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Synthesis of arylethynylated cyclohexa-*m*-phenylenes via sixfold Suzuki coupling

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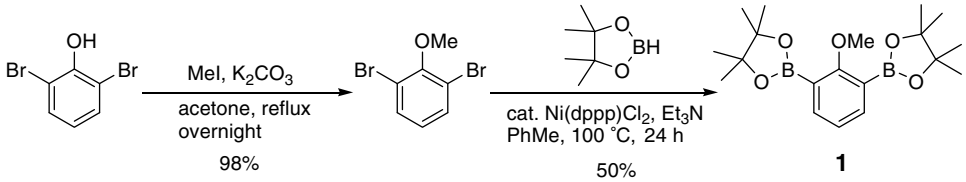
ABSTRACT

A one-step, one-pot assembly of arylethynylated cyclohexa-*m*-phenylenes from *meta*-dibromide and *meta*-diboronic acids has been accomplished using a sixfold Suzuki macrocyclization, without the need for high dilution or slow-addition techniques.

Cyclohexa-*m*-phenylenes are cyclic oligomers possessing the same benzene ring-based backbone as poly(*p*-phenylene)s (PPPs). Since the first syntheses of cyclohexa-*m*-phenylenes by Staab in the 1960s[1] and some later work on cyclohexa-*m*-phenylene-based cation hosts by Cram et al.,[2] there has generally been little attention given to these interesting macrocycles. With the exception of a recent paper[3] by the Klaus Müllen group, there have been no reports of cyclohexa-*m*-phenylenes bearing functional groups more complex than alkyl and alkoxy substituents. Furthermore, all previous strategies for cyclohexa-*m*-phenylene syntheses involve the cumbersome pre-synthesis of terphenyl precursors prior to the final macrocyclization step (reductive coupling). The terphenyl strategy restricts the diversity of symmetries that can be achieved in the final product, and the harsh conditions of the final coupling step also restrict the range of functional groups that can be present. Given recent interest in designing various novel functional materials, more efficient syntheses are needed to advance the development of cyclohexa-*m*-phenylenes.

In this Letter, we report an efficient approach for the one-step assembly of the cyclohexa-*m*-phenylene framework via a sixfold Suzuki coupling between *meta*-difunctionalized, monobenzenoid building blocks. For the macrocyclization experiment, we prepared the two necessary building blocks, namely pinacol-protected diboronic acid **1** and dibromide **2**. The synthesis of the dibromide is described in previous work performed in our group,[4] whilst the diboronic acid had to be prepared in two steps (Scheme 1). The first step involved a simple O-methylation, followed by a nickel-catalyzed double borylation in the second step, using a method described by Tour and co-workers.[5] It is worth noting that the use of pinacol protecting groups enabled the complete purification of the diboronic acid coupling partner by column chromatography, in contrast to a structurally similar but unprotected 1-alkoxyphenyl-2,6-diboronic acid employed by Cram et al.,[2a] which could only be used in a subsequent step without further purification. In our macrocyclization step (Scheme 2), equimolar amounts of both coupling partners were mixed together with catalytic $Pd(PPh_3)_4$ (6 mol %), cesium carbonate and toluene (water was excluded), and refluxed for 27 h to give the desired cyclohexa-*m*-phenylene in 13% isolated yield (as a white powder),[9] along with some oligomeric byproducts (ca. 37%). Increasing the scale of the reaction tenfold appears to decrease the yield to about 9–10%. Empirically, this set of conditions appears to be crucial to the success of the reaction. Following the isolation of the less polar cyclohexa-*m*-phenylene, the majority of the oligomeric mixture was successfully flushed out of the silica gel column, and subsequently analyzed by NMR and gel permeation chromatography (GPC). Chemical shifts from the ^1H NMR spectrum suggested that the functionality present in the oligomers was the same as those present in the



Scheme 1. Synthesis of the protected diboronic acid precursor.

