

Streamlining Organic Synthesis

Accessing Cycloparaphenylenes and Azobenzenes via
Advanced Synthetic Techniques

Inauguraldissertation zur Erlangung des Doktorgrades (Dr. rer. nat.) der
Naturwissenschaftlichen Fachbereiche im Fachgebiet Chemie der

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Gießen 2024

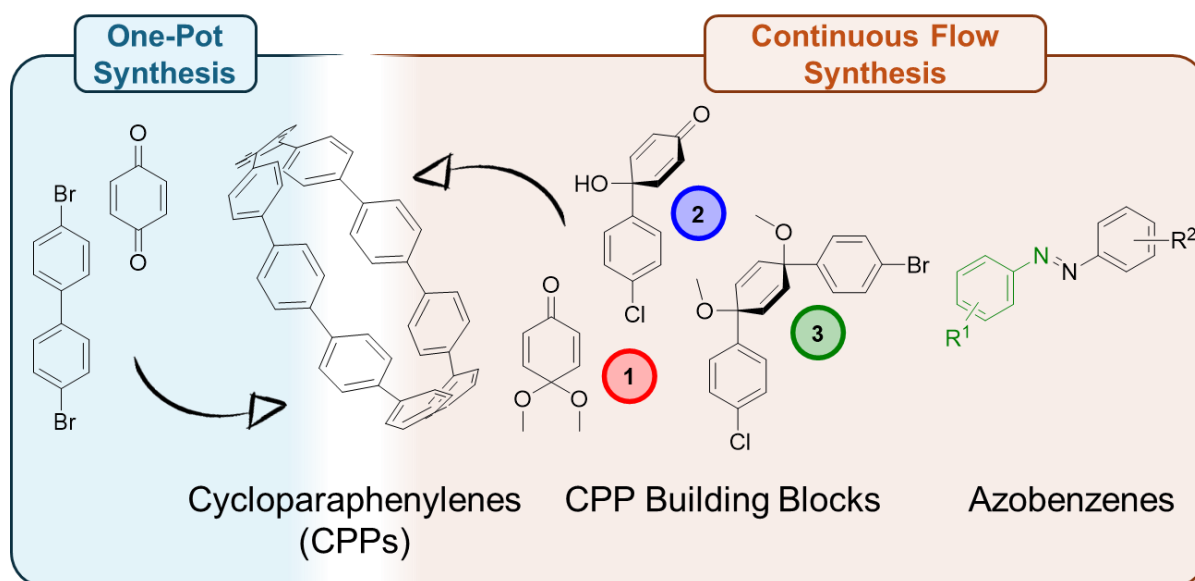
“I would rather have questions that can't be answered than
answers that can't be questioned.”

— Richard Feynman

Für meine Familie.

Abstract

The synthesis of organic molecules can be a challenging and tedious task. These compounds, which are not necessarily large or complex, may require long, multi-step syntheses. This hampers research and complicates access to important drugs or new materials. Over time, strategies have been developed towards shorter, more efficient, and faster accesses to molecules of interest. Since the purification of substances accounts for a huge part of the work, so-called one-pot reactions were developed, which combine successive reactions without intermediate purification.



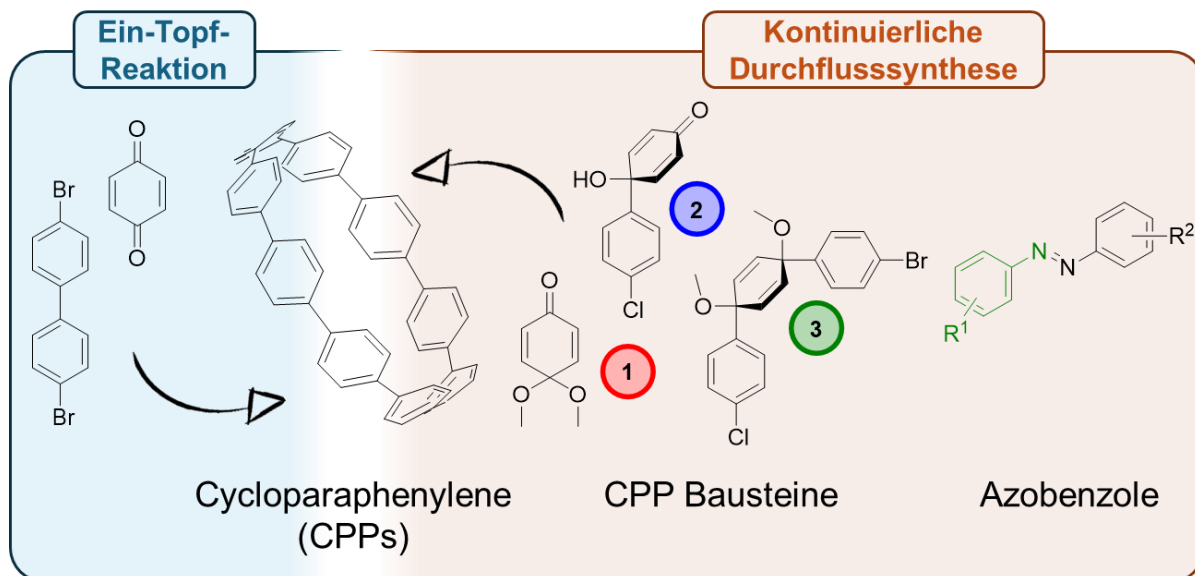
In the first part of this thesis, a one-pot reaction has been developed for the substance class of cycloparaphenylenes (CPPs). Their synthesis is usually achieved by a multi-step process, which relies on the combination of smaller building blocks. The developed method provides rapid and selective access to CPPs with different ring sizes via the in-situ formation of macrocyclic precursors and their subsequent aromatization in a single flask. However, this method is only suitable to obtain small amounts of these compounds.

To provide access to large amounts of different sized and functionalized CPPs, key building blocks for their synthesis have been prepared using continuous flow chemistry. Self-built reactors were optimized and utilized to obtain substance quantities on up-to kilogram scale. By this, the investigation of known and novel CPPs and related macrocycles is no longer limited by multi-step syntheses and the resulting small amounts of material.

Continuous flow chemistry can not only be used to produce large quantities of a compound but can also be applied to safely handle a hazardous substance. The critical compound will only exist in small quantities at a time and is safely contained inside the flow reactor. This feature was utilized to synthesize different non-symmetric substituted azobenzenes (ABs) via a Baeyer-Mills reaction. The toxic nitrosobenzene was accessed in a continuous flow reactor and allowed to react immediately. By this, multiple substituted ABs were obtained in a fast and safer way, compared to traditional (multi-step) batch synthesis.

Zusammenfassung

Die Synthese organischer Moleküle kann eine herausfordernde und langwierige Aufgabe sein. Diese Verbindungen müssen nicht zwangsläufig besonders groß oder komplex sein, um lange, mehrstufige Synthesen zu erfordern und somit die Forschung auszubremsen und den Zugang zu wichtigen Medikamenten oder neuen Materialien zu erschweren. Daher wurden im Laufe der Zeit Strategien entwickelt, um kürzere, effizientere und schnellere Wege für den Zugang zu bestimmten Molekülen zu finden. Da insbesondere die Aufreinigung von Substanzen einen Großteil des Arbeitsaufwands ausmacht, wurden so genannte Ein-Topf-Reaktionen entwickelt, bei denen aufeinanderfolgende Reaktionen ohne zwischenzeitliche Aufreinigung kombiniert werden.



Im ersten Abschnitt dieser Thesis wurde für die Substanzklasse der Cycloparaphenylen (CPPs), deren Synthese üblicherweise in einem mehrstufigen Prozess erfolgt, der auf der Kombination kleinerer Bausteine beruht, eine Ein-Topf-Reaktion entwickelt. Durch die in-situ Darstellung von Makrozyklen und deren direkter Aromatisierung in einem Kolben, ermöglicht die entwickelte Methode einen schnelleren und selektiven Zugang zu CPPs mit unterschiedlichen Ringgrößen. Allerdings ist diese Methode nur geeignet, um kleine Mengen dieser Verbindungen zu erhalten.

Um Zugang zu großen Mengen unterschiedlich großer und funktionalisierter CPPs zu erhalten, wurden die Grundbausteine für deren Synthese mit Hilfe der kontinuierlichen Durchflusschemie dargestellt. Selbstgebaute Reaktoren wurden optimiert und eingesetzt, um

Bausteine in bis zum Kilogramm-Maßstab zu erhalten. Damit ist die Untersuchung bekannter und neuartiger CPPs, ebenso wie verwandter Makrozyklen, nicht mehr durch mehrstufige Synthesen und die daraus resultierenden geringen Materialmengen begrenzt.

Die kontinuierliche Durchflusschemie kann nicht nur für die Herstellung großer Substanzmengen eingesetzt werden, sondern auch für den sicheren Umgang mit einem gefährlichen Stoff. Die betreffende Verbindung liegt stets in nur geringen Mengen vor und ist in dem Durchflussreaktor sicher eingeschlossen. Diese Technik wurde für die Synthese verschiedener nicht-symmetrisch substituierter Azobenzole (ABs) mittels Baeyer-Mills-Reaktion genutzt. Das giftige Nitrosobenzol wurde in einem kontinuierlichen Durchflussreaktor zugänglich gemacht und sofort zur Folgereaktion gebracht. Auf diese Weise wurden mehrfach substituierte AB im Vergleich zur traditionellen (mehrstufigen) Batch-Synthese auf schnelle und sichere Weise erhalten.

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1 Multi-Step Syntheses

Today's organic chemistry has its early beginnings in the first half of the 19th century. Starting with simple transformations and techniques, a broad field has quickly developed. This has become the fundament of organic chemistry in academia, fine chemical industry, and medicinal chemistry.^[1-3]

Over the time scientists developed not only single step transformations, but realized multi-step syntheses of complex molecules.^[2,4] By using a large toolbox of different reactions, the synthesis of natural products has become an own discipline.^[1,3]

Total synthesis of natural products was pushed forward from the middle of the 20th century around famous scientists like Vigneaud, Woodward, Eschenmoser and Corey among others. With great effort, hundreds of different natural products have been targeted and obtained by their groups.^[5-10] For example, vitamin B₁₂ was synthesized over more than 70 steps by the groups of Woodward and Eschenmoser (Figure 1).^[6,7] The latter also reported the synthesis of colchicine over 20 steps.^[9] In 1969 Corey published the synthesis of prostaglandin F₂α over 17 linear steps.^[10]

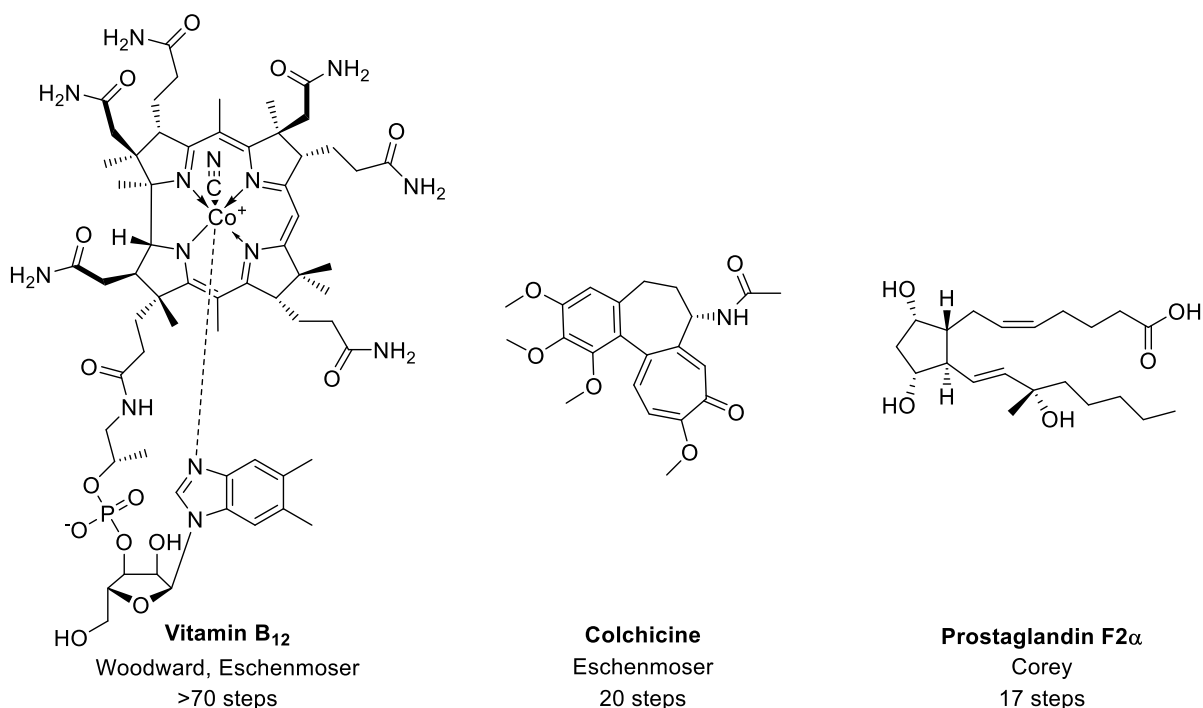
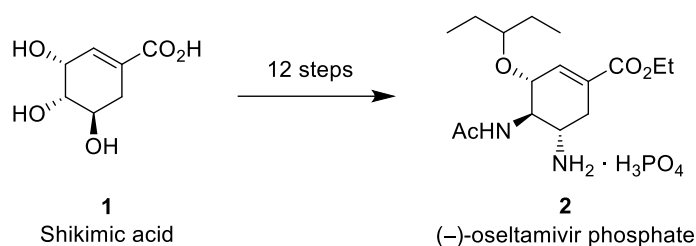


Figure 1: Examples of some selected natural products and the number of synthetic steps during their total synthesis.^[6,7,9,10]

While some natural products are used to cure specific diseases, there are also synthetic active pharmaceutical ingredients (APIs), that require long, multi-step syntheses to be obtained. One famous example is the synthesis of the antiviral drug (-)-oseltamivir (Tamiflu®). Its first scalable synthesis starting from naturally occurring quinic acid or shikimic acid (**1**) was

reported in 1998.^[11] The synthesis was slightly modified and is now used for the commercial production by Roche (Scheme 1).^[12] In recent years, several syntheses of (–)-oseltamivir were reported. However, the synthesis by Trost is the only yet reported synthesis with less than 10 linear steps (8 steps).^[13] A huge drawback of long linear multi-step syntheses is the potential low yield and excessive work load. According to Roche, the production time is 6 - 8 months, which is very long and laborious, if there is the need to react on an urgent scenario.^[12]



Scheme 1: Total synthesis of (–)-oseltamivir phosphate from shikimic acid.^[12]

1.1 Organic Materials

Multi-step syntheses do not only play a role in medicinal chemistry or natural product synthesis. Even small organic molecules, sometime, are only accessible via long syntheses. For instance, [1.1.1]propellane (**3**) contains only five carbon atoms and the same number of steps was necessary to synthesize it (Figure 2).^[14]

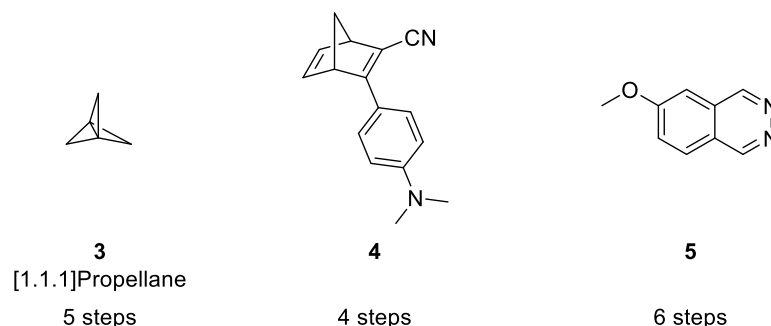


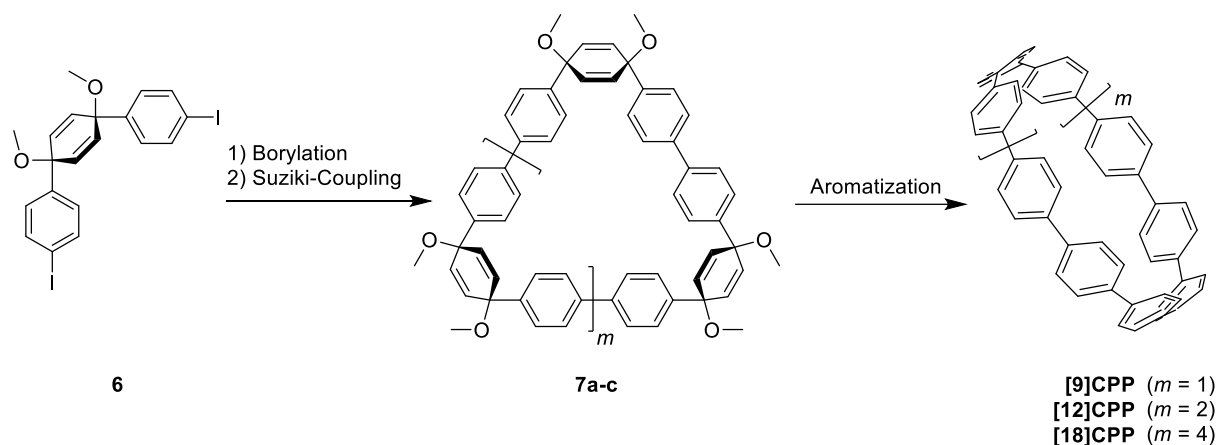
Figure 2: Examples of other organic molecules and the number of steps of their synthesis.^[14-16]

Although the π -conjugated small molecules **4** and **5** do not appear particularly complex, the norbornadiene **4** and the phthalazine **5** require a synthetic procedure with four and six steps, respectively.^[15,16]

1.1.1 Conjugated Aromatic Materials

Conjugated aromatic compounds are of rising interest in material research as molecular electronics components or in the context of development of renewable energy conversion and storage technology.^[17] A compound class of high interest are bent three dimensional aromatic structures.^[18–20]

Cycloparaphenylenes ($[n]$ CPPs, n = number of phenyl rings) are just one example out of numerous different compounds.^[20] Their synthesis is usually realized via pre-angled building blocks. Multiple of those precursors are combined to obtain less strained macrocycles, which are aromatized in the final step.^[18] By the use of different combinations of building blocks, various ring sizes can be realized.^[18,21,22] Even though the building block approach saves linear steps, the synthesis involves several stages and is labor-intensive.



Scheme 2: Synthesis of [9]-, [12]-, and [18]CPP by Jasti and Bertozzi in 2008.^[23]

The first synthesis of CPPs was realized by Jasti and Bertozzi based on cyclohexadiene containing building blocks (Scheme 2).^[23] Besides other, predominantly Jasti and his group published several synthetic routes towards different sized CPPs using the same building block approach in the course of the following years (Figure 3).^[22,24–26] Itami and co-workers published several syntheses based on cyclohexane-containing building blocks.^[27] The group of Yamago reported the synthesis of cycloparaphenylenes via macrocycles with planar platinum-complex as strain reducing unit.^[28] A gold mediated synthesis was reported by Tsuchido and co-workers in 2020.^[29] The gold complexes offer the possibility to form even small macrocycles, which were not accessible via planar platinum complexes.^[29] While the two latter attempts are synthetically concise (2 - 4 linear steps), the more common approaches are more elaborate (6 - 9 linear steps). Unfortunately, the macrocyclization of those building blocks only succeeds in high dilution and often suffer from low yields.^[21] This, and the need for cryogenic cooling during multiple reaction steps are the main reasons that prohibit a large-scale synthesis of such compounds.

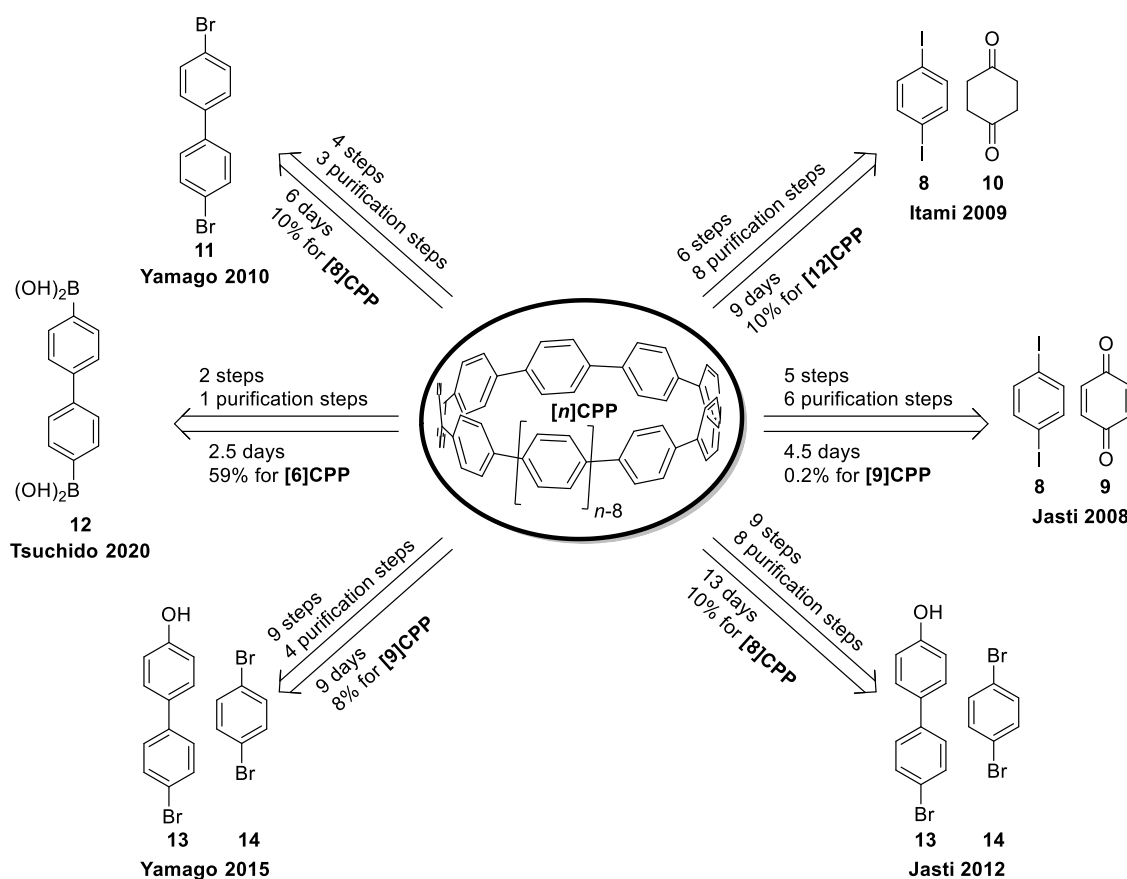
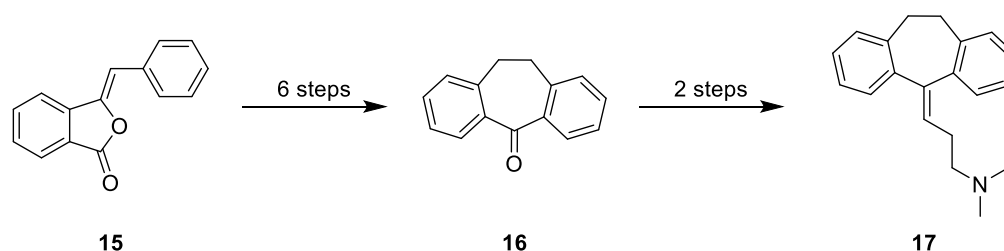


Figure 3: Overview of different synthesis routes towards $[n]$ CPPs and their characteristics. Adapted from [64].

