Aromatic Rings

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Selective Synthesis of [12]Cycloparaphenylene**

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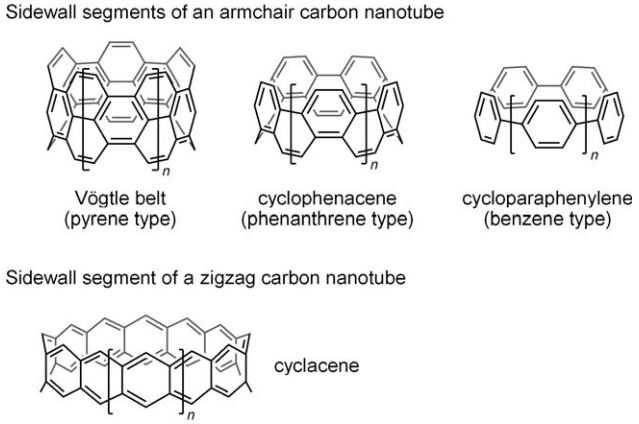
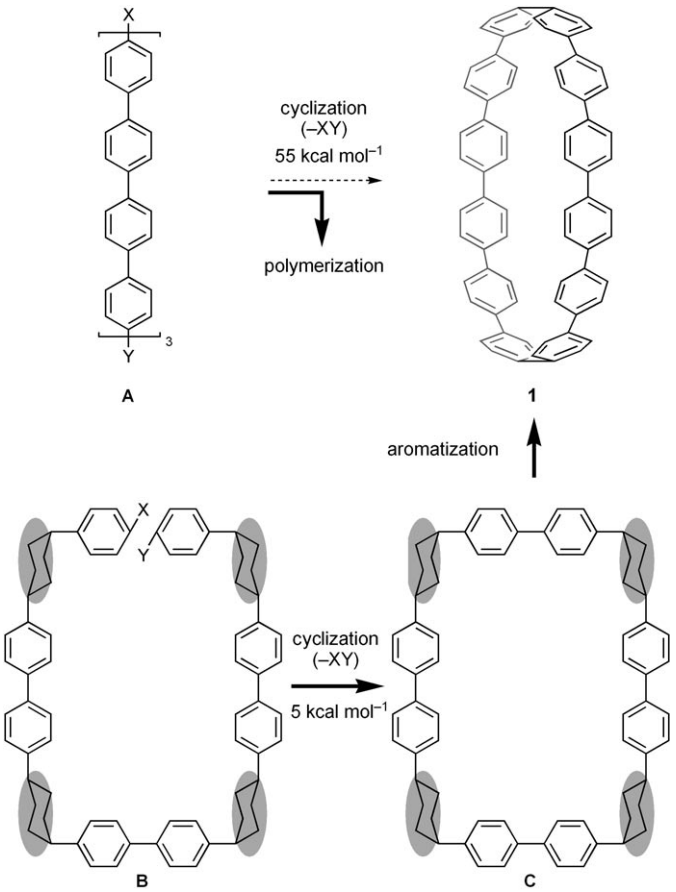
In memory of Professor Kazuhiko Seki

Shape-persistent, nanosized macrocycles that are composed of only sp- and sp^2-hydridized carbon atoms on their perimeter (conjugated molecular loops and belts) have attracted significant attention because of their potential applications in materials science and supramolecular chemistry.[1,2] Particularly interesting and challenging among these are aromatic belts[1] and rings as exemplified by the Vögtle belts,[3,4] cyclophenacenes,[5,6] cycloparaphenylenes,[7–9] and cyclacenes [10,11]. Adding to their sheer aesthetic appeal,[1] these unusual hydrocarbons represent structural models for carbon nanotube segments, and can be envisioned as potential precursors in the preparation of structurally uniform armchair or zigzag carbon nanotubes (Scheme 1).[12,13] However, despite extensive trials the synthesis of these molecules remains a formidable challenge.[1]



Scheme 1. Aromatic belts/rings related to the carbon nanotube structure.

In 2005, as a part of our research program exploring new synthetic methods and properties of oligoarenes[14] and nanocarbons,[15] we initiated a synthetic study of these aromatic belts/rings that aims at contributing to a bottom-up organic synthesis of structurally uniform single-walled carbon nanotubes. We selected cycloparaphenylene[7–9] as a first target in view of a comparatively straightforward approach to their synthesis through aryl–aryl bond formation. Despite its structural simplicity, no successful synthesis had been reported at the inception of our work. Very recently, Bertozzi and co-workers have accomplished the elegant first synthesis of [9]-, [12]-, and [18]cycloparaphenylenes and coined them as "carbon nanohoops".[9] Herein, we report a selective synthesis of [12]cycloparaphenylene (**1**) through stepwise palladium-catalyzed coupling reactions.



