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Synthetic Methods

Rational Synthesis for All *All*-Homocalixarenes**

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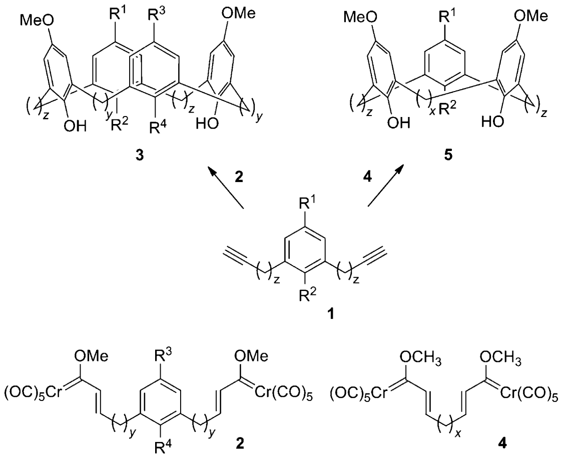
Calixarenes and related compounds are established scaffolds useful as ligands and very popular as building blocks for molecular design.[1,2] At the same time, the use of these compounds is virtually always defined by the ability of researchers to prepare them efficiently in useful quantities, and in a controlled fashion. As an example, calix[4]arenes, calix[6]arenes, and calix[8]arenes gained popularity very quickly after Gutsche et al. developed and perfected one-step methods for their preparation.[3] Fitting geometry, namely appropriate ring size and dominant conformation, are of paramount importance in most macrocycle applications, yet the overwhelming majority of publications still only report modifications of the three above-mentioned easily prepared calixarene cores.

Homocalixarenes have been a subject of scientific interest for a couple of decades.[1c,4] Whereas calixarenes have only one carbon atom between the aromatic rings, the presence of extra linkers between the aromatic rings allows the tuning of the desired cavity size, symmetry, and conformational mobility of the molecule. *All*-homocalixarenes have been defined by Vögtle and co-workers as those in which all aromatic rings are separated by two carbon atoms. *All*-bis(homocalixarene)s are those separated by three carbon atoms, *All*-tris(homocalixarene)s separated by four carbon atoms, etc.[4] We use the term homocalixarenes to refer to all calixarenes which have tether lengths greater than one carbon atom for at least one of the tethers and *all*-homocalixarenes for all calixarenes in which each of the tethers is greater than one carbon atom. The most direct method for the synthesis of *all*-homocalixarenes is the Müller–Röscheisen cyclization which gives mixtures of calixarenes in low yields.[5,6] *All*-homocalixarenes have also been made in a multistep synthesis by sulfur extrusion upon thermolysis of the corresponding sulfone.[7] Several methods have been used in the synthesis of *all*-bis(homocalixarene)s, including alkylation of bis(bromomethyl) benzenes with tosylmethyl isocyanide[8] and diethyl malonate,[9] a Claisen rearrangement,[10] and aryllithium/alkyl halide coupling.[11] Larger *all*-homocalixarenes ($n \geq 4$) have been made by the reaction of a bis(benzyllithium) with α,ω-dihalides,[12] and by the trimerization of a Fischer carbene complex.[13]

Homocalixarenes with heteroatoms in the linkers are much more widely studied compared to those with all-carbon linkers. The most popular of these are the bis(homooxacalix[3]arene)s which have enjoyed significant attention from researchers only after the discovery of a direct method for their preparation.[14–16]

Earlier reports from our laboratory have shown that the benzannulation reaction[17] of Fischer carbene complexes can be used to synthesize paracyclophanes with various tether lengths.[18] This chemistry was extended to the synthesis of calix[4]arenes,[19] having various substituents, in a highly regiocontrolled triple annulation, and later extended to chiral calix[4]arenes.[20] The purpose of the present work is to test the viability of this method to serve as a very general approach to *all*-homocalixarenes, having tethers with any number of desired carbon atoms, on a gram scale.

