Method Development, Synthesis and Mechanistic Investigations of Heteroaromatic Compounds

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Dekan

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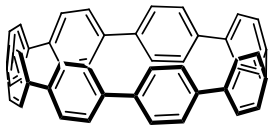
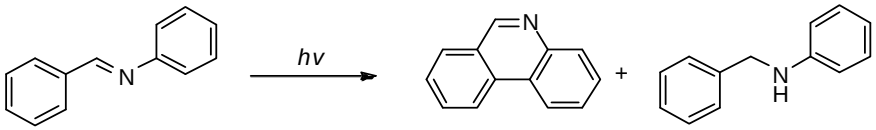
Abstract

The presented thesis describes three different projects related to method development, synthesis and mechanistic investigations of hetereoaromatic compounds.

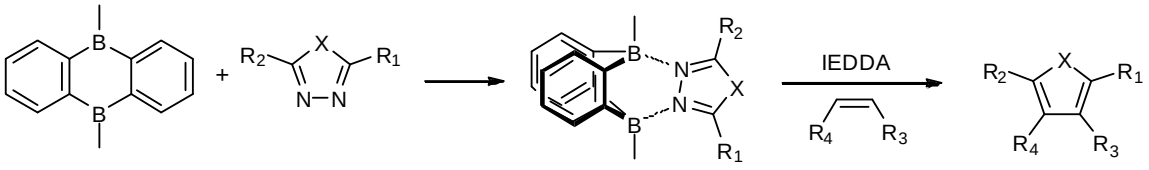
Chapter 1 describes the endeavors towards the synthesis of cycloparaphenylenes, which are fragments of armchair carbon nanotubes. The retrosynthetic approach is discussed, as well as our synthetic strategy which provides a highly flexible synthesis for various sizes of cycloparaphenylenes via Sonogashira cross-coupling reactions and [2+2+2]-cycloadditions. After some preliminary experiments two generations of syntheses are discussed in detail. The first generation synthesis was based on an unfunctionalized alkyne and offers a concise seven-step procedure to the cycloparaphenylenes. The second generation synthesis utilized customized building blocks, a functionalized alkyne and a masked iodoaryl, and offers a 15-step synthesis of functionalized cycloparaphenylenes. Both synthetic pathways have been explored and led to good to excellent yields for all steps. During this endeavor several challenges especially during the macrocyclization attempts were encountered. Until now the macrocycles could not be isolated from complex multiple-compound mixtures. This challenge, as well as the final [2+2+2]-cycloaddition reaction, remain the focus of the future work and have to be overcome to finally complete the synthesis successfully.



Chapter 2 gives a description of the research concerning the photocyclization of Schiff' Bases. Based on an optimization of the method, detailed mechanistic investigations of each step of the photocyclization sequence were conducted. All results combined led to the proposal of a new mechanism: Starting with a Lewis acid induced *E*/*Z* isomerization, followed by a conrotatory photocyclization the dihydrophenanthridine is formed. This intermediate cannot be trapped by oxidants or hydrogen absorbers but transfers the two hydrogen atoms directly to another molecule of the Schiff' Base to form phenanthrindine and *N*-benzylphenylamine. The photocyclization occurs probably in a pre-equilibrium. Deuteration experiments indicated that the hydrogen atoms are transferred in a non rate-determining step. This hydrogen transfer might take place via an excimer in an intramolecular fashion. Moreover, the method was applied to the synthesis of Trisphaeridine, a biological active natural product.



Chapter 3 describes the application of a bidentate Lewis acid catalyst to the inverse electron-demand Diels-Alder reaction of five-membered heterocycles. The limitations of the uncatalyzed reactions were grasped and the application of a bidentate Lewis acid catalyst to expand the scope of the reaction towards less reactive dienes and dienophiles was studied. The coordination of the Lewis acid to the diazene moiety was observed in several cases via NMR-spectroscopy. Quantum chemical calculations indicated the required lowering of the energy of the LUMO orbitals. Unfortunately, in the experiments the accelerating effect of the catalyst was rather small in comparison to uncatalyzed reactions. To overcome this drawback, different more reactive catalysts will be developed in our group in the future.



X= O, S, NR

The experimental data and characterization of the compounds listed in this thesis are summarized in Chapter 4.

Chapter 1

Towards the Synthesis of Carbon Nanotubes Fragments

1.1 Introduction[1]

Carbon is a nonmetallic tetravalent element which occurs in three mayor isotopes ^{12}C, ^{13}C and ^{14}C. Carbon is named after the Latin *carbo* which means coal. As it exist as pure element in nature it is known since the beginning of mankind.[2] There are several allotropes of carbon known, the most abundant are graphite, diamond, amorphous carbon and fullerenes (Figure 1)

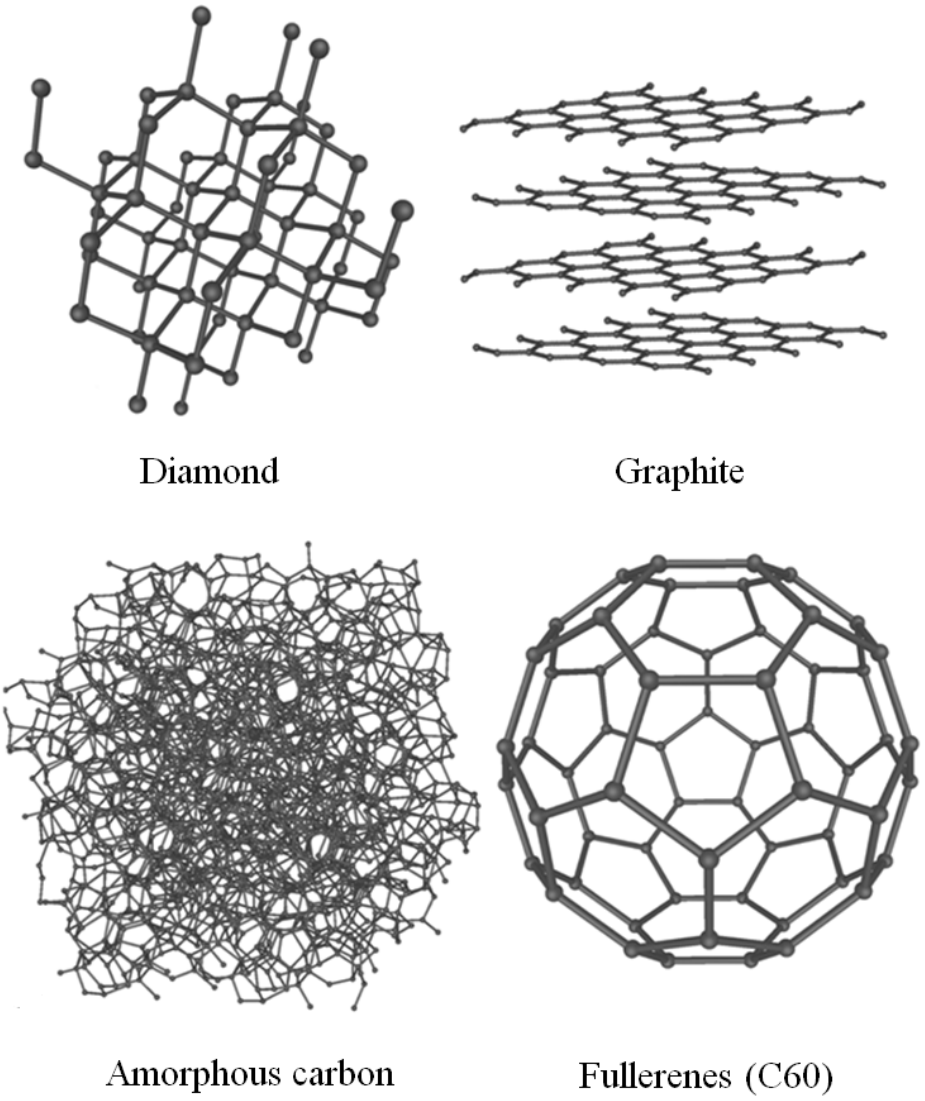


Figure 1[3]

It is important to state, that the most stable allotrope is graphite, so all other allotropes will slowly be converted to graphite. In difference to the other three major allotropes Fullerenes are not known since centuries but have been discovered in 1985 by R. F. Curl, H. W. Kroto

and R. E. Smalley. They reported the formation of Buckminsterfullerene via laser evaporation of graphite.[4]

For their research these three scientists have been awarded the Nobel Prize 1996 in Chemistry. Fullerenes are a family of carbon-materials with sphere-, ellipsoid- or tube like structures. Besides these buckyballs, carbon nanotubes have fascinated scientist over the last decades because of their interesting structures and properties.

1.1.1 Carbon Nanotubes

Carbon nanotubes (CNTs) have first been discovered by L. V. Radushkevich and V. M. Lukyanovich in 1952.[5] Due to the cold war their reports where only available at a later stage to the western civilization. Therefore, S. Ilijima is often credited with their discovery.[6] Nanotubes are as their name say literally tubes out of pure carbon. Their diameter is usually smaller than 10 nm. Carbon nanotubes can be categorized into single-walled and multi-walled nanotubes. The latter were first discovered and consist of multiple rolled layers (concentric tubes) of graphite which are packed into each other (Figure 2).

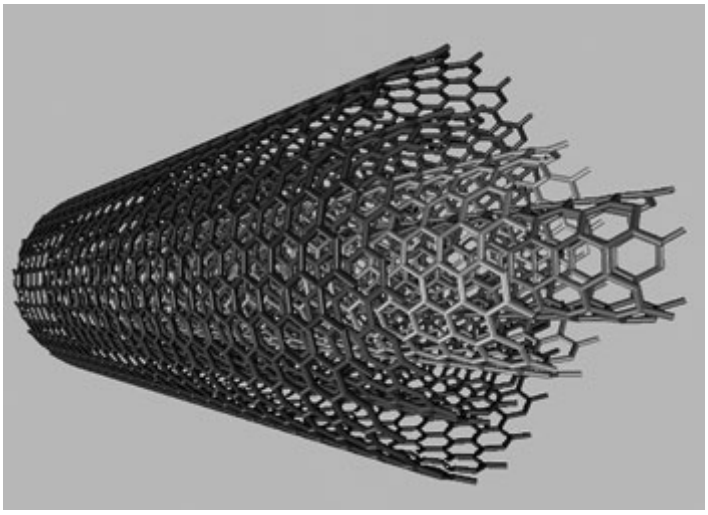


Figure 2[7]

1.1.1.1 Structure of Single-Walled Carbon Nanotubes

Single-walled carbon nanotubes (SWNTs) are graphene sheets which are rolled to form a tube. In principle there are 3 ways how to roll a graphene sheet. Consequently, there are also

three types of single-walled carbon nanotubes known (Figure 3). If you roll a graphene sheet along one of its two symmetry axes you form a zig-zag or armchair nanotubes, depending on the axis. If you roll it around no symmetry axis you form chiral nanotubes. Nanotubes are defined precisely by a vector (*n*,*m*). The integers *n* and *m* indicate the number of unit vectors along two directions in the graphene sheet. The (0,n) or (n,0) type of nanotubes are called zigzag nanotubes, whereas the (*n*,*n*) type are called armchair nanotubes and all other will be named chiral nanotubes.

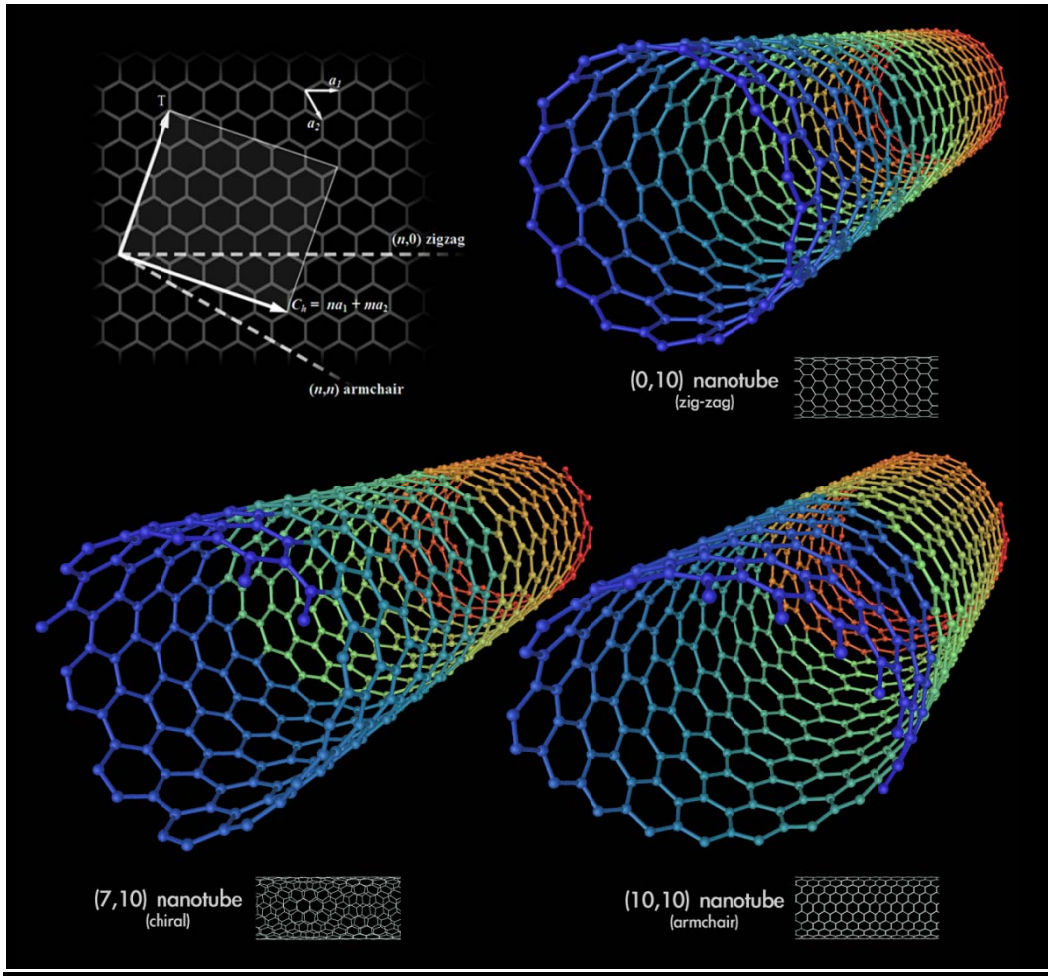


Figure 3[8]

Each type of nanotubes, armchair, zig-zag and chiral, has its own distinct properties. Single-walled carbon nanotubes are usually above 1 μm long and their diameters range typically from 1 to 2 nm.

1.1.1.2 Properties of Carbon Nanotubes

The electronic properties of SWNTs varies substantially. Only armchair carbon nanotubes show fully metallic properties. In contrast, chiral and zigzag nanotubes show either semi-metallic or semiconducting properties. There is an easy rule how to distinguish between nanotubes with those two properties: if the difference of the subtraction of "n-m" is a multiple of three, then the CNTs will be semi-metallic, otherwise the CNTs are moderate semiconductors.

Furthermore, carbon nanotubes are the stiffest and strongest materials in term of tensile strength and elastic modulus discovered so far. Carbon nanotubes are 24 times harder than steel, but are only one fourth as heavy. Additionally, armchair carbon nanotubes have a, in theory, 1000 times higher current density than copper.[9]

Those two properties open the way to many applications. The lightweight and stability of nanotubes can be used for applications like tennis rackets, baseball bats and bicycle frames. Moreover, the electronic properties are very promising for high-performance and flexible electronic devices.

Finally, carbon nanotubes are biocompatible which makes them suitable for various applications in living organisms. For example, protein-encapsulated single-walled carbon nanotubes can alter their fluorescence in the presence of biomolecules (e.g. glucose), which can be used for new types of biological sensors.[10]

1.1.1.3 Synthesis of Carbon Nanotubes

Carbon nanotubes have been synthesized by various methods. The first technique is ark-discharge under helium atmosphere, which can afford multi-gram quantities of carbon nanotubes.[11] The second technique is laser ablation, a condensation of a laser-vaporized carbon-nickel-cobalt mixture at 1200°C.[12] Usually, the quality of carbon nanotubes which are produced via the first two methods is very high. Finally, chemical vapor deposition (CVD) is one of the most promising methods to synthesize carbon nanotubes.[13] Especially as they can be grown in a controlled process on a surface.

The downside of the CVD method is its lack of selectivity. Usually, nanotubes of various length, diameter and structure (zig-zag, armchair, chiral) are synthesized at the same time. As mentioned above, each of this type of carbon nanotubes has different properties. Until now no selective synthesis or suitable purification method was available. From the organic chemists' viewpoint, it is desired to synthesize carbon nanotubes fragments selectively to study their structure-properties relationship. As armchair nanotubes were of special interest in molecular electronics due to their metallic properties we focused our efforts to the synthesis of such carbon nanotubes fragments. The smallest organic fragments that resembles an armchair carbon nanotubes are the [n]-cycloparaphenylenes (Figure 4).

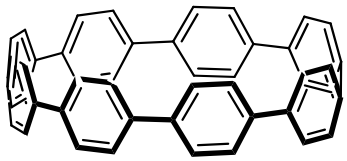
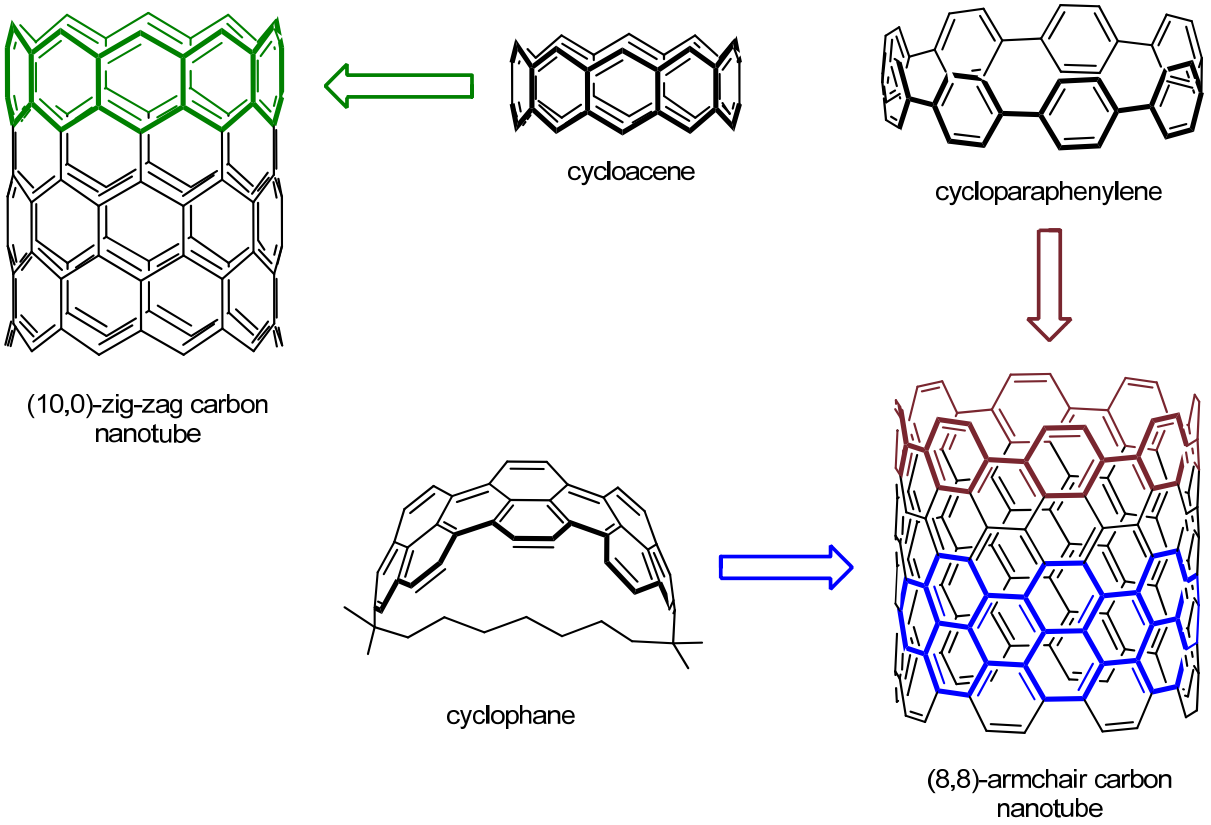


Figure 4

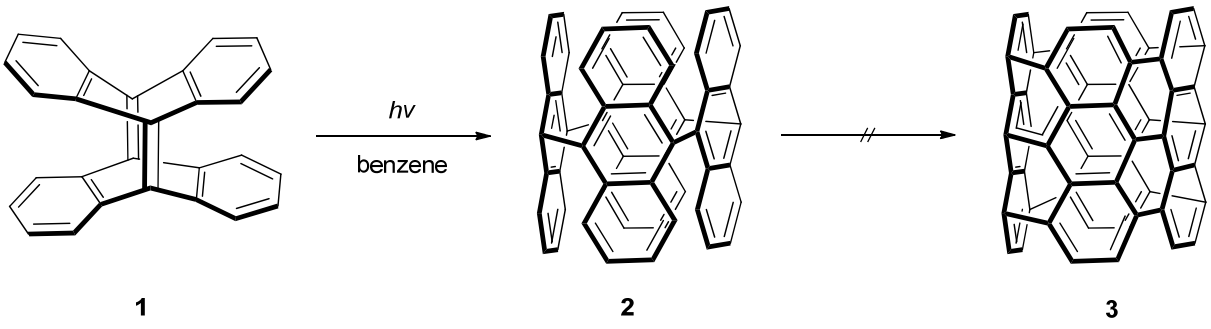
1.1.2 Cycloparaphenylenes and Other Nanotubes Fragments

The synthesis of carbon nanotubes fragments is in the focus of many research groups worldwide. Although each group has its own ideas and approach for the synthesis, the basic molecules they aim to prepare stay the same (Scheme 1). Usually, either cycloacenes, cycloparaphenylenes or polyaromatic cyclophanes are the desired molecules as they all can be mapped onto carbon nanotubes.[14]



Scheme 1

A very famous example is the picotube (**1**, Scheme 2) synthesis from R. Herges and co-workers.[15] The picotube, [0_4]-paracyclophane, was synthesized from 9.9',10,10'-tetradehydrodianthracene (**2**) in a photochemical [2+2]-cycloaddition.



Scheme 2

Unfortunately, all efforts to oxidatively close the molecule and synthesize a (4,4)-armchair carbon nanotubes were unsuccessful.[16] Nonetheless, it is important to mention that the picotube is a fascinating molecule, as its p-orbitals are all conjugated and radially oriented.