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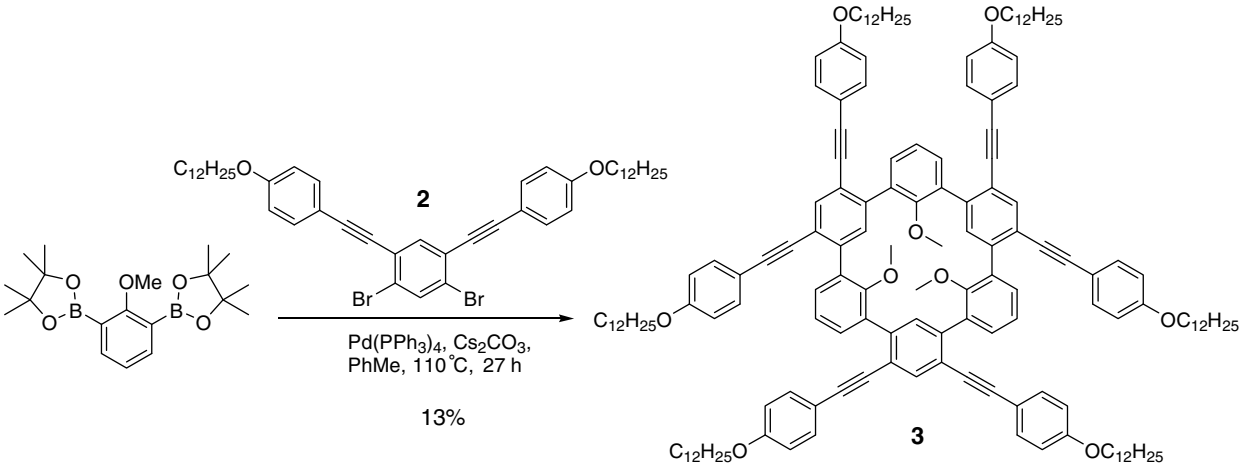
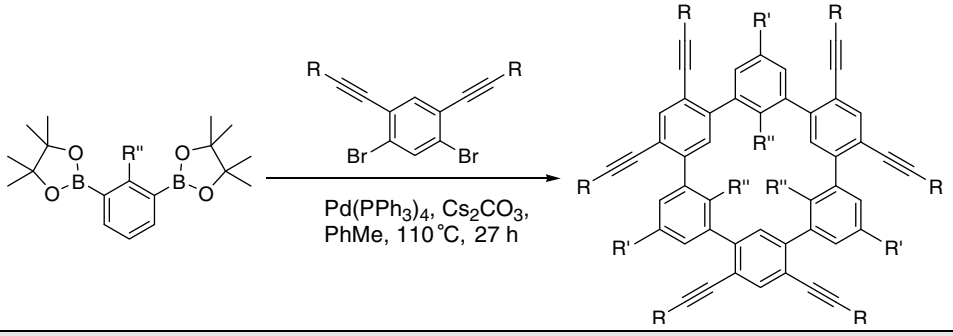
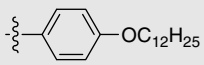
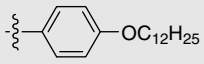
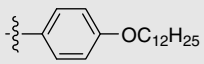


Scheme 2. Synthesis of hexa-*m*-phenylene via sixfold Suzuki coupling.

