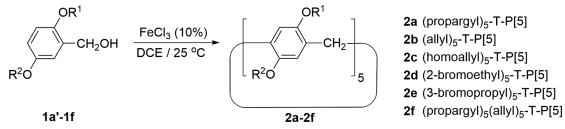
deviation from the statistical protocol. Other Lewis acids (0.1 equiv) such as $AlCl_3$, $FeCl_3$, and $FeBr_3$ (Table 1, Entries 2 to 4) were also screened with DCE as solvent. With $FeCl_3$ and $FeBr_3$ as the Lewis acid, the selectivity of T-P[5] **2a** increased to >50% (Figure 2c, also see Supporting Information), whereas in contrast several other metal salts (FeF_3, $AuCl_3$, $InCl_3$, $Sc(OTf)_3$, $ZnCl_2$, AgOTf) did not lead to any P[5] formation under the same reaction conditions.

In addition to DCE, various other solvents, such as chloroform, dichloromethane, acetonitrile, and tetrahydrofuran, were examined. Generally, chlorinated solvents lead to similar yields and selectivity (Table 1, Entry 3, 6, 7). When the reaction time was extended to 4 h (Table 1, Entry 8), the yield of P[5]s improved slightly, but further elongation of the reaction time showed no enhancement (Table 1, Entry 9). The optimized reaction conditions for the "preoriented" T-P[5] synthesis, which employs DCE as solvent and $FeCl_3$ as the weak Lewis acid, lead to a 35% total yield of all constitutional isomers, in which the T-P[5] **2a** is the major product with 55% selectivity (Figure 2c). Because purification of thus prepared T-P[5] can simply be achieved by flash column chromatography followed by recrystallization without the need for HPLC, this new method enhances the isolated yield of **2a** to ~20%, typically one order of magnitude improvement over previous synthetic protocols, and significantly simplifies the purification. The formation of the other three non-T-P[5] constitutional isomers in the "preoriented" strategy can be attributed to the parallel dealkylation/realkylation side reactions on the hydroxymethylene handle of $\mathbf{M}_A$ in the presence of Lewis acids (see Supporting Information Scheme S6). It is this dynamic covalent process which prevents the exclusive formation of the linear all-*syn* oligomeric intermediates.

The ^1H NMR spectrum of $(propargyl)_5$-T-P[5] **2a** is shown in Figure 2d. The relatively simple spectrum without splitting in the aromatic region reflects the high C_5-symmetry of this T-P[5] in solution. X-ray crystallography (Figure 3a) further unambiguously confirms that all five propargyl constituents are positioned on the same rim of the P[5] scaffold.

In order to investigate the scope of this novel strategy, as well as to further increase the diversity of chemical functionalities on T-P[5] scaffolds, several different monomers containing either "clickable" moieties or good leaving groups were prepared. Specifically, monomers with allyl (**1b**), homoallyl (**1c**), 2-bromoethyl (**1d**), and 3-bromopropyl (**1e**) moieties, were subjected to the optimized reaction conditions. In general, rim-differentiated T-P[5]s **2b-2e** were obtained in good isolated yields (up to ~20%; see Table 2, Entries 2 to 5). Furthermore, a

Table 2. Syntheses of Various Tiara-Pillar[5]arenes 2a–2f[a]



Entry	Substrate	R^1/R^2	Yield[b] of P[5]s (%)	Yield[c] of 2 (%)
1	**1a′**	$Me/CH_2C{\equiv}CH$	34	19
2	**1b**	$CH_2CH{=}CH_2/Me$	32	16
3	**1c**	$CH_2CH_2CH{=}CH_2/Me$	38	18
4	**1d**	CH_2CH_2Br/Me	30	15
5	**1e**	$CH_2CH_2CH_2Br/Me$	19	9
6	**1f**	$CH_2CH{=}CH_2/CH_2C{\equiv}CH$	17	8

[a]The reaction was performed by employing compounds **1a′–1f** (2.0 mmol) and $FeCl_3$ (0.2 mmol, 10%) in DCE (10.0 mL) for 4 h at room temperature. See Supporting Information for details. [b]Isolated yields of four constitutional isomers combined. [c]Yield of **2a** is calculated based on the isolated yield of all P[5] isomers combined and the fraction of T-P[5] determined by HPLC analysis. Entries 2 to 6 are isolated yields of **2b–2f** after flash chromatography.

