Organic LETTERS

Letter

pubs.acs.org/OrgLett

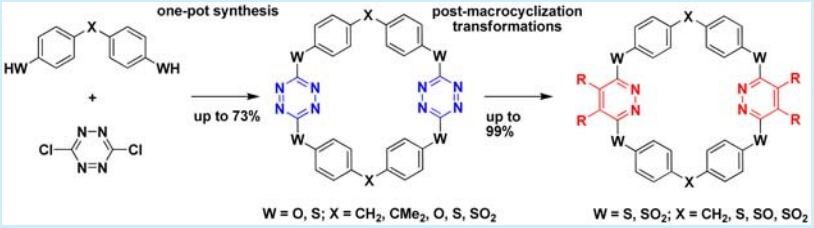
Synthesis and Structure of Corona[6](het)arenes Containing Mixed Bridge Units

Zhan-Da Fu,[†,§] Qing-Hui Guo,[†,‡,§] Liang Zhao,[†] De-Xian Wang,[‡] and Mei-Xiang Wang*[,†]

[†]Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology (Ministry of Education), Tsinghua University, Beijing 100084. China

[‡]Beijing National Laboratory for Molecular Sciences, CAS Key Laboratory of Molecular Recognition and Function, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China

Supporting Information



ABSTRACT: A one-pot nucleophilic aromatic substitution reaction of 3,6-dichlorotetrazine with various diphenols and dibenzenethiols produced corona[4]arene[2]tetrazines that contain mixed oxygen, sulfide, methylene, and sulfone linkages. Macrocyclic ring transformations employing an inverse-electron-demand Diels–Alder reaction of tetrazine moieties with enamines and the subsequent sulfide oxidation reaction afforded diverse corona[4]arene[2]pyridazines. The acquired corona[6]arenes adopted three types of conformational structures in the crystalline state.

Development of novel synthetic macrocycles has always been a central focus in the study of supramolecular chemistry.[1] Macrocycles provide powerful molecular tools to investigate noncovalent bond interactions, molecular recognition, and self-assembly. They are also invaluable building blocks in the fabrication of sophisticated (supra)molecular architectures and advanced functional materials. In the past decade, we have endeavored to develop heteracalixaromatics or heteroatom-bridged calix(het)arenes **A** (Figure 1).[2−6] Owing to

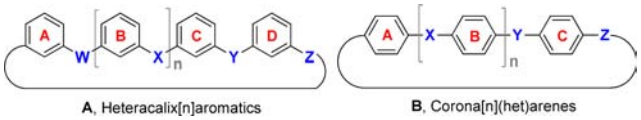


Figure 1. General structures of heteracalix[*n*]aromatics and X_n-corona[*n*](het)arenes.

their easy availability, self-tunability of unique conformation and cavity structures and versatility in molecular recognition, heteracalixaromatics have been regarded as a type of privileged synthetic macrocycles that are finding more and more applications.[3,7]

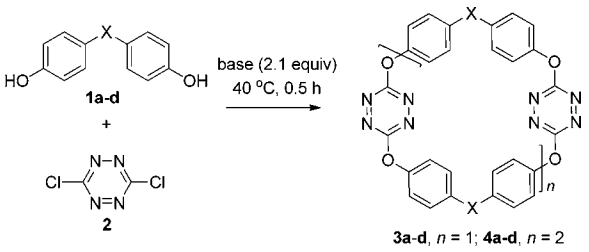
To engineer the cylindroid cavity from the V-shaped cavity or cleft of 1,3-alternate heteracalix[4]aromatics, we have recently devised a new family of macrocycles based on the alteration of bond connectivity of bridging heteroatoms to (het)arylenes.[8−10] The change of *meta* substitution of (het)arylenes in heteracalixaromatics into *para* ones engenders coronarenes **B** (Figure 1), the macrocycles that are composed of heteroatoms and *para*-(het)arylenes in an alternative fashion. We have established a convenient one-pot nucleophilic aromatic substitution reaction of *p*-benzenediol and dithiol derivatives with 3,6-dichlorotetrazine to synthesize O_6- and S_6-corona[3]arene[3]tetrazines, respectively.[8−10] The macrocyclic ring transformation of S_6-corona[3]arene[3]tetrazines into S_6-corona[3]arene[3]pyridazines has also been realized.[9,10] The C_3-symmetric O_6-corona[3]arene[3]tetrazine and S_6-corona[3]arene[3]pyridazine appeared as powerful hosts to complex chloride[8] and organic cation guests,[9,10] respectively. To develop the diversity of coronarenes and also to shed light on the effect of bridging units on the structure and property of this new type of synthetic macrocycles, we conducted the current study. We report herein the efficient synthesis of corona[4]arene[2]tetrazines and corona[4]arene[2]pyridazines that contain mixed bridging units by means of one-pot nucleophilic aromatic substitution reaction, macrocycle-to-macrocycle transformation, and postmacrocyclization oxidation reaction. Structures of the acquired macrocycles in the solid state and in solution are also discussed.

