Charles University in Prague
Faculty of Science

Organic Chemistry

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Π-Konjugované oligomery obsahující helikálně chirální jednotky

Π-Conjugated Oligomers Comprising Helically Chiral Units

Diploma Thesis

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Prague, 2015

Prohlášení:

Prohlašuji, že jsem závěrečnou práci zpracoval samostatně a že jsem uvedl všechny použité informační zdroje a literaturu. Tato práce ani její podstatná část nebyla předložena k získání jiného nebo stejného akademického titulu.

V Praze, 13. 5. 2015

Václav Houska

Acknowledgement:

It would not be possible to finish this work without help of many people. Every single person was irreplaceable in this process but few of them really stand apart. These are my parents and my whole family who have been supporting me in my scientific endeavor since my childhood and without whose help I would not be able to finish my Bachelor and Master studies. The same thanks belong to my supervisors Dr. Irena G. Stará and Dr. Ivo Starý who not only were helping me to overcome theoretical and experimental problems but gave me an enormous freedom in my research and overall support. I also would like to thank all other members of our research group who created an intellectually stimulating and friendly atmosphere, especially to Dr. Jiří Rybáček. Furthermore, I would like to acknowledge the analytical department of IOCB, particularly Dr. David Šaman and Dr. Miroslav Fiedler and the members of the MS team for their help with NMR, IR and MS analysis. I am also grateful to my chemistry teachers Mgr. Vlastimil Michalec and Dr. Hana Malaníková who introduced me to chemistry and made sure that I would survive my chemical puberty with all my limbs and eyes still functional. Last but not least, I would like to express my gratitude to all my friends who helped to create the non-chemical part of my life.

Abstract:

The synthesis of large, shape-persistent, trimeric macrocycles comprising helical units was investigated. Since the previous synthetic approaches studied in our group failed (mainly alkene and alkyne ring closing metathesis), a more robust route toward the desired macrocycle was sought. A sequential construction of an acyclic trimer employing cross-coupling reactions was expected to overcome the unwanted oligomerization encountered in the case of the earlier metathesis approaches. The closure of the trimer would be accomplished *via* the intramolecular McMurry reaction or alkene metathesis. An optimized synthesis of the solubilized dibenzo[5]helicene and its derivatives was developed. These compounds served as proposed building blocks of the acyclic trimer. Both Heck and Suzuki-Miyaura couplings used for the preparation of the acyclic trimers provided mixtures containing the desired trimers but the Suzuki-Miyaura reaction proved to be much more efficient. However, the solubility of the trimers turned out to be very low, making the separation of the pure products from the mixture impossible and seriously limiting the further synthetic progress. Only alkene metathesis of the corresponding divinyltrimer was accomplished and despite a low solubility of the starting material, the MS analysis of the resulting mixture confirmed a preferential formation of the desired trimeric macrocycle. Despite the encountered problems, the achieved results proved the synthetic concept to be correct and left a room for further development in the project.

Key words:
Shape persistent macrocycles, dibenzohelicenes, Heck reaction, Suzuki-Miyaura reaction, alkene metathesis, McMurry reaction.

V rámci diplomové práce byl výzkum zaměřen na syntézu velkých rigidních makrocyklů obsahujících helikální jednotky. Dřívější syntetické přístupy studované v naší skupině (využívající zejména metathesi alkenů a alkynů) selhaly a bylo proto zapotřebí hledat robustnější syntetickou cestu. Postupná konstrukce acyklického trimeru za použití cross-couplingových reakcí se zdála být vhodným postupem eliminujícím nechtěnou oligomerizaci, jež byla pozorována u syntéz využívajících metathesi. Pro uzavření makrocyklu se jevilo použití intramolekulární McMurryho reakce nebo metathese alkenů jako vhodné řešení. V rámci této práce byla vyvinuta optimalizovaná syntéza solubilizovaného dibenzo[5]helicenu a jeho derivátů, které měly sloužit jako stavební bloky zamýšleného acyklického trimeru. Jak Heckova, tak Suzukiho-Miyaurova reakce vedly ke směsím obsahujím žádaný trimer, ovšem pouze Suzukiho-Miyaurova reakce poskytla uspokojivé výsledky. Rozpustnost připravených směsí však byla velice nízká, což znemožňovalo izolaci čistých produktů a další syntetický postup. V případě divinyltrimeru se podařilo provést finální metathesi. Vzniklá směs byla analyzována pomocí hmotnostní spektrometrie, která prokázala preferovaný vznik žádaného makrocyklu. Navzdory uvedeným problémům ponechávají dosažené výsledky prostor pro další postup v tomto projektu.

Klíčová slova:
Rigidní makrocykly, dibenzoheliceny, Heckova reakce, Suzukiho-Miyaurova reakce, metathese alkenů, McMurryho reakce.

Tato práce je věnována mému dlouholetému učiteli a příteli Vlastovi Michalcovi, neboť bez něj by vůbec nevznikla.

This work is dedicated to my long-time teacher and friend Vlasta Michalec, without whom it would not be created at all.

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1. Theoretical background and review of current literature

1.1. The world is made of cyclic molecules

The world around us is full of cyclic compounds. DNA, for instance, is a chain of nucleotides that all consist of cyclic deoxyribose and a cyclic nucleobase. And even the DNA chain itself can be cyclic like that of plasmids found in bacteria (Figure 1). Similarly, a lot of amino acids contain cyclic structures, the most common sugars form cycles and many terpenes, like steroid hormones, for instance, are another example of cyclic molecules. We can find cycles in many synthetic organic compounds produced in chemical industry too.

Figure 1. Structure of DNA consisting of many cyclic molecules – deoxyribose and four types of heterocyclic bases and a picture of plasmidic DNA – examples of natural cyclic structures [1]

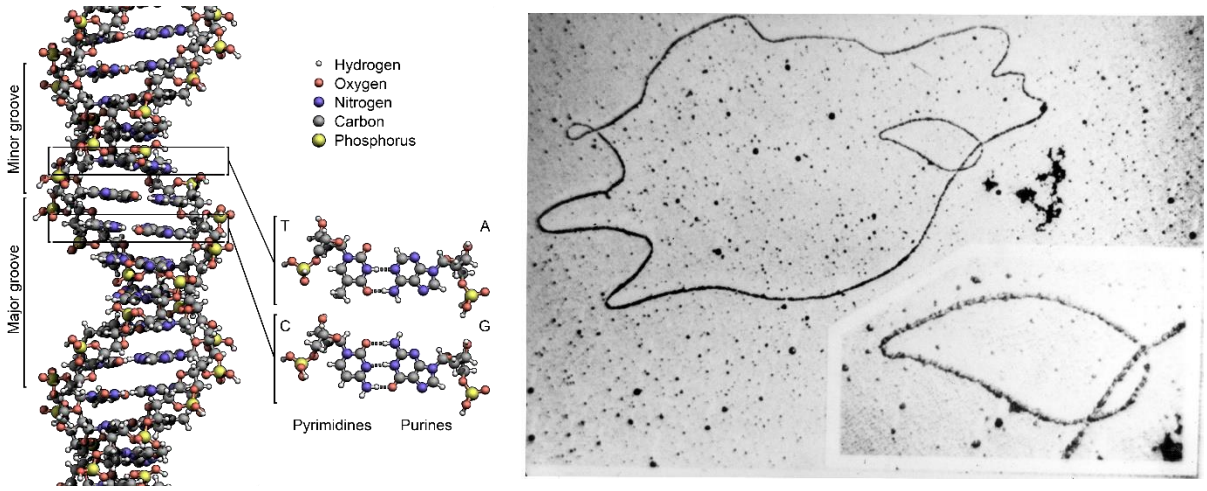
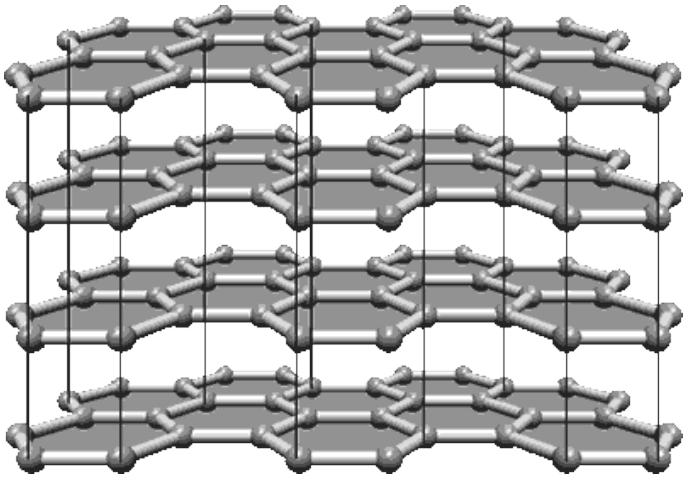


Figure 2. Structure of graphite. Graphene sheets are, in fact, polycyclic molecules. [2]



On the other hand, graphite, an example of a typically inanimate material found in nature, consists of carbon atoms arranged in six membered rings, endlessly repeating to form graphene sheets (Figure 2). Likewise, sulfur's most common modification consists of eight membered rings. And the list could go on. In many of these examples, cycles are rather small, comprising just few atoms, in other instances, such as the aforementioned cyclic DNA, the

cycles can be of such a size that it is hard to believe that they are actually formed by just one single molecule!

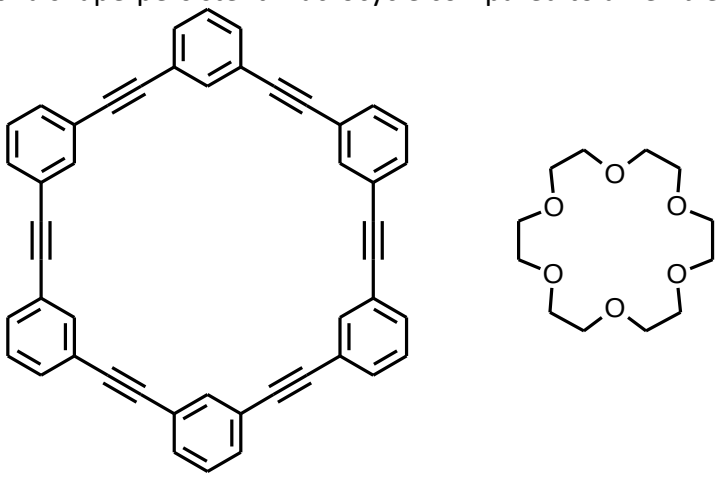
But why is it that so many natural materials, either of biological or other origin, are based on cyclic structures? There are probably several reasons for that. The most obvious one is that bonding properties of carbon, nitrogen, oxygen or sulfur, elements usually built into cyclic molecules, allow such a topology. But perhaps more important is the shape and rigidity that the cyclic building blocks bring into the material. In some cases a steric bulk associated with a cyclic structure, can play a vital role in an active site of an enzyme, [3] something that would not be possible with a linear chain. In other cases, cycles can be very robust, both chemically and mechanically, and that is why, for example, cellulose is formed of long chains of cyclic glucose units of remarkable chemical and mechanical resistance. It was found that some forms of cellulose fibers have tensile strength comparable to iron, far behind the values for linear polymers such as polyethylene. [4] Of course, the presence of cyclic glucose units in cellulose is not a sole origin of such properties (hydrogen bonding is very important for this too) but it is difficult to imagine such features without the cyclic structure. Cyclic topology has obviously many advantages.

On the other hand, no matter how robust molecules of DNA and cellulose (used here as examples) are, it still allows them to bend and change their shape when needed. This fact is vital for their biological functions. These molecules are quite flexible due to their flexible building blocks. Saccharide units, both in DNA and cellulose, can be stretched and can rotate about the bonds that connect them together to some extent. [5] In other words, these cycles and the whole structures they are forming are examples of shape non-persistent molecules. It is important for their function, of course, to behave like this. On the other hand, in many applications it is necessary to have almost completely rigid structure that does not bend or rotate. Graphite, mentioned above, could not be used in pencils if it was flexible. Graphite structure is thus an example of so-called shape-persistent architecture - its shape and size remain relatively intact to the external forces.

1.2. Shape-persistent macrocycles

As shown in the previous Chapter, cyclic molecules play an important role both in nature and industry. A special class of new compounds that have been studied during past decades are so called shape-persistent macrocycles (SPMs). As their name suggests, they are large cyclic molecules of low flexibility which ensures the aforementioned shape-persistence. Rigidity of SPMs is mostly due to the presence of an extensive π-conjugated system. This conjugation, however, is also a source of other rather unusual electrical, magnetic and optical properties. [6], [7] Apart from very appealing applications of SPMs in the future, their synthesis is no less interesting and, especially for large macrocycles or structures with unusual shape and functionality, poses a real challenge. Various possible methods for the synthesis of SPMs have been extensively reviewed in several articles as well as in my Bachelor Thesis and will be discussed here only in general terms.[6], [7], [8]

Figure 3. Example of a shape-persistent macrocycle compared to a flexible crown[6]ether



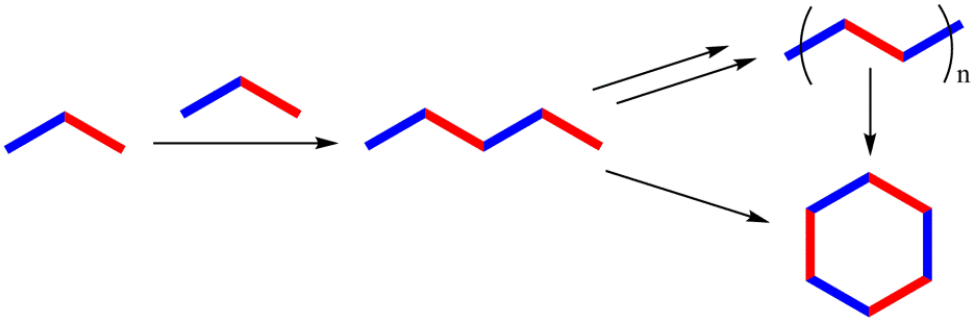
1 **2**

1.2.1. Synthesis of shape persistent macrocycles

The synthesis of SPMs is an interesting chemical problem. Generally, the synthetic strategies can be divided into two main groups: kinetically and thermodynamically controlled. While the kinetic approach relies on the relative reaction rate of product formation, the thermodynamic approach is based on the relative free energy of products formed. The most preferred molecule is formed in the largest amount.

There are many various strategies using kinetically controlled reactions. In most cases, metal catalyzed coupling reactions are used for this purpose. In the simplest strategy, a monomer containing two complementary functional groups is allowed to oligomerize to afford a mixture of various oligomers. The desired macrocycle is one of many products and the yield of such a reaction is therefore low. (Figure 4).

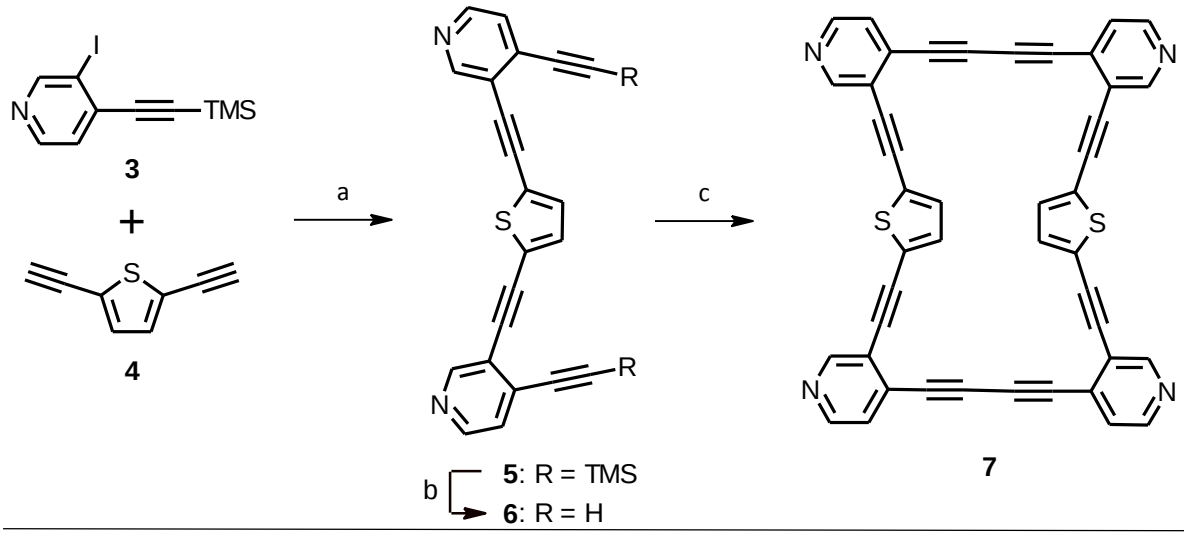
Figure 4. Schematic representation of kinetic and thermodynamic formation of macrocycles



A disadvantage of such a way is obvious and attempts to overcome it by various means have been made. Usually, the macrocycle is built from two or more large building blocks and the cyclization step is postponed to the latest stage of the synthesis where a high dilution cyclisation, a common way to avoid formation of linear oligomers, can be used. The structure of the final product is encoded by the right choice of functionalities of the building blocks. More complicated target molecules usually require a time demanding and laborious synthesis involving many steps and giving low overall yields. Conversely, it is the most general approach allowing to prepare molecules of enormous complexity with no symmetric prerequisites.

Scheme 1 shows a typical example. [9] The starting material for macrocycle **7** were pyridine and thiophene precursors **3** and **4** which had been prepared *via* a sequence of Sonogashira and deprotection reactions. Compounds **3** and **4** were connected *via* Sonogashira coupling and a subsequent removal of trimethylsilyl groups afforded compound **6**. The final cyclization was accomplished using Glazer coupling in 46 % to give the target compound **7**.

Scheme 1. Step by step synthesis of a macrocycle

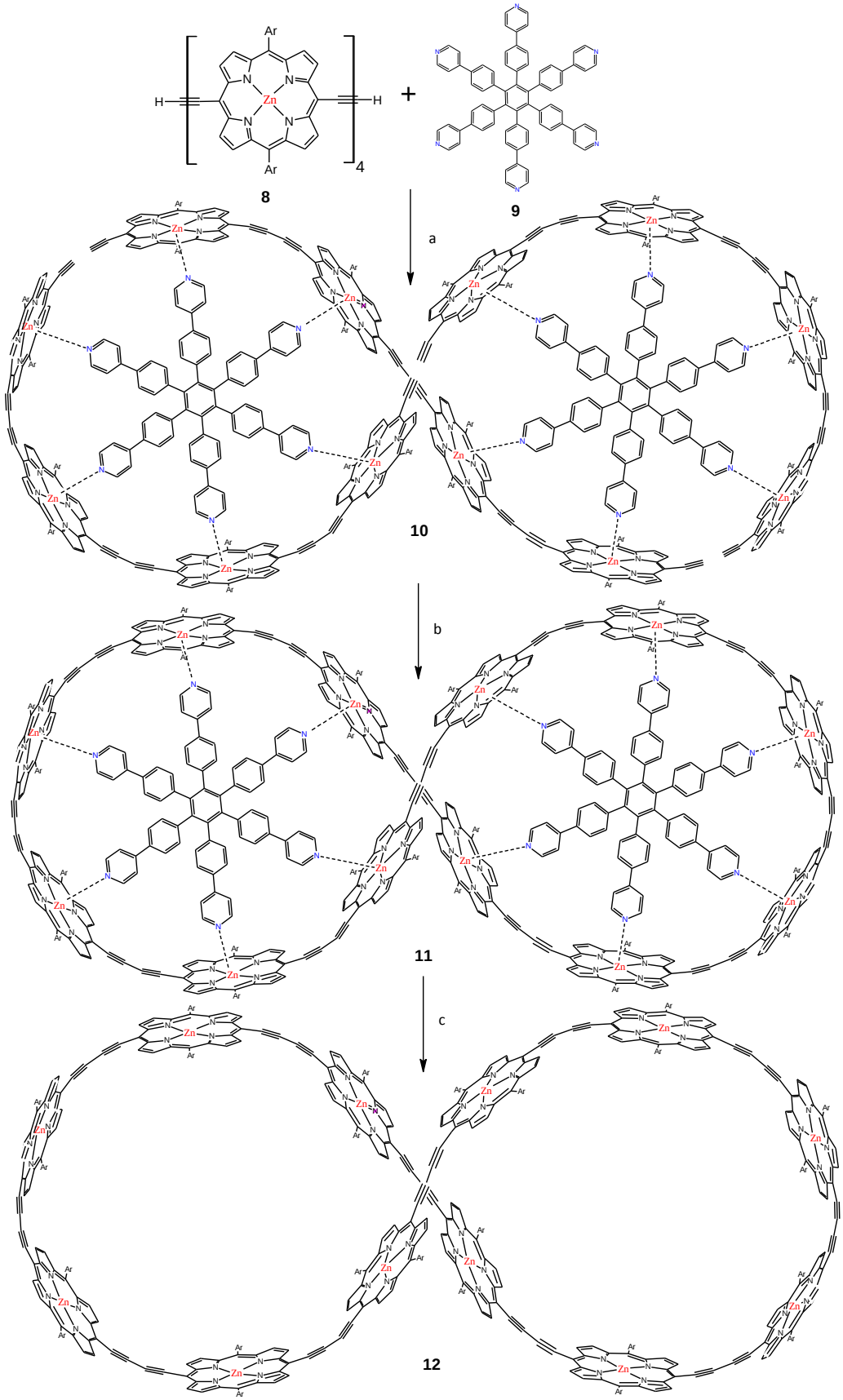


a) $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, toluene, rt, 120 h, 54 %; b) TBAF, THF, H_2O, rt, 20 h 88 %; c) $Cu_2(OAc)_4.2H_2O$, pyridine, rt, 168 h, 46 %. [9]

In this example, the structure of the final macrocycle was preset by the position of the substituents in the starting compounds **3** and **4** and by the appropriate order in the sequence of deprotection and Sonogashira couplings. A different order of the individual steps would not lead to the desired product.

Another way to control the geometry of the final product is to use a template. Significantly fewer steps is usually required compared to the previous example, since the desired geometry is transferred from the template to the product. The binding sites of the template match the complementary sites of the building blocks and then some suitable reaction is used to close the cycle in one step. The disadvantage of this strategy is that the product's symmetry is limited by the symmetry of the template and therefore macrocycles prepared this way are usually highly symmetric. An amazing example is a synthesis of an enormous porphyrin macrocycle **12** containing 12 porphyrin units developed by Anderson et al (Scheme 2). [10] In this case, a unique Vernier principle was applied to build a macrocycle having more binding sites than the template. This truly ingenious strategy allows to prepare molecules significantly bigger compared to the size of the template (whose synthesis can be also laborious) while keeping the precise geometry of the product. The principle behind this is very simple. The number of reacting molecules of the template and building blocks are dictated by the least common multiple of the numbers of their binding sites. So for instance, in Scheme 2, four binding sites of the porphyrin building block **8** combine with six binding sites of the template **9** to form a twelve membered complex **10**. The following Glaser coupling of the free alkyne groups on **10** and subsequent removal of the templates gives the final porphyrin ring **12**.

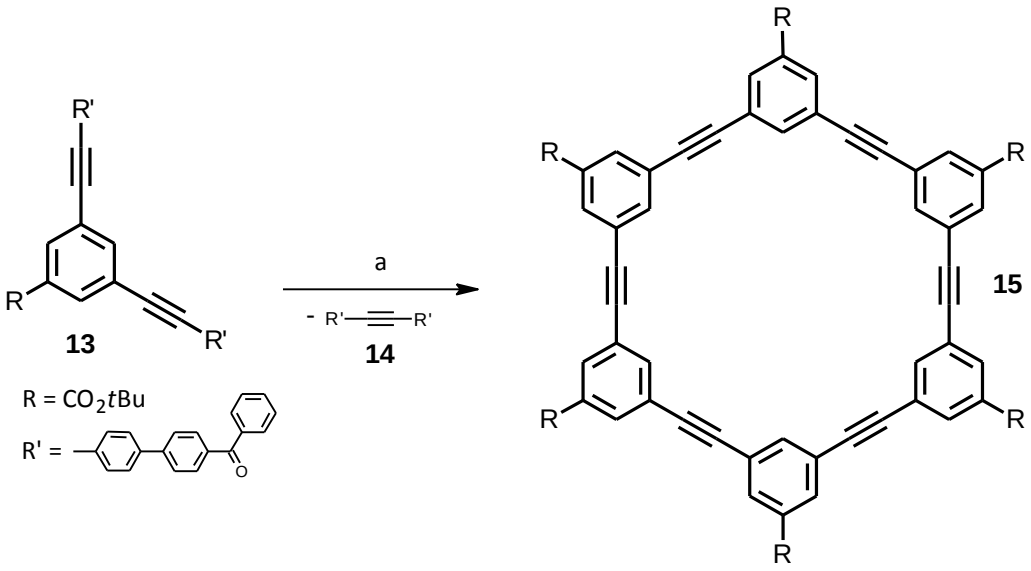
Scheme 2. Synthesis of a large **12**-porphyrin macrocycle



a) $CHCl_3$, sonication, rt, 1 h; b) $Pd(PPh_3)_2Cl_2$, CuI, benzoquinone, CHCl3, 20 - 50 °C, 2.5 h, 39 % over 2 steps; b) GPC using pyridine – toluene eluent, rt, 98 %. [10]

As stated above, another common strategy for the synthesis of SPM's, popular especially in recent years, is to use thermodynamically controlled reactions. A typical example can be the synthesis of *m*-phenyleneethynylene macrocycles using alkyne metathesis introduced by Moore and co-workers (Scheme 3). Since alkyne metathesis is in principle a reversible reaction, provided several products can be formed, the one with the largest relative free energy of formation is preferred. Such a reaction is especially efficient if the equilibrium is shifted by removal of the alkyne by-product. Moore and his group developed a protocol where the starting alkynes **13** were equipped with benzoylbiphenyl groups to shift the equilibrium of the reaction by the formation of insoluble alkyne **14**. The efficiency of the synthesis was thus greatly improved, allowing a gram-scale preparation of the *m*-phenyleneethynylene macrocycles such as **15** for the first time. [11]

Scheme 3. Synthesis of *m*-phenyleneethynylene macrocycle *via* alkyne metathesis



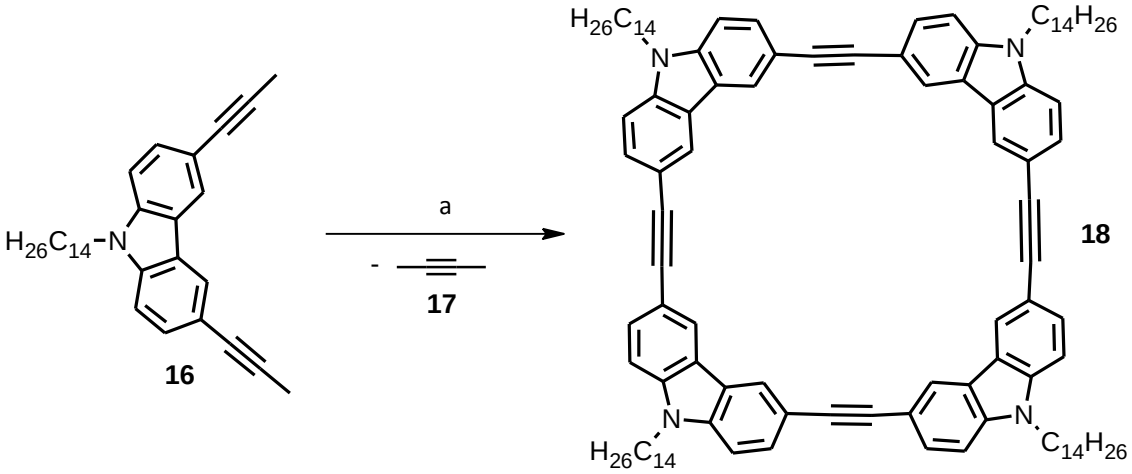
a) {EtC≡Mo[NAr(*t*-Bu)]$_3$}, *p*-nitrophenol, CCl_4, 30 °C, 22 h, 79 %. [11]

On the other hand, Fürstner et al decided to terminate the alkyne groups of **16** with methyls. 2-Butyne formed during the reaction to afford macrocycle **18** was then removed by adsorption on molecular sieves (Scheme 4). [12]

In both instances, shifting the equilibrium along with the thermodynamically preferred structure allowed the preparation of the macrocycles in high yields. The disadvantage of the letter method is that the thermodynamic preference of the product is given by its structure, especially by the amount of strain present in the product along with entropy increase generated during the reaction. Therefore, more strained molecules with unusual geometries are usually inaccessible by this method.

Only a brief overview of synthetic approaches was discussed in the preceding paragraphs. For more detailed information see the references. [6], [7], [8]

Scheme 4. Fürstner's synthesis of a shape-persistent macrocycle

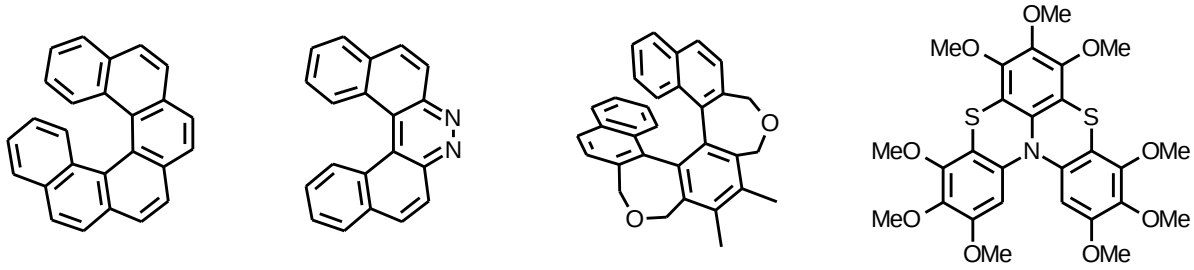


a) {N≡Mo[OSiPh$_3$]$_3$phen}, MnCl$_2$, toluene, MS 5A, 80 °C, 24 h, 83 %. [12]

1.3. Helicenes and their synthesis

Helicenes are *ortho*-fused polycyclic aromatic compounds with a screw-like geometry. Examples of various helicenes are shown in Figure 5. As can be seen, the structural variety of helicenes is almost endless. Helicenes are often conjugated systems and they possess interesting electronic, magnetic and optical properties. Their shape is also a source of their chirality and helicenes therefore exhibit unusually high optical rotation. [13], [14], [15]

Figure 5. Various kinds of helicenes



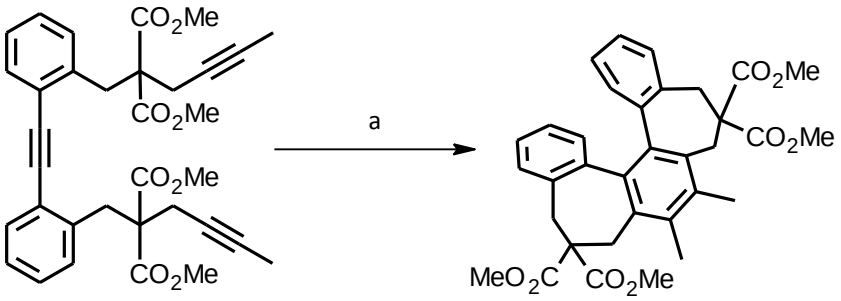
19 **20** **21** **22**

Helicenes might be applied to different areas of science. First, in material science some helicenes are intensively studied as possible molecular wires due to their electrical conductance. [16], [17] Similarly, helicenes have been proposed to act as nano electromagnets, which relates to their coil-like shape. [18] Application of helicenes as ligands has been a long time interest within the synthetic community. Some heterohelicenes have been used as chiral ligands under both metal catalyzed [19], [20] and organocatalytic conditions [21] and, indeed, high enantiomeric excess was achieved in some cases.

1.3.1. Synthesis of helicenes using [2+2+2] cyclotrimerization

It is not the aim of this Introduction to provide a comprehensive review of the whole area of helicene synthesis. However, [2+2+2] cyclotrimerization approach, developed in our group, represents a very convenient route to helicenes and was also used in this study. A brief review of this methodology is therefore presented below.

Scheme 5. Synthesis of helicene-like compound using [2+2+2] cyclotrimerization

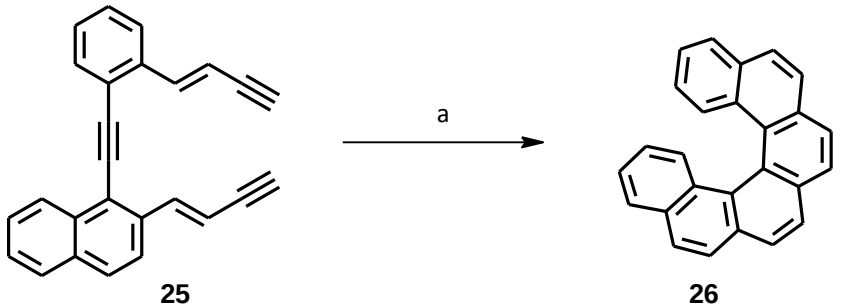


23 **24**

a) $CpCo(CO)_2$, PPh_3, decane, 140 °C, 30 min, 83 %. [22]

First synthesis of helicene-like compounds *via* [2+2+2] cyclotrimerization of alkynes using Co^I catalysis was published by Starý and Stará et al in 1998 (Scheme 5). [22] A whole new class of helically chiral molecules having incorporated seven-membered rings was thus prepared demonstrating the versatility and effectiveness of this new method. One of the drawbacks of the previously utilized photodehydrocyclization was the need for a highly diluted reaction mixture. [23] In the case of alkyne cyclotrimerization, this was no longer needed. Helicenes and their analogues could be prepared in larger quantities with a great variety of functional groups present in the molecules. Syntheses of more complex structures soon followed. Fully conjugated helicenes were first prepared by dehydrogenation of the corresponding tetrahydro precursors obtained by the cyclotrimerization. [24] Probably the most straightforward route towards these compounds leads through dienetriynes (Scheme 6). [25] However, the difficulties encountered during the course of the synthesis, mainly instability of the starting dienetriynes, were stimuli to develop a more robust approach. An alternative was to introduce acetoxy groups that could be easily eliminated after the cyclotrimerization step to aromatize the helicene backbone. [26] Thus diacetyloxy triynes were

Scheme 6. Starý and Stará's approach to the synthesis of helicenes *via* dienetriynes

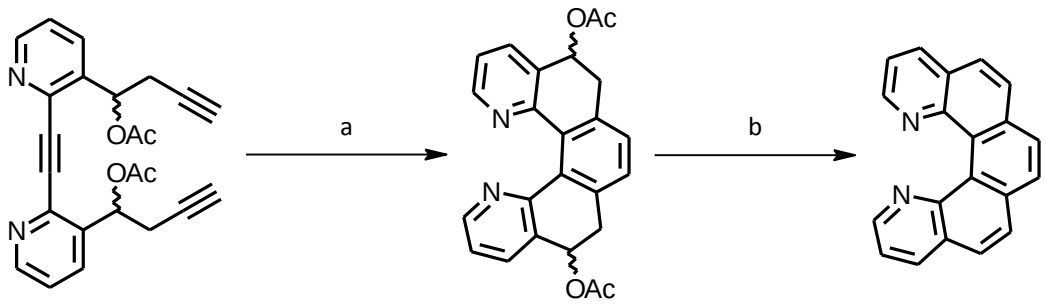


25 **26**

a) $Ni(cod)_2$, THF, rt, 15 min, 86 %. [25]

prepared, followed by their cyclotrimerization (Scheme 7). Acetic acid was further eliminated by means of silica gel to afford the desired helicenes. A number of variously functionalized helicenes were prepared, demonstrating the versatility of this method.

Scheme 7. Synthesis of diazahelicenes by elimination of acetic acid

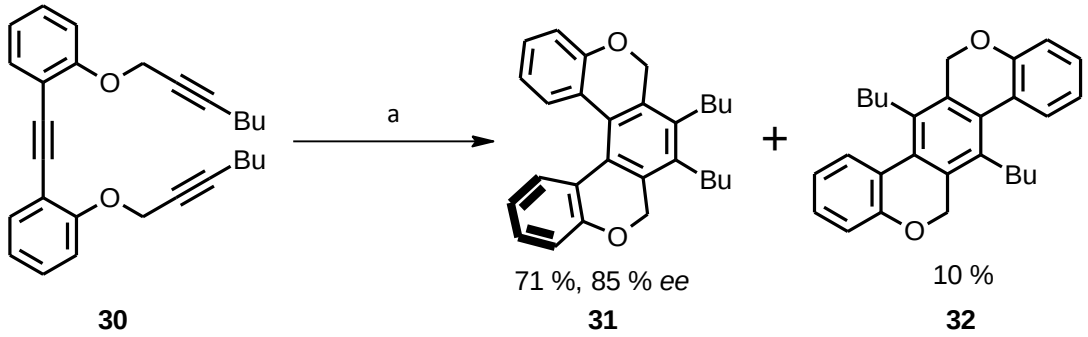


27 **28** **29**

a) $CpCo(CO)_2$, PPh_3, decane, 140 °C, 3 h, 83 %; b) SiO_2, TfOH, 120 °C, 2 h, 67 %. [26]

Enantioselective syntheses of helicenes have been developed as well. Starý, Stará et al published the first enantioselective synthesis of helicene in 1999 using Ni^0 catalyst with Hayashi's axially chiral monodentate phosphine *BOP* ligand. [27] Later on, Tanaka and co-workers successfully used Rh^I and phosphine ligands to obtain helicene-like molecules in good yields and high enantiomeric excess (Scheme 8). [28]

Scheme 8. Tanaka's enantioselective synthesis of helical compounds



71 %, 85 % *ee* 10 %

30 **31** **32**

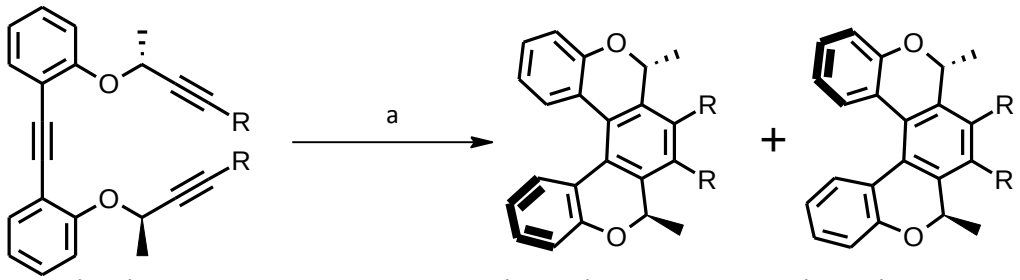
a) $[Rh(cod)_2]BF_4$, (*R*,*R*)-Me-*DuPhos*, DCM, 40 °C, 15 h, 85 % *ee*. [28]

An efficient and general asymmetric synthesis of helical compounds was introduced by Starý, Stará and co-workers. In a series of articles, they described a novel and general strategy where the formation of a specific diastereomer during Co^I mediated cycloisomerization is controlled by the presence of a stereogenic center in the starting triyne (Scheme 9). Not only carbohelicene-like molecules but also their aza counterparts could be obtained this way. [29] Thus, the [2+2+2] cyclotrimerization of aromatic triynes has been established as a standard method for the construction of helicene backbone as documented by work of other laboratories.

Interesting analogues of helicenes, Vollhardt's heliphenes, were prepared in 2002 by cyclotrimerization, (Scheme 10). [30] Teplý's helquats may also serve as an example. [31] In 2013 Starý, Stará and colleagues reported a rapid synthesis of dibenzohelicenes. [32] Since

dibenzohelicenes are the key building blocks of the target macrocycles of this Diploma Thesis, a separate and more detailed Chapter is dedicated to their synthesis and physiccochemical properties.

