

A New Convergent Strategy for the Synthesis of Calixarenes via a Triple Annulation of Fischer Carbene Complexes

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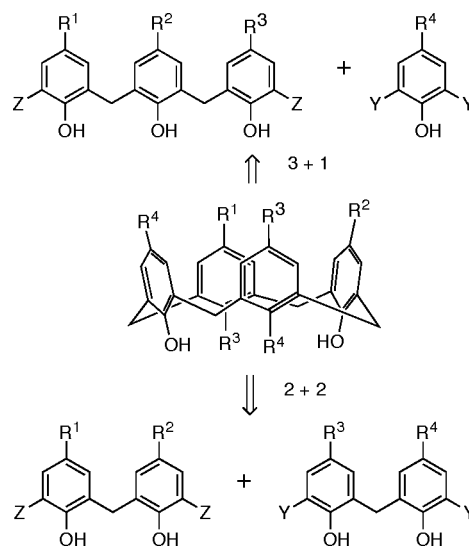
Calix[4]arenes have become a popular template for a number of chemical investigations.¹ Symmetrical calix[4]arenes with four identically substituted phenol rings can be prepared in one step from the base-catalyzed condensation of 4 equiv of a phenol and of formaldehyde. The yields for this one-step synthesis can be moderate to high, but only for phenols with para-substituted tertiary alkyl groups. Unsymmetrical calixarenes can be fashioned from these readily available materials by desymmetrization reactions. More convergent and more synthetically flexible routes to unsymmetrical calixarenes have been developed, and the two most important are the 3 + 1 strategy and the 2 + 2 strategy indicated in Scheme 1. These routes are necessarily longer but are often the route of choice for the construction of calixarenes designed for specific applications.

In the past few years, we have been exploring the intramolecular reaction of Fischer carbene complexes with alkynes as a method for the preparation of macrocycles.² On the basis of the success of experiments in simple systems, we envisioned a new approach to calixarenes, which would involve the reaction of a bis-carbene complex of the type **1** with bis-propargyl benzene of the type **2** (Scheme 2). If viable, this reaction would result in the assembly of two of the phenol rings of the calixarene and the macrocycle of the calixarene in one step. We report here the first method for the synthesis of calixarenes where one or more of the benzene rings are formed convergent with the annulus.

The syntheses of the starting materials are convergent in the sense that the bis-propargyl benzene derivatives **2** are constructed and then in turn utilized in the synthesis of the bis-carbene complex **1**. Four different bis-propargyl benzenes were prepared from the bis-bromomethyl analogues **4**. The latter are prepared in 2–4 steps in 20–62% overall yield from commercially available starting materials; their preparation is presented in the Supporting Information. After investigating a (large) number of methods for the coupling of alkynes with the bis-benzyl bromides **4**, we found two that gave high yields. The palladium-catalyzed cross-coupling of **4** with tris(trimethylsilylethynyl)indium³ gave high yields of **5**, but the extreme air and moisture sensitivity of indium trichloride together with the necessity to do this transformation on a larger scale rendered this protocol operationally inconvenient. The method of choice was the copper-catalyzed coupling⁴ of **4** with the trimethylsilylethynyl Grignard that gave high yields of **5** and, after desilylation, high yields of the bis-propargyl benzenes **2** (Table 1).

The bis-propargyl benzenes **2** could be converted to the bis-carbene complex **1** in two steps, as outlined in Table 2. Hydrozirconation of **2** with 2 equiv of zirconocene chlorohydride followed by a quench with NIS gave the bis-*trans*-vinyl iodides **6** in good to excellent yields. These diiodides could be converted into the bis-carbene complexes **1** by treatment with *tert*-butyllithium to generate the bis-vinylolithium and then sequentially with chromium carbonyl and trimethyloxonium tetrafluoroborate to give the bis-carbene complexes in moderate yields. The complexes were isolated

Scheme 1



Scheme 2

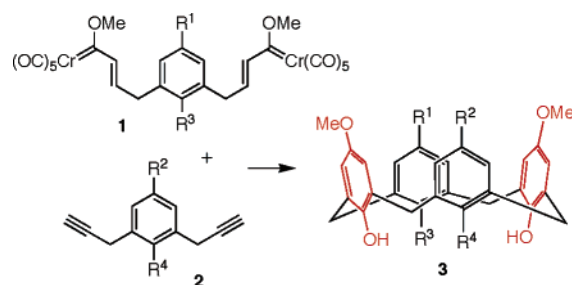
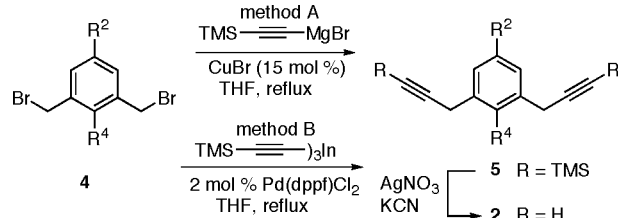
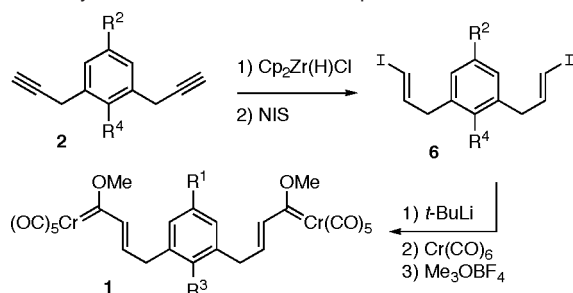