Another noteworthy multi-step process is the synthesis of the polyaromatic tricyclic antidepressant amitriptyline **17**, which was originally discovered by Merck in 1958,^[30,31] and synthesized over 8 steps from benzalphthalid **15** by Protiva et al. in 1961 (Scheme 3).^[32–34] Driven by the success of this compound class as antidepressant drugs, further research was carried out, but limited by the scalability of the synthesis. Thus, further optimization and development of the synthetic accessibility for these compounds is required. In an ideal case, no work-up and purification steps in between two transformations would be necessary. These studies led to a faster and more convenient synthesis as shown by the report of a one-pot synthesis of different dibenzosuberones **16**, a key intermediate in the synthesis of amitriptyline **17** in 1980.^[35]



Scheme 3: Synthesis of amitriptyline **17** via dibenzosuberone **16**.^[32–34]

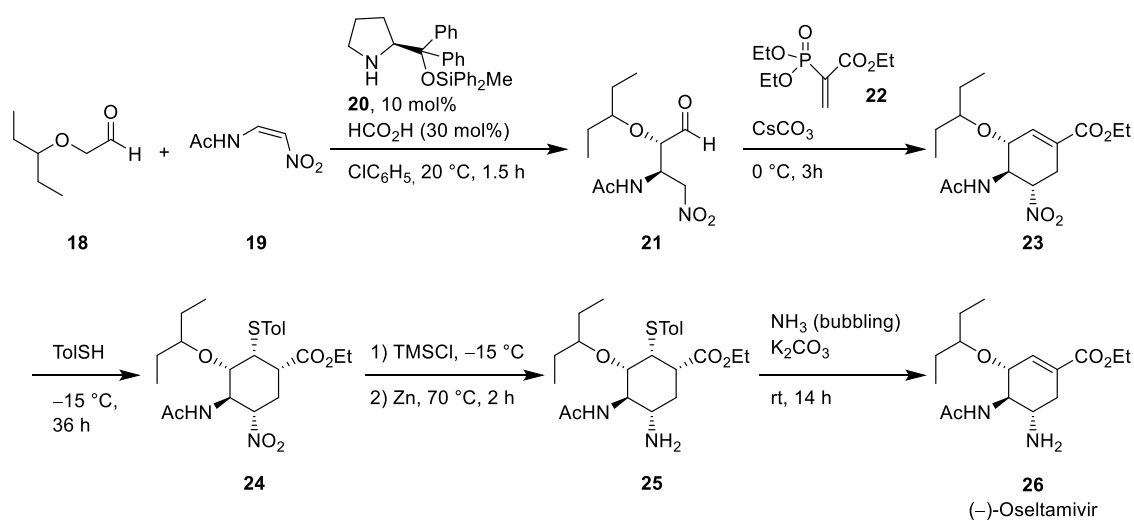
2 One-Pot Reactions

A one-pot reaction is defined, by its very name, as a reaction that is carried out in a single vessel. This, of course, includes “cascade”, “domino” and “tandem” reactions, but its definition is broader and is not confined to these.^[36]

The successive sequence of reactions within one pot, which is not interrupted by work-ups or purification steps, may bring a significant reduction in time effort and costs. However, the complexity of these successive reactions makes the planning and implementation more challenging and makes these key steps indispensable.

There are several restrictions which must be considered planning to transfer a multi-step synthesis towards a one-pot process. Starting with the type of reaction, which should not suffer from side reactions and give high yields. Moreover, all reagents have to be compatible with each other or have to be removed during the synthesis (e.g. distillation, quenching).^[36,37]

An example of a successful implementation of a multi-step synthesis in a one-pot process was reported by Hayashi (Scheme 4). His group realized the (-)-oseltamivir one-pot synthesis over six steps.^[38] Starting from (*Z*)-nitroalkene **19** in chlorobenzene, an enantioselective Michael addition was followed by an intramolecular Horner-Wadsworth-Emmons reaction.

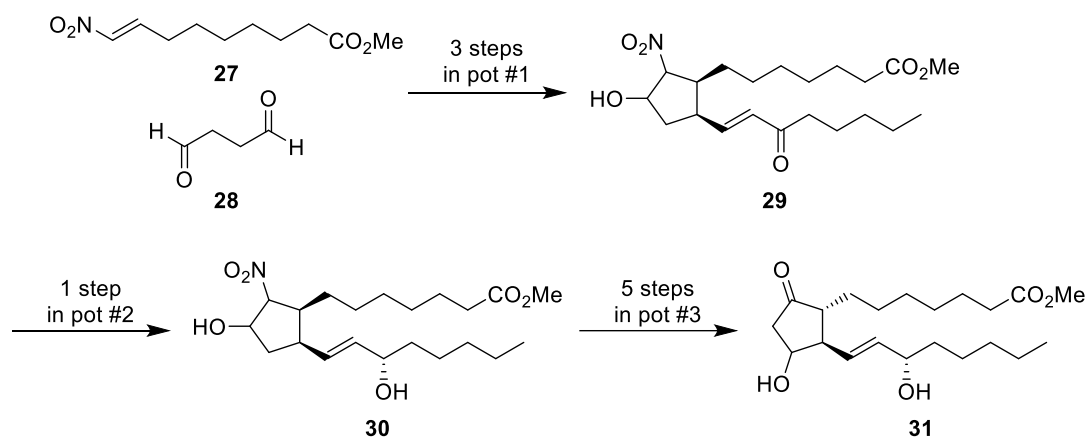


Scheme 4: One-pot synthesis of (-)-oseltamivir by Hayashi and co-workers.^[38]

The stereochemistry of the nitro group was controlled by the addition of toluenethiol, which was eliminated under basic conditions after the reduction of the nitro group. This one-pot method gave a total yield of 28% at a gram scale without the need for solvent exchanges or

evaporations, being competitive in yield with commercial or other reported routes.^[39] This work was the final outcome of enormous optimizations by multiple groups, which demonstrates the extent of the preliminary work required for one-pot processes.^[40–44]

A report of the synthesis of prostaglandins is another example of an one-pot reactions by the same group (Scheme 5).^[45] The synthesis includes a total of nine steps, split up in parts of three, one and five reactions, which then are carried out in one vessel.^[45]



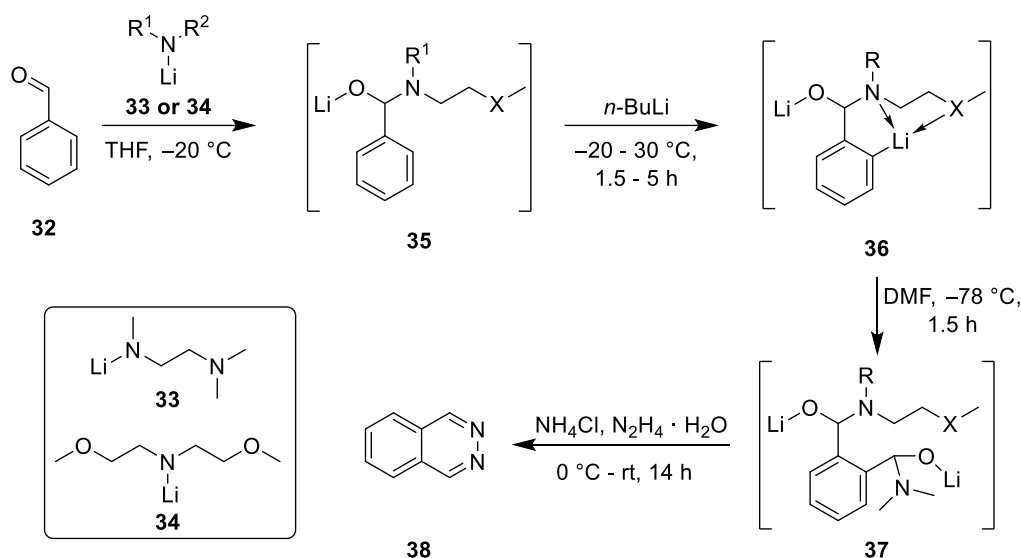
Scheme 5: One-pot approach towards the synthesis of prostaglandin **31** by Hayashi and co-worker.^[45]

The advantages of one-pot reactions were not only applied for APIs or natural products, but also in material science to access key-compounds in a shorter period of time with less preparative workload.^[36]

The previously mentioned phthalazines depict a common scaffold in biological active compounds.^[46,47] Moreover, they are a starting material for multiple reactions including the inverse electron demand Diels-Alder reactions,^[47–54] and used as ligands in the Sharpless asymmetric dihydroxylation.^[55] However, their synthesis, especially with specific substitution pattern, can be challenging.^[53]

The synthesis of phthalazine derivatives typically involves multistep procedures that conclude with ring-closing reactions, ring enlargement, cycloadditions, or aromatization of saturated precursors.^[56–59] In 1893, Gabriel et al. reported the first synthesis of phthalazine, which involved the ring-closing reaction of *ortho*-carbonylbenzaldehyde or 1,2-bis-dichloromethylbenzene with hydrazine.^[60,61] The ring closure of *ortho*-dicarbonyl compounds with hydrazine is still a common route^[62,63] for the preparation of phthalazines.^[62,63] All methods, however, are often preceded by many synthetic steps, depending on the degree of substitution of the formed phthalazine.

The one-pot approach by Kessler and Wegner uses (substituted) aromatic aldehydes as starting materials (Scheme 6).^[53] In the first step, the aldehyde was converted into a directed *ortho*-metalation group using different lithium amides. Next *n*-Butyllithium (*n*-BuLi) was added at $-20\text{ }^{\circ}\text{C}$ and warmed up to $30\text{ }^{\circ}\text{C}$. *N,N*-Dimethylformamide (DMF) was added to the *ortho*-lithiated species to generate *ortho*-bis(amino alkoxide) **37** at temperatures of $-78\text{ }^{\circ}\text{C}$ to $0\text{ }^{\circ}\text{C}$ and subsequent addition of hydrazine liberated the corresponding phthalazine. This method gives access to a broad range different phthalazines in yields of 36% - 91% and, moreover, reduces the time and workload drastically.^[53]

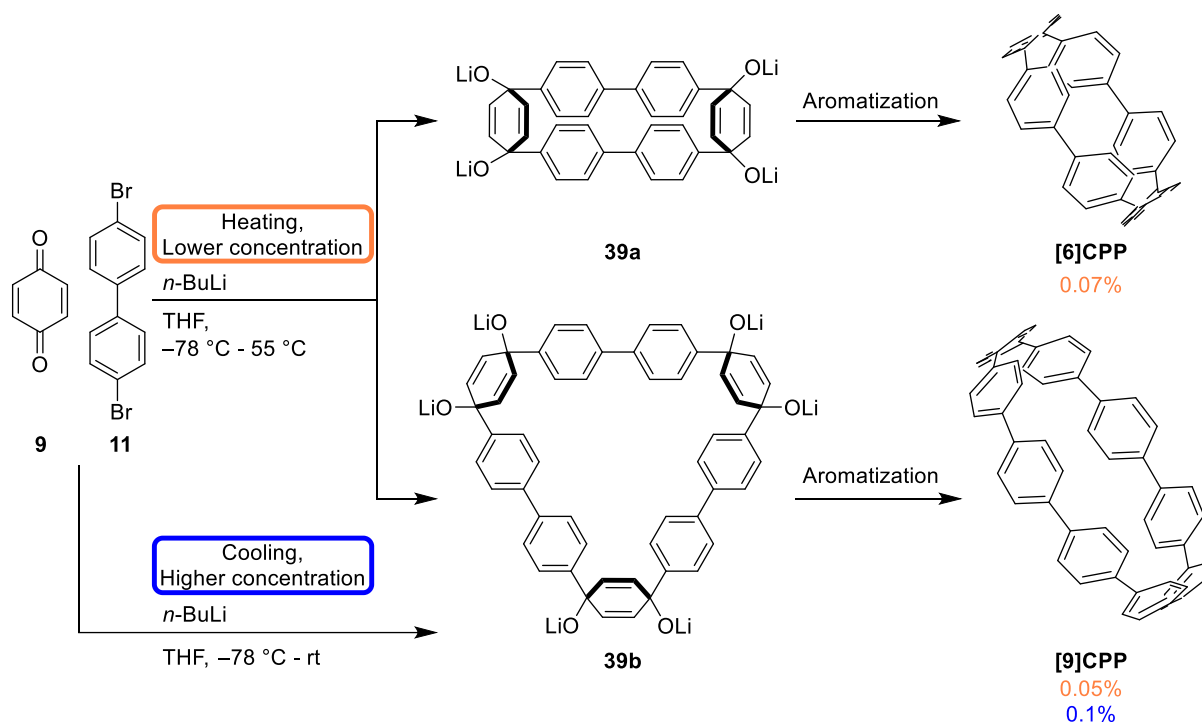


Scheme 6: One-pot synthesis of phthalazines by Wegner and co-workers.^[53]

By saving multiple steps, the one-pot approach towards phthalazines is a good example of the utility of a well-developed one-pot synthesis of an organic molecule, which can be used to obtain organic materials.

Driven by this motivation, we investigated a one-pot synthesis of different sized CPPs (Scheme 7).^[64] Especially in a scientific context where usually small quantities of a compound are required, the advantageous properties of CPPs are imbalanced with the synthetic effort.^[65–69] The reported work demonstrates the size selective synthesis of two different CPPs starting from *p*-benzoquinone **9** and dibromobiphenyl **11**.

After lithiation of dibromobiphenyl **11** with *n*-BuLi at $-78\text{ }^{\circ}\text{C}$, *p*-benzoquinone **9** was added as a solid. According to the targeted nanostructure, the reaction temperature was controlled.



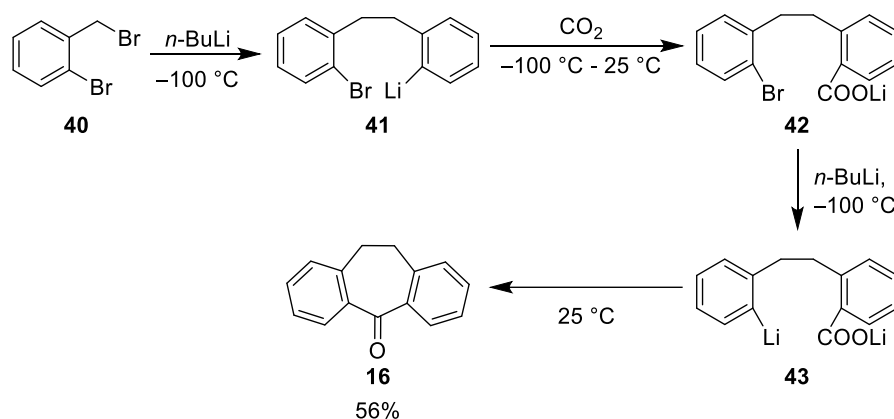
Scheme 7: One-pot synthesis of [6]CPP and [9]CPP starting from benzoquinone **9** and biphenyl **11**. Adapted from [64].

Depending on the reaction temperature, either [9]CPP (low temperatures, 0.1% yield) or [6]CPP (higher temperatures, 0.07% yield) were obtained (Scheme 7). With completion of the reaction time (5 - 24 h), a solution of SnCl_2 in concentrated aqueous HCl was added to aromatize the in-situ formed macrocycles. However, it was also to be expected that large quantities of linear by-products would be generated. Therefore, an effective purification method was developed. Using the low solubility of CPPs in alkanes, a Soxhlet extraction with *n*-pentane was executed to remove nonpolar by-products and starting materials. An additional extraction with toluene and two column chromatographic purifications enabled isolation of the pure CPP on a milligram-scale.

Despite the very low yield, the one-pot approach gives access to different sized CPPs in a single reaction step in just 2.5 days. Especially, if only small quantities are necessary for further studies, this method is very useful. Moreover, in the pursuit of sustainability, it must also be emphasized that this approach does not use any transition metals during synthesis. To further use the method for the synthesis of other ring sizes or substitution pattern, it is possible to use for example a terphenyl or higher substituted biphenyls as starting materials.

In this approach the reactivity of the formed lithiated biphenyl was controlled by the reaction temperature. The same was applied in the previously mentioned one-pot synthesis of dibenzosuberone **16**, which relies on lithium-halogen exchanges of compound **40** in the first

step (Scheme 8). To minimize the formation of side products, a temperature as low as $-100\text{ }^{\circ}\text{C}$ had to be applied. After a Wurtz reaction, the carboxylation using CO_2 was carried out at $-100\text{ }^{\circ}\text{C}$ to $25\text{ }^{\circ}\text{C}$ for 3 h. After a second addition of $n\text{-BuLi}$, the Perham-type cyclization occurred. The one-pot procedure was reported to give (substituted) dibenzosuberone in yields of (30% -) 56%, being suitable to access dibenzosuberone **16** at gram scale. Still, this synthesis is sensitive to higher temperatures and has a low scalability.^[31,35]



Scheme 8: One-pot synthesis of dibenzosuberone **16**.^[35]

3 Continuous Flow Chemistry

Based on the one-pot approach towards dibenzosuberone **16**, Kirschning and co-worker reported a continuous flow synthesis of amitriptyline **17**, having dibenzosuberone **16** as an intermediate (Figure 4).^[31] Starting from compound **40**, the temperature for lithiation and Wurtz reaction was first optimized. They reported the highest yield at $-50\text{ }^{\circ}\text{C}$ at a residence time of 5 s. To enable that short reaction times, rapid mixing was ensured using a narrow T-shaped mixer. Carbon dioxide was introduced at room temperature via a tube-in-tube reactor, followed by a gas removing unit. This reactor, developed by the Ley group, allows gas-liquid reactions without the formation of gas-bubbles.^[70] The final lithiation and Perham type cyclization took place at room temperature in a third reactor. After a total reaction time of 33 s, dibenzosuberone **16** was isolated in a yield of 76% with a throughput of 127 mg min^{-1} .

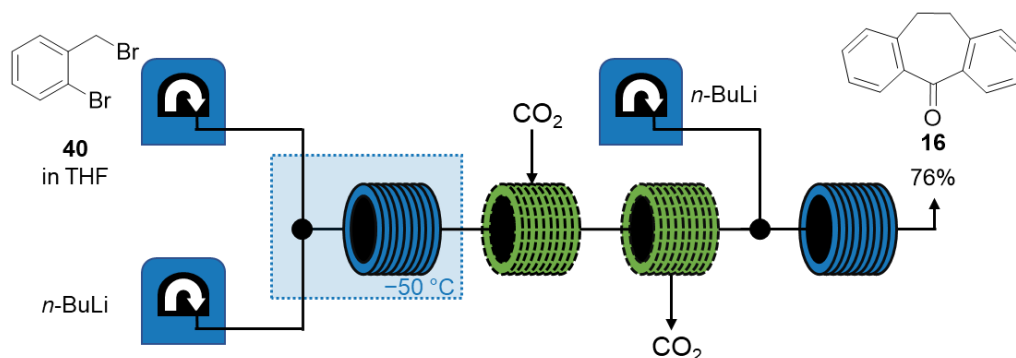


Figure 4: Continuous flow synthesis of dibenzosuberone **16** by the group of Kirschning.^[31]

Amitriptyline **17** was obtained after a Grignard addition and elimination in a second flow reactor in a yield of 71%.^[31] Compared with the one-pot procedure by Bradsher and co-workers, this continuous flow synthesis of **16** is superior in terms of yield and scalability.^[35] Moreover, it offers a higher practicability due to the increased temperatures and the fact that two reaction stages are even carried out at room temperature.

3.1 Advantages and Disadvantages of Continuous Flow Chemistry

The scalability of reactions incorporating reactive intermediates (e.g. aryl lithium compounds) in traditional batch reactors may be problematic. Cooling or heating a solution in a round bottom flask at large scales, is very inefficient and results in a large temperature gradient. Therefrom follows a broad energy distribution, which possibly leads to side reactions or decomposition.^[71]

Continuous flow chemistry may provide a solution to this issue. It involves pumping and mixing two or more reagents continuously, ensuring a constant concentration of reactants at any given point in the system. As a result, the reaction time is solely dependent on the flow rate of the pumped solutions or reactants and the volume of the reactor. Thus, changes in the total runtime of the system do not affect the reaction conditions or percentage yields. Easy scalability is possible by increasing the total reactor runtime and flow rate accordingly. The reaction itself primarily occurs in tubular reactors, which provide a high surface-to-volume ratio that benefits temperature control. This results in a sharper energy distribution and increased selectivity against competing reactions (Figure 5).^[71,72]

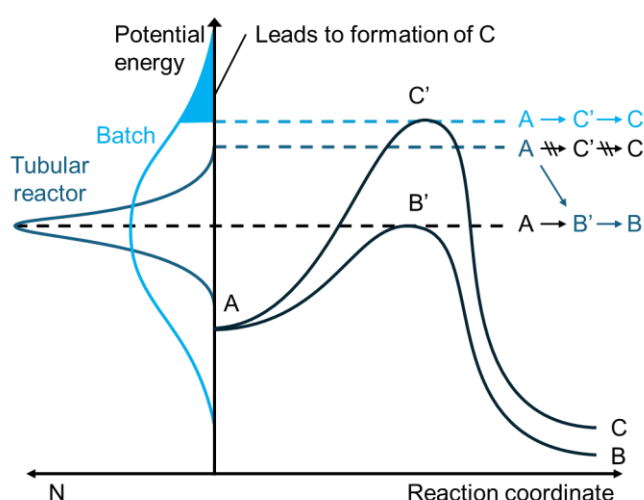


Figure 5: Schematic energy diagram of two competing reactions and the energy distribution within a batch (broad) and a tubular reactor (narrow). Adapted from [72].

In addition to the tubular reactors, there are chip and packed bed reactors (Figure 6). For low flow rates and a simple but inflexible set-up, a chip reactor can be used. Tube reactors offer better accessibility to reaction time and the possibility of higher flow rates. Both, chip and tube reactors allow photochemical reactions due to their construction from glass or transparent polymers such as fluorinated ethylene propylene (FEP) polymers. Implementing solid reagents into a flow chemistry system can be challenging, but one solution is to use a packed bed reactor. The solid is filled into a small pipe, which is then connected to the flow system, allowing dissolved reagents to react with the solid while passing through the packed bed reactor.^[71,73]

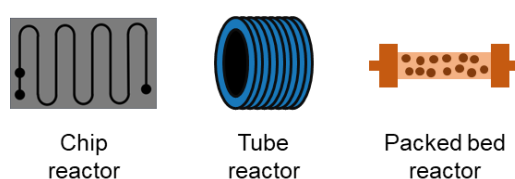


Figure 6: Schematic drawing of different flow reactor types.