Scheme 9. Starý and Stará's diastereoselective synthesis of helicene-like molecules



(*R*,*R*)-**33** R = H R = H *(M,R,R)*-**35** *(P,R,R)*-**35**

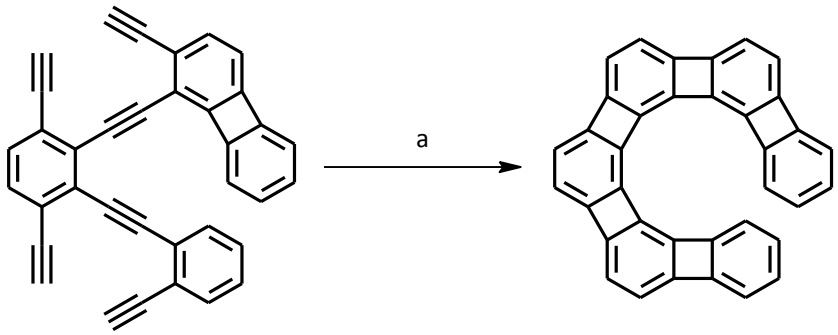
d.r. = 34 : 66

(*R*,*R*)-**34** R = Tol R = Tol *(M,R,R)*-**36** *(P,R,R)*-**36**

d.r. = 100 : 0

a) CpCo(CO)(fum), THF, microwave reactor, 180 °C, 20 min, 96 %. [29]

Scheme 10. Vollhardt's synthesis of heliphenes



37 **38**

a) $CpCo(CO)_2$, m-xylene, hv, DMTS, 30 min, 12 %. [30]

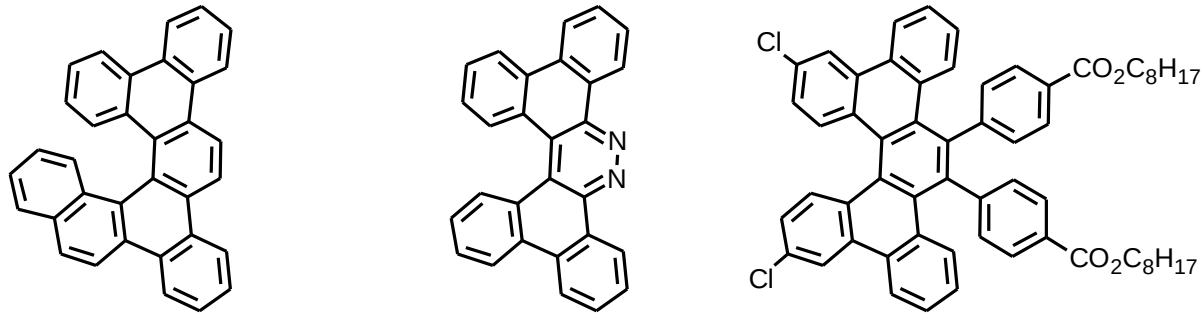
1.3.2. Synthesis and properties of dibenzohelicenes

The idea of the synthesis of dibenzohelicenes (DBHs) originated from several reasons. The previously mentioned synthesis of helicenes from dienetriynes was, in principle, very simple, albeit limited by the instability of the precursors. The synthesis of dibenzohelicenes successfully overcomes this problem by incorporating the vinylene fragments into the chemically stable *ortho*-phenylene rings. Moreover, the lateral extension of the helicene backbone might amplify its chiroptical properties compared to classical helicenes and makes dibenzohelicene based ligands perhaps more suitable in enantioselective reactions. [32]

A large number of functionalized DBHs of various lengths have been prepared. Some examples are shown in Figure 6. Scheme 11 shows an outline of the synthesis of DBHs demonstrated on the preparation of a simple dibenzo[5]helicene. The strength of this approach lies in the shortest access to these complex molecules from commercially available starting materials, usually requiring four or five steps. In this case, the synthesis of compound **48** or **49**, respectively, comprised of double Sonogashira coupling of 1-bromo-2-iodobenzene

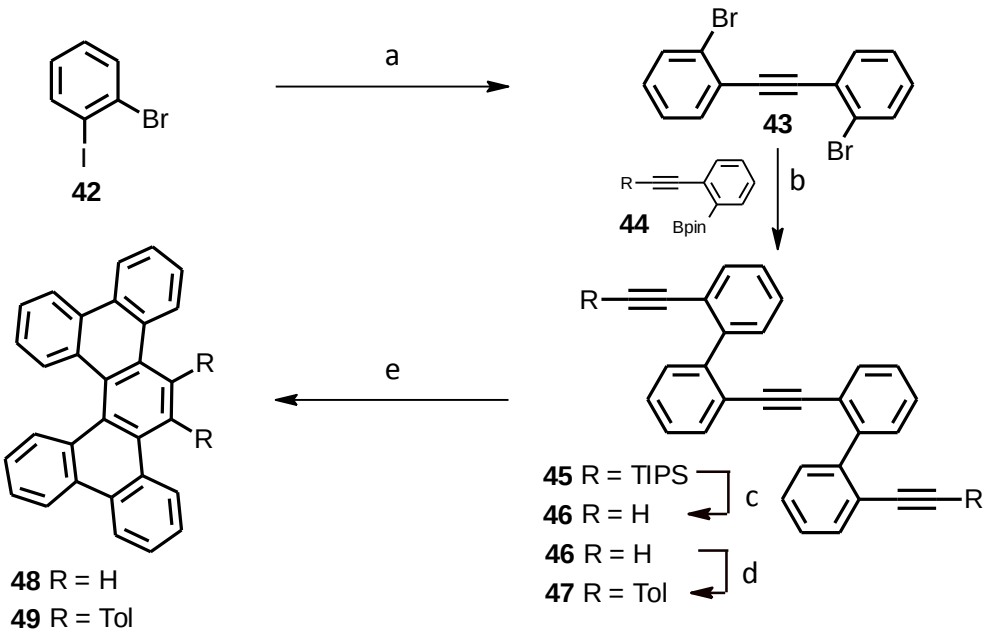
42 with gaseous acetylene to afford dibromoalkyne **43** that was further coupled with boronic acid **44** in a double Suzuki-Miyaura reaction. After removal of the TIPS-protecting groups, the free triyne **46** was cycloisomerized using Ni^0 or Co^I catalysts to afford the desired dibenzo[5]helicene **48**. The Scheme also shows an introduction of phenyl substituents by Sonogashira coupling of terminal triyne to give rise to the helicene structure **49**.

Figure 6. Examples of various dibenzohelicenes



39 **40** **41**

Scheme 11. Synthesis of dibenzo[5]helicene



42 **43** **44** **45** R = TIPS **46** R = H **46** R = H **47** R = Tol **48** R = H **49** R = Tol

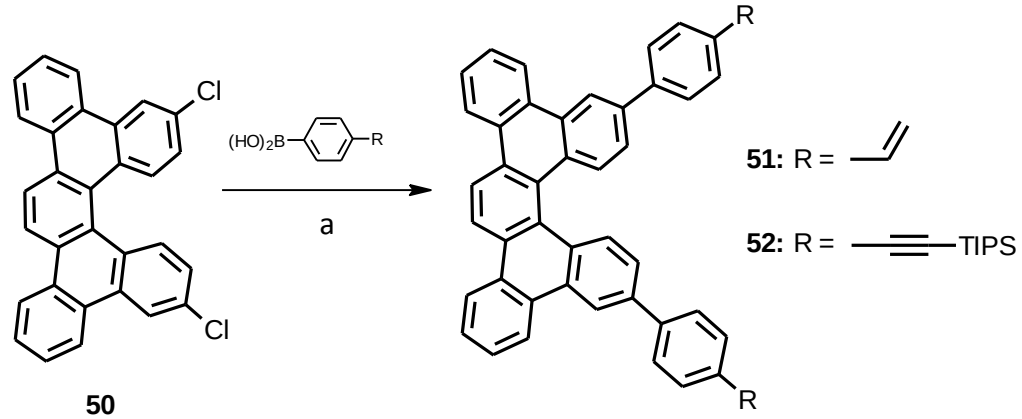
a) C_2H_2, $Pd(PPh_3)_4$, CuI, DIPA, 60 °C, 3 h, 74 %; b) $Pd(PPh_3)_2Cl_2$, K_2CO_3, toluene, ethanol, water, 90 °C, 3 h, 98 %; c) TBAF, THF, rt, 15 min, 96 %; d) iodobenzene, $Pd(PPh_3)_4$, CuI, DIPA, THF, rt, 3 h, 94 %; e) $Ni(cod)_2$, PPh_3, THF, rt, 10 min, 96 % for **48**, 30 min, 88 % for **49**. [32]

The synthesis provided high yields. Functionalization of the used building blocks afforded a corresponding functionalized DBH, sometimes in lower yields, but the robustness and efficiency of the synthesis is still preserved. An enantioselective route toward DBHs was also presented in the same work. Thus, dibenzo[6]helicene was prepared in an excellent 90 % yield and enantiomeric excess 80 – 87 % using Ni^0-(*R*)-*QUINAP* catalytic system.

Most DBHs prepared in our laboratory were prepared in high yields and in a few steps. However, as discussed in my Bachelor Thesis, synthesis of 3,16-dichlorodibenzo[5]helicene **50** was complicated by a difficult chromatographic separation of the product due to its

unusually low solubility. Therefore, appropriate means of solubilisation was sought. Installing the branch TIPS groups turned out to be an efficient way to increase the solubility of the product but, on the other hand, lowered the yield of the cyclotrimerization. [8]

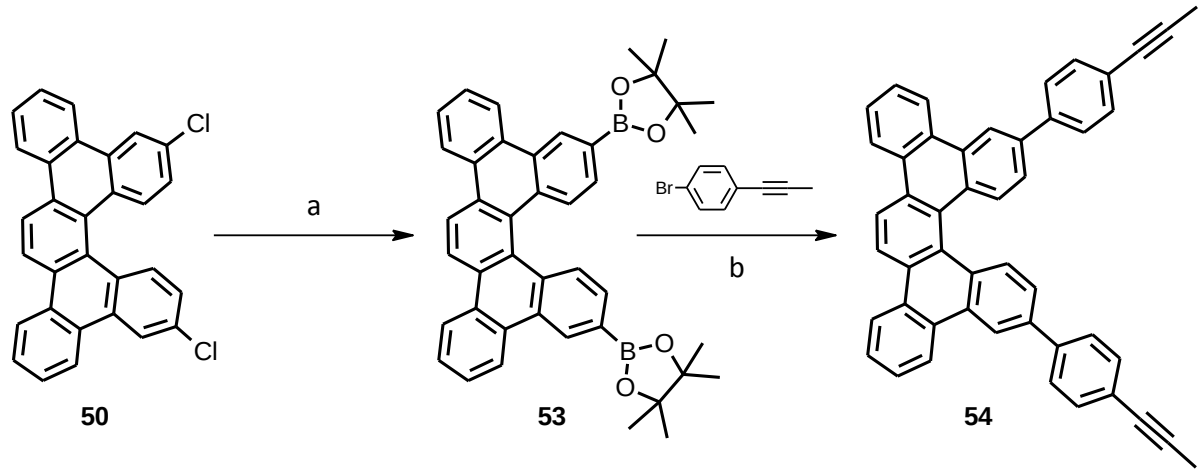
Scheme 12. Suzuki-Miyaura coupling of 3,16-dichlorodibenzo[5]helicene



a) for **51**: $Pd(OAc)_2$, *XPhos*, K_3PO_4, dioxane, water, reflux, 6 h, 56 %; for **52**: $Pd(OAc)_2$, *DavePhos*, Cs_2CO_3, dioxane, 85 °C, 17 h, 83 %. [8]

Further, functionalization of helicene **50** was investigated. Inspired by a similar work done on dichloropentahelicene, [26] the dichloroDBH **50**, mentioned above, was subjected to Suzuki-Miyaura reaction and smoothly afforded DBH derivatives **51** and **52** (Scheme 12). In the case of bis(4-propenylphenyl) derivative, the reaction did not work. Therefore, the helicene **50** was instead converted into a corresponding bis(pinacolboronate) **53** that gave the desired product **54** in the reaction with propynylphenylbromide (Scheme 13). *XPhos* turned out to be the best ligand for this transformation.

Scheme 13. One-pot preparation of a DBH derivative



a) B_2pin_2, $Pd(OAc)_2$, *XPhos*, KOAc, dioxane, reflux 2.5 h; b) 4-propynylphenylbromide, K_3PO_4 aq., reflux, 2 h, 74 % over 2 steps. [8]

1.4. Transformations for the synthesis of complex organic molecules

1.4.1. General principles

The preparation of a number of Shape-persistent macrocycles and of helicenes using [2+2+2] cyclotrimerization has already been discussed in the preceding text. The chosen examples in the following Chapter reflect the actual problems that have been solved in the course of the project and can be also used as a reference for the discussion section.

To synthesize an unknown complex organic molecule is often a challenging task. It is like looking for the way out of a large maze, the bigger and more complicated the molecule, the bigger the maze. Synthesis usually follows a certain plan but only rarely is the chemist allowed to go the whole way as originally proposed without some necessary changes. The opposite is often true – if one encounters an unexpected reactivity, formation of by-products or difficulties with purification of the products, it is necessary to go back one or more steps and modify the original plan. In the course of the synthesis, there are usually a few key steps on which the whole synthesis relies and if these fail, there is no other option but to redesign the whole synthetic plan.

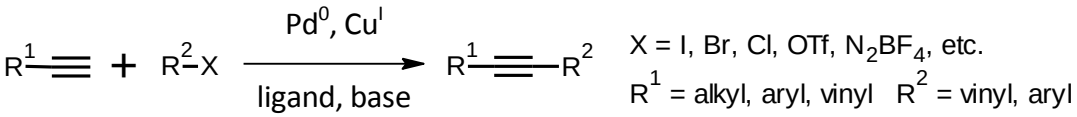
Concerning large molecules such as the target macrocycle, certain special considerations must be taken into account. Perhaps the most important one is that the reactivity of large molecules usually decreases and the possibility of by-product formation increases. Sometimes, this obstacle can be solved, by increasing the concentration of the reaction mixture, but since shape-persistent macrocycles have often low solubility, it poses a significant problem. The isolation of the desired product from the reaction mixture represents another problem. The changes brought about by the chemical transformation often do not change its separation properties enough. Separation of the product from the starting material thus can be difficult. This is especially apparent in the case of molecules equipped with long solubilizing chains. In the absence of these long chains, large π-conjugated compounds are desperately insoluble. When the chains are too long, it is almost impossible to crystalize the compound and separation on silica gel is more problematic as well. A good compromise in the initial design of the molecule is therefore very important.

Building a large molecule is almost always many step process involving various chemical transformations. Over the recent years, various metal-catalyzed reactions have enormously extended in their scope and applicability, particularly in the synthesis of π-conjugated systems and are basic tools of today's organic chemist and that is why most following chapters in this section concern this area of chemistry.

1.4.2. Sonogashira reaction

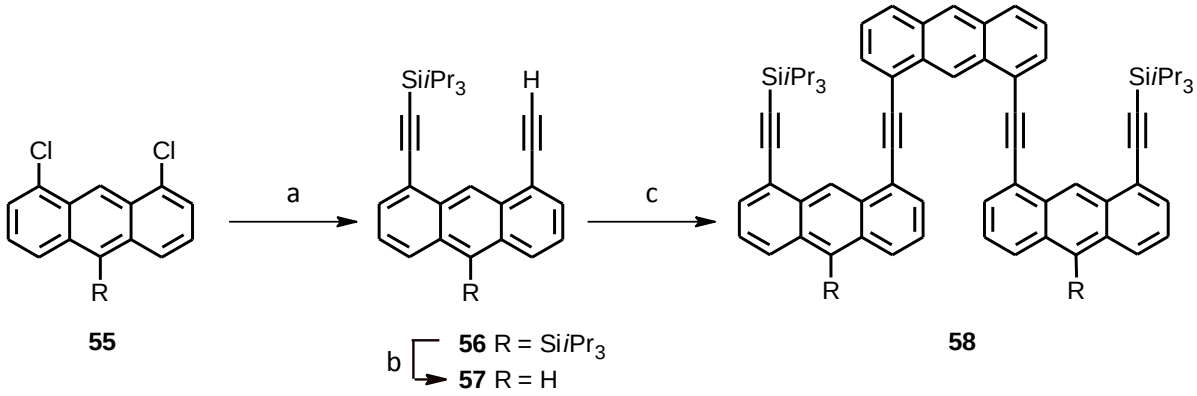
The Sonogashira reaction is a type of cross-coupling reaction between aryl or vinyl halides (or pseudohalides) and terminal acetylenes. It is usually catalyzed by Pd^0 and Cu^I in the presence of a base, most often an amine. For at least last ten years, it has been possible to couple also very unreactive partners due to development of new active catalysts mainly by Buchwald and co-workers. Thus, even hindered aryl chlorides pose no problem anymore and can be coupled giving high yields.

Scheme 14. General scheme of Sonogashira reaction



Often when building a complex molecule bearing an alkyne moiety, it is necessary to attach a protected terminal acetylene, remove the protecting group and let the resulting compound couple to another molecule. This is usually a safe way to obtain the desired product but involves three steps and is therefore time and labor expensive. An example of such a procedure is shown in Scheme 15. [33] This three-step sequence can be avoided in the case of symmetrical acetylenes where gaseous acetylene can sometimes be used. [24] But this

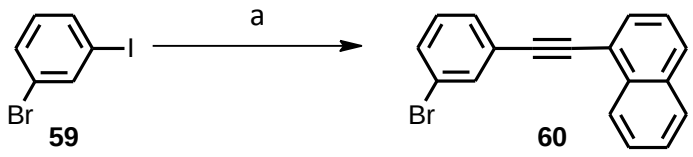
Scheme 15. Sequential synthesis of a macrocycle precursor using multiple Sonogashira reaction



a) *i*-$Pr_3SiC{\equiv}CMgBr$, $Ni(acac)_2$, THF, reflux, 48 h, 99 %; b) TBAF, DCM, 20 min, 33 %; c) 1,8-diiodoanthracene, $Pd(PPh_3)_4$, CuI, Et_3N-THF, 48 h, 92 %. [33]

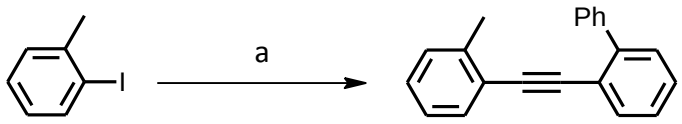
is obviously not possible for unsymmetrical biarylacetylenes and various one-pot procedures have been developed. Nishihara and co-workers utilized an interesting Sonogashira-Hagihara coupling to avoid the deprotection step. [34] In this reaction, TMS-protected alkyne is directly transmetalated to Cu^I and involved in the usual Sonogashira catalytic cycle. Grieco et al. developed a one pot protocol suitable for preparation of both symmetrical and unsymmetrical biarylacetylenes using Pd^0-Cu^I catalyst system, trimethylsilylacetylene and DBU/water (Scheme 16). [35] An appealing approach was followed by Lee et al. who took advantage of a sequential Sonogashira reaction and a decarboxylative coupling using $Pd_2(dba)_3$-dppf with TBAF as a base. Propiolic acid was used as an alkyne building block giving the desired biaryl products in good to high yields (Scheme 17). [36]

Scheme 16. One-pot synthesis of biarylacetylenes



a) 1. TMSA, $Pd(PPh_3)_2Cl_2$, CuI, NEt_3, benzene, rt, 18 h; 2. 1-iodonaphtalene, DBU, water, rt, 18 h, 81 %. [35]

Scheme 17. One-pot synthesis of biarylacetylenes using decarboxylative coupling



61 **62**

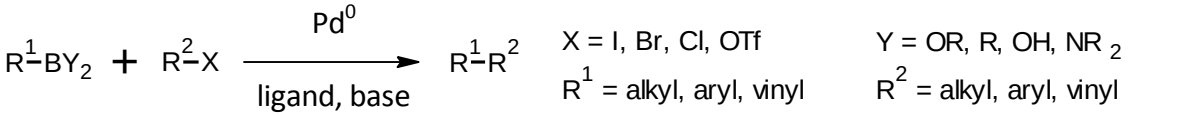
a) 1. propiolic acid, $Pd_2(dba)_3$, dppf, TBAF, NMP, rt, 12 h; 2. 2-bromobiphenyl, 90 °C, 12 h, 81 %. [36]

A common problem associated with the Sonogashira reaction is a Glazer-type homocoupling occasionally occurring during the reaction. [37] Sometimes, the extent of this side-reaction even prevents the main reaction from proceeding because the alkyne is consumed before it can deliver the desired product. A number of strategies have been developed to overcome this complication. Ho and co-workers suggested to use hydrogen-argon atmosphere to prevent the homocoupling. [37] However, the results of this study are questionable. We repeatedly have not observed any noticeable effect on the reaction course in our lab. On the other hand, it was observed that a correct and careful degassing of the reaction media along with an airproof apparatus significantly affect the reaction outcome, giving substantially higher yields. [8] Based on our observation, even despite such rigorous precautions homocoupling product may sometimes form. This suggest that the mechanism of the homocoupling is probably more complex and needs to be further studied. A different way to avoid Glazer-type side reactions is to use a copper-free catalytic systems. [38] Indeed, the side products were successfully reduced to minimum and some of these catalytic systems allow even coupling of usually unreactive aryl chlorides.

1.4.3. Suzuki-Miyaura and borylation reactions

The Suzuki-Miyaura reaction also belongs to the group of cross-couplings. Usually, aryl or alkenyl halides are coupled with aryl or alkenyl boron compounds to form sp^2-sp^2 C-C bond, although compounds bearing sp^3 and sp carbons can be coupled as well. [39], [40], [41] Apart from halides, other functional groups are eligible such as triflates, nonaflates or diazonium tetrafluoroborates. Similarly, the boron functional groups can range from boranes, boronic acids and their esters, trialkylboronate salts or trifluoroborate salts.

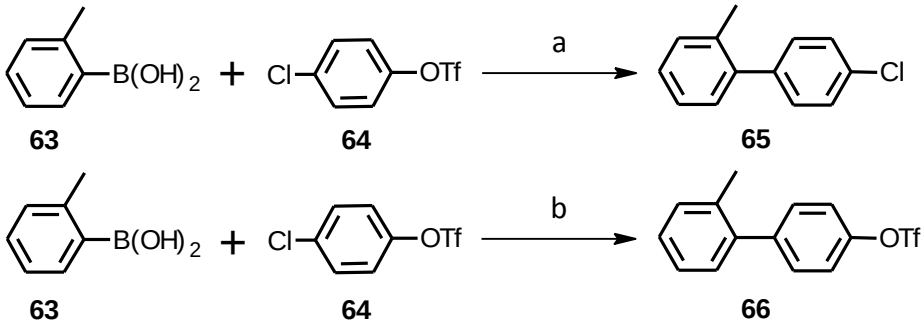
Scheme 18. General scheme of Suzuki-Miyaura reaction



The scope of the Suzuki-Miyaura reaction is huge and has enormously expanded since its discovery. Unlike other couplings such as the Negishi or Sonogashira reactions, the Suzuki-Miyaura reaction is not particularly sensitive to oxygen and can be performed in water (actually water is often essential for its smooth course). The choice of available catalytic systems is very wide and covers practically all areas a synthetic chemist can imagine. Usually, palladium source accompanied by a phosphine ligand is used, but Ni^0 can be used as well. [42]

A common order of reactivity for oxidative addition often followed is Cl < Br < Tf < I although it can be sometimes reversed. For instance, Scheme 19 shows that if $Pd_2(dba)_3$ and P(*t*-Bu)$_3$ is used, triflate group reacts prior to chloride while the reactivity is reversed if $Pd(OAc)_2$ and PCy_3 is applied. [43]

Scheme 19. Examples of selectivity of different catalytic systems



a) $Pd(OAc)_2$, PCy_3, KF, THF, rt, 48 h, 87 %; b) $Pd_2(dba)_3$, P(*t*-Bu$_3$)$_3$, KF, THF, rt, 24 h, 95 %. [43]

The ability to differentiate between halide groups in a number of ways makes possible the synthesis of very complex molecules. For example the dichlorohelicene **50** (Scheme 11, Chapter 1.3.2) was prepared in three steps taking advantage of decreased reactivity of iodo vs. bromo vs. chloro substituents.

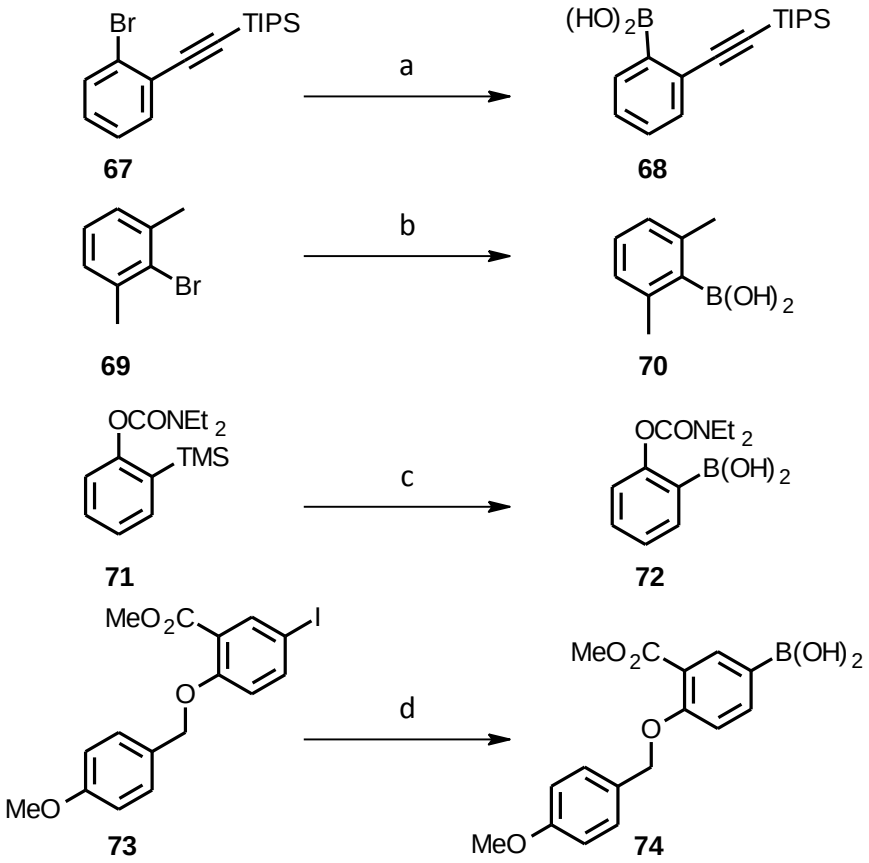
Chlorine, as the least reactive halogen, has long been problematic for the Suzuki-Miyaura reaction. Since the discovery of very active catalysts, this is not a problem anymore. At first, electron-rich ligands with a wide cone angle such as P(*t*-Bu)$_3$ were used. Especially chloroaromatics containing electron-withdrawing groups gave very good yields, but sterically hindered electron-rich chlorides remained problematic. [44] Introduction of biphenyl phosphine ligands by Buchwald et al provided solution to these issues. Since then, even electron rich and sterically hindered chlorides can be coupled at room temperature in excellent yields. [45]

As mentioned above, a lot of different boron groups can be utilized in the Suzuki-Miyaura reactions. The discussion in this Chapter will focus only on a limited area of boronic acids and related compounds. Boronic acids are usually quite stable under ambient conditions, easily prepared in many ways and relatively non-toxic. This combination makes them very appealing substrates and together with their excellent reactivity make the Suzuki-Miyaura reactions one of the most popular cross-couplings used today. [46]

Boronic acids can be prepared by various means (Scheme 20). The most common way is a sequential metalation – borylation. In this protocol, lithium – halogen exchange is performed on an aryl or alkenyl bromide or iodide, followed by addition of the boron source. Boronic acid is then isolated after an acidic work-up. [47] All other means of lithiation can be utilized instead of lithium-halogen exchange, such as *ortho*-lithiation or reductive lithiation. The latter can be particularly beneficial for lithiation of aryl chlorides which usually don't undergo chlorine-lithium exchange. Thus, lithium – anthracene radical anion can serve that purpose. [48] Despite lithiation being the preferred choice, other metalations are also possible, Grignard reaction being the most popular one. [49] Concerning the boron source,

trimethylborate has been a typical reagent although nowadays it has been replaced with triisopropylborate which gives much higher yields. [50] Transmetalation of trimethylsilyl arenes with BBr_3 followed by acidic hydrolysis can serve as a viable means of boronic acid synthesis too. [51] A different approach is the use of metal catalyzed borylation reaction leading to boronic acids. This can be of a special advantage if the boronic acid is sensitive to acidic conditions and it is very atom-economic compared to the similar pinacolborylation. [52], [53]

Scheme 20. Various means of the preparation of boronic acids



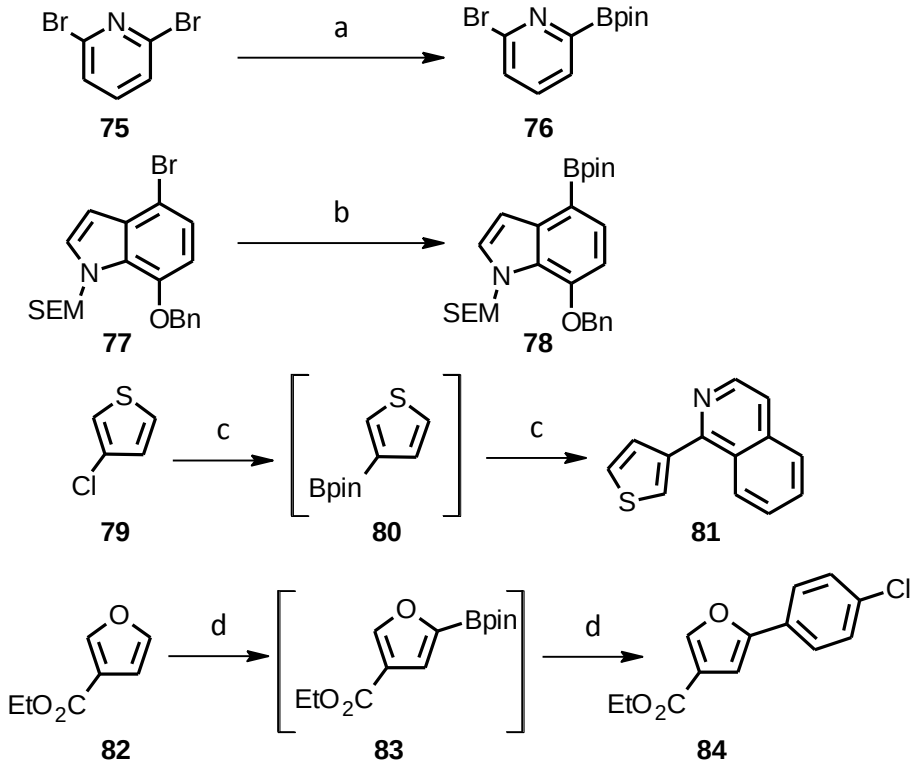
a) 1. n-BuLi, THF, -78 °C, 75 min, 2. B(O-*i*-Pr)$_3$, rt, 20 h, 3. HCl aq., 3 h, 93 %; [6] b) 1. Mg, THF, 50 °C, 2. B(OMe)$_3$, -78 °C, 66 %; [49] c) 1. BBr_3, DCM, -78 °C, 2. HCl, 85 %; [51] d) $B_2(OH)_4$, *XPhos* Pd G2, *XPhos*, KOAc, MeOH, reflux, 4 h, 75 %. [53]

Boronic acids are very good substrates for the Suzuki-Miyaura reactions but they are sometimes prone to protodeboronation or the isolation from the reaction mixture is problematic. These complications may be sometimes avoided using analogous esters (Scheme 21). [46] Especially pinacol esters of boronic acids found wide use in the synthesis for their remarkable stability and ease of preparation. They can be easily chromatographed on silica gel or distilled under *vacuum*. [46] Pinacolboronate esters can be prepared by esterification of the corresponding boronic acids directly after the transmetalation, all in one step. [54] A more appropriate way is, however, to use isopropylpinacolborane in reaction with a lithium compound. This reagent affords pinacolboronates directly in a reaction analogous to the preparation of free boronic acids. [55] Although the preparation of pinacolboronates *via* the routes described above is sometimes necessary, preparing pinacolboronates by use of metal catalyzed reactions is much more common. A Pd^0 catalyzed reaction of

bis(pinacolato)diboron with aryl halides is a typical example. Recently, when very active catalysts became available, even hindered aryl chlorides react well. [56] Since the mechanism of Pd^0 catalyzed borylation is related to that of the Suzuki-Miyaura reaction, it can be combined in one-pot setup and unsymmetrical biaryls can be prepared. One reactant is borylated and the second partner is then added along with a base during the course of the reaction. [56]

Another possibility is to prepare pinacolboronates *via* Ir^I catalyzed C-H activation (Scheme 21). This route is amazingly simple and efficient, in many cases allowing a good control of regiochemistry. As in the case of the borylation starting from halides, a one-pot protocols for the subsequent Suzuki-Miyaura reaction have been developed. [57]

Scheme 21. Examples of preparation of various pinacolboronates

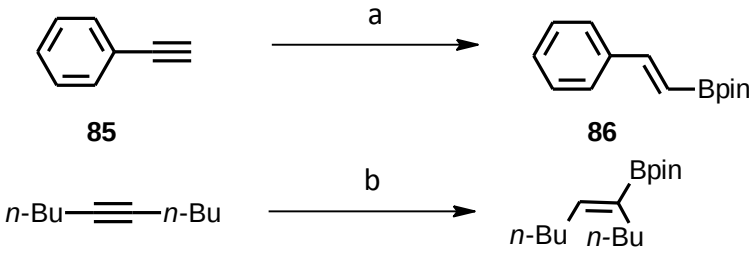


a) 1. *n*-BuLi, THF, -78 °C, 45 min, 2. $B(O\text{-}i\text{-}Pr)_3$, rt, 2 h, 3. pinacol, AcOH, 5 min, 4. NaOH aq., 56 %; [54] b) 1. *t*-BuLi, THF, -78 °C, 15 min, 2. *i*-PrOBpin, 1.5 h, 68 %; [55] c) 1. $Pd_2(dba)_3$, *XPhos*, B_2pin_2, KOAc, dioxane, 110 °C, 3 h, 2. 1-bromoisoquinoline, K_3PO_4 aq., dioxane, 110 °C, 15 h, 71 %; [56] d) 1. $[Ir(cod)OMe]_2$, dtbpy, THF, 80 °C, 18 h, 2. 4-bromochlorobenzene, $Pd(dba)_2$, $P(o\text{-}tol)_3$, Na_2CO_3, THF-H_2O, rt, 18 h, 89 %. [57]

Concerning the preparation of alkenyl pinacolboronates, they can be obtained by metal catalyzed hydroboration of alkynes using bis(pinacolato)diboron (Scheme 22). For instance, Yun and co-workers used CuCl and *DPEPhos* as a catalyst. [58] Although the procedure was originally designed for addition to α,β-acetylenic esters, ethynylbenzene reacted also almost quantitatively. In a different study, Fe_3O_4 nanoparticles or $FeCl_3$ was utilized to prepare pinacolboronates. [59] Despite the efficiency of this method, the use of $FeCl_3$ raises a concern of possible Scholl reaction in the case of large electron rich aromatic systems and thus may not be suitable for the synthesis of large aromatic macrocycles.

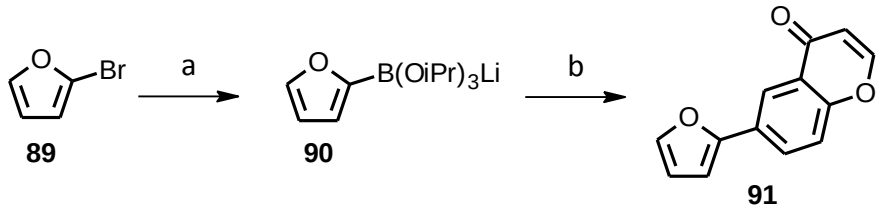
The reason why a base is needed for the Suzuki-Miyaura reaction is not only to remove the formed hydrogen halide but also to activate the boron compound. The addition of a nucleophile, usually hydroxide or alkoxide anion to the boron atom makes it a better leaving group and it can be easily transmetalated to the palladium catalyst. [60] Such an activated substrate is also formed during the reaction of a lithium compound with triisopropylborate resulting in the formation of lithium triisopropylboronate salt. As stated above, boronic acids can be synthesized by acidic hydrolysis of lithium triisopropylboronates but these addition intermediates can be also isolated and stored under inert gas for a long time and even weighed in the air. Thus, in the cases where the isolation of the boronic acid or its ester is not crucial, the lithium triisopropylboronate salt is an excellent alternative. One pot reactions are also possible. This approach was developed by Buchwald and co-workers in order to couple boronic acids prone to decomposition during the course of the reaction (Scheme 23). [61]

Scheme 22. Catalytic hydroboration of terminal alkynes



a) B_2pin_2, CuCl, *DPEPhos*, NaO*t*-Bu, MeOH, rt, 24 h, 99 %; [58] b) $FeCl_3$, Cs_2CO_3, Me_2CO, 60 °C, 12 h, 65 %. [59]

Scheme 23. One-pot lithiation-borylation-Suzuki-Miyaura synthesis of biaryls

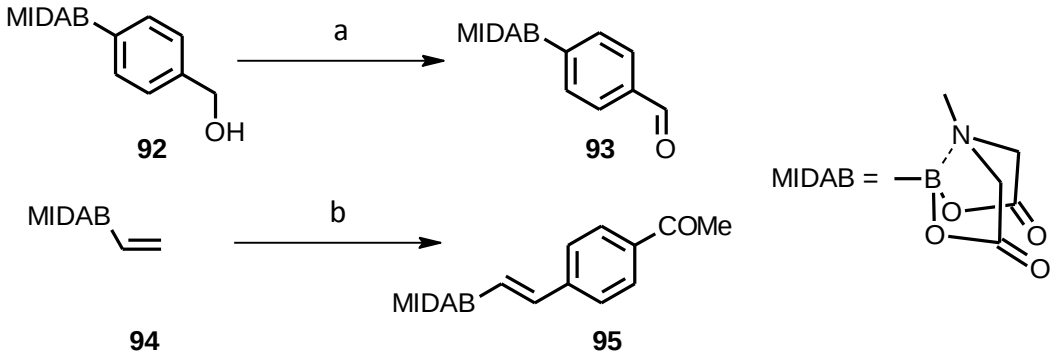


a) *n*-BuLi, THF, -78 °C, 8 h, 99 %; aryl bromide, *XPhos* Pd G2, K_3PO_4 aq., 40 °C, 2 h, 87 %. [61]

Boronic acids and related esters are usually quite reactive compounds that react with a number of reagents. Therefore, boronic function is usually installed before the Suzuki-Miyaura step. This, however, is quite limiting and such a disadvantage can be avoided if the lithium boronate salt is protected as N-metyliminodiacetic boronate (MIDA, Scheme 24). MIDA boronates are very stable compounds compared to many of their unprotected counterparts and can withstand very harsh reagents such as CrO_3 or $COCl_2$. Similarly, the group can be used as a protection during the Heck coupling (Scheme 24). [62] For couplings of highly unstable boron compounds, MIDA boronates can be slowly hydrolyzed during the Suzuki-Miyaura reaction to release the free boronic acid that enters immediately the catalytic cycle. To achieve this, a highly efficient catalyst must be used, such as Pd^0-*XPhos* along with Cu^I additive. Presence of copper makes the reaction very efficient as the released boronate is immediately transmetalated and only then the slow process of transfer to palladium

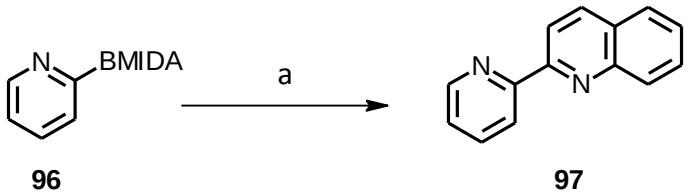
proceeds. By this protocol, high yields have been achieved even in the case of 2-pyridyl moiety that is notorious for its protodeboronation (Scheme 25). [63]

Scheme 24. Demonstration of the resistance of MIDA boronates to different reagents



a) $(COCl)_2$, DMSO, DCM, EtaN, -78 °C to rt, 2 h, 90 %; [62] b) 4-bromoacetophenone, $Pd(PPh_3)_4$, Ag_3PO_4, THF, 100 °C, 24 h, 64 %; [62]

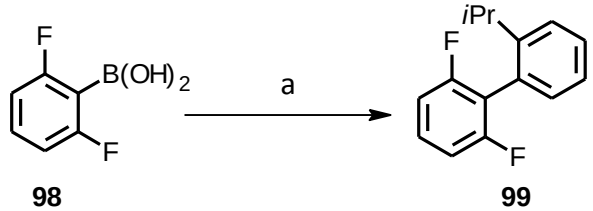
Scheme 25. Slow-release Suzuki-Miyaura coupling of 2-pyridyl MIDA boronate



a) *XPhos* Pd G1, $Cu(OAc)_2$, DEA, K_3PO_4, DMF, 100 °C, 64 %; [63]

Making the Suzuki-Miyaura reaction efficient for couplings of unstable boron compounds is crucial. The whole problem is to make the coupling reaction faster than the protodeboronation one. Buchwald et al introduced many extremely efficient catalytic systems using Pd^0 in combination with *XPhos* or *SPhos* which, under specific conditions, can be used for extraordinarily fast Suzuki-Miyaura reactions. [56] This catalytic system was applied to couple 2-heteroaryl boronic acids such as 2-furyl- and 2-indyl- or polyfluorophenyl boronic acids, albeit it was unable to couple 2-pyridyl boronic acid. [64] The reaction can be even faster and proceed under milder conditions employing Pd^0 precatalysts. Thus chlorides and bromides (surprisingly not iodides) can be coupled at room or slightly elevated temperature with many 2-heteroarylboronic acids (Scheme 26). [65]

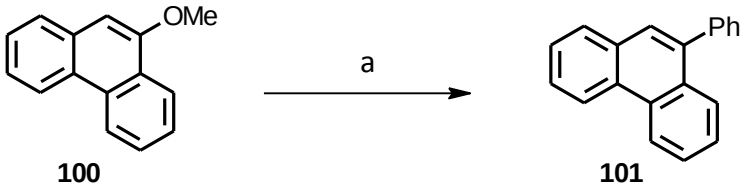
Scheme 26. Example of an application of the extremely active *XPhos* Pd G2 precatalyst



a) 2-isopropylphenyltriflate, *XPhos* Pd G2, K_3PO_4, THF, rt, 30 min, 89 %. [65]