cyclohexa-*m*-phenylene. The GPC results indicated a number-average molecular weight of 4400 amu, and a polydispersity index of about 1.2. This corresponds to species containing about six repeat units (or 12 benzene rings) in their structure. The use of high-dilution/slow-addition techniques was found to be unnecessary (and in fact detrimental) to macrocycle formation. When such conditions were applied, a grand mixture of inseparable products was obtained, with the distinctive absence of the desired cyclohexa-*m*-phenylene. A multitude of emissive (under UV) and non-emissive spots was observed on TLC, with the dibromide starting material being one of the components in the crude mixture. The emissive species were presumed to be oligomers, and subsequent analysis of the crude mixture by MALDI-TOF did reveal the presence of molecules in the 4900–4950 amu mass range, which could correspond to oligomers containing about 6.5 repeat units. Trials employing tetrahydrofuran or dioxane as solvent did not give succesful reactions. The use of cesium carbonate under anhydrous conditions was also found to be effective compared with the use of potassium and sodium carbonates in the presence of water. The introduction of water to the reaction mixture proves deleterious to the formation of cyclohexa-*m*-phenylene. For example, when K_2CO_3/H_2O was used instead of Cs_2CO_3, no macrocycle was obtained. Instead, up to 60% of the starting dibromide could be recovered after column chromatography, and an analysis of the remaining mixture of substances by MALDI-TOF revealed only very low molecular weight species (i.e., <1150 amu). It is highly likely that under protic conditions, hydrolytic deborylation of the pinacolboronate ester predominates, leading to very little coupling being effected. An additional experiment in which the methoxy group of the diboronic acid component was deliberately omitted was performed, keeping all other reaction conditions unchanged. In this case (Table 1, entry 4), no macrocycle was detected by either TLC or MALDI-TOF. Instead, numerous unresolvable emissive spots were observed on TLC. After partial purification and attempted

Table 1
Scope of the one-step macrocyclization



Entry	R	R′	R″	Yield[a] (%)
1		H	OMe	13
2		Me	OMe	ca. 5[b]
3	–*n*-$C_{10}H_{21}$	H	OMe	15
4		H	H	0

[a] Isolated yields based on 0.14 mmol scale.
[b] Yield could not be determined with sufficient accuracy.

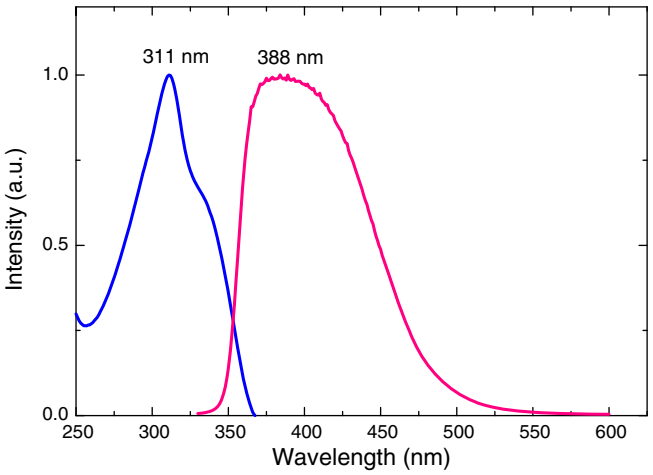


Figure 1. Normalized absorbance (blue line) and emission (pink line) spectra of **3**.

separation by silica gel column chromatography, several (emissive) fractions were analyzed by NMR and MALDI. The ^{1}H NMR spectra of the partially purified mixtures showed typical aromatic peaks between 6.5 and 8.0 ppm, as well as signals around 3.5 and 4.0 ppm (OCH_2), suggesting the kind of functionality that would be expected in any oligomer or macrocycle formed. MALDI studies on these fractions indicated the presence of numerous species with exact masses ranging from 1100 to 4900 amu. These could correspond to oligomers containing between 2 and 7 repeat units. When the methoxy groups were kept in place, macrocyclization occurred even as the ethynyl substituents were varied. Isolated yields tended to be below 20%, with greater steric hindrance (bulkier substituents) resulting in lower yields. Finally, a macrocyclization reaction between pinacolboronate **1** and 1,3-dibromobenzene was attempted. This reaction did not proceed cleanly, leading to the formation of numerous products. TLC showed no less than ten unresolvable non-emissive spots, and MALDI analysis failed to show any peak that would correspond to the desired target. Thus, the reaction appears to be quite sensitive to the type of substituents employed in the coupling partners.