If a solid reagent must be used in an exact stoichiometric ratio, it cannot be packed into a bed reactor, but has to be pumped as a solution or slurry. The latter can easily cause clogging of the reactor or mixers. However, there are reported procedures and special techniques to pump slurries without clogging, such as the use of peristaltic pumps or ultrasonic baths.^[74–77]

Another general downside of flow chemistry is the inevitable and time-consuming effort, to optimize the process. But these optimizations are worth the effort if a preparative production of a compound (class) is needed frequently. Another obstacle to use flow chemistry are the high costs associated with purchasing pumps and reactors.^[73,78]

Nevertheless, flow chemistry offers advantages that justify its use and compensates for all efforts. In contrast to reactions in flasks, reactive intermediates exist for a well-defined time and are not longer in contact with the starting material, as necessary. Instable reactive intermediates may be consumed by a consecutive reaction and are not exposed to the previous conditions any longer.^[71] Furthermore, it is in the nature of continuous flow chemistry that intermediates are only present within the reactor. This leads to increased safety, as no direct operator contact can occur, and only small quantities of the potentially hazardous substance exist at any one time.^[71,79]

A good example, to be mentioned, is the in-situ generation and reaction of diazomethane in continuous flow.^[80,81] Maggini and Woehl reported a modular continuous flow platform to

produce and use up-to 19 mol diazomethane per day, while limiting the amount of diazomethane in the reactor to 6.5 mmol at a time.^[81] This opens up the way towards large scale processes in chemical or pharmaceutical industries.^[78,82]

The precisely defined reaction times allow the use of other reaction conditions, compared to batch reactions. For example, the short residence time of 5 seconds of the lithiated species during the synthesis of dibenzosuberone **16** (Figure 4) should be highlighted here.^[31,83] By that short reaction time, side reactions or decomposition do not occur even at temperatures which are 50 °C higher compared to the reported batch synthesis.^[31,35] Less cooling or heating leads to lower energy consumption. This is one important aspect and especially the chemical industry is using flow chemistry for this reason.^[78] Additionally, as they need to produce specific reagents and commodities all the time, flow chemistry is the method of choice in some cases. Due to the lack of available flow chemistry equipment in laboratory scale, the research was often disconnected from process chemistry. As this is no longer the case, flow chemistry is undergoing a renaissance in recent years, and it was stated that ~50% of the reactions in chemical industry could benefit from flow chemistry.^[84–86]

3.2 Continuous Flow Synthesis of Organic Materials

The high investment costs and perceived complexity has led to a slow growth of the number of academic researchers, working with flow chemistry.^[73] Due to this, only few examples of continuous flow syntheses of novel organic molecules are reported in literature.^[87–90]

One prominent example is the continuous flow-assisted synthesis of [10]CPP by Kim and co-workers.^[91] The synthesis follows the concept of the approach reported by the group of Itami in 2009, based on cyclohexane-incorporated macrocycles.^[27] The first part of the synthesis is the mono-lithiation of dibromobenzene **14** by *n*-BuLi followed by the addition to 1,4-cyclohexandione (**10**, Figure 7). The formed alcoholate is protected as a methoxymethyl

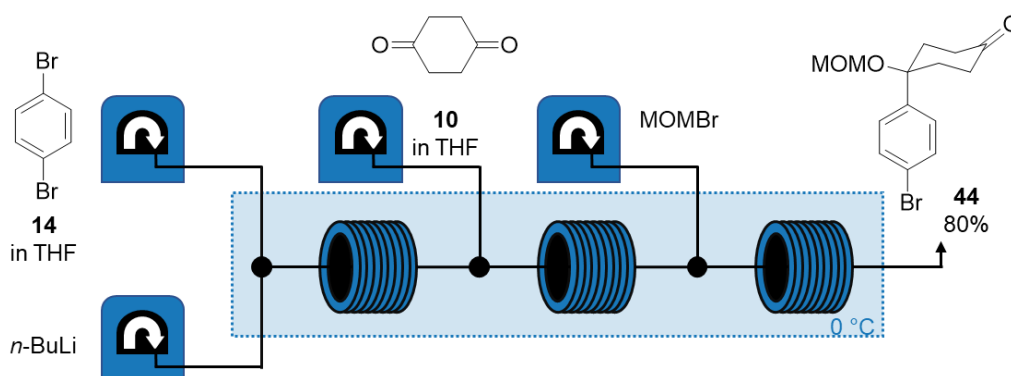


Figure 7: Continuous flow synthesis of CPP building block **44**.^[91]

(MOM) ether by the addition of MOMBr and stirring in a flask for additional 4 h. The ketone **44** was obtained in 80% yield and used in the second reactor stage. The reduced cooling to 0 °C, is a great advantage compared to the usual -78 °C used in batch lithiations.^[27]

The continuous flow synthesis of the U-shaped building block **45** was realized by the double-lithiation of dibromobenzene **14** using *tert*-butyllithium followed by a twofold addition of the previously synthesized ketone **44** at 25 °C (Figure 8). After MOMBr addition and stirring in a vial for 6 h, MOM protected U-shaped building block **45** was obtained in 68% yield (7.7 g/h). The last two synthetic steps toward [10]CPP were conducted using batch reactions. With an overall yield of 11%, the synthesis offers access to [10]CPP without the need for cryogenic cooling.^[91]

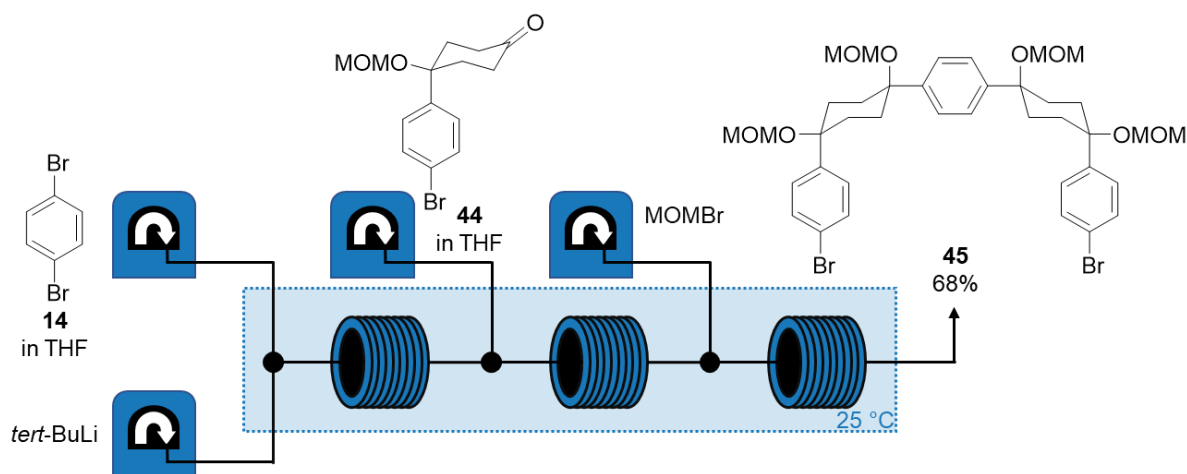
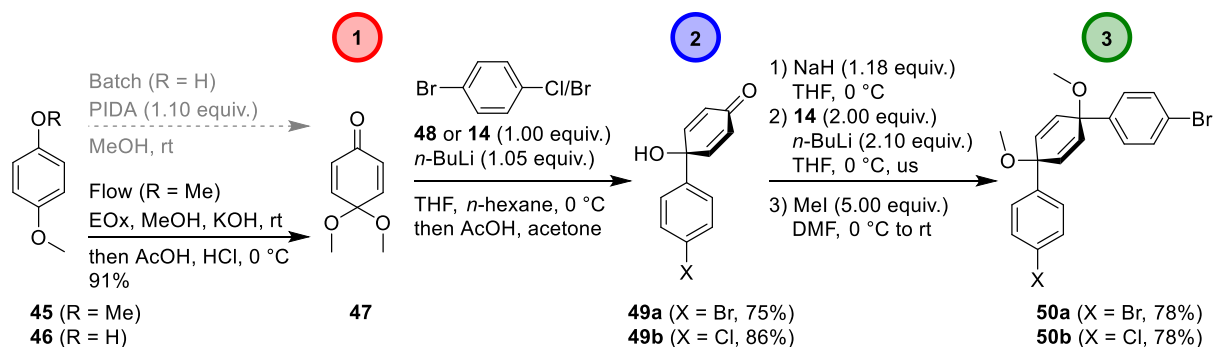


Figure 8: Continuous flow synthesis of CPP building block **45**.^[91]

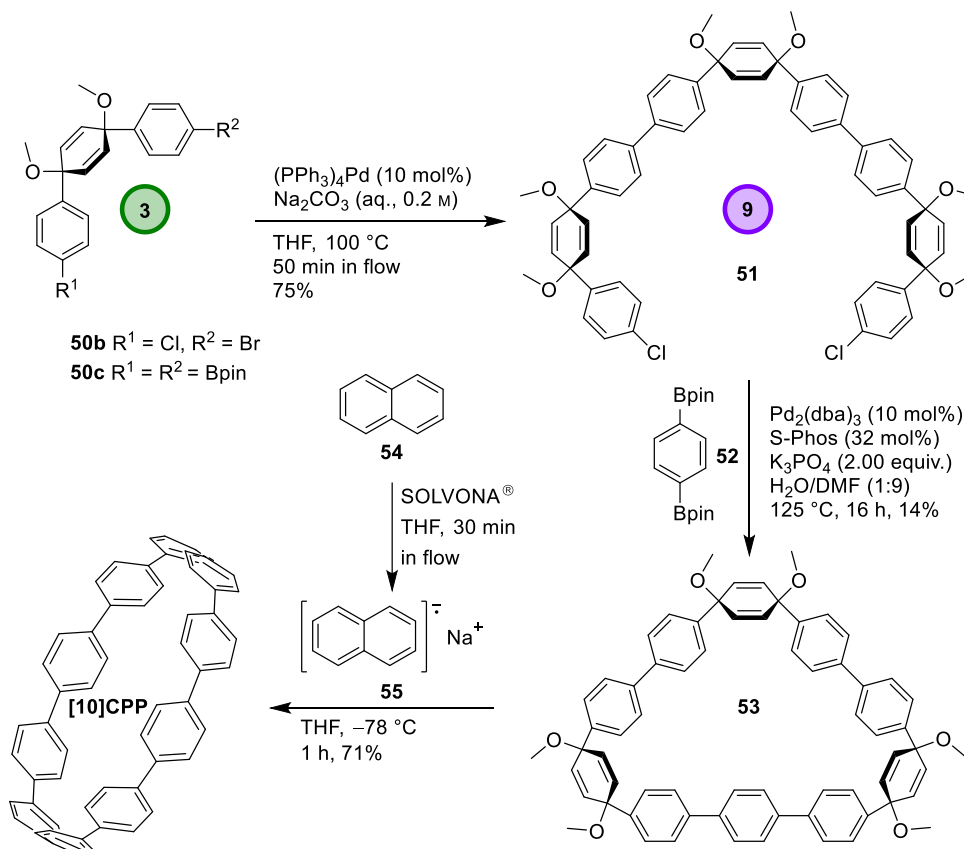
This synthetic approach via cyclohexane suffers from lower yields for aromatization to the corresponding CPP.^[92–94] Therefore, this approach has not been widely used recently. Moreover, unsubstituted CPPs are limited in their applications. As a result, a growing field of substituted cycloparaphenylenes or hybrid CPPs has been developed. Multiple of their syntheses are based on the same or analogous building blocks.^[21,95] An efficient and fast access to these building blocks would facilitate the synthesis of these nano hoops and their application. Inspired by this circumstance, we have developed self-built flow reactors and optimized a continuous synthesis of CPP building blocks, analogous to the work of Jasti's group (Scheme 9).^[21,96]

The ketone **47** is usually obtained by oxidation of 4-hydroxyanisole (**46**) with (diacetoxyiodo)-benzene (PIDA). However, the purification process is challenging, due to iodobenzene, which is formed as a side product. An electrochemical oxidation of anisole **45** was developed in a continuous flow cell, providing acetal **47** in high yields and purity. The 2- and 3- membered



Scheme 9: Building Block approach realized in continuous flow. Adapted from [96].

building blocks were synthesized in separate flow reactors. Analogous to previously reported procedures, the lithium-halogen exchanges gave quantitative conversions at temperatures as high as 0 °C and a reaction time of 1.6 s. As the high temperature allowed higher concentrations of all reagents, *n*-BuLi (1.6 M in hexanes) was used directly of the commercial bottle. Both, less cooling and higher concentrations, in line with high yields ensure a great scalability. Syntheses at scales of 100 g (larger building blocks) to a kilogram were realized. Those building blocks were combined to an even larger 9-membered building block **51** via a continuous flow Suzuki coupling (Scheme 10). In contrast to the reported batch procedure, no column chromatography was necessary.^[21,96] All of the synthesized building blocks can be used to access different sized and functionalized CPPs.^[21,26,95–100]



Scheme 10: Combination of 3-membered building blocks towards larger and macrocyclic precursors and their final aromatization to obtain [10]CPP.^[96]

Furthermore, a packed bed reactor for the synthesis of sodium naphthalenide **55** was developed. Usually, the generation of sodium naphthalenide **55** is a labor-intensive and time-consuming process.^[23] By pumping solution of naphthalene **54** in THF through the reactor, filled with a sodium coated molecular sieve (SOLVONA[®]), gave sodium naphthalenide **55** in constant concentrations within 30 minutes. To demonstrate the usability of the method, a 10-membered macrocycle **53** was synthesized by combination of the building blocks. This macrocycle was aromatized using in-flow generated sodium naphthalenide **55** in 71% yield.^[96]

The purpose of building a stock of CPP building blocks is to save time during synthesis of (novel) nano hoops. Moreover, the continuous flow setup for synthesizing sodium naphthalenide is particularly useful for handling a reactive intermediate in a safe and convenient manner.

3.3 Reactive Intermediates in Continuous Flow

Continuous flow chemistry is a versatile tool for handling reactive intermediates. The already mentioned diazomethane synthesis and sodium naphthalenide preparation are just two examples. The reactor provides an enclosed space wherein a small amount of the species is formed but also separated from the environment.^[80,101]

Azides display a potential risk during the synthesis of (-)-oseltamivir. Therefore, many synthetic routes avoid those explosive intermediates during the process. One example is the continuous flow synthesis of (-)-oseltamivir by Ogasawara and Hayashi (Figure 9).^[102] The

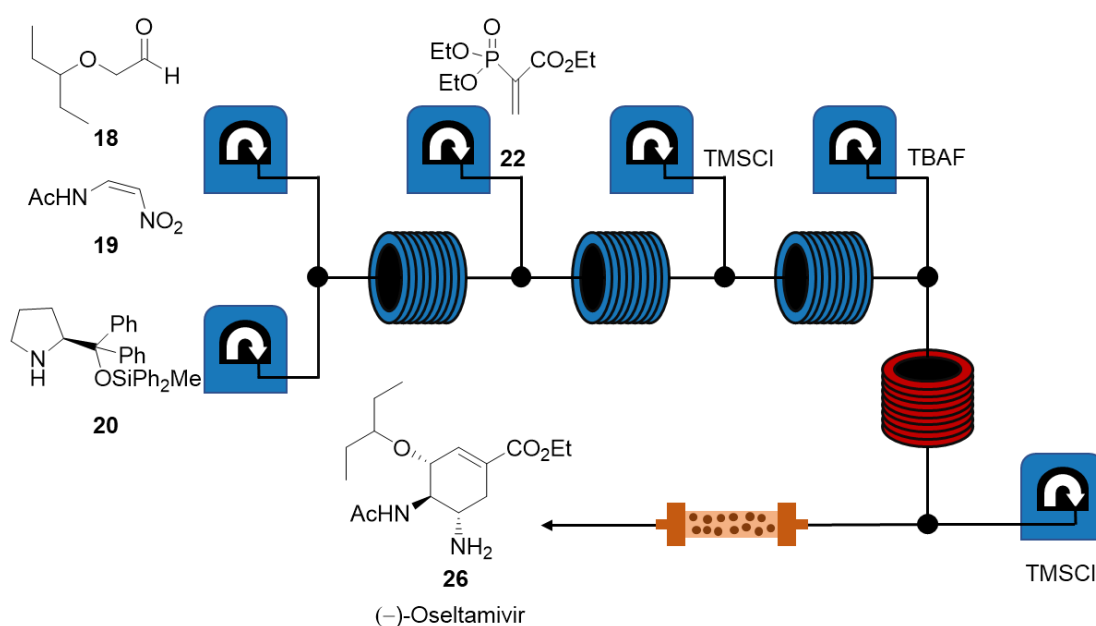


Figure 9: Continuous flow synthesis of (-)-Oseltamivir by Hayashi and co-worker.^[102]

synthesis is based on their previously reported one-pot approach.^[38] Oseltamivir was obtained in a yield of 13% after a total residence time of 310 minutes through a single flow procedure. However, the throughput of 3.7 mg per hour is insufficient for an industrial use.^[102,103]

In 2020, Watts and co-worker reported a semi-telescoped flow synthesis of (–)-oseltamivir based on azide intermediates (Figure 10).^[103] Starting from mesylated shikimic acid ethylester **56**, azidation agents were screened. Aqueous sodium azide was most efficient, but not suitable for a telescoped process. Therefore, water-free conditions using diphenylphosphoryl azide (DPPA) in acetonitrile were applied, enabling the in-situ formation and consumption of azide **57**. The drawback of this telescoped approach are higher reagent costs and lower yields. Nevertheless, even carrying out a consecutive reaction of azides in a small continuous flow reactor, increases the process safety. Isolated azide **57** undergoes formation of hazardous aziridine **58**, which was consumed in-situ towards a 3-pentyl ether **59**. The formed phosphoramidate was cleaved and the amine acetylated in two separate continuous flow reactors. A second azide formation was conducted using aqueous sodium azide. (–)-Oseltamivir phosphate **2** was obtained after reduction and salt formation in an overall yield of 48-54% in only 3.5 min total residence time.^[103]

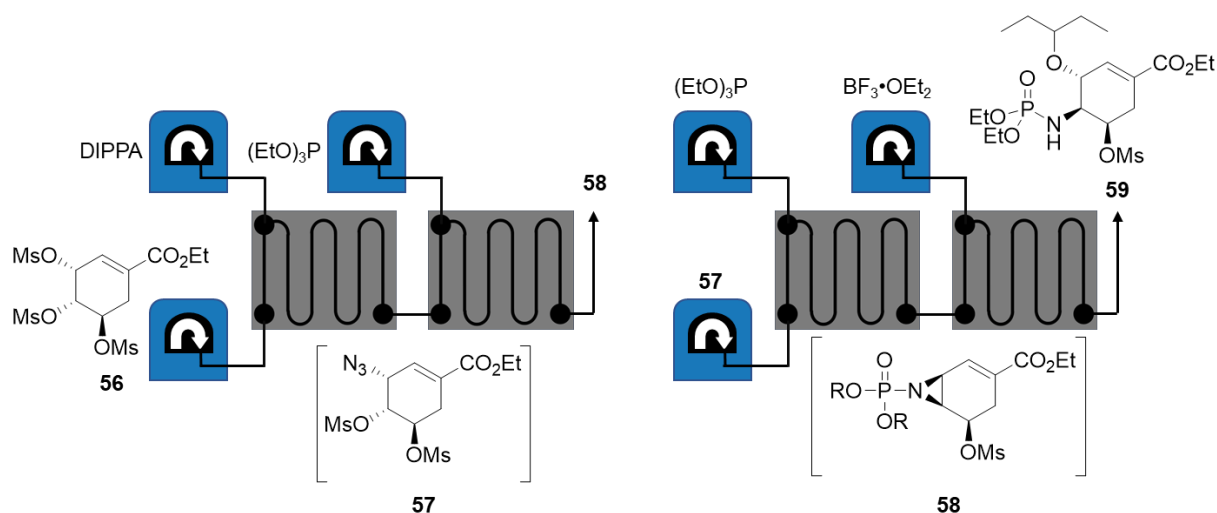


Figure 10: Continuous flow synthesis of azide intermediates by Watts and co-worker.^[103]

Another poisonous and also thermally instable compound class are diazonium salts.^[101,104] De Mello's group developed one of the earliest examples of in-situ generation and use of reactive diazonium salts in an azo coupling. They reported the continuous diazotation of aniline (**60**) with sodium nitrite in a microchip reactor (Figure 11). The generated diazonium chloride **61** was then immediately mixed with a basic solution of β -naphthol **62** in a second reactor to obtain an azobenzene derivative (**63**, Sudan I dye) with a yield of 52%.^[105]

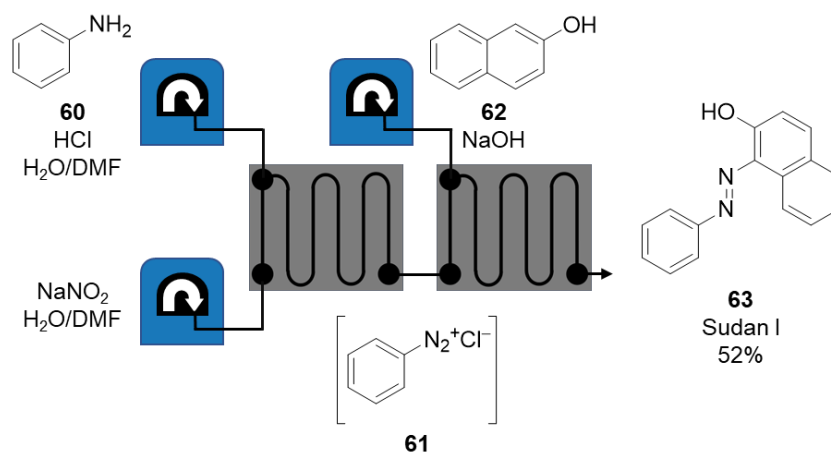


Figure 11: Continuous flow synthesis of Sudan I dye **62** starting from aniline **59**.^[105]

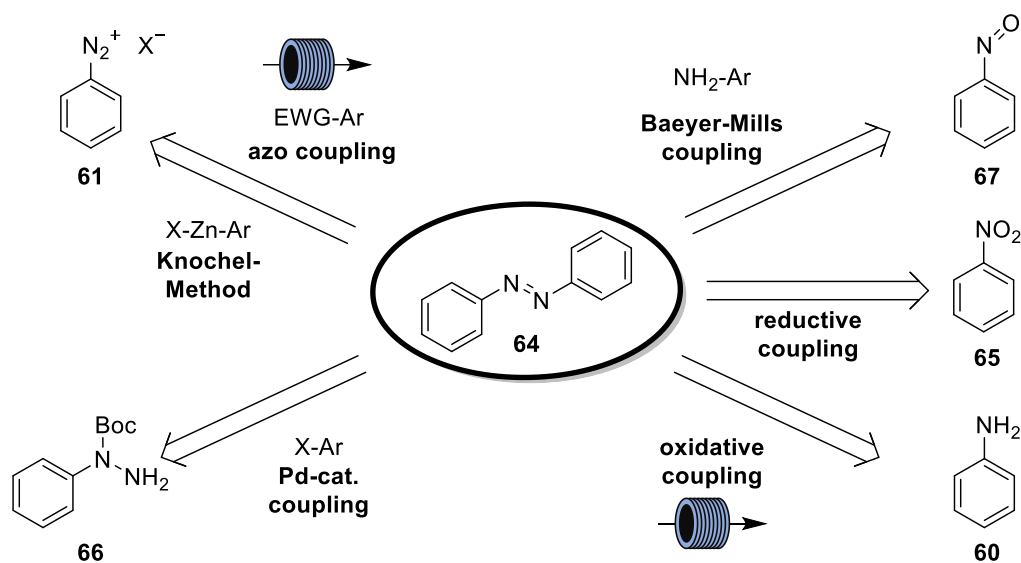
3.4 Azobenzene Synthesis

Azobenzenes (ABs) were originally known primarily for their use as dyes and even as food colorants.^[106–108] They have experienced a significant surge in popularity due to their versatile applications as molecular switches in recent years.^[109–111] These switches can (potential) be used in energy and information storage,^[112–118] organocatalysis,^[119] photobiology and photopharmacology^[120] to soft robotics^[121,122] and molecular machines.^[123] Most of these applications are primarily based on their isomerization capability, which allows reversible conversion between the energetically stable (*E*)-configuration and the metastable (*Z*)-isomer upon exposure to light, thermal or chemical stimuli.^[124,125] Apart of their change in molecular geometry, from an extended planar (*E*)-AB to a twisted (*Z*)-AB, they also alter their physical properties, including dipole moment and polarity during isomerization.^[126,127]

As the AB properties are influenced by substitution, strategies to access various patterns and degrees of substitution are essential for their application. When designing the target compound, a wide range of methods can be chosen from, and the optimal synthesis method must be carefully selected (Scheme 11).^[128,129]

Symmetric ABs are characterized by identical substitutions on both phenyl units. They can be accessed by dimerization. For example, oxidative or reductive coupling can be used, in which

two anilines or nitro-substituted aryl compounds are used as starting materials.^[129–134] Although these strategies can be used for the synthesis of non-symmetric ABs, a reduction in yield is expected due to the potentially coupling toward symmetric compounds.



