Microreactors

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Flow-Assisted Synthesis of [10]Cycloparaphenylene through Serial Microreactions under Mild Conditions

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Abstract: *Cycloparaphenylene (CPP) has been recognized as an attractive template for the bottom-up synthesis of carbon nanotubes with uniform diameter, and is important for the chemistry of graphitic as well as ring-shaped macromolecules. However, the reported routes from halogenated benzenes have suffered from low yields even under time- and labor-consuming multistep conditions. Herein we report a flow-assisted synthesis of [10]CPP in four steps under mild conditions. For the synthesis, a selective nucleophilic addition of the unprotected diketone without the double-added byproduct was achieved within 3 s in high yield. Subsequently, the obtained compound was reacted with dilithiated benzene at 25°C to form a U-shaped precursor for CPP in a separate microreactor, which was finally dimerized and aromatized to obtain [10]CPP by a two-step in-flask reaction. Precise control of time and flow facilitated by the flow-assisted system enabled the development of an efficient synthetic route for [10]CPP.*

Carbon nanotubes (CNTs) are a well-known nanomaterial with various functions for applications in sensors, tissue engineering, solar cells, transistors, and transparent electrodes.[1–5] Precise control of tube diameter and side-wall structures is important to determine the properties of carbon nanotubes.[6] Chemists have taken a bottom-up approach towards the synthesis of CNTs to more efficiently and exactly control the desired length and diameter. Cycloparaphenylene (CPP) molecules,[7] subunit of CNTs, are commonly known as “carbon nanohoops”, and can be employed for the rational construction of a CNT from a single subunit with a well-controlled diameter.[8] Moreover, the emergence of these molecules as the smallest unit of CNTs has provided an opportunity to understand the detailed chemistry of these graphitic materials as well as that of ring-shaped π-conjugated macromolecules[9] and a light-emitting fluorophore.[10]

Efforts towards the synthesis of CPP have been attempted over the past seven decades since the work reported by Parekh and Guha in 1934.[11] The pioneering synthesis of CPP as a single molecule,[8a,b] however, has been achieved only in the last seven years. A molecular approach has been taken to synthesize different sizes of [*n*]CPPs ($n = 5$ to 16, where n is the number of benzene rings) with uniform diameter.[12] A batch process involving a flask is typically utilized to synthesize CPPs, as reported in recent studies,[13–15] with dihalobenzene and protected 1,4-cyclohexanedione as starting reagents. This in-flask synthesis requires low-temperature conditions, such as -78°C, or reflux conditions, leading to a low yield. Furthermore, these routes invariably produce only a small amount of CPP products.

Flask reactors, in general, have to be run at low temperature when the synthesis-of-interest involves an unstable intermediate, such as diazo compounds[16] or organolithium compounds.[17] In contrast, the continuous-flow reactors[18] based on microfluidic systems can be run under mild conditions because of the precise control of reaction time (milliseconds to seconds) and temperature, which leads to good performance. In particular, various types of flash chemistry[19] have been demonstrated in one-flow microreactors for efficient utilization of short-lived intermediates, such as organolithium compounds bearing highly electrophilic groups,[20] for discovering new synthetic routes that were impossible in batch reactors. This continuous-flow method has been broadly applied for synthesizing various biologically active molecules such as pharmaceutical compounds or natural products. To date, however, there has been no attempt to synthesize CPP using a flow system. A continuous-flow route for CPP synthesis is needed to integrate the sequential reactions involving reactive intermediates, which significantly alleviates the difficulties in handling multistep reactions.

Herein, we report a flow-assisted synthesis of [10]CPP in four steps under mild conditions (Scheme 1). [10]CPP can be prepared from the U-shaped molecule **6**, obtained by serial reactions in microreactors (Scheme 1). In the first step, the L-shaped subunit compound **3** is produced by the selective reaction of efficiently generated monolithiated arene with unprotected ketone within 3 s at 0°C and subsequent alcohol protection. The product **3** thus produced is employed in the synthesis of U-shaped molecule **6**, achieved by the reaction of **3** with a dilithiated arene at room temperature and subsequent alcohol protection. This U-shaped precursor of CPP is then dimerized and aromatized to finally synthesize CCP.

