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Efficient Post-Macrocyclization Functionalizations of Oxacalix[2]arene[2]pyrimidines

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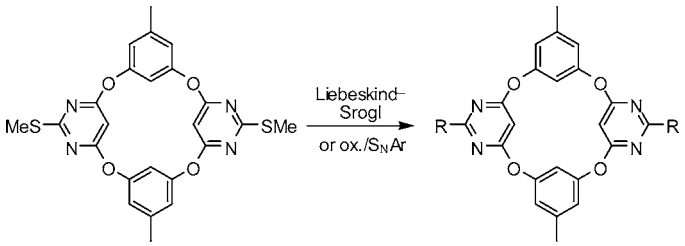
ABSTRACT



Diversely functionalized oxacalix[2]arene[2]pyrimidines have been synthesized starting from a bis(methylsulfanyl)-substituted oxacalix[4]arene by two efficient post-macrocyclization pathways. Functionalized aryl groups were introduced on the pyrimidine building block via Liebeskind–Srogl cross-coupling reactions, while a variety of O-, S-, N-, and C-nucleophiles were inserted on the calixarene skeleton by nucleophilic aromatic substitution reactions on the bis(methylsulfonyl)oxacalix[4]arene analogue.

Calix[*n*]arenes are [1$_n$]metacyclophanes that are relatively easy to prepare and functionalize, and due to their high level of preorganization and conformational preferences, they have been widely used as molecular platforms and hosts in supramolecular chemistry.[1] Heteracalixarenes, in which the carbon linkages between the aromatic units are replaced by heteroatoms, are less prevalent, although they inherently possess different properties that might expand the scope of "classical" calixarene chemistry.[2,3] Thiacalixarenes have been studied extensively,[4] mainly due to their synthetic availability, while aza- and oxacalixarenes, until recently, have been underexposed. Publications of novel synthetic procedures toward both aza- and oxacalixarenes have, however, created a renewed interest in these macrocycles. Azacalix[*n*](hetero)arenes have been obtained by Pd-catalyzed amination or nucleophilic aromatic substitution (S_NAr) reactions.[5] Oxacalixarenes were prepared as early as 1966, but up until a few years ago the field has been very quiet.[6] More recently, a number of groups have reinvestigated synthetic S_NAr protocols toward oxacalix[4]arenes.[7,8] Katz et al. optimized the S_NAr conditions to obtain oxacalix[4]arenes in a single step from 1,5-difluoro-2,4-dinitrobenzene and various *m*-dihydroxybenzenes in very high yields,[7e] and a number of

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(1) (a) Gutsche, C. D. *Calixarenes Revisited*; Royal Society of Chemistry: Cambridge 1998. (b) Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds. *Calixarenes 2001*; Kluwer Academic Publishers: Dordrecht, 2001. (c) Vicens, J., Harrowfield, J., Eds. *Calixarenes in the Nanoworld*; Springer: Dordrecht, 2006.

(2) We prefer the term heteracalixarenes to distinguish this class of heteroatom-bridged macrocycles from heterocalixarenes, the heterocyclic analogues of classical C-bridged calixarenes, e.g., calixpyrroles (calixhetarenes).

(3) König, B.; Fonseca, M. H. *Eur. J. Inorg. Chem.* **2000**, 2303.

(4) (a) Lhotak, P. *Eur. J. Org. Chem.* **2004**, 1675. (b) Morohashi, N.; Narumi, F.; Iki, N.; Hattori, T.; Miyano, S. *Chem. Rev.* **2006**, *106*, 5291.

(5) Some examples: (a) Ito, A.; Ono, Y.; Tanaka, K. *J. Org. Chem.* **1999**, *64*, 8236. (b) Miyazaki, Y.; Kanbara, T.; Yamamoto, Y. *Tetrahedron Lett.* **2002**, *43*, 7945. (c) Wang, M.-X.; Zhang, X.-H.; Zheng, Q.-Y. *Angew. Chem., Int. Ed.* **2004**, *43*, 838. (d) Tsue, H.; Ishibashi, K.; Takahashi, H.; Tamura, R. *Org. Lett.* **2005**, *7*, 2165.

(6) (a) Sommer, N.; Staab, H. A. *Tetrahedron Lett.* **1966**, *7*, 2837. (b) Lehmann, F. P. A. *Tetrahedron* **1974**, *30*, 727. (c) Gilbert, E. E. *J. Heterocycl. Chem.* **1974**, *11*, 899. (d) Bottino, F.; Foti, S.; Papalardo, S. *Tetrahedron* **1976**, *32*, 2567.