The Ni^0 catalyzed Suzuki-Miyaura reaction is also worth mentioning since it can be very efficient and offers an interesting reactivity, usually not found in Pd^0 catalyzed reactions. For example, reaction of aryl chlorides with boronic acids can be performed at ambient temperature in good yields. [66] Similarly, tosylates, [67] carbamates [68] as well as other less common functional groups including methoxyl [69] can all serve instead of halides (Scheme 27). Quite interesting might be also the use of methoxyl as a temporary directing group that could be later removed in Ni^0 catalyzed reductive demethoxylation. [70]

Scheme 27. Unusual reactivity of Ni^0-catalyzed Suzuki-Miyaura reaction



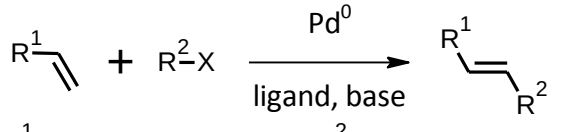
100 **101**

a) $Ni(cod)_2$, PCy_3, CsF, toluene, rt, 12 h, 92 %. [70]

1.4.4. Heck reaction

The Heck reaction is a coupling of aryl or alkenyl halides with alkenes (Scheme 28). The reaction is usually catalyzed by Pd^0 in the presence of a ligand. Since no functional group is required on the alkene part, this reaction stands out having very good atom economy. This advantage is, however, at the expense of quite harsh reaction conditions, with temperatures often exceeding 100 °C (in the case of inactivated halides). The reaction mechanism involves the usual oxidative addition of palladium complex to a halide followed by an insertion of the alkene and by a subsequent β-elimination of the hydridopalladium complex. [71] The mode of Pd insertion, which means the orientation of the double bond towards the Pd complex, depends on many factors, steric as well as electronic effects play both an important role. The electron-withdrawing substituent on the double bond leads usually to a *syn*-1,2 product while electron donating substituents often afford mixtures of 1,2 and 1,1 regioisomers together with other by-products, [72] but even these problems have been recently surmounted by new very active catalysts. [73] Since the β-elimination step is *syn* in respect to the palladium, *trans* double bonds are usually formed. [72] If more sp^3 carbons allow the elimination, more possible products can be formed. This is certainly not a problem where a vinyl group is connected to a conjugated system such as aryl since there is only one possibility of β-elimination. [72]

Scheme 28. General scheme of Heck coupling



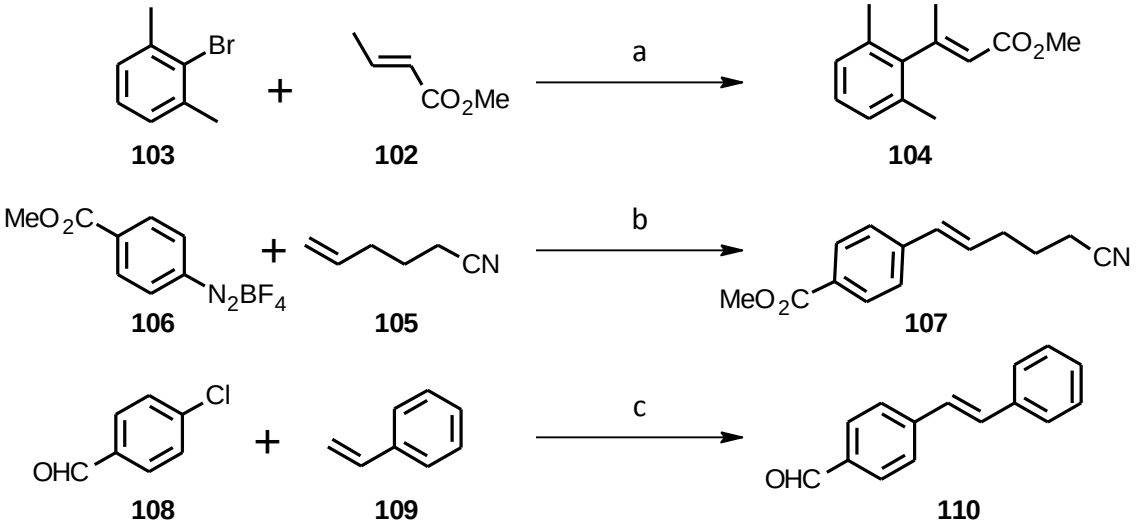
R^1 = alkyl, aryl, vinyl R^2 = alkyl, vinyl, aryl

X = I, Br, Cl, OTf

Although with older catalytic systems the high reaction temperatures and long reaction times made the reaction inappropriate for thermally labile compounds, employing highly active catalysts in recent years has overcome these complications. For example, Fu et al discovered

that combination of $Pd_2(dba)_3$, P(*t*-Bu)$_3$ and Cy_2NMe as a base promotes Heck coupling of activated aryl chlorides and even inactivated halides could be used at temperatures around 100 °C (Scheme 29). [73] Another approach to avoid harsh conditions is to use aryl diazonium tetrafluorobrate salts that undergo oxidative addition at room temperature without use of any special ligand. Sigman et al used this conditions to develop a mild protocol for Heck reaction where he took advantage of coordinating properties of DMA used as a solvent. [74] The procedure gave the products in high to excellent yields and alkenes with no particular electronic features could be employed while still preserving the excellent *trans* styrenyl selectivity. A different step towards milder conditions made Xu and colleagues, who applied basic tetraalkylammonium salts in combination with highly active systems like Pd^0-*DavePhos* to couple wide range of both electron-rich and electron poor alkenes with chlorides. [75]

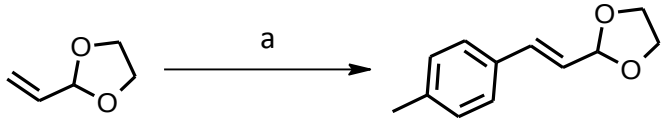
Scheme 29. Various examples of Heck couplings



a) $Pd_2(dba)_3$, P(*t*-Bu)$_3$, Cy_2NMe, dioxane, rt, 83 %; [73] b) $Pd_2(dba)_3$, DMA, rt, 20 min, 98 %; [74] c) $Pd(OAc)_2$, *DavePhos*, TBAE, dioxane, 80 °C, 24 h, 92 %. [75]

A very interesting option is also an oxidative variant of Heck coupling. Its mechanism is different from the usual mode of Heck reaction and involves transmetalation as the first step instead of the usual oxidative addition. Sometimes C-H activation can be employed instead of the transmetalation although it often requires more active catalysts or harsher reaction conditions. Boronic acids are excellent substrates for the transmetalation that allow relatively mild reaction conditions (Scheme 30). Cu^{II} is commonly used as an additive to reoxidise the formed Pd^0 species but pure or atmospheric oxygen can be also used for that purpose. [76]

Scheme 30. Example of an oxidative Heck reaction

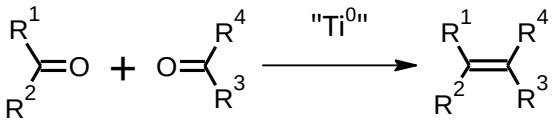


a) 4-tolylboronic acid, $Pd(OAc)_2$, dmphen, N-methylmorpholine, MeCN, rt, 96 h, 63 %. [76]

1.4.5. McMurry reaction

McMurry reaction is a reductive coupling of two carbonyl groups to afford alkenes by use of low-valent titanium ("Ti^0") (Scheme 31). Since in this Diploma Thesis McMurry reaction was intended for the final cyclization step, main focus will be put on this application.

Scheme 31. General scheme of McMurry reaction

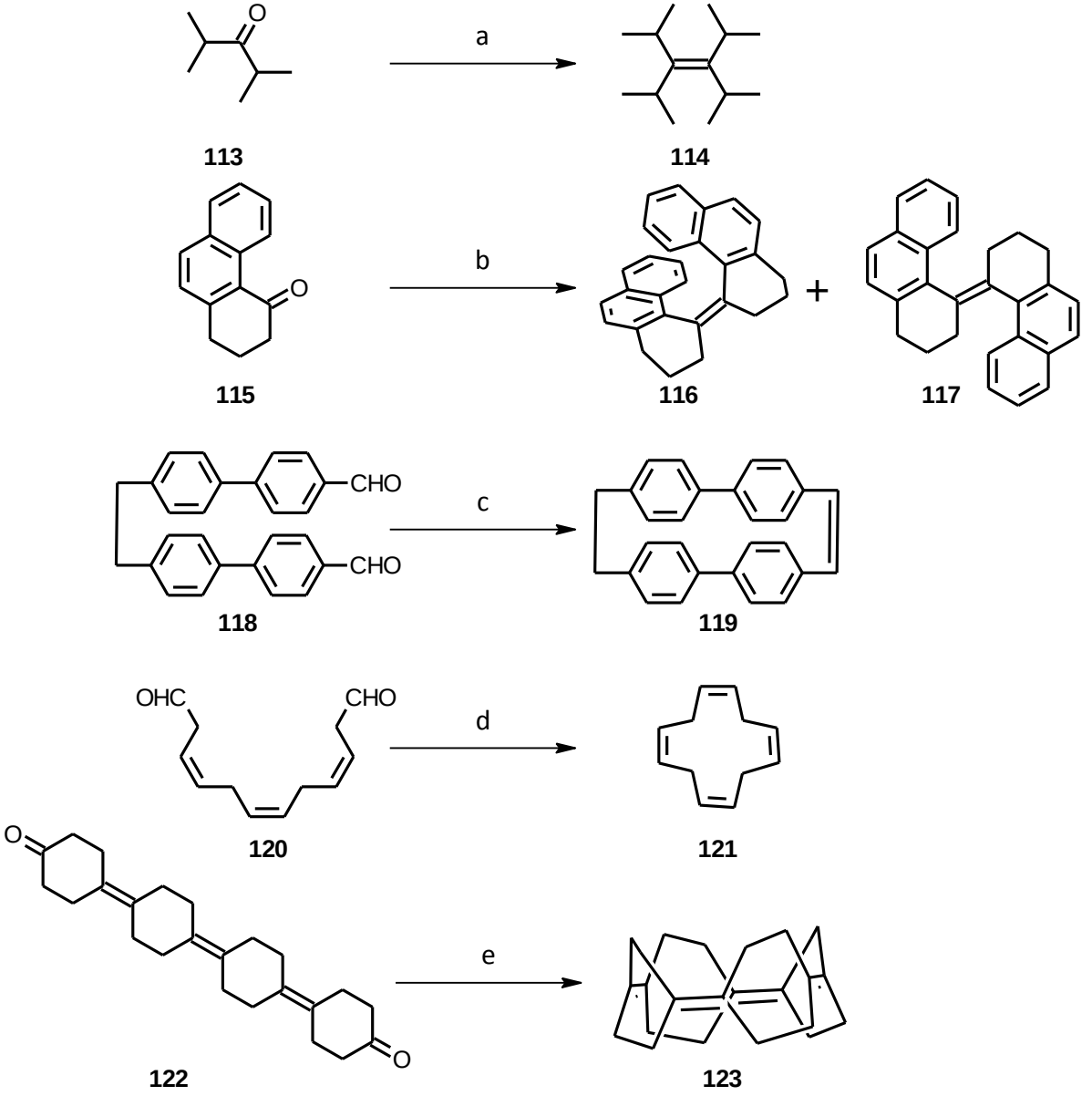


Mechanism of McMurry reaction is very different from the previous couplings and still remains not entirely understood. [77], [78] It is known that the first step involves reduction of the carbonyl group to form radical anion which dimerizes into a pinacol double-anionic product. Until this point, the mechanism is no different from the usual dissolving metal reductions that are carried out at low temperatures. [77] However, unlike most other metals, "Ti^0" is unique in being able to deoxygenate the formed pinacol product to deliver an alkene. How this process actually works is not clear. The "Ti^0" can be obtained in various ways, the most common example is a reduction of $TiCl_4$ or $TiCl_3$ by $LiAlH_4$, Zn or Zn-Cu couple. [77] The reaction is heterogeneous and very fine particles of titanium are probably formed. [79] The reduction probably proceeds at the surface of these particles. The fact that the pinacol product is bound to the surface is crucial for this unique reaction course.

Although the research in recent years has not been as intensive as, perhaps, in the field of Pd-mediated couplings, McMurry reaction still possesses numerous significant advantages over many other similar transformations. First of all, it is very suitable for both inter- and intramolecular synthesis of strained double bonds. [77] If a cycle is being closed during the reaction, the efficiency of cyclization is not so dependent on the ring size. Therefore, McMurry reaction can efficiently close both small and very large rings. The amount of strain that can be brought into the double bond is remarkable and it is no coincidence that the most strained molecules with double bonds were prepared by McMurry reaction. The reason behind this special reactivity probably lies in the enormous strength of the Ti-O bonds that are formed during the process. [77]

Unfortunately, a serious problem of McMurry reaction is poor reproducibility of results. [80] What works for one molecule can fail in the case of another one, what works in one lab, does not work in a different one. This unpredictable behavior is probably due to the way how the fine particles of "Ti^0" are prepared. The quality of the reaction surface of titanium has a large influence on the reaction outcome. Protocols to avoid the reproducibility problems have been developed, but the reaction conditions still must be tuned for a particular transformation, no general reagent is available. [81], [82]

Scheme 32. Various applications of McMurry coupling



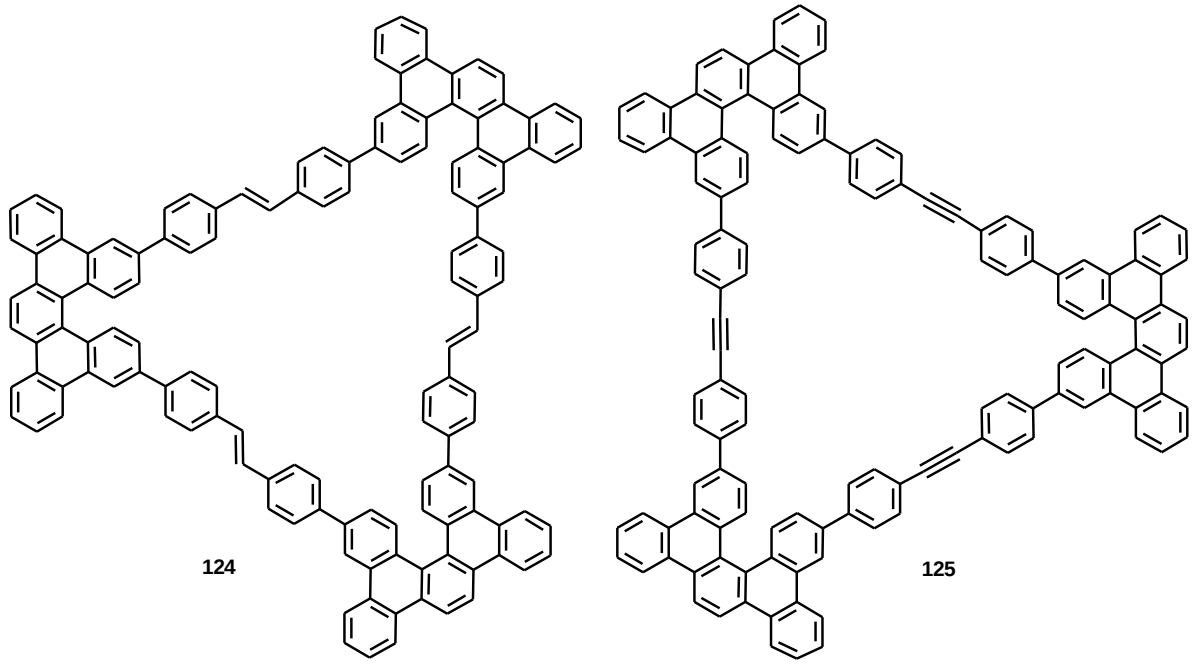
a) $TiCl_4$, Li, I_2, THF, rt, 8 h, 59 %;[83] b) $TiCl_3$, $LiAlH_4$, THF, reflux 4 h;[84] c) $TiCl_4$, Zn, pyridine, THF, reflux, 13 %; [85] d) $TiCl_3$, Zn-Cu, EGDE, reflux, 15 h, 2 %; [86] e) $TiCl_3$, Zn-Cu, DME, reflux, 48 h, 90 %; [87]

A number of very interesting molecules have been synthesized up to now employing McMurry reaction. Tetraisopropylethylene, a molecule otherwise difficult to obtain, is a nice example of applying McMurry coupling (Scheme 32). [83] Other tetrasubstituted, highly strained alkenes have been synthesized this way. [77] Similarly, McMurry reaction has been used for the synthesis of many mono and polycyclic molecules, often with very strained double bonds such as molecules **121** and **123** (Scheme 32). [84], [85], [86], [87] The connected rings of **123** form a macrocycle whose deformed double bonds act as strong ligands for metal ions that can be trapped in the cycle. [77] It has been also shown by Stuhr-Hansen that microwave heating can promote McMurry coupling. The reactions proceeded very rapidly compared with the usual setup and delivered the desired products in high yields. [88]

2. Objectives of the study

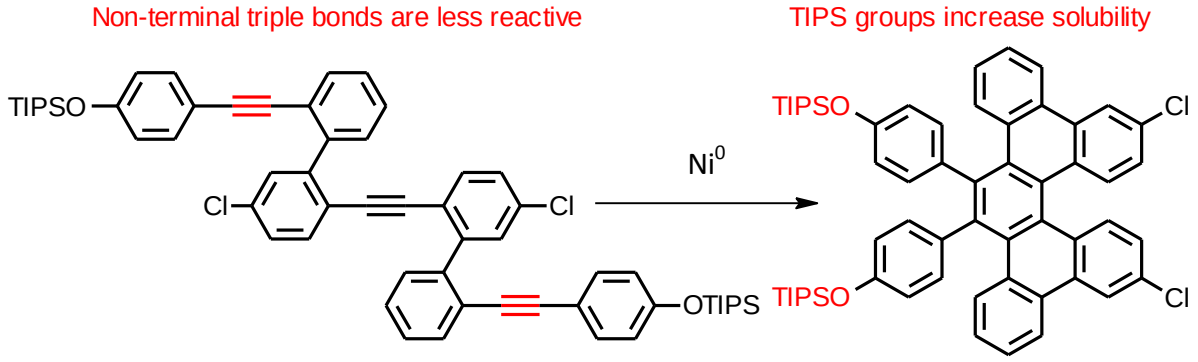
It has already been mentioned in the preceding paragraphs that the project solved in this Thesis relates to the previous work done during my Bachelor project. The original idea concerned a synthesis of a large macrocycle consisting of dibenzo[5]helicene units. These units would have been connected by either double or triple bonds formed *via* alkene or alkyne metathesis. Unfortunately, despite a great effort the metathesis did not turn out to be the best choice for the synthesis of the target compound. Even though the macrocycle was under certain conditions detected, it was practically impossible to isolate it in a pure form. The strategy had to be redesigned and it soon turned into a totally new project.

Figure 7. Structures of the target macrocycles from the Bachelor project



Significant changes were made to overcome the problems encountered during the Bachelor project. First, it was obvious that the helicene building blocks had to be decorated with solubilizing groups. The previous solution to introduce the phenyls with attached solubilizing groups and connected to the triple bonds of triyne **126** (Scheme 33) did help and the solubility of the helicene **127** was greatly increased but at the expense of a much lower yield of cyclotrimerization. This is obvious since the phenyl groups greatly increase the steric hindrance of the alkynes and make their cyclotrimerization much more difficult. Scheme 34 shows the newly designed helicene **129**. Note that the solubilizing groups are placed on the periphery of the molecule not to interfere with the free alkynes during the cyclotrimerization. Moreover, the free alkyne groups are still available for Sonogashira coupling, if needed.

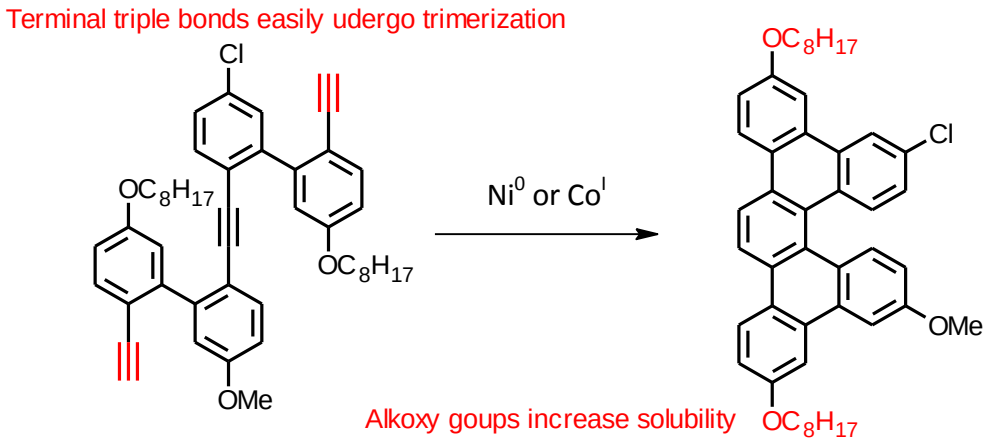
Scheme 33. Features of solubilizing groups on helicene from the Bachelor project



126 **127**

Accordingly, the whole synthetic strategy of the macrocycle had to be changed. Its retrosynthetic analysis is presented in Scheme 35. An older, but more certain, route was chosen whose idea is to prepare the macrocycle *via* the McMurry reaction (or another suitable coupling) from trimer **131**. There are several reasons for this choice. First, the starting material for the macrocyclization would be a molecule already containing all necessary parts of the macrocycle. Second, since high dilution conditions could be used for the final cyclization, it would hopefully prevent the formation of a larger amount of undesired oligomers. Third, the McMurry reaction is known to be efficient in closing even large strained cycles (cf. Chapter 1.4.5). To prepare the trimer **131**, the Heck reaction is considered as the primary choice, offering a high atom economy compared to other couplings. Unfortunately, the Heck reaction usually requires harsh reaction conditions (cf. Chapter 1.4.4) and if it fails, the Suzuki-Miyaura coupling would be the second choice (with the corresponding changes in the synthesis of the building blocks) (cf. Chapter 1.4.3).

Scheme 34. New design of the key helicene building block



128 **129**

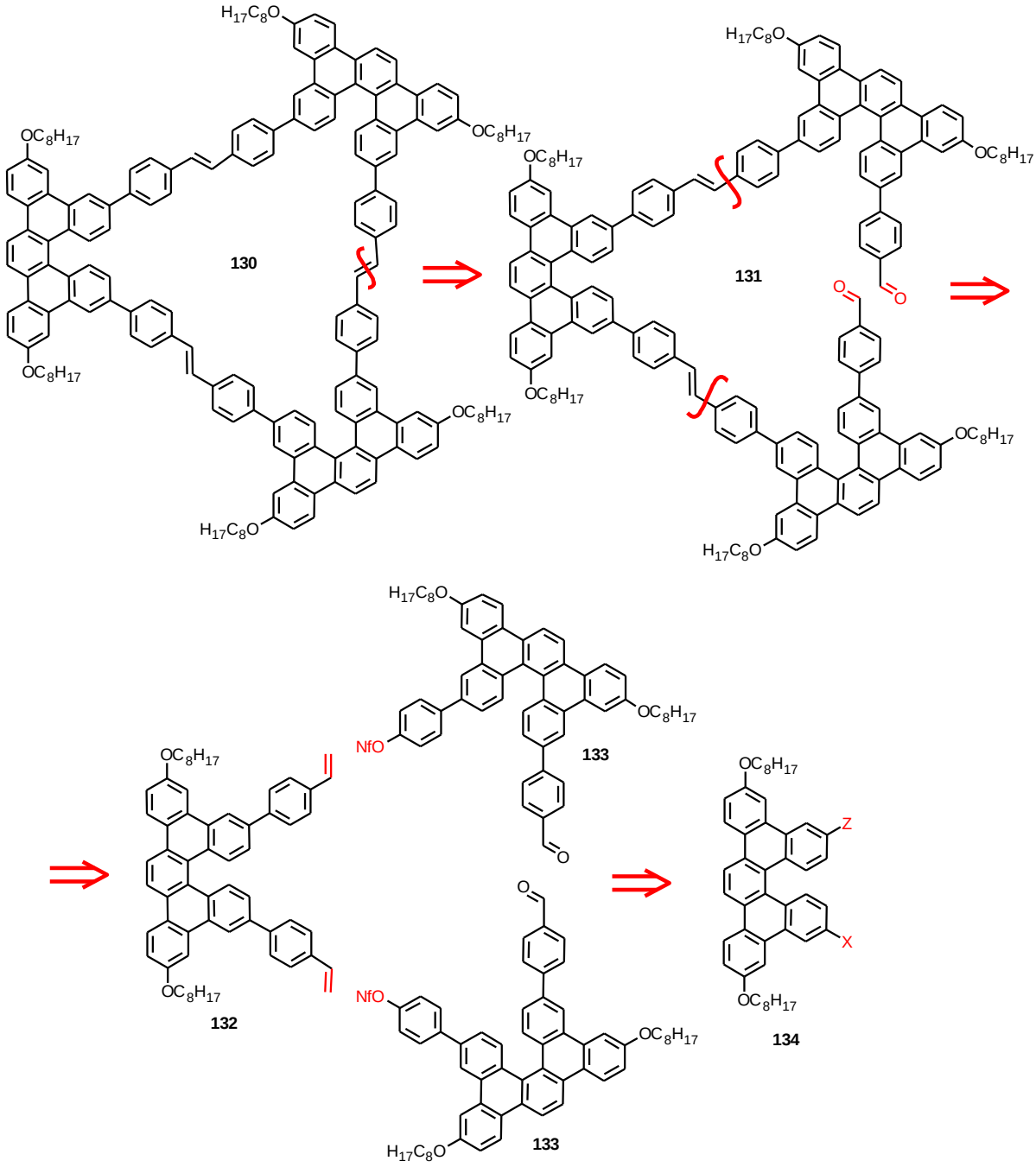
Thus, the objections of the Diploma project can be summarized as follows:

- **To develop an optimized synthesis of helicene 134 with long alkyl chain solubilizing groups as a key building block.**

- **To prepare divinyl building block 132 and nonaflate aldehyde 133 for the synthesis of dialdehyde 131.**

- **To synthesize the final macrocycle 130.**

Scheme 35. Retrosynthetic analysis of the synthesis of the target macrocycle



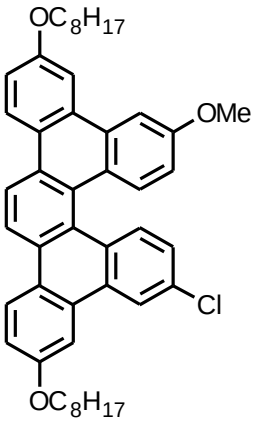
Helically chiral π-conjugated shape-persistent macrocycles such as **130** will be highly attractive for the subsequent chiroptical, physical, material and on-surface studies. The motivation for this project stems, *inter alia*, from unsolved fundamental questions about the role of symmetry breaking in charge transport and formation of molecular electromagnets.

3. Results and discussion

3.1. Synthesis of helicene building blocks – helicene 129

In accordance with the Diploma Thesis goals, the project began with the synthesis of helicene **129** (Figure 8). The structure's designed is based on the previous experience and chlorine and methoxyl groups were installed in order to allow a smooth synthesis of the unsymmetrical building blocks. Although the methoxyl can undergo the Suzuki-Miyaura reaction under specific conditions, this cannot be considered as a viable option due to the simultaneous presence of octyloxy solubilizing groups. Nevertheless, the presence of the methoxyl group has several reasons. First of all, it is required as a directing group at the beginning of the synthesis and, more important, it serves as a protecting group during the whole synthetic sequence. Free phenols are not only prone to oxidation but their chromatographic separation may sometimes by difficult, especially in the case of larger arenes (like helicene **129**). It was supposed that the methoxyl would be eventually deprotected to free phenol which would be transformed to a pseudohalide group capable of undergoing the Suzuki-Miyaura coupling.

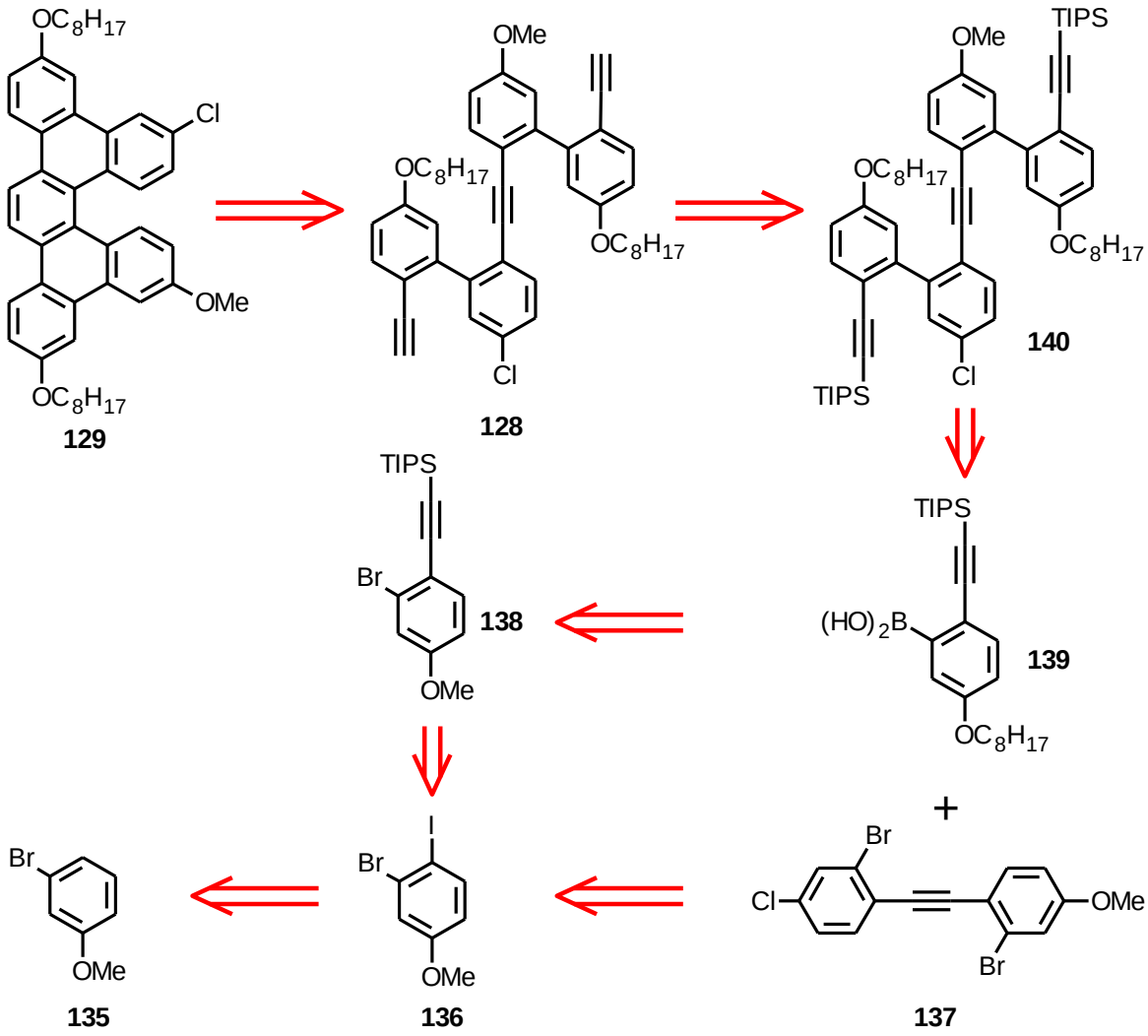
Figure 8. Structure of the target dibenzohelicene **129**



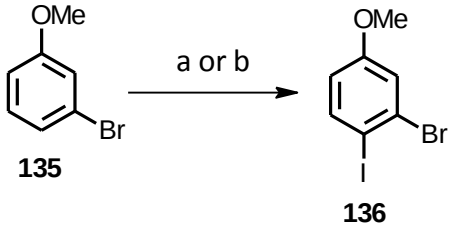
129

The outline of the whole synthesis of helicene **129** is shown in Scheme 36. The preliminary attempts to directly iodinate 3-bromophenol **135** failed resulting in a complex mixture of various isomers and polyiodinated products. According to the literature, [89] however, 3-bromoanisole can be iodinated to form 4-iodo-3-bromoanisole in excellent yield using iodine, acetic anhydride and HgO. Repeating the published procedure led to a complex mixture of products and only a small conversion of the starting material (based on a GC-MS analysis). However, the use of iodine in the presence of mercuric acetate gave the product **136** in very good 89 % yield (Scheme 37). Although the methyl ether **136** could be cleaved at this point, the deprotection was postponed until the later stage of the synthesis to avoid the expected complications discussed above.

Scheme 36. Outline of the synthetic strategy of helicene **129**



Scheme 37. Regioselective iodination of 3-bromoanisol

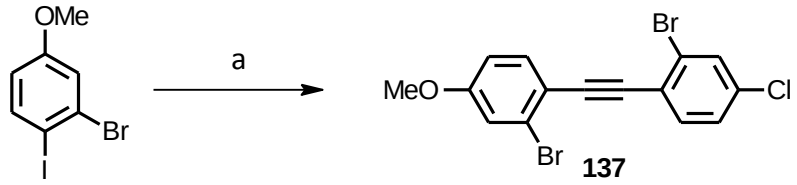


a) I_2, HgO, Ac_2O, DCM, rt, yield not estimated; b) I_2 (1.3 eq.), $Hg(OAc)_2$ (1.2 eq.), DCM, rt, 3 h, 89 %.

At this point the synthesis divided into two branches. To prepare bisarylacetylene **137**, the Sonogashira reaction was utilized. Usually, the synthesis of such a compound involves three steps: the Sonogashira coupling to introduce trimethylsilyl-protected acetylene, removal of the silyl group and the second Sonogashira coupling. A one-pot protocol, however, could be a very convenient way to simplify the whole reaction sequence. As discussed in Chapter 1.4.2., a number of one-pot protocols have been introduced but these procedures usually involve the use of several reagents and co-solvents which make the procedures rather complicated and sometimes unreliable. It was therefore decided to develop our own

approach. After some optimization a simple, high yielding protocol was developed (Scheme 38). First, iodide **136** was subjected to the Pd^0 catalyzed Sonogashira coupling in diisopropylamine. This reaction proceeded rapidly in a standard way and when the starting material was consumed, the solution of tetra-*n*-butylammonium fluoride in THF was introduced to remove the trimethylsilyl group. The deprotection usually took only a few minutes and after this period, 2-bromo-4-chloroiodobenzene was added to the reaction mixture that rapidly coupled to the free alkyne to give the desired product **137**. This protocol proved to be very reliable and gave the product in very good 87 % yield after three steps.

Scheme 38. One-pot synthesis of unsymmetrical biarylacetylene **137**

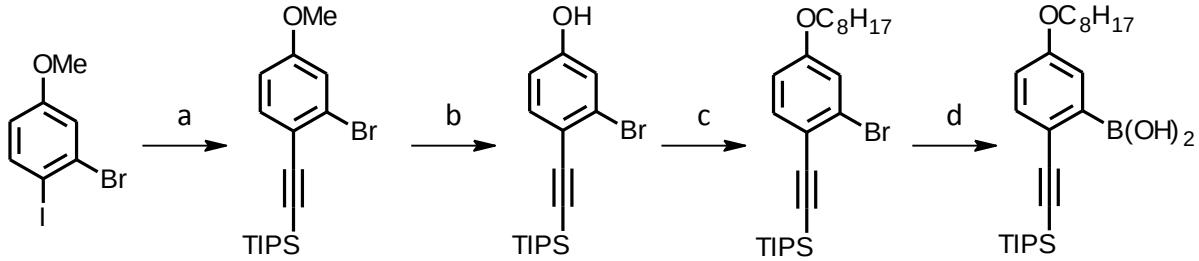


136 **137**

a) 1. TMSA (1.05 eq.), $Pd(PPh_3)_2Cl_2$ (2 mol %), CuI (4 mol %), DIPA, rt, 2 h; 2.TBAF (1.5 eq., THF), 30 min; 3. 2-bromo-4-chloroiodobenzene (1.05 eq.), rt, 2 h, 87 %.

In the second branch of the synthesis, compound **136** was subjected to Sonogashira reaction to quantitatively afford alkyne **138** (Scheme 39). The subsequent removal of the methyl group by means of BBr_3 was, however, problematic. The reaction had to be carried out at low temperature in order to obtain high yield because otherwise the reagent obviously attacked the silyl group. If the reaction was performed cautiously, the reaction yield reached up to 95 %. In order to introduce the long solubilizing chain, the resulting compound **142** was subjected to Williamson reaction with octyl iodide to give compound **143** in excellent 93 % yield.

Scheme 39. Synthetic sequence for the preparation of the boronic acid **139**



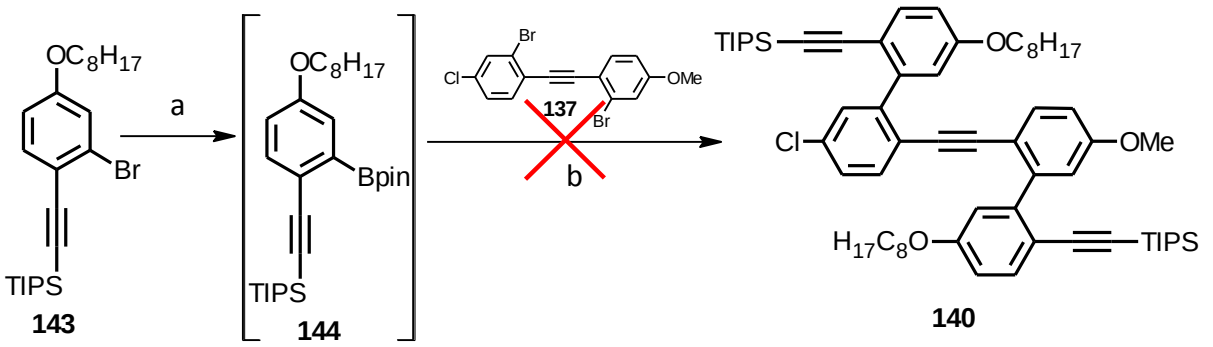
136 **138** **142** **143** **139**

a) TIPSA (1.05 eq.), $Pd(PPh_3)_2Cl_2$ (2 mol %), CuI (4 mol %), DIPA, rt, 2 h; 99 %; b) BBr_3 (1.3 eq.), DCM, rt, 18 h, 95 %; b) $C_8H_{17}I$ (1.1 eq.), Cs_2CO_3 (3 eq.), DMF, 95 °C, 93 %; c) 1. *n*-BuLi (1.3 eq.), B(O-*i*-Pr)$_3$ (1.4 eq.), -78 °C to rt, 16 h; 2. HCl (1 M, aq.), 1 h; 91 %.

To prepare triyne **140**, the Suzuki-Miyaura reaction was employed. Usually, boronic acid or a corresponding pinacol esters are used as coupling partners. In order to avoid the preparation of these compounds, a one-pot protocol was tried (Scheme 40). Bromide **143** was subjected to the Pd^0 catalyzed borylation with bis(pinacolato)diboron to furnish pinacolboronate **144** that would be further coupled to biarylacetylene **137** immediately after the borylation. Unfortunately, the reaction provided only trace amounts of the expected

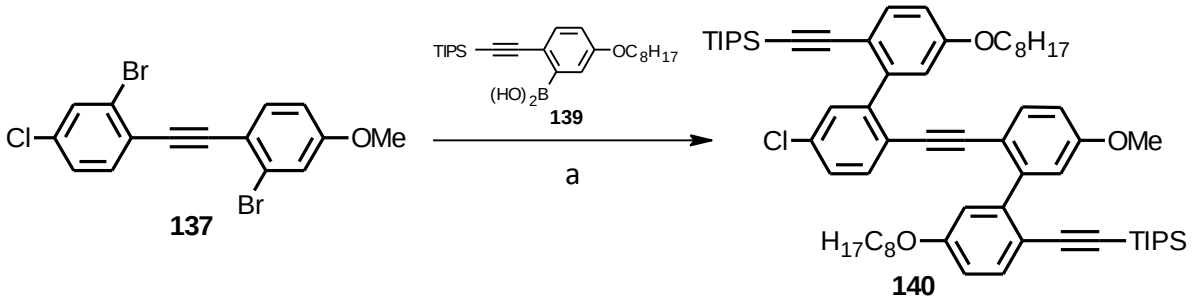
boronate **144**. The opposite process to borylate the dibromide **137** was found impossible due to the presence of chlorine in the molecule. Based on these findings, it was obvious that the one-pot protocol was beyond reach and the boronic acid had to be prepare separately. To do this, a classical lithium-halogen exchange followed by the addition of triisopropyl borate was employed giving the boronic acid in excellent yield of 91 % (Scheme 39). This reaction showed a strong scale – yield dependence and at scales of about 5 g, the yield dropped to 70 %. The boronic acid **139** could be recrystallized from an acetone – water mixture to give crystals whose NMR spectrum confirmed to be a free acid. Otherwise the compound was obtained as amorphous powder containing a variable amount of anhydride, which, however, did not have any negative effect on the following reaction step. With the boronic acid in hand, the Suzuki-Miyaura reaction of the bisarylacetylene **137** was performed giving the desired triyne in 75 % (Scheme 41). Moreover, the reaction went cleanly and the chromatographic separation of the product was very simple.