Our interest in the synthesis of cycloparaphenylenes led us in summer 2008 to start investigating a possible synthetic strategy. At this point no report of any synthesis of cycloparaphenylenes was published. We became very interested in the cycloparaphenylenes because of their distorted aromatic system and their radially oriented p-orbitals. Moreover, we planned to use the cycloparaphenylenes for the synthesis of smaller carbon nanotubes fragments, by connecting multiple cycloparaphenylenes to each other.

1.1.2.1 Cycloparaphenylene — Properties, Structure and Definition

Cycloparaphenylene is a cyclic molecule where multiple phenyl units are connected to each other in *para*-position. The cycloparaphenylenes are classified by the index [n] corresponding to the number of phenyl units. The [10]-cycloparaphenylene is a cyclic molecule, where all ten phenyl units are connected in *para*-postion. These cycloparaphenylene have very interesting properties due to their distorted aromatic system and their radially oriented p-orbitals (Figure 5).

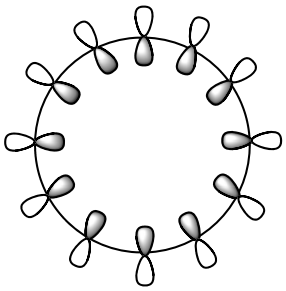


Figure 5

Cycloparaphenylenes were investigated theoretically by several groups, out of which K. Itami and co-workers investigated the strain energies of cycloparaphenylenes via DFT calculations.[17] They reported that there are 15 stable conformations (local minima) of [12]-cycloparaphenylene. All these conformations are within an energy difference of 5.7 kcal/mol which shows that at least in [12]-cycloparaphenylene all phenyl units can rotate freely. The lowest energy conformation consists of 12 phenyl units which are twisted alternatingly with a dihedral angle of 33°. Moreover, they reported the diameters and strain energy of a series of [n]-cycloparaphenylenes from 6 to 20 phenyl units. Furthermore, they showed the correlation between strain energy and diameter which is depicted in Figure 6.

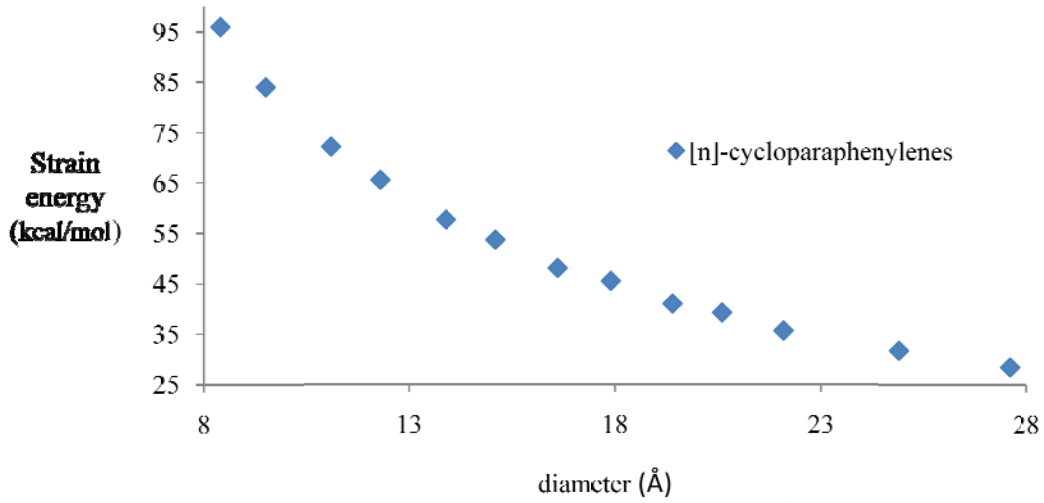


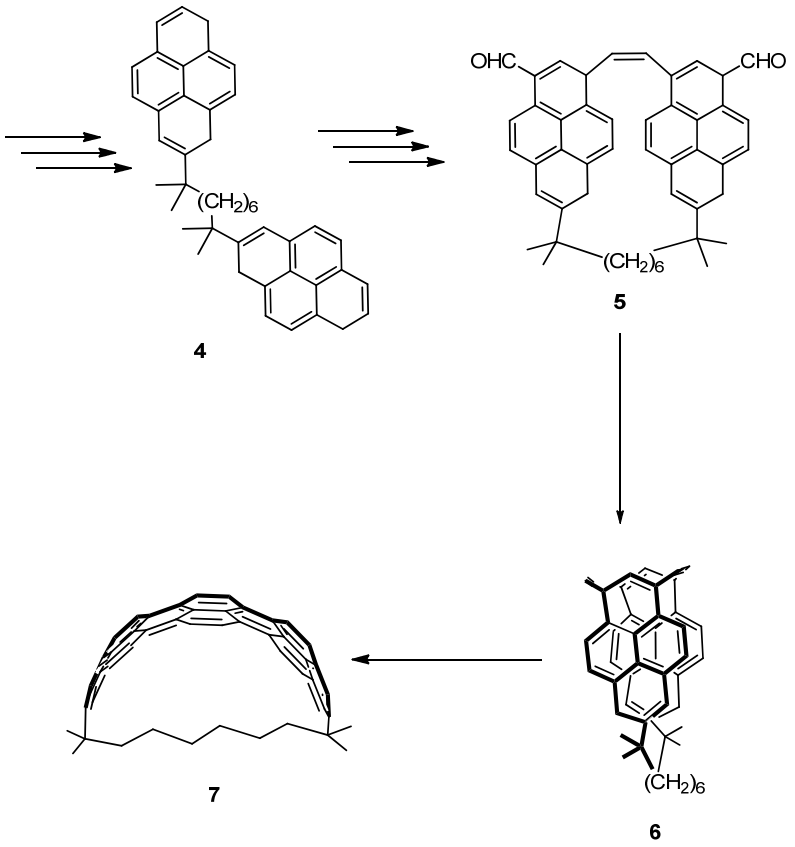
Figure 6

The strain energy is one of the challenges in the synthesis of cycloparaphenylenes. In any synthesis a smart solution for the introduction of the strain has to be found. Among others, sequential introduction of strain or forcing conditions can be employed. On the other hand the aromatic stabilization (and conjugation) is gained as soon as all phenyl units are more or less in plane with their neighboring phenyls. The other major challenge to overcome was the decreasing solubility, which is known to decrease for all polyaromatic molecules, the larger they become.

1.1.2.2 The Bodwell Half-Belt

Bodwell and co-workers had an interesting strategy to create half of an aromatic belt-shaped molecule in a 12-steps pathway with an overall yield of 10% (Scheme 3).[18] They prepared the enedialdehydes **5** in a Riche formylation, followed by a McMurry coupling and a second Riche formylation of 2,9-dimethyl-2,9-bis(2-pyrenyl)decane (**4**). After a further McMurry coupling of **5**, the cyclophanediene **6** was obtained. The desired product, (2,11)-teropyrenophane (**7**), was formed via valence isomerization and dehydrogenation of cyclophanediene **6** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). As mentioned above (Scheme 1), their half belt molecule can be perfectly mapped on the wall of a (8,8)-

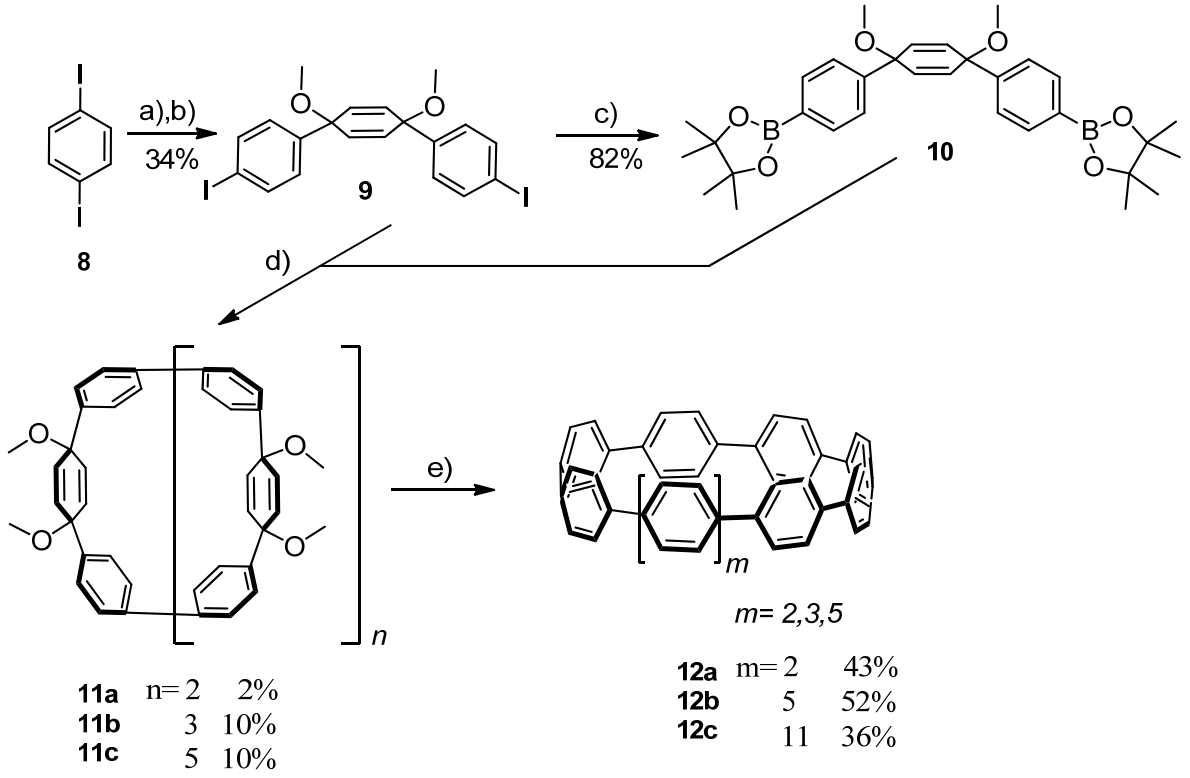
armchair carbon nanotubes and is, therefore, one of the largest fragments which have been synthesized until now.



Scheme 3

1.1.2.3 Synthesis by Bertozzi

The first successful synthesis of a cycloparaphenylene was reported by C. Bertozzi and co-workers in December 2008.[19] They reported the synthesis of [9]-,[12]- and [18]-cycloparaphenylenes in 0.2-1.4% yields in a 5 step procedure (Scheme 4).



a) *n*-BuLi, then Benzochinon; b) NaH, then MeI; c) *n*-BuLi, then *iso*propyl pinacol borate; d) $Pd(PPh_3)_4$, $CsCO_3$; e) Li-Naphthalenide

Scheme 4

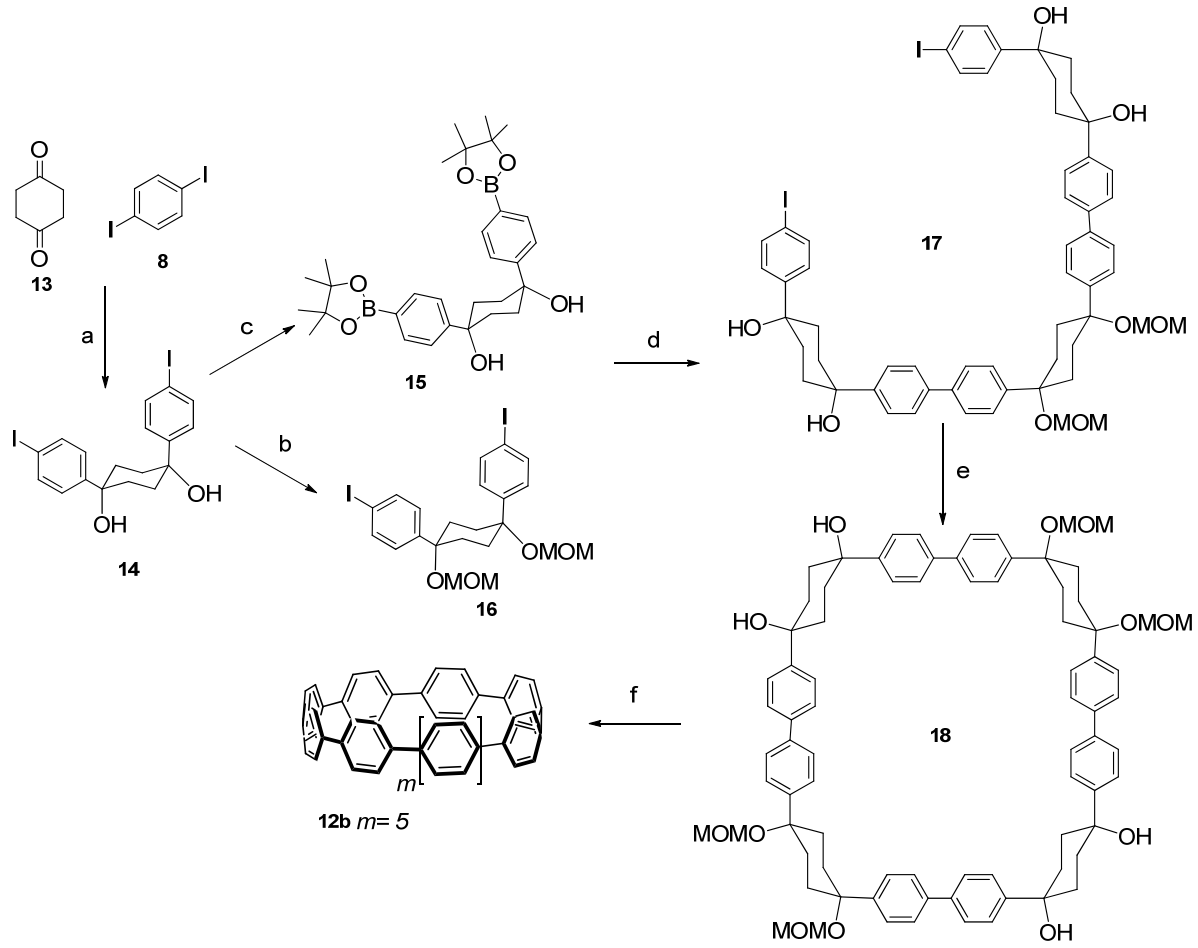
The first step of their synthesis is a lithium-halogen exchange and the addition of this organometallic species to benzophenone. The formed alcohol is then alkylated with sodium hydride and methyl iodide to form bisiodide **9**. This bisiodide is partly transformed to the corresponding diboronate **10**. A Suzuki coupling of the bisiodide **9** and the diboronate **10** afforded three macrocycles **11a**, **11b**, **11c** which are the key intermediates of the synthesis. The final step had to introduce the aromaticity and overcome the strain to form the cycloparaphenylenes. Reductive elimination of all methoxy groups with lithium naphthalenide at -78°C afforded the [9]-,[12]- and [18]-cycloparaphenylenes (**12a**, **12b**, **12c**) in overall yields of 0.4 to 1.2%.

1.1.2.4 Synthesis by Itami

K. Itami and co-workers published a selective synthesis of [12]-cycloparaphenylene (Scheme 5).[20] They used similar methods like Bertozzi *et al.* to build up the molecule. The initial

reaction between 1,4-diiodobenzene (**8**) and cyclohexane-1,4-dione (**13**) afforded 1,4-diphenylcyclohexane (**14**).

The key building block was then on one hand converted to the corresponding dipinacol borate **15** and on the other hand to the MOM-protected dioxide **16**. These two molecules were combined by two Suzuki coupling to form the macrocycle **18**. A domino deprotection and eight-fold dehydrative oxidation with *p*-TsOH under microwave irradiation afforded [12]-cycloparaphenylene (**12b**) in 10% overall yield.



a) *n*-BuLi; b) MOM-Cl, Hunigs Base; c) $[PdCl_2(dppf)]$, $B_2(pin)_2$, KOAc; d) $[PdCl_2(dppf)]$, NaOH; e) $Pd(OAc)_2$, X-Phos, NaOH; f) *p*-TsOH, microwave

Scheme 5

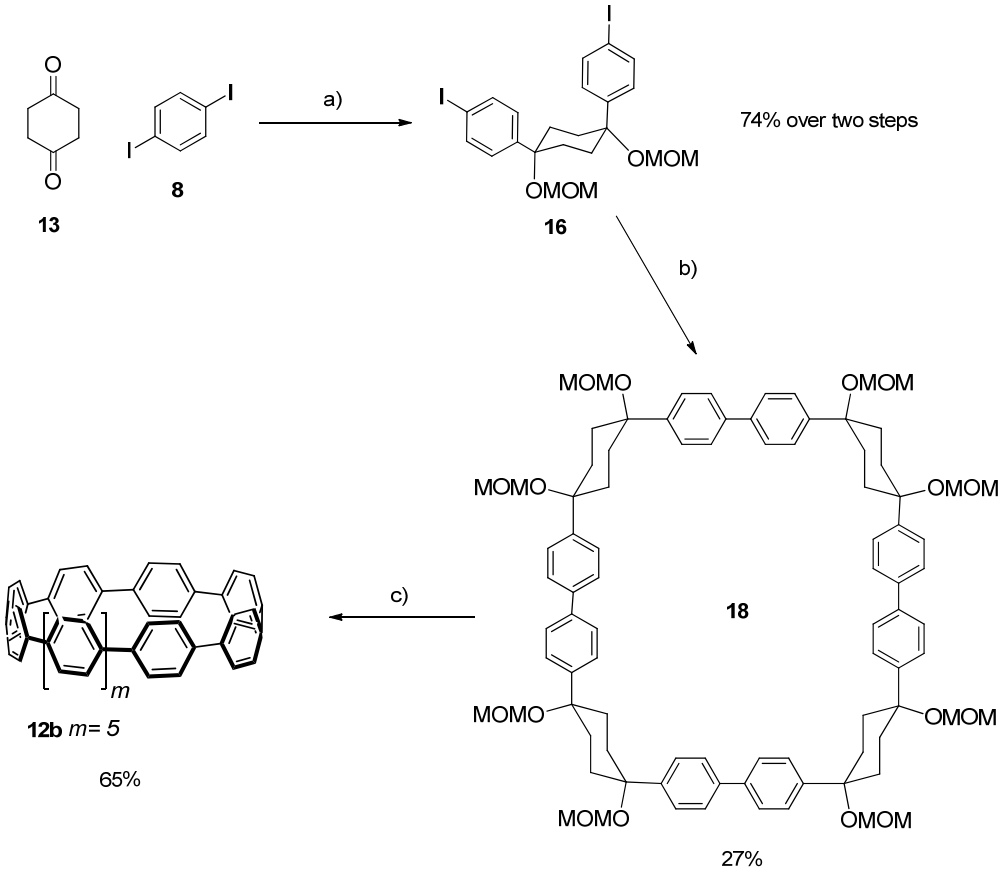
Moreover, they showed the flexibility of their synthesis by using the same protocols for the selective synthesis of [14]-,[15]- and [16]-cycloparaphenylene, just few months after the report of their first synthesis.[21] As the microwave conditions, which they reported for the

synthesis of [12]-cycloparaphenylene were not easily controllable they established a new protocol for the final aromatization step. They reported that $NaHSO_4{}^*H_2O$ in refluxing *m*-xylene/DMSO yielded the cycloparaphenylenes even under non-inert conditions. The use of DMSO was crucial to dissolve the highly polar intermediates which are formed during the eightfold MOM-deprotection, dehydration and oxidation sequence.

Recently, they were the first to report a crystal structure of a cycloparaphenylene.[22]

Figure 7

In the same context, they also developed a so called shotgun approach to cycloparaphenylenes. They obtained multiple grams of [12]-cycloparaphenylene in only four steps with overall 13 % yield via a Nickel catalyzed homocoupling reaction (Scheme 6).

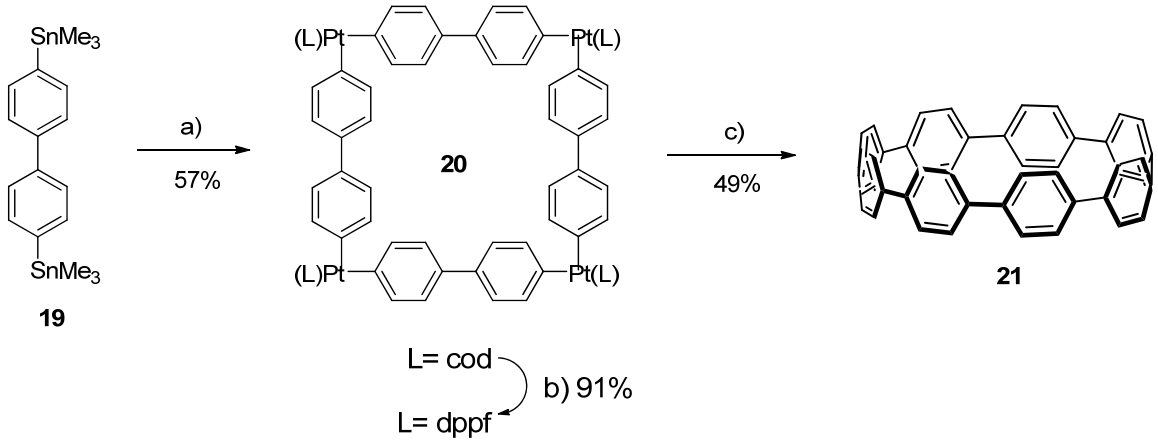


a) 1. *n*BuLi, then $CeCl_3$, LiCl, then cyclohexane-1,4-dione; 2. MOM-Cl, *i*Pr_2NEt, CH_2Cl_2;
b) $[Ni(cod)_2]$, bpy, (with or without cod); c) $NaHSO_4{}^*H_2O$, m-xylene/DMSO, under air.

Scheme 6

1.1.2.5 Synthesis by Yamago

The third researchers reporting a synthesis of cycloparaphenylene was the group of S. Yamago (Scheme 7).[23] They published the selective synthesis of [8]-cycloparaphenylene in 18% overall yield. Starting from a 4,4'-di(tin)-substituted biphenyl **19** they formed the tetraplatinum complex **20** in 57% yield. After a ligand exchange (cod→dppf) they used an already known[24] bromine induced reductive elimination to form the [8]-cycloparaphenylene (**21**).