The single addition reaction of organolithium reagents with diketone molecules under batch conditions is known to require the protection/deprotection of a single ketone group, necessary to prohibit the undesired overreaction that leads to a double-added byproduct.[21] When the Br–Li exchange

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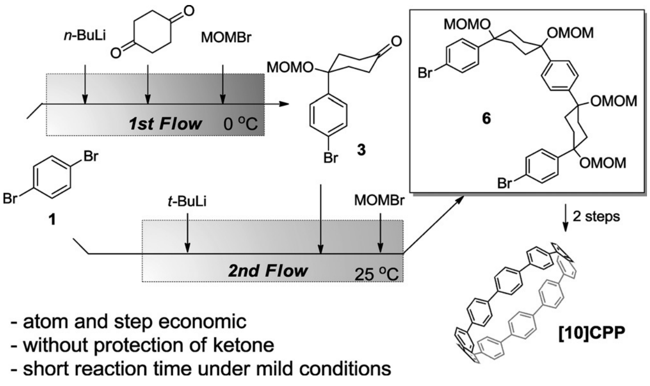
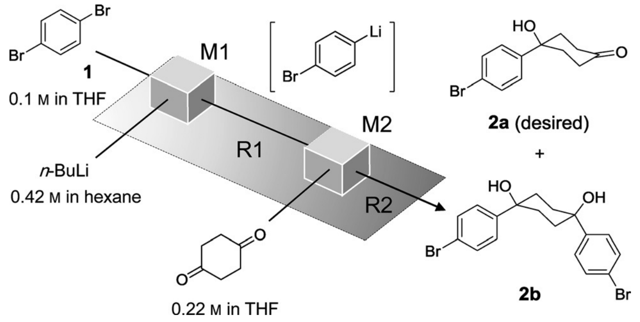


Scheme 1. Flow-assisted approach for the synthesis of [10]cycloparaphenylene (CPP) through integrated sequential reactions under mild conditions. MOM = methoxymethyl.

reaction of 1,4-dibromobenzene was followed by the reaction with unprotected 1,4-cyclohexanedione at −78 °C in a batch reactor, the yield of the mono-addition product **2a** was only 11 % while that of the double-addition byproduct **2b** was 26 % (Table 1, entry 1). Clearly, selective nucleophilic reaction could not be easily achieved when the electrophile had two of the same functional groups.

Therefore, we first focused on the selective nucleophilic addition of aryllithium to 1,4-cyclohexanedione (without protection of the diketone) in a continuous-flow microreactor (Table 1). The flow microreactor, consisting of two T-shaped micromixers (inner diameter $\phi = 250\ \mu m$ for M1 and $\phi = 500\ \mu m$ for M2) and two microtube reactors (R1: $\phi = 250\ \mu m$, length $L = 4$ cm; R2: $\phi = 1000\ \mu m$, $L = 50$ cm), was used with the total flow rates varying in the range from 1.75 mL min^{-1} to 10.50 mL min^{-1}. The yield of the desired product **2a** was improved with increasing the flow rate, presumably because of the fast-flow-induced mixing effect[20] (Table 1, entries 2–7). When the total flow rate was set at 10.5 mL min^{-1}, a completely selective reaction was achieved to give **2a** as the sole product within 3 s from the beginning of the reaction at 0 °C (92 % yield of isolated product; Table 1, entry 7). For the reaction at room temperature, both the conversion and yield were slightly decreased (Table 1, entry 8). From this result, we showed that an extremely fast flow rate for highly efficient vortex mixing is crucial, even at room temperature, for selective nucleophilic addition to unprotected 1,4-cyclohexanedione as well as for the generation of *para*-lithiated bromobenzene by means of a single Br–Li exchange. Similarly, Yoshida et al. recently reported that chemoselective nucleophilic reactions with electrophiles bearing two different functional groups could be performed through fast mixing in a flow microreactor.[22]

Table 1: Selective reaction of 4-bromophenyllithium with 1,4-cyclohexadione in a flow microreactor.