One can envisage that both the homocalix[4]arenes **3** and homocalix[3]arenes **5** can be prepared by the triple annulation method[19,20] (Scheme 1) involving the formation of two aromatic rings and a macrocyclic ring by two tandem benzannulations. The key starting material common to these reactions is the aromatic diyne **1** which should give **5** upon reaction with the bis(carbene) complex **4** and **3** upon reaction with the bis(carbene) complex **2**. In theory, any size homocalixarene could be accessed by this approach by just programming in the proper number of methylene spacers between the alkyne and arene ring in the diyne **1** and between the double bond and the arene ring in the bis(carbene) complexes **2** or **4**.



Scheme 1. Homocalix[4]arenes and homocalix[3]arenes by a triple annulation of bis(carbene) complexes.

The key diyne **1** can be prepared in high yield and in a convergent manner by a Suzuki coupling reaction using 2,6-

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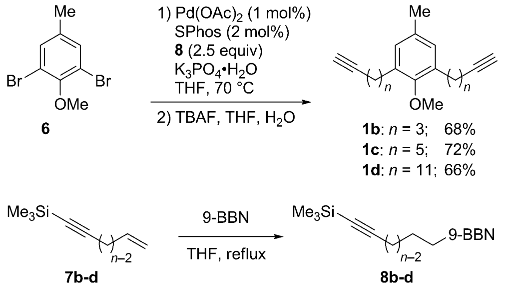
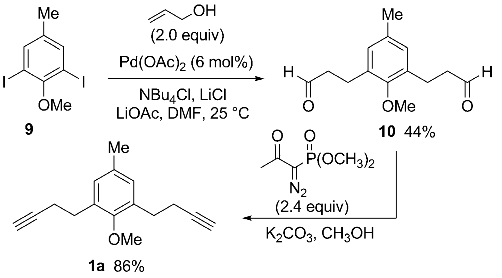
dibromo-4-methylanisole (**6**; Scheme 2). The enynes **7b–d** with 3, 5, and 11 methylene spacers, respectively, were prepared by alkylation of trimethylsilyl acetylene with the proper α,ω-haloalkene (see the Supporting Information). Then, using the coupling protocol of Buchwald et al.[21] the 9-BBN derivatives **8b–d** were prepared and then coupled with **6**.[22] This Suzuki coupling was performed at 70 °C and required freeze-thaw deoxygenation; 2 mol% SPhos and 1 mol% $Pd(OAc)_2$ were used to generate the catalyst, and potassium triphosphate monohydrate was the base. The resulting mixture was deprotected with catalytic TBAF in wet THF to afford good yields of **1b–d** in a one-pot procedure.



Scheme 2. Preparation of the diynes **1b–d**. 9-BBN = 9-borabicyclo-[3.3.1]nonane, TBAF = tetra-*n*-butylammonium fluoride.

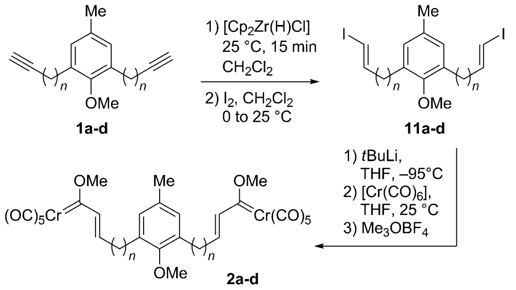
There was a desire to extend the substrate scope study to the *all*-homocalix[4]arene **3a** ($n = 2$) and the *all*-homocalix[3]arene **5a** ($n = 2$; see Tables 3 and 4 for structures). The requisite diyne **1a** for this job required special preparation (Scheme 3) since the appropriate enyne **7a** ($n = 2$) is not as readily available, and the presence of the β-alkyne function in **8a** could potentially complicate the Suzuki coupling. As an alternative, 2,6-diiodo-4-methylanisole (**9**) was converted into the dialdehyde **10** in 44% yield using the Heck reaction under Larock's conditions (in presence of quaternary ammonium salt and lithium acetate as a base).[23] In the course of this reaction the double bond of the allylic alcohol is shifted towards the end of the chain, thus giving the unbranched bis(aldehyde) as the major product. Finally, **1a** was prepared in 86% yield by treatment of the bis(aldehyde) with the Bestmann–Ohira reagent, dimethyl-1-diazo-2-oxopropylphosphonate, and potassium carbonate.[24]



Scheme 3. Preparation of the diyne **1a**. DMF = *N*,*N*-dimethylformamide.