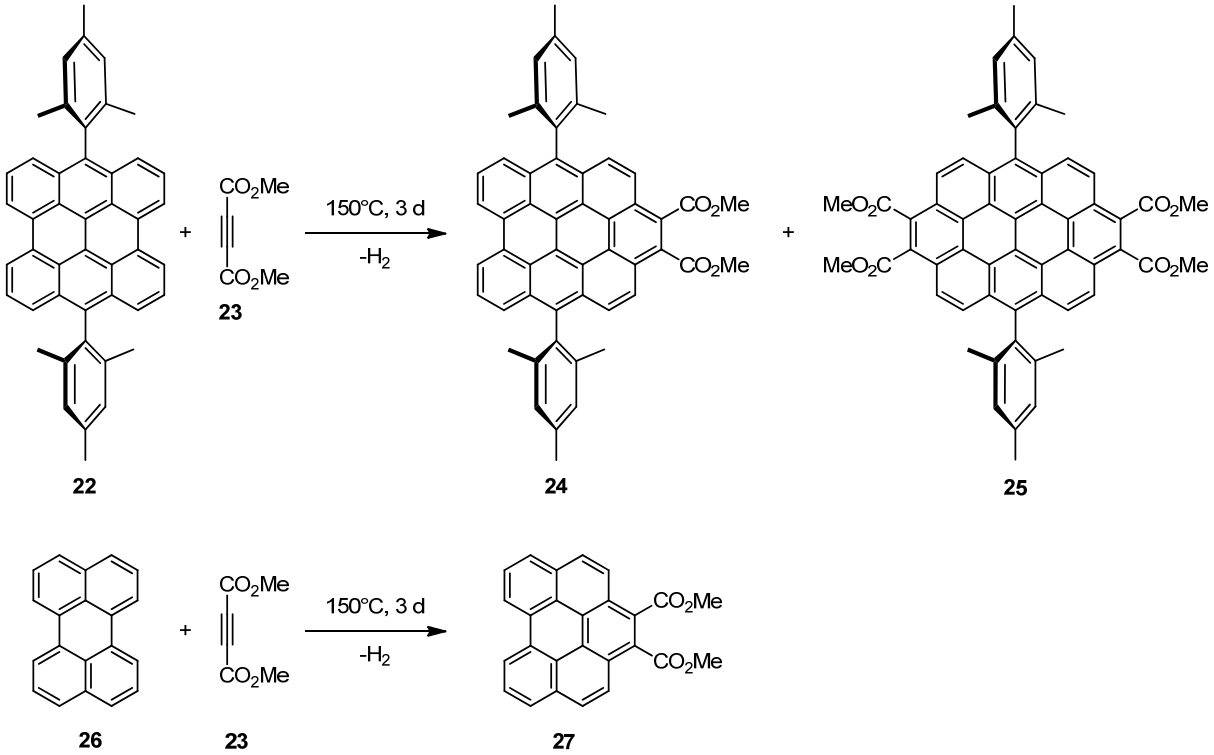
a) [$PtCl_2$(cod)], THF; b) dppf, DCM; c) Br_2, toluene

Scheme 7

The major drawback of their very concise synthesis is the stoichiometric use of Platinum. On the other hand, they could synthesize the smallest cycloparaphenylene until now and could overcome the highest strain.

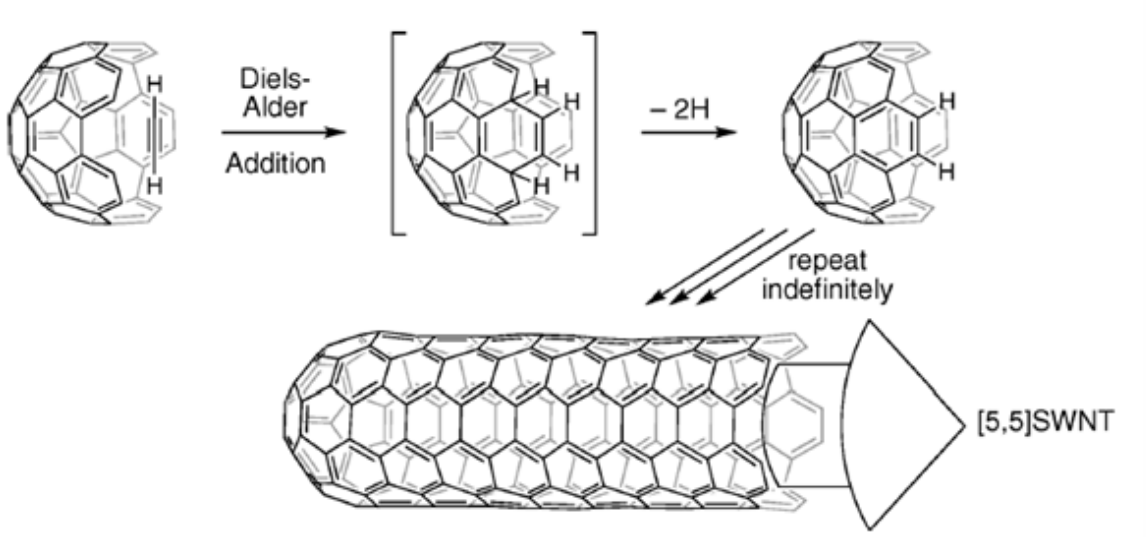
1.1.2.6 From Cycloparaphenylenes to Nanotubes

L. T. Scott and co-workers proposed a synthesis of (5,5)-armchair nanotubes by multiple Diels-Alder reactions.[25] They investigated reactions (Scheme 8) at the bay region of 4,11-dimesitylbisanthene (**22**) and perylene (**26**) with diethyl acetylenedicarboxylate (**23**). The reactions were successfully performed, whereas the reaction with **22** afforded two products **24** and ; the Diels-Alder reaction with **26** yielded molecule **27** as single product. During a competition experiment with diethyl acetylenedicarboxylate (**23**) and equal amounts of 4,11-dimesitylbisanthene (**22**) and perylene (**26**), only **22** was able to undergo the Diels-Alder reaction.



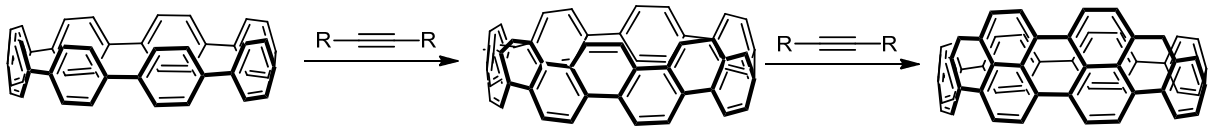
Scheme 8

The experimental results confirmed the calculations that Diels-Alder reactions are easier at bay regions at the end of longer polycyclic aromatic hydrocarbon. Based on the presented techniques and approaches, it will be soon possible to create armchair as well as chiral nanotubes with belt-shaped molecules (Scheme 9). Nevertheless, it is important to mention, that the Diels-Alder reaction at bay regions of aromatic belts are energetically more challenging than for the linear systems, especially for smaller, more bended systems.



Scheme 9

From synthesized cycloparaphenylene there can be envisioned a similar protocol to "grow" the aromatic framework (Scheme 10). With this strategy in mind selective synthesis of cycloparaphenylenes become very important as they define the structure (diameter) of the later nanotubes molecule. Therefore, we became interested in developing our own synthesis of cycloparaphenylenes even before the first report by Bertozzi and co-workers was published in 2008.



Scheme 10

1.1.3 The Sonogashira Reaction for the Synthesis of Macrocycles

The Sonogashira reaction is one of the most important C-C bond forming reaction in organic chemistry. As mentioned above, in all synthesis of cycloparaphenylenes there was used a macrocyclic precursor. As, the Sonogashira reaction is a very powerful method to synthesize such macrocycles we became very interested in its use in our synthetic approach.

Fascinating examples are the macrocycles reported by S. Höger and co-workers, where in all case the Sonogashira cross coupling reaction was applied to synthesize the framework of a macrocycle (Figure 8).[26]

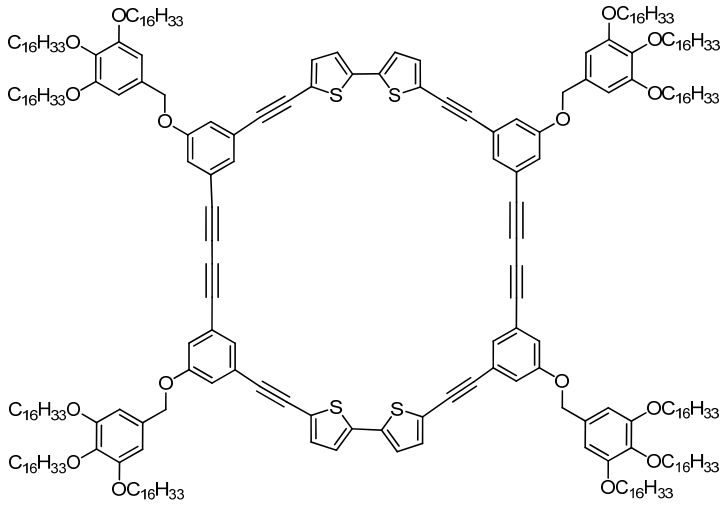
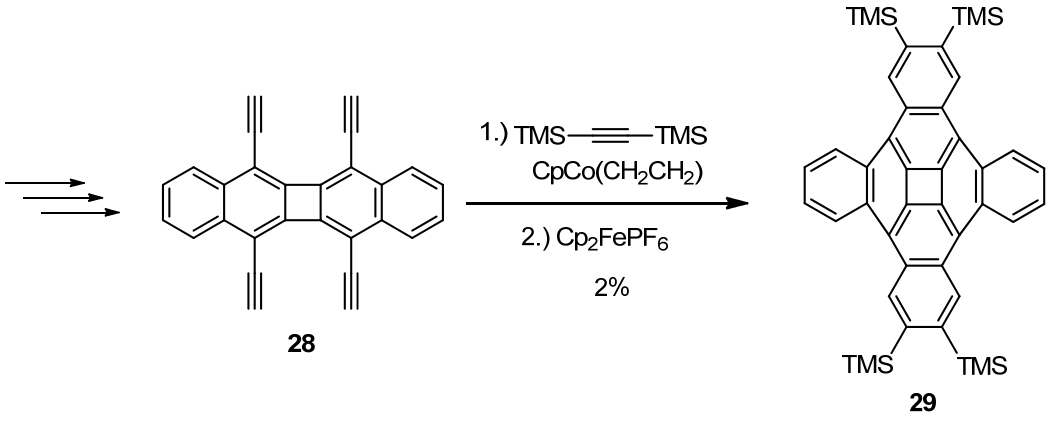


Figure 8

1.1.4 The [2+2+2]-Cycloaddition in the Synthesis of Strained Molecules

The [2+2+2]-cycloaddition is, as indicated by the name, a reaction where 6 π-electrons interact to form a new usually 6-membered ring. For our synthesis of cycloparaphenylenes we wanted to introduce the aromaticity and the strain via [2+2+2]-cycloadditions. Therefore, we were very interested in examples where this reaction was used to synthesize strained systems. A very interesting molecule, quadrannulene, which is a non-classical fullerene fragment was synthesized by B. T. King and co-workers using a [2+2+2]-cycloaddition.[27] In their work the tetraalkyne **28** reacted with a cobalt catalyst and bis(trimethylsilyl)acetylene to form the highly strained and bowl shape quadrannulene in 2% yield (**29**, Scheme 11).



Scheme 11

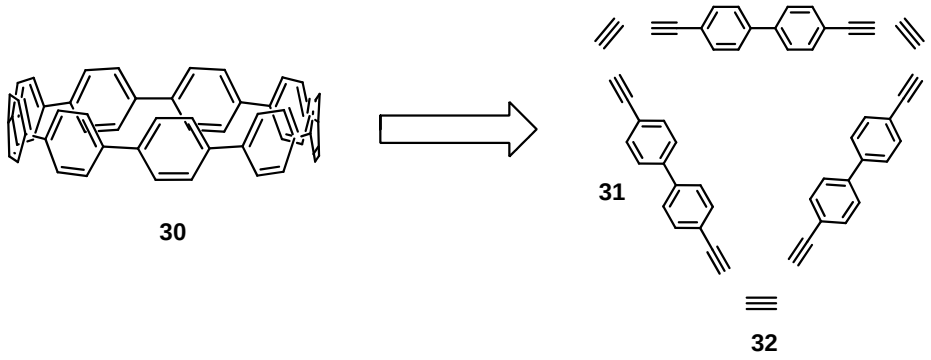
Their highly innovative work is a perfect example of a [2+2+2]-cycloaddition where the strain could be overcome by stabilization though conjugation, a concept we also wanted to use for our approach.

1.2 Results and Discussion

1.2.1 Retrosynthetic Analysis and Synthetic Strategy

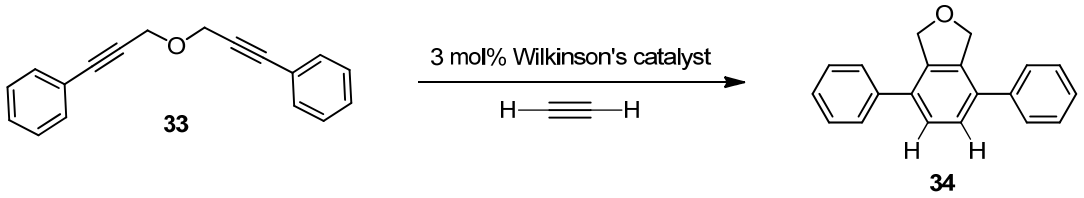
For our bottom-up approach towards carbon nanotubes, we were very interested in designing a highly flexible as well as a selective strategy for the synthesis of cycloparaphenylenes.

Our retrosynthetic analysis started with the cycloparaphenylene and our first disconnection was performed at every third aromatic ring. We anticipated, that a sequential build up of the strain and aromaticity was the key to achieve the synthesis. If you disconnect a cycloparaphenylene at ever third aromatic ring via a retro-[2+2+2]-cycloaddition you get two very simple molecules, acetylene (**32**) and 4,4'-bis(ethynyl)-biphenyl (**31**, Scheme 12).



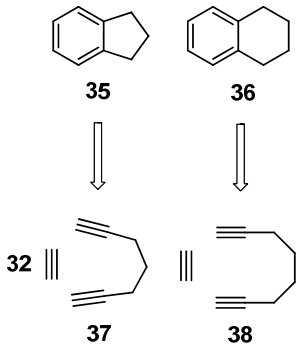
Scheme 12

On one hand, this approach would be very practical, on the other hand we expected severe selectivity problems during the [2+2+2]-cycloadditions as in principal all acetylene units could react with each other to form various oligomers or polymers. F. E. McDonald and V. Smolentsev developed an interesting synthesis for linear oligo-*p*-phenylenes via a rhodium-catalyzed alkyne cyclotrimerization.[28] They used a three atom-connection between the two alkynes to overcome the entropic challenges of a trimerization (Scheme 13).



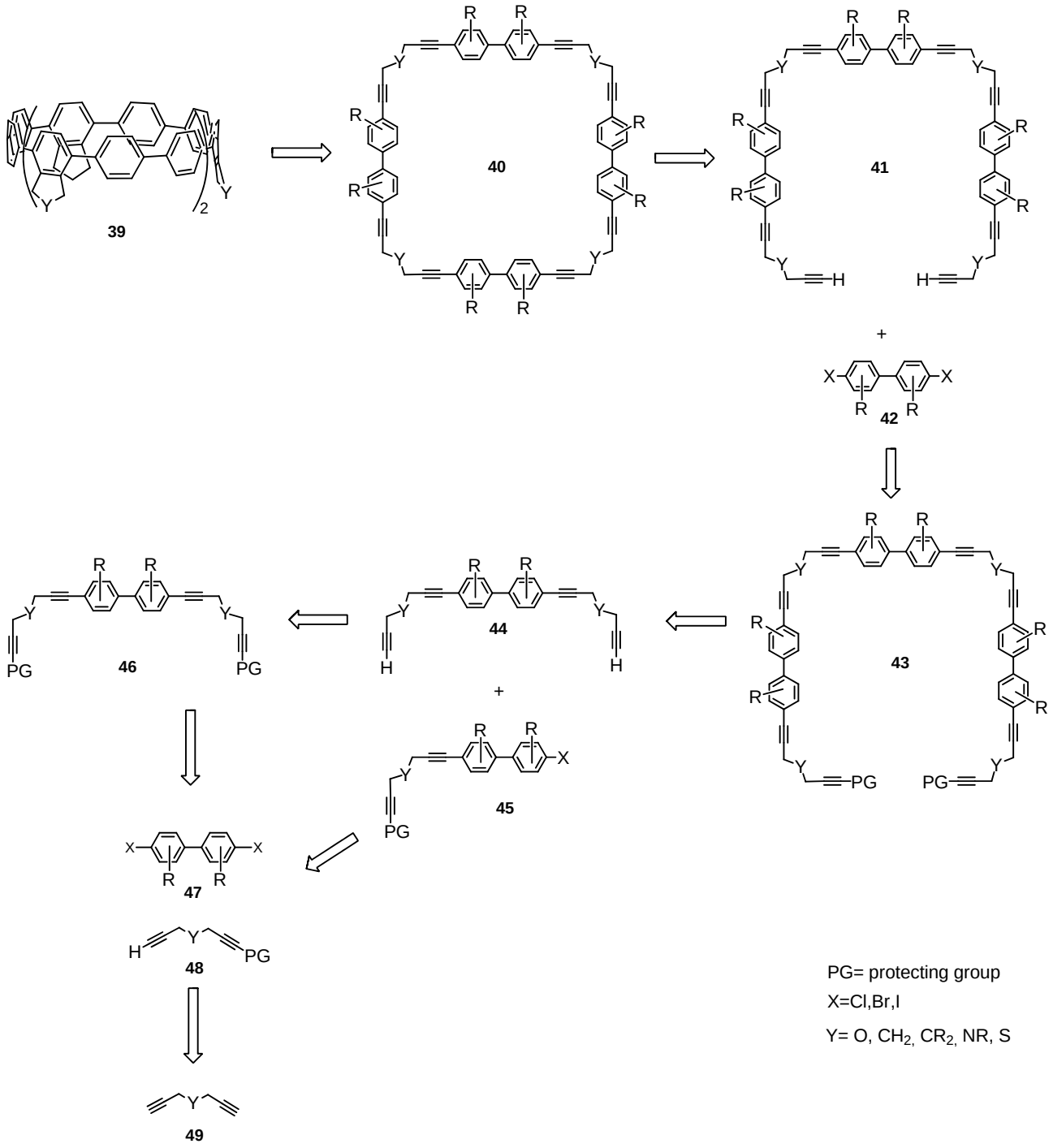
Scheme 13

With their report in mind, we thought about a similar possible connection between the multiple biphenyl units. If you could use an indane (**35**) or tetraline (**36**) moiety (Scheme 14) for every third aromatic ring you could imagine a 3-4 carbon atom connection between the biphenyls.



Scheme 14

For the synthesis of e.g. [12]-cycloparaphenylene with a three carbon bridge between the acetylene units you would be disconnected as depicted in Scheme 15 to obtain the arylalkenyl macrocycle **40**. A macrocyclic compound of this structure can be assembled readily via multiple Sonogashira cross coupling reactions. The disconnection of the macrocycle **40** would lead after several steps to a bisalkyne **49** and a bis(halo)-biphenyl **47**. Additionally, the alkyne should be protected due to selectivity issues, as otherwise the bis(halo)aryl building block and a unprotected bisalkyne could react to form oligomers.



Scheme 15

The structure of the macrocycle was expected to be square like and mm2 optimizations confirmed a square like structure (Figure 9). We anticipated, that it should be possible to synthesize structures of this type and then perform a [2+2+2]-cycloaddition with an alkyne to

introduce the final aromatics and compensate the strain energy by the aromatic stabilization of the newly formed aromatic rings.

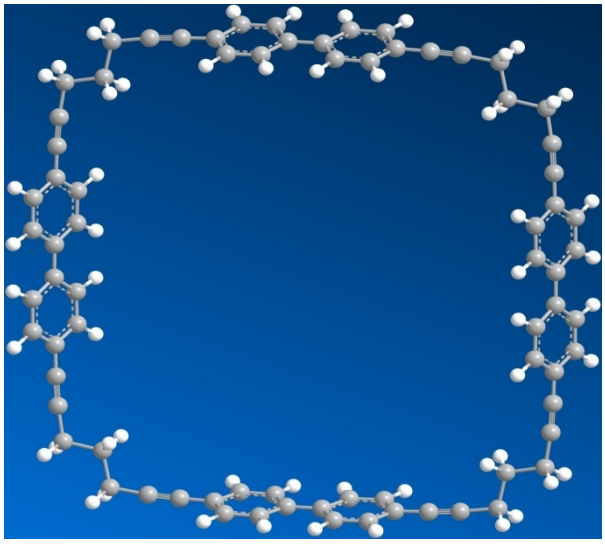
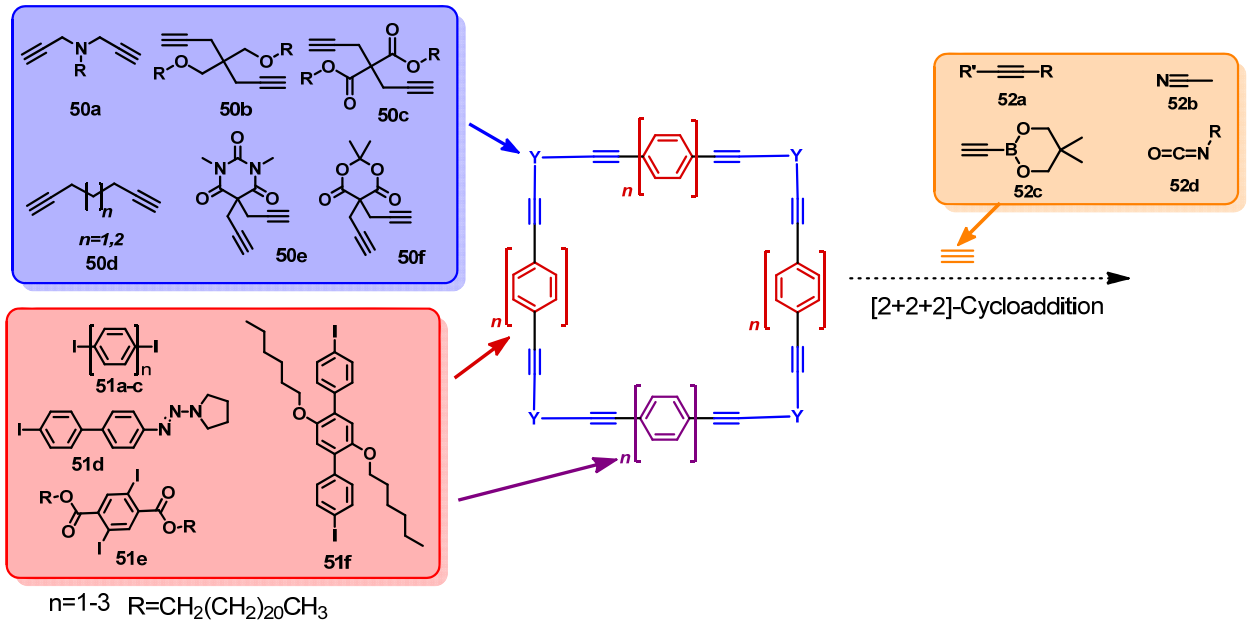


Figure 9

Our synthetic strategy was designed to be the following: synthesis of an arylalkynyl macrocycle via multiple Sonogashira reactions and transition metal catalyzed [2+2+2]-cycloaddition to synthesize the substituted cycloparaphenylene. Our strategy (Scheme 16) basically uses three building blocks, an alkyne, a bis(halo)biphenyl and a bisalkyne. As the build-up of the macrocycle is sequential a higher flexibility of varying building blocks to adjust the properties or size of the formed macrocycle is available. On Scheme 16 the impact of different building blocks on the final molecule is demonstrate, using the examples of different building blocks used in our group. The ring size of the cycloparaphenylene is in principal decided by the size of the halo-phenyl building blocks (**51a-f**), e.g. by using phenyl, biphenyl or terphenyl moieties. On the other hand you have a huge flexibility in your choice of suitable bisalkynes (**50a-f**) to adjust parameters like polarity or solubility. Finally, even in the last step, the [2+2+2]-cycloaddition, various side-chains on the acetylene can be introduced (**52a**). In addition, even pyridines or pyridines, by the use of nitriles (**52b**) or isocyanates (**52d**) instead of the alkyne building block, can be synthesized. The cycloparaphenylene could also be functionalized for further reactions, e.g. by the use of a boronic ester substituted alkyne (**52c**).