We commenced our study by examining the nucleophilic aromatic substitution (S_NAr) reaction of bis-phenol derivatives **1a–d** with 3,6-dichlorotetrazine **2**[11] (Table 1). In the presence of triethylamine as an acid scavenger, 4,4′-methylenediphenol **1a** reacted smoothly at 40 °C in acetonitrile to afford $(CH_2)_2$,O_4-corona[4]arene[2]tetrazine **3a** as a major product

Received: April 18, 2016
Published: May 16, 2016

DOI: 10.1021/acs.orglett.6b01112
Org. Lett. 2016, 18, 2668–2671

Table 1. Synthesis of Corona[4]arene[2]tetrazines 3a–d



entry	1 (X)	conditions	3[a] (%)	4[a] (%)
1	**1a** (CH_2)	Et_3N, 40 °C, CH_3CN	**3a** (54)	**4a** (5)
2	**1b** (CMe_2)	Et_3N, 40 °C, CH_3CN	**3b** (73)	**4b** (13)
3	**1c** (SO_2)	Et_3N, 40 °C, CH_3CN	**3c** (59)	**4c** (0)
4	**1d** (S)	Et_3N, 40 °C, CH_3CN	**3d** (67)	**4d** (13)
5	**1d** (S)	DIPEA, 40 °C, CH_3CN	**3d** (74)	**4d** (12)

[a]Isolated yields.

in 54% yield. A larger macrocyclic ring homologue, $(CH_2)_3,O_6$-corona[6]arene[3]tetrazine **4a**, was also isolated in 5% yield (entry 1, Table 1). Under the same reaction conditions, 4,4′-(propane-2,2-diyl)diphenol **1b** underwent the macrocyclization reaction more efficiently, producing a high yield of $(CMe_2)_2,O_4$-corona[4]arene[2]tetrazine **3b** along with 13% of $(CMe_2)_3,O_6$-corona[6]arene[3]tetrazine **4b** (entry 2, Table 1). Pleasingly, the one-pot reaction of 4,4′-sulfonyldiphenol with **2** proceeded equally well to furnish the formation of $O_4,(SO_2)_2$-corona[4]arene[2]tetrazine **3c** as the sole macrocyclic product (entry 3, Table 1). When 4,4′-thiodiphenol **1d** was used as the dinucleophilic reactant, the same reaction gave O_4,S_2-corona-[4]arene[2]tetrazine **3d** and O_6,S_3-corona[6]arene[3]tetrazine **4d** in 67% and 13% respectively (entry 4, Table 1). The use of DIPEA instead of triethylamine resulted in the improvement of chemical yield of **3d** to 74% (entry 5, Table 1).

We extended the synthesis to S_6- and $(CH_2)_2,S_4$-corona[4]-arene[2]tetrazines employing 4,4′-thiodibenzenethiol **1e** and 4,4′-methylenedibenzenethiol **1f** as substrates. As illustrated in Figure 2, both **1e** and **1f** reacted effectively with **2** at 75 °C in a