Scheme 11: Synthetic routes towards symmetric and non-symmetric AB derivatives.

Other couplings are capable for synthesizing both non-symmetric and symmetric substituted AB derivatives. These reactions can be achieved through various methods, such as the Knochel method, which involves the reaction between diheteroaryl zinc and aryl diazonium salts,^[135,136] or Pd-catalyzed couplings of aryl halides with hydrazines followed by oxidation.^[137] The conventional method for AB synthesis involves the azo coupling of diazonium salts with electron-rich aromatic nucleophiles as already mentioned before. This substitution occurs in the *para* or *ortho* position, which limits the accessible patterns.^[105,138]

A condensation of a nitrosobenzene (**67**) with an aniline (**60**) to form a symmetric or non-symmetric AB (**64**) is called Baeyer-Mills reaction. Although first published by Baeyer in 1874,^[139] Mills subsequently carried out a more detailed investigation of this reaction.^[140] The resulting ABs are formed by the nucleophilic attack of aniline on nitrosobenzene under acidic or basic conditions, thus best results are observed when using electron-poor nitrosobenzenes with electron-rich anilines.^[141,142] Nitrosobenzenes, which are essential in this reaction, can be easily accessed by oxidation of anilines with agents such as hydrogen peroxide, *meta*-chloroperbenzoic acid, or OXONE®.^[143] The latter one tolerates a variety of functional groups and is environmental friendly.^[144]

As ABs are investigated as functional organic materials, it is crucial that the potential compounds are not only accessible on a large scale but can also be synthesized fast and efficiently.^[15,145–151] To circumvent the challenges associated with large scale batch synthesis, flow synthesis is proving to be a viable alternative.

Besides the already mentioned azo coupling in continuous flow, there are reports of a continuous flow oxidative coupling of anilines using copper reagents.^[130,152,153] The first example uses a packed bed reactor filled with copper powder (Figure 12).^[152]

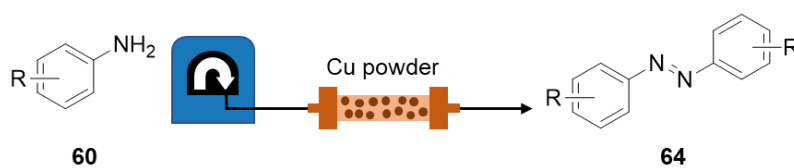


Figure 12: Continuous flow synthesis of symmetric ABs using Cu powder.^[152]

The homocoupling of multiple aniline derivatives was screened. The method was demonstrated to give high yields for electron-rich alkyl- or methoxy-substituted starting materials. Halides, especially *ortho*-substituted, gave moderate to poor yields. Probably, not Cu⁰, but Cu(I) or Cu(II) traces on the surface will catalyze the reaction.^[130,152] Therefore, the reaction may lack in scalability and reproducibility.

This circumstance can be avoided by using a copper(I) salt. The group around Fang and Guo reported a continuous flow synthesis of azobenzene compounds catalyzed by previously prepared CuBr (Figure 13).^[153] In the first step, copper(II)sulfate was reduced to obtain reactive copper(I)bromide. After washing with water and ethanol, the prepared packed bed reactor was used in the second step. A solution of aniline **60** and pyridine in toluene was pumped through a tube-in-tube reactor to introduce dioxygen into the solution. Afterwards,

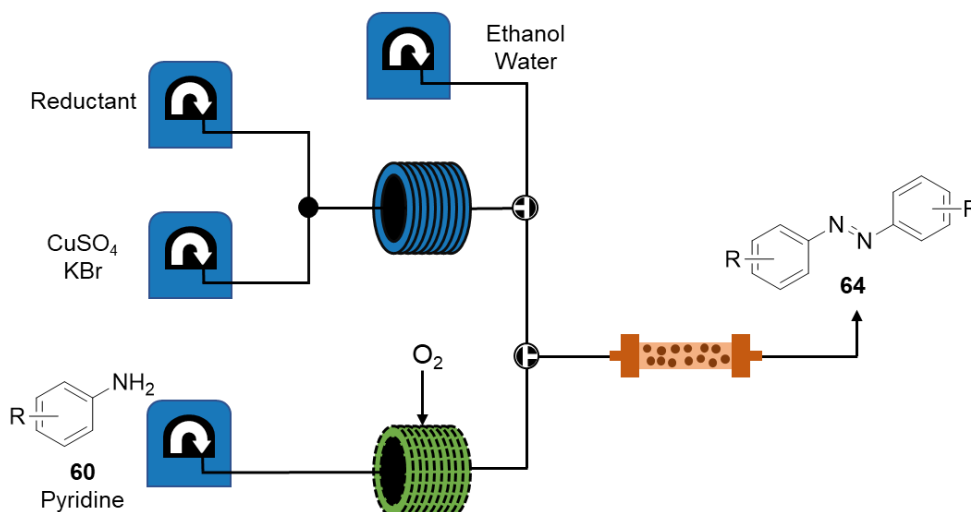


Figure 13: Continuous flow synthesis of CuBr and subsequent synthesis of AB derivatives by Qin and co-workers.^[153]

the solution passes through the packed bed reactor. This method was suitable for the synthesis of different symmetric ABs. Anilines with electron-donating groups performed best, while nitro-substituted (electron-withdrawing) ABs could not be obtained with this route.^[153]

To control the substitution pattern of both phenyl rings, a continuous flow Baeyer-Mills reaction was targeted by our group. A preliminary study focused on the coupling of substituted anilines with parent nitrosobenzene (**67**).^[154] Therefore, temperature and residence time were optimized for the synthesis of unsubstituted AB **64**. To speed up the working procedure, cyclohexane was added in a second mixer after the tube reactor. By this, azobenzene **64** was obtained in a reasonable purity after separation of the organic layer and solvent removal (Figure 14).^[154]

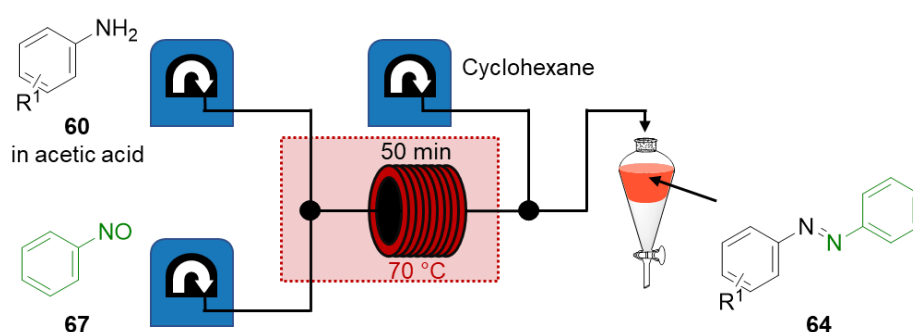


Figure 14: Continuous flow synthesis of non-symmetric ABs via Baeyer-Mills reaction. Adapted from [154].

Using the optimized conditions of 50 minutes reaction time at 70 °C, a scope of more than 20 different substituted ABs was synthesized. Electron-rich anilines delivered good to excellent yields. Furthermore, a large-scale synthesis (72 g in 3 days) of a liquid AB used for molecular solar thermal energy storage (MOST) was demonstrated. In most of the presented examples, there was no need for further purification. However, the method is not suitable for the synthesis of ABs starting from electron-poor anilines.^[154]

To extend the accessible AB scope, in a follow-up study substituted nitrosobenzenes were applied. As some nitrosobenzene derivatives are prone to oxidation and are not stable at ambient conditions, an in-situ preparation of substituted nitrosobenzenes was developed. Using a biphasic oxidation with OXONE®, multiple anilines were efficiently oxidized to their nitroso analogues. By an in-line phase separator (Zaiput SEP-10), the aqueous phase was removed and the organic phase, containing the target compound was analyzed by an in-line IR-spectrometer (Mettler Toledo ReactIR 702L) before being applied to the subsequent Baeyer-Mills reaction (Figure 15).^[155]

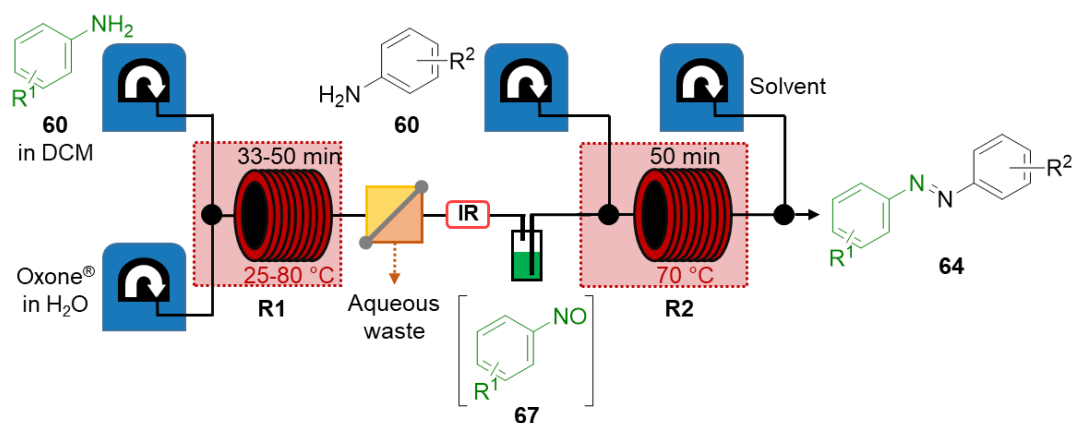


Figure 15: In-situ oxidation and coupling of anilines towards non-symmetric ABs using flow chemistry. Adapted from [155].

The telescoped Baeyer-Mills reaction gave access to multiple ABs in moderate to high yields. Electron rich substituted anilines (e.g. alkyl-, methoxy-substituted) provided, as expected, only moderate yields and underwent over-oxidation to their nitro-analogues at elevated temperatures during the nitrosobenzene formation (reactor R1). The process offers a modular and time-saving alternative to the synthesis of azobenzene derivatives, as the selection of anilines for nitroso synthesis can be conveniently changed according to their reactivity with the desired substrate. This method has proven to be suitable for the synthesis of highly substituted non-symmetric ABs.^[155] Additionally, this technique provides a safer access to different hazardous nitrosobenzenes and can also be used in a variety of other transformations apart from AB synthesis.^[156]

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4 Contributions to the Literature

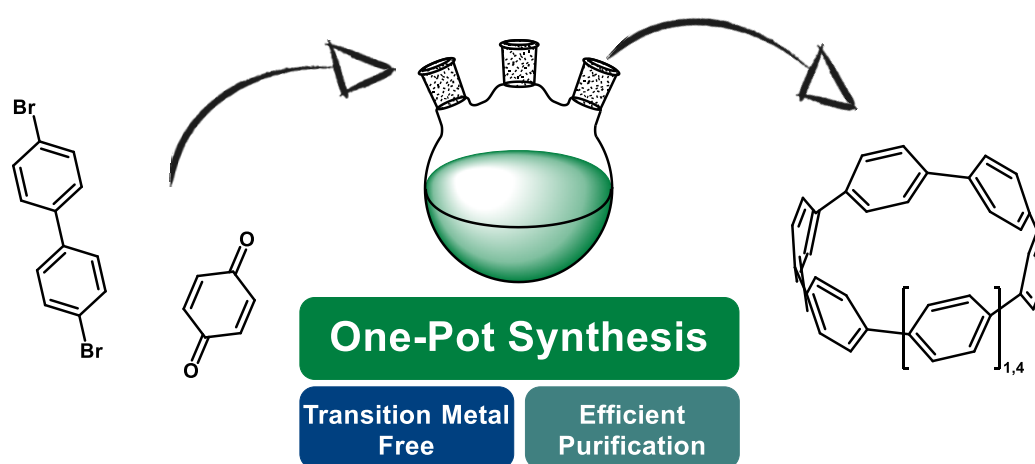
4.1 One-Pot Synthesis of Cycloparaphenylenes

Reference: J. H. Griwatz, H. A. Wegner, *Organic Materials* **2020**, *02*, 306.

DOI: 10.1055/s-0040-1721082

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Organic Materials published by Thieme.



“The preparation of cycloparaphenylenes ($[n]$ CPPs) with their bent π -system poses a long-standing challenge in organic synthesis. In the current multi-step approaches to access CPPs, pre-angulated precursors were combined using transition metal-catalysed or mediated coupling reactions. Therefore, there is a long way to the realisation of the idea of an ‘*ideal synthesis*’. An easy and efficient synthesis of different $[n]$ CPPs would represent a breakthrough, also pushing their incorporation into organic materials. By combining multiple steps in a one-pot approach, the overall time and workload can be drastically shortened. Herein, we present the application of this concept for the preparation of **[6]** and **[9]CPP** as a simple and fast alternative to current methods. By tuning the reaction conditions the selective synthesis of both **[6]** and **[9]CPP** was demonstrated.”

One-Pot Synthesis of Cycloparaphenylenes

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Received: 31.08.2020

Accepted after revision: 29.09.2020

DOI: 10.1055/s-0040-1721082; Art ID: om-20-00290a

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Abstract The preparation of cycloparaphenylenes ($[n]$ CPPs) with their bent π -system poses a long-standing challenge in organic synthesis. In the current multi-step approaches to access CPPs, pre-angled precursors were combined using transition metal-catalysed or mediated coupling reactions. Therefore, there is a long way to the realisation of the idea of an ‘ideal synthesis’. An easy and efficient synthesis of different $[n]$ CPPs would represent a breakthrough, also pushing their incorporation into organic materials. By combining multiple steps in a one-pot approach, the overall time and workload can be drastically shortened. Herein, we present the application of this concept for the preparation of **[6]** and **[9]CPP** as a simple and fast alternative to current methods. By tuning the reaction conditions the selective synthesis of both **[6]** and **[9]CPP** was demonstrated.

Key words cycloparaphenylenes, nanorings, organic synthesis, transition metal-free, carbon allotropes, macrocyclisation

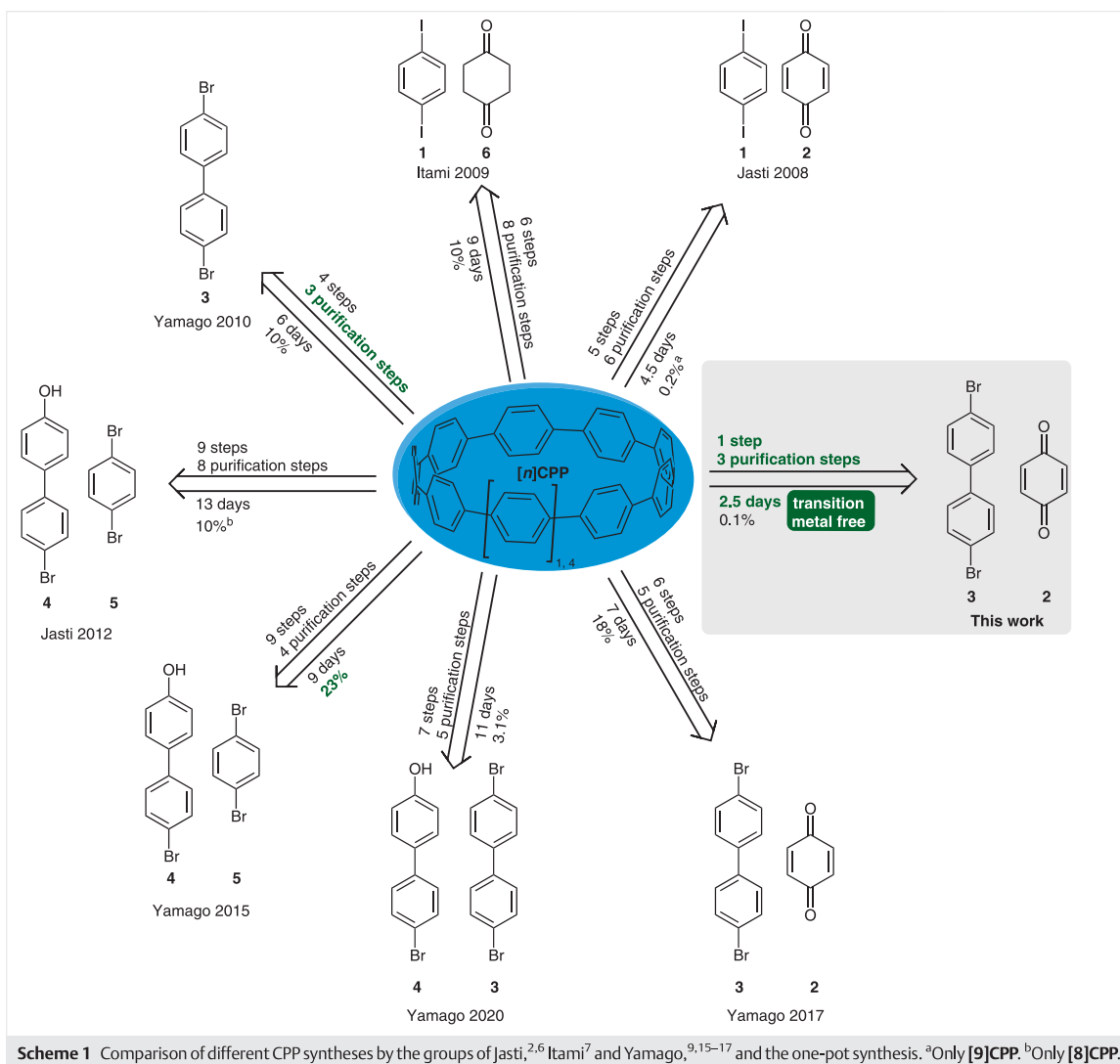
Introduction

The preparation of complex structures, starting from sustainable materials, in 100% yield – the ‘ideal synthesis’ – is every chemist’s dream.¹ The concept is mostly discussed in the context of natural products’ synthesis. However, there are also highly elaborate compounds beyond natural resources, which in no regards rank behind total syntheses of natural products in terms of number of steps, complexity and synthetic challenges. One example in this respect is the class of $[n]$ cycloparaphenylenes ($[n]$ CPPs). These nano hoops consist of *para*-connected benzene rings in a cyclic arrangement resulting in considerable strain due to the bending of the phenyl units. CPPs represent the conceivably shortest segment of an armchair carbon nanotube.^{2,3} Early

on, the unique geometry of CPPs has attracted the creativity of organic chemists. Already in the 1980s, Vögtle proposed a synthetic strategy using pre-angled building blocks, however, without being able to succeed in its achievement.⁴ It lasted until 2008, when Jasti and Bertozzi realized Vögtle’s concept in the first synthesis of **[9]**, **[12]** and **[18]CPP** (Scheme 1).² Their approach relies on a statistical palladium-catalysed Suzuki macrocyclisation followed by reductive aromatisation using lithium naphthalenide. In the following years, several syntheses based on similar methodologies were reported.^{5,6} Itami’s strategy relying on a cyclohexanedione moiety as angular building blocks offers a selective access to a variety of different-sized CPPs.^{7,8} However, it suffers from harsh oxidative aromatisation conditions, which are only practicable on smaller scales.⁷ The group of Yamago reported a different approach for the first time in 2010.^{9,10} They made use of the formation of a stoichiometric Pt-complex to access an unstrained square-shaped macrocycle ultimately leading to a CPP in only four steps. Another approach based on stoichiometric transition metal complexes was reported by Osakada and co-workers. By using a gold complex, they obtained **[6]CPP** in good yields.¹¹ Various strategies were reported in the due course to obtain also substituted CPPs using $[2 + 2 + 2]$ ¹² or Diels–Alder cycloadditions.¹³ All approaches are limited to specific substitution patterns, though.