Scheme 16

With our strategy in hand we started the synthesis of substituted cycloparaphenylenes.

1.2.2 Review on the Previous Work in our Group

The first investigations of our synthetic strategy where performed by Hermann A. Wegner and Joel Riverendo during his work in our group.[29] First they found that a silyl protection strategy for the alkynes is necessary to overcome selectivity problems during the Sonogashira cross coupling reactions. To overcome challenges during the separation of protected and unprotected alkynes, it was found, that the use of a polar analoga for the TMS-group developed by S. Höger and his group: the 3-(cyanopropyl)-dimethylsilyl protecting group (CPDMS) (Figure 10) was suitable.[30]

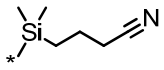
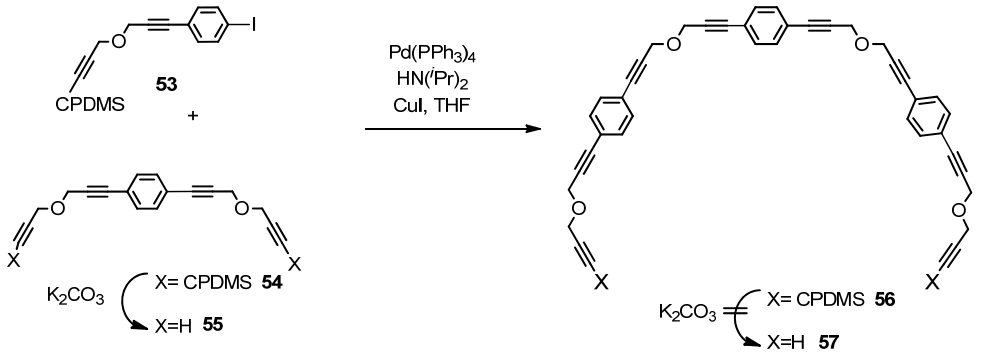


Figure 10

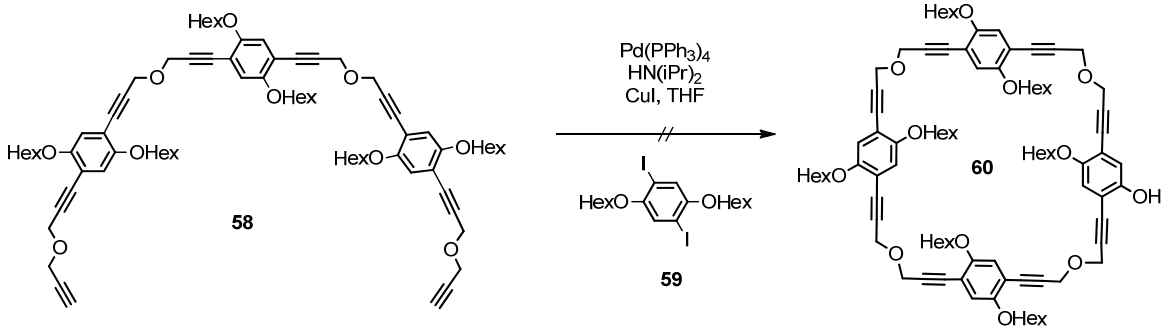
When this new protecting group was applied, the separation after the deprotection was significantly simplified as the polarities were now very different. Unfortunately, we were

unable to purify the product of the reaction **57** from the second deprotection step from side-products (Scheme 17).



Scheme 17

To overcome solubility changes we also used a substituted 1,4-diiodobenzene (**59**). This time we could complete all deprotections. Unfortunately, we could not complete the final Sonogashira coupling to the arylalkynyl macrocycle **60**, as no product could been isolated (Scheme 18).



Scheme 18

As all our attempts with the bisalkyneether failed we switched to the dimethyl malonate alkyne building block **50c**. Unfortunately, this approach did not lead to the desired macrocycle.[30]

To overcome the solubility challenges we switched from the methyl malonate building block to the octyl malonate and *iso*-pentyl malonate building blocks. Unluckily, during the CPDMS deprotection we observed a partial transesterification. As, we used potassium carbonate in

methanol the octylester was transesterified to the methyl ester. Moreover, when we used the *iso*-pentyl malonate we got mixtures of stereoisomers after the first Sonogashira reaction.

In conclusion, a lot was learnt from the first investigations. A suitable protecting group was found in the CPDMS-group. Moreover, we discovered the tendency of malonates to transesterification. Finally, several times problems during the macrocyclization reaction were encountered. These problems on one hand occurred from the low solubility. Moreover, they were supposed to arise from the small ring sizes which would have been formed when the diiodophenyl building block **59** was used.[30]

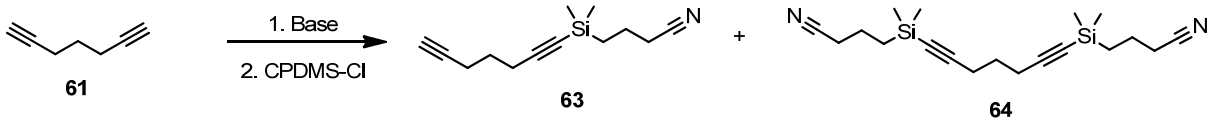
Therefore, a synthesis was designed, choosing a non-functionalized alkyne and a larger haloaryl building block.

1.2.3 First Generation Synthesis

1.2.3.1 First Generation Synthesis — 3-Cyanopropyldimethylsilyl Protection Strategy

For the first generation synthesis we chose 1,6-heptadiyne (**61**) as alkyne building block. Moreover, we switched from 1,4-diiodobenzene (**8**) to 4,4'-diiodobiphenyl (**62**) to synthesize larger less strained macrocycles.

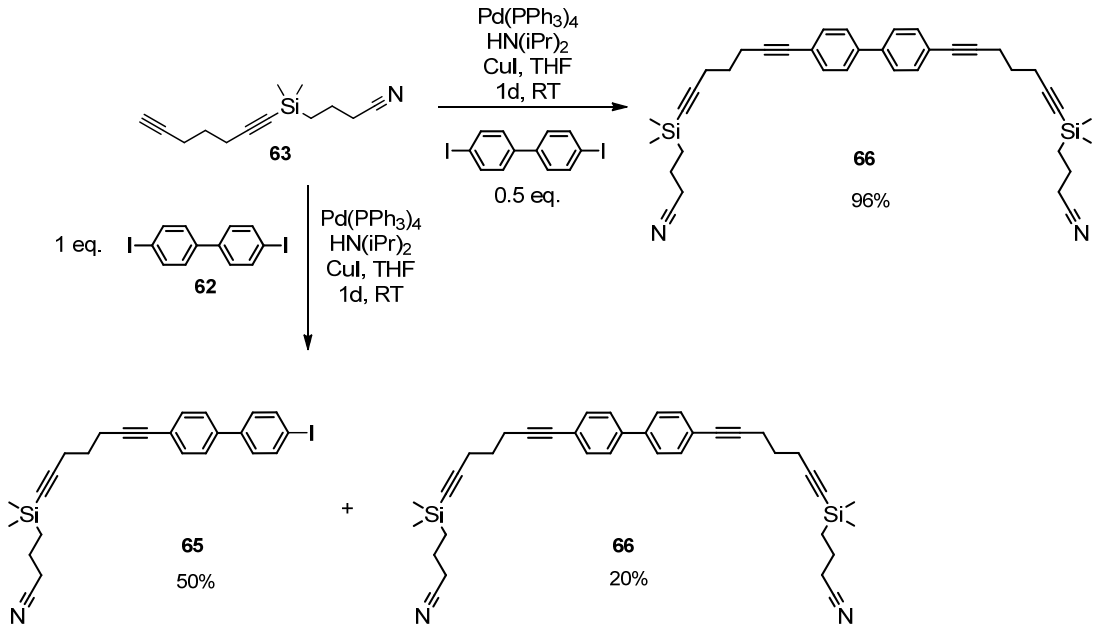
The first step of the pathway was the mono protection of 1,6-heptadiyne (**61**) with CPDMS-Cl (Scheme 19). When the reaction was performed for the first time with LiHMDS as base about 45% of the desired monoprotected compound **63** were isolated. Moreover, 32% of the double-protected alkyne **64** and some starting material were isolated. The influence of the base is obvious in the protection, as the terminal alkyne has a pKa of 26, LiHMDS (pKa 29 in DMSO) is basically a strong enough base (pKa difference of 3 units). In an optimization attempt we used sodium hydride as base (pKa 40). Unfortunately, the starting material decomposed and neither product **63** nor side-product **64** were isolated. On the other hand, more basic reagents like Grignard reagents are as well used for the deprotonation of alkynes.[31] The use of ethylmagnesium bromide increased the yield to up to 55%. Finally using a substoichiometric amount of EtMgBr (0.9 eq) and CPDMS-Cl (0.85 eq) afforded yields of monoprotected alkyne **63** up to 65%.



Base = LiHMDS	45%		32%
Base = NaH		decomposition	
Base = EtMgBr	65%		17%

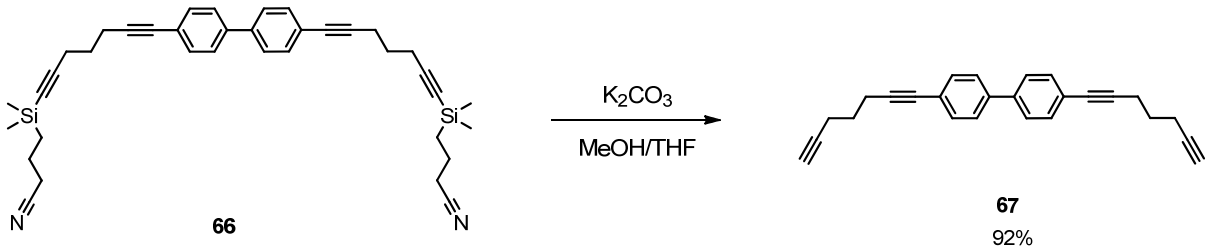
Scheme 19

This alkyne **63** was then used in two Sonogashira reactions. One to form the monocoupled product **65** and another one to synthesize the biscoupled building block **66** (Scheme 20). The double Sonogashira reaction worked well in all case (usually above 90% yield), especially as the two CPDMS groups made the molecule polar and facilitate the purification via column chromatography. The monocoupling has two major drawbacks: first, there is no selectivity and a significant amount of double coupled product **66** is always formed. Luckily, in this case this was not a problem as this molecule was needed anyways for the synthesis. Second, as the starting material **63** and the monocoupled product **65** both have one CPDMS group, their polarities are very similar. This made control of the reaction via TLC challenging which led in some cases to the reisolation of starting material, because the reaction was worked up too early. Nonetheless, the overall reaction is quite efficient, as in combination of both products, around 90% of the monoprotected alkyne **63** are converted into products which are used for the synthesis.



Scheme 20

The next step, the double CPDMS deprotection with potassium carbonate, worked quite well in the first attempt (Scheme 21). The free alkyne **67** could be isolated in 92% yield on 100 mg scale. As the product is very apolar compared to the starting material easy separation via column chromatography was performed.



Scheme 21

After this test reaction we wanted to convert 900 mg of starting material **66** using the same protocol. Unfortunately, only 37% yield were achieved under unchanged reaction conditions. As, this effect dramatic yield decrease during upscaling was unexpected we investigated the influence of the scale on the yield (Table 1, Figure 11)

Table 1

Scale (compound **66**)	100 mg	200 mg	450 mg	800 mg	900 mg
Yield (compound **67**)	92%	85%	76%	54%	37%

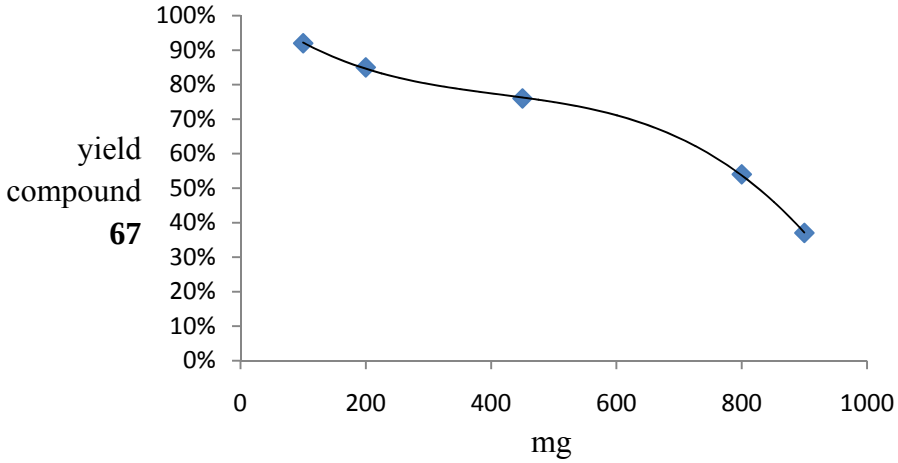
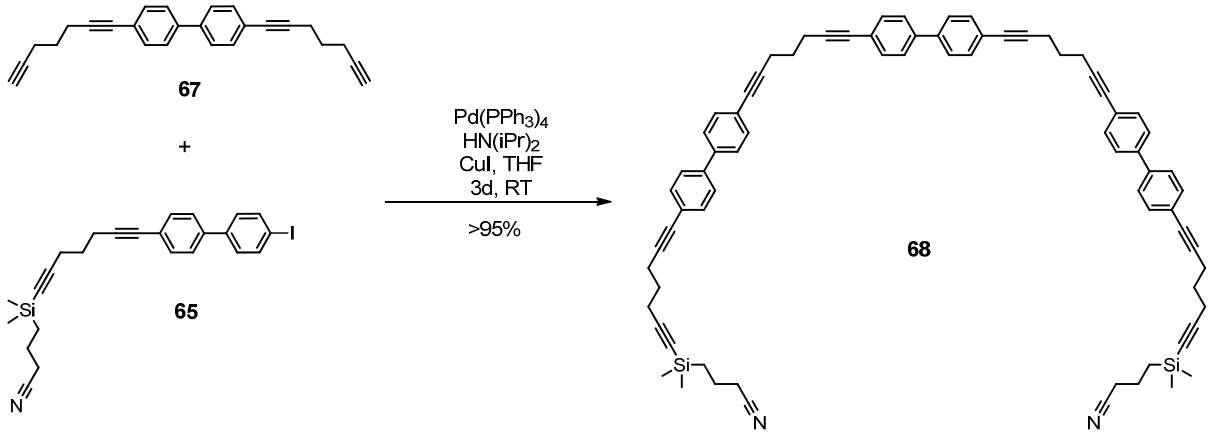


Figure 11

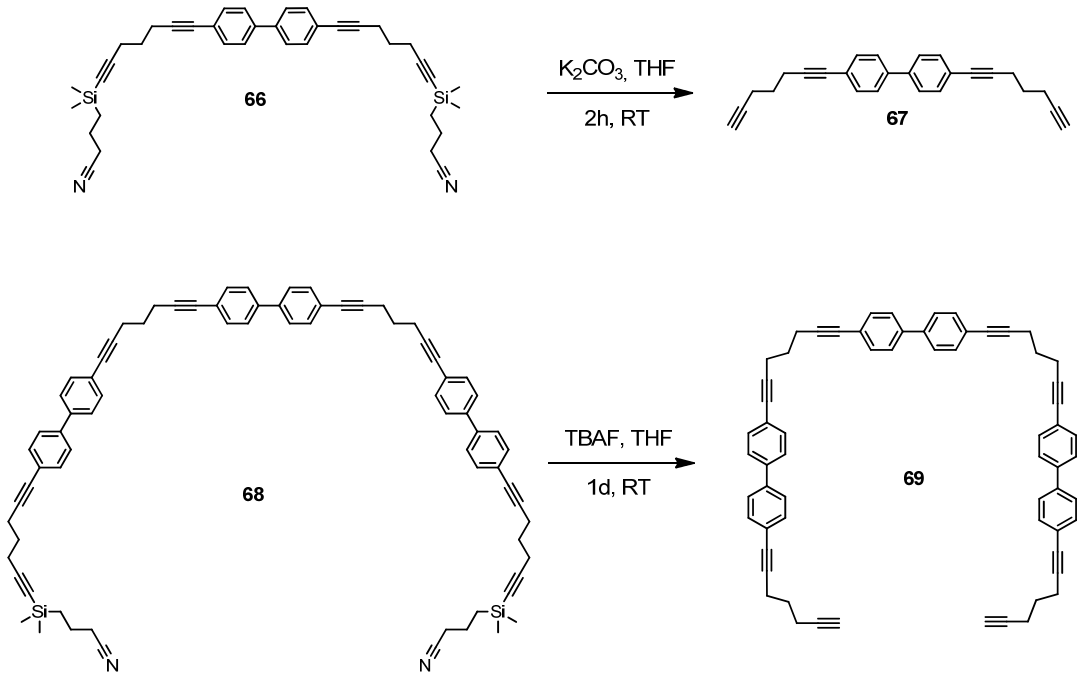
These results were interesting, as you could see a clear trend, that larger scale lowers the yield. Moreover, we found that the reaction time had also a significant influence on the yield. If the reaction was stopped after TLC indicated full conversion the yields were much higher, than when the reaction was continuously stirred for longer time. Usually after 2-3 h the workup had to be performed to achieve maximum yields. To overcome this drawback and to perform the reaction on larger scale we divided the starting material into 200 mg portions and performed the reaction in several vials. The workup and column chromatography could be performed for all vials together and reliable yields around 85% were obtained.

The next step was another Sonogashira reaction to couple to monoprotected compound **65** with free alkyne **67** (Scheme 22). The only mediocre yields (around 50%) which were obtained at the beginning could be overcome by longer reaction time (3 d instead of 1 d) and in the end high (above 95%) to quantitative yields were reached regularly.



Scheme 22

After completion of the Sonogashira reaction the formed bisprotected alkyne **68** had to be deprotected for the macrocyclization step (Scheme 23). When we used the developed condition for the first deprotection step (potassium carbonate in MeOH/THF), no deprotection could be achieved. This was astonishing, as in principal the only difference between the two molecules was, that now a trimer (**69**) of the central building block was submitted to deprotection, whereas the monomer (**66**), was found to react well. As the starting material was completely dissolved we did not expect such a difference in the deprotection of the same protection-group.



Scheme 23

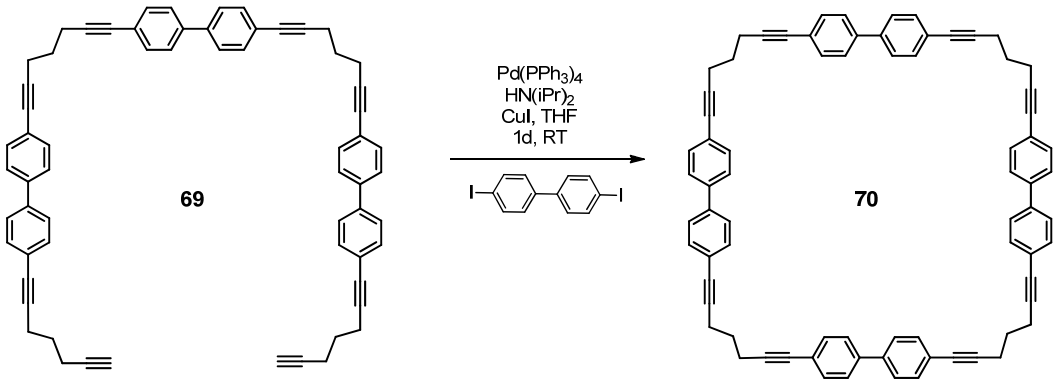
To find suitable deprotection conditions several protocols were applied:[1]

Table 2

Entry	Reagent	Solvent	Yield 69 (%)
1	K_2CO_3	MeOH/THF	0
2	AgF	DMF	low
3	TBAF (1M in THF)	dry THF	low
4	KOH	Dioxan	low
5	KF	THF	0
6	18-crown-6, KF	dry MeCN	3
7	HF*pyr	dry THF	0
8	anhyd. TBAF (1M in THF)	dry THF	10
9	TBAF salt	dry THF	80–94

Cleavage of the protecting group by the use of silver fluoride[32], followed by acidic work-up (Entry 2), and the reaction with TBAF (1M in THF; Entry 3) only afforded low yields of impure product. Additionally, the use of potassium hydroxide (Entry 4) for the deprotection were investigated. A low conversion was observed with potassium hydroxide. Methods like stirring potassium fluoride in a solution of tetrahydrofuran (Entry 5), or using a mixture of 18-crown-6-ether[33], [34] to activated the potassium fluoride (Entry 6) and the pretty harsh method using hydrogen fluoride in pyridine[35] (Entry 7) did not lead to the desired product in good yield. In literature, it was reported that anhydrous TBAF[36] should increase the basicity of fluoride. Therefore, TBAF salt was dried under high vacuum at 45°C oil bath temperature for 49 h, then diluted with dry tetrahydrofuran and stirred over night (Entry 8). Regrettably, this method was not as satisfactory as the product was isolated in low yield and contaminated with impurities. Finally, it was found that TBAF salt in dry tetrahydrofuran (Entry 9) led to the pure formation of the terminal bisalkyne **69**. The key to obtain pure product was to precipitate it out of the reaction mixture by addition of water. The reaction was divided in vials (400 mg portions) on large scale (4 g), similar to the deprotection of bisprotected monomeric compound **67**. The product was always isolated in yields between 80 and 94%.