Cyclohexa-*m*-phenylene **3** was characterized by ^{1}H NMR, ^{13}C NMR, high-resolution mass spectrometry (MALDI-TOF), UV/vis, and fluorescence spectroscopy. The ^{1}H NMR spectrum showed all the expected splitting patterns and chemical shifts. The three sets of methoxy protons within the macrocycle cavity turned out to be magnetically equivalent (δ = 3.33 ppm), suggesting a symmetrical optimum conformation that placed the internal substituents in identical environments, or that the ring system was reasonably fluxional. Figure 1 shows the normalized absorbance and emission spectra of **3**, with the absorption and emission maxima at 311 nm and 388 nm, respectively. The large bandgap of the material (3.4 eV) suggests the lack of conjugation between the rings of the cyclic system due to twisting relative to each other, not unlike the rings of unsubstituted cyclohexa-*m*-phenylene (bandgap = 3.9 eV, based on its 320 nm band edge).[6] Further synthetic manipulations involving the cyclohexa-*m*-phenylene targets are envisioned and we were particularly interested in cyclization reactions promoted by electrophilic additions to the acetylene groups.[7] The appeal of these reactions is that they would provide an efficient synthesis of Kekulene structures.[8] Unfortunately, to date our efforts via various electrophilic cyclizations have been unsuccessful, giving complex inseparable mixtures.

In summary, we have discovered a one-step Suzuki coupling-based construction of arylethynylated cyclohexa-*m*-phenylenes from simple building blocks. Compared with previous preparations of oligophenylene macrocycles, all carbon–carbon bond formations can be accomplished within a single step. Besides allowing for the quick assembly of the cyclohexa-*m*-phenylene framework, the relatively mild conditions used also accommodate the introduction of complex functionality, and thus provides access to a wide range of potentially useful materials.

Acknowledgments

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9. Typical experimental details: Preparation of cyclohexa-*m*-phenylene **3**. A two-neck round-bottomed flask containing a magnetic stir-bar was charged with 1,5-dibromo-2,4-*bis*(*p*-dodecyloxyphenylethynyl)benzene (0.112 g, 0.14 mmol), 1-methoxy-2,6-benzenedipinacolboronate (0.050 g, 0.14 mmol), *tetrakis*-(triphenylphosphine)palladium (4.8 mg, 0.0042 mmol), cesium carbonate (0.113 g, 0.35 mmol), and dry toluene (8 mL). After sparging the stirred mixture with argon gas over 10 min, the reaction mixture was refluxed under argon at 110 °C for 27 h. Upon cooling, the crude mixture was partitioned between diethyl ether and deionized water. After three rounds of extraction with diethyl ether, the combined organic extracts were dried over anhydrous magnesium sulfate, before being concentrated in vacuo to give a viscous brown oil. This was then subjected to flash chromatography on a silica gel column (3:2 v/v hexane/dichloromethane). Upon the complete removal of solvent from the desired fractions, the target cyclohexa-*m*-phenylene **3** (13.7 mg, 0.0061 mmol) is obtained as an off-white solid. ^{1}H NMR (300 MHz, CH_2Cl_2-d_2): δ 7.96 (s, 3H), 7.94 (s, 3H), 7.81 (d, 6H, J = 7.8 Hz) 7.38 (d, 12H, J = 9.0 Hz), 7.29 (t, 3H, J = 7.8 Hz), 6.85 (d, 12H, J = 9.0 Hz), 3.97 (t, 12H, J = 6.6 Hz), 3.33 (s, 9H), 1.80 (m, 12H), 1.2–1.6 (108H), 0.90 (t, 18H, J = 6.9 Hz). ^{13}C NMR (300 MHz, CH_2Cl_2-d_2): δ 159.62, 138.76, 133.96, 133.09, 131.39, 120.84, 115.29, 114.71, 93.22, 87.37, 68.35, 32.17, 29.94, 29.91, 29.86, 29.70, 29.62, 29.49, 26.26, 22.94, 14.14. HRMS (MALDI-TOF): m/z calcd for $C_{159}H_{198}O_9$ 2253.2680, found 2252.9891 (M^+).