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Hot Paper

Continuous-Flow Synthesis of Cycloparaphenylene Building Blocks on a Large Scale

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The synthesis of [*n*]cycloparaphenylenes ([*n*]CPPs) and similar nanohoops is usually based on combining building blocks to a macrocyclic precursor, which is then aromatized in the final step. Access to those building blocks in large amounts will simplify the synthesis and studies of CPPs as novel functional materials for applications. Herein, we report a continuous-flow synthesis of key CPP building blocks by using versatile synthesis techniques such as electrochemical oxidation, lithiations and Suzuki cross-couplings in self-built reactors on up-to kilogram scale.

Introduction

Since Jasti and Bertozzi published the first synthesis of [*n*]cycloparaphenylenes ([*n*]CPPs) 15 years ago,[1] a continuously evolving field of nanohoop-based curved aromatics has emerged. [*n*]CPPs excel due to their size-dependent photophysical properties and the ability to form complexes as macrocyclic hosts.[2,3] Based on these properties, various applications, such as components in organic solar cells,[4] as a white-light emitter,[5] for selective fullerene functionalization as well as radical shielding have been proposed.[6] Those systems are not limited to the parent unsubstituted [*n*]CPPs but have been taken further towards more complex systems. On the one hand, CPPs with a substituted backbone were prepared to introduce certain functional groups or change specific properties.[7,8–10] These substituted CPPs allowed CPP-based polymers to be built-up,[11,12] and CPPs to be incorporated into metal–organic frameworks or noncovalent tubes.[13,14,15] On the other hand, hybrid systems were designed in which CPP cut-outs have been connected to other function entities. Those systems combine properties of the strained nanohoops as well of the introduced moiety. For example, von Delius and Anderson presented the incorporation of porphyrin units into such hybrid CPPs.[16,17] Recently, boron cluster embedded nanohoops were reported showing excellent fluorescence emission properties.[18] Variants of the parent [*n*]CPPs result by exchanging one of the *para*-connected phenyl units by a *meta*-connected one. These [*n*]*m*CPPs exhibit changed properties and are easier to functionalize. For example, a water soluble [*n*]*m*CPP was applied as a fluorescence marker in cells by the group of Jasti.[19] Moreover, [*n*]*m*CPP based rotaxanes were successfully demonstrated as sensors for small ions.[20]

Despite all the promising results, the breakthrough of an application of a CPP-containing material did not come yet. This could be due to the tedious multistep synthesis of the mentioned systems. To build up those strained molecules, it is not possible to simply bend a linear chain of phenylenes. The pre-bent building blocks were assembled to macrocyclic precursors, which are aromatized later on. For most systems, the building blocks are the same or very similar and interchangeable (Figure 1).[8,10,16,17,21]

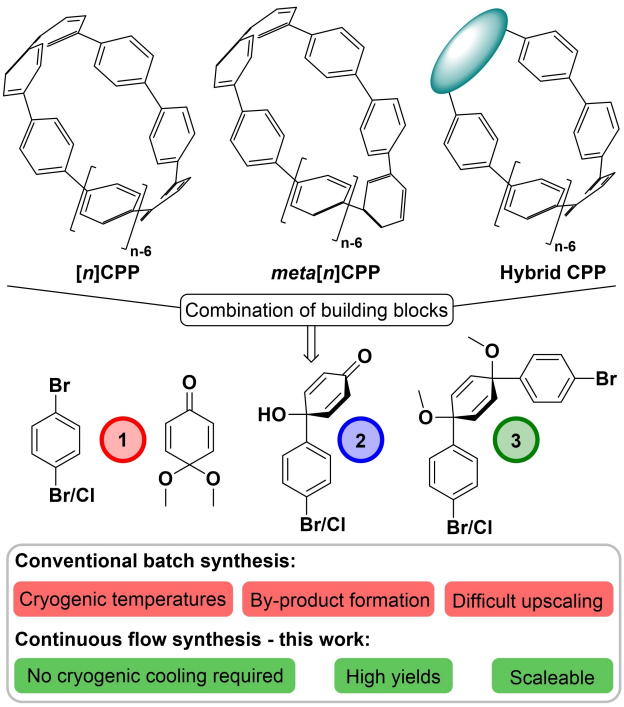

Figure 1. The synthesis of [*n*]CPPs and similar nanohoops is often based on the same or interchangeable building blocks.