With the free alkyne **69** available, we started to investigate the macrocyclization reaction (Scheme 24). The first results were quite promising. When we used our standard Sonogashira conditions we obtained a mixture of starting material and an unknown symmetric aromatic compound (NMR).



Scheme 24

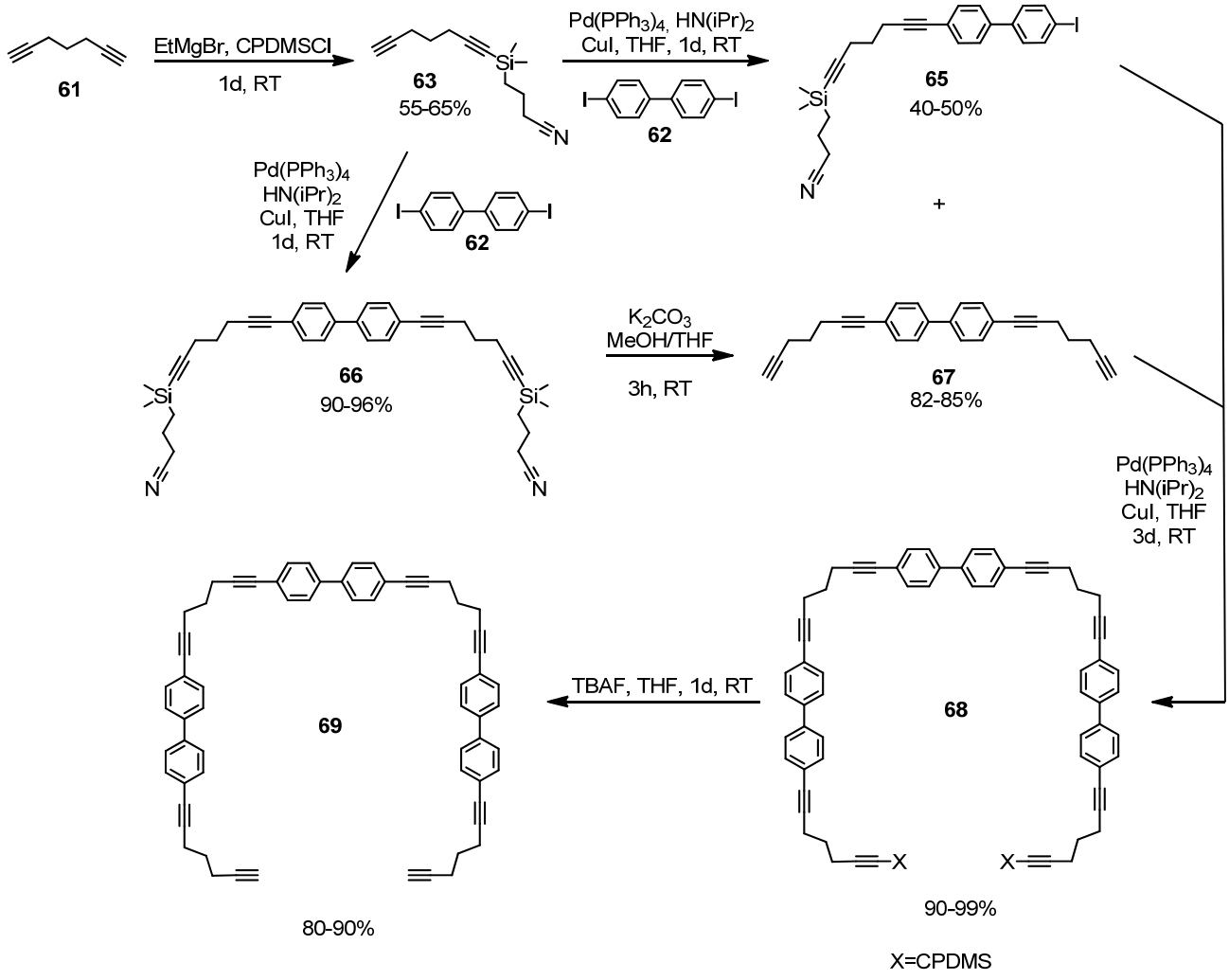
When we investigated this mixture via MALDI-MS we found three signals (405 m/z, 816 m/z and 968 m/z) which could be assigned to 4,4'-bis(iodo)biphenyl (**62**), starting material **69** and macrocycle **70**. The major challenge was the low solubility of the starting material and the macrocycle. No separation via column chromatography or recrystallization could be done. We were not able to perform TLC: neither the starting material **69** nor the mixture were eluted by any solvent mixture.

In his Master thesis Pascal Hess studied this macrocyclization, changing solvents, catalyst, base reaction time and temperature. As, the alkyne homocouplings are often copper-catalyzed we wanted to avoid this possible side reaction by not adding a copper salt. Due to our experiments, we proved that no product was formed without the copper cocatalysis.

Moreover, he found out that the reaction in toluene works quite decently, but in all cases he isolated a mixture of starting material and product.

Furthermore, all attempts to separate those two compounds via gel permeation chromatography (GPC) were not successful.

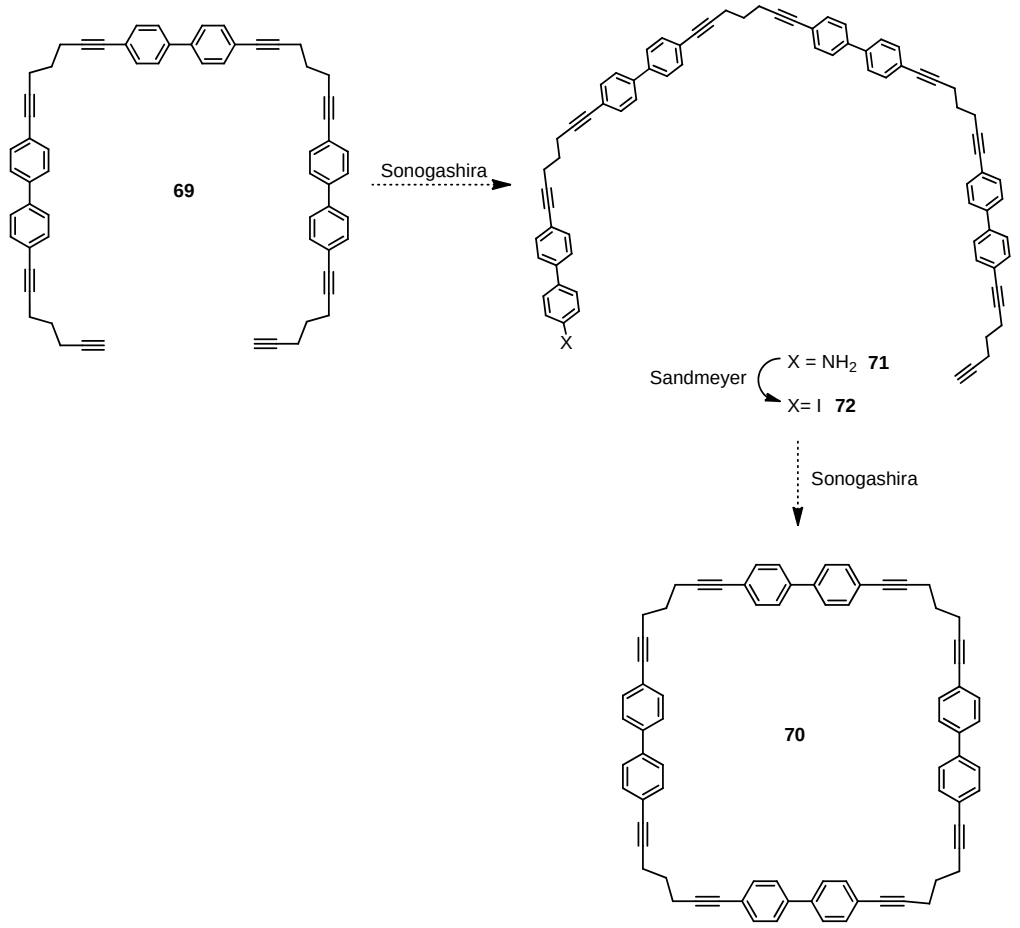
The final step the [2+2+2]-cycloaddition was performed several times with the crude mixture from the macrocyclization reaction. Unfortunately, only very complex mixtures were obtained and the product could not be detected in NMR or MALDI-MS. An overview of the complete synthesis is presented in Scheme 25:



Scheme 25

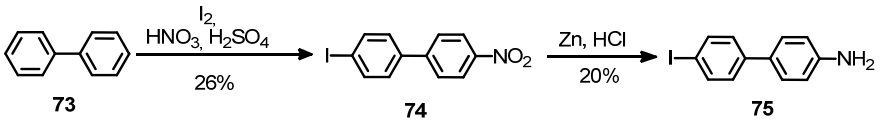
To overcome the challenges of the macrocyclization we attempted several workarounds:

Our first attempt was aiming for an intramolecular ring closing instead of the intermolecular reaction from Scheme 26. Therefore, we wanted to react the macrocycle precursor **69** with 4'-iodo-4-aminobiphenyl (**75**). After the Sonogashira reaction we wanted to perform a Sandmeyer type amine-iodo exchange and then an intramolecular ring closure with a final Sonogashira reaction.



Scheme 26

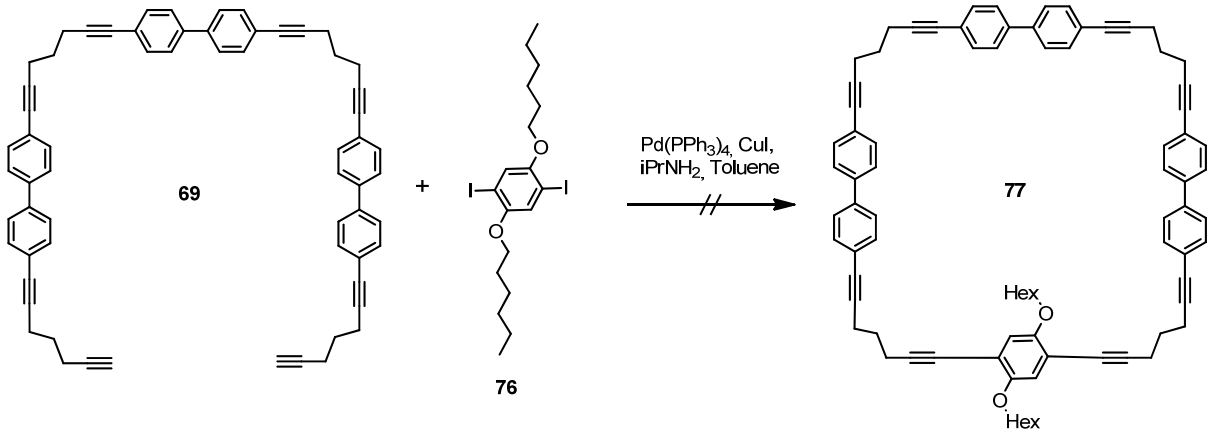
Therefore we performed the synthesis of 4'-iodo-4-aminobiphenyl (**75**) according to a procedure from Zhang *et al*.[37]



Scheme 27

Then we carried out the Sonogashira reaction with the free bisalkyne **69** and the synthesized 4'-iodo-4-aminobiphenyl (**75**). The same problems as in the original synthesis occurred. We could not monitor the reaction via TLC because of the low solubility. Unfortunately, the reaction did not yield any product even after prolonged reaction times.

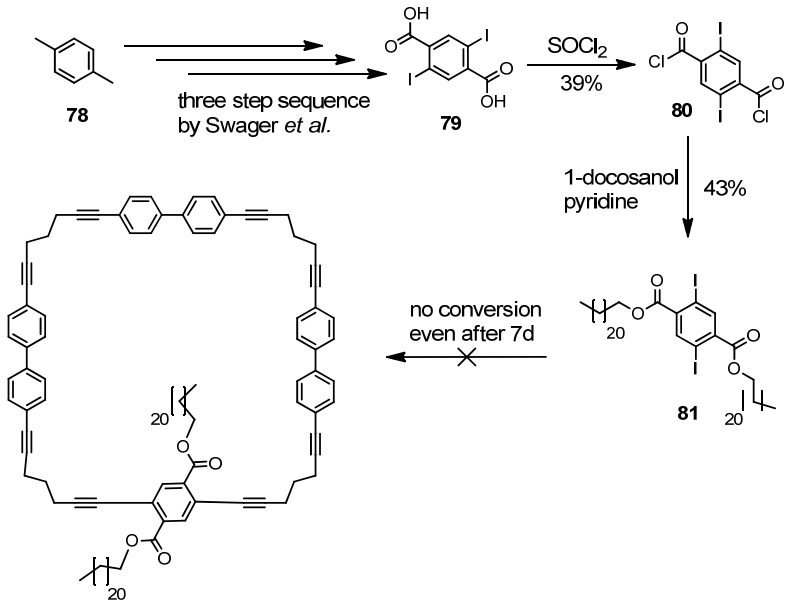
As the solubility was a great challenge, we decided to use derivatives of iodobiphenyl **62** with solubility enhancing properties. The use of 1,4-bis(hexyloxy)-2,5-diiodobenzene (**76**) should increase the solubility of the molecule after the first Sonogashira reaction. Regrettably, the reaction did not work and no product (**77**) could be isolated.



Scheme 28

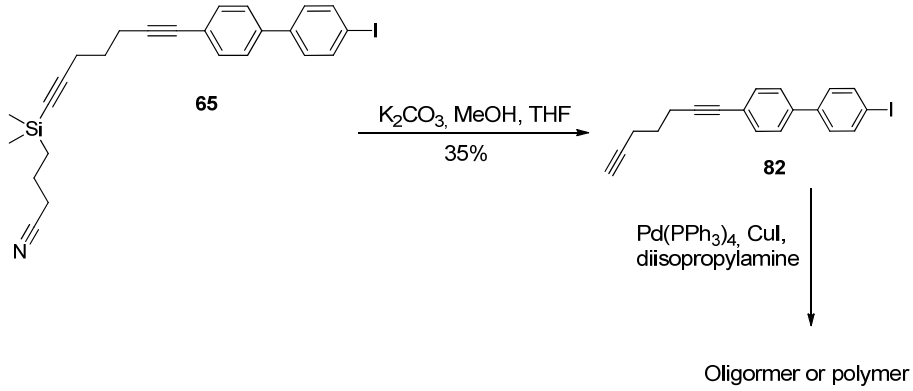
As the ether ligands, which increase the solubility, are on the other hand deactivating for the oxidative addition to the palladium during the Sonogashira reaction we intended to use another building block which should increase the solubility without strengthening the carbon-iodine bond and deactivating the molecule towards cross coupling reactions. Therefore, we synthesized the bis(iodo)-diester **81** (Scheme 29).

Following a three step sequence by T. M. Swager and co-workers we obtained 2,5-diiodoterephthalic acid (**79**).[38] As the direct esterification was not successful, we converted the acid to a bisacid chloride **80** in 39%. Finally reaction with 1-docosanol in pyridine afforded the desired diester **81** in 43% yield. When we used this building block **81** for the Sonogashira reaction with our macrocycle precursor **69** no reaction was detected even after 7 days.



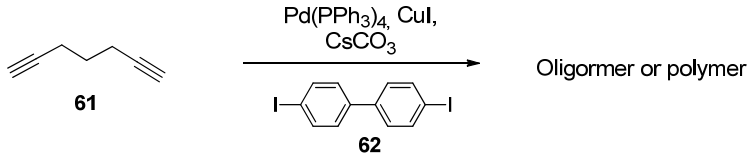
Scheme 29

Furthermore, we also investigated the possibility to synthesize the macrocycle starting with a smaller building block directly via tri- or tertramerization. Therefore, we deprotected the iodoaryl compound **65** in 35% yield (Scheme 30). The free iodoalkyne **82** was then used in a Sonogashira cross coupling reaction but only oligomeric or polymeric products were found in the reaction mixture.



Scheme 30

Moreover, we performed a Sonogashira reaction with the unprotected 1,6-heptadiyne (**61**) and 4,4'-iodobiphenyl (**62**) with the same result of oligomer or polymer formation.



Scheme 31

Altogether the free bisalykne **69** seems to be very insoluble and all Sonogashira reactions with this alkyne seem to proceed very slowly. Even though the first 6 steps of the synthesis could be developed and would offer a large scale synthesis with 47% overall yield for the longest linear sequence, we could not isolated the product **70** from the macrocyclization making the whole pathways unfeasible.

1.2.3.2 First Generation Synthesis — Other Protection Strategies

When we encountered the first problems with the deprotection of the CPDMS-group we started the sequence twice again with two new protecting groups: the 3-(cyanopropyl)-di*iso*propylsilyl (CPDIPS) and dimethylhydroxy (DMH) groups (Figure 12).[39]

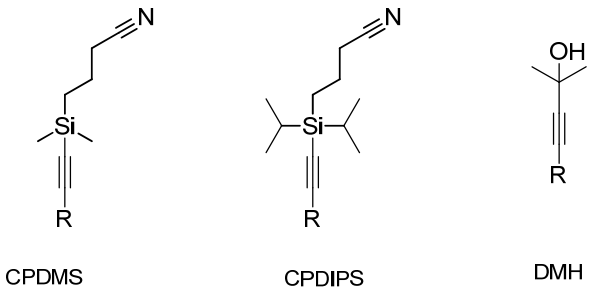
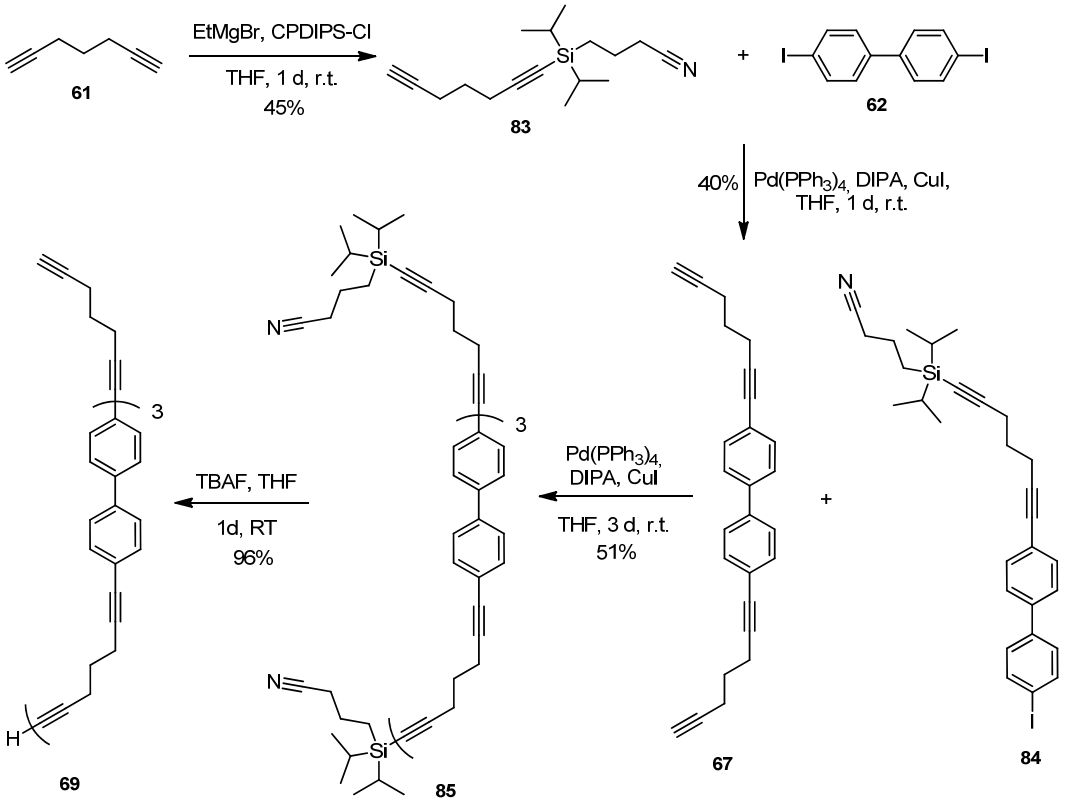


Figure 12

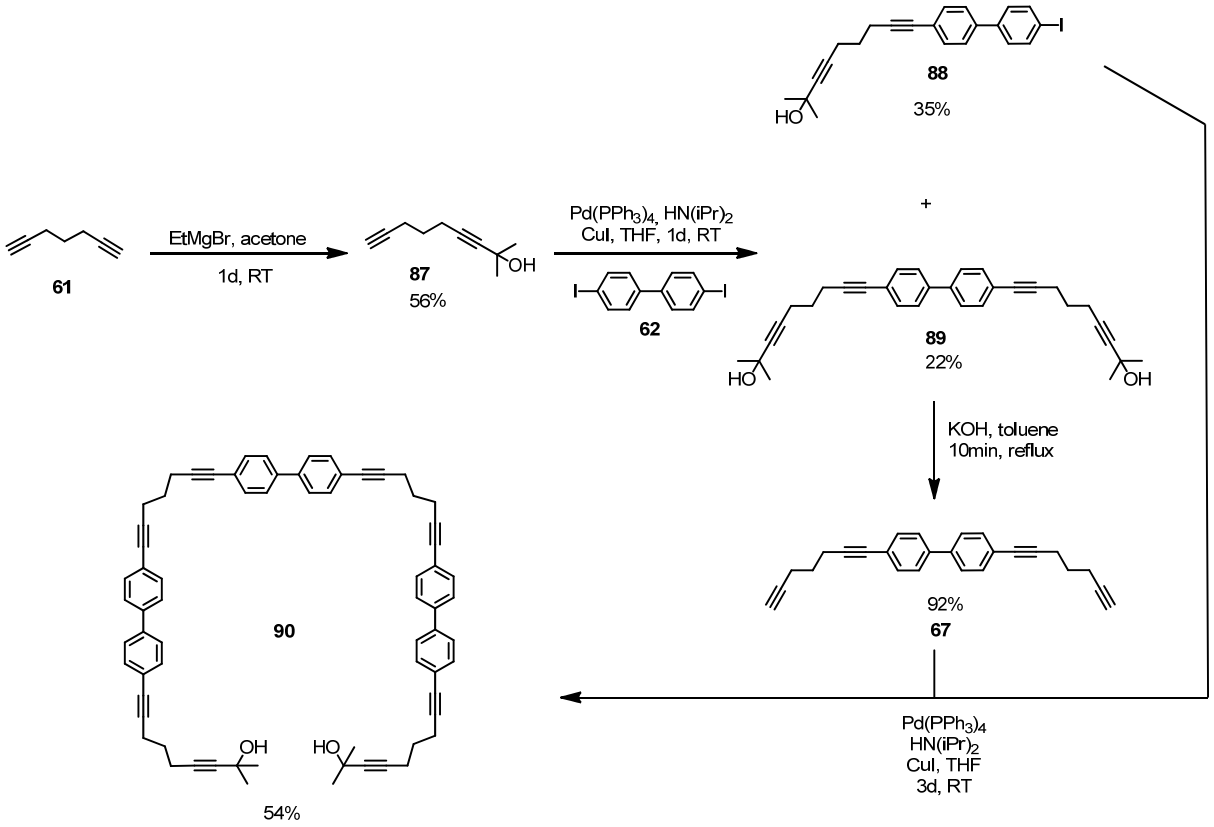
This work was performed in collaboration with Pascal Hess during his Master thesis. First we started with a derivative from our original protecting group the 3-(cyanopropyl)-di*iso*propylsiliyl protecting group (Scheme 32):



Scheme 32

The monoprotected bisalkyne **83** was afforded in 45% yield in analogy to the preparation for the CPDMS protecting group (Scheme 32). The Sonogashira coupling of monoprotected bisalkyne **83** and 4,4'-diiodobiphenyl (**62**) gave primary the monoprotected iodobiphenylalkyne **84** in 40% yield and as byproduct the bisprotected biphenylbisalkyne (**86**) in 23% yield. The Sonogashira coupling of the terminal biphenylbisalkyne **67** with the monoprotected iodobiphenylalkyne **84** afforded the bisprotected hexaphenylbisalkyne **85** in 51% yield. The yield was decent, since no optimization on the reaction had been done. The cleavage of the two CPDIPS protecting groups of the bisprotected hexaphenylbisalkyne **85** to the terminal hexaphenylbisalkyne **69** was performed by precipitation out of the reaction mixture of TBAF salt in dry THF by the addition of water in 96% yield. As the overall yields were inferior to the CPDMS-strategy and the CPDIPS-Cl was much more expensive, we discarded this synthetic route.