An attractive feature of the synthesis of the bis(carbene) complexes **2a–d** is that it is convergent with the synthesis of the diynes **1a–d** in that they can be converted to the corresponding bis(carbene) complexes in two steps via the bis(*trans*-vinyl iodide) **11a–d** (Table 1). For the preparation of bis(*trans*-vinyliodide)s **11** and **13** (Table 2), a variation of Schwartz's hydrozirconation/iodination sequence reported by Jacobsen and co-workers was found to be highly beneficial.[25] The addition of Schwartz's reagent to both alkynes was found to be very fast in dichloromethane and, more importantly, the success of the addition was much less sensitive to the quality of Schwartz reagent. Quenching the reaction mixture with iodine affords very reproducibly high yields of **11** and **13**.

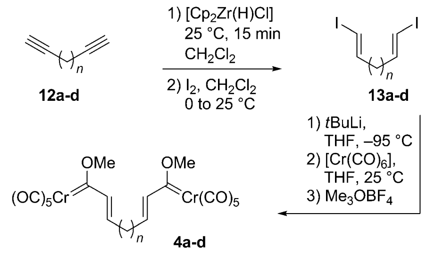
Table 1: Preparation of aryl-tethered bis(carbene) complexes **2**.[a]



Entry	n	**11**	Yield [%]	**2**	Yield [%]
1	2	**11a**	89	**2a**	67
2	3	**11b**	77	**2b**	79
3	5	**11c**	80	**2c**	68
4	11	**11d**	93	**2d**	49

[a] See the Supporting Information for experimental details. Yield is that of the isolated product. Cp = cyclopentadienyl.

Table 2: Preparation of the alkyl-tethered bis(carbene) complexes **4**.[a]



Entry	n	**13**	Yield [%]	**4**	Yield [%]
1	2	**13a**	90	**4a**	65
2	3	**13b**	86	**4b**	71
3	5	**13c**	79	**4c**	75
4	11	**13d**	90	**4d**	67

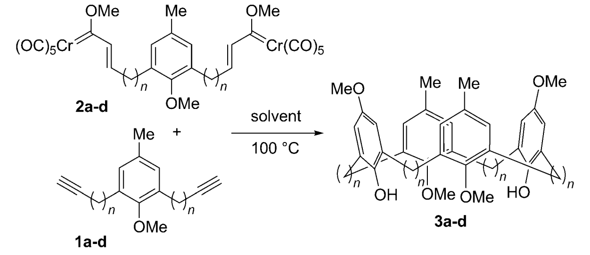
[a] See the Supporting Information for experimental details. Yield is that of the isolated product.

The bis(carbene) complexes **2** and **4** were initially prepared by a procedure following the Fischer method we had reported earlier for related bis(carbene) complexes.[19]

However, this procedure was plagued with low and unreproducible yields. It was suspected that the low yields were a result of Michael-type polymerization reactions or protonation of the bis(vinyllithium) intermediates by traces of water and, in some cases, the solvent. Thus, after a thorough search for optimal reaction conditions, an improved synthetic procedure was developed. Lithium–iodine exchange at −95 °C in THF and the subsequent rapid transfer of the resulting slurry into a chromium carbonyl THF solution at room temperature was the protocol of choice (Tables 1 and 2). All complexes but one could be prepared in 65–79 % yield, which constitutes, in many cases, more than a twofold increase in efficiency compared to previous syntheses of this class of bis(carbene) complexes.[19,20]

The triple annulation giving the homocalix[4]arenes **3a**–**d** was found to be more sensitive to the reaction conditions than would have been expected based on our experience with the synthesis of calix[4]arenes.[19,20] For example, the reaction of **1b** and **2b** did not give any detectable products in benzene, acetonitrile, or dichloromethane. In contrast, reactions in 1,2-dichloroethane, 1,4-dioxane, and THF all gave the bis(homocalix[4]arene) **3b** in 25–39 % yield, and it was the only product that was mobile on silica gel (Table 3). This result is to be compared to a 36 % yield for the calix[4]arene **3** ($n = 1$) in 1,2-dichloroethane.[19] To our delight, the extension of these reaction conditions to the other tether lengths afforded all of the *all*-homocalix[4]arenes **3a**–**3d**.