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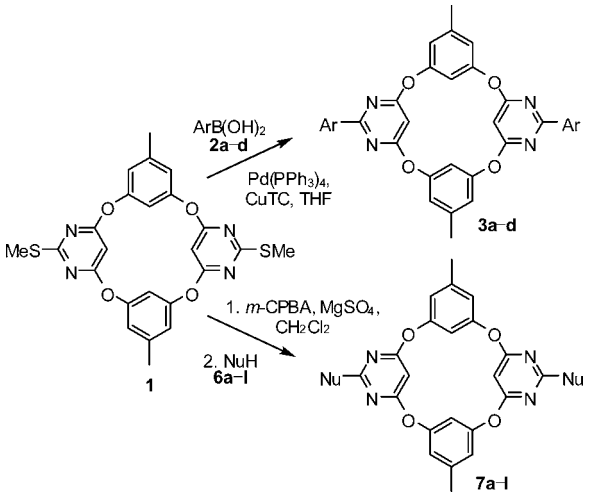
groups have elaborated on this work.[7g,j−m] The main limitation of all oxacalix[4]arenes derived from 1,5-difluoro-2,4-dinitrobenzene is, however, the fact that variation of the substitution pattern can only be achieved via the resorcinol component. In order to vary the electrophilic building block, numerous activated N-heterocycles, such as triazines,[7d,o−s] pyridines,[7f,i,p] pyrazines,[7i] pyrimidines,[7i,8] and naphthyridines,[7n] have been used for the synthesis of oxacalix[4]arenes. The scope of functional electrophilic components remains, however, rather limited. So far, the only oxacalixarene platform that enables post-macrocyclization modifications at the electrophilic component is the oxacalix[2]arene[2]triazine framework.[7d,o−s] These heteroaromatic oxacalixarenes have, however, to be prepared by a fragment coupling strategy, and, although efficient functionalization with a number of (bis)nucleophiles has recently been achieved,[7o,q] the possibilities are rather limited due to the inherent lower stability of triazine-based systems.[9]

Synthetic pyrimidine chemistry is a well-studied part of organic chemistry since the pyrimidine skeleton is commonly found in pharmaceutical drugs, fungicides, and herbicides.[10a] Dihalopyrimidines have been used for the synthesis of multitopic ligands suitable for the generation of grid-type materials.[10b] In previous work, we have been studying 4,6-dichloropyrimidines as structural components of both porphyrinoids and dendrimers,[11,12] and this research has recently been extended to oxacalixarenes. Oxacalix[*m*]arene[*m*]pyrimidines have been synthesized by S_NAr reactions on halogenated pyrimidine building blocks, and depending on the conditions, either a mixture of oxacalix[*n*]arenes, ranging from oxacalix[4]- up to oxacalix[12]arene, could be prepared or the thermodynamically favored 1,3-alternate oxacalix[4]-arene could be synthesized selectively in a high yield (up to 80%).[8] Both the pyrimidine and the nucleophilic component could be varied, allowing the preparation of variously functionalized oxacalix[4]arenes. Although the use of dihalopyrimidine building blocks offers a distinct advantage compared to analogous systems, by allowing variation of both reaction components, and, hence, introduction of functional groups on the oxacalixarene skeleton, a more general functionalization strategy has been pursued. The main limitation of our previous procedure is the fact that the desired functions have to be introduced in advance on the dihalopyrimidines, and although pyrimidine chemistry is versatile, this is not trivial for all substituents. Moreover, the desired functional groups have to be compatible with the applied S_NAr conditions. Another limiting factor is the yield of the desired oxacalix[4]arene, which is highly dependent on the substitution pattern of both reaction partners.[8] Therefore, it might be beneficial to introduce functional groups at the calixarene stage, after macrocyclization. The introduced functions can be used later on for specific applications of oxacalixarenes.