The necessity to access CPPs in a convenient and efficient way was recognised early on. Hence, some of these syntheses have been optimised to a large scale. However, most of the drawbacks of the initial attempts could not be overcome. Yamago’s large-scale syntheses of **[5]**,¹⁴ **[6]**,¹⁵ **[8]**¹⁶ and **[10]CPP**¹⁷ offer high overall yields, but are still based on stoichiometric amounts of transition metals (Scheme 1). The modular gram-scale synthesis of **[8]** and **[10]CPP** by Jasti and co-workers requires multiple steps including protection and deprotection. These time-consuming steps increase the total synthesis duration to almost 2 weeks.⁶

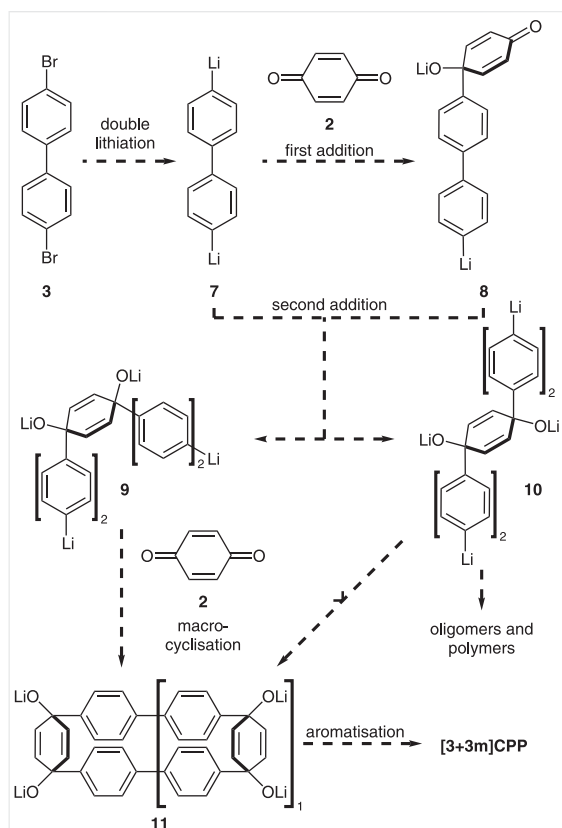
All preparations of CPPs mentioned in this article do not even remotely touch the idea of an ‘ideal synthesis’,¹ in terms of number of steps, the need for protection groups or the utilisation of large amounts of expensive reagents or



starting materials. The combination of multiple steps in a one-pot procedure would offer the possibility to drastically shorten the overall time and workload. The design of such a one-pot synthesis bears the challenge to ensure the compatibility of all reagents and intermediates. The application of the concept to CPPs has to combine firstly the formation of a less strained macrocyclic precursor and secondly the difficult aromatisation. Starting from cheap starting materials (<0.2 \$/g)¹⁸ in combination with an easy and non-labour-intensive purification, we herein report a fast and simple method to access different-sized CPPs. Furthermore, our method is the first example of a transition metal-free synthesis of CPPs.

Results and Discussion

The consecutive addition of a biphenyl building block to benzoquinone analogous to Yamago's gram-scale synthesis should provide the first intermediate.¹⁷ If this precursor is lithiated again at the terminal positions, a successive addition to another quinone will be possible (Scheme 2). However, here multiple problems arise: the double addition to benzoquinone could occur from either the same or different sides leading to the *syn*- or the *anti*-adduct. If the addition happens only once in the undesired *anti*-fashion, it will inevitably end up with oligomers or polymers. The ratio of *syn*- and *anti*-attack is reported to be around 95:5 and the



Scheme 2 Synthetic strategy towards a one-pot CPP synthesis.

yield of the double addition is about 77%.^{17,19,20} Another pitfall is the intramolecular macrocyclisation, which is entropically inherently disfavoured. Even if all steps are proceeded according to plan, the final aromatisation has to work without interaction with previously used reagents or intermediates. In spite of all these challenges, we initiated the development of a one-pot synthesis of CPPs, as a success would be of high value.

In the first attempt, biphenyl **3** was dilithiated by 2 equivalents of *n*-butyllithium (*n*-BuLi) at $-78\text{ }^{\circ}\text{C}$ similarly to the procedure reported by Yamago (Table 1, entry 1).¹⁴ To this slurry, a solution of benzoquinone **2** was added. The mixture was warmed up to $-40\text{ }^{\circ}\text{C}$ over 30 min. To ensure a complete conversion of the arylhalide, the excess of *n*-BuLi was increased further and 1 equivalent of quinone **2** was added. The reaction mixture was quenched with an aqueous solution of tin(II) chloride dihydrate and hydrochloric acid to aromatised the proposed macrocyclic intermediate. After extraction with dichloromethane and purification by column chromatography, crude **[9]CPP** was obtained. After performing gel permeation chromatography (GPC) using chloroform as the eluent, gratefully **[9]CPP** was obtained in 0.1% yield (5.1 mg). This is the first example of a transition metal-free CPP synthesis. As expected, the synthesis provided a large amount of side products and the column chromatography was complex. Therefore, we established a fast and selective separation technique to isolate the pure CPP (Figure 1). The crude reaction mixture was extracted with dichloromethane and adsorbed onto silica gel. The resulting solid was purified via Soxhlet extraction. Firstly, *n*-pentane was used to elute some of the side-products. No CPP was washed out under this condition [controlled by thin layer chromatography (TLC)]. Secondly, the solvent was switched to toluene continuing the Soxhlet extraction. The

Table 1 Overview of the different optimisation conditions

	c ^a (mol/L) and Solvent	Addition of 2 ^b	Temperature ^c	Time ^d	Yield	
					[6]CPP	[9]CPP
1	3×10^{-2} THF	2×1.00 equiv	$-78\text{ }^{\circ}\text{C}$	2 h	–	0.1%
2	7×10^{-2} THF	4×0.25 equiv	$-40\text{ }^{\circ}\text{C}$	5 h ^e	traces	0.01%
3	2×10^{-2} THF	1.00 equiv	$-78\text{ }^{\circ}\text{C}$	20 h	–	0.03%
4	2×10^{-2} THF	1.00 equiv	$50\text{ }^{\circ}\text{C}$	4 h	0.07%	0.05%
5	2×10^{-2} THF	2×0.50 equiv ^f	$50\text{ }^{\circ}\text{C}$	4 h	–	0.03%
6	2×10^{-2} THF	1.00 equiv ^f	$50\text{ }^{\circ}\text{C}$	4 h	–	–
7	2×10^{-2} 1,4-dioxane	1.00 equiv	$50\text{ }^{\circ}\text{C}$	4 h	traces	traces
8	2×10^{-2} THF/TMEDA	1.00 equiv	$50\text{ }^{\circ}\text{C}$	4 h	–	–
9	2×10^{-2} THF/benzene	1.00 equiv	$50\text{ }^{\circ}\text{C}$	4 h	0.04%	traces

^aFinal concentration (c) after the addition of **2**.

^bSteps of the addition of **2** to the reaction mixture.

^cReaction temperature (temperature) after the addition of **2**.

^dReaction time after the addition of **2** before aromatisation.

^e1 h after every addition.

^fAddition to monolithiated **3**.

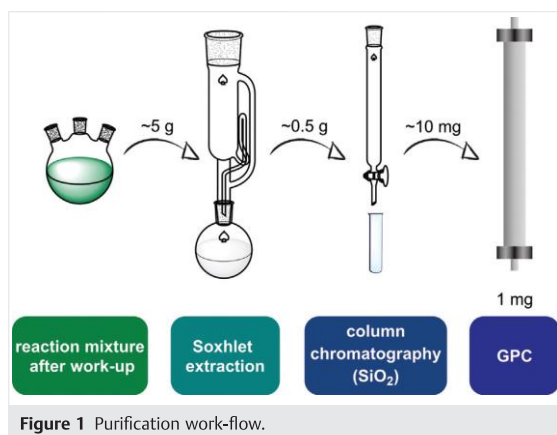


Figure 1 Purification work-flow.

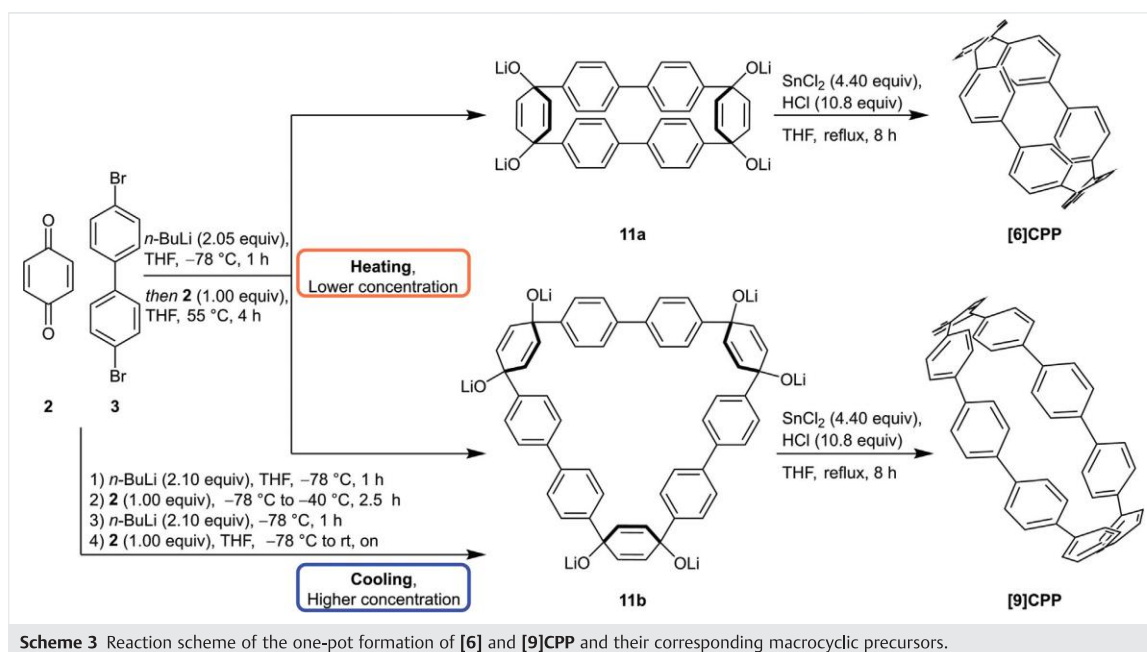
crude CPP was completely extracted (TLC control). By this, the total amount of material was reduced by roughly 90% by weight and column chromatography became feasible.

After this encouraging result and an efficient purification method in hand, the one-pot approach was further optimised (Table 1). In a first attempt, the addition of benzoquinone **2** was varied. Usage of an excess of the lithiated species led to a higher conversion rate as reported by the groups of Jasti and Yamago.^{17,19} Benzoquinone was added successively to monolithiated dibromobiphenyl,

which increased the relative concentration of biphenyl favouring the double addition (Table 1, entry 2).

After adding one additional equivalent of *n*-BuLi, the remaining quinone **2** was added in three portions to the reaction mixture. The reaction mixture was quenched as mentioned before. The Soxhlet extract (see description above) was further purified by column chromatography, providing a mixture of [6]CPP and [9]CPP. Finally, [9]CPP was isolated in a yield of 0.01% and [6]CPP in traces (<<0.5 mg) after purification using GPC. Next, the reaction time was altered (Table 1, entry 3). TLC analysis showed no more change after 18 h. Due to stirring problems using magnetic stirrers, an overhead stirrer was introduced. Afterwards H₂SnCl₄ was added to aromatise the expected macrocyclic intermediate. The reaction mixture was purified by Soxhlet extraction as mentioned before and column chromatography. After GPC purification, [9]CPP was obtained in 0.03% isolated yield. The yield was higher than that in the successive approach, but lower compared to the first synthesis. In order to increase the reactivity even more, the reaction mixture of the dilithiated biphenyl **7** and quinone **2** was heated to 50 °C immediately after the addition of **2** and stirred for 4 h (Table 1, Scheme 3). The reaction mixture was again purified by Soxhlet extraction and column chromatography. [9]CPP was obtained in 0.05% (1.2 mg) and [6]CPP in 0.07% (1.7 mg) isolated yield after GPC.

To further investigate the formation of the corresponding macrocycles, stepwise lithiation of biphenyl **3** was performed (Table 1, entries 5 and 6). First, double addition



Scheme 3 Reaction scheme of the one-pot formation of [6] and [9]CPP and their corresponding macrocyclic precursors.

of monolithiated biphenyl **3** to quinone **2** was tested. In theory, this would lead to a 5-membered precursor, which then could react to macrocycles by further lithiation and addition of **2**. Using the same procedure as mentioned before, only **[9]CPP** was obtained in 0.03% (0.7 mg) isolated yield. Moreover, 1:1 addition of monolithiated biphenyl **3** to quinone **2** was performed. After further lithiation, followed by the standard procedure of aromatisation, no CPP was obtained (TLC control).

Next, different solvents were screened. Following the highest yielding procedure (Table 1, entry 4), the solvents 1,4-dioxane, THF/TMEDA (9:1) and THF/benzene (1:1) were tested. In the case of 1,4-dioxane the addition of *n*-BuLi was carried out at room temperature (rt). The use of 1,4-dioxane and TMEDA as a (co-)solvent did not lead to the isolation of CPPs. However, the mixture of THF/benzene (1:1) led to the isolation of **[6]CPP** in 0.04% yield (0.9 mg) as well as **[9]CPP** in traces.

By adding *p*-benzoquinone (**2**) successively to the reaction mixture, the yield dropped dramatically compared to the first approach. Nevertheless, this reaction yielded the highly strained **[6]CPP** under these one-pot conditions. Moreover, subsequent lithiation of biphenyl **3** (entries 5 and 6) combined with different addition sequences of **2** did not give higher yields. This could be explained by the stepwise lithiation and it has been reported that the lithiation of the double addition product to benzoquinone leads to decomposition.² Also elongating the reaction time at a low temperature (−78 °C) did not increase the initial yield of the first approach (Table 1, entry 3). The longer reaction time and lower temperature could favour linear adducts or rearrangements to less strained *meta*-connected side-products.²¹

The highest total isolated yield was observed when heating the reaction mixture to 50 °C in THF for 4 h in this study (Table 1, entry 4). Furthermore, **[6]CPP** was the main product, which led to the hypothesis that heating increases the total yield and also favours the formation of more strained cyclic precursor **11a** (Scheme 3). In comparison to the first approach, the concentration was lowered in this case to favour intra- over intermolecular reactions. By reducing the concentration in combination with a higher reaction temperature, the one-pot synthesis showed a preference for the smaller **[6]CPP** (Scheme 3). Furthermore, the formation of **[6]CPP** was also favoured using THF/benzene as the solvent. This could lower the total reactivity of all lithiated species and favour intramolecular reactions.

Conclusions

In summary, we describe a transition metal-free one-pot synthesis of **[6]** and **[9]CPP**. This is the fastest and easiest way to access cycloparaphenylenes reported so

far. By developing a convenient purification work-flow, the targeted CPPs could be easily separated from the complex reaction mixtures. Starting from cheap materials, it opens up new ways and strategies for CPP synthesis.

Experimental Section

All reactions were carried out under inert conditions. Dry solvents were purchased from Acros Organics and stored under a nitrogen atmosphere. Technical grade solvents for column chromatography and extraction were distilled once prior to use. All reagents were purchased at reagent grade from commercial suppliers and were used without further purification. For column chromatography, silica gel 60 (0.04–0.063 mm) from Macherey-Nagel GmbH & Co. was used. For TLC, SIL G/UV254 with 0.2-mm SiO₂-layer thickness from Macherey-Nagel GmbH & Co. was used. Spots were detected with a UV-lamp at the wavelength of 254 nm or 366 nm. Proton-nuclear magnetic resonance (¹H NMR) spectra were measured on a Bruker Avance 400 (400 MHz) or a Bruker Avance 600 (600 MHz) spectrometer. Carbon-nuclear magnetic resonance (¹³C NMR) spectra were measured on a Bruker Avance 400 (101 MHz) or a Bruker Avance 600 (151 MHz) spectrometer. All measurements were performed at rt. For GPC, a Shimadzu instrument (consisting of an LC-20AD pump unit, an SPD-20A detector unit (D2 lamp) and a CTO-20AC column oven) equipped with a PSS SDV preparative column (100 Å, 300 mm length, 20.0 mm diameter) was used. As eluent 'Chloroform for HPLC stabilised with amylene' by Acros Organics (charge number: 268320025) was used.

Procedures

Selective synthesis of [9]CPP (Table 1, entry 1): Dibromobiphenyl **3** (6.37 g, 20.0 mmol, 1.00 equiv) was dissolved in dry THF (500 mL). The solution was cooled to −78 °C. A solution of *n*-BuLi (1.6 M in hexanes, 26.3 mL, 2.1 equiv) was added slowly. The resulting light-green coloured suspension was stirred for 60 min at −78 °C. Then, *p*-benzoquinone (**2**) (2.16 g, 20 mmol, 1.00 equiv) was dissolved in dry THF (100 mL, in a second flask) and cooled to −78 °C. The solution of quinone **2** was transferred to the first flask via a cannula and the solution was stirred for 2 h at −78 °C, then allowed to warm to −40 °C for 30 min and again cooled to −78 °C. Again, a solution of *n*-BuLi (1.6 M in hexanes, 26.3 mL, 2.10 equiv) was added slowly and stirring was continued for 60 min at −78 °C. Quinone **2** (2.16 g, 20 mmol, 1.00 equiv) was added as mentioned before, followed by stirring for 2 h at −78 °C.



The mixture was allowed to warm to rt. Tin(II)chloride dihydrate (39.7 g, 176 mmol, 8.80 equiv) was dissolved in HCl (38%, 35.0 mL, 434 mmol, 21.7 equiv) and stirred for 30 min. The resulting solution was slowly added to the reaction mixture, which was heated under reflux for 1 day. The yellow-white solution was allowed to cool to rt. Water (100 mL) and CH₂Cl₂ (100 mL) were added. The organic layer was separated and washed with water (100 mL) and brine (100 mL). The organic layer (very viscous) was dried with MgSO₄, filtered off and washed with CH₂Cl₂ (3 × 200 mL). The solvent was removed under reduced pressure and column chromatography was performed (SiO₂, 400 g, cyclohexane/CH₂Cl₂ = 1:1). Fractions containing [9]CPP (green spot, R_f = 0.45) were combined and further purified by GPC (6 mL/min, retention time = 12.29 min). [9]CPP was obtained as a green solid (5.1 mg, 7.5 μmol, 0.1%). The analytical data correspond to the literature data.²

Synthesis of [6] and [9]CPP (entry 4): Dibromobiphenyl **3** (3.18 g, 10.0 mmol, 1.00 equiv) was dissolved in dry THF (500 mL). The solution was cooled to –78 °C. A solution of *n*-BuLi (1.6 M, 12.8 mL, 20.5 mmol, 2.05 equiv) was added slowly and the resulting mixture was stirred (mechanical stirrer) for 1 h at –78 °C. Quinone **2** (1.08 g, 10.0 mmol, 1.00 equiv) was added neat. The resulting solution was warmed up to 50 °C and was stirred for 4 h at that temperature. Tin(II)chloride dihydrate (9.93 g, 44.0 mmol, 4.40 equiv) and HCl (38%, 8.72 mL, 108 mmol, 10.8 equiv) were mixed and slowly added to the reaction mixture followed by heating under reflux for 1.5 h. The reaction was quenched by adding water (100 mL) and CH₂Cl₂ (200 mL). The layers were separated, and the aqueous layer was washed with CH₂Cl₂ (3 × 100 mL). The combined organic layers were washed with brine (200 mL) and dried with MgSO₄ and concentrated under reduced pressure. The residue was taken up in CH₂Cl₂ and loaded onto silica gel (20 g). This solid was used for Soxhlet extraction with pentane (10 h), followed by toluene (4 h). TLC analysis showed a spot for [9]CPP (green, R_f = 0.45) only in the toluene extract. Column chromatography (SiO₂, 100 g, toluene/cyclohexane = 1:1) provided crude [9]CPP and [6]CPP. GPC was performed (6 mL/min, retention time = 12.29 and 13.57 min) and pure [6]CPP (1.7 mg, 3.72 μmol, 0.07%) and [9]CPP (1.2 mg, 1.75 μmol, 0.05%) were obtained. Analytical data correspond to the literature data.^{2,15}

Please see Supporting Information for other entries (Table 1, entries 2, 3, and 5–9).

Funding Information

Financial support was provided by the Justus Liebig University Giessen.

Acknowledgments

We thank Domenic Dreisbach and Prof. Bernhard Spengler for MALDI-MS measurements. Furthermore, we thank Daniel Kohrs and Jannis Volkmann for fruitful discussions.

Supporting Information

Supporting information for this article is available online at <http://doi.org/10.1055/s-0040-1721082>.

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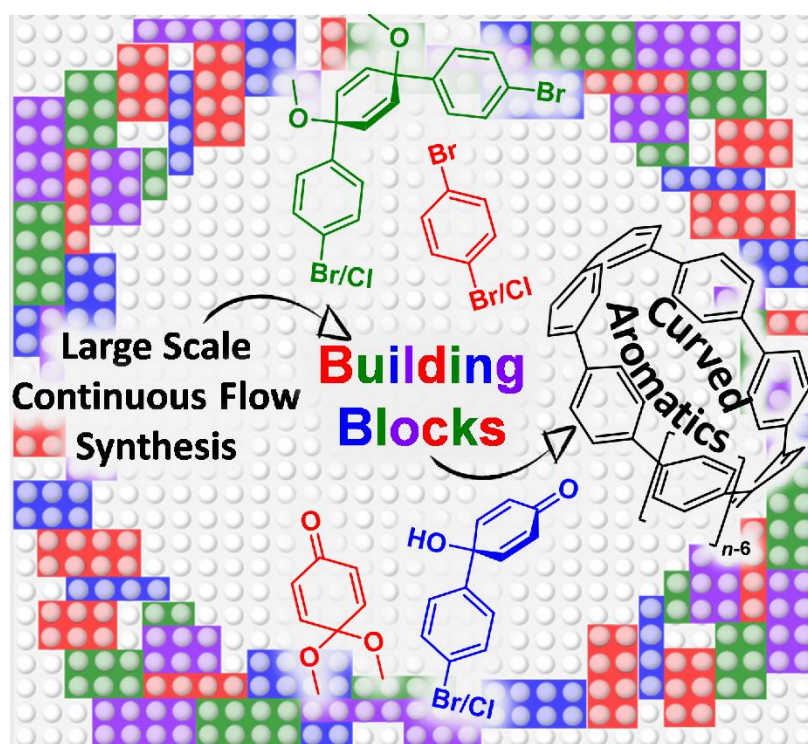
4.2 Continuous-Flow Synthesis of Cycloparaphenylene Building Blocks on a Large Scale

Reference: J. H. Griwatz, M. L. Kessler, H. A. Wegner, *Chem. Eur. J.* **2023**, *29*, e202302173.

DOI: 10.1002/chem.202302173

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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.”

Cover Feature: Continuous-Flow Synthesis of Cycloparaphenylene Building Blocks on a Large Scale (Chem. Eur. J. 63/2023)

Reference: J. H. Griwatz, M. L. Kessler, H. A. Wegner, *Chemistry A European J* **2023**, 29.