Scheme 40. One-pot borylation-Suzuki-Miyaura reaction



a) bromide **143** (2.4 eq.), B_2pin2 (2.6 eq.), Pd(OAc)2 (5 mol %), *XPhos* (20 mol %), KOAc (4 eq.), dioxane, 110 °C, 16 h; b) alkyne **137** (1 eq.), K3PO4 (aq., 10 eq.), 110 °C, 4 h, 0 %.

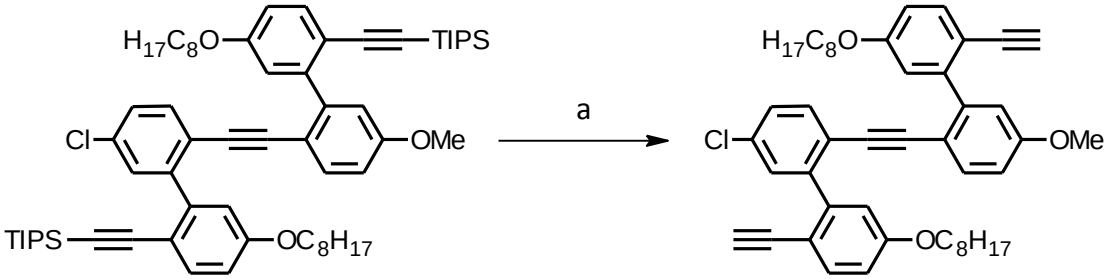
Scheme 41. Synthesis of the triyne *via* Suzuki-Miyaura reaction



a) boronic acid **139** (2.5 eq.), $Pd(PPh_3)_2Cl_2$ (10 mol %), K_2CO_3 (3.5 eq.), toluene : 1-*PrOH* : water = 4 : 4 : 1, reflux, 3 h; 75 %.

The synthesis then followed a usual course. The triisopropylsilyl groups of compound **140** were removed using (Scheme 42). To avoid polymerization of the free alkynes (a reaction that often significantly decreases yield), methanol was added into the reaction mixture. When a large excess of methanol (25 eq.) was used, the conversion of the starting material was not complete. In the case of 5 equivalents of methanol, 3 equivalents of tetra-*n*-butylammonium fluoride were sufficient to achieve a full conversion of the starting material.

Scheme 42. Removal of the TIPS protecting groups

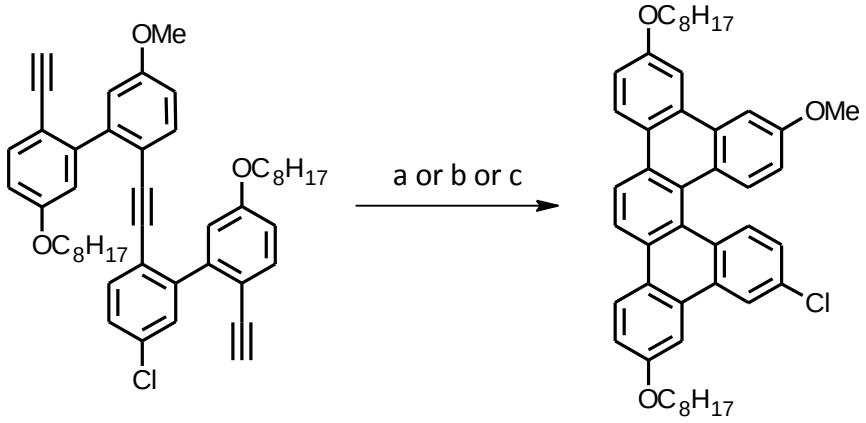


140 **128**

a) TBAF (3 eq.), MeOH (5 eq.), THF, rt, 1 h; 73 %.

The final transformation was [2+2+2] cycloisomerization of triyne **128** to obtain the desired helicene **129** (Scheme 43). Experiments with $Ni(cod)_2$ and PPh_3 or PCy_3 failed giving only small conversion of the starting triyne even when a large amount of catalyst was used. Conversely, $CpCo(CO)_2$ in a flow reactor provided the helicene **129** in 85 % yield using just 20 mol % of the catalyst. Moreover, the separation of the product *via* chromatography was very easy owing to the presence of the solubilizing groups.

Scheme 43. Preparation of the desired helicene *via* cyclotrimerization

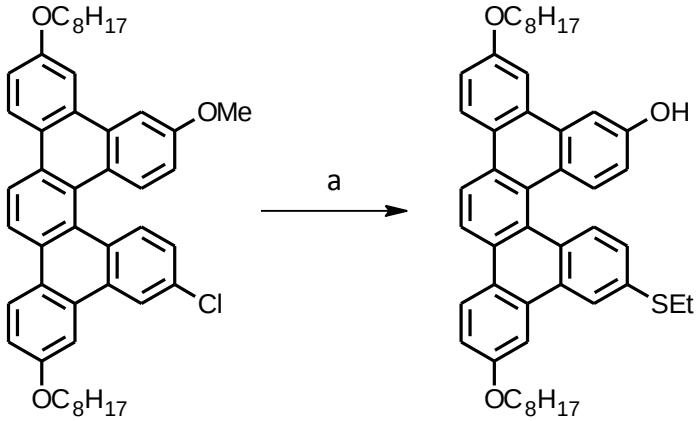


128 **129**

a) $Ni(cod)_2$ (1 eq.), PPh_3 (2 eq.), THF, rt, 24 h; 0 %; b) $Ni(cod)_2$ (1 eq.), PCy_3 (2 eq.), THF, rt, 24 h; 0 %; c) $CpCo(CO)_2$ (20 mol %), THF, flow reactor, 240 °C, 8 min, 85 %.

There were no major problems along the whole synthetic sequence and the final helicene **129** was synthesized in overall 34 % yield. The last step was to remove the methyl and transform the resulting free hydroxyl group into a substituent suitable for the Suzuki-Miyaura reaction. Unfortunately, the demethylation step turned out to be a very difficult problem.

Scheme 44. Attempt at demethylation using sodium ethanethiolate



129 **145**

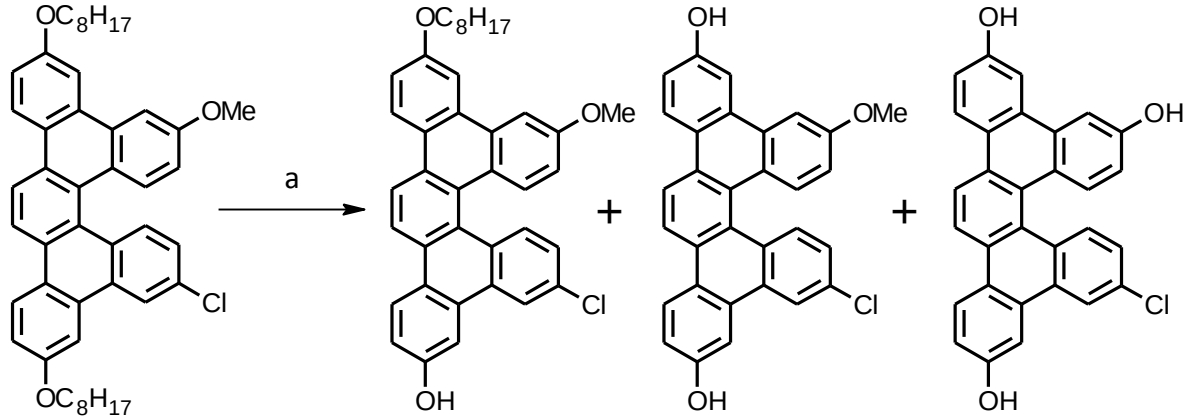
a) EtSH (8 eq.), NaH (8 eq.), DMF, 130 °C, 16 h; yield was not estimated.

First, sodium ethanethiolate, prepared by the reaction of ethanethiol with sodium hydride, was employed (Scheme 44). At 130 °C, the demethylation proceeded as confirmed by ESI mass spectrometry but at the same time, the chlorine substituent underwent substitution by the thiolate to afford a corresponding thioether. The octyloxy groups remained intact, only the methyl was selectively removed. The thioether was not isolated because it co-eluted with other by-products during a chromatography and could not be crystallized. For obvious reasons, the attention was turned to demethylation using BBr_3, another common reagent for demethylation.

The reaction of BBr_3 with helicene **129** was unsuccessful as well (Scheme 45). At -78 °C, there was no reaction at all, even despite the addition of excess reagent. In the subsequent experiments, it was found that the reaction proceeds at 40 °C to give a mixture of three main products. The MS ESI analysis showed signals corresponding to the unreacted starting material along with compound **146** bearing only one solubilizing chain and methoxyl; bearing no solubilizing chain and methoxyl (compound **146**) and with all the ether bonds cleaved (compound **147**). The conclusion which can be drawn from this observation is that the reactivity of the octyloxy groups towards dealkylation is, surprisingly, higher compared to that of methoxy groups. These results suggested that the optimization of the reaction conditions to selectively remove only the methyl group was practically impossible.

At this point it was obvious that the strategy to keep the hydroxyl group protected in the form of methyl ether was not a good decision. The following chapter describes a solution to this problem.

Scheme 45. Attempt at demethylation of methoxyhelicene **129** using BBr_3



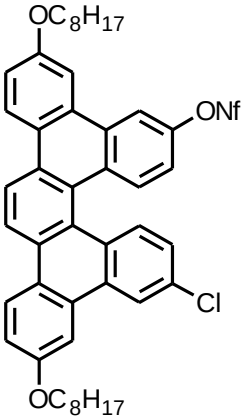
129 **129** **146** **147**

a) BBr_3 (1 eq.), DCM, 40 °C, 30 min; yield was not estimated.

3.2. Synthesis of helicene building blocks – helicene 148

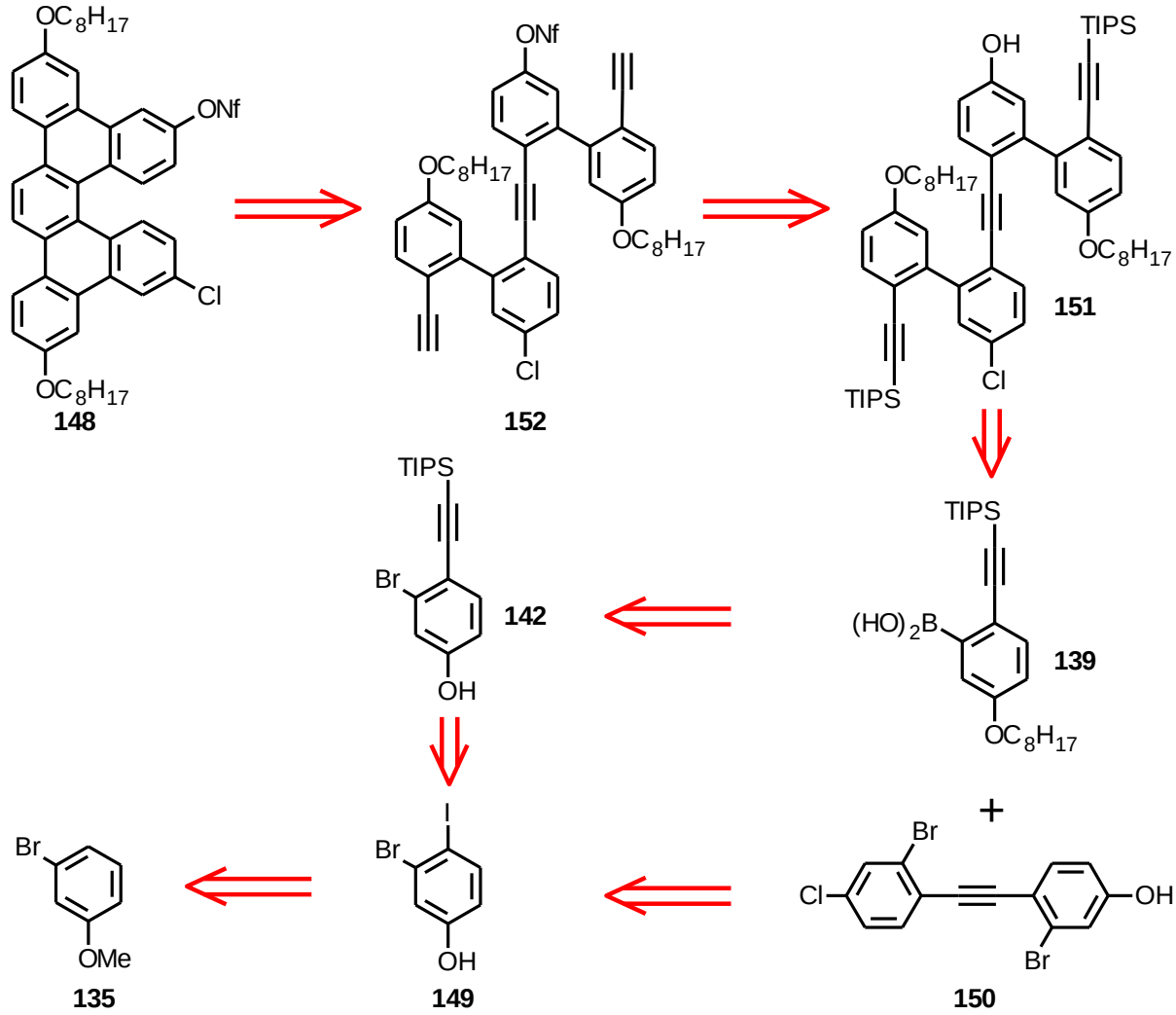
As described in the previous Chapter, an original idea was to prepare helicene with two functional groups of different reactivity that could be later employed in the Suzuki-Miyaura reaction to introduce further functionality. One of these groups was chlorine, the other one could be some pseudohalide. It was decided that nonafluorobutane sulfonate group (nonaflate) is a good candidate for that purpose. We observed in our group that nonaflates are usually more stable compared to triflates and can be chromatographed on silica gel without any concerns. Its introduction is trivial and is done by the reaction of nonaflyl fluoride with phenols under basic conditions. Unlike triflic anhydride used to prepare triflates, this reagent is not particularly corrosive and is relatively non-toxic. Moreover, nonaflates seem to be as reactive as triflates in coupling reactions.

Figure 9. Structure of target dibenzohelicene **148**



148

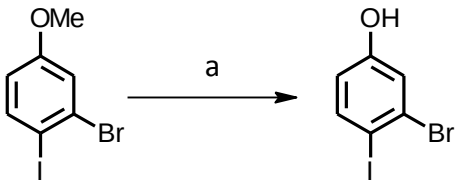
Scheme 46. Outline of the synthetic strategy of helicene **148**



The updated structure of the target helicene **148** is shown in Figure 9. Of course, there might be a reasonable question why such a functionality was not considered in the first place. At the beginning of the project, it was not clear whether the nonaflate would be compatible with the Ni^0 or Co^I catalysts (especially at high temperatures) or with tetra-*n*-butylammonium fluoride. Since it was supposed that the demethylation would not pose any problems, the reaction path using nonaflate was considered as the second possibility.

The outline of the modified synthesis is displayed in Scheme 46. The synthesis of the target helicene **148** started in a very similar manner as the previous strategy. Iodo compound **136** was transformed into a free phenol **149** by the use of BBr_3 (Scheme 47). The reaction mixture work-up had to be done very carefully since the product was obviously prone to acidic ypso – substitution. A chromatographic separation of the desired product was improved by the addition of approximately 1 % acetic acid to decrease the large affinity of phenol to silica gel. The use of this additive also improved the overall separation and proved to be a good way to overcome complications associated with chromatography of free phenols. Acetic acid was then utilized for chromatography of all compounds containing a free hydroxyl group resulting in much better separation.

Scheme 47. Demethylation of methoxy derivative **136** using BBr_3

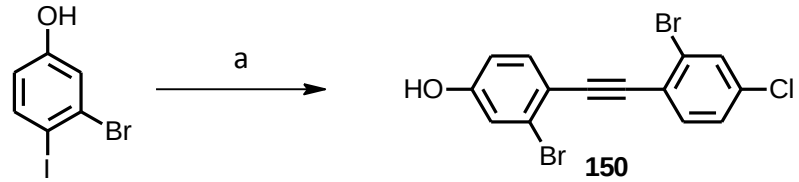


136 **149**

a) BBr_3 (1 eq.), DCM, rt, 18 h, 85 %.

In the next step, bisarylacetylene **150** was prepared *via* the one-pot Sonogashira reaction using commercially available 2-bromo-4-chloroiodobenzene in 60 % yield (Scheme 48). It was observed that the hydroxyl group was prone to oxidation when exposed to the atmosphere for a prolonged period. This turned out to be the case for basically all compounds containing a free phenol group and these compounds had to be stored in the freezer under inert gas.

Scheme 48. Sonogashira coupling for the synthesis of biarylacetylene compound **150**

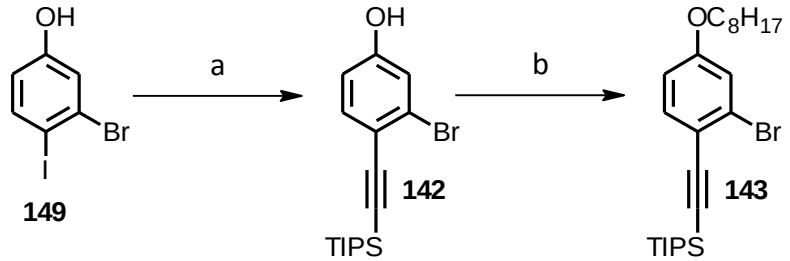


149 **150**

a) 1. TMSA (1.1 eq.), $Pd(PPh_3)_2Cl_2$ (4 mol %), CuI (8 mol %), DIPA, rt, 2 h; 2.TBAF (1.5 eq., THF), 30 min; 3. 2-bromo-4-chloroiodobenzene (1.05 eq.), rt, 2 h, 60 %.

The second branch of the synthesis involved the Sonogashira coupling of iodide **149** to deliver alkyne **142** in 75 % yield (Scheme 49). Since the reaction was very clean both according to TLC and GC-MS analysis, the product was used directly after aqueous work-up in the next step. Free phenol **142** was submitted to the Williamson reaction to provide octyloxy derivative **143** in satisfying 69 % overall yield from iodide **149** (Scheme 49). To our disappointment, when the reaction was repeated on a multi-gram scale, a large amount of various by-products was formed, probably owing to the trace amounts of the copper catalysts from the previous reaction contained in the starting material. Moreover, the by-products were difficult to separate from the desired product. The boronic acid **139** was then prepared in the same way as during the first synthesis discussed in Chapter 3.1 (cf. Scheme 39).

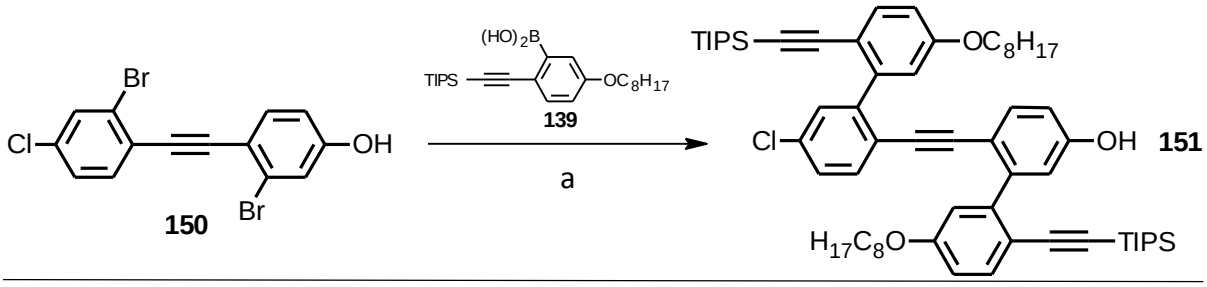
Scheme 49. Synthesis of the octyloxy derivative **143**



149 **142** **143**

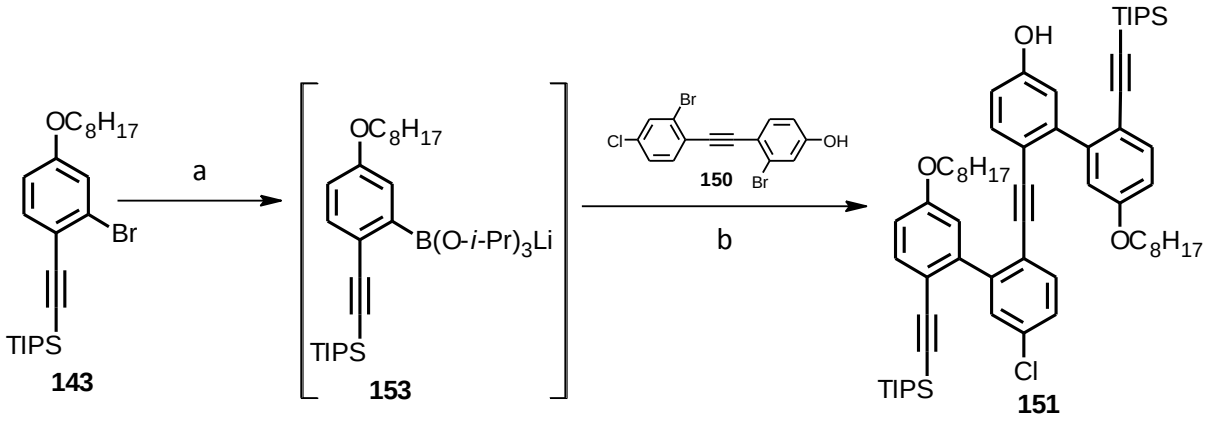
a) TIPSA (1.1 eq.), $Pd(PPh_3)_2Cl_2$ (4 mol %), CuI (8 mol %), DIPA, rt, 2 h; b) $C_8H_{17}I$ (0.95 eq.), Cs_2CO_3 (3 eq.), DMF, 90 °C, 69 % over 2 steps.

Scheme 50. Synthesis of triyne **151** *via* the Suzuki-Miyaura reaction



a) boronic acid **139** (2.5 eq.), $Pd(PPh_3)_2Cl_2$ (10 mol %), K_2CO_3 (3 eq.), toluene : 1-*PrOH* : water = 4 : 4 : 1, reflux, 3 h; 85 %.

Scheme 51. One-pot lithiation-borylation-Suzuki-Miyaura reaction



a) **143** (2.2 eq.), *n*-BuLi (2.5 eq.), $B(O\text{-}i\text{-}Pr)_3$ (2.5 eq.), THF, -78 °C to rt, 4 h; b) **150** (1 eq.), *XPhos* Pd G2 (7 mol %), K_3PO_4 (3 eq.), 40 °C, 2 h; 53 % over 2 steps.

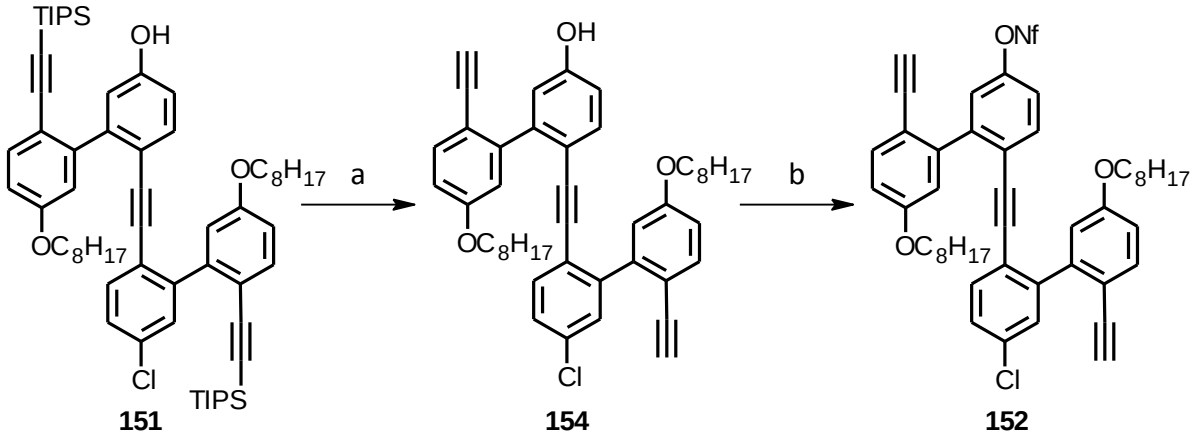
Once the alkyne **150** and the boronic acid **139** were available, they were subjected to the Suzuki-Miyaura reaction under the same reaction conditions as in the case of **140** (Scheme 50, cf. Scheme 41, Chapter 3.1). The yield of this step was surprisingly high, 85 %, with a minimum amount of by-products which made the separation of the product trivial.

The one-pot procedure for the preparation of triisopropylsilyl triyne **151** involving lithium triisopropylboronate was also tried (Scheme 51). The reaction gave the product in only 53 % yield, perhaps due to the reaction of the boronate **153** in the presence of the chlorine substituent. On the other hand, if there was no chlorine, this protocol might be very useful.

The obtained triyne **151** could be easily converted to nonaflate **152** but the subsequent removal of triisopropylsilyl groups to obtain triyne **154** was complicated by a concomitant cleavage of the nonaflyl group, as indicated by TLC analysis. Conversely, treating **151** with tetra-*n*-butylammonium fluoride led smoothly to the deprotected triyne **154** in almost quantitative yield which was then converted to nonaflate **152** by the use of nonaflyl fluoride in 92 % yield (Scheme 52). A legitimate question could be asked why it was better to convert the hydroxyl group of **154** to nonaflate before the final cyclotrimerization. The first reason for this choice was that we had had a bad experience with the cyclotrimerization of hydroxyl-containing compounds using $CpCo(CO)_2$. $Ni(cod)_2$ could be used instead but we

already knew that the preparation of helicene **129** using $Ni(cod)_2$ was tricky and the same result could be anticipated in this case. The second reason for introducing the nonaflate prior the cyclotrimerization was to avoid a free hydroxyl group that might complicate its chromatographic separation.

Scheme 52. Removal of the TIPS protecting groups

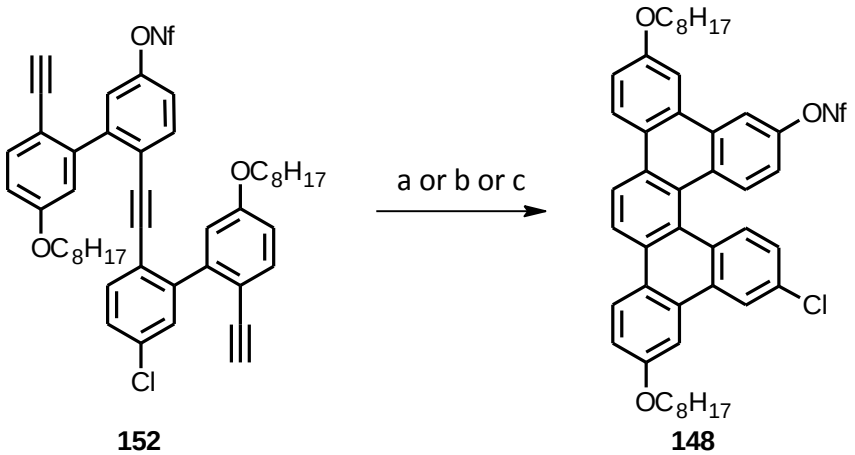


151 **154** **152**

a) TBAF (5 eq.), MeOH (5 eq.), THF, rt, 16 h; 98 %; b) NfF (3 eq.), Cs_2CO_3 (4 eq.), THF, rt, 1 h; 92 %.

With triyne **152** in hand, the experiments to prepare the corresponding helicene **148** began (Scheme 53). The cyclotrimerization using $CpCo(CO)_2$ in a flow reactor was successful after some optimization of the reaction temperature, catalyst loading and concentration of the starting materials, and the helicene **148** was isolated in 53 %. The best results were obtained with 1 equivalent of the cobalt reagent at 230 °C. Higher temperatures led only to a higher content of by-products, mainly due to hydrolysis of the nonaflate to give back the compound **154**. Micro-scale experiments (0.15 mmol) using $Ni(cod)_2$ in combination with PPh_3 or PCy_3 ligands never gave full conversion of the starting material according to TLC.

Scheme 53. Preparation of the helicene **148**



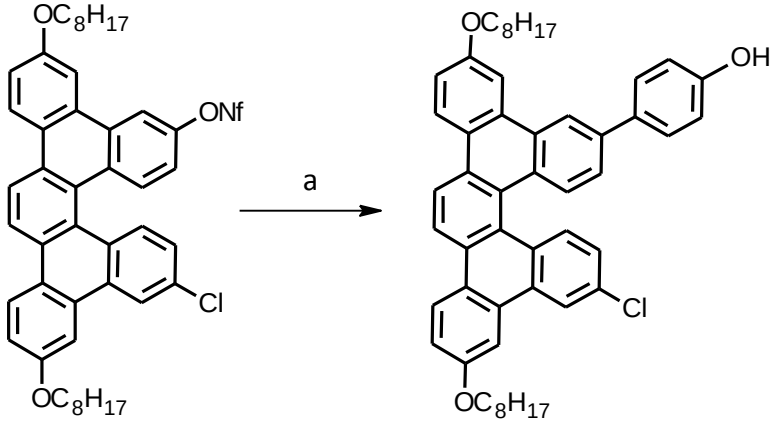
152 **148**

a) $Ni(cod)_2$ (1 eq.), PPh_3 (2 eq.), THF, rt, 24 h; yield was not estimated; b) $Ni(cod)_2$ (1 eq.), PCy_3 (2 eq.), THF, rt, 24 h; yield was not estimated; c) $CpCo(CO)_2$ (1 eq.), THF, flow reactor, 235 °C, 8 min, 53 %.

This helicene **148** was equipped with chlorine and nonaflyl groups that served in the following steps for introduction of phenyls with appropriate functionalities. The structure of

this helicene allowed to prepare the unsymmetrical building blocks due to the different reactivity of chlorine and nonaflyl group.

Scheme 54. Selective Suzuki-Miyaura reaction of the nonaflyl helicene



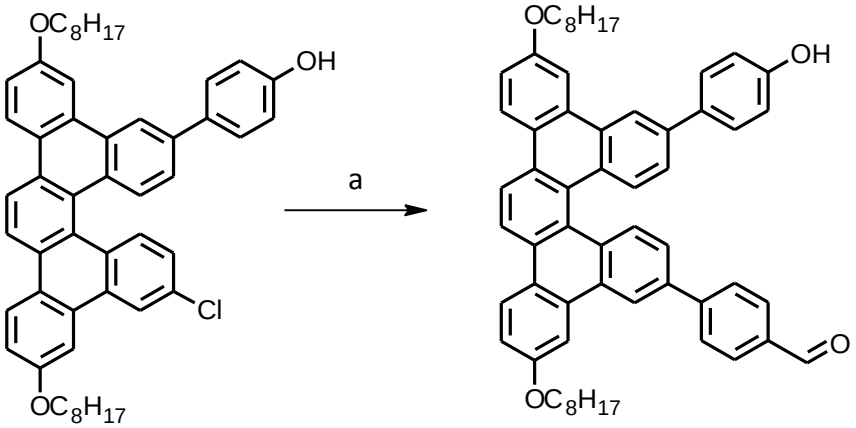
148 **155**

a) 4-hydroxyphenylboronic acid (1.5 eq.), *XPhos* Pd G2 (5 mol %), 0.5 M K_3PO_4 (6 eq.), THF, 40 °C, 2 h; 81 %.

The synthesis of the unsymmetrical helicene building block started with the Suzuki-Miyaura coupling of **148** with commercial 4-hydroxyphenylboronic acid to provide compound **155** in 81 % (Scheme 54). This reaction was catalyzed by $Pd(PPh_3)_2Cl_2$ whose low activity allowed to perform this transformation selectively without affecting the present chlorine group.

The chloride **155** was further coupled to commercially available 4-formylphenylboronic acid giving the building block **156** in excellent 90 % yield (Scheme 55). *XPhos* Pd G2 pre-catalyst was used for this purpose. Mild reaction temperature 40 °C, allowed by the use of this catalyst, was vital to prevent nucleophilic addition to the formyl group. Despite the presence of both formyl and hydroxyl groups, the product was easily separated by column chromatography with addition of a minute amount of acetic acid to the eluent, demonstrating a powerful solubilizing ability of the octyl chains.

Scheme 55. Highly efficient Suzuki-Miyaura reaction under mild conditions

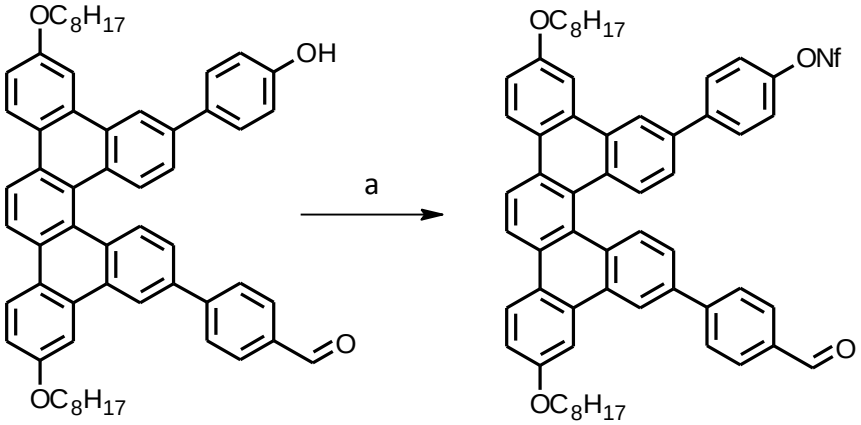


155 **156**

a) 4-formylphenylboronic acid (1.5 eq.), *XPhos* Pd G2 (5 mol %), 0.5 M K_3PO_4 (2 eq.), THF, 40 °C, 2 h; 90 %.

The hydroxyl group in the compound **156** was finally converted to nonaflate according to a standard protocol using nonaflyl fluoride (Scheme 56). Surprisingly, the nonaflate turned out to be unstable during chromatography and was isolated only in 54 % yield.

Scheme 56. Nonaflation of the unsymmetrical building block

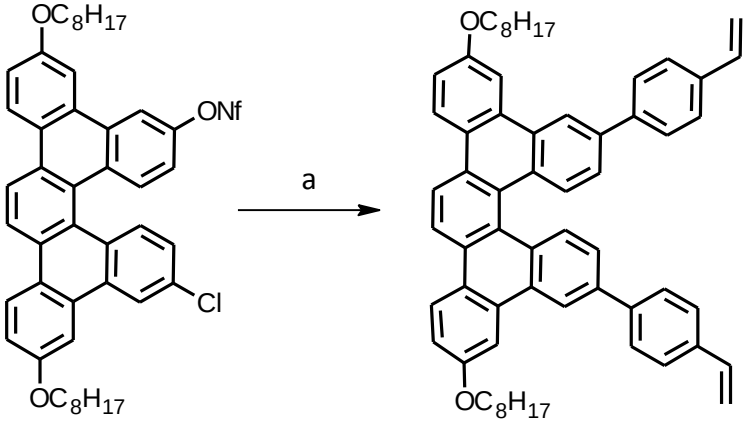


156 **133**

a) NfF (4 eq.), Cs_2CO_3 (3 eq.), THF, rt, 1 h; 54 %.

The synthesis continued with the preparation of the divinyl building block **132**. For this purpose, helicene **148** was subjected to Suzuki-Miyaura coupling with commercial 4-vinylphenylboronic acid to furnish only 54 % of the product (Scheme 57).

Scheme 57. Preparation of the symmetrical divinyl building block

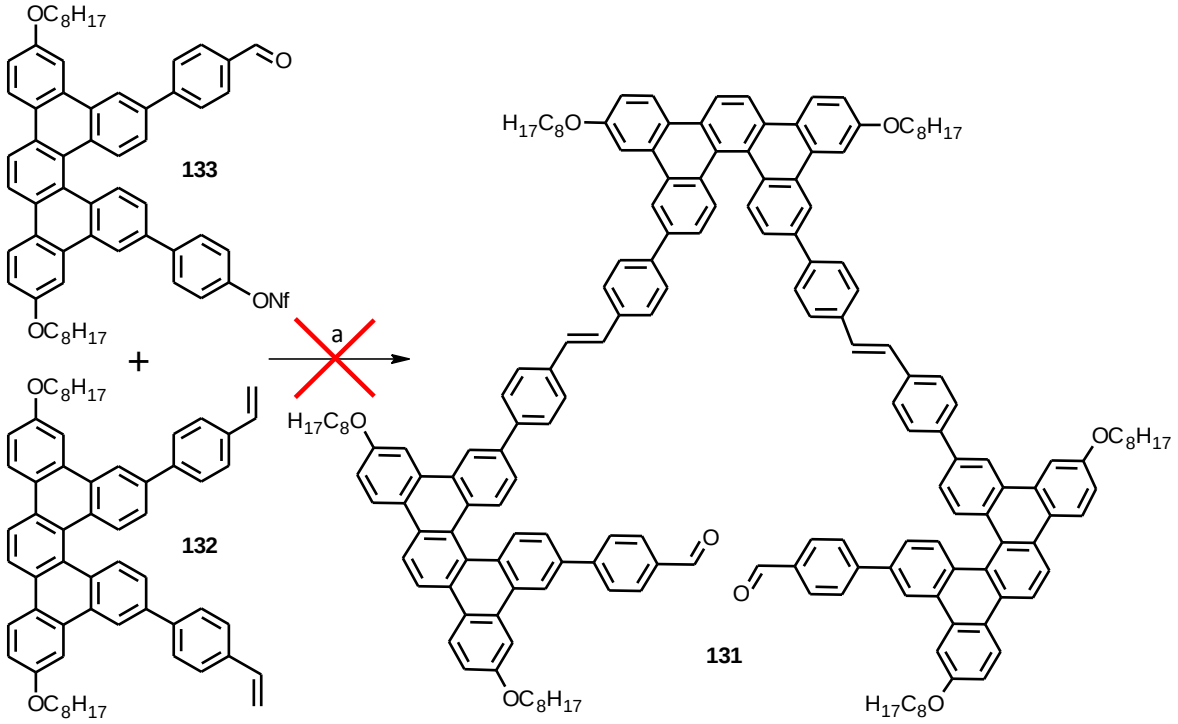


148 **132**

a) 4-vinylphenylboronic acid (3 eq.), *XPhos* Pd G2 (5 mol %), 0.5 M K_3PO_4 (4 eq.), THF, 50 °C, 2 h; 54 %.

At this stage, both building blocks **132** as well as **133** necessary for the construction of the target macrocycle were available. As outlined in Chapter 2, the reaction chosen for the construction of the trimer **131** was primarily Heck coupling. It is obvious that this step is, along with the final cyclization, a key point of the whole synthesis where the chemistry is being pushed to its limits mainly due to small amounts of the starting materials available and their low solubility. The volume of the reaction mixture was kept minimal to reach a sufficient molar concentration of the reactants and thus increase the reaction rate as much as possible. Even with such effort the molar concentration of the reactants stayed at least 5 to 10 times lower compared to usual Heck coupling protocols [(74),(75)] while the mass fraction remained quite high.

Scheme 58. First attempt of the trimer synthesis



a) *XPhos* Pd G2 (10 mol %), Et_3N (6 eq.), toluene, 100 °C, 24 h; 0 %.

The first attempt to prepare the trimer **131** involved the reaction of **132** with **133**, catalyzed by *XPhos* Pd G2 precatalyst (Scheme 58). This protocol had been specially designed for coupling of chlorides so it was anticipated that more reactive nonaflates would be even more suitable for this purpose. Unfortunately, despite all the precautions (very active catalyst, small reaction volume) the reaction resulted only in the hydrolysis of the nonaflate with no signs of the coupling (based on MALDI analysis). Nonaflates were obviously too unstable at elevated temperature in the presence of palladium. This outcome suggested that instead of searching for optimal conditions, it would be better to replace nonaflyl group with a more robust chlorine. The structure of the starting helicene **157** allowed such an approach albeit in several more steps and it is described in the next chapter.

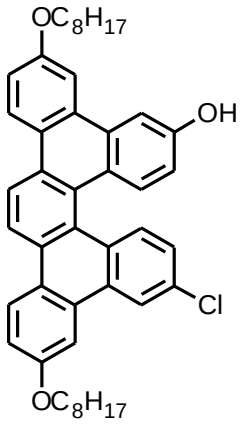
3.3. Synthesis of helicene building blocks – helicene 157

Figure 10 shows the structure of helicene **157**, a key molecule of the third synthetic strategy (Scheme 59). Based on the previous experience, the free hydroxyl group in combination with dibenzohelicene moiety was first considered problematic due to expected low solubility of dibenzohelicenes. On the other hand, it was very important to keep the free hydroxyl for later steps in the synthesis. Quite surprisingly, the problems turned out eventually not to be so serious and could be surmounted.