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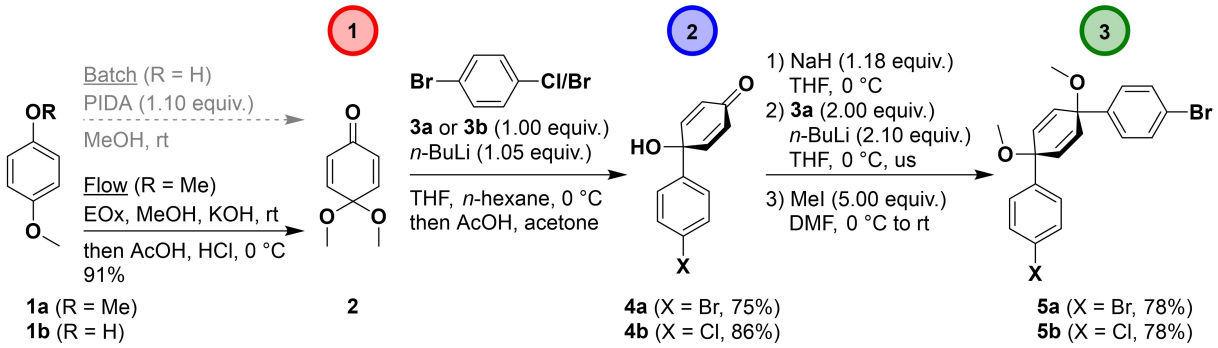

Scheme 1. Overview of the synthesis of the building blocks.

By a combinatorial approach, small building blocks allow the assembly of novel systems, which can be as simple as making up new constructions with toy bricks. Therefore, a fast and easy access to large amounts of different sized building blocks is key for efficiently exploring the chemical space of CPPs, opening new fields of materials application and to take research in the field of CPP based curved aromatics to the next level.

Continuous flow represents an ideal technique to fulfill all necessary requirement for the envisioned building block synthesis. The reaction conditions of a continuous synthesis are highly reproducible and reliably controllable. Another advantage is scalability: The reaction scale is not limited by the size of the largest flask in the laboratory, since only part of the total reaction mixture passes the reactor at any given time.[22]

A flow-assisted synthesis of CPP building blocks has been presented by Kim and co-workers based on the cyclohexyl moiety.[23] This synthesis approach suffers from lower yields for the aromatization toward the corresponding CPP.[24,25] Therefore, this approach has not been used much lately. We developed self-built flow reactors and optimized a continuous synthesis of CPP building blocks analogous to the work presented by the group of Jasti.[21] Using this reactor, we herein report a multigram and easily scalable synthesis of key [*n*]CPP building blocks and their conversion to CPPs.

Results and Discussion

The building blocks **2**, **4** and **5** are synthesized stepwise, starting from small commercially available compounds. (Scheme 1) Traditionally, the synthesis suffers from large amounts of side products and the need for cryogenic cooling. While this is not a problem at small scales, it complicates the upscaling of synthesis steps. The synthesis of mono-acetal **2** (Scheme 1) is usually achieved by the oxidation with phenyliodine(III) diacetate (PIDA).[26–28] This transformation has the drawback of the equimolar formation of iodobenzene, which has to be removed. We made use of a continuous flow electrochemical oxidation to avoid large amounts of iodobenzene as a side product. The electrochemical oxidation of *p*-methoxyanisole (**1**) was previously reported by different groups.[29]

Nickel and graphite electrodes (IKA ElectraSyn Flow) allowed the use of an expensive Pt electrode to be avoided. The oxidation was directly followed by an acid catalyzed acetal cleavage in the same flow set-up (Figure 2). The formed hydrogen gas was removed by a gas outlet, to have a constant flow rate for the second reaction step. The addition of aqueous hydrochloric acid (HCl) turned out to be crucial to neutralize the basic methanolic solution of the first reaction step and avoid buffer formation. However, large excess of hydrochloric acid led to formation of benzoquinone. After optimization of flow rates and acid concentrations, a long-time run was performed. The flow reactor was operated for four weeks continuously to obtain more than 1 kg of **2** in an overall yield of 91%. With larger reactors this could be even further scaled up or accelerated linearly.

Mono-acetal **2** was used as a starting material for the flow synthesis of two-membered building blocks **4a** and **4b** (Scheme 1, Figure 3). This flow reactor combines three reaction steps: the lithiation of 1,4-dibromo- (or 1-bromo-4-chloro-)benzene **3a** (**3b**) is followed by the addition to acetal **2** and, consecutively, the acetal cleavage. The reactor is fully assembled from liquid chromatography equipment and is not larger than a postcard. Each of the steps was optimized separately and monitored by GC-MS. *n*-Butyllithium (*n*BuLi) was used as a commercial 1.6 M solution in hexanes with a flow rate of 1.0 mL min^{-1} (1.05 equiv.). The bromobenzene derivatives were pumped as solution in THF (0.38 mol L^{-1}) with a flow rate of 4 mL min^{-1}. As the lithiated species has only a short residence time (1.6 s) prior to the next reaction step, it was not necessary to cool down the reactor lower than 0 °C. This is an important

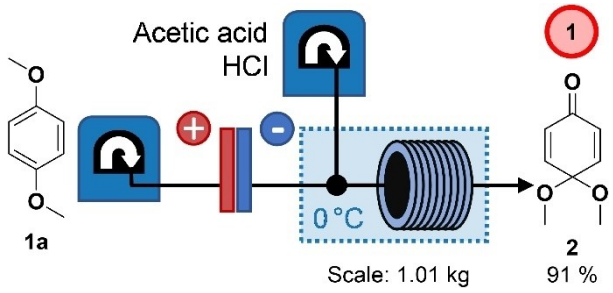

Figure 2. The continuous-flow reactor used for the synthesis of acetal **2**.