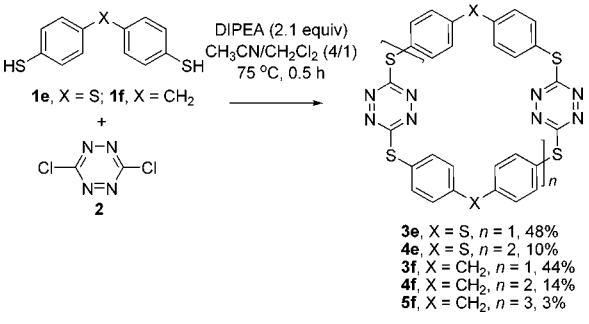
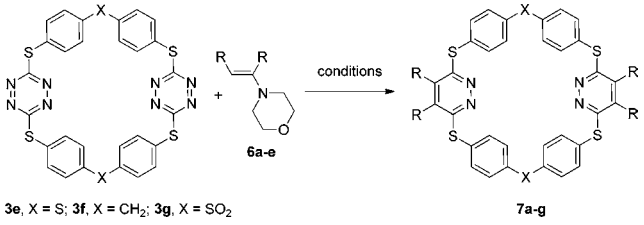


Figure 2. Synthesis of S_6- and $(CH_2)_2,S_4$-corona[4]arene[2]tetrazines **3e** and **3f**.

mixture of CH_3CN and CH_2Cl_2 in a sealed tube. The desired S_6-corona[4]arene[2]tetrazine **3e** was obtained in 48% yield. In addition, S_9-corona[6]arene[3]tetrazine **4e** was formed as a byproduct. In the case of **1f**, the reaction produced a mixture of targeted $(CH_2)_2,S_4$-corona[4]arene[2]tetrazine **3f** and its giant macrocyclic homologues, corona[9]- and [12]-(het)arenes **4f** and **5f**, in yields of 44%, 14%, and 3%, respectively. It is worth mentioning that the construction of corona[4]arene[2]-tetrazines **3a–f** from diphenols and dibenzenethiols involves the formation of four new C–O or C–S chemical bonds. The good chemical yields (44–74%) obtained for them indicated high efficiency in each of the bond-forming reactions. The high selectivity for the assembly of corona[4]arene[2]tetrazines **3** from a one-pot reaction implied most likely a thermodynamic-controlled process due to the stability of corona[6]arene products.

Since tetrazine is a powerful latent diene component able to undergo an inverse-electron-demand Diels–Alder reaction,[12] we then attempted synthesis of corona[4]arene[2]pyridazines from the reaction of corona[4]arene[2]tetrazines with enamines as electron-rich dienophiles. As summarized in Table 2, macrocyclic transformation of corona[4]arene[2]-

Table 2. Synthesis of Corona[4]arene[2]pyridazines 7a–g[a]



entry	3	6	R,R	conditions	7	yield[b] (%)
1	**3e**	**6a**	R = *n*-Pr	A	**7a**	85
2	**3e**	**6b**	R = *n*-Bu	A	**7b**	87
3	**3e**	**6c**	R = *n*-pentyl	A	**7c**	75
4	**3e**	**6d**	R, R = $(CH_2)_3$	B	**7d**	90
5	**3e**	**6e**	R, R = $(CH_2)_4$	C	**7e**	75
6	**3f**	**6d**	R, R = $(CH_2)_3$	B	**7f**	99
7	**3g**	**6d**	R, R = $(CH_2)_3$	B	**7g**	80

[a]Conditiona A: (a) $CHCl_3$, reflux 2 h; (b) CH_3CO_2H/benzene, rt, 3 h. Conditions B: (a) $CHCl_3$, rt 1 h; (b) *p*-TsOH/CH_3CO_2H, $CHCl_3$, rt, 2 h. Conditions C: (a) $CHCl_3$, rt 5 h; (b) *p*-TsOH/CH_3CO_2H, $CHCl_3$, rt, 12 h. [b]Isolated yields.

tetrazine **3e** proceeded efficiently to produce **7a–e**. Notably, the use of more reactive enamines led to higher yields of the products (entries 4 and 5, Table 2). Being similar to **3e**, $(CH_2)_2,S_4$-corona[4]arene[2]tetrazine **3f** and $S_4,(SO_2)_2$-corona[4]arene[2]tetrazine **3g** (vide infra) were converted into the corresponding corona[4]arene[2]pyridazines **7f** and **7g** in good to excellent yields upon treatment with enamine **6d** (entries 6 and 7, Table 2).