The synthesis started as in the previous cases with two main differences. The first one was the final optimization of the synthesis of **143**. To avoid the risk of side reactions caused

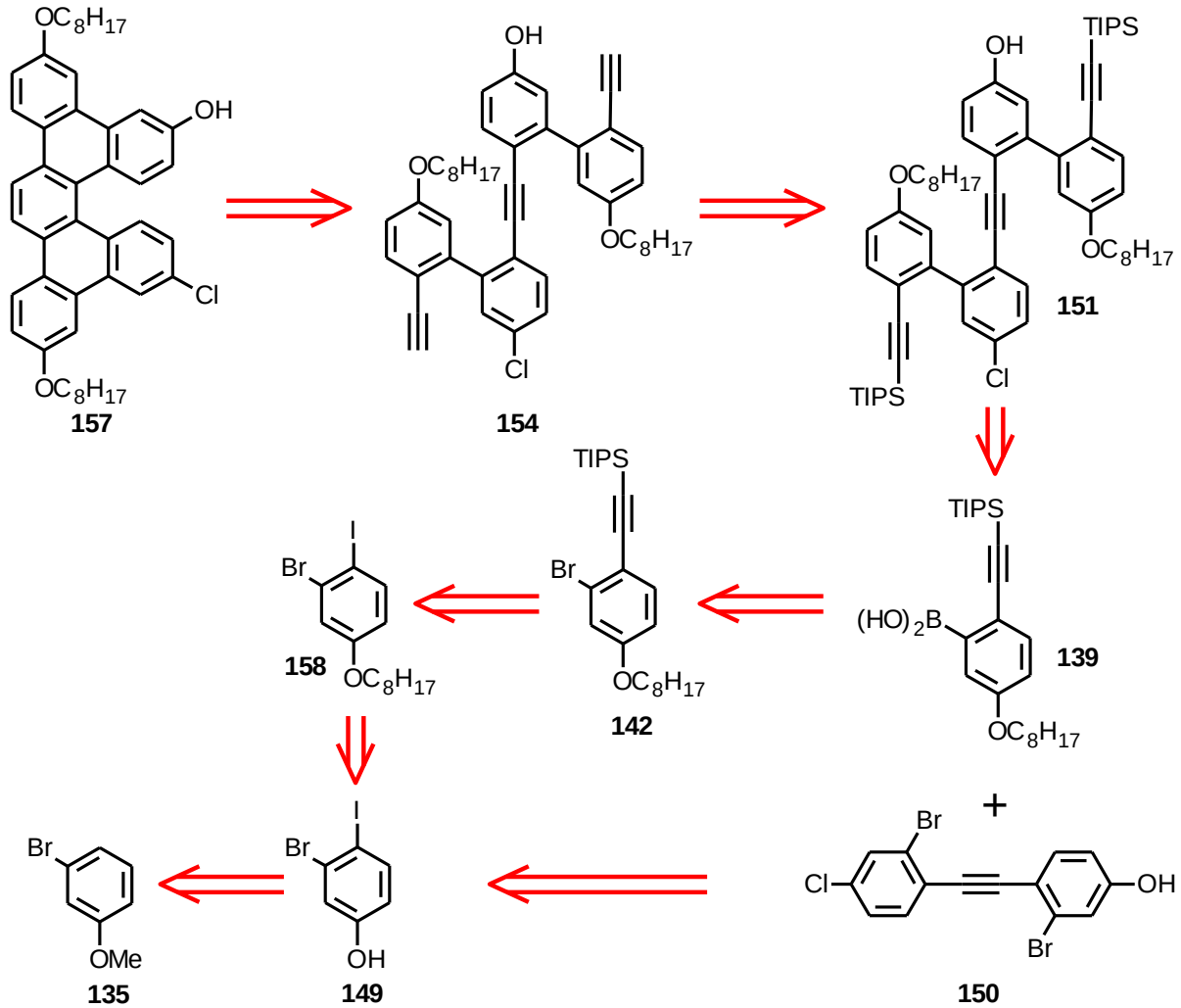
by the traces of catalyst present in the crude material **142** (cf. Scheme 49, Chapter 3.2) the order of the reactions was switched and the compound **143** was thus obtained in almost quantitative yield 97 % over two steps (Scheme 60).

Figure 10. Structure of target helicene 157

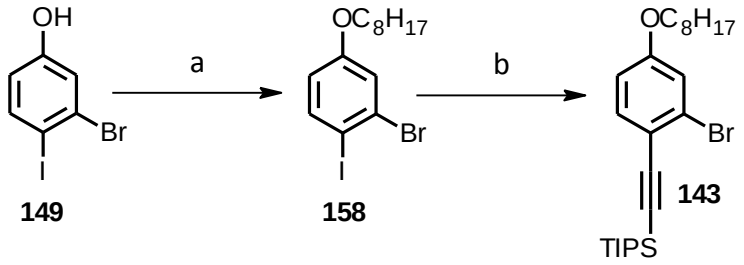


157

Scheme 59. Outline of the synthetic strategy of helicene **157**



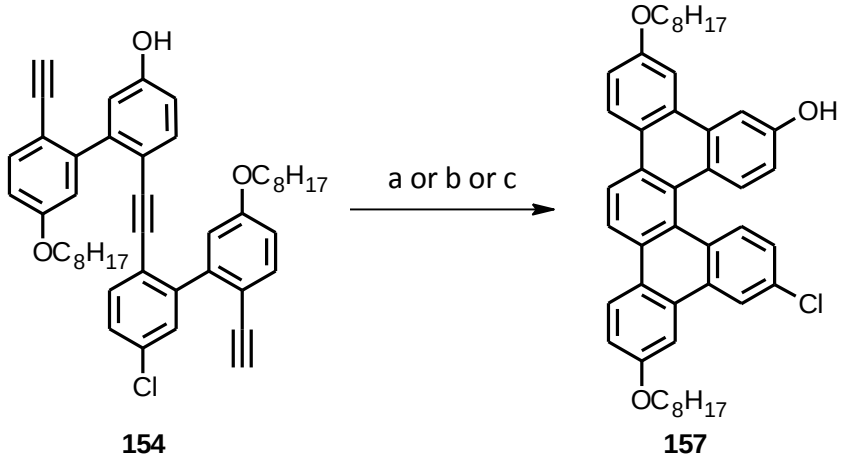
Scheme 60. Optimization of the synthesis of **143**



a) $C_8H_{17}I$ (1.05 eq.), Cs_2CO_3 (2.9 eq.), DMF, 90 °C; b) TIPSA (1.05 eq.), $Pd(PPh_3)_2Cl_2$ (5 mol %), CuI (10 mol %), DIPA, rt, 17 h; 97 % over 2 steps.

The second difference was in the order of cyclotrimerization and nonaflation reaction. While in the previous approach the triyne **151** was first nonaflated and then cyclotrimerized (cf. Scheme 52 and 53, Chapter 3.2), in the new strategy, the order was reversed. Concerns whether the presence of the free hydroxyl group would affect the catalyst performance were one of the reasons why this structure was not considered initially. The cyclotrimerization of **154** using $Ni(cod)_2$ and PPh_3 did not give a full conversion of the starting compound (Scheme 61). Better results were achieved using PCy_3 as a ligand but the yield was still low (49 %). Conversely, $CpCo(CO)_2$ in a flow reactor gave the helicene in 70 % yield regardless of the reaction scale. To our delight, the separation of the product *via* column chromatography was also efficient using acetic acid as an additive.

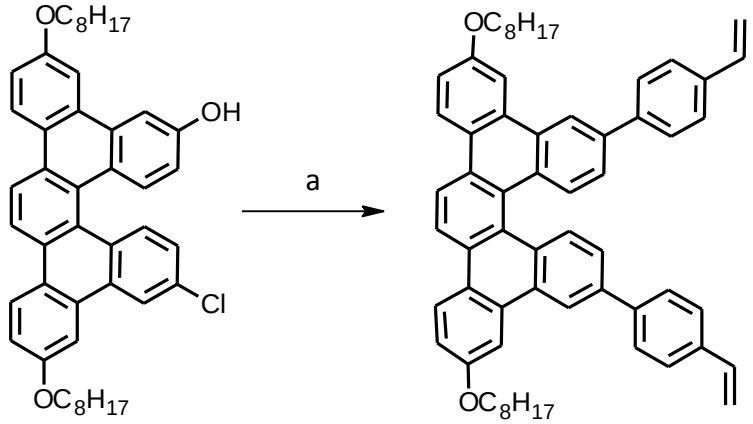
Scheme 61. Preparation of helicene **157**



a) $Ni(cod)_2$ (1 eq.), PPh_3 (2 eq.), THF, rt, 24 h; yield was not estimated; b) $Ni(cod)_2$ (1 eq.), PCy_3 (2 eq.), THF, rt, 24 h; 49 %; c) $CpCo(CO)_2$ (1 eq.), THF, flow reactor, 240 °C, 8 min, 70 %.

For the preparation of the divinyl derivative **132**, helicene **157** had to be first converted into the nonaflyl derivative **148** which had been already prepared (Scheme 62, cf. Scheme 57, Chapter 3.2). The reaction of **157** with nonaflyl fluoride was absolutely clean and to avoid chromatography, the crude product was directly employed in the following Suzuki-Miyaura reaction with commercially available 4-vinylphenylboronic acid. At 40 °C and 5 mol % of *XPhos* Pd G2, the reaction gave a mixture of unreacted starting compound along with products of mono and double coupling (based on TLC analysis). Increasing the catalyst loading to 10 % and temperature to 80 °C, the reaction was practically quantitative.

Scheme 62. Preparation of the symmetrical divinyl building block



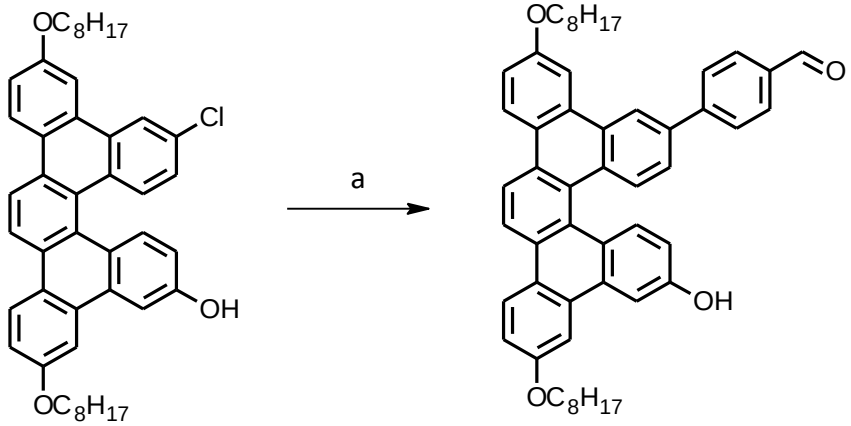
157 **132**

a) 1. NfF (3 eq.), Cs_2CO_3 (3 eq.), THF, rt, 1 h; 2. 4-vinylphenylboronic acid (3 eq.), *XPhos* Pd G2 (10 mol %), 0.5 M K_3PO_4 (4 eq.), THF, 80 °C, 1.5 h; 99 % over two steps.

The synthesis of the unsymmetrical building block **159** was a bigger challenge. Based on the conclusions made in Chapter 3.2, it was necessary to decorate the building block with 4-chlorophenyl moiety in place of the labile 4-nonaflylphenyl. Since there was already a chlorine atom in the molecule of the starting helicene **157**, the order of the consecutive Suzuki-Miyaura reactions had to be changed and that is why it was necessary to keep the free hydroxyl group in the molecule.

The first attempt was made by coupling **157** and 4-formylphenylboronic acid to get derivative **159** (Scheme 63). In spite of very mild reaction conditions, a mixture of compounds was formed with the desired aldehyde obtained in 54 % yield, perhaps owing to a nucleophilic addition to the free formyl group. Considering the harsh conditions of the future Heck coupling, also performed under basic conditions, it was clear that the formyl group had to be protected.

Scheme 63. First step in the preparation of the unsymmetrical building block



157 **159**

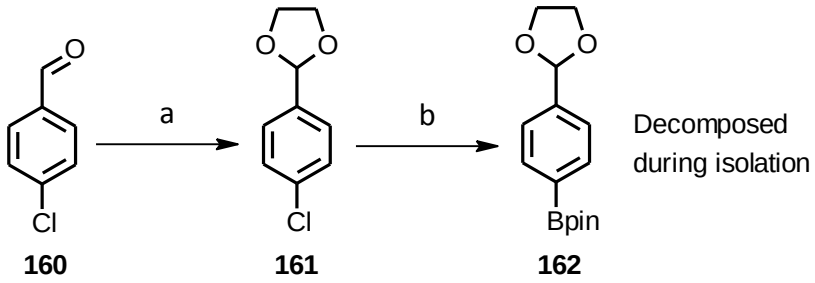
a) 4-formylphenylboronic acid (1.5 eq.), *XPhos* Pd G2 (5 mol %), 0.5 M K_3PO_4 (2 eq.), THF, 40 °C, 19 h; 54 %.

Dioxolane protecting group was considered as an ideal choice because it is stable under basic conditions. The synthetic sequence was therefore correspondingly modified. The

first step was acetalyzation of 4-chlorobenzaldehyde **160** to provide the desired dioxolane **161** (Scheme 64). To purify the product, chromatography could not be used because the compound **161** decomposed in acidic environment. Therefore, Kugelrohr distillation was applied instead, giving the product quantitatively in high purity.

In order to prepare pinacolboronate **162**, suitable for the subsequent Suzuki-Miyaura coupling, the protected aldehyde **161** was further submitted to Pd^0 catalyzed borylation (Scheme 64). GC-MS showed a complete reaction within 30 minutes. Unfortunately, the product was totally unstable even on a TLC plate so chromatographic purification was not feasible. However, compound **162** could still be used in a one-pot reaction to prepare **163**.

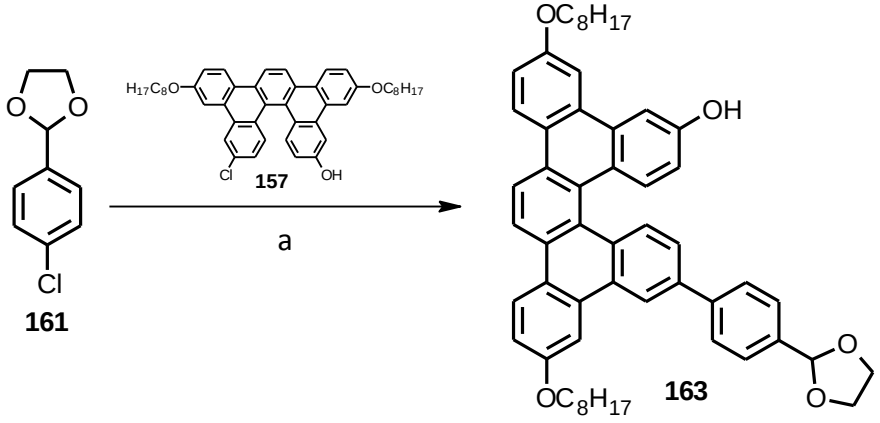
Scheme 64. Unsuccessful borylation of **161**



a) $(CH_2OH)_2$ (10 eq.), *p*-TsOH (10 mol %), toluene, reflux, 2 d; 99 %; b) B_2pin_2 (1.5 eq.), $Pd(OAc)_2$ (5 mol %), *XPhos* (10 mol %), KOAc (3 eq.), dioxane, 110 °C, 16 h, 0 %.

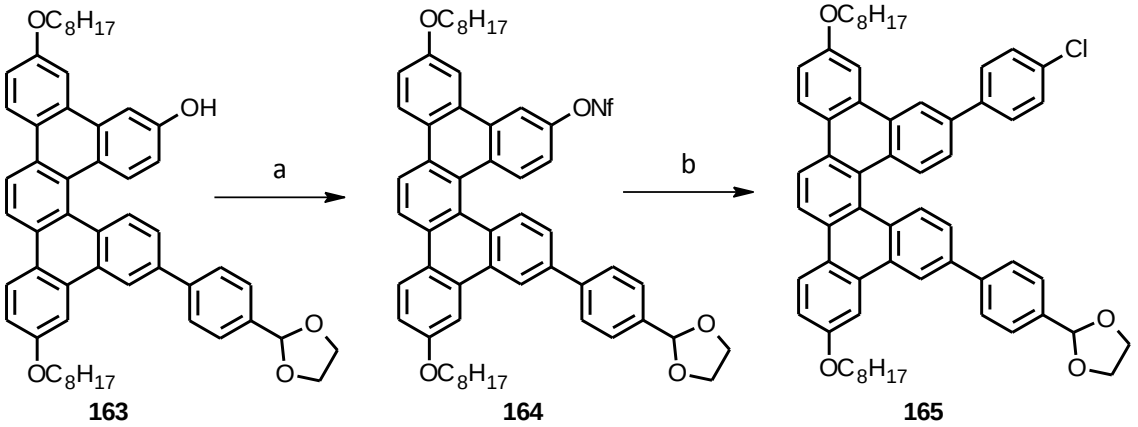
For its preparation, chloride **161** was converted to pinacolboronate **162** followed by the addition of helicene **157**. The reaction afforded the desired product **163** in 76 % yield. The obtained hydroxyl derivative **163** was then converted to nonaflate **164** (Scheme 66) and since this reaction was practically quantitative, it was used after an aqueous work-up directly in the subsequent Suzuki-Miyaura reaction with 4-chlorophenylboronic acid to give the unsymmetrical building block **165** in almost quantitative yield.

Scheme 65. One-pot Suzuki-Miyaura coupling for the synthesis of **163**



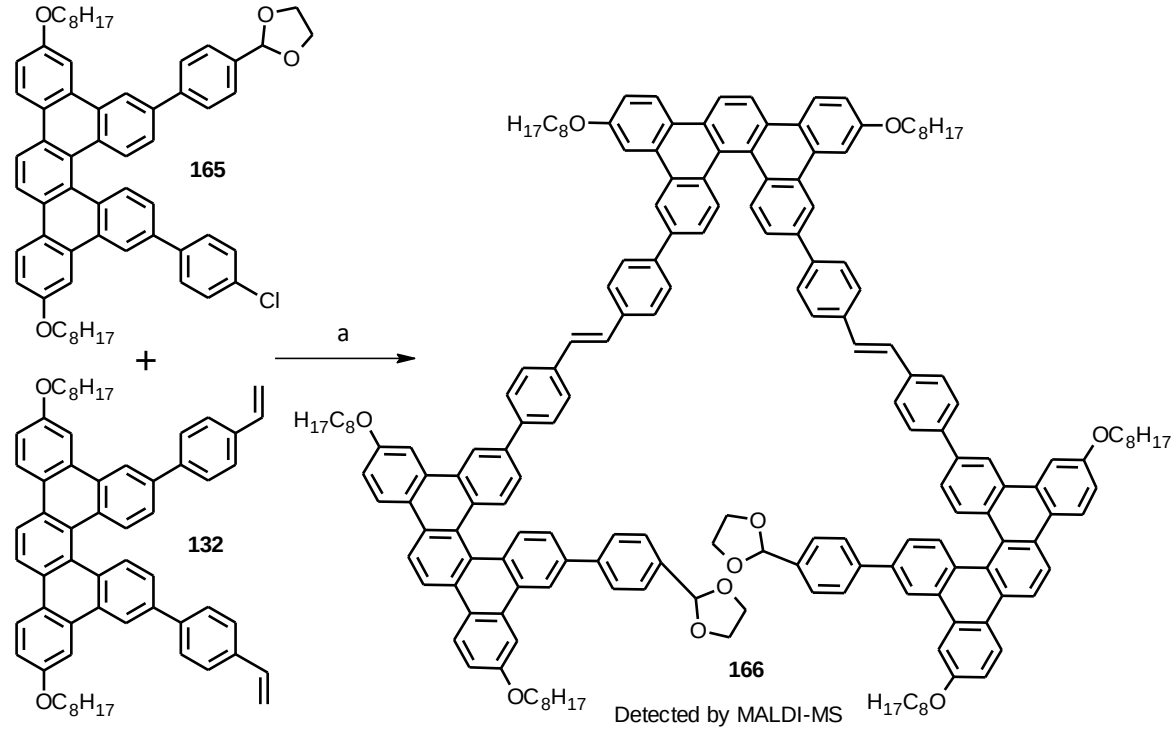
a) 1. B_2pin_2 (1.1 eq.), $Pd(OAc)_2$ (3 mol %), *XPhos* (12 mol %), KOAc (1.3 eq.), dioxane, 110 °C, 30 min; 2. **135** (0.7 eq.), 110 °C, 1 h, 76 %.

Scheme 66. Synthesis of the unsymmetrical building block with protected formyl group



a) NfF (3 eq.), Cs_2CO_3 (3 eq.), THF, 40 °C, 40 min; b) 4-chlorophenylboronic acid (2 eq.), $Pd(PPh_3)_2Cl_2$ (10 mol %), K_2CO_3 (2 eq.), toluene : 1-*PrOH* : water = 4 : 4 : 1, reflux, 2 h; 99 % after 2 steps.

Scheme 67. Synthesis of trimer **166**



a) $Pd(OAc)_2$ (10 mol %), *DavePhos* (30 mol %), Bu_4NOAc (6 eq.), dioxane, 110 – 130 °C, 72 h, traces of product, not isolated.

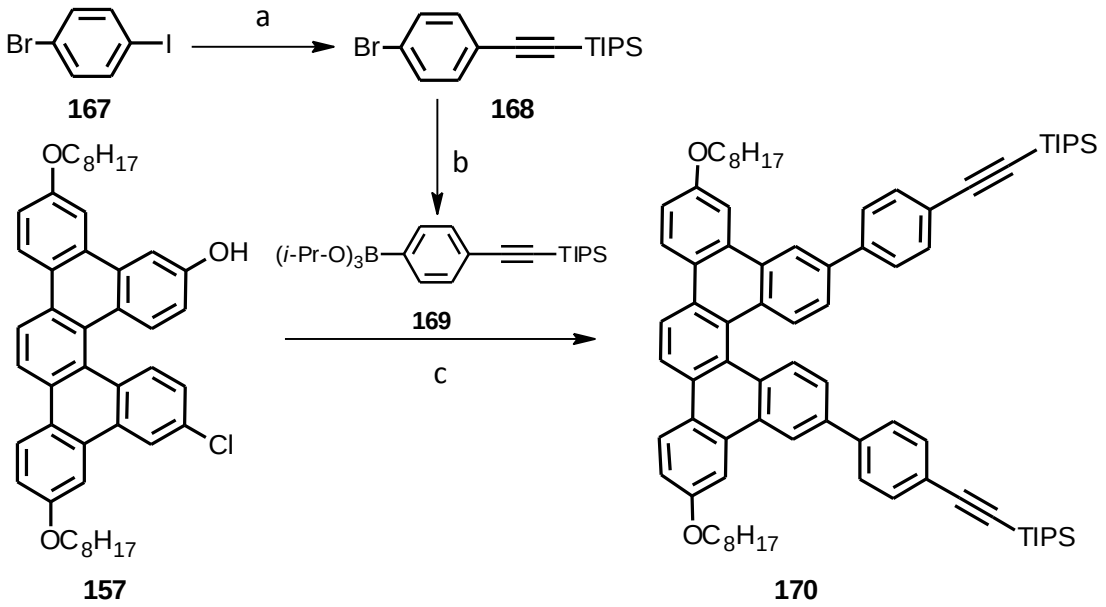
At this point, both necessary building blocks **132** and **165** were synthesized and the Heck reaction to prepare trimer **166** could be realized (Scheme 67). A catalytic system utilizing *DavePhos* ligand was chosen since it has been reported to be especially suitable for the Heck coupling of aryl chlorides (cf. Chapter 1.4.4). For the reasons mentioned above, this reaction was carried out in a pressure tube in less than 100 µL of solvent. The pressure tube had to be very tightly closed to reduce evaporation of the solvent since the reaction was performed above its boiling point. After one day heating at 110 °C, the color of the reaction mixture turned from yellow to bright fluorescent yellow-green which usually indicates an increased

conjugation. Additionally, there was clearly visible precipitation which was also in accordance with expectation. The MALDI-MS analysis showed the formation of the expected primarily formed dimer and the desired trimer **166**. The TLC analysis, however, showed that the conversion was rather poor and many by-products were formed. The reaction temperature was therefore increased to 130 °C and the mixture was left for additional two days to increase the conversion. Unfortunately, MALDI-MS showed a complete decomposition of the initially formed products. Since the separation of the mixture would not be efficient due to the bad separation at a TLC plate and the attempts to crystallize the products failed, it was obvious that Heck coupling, despite all its advantages, is not a good choice for this purpose.

3.4. Synthesis of the trimer based on the Suzuki-Miyaura reaction

To avoid problems encountered during the syntheses of trimers **131** and **166** *via* Heck coupling (cf. Chapter 3.3), the Suzuki-Miyaura reaction was seen as another option for the synthesis of trimer **166**, hopefully providing only the desired product. Its conditions are usually milder compared to those of the Heck coupling, with the lower formation of unwanted by-products. For this purpose, bis(pinacolboronate) **172** was anticipated as an ideal coupling partner. This compound was prepared in several steps as shown in Schemes 68 and 69. The Sonogashira coupling of 4-iodobromobenzene with (triisopropylsilyl)acetylene afforded alkyne **168** in a quantitative yield (Scheme 68). This compound was then converted to the corresponding lithium triisopropylboronate **169** that was employed directly in the subsequent Suzuki-Miyaura coupling with helicene **157** to deliver diyne **170** in excellent 95 % yield.

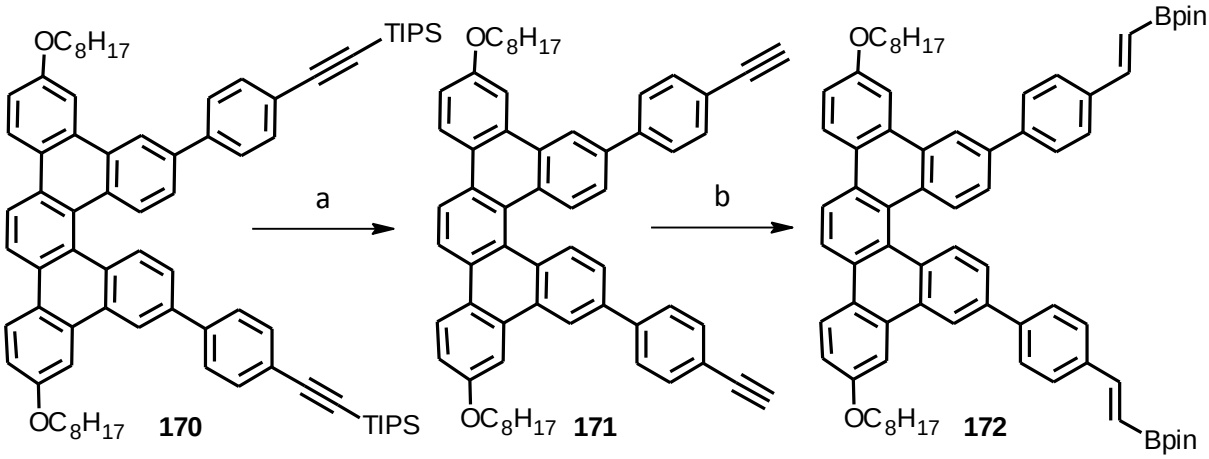
Scheme 68. Reaction sequence leading to the protected diyne **170**



a) TIPSA (1.05 eq.), $Pd(PPh_3)_2Cl_2$ (1 mol %), CuI (2 mol %), DIPA, rt, 23 h, 99 %; b) *n*-BuLi (3.3 eq.), $B(O\text{-}i\text{-}Pr)_3$ (3.3 eq.), THF, -78 °C to rt, 1 h, yield not estimated; c) 1. NfF (3 eq.), Cs_2CO_3 (3 eq.), THF, 40 °C, 1 h; 2. **169** (3 eq.), *XPhos* Pd G2 (10 mol %), 0.5 M K_3PO_4 (4 eq.), THF, 60 °C, 1 h, 95 % over 2 steps.

To introduce the boron functional groups suitable for the Suzuki-Miyaura reaction, the triisopropylsilyl groups of the compound **170** were first removed using tetra-*n*-butylammonium fluoride to give diyne **171** in 79 % yield and then Cu^{I} catalyzed hydroboration of the free diyne **171** using bis(pinacolato)diboron was employed (Scheme 69). When *DPEPhos* was used as a ligand, the reaction resulted in a mixture of unreacted starting material and products of mono- and dihydroboration. Replacing *DPEPhos* with *XantPhos* led to the clean formation of the desired diborylated product **172**, as confirmed by the TLC analysis the ESI mass spectrometry. Unfortunately, attempts to isolate this compound failed due to its low stability on silica gel. Since the reaction led to a single product, it was, however, supposed that it could be used directly in the following Suzuki-Miyaura reaction.

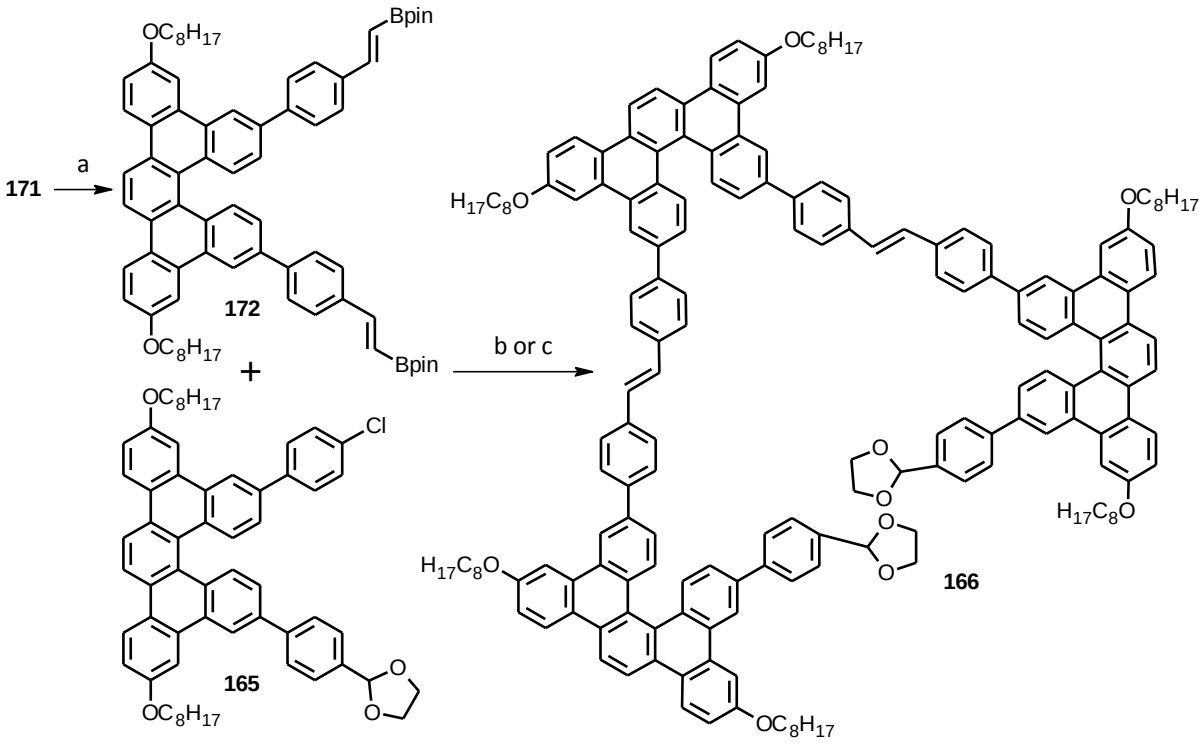
Scheme 69. Preparation of bis(pinacolboronate) **172**



a) TBAF (10 eq.), MeOH (3.5 eq.), THF, rt, 30 min, 79 %; b) B_2pin_2 (2.5 eq.), CuCl (7.5 mol %), *XantPhos* (7.5 mol %), KO*t*-Bu (15 mol %), MeOH (6 eq.), THF, rt, 24 h, yield not estimated.

To obtain trimer **166**, the previously prepared solution of bis(pinacolboronate) compound **172** was allowed to react with chloride **165** (Scheme 70). In order to ensure a smooth course of the reaction and thus avoid the separation problems discussed in Chapter 3.3, very active *XPhos* Pd G2 precatalyst was used. The reaction at 40 °C led to the formation of a green precipitate within 1 hour. As expected, the TLC showed a complete consumption of the starting compound **172** along with the remaining chloride **165** which was used in a slight excess. However, the low solubility of the products made the TLC analysis very unreliable since all the desired products were eluted only poorly by 1,2,4-trichlorobenzene or N-methylpyrrolidone. The mixture could be sequentially triturated with chloroform to provide three fractions of decreasing solubility. The fractions were individually analyzed by MALDI-MS (as the only viable analytical tool in this case) which showed that the insoluble fractions contained the desired trimer **166** along with dimer **173** containing an unreacted pinacolboronate group and the product of protodeboration **174** (Figure 11 and Figure 12). On the other hand, the soluble fraction composed mainly of the unreacted starting compounds **165** and **172**.

Scheme 70. Suzuki-Miyaura reaction leading to trimer **16**



a) B_2pin_2 (2.5 eq.), CuCl (7.5 mol %), *XantPhos* (7.5 mol %), KO*t*-Bu (15 mol %), MeOH (6 eq.), THF, rt, 24 h, yield not estimated; b) **165** (2.2 eq.), *XPhos* Pd G2 (10 mol %), K_3PO_4 (4 eq.), THF, 50 °C, 18 h, yield not estimated; c) **165** (3 eq.), *XPhos* Pd G2 (10 mol %), CuCl (2 eq.), *n*-Bu_4NBr (20 mol %), K_3PO_4 (5.5 eq.), NMP, 140 °C, 2 h, yield not estimated.

Figure 11. Intermediate **173** and product of protodeboration **174**

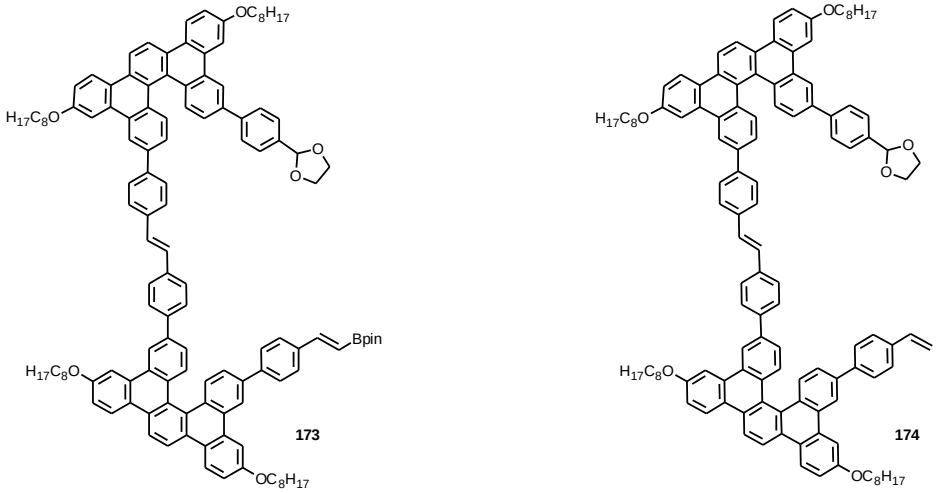
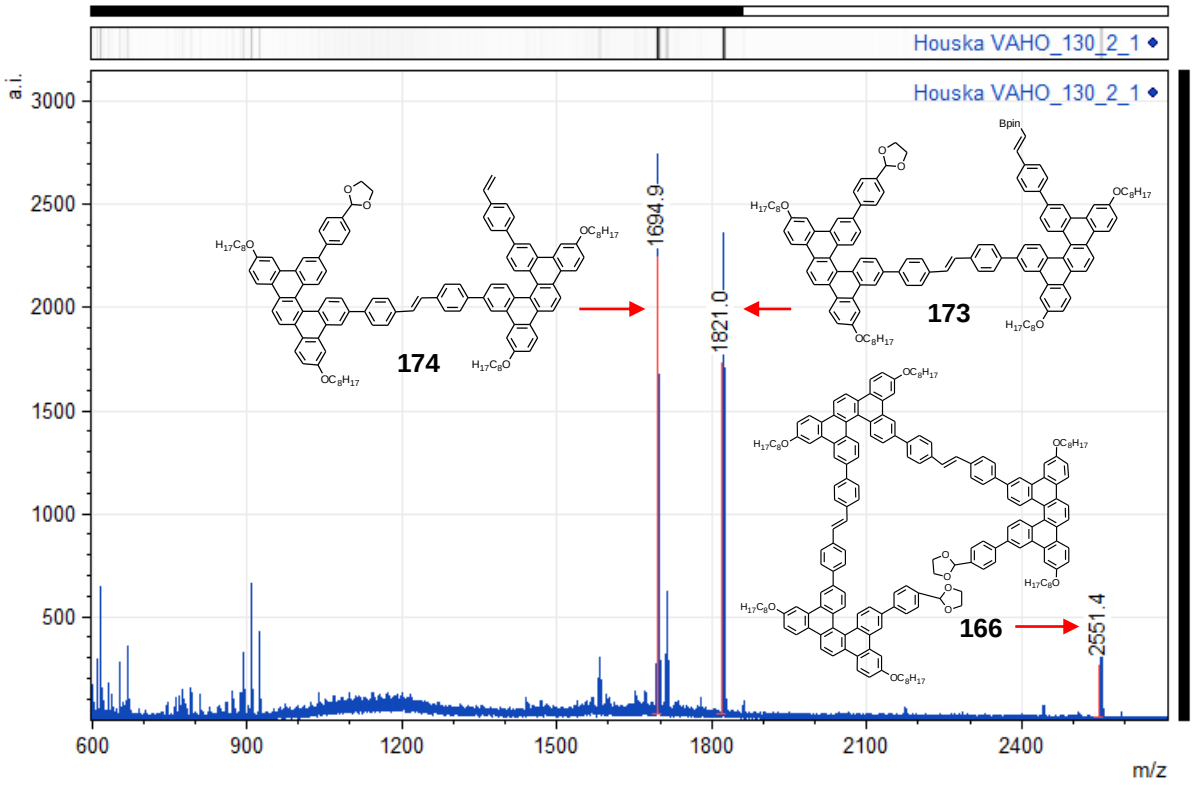


Figure 12. MALDI-MS spectrum corresponding to the insoluble fraction of products of the Suzuki-Miyaura reaction of **165** and **172** in THF as a solvent



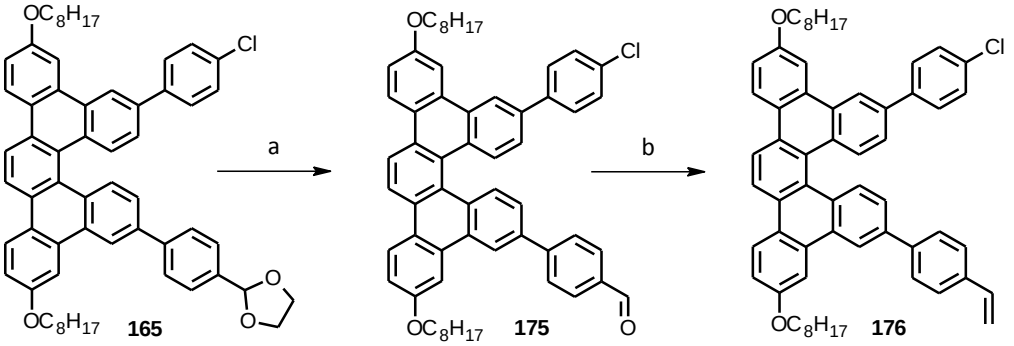
The spectrum shows the formation of the desired trimer **166** at mass 2551.4 m/z along with the unreacted intermediate **173** at mass 1821.0 m/z and the product of protodeboration **174** at mass 1694.9 m/z.

Assuming that the conversion of the starting materials **165** and **172** was incomplete due to the bad solubility of the intermediates (mainly the product of a one-fold Suzuki-Miyaura reaction **173**), attempts to surmount this complication were made. It was found that the only solvents that satisfyingly dissolve the trimer **166** are 1,2,4-trichlorobenzene and N-methylpyrrolidone. The next experiment therefore employed N-methylpyrrolidone as a solvent (as 1,2,4-trichlorobenzene is incompatible with the conditions of the Suzuki-Miyaura reaction) (Scheme 70). The reaction was performed at 140 °C using *XPhos* Pd G2 precatalyst along with CuCl and tetra-*n*-butylammonium bromide as additives (both known to increase the rate of the Suzuki-Miyaura reaction [90]). However, the MALDI-MS spectrum did not show any significant changes in the composition of the reaction mixture. Due to the very low solubility of the products, their chromatographic separation was not feasible but recrystallization from N-methylpyrrolidone afforded yellow crystals. Unfortunately, it had no effect on the composition of the mixture and the material still contained impurities.

Considering the fact that this project was specially designed to overcome the previously encountered solubility problems, the aforementioned findings were a big disappointment. Moreover, none of the solvents that dissolve trimer **166** could be used for the intended McMurry reaction. At this point, the optimization of the synthesis of trimer **166** was therefore meaningless. Instead, the attention was turned to the intramolecular alkene metathesis of divinyl trimer **177** (for the structure of trimer **177** see Scheme 73).

The first step to prepare the new trimer **177** was a synthesis of its vinyl building block **176**. Thus, dioxolanyl derivative **165** was quantitatively converted to a free aldehyde **175** by an acid catalyzed transacetalization (Scheme 71). This compound was further transformed into vinyl derivative **176** in 55 % yield using the Wittig reaction. With the introduction of the vinyl group, a dramatic decrease in solubility of the compound **176** was observed which indicated the possible more serious solubility problems in the following steps of the synthesis.