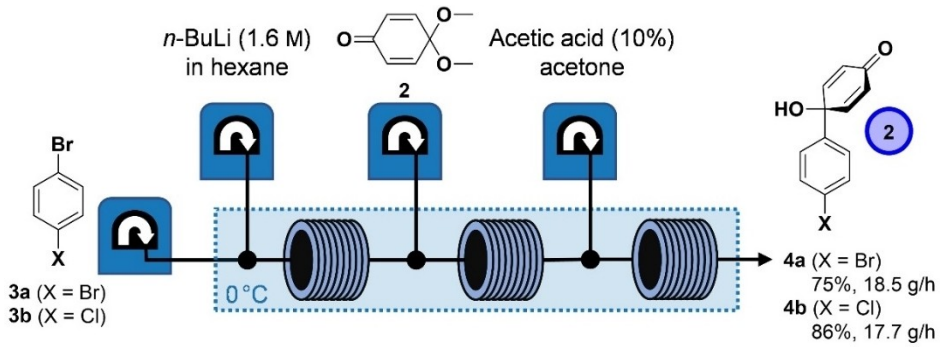

Figure 3. Schematic representation of the continuous-flow reactor used for the synthesis of two-membered building blocks **4a** and **4b**.

benefit compared to the cryogenic temperature for the conventional batch synthesis in terms of costs and workload. Moreover, the increased temperature makes it possible to use higher concentrations, as the solubility of lithiated **3a** and **3b** is much lower at the commonly employed reaction temperature of −78 °C. However, if the temperature rises above 0 °C, the reaction mixture in the tube reactor turns black indicating decomposition. Acetal **2** was introduced as THF solution (1.0 mol L^{-1}) with a flow rate of 2.0 mL min^{-1} to have an excess amount (1.30 equiv.) for higher yields. The conversion was monitored by in-line infrared spectroscopy (ReactIR 702 L, Mettler Toledo). To cleave the remaining acetal moiety, a mixture of aqueous acetic acid (10%) and acetone was added with a flow rate of 5 mL min^{-1}. As the optimized conditions enable high yields up to 86%, the work up could be limited to washing the crude product with chloroform. Within a normal working day, it is possible to run this reaction on a > 100 g scale with a throughput of up to 18.5 g/h. The set-up is capable of being turned off at one point and resumed a few days later without any problems and comparable yields. Using this method, more than 500 g of the two-membered building blocks were synthesized during the project.

Next, the three-membered building blocks **5a** and **5b** were targeted (Scheme 1, Figure 4), which are key compounds for the synthesis of [6]- to [12]CPP and various substituted or hybrid nanohoops.[1,3,12,17,18,21,25,26,30,31–33] However, it is important to have both phenyl units orientated in a *syn* arrangement. There are different strategies to achieve this selectivity. On the one hand it is possible to shield one side with a sterically demanding protection group. On the other hand, deprotonation of the alcohol moiety prevents a nucleophilic attack from that side.[34] To minimize the synthesis step counts, we decided to apply the deprotonation route using sodium hydride. However, it was not successful to pump the already deprotonated building block, due to its poor stability at temperatures around room temperature. Therefore, it was necessary to add sodium hydride as a slurry in THF to **4a** or **4b** under continuous flow conditions (Figure 4). The slurry was pumped by a peristaltic pump (SF-10, Vapourtec). To ensure a uniform dispersion the reagent stock of sodium hydride was stirred permanently. In a parallel stream, *n*BuLi was used to lithiate dibromobenzene **4a**. As the group of Jasti reported previously, two equivalents of mono-lithiated dibromobenzene are needed to achieve a good conversion.[34] The conditions of the lithiation reactor are exactly the same as described before. Both streams were merged followed by a tube reactor. The last step included in this flow set-up is the methoxy protection of the formed alcoholates by methyl iodide. Due to the high amount of (formed) solids within the tubing, this reactor is very likely to clog. This was prevented effectively by placing