Scheme 2. Strategy for the synthesis of [12]cycloparaphenylene (**1**).

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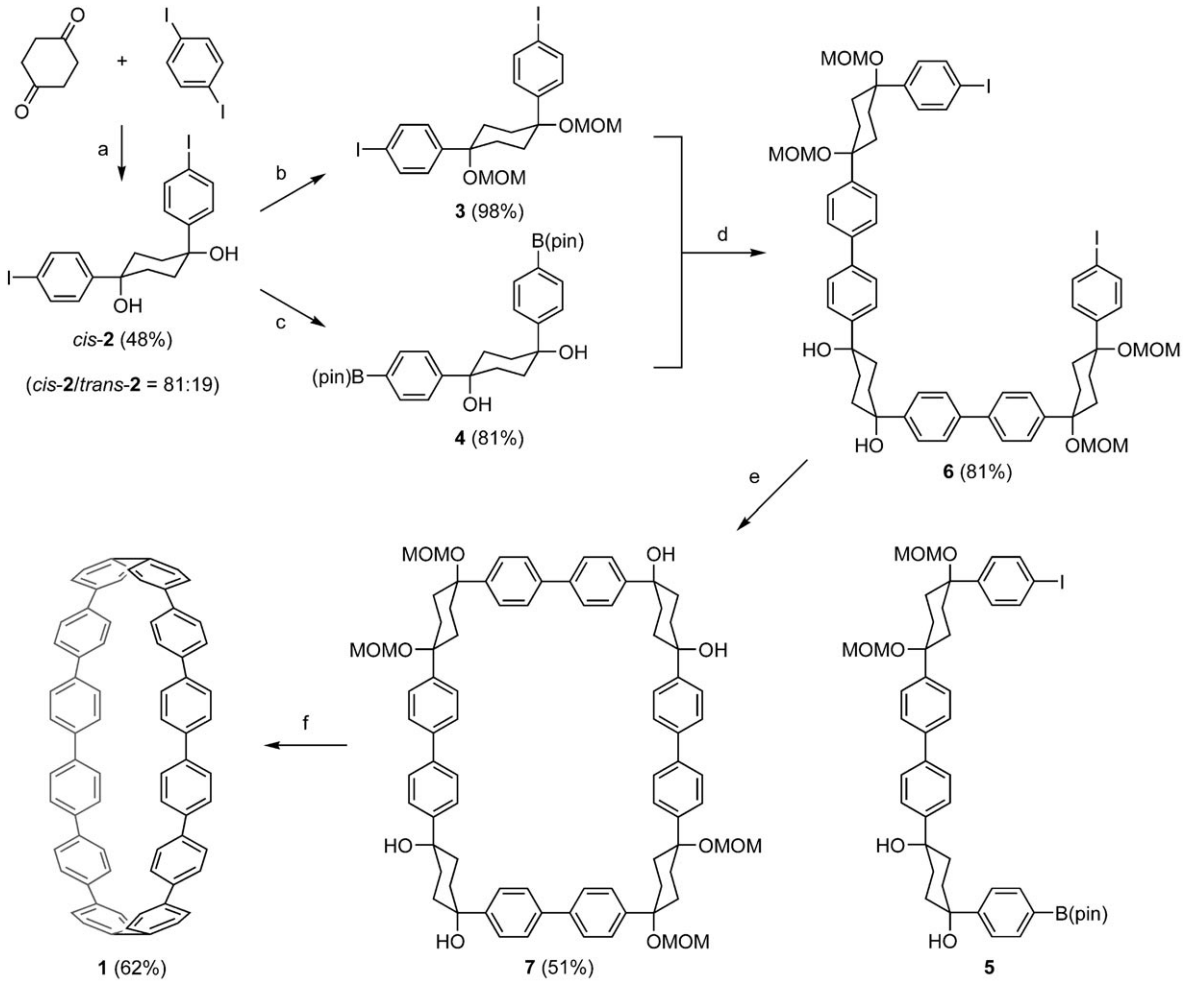
The challenge for synthesizing cycloparaphenylenes lies in the increased strain energy that results from ring closure.[16] For example, the strain energy for aryl–aryl bond-forming cyclization at the two ends of -(p-C_6H_4)$_{12}$- to furnish [12]cycloparaphenylene (**1**) is calculated to be 55 kcal mol^{-1}.[17] Thus, polymerization is, as expected, the observed outcome of these reactions (Scheme 2). Inspired by the insightful works of Vögtle and co-workers,[7b] we hypothesized that a suitably substituted cyclohexane moiety could function as a bent benzene-convertible unit in the synthesis of [12]cycloparaphenylene (**1**). By inserting four *cis*-cyclohexane-1,4-diyl units, the cyclization of **B** to give **C** becomes synthetically viable (calculated strain energy = 5 kcal mol^{-1}).[17] The transformation of cyclohexane moieties of **C** to give benzene rings (aromatization) would then provide **1**, but the balance between aromatic stabilization energy and macrocyclic strain energy would be critically important in this final step.