Entry	Flow rate[a] [mL/min]	Conv. of **1**[b] [%]	Yield of **2a**[b] [%]	Yield of **2b**[b] [%]
1	–[c]	73	11	26
2	1.75	42	20	0
3	3.5	82	62	24
4	5.25	94	69	19
5	7	96	82	14
6	8.75	96	84	10
7	10.5	99	97 (92)[d]	0
8[e]	10.5	96	95	3

[a] The ratio of the flow rates for 1,4-diboromobenzene, *n*-butyllithium, and 1,4-cyclohexadione was kept at 4:1:2. [b] GC yield. [c] The reaction was conducted in a flask reactor at −78 °C. [d] Yield of isolated product. [e] The reaction was conducted at 20 °C.

We then focused on the alcohol protection of the produced compound **2a** using the microfluidic device. The MOM (methoxy methyl) protection of alcohol using in-flask chemistry is typically conducted with an additional base (for example, Et_3N) in a different solvent system (such as CH_2Cl_2) as an overnight reaction. Based on the optimized flow conditions (10.5 mL min^{-1} of total flow rate at 0 °C), we conducted a sequential protection of the alcohol in the flow microreactor (Figure 1). Because the MOM protection typically requires a long reaction time, bromomethyl methyl ether (MOMBr) was sequentially introduced into the flow system and the resulting solution of the flow reaction was stirred in a vial for 4 h for full conversion of the alcohol. This method led to the production of the L-shaped product **3**, a subunit of CPP, which was isolated 80 % in yield.

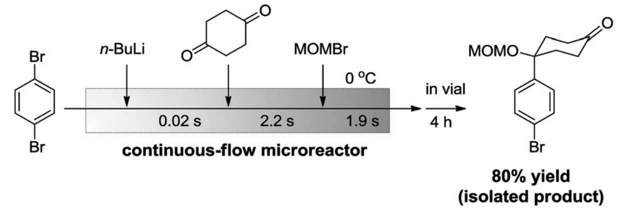


Figure 1. Flow-assisted synthesis of the L-shaped compound **3** by means of a single Br–Li exchange reaction of 1,4-dibromobenzene, followed by selective reaction with unprotected 1,4-cyclohexandione and MOM protection.

Next, we examined the dilithiation of 1,4-dibromobenzene **1**, by means of a double Br–Li exchange reaction, for the synthesis of the U-shaped unit **6** (a core precursor of [10]CPP; Figure 2). The reaction, when conducted in a flask, requires an excess of *t*-BuLi. Under these conditions, *t*-BuLi should be carefully handled because of its strong flammability at an extremely low temperature (between −78 and −100 °C). Thus, it was necessary to develop a safe and mild method for the generation of dilithiated benzene using *t*-BuLi.

To optimize the reaction conditions for the dilithiation and the subsequent formation of compound **5** (see Figure 2

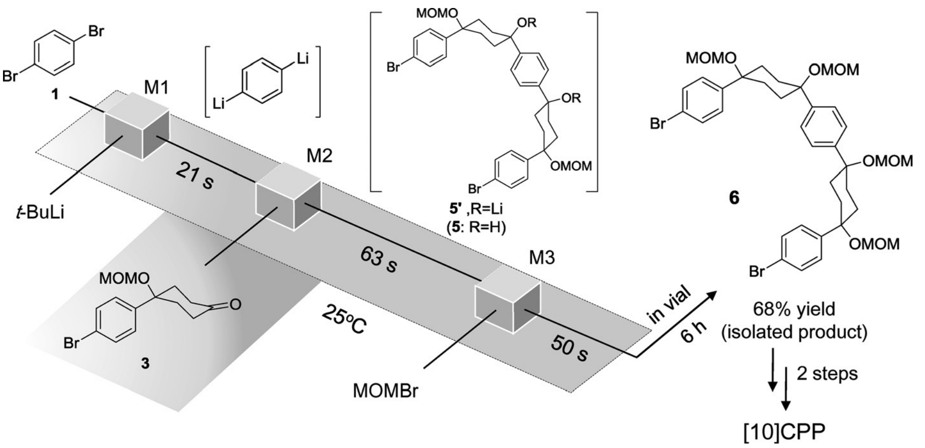
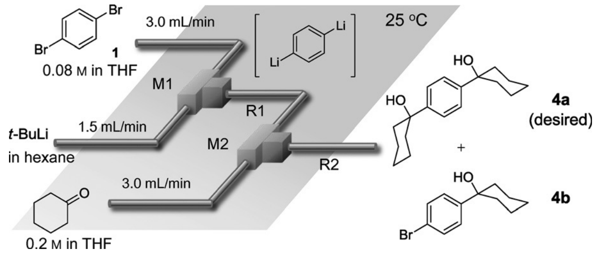