Table 1. Synthesis of Bis-Propargyl Arenes

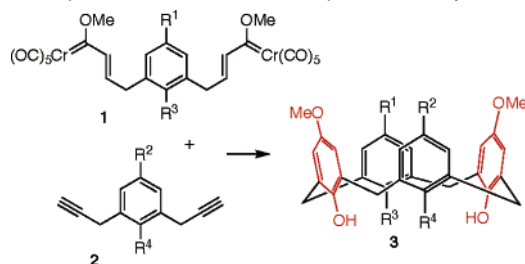


series	R ²	R ⁴	method	% yield 5	% yield 2
a	Me	Ph	A	79	77
b	Me	<i>n</i> -C ₆ H ₁₃	A	73	73
c	Me	OMe	B	80	91
d	Ph	OMe	B	77	90

as red oils and normally were directly taken onto the benzannulation with the diynes **2**. Improved overall yields of these complexes were not realized by employing the intermediate bis-*trans*-bromo analogue of **6**.

Table 2. Synthesis of Bis-Carbene Complex **1**

R ²	R ⁴	6	% yield 6	R ¹	R ³	1	% yield 1
Me	Ph	6a	73	Me	Ph	1a	47
Me	<i>n</i> -C ₆ H ₁₃	6b	77	Me	<i>n</i> -C ₆ H ₁₃	1b	44
Me	OMe	6c	86	Me	OMe	1c	36
Ph	OMe	6d	78	Ph	OMe	1d	32

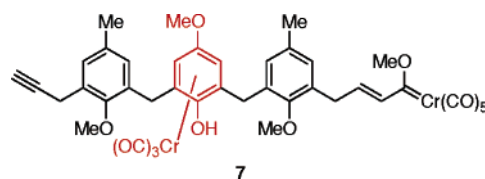
Table 3. Triple Benzannulation of Complex **1** and Diyne **2**^a

entry	complex 1	R ¹	R ³	arene 2	R ²	R ⁴	3	% yield 3
1	1a	Me	Ph	2a	Me	Ph	3a	35 ^b
2	1b	Me	<i>n</i> -C ₆ H ₁₃	2b	Me	<i>n</i> -C ₆ H ₁₃	3b	22
3	1c	Me	OMe	2c	Me	OMe	3c	36
4	1d	Ph	OMe	2d	Ph	OMe	3d	41
5	1c	Me	OMe	2a	Me	Ph	3e	31 ^c
6	1d	Ph	OMe	2a	Me	Ph	3f	35 ^d
7	1c	Me	OMe	2b	Me	<i>n</i> -C ₆ H ₁₃	3g	22 ^e
8	1b	Me	<i>n</i> -C ₆ H ₁₃	2d	Ph	OMe	3h	35 ^e
9	1c	Me	OMe	2d	Ph	OMe	3i	40

^a All reactions were carried out in 1,2-dichloroethane at 100 °C at 2.5 mM in **1** with 1.0 equiv of alkyne **2** for 20–40 min. ^b Isolated as a separable 1.7:1 mixture of two conformers. ^c Isolated as a nonseparable 3.8:1 mixture of two conformers. ^d Isolated as a nonseparable 3.3:1 mixture of two conformers. ^e Isolated as a nonseparable 7.9:1 mixture of two conformers.

We were delighted to find that the reaction of the carbene complex **1c** with diyne **2c** gave the unsymmetrical calixarene **3c** in 36% yield. While all but two of the yields in Table 3 are in the 30–40% range, this is well above the yields normally seen for the cyclization event for either the 2 + 2 or 3 + 1 strategies.⁵ Since it is well known that the synthesis of phenols via the benzannulation reaction of Fischer carbene complexes and alkynes can be very sensitive to the reaction conditions,⁶ an optimization regimen was explored for the reaction of bis-complex **1c** with diyne **2c** (entry 3). Since this macrocyclization likely involves the intramolecular

cyclization of the intermediate carbene complex **7**, it is not



surprising that it is sensitive to the concentration. The yield drops to 16% at 0.025 M. It was surprising that the yield could not be improved when a mixture of **1c** and **2c** was added via syringe pump to hot 1,2-dichloroethane. Given the effects of solvent that we have seen on other macrocyclizations of carbene complexes,² it was surprising to find little solvent effect on this reaction. The yields of **3c** in THF, acetonitrile, benzene, and 1,4-dioxane were all in the range of 26–30%. Higher temperature is optimal: the reaction at 83 °C gives a 33% yield of **3c** with a reaction time of 90 min, but this falls to 25% yield at 50 °C with a reaction time of 2 days.

The benzannulation reaction of Fischer carbene complexes with alkynes provides for a highly regiocontrolled synthesis of unsymmetrical calix[4]arenes in a process that constructs two of the benzene rings of the calixarene simultaneously with the macrocyclization event that creates the 16-membered ring of the calixarene. Furthermore, the overall yields from commercially available materials of the unsymmetrical calixarenes so generated are comparable with the overall yields of existing methods via either the 2 + 2 or the 3 + 1 strategies that have been previously developed.⁵

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Supporting Information Available: Experimental procedures and spectral data for all new compounds, ¹H NMR spectra for calixarenes **3a–3i**; X-ray structural data for **3a-I**, **3a-II**, and **3c** (PDF); X-ray crystallographic data (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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