The important elements in this synthetic strategy are: 1) How can a cyclohexane-inserted macrocycle **C** be accessed? 2) What could be a suitable cyclohexane unit? Our approach to satisfying this first issue has been to connect four 1,4-diphenylcyclohexane monomers by palladium-catalyzed Suzuki–Miyaura cross-coupling reactions.[18] As for the suitable cyclohexane moiety, we chose *cis*-1,4-dihydroxycyclohexane-1,4-diyl because the corresponding monomers can be readily made by two-fold carbonyl addition to the commercially available cyclohexane-1,4-dione. We expected the transformation of a *cis*-1,4-dihydroxy-cyclohexane-1,4-diyl unit to give a benzene ring could be accomplished as a final step by an acid-mediated eight-fold dehydration and subsequent oxidation. In the synthesis by Bertozzi and co-workers, *cis*-1,4-dimethoxy-2,5-cyclohexadiene-1,4-diyl was utilized as a similar bent unit, where the final aromatization step was accomplished with lithium naphthalenide; most likely through a stepwise electron transfer mechanism.[9]

The selective synthesis of [12]cycloparaphenylene (**1**) began with the preparation of 1,4-diphenylcyclohexane monomers. The two-fold addition of 4-iodophenyllithium,



Scheme 3. Synthetic route toward **1**. Conditions and reagents: a) 1. 1,4-diiodobenzene (3.0 equiv), *n*BuLi (3.0 equiv), THF, –78 °C, 1 h; 2. cyclohexane-1,4-dione (1.0 equiv), RT, 2 h; b) *cis*-**2** (1.0 equiv), CH_3OCH_2Cl (7.6 equiv), iPr_2NEt (7.6 equiv), CH_2Cl_2, RT, 19 h; c) *cis*-**2** (1.0 equiv), $B_2(pin)_2$ (2.4 equiv), [$PdCl_2$(dppf)] (3 mol%), KOAc (6.0 equiv), DMSO, 80 °C, 13 h; d) **3** (10 equiv), **4** (1.0 equiv), [$PdCl_2$(dppf)] (10 mol%), NaOH (5.0 equiv), H_2O (16 equiv), 1,4-dioxane (8 mM with respect to **4**), 60 °C, 24 h; e) **6** (1.0 equiv), **4** (1.4 equiv), $Pd(OAc)_2$ (20 mol%), X-Phos (20 mol%), NaOH (5.0 equiv), H_2O (26 equiv), 1,4-dioxane (2 mM with respect to **6**), 80 °C, 24 h; f) **7** (1.0 equiv), *p*TsOH (1.0 equiv), *m*-xylene, 150 °C (microwave), 30 min. DMSO = dimethyl sulfoxide, pin = pinacol, THF = tetrahydrofuran.

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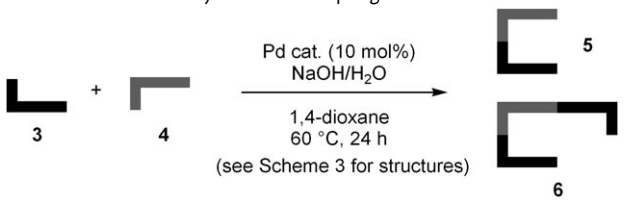
prepared from 1,4-diiodobenzene and *n*BuLi, to cyclohexane-1,4-dione afforded the common 1,4-diphenylcyclohexane scaffold (*cis*-**2**) in 48% yield (Scheme 3). This common unit was then converted into the methoxymethyl (MOM)-protected diiodide **3** (98% yield) and diboronate **4** (81% yield) by using literature procedures.[19] Through the repetitive cross-coupling of these units (**3** and **4**), the cyclic tetramer **7** was synthesized (Scheme 3). The combination of the free hydroxy and MOM-protected monomers greatly simplified the purification of the trimer and cyclic tetramer (vide infra). The MOM group turned out to be beneficial in the mid-stage synthesis (e.g., the silyl protecting groups are labile under some cross-coupling reaction conditions).