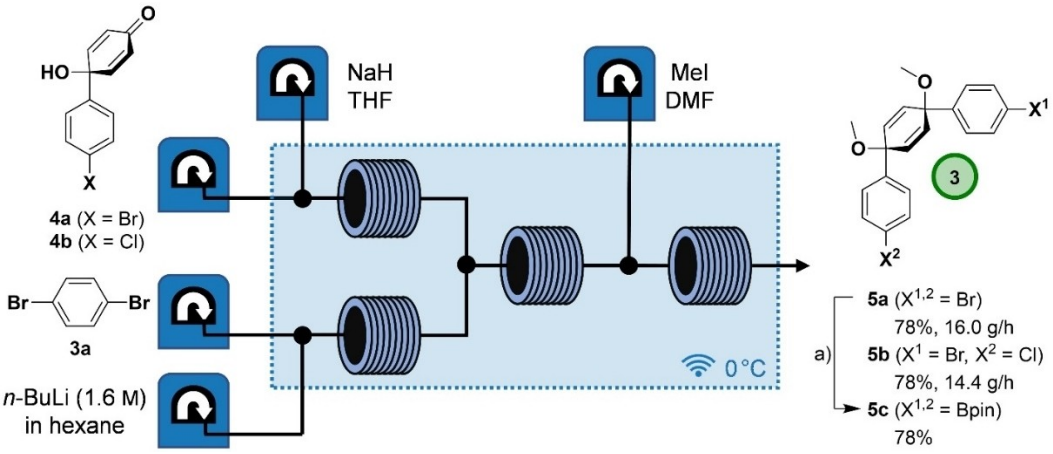

Figure 4. Schematic representation of the continuous-flow reactor used for the synthesis of three-membered building blocks **5a** and **5b**. Reaction conditions for the synthesis of **5c**: a) *n*BuLi (2.1 equiv.), 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.0 equiv.), THF, −78 °C.

the entire reactor in an ultrasonic bath. The three-membered building blocks **5a** and **5b** were obtained in good yields of 78% with a throughput of up to 16 g h^{-1}. This made it possible to synthesize more than 130 g of the three-membered building blocks during the project.

These three-membered building blocks can be assembled towards larger CPP precursors via Suzuki coupling reactions. One prominent building block, the nine-membered building block **6**, is often used for the synthesis of larger CPPs or hybrid nanohoops.[21,32,33,35,36] To target this building block, it was necessary to borylate the dibromo building block **5a**. However, we were not able to perform this reaction in flow.[37] Therefore, boronic ester **5c** was synthesized in conventional batch synthesis analogous to the literature.[21]

The nine-membered building block **6** was synthesized via Suzuki coupling from boronic ester **5c** and three-membered building block **5b** (Figure 5). The conversion was monitored via NMR. Compared to the literature procedure by the group of Jasti, sodium carbonate was used instead of sodium bicarbonate allowing a higher concentration. Moreover, THF was applied as solvent for the same reason. Firstly, the reaction temperature was screened between 80 and 120 °C. A temperature of 100 °C turned out to be the sweet spot with a fast conversion and no decomposition of the palladium catalyst. With that temperature, the reaction time was screened. The use of lower flow rates led to clogging next to the mixers. Therefore, different reactor lengths had to be applied. With a reaction time of 50 min the highest yield was obtained, which could not be increased by even longer reaction times. This led to a throughput of 0.8 g h^{-1} and a yield of 75%. Compared to the previous mentioned reactors the low throughput was caused by the need for long reaction times and therefore low flow rates. The use of a heterogeneous catalyst was not successful. To have a scalable synthesis it is important to not have any tedious purification step. Therefore, a three-step washing process was developed to obtain pure nine-membered building block **6** without the need for column chromatography.

By the combination of building blocks, macrocycles in different sizes and functionality are accessible. Moreover, a late-stage introduction of substituted phenyl units or more complex systems is possible. Initial efforts to implement this assembling step in a continuous flow as well turned out to be insufficiently successful.[38] In addition, the fact that different reaction conditions are often required, especially for more complex (hybrid) systems, makes the development of a general method unreasonable. Starting from nine-membered building block **6**, macrocycle **9** was synthesized in a single step following an already reported procedure.[21]

Once a macrocycle has been synthesized, on the way towards full aromatic systems, an important step is missing-the aromatization. There are multiple strategies to achieve this challenging task. Jasti and Bertozzi demonstrated the first successful approach using lithium naphthalenide, which is used frequently since then.[1,9,12,14,15,33,35]

The preparation of the naphthalenide reagent is laborious and time consuming. Herein, we have developed a method to simplify and speed-up this procedure. By pumping a 0.5 M naphthalene solution through a packed bed reactor containing SOLVONA® (sodium on molecular sieve) followed by an in-line filter, sodium naphthalenide (**8**) was obtained after a residence time of 37.5 min (Figure 6, top). The conversion was confirmed by titration with menthol. Moreover, we were able to flush the column with anhydrous THF (not stabilized) and reuse the packed bed reactor after multiple days. In order to demonstrate the usability of this method, ten-membered macrocycle **9** was aromatized to [10]CPP in a yield of 71% (Figure 6, bottom).

Conclusions

An efficient process starting from commercially available compounds and providing a fast, high-yielding and easily scalable synthesis of CPP precursors for differently sized CPPs and other nanohoops is presented. Versatile synthesis techniques, including electrochemical oxidation, lithiations and Suzuki cross-couplings were demonstrated in a continuous flow. The modular self-built flow reactors are no larger than 10 cm×15 cm and capable of throughputs up-to 18 g h^{-1}. These reactors were used to synthesize more than 1.7 kg of different CPP building blocks. This opens new possibilities for further research in the field of curved aromatic compounds, not being limited or delayed by the fast accessibility of those building blocks.