Table 3: Homocalix[4]arenes through the triple annulation of **1** and **2**.[a]



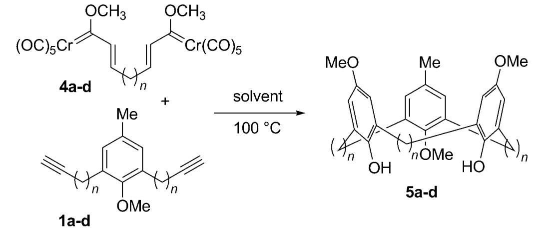
3	n	THF	Yield [%] 1,2-DCE	1,4-dioxane
3a	2	25	35	22
3b	3	25	39	25
3c	5	27	10	17
3d	11	13	0	18[b]

[a] Unless otherwise specified, all reactions were carried out on 1.0 mmol of **2** with 1.0 equiv of **1** at 0.0025 M at 100 °C for 24 h in THF and 1,4-dioxane, and for 0.5–1 h in 1,2-DCE. Yield is that of the isolated product. [b] This reaction was conducted at 115 °C. The yield for the reaction run at 100 °C is 13 %. 1,2-DCE = 1,2-dichloroethane.

The choice of the solvent for the triple annulation reaction is defined by several factors. While 1,2-dichloromethane gives the highest yield for tether lengths of two and three (**3a** and **3b**,respectively; Table 3), the yield drops to 10 % in case of $n = 5$, and the cyclization fails completely when $n = 11$. It is also worth noting that only high purity 1,2-dichloroethane works in this reaction. Even when a lower grade purity solvent is purified by distillation over calcium hydride, the reaction still fails, possibly because of the presence of chloroform (see the Supporting Information). Tetrahydrofuran and 1,4-dioxane, in contrast, provide more reproducible and reliable reactions. Furthermore, 1,4-dioxane can be deoxygenated by simply purging of the solvent with nitrogen, while the use of both THF and 1,2-dichloroethane require freeze-thaw deoxygenation. Thus, 1,4-dioxane allows greater operational convenience and the preparation of **3** on a gram scale. It is also to be noted that, while increased temperature does not benefit the reactions with smaller tethers, the yield of **3d** increases from 13 to 18 % when the reaction is conducted at 115 °C rather than at 100 °C. The macrocycle in **3d** consists of a 56-membered ring.

The triple annulation strategy could be extended to the synthesis of the homocalix[3]arenes **5** in which two of the three benzene rings were constructed simultaneously with the macrocycle (Table 4). Slightly higher yields were observed in THF and 1,4-dioxane for the three and five methylene tethers compared to those for the corresponding homocalix[4]arenes (Table 3 versus Table 4). However, lower yields were observed for the smallest macrocycle **5a**, and this might be attributed to steric congestion in the 15-membered macrocycle having three aromatic rings when one considers that the two-rings generated in the coordination sphere of the chromium will maintain an η^6 coordination of a chromium tricarbonyl to these two rings until the reaction is stopped and exposed to air. In contrast to **3d**, the yield of **5d** could not be improved by increasing the temperature from 100 to 115 °C. Like the homocalix[4]arenes **3a**–**3d**, the homocalix[3]arenes **5a**–**5d** are all conformationally mobile and no evidence could be found for hindered rotation of the benzene rings through the annulus. However, the pseudosymmetry of the aromatic protons present in **5c** and **5d** is broken when the size of the spacer is reduced to two or three methylenes (**5b** and **5a**; see the Supporting Information).