Furthermore, we investigated the strategy with the dimethylhydroxy protecting group:



Scheme 33

The initial reaction was a protection reaction from 1,6-heptadiyne (**61**) with EtMgBr and acetone to afford the monoprotected bisalkyne **87**. The product was isolated in 56% yield (Scheme 14). The separation was difficult since the mono- and or the bisprotected arylalkyne stuck to the silica gel during the separation.

The Sonogashira coupling with 4,4'-diiodobiphenyl (**62**) and monoprotected bisalkyne **87** to form the monoprotected iodobiphenylalkyne **88** or the bisprotected biphenylbisalkyne **89** was performed in 35% and 22% yield respectively, which was inferior compared to the silyl strategy. The deprotection of molecule **89** was first performed with NaOH in refluxing absolute toluene but even after a few hours (West et al. reported complete deprotection after 10 min complete deprotection[40]) only starting material was observed in the reaction control (TLC). Nonetheless, preparative TLC led to isolation of 3% of desired molecule **67**. As, the solubility of NaOH is quite low in toluene, the reaction was repeated with KOH and 18-Crown-6. Additionally, it seems from the possible deprotection mechanism, that a proton

source is needed, therefore 0.5 ml of water were added. This time the reaction was complete after 90 min and the deprotected molecule **67** was isolated in 21% yield. The low yield could be a consequence of prolonged heating (90 min compared to 10 min in literature) as it is known, that terminal alkynes are heat sensitive. As we could readily monitor the reaction (the starting material was strongly stained with vaniline) we performed the deprotection again at reflux with KOH until no more starting material could be observed (TLC control, 25 min) to afford deprotected molecule **67** in 69 % yield. The quite good yield could be ascribed to the shorter reaction time and the heat sensitivity of oligoalkynes. Therefore, another reaction was stopped after 10 minutes to yield after column chromatography 86% of the free alkyne **67**.

The Sonogashira coupling between the terminal biphenylbisalkyne **67** and a monoprotected iodobiphenylalkyne **88** led to the bisprotected hexaphenylbisalkyne **90** in a moderate yield of 54%. Unfortunately, the deprotection of bisprotected hexaphenylbisalkyne **90** to the terminal hexaphenylbisalkyne **69** was only performed once and did not lead to pure formation of the desired product. The usual key to the purification, during the other two strategies, was precipitation out of the solution which was not possible because toluene was used in this reaction. Moreover, column chromatography on the very apolar free alkyne **69** was not possible, as described above, for solubility reasons.

Even though this protecting group is really cheap (acetone), the overall yields were inferior throughout the whole synthesis therefore, this protection strategy was discarded as well.

In conclusion, we learned a lot from the first generation synthesis. Unfortunately, we encountered the frontier of solubility with the non-functionalized building blocks right at the macrocyclization step. Even though some conversion took place (MALDI-MS signal for the macrocycle) the isolation and purification could not be performed by any means. Finally, we could compare the CPDMS, the DMH and CPDIPS protecting groups. In this comparison the CPDMS group was found to have superior properties.

1.2.4 Second Generation Synthesis

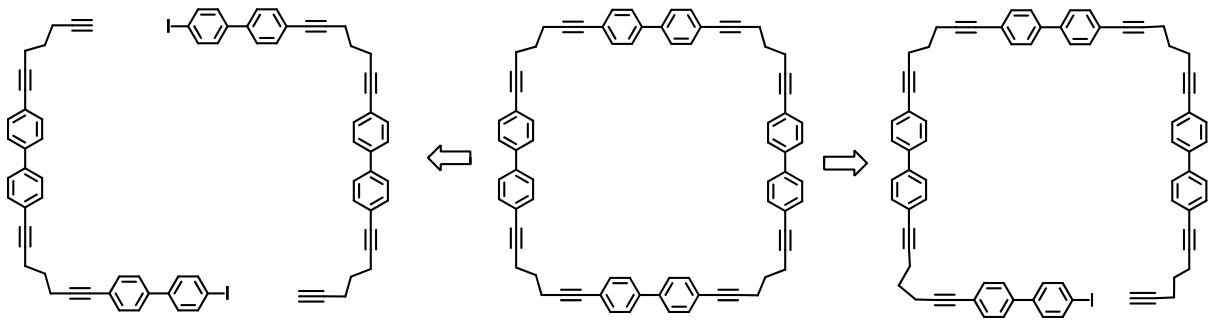
When we started the second generation synthesis we had several requirements on the building blocks we wanted to use, based on our past experience in the first generation synthesis.

First we wanted to overcome the selectivity problems with the first Sonogashira reaction, as when we used 4,4'-iodobiphenyl always a side-product (the double coupled compound) was formed.

Secondly, we wanted to enhance our chances to succeed by using building blocks which increase the solubility, compared to the non-functionalized first generation approach.

Third, we were interested in using functionalizes side-chains which can be transformed chemically into functional moieties. Especially, useful in context of analysis and purification of the macrocycle. An amine for example could enable the use of ESI-MS (LC-MS), the same is true for multiple ether functionalities, which could coordinate cations to facilitate the mass spectrometry (ESI-MS) as well.

Finally, we wanted to improve our pathway, towards either a more convergent approach or in direction of an intramolecular ring-closing (Scheme 34). The convergence could improve the separation via GPC as the size difference between starting material and products is much more significant.

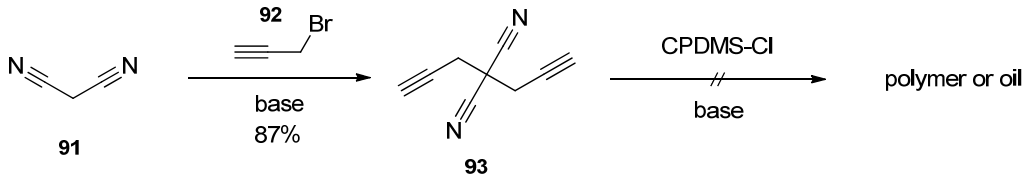


Scheme 34

1.2.4.1 Second Generation Synthesis ─ Synthesis of Several Alkyne Building Blocks

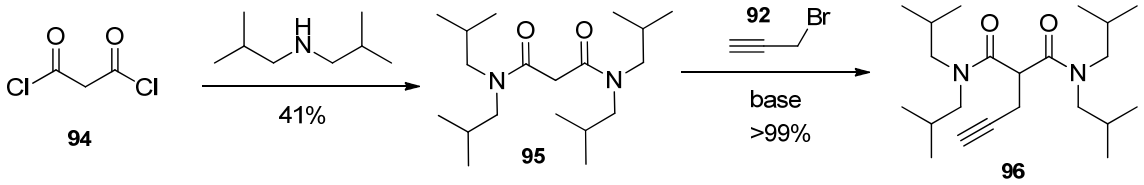
Our choice of possible alkyne building blocks was heavily influenced by our experience from the first two synthetic approaches. On one hand, we wanted to have side-chains on the alkyne to enhance solubility on the other hand we had to find suitable groups which do not interfere with the whole sequence. In the first generation synthesis we found that esters are not optimal, as during the CPDMS deprotection transesterification takes place.

Therefore, we started with the synthesis of an amine substituted alkyne. Indeed we did not want to have a free amine or amide because of possible side reaction and purification problems. We also wanted to use nitriles as amine mimics. We synthesized the bis nitrile **93** (Scheme 35) in 87% yield from malonitrile (**91**). Unfortunately, two attempts (with EtMgBr and LiHMDS as base) to protect the alkyne with the CPDMS protecting group only afforded black oils (polymers).



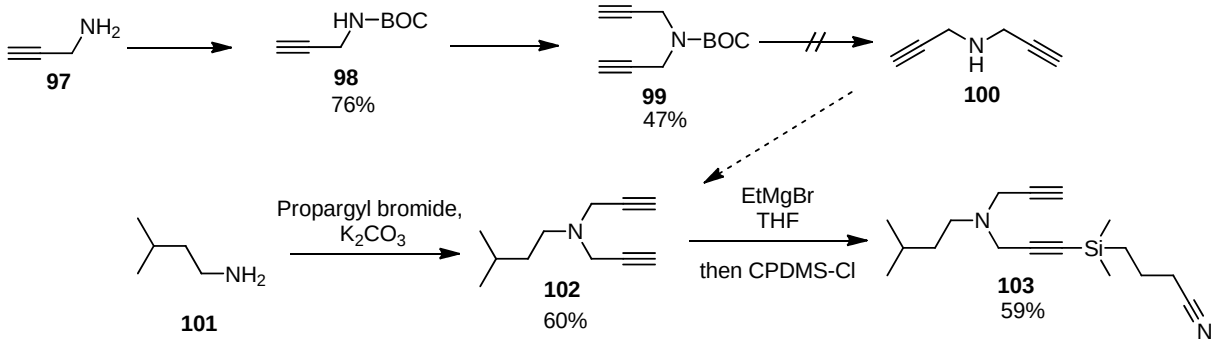
Scheme 35

Our next attempt was to use an amide, with for solubility reasons branched side-chains (Scheme 36). Starting with malonyl chloride (**94**) we synthesized the bisamide **95** in 41% yield. The Propargylation of **95** led to difficulties. The reaction was performed, but after workup and separation only monopropargyl amide **96** was isolated via column chromatography. This molecule was then again reacted with propargyl bromide and potassium carbonate. Still, only monopropargylated product **96** was isolated. Therefore, sodium hydride was used as stronger base, both sodium hydride and propargyl bromide were added twice to amide **96**, but this sequence led to no further reaction, probably due to steric hindrance.



Scheme 36

As both the nitrile and the amide pathway did not afford the desired building block we started to investigate a synthesis for a tertiary bispropargyl amine **102** (Scheme 37). BOC protection of propargyl amine (**97**) worked quite well in 76% yield. The following propargylation afforded the BOC protected amine **99** in 47% yield. The deprotection was unfortunately not successful as we could not isolate the very volatile secondary amine **100**. After an intensive literature research it was found that simple alkylation of a primary amine can offer a direct pathway to bis(propargyl)amines.[41] In the literature only examples with the *n*-alkyl amines were reported, nonetheless, it was possible to alkylated isoamyl amine (**101**) in 60% yield. Subsequent mono-protection afforded the CPDMS-bis(propargyl)-isoamyl amine **103** in 59% yield.

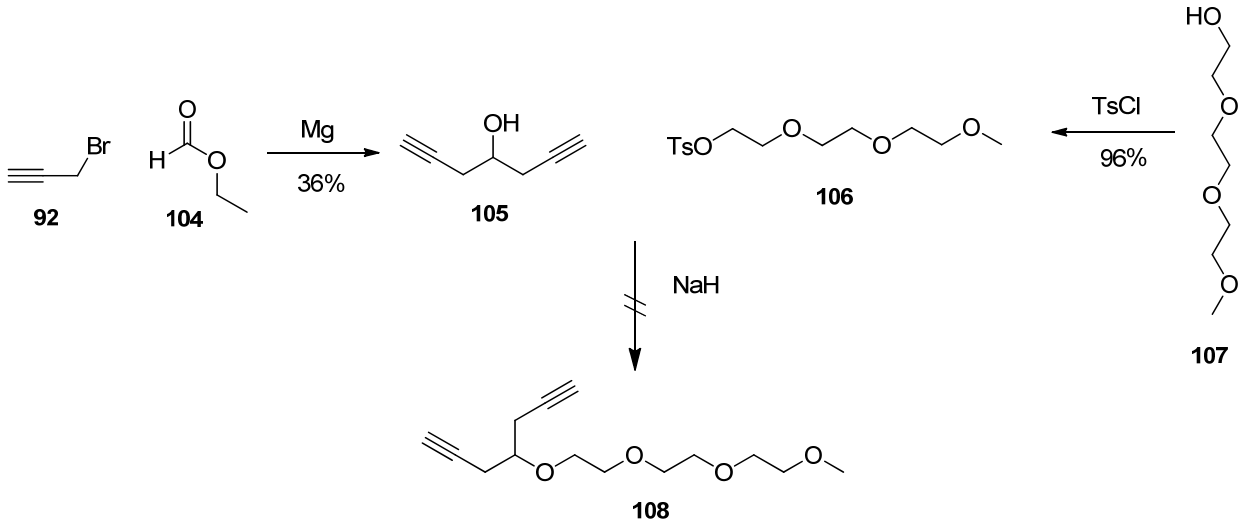


Scheme 37

Besides, the substituted amines, we also became interested in the synthesis of polyether-substituted alkynes.

The synthesis of dipropargylalcohol **105** was not easily achieved in good yields (Scheme 38). The first attempt to synthesize the alcohol **105** failed because after successful formation of

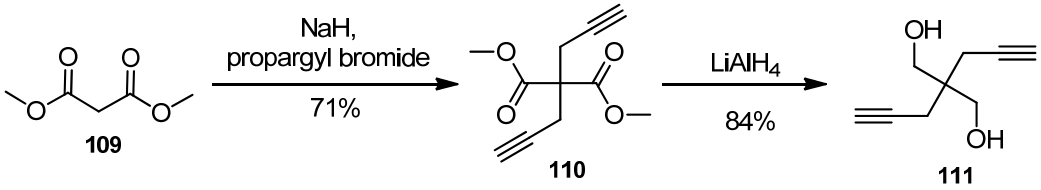
propargylmagnesium bromide the reaction with ethylformate (**104**) led to an unstirrable slurry. Therefore, isolation via column chromatography of the desired alcohol **105** failed. In a second attempt a slightly adjusted procedure was used (different temperature) and a mechanic stirrer helped to mix the sticky solution after addition of the Grignard reagent. This time the dipropargylalcohol **105** could be isolated in 36% yield. As the procedures which were reported in literature afforded yields around 37% and the starting materials were quite cheap this only mediocre yield was acceptable.[42]



Scheme 38

For the same pathway the triethylenemethylglycol tosylate **106** had to be synthesized. This was achieved using commercially available monomethoxytriethyleneglycol **107** and tosyl chloride in 69% yield. The first attempt to attach the triethyleneglycol moiety to the alcohol **105** led to the full consumption of the alcohol but the product was not separated or detected in the mixture even though plenty of compounds were detected on TLC and observed in the NMR-spectrum. Several unknown compound were isolated after column chromatography. The base used, sodium hydride, could also deprotonated the alkyne which might explain the mixture obtained. This reaction was repeated, but did not afford the desired polyether **108**.

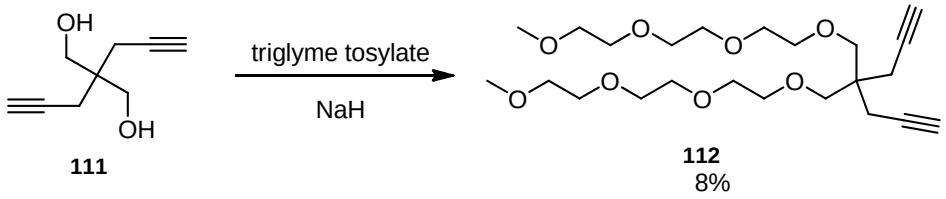
Therefore, we shifted our efforts to the synthesis of the bis(homopropargyl) alcohol **111**:



Scheme 39

The synthesis of the dipropargyl methylmalonate **110** was achieved in 71% yield following already developed procedures from Joel Riverendo. The reduction of this diester with $LiAlH_4$ was performed to isolate the bis(homopropargyl) alcohol **111** in 84% yield.

The attachment of the triglyme moieties with triglyme tosylate led to problems (Scheme 40). The reaction seemed to proceed very slowly as even after two days at reflux still both starting materials were detected in the reaction mixture (TLC control). Consequently, after the workup a mixture of triglyme tosylate (**106**), dialcohol **111**, mono-triglyme-alcohol **113** and the desired bis(triglyme) ether **112** was isolated. Recrystallization was unsuccessful and column chromatography led to a large mixed fraction of compounds **112** and **113** besides, two minor separated fractions of each compound. (Yield of isolated crude **112** is 8 %) The triglyme-group made both compounds very polar and led to major smearing of the compounds on the silica gel. (TLC and column chromatography).

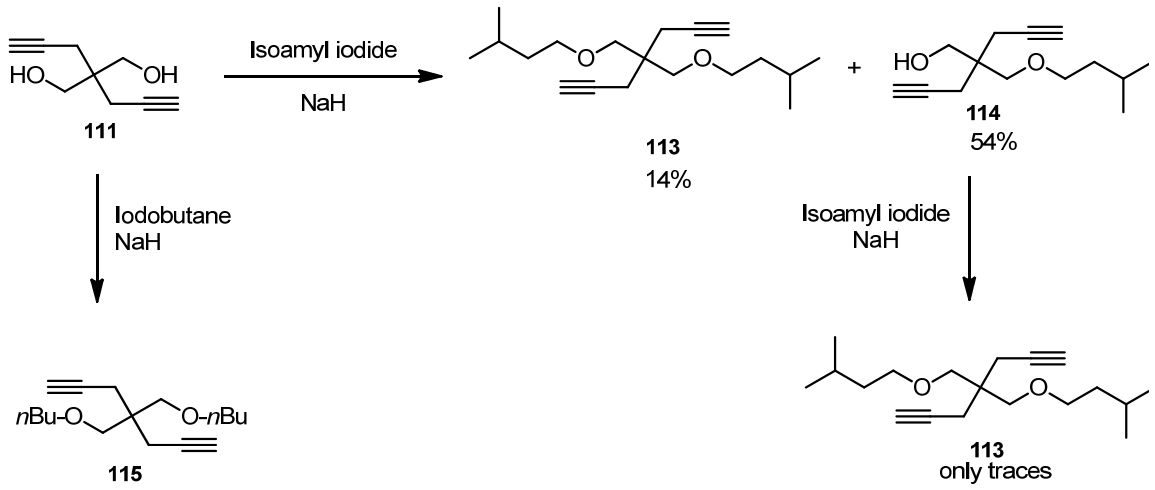


Scheme 40

As a result it seemed, as the etherification with the triglyme tosylate has two major drawbacks. Full conversion was hard to achieve and product mixtures and the compounds tended to get very polar and highly affine to silica gel. Altogether, it seems more convenient to use alkyl ethers instead of triglyme ethers, as e.g. the isoamyl moiety should also increase the solubility with a smaller tendency to make the compounds too polar.

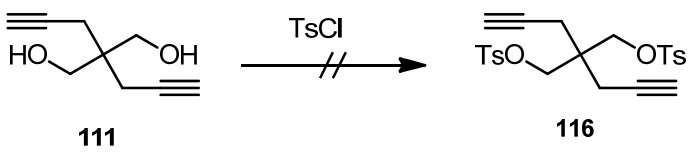
With the free bisalcohol **111** available we wanted to synthesize the bisbutylether **115** (Scheme 41). Unfortunately, only low yields of the desired product **115** were isolated even though the reagents were used in large excess. The major product of the reaction was the monoalkylated side-product.

The alkylation was also performed with isoamyl iodide. The results were very similar to the butylation reaction. Only 14% of bisalkylated compound **113** were isolated, whereas 54% monoalkylated ether **114** were obtained. When we used the monoalkylated ether and performed a second alkylation, only trace amounts of the bisalkylated compound were detected. The main fraction remained the monoalkylated starting material **114**.



Scheme 41

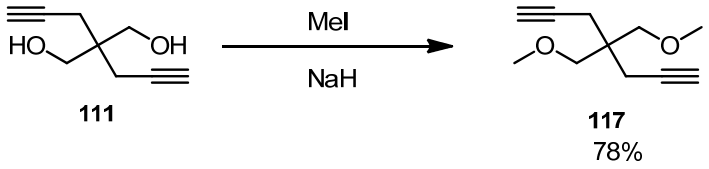
As the alkylation strategy was not satisfactory we wanted to switch to an S_N2 reaction to establish the ether. Consequently, we wanted to tosylate the two alcohol functions to transform them into good leaving groups (Scheme 42). The reaction of the bisalcohol **111** with tosyl chloride did not afford any tosylated compound **116**, even after prolonged reaction times.



Scheme 42

This entire setback could in principal be traced back to a steric hindrance of the two alcoholic groups. Especially, when the first alcohol is substituted the second OH-group seemed to be much hindered, as all reactions to the bisalkylated compound failed. The alcohol groups are in principal primary alcohols which is in contrast to the observed steric hindrance. On the other hand, if you consider the entire molecule the alcohol groups are actually in a neopentyl-like surrounding. The neopently group is known for its steric demand which is in accordance to our experimental results.