Out of our small library of oxacalix[*m*]arene[*m*]pyrimidines,[8] a calixarene platform suitable for various post-macrocyclization synthetic functionalizations had to be selected. An oxacalixarene with high potential toward such modifications is oxacalix[4]arene **1**, carrying two thiomethyl groups on the 2-pyrimidinyl positions. Such activated methylsulfanyl groups can conveniently be exchanged for other substituents by Liebeskind−Srogl cross-coupling reactions, or, after oxidation to the sulfonyl analogues, by S_NAr reactions (Scheme 1). 5,17-Bis(methylsulfanyl)oxacalix[2]-

Scheme 1. Variation of the Substitution Pattern of Oxacalix[2]arene[2]pyrimidines via Liebeskind−Srogl or S_NAr Reactions



(7) (a) Chambers, R. D.; Hoskin, P. R.; Khalil, A.; Richmond, P.; Sandford, G.; Yufit, D. S.; Howard, J. A. K. *J. Fluorine Chem.* **2002**, *116*, 19. (b) Chambers, R. D.; Hoskin, P. R.; Kenwright, A. R.; Khalil, A.; Richmond, P.; Sandford, G.; Yufit, D. S.; Howard, J. A. K. *Org. Biomol. Chem.* **2003**, *1*, 2137. (c) Li, X.; Upton, T. G.; Gibb, C. L. D.; Gibb, B. C. *J. Am. Chem. Soc.* **2003**, *125*, 650. (d) Wang, M.; Yang, H. *J. Am. Chem. Soc.* **2004**, *126*, 15412. (e) Katz, J. L.; Feldman, M. B.; Conry, R. R. *Org. Lett.* **2005**, *7*, 91. (f) Katz, J. L.; Selby, K. J.; Conry, R. R. *Org. Lett.* **2005**, *7*, 3505. (g) Hao, E.; Fronczek, F. R.; Vicente, M. G. H. *J. Org. Chem.* **2006**, *71*, 1233. (h) Yang, F.; Yan, L.; Ma, K.; Yang, L.; Li, J.; Chen, L.; You, J. *Eur. J. Org. Chem.* **2006**, 1109. (i) Katz, J. L.; Geller, B. J.; Conry, R. R. *Org. Lett.* **2006**, *8*, 2755. (j) Csokai, V.; Kulik, B.; Bitter, I. *Supramol. Chem.* **2006**, *18*, 111. (k) Konishi, H.; Tanaka, K.; Teshima, Y.; Mita, T.; Morikawa, O.; Kobayashi, K. *Tetrahedron Lett.* **2006**, *47*, 4041. (l) Konishi, H.; Mita, T.; Morikawa, O.; Kobayashi, K. *Tetrahedron Lett.* **2007**, *48*, 3029. (m) Jiao, L.; Hao, E.; Fronczek, F. R.; Smith, K. M.; Vicente, M. G. H. *Tetrahedron* **2007**, *63*, 4011. (n) Katz, J. L.; Geller, B. J.; Foster, P. D. *Chem. Commun.* **2007**, 1026. (o) Yang, H.-B.; Wang, D.-X.; Wang, Q.-Q.; Wang, M.-X. *J. Org. Chem.* **2007**, *72*, 3757. (p) Zhang, C.; Chen, C.-F. *J. Org. Chem.* **2007**, *72*, 3880. (q) Hou, B.-Y.; Wang, D.-X.; Yang, H.-B.; Zheng, Q.-Y.; Wang, M.-X. *J. Org. Chem.* **2007**, *72*, 5218. (r) Wang, Q.-Q.; Wang, D.-X.; Zheng, Q.-Y.; Wang, M.-X. *Org. Lett.* **2007**, *9*, 2847. (s) Hou, B.-Y.; Zheng, Q.-Y.; Wang, D.-X.; Wang, M.-X. *Tetrahedron* **2007**, *63*, 10801.

(8) Maes, W.; Van Rossom, W.; Van Hecke, K.; Van Meervelt, L.; Dehaen, W. *Org. Lett.* **2006**, *8*, 4161.

(9) This lower stability was also observed on comparison of triazine and pyrimidine-based dendrimers (with aryl ether linkages): Verheyde, B.; Maes, W.; Dehaen, W. *Mater. Sci. Eng. C* **2001**, *18*, 243, and ref. 12a.

(10) (a) von Angerer, S. In *Science of Synthesis*; Yamamoto, Y., Ed.; Georg Thieme Verlag: Stuttgart, 2004; Vol. 16, p 379 and references cited therein. (b) Ruben, M.; Rojo, J.; Romero-Salguero, F. J.; Uppadine, L. H.; Lehn, J.-M. *Angew. Chem., Int. Ed.* **2004**, *43*, 3644.