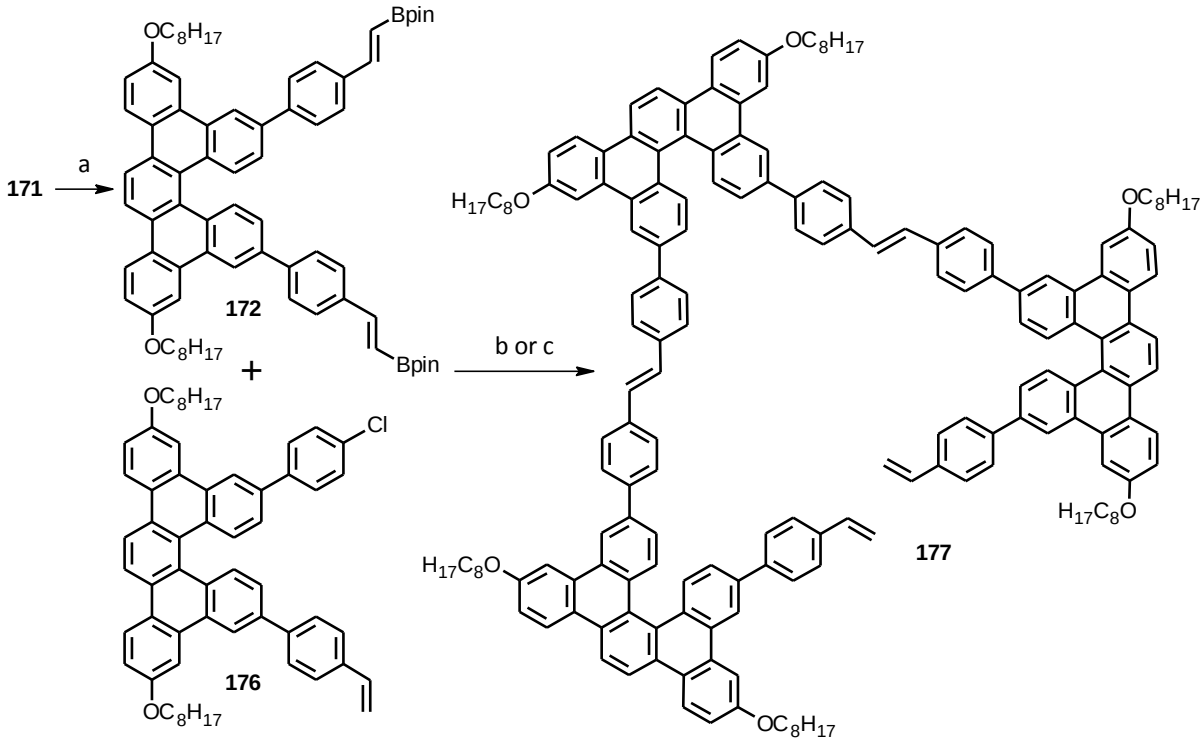
Scheme 71. Reaction sequence leading to vinyl compound **176**



a) *p*-TsOH (1 eq.), Me_2CO, THF, rt, 10 min, 99 %; b) 1. $MePPh_3I$ (1.6 eq.), *n*-BuLi (1.5 eq.), THF, 0 °C to rt, 15 min. 2. **175** rt, 2 h; 55 %.

The subsequent Suzuki-Miyaura coupling of the vinyl derivative **176** and the diboronyl compound **172** was realized in a similar way as in the previous cases (cf. Scheme 70). First, compound **172** was prepared and used without the separation from the reaction mixture directly in the coupling with the vinyl compound **176** (Scheme 72). The reaction was catalyzed by *XPhos* Pd G2 precatalyst and carried out at 80 °C under sonication to ensure the dissolution of the intermediates. Yellow-green products precipitated out of the reaction mixture within one hour and the mixture was left to react overnight to ensure the highest possible yield. Similarly as in the case of the previous preparations of the key trimer, this reaction afforded a mixture of products containing the desired trimer **177** in a mixture with the intermediate **178** and other by-products, as evidenced by the MALDI-MS analysis (Figure 13 and Figure 14).

Scheme 72. Suzuki-Miyaura reaction leading to divinyl trimer **177**



a) B_2pin_2 (2.5 eq.), CuCl (7.5 mol %), *XantPhos* (7.5 mol %), KO*t*-Bu (15 mol %), MeOH (6 eq.), THF, rt, 24 h, yield not estimated; b) **176** (2.5 eq.), *XPhos* Pd G2 (10 mol %), K_3PO_4 (8.5 eq.), THF, sonication, 80 °C, 18 h, yield not estimated.

Figure 13. Main intermediate of the Suzuki-Miyaura reaction of **172** and **176**

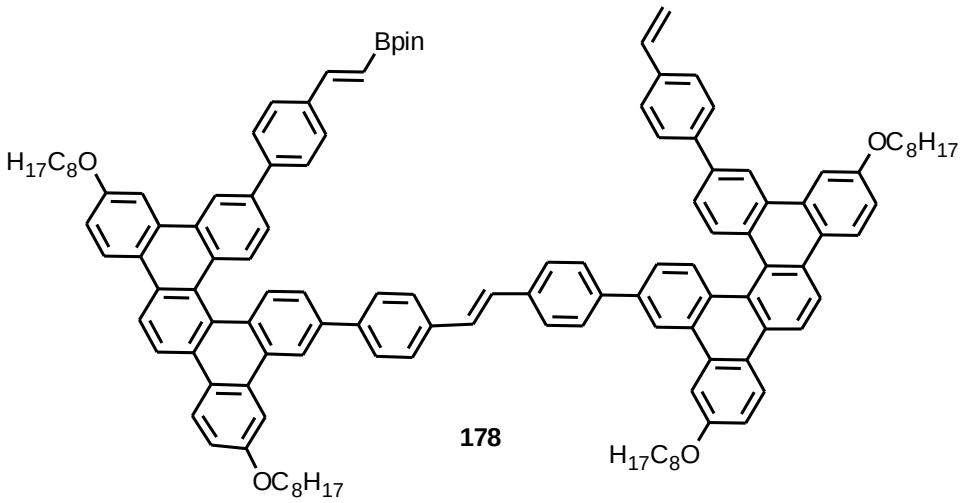
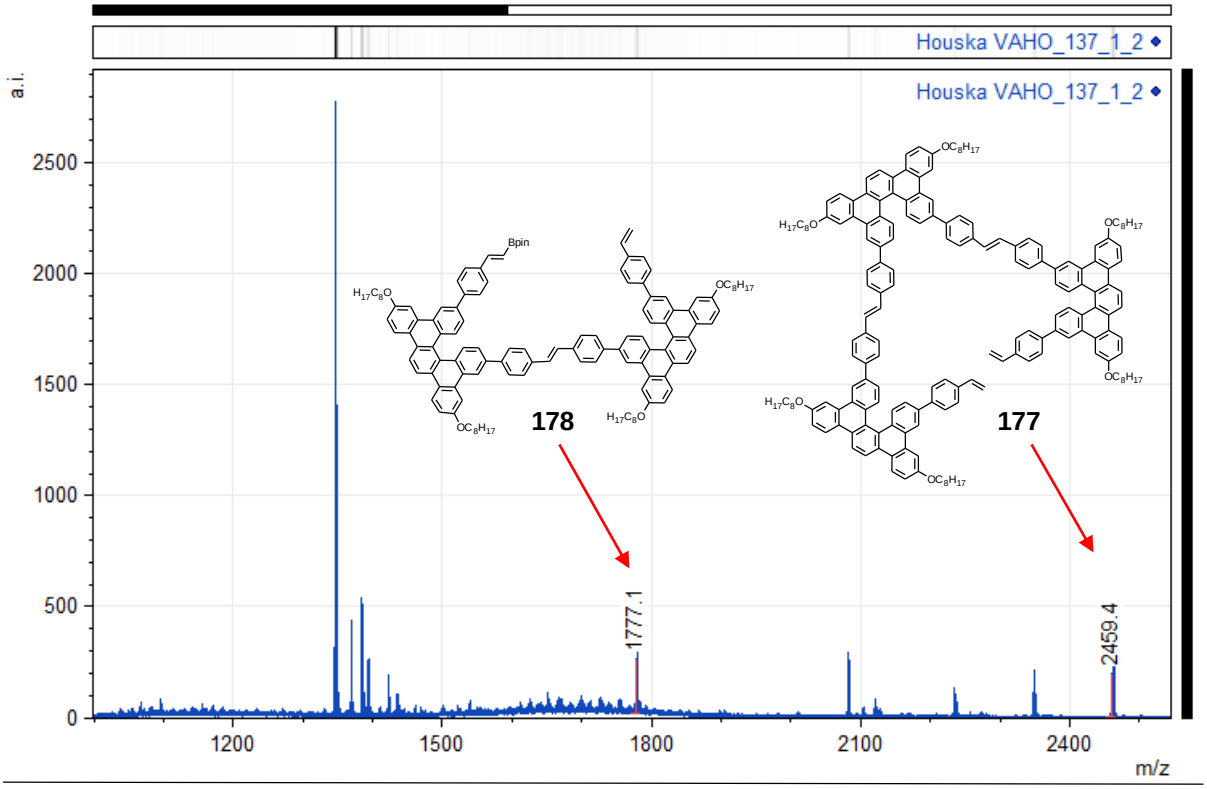


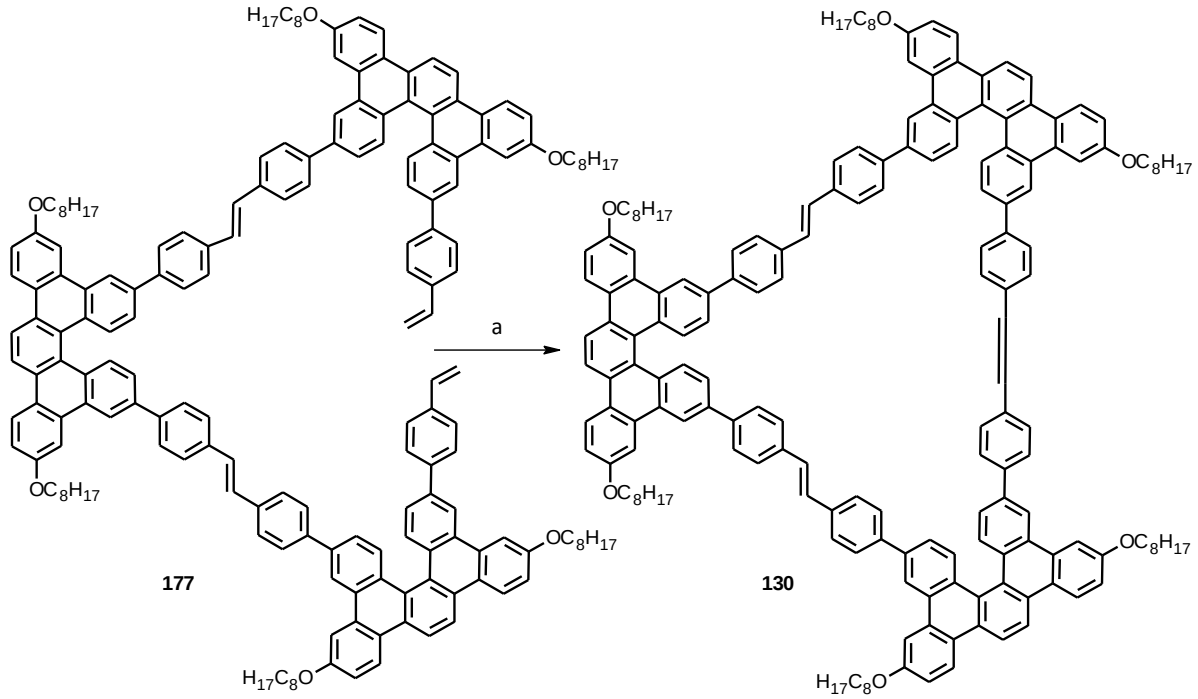
Figure 14. MALDI-MS showing the products of the Suzuki-Miyaura reaction of **172** and **176**



The spectrum shows the formation of the desired divinyl trimer **177** at mass 1777.1 m/z along with the unreacted intermediate **178** at mass 1459.4 m/z.

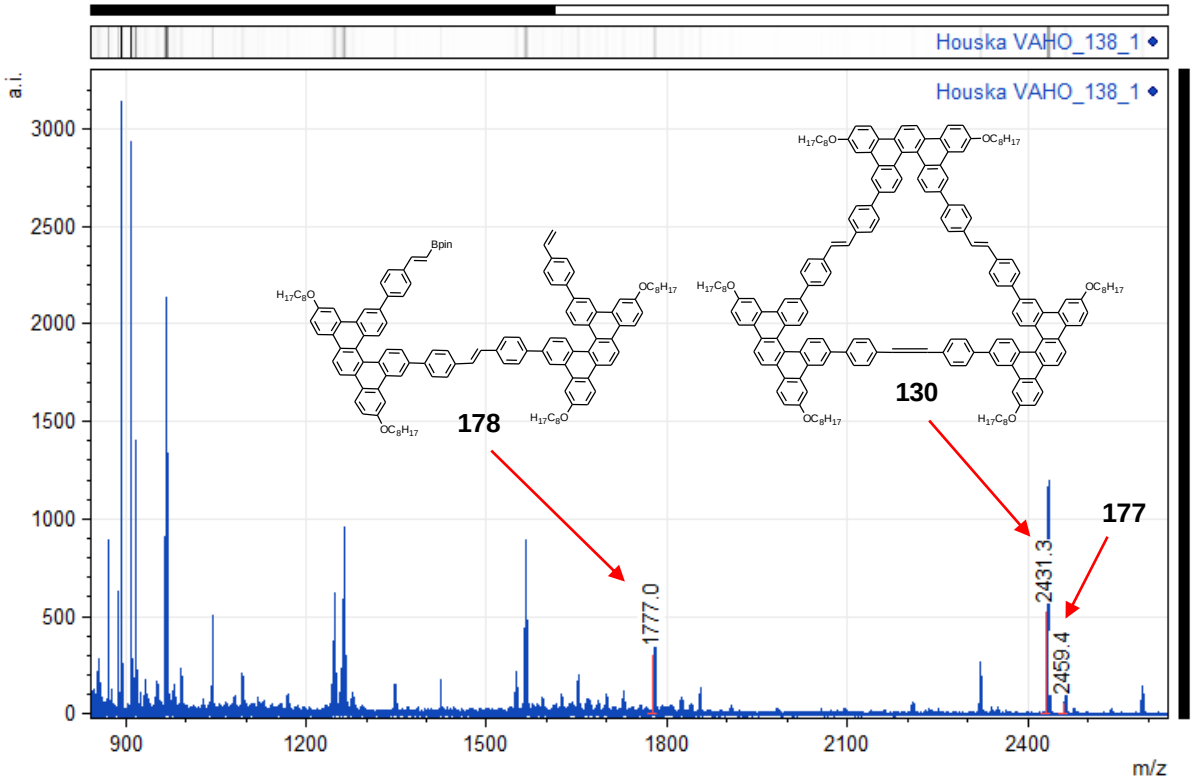
Even though the divinyl trimer **177** was obtained only in a mixture, it was submitted to alkene metathesis in the hope of forming the target macrocycle **130** (Scheme 73). Based on the good solubility of **166** in 1,2,4-trichlorobenzene, it was supposed that this solvent could be also used for the metathesis of the divinyl trimer **177**. The reaction was therefore performed using Grubbs 2nd generation catalyst in 1,2,4-trichlorobenzene but, unlike trimer **166**, the starting material did not dissolve sufficiently in this solvent. The reaction mixture was stirred at 100 °C for 2 days while being purged with a stream of argon to remove the produced ethylene. Since most by-products contained in crude **177** should, in principle - due to its suitable structure, undergo alkene metathesis, it was expected that they would eventually transform into the desired macrocycle **130**. The MALDI-MS analysis of the obtained material showed that this expectation was fulfilled to a certain extent (Figure 15). The comparison of the spectra of the starting mixture (cf. Figure 14) and the mixture after metathesis clearly showed the formation of the desired macrocycle **130** along with the decreased signals of some other by-products. In addition to that, no signals of a cyclic dimer or higher oligomers were detected. Unfortunately, the resulting material was absolutely insoluble in any solvent and all attempts to purify it failed.

Scheme 73. Metathesis of **177** leading to the desired macrocycle **130**



a) Grubbs II catalyst (20 mol %), 1,2,4-trichlorobenzene, 100 °C, 24 h, yield not estimated.

Figure 15. MALDI-MS of the mixture after metathesis proving the formation of the desired macrocycle **130**



The spectrum shows the formation of the desired macrocycle **130** along with the remaining intermediate trimer **177** and intermediate **178**.

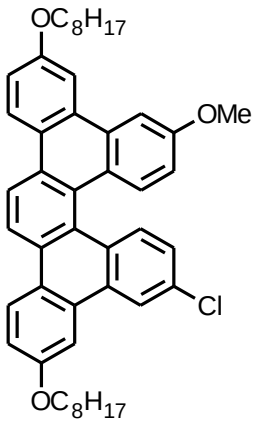
4. Conclusion and outlook

A number of various dibenzo[5]helicene derivatives based on the structure **134** were synthesized. Compared to the previous approach, the dibenzo[5]helicenes **134** were solubilized with long alkyl chains which proved to be an efficient means for solubilisation of small dibenzohelicene building blocks. The synthesis of the derivatives was progressively optimized resulting in the synthesis of helicene **157** in the highest yield and was not complicated by various problems encountered during the syntheses of **129** and **148**. The helicene **157** served as a starting material for the preparation of macrocycle building blocks. Thus, divinyl compound **132** and nonaflate **133** were prepared. The attempt at the Heck coupling of these compounds was, however, unsuccessful mainly due to the hydrolysis of the present nonaflyl group. Moreover, the aldehyde group of **133** turned out to be unstable under basic conditions. As a solution to these complications, the nonaflate in **133** was replaced with a far more robust chlorine substituent and the aldehyde group was protected as a dioxolane. The Heck coupling of the divinyl compound **132** and the protected aldehyde **165** indeed proceeded but the formation of the desired trimer **166** was minimal and the produced compound eventually decomposed after prolonged heating under the reaction conditions. In light of these problems, the Heck coupling was replaced with a much milder Suzuki-Miyaura reaction. While the compound **165** could be used, the divinyl compound **132** was replaced by bis(pinacolboronate) **172**. As expected, the Suzuki-Miyaura coupling of these compounds was much more efficient but it provided a mixture of the trimer **166** along with the dimer **174** and other by-products. Unfortunately, the solubility of these large compounds was unexpectedly low, despite the present solubilizing groups and twisted backbones of the helicene segments. Since no suitable solvent for the McMurry reaction was found, this concept was abandoned and the attention was turned to an intramolecular alkene metathesis. For this purpose, vinyl derivative **176** was prepared that was submitted to the Suzuki-Miyaura reaction to prepare the corresponding trimer **177**. As in the previous cases of the trimer synthesis, the reaction gave a complex mixture of products. The alkene metathesis of this mixture, however, provided evidence of the favorable target macrocycle **130** formation and this synthetic route is therefore open for further investigation.

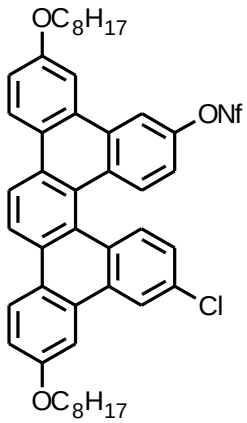
The future direction of the project will have to address mainly the solubility issues. As the present alkyl chains were clearly not sufficient in solubilizing the large trimer molecules, we hope to improve the solubility by the introduction of 4-alkoxyphenyl moiety to the dibenzohelicene molecule to increase the distortion of the helical backbone as well as to introduce additional solubilizing chains. If the new trimer shows to be sufficiently soluble, the intramolecular alkene metathesis will be utilized, hopefully to close the trimer to the desired macrocycle.

Figures 16 – 19 show the key compounds synthesized or detected during the Diploma project.

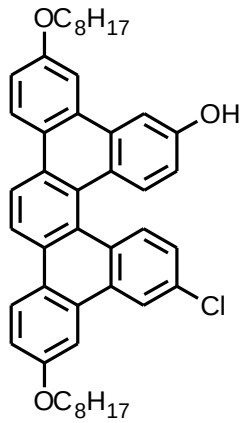
Figure 16. Synthesized functionalized helicenes



129

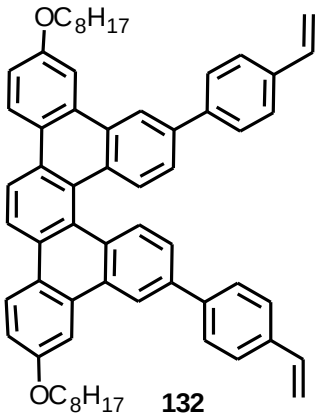


148

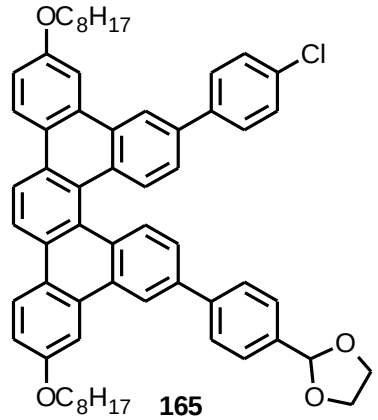


157

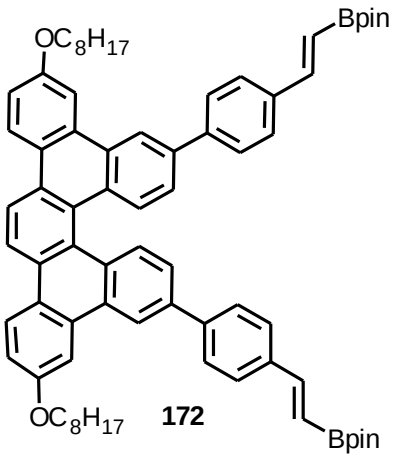
Figure 17. Synthesized building blocks for the synthesis of trimers **166** and **177**



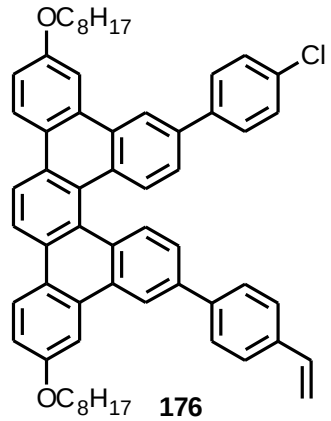
132



165

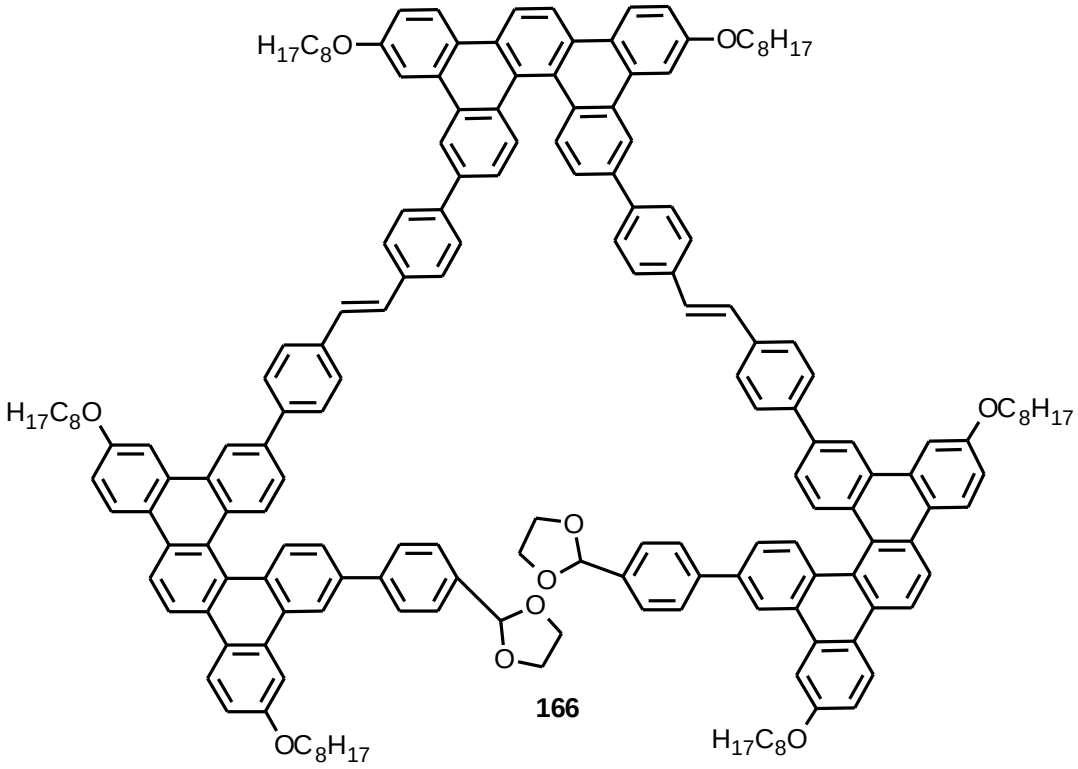


172

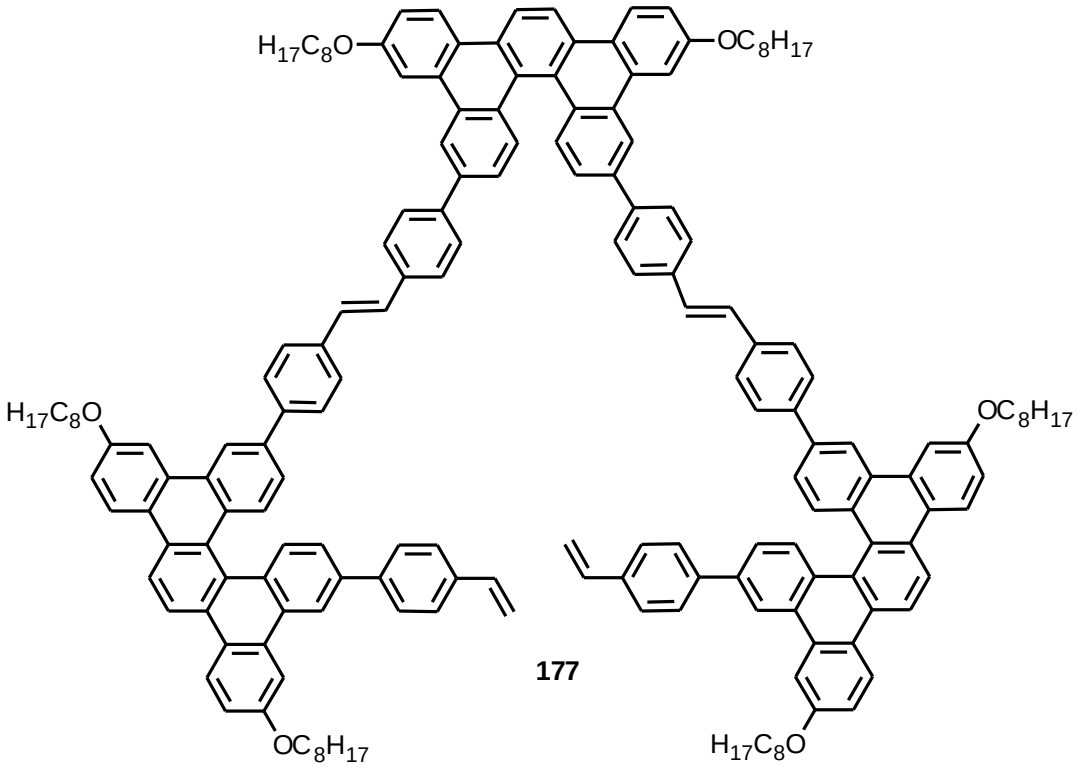


176

Figure 18. Synthesized trimers **166** and **177** obtained in mixtures and detected by MALDI-MS

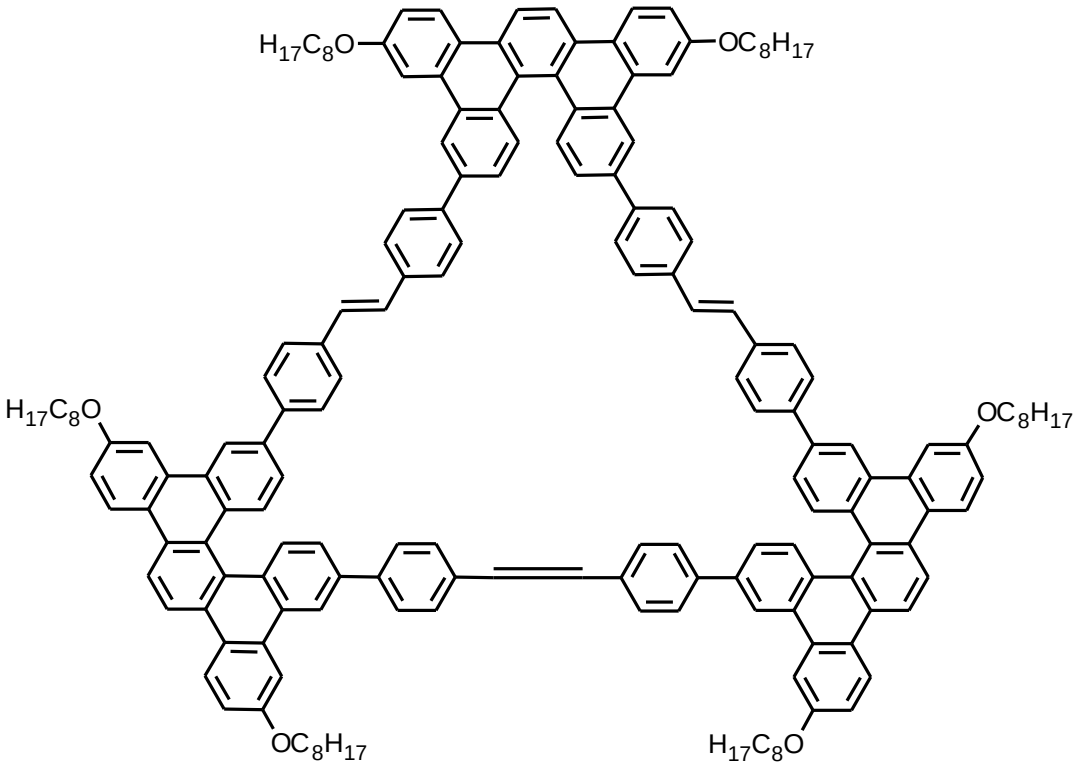


166



177

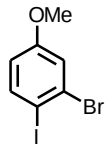
Figure 19. Target macrocycle **130** obtained in a mixture and detected by MALDI-MS



5. Experimental part

General: Unless otherwise noted, all reactions were carried out under argon in an oven-dried glassware. The solvents used for reactions were distilled from drying agents indicated and were transferred under argon: THF, 1,4-dioxane (Na/benzophenone); toluene (Na); DIPA, DCM (P_4O_{10}), NMP (CaH_2). Chromatography was performed either classically or using HPFC Biotage Isolera One system, using Fluka silica gel 60 (0.040 – 0.063 mm) or Merck silica gel 60 (0,015-0,040 mm), if noted. For TLC analysis, Merck silica gel 60 F_{254}, or Merck silica gel 60 RP-18 F_{254} -coated aluminum sheets were used. The spots were detected both in UV and by the solution of $Ce(SO_4)_2.4\ H_2O$ (1 %) and $H_3P(Mo_3O_{10})_4$ (2 %) in 10 % sulfuric acid (10 %). All starting materials were used as purchased (Sigma Aldrich, Alfa Aesar, Strem Chemicals), unless otherwise indicated. The standard EI spectra were recorded in the positive ion mode. The ^{1}H-NMR spectra were measured at 400.13 or 600.13 MHz, the ^{13}C-NMR spectra at 100.61 or 150.90 MHz in $CDCl_3$, $(CD_3)_2CO$ or CD_2Cl_2, with tetramethylsilane or solvent peaks as an internal standard. The chemical shifts are given in δ-scale, coupling constants J are given in Hz. The IR spectra were measured in $CHCl_3$ or in KBr tablet in the range 400 – 3800 cm^{-1} using Nicolet 6700 system. GC-MS analysis was performed on Agilent 5975C series with DB-5MS (JW & Scientific) column at temperature gradient from 60 °C to 320 °C. The spray temperature was 320 °C with 10 : 1 split. The column length was 30 m, internal diameter was 0.25 mm, and film thickness was 0.25 µm. Helium was used as carrying gas at 1 mL/min flow rate. The MS used quadrupole analyzer which operated at 150 °C. The EI mass spectra were determined at an ionizing voltage of 70 eV, the m/z values are given along with their relative intensities (%). The TOF EI spectra were measured using an orthogonal acceleration time-of-flight mass spectrometer GCT Premier (Waters). The sample was dissolved in chloroform, loaded into a quartz cup of the direct probe and inserted into the ion source. The source temperature was 220 °C. For exact mass measurement, the spectra were internally calibrated using perfluorotri-*n*-butylamine (Heptacosa). The ESI mass spectra were recorded using ZQ micromass mass spectrometer (Waters) equipped with an ESCi multi-mode ion source and controlled by MassLynx software. Methanol was used as solvent. Accurate mass measurements were obtained by the EI, TOF EI, CI or APCI MS. The CI mass spectra were determined at an ionizing voltage of 70 eV and recorded using CTC Premiere (Waters) with TOF analyzer. The source temperature was 130 °C and the carrying gas was methane. The MALDI-TOF spectra were measured on UltrafleXtreme™ MALDI-TOF/TOF mass spectrometer (Bruker Daltonics, Germany) with 1 kHz smartbeam II laser. The measurements were done in reflectron mode by dried droplet technique, with the mass range 400_4000Da, (Dried Droplet matrix 2,5-DHB, sample solvent - chloroform, matrix solution of 10 mg/mL 2,5-DHB in acetone, 1 : 1 mixture of the matrix solution and the sample solution, 1 µL of the matrix-analyte mixture deposited onto the MALDI target and allowed to dry.)

2-Bromo-1-iodo-4-methoxybenzene (136)

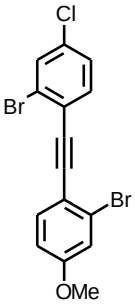


A round bottom flask was charged with iodine (57.3 g, 209 mmol, 1.3 eq.), $Hg(OAc)_2$ (50.5 g, 1.2 eq.) and DCM (600 mL, dried over 3Å mol. sieves) was added. 3-Bromoanisole (30.0 g, 160 mmol) was added in one portion. The resulting purple solution was stirred at RT for 3 h after which time the precipitate was removed *via* suction filtration and the solution was washed with a saturated solution of $Na_2S_2O_3$ (3 x 100 mL), and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* and the residue was filtered through a short pad of silica gel using hexane, the solvent evaporated and the residue was distilled under reduced pressure using a Kugelrohr apparatus to provide the product **136** as an orange liquid (44.8 g, 89 %).

The analytical data were in agreement with published data. [89]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (dd, *J* = 8.8, 5.2, 1H), 7.19 (d, *J* = 2.9, 1H), 6.60 (dd, *J* = 8.8, 2.9, 1H), 3.78 (s, 3H).

2-Bromo-1-[(2-bromo-4-chlorophenyl)ethynyl]-4-methoxybenzene (137)



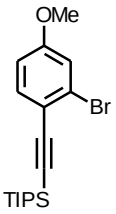
A Schlenk flask equipped with a magnetic stir bar was charged with **136** (500 mg, 1.60 mmol), $Pd(PPh_3)_2Cl_2$ (22.4 mg, 0.032 mmol, 2 mol %), and CuI (12.2 mg, 0.064 mmol, 4 mol %). The flask was backfilled with argon 3 times and DIPA was added (11 mL) *via* syringe under a stream of argon. The flask was sealed with a greased glass stopper and the mixture was degassed using a freeze-pump-thaw cycle 3 times. The mixture was warmed to RT and TMSA (165 mg, 1.68 mmol) was added under a stream of argon. The reaction was completed after 2 h, and then a degassed solution of TBAF (627 mg, 2.40 mmol, 1 M) was added to the reaction mixture. After 15 min, a degassed solution of 4-chloro-3-bromoiodobenzene (532 mg, 1.68 mmol, 1.05 eq.) in DIPA (5 mL) was added to the reaction mixture. The reaction was left stirring overnight. The solvent was removed *in vacuo* and the residue was dissolved in DCM (20 mL), washed with water (20 mL), dried over anhydrous $MgSO_4$ and evaporated *in vacuo*. Chromatography on silica gel (hexane) afforded the product **137** as a white solid (554 mg, 87%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J* = 2.0, 1H), 7.51 (dd, *J* = 8.5, 2.8, 2H), 7.29 (d, *J* = 2.1, 1H), 7.17 (d, *J* = 2.5, 1H), 6.85 (dd, *J* = 8.7, 2.5, 1H), 3.83 (s, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.32, 134.45, 134.35, 133.85, 132.29, 131.87, 127.46, 126.38, 125.69, 117.94, 113.67, 109.98, 91.29, 89.86, 55.66.

Full characterization is in progress.

((2-Bromo-4-methoxyphenyl)ethynyl)triisopropylsilane (138)



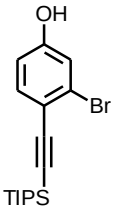
A Schlenk flask equipped with a magnetic stir bar was charged with **136** (2.10 g, 6.70 mmol), $Pd(PPh_3)_2Cl_2$ (93.4 mg, 0.134 mmol, 2 mol %), and CuI (50.0 mg, 0.268 mmol, 4 mol %). The flask was backfilled with argon 3 times and then DIPA was added (25 mL) *via* syringe under a stream of argon. The flask was sealed with a greased glass stopper and the mixture was degassed three times using a freeze-pump-thaw cycle and TIPSA (1.60 mL, 6.79 mmol, 1.01 eq.) was added under a stream of argon. The reaction mixture was left to stir overnight. The precipitate was filtered off and washed with hexane. Volatiles were removed *in vacuo* and the residue chromatographed on silica gel (hexane : AcOEt = 85 : 15) to give the product **138** as a light brown oil (2.45 g, 99 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.6, 1H), 7.11 (d, *J* = 2.5, 1H), 6.78 (dd, *J* = 8.6, 2.6, 1H), 3.80 (s, 3H), 1.15 – 1.12 (m, 21H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.05, 134.77, 126.48, 119.45, 118.16, 114.48, 104.65, 93.96, 60.54, 18.67, 11.34.

Full characterization is in progress.

3-Bromo-4-((triisopropylsilyl)ethynyl)phenol (142)



A Schlenk flask equipped with a magnetic stir bar was charged with **138** (2.19 g, 5.98 mmol) and dissolved in DCM (36 mL) under argon. BBr_3 (24.8 mL, 1 M solution in DCM, 6.58 mmol, 1.1 eq.) was added *via* syringe through a septum. The resulting dark mixture was stirred at RT for 18 h and subsequently quenched with water (20 mL) at 0 °C. The organic layer was separated and the water layer extracted with diethyl ether (3 x 25 mL), the extracts combined, washed with a saturated solution of $NaHCO_3$ (50 mL) and dried over anhydrous $MgSO_4$. The volatiles were removed *in vacuo* and the oily residue was filtered through a pad of silica gel (hexane : AcOEt = 9 : 1) to give the desired product **142** as a brown oily liquid (2.0 g, 95 %).

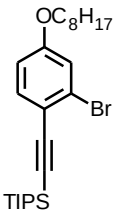
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, *J* = 8.5, 1H), 7.08 (d, *J* = 2.5, 1H), 6.72 (dd, *J* = 8.5, 2.5, 1H), 5.17 (d, *J* = 20.2, 1H), 1.11 (d, *J* = 20.0, 21H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.13, 134.76, 126.46, 119.46, 118.07, 114.50, 104.73, 93.82, 18.67, 11.35.

Full characterization is in progress.

((2-Bromo-4-methoxyphenyl)ethynyl)triisopropylsilane (143)

Method A



A Schlenk flask equipped with a magnetic stir bar was charged with **142** (6.10 g, 17.3 mmol), Cs_2CO_3 (17.0 g, 52.0 mmol, 3 eq.) and DMF (113 mL) was added under argon. Subsequently, octyl iodide (4.58 g, 19.1 mmol, 1.1 eq.) was added *via* syringe. The mixture was left stirring at 95 °C for 3 h after which time the solvent was removed *in vacuo* and the residue was partitioned between DCM and water, the organic layer was separated and the water layer extracted with DCM (3 x 20 mL). The organic layers were combined, dried over anhydrous $MgSO_4$ and the volatiles removed *in vacuo*. The residue was chromatographed on silica gel (hexane) to provide the product **143** as light yellow oil (7.45 g, 93 %).