The one-pot method allowed the synthesis of coronarenes that contain sulfone bridges when a sulfone-bearing dinucleophile was applied. This has been exemplified by the preparation of **3c** (entry 3, Table 1). Alternatively, (SO_2)-linked coronarenes were also obtainable by oxidizing sulfide moieties of the macrocycles. Shown in Figure 3, for instance is the synthesis of $S_4,(SO_2)_2$-corona[4]arene[2]tetrazine **3g** from

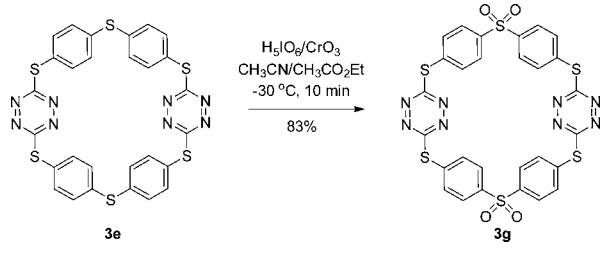


Figure 3. Synthesis of $S_4,(SO_2)_2$-corona[4]arene[2]tetrazine **3g**.

DOI: 10.1021/acs.orglett.6b01112
Org. Lett. 2016, 18, 2668–2671

partial oxidation of S_6-corona[4]arene[2]tetrazine **3e**. Remarkably, oxidation using a combination of H_5IO_6 and CrO_3 at −30 °C selective transformed diphenylsulfide segment into diphenylsulfone while phenyltetrazinylsulfide remained intact. The result is in accordance with the electron-withdrawing effect of the tetrazine ring.

When corona[4]arene[2]pyridazines **7b,c** and **7f** were reacted with *m*-CPBA, all phenylpyridazinylsulfides were oxidized into sulfones, yielding $(SO_2)_6$- and $(CH_2)_2,(SO_2)_4$-linked corona[4]arene[2]pyridazines **8b–d** (Figure 4). The

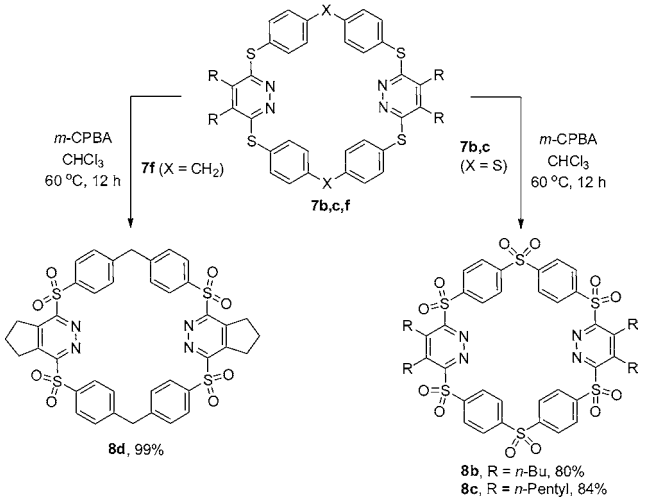


Figure 4. Synthesis of partially and fully $(SO_2)_2$-linked corona[4]arene[2]pyridazines **8**.

oxidation did not stop at the sulfoxide stage. We found that the degree of oxidation seemed to be dependent on the solubility of the product. In the case of the oxidation of **7a** and **7d**, for example, oxidation reaction gave an inseparable mixture of partially oxidized products as precipitates.

Finally, controlled oxidation of sulfide-bridged coronarenes was performed purposefully in order to obtain sulfoxide-containing coronarenes. We were pleased discover that the interaction of S_6-corona[4]arene[2]pyridazine **7d** with Selectfluor at ambient temperature in wet acetonitrile resulted in the generation of $S_4,(SO)_2$-corona[4]arene[2]pyridazine **9** albeit in a moderate yield (Figure 5).