(11) (a) Smeets, S.; Asokan, C. V.; Motmans, F.; Dehaen, W. *J. Org. Chem.* **2000**, *65*, 5882. (b) Asokan, C. V.; Smeets, S.; Dehaen, W. *Tetrahedron Lett.* **2001**, *42*, 4483. (c) Maes, W.; Dehaen, W. *Synlett* **2003**, 79. (d) Maes, W.; Vanderhaeghen, J.; Dehaen, W. *Chem. Commun.* **2005**, 2612. (e) Maes, W.; Ngo, H. T.; Vanderhaeghen, J.; Dehaen, W. *Org. Lett.* **2007**, *9*, 3163.

(12) (a) Maes, W.; Amabilino, D. B.; Dehaen, W. *Tetrahedron* **2003**, *59*, 3937. (b) Chavan, S. A.; Maes, W.; Gevers, L. E. M.; Wahlen, J.; Vankelecom, I. F. J.; Jacobs, P. A.; Dehaen, W.; De Vos, D. E. *Chem. Eur. J.* **2005**, 6754. (c) Maes, W.; Vanderhaeghen, J.; Smeets, S.; Asokan, C. V.; Van Renterghem, L.; Du Prez, F. E.; Smet, M.; Dehaen, W. *J. Org. Chem.* **2006**, *71*, 2987.

arene[2]pyrimidine **1** could be synthesized in 70% yield starting from orcinol and 4,6-dichloro-2-methylsulfanylpyrimidine, which is easily available from thiobarbituric acid.[8]

Initially, the substitution of both 2-(methylsulfanyl) groups by Liebeskind−Srogl cross-coupling reactions was studied.[13,14] A number of different aryl groups were introduced on the upper rim of the calixarene skeleton (extra-annular) in good yields (68−78%) on reacting oxacalix[4]arene **1**, the respective arylboronic acid **2a**−**d**, $Pd(PPh_3)_4$, and copper(I) thiophene-2-carboxylate (CuTC) in THF (Scheme 1, Table 1). To avoid the reaction to stop at the monosubstituted oxacalix[4]arenes, 3 equiv of arylboronic acid were used.

Table 1. Functionalized Oxacalix[2]arene[2]pyrimidines Synthesized via Liebeskind−Srogl Cross-Coupling Reactions[a]

entry	$ArB(OH)_2$	oxacalix[4]	yield (%)
1	4-*tert*-butylphenylboronic acid (**2a**)	**3a**	68
2	4-methoxyphenylboronic acid (**2b**)	**3b**	78
3	4-cyanophenylboronic acid (**2c**)	**3c**	75
4	2-methylphenylboronic acid (**2d**)	**3d**	76

[a] General conditions: oxacalix[4]arene **1** (1 equiv), $ArB(OH)_2$ (3 equiv), $Pd(PPh_3)_4$ (5 mol %), CuTC (3.5 equiv), THF, 24 h reflux.

Although some aryl groups can also be introduced directly on the dihalopyrimidine component, this is not trivial for all substituted aryl groups (e.g., 4-CN-Ph), since the pyrimidine precursors have to be prepared by a multistep sequence starting from the respective amidines. The current one-step post-macrocyclization arylation procedure is obviously more efficient. Moreover, the yield of the macrocyclization step can be quite low depending on the substitution pattern. A striking example is oxacalix[2]arene[2]pyrimidine **3b**. This macrocycle can alternatively be generated directly from orcinol and 4,6-dichloro-2-(*p*-methoxyphenyl)pyrimidine, but the observed yield is only 20%, while it can now be obtained in a high yield by reaction on the much more accessible bis(methylsulfanyl)oxacalix[4]arene **1**.

A second pathway to substitute the thiomethyl groups involves an S_NAr strategy. In this way, a variety of O-, S-, N-, and C-nucleophiles can be bound to the oxacalixarene platform (Scheme 1, Table 2). To be able to perform S_NAr reactions on oxacalix[4]arene **1**, the 2-(methylsulfanyl) groups have to be activated for nucleophilic displacement by oxidizing them to their methylsulfonyl analogues.[10a,15] Oxacalix[4]arene **1** was oxidized to bis(methylsulfonyl)oxacalixarene **4** nearly quantitatively (96%), and without the need of chromatography, using *m*-CPBA as an oxidant.