With suitable monomers in hand, we first attempted the synthesis of dimer **5** by the Suzuki–Miyaura coupling of **3** and **4** (Table 1). However, in early experiments we identified that

Table 1: Palladium-catalyzed cross-coupling of **3** and **4**.[a]



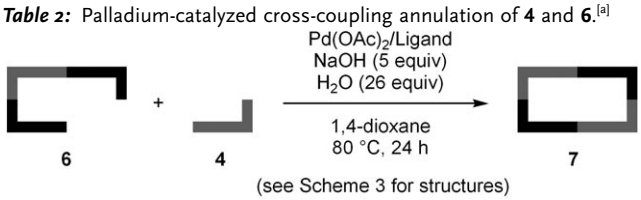
Entry	Pd catalyst	Base (equiv)	[**3**]/[**4**]	Results
1[b]	[Pd(P*t*Bu$_3$)$_2$]	NaOH (5), H$_2$O (5)	1	**5** (18%), **6** (27%)
2[c]	[Pd(P*t*Bu$_3$)$_2$]	NaOH (5), H$_2$O (5)	1	oligomerization
3[c]	[Pd(P*t*Bu$_3$)$_2$]	NaOH (5), H$_2$O (5)	10	**6** (28%)
4[c]	[Pd(P*t*Bu$_3$)$_2$]	NaOH (5), H$_2$O (16)	10	**6** (43%)
5[c]	[Pd(PPh$_3$)$_4$]	NaOH (5), H$_2$O (16)	10	**6** (40%)
6[c]	[PdCl$_2$(dppf)]	NaOH (5), H$_2$O (16)	10	**6** (67%)
7[d]	[PdCl$_2$(dppf)]	NaOH (5), H$_2$O (16)	10	**6** (81%)[e]

[a] Reaction conditions: **3**, **4**, Pd catalyst (10 mol%), NaOH, H$_2$O, 1,4-dioxane, 60°C, 24 hours. [b] [**4**] = 110 mM (in toluene). [c] [**4**] = 5 mM. [d] [**4**] = 8 mM. [e] 91% of unchanged starting material **3** was recovered after the reaction.

this is not an easy task. For example, the use of [Pd(P*t*Bu$_3$)$_2$] catalyst[20] in combination with NaOH/H$_2$O[21] in toluene gave dimer **5** (18% yield), but non-negligible amounts of trimer **6** (27% yield) were also observed, even when using a 1:1 ratio of the coupling partners (Table 1, entry 1). Although it was found that the use of 1,4-dioxane as a solvent facilitated the cross-coupling reaction, undesired mixtures of oligomers were formed even under dilute conditions (5 mM; Table 1, entry 2). At this point, we changed our target to trimer **6**. When an excess of **3** ([**3**]/[**4**] = 10) was employed, **6** was obtained in reasonable yields (Table 1, entries 3 and 4). After the screening of various Pd catalysts, we found that the use of [PdCl$_2$(dppf)] (dppf = 1,1′-bis(diphenylphosphanyl)ferrocene) led to a very clean 2:1 cross-coupling reaction and afforded **6** in 81% yield after isolation (Table 1, entry 7). Notably, 91% of the unchanged starting material **3** (based on the consumption for trimer **6**) was recovered (Table 1, entry 7).

Next, the synthesis of cyclic tetramer **7** by the cross-coupling annulation (inter/intramolecular cross-coupling) of trimer **6** and monomer **4** was investigated (Table 2). We first screened several bases with the Pd(OAc)$_2$/PPh$_3$ catalyst in 1,4-dioxane and identified NaOH/H$_2$O to be a reasonable basic

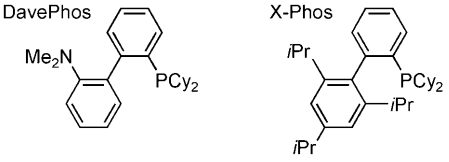
Table 2: Palladium-catalyzed cross-coupling annulation of **4** and **6**.[a]



(see Scheme 3 for structures)