Method B

A Schlenk flask equipped with a magnetic stir bar was charged with **149** (1.50 g, 5.02 mmol), $Pd(PPh_3)_2Cl_2$ (141 mg, 0.201 mmol, 4 mol %), and CuI (76.5 mg, 0.401 mmol, 8 mol %). The flask was backfilled with argon 3 times and DIPA was added (35 mL) *via* syringe under a stream of argon. The flask was sealed with a greased glass stopper. The mixture was degassed three times using a freeze-pump-thaw cycle and TIPSA (1.24 mL, 5.52 mmol, 1.01 eq.) was added under a stream of argon. The reaction mixture was left to stir overnight. The solvents were removed *in vacuo* and the residue was partitioned between water and AcOEt. The water layer was extracted with AcOEt (3 x 20 mL), the organic layers were combined, washed with brine, dried over anhydrous $MgSO_4$ and the solvents were removed *in vacuo*. The solid residue containing **142** was transfered to a Schlenk flask along with Cs_2CO_3 (4.92 g, 15.1 mmol, 3 eq.). DMF (33 mL) was added, followed by *n*-octyliodide (1.15 mL, 4.78 mmol, 0.95 eq.). The mixture was stirred at 90 °C for 2 h. The solvent was removed *in vacuo* and the residue partitioned between water (10 mL) and AcOEt (20 mL), the water layer extracted with AcOEt (3 x 15 mL), the extracts were combined and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* and the brown oily residue was chromatographed on silica gel (Davisil 20-45 microns, Biotage, hexane to hexane : AcOEt = 95 : 5). The product **143** was obtained as a pale yellow oil (1.54 g, 69 %).

Method C

To a suspension of **149** (8.68 g, 29.04 mmol) and Cs_2CO_3 (27.4 g, 84.2 mmol, 2.9 eq.) in DMF, (190 mL) *n*-octyliodide (5.5 mL, 30.5 mmol, 1.05 eq.) was added. The mixture was stirred at 60 °C for 2 h. The solvent was removed *in vacuo*, the residue partitioned between water (50 mL) and AcOEt (50 mL) and the water layer extracted with AcOEt (3 x 30 mL), the extracts were combined and dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo* and the yellow oily residue containing **158** was used directly without purification in the next step (11.87 g)

A Schlenk flask was charged with **158** (11.6 g, 28.3 mmol), $Pd(PPh_3)_2Cl_2$ (854 mg, 1.22 mmol, 5 mol %) and CuI (463 mg, 2.43 mmol, 10 mol %) and left under *vacuum* for ca 10 min. Then, DIPA (120 mL) was added *via* cannula. The resulting yellow suspension was quickly evacuated, sealed and sonicated for ca 3 min, then filled with argon. This procedure was repeated three times. To the resulting mixture, TIPSA (6.00 mL, 26.8 mmol, 1.1 eq.) was added *via* syringe. The solution was left stirred at RT (the reaction is slightly exothermic). After ca 30 min, the

solvents were removed *in vacuo* and the residue partitioned between water (ca 50 mL) and AcOEt (50 mL). The water layer was subsequently extracted with AcOEt (3 x 20 mL), the extracts were combined, washed with brine and dried over anhydrous $MgSO_4$. The solvents were removed and the residue was chromatographed on silica gel (8 x 20 cm column, Fluka, 40-65 µm, 60 A, hexane) to provide **143** as a pale yellow oil (12.7 g, 97 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, *J* = 8.6 Hz, 1H), 7.10 (d, *J* = 2.5 Hz, 1H), 6.77 (dd, *J* = 8.6, 2.5 Hz, 1H), 3.93 (t, *J* = 6.6 Hz, 2H), 1.76 (dt, *J* = 14.6, 6.6 Hz, 2H), 1.43 (s, 3H), 1.30 (d, *J* = 10.6 Hz, 11H), 1.14 (s, 22H), 0.92 – 0.86 (m, 4H).

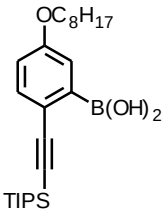
^{13}C NMR (100 MHz, $CDCl_3$): δ 159.40, 134.46, 126.47, 118.20, 117.71, 113.83, 104.90, 93.78, 31.79, 29.29, 29.20, 29.04, 25.93, 22.64, 18.69, 14.08, 11.37.

IR ($CHCl_3$): 2958 s, 2943 vs, 2930 vs, 2865 vs, 2157 m, 1597 s, 1546 w, 1489 s, 1468 s, 1434 w, 1384 w, 1367 w, 1287 s, 1270 wm, 1262 w, 1071 w, 1032 m, 997 m, 883 m, 866 w, 678 m, 660 m, 571 w cm^{-1}.

EI MS: 464 ($M^{+\cdot}$, 16), 424 (30), 423 (100), 422 (29), 421 (93), 395 (13), 381 (20), 379 (19), 367 (7), 353 (22), 351 (21).

TOF HR EI MS: calcd. 464.2110 for $C_{25}H_{41}O^{79}BrSi$, found 464.2113.

(5-(Octyloxy)-2-((triisopropylsilyl)ethynyl)phenyl)boronic acid (139)



To a solution of **143** (1.37 g, 2.95 mmol, dried over 3Å mol. sieves) in THF (20 mL), BuLi (2.44 mL, 3.83 mmol, 1.3 eq., 1.6 M in hexane) was added at -78 °C. The color slowly turned light purple. The resulting solution was stirred for 1 h and then B(O-*i*-Pr)$_3$ (1.70 mL, 7.37 mmol, 2.5 eq., stored under argon over 3Å mol. sieves) was added drop wise. The solution was left stirred for 10 min and then left to reach RT. A pale yellow precipitate formed. The mixture was stirred overnight at RT and then quenched with HCl (25 mL, 1 M aq.). The formed precipitate dissolved to pale yellow solution. The mixture was extracted with diethyl ether (3 x 30 mL), extracts washed with brine, dried over anhydrous $MgSO_4$ and the solvents removed *in vacuo*. The pale yellow oily residue was chromatographed on silica gel (hexane : AcOEt = 1 : 0 to 95 : 5) to provide the product as a white amorphous powder (1.15 g, 91 %).

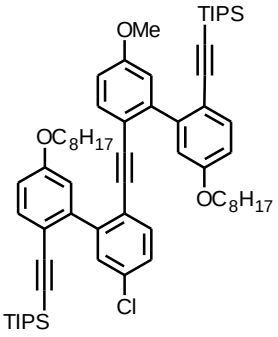
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (s, 1H), 7.46 (d, *J* = 8.5, 1H), 6.94 (dd, *J* = 8.5, 2.8, 1H), 6.27 – 6.16 (m, 2H), 4.00 (q, *J* = 6.7, 2H), 1.83 – 1.73 (m, 2H), 1.50 – 1.40 (m, 2H), 1.36 – 1.25 (m, 9H), 1.18 – 1.11 (m, 21H), 0.89 (t, *J* = 6.9, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.12, 134.64, 120.44, 118.74, 117.63, 108.66, 93.93, 68.09, 31.80, 29.33, 29.22, 29.18, 25.99, 22.65, 18.60, 14.08, 11.32.

IR ($CHCl_3$): 3623 m, 3500 m, 2958 sb, vs-s; 2944 vs, 2894 s-m, 2867 s-vs, 2757 w, 2726 w, 2139 s-m, 1389 m, 1368 s, 1337 vs, 1287 m, 1235 s, 1140 w, 1075 m, 1000 br, w-m; 997 m, 883 m-s, 834 m, 679 m, 662 m, cm^{-1}.

TOF HR CI MS: calcd. 453.2967 for $C_{25}H_{43}O_3BNaSi$, found. 453.2967.

((5'-Chloro-2'-((5-methoxy-5'-(octyloxy)-2'-((triisopropylsilyl)ethynyl)-[1,1'-biphenyl]-2-yl)ethynyl)-5-(octyloxy)-[1,1'-biphenyl]-2-yl)ethynyl)triisopropylsilane (140)

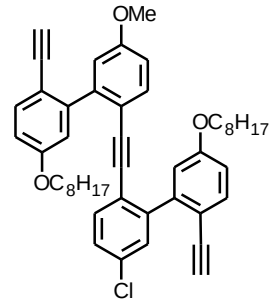


A flask equipped with a Schlenk adapter and a reflux condenser was charged with **137** (400 mg, 1.00 mmol), $Pd(PPh_3)_2Cl_2$ (70 mg, 0.1 mmol, 10 mol %), and K_2CO_3 (483 mg, 3.5 mmol, 3.5 eq.). A solution of **139** (1.07 g, 2.50 mmol, 2.5 eq.) in toluene (9.5 mL) was added, followed by the addition of *n*-PrOH (9.5 mL) and water (2.4 mL). The apparatus was closed and backfilled with argon three times. The resulting yellow solution was then purged with argon for 10 min and subsequently stirred at reflux (105 °C bath) for 2 h. The solution was diluted with DCM (ca 10 mL) and water was added (ca 10 mL). The organic phase was separated and the aqueous phase extracted with chloroform (3 x 20 mL), the extracts were combined and washed with brine. The solution was dried over anhydrous $MgSO_4$, solvents removed *in vacuo* and the dark brown resin was chromatographed on silica gel (Davisil 20-45 microns, Biotage, hexane to hexane : THF = 100 : 1). The product **140** was obtained as a yellow resin (757 mg, 75 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (dd, *J* = 8.6, 1.8, 2H), 7.42 (d, *J* = 2.1, 1H), 7.14 (dd, *J* = 8.3, 2.2, 1H), 7.07 (dd, *J* = 14.9, 8.5, 2H), 6.94 (dd, *J* = 5.1, 2.6, 2H), 6.90 (d, *J* = 2.5, 1H), 6.86 – 6.82 (m, 2H), 6.73 (dd, *J* = 8.6, 2.7, 1H), 3.93 (dd, *J* = 13.9, 7.3, 4H), 3.78 (s, 3H), 1.83 – 1.71 (m, 4H), 1.43 (s, 4H), 1.27 (d, *J* = 9.8, 16H), 0.96 – 0.88 (m, 42H).

Full characterization is in progress.

5-Chloro-2'-ethynyl-2-((2'-ethynyl-5-methoxy-5'-(octyloxy)-[1,1'-biphenyl]-2-yl)ethynyl)-5'-(octyloxy)-1,1'-biphenyl (128)



To a solution of **140** (757 mg, 0.748 mmol) in THF (21 mL), MeOH (150 µL, 3.74 mmol, 3 eq.) was added and a solution of TBAF (587 mg, 2.24 mmol, 3 eq.) in THF (3 mL) was added at RT. The pale orange solution was stirred for 1 h, then diluted with MeOH (ca 10 mL, the solution turned to pale yellow) and the solvents were removed *in vacuo*. The oily residue was chromatographed on silica gel (Davisil 20-45 microns, Biotage, hexane to hexane : THF = 15 : 1). The product **128** was obtained as a yellow resin (382 mg, 73 %).

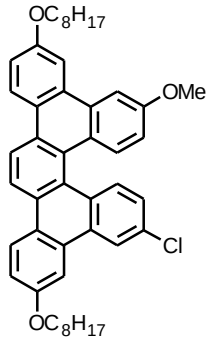
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (dt, *J* = 4.4, 2.2, 2H), 7.42 (d, *J* = 2.1, 1H), 7.22 – 7.12 (m, 3H), 6.99 (d, *J* = 2.6, 1H), 6.93 (dd, *J* = 9.8, 2.6, 2H), 6.85 (dt, *J* = 8.6, 2.4, 2H), 6.80 (dd, *J* = 8.6, 2.7, 1H), 3.96 – 3.90 (m, 4H), 3.81 (d, *J* = 3.3, 3H), 2.88 (s, 1H), 2.87 (s, 1H), 1.82 – 1.70 (m, 4H), 1.46 – 1.37 (m, 4H), 1.33 – 1.25 (m, 16H), 0.92 – 0.85 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.91, 158.77, 158.70, 144.47, 143.67, 143.44, 143.20, 134.48, 134.42, 133.73, 133.19, 132.81, 130.09, 127.51, 121.69, 115.98, 115.80, 115.32, 114.69,

114.62, 114.31, 113.82, 113.26, 113.20, 93.06, 89.62, 82.88, 82.52, 78.83, 78.54, 68.17, 55.36, 31.80, 29.34, 29.24, 29.21, 26.05, 26.04, 22.65, 14.08.

Full characterization is in progress.

3-Chloro-16-methoxy-6,13-bis(octyloxy)dibenzo[5]helicene (129)



To a solution of **128** (200 mg, 0.286 mmol) in THF (20 mL) was added $CpCo(CO)_2$ (7.6 µL, 0.057 mmol, 20 mol %). The solution was trimerized in a flow reactor at 240 °C, 1 mL.min^{-1}, 8 mL loop (8 min reaction time). The resulting brown solution was evaporated and the residue chromatographed on silica gel (Davisil 20-45 microns, Biotage, cyclohexane : THF = 50 : 1). The product **129** was obtained as an orange resin (170 mg, 85 %).

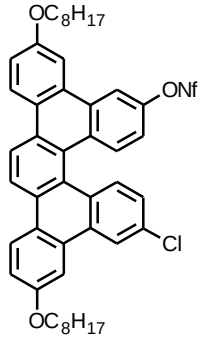
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (dd, *J* = 9.1, 4.1, 3H), 8.46 (d, *J* = 9.0, 1H), 8.41 (d, *J* = 2.1, 1H), 8.22 (d, *J* = 8.9, 1H), 8.12 (d, *J* = 9.1, 1H), 7.97 (dd, *J* = 14.7, 2.5, 2H), 7.86 (d, *J* = 2.6, 1H), 7.36 – 7.31 (m, 2H), 7.12 (dd, *J* = 8.9, 2.2, 1H), 6.84 (dd, *J* = 9.1, 2.6, 1H), 4.22 (t, *J* = 5.5, 4H), 4.00 (s, 3H), 1.98 – 1.87 (m, 4H), 1.57 (d, *J* = 8.1, 4H), 1.36 (dd, *J* = 36.1, 20.8, 16H), 0.91 (dd, *J* = 7.0, 5.9, 6H).

^{13}C NMR (101 MHz, CDCl3): δ 158.56, 158.43, 158.41, 132.29, 132.22, 131.96, 131.28, 130.96, 130.48, 129.95, 129.71, 128.74, 126.42, 125.39, 125.25, 125.19, 123.86, 123.69, 123.08, 121.74, 120.54, 117.20, 116.32, 113.96, 106.83, 106.26, 105.87, 68.40, 55.44, 31.86, 29.70, 29.46, 29.42, 29.30, 26.16, 22.69, 14.12.

IR ($CHCl_3$): 2930 s-vs, 2857 s-m, 1624 vs, 1470 sh, s; 1465 s, 1438 m, 1389 m, 1235 s, 1078 m, 1036 m, 1025 sh, m; cm^{-1}.

TOF HR APCI MS: calcd. 699.35995 for $C_{47}H_{52}O_3{}^{35}Cl$, found 699.35977

3-Chloro-16-nonafluorobutanesolfonyl-6,13-bis(octyloxy)dibenzo[5]helicene (148)



To a solution of **152** (312 mg, 0.323 mmol) in THF (13 mL) was added $CpCo(CO)_2$ (43 µL, 0.323 mmol, 1 eq.) and the resulting solution was trimerized in a flow reactor at 235 °C, 1 mL.min^{-1}, 8 mL loop (8 min reaction time). The resulting solution was evaporated and the residue filtered through a pad of silica gel using toluene. After evaporation of the solvent, the residue was chromatographed on reversed phase silica gel (Biotage, MeCN : chloroform = 9 : 1 to 7 : 3) to yield the product **148** as a yellow resin (164 mg, 53 %).

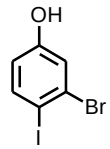
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 – 8.54 (m, 3H), 8.53 (s, 1H), 8.44 (s, 1H), 8.32 (d, *J* = 2.5, 1H), 8.29 (d, *J* = 9.1, 1H), 8.09 (d, *J* = 9.0, 1H), 7.96 (s, 1H), 7.91 (s, 1H), 7.42 – 7.35 (m, *J* = 9.6, 2H), 7.15 (d, *J* = 9.0, 1H), 7.10 (d, *J* = 9.1, 1H), 4.24 (d, *J* = 4.2, 4H), 1.94 (s, 4H), 1.58 (d, *J* = 7.7, 4H), 1.39 (s, 4H), 1.29 (d, *J* = 32.0, 16H), 0.96 – 0.86 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): 158.83, 148.06, 132.85, 132.78, 132.03, 131.27, 131.23, 130.67, 130.54, 130.48, 130.20, 129.94, 129.18, 125.67, 125.62, 125.31, 125.19, 124.97, 123.68, 123.46, 123.34, 122.29, 121.48, 117.99, 117.63, 117.45, 116.12, 106.28, 106.53.

IR ($CHCl_3$): 2956 m, 2929 s, 2872 w, 2857 m, 1615 s, 1590 vw, sh; 1569 w, 1502 w, 1480 m, 1469 m, 1443 m, 1425 m, 1406 m, 1391 m, 1352 m, 1295 m, 1242 vs, 1230 vs, 1146 s, 1032 m, 1011 w, 833 w, 588 w, 532 w; cm^{-1}.

TOF HR APCI MS: calcd. 967.2840 for $C_{50}H_{49}O_5{}^{35}ClF_9S$, found 967.2841.

3-Bromo-4-iodophenol (149)

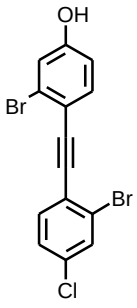


To a solution of **136** (2.66 g, 8.50 mmol) in DCM (85 mL, 3Å mol. sieves), a solution of BBr_3 (8.5 mL, 1.0 eq., 1 M in DCM) was added at RT. The mixture was left stirred for 18 h. The dark red solution was poured into ice and pH of the water layer was adjusted to 5 by a portionwise addition of KOH (10 %, aq.). The organic phase was separated and the water layer was extracted with AcOEt (3 x 20 mL). The extracts were combined, washed with $Na_2S_2O_3$ (50 mL), brine and the solvents removed *in vacuo*. The oily dark brown residue was chromatographed on silica gel (Fluka, 40-65 µm, hexane : AcOH = 100 : 1 to hexane : AcOEt : AcOH = 80 : 20 : 1) and subsequently dried under high *vacuum* for one day to provide the desired product **149** as a beige solid (2.17 g, 85 %).

The analytical data were in agreement with published data. [91]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.6, 1H), 7.17 (d, *J* = 2.8, 1H), 6.55 (dd, *J* = 8.6, 2.8, 1H), 5.00 (s, 1H).

3-Bromo-4-((2-bromo-4-chlorophenyl)ethynyl)phenol (150)



A Schlenk flask equipped with a magnetic stir bar was charged with **149** (9.63 g, 32.2 mmol), $Pd(PPh_3)_2Cl_2$ (905 mg, 1.29 mmol, 2 mol %), and CuI (491 mg, 2.58 mmol, 4 mol %). The flask was backfilled with argon 3 times, and then DIPA (200 mL) was added *via* syringe under stream of argon. The flask was closed with a greased glass stopper and the mixture was degassed three times using freeze-pump-thaw cycle. To this mixture, TMSA (5.0 mL, 35.4 mmol, 1.1 eq.) was added under a stream of argon. The resulting mixture was stirred at RT for 2 h and then a solution of TBAF (16.6 g, 48.3 mmol, 1.5 eq., 1 M in THF, degassed) was added to the reaction mixture. After 15 min, solid 4-chloro-3-bromoiodobenzene (10.7 g, 33.8 mmol, 1.05 eq.) was added to the reaction mixture. After two hours, the mixture was extracted with DCM (3 x 50 mL), the organic layers combined, washed with brine, dried over anhydrous $MgSO_4$, the solvents removed *in vacuo* and the residue chromatographed on silica gel (Fluka, 40-65 µm, hexane : AcOEt : AcOH = 90 : 10 : 1). The product **150** was dried under high *vacuum* for one day and was obtained as a white amorphous solid (7.41 g, 60 %).

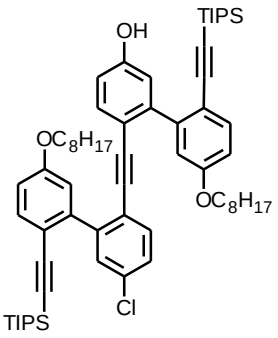
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J* = 2.0, 1H), 7.49 (t, *J* = 8.3, 2H), 7.28 (dd, *J* = 8.2, 1.9, 1H), 7.13 (d, *J* = 2.5, 1H), 6.79 (dd, *J* = 8.5, 2.5, 1H), 5.17 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.36, 134.63, 134.50, 133.86, 132.29, 127.47, 126.35, 125.69, 124.03, 119.73, 117.38, 114.79, 93.08, 89.85.

IR ($CHCl_3$): 3586 m, 3357 vw, vb; 3092 vw, 3065 vw, 2225 vw, 2211 vw, 1603 m, 1583 w, 1560 w, 1543 w, 1497 vs, 1467 w, 1419 w, 1288 w, 1246 vw, 1373 w, 1278 m, 1172 m, 1158 w, 1138 vw, 1098 m, 1045 w, 1033 w, 951 vvw, 895 w, 871 w, 839 vw, 822 m, 706 vw, 679 vw, 566 vw, 446 vw, 409 vw cm^{-1}.

TOF HR APCI MS: calcd. 384.8625 for $C_{14}H_8O^{79}Br_2Cl$, found 384.8622.

6-((5-Chloro-5'-(octyloxy)-2'-((triisopropylsilyl)ethynyl)-[1,1'-biphenyl]-2-yl)ethynyl)-5'-(octyloxy)-2'-((triisopropylsilyl)ethynyl)-[1,1'-biphenyl]-3-ol (151)



Method A

A flask equipped with a Schlenk adapter and a reflux condenser was charged with **150** (3.60 g, 9.32 mmol), **139** (10.0 g, 13.3 mmol, 2.5 eq.), $Pd(PPh_3)_2Cl_2$ (654 mg, 0.932 mmol, 10 mol %), and K_2CO_3 (3.86 g, 28 mmol, 3 eq.). The flask was backfilled with argon three times and toluene (89 mL), *n*-PrOH (89 mL), and water (22 mL) were added. The resulting yellow solution was then purged with argon for 10 min and subsequently stirred at reflux (105 °C bath) for 3 h. The resulting black solution was diluted with DCM (20 mL) and the water layer extracted with DCM (3 x 30 mL), the extracts were combined and washed with brine, dried over anhydrous $MgSO_4$, solvents were removed *in vacuo* and the dark brown resin chromatographed on silica gel (Davisil 20-45 microns, Biotage, hexane : AcOH = 100 : 1 to hexane : THF : AcOH = 100 : 1 : 1). The product **151** was obtained as a yellow resin (7.91 g, 85 %).

Method B

A Schlenk flask equipped with a magnetic stir bar was charged with **143** (100 mg, 0.215 mmol, 2.2 eq.) and dissolved in THF (0.5 mL). The solution was cooled to -78 °C and *n*-BuLi (155 µL, 0.244 mmol, 2.5 eq., 1.6 M in hexane) was added drop wise followed by the addition of B(O-*i*-Pr)$_3$ (56 µL, 0.244 mmol, 2.5 eq.). The mixture was left stirring for 1 h and then left to warm to RT to provide a solution of the boronate salt **153**.

Another Schlenk flask was charged with **150** (38 mg, 0.098 mmol), *XPhos* Pd G2 (5.4 mg, 0.007 mmol, 7 mol %) and backfilled with argon. THF (0.5 mL) was added followed by addition of a solution of K_3PO_4 (590 µL, 0.293 mmol, 3 eq., 0.5 M aq.). Subsequently, the borylation product **153** was transfered to the second Schlenk flask *via* cannula and the resulting mixture was stirred at 40 °C for 2 h. The mixture was then diluted with DCM (5 mL), the water layer separated and the water layer extracted with DCM (3 x 2 mL), the organic extracts were combined, dried over anhydrous $MgSO_4$ and the solvents were removed *in vacuo*. The residue was chromatographed on silica gel (Davisil 20-45 microns, Biotage, hexane to hexane : THF = 20 : 1) to provide the product **151** as a pale yellow resin (52 mg, 53 %.).

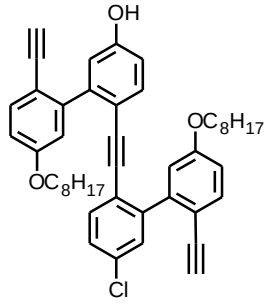
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, *J* = 8.5, 2H), 7.42 (d, *J* = 2.1, 1H), 7.14 (dd, *J* = 8.3, 2.2, 1H), 7.06 (d, *J* = 8.5, 2H), 6.92 (dd, *J* = 5.9, 2.6, 2H), 6.89 (d, *J* = 2.6, 1H), 6.84 (dt, *J* = 8.5, 2.6, 2H), 6.68 (dd, *J* = 8.4, 2.6, 1H), 4.86 (s, 1H), 3.94 (t, *J* = 6.1, 4H), 1.81 – 1.70 (m, 4H), 1.43 (m, 4H), 1.35 – 1.24 (m, 16H), 0.96 (dd, *J* = 19.9, 2.2, 42H), 0.90 – 0.83 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.37, 154.94, 144.26, 143.99, 143.44, 143.21, 134.26, 134.19, 133.93, 133.16, 132.74, 130.13, 127.24, 121.76, 117.12, 115.64, 115.25, 114.93, 114.92, 114.48, 114.20, 105.98, 105.69, 93.05, 92.18, 91.73, 89.75, 68.15, 31.82, 29.38, 29.37, 29.26, 26.11, 26.09, 22.66, 18.52, 14.09, 11.24, 11.22.

IR ($CHCl_3$): 3594 w, 3397 vw, 3065 vw, 3040 vw, 2957 s, 2942 vs, 2930 vs, 2865 vs, 2215 vw, 2152 m, 1601 s, 1586 w, sh; 1507 w, sh;, 1485 m, 1468 s, 1437 w, 1408 vw, 1388 w, 1383 w, 1367 w, 1235 m, 1172 m, 1071 w, 1032 w, 996 m, 883 m, 860 w, 825 m, 678 m, 660 m, 571 w; cm^{-1}.

TOF HR MALDI MS: calcd. 997.6115 for $C_{64}H_{90}{}^{35}Cl_3S_2$, found 997.6112.

6-((5-Chloro-2'-ethynyl-5'-(octyloxy)-[1,1'-biphenyl]-2-yl)ethynyl)-2'-ethynyl-5'-(octyloxy)-[1,1'-biphenyl]-3-ol (154)



151 (3.33 g, 3.38 mmol) was dissolved in THF (94 mL), MeOH (680 µL, 16.7 mmol, 5 eq.) was added *via* syringe and a solution of TBAF (16.7 mL, 16.7 mmol, 5 eq., 1 M in THF) was added *via* syringe. The resulting bright yellow solution was stirred under argon for 16 h after which time the solution was quenched with MeOH (ca 10 mL) and the solvents were removed *in vacuo*. The bright yellow oily residue was chromatographed on silica gel (Davisil 20-45 microns, Biotage, hexane : AcOEt : AcOH = 90 : 10 : 1) to yield the compound as a pale yellow resin (2.25 g, 98 %).

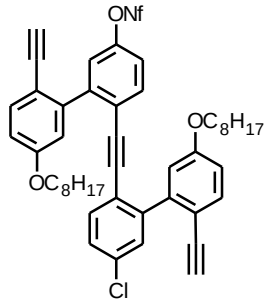
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, *J* = 1.7, 1H), 7.48 (d, *J* = 1.7, 1H), 7.41 (d, *J* = 2.1, 1H), 7.20 (dd, *J* = 8.3, 2.2, 1H), 7.14 (s, 1H), 7.12 (s, 1H), 6.91 (t, *J* = 2.5, 2H), 6.90 (d, *J* = 2.6, 1H), 6.87 – 6.85 (m, 1H), 6.85 – 6.82 (m, 1H), 6.73 (dd, *J* = 8.4, 2.6, 1H), 5.17 (s, 1H), 3.93 (td, *J* = 6.5, 3.2, 5H), 2.88 (s, 1H), 2.86 (s, 1H), 1.81 – 1.69 (m, 5H), 1.41 (s, 5H), 1.34 – 1.23 (m, 20H), 0.88 (t, *J* = 6.7, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.77, 158.71, 155.06, 144.13, 143.95, 143.44, 143.21, 134.45, 134.41, 134.00, 133.21, 132.86, 130.08, 127.52, 121.64, 117.12, 115.88, 115.80, 114.97, 114.80, 114.60, 114.38, 113.28, 113.17, 92.86, 89.59, 82.78, 82.51, 78.84, 78.56, 68.19, 68.18, 31.80, 29.34, 29.23, 29.21, 26.05, 26.02, 22.65, 14.09.

IR ($CHCl_3$): 3591 m, 3312 m, 3300 m, sh; 3065 vw, 3038 vw, 2956 s, 2929 vs, 2872 m, 2857 s, 2214 w, 2104 w, 1602 vs, sh; 1587 m, 1571 w, sh; 1560 m, 1503 m, 1484 s, 1468 s, 1456 m, sh; 1449 m, sh; 1437 w, 1409 vw, 1390 w, 1380 w, 1235 s, 1173 m, 1032 m, 861 w, 826 m, 654 m, 604 m, sh; 571 vw; cm^{-1}.

TOF HR MALDI MS: calcd. 648.3370 for $C_{46}H_{49}{}^{35}ClO_3$, found 684.3365.

6-((5-Chloro-2'-ethynyl-5'-(octyloxy)-[1,1'-biphenyl]-2-yl)ethynyl)-2'-ethynyl-5'-(octyloxy)-[1,1'-biphenyl]-3-yl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (152)



A Schlenk flask equipped with a magnetic stir bar charged with **154** (366 mg, 0.534 mmol) and Cs_2CO_3 (522 mg, 1.60 mmol, 3 eq.) and THF (11 mL) and NfF (380 µL, 2.14 mmol, 4 eq.) was added *via* syringe under argon. The initially bright yellow solution turned faint yellow immediately. The suspension was stirred at RT for 1 h after which time the solvent was removed *in vacuo* and the residue was suspended in a mixture of hexane and AcOEt (hexane : AcOEt = 9 : 1) and filtered through a pad of silica gel. The solvent was removed and the yellow oil was dried under high *vacuum* to yield the compound as a yellow resin (473 mg, 92 %).

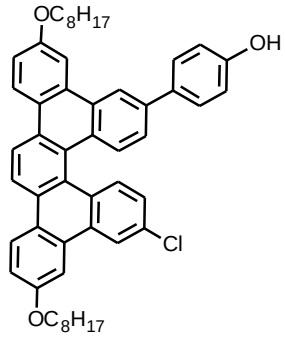
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 3.3, 1H), 7.51 – 7.49 (m, 1H), 7.42 (d, *J* = 2.1, 1H), 7.40 (d, *J* = 2.6, 1H), 7.28 (d, *J* = 8.6, 1H), 7.23 (d, *J* = 2.1, 1H), 7.19 – 7.17 (m, 1H), 7.17 – 7.14 (m, 1H), 6.96 (d, *J* = 2.6, 1H), 6.91 – 6.85 (m, 3H), 3.93 (td, *J* = 6.5, 1.5, 5H), 2.88 (s, 2H), 1.82 – 1.68 (m, 5H), 1.42 (d, *J* = 6.8, 5H), 1.35 – 1.24 (m, 19H), 0.88 (dt, *J* = 7.0, 3.4, 7H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.87, 158.81, 148.34, 144.15, 143.94, 143.19, 142.36, 134.63, 134.45, 134.06, 133.97, 133.38, 130.17, 127.69, 123.28, 123.01, 120.72, 120.35, 116.04, 115.86, 114.88, 114.53, 113.36, 113.14, 109.98, 92.80, 90.93, 82.32, 81.94, 79.45, 78.99, 68.27, 68.24, 31.80, 31.79, 29.33, 29.24, 29.21, 29.19, 26.03, 22.65, 22.62, 14.08, 14.04.

IR ($CHCl_3$): 3300 w, sh; 3311 w, 2956 m, 2929 s, 2872 w, 2857 m, 2219 vw, 2105 w, 1604 m, 1598 m, sh; 1587 w, 1559 w, 1546 vw, sh; 1500 m, sh; 1483 m, 1469 m, 1427 s, 1394 w, 1380 w, 1353 w, 1297 m, 1242 vs, 1146 s, 1033 m, 1010 w, 827 m, 655 w, 606 w, 587 w, 532 w; cm^{-1}.

TOF HR MALDI MS: calcd. 966.2767 for $C_{50}H_{48}{}^{35}ClF_9O_5S$, found 966.2762.

3-Chloro-6,13-bis(octyloxy)-16-(4-hydroxyphenyl)dibenzo[5]helicene (155)



A flask equipped with a Schlenk adapter and a reflux condenser was charged with **148** (72 mg, 0.074 mmol), 4-hydrohyphenylboronic acid (15.4 mg, 0.112 mmol, 1.5 eq.), $Pd(PPh_3)_2Cl_2$ (5.2 mg, 0.007 mmol, 10 mol %), and K_2CO_3 (36 mg, 0.26 mmol, 3.5 eq.). The apparatus was backfilled with argon three times and toluene (0.7 mL), *n*-PrOH (0.7 mL), and water (0.2 mL) were added. The resulting yellow solution was purged with argon for 10 min and then stirred at reflux (110 °C bath) for 2 h. The solution was subsequently evaporated and the brown oily residue chromatographed on silica gel (Davisil 20-45 microns, Biotage, hexane : THF = 50 : 1 to hexane : THF = 20 : 1). The product **155** was obtained as a pale yellow resin (46 mg, 81 %).

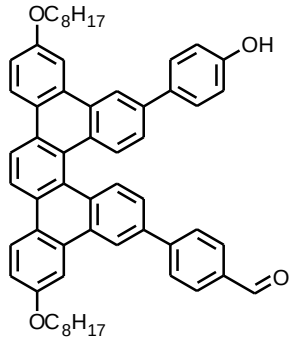
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (s, 1H), 8.55 (d, *J* = 2.7, 1H), 8.53 (d, *J* = 4.9, 3H), 8.43 (d, *J* = 2.1, 1H), 8.25 (d, *J* = 8.9, 1H), 8.22 (d, *J* = 8.7, 1H), 8.12 (d, *J* = 2.4, 1H), 7.96 (d, *J* = 2.4, 1H), 7.66 (d, *J* = 8.6, 2H), 7.40 (dd, *J* = 19.5, 9.0, 3H), 7.14 (dd, *J* = 8.9, 2.1, 1H), 6.98 (d, *J* = 8.6, 2H),

5.02 – 4.87 (m, 1H), 4.29 – 4.18 (m, 4H), 1.99 – 1.89 (m, 4H), 1.58 (s, 4H), 1.41 – 1.22 (m, 18H), 0.90 (dd, *J* = 9.1, 5.3, 6H).

TOF HR APCI MS: calcd. 760.3683 for $C_{52}H_{53}{}^{35}ClO_3$, found 760.3678.

Full characterization is in progress.

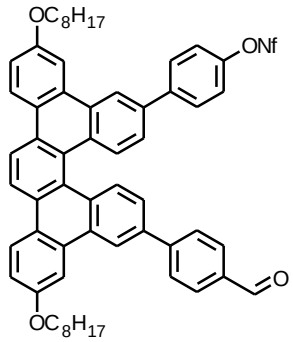
3-(4-Formylphenyl)-16-(4-hydroxyphenyl)-6,13-bis(octyloxy)-dibenzo[5]helicene (156)



A Schlenk flask was charged with **155** (46 mg, 0.06 mmol), *XPhos* Pd G2 (2.4 mg, 0.003 mmol, 5 mol %), and 4-formylphenylboronic acid (14 mg, 0.091 mmol, 1.5 eq.) The flask was capped with a septum and backfilled with argon three times. THF (0.5 mL) was added *via* syringe followed by the addition of K_3PO_4 (242 µL, 0.5 M aq., 2 eq.). The resulting mixture was stirred at 40 °C for 2 h and subsequently extracted with AcOEt (3 x 1 mL), the combined extracts dried over anhydrous $MgSO_4$, solvents removed *in vacuo* and the oily residue chromatographed on silica gel (Davisil 20-45 microns, Biotage, hexane : AcOEt : AcOH = 90 : 10 : 1 to 70 : 30 : 1) to yield the product as a yellow resin (45 mg, 90 %) which was used immediately in the next step.

Full characterization is in progress.

3-(4-Formylphenyl)-16-(4-nonaflurobutanesulfonylphenyl)-6,13-bis(octyloxy)dibenzo[5]helicene (133)



A Schlenk flask was charged with **156** (50 mg, 0.06 mmol), Cs_2CO_3 (59 mg, 0.18 mmol, 3 eq.), THF (1.2 mL) was added under argon followed by the addition of NfF (43 µL, 0.24 mmol, 4 eq.). The initially bright yellow solution turned faint yellow immediately. The suspension was stirred at RT for 1 h after which time the solvent was removed *in vacuo*, the residue adsorbed on silica gel and chromatographed on silica gel (Fluka, 40-65 µm, hexane to hexane : AcOEt = 9 : 1). The obtained yellow oil was dried under high *vacuum* to yield the compound **133** as a bright yellow resin (36 mg, 54 %)

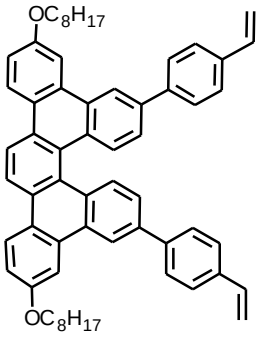
^{13}C NMR (100 MHz, $CDCl_3$): δ 191.80, 158.68, 149.24, 146.83, 141.38, 137.51, 137.19, 135.27, 131.53, 131.48, 131.45, 131.27, 130.89, 130.31, 130.15, 130.07, 128.96, 127.72, 126.02, 125.98, 125.28, 124.12, 124.05, 123.69, 123.67, 122.33, 122.06, 121.87, 121.78, 121.74, 116.51, 116.35, 106.97, 106.77, 68.46, 31.86, 29.70, 29.48, 29.30, 26.20, 22.69, 14.11, 14.10.

TOF HR APCI MS: calcd.1113.3805 for $C_{63}H_{58}O_6F_9S$, found. 1113.3808

Full characterization is in progress.

3,16-Bis(4-vinylphenyl)-6,13-bis(octyloxy)dibenzo[5]helicene (132)

Method A



A Schlenk flask was charged with **148** (235 mg, 0.243 mmol), *XPhos* Pd G2 (9.6 mg, 0.012 mmol, 5 mol %), and 4-vinylphenylboronic acid (108 mg, 0.729 mmol, 3 eq.), the flask was capped with a septum and backfilled with argon three times. THF (3 mL) was added *via* syringe followed by the addition of K_3PO_4 (1.94 mL, 0.5 M aq., 4 eq.). The resulting mixture was stirred at 40 °C for 2 h. The mixture was diluted with water (5 mL), extracted with DCM (3 x 5 mL), the extracts dried over anhydrous $MgSO_4$, solvents removed and the residue chromatographed on silica gel (Davisil 20-45 microns, Biotage, hexane : THF = 9 : 1 to hexane : THF = 3 : 1) to yield the product **132** as a yellow resin (110 mg, 54 %).

Method B

A Schlenk flask was charged with **157** (100 mg, 0.146 mmol) and Cs_2CO_3 (143 mg, 0.438 mmol, 3 eq.). THF (2.5 mL) was added, followed by the addition of NfF (80 µL, 0.44 mmol, 3 eq.) *via* syringe under argon. The initially bright yellow solution turned faint yellow immediately. The suspension was stirred for 1 h at 40 °C after which time the mixture was diluted with water (2 mL) and extracted with DCM (3 x 5 mL). The solvents were removed *in vacuo* and the residue was transferred to a pressure Schlenk flask which was charged with 4-vinylphenylboronic acid (72 mg, 0.487 mmol, 3 eq.) and *XPhos* Pd G2 (13 mg, 0.016 mmol, 10 mol %). The flask was backfilled with argon three times and THF (0.7 mL) was added *via* syringe followed by the addition of K_3PO_4 (1.3 mL, 0.649 mmol, 0.5 M aq., 4 eq.). The Schlenk flask was sealed and the solution was stirred at 80 °C for 1.5 h. The resulting mixture was diluted with water (5 mL) and extracted with DCM (3 x 5 mL). The extracts were washed with brine, dried over anhydrous $MgSO_4$ and the solvents removed *in vacuo*. The residue was chromatographed on silica gel (Davisil 20-45 microns, Biotage, hexane : THF = 9 : 1 to hexane : THF = 3 : 1) to afford the product **132** as a yellow resin (135 mg, 99 % over 2 steps).

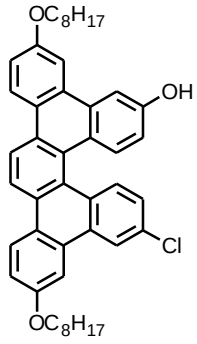
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.67 (s, 1H), 8.55 – 8.48 (m, 2H), 8.34 (d, *J* = 8.6, 1H), 8.13 (d, *J* = 2.4, 1H), 7.74 (d, *J* = 8.3, 2H), 7.54 (d, *J* = 8.3, 2H), 7.44 (d, *J* = 8.7, 1H), 7.36 – 7.30 (m, 1H), 6.79 (dd, *J* = 17.6, 10.9, 1H), 5.83 (d, *J* = 17.6, 1H), 5.31 (d, *J* = 11.2, 1H), 4.22 (s, 2H), 1.99 – 1.87 (m, 2H), 1.58 (d, *J* = 7.8, 2H), 1.36 (d, *J* = 17.4, 8H), 0.98 – 0.86 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.52, 140.34, 138.61, 136.76, 136.41, 131.68, 131.35, 130.59, 129.96, 129.84, 127.34, 126.74, 126.25, 125.21, 124.14, 123.74, 121.53, 116.30, 113.97, 106.79, 68.41, 31.93, 31.86, 29.72, 29.48, 29.47, 29.31, 26.19, 22.70, 14.13.