Figure 2. Flow-assisted synthesis of U-shaped compound **6** by double Br–Li exchange reaction of 1,4-dibromobenzene, reaction with L-shaped subunit compound **3**, and MOM protection.

for the structure), the reactions shown in Table 2 were conducted in a microreactor where the readily available compound cyclohexanone was used as a model compound in place of compound **3** (see Figure 2). This microreactor consisted of two T-shaped micromixers and two microtube reactors with different dimensions (R1: $L = 4$ cm to 200 cm, $\phi = 1000$ μm; R2: $L = 1000$ cm, $\phi = 1000$ μm). Initially, the dilithiation reaction was conducted using 5 equivalents of *t*-BuLi at 0 °C (residence time in R1 = 23 ms), which resulted in 13 % yield of the desired product **4a** from dilithiated benzene and 75 % yield of the undesired product **4b** from monolithiated benzene (Table 2, entry 1). These results indicate that a 23 ms reaction time at 0 °C was insufficient for full conversion. Thus, the reaction time for dilithiation was increased from 23 ms to 5.2 s by changing the diameter and length of R1 at room temperature, resulting in an increase of the yield of **4a** from 27 % to 83 % (Table 2, entry 2–5). Moreover, 4.5 equiv of *t*-BuLi was found to be sufficient for full conversion of starting compound **1** to give **4a** in 82 % yield without the formation of the undesirable byproduct **4b**, achieved upon increasing the reaction time to 20.9 s (Table 2, entry 6–8).

Table 2: Generation of 1,4-dilithiated benzene by means of a double Br–Li exchange reaction of 1,4-dibromobenzene followed by reaction with cyclohexanone in a flow microreactor.



Entry	Residence time in R1 [s]	*t*-BuLi [equiv]	Yield of **4a**[a] [%]	Yield of **4b**[a] [%]
1[b]	0.03	5.0	13	75
2	0.03	5.0	27	64
3	0.42	5.0	60	35
4	3.1	5.0	75	13
5	5.2	5.0	83	3
6	5.2	4.5	70	13
7	10.5	4.5	76	7
8	20.9	4.5	82 (73)[c]	0

[a] GC yield. [b] At 0 °C. [c] Ketone **3** was used instead of cyclohexanone as the electrophile.

Utilizing the best reaction conditions (20.9 s for dilithiation at 25 °C), the U-shaped unit **5** was synthesized by the reaction with the L-shaped electrophile **3** (Figure 2). For a gram-scale synthesis, the flow operation was continued for 10 min to give product **5** which was isolated in 73 % yield (1.23 g of **5** isolated). This result clearly demonstrates that a combination of fast mixing and controlled reaction time in the microreactor is effective for the generation of the dilithiated intermediate and the subsequent reaction with the ketone under safe and mild reaction conditions. The protection of the thus-generated alkoxide of the compound **5′** was further integrated in the series of microreactions (Figure 2). The generated 1,4-dilithiated benzene, obtained through double Br–Li exchange, was reacted with 2 equivalents of ketone **3** to form the alkoxide **5′**. This molecule was subsequently protected by reaction with MOMBr in the microfluidic device.