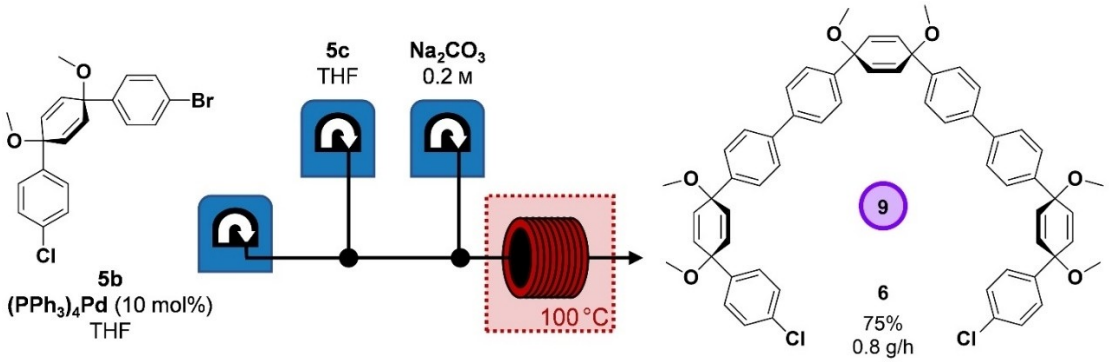

Figure 5. Schematic drawing of the continuous-flow reactor used for the synthesis of nine-membered building block **6**.

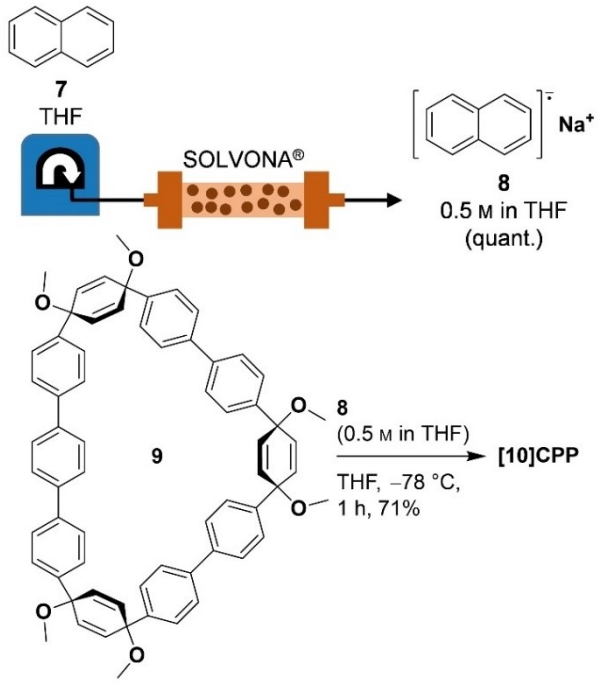

Figure 6. The preparation of sodium naphthalenide (**8**) from naphthalene (**7**) by using SOLVONA® (sodium on molecular sieve) in a packed bed reactor (top). Aromatization of macrocycle **9** to [10]CPP with a yield of 71 %. (bottom).

Experimental Section

Synthesis of acetal 2 (4,4-dimethoxycyclohexa-2,5-dien-1-one): 1,4-Dimethylbenzene **1 a** (1.00 kg, 7.17 mol, 1.00 equiv.) and KOH (200 g, 3.56 mol) were dissolved in methanol (10.0 L). Separately, the quenching solution was prepared from acetone (12.5 L) and an aqueous solution (7.5 L) containing acetic acid (150 mL) and concentrated hydrochloric acid (148 mL, 1.78 mol). The reagent solution was pumped with a flow rate of 300 μL min^{-1}. Two electrochemical cells (IKA Electrasyn Flow, Ni cathode, graphite anode) were set up in a row. Each cell was followed by a gas release (open bottle and peristaltic pump, same flow rate). Both cells were run in constant current mode ($A = 1.00$ A). Next, the quenching solution (flow rate of 600 μL min^{-1}) was added via a T-mixer (1.0 mm) connected to a tubular reactor (1.6 mm inner diameter, $V = 10$ mL). The T-mixer and reactor were placed in an ice bath and cooled to 0 °C. The reactor output was collected and split for work up. Dichloromethane was added until a phase separation occurred. Phases were separated and the aqueous phase was extracted with dichloromethane. The combined organic phase was washed with water and brine. The organic phase was dried with sodium sulfate and filtered. The solvent was removed under reduced pressure. The crude product was purified by distillation under reduced pressure (0.2 mbar, 50 °C). Acetal **2** was obtained as a light-yellow oil in a yield of 91 % (1.01 kg, 6.55 mol). Analytical data correspond to literature.[28] ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 6.87$–6.75 (m, 2H), 6.31–6.20 (m, 2H), 3.36 (s, 6H). ^{13}C{1H} NMR (50 MHz, $CDCl_3$): $\delta = 185.2$, 143.4, 130.1, 92.6, 50.5. HRMS (ESI) *m/z* calc. for $C_8H_{10}O_2 + Na^+$: 177.0522; found: 177.0525. Boiling point: 50 °C (0.2 mbar).