DOI: 10.1002/chem.202303222

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[n]Cycloparaphenylene

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

Jan H. Griwatz,^[a, b] Mika L. Kessler,^[a] and Hermann A. Wegner^{*[a, b]}

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 photo-physical 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 $[n]$ mCPPs exhibit changed properties and are easier to functionalize. For example, a water soluble $[n]$ mCPP was applied as a fluorescence marker in cells by the group of Jasti.^[19] Moreover, $[n]$ mCPP 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]

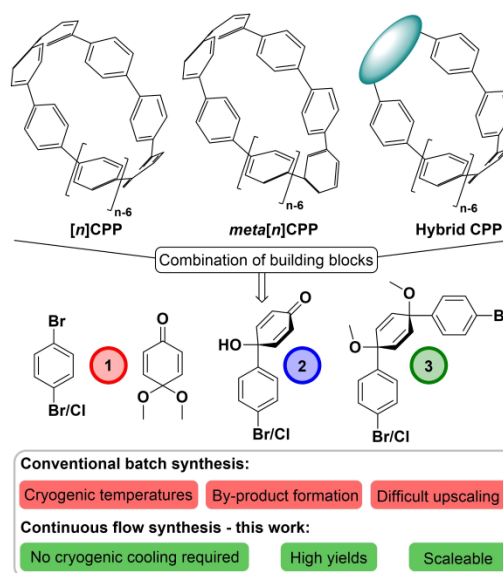


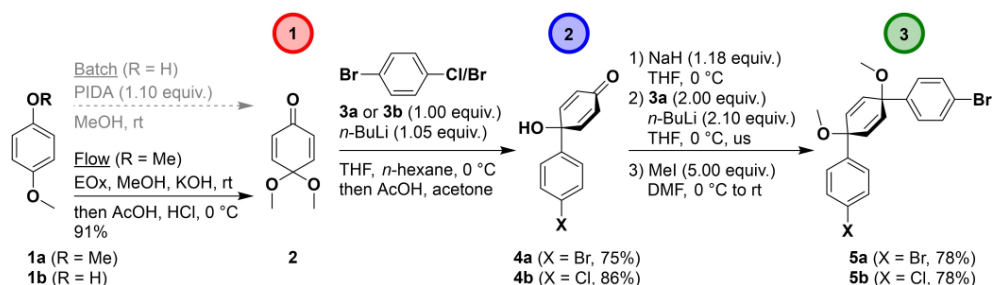
Figure 1. The synthesis of $[n]$ CPPs and similar nanohoops is often based on the same or interchangeable building blocks.

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Supporting information for this article is available on the WWW under <https://doi.org/10.1002/chem.202302173>

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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]

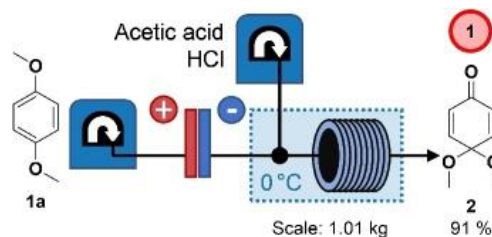
A flow-assisted synthesis of CPP building blocks has been presented by Kim and co-workers based on the cyclohexyl moiety.^[23] This synthesis approach suffers from lower yields for the aromatization toward the corresponding CPP.^[24,25] Therefore, this approach has not been used much lately. We developed 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 multi-gram 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 molL⁻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**.

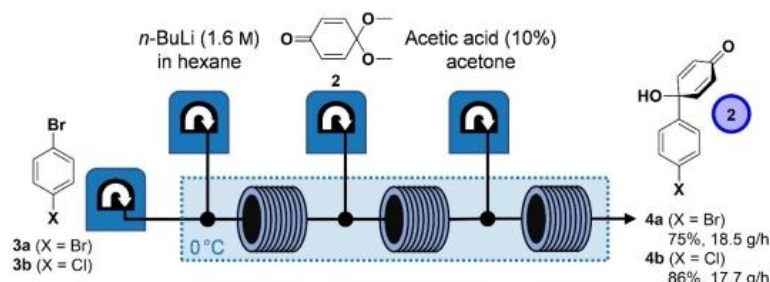


Figure 3. Schematic representation of the continuous-flow reactor used for the synthesis of two-membered building blocks **4a** and **4b**.

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 $>100\text{ g}$ 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

nano hoops.^[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

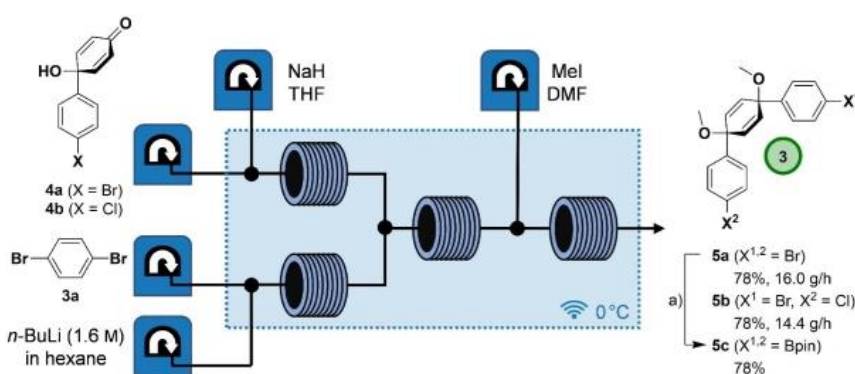


Figure 4. Schematic representation of the continuous-flow reactor used for the synthesis of three-membered building blocks **5a** and **5b**. Reaction conditions for the synthesis of **5c**: a) *n*BuLi (2.1 equiv.), 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.0 equiv.), THF, -78°C .

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 nano-hoops.^[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 nano-hoops 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 $10 \text{ cm} \times 15 \text{ cm}$ 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.

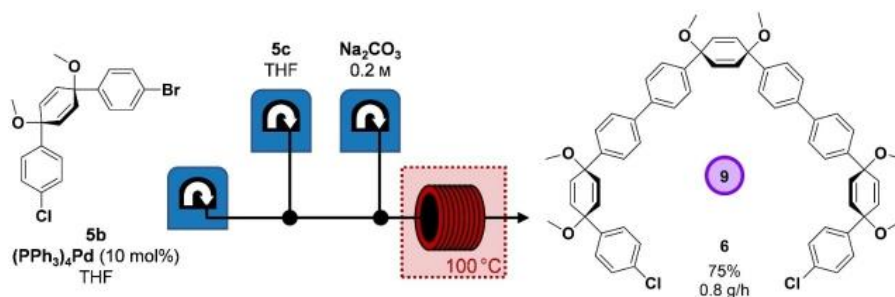


Figure 5. Schematic drawing of the continuous-flow reactor used for the synthesis of nine-membered building block **6**.

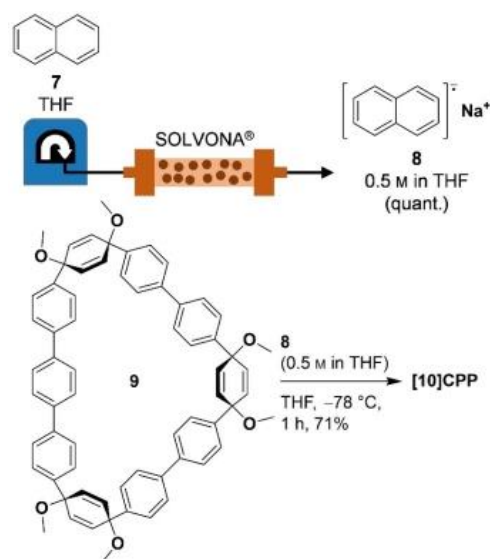


Figure 6. The preparation of sodium naphthalenide (**8**) from naphthalene (**7**) by using SOLVONA® (sodium on molecular sieve) in a packed bed reactor (top). Aromatization of macrocycle **9** to [10]CPP with a yield of 71% (bottom).

Experimental Section

Synthesis of acetal 2 (4,4-dimethoxycyclohexa-2,5-dien-1-one): 1,4-Dimethylbenzene **1a** (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 $\mu\text{L min}^{-1}$. 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 $\mu\text{L min}^{-1}$) 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] ^1H NMR (200 MHz, CDCl_3): $\delta=6.87\text{--}6.75$ (m, 2H), 6.31–6.20 (m, 2H), 3.36 (s, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (50 MHz, CDCl_3): $\delta=185.2$, 143.4, 130.1, 92.6, 50.5. HRMS (ESI) m/z calc. for $\text{C}_8\text{H}_{10}\text{O}_2 + \text{Na}^+$: 177.0522; found: 177.0525. Boiling point: 50 °C (0.2 mbar).

Synthesis of two-membered building blocks 4a and 4b: 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 (**3a**) or 1-bromo-4-chlorobenzene (**3b**) 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 (**4a** (Br): 75% (257 mmol, 51.7 g); **4b** (Cl): 86% (113 mmol, 21.5 g). Analytical data correspond to literature (**4a**,^[39] **4b**^[26]).

4-(4-Bromophenyl)-4-hydroxy-2,5-cyclohexadien-1-one (4a): ^1H NMR (400 MHz, $[\text{D}_6]\text{DMSO}$): $\delta=7.62\text{--}7.53$ (m, 2H), 7.41–7.31 (m, 2H), 6.95–6.85 (m, 2H), 6.64 (s, 1H), 6.20–6.10 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, $[\text{D}_6]\text{DMSO}$): $\delta=185.3$, 152.0, 139.8, 131.5, 127.7, 125.8, 121.0, 69.8. HRMS (ESI) m/z calc. for $\text{C}_{12}\text{H}_9\text{OBr} + \text{Na}^+$: 286.9678; found: 286.9677. Melting point: 173 °C.

4-(4-Chlorophenyl)-4-hydroxy-2,5-cyclohexadien-1-one (4b): ^1H NMR (400 MHz, $[\text{D}_6]\text{DMSO}$): $\delta=7.43$ (s, 4H), 6.93–6.88 (m, 2H), 6.64 (s, 1H), 6.18–6.12 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, $[\text{D}_6]\text{DMSO}$): $\delta=185.3$, 152.1, 139.4, 132.5, 128.6, 127.4, 125.8, 69.7. HRMS (ESI) m/z calc. for $\text{C}_{12}\text{H}_9\text{OCl} + \text{Na}^+$: 243.0183 [$M + \text{Na}$] $^+$; found: 243.0184. Melting point: 170 °C.

Synthesis of three-membered building blocks 5a and 5b: The reaction was performed under inert atmosphere. Ketone **4a** or **4b** (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 (**3b**) 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 (**3b**; 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 **4a** or **4b** (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. (**5a** (Br): 78% (17.8 mmol, 8.00 g); **5b** (Cl/Br): 78% (17.7 mmol, 7.20 g). Analytical data correspond to literature (**5a**,^[21] **5b**^[31]).

1,1'-(cis-1,4-Dimethoxycyclohexa-2,5-diene-1,4-diy)bis(4-bromobenzene) (5a): ^1H NMR (400 MHz, CDCl_3): $\delta = 7.46\text{--}7.41$ (m, 4H), $7.26\text{--}7.22$ (m, 4H), 6.07 (s, 4H), 3.41 (s, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): $\delta = 142.5, 133.5, 131.7, 127.9, 121.9, 74.6, 52.2$. HRMS (ESI) m/z calc. for $\text{C}_{20}\text{H}_{18}\text{O}_2\text{Br}_2 + \text{Na}^+$: 470.9566; found: 470.9563. Melting point: 131°C .

1-Bromo-4-[cis-4-(4-chlorophenyl)-1,4-dimethoxy-2,5-cyclohexadien-1-yl]benzene (5b): ^1H NMR (400 MHz, CDCl_3): $\delta = 7.47\text{--}7.39$ (m, 2H), $7.34\text{--}7.20$ (m, 6H), 6.07 (s, 4H), 3.41 (s, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): $\delta = 142.5, 141.9, 133.7, 133.54, 133.45, 131.6, 128.7, 127.9, 127.5, 121.9, 74.6, 74.5, 52.2$. HRMS (ESI) m/z calc. for $\text{C}_{20}\text{H}_{18}\text{O}_2\text{BrCl} + \text{Na}^+$: 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-diy)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 $n\text{BuLi}$ (1.6 m in hexanes, 45.5 mL, 72.9 mmol, 2.10 equiv.) over 5 min. Immediately after the addition of $n\text{BuLi}$, 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]

^1H NMR (400 MHz, CDCl_3): $\delta = 7.78\text{--}7.72$ (m, 4H), $7.41\text{--}7.38$ (m, 4H), 6.09 (s, 4H), 3.43 (s, 6H), 1.34 (s, 24H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): $\delta = 146.5, 135.1, 133.4, 125.5, 83.9, 75.1, 52.1, 25.0$. HRMS (ESI) m/z calc. for $\text{C}_{32}\text{H}_{42}\text{B}_2\text{O}_6 + \text{Na}^+$: 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-diy)bis[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 ($V = (0.75 \cdot V_{\text{THF}})$ 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 ($525\text{ }\mu\text{L min}^{-1}$) and solution B ($300\text{ }\mu\text{L min}^{-1}$) 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] ^1H NMR (400 MHz, CD_2Cl_2): $\delta = 7.59\text{--}7.53$ (m, 8H), $7.51\text{--}7.46$ (m, 4H), $7.45\text{--}7.41$ (m, 4H), $7.38\text{--}7.33$ (m, 4H), $7.31\text{--}7.25$ (m, 4H),

$6.18\text{--}6.11$ (m, 8H), $6.10\text{--}6.05$ (m, 4H), 3.45 (s, 6H), $3.43\text{--}3.41$ (m, 12H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CD_2Cl_2): $\delta = 143.4, 143.1, 142.9, 140.3, 140.1, 134.2, 133.9, 133.54, 133.53, 128.8, 128.0, 127.31, 127.28, 127.0, 126.9, 75.1, 75.0, 74.8, 52.3$. HRMS (ESI) m/z calc. for $\text{C}_{60}\text{H}_{54}\text{Cl}_2\text{O}_6 + \text{Na}^+$: 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] ^1H NMR (200 MHz, CD_2Cl_2): $\delta = 7.68$ (s, 4H), $7.66\text{--}7.41$ (m, 20H), $7.41\text{--}7.27$ (m, 4H), $6.31\text{--}6.03$ (m, 12H), $3.49\text{--}3.36$ (m, 18H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CD_2Cl_2): $\delta = 143.7, 142.9, 142.8, 140.4, 140.2, 139.96, 139.93, 134.1, 134.0, 133.4, 127.9, 127.3, 127.24, 127.18, 127.1, 127.0, 126.9, 75.55, 75.52, 74.3, 52.4, 52.2, 52.1$. HRMS (ESI) m/z calc. for $\text{C}_{66}\text{H}_{58}\text{O}_6 + \text{Na}^+$: 969.4125; found: 969.4121. Melting point: decomposition at $> 250^\circ\text{C}$.

Synthesis of [10]cycloparaphenylene: A column (250 mm \times 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 ($200\text{ }\mu\text{L min}^{-1}$, residence time 37.5 min) and an in-line filter (PTFE, $4\text{ }\mu\text{m}$) to obtain a dark green solution. Ten-membered macrocycle **9** (40.0 mg, $42.2\text{ }\mu\text{mol}$, 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, $30.0\text{ }\mu\text{mol}$). Analytical data correspond to literature.^[21] ^1H NMR (200 MHz, CDCl_3): $\delta = 7.56$ (s, 40H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): $\delta = 138.3, 127.5$. HRMS (LDI) m/z calc. for $\text{C}_{60}\text{H}_{40}^+$: 760.3130; found: 760.3122. Melting point: decomposition at $> 250^\circ\text{C}$.

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]

Acknowledgements

The authors thank Simon Weiß for assistance with synthesis. Moreover, the authors thank TCI and the European and Hessian Government (EFRE, 20005599) for financial support. The authors thank Prof. Bernhard Spengler and Carolin Marta Morawietz for MALDI MS measurements. Finally, the authors thank Jannis Volkmann, Daniel Kohrs, and Felix Bernt for fruitful discussions. Open Access funding enabled and organized by Projekt DEAL.

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.

Keywords: cross-coupling · cycloparaphenylene · flow chemistry · reactive intermediates · synthetic methods

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Manuscript received: July 7, 2023
Accepted manuscript online: August 3, 2023
Version of record online: September 27, 2023

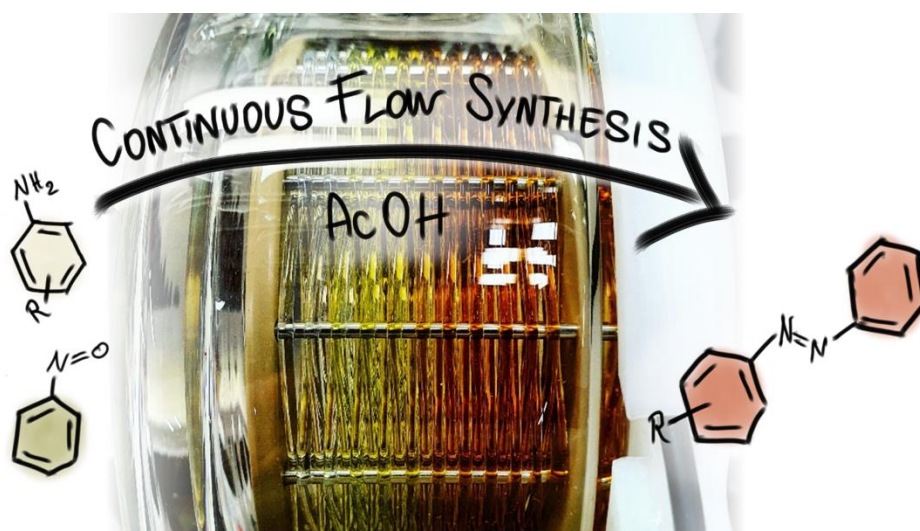
4.3 Continuous Flow Synthesis of Azobenzenes via Baeyer–Mills Reaction

Reference: J. H. Griwatz[‡], A. Kunz[‡], H. A. Wegner, *Beilstein J. Org. Chem.* **2022**, *18*, 781.

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DOI: 10.3762/bjoc.18.78

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“Azobenzene, as one of the most prominent molecular switches, is featured in many applications ranging from photopharmacology to information or energy storage. In order to easily and reproducibly synthesize non-symmetric substituted azobenzenes in an efficient way, especially on a large scale, the commonly used Baeyer–Mills coupling reaction was adopted to a continuous flow setup. The versatility was demonstrated with a scope of 20 substances and the scalability of this method exemplified by the synthesis of >70 g of an azobenzene derivative applied in molecular solar thermal storage (MOST) systems.”



Continuous flow synthesis of azobenzenes via Baeyer–Mills reaction

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Full Research Paper

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Keywords:

azobenzenes; Baeyer–Mills reaction; continuous flow; molecular switches; solar fuel

Beilstein J. Org. Chem. **2022**, *18*, 781–787.

<https://doi.org/10.3762/bjoc.18.78>

Received: 26 April 2022

Accepted: 15 June 2022

Published: 30 June 2022

This article is part of the thematic issue "Platform and enabling technologies in organic synthesis".

Guest Editor: P. Heretsch

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Abstract

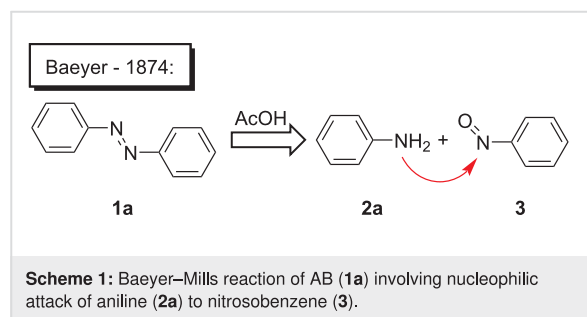
Azobenzene, as one of the most prominent molecular switches, is featured in many applications ranging from photopharmacology to information or energy storage. In order to easily and reproducibly synthesize non-symmetric substituted azobenzenes in an efficient way, especially on a large scale, the commonly used Baeyer–Mills coupling reaction was adopted to a continuous flow setup. The versatility was demonstrated with a scope of 20 substances and the scalability of this method exemplified by the synthesis of >70 g of an azobenzene derivative applied in molecular solar thermal storage (MOST) systems.

Introduction

Although the red-colored azobenzenes (AB) have been known for years as dyes, their applications nowadays span from energy and information storage [1–5], organocatalysis [6], photobiology and photopharmacology [7], host–guest chemistry [8], molecular mechanics [9,10], to molecular machines [11]. This popularity is due to the ability of ABs to isomerize from their energetically more stable (*E*)- to the meta-stable (*Z*)-isomer by irradiation with light [12]. During this isomerization, not only the geometry is altered from the planar (*E*)-AB to its twisted (*Z*)-AB form, but also its properties change (e.g., dipole

moment and polarity) [13,14]. Furthermore, the (*Z*)-AB can be reversibly switched back by visible light or thermally [15]. To synthesize ABs a variety of reactions can be chosen from, each having both advantages and disadvantages. The best synthesis must be individually selected for the respective use [16]. There are various ways to access symmetric and non-symmetric AB compounds in a convenient way in batch size, as it has been summarized in detail [16]. One example is the reliable synthesis of symmetric ABs in high yields via a Cu-catalyzed oxidative coupling of aniline derivatives [17]. This synthesis can be

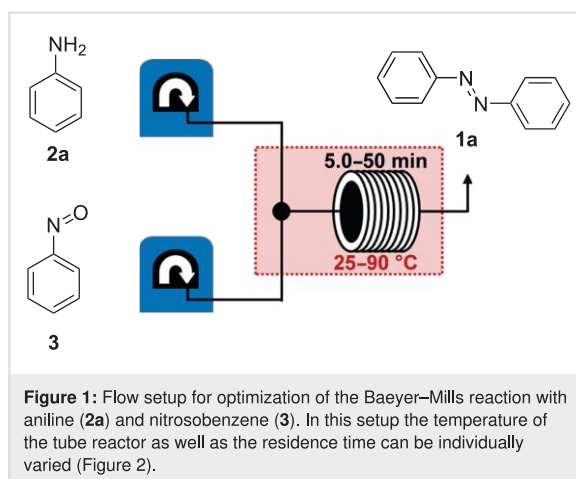
also used for the formation of non-symmetric AB, however, only for a selected set of anilines. One of the most applied methods to access non-symmetric azobenzenes is based on the condensation of nitrosobenzenes with anilines (Scheme 1). This so-called Baeyer–Mills reaction, which was first published by Baeyer in 1874 and further investigated by Mills, proceeds best for electron-rich anilines with electron-poor nitrosobenzenes. The reactivity can be rationalized by the proposed mechanism, which involves nucleophilic attack of the aniline on the nitrosobenzene derivatives in acidic or basic media (Scheme 1) [18–21]. However, in order to use azobenzenes as functional materials, access to a large-scale process is necessary. In this context continuous flow synthesis is frequently discussed as potential solution to address this challenge. This technique is neither limited by the size of the reaction vessel nor the stirring as the reagents are pumped continuously through the reactor. The set-up also allows precise control of the reaction time and temperature, which can lead to higher yields and purity [22]. Flow chemistry to prepare azobenzenes has been previously applied to the Cu-catalyzed synthesis of symmetric substituted AB derivatives [23,24]. However, non-symmetric substituted ABs are not accessible by this method in an efficient way. Herein, we report a continuous flow synthesis of non-symmetric AB compounds via the Baeyer–Mills reaction, which allows to obtain large quantities of products from different substrates in a fast and efficient manner.