At the outlet, the resulting solution was stirred for 6 h in a vial at room temperature to achieve completion of the protection step using the MOM reagent (for details see the Supporting Information). The desired U-shaped unit **6** was obtained in good yield (68 %, Figure 2) in the integrated microfluidic system. Compound **6** was then converted into [10]CPP in two steps through cyclic dimerization and aromatization (as previously reported).[22] Employing this method provides not only the highest overall yield (11 %) of [10]CPP reported to date but is also the simplest route (four steps), requiring a short reaction time (circa 70 h) under mild conditions. This method is in direct contrast to previously reported routes that required seven steps, including very low temperatures (−78 °C), to render only 5 % yield in circa 160 h.[15,23]

In conclusion, we have demonstrated a novel flow-assisted reaction route for the synthesis of [10]CPP. The generation and utilization of mono- and dilithiated benzene was optimized by precise time and flow control under mild conditions in the microreactor. In particular, the selective nucleophilic addition of the lithiated benzene derivative to a diketone was achieved in high yield without requiring a protection/deprotection step. The U-shaped unit **6**, a precursor to CPP, was obtained by two steps of serial reactions in microreactors under mild conditions, and was subsequently dimerized and aromatized to form [10]CPP using two reaction steps in reaction carried out in a flask. The flow-assisted approach taken here could be utilized to synthesize CPPs of various sizes in a continuous manner.

Experimental Section

Synthesis of **3**: A microfluidic system consisting of three T-shaped micromixers (M1, M2, and M3), three microtube reactors (R1, R2, and R3) and four tube pre-temperature retaining units (P1, P2, P3, and P4; inner diameter $\phi = 1000$ μm, length $L = 50$ cm) were used. A solution of 1,4-dibromobenzene (0.10 M in THF, flow rate: 6.0 mL min^{-1}) and a solution of *n*-BuLi (0.42 M in hexane, flow rate: 1.5 mL min^{-1}) were introduced to M1 ($\phi = 250$ μm) by syringe pumps. The resulting solution was passed through R1 ($\phi = 250$ μm, $L =$ 3.5 cm) and was mixed with a solution of 1,4-cyclohexanedione (0.22 M in THF, flow rate: 3.0 mL min^{-1}) in M2 ($\phi = 500$ μm). The resulting solution was passed through R2 ($\phi = 1000$ μm, $L = 50$ cm) and was mixed with a solution of bromomethyl methyl ether (2.4 M in DMF/THF, flow rate: 2.0 mL min^{-1}). The resulting solution was passed through R3 ($\phi = 1000$ μm, $L = 1$ m). After a steady state was reached, the product solution was collected and further stirred for 4 h at 25 °C. The reaction mixture was quenched using a saturated NH$_4$Cl aqueous solution. The crude product was extracted with CH$_2$Cl$_2$ (3 × 15 mL) and was washed with brine (15 mL). The organic phase was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: 30 % to 100 % ethyl acetate in hexane) to give desired product **3** in 80 % yield.

Synthesis of **6**: A solution of 1,4-dibromobenzene (0.08 M in THF, flow rate: 3.0 mL min^{-1}) and a solution of *t*-BuLi (0.72 M in hexane, flow rate: 1.5 mL min^{-1}) were introduced to M1 ($\phi = 250$ μm) by syringe pumps. The resulting solution was passed through R1 ($\phi =$ 1000 μm, $L = 1$ m) and was mixed with a solution of functionalized **3a** (0.2 M in THF/HMPA, flow rate: 3.0 mL min^{-1}; HMPA = hexamethylphosphoramide) in M2 ($\phi = 500$ μm). The resulting solution was passed through R2 ($\phi = 1000$ μm, $L = 50$ cm) and was mixed with a solution of bromomethyl methyl ether (4.8 M in DMF/THF, flow rate: 2.0 mL min^{-1}). The resulting solution was passed through R3 ($\phi = 1000$ μm, $L = 1$ m). After a steady state was reached, the product solution was collected and further stirred for 6 h at 25 °C. The crude product was extracted with ethyl acetate (3 × 15 mL), dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography (eluent: 20 % to 50 % ethyl acetate in hexane) to give desired product **6** in 68 % yield.

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