Finally, we were able to methylate both alcohol functions in 78% yield (Scheme 43). This result shows, that the methyl groups are just small enough to perform a successful double-alkylation.



Scheme 43

Overall this molecule should increase the solubility significantly compared to the unsubstituted alkyne.

In summary, we could synthesize two new functionalized alkynes (**102**, **117**) which both should increase the solubility of the macrocycle and enable the detection via ESI-MS.

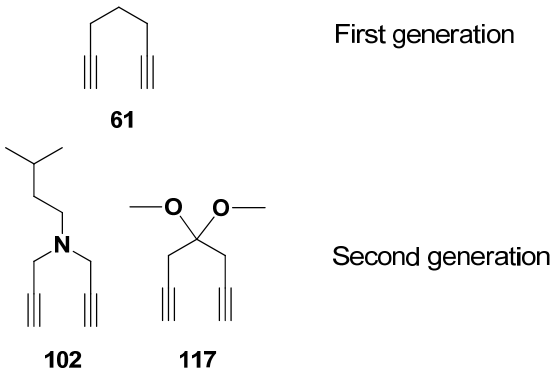
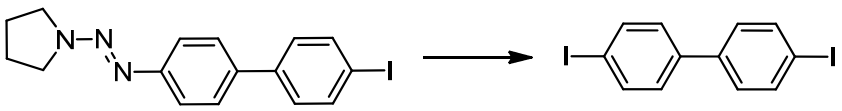


Figure 13

1.2.4.2 Second Generation Synthesis – Synthesis of the Aryl Building Block

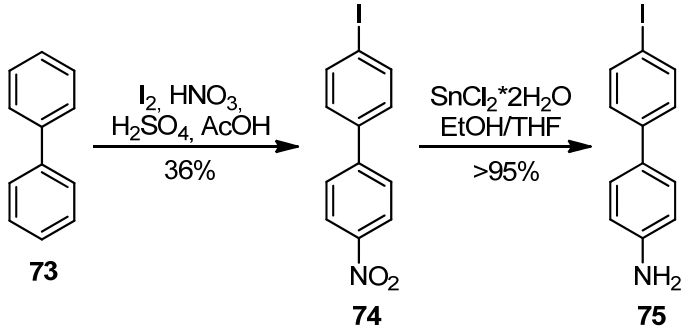
As mentioned above we wanted to synthesize a building block which should overcome the selectivity challenges of the Sonogashira reaction. Therefore, we decided to use a masking group for one of the two iodide functionalities. A common masking group for the iodides are triazenes, which can be easily interconverted to the iodides:



118 **62**

Scheme 44

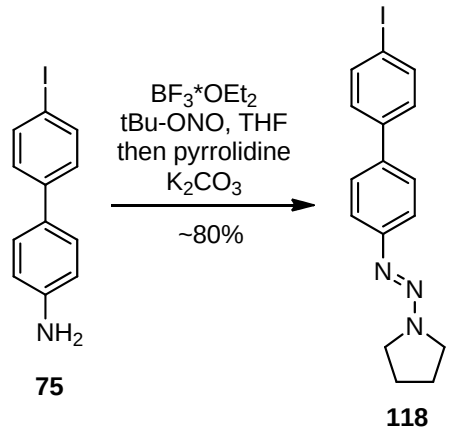
The first two steps the iodonitration of biphenyl (**73)** to molecule **74** and the following reduction to the 4-iodo-4'-aminobiphenyl (**75**) were already performed for the first generation synthesis. The sequence was started with the iodonitration to yield the desired molecule **74** in 37% yield. The reduction with Zn/HCl in EtOH led to a very challenging workup and to isolation of amino-iodobiphenyl **75** in 21 % yield. As this yield was too low for the whole sequence which would follow, the reaction was performed with another protocol. This time $SnCl_2$ was used in a 1:1 EtOH/THF mixture. This yielded the amino compound in 93% yield on 1.3 g scale. In a second reaction on large scale (5.2 g) still 81% yield were achieved. This slightly reduced yield is probably due to problems with the workup on larger scale, as the formed tin oxide is difficult to remove. Nonetheless, this is a significant improvement to the literature procedure where only 36% of the amine are formed.[37] During our repeated synthesis of this starting material for the synthesis we were able to improve the yields and usually the amine **75** was afforded in yields above 95%.



Scheme 45

As, a two-step synthesis for larger quantities of 4-iodo-4'aminobiphenyl was developed we began to investigate the triazole formation. The first three attempts to form, first the diazonium salt and then the triazene **118** in aqueous solutions led to yields between 4% and 20%. Usually, a mixture of the triazene with the amine was obtained. When the amount of water was increased in the formation of the diazonium salt a ratio of 2:1 between the product and the starting material was obtained. Altogether, it seemed that the low solubility in water was leading to only partial conversion.

Therefore, tBu-ONO and BF_3*OEt_2 in THF were used in a non aqueous approach to form the diazonium salt. The formed diazonium tetrafluoroborate was precipitated out of the solution, washed with ether and directly dissolve in MeCN to react with pyrrolidine. This time the product **118** was isolated after workup in 71% yield. On repetition the yield could be improved to 80%.



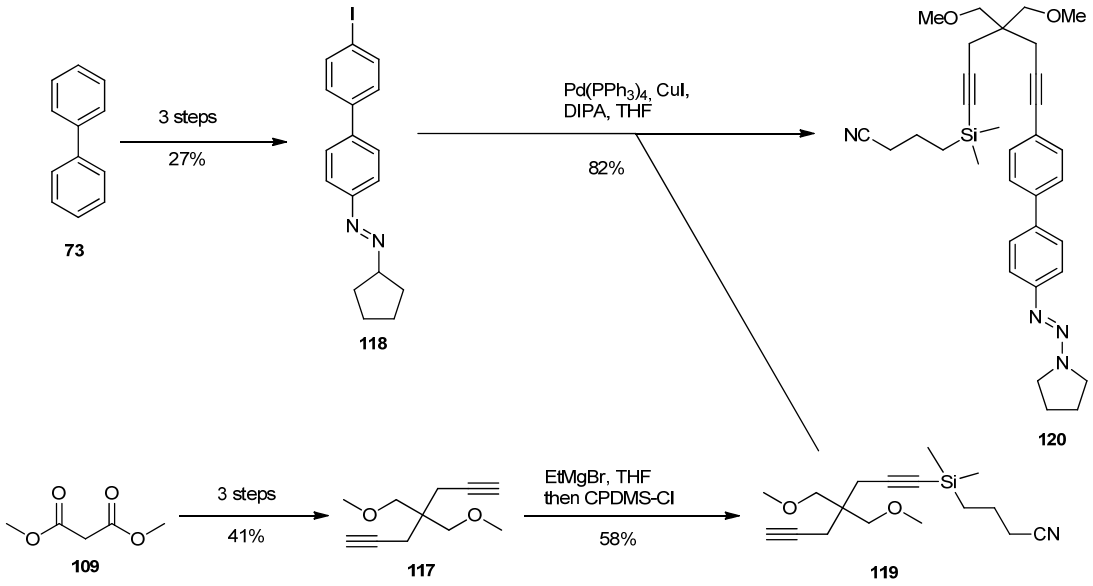
Scheme 46

After we finished the development of the synthesis of this building block **118**, we had a three step procedure in hand to synthesize multiple grams in overall yields of 27%. This number is mainly limited by the first step, the iodonitration of biphenyl. As all the reactants (biphenyl) and reagents (sulfuric acid, nitric acid iodine) are very cheap, this step could be performed at 30 g scale and no further optimization was performed.

1.2.4.3 Second Generation Synthesis ─ Synthesis of the Macrocycle

The first reaction was the mono-protection of the alkyne **117** with EtMgBr and CPDSM-Cl, which afforded the CPDMS-alkyne **119** in 58% yield. As usual, also the double-protection, as side-reaction took place.

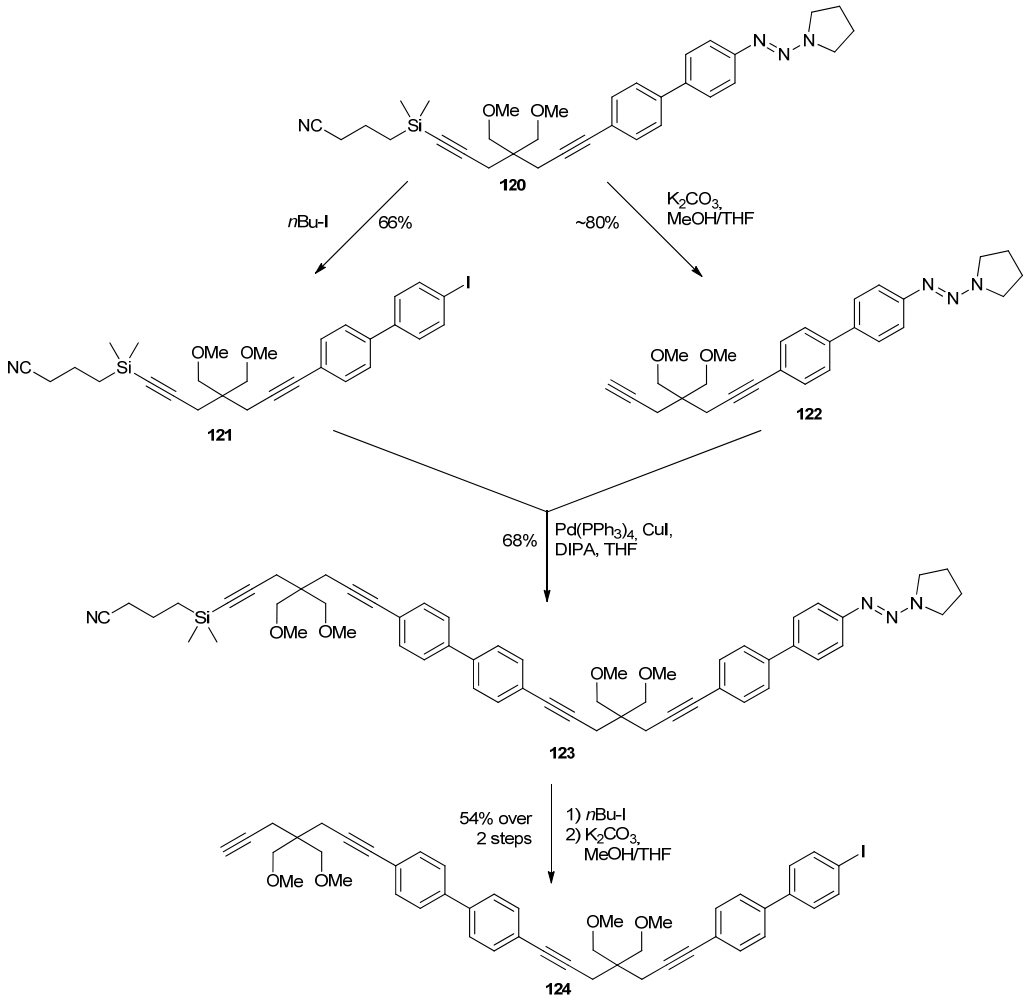
With the aryl and alkyne building block in hand, the first Sonogashira reaction was performed and the compound **120** could be isolated in 82% yield after 1 day (Scheme 47).



Scheme 47

The silyl-deprotection reaction with potassium carbonate gave the free alkyne **122** in 80% yield (Scheme 48). Moreover, also the triazene conversion to the iodide was performed for the

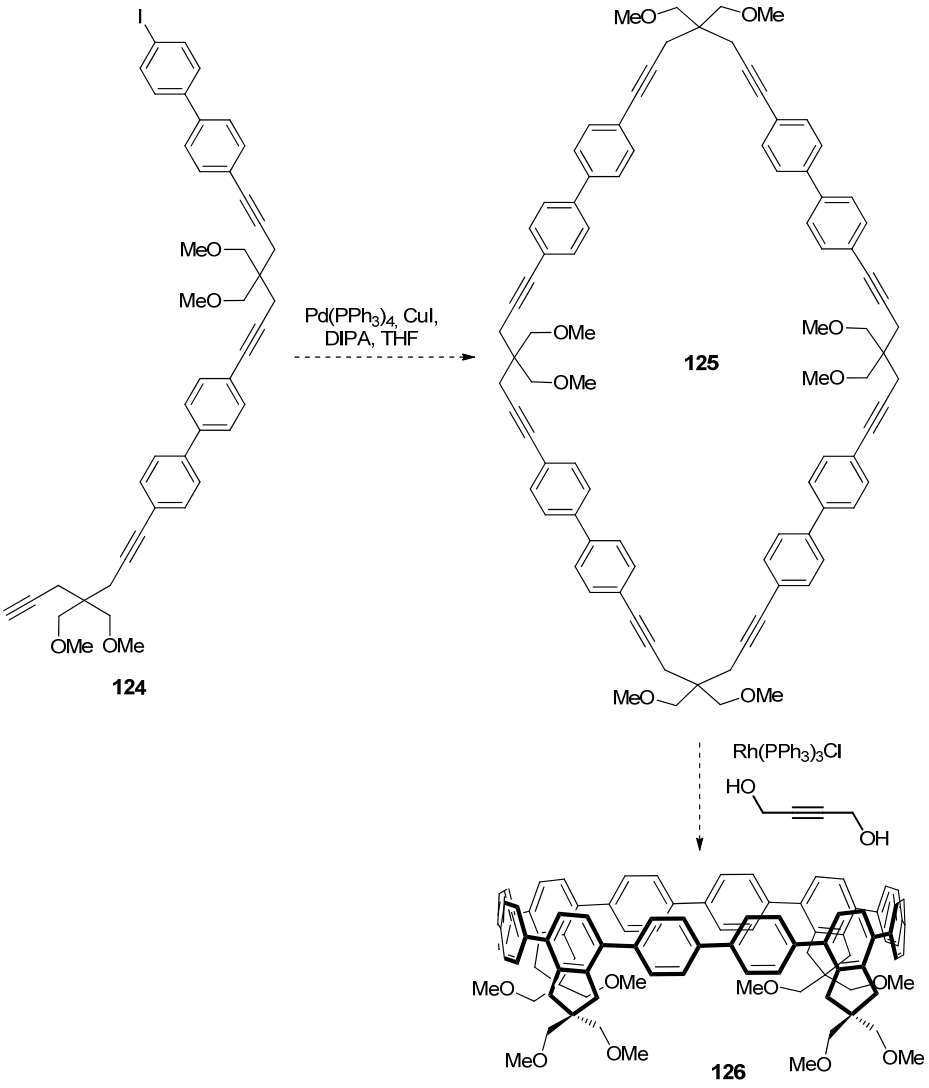
first time. Out of the three mayor protocols: high-pressure heating in methyl iodide[43], heating in diiodomethane with elemental iodine[44] and refluxing in 1-iodobutane[45], the latter was used because elemental iodine could react with the triple bonds and the methyl iodide protocol demands high pressure. The reaction with 1-iodobutane yielded the aryl iodide **121** in 66% yield. The next Sonogashira reaction was complete, after 3 days at 45°C and afforded the desired CPDMS-triazene **123** in 68% yield. In this case elevated temperatures were required as the reaction at room temperature was still incomplete after 3 days. The next two steps, again a triazene iodide exchange and silyl deprotection, proceeded smoothly in 72% and 75% yield respectively to form the macrocycle precursor **124**.



Scheme 48

The macrocyclization/Sonogashira coupling reaction led to several fractions after three days reaction time (Scheme 49). Some starting material **124** was re-isolated but even after one

column and two preparative TLCs no fraction could be found which could clearly be assigned to the desired cycle **125**. Several fractions showed symmetrical NMR-signals, which were expected from the macrocycle, but the mass analysis could not confirm the formation of the ring. Nonetheless, those fractions were used in the last step, a [2+2+2]-cycloaddition with 1,4-butynediol. Unfortunately, no Mass corresponding to the cycloparaphenylene could be found via ESI or MALDI-MS after workup. The reaction was performed three times with different conditions (reaction times). Overall no macrocycle could be isolated even by use of recycling GPC.



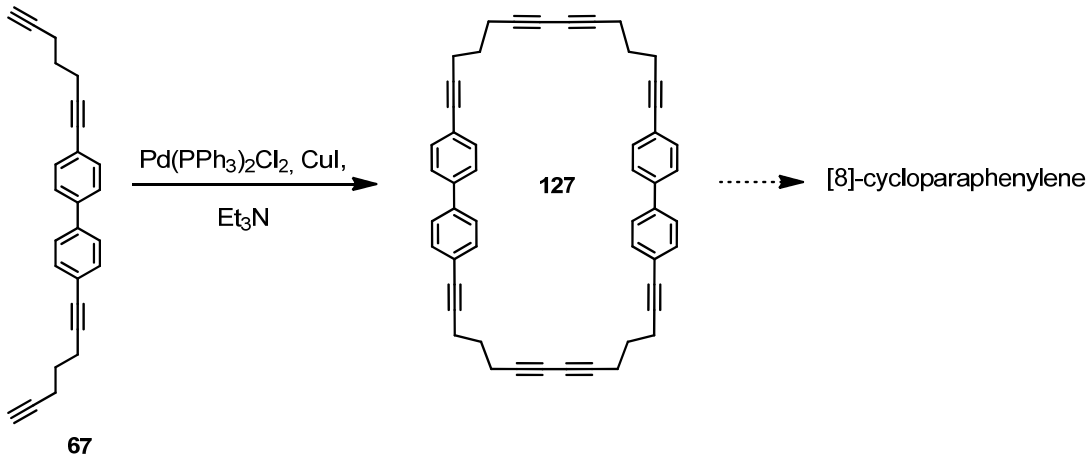
Scheme 49

At this time of the project the results from the investigations of the [2+2+2]-cycloaddition (Chapter 1.2.6) were discovered by Anne-Florence Stoessel, therefore further experiments were postponed until the optimization of the [2+2+2]-cycloaddition would have been completed.

1.2.5 Homocoupling and Half-Belt Approaches

1.2.5.1 Smaller Cycloparaphenylenes via a Glaser-Hay type Homocoupling

From the readily available terminal bisalkyne **67** which was obtained during the first generation synthesis one could form a dimeric molecule **127** via a Glaser-Hay type coupling. This dimer **127** would be itself a precursor of [8]-cycloparaphenylene (Scheme 50). Two attempts were performed, whereas the reaction with copper chloride and tetramethylethylenediamine (TMEDA) and oxygen atmosphere led only to reisolation of the starting material (88%). The reaction with Bis(triphenylphosphine)palladium(II) dichloride, copper iodide and triethylamine led to the formation of a precipitate of the desired product **127**.



Scheme 50

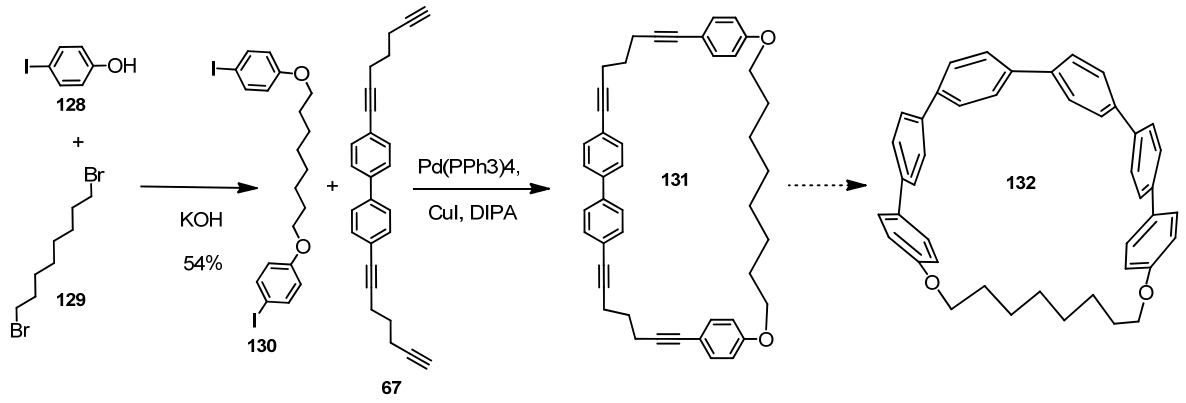
Unfortunately, the solid was very insoluble but still the ^{1}H-NMR looked quite promising as the terminal alkyne signals vanished and a symmetrical product was obtained. Moreover, the HMBC-spectra showed the expected signals as well. Furthermore, the MALDI spectra

showed the peak of the product at 665 m/z. Regrettably all attempts to purify the insoluble compound via crystallization or soxhlet extraction were unsuccessful.

In conclusion, we found that the non-functionalized building blocks are themselves already insoluble the products of their reactions, are usually completely insoluble and cannot be purified.

1.2.5.2 Synthetic Approach to a Tethered Half-Ring[46]

During our synthesis of the unfunctionalized cycloparaphenylene the idea was born to synthesize a tethered half ring (Scheme 51), which should also have a distorted aromatic system. In this approach an early investigation of the [2+2+2]-cycloaddition on strained systems could be performed. In this case only two aromatic systems would be formed during the [2+2+2]-cycloaddition, which should lead to higher reaction yields compared to the strategy leading to the full macrocycle. Moreover, the tether would give the molecule a minor flexibility. The synthesis was started and the diiodocompound **130** could be obtained in 54% yield. This molecule was coupled with dialkyne **67** in a Sonogashira reaction with slow addition of alkyne via a syringe pump. This reaction led to no conversion, therefore it was performed again without the use of a syringe pump. This time, the reaction yielded an orange precipitate which was collected. The crude ^{1}H-NMR of this precipitate clearly showed, that the product **131** was formed, but recrystallization from toluene led to the spontaneous formation of an insoluble compound on the surface of the solvent (probably polymerization or decomposition). The newly formed substance could be collected by filtration, but we were unable to dissolve it in any solvent.

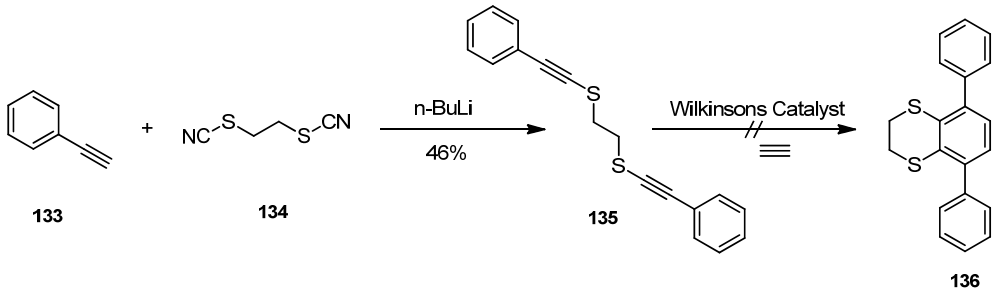


Scheme 51

Due to time constraints this half-belt approach was continued by Anne-Florence Stoessel:[46] Based on dimethoxy bisalkyne **117** and the bis(propargyl)-isoamyl amine **102** as alkyne building blocks she successfully developed a synthesis of tethered macrocycles to investigate the synthesis of half-belts.