Table 2. Functionalized Oxacalix[2]arene[2]pyrimidines Synthesized via S_NAr Reactions

entry	nucleophile	oxacalix[4]	yield (%)
1	phenol (**6a**)	**7a**	85
2	4-*tert*-butylphenol (**6b**)	**7b**	89
3	benzyl alcohol (**6c**)	**7c**	65
4	ethanol (**6d**)	**7d**	57
5	thiophenol (**6e**)	**7e**	95
6	benzyl mercaptan (**6f**)	**7f**	72
7	aniline (**6g**)	**7g**	48
8	piperidine (**6h**)	**7h**	67
9	ammonia (**6i**)[a]	**7i**	91
10	diethyl malonate (**6j**)	**7j**	67
11	**6k**[b]	**7k**	77
12	L-cysteine ethyl ester (**6l**)	**7l**	71
13[c]	4,4′-biphenol (**8**)	**9**	62

[a] 2.0 M in 2-propanol. [b] 1,8-Bis(2-hydroxyphenoxy)-3,6-dioxaoctane. [c] Reaction with mono(methylsulfonyl)oxacalix[4]arene **5**.

Initially, oxacalix[4]arene **4** was reacted with phenol (2 equiv) in DMF, with the addition of K_2CO_3 base and 18-crown-6, and the reaction mixture was stirred at 70 °C for 24 h.[16] After column chromatographic purification, the desired oxacalix[4]arene **7a** was obtained in 85% yield (entry 1).[17] To confirm this result, 4-*tert*-butylphenol and **4** were reacted under the same conditions, affording **7b** in 89% yield (entry 2). However, when these conditions were used to introduce alkoxides, poor results were obtained. On changing the base to NaH, benzyloxy groups could be introduced in 64% yield, and, on changing the solvent to acetonitrile, the reaction could be performed in only 15 min in a similar yield (entry 3). Ethanol could also be used as an O-nucleophile, affording 57% of oxacalix[4]arene **7d** (entry 4). S_NAr of thiophenol on **4** could be performed in a very high yield (95%) using the conditions optimized for phenols (entry 5), while benzylsulfanyl groups were introduced via the conditions used for benzyl alcohol (72%, entry 6). The introduction of N-nucleophiles appeared to be more challenging. Using different conditions with temperatures up to 150 °C, no satisfying results were obtained for the substitution of aniline. Only at 170 °C reaction between oxacalixarene **4** and aniline was observed. When an excess (7 equiv) of aniline was added to **4** in DMSO, and the reaction was kept at 170 °C for 4 h, oxacalix[4]arene **7g** was obtained in 48% yield (entry 7).[18] Piperidine could also be used for substitution reactions on oxacalixarene **4**. Using 2.2 equiv of piperidine in 1,4-dioxane at reflux, the reaction was not completed after a few h. Therefore, 5 equiv were used to obtain 67% of oxacalixarene **7h** within 2 h (entry 8). Another functional oxacalix[4]arene could be synthesized on using ammonia as a nucleophile. To obtain bis(amino)oxacalix[4]arene **7i**, a solution of

(13) (a) Liebeskind, L. S.; Srogl, J. *Org. Lett.* **2002**, *4*, 979. (b) Kusturin, C.; Liebeskind, L. S.; Rahman, H.; Sample, K.; Schweitzer, B.; Srogl, J.; Neumann, W. L. *Org. Lett.* **2003**, *5*, 4349.

(14) Similar conditions were already used on the 2-(methylsulfanyl) group of a *meso*-pyrimidinyl-substituted A_2B-corrole (ref 11e).

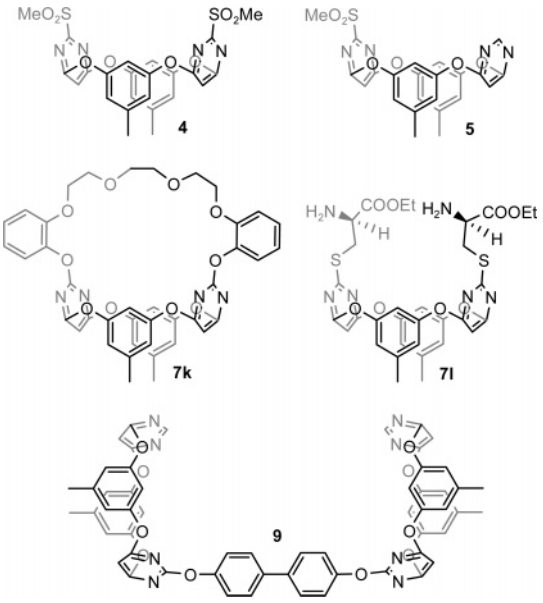
(15) Some examples: (a) Morimoto, H.; Shimadzu, H.; Hosaka, T.; Kawasa, Y.; Yasuda, K.; Kikkawa, K.; Yamauchi-Kohno, R.; Yamada, K. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 81. (b) Taddei, D.; Slawin, A. M. Z.; Woollins, J. D. *Eur. J. Org. Chem.* **2005**, 939. (c) Herrera, A.; Martinez-Alvarez, R.; Chioua, M.; Chatt, R.; Chioua, R.; Sanchez, A.; Almy, J. *Tetrahedron* **2006**, *62*, 2799.