Entry	Ligand (mol%)	**4** [mM]	Yield of **7** [%][d]
1[b]	PPh$_3$ (30)	5	15
2	DavePhos (40)	5	16
3	DavePhos (40)	2	34
4	DavePhos (40)	0.5	17
5	X-Phos (40)	2	46
6[c]	X-Phos (20)	2	51

[a] Reaction conditions: **6** (1.0 equiv), **4** (1.2 equiv), Pd(OAc)$_2$ (20 mol%), ligand, NaOH (5 equiv), H$_2$O (26 equiv), 1,4-dioxane, 80°C, 24 hours. [b] Pd(OAc)$_2$ (30 mol%). [c] **4** (1.4 equiv). [d] Yield of isolated product. Cy = cyclohexyl.



promoter (Table 2, entry 1). Further screening of phosphane ligands and concentrations (Table 2, entry 2–5) led to the use of Buchwald's X-Phos[22] as the optimal ligand to furnish the target cyclic tetramer **7** in 51% yield (Table 2, entry 6). The cyclic structure of **7** was confirmed by the X-ray crystal structure analysis of a crystal grown from CHCl$_3$/MeOH/*n*-hexane (Figure 1).[23] It should be noted that unlike Bertozzi's synthesis, where a mixture of three different macrocycles was obtained,[9] our procedure provides **7** as the sole cyclic product.

Finally, the transformation of cyclic tetramer **7** to give **1** was examined (Scheme 3). We anticipated that the treatment of **7** with acid would lead to a sequence of 1) removal of the

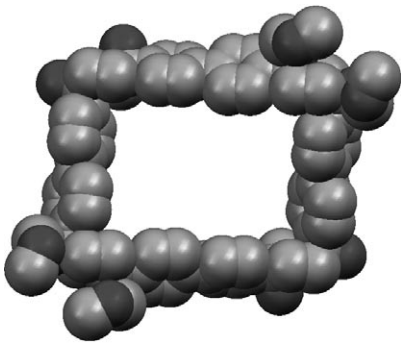


Figure 1. X-ray crystal structure of **7** (*n*-hexane and methanol molecules in the crystal are omitted for clarity).

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MOM groups, 2) eight-fold dehydration (dihydroxycyclohexane→cyclohexadiene), and 3) oxidation (cyclohexadiene→benzene) to provide the target [12]cycloparaphenylene (**1**). Although we were aware of a number of unsuccessful examples of acid-mediated aromatization in the synthetic study of aromatic macrocycles,[10] we were finally able to develop a satisfactory protocol for this transformation. Thus, treatment of **7** with a stoichiometric amount of *p*-toluenesulfonic acid (*p*TsOH) in *m*-xylene under microwave irradiation (150 °C, 30 min) afforded **1** in 62 % yield after isolation.[24] The reaction when performed at a lower temperature (100 °C) did not give rise to the product. The use of protic solvents led to complex mixtures of unidentified products. Gratifyingly, the spectroscopic data of the product isolated from our synthesis match those of **1** as reported by Bertozzi and co-workers (^{1}H NMR: $\delta = 7.61$ ppm in $CDCl_3$; ^{13}C NMR: $\delta = 127.3$, 138.5 ppm in $CDCl_3$; MALDI-TOF MS, 912.37 for $C_{72}H_{48}$).[9]

In summary, an efficient method that selectively produces [12]cycloparaphenylene (**1**) has been established. Our synthesis capitalizes on the ability of *cis*-1,4-dihydroxycyclohexane-1,4-diyl to attenuate the build-up of strain energy during the macrocyclization, and exploits its benzene-convertible nature. Our method, along with that of Bertozzi and co-workers (utilizing 1,4-dimethoxy-2,5-cyclohexadiene-1,4-diyl unit), can be categorized as belonging to a family of syntheses inspired by the seminal work of Vögtle.[7b] However, we stress that putting these ideas into practice required extensive optimization of the reaction conditions, even for modern palladium-catalyzed cross-coupling reactions. Although here we have focused on the selective synthesis of one specific cycloparaphenylene, we believe that the strategy of stepwise assembly would provide a synthetic platform for the preparation of other [*n*]cycloparaphenylenes. By carefully selecting monomers with variable numbers of linear (arene) and bent (cyclohexane) units in the trimerization and cross-coupling annulation steps, a range of cycloparaphenylenes of discrete ring size could be accessed. This synthetic campaign is now the focus of our ongoing efforts.

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[24] The oxidant that is responsible for producing **1** in the final step is yet to be identified.

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