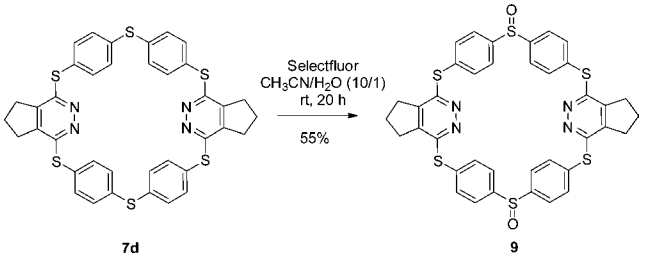


Figure 5. Oxidation of S_6-corona[4]arene[2]pyridazine **7d**.

All coronarenes synthesized are crystalline compounds. The structure of all products was supported by spectroscopic and microanalytic data. To gain a deeper insight into the macrocyclic conformation, single crystals of some products were cultivated and their X-ray molecular structures were determined. On the basis of the position of bridging atoms, corona[4]arene[2]tetrazines and corona[4]arene[2]pyridazines can be classified into three kinds of conformational structures in the solid state. As depicted in Figure 6 and Figures S1–3, all

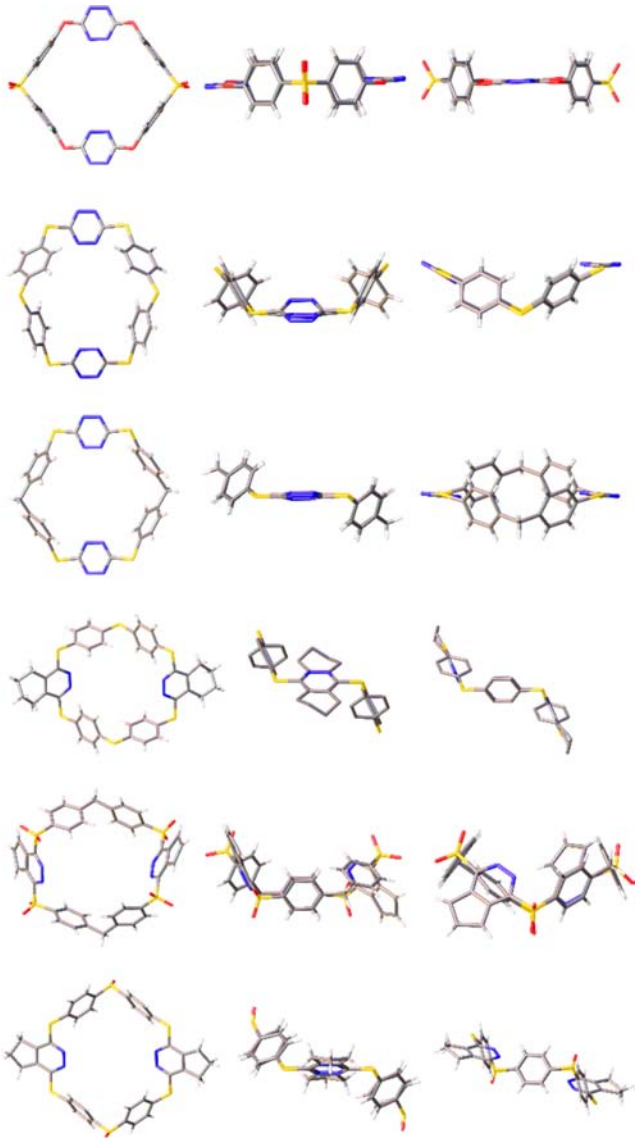


Figure 6. X-ray molecular structures of **3c**, **3e**, **3f**, **7e**, **8d**, and **9** (from top to bottom) with top (left) and side (middle and right) views.

linking units such as oxygen, sulfur, and carbon atoms in macrocycles **3a–d** are located almost on the same plane, yielding similar macrocyclic conformation in which two tetrazine subunits are nearly procumbent on the plane while the four benzene rings tend to be orthogonally orientated. In the cases of $(CH_2)_2,S_4$-corona[4]arene[2]tetrazine **3f** and S_6-, $(CH_2)_2,S_4$-, and $S_4,(SO)_2$-corona[4]arene[2]pyridazines **7d–f** and **9**, the linking atoms adopt the chair conformation. The boat and distorted boat conformations were observed in the X-ray molecular structure of S_6- and $S_4,(SO_2)_2$-corona[4]arene[2]tetrazines **3e** and **3g** and S_6- and $(CH_2)_2,(SO)_4$-corona[4]arene[2]pyridazines **7a** and **8d**. Evidenced clearly by the X-ray crystallography, all corona[6](het)arenes obtained gave analogous hexagon-like cavity. The cavity size and, more importantly, the electronic feature of macrocycles varied, however, depending on the nature of bridging atoms and constitutional aromatic components. Unlike corona[6](het)arenes, the larger macro-