IR ($CHCl_3$): 3090 w, 3047 m, 2956 m, 2929 s, 2872 m, 2859 m, 1627 m, sh; 1614 s, 1568 w, 1519 w, 1499 m, 1469 s, 1424 w, sh; 1406 m, 1390 m, 1288 m, 1172 m, 1121 w, 1107 w, 1039 w, 1033 m, 990 w, 912 w, 830 m, 533 w; cm^{-1}.

TOF HR CI MS: calcd. 838.4750 for $C_{62}H_{62}O_2$, found 838.4744.

3-Chloro-16-hydroxy-6,13-bis(octyloxy)dibenzo[5]helicene (157)



To a solution of **154** (50 mg, 0.073 mmol) in THF (2.9 mL), $CpCo(CO)_2$ (10 µL, 0.073 mmol, 1 eq.) was added and the resulting solution was trimerized in a flow reactor at 240 °C, 1 mL.min^{-1}, 8 mL loop, (8 min reaction time). The resulting solution was evaporated and chromatographed on silica gel (Davisil 20-45 microns, Biotage, hexane : THF : AcOH = 90 : 10 : 1 to hexane : THF : AcOH = 75 : 25 : 1) to yield the product **157** as a pale yellow amorphous solid (35 mg, 70 %).

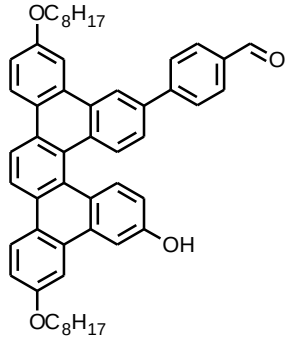
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.51 (d, *J* = 8.9, 2H), 8.45 (d, *J* = 9.3, 1H), 8.40 (d, *J* = 2.3, 1H), 7.32 (dd, *J* = 2.6, 8.9, 1H), 7.92 (d, *J* = 2.6, 1H), 7.85 (d, *J* = 2.6, 1H), 6.74 (dd, *J* = 2.6, 8.9, 1H), 8.08 (d, *J* = 8.9, 1H), 8.51 (d, *J* = 9.3, 1H), 8.21 (bd, *J* = 9.0, 1H), 7.11 (dd, *J* = 2.3, 9.0, 1H), 7.34 (dd, *J* = 2.6, 8.9, 1H), 7.94 (d, *J* = 2.6, 1H), 5.11 (s, 1H), 4.28 – 4.17 (m, 4H), 1.93 (s, 4H), 1.57 (s, 4H), 1.33 (m, 16H), 0.90 (m, 6H).

^{13}C NMR (151 MHz, $CDCl_3$): 158.60, 158.47, 154.49, 132.55, 132.26, 131.97, 131.64, 131.05, 131.00, 130.51, 129.96, 129.75, 128.79, 126.43, 125.42, 125.31, 125.23, 125.22, 125.18, 123.88, 123.67, 123.12, 121.81, 120.61, 117.27, 117.00, 114.80, 108.06, 106.38, 106.30.

IR ($CHCl_3$): 3594 w, 3087 vw, 2956 m, 2929 s, 2872 m, 2858 m, 1614 vs, 1598 m, 1570 w, 1536 w, 1506 w, 1498 w, 1482 m 1469 m, 1454 m, 1444 n, 1438 m, 1230 vs, sh; cm^{-1}.

TOF HR APCI MS: calcd. 685.3443 for $C_{46}H_{50}O_3{}^{35}Cl$, found 685.3443.

3-(4-Formylphenyl)-16-hydroxy-6,13-bis(octyloxy)dibenzo[5]helicene (159)



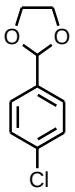
A Schlenk flask was charged with **157** (35.0 mg, 0.051 mmol), *XPhos* Pd G2 (2 mg, 0.003 mmol, 5 mol %) and 4-formylphenylboronic acid (12 mg, 0.077 mmol, 1.5 eq.), the flask was capped with a septum and backfilled with argon three times. THF (0.5 mL) was added *via* syringe followed by the addition of K_3PO_4 (200 µL, 2 eq., 0.5 M aq., degassed). The resulting mixture was stirred at 40 °C for 19 h. The mixture was extracted with AcOEt (3 x 5 mL), the extract was washed with brine, dried over anhydrous $MgSO_4$, the solvents were removed *in vacuo* and the residue was chromatographed on silica gel (Davisil 20-45 microns, Biotage, hexane : AcOEt : AcOH = 100 : 0 : 1 to hexane : AcOEt : AcOH = 60 : 40 : 0.6). The obtained crude product was purified *via* reversed phase chromatography to yield the product **159** as a yellow resin (21 mg, 54 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.08 (s, 1H), 8.68 (d, *J* = 1.9, 1H), 8.57 – 8.51 (m, 3H), 8.48 (d, *J* = 9.0, 1H), 8.36 (d, *J* = 8.7, 1H), 8.18 (d, *J* = 9.0, 1H), 8.12 (d, *J* = 2.5, 1H), 8.00 (d, *J* = 8.4, 2H), 7.94 (d, *J* = 2.5, 1H), 7.91 (d, *J* = 8.3, 2H), 7.88 (d, *J* = 2.6, 1H), 7.43 (dd, *J* = 8.6, 1.9, 1H), 7.38 – 7.31 (m, 2H), 6.76 (dd, *J* = 9.0, 2.5, 1H), 5.22 (s, 1H), 4.23 (m, 4H), 1.99 – 1.87 (m, 4H), 1.58 (m, 4H), 1.48 – 1.27 (m, 16H), 0.91 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.97, 158.58, 158.47, 154.43, 147.03, 137.32, 135.19, 132.80, 131.67, 131.48, 131.22, 131.05, 130.38, 130.13, 129.96, 128.80, 127.76, 126.66, 125.50, 125.34, 125.21, 124.09, 123.90, 123.73, 122.38, 121.95, 120.68, 117.01, 116.31, 114.77, 108.03, 106.99, 106.38, 68.48, 68.40, 31.88, 29.71, 29.48, 29.42, 29.32, 26.20, 26.17, 22.71, 14.14.

Full characterization is in progress.

2-(4-Chlorophenyl)-1,3-dioxolane (161)

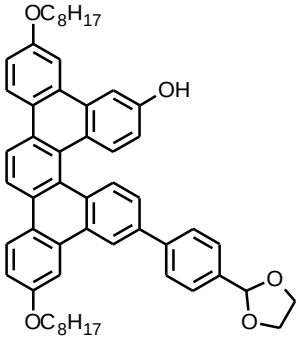


A round bottom flask equipped with a magnetic stir bar was charged with 4-chlorobenzaldehyde (8.00 g, 56.9 mmol) and *p*-TsOH (1.08 g, 5.69 mmol, 10 mol %). Ethylene glycol was added (32 mL, 569 mmol, 10 eq.), followed by the addition of toluene (170 mL). The mixture was stirred at reflux (130 °C bath) using Dienst-Stark trap for 2 days, after which time the bulk of toluene was distilled off and the concentrated residue washed with a $NaHCO_3$ solution followed by the extraction with diethyl ether. The extracts were washed with brine and dried over anhydrous K_2CO_3. The solvent was removed *in vacuo* and the residue was distilled under reduced pressure using a Kugelrohr apparatus to provide the product **161** as a colorless liquid (10.5 g, 99 %).

The analytical data were in agreement with published data. [92]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 – 7.39 (m, 2H), 7.38 – 7.33 (m, 2H), 5.79 (s, 1H), 4.15 – 4.07 (m, 2H), 4.07 (s, 2H).

3-(4-(1,3-Dioxolan-2-yl)phenyl)-16-hydroxy-6,13-bis(octyloxy)dibenzo[5]helicene (163)



A round bottom flask equipped with a Schlenk adapter and a magnetic stir bar was charged with **161** (269 mg, 1.46 mmol, 2.0 eq.), $Pd(OAc)_2$ (8.2 mg, 0,036 mmol, 5 mol %), *XPhos* (70 mg, 0.15 mmol, 20 mol %), B_2pin_2 (407 mg, 1.603 mmol, 2.2 eq.) and KOAc (286 mg, 2.91 mmol, 4 eq.). The apparatus was backfilled with argon three times and THF (7 mL) was added *via* syringe. The solution was purged with a stream of argon for 10 min and then stirred at reflux (110 °C bath) for 30 min, after which time an aqueous solution of K_3PO_4 (730 µL, 3.64 mmol, 5 eq., 0.5 M aq.) was added, followed by the addition of solid **157** (500 mg, 0.729 mmol) under a stream of argon. The resulting mixture was refluxed for further 1 h. The mixture was then extracted with DCM (3 x 10 mL), the extract was dried over anhydrous $MgSO_4$, solvents removed *in vacuo* and the residue chromatographed on silica gel (Davisil 20-45 microns, Biotage, hexane : THF : AcOH = 90 : 10 : 1 to hexane : THF : AcOH = 75 : 25 : 1) to provide the product **163** as a yellow resin (438 mg, 75 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (d, *J* = 1.8, 1H), 8.52 – 8.41 (m, 4H), 8.31 (d, *J* = 8.7, 1H), 8.18 (d, *J* = 9.0, 1H), 8.07 (d, *J* = 2.5, 1H), 7.92 (d, *J* = 2.5, 1H), 7.84 (d, *J* = 2.5, 1H), 7.75 (d, *J* = 8.3, 2H), 7.60 (d, *J* = 8.1, 2H), 7.36 (dd, *J* = 8.6, 1.9, 1H), 7.33 – 7.27 (m, 2H), 6.68 (dd, *J* = 9.0, 2.5,

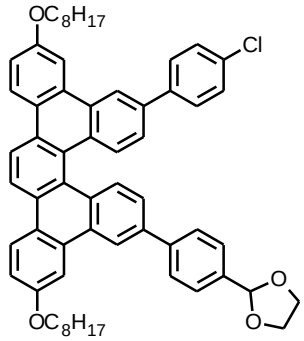
1H), 5.90 (s, 1H), 5.75 (s, 1H), 4.24 – 4.15 (m, 4H), 4.13 – 4.04 (m, 4H), 1.96 – 1.84 (m, 4H), 1.54 (m, 4H), 1.43 – 1.30 (m, 16H), 0.95 – 0.85 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.42, 158.33, 154.59, 145.64, 142.02, 138.48, 136.91, 132.68, 131.59, 131.51, 131.06, 130.95, 130.89, 129.84, 128.63, 127.29, 126.97, 126.62, 125.66, 125.41, 125.21, 125.13, 124.19, 123.82, 123.76, 121.87, 121.57, 120.55, 116.84, 116.32, 114.83, 107.91, 106.64, 106.33, 103.63, 68.37, 68.33, 65.35, 31.85, 29.47, 29.45, 29.41, 29.29, 26.15, 22.69, 14.12.

TOF HR MALDI MS: calcd. 798.4284 for $C_{55}H_{58}O_5$, found 798.4279.

Full characterization is in progress.

3-(4-(1,3-Dioxolan-2-yl)phenyl)-16-(4-hydrohyphenyl)-6,13-bis(octyloxy)dibenzo[5]helicene (165)



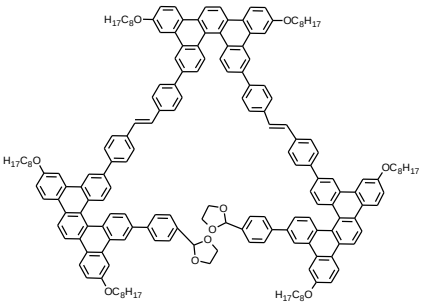
A Schlenk flask equipped with a magnetic stir bar was charged with **163** (348 mg, 0.436 mmol), Cs_2CO_3 (426 mg, 1.31 mmol, 3 eq.), and THF (7.4 mL) was added under argon followed by the addition of NfF (235 µL, 1.31 mmol, 3 eq.). The initially bright yellow solution turned faint yellow immediately. The suspension was stirred at 40 °C for 40 min after which time the mixture was diluted with water (5 mL) extracted with DCM (3 x 10 mL), the combined extracts dried over anhydrous $MgSO_4$, solvents removed *in vacuo* and the residue was transferred to a flask equipped with a Schlenk adapter and a reflux condenser. This flask was further charged with 4-chlorophenylboronic acid (136 mg, 0.871 mmol, 2 eq.), $Pd(PPh_3)_2Cl_2$ (31 mg, 0.044 mmol, 10 mol %), and K_2CO_3 (120 mg, 0.871 mmol, 2 eq.). The apparatus was backfilled with argon three times and toluene (4 mL), *n*-PrOH (4 mL) ,and water (1 mL) were added. The resulting yellow solution was purged with argon for 10 min and subsequently stirred at reflux (100 °C bath) for 2 h. The solution was subsequently evaporated and the brown oily residue chromatographed on silica gel (Davisil 20-45 microns, Biotage, hexane : THF = 9 : 1 to hexane : THF = 3 : 1). The product **165** was obtained as a yellow resin (386 mg, 99 % over 2 steps).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.66 (d, *J* = 1.8, 1H), 8.61 (d, *J* = 1.9, 1H), 8.54 (d, *J* = 9.1, 2H), 8.52 (s, 2H), 8.34 (dd, *J* = 8.6, 5.8, 2H), 8.12 (dd, *J* = 4.4, 2.5, 2H), 7.78 (d, *J* = 8.3, 2H), 7.71 – 7.67 (m, 2H), 7.62 (d, *J* = 8.2, 2H), 7.49 – 7.45 (m, 2H), 7.40 (ddd, *J* = 16.6, 8.7, 1.9, 2H), 7.34 (dd, *J* = 9.0, 2.5, 2H), 5.91 (s, 1H), 4.26 – 4.19 (m, 4H), 4.19 (m, 4H), 1.93 (m, 4H), 1.64 – 1.52 (m, 4H), 1.45 – 1.24 (m, 16H), 0.96 – 0.86 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.55, 141.92, 139.44, 138.76, 137.84, 137.11, 133.51, 131.65, 131.56, 131.46, 131.32, 130.73, 130.60, 129.97, 129.89, 128.99, 128.51, 127.31, 126.98, 126.21, 126.13, 125.24, 124.45, 124.34, 124.05, 123.96, 123.74, 123.68, 121.92, 121.64, 121.55, 116.42, 116.28, 106.85, 106.70, 103.59, 68.42, 65.36, 31.85, 29.47, 29.30, 26.17, 22.69, 14.12.

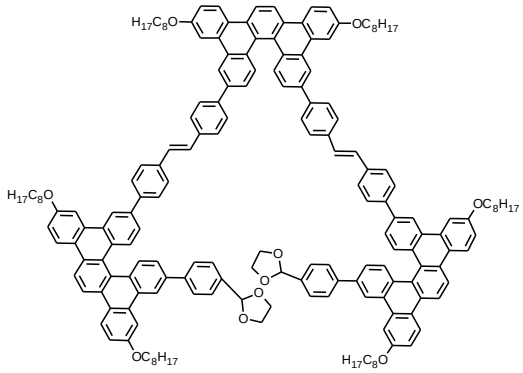
TOF HR MALDI MS: calcd. 892.4258 for $C_{61}H_{61}ClO_4$, found 892.4253.

Heck coupling for the preparation of the dioxolane trimer (166)



A small pressure Schlenk tube equipped with a magnetic stir bar was charged with **132** (10.0 mg, 0.012 mmol), **165** (32 mg, 0.036 mmol, 3 eq.), $Pd(OAc)_2$ (0.5 mg, 0.002 mmol, 10 mol %), *DavePhos* (1.4 mg, 0.004 mmol, 30 mol %), and *n*-Bu_4NAc (22 mg, 0.072 mmol, 6 eq.). The flask was backfilled with argon three times and dioxane (100 µL) was added *via* syringe. The resulting suspension was stirred at 100 °C overnight. TLC showed both remaining starting materials along with a bright yellow fluorescent spot on start that could not be eluted with common solvents. The only solvents in which **166** was satisfyingly soluble was 1,2,4-trichlorobenzene and N-methylpyrrolidone. The sample of the reaction mixture was submitted to MALDI-MS analysis which confirmed the formation of the desired product **166** (2551.4 m/z) along with the product of one-fold Heck reaction **174** (1694.9 m/z). A prolonged heating of the mixture for 3 days in order to achieve a full conversion of the starting materials ended up in decomposition of the products, as evidenced by MALDI-MS.

Suzuki-Miyaura reaction for the preparation of dioxolane trimer (166)



Experiment 1

A small pressure Schlenk tube equipped with a magnetic stir bar was charged with **165** (25 mg, 0.028 mmol, 2.2 eq.), *XPhos* Pd G2 (1 mg, 0.001 mmol, 10 mol %), the flask was closed and backfilled with argon three times. An aqueous solution of K_3PO_4 (10 µL, 0.051 mmol, 4 eq., 5 M aq.) was added *via* syringe and a solution of previously prepared **172** (14 mg, 0.013 mmol) was added *via* syringe. The resulting mixture was stirred at 50 °C overnight. A yellow-green fluorescent precipitate was formed after ca 1 h. TLC of the mixture showed a consumption of **172**, unreacted **165** and a bright-yellow fluorescent spot at the start that could not be eluted with common solvents. The only solvents in which **166** was satisfyingly soluble was 1,2,4-trichlorobenzene and N-methylpyrrolidone. The sample of the reaction mixture was submitted to MALDI-MS analysis which confirmed the formation of the desired product **166** (2551. 4 m/z) along with the product of one-fold Suzuki reaction **173** (1821.0) as well as the products of protodeboration **174** (1694.9). The precipitate was obtained by filtration, rinsed with DCM and chloroform at RT and boiling chloroform, most of the compound was insoluble even in hot chloroform. The chloroform and the insoluble fractions were analyzed by MALDI-MS to confirm that the insoluble fraction contains the largest proportion of the desired trimer. Of all common solvents, the compound was soluble only in 1,2,4-trichlorobenzene and N-methylpyrrolidone.

Experiment 2

A small pressure Schlenk tube equipped with a magnetic stir bar was charged with 165 (25 mg, 0.028 mmol, 2.2 eq.), *XPHOS* Pd G2 (0.7 mg, 0.001 mmol, 10 mol %), n-Bu4NBr (0.6 mg, 0.002 mmol, 20 mol %) and CuCl (1.8 mg, 0.08 mmol, 2 eq.). The flask was closed and

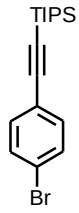
backfilled with argon three times. An aqueous solution of K_3PO_4 (10 µL, 0.051 mmol, 4 eq., 5 M) was added *via* syringe and the solution of previously prepared **172** (10 mg, 0.009 mmol) was added *via* syringe. The resulting dark brown blue-fluorescent solution was stirred at 140 °C for 2 h. A yellow-green fluorescent precipitate formed after cooling to RT. TLC of the mixture showed a consumption of **172**, unreacted **165** and a bright-yellow fluorescent spot at the start that could not be eluted with common solvents. The sample of the reaction mixture was submitted to MALDI-MS analysis which confirmed the formation of the desired product **166** (2551. 4 m/z) along with the product of one-fold Suzuki reaction **173** (1821.0) as well as the products of protodeboration **174** (1694.9). The MALDI-MS analysis showed a much smaller proportion of the intermediate pinacolboronate dimer but a lot of other by-products formed.

The compound was insoluble in the following solvents: acetone, benzene, carbon disulfide, chlorobenzene, chloroform, dichloromethane, diethyl ether, dimethylformamide, dimethylsulfoxide,diphenyl, ether ethyl acetate, hexane, N-methylpyrrolidone, tetrachloromethane, 1,2,4-trichlorobenzene, toluene.

TOF HR MALDI MS: calcd. 2511.3733 for $C_{184}H_{182}O_{10}$, found 2551.3728.

Full characterization is in progress.

((4-Bromophenyl)ethynyl)triisopropylsilane (168)



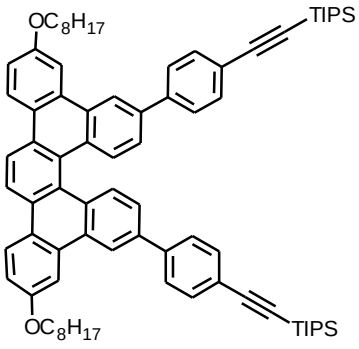
A Schlenk flask equipped with a magnetic stir bar was charged with *p*-bromoiodobenzene (500 mg, 1.77 mmol), $Pd(PPh_3)_2Cl_2$ (12.4 mg, 0.0177 mmol, 1 mol %), CuI (6.7 mg, 0.35 mmol, 2 mol %) and backfilled with argon three times. DIPA was added *via* syringe (8 mL), the mixture was degassed three times using freeze-pump-thaw cycle and (triisopropylsilyl)acetylene (420 µL, 1.86 mmol, 1.05 eq.) was added *via* syringe. The mixture was stirred at 40 °C for 23 h. The precipitate was filtered off by suction and rinsed with hexane (20 mL). The solvent was removed *in vacuo* and the residue was chromatographed on silica gel (hexane) to obtain to product **168** as a pale yellow liquid (590 mg, 99 %).

The analytical data were in agreement with published data. [6]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.4, 2H), 7.33 (d, *J* = 8.4, 2H), 1.11 (d, *J* = 11.7, 22H).

3,16-Bis(4-(2-triisopropylsilylethyn-1-yl)phenyl)-6,13-bis(octyloxy)dibenzo[5]helicene (170)

A Schlenk flask was charged with **157** (100 mg, 0.146 mmol) and Cs_2CO_3 (143 mg, 0.438 mmol, 3 eq.). THF (2.5 mL) was added, followed by the addition of NfF (80 µL, 0.44 mmol, 3 eq.) *via* syringe under argon. The initially bright yellow solution turned faint yellow immediately. The



suspension was stirred at 40 °C for 1 h after which time the mixture was diluted with water (2 mL) and extracted with DCM (3 x 5 mL). The solvents were removed *in vacuo* and the residue containing **148** was used directly without purification in the next step.

To a solution of **168** (147 mg, 0.436 mmol) in THF (0.5 mL) and B(O-*i*-Pr)$_3$ (110 µL, 0.479 mmol, 3.3 eq., stored under Ar over 3Å mol. sieves), *n*-BuLi (300 µL, 0.479 mmol, 3.3 eq., 1.6 M in Hexane) was slowly added at -78 °C. The resulting solution was stirred for 1 h and then allowed to reach RT to provide a solution of boronate salt **169**.

Another Schlenk flask was charged with previously prepared **148** (141 mg, 0.145 mmol) and *XPhos* Pd G2 (11 mg, 0.015 mmol, 10 mol %), the flask was backfilled with argon three times and THF (0.5 mL) was added followed by an aqueous solution of K_3PO_4 (1.2 mL, 0.58 mmol, 4 eq., 0.5 M aq.). The previously prepared solution of the boronate salt **169** was transferred *via* cannula to the mixture which was subsequently stirred at 60 °C 1 h. Then it was diluted with water (2 mL), extracted with DCM (3 x 5 mL), the extracts were dried over anhydrous $MgSO_4$, solvents removed and the residue chromatographed on silica gel (Davisil 20-45 microns, Biotage, hexane : AcOEt = 95 : 5) to yield **170** as a yellow resin (158 mg, 95 %).

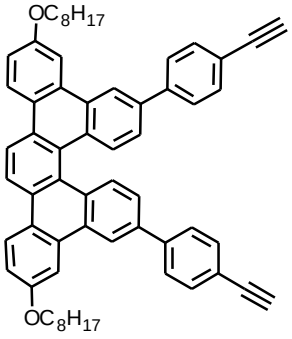
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.66 (d, *J* = 1.9, 2H), 8.58 (d, *J* = 8.9, 4H), 8.37 (d, *J* = 8.6, 2H), 8.14 (d, *J* = 2.6, 2H), 7.75 – 7.70 (m, 4H), 7.63 – 7.59 (m, 4H), 7.45 (dd, *J* = 8.6, 1.9, 2H), 7.37 (dd, *J* = 9.0, 2.5, 2H), 4.25 (m, 4H), 2.00 – 1.88 (m, 4H), 1.59 (m, 4H), 1.33 (m, 16H), 1.16 (m, 42H), 0.95 – 0.87 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.44, 140.72, 138.48, 138.16, 132.52, 131.52, 131.34, 130.66, 129.89, 129.82, 126.94, 126.05, 125.18, 124.03, 123.97, 123.63, 122.54, 121.65, 121.52, 116.18, 106.96, 106.68, 91.48, 68.33, 31.88, 29.51, 29.46, 29.33, 26.18, 22.71, 18.70, 14.16, 11.33.

IR ($CHCl_3$): 3085 w, 3057 w, 3037 w, 2958 s, 2943 s, 2893 sh, 2866 s, 2154 s, 1614 s, 1568 m, 1517w, 1495 m, 1469 m, 1445 m, 1388 m, 1305 m, 1285 w, 997 m, 679 s; cm^{-1}.

TOF HR MALDI MS: calcd. 1146.7105 for $C_{80}H_{98}O_2Si_2$, found 1146.7100.

3,16-Bis(4-ethynylphenyl)-6,13-bis(octyloxy)dibenzo[5]helicene (171)



170 (84 mg, 0.073 mmol) was dissolved in THF (1 mL) and MeOH (10 µL, 0.26 mmol, 3.5 eq.) was added *via* syringe, followed by the addition of a solution of TBAF (730 µL, 0.73 mmol, 10 eq., 1 M in THF). The resulting bright yellow solution was stirred under argon for 30 min. The product was precipitated by addition of *i*-PrOH (2 mL), which was removed by suction and rinsed with *i*-PrOH (2 mL) to yield the compound as a pale yellow powder (48 mg, 79 %).

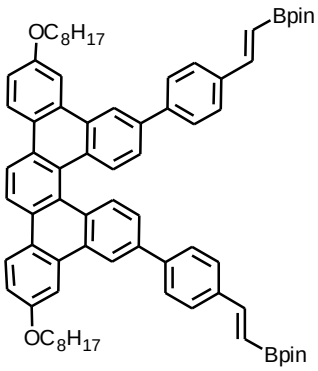
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.63 (m, 2H), 8.53 – 8.45 (m, 4H), 8.30 (d, *J* = 8.6, 2H), 8.11 (s, 2H), 7.72 (d, *J* = 7.8, 4H), 7.62 (d, *J* = 7.8, 4H), 7.39 (d, *J* = 8.5, 2H), 7.32 (d, *J* = 8.7, 2H), 4.22 (m, 4H), 3.17 (s, 2H), 1.93 (m, 4H), 1.59 (m, 4H), 1.34 (s, 16H), 0.92 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.56, 141.29, 138.09, 132.64, 131.57, 131.42, 130.78, 129.98, 129.94, 127.09, 126.12, 125.23, 124.06, 123.69, 121.76, 121.64, 121.10, 116.29, 106.84, 83.58, 77.96, 68.42, 31.86, 29.48, 29.46, 29.31, 26.19, 22.69, 14.13.

IR ($CHCl_3$): 3302 m, 2108 w, 656 w, 1614 s, 1517 w, 1569 w, 1469 s, 1413 m, 1285 m, 1127 w, 1083 m, 998 w, 935 w; cm^{-1}.

Full characterization is in progress.

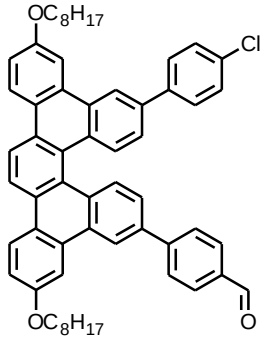
3,16-Bis(2-((E)-4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinylphenyl)-6,13-bis(octyloxy)dibenzo[5]helicene (172)



A Schlenk flask equipped with a magnetic stir bar was charged with *XantPhos* (0.78 mg, 0.001 mmol, 7.5 mol %), CuCl (0.1 mg, 0.001 mmol, 7.5 mol %), and KO*t*-Bu (0.3 mg, 0.003 mmol, 15 mol %), the flask was equipped with a septum and backfilled with argon three times. THF (30 µL) was added *via* syringe and the resulting suspension was sonicated for at RT 30 min. Then, B_2pin_2 (12.5 mg, 0.049 mmol, 2.75 eq.) was added dissolved in THF (30 µL) and the resulting dark brown solution was sonicated for another 30 min. Subsequently, **171** (15 mg, 0.018 mmol) was added as a solution in THF (250 µL), followed by the addition of MeOH (3 µL). The solution was stirred at RT for 18 h. The obtained mixture containing **172** was used directly in the following step.

ESI MS: calcd. 1155.9 for $C_{74}H_{86}O_6B_2Cu$, found 1155.4 ($[M + Cu + 2\ H]^{+\cdot}$).

3-(4-Chlorophenyl)-16-(4-formylphenyl)-6,13-bis(octyloxy)dibenzo[5]helicene (175)



A flask equipped with a magnetic stir bar was charged with **165** (50 mg, 0.056 mmol) and *p*-TsOH (11 mg, 0.056 mmol, 1 eq.). THF (0.2 mL) and acetone (0.2 mL) were added and the mixture was stirred at RT for 10 min. A yellow precipitate formed. The mixture was diluted with DCM (2 mL) and water was added (2 mL). The water phase was extracted with DCM (3 x 5 mL), the extracts were combined and dried over anhydrous $MgSO_4$. The removal of the solvents *in vacuo* provided a pure product **175** as a yellow resin (47 mg, 99 %).

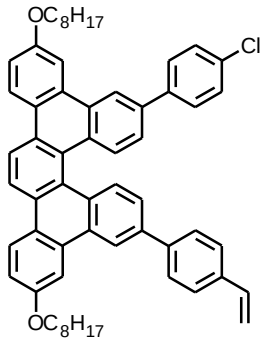
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.07 (s, 1H), 8.66 (d, *J* = 1.7, 1H), 8.58 (d, *J* = 1.7, 1H), 8.48 (d, *J* = 8.6, 2H), 8.45 (s, 2H), 8.30 (d, *J* = 8.7, 1H), 8.26 (d, *J* = 8.7, 1H), 8.09 (dd, *J* = 4.4, 2.5, 2H), 7.98 (d, *J* = 8.4, 2H), 7.88 (d, *J* = 8.3, 2H), 7.66 (m, 2H), 7.44 (d, *J* = 8.5, 2H), 7.40 (dd, *J* = 8.7, 1.8, 1H), 7.36 – 7.28 (m, 3H), 4.21 (m, 4H), 1.99 – 1.87 (m, 4H), 1.64 – 1.51 (m, 4H), 1.47 – 1.31 (m, 16H), 0.95 – 0.87 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.89, 158.55, 158.54, 146.84, 139.29, 137.86, 137.38, 135.16, 133.55, 131.50, 131.48, 131.42, 131.39, 131.30, 130.52, 130.31, 130.06, 129.99, 129.96, 129.90, 128.99, 128.45, 127.70, 126.11, 125.89, 125.25, 125.21, 124.09, 124.01, 123.66, 123.59, 122.27, 121.83, 121.64, 121.59, 116.24, 106.87, 106.78, 68.38, 31.86, 29.48, 29.45, 29.31, 26.18, 22.70, 14.15.

IR ($CHCl_3$): 3090 m, 3060 w, 1614 s, 1604 s, 1535 m, 1574 m, 1489 w, 1171 m, 1018 m, 821 s, 2956 m, 2929 s, 2872 m, 2857 m, 1469 m, 1388 m, cm^{-1}.

TOF HR MALDI MS: calcd. 848.3996 for $C_{59}H_{57}{}^{35}ClO_3$, found 846.3991.

3-(4-Chlorophenyl)-16-(4-vinylphenyl)-6,13-bis(octyloxy)dibenzo[5]helicene (176)



A Schlenk flask equipped with a magnetic stir bar was charged with $MePPh_3I$ (36 mg, 0.089 mmol, 1.6 eq.), THF was added (0.6 mL) and *n*-BuLi (41 µL, 0.066 mmol, 1.2 eq., 1.6 M in hexane) was added drop wise at 0 °C. The yellow solution was stirred at RT for 15 min and then a solution of **177** (47 mg, 0.055 mmol) in THF (0.6 mL) was added drop wise. The resulting mixture was stirred for at RT 2 h and then was quenched with water (2 mL), followed by the addition of DCM (2 mL). The aqueous phase was extracted with DCM (3 x 5 mL), the solvents were removed *in vacuo* and the residue chromatographed on silica gel (Davisil 20-45 microns, Biotage, hexane : DCM = 7 : 3 to hexane : DCM = 1 : 4) to provide the product **176** as a yellow resin (26 mg, 55 %).

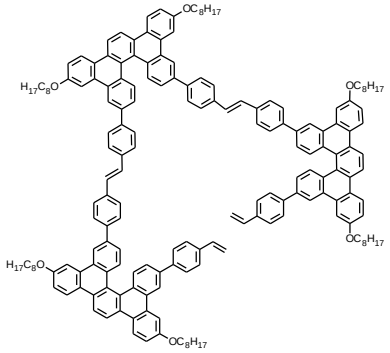
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.65 (d, *J* = 1.7, 1H), 8.59 (d, *J* = 1.7, 1H), 8.50 (d, *J* = 9.1, 2H), 8.47 (s, 2H), 8.31 (t, *J* = 8.5, 2H), 8.10 (dd, *J* = 9.1, 2.5, 2H), 7.73 (d, *J* = 8.3, 2H), 7.69 – 7.64 (m, 2H), 7.54 (d, *J* = 8.3, 2H), 7.48 – 7.43 (m, 2H), 7.41 (dd, *J* = 8.7, 1.8, 1H), 7.36 (dd, *J* = 8.7, 1.8, 1H), 7.32 (dd, *J* = 9.0, 2.4, 2H), 6.79 (dd, *J* = 17.6, 10.9, 1H), 5.83 (d, *J* = 18.2, 1H), 5.31 (d, *J* = 11.4, 1H), 4.21 (m, 4H), 1.98 – 1.88 (m, 4H), 1.63 – 1.53 (m, 4H), 1.48 – 1.28 (m, 16H), 0.92 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.41, 140.21, 139.35, 138.50, 137.67, 136.69, 136.34, 133.43, 131.57, 131.45, 131.38, 131.25, 130.65, 130.42, 129.89, 129.87, 129.78, 129.76, 128.95, 128.44, 127.28, 126.70, 126.11, 125.98, 125.17, 124.03, 123.93, 123.65, 123.60, 121.54, 121.46, 121.43, 116.12, 116.08, 113.99, 106.74, 106.68, 68.31, 31.87, 29.50, 29.46, 29.32, 26.18, 22.71, 14.16.

TOF HR MALDI MS: calcd. 846.4204 for $C_{60}H_{59}{}^{35}ClO_2$, found 846.4198.

Full characterization is in progress.

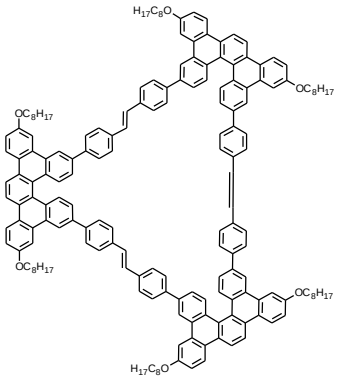
Suzuki-Miyaura reaction for the preparation of the divinyl trimer (177)



A small pressure Schlenk tube equipped with a magnetic stir bar was charged with **176** (25 mg, 0.03 mmol, 2.5 eq.), *XPhos* Pd G2 (1.7 mg, 0.002 mmol, 18 mol %), the flask was closed and backfilled with argon three times. An aqueous solution of K_3PO_4 (20 µL, 0.10 mmol, 8.5 eq., 5 M aq.) was added *via* syringe and a solution of previously prepared **172** (13 mg, 0.012 mmol, 0.8 mL) was added *via* syringe. The resulting mixture was sonicated at 80 °C overnight. A yellow-green fluorescent material precipitated out after ca 1 h. TLC of the mixture showed a consumption of **172**, unreacted **176** and a bright- yellow fluorescent spot at the start that could not be eluted with common solvents The sample of the reaction mixture was submitted to MALDI-MS analysis which confirmed the formation of the desired product **177** (2459.4 m/z) along with the product of one-fold Suzuki-Miyaura **178** (1777.1 m/z) reaction. The precipitate was obtained by filtration, rinsed with chloroform (1 mL) and dried under *vacuum* (14 mg of the mixture). The mixture was only partially soluble in 1,2,4-trichlorobenzene. Other solvents tried were: acetone, benzene, carbon disulfide, chlorobenzene, chloroform, dichloromethane, diethyl ether, dimethylformamide, dimethylsulfoxide, diphenyl, ether ethyl acetate, hexane, N-methylpyrrolidone, tetrachloromethane, 1,2,4-trichlorobenzene, toluene.

TOF HR MALDI MS: calcd. 2459.3623 for $C_{182}H_{178}O_6$, found 2459.3618.

Metathesis for the preparation of the target macrocycle (130)



A Schlenk flask equipped with a magnetic stir bar was charged with **177** (14 mg) and Grubbs II gen. cat. (1.0 mg, 0.001 mmol). The flask was equipped with a septum and backfilled with argon three times. 1,2,4-trichlorobenzene (5 mL) was added *via* syringe and the resulting suspension was stirred at 100 °C for 1 day. The insoluble material was filtered off, rinsed with chloroform (1 mL) and dried under *vacuum*. The MALDI-MS analysis of the mixture showed the formation of the target macrocycle as one of the main products. No signals of a cyclic dimer or higher oligomers were detected. The compound was insoluble in the following solvents: acetone, benzene, carbon disulfide, chlorobenzene, chloroform, dichloromethane, diethyl ether, dimethylformamide, dimethylsulfoxide,diphenyl, ether ethyl acetate, hexane, N-methylpyrrolidone, tetrachloromethane, 1,2,4-trichlorobenzene, toluene.

TOF MALDI MS: calcd. 2431.3310 for $C_{180}H_{174}O_6$, found 2431.3.

6. List of abbreviations

Ac	acetyl
BOP	(Z)-7-((*1S,4R,5R,6R*)-5-(E,*3R*)-3-hydroxy-4-(4-iodophenoxy)but-1-enyl)-7-oxabicyclo[2.2.1]heptan-6-yl]hept-5-enoic acid
Bu	butyl
t-Bu	*tert*-butyl
calcd.	calculated
cod	cyclooctadiene
Cp	cyclopentadienyl
Cy	cyclohexyl
d	doublet (NMR)
DavePhos	2-dicyclohexylphosphino-2`-(*N*,*N*-dimethylamino)biphenyl
DBH	dibenzohelicene
DCM	dichloromethane
DEA	diethyl azodicarboxylate
2,5-DHB	2,5-dihydroxybenzoic acid
DIPA	diisopropylamine
DMA	5-(N,N-dimethyl)amiloride hydrochloride
DMF	dimethylformamide *DUPhos* (−)-1,2-bis((*2R,5R*)-2,5-diethylphospholano)benzene
Dmphen	2,9-dimethyl-1,10-phenanthroline
DMTS	dimethyltrisulfide
DPEPhos	bis-[2-(diphenylphosphino)phenyl]ether
Dppf	1,1'-bis(diphenylphosphino)ferrocene
Dtbpy	di-*t*-butylbipyridyl
EI	electron impact
Et	ethyl
ESI	electrospray ionization
GC-MS	gas chromatography – mass spectrometry
Grubbs II	(1,3-Bis(2,4,6-trimethylphenyl)-2-

	imidazolidinylidene)dichloro(phenylmethylene)(tricyclohexylphosphine)ruthenium
HPLC	high performance liquid chromatography
HR-MS	high resolution mass spectrometry
IR	infrared spectrometry
m	medium (infrared spectrometry), multiplet (NMR)
MALDI-MS	matrix-assisted laser desorption-ionization – mass spectrometry
Me	methyl
MS	mass spectrometry
Nf	nonaflyl
NMR	nuclear magnetic resonance
NMP	N-methylpyrrolidone
Pr	Propyl
Ph	phenyl
phen	phenantroline
pin	pinacol
PPh3	triphenylphosphine
i-Pr	isopropyl
Quinap	1-(2-diphenylphosphino-1-naphthyl)isoquinoline
q	quadruplet (NMR)
RT	room temperature
s	strong (infrared spectrometry)
SEM	[2-(Trimethylsilyl)ethoxy]methyl acetal
s-m	strong to medium (infrared spectrometry)
SPMs	shape-persistent macrocycles
s-vs	strong to very strong (infrared spectrometry)
t	triplet (NMR)
Tg	$-(CH_2CH_2O)_3CH_3$
TBAF	tetra-*n*-butylammonium fluoride
TfOH	triflic acid
THF	tetrahydrofurane
TIPS	triisopropylsilyl

TIPSA	(triisopropylsilyl)acetylene
TIPSCl	triisopropylsilyl chloride
TLC	thin-layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
TMSA	(trimethylsilyl)acetylene
UV	ultraviolet
vs	very strong (infrared spectrometry)
w	weak (infrared spectrometry)
XPhos Pd G1	chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl)]palladium(II)
XPhos Pd G2	chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II)

7. References

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