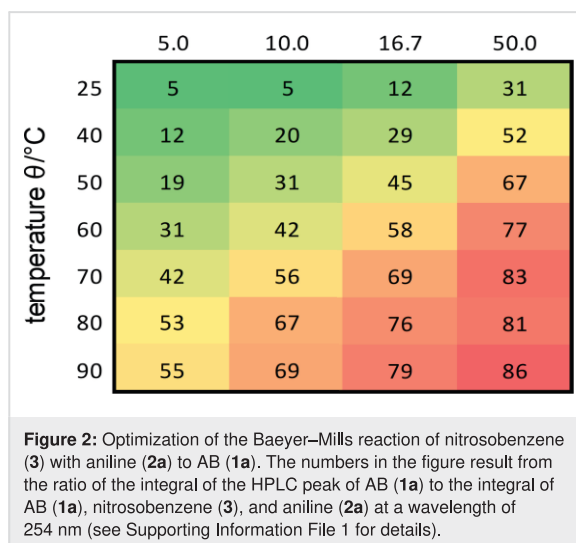
Results and Discussion

For optimization of the Baeyer–Mills coupling in continuous flow the reaction to generate unsubstituted AB (**1a**) was performed with freshly distilled aniline (**2a**) and commercially available nitrosobenzene (**3**), dissolved separately in acetic acid. Both starting materials had the same concentration and were pumped by a Vapourtec E-Series system (for details, see experimental part in Supporting Information File 1). After mixing, the solution was passed through a tube reactor, in which the temperature as well as the residence time can be easily modified. Afterwards the respective reaction mixture was collected and analyzed (Figure 1). In order to optimize the reaction, both the temperature and the residence time were successively changed

to achieve the highest conversion to AB. The residence time was increased from 5.0 to 50.0 min and the temperature was raised stepwise from 25 °C up to 90 °C (Figure 1). After the set residence time an aliquot was collected, diluted with acetonitrile, and subsequently examined by HPLC analysis (for details, see Supporting Information File 1).



At lower temperature, AB (**1a**) could be detected, but only a low conversion of the starting materials was observed (Figure 2). At higher temperature, the product/starting material ratio was improved but was still not satisfactory. Therefore, not only the temperatures, but also the residence time was gradually changed (Figure 2). At 70–90 °C and a residence time of 50.0 min the best results were observed. However, heating to 80–90 °C provided increasing amounts of azoxybenzene, which is a known side product of the Bayer–Mills reaction [25]. Hence, these parameters (70 °C, 50.0 min) were chosen to do



the synthesis on a preparative scale. The setup was slightly modified to include an aqueous workup and extraction of the organic phase. For this purpose, a third pump was implemented which adds cyclohexane to the reaction mixture after the tube reactor (Figure 3). The reaction solution with cyclohexane was continuously fed into a separating funnel containing brine. After phase separation, drying of the organic phase with MgSO_4 , and evaporation of the solvent, AB (**1a**) could be obtained in 98% yield under the previously optimized conditions. By collection of the reactor output for 2 h, 582 mg of AB were obtained.

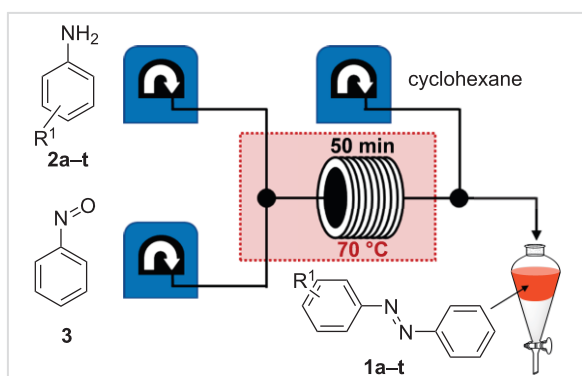


Figure 3: Flow setup after prior optimization with unsubstituted aniline (**2a**) and nitrosobenzene (**3**) to AB (**1a**).

Further purification was not necessary as the product was satisfactorily pure with the described workup. After successful optimization of the synthesis of unsubstituted AB (**1a**) the setup was also tested for a large number of other azobenzene derivatives to determine the scope of the method (Table 1). All aniline derivatives **2a–s** were commercially available and the corresponding azobenzenes **1a–s** were synthesized according to the general procedure in continuous flow as described before. The optimized flow and workup conditions gave the products in high purity for most of the synthesized AB derivatives (see Supporting Information File 1 for details). Only in a few cases flash column chromatography was necessary to isolate the pure products (see Table 1). As expected, the method worked excellently for most of the electron-rich anilines due to their increased nucleophilicity.

A comparison of *ortho*-, *meta*- and *para*-substituted derivatives revealed that for electron-rich anilines, the *para*-substituted ABs are formed in better yields as their *ortho*- and *meta*-analogues. For example, the synthesis of AB **1i** from *m*-anisidine (**2i**) gave only 7% yield, due to the formation of large amounts of azoxybenzene and purification issues therefrom. The moderate product yields from the *ortho*-substituted aniline derivatives are presumably caused by the higher steric hindrance of the nucleophilic attack. Low yields in case of electron-poor aniline

Table 1: Substrate scope of the Baeyer–Mills reaction under the optimized conditions in continuous flow.

entry	aniline 2	product 1	yield [%]
1			98
2			89
3			77
4			94

Table 1: Substrate scope of the Baeyer–Mills reaction under the optimized conditions in continuous flow. (continued)

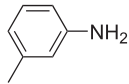
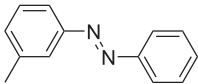
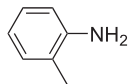
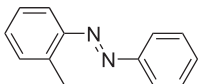
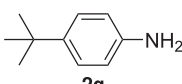
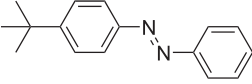
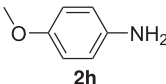
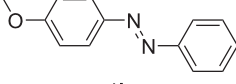
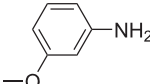
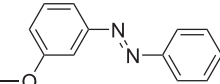
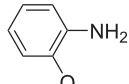
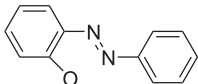
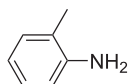
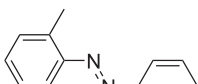
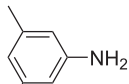
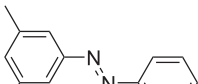
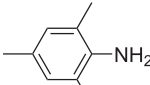
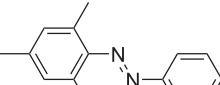
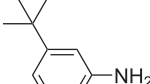
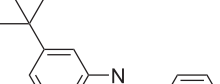
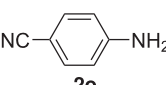
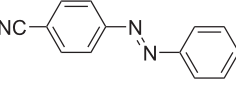
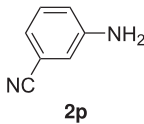
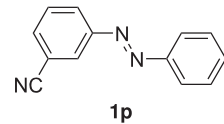
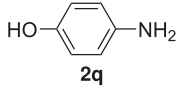
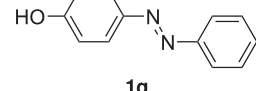
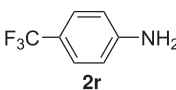
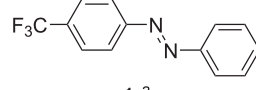
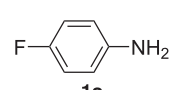
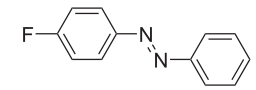
5	 2e	 1e^a	79
6	 2f	 1f^a	67
7	 2g	 1g	>99
8	 2h	 1h	96
9	 2i	 1i^a	7
10	 2j	 1j^a	72
11	 2k	 1k^a	23
12	 2l	 1l^a	65
13	 2m	 1m	70
14	 2n	 1n	99
15	 2o	 1o	7

Table 1: Substrate scope of the Baeyer–Mills reaction under the optimized conditions in continuous flow. (continued)

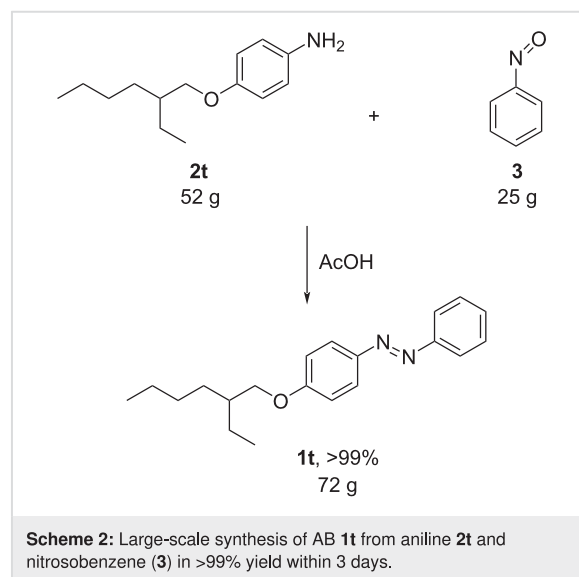
16			54
17			68
18			33
19			95

^aPurified by chromatography.

derivatives can be explained by the reduced nucleophilicity. To exemplarily demonstrate the optimization for electron-poor derivatives, the synthesis of *p*-cyano-substituted AB **1o** was repeated at higher temperatures. Thereby the yield of **1o** could be increased to 17% (90 °C) and 19% (110 °C), respectively. However, since larger amounts of azoxybenzene were formed, column chromatography became necessary relativizing this improvement in yield (see Supporting Information File 1 for spectra). Substrates, which did not result in AB formation, were anilines with a nitro-substituent. Moreover, some further cases of *ortho*-substituted anilines were unsuccessful, for which steric effects could serve as an explanation (see Supporting Information File 1 for details). In comparison with published batch syntheses, the herein reported continuous flow synthesis usually gives similar or improved yields and eliminates the shortcomings in scalability.

For the applications of ABs as molecular materials often larger amounts are required, for example, as active compounds in molecular solar thermal energy storage (MOST) systems. Therefore, we utilized the set-up for the preparation of large amounts of AB **1t** (Scheme 2). This AB analogue was first synthesized by Masutani et al. in 2014 and was examined by them as well as in further studies by other groups regarding their potential for MOST applications, e.g., in a fluidic chip device by Wang et al. [1,26,27]. For the large-scale synthesis both, aniline **2t** as well as nitrosobenzene (**3**), were dissolved in acetic acid and, as described before, pumped through the flow setup (Figure 3). Every 12 h, the organic phase was separated from the aqueous phase, dried over MgSO₄, and the solvent was subsequently re-

moved. The solvent was recycled to minimize waste. After a total runtime of 3 days 72 g of AB **1t** were obtained as pure red oil which corresponds to a yield of >99%. Therefore, the method should be suitable for the preparation of easily several 100 grams of azobenzene compounds.



Conclusion

In summary, the Baeyer–Mills reaction was successfully transferred to a continuous flow setup. The method can be used for various anilines as starting materials to access the desired ABs. A scope of 20 different anilines (**2a–t**) resulting in the corre-

sponding azobenzenes **1a–t** was investigated and especially electron-rich azobenzenes were prepared in yields up to >99%. Furthermore, the setup was demonstrated to be applicable for a large-scale synthesis, where azobenzene **1t** was obtained in 72 g within 3 days without the need of further purification. With this process a large number of non-symmetric substituted azobenzenes can be prepared in high yields and large quantities which opens new possibilities for applications of AB as molecular materials in general.

Supporting Information

Supporting Information File 1

General information, experimental data of all isolated products, ^1H and ^{13}C NMR spectra, and structures of unsuccessful substrates.

[<https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-18-78-S1.pdf>]

Acknowledgements

The authors thank Chiara Eleonora Campi for help with the graphical abstract.

Funding

This project was partially funded by the European Regional Development Fund (ERDF), the Germans Research Council DFG (WE5601/12-1) and TCI.

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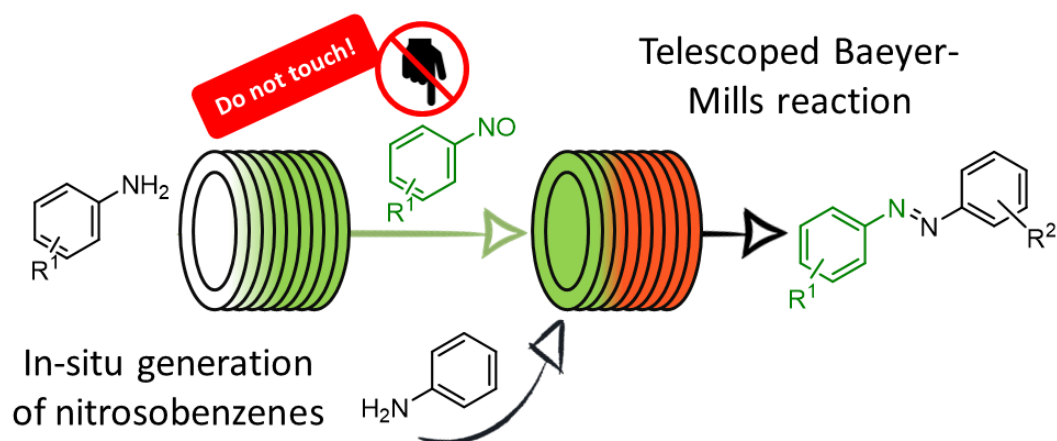
4.4 In-situ Oxidation and Coupling of Anilines towards Unsymmetric Azobenzenes Using Flow Chemistry

Reference: J. H. Griwatz[‡], C. E. Campi[‡], A. Kunz, H. A. Wegner, *ChemSusChem* **2024**, e202301714.

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DOI: 10.1002/cssc.202301714

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“Molecular switches, especially azobenzenes, are used in numerous applications, such as molecular solar thermal storage (MOST) systems and photopharmacology. The Baeyer-Mills reaction of anilines and nitrosobenzenes has been established as an efficient synthetic method for non-symmetric azobenzenes. However, nitrosobenzenes are not stable, depending on their substitution pattern and pose a health risk. An in situ oxidation of anilines with Oxone[®] was optimized under continuous flow conditions avoiding isolation and contact. The in-situ generated nitrosobenzene derivatives were subjected to a telescoped Baeyer-Mills reaction in flow. That way azobenzenes with a broad substituent spectrum were made accessible.”

In-situ Oxidation and Coupling of Anilines towards Unsymmetric Azobenzenes Using Flow Chemistry

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Molecular switches, especially azobenzenes, are used in numerous applications, such as molecular solar thermal storage (MOST) systems and photopharmacology. The Baeyer-Mills reaction of anilines and nitrosobenzenes has been established as an efficient synthetic method for non-symmetric azobenzenes. However, nitrosobenzenes are not stable, depending on

their substitution pattern and pose a health risk. An in-situ oxidation of anilines with Oxone[®] was optimized under continuous flow conditions avoiding isolation and contact. The in-situ generated nitrosobenzene derivatives were subjected to a telescoped Baeyer-Mills reaction in flow. That way azobenzenes with a broad substituent spectrum were made accessible.

Introduction

In recent years, colored azobenzenes (AB), originally known primarily for their use as dyes even as food additives,^[1] have gained great popularity due to their wide range of applications as molecular switch.^[2] These applications range from energy and information storage,^[3] organocatalysis,^[4] photobiology and photopharmacology^[5] to host-guest chemistry,^[6] molecular mechanics^[7] and molecular machines.^[8] This surge in popularity is primarily attributed to the remarkable isomerization ability of ABs, which can undergo reversible conversion between the energetically stable (*E*)-configuration and the metastable (*Z*)-isomer upon exposure to either light or thermal stimuli.^[9] This isomerization process not only changes the geometry of the molecule from an extended planar (*E*)-AB to a twisted (*Z*)-AB, but also modifies its physical properties, including dipole moment and polarity.^[10]

Various methods for the synthesis of ABs have been reported in literature over time,^[11,12] making the choice of the most suitable synthetic approach dependent on the required substitution pattern. Traditionally, ABs are synthesized through azo coupling reactions, which involve the electrophilic aromatic substitution of a diazonium compounds with an electron rich aromatic system.^[13] Although this method provides fast reaction

rates and high yields, its narrow substrate scope and hazardous nature pose significant limitations on its applicability.^[13] An effective alternative for the synthesis of symmetrical ABs is represented by the Cu-catalyzed oxidative coupling of aniline derivatives.^[14] While this method can be applied to produce wide range of symmetrical ABs, its application to unsymmetric compounds is restricted to specific aniline substrates. Therefore, a more selective approach for the preparation of unsymmetric azobenzenes is based on the well-established Baeyer-Mills reaction, firstly described by Baeyer in 1874 and further investigated by Mills.^[15] This reaction involves a nucleophilic attack of anilines on nitrosobenzene derivatives in acidic or basic media and proves particularly efficient when electron-rich anilines react with electron-poor nitrosobenzenes.^[16]

Despite the availability of numerous synthetic routes, suitable methods for a modular and large-scale production process, crucial for the practical application of azobenzenes in functional materials, are still limited. Continuous flow synthesis has emerged as a possible solution to this challenge. This technique offers several advantages, including the absence of size limitations for reaction vessels and stirring, as the reagents are continuously pumped through the reactor. In addition, it enables precise control over reaction time and temperature, resulting in higher yields and purity.^[17]

Over the past years, continuous flow chemistry has been employed for Cu-catalyzed synthesis of symmetric AB derivatives and azo coupling for non-symmetric ABs (Figure 1).^[18] However, these syntheses faced challenges in the efficient preparation of unsymmetrically substituted ABs and encounters limitations in terms of accessible substrates. Therefore, a continuous flow synthesis method for non-symmetric AB compounds *via* the Baeyer-Mills reaction was developed by us.^[19] This approach enabled the rapid and efficient preparation of large quantities of AB products from various substrates. Nonetheless, this method was limited to the use of electron-rich anilines, resulting in low or no yields for the corresponding ABs synthesized from electron-deficient anilines. Additionally, the use of nitrosobenzenes raises concerns due to their potential low stability and susceptibility to oxidation during the isolation process. Moreover, nitrosobenzenes pose a health

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Supporting information for this article is available on the WWW under <https://doi.org/10.1002/cssc.202301714>

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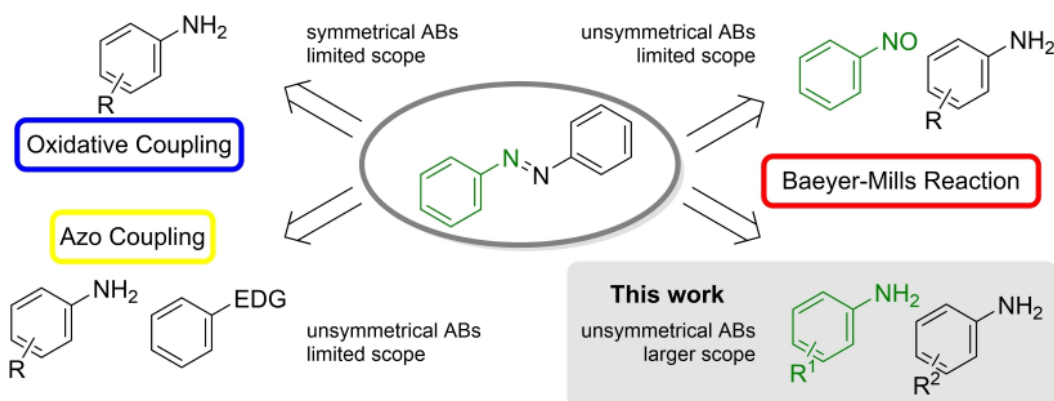


Figure 1. Overview of azobenzene syntheses in continuous flow via oxidative coupling, azo coupling, Baeyer-Mills reaction and this work.^[17,18]

hazard as they have been shown to be toxic and can damage DNA strains.^[20,21] To circumvent these drawbacks and to increase work safety,^[22] an in-situ oxidation of anilines to nitrosobenzenes was developed and is presented herein. This versatile compound class has been applied in a number of other transformations as either electrophile or nucleophile as well as in cycloaddition reactions.^[20] As an example of a telescopic reaction of these in situ generated intermediates, the coupling to unsymmetric azobenzenes was demonstrated.

Results

In our initial attempt to broaden the scope of azobenzenes using our previously reported method, we explored substituted nitrosobenzene derivatives within the same flow set-up.^[19] Remarkably, this approach successfully led to the formation of the targeted ABs in high yields under the same optimized conditions. However, as anticipated, the freshly prepared nitrosobenzene derivatives displayed limited stability when stored for extended periods at ambient conditions. An in-situ preparation of nitrosobenzenes was targeted to overcome this obstacle and would also eliminate any health risks connected with the direct contact.

The oxidation of anilines towards their corresponding nitrosobenzene derivatives can be achieved through a biphasic reaction involving Oxone[®] to minimize side reactions.^[11,23] This approach aligns perfectly with our methods, as biphasic reactions profit from a continuous flow set-up due to the extended surface area between the phases compared to batch reactions. For this purpose, the aniline derivative was dissolved in dichloromethane (DCM) and Oxone[®] was dissolved in water. Both solutions were separately pumped and joined in a T-Mixer followed by a tube reactor (10 mL volume). The output of the reactor was fed into an in-line phase separator (Zaiput SEP-10, Figure 2). The organic phase was analysed by an in-line IR spectrometer (Mettler Toledo ReactIR 702L) and collected. This reaction was tested first for a *meta*-nitro-substituted aniline **1b**.

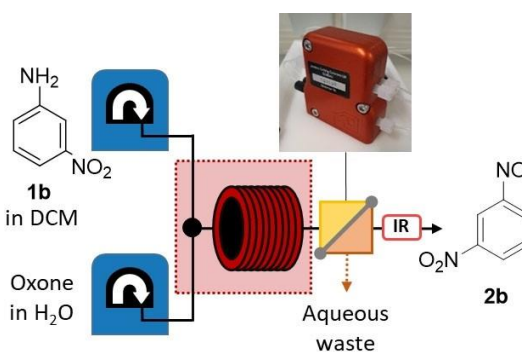


Figure 2. Schematic representation of the continuous flow synthesis of nitrosobenzenes.

The continuous flow reaction showed full conversion after a residence time of 50 min at room temperature and gave reasonable pure nitrosobenzene **2b** without the need for any further purification (Figure 2).