DOI: 10.1021/acs.orglett.6b01112
Org. Lett. 2016, 18, 2668–2671

cyclic homologues such as corona[9](het)arenes **4a,b,d,f** and corona[12](het)arene **5f** adopted different loop structures in the crystalline state (Figure 7 and Figures S7−10). It should be

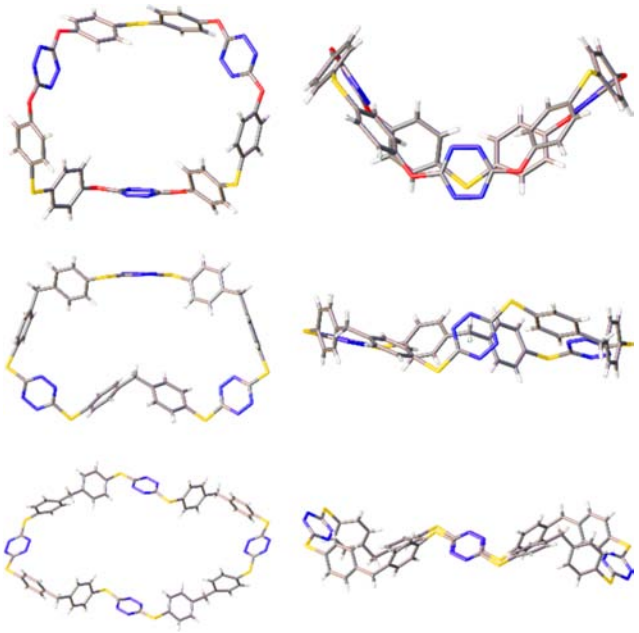


Figure 7. X-ray molecular structures of **4d**, **4f**, and **5f** with top (left) and side (right) views.

addressed that except for **7a−c** and **8b,c**, which contain many aliphatic chains, all coronarenes obtained gave simple and single sets of proton and carbon resonance signals in their ^{1}H and ^{13}C NMR spectra, respectively (Supporting Information). The outcomes suggested most likely the presence of an equilibrium mixture of macrocyclic conformers which are able to undergo very rapid interconversions at ambient temperature relative to the NMR time scale. It may also be interesting to note that all tetrazine-bearing coronarenes were red colored while pyridazine-bearing macrocycles were colorless. All oxygen-linked macrocycles exhibited strong UV−vis absorption bands at 298−339, 340−342, and 528−534 nm. In the case of sulfer-bridged analogues, two strong absorption bands at 254−288 and 290−299 nm and two weak bands at 403−417 and 531−533 nm were observed.

In summary, we have developed an operationally simple one-pot reaction method for the synthesis of corona[4]arene[2]-tetrazines that contain different bridging units including oxygen, sulfide, methylene, and sulfone based on nucleophilic aromatic substitution reaction. We have also demonstrated efficient synthesis of diverse corona[4]arene[2]pyridazines via macrocyclic ring transformations employing inverse-electron-demand Diels−Alder reaction and sulfide oxidation reaction. The easy availability and interesting conformational behaviors would render these novel synthetic macrocycles useful in study of supramolecular chemistry. Their applications as macrocyclic hosts to recognize varied electron-neutral and charged guest species are being actively pursued, and results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01112.

X-ray crystallographic files of **3−5**, and **7−9** (CIF)
Detailed experimental procedures, characterization of all products, and ^{1}H and ^{13}C NMR spectra of products (PDF)

■ AUTHOR INFORMATION

Corresponding Author

* wangmx@mail.tsinghua.edu.cn

Author Contributions

§Z.-D.F. and Q.-H.G. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We also thank the National Natural Science Foundation of China (21132005, 91427301, 21421064) and Tsinghua University for financial Support.

■ REFERENCES

(1) *Comprehensive Supramolecular Chemistry*; Lehn, J.-M., Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Vögtle, F., Eds.; Pergamon: Oxford, 1996.