Synthesis of two-membered building blocks 4 a and 4 b: The reaction was performed under inert atmosphere. Acetal **2** (1.30 equiv.) was dissolved in anhydrous THF (993 mmol L^{-1}). In a separate bottle 1,4-dibromobenzene (**3 a**) or 1-bromo-4-chlorobenzene (**3 b**) was dissolved in anhydrous THF (380 mmol L^{-1}). *n*-Butyllithium (1.6 m in hexanes) was used directly from the purchased bottle. The whole reactor was placed in an ice bath (0 °C) and all reagent solutions were pumped through cooling loops before entering the mixers. The solution of the bromobenzene derivative (4.00 mL min^{-1}) was first mixed with *n*-butyllithium (1.00 mL min^{-1}) in a first mixer before entering a tubular reactor ($L = 30$ cm, $V =$ 0.13 mL). A second mixer followed this reactor, where the solution of acetal **2** (2.00 mL min^{-1}) was added. After another tubular reactor ($L = 50$ cm, $V = 0.22$ mL), a third mixer was used to introduce the quenching solution (1 : 1 mixture of acetone and 10 % aqueous acetic acid) with a flow rate of 5.00 mL min^{-1}. This mixer was followed by a tubular reactor ($L = 200$ cm, $V = 0.88$ mL) after which the reactor output was collected and stirred for 1 h. CH_2Cl_2 was added until a phase separation occurred. Phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phase was washed with water and brine. The organic phase was dried with sodium sulfate and filtered. The solvent was removed under reduced pressure. The crude product (light yellow solid) was washed with $CHCl_3$. The product was obtained as a white solid (**4 a** (Br): 75 % (257 mmol, 51.7 g); **4 b** (Cl): 86 % (113 mmol, 21.5 g). Analytical data correspond to literature (**4 a**,[39] **4 b**[26]).

*4-(4-Bromophenyl)-4-hydroxy-2,5-cyclohexadien-1-one (**4 a**)*: ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = 7.62$–7.53 (m, 2H), 7.41-7.31 (m, 2H), 6.95–6.85 (m, 2H), 6.64 (s, 1H), 6.20–6.10 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, [D$_6$]DMSO): $\delta = 185.3$, 152.0, 139.8, 131.5, 127.7, 125.8, 121.0, 69.8. HRMS (ESI) *m/z* calc. for $C_{12}H_9OBr + Na^+$: 286.9678; found: 286.9677. Melting point: 173 °C.

*4-(4-Chlorophenyl)-4-hydroxy-2,5-cyclohexadien-1-one (**4 b**)*: ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = 7.43$ (s, 4H), 6.93–6.88 (m, 2H), 6.64 (s, 1H), 6.18–6.12 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, [D$_6$]DMSO): $\delta = 185.3$, 152.1, 139.4, 132.5, 128.6, 127.4, 125.8, 69.7. HRMS (ESI) *m/z* calc. for $C_{12}H_9OCl + Na^+$: 243.0183 $[M + Na]^+$; found: 243.0184. Melting point: 170 °C.

Synthesis of three-membered building blocks 5 a and 5 b: The reaction was performed under inert atmosphere. Ketone **4 a** or **4 b** (1.00 equiv.) was dissolved in anhydrous THF (238 mmol L^{-1}). In a separate bottle NaH was suspended in anhydrous THF (0.500 mol L^{-1}) and continuously stirred. In a third bottle 1,4-dibromobenzene (**3 b**) was dissolved in anhydrous THF (380 mmol L^{-1}). Methyl iodide (5.00 equiv.) was dissolved in anhydrous dimethylformamide (DMF, 475 mmol L^{-1}). *n*-Butyllithium (1.6 m in hexanes) was used directly from the purchased bottle.