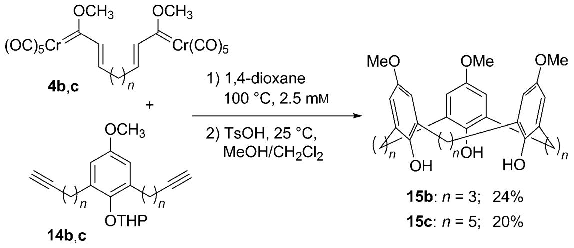
Table 4: Homocalix[3]arenes through the triple annulation of **1** and **4**.[a]



5	n	THF	Yield [%] 1,4-dioxane
5a	2	9	17
5b	3	30	31
5c	5	28	25
5d	11	10	11[b]

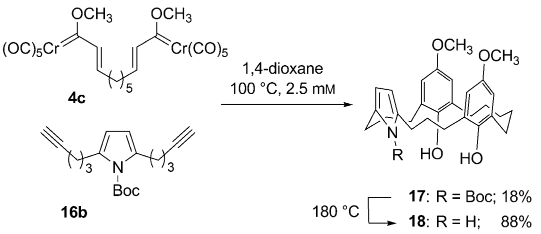
[a] Unless otherwise specified, all reactions were carried out on 1.0 mmol of **4** with 1.0 equiv of **1** at 0.0025 M at 100 °C for 24 h. Yield is that of the isolated product. [b] This reaction was conducted at 115 °C.

Calixarenes and homocalixarenes are characterized by the presence of a phenol function on each of the benzene rings projecting from the lower rim of the calixarene and these are crucial for the recognition and binding of substrates, and for covalent modifications. In an effort to provide access to unfunctionalized symmetrical homocalixarenes by the triple annulation methodology, the THP-protected diynes **14b** and **14c** where prepared and reacted with the corresponding bis(carbene) complexes **4b** and **4c** (Scheme 4). The initially formed homocalix[3]arenes were not isolated but directly deprotected to give the symmetrical molecules **15b** and **15c** in 24 and 20 % yield, respectively, upon isolation. The reactions were performed on 10 mmol scale and provided 1.18 g of **15b** and 1.15 g of **15c.**



Scheme 4. Synthesis of symmetrical homocalix[3]arenes. THP = tetrahydropyran, Ts = 4-toluenesulfonyl.

Calix[4]pyrroles are widely studied and their attractive properties have been used for a variety of applications including as optical sensors for anions.[26] To put our method to a final test, the previously unknown pyrrole/calixarene hybrid **17** with linkers of different lengths (three and five methylene groups) was prepared from the protected diyne **16b** in 18 % yield (Scheme 5). The Boc group was removed by heating the macrocycle as a thin film in an inert atmosphere at 180 °C,[27] thus affording the homocalix[3]arene **18** in 88 % yield. Interestingly, even though the triple annulation was performed at 100 °C, **18** was not detected in the initial reaction mixture (≤ 5 %). The air-sensitive macrocycle **18** was prepared on a 200 mg scale, thus allowing us to grow a single crystal and perform X-ray analysis.[28]



Scheme 5. Synthesis of a pyrrole/benzene calix[3]arene hybrid. Boc = *tert*-butoxycarbonyl.

In conclusion, the reaction of bis(carbene) complexes with bis(alkyne)s in a triple annulation provides direct access to homocalixarenes with three and four aromatic rings. Through proper choice of tether length, these macrocycles were assembled with ring sizes ranging from 15 to 56 carbon atoms. The method allows full control over the ring size and symmetry, and its ability to provide the synthesis of a series of *all*-homocalixarenes was illustrated for compounds having 2, 3, 5, and 11 methylene linkers between each ring. The method is also flexible enough to allow the incorporation of a pyrrole unit in place of one of the benzene rings in the calixarene. The macrocycles are always isolated as a single product and can be prepared conveniently on a gram scale. Six of the twelve homocalixarenes that were prepared were characterized by single-crystal X-ray analysis.[28]

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Keywords: annulation · calixarenes · carbenes · macrocycles · synthetic methods

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[28] CCDC 897168–897173 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Please see the Supporting Information for additional details regarding the X-ray structures obtained for the compounds presented herein.