(2) (a) Wang, M.-X.; Zhang, X.-H.; Zheng, Q.-Y. *Angew. Chem., Int. Ed.* **2004**, *43*, 838. (b) Wang, M.-X.; Yang, H.-B. *J. Am. Chem. Soc.* **2004**, *126*, 15412.

(3) For reviews, see: (a) Wang, M.-X. *Chem. Commun.* **2008**, 4541. (b) Wang, M.-X. *Acc. Chem. Res.* **2012**, *45*, 182.

(4) For a review of oxacalixaromatics, see: Maes, W.; Dehaen, W. *Chem. Soc. Rev.* **2008**, *37*, 2393.

(5) For a review of azacalixaromatics, see: Tsue, H.; Ishibashi, K.; Tamura, R. *Top. Heterocycl. Chem.* **2008**, *17*, 73.

(6) For a review of thiacalixarenes, see: Morohashi, N.; Narumi, F.; Iki, N.; Hattori, T.; Miyano, S. *Chem. Rev.* **2006**, *106*, 5291.

(7) For recent applications of heteracalixaromatics, see: (a) Tsue, H. *Nippon Kessho Gakkaishi* **2013**, *55*, 37. (b) Wu, J.-C.; Zhao, L.; Wang, D.-X.; Wang, M.-X. *Inorg. Chem.* **2012**, *51*, 3860. (c) Fa, S.-X.; Chen, X.-F.; Yang, S.; Wang, D.-X.; Zhao, L.; Chen, E.-Q.; Wang, M.-X. *Chem. Commun.* **2015**, *51*, 5112. (d) He, Q.; Ao, Y.-F.; Huang, Z.-T.; Wang, D.-X. *Angew. Chem., Int. Ed.* **2015**, *54*, 11785. (e) Gao, C.-Y.; Zhao, L.; Wang, M.-X. *J. Am. Chem. Soc.* **2011**, *133*, 8448. (f) Gao, C.-Y.; Zhao, L.; Wang, M.-X. *J. Am. Chem. Soc.* **2012**, *134*, 824. (g) Zhang, C.; Wang, Z.; Tan, L.; Zhai, T.-L.; Wang, S.; Tan, B.; Zheng, Y.-S.; Yang, X.-L.; Xu, H.-B. *Angew. Chem., Int. Ed.* **2015**, *54*, 9244. (h) Manganaro, N.; Lando, G.; Gargiulli, C.; Pisagatti, I.; Notti, A.; Pappalardo, S.; Parisi, M. F.; Gattuso, G. *Chem. Commun.* **2015**, *15*, 12657. (i) Hu, K.; Feng, S.; Wu, M.; Wang, S.; Zhao, W.; Jiang, Q.; Yu, A.; Zhang, S. *Talanta* **2014**, *130*, 63.

(8) Guo, Q.-H.; Fu, Z.-D.; Zhao, L.; Wang, M.-X. *Angew. Chem., Int. Ed.* **2014**, *53*, 13548.

(9) Guo, Q.-H.; Zhao, L.; Wang, M.-X. *Angew. Chem., Int. Ed.* **2015**, *54*, 8386.

(10) Guo, Q.-H.; Zhao, L.; Wang, M.-X. *Chem. - Eur. J.* **2016**, *22*, 6947.

(11) (a) Coburn, M. D.; Buntain, G. A.; Harris, B. W.; Hiskey, M. A.; Lee, K. Y.; Ott, D. G. *J. Heterocycl. Chem.* **1991**, *28*, 2049. (b) Chavez, D. E.; Hiskey, M. A. *J. Heterocycl. Chem.* **1998**, *35*, 1329. (c) Chavez, D. E.; Hiskey, M. A. *J. Energ. Mater.* **1999**, *17*, 357. (d) Helm, M. D.; Plant, A.; Harrity, J. P. A. *Org. Biomol. Chem.* **2006**, *4*, 4278.

(12) Saracoglu, N. *Tetrahedron* **2007**, *63*, 4199.

DOI: 10.1021/acs.orglett.6b01112
Org. Lett. 2016, 18, 2668−2671