The whole reactor was placed in an ultrasonic bath filled with ice and water (0 °C) and all reagent solutions were pumped through cooling loops before entering the mixers. The reactor consists of two parallel streams, which are joined later on. First, the solution of 1,4-dibromobenzene (**3 b**; 4.00 mL min^{-1}) was mixed with *n*-butyllithium (1.00 mL min^{-1}) before entering a tubular reactor ($L = 30$ cm, $V =$ 0.13 mL). In the parallel stream, the solution of ketone **4 a** or **4 b** (3.20 mL min^{-1}) was mixed with the NaH suspension (1.80 mL min^{-1}) before entering a tubular reactor (inner diameter 1.6 mm, $L = 50$ cm, $V = 1.0$ mL). In the following mixer, both streams were combined. The mixer is followed by a tubular reactor (inner diameter 1.6 mm, $L = 50$ cm, $V = 1.0$ mL). Afterwards, a MeI solution (8.00 mL min^{-1}) is added via a fourth mixer. After a tubular reactor (inner diameter 1.6 mm, $L = 200$ cm, $V = 4.0$ mL) the output is collected under inert atmosphere and stirred for 16 h. The mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with water and brine. The solvent was removed under reduced pressure. The crude product was obtained as a yellow oil. Crude product was triturated with *n*-hexane, filtered off and dried under reduced pressure. The product was obtained as an off-white solid. (**5 a** (Br): 78 % (17.8 mmol, 8.00 g); **5 b** (Cl/Br): 78 % (17.7 mmol, 7.20 g). Analytical data correspond to literature (**5 a**,[21] **5 b**[31]).

*1,1′-(*cis*-1,4-Dimethoxycyclohexa-2,5-diene-1,4-diyl)bis(4-bromobenzene) (**5a**)*: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.41 (m, 4H), 7.26–7.22 (m, 4H), 6.07 (s, 4H), 3.41 (s, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 142.5, 133.5, 131.7, 127.9, 121.9, 74.6, 52.2. HRMS (ESI) *m/z* calc. for $C_{20}H_{18}O_2Br_2 + Na^+$: 470.9566; found: 470.9563. Melting point: 131 °C.

*1-Bromo-4-[*cis*-4-(4-chlorophenyl)-1,4-dimethoxy-2,5-cyclo-hexadien-1-yl]benzene (**5b**)*: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47–7.39 (m, 2H), 7.34–7.20 (m, 6H), 6.07 (s, 4H), 3.41 (s, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 142.5, 141.9, 133.7, 133.54, 133.45, 131.6, 128.7, 127.9, 127.5, 121.9, 74.6, 74.5, 52.2. HRMS (ESI) *m/z* calc. for $C_{20}H_{18}O_2BrCl + Na^+$: 427.0071; found: 427.0073. Melting point: 132 °C.

Synthesis of boronic ester 5c (2,2′-[(*cis*-1,4-dimethoxycyclohexa-2,5-diene-1,4-diyl)di-4,1-phenylene]bis[4,4,5,5-tetramethyl-1,3,2-dioxaborolane]): The three-membered building block **5a** (15.6 g, 34.7 mmol, 1.00 equiv.) was dissolved in anhydrous THF (500 mL) and cooled down to −78 °C. To this solution was added *n*BuLi (1.6 m in hexanes, 45.5 mL, 72.9 mmol, 2.10 equiv.) over 5 min. Immediately after the addition of *n*-BuLi, isopropyl pinacol borate (29 mL, 139 mmol, 4.01 equiv.) was added and the solution was stirred for 30 min at −78 °C. The reaction mixture was warmed up to RT. Water (350 mL) was added to the solution and the mixture was allowed to stir for 15 min before extracting with CH_2Cl_2 (3×200 mL). The combined organic layers were washed with brine and then dried over magnesium sulfate. After removing the solvent under vacuum, the crude product was boiled in *n*-hexane (75 mL). The solid was filtered off (product). To further increase the isolated yield, the filtrate was concentrated under reduced pressure. The solid was washed with *n*-hexane (ultrasonic bath) and filtered off. The product was isolated as colorless solid in a yield of 78 % (14.7 g in total). Analytical data correspond to literature.[21]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78–7.72 (m, 4H), 7.41–7.38 (m, 4H), 6.09 (s, 4H), 3.43 (s, 6H), 1.34 (s, 24H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 146.5, 135.1, 133.4, 125.5, 83.9, 75.1, 52.1, 25.0. HRMS (ESI) *m/z* calc. for $C_{32}H_{42}B_2O_6 + Na^+$: 567.3060; found: 567.3057. Melting point: 245 °C.