(16) The S_NAr conditions used for macrocyclization (ref 8).

(17) Application of the same conditions on oxacalix[4]arene **1** did not afford any substituted product, even after 3 days of reaction.

(18) Longer reaction times caused a gradual drop in the yield.

ammonia in 2-propanol was added to **4**, and this mixture was stirred at 65 °C during 60 h. After simple filtration, the desired oxacalixarene **7i** was obtained in 91% yield (entry 9).[19] This oxacalix[4]arene is an extremely versatile starting material to introduce novel functions on the calixarene skeleton toward applications. Finally, we also explored a C-nucleophile. Treatment of **4** with diethyl malonate (NaH, CH_3CN) afforded 67% of oxacalix[4]arene **7j** (entry 10).



Since good results were observed for the introduction of various nucleophiles, a few more challenging examples were pursued to demonstrate the wide scope and versatility of the post-macrocyclization functionalization procedure. Oxacalix[4]arene **4** was combined with a bisphenol derivative **6k**, under the same conditions as optimized for regular phenols, but using a high-dilution procedure, affording oxacalixcrown **7k** in 77% yield (entry 11).[7j] A single-crystal X-ray structure was obtained for this novel oxacalixcrown, showing a 1,3-alternate conformation, as generally observed for oxacalix[4]arenes (Figure 1). A chiral oxacalix[2]arene[2]pyrimidine **7l** was prepared in 71% yield on introducing two L-cysteine moieties on the calixarene skeleton (entry 12). This reaction can be regarded as a preliminary test reaction for the construction of polypeptide chains on an oxacalixarene scaffold. An oxacalix[4]arene dimer **9** could be synthesized starting from 4,4′-biphenol (**8**) and mono(methylsulfonyl)-

(19) Direct macrocyclization of 2-amino-4,6-dichloropyrimidine did not afford any oxacalix[*n*]arene.

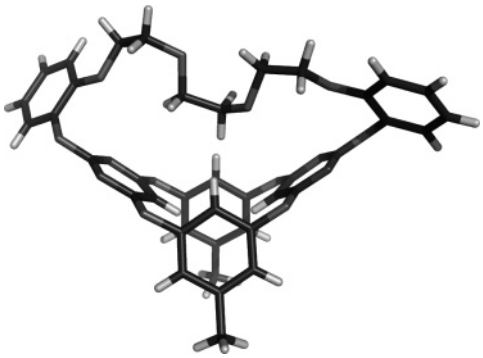


Figure 1. Single-crystal X-ray structure of oxacalixcrown **7k**.

oxacalix[4]arene **5** (62%, entry 13). Monofunctional oxacalixarene **5** was prepared by oxidation of the mono(methylsulfanyl) analogue (93%), which was synthesized on combining 4,6-dichloropyrimidine and 4,6-dichloro-2-methylsulfanylpyrimidine with orcinol (43%).[8] Monosubstituted oxacalix[4]arenes can be important in view of potential applications, e.g., attachment to fluorophores (sensors) and all kinds of supports, or the construction of monolayers.

In conclusion, novel functionalized oxacalix[2]arene[2]pyrimidines have been synthesized by two different post-macrocyclization strategies. Functionalized aryl groups could be introduced via Liebeskind−Srogl cross-coupling reactions, while diverse nucleophiles were inserted by a very straightforward S_NAr procedure. Some more advanced structures could also be prepared, illustrating the wide (and unprecedented) scope of the procedures. The high-yielding synthesis, the tunable macrocycle size, and the ease of elaboration of the substitution pattern make oxacalix[*m*]arene[*m*]pyrimidines versatile and unique platforms for the exploration of various supramolecular applications of oxacalixarenes.

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Supporting Information Available: Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra for all novel oxacalix[4]arenes. X-ray structure for **7k** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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