"dual-functionalized" $(propargyl)_5(allyl)_5$-T-P[5] **2f** was successfully synthesized and isolated in 8% yield (Table 2, Entry 6) using precursor **1f**. The lower yields of **2e** and **2f** are presumably because of the steric hindrance caused by the relatively bulky groups attached to the monomer during the cyclization processes. All these T-P[5]s have the potential to be further derivatized through many routine reactions, including copper-catalyzed azide–alkyne cycloaddition (CuAAC), thiol–yne/thiol–ene click chemistry, alkene metathesis, as well as simple S_N2 reactions. For example, $(3\text{-}azidopropyl)_5$-T-P[5] **3**, which itself can be used in further CuAAC reactions, could be obtained (see Supporting Information) from reacting penta-bromide T-P[5] **2e** with NaN_3 in DMF in ~90% yield. Single crystal samples of T-P[5]s, **2a–2f** and **3**, were obtained by slow vapor diffusion of hexane into ethyl acetate or dichloromethane solutions of the isolated compounds. The solid-state structures of T-P[5] **2a–2f** and **3**, elucidated by X-ray crystallography (shown in Figure 3), again confirm their rim-differentiated nature. It is noteworthy that the X-ray snapshots of these T-P[5]s **2a–2f** and **3** do not

DOI: 10.1021/jacs.7b10767
J. Am. Chem. Soc. 2018, 140, 74–77

have perfect C_5-symmetry in the solid state as a result of the different orientations adopted by the functional groups, whereas all pentagonal cavities were filled with hexane guest molecules inside (omitted in Figure 3 for clarity).

In summary, an $FeCl_3$-catalyzed cyclization of asymmetrically substituted 2,5-dialkoxybenzyl alcohols has been developed[23] for convenient and selective syntheses of rim-differentiated C_5-symmetric tiara-pillar[5]arenes. This preoriented synthetic protocol for tiara-pillar[5]arenes, which takes advantage of the hydroxymethylene handle to orient the oligomerization processes, pushes the selectivity to ~55% and isolated yields to ~20%, both showing significant improvement from the results obtained by previous statistical syntheses. By applying this "preoriented" strategy, a series of tiara-pillar[5]arene derivatives was synthesized, isolated, and crystallized. Further studies toward expansion of chemical functionalities on tiara-pillar[5]arenes and their applications in supramolecular assemblies, bioconjugation, and surface functionalization are underway in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b10767.

Synthetic procedures, HPLC analyses, mechanism and reaction pathways discussions (PDF)
Crystallographic Information (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*andrew.sue@tju.edu.cn
*han.zuilhof@wur.nl

ORCID

Mark A. Olson: 0000-0003-0398-5063
Han Zuilhof: 0000-0001-5773-8506
Andrew C.-H. Sue: 0000-0001-9557-2658

Author Contributions

#These authors contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the 973 National Basic Research Program of China (2015CB856500).