Synthesis of nine-membered building block 6 (4,4″-(*cis*-1,4-dimethoxycyclohexa-2,5-diene-1,4-diyl)bis[4′-[*cis*-4-(4-chlorophenyl)-1,4-dimethoxy-2,5-cyclohexadien-1-yl]-1,1′-biphenyl]: Boronic ester **5c** (2.68 g, 4.92 mmol, 1.00 equiv.) was dissolved in THF (80 mL, 61.5 mmol L^{-1}, degassed) and aqueous sodium carbonate (V = (0.75·V_{THF}) mL, 0.2 m, degassed) was added (solution A). The solution was stirred continuously. A second solution (solution B) was prepared by dissolving three-membered building block **5b** (2.00 equiv.) in THF (80 mL, 12.3 mmol L^{-1}, degassed). Both solutions were purged separately with a stream of nitrogen for 1 h. Tetrakis(triphenylphosphine) palladium(0) (10 mol %) was added to solution B. Solution A (525 µL min^{-1}) and solution B (300 µL min^{-1}) were pumped from reservoirs using peristaltic pumps (E-Series, Vapourtec). The mixer was placed in an ultrasonic bath filled with water (heated to 70 °C) and all reagent solutions were pumped through loops and check valves before entering the mixer. The mixer (inner diameter 1.0 mm) was followed by a tubular reactor (V = 40 mL, heated to 100 °C) and a cooling loop (V = 4 mL). A peristaltic pump (E-Series, Vapourtec) was used as a back-pressure regulator (BPR, 2.5 bar). The reactor output was collected for 200 min. Ethyl acetate (20 mL) and water (50 mL) were added to the reactor output. The organic phase was separated and treated with methanol (50 mL) to obtain the precipitation of a black oily solid. The solvent was decanted. The solid was then dissolved in ethyl acetate, activated coal was added and filtered through a pad of celite. The solvent was removed under reduced pressure to obtain an off-white solid in a yield of 75 % (2.62 g, 2.78 mmol). Analytical data correspond to literature.[21] ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.59–7.53 (m, 8H), 7.51–7.46 (m, 4H), 7.45–7.41 (m, 4H), 7.38–7.33 (m, 4H), 7.31–7.25 (m, 4H), 6.18–6.11 (m, 8H), 6.10–6.05 (m, 4H), 3.45 (s, 6H), 3.43–3.41 (m, 12H). $^{13}C\{^1H\}$ NMR (101 MHz, CD_2Cl_2): δ = 143.4, 143.1, 142.9, 140.3, 140.1, 134.2, 133.9, 133.54, 133.53, 128.8, 128.0, 127.31, 127.28 127.0, 126.9, 75.1, 75.0, 74.8, 52.3. HRMS (ESI) *m/z* calc. for $C_{60}H_{54}Cl_2O_6 + Na^+$: 963.3189; found: 963.3181. Melting point: 150 °C.

Synthesis of ten-membered macrocycle 9: The synthesis of **9** was performed according to literature.[21] Compound contained unknown impurities and was used without further purification. Analytical data correspond to literature.[21] ^{1}H NMR (200 MHz, CD_2Cl_2): δ = 7.68 (s, 4H), 7.66–7.41 (m, 20H), 7.41-7.27 (m, 4H), 6.31–6.03 (m, 12H), 3.49–3.36 (m, 18H). $^{13}C\{^1H\}$ NMR (101 MHz, CD_2Cl_2): δ = 143.7, 142.9, 142.8, 140.4, 140.2, 139.96, 139.93, 134.1, 134.0, 133.4, 127.9, 127.3, 127.24, 127.18, 127.1, 127.0, 126.9, 75.55, 75.52, 74.3, 52.4, 52.2, 52.1. HRMS (ESI) *m/z* calc. for $C_{66}H_{58}O_6 + Na^+$: 969.4125; found: 969.4121. Melting point: decomposition at > 250 °C.

Synthesis of [10]cycloparaphenylene: A column (250 mm×10 mm, stainless steel) was packed with SOLVONA® (7.6 g) under inert atmosphere (glovebox). The column was filled with anhydrous THF to determine the remaining volume (7.5 mL). A solution of naphthalene (0.50 m) in anhydrous THF (distilled, not stabilized) was prepared. This solution was pumped through the packed bed reactor (200 µL min^{-1}, residence time 37.5 min) and an in-line filter (PTFE, 4 µm) to obtain a dark green solution. Ten-membered macrocycle **9** (40.0 mg, 42.2 µmol, 1.00 equiv.) was mixed with anhydrous THF (distilled, not stabilized) to obtain a colorless suspension. The mixture was cooled to −78 °C. The reactor output was added to this flask for 7:36 min (18.0 equiv.) to obtain a purple solution. The reaction mixture was allowed to stir at −78 °C for 1 h. The reaction was quenched by the addition of I_2 (0.3 mL of a 1 m solution in THF) and warmed up to RT. The resulting mixture was added to sodium thiosulfate (saturated solution, 10 mL). Water (20 mL) was then added and the mixture was extracted with dichloromethane (3×20 mL). The combined organic layers were washed with brine (30 mL), dried over magnesium sulfate and filtered. The crude product was purified by column chromatography (SiO_2, cyclohexane/CH_2Cl_2 1:1). Small traces of grease could be removed by washing with pentane to obtain a bright yellow solid in a yield of 71 % (22.8 mg, 30.0 µmol). Analytical data correspond to literature.[21] ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.56 (s, 40H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 138.3, 127.5. HRMS (LDI) *m/z* calc. for $C_{60}H_{40}{}^+$: 760.3130; found: 760.3122. Melting point: decomposition at > 250 °C

Supporting Information

General information, NMR spectra of all compounds, HPLC data, photographs of the reactor set-ups and a comparison with literature yields are given in the Supporting Information. Furthermore, the authors have cited an additional reference here.[40]

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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