In the next step, we developed a flow system able to combine the oxidation of anilines to nitrosobenzenes with the subsequent Baeyer-Mills coupling to form ABs (Figure 3). Even though the oxidation was successful at room temperature, the reactor R1 was placed in an oil bath to ensure the possibility of increasing the temperature for less reactive starting materials. The output of the first reactor (R1, formation of the nitrosobenzene) was connected through a back-pressure generator (BPR) to an in-line phase separator. In-line reaction control was realized *via* an IR spectrometer and the output collected in a nitrogen-flushed container at 0 °C, as soon as a steady state was reached with a high conversion. The bright green solution of nitrosobenzene was then pumped into a second reactor to undergo the Baeyer-Mills reaction with a second aniline derivative (Figure 3). Also in this case, the reactor was placed into an oil bath to provide flexibility in temperature control. Additionally, more solvent was added after the second reactor

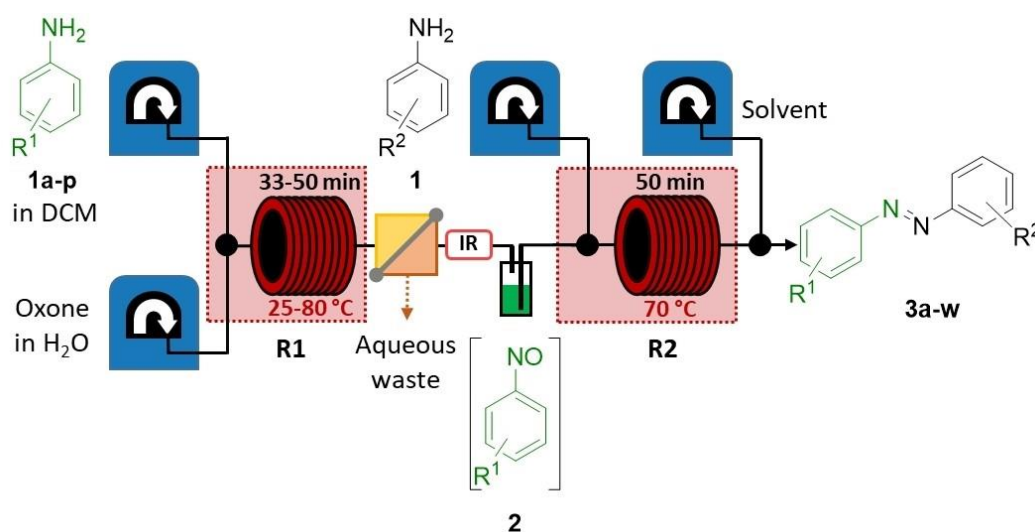


Figure 3. Schematic representation of the continuous flow synthesis of nitrosobenzenes followed by the telescoped Baeyer-Mills reaction.

to dilute the azobenzene solution and facilitates the reaction work up. To realize a reaction temperature of 70 °C, an additional BPR was used prior the collection valve.

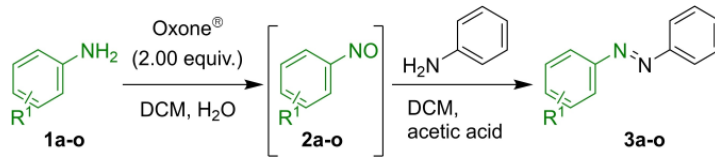
Accordingly, the in-situ synthesis of different nitrosobenzenes was performed using unsubstituted aniline as coupling partner. The procedure proved to be highly effective starting from electron-poor anilines ($-\text{NO}_2$, $-\text{CN}$, Table 1, entries 1–6). For each aniline, the reaction temperature of the first step was screened and the conversion was analysed by in-line IR spectroscopy or thin layer chromatography (Table 1). Despite of the use of dichloromethane as solvent, temperatures up to 80 °C were possible by the use of a BPR (75 psi), which represent an advantage over conventional batch synthesis. For most of the anilines, it was possible to increase the concentration up to 0.32 M. Attempts with a higher concentration of Oxone[®] resulted in reactor blockages. To keep the stoichiometric ratio, the flow rate was increased from 100 to 200 $\mu\text{L}/\text{min}$ and the reaction time ranged from 33 min to 50 min. The telescoped Baeyer-Mills reaction was performed at 70 °C for 50 min, as optimized during the previous studies.^[19] The products were extracted with cyclohexane and finally obtained as red compounds after solvent evaporation. To further explore the applicability of this method, additional anilines were tested.

Halide substituted anilines exhibited high yields for bromides and fluorides (Table 1, entries 8 and 9). In contrast, iodoaniline **1g** only gave moderate yields and led to reactor blockages, necessitating the use of less concentrated solutions (Table 1, entry 7). Electron rich substituted anilines (**1j–1o**) provided, as expected, only moderate yields and displayed over-oxidation to their nitro-analogues at elevated temperatures (Table 1, entries 10–15). Attempts to use larger alkyl groups, such as *n*-butyl, proved futile as they also resulted in over-oxidation even at low temperatures. Similar outcomes

were observed for moieties with a +M-effect, such as $-\text{OMe}$. Nevertheless, these electron-rich anilines exhibited good yields when employed as the coupling partner in the second step of the reaction, due to the electronic requirements of the Baeyer-Mills reaction, particularly with regard to nucleophilic attack.^[18] As a limitation, substituents that could undergo oxidations with Oxone[®] may cause low yields. However, it has been reported that Oxone[®] has been successfully used for the synthesis of nitrosobenzenes in the presence of a benzylic alcohol or an aldehyde.^[24]

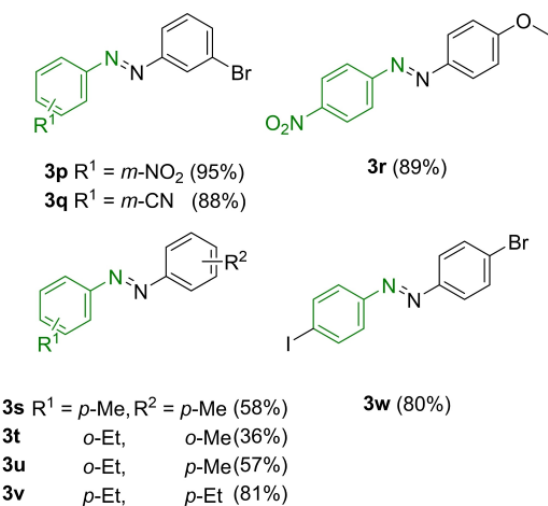
To further investigate the applicability of the method, unsymmetric ABs with more complex substitution pattern were synthesized (Figure 4). As mentioned before, electron-poor anilines are particularly suitable for the in-situ formation of nitrosobenzenes. Consequently, nitro- and cyano-substituted anilines were employed in the first reactor, while anilines, such as bromo-substituted (Figure 4, **3p–q**) and the electron-rich methoxy-substituted (Figure 4, **3r**), were used as second coupling partner. Those combinations gave excellent yields and depict an efficient and fast way to access the corresponding azobenzenes **3p–3v**. The synthesis of unsymmetric alkyl-alkyl-substituted azobenzenes resulted in a broad range of moderate yields, strongly influenced by the substitution pattern (Figure 4, **3s–3v**). Although the achieved yields were not excellent, this pathways proved to be a valid alternative for the synthesis of alkyl-alkyl-substituted ABs, reducing consistently the reaction time and work load for their synthesis from days to hours.^[25]

Finally, an asymmetric azobenzene containing two different halides was targeted as a modular building block for the synthesis of larger azobenzene-containing systems (Figure 4, **3w**). This specific substitution pattern enables to perform two selective cross-couplings with a minimal loss of selectivity.^[26] At first, the synthesis was done with the same conditions reported

Table 1. Optimized condition for the oxidation of different anilines and the yield after the telescoped Baeyer-Mills reaction in continuous flow.


Entry	1 st Aniline (R ¹ =)	c(Aniline)/m	T (R1)/°C	Reaction time R1/min	Yield of AB/%		
1	1a	<i>o</i> -NO ₂	0.16	80	50.0	3a	51
2	1b	<i>m</i> -NO ₂	0.16	25	50.0	3b	76
3	1c	<i>p</i> -NO ₂	0.16	50	50.0	3c	79
4	1d	<i>o</i> -CN	0.32	60	33.3	3d	85
5	1e	<i>m</i> -CN	0.32	50	33.3	3e	99
6	1f	<i>p</i> -CN	0.32	40	33.3	3f	71
7	1g	<i>o</i> -I	0.16	60	50.0	3g	59
8	1h	<i>o</i> -Br	0.32	55	33.3	3h	98
9	1i	<i>o</i> -F	0.32	55	33.3	3i	95
10	1j	<i>o</i> -Me	0.32	40	33.3	3j	69
11	1k	<i>p</i> -Me	0.32	45	33.3	3k	66
12	1l	<i>o</i> -Et	0.32	40	33.3	3l	59
13	1m	<i>p</i> -Et	0.32	50	33.3	3m	72
14	1n ¹	<i>p</i> - ^t Bu	0.32	42	40.0	3n	54
15	1o ²	3,5-di ^t Bu	0.27	50	50.0	3o	50

¹ Aniline 1n was dissolved in DCM/acetic acid (7/3) and Oxone[®] was pumped with 150 μL (1.5 equiv.). ² Oxone[®] was pumped with a flow rate of 100 μL (1.18 equiv.). See general procedure for further reaction conditions.

**Figure 4.** Substituted ABs, which were synthesized from substituted anilines using the same continuous flow set-up.

above. However, the target azobenzene crushed out in the second reactor causing a blockage in the flow set-up. Therefore, the solvent for the second aniline (4-bromoaniline) was

changed to a mixture acetic acid and dichloromethane (1:9). This adjustment proved to be successful, resulting in the formation of AB 3w in a yield of 80%.

Most of the synthesized ABs showed small amounts of substituted nitrobenzenes from over-oxidation or azoxybenzenes as impurity. The crude products were purified or flash column chromatography. However, good results were already obtained by filtration through a pad of silica in some cases.

Conclusions

In conclusion, a continuous flow method for the synthesis of nitrosobenzene compounds through oxidation using Oxone[®] was developed. The reaction conditions were optimized for a variety of different electron-poor and electron-rich anilines. These reactive intermediates were further used in a telescoped Baeyer-Mills reaction to obtain different ABs in moderate to high yields. This method represents a safer access to substituted nitrosobenzenes, which finds application in a variety of other transformations. The application of flow chemistry does not only allow accessing larger amounts of material, the in-situ generation of the hazardous and instable nitrosobenzene intermediate minimizes the health risk. Moreover, it provides an alternative modular and timesaving way to synthesize azobenzene derivatives as the choice of anilines for the nitroso

synthesis can be conveniently altered depending on its reactivity for the desired substrate.

Experimental Section

1-Nitro-3-nitrosobenzene 2b

A solution of 3-nitroaniline (1b) in dichloromethane (0.32 M) and a solution of Oxone® in water (0.16 M) were pumped individual with a flow rate of 100 $\mu\text{L}/\text{min}$ for the aniline solution (1.00 equiv.) and 200 $\mu\text{L}/\text{min}$ for the Oxone® solution (2.00 equiv.). The streams were joined in a T-mixer, followed by a tube reactor (10 mL, 33.3 min residence time). The biphasic reactor output was separated by an in-line phase separator (SEP-10, hydrophobic OB-900 membrane). After equilibration, the green organic phase was collected for 30 min and the solvent was removed using a stream of nitrogen. An off-white solid was obtained (117 mg, 0.769 mmol, 79%).

^1H NMR (200 MHz, CDCl_3) δ 8.65–8.55 (m, 2H), 8.38–8.30 (m, 1H), 7.95–7.83 (m, 1H).

Due to the low stability only ^1H NMR data were recorded. Analytical data correspond to the literature.^[27]

General procedure for the synthesis of AB derivatives 3a–3w

Aniline was dissolved in dichloromethane (0.16 M or 0.32 M, see Table 1). Oxone® was dissolved in water (0.32 M). Both solutions were pumped individual with a flow rate of 100 $\mu\text{L}/\text{min}$ for the aniline solution (1.00 equiv.) and 200 $\mu\text{L}/\text{min}$ for the Oxone® solution (1.18–2.00 equiv., see Table 1). The streams were joined in a T-mixer, followed by a tube reactor (10 mL, 33.3 min–50.0 min residence time). A BPR (75 psi) was used after the reactor. The biphasic reactor output was separated by an in-line phase separator (SEP-10, hydrophobic OB-900 membrane). After equilibration, the green organic phase was collected in a container (cooled to 0 °C). A second aniline was dissolved in acetic acid (0.16 M or 0.32 M) and pumped with a flow rate of 100 $\mu\text{L}/\text{min}$ (1.00 equiv.). Both, the nitrosobenzene solution (flow rate of 100 $\mu\text{L}/\text{min}$) and the second aniline solution were pumped through a second mixer followed by a tube reactor at 70 °C (10 mL, 50.0 min residence time). After this reactor, cyclohexane was added in a third mixer with a flow rate of 1.00 mL/min. A BPR (75 psi) was used after the third mixer. The output was collected in a separatory funnel. The organic phase was extracted with dichloromethane and dried over sodium sulfate. The solvent was removed under reduced pressure. Crude products were purified by column chromatography [SiO_2 , cyclohexane/toluene ($v/v = 2/1$ or $1/1$)]. Yields are given in Table 1 or Figure 4. Further experimental details, spectra and analytical data are reported in the supporting information.

The authors have cited additional publications as a reference for analytical data in the supporting information.^[28]

Acknowledgements

The authors acknowledge financial support by the Deutsche Forschungsgemeinschaft (DFG) within the Research Unit FOR 5499 “Molecular Solar Energy Management - Chemistry of MOST Systems”. Open Access funding enabled and organized by Projekt DEAL.

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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Manuscript received: November 21, 2023

Revised manuscript received: January 17, 2024

Accepted manuscript online: January 19, 2024

Version of record online: ■■, ■■

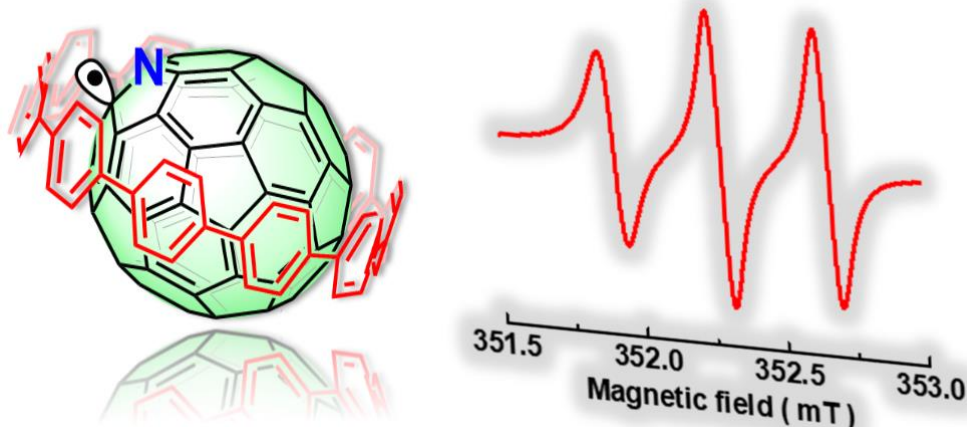
5 Additional Contributions to the Literature

A Long-Lived Azafullerenyl Radical Stabilized by Supramolecular Shielding with a [10]Cycloparaphenylene

Reference: A. Stergiou, J. Rio, J. H. Griwatz, D. Arčon, H. A. Wegner, C. P. Ewels, N. Tagmatarchis, *Angew. Chem. Int. Ed. Engl.* **2019**, *58*, 17745.

DOI: 10.1002/anie.201909126

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“A major handicap towards the exploitation of radicals is their inherent instability. In the paramagnetic azafullerenyl radical C₅₉N[•], the unpaired electron is strongly localized next to the nitrogen atom, which induces dimerization to diamagnetic bis(azafullerene), (C₅₉N)₂. Conventional stabilization by introducing steric hindrance around the radical is inapplicable here because of the concave fullerene geometry. Instead, we developed an innovative radical shielding approach based on supramolecular complexation, exploiting the protection offered by a [10]cycloparaphenylene ([10]CPP) nanobelt encircling the C₅₉N[•] radical. Photoinduced radical generation is increased by a factor of 300. The EPR signal showing characteristic ¹⁴N hyperfine splitting of C₅₉N[•] ⊂ [10]CPP was traced even after several weeks, which corresponds to a lifetime increase of >10⁸. The proposed approach can be generalized by tuning the diameter of the employed nanobelts, opening new avenues for the design and exploitation of radical fullerenes.”

6 Abbreviations

AB	Azobenzene
AcOH	Acetic acid
Aq.	Aqueous
Ar	Aryl
<i>n</i> -BuLi	<i>n</i> -Butyllithium
<i>tert</i> -Buli	<i>tert</i> -Butyllithium
Bpin	Pinacolborane
cat.	catalyzed
CPP	Cycloparaphenylene
d	Day
δ	Chemical shift
DMF	<i>N,N</i> -Dimethylformamide
DPPA	Diphenylphosphoryl azide
EOx	Electrochemical oxidation
Et-	Ethyl-
e.g.	<i>Exempli gratia</i> , for example
Equiv.	Equivalents
g	Gram
h	Hour
IR	Infrared
L	Liter
<i>m</i>	<i>meta</i>
M	Molar
Me-	Methyl-
min	Minute
MOM	Methoxymethyl
MOST	Molecular solar thermal energy storage
NMR	Nuclear magnetic resonance
<i>O</i>	<i>ortho</i>
PIDA	(Diacetoxyiodo)benzene
R1/R2	Reactor 1/2

s	Second
S-Phos	Dicyclohexyl(2',6'-dimethoxy[1,1'-biphenyl]-2-yl)phosphane
TBAF	Tetrabutylammonium fluoride
THF	Tetrahydrofuran
TMSCl	Trimethylsilyl chloride
us	Ultrasonic
rt	Room temperature
UV	Ultraviolet
VIS	Visible
X	Halogen (F, Cl, Br, I)

7 Danksagung

Zu Beginn möchte ich mich bei meinem Doktorvater Prof. Dr. Hermann A. Wegner bedanken für die Möglichkeit meine Doktorarbeit in der AG Wegner anzufertigen. Ich bin dankbar für die vertrauensvolle Unterstützung und Hilfe bei der Bearbeitung dieser spannenden und immer wieder anspruchsvollen Forschung, zu deren Erfolg er mit seinen hilfreichen und kreativen Ideen maßgeblich beigetragen hat.

Außerdem möchte ich mich herzlich bei Prof. Dr. Bernd Smarsly für das Anfertigen des Zweitgutachtens bedanken.

Ein besonderer Dank gilt meiner Frau Celine, ohne die ich diese Zeit mit Sicherheit nicht so hätte meistern können. Mit ihrem Verständnis, gerade auch in den stressigen und frustrationsreichen Zeiten, und dem Gefühl für die richtigen Worte, hat sie mich immer wieder aufgebaut und mir Kraft gegeben.

Auch meinem Sohn Felix möchte ich von Herzen für die vielen schönen Augenblicke danken und dafür, dass ein Lächeln von ihm reicht, um Stress und Zeitdruck für einen Moment zu vergessen.

Aufrichtiger Dank gilt meinen Eltern, meinem Bruder David und meiner gesamten Familie. Durch ihre beständige Unterstützung haben sie mir das Studium und Promotion erst ermöglicht und ich konnte mich zu jeder Zeit auf ihre Hilfe und Unterstützung verlassen.

Ich danke von Herzen der gesamten Arbeitsgruppe Wegner. Besonders bedanken möchte ich mich bei der „Nanocarbon-Subgroup“ Dr. Jannis Volkmann, Dr. Daniel Kohrs, Felix Bernt und Nathaniel Ukah. Eure Hilfe in Theorie und Praxis, eure guten Ideen und eure kritischen Nachfragen haben mir sehr geholfen und dadurch zum Erfolg dieser Arbeit beigetragen. Für die großartige Zeit, die entspannte, freundschaftliche Atmosphäre im Labor und in der Arbeitsgruppe, ebenso wie die schönen Kaffeepausen, und Feierabendbiere, danke ich den ehemaligen und aktuellen Mitgliedern der Arbeitsgruppe Dr. Andreas Heindl, Dr. Sebastian Schmalisch, Sebastian Beeck, Dr. Sebastian Ahles, Dr. Long-Chen Hong, Dr. Anne Kunz, Dr. Julia Ruhl, Dr. Marcel Strauß, Dr. Atanu Patra, Dr. Jan Geldsetzer, Mari Janse van Rensburg, Katinka Grimmeisen, Elena Berger, Finn Schneider, Giovanni Parolin, Chiara di Berardino, Chiara Campi, Dominik Schatz, Conrad Averdunk, Christopher Leonhardt, Michel Große und Kai Hanke, Pia Mader, Silke Müsse und Rouven Fritzius. Weiterer Dank gilt meinen ehemaligen

Studenten Mika Keßler, Christian Wolf und Paul Wiebe von und mit denen ich immer wieder neues lernen konnte.

Unseren Kooperationspartnern bin ich für die konstruktive und freundschaftliche Zusammenarbeit dankbar. Besonderer Dank gilt hierbei Dr. Nikos Tagmatarchis, Dr. Anika Tarasewicz und Dr. María Méndez Pérez, ebenso wie ihren Mitarbeitern für die herzliche Aufnahme in ihren Laboren.

Ich möchte auch den anderen Arbeitsgruppen des Instituts, der AG Schreiner, der AG Gellrich sowie der AG Göttlich für die gute Zusammenarbeit, Hilfsbereitschaft und freundschaftliche Atmosphäre danken.

Des Weiteren gilt ein großer Dank allen Mitarbeiter:innen des organischen Instituts der JLU, die mir mit technischer und administrativer Hilfe zur Seite standen und die diese Arbeit mit ihrer Hilfe und ihren Messungen erst möglich gemacht haben. Dabei danke ich Dr. Heike Hausmann, Anika Bernhardt, Anja Platt und Inna Klein für die Messung aller NMR-Spektren, auch wenn die Proben oft tückisch waren, oder es schnell gehen musste. Außerdem danke ich Dr. Raffael Wende, Stefan Bernhardt, Steffen Wagner, Brigitte Weinl-Boulakhrouf und Edgar Reitz. Des Weiteren danke ich dem Team der Chemikalienausgabe: Eike Santowski und Mario Dauber, sowie dem Team der Materialienausgabe und Glasbläserei: Anja Beneckenstein, Dr. Wolfgang Herrendorf, Hans-Jürgen Wolf, Michaela Jäkel und Petra Grundmann für die Bereitstellung und Bestellungen von Chemikalien und Laborausstattung. Vielen Dank auch an Dr. Jörg Neudert, der bei der allgemeinen Organisation des Instituts sowie der OC-Praktika immer zuvorkommend und unterstützend handelte.

Zuletzt geht ein großer Dank an Anika Jäger, Michaela Richter, Doris Verch und Maurice Monnard, die mir bei organisatorischen und verwaltungstechnischen Fragen und Abläufen immer helfend zur Seite standen.

NACH §17 DER PROMOTIONSORDNUNG

Ich erkläre: Ich habe die vorgelegte Dissertation selbstständig und ohne unerlaubte fremde Hilfe und nur mit den Hilfen angefertigt, die ich in der Dissertation angegeben habe. Alle Textstellen, die wörtlich oder sinngemäß aus veröffentlichten Schriften entnommen sind, und alle Angaben, die auf mündlichen Auskünften beruhen, sind als solche kenntlich gemacht. Ich stimme einer evtl. Überprüfung meiner Dissertation durch eine Antiplagiat-Software zu. Bei den von mir durchgeführten und in der Dissertation erwähnten Untersuchungen habe ich die Grundsätze guter wissenschaftlicher Praxis, wie sie in der „Satzung der Justus-Liebig-Universität Gießen zur Sicherung guter wissenschaftlicher Praxis“ niedergelegt sind, eingehalten.

Jan Henning Griwatz

Ort, Datum

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Erstgutachter: Prof. Dr. Hermann A. Wegner

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