■ REFERENCES

(1) Ogoshi, T.; Kanai, S.; Fujinami, S.; Yamagishi, T.; Nakamoto, Y. *J. Am. Chem. Soc.* **2008**, *130*, 5022−5023.
(2) (a) Xue, M.; Yang, Y.; Chi, X.; Zhang, Z.; Huang, F. *Acc. Chem. Res.* **2012**, *45*, 1294−1308. (b) Ogoshi, T.; Yamagishi, T.; Nakamoto, Y. *Chem. Rev.* **2016**, *116*, 7937−8002.
(3) Pedersen, C. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1021−1027.
(4) Lehn, J. M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 89−112.
(5) Bruns, C.; Stoddart, J. F. *The Nature of the Mechanical Bond*; Wiley: Weinheim, 2017.
(6) (a) Cao, D.; Kou, Y.; Liang, J.; Chen, Z.; Wang, L.; et al. *Angew. Chem., Int. Ed.* **2009**, *48*, 9721−9723. (b) Ogoshi, T.; Aoki, T.; Kitajima, K.; Fujinami, S.; Yamagishi, T.; et al. *J. Org. Chem.* **2011**, *76*, 328−331. (c) Holler, M.; Allenbach, N.; Sonet, J.; Nierengarten, J.-F. *Chem. Commun.* **2012**, *48*, 2576−2578. (d) Wang, K.; Tan, L.-L.; Chen, D.-X.; Song, N.; Xi, G.; et al. *Org. Biomol. Chem.* **2012**, *10*, 9405−9409.
(7) Cram, D. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1009−1020.
(8) Strutt, N. L.; Zhang, H.; Schneebeli, S. T.; Stoddart, J. F. *Acc. Chem. Res.* **2014**, *47*, 2631−2642.
(9) (a) Szejtli, J. *Chem. Rev.* **1998**, *98*, 1743−1754. (b) Crini, G. *Chem. Rev.* **2014**, *114*, 10940−10975.
(10) Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 2495−2496.
(11) Freeman, W. A.; Mock, W. L.; Shih, N. Y. *J. Am. Chem. Soc.* **1981**, *103*, 7367−7368.
(12) Gutsche, C. D. *Calixarenes Revisited*; The Royal Society of Chemistry: Cambridge, 1998.
(13) (a) Ogoshi, T.; Umeda, K.; Yamagishi, T.; Nakamoto, Y. *Chem. Commun.* **2009**, 4874−4876. (b) Ogoshi, T.; Shiga, R.; Hashizume, M.; Yamagishi, T. *Chem. Commun.* **2011**, *47*, 6927−6929. (c) Nierengarten, I.; Nothisen, M.; Sigwalt, D.; Biellmann, T.; Holler, M.; et al. *Chem. - Eur. J.* **2013**, *19*, 17552−17558.
(14) (a) Strutt, N. L.; Forgan, R. S.; Spruell, J. M.; Botros, Y. Y.; Stoddart, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 5668−5671. (b) Ogoshi, T.; Demachi, K.; Kitajima, K.; Yamagishi, T. *Chem. Commun.* **2011**, *47*, 7164−7166.
(15) (a) Zhang, Z.; Xia, B.; Han, C.; Yu, Y.; Huang, F. *Org. Lett.* **2010**, *12*, 3285−3287. (b) Strutt, N. L.; Fairen-Jimenez, D.; Iehl, J.; Lalonde, M. B.; Snurr, R. Q.; et al. *J. Am. Chem. Soc.* **2012**, *134*, 17436−17439. (c) Liu, Z.; Cao, D.; Jin, Y.; Tao, H.; Kou, Y.; et al. *Org. Biomol. Chem.* **2011**, *9*, 7007−7010.
(16) (a) Kou, Y.; Tao, H.; Cao, D.; Fu, Z.; Schollmeyer, D.; et al. *Eur. J. Org. Chem.* **2010**, *2010*, 6464−6470. (b) Zhang, Z.; Luo, Y.; Xia, B.; Han, C.; Yu, Y.; et al. *Chem. Commun.* **2011**, *47*, 2417−2419. (c) Yu, G.; Zhang, Z.; Han, C.; Xue, M.; Zhou, Q.; et al. *Chem. Commun.* **2012**, *48*, 2958−2960. (d) Shu, X.; Chen, W.; Hou, D.; Meng, Q.; Zheng, R.; et al. *Chem. Commun.* **2014**, *50*, 4820−4823. (e) Zhou, Y.; Yao, Y.; Huang, F. *Chin. J. Chem.* **2015**, *33*, 356−360.
(17) (a) Yao, Y.; Xue, M.; Chen, J.; Zhang, M.; Huang, F. *J. Am. Chem. Soc.* **2012**, *134*, 15712−15715. (b) Yu, G.; Ma, Y.; Han, C.; Yao, Y.; Tang, G.; et al. *J. Am. Chem. Soc.* **2013**, *135*, 10310−10313. (c) Zhang, H.; Ma, X.; Nguyen, K. T.; Zhao, Y. *ACS Nano* **2013**, *7*, 7853−7863. (d) Nishimura, T.; Sanada, Y.; Matsuo, T.; Okobira, T.; Mylonas, E.; et al. *Chem. Commun.* **2013**, *49*, 3052−3054. (e) Yao, Y.; Xue, M.; Zhang, Z.; Zhang, M.; Wang, Y.; et al. *Chem. Sci.* **2013**, *4*, 3667−3672.
(18) (a) Si, W.; Chen, L.; Hu, X.-B.; Tang, G.; Chen, Z.; et al. *Angew. Chem., Int. Ed.* **2011**, *50*, 12564−12568. (b) Hu, X.-B.; Chen, Z.; Tang, G.; Hou, J.-L.; Li, Z.-T. *J. Am. Chem. Soc.* **2012**, *134*, 8384−8387. (c) Chen, L.; Si, W.; Zhang, L.; Tang, G.; Li, Z.-T.; et al. *J. Am. Chem. Soc.* **2013**, *135*, 2152−2155.
(19) (a) Pujari, S. P.; Scheres, L.; Marcelis, A. T. M.; Zuilhof, H. *Angew. Chem., Int. Ed.* **2014**, *53*, 6322−6356. (b) de Smet, L. C. P. M.; Pukin, A. V.; Sun, Q.-Y.; Eves, B. J.; Lopinski, G. P.; et al. *Appl. Surf. Sci.* **2005**, *252*, 24−30. (c) Escorihuela, J.; Zuilhof, H. *J. Am. Chem. Soc.* **2017**, *139*, 5870−5876.
(20) Luo, L.; Nie, G.; Tian, D.; Deng, H.; Jiang, L.; et al. *Angew. Chem., Int. Ed.* **2016**, *55*, 12713−12716.
(21) Zhou, J.; Chen, M.; Xie, J.; Diao, G. *ACS Appl. Mater. Interfaces* **2013**, *5*, 11218−11224.
(22) Ma, Y.; Zhang, Z.; Ji, X.; Han, C.; He, J.; et al. *Eur. J. Org. Chem.* **2011**, *2011*, 5331−5335.
(23) After the acceptance of this manuscript, it was brought to our attention that a similar protocol was developed independently by Professor Da Ma's group. See Ding, J.; Chen, J.; Mao, W.; Huang, J.; Ma, D. *Org. Biomol. Chem.* **2017**, *15*, 7894−7897.

DOI: 10.1021/jacs.7b10767
J. Am. Chem. Soc. 2018, 140, 74−77