1.2.6 Investigation of the [2+2+2]-Cycloaddition[46]

During our macrocycle synthesis we already started to investigate the key step of our sequence, the [2+2+2]-cycloaddition. As mentioned above we made several attempts to synthesis the cycloparaphenylenes out of the crude macrocycle mixture without any clear results, as usually mixtures of several insoluble compounds were isolated. To gain clear insights into the [2+2+2]-cycloaddition we wanted to synthesize test substrates, which then could be extensively studied.



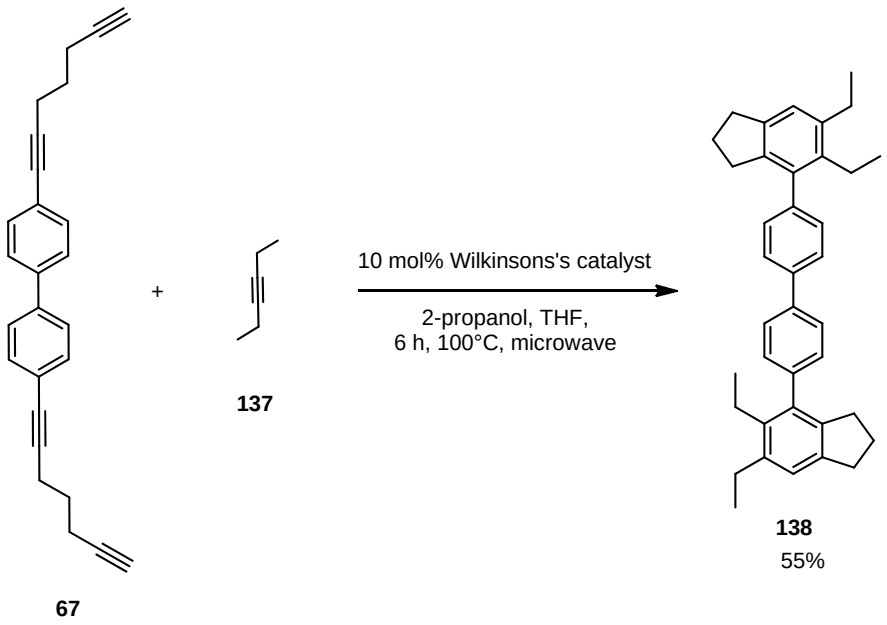
Scheme 52

One example is shown in Scheme 52. We were interested whether or not sulfur containing building blocks are interfering with the [2+2+2]-cycloaddition. Especially, if sulfur is poisoning the Wilkinson catalyst, used for the [2+2+2]-cycloaddition. Therefore, phenylacetylene (**133**) was coupled with two equivalents ethylene dithiocyanate (**134**) to yield molecule **135** in 46% yield. With the desired intermediate in hands, the [2+2+2]-cycloaddition was performed. Unfortunately, no product **136** was obtained after workup.

After this preliminary result, Anne-Florence Stoessel started to investigated the [2+2+2]-cycloaddition systematically, as both the synthesis of the macrocycles and the optimization of

the [2+2+2]-cycloaddition on test substrates would have been impossible due to time constraints.

After she optimized the reaction conditions for the linear bisalkynes, they were successfully applied to the free bisalkyne **67** (Scheme 53). We could successfully isolated the product **138** of the [2+2+2]-cycloaddition in 55% yield



Scheme 53

Moreover, Anne-Florence Stoessel discovered the very interesting shift in reactivity from linear to strained systems. Whereas the linear molecules reacted in the expected [2+2+2]-cycloaddition, the strained system reacted indeed via a different pathway. Different solvent systems, concentrations and catalysts are currently under investigations in order to see if the [2+2+2]-cycloaddition product can be obtained on strained systems as well. This is a requirement, as under the current condition our synthesized macrocycles would not react in the desired [2+2+2]-cycloaddition pathway to the cycloparaphenylenes.

1.3 Conclusion

In summary, we developed a synthetic strategy (Scheme 15, Scheme 16) for the synthesis of cycloparaphenylenes with multiple Sonogashira couplings. The key-step of our strategy is the transition metal catalyzed [2+2+2]-cycloaddition to form the final aromatic building blocks.

In the first generation synthesis an unfunctionalized alkyne (**61**) and 4,4'-iodobiphenyl (**62**) were used as starting materials. As during this approach several challenges concerning the deprotection were discovered, we also investigated the CPDIPS and DMH protecting groups. We found that the CPDMS group remains the overall best choice for our synthesis. Moreover, we were able to achieve good to very good yields through all steps of the synthesis. The macrocyclization step seemed to work, but unfortunately, the solubility of the obtained mixture was too low for purification. During optimization of this step we could show that copper cocatalysis is needed for our Sonogashira reactions. As, all attempts to purify the macrocycle or to cyclize the crude macrocycle via a [2+2+2]-cycloaddition were not successful, we developed a second generation synthesis

In the second generation synthesis we synthesized property-tailored alkyne building blocks (**102**, **117**) according to our previous experience. Moreover, we faced the selectivity issues of the previous synthesis by masking one aryl iodide functionality with a triazene (**118**). Furthermore, we approached the synthesis of the cycloparaphenylene in a more convergent way. Our thirteen step synthesis led us again to problems during the macrocyclization reaction as no product could be isolated from a complex mixture. When the mixture of compounds was submitted to the [2+2+2]-cycloaddition no cycloparaphenylene was found or could be isolated.

Moreover, the optimized conditions for the [2+2+2]-cycloaddition, developed by Anne-Florence Stoessel were successfully applied to the synthesis of a linear oligophenylene (**138**). This experiment demonstrates that our approach will remain a promising pathway to cycloparaphenylenes.

Until now we were not able to find appropriate conditions which favor the [2+2+2]-cycloaddition for our strained system. As a consequence, the synthesis of further macrocycles had to be postponed until a suitable method for the final cyclization step is developed.

In conclusion, we synthesized several key compounds towards the synthesis of substituted cycloparaphenylenes. During the synthesis we encountered several challenges especially during the macrocyclization attempts. Moreover, it was found that strained bisalkynes react via a different reaction pathway than the [2+2+2]-cycloaddition.

These two challenges remain the focus of the future work and have to be overcome to finally complete the synthesis successfully.

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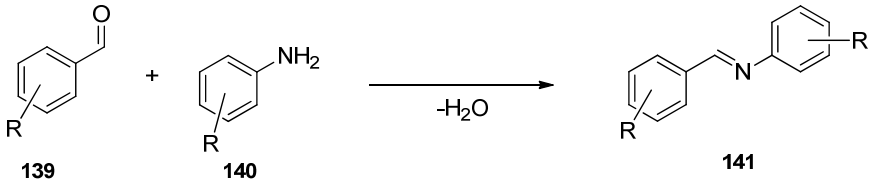
Chapter 2

Mechanistic Investigation of the Photocyclization of Schiff' Bases.

2.1 Introduction

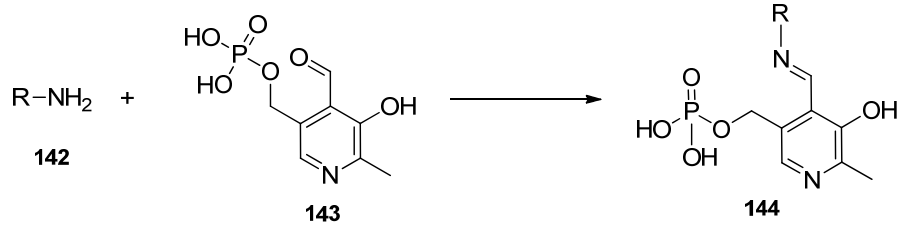
2.1.1 Schiff' Bases

Since their first discovery and preparation in 1864 Schiff' Bases (SB, **141**) have become extensively used and studied in organic chemistry.[1] Hugo Schiff, their discoverer, already used the condensation reaction of aldehydes (**139**) and anilines (**140**) for their preparation, which remains also up to now still one of the most applied procedures (Scheme 54).[2]



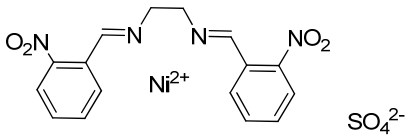
Scheme 54

Schiff' Bases occur in almost every area of chemistry, e.g. classical biomolecules, like Rhodopsin where the lysine residue of Scotopsin is linked to retinal via an imine function.[3] Furthermore, in the human body a Schiff' Base is formed whenever pyridoxal-phosphate (PLP, **143**), a transamination coenzyme, reacts with an amine (Scheme 55).



Scheme 55

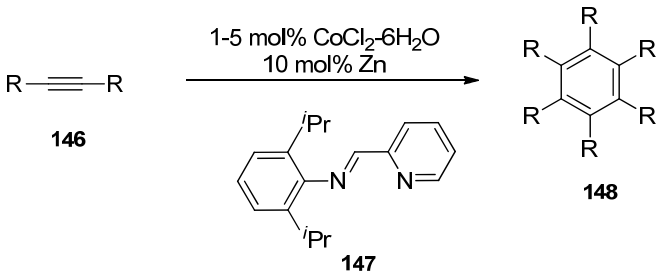
Moreover, there are several different imine dyes, of which many are frequently used in analytical chemistry as redox, acid-base, adsorption, and solvent polarity indicators.[4] They are useful intermediates in the synthesis of heterocycles and non-natural β-amino acids. Besides, there are plenty of different imine-function containing compounds showing liquid crystal properties.[5] Finally, Schiff' Bases are also used as ligands in transition metal complexes. Figure 14 shows a bidentate Schiff'Base ligand which can coordinate to Nickel.[6]



145

Figure 14

Another Schiff' Base ligand (**147**) can be used as ligand for cobalt(0) in [2+2+2]-cycloadditions. In this system cheap and easy to handle cobalt chloride hexahydrate can be utilized as precatalyst and be reduced by zinc to form the complex with the imine (Scheme 56).[7]



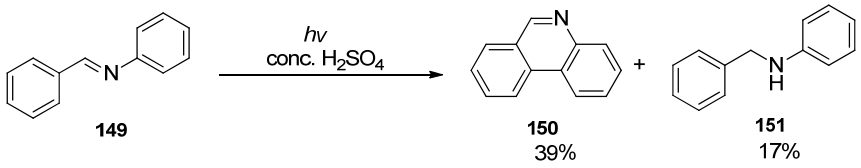
Scheme 56

2.1.2 The Photocyclization of Schiff' Bases

As described above, theses synthetically versatile imines can be used for various reactions. The oxidative photocyclization of *N*-benzylideneaniline (**149**) to phenanthridine (**150**), described by G.E. Lewis *et al.* in 1964 is especially interesting.[8] The importance of such atom economic bond forming processes recently gained in importance in view of shortage of resources as it formally resembles a coupling of two unfunctionalized carbon atoms.

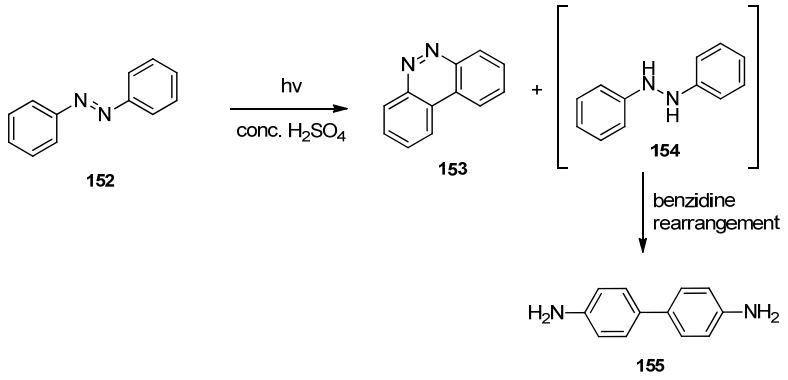
The original procedure involves irradiation of Schiff' Bases in concentrated sulfuric acid to form the phenanthridine in 39% yield. Besides phenanthridine, the isolation of the *N*-benzylphenylamine (**151**) in 17% yield showed that a disproportionation of the imine takes place. Due to this side-product formation the theoretical yield is limited to 50% of phenanthridine limiting this method in its application. The photocyclization of Schiff' Bases is very tolerant towards various substituents and offers an atom economic pathway to phenanthridine and benzo[*c*]phenanthridine alkaloids which show various biological

activities.[9] Therefore, we decided to investigate this powerful reaction to optimize the yields by avoiding side-product formation.



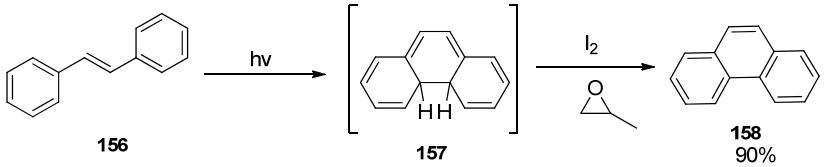
Scheme 57

Similar results were obtained when azobenzene (**152**) was irradiated under similar conditions to afford benzo[*c*]quinoline (**153**) in 42% yield.[10] In parallel, to the Schiff' Base cyclizaton, a reduced side-product, diphenylhydrazine (**154**), is formed and isolated as its benzidine rearrangement product **155**.



Scheme 58

Another prominent example of these oxidative photocyclization is the stilbene-phenanthrene system.



Scheme 59

Here, a major improvement was found by T. J. Katz *et al.* when they increased the yields significantly by using iodine (stoichiometric oxidant) and propylene oxide (quenching the formed hydroiodic acid).[11]

2.1.3 Short Overview of the Phenanthridine and Benzo[*c*]phenanthridine Alkaloids

Phenanthridine and benzo[*c*]phenanthridine alkaloids are common ingredients of medical plants which were used over centuries in different parts of the world. For example, alkaloids from the family *Amaryllidaceae* usually have a phenanthrene-like framework. One of the alkaloids isolated from these plants, Trisphaeridine (**159**) is a representative with such a framework (Figure 15)

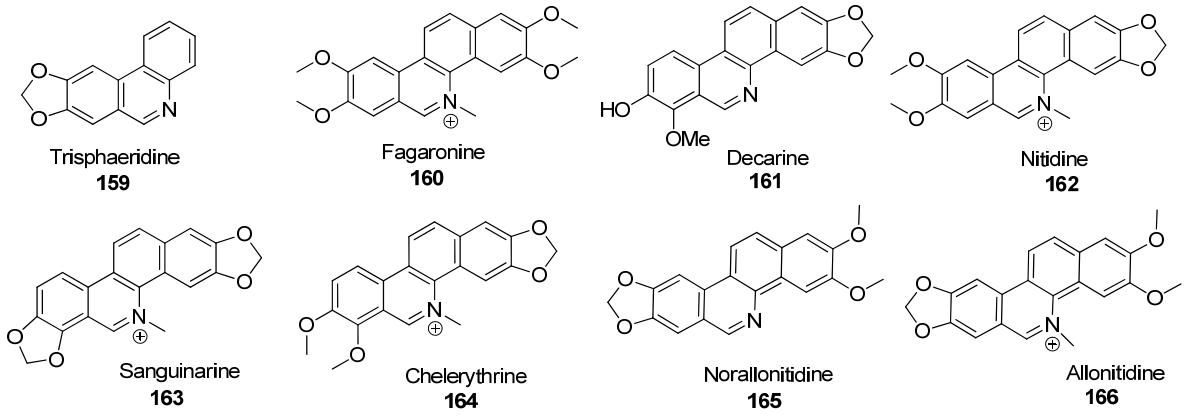


Figure 15

Medicinal plants like bloodroot (*Sanguinaria Canadensis*), greater celadine (*Chelidonium majus*), macleaya cordata have been used in traditional medicine in North America, Europe and China for a long time. Nowadays, the active ingredients of these plants, the benzo[*c*]phenanthridine alkaloids Sanguinarine (**163**) and Chelerythrine (**164**) have been isolated and show anti-inflammatory, adrenolytic, sympatholytic, cytostatic and local aneasthetic properties.[9] Chelidonine, Sanguinarine and Chelerythrine were reported as possible agents in treatment of uveal melanomas (eye cancer). However, further studies are required to unravel the exact mechanism of the effect and the effectiveness of these alkaloids.[13]

Moreover, they show cytotoxic properties. Especially Sanguinarine has very low minimum inhibitory concentrations (MIC) for cell cultures of S. aureus and E. coli bacteria as reported by Stermitz et al.[14] Additionally, Stermitz and co-workers discuss the general trend that benzo[*c*]phenanthridine alkaloids with alkoxy substituents on the A ring, where the substituents have the highest influence on the activity (Figure 16), show better cytostatic abilities than such with the methylenedioxy substitution pattern.

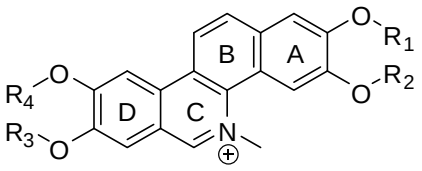
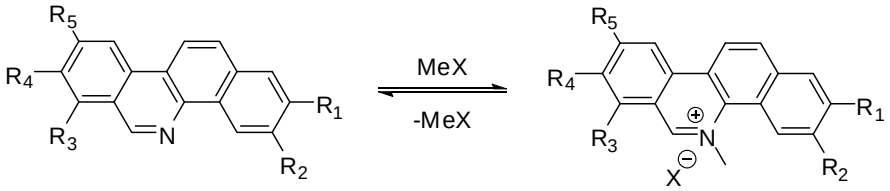


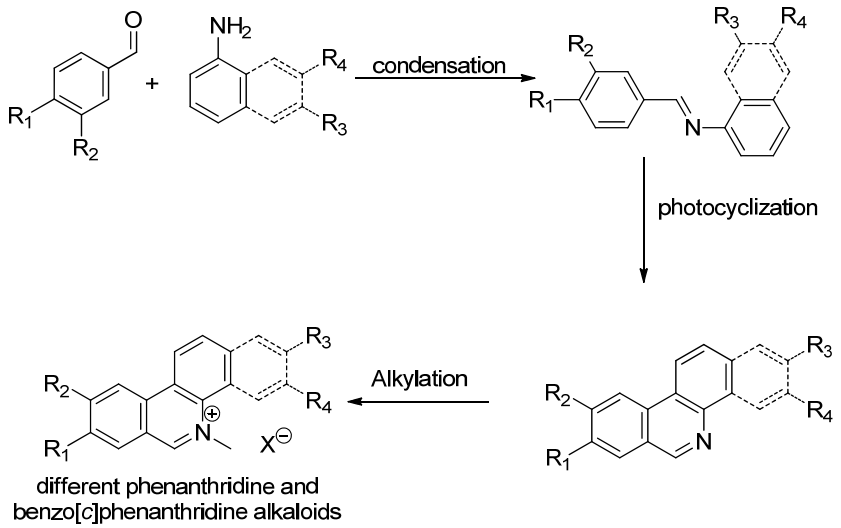
Figure 16

Fagaronine (**160**), which is isolated from the *Rutaceae* (*Fagara zanthoxyloides*), a member of the Rue or Citrus family, shows the highest T/C values (in vivo experiments against L1210 and p388 mouse leukemias) out of the benzo[*c*]phenanthridine alkaloids. Furthermore, another study suggests that *Fagara zanthoxyloides* root extracts have antimalaria activity, supposably because of Fagaronine.[15] Almost all benzo[*c*]phenanthridine alkaloids like Fagaronine, Sanguinarine and Chelerythrine interconvert between a neutral form to penetrate into cells and the pharmaceutical active cationic form as depicted in Scheme 60.



Scheme 60

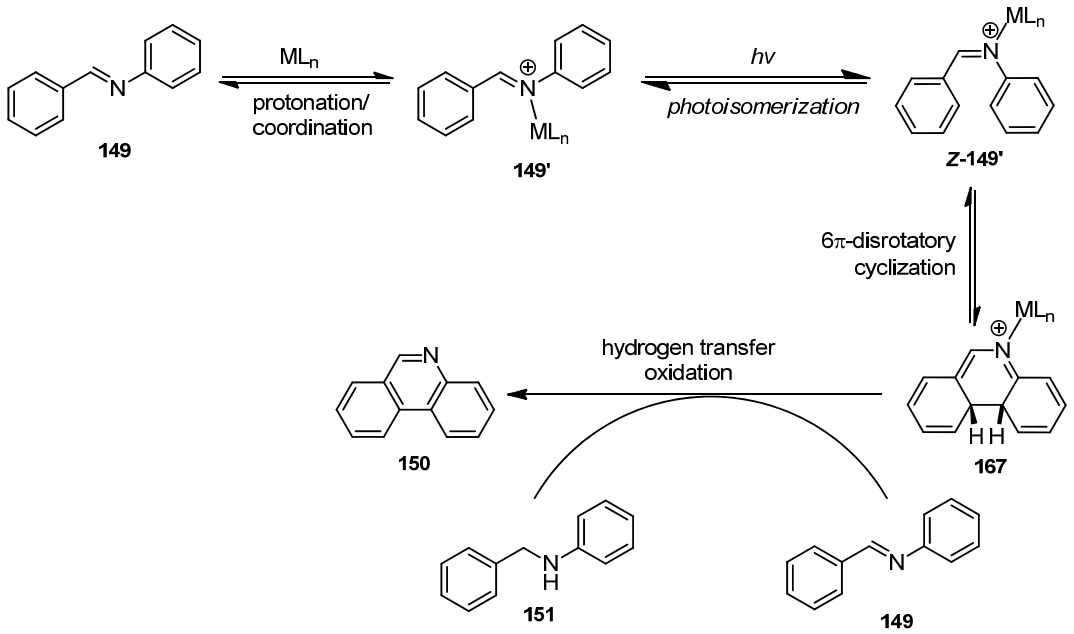
Benzo[*c*]phenanthridine alkaloids have been synthesized by several methods, like palladium-catalyzed couplings[16] and further cyclization, radical cyclization,[17] benzyne-mediated condensations[18], [19] and some other strategies.[20] These methods usually require functional groups e.g. halogens, for the cyclization steps. The phenanthridine and benzo[*c*]phenanthridine alkaloids ere of special interest to us, as the photocyclization of Schiff' Base could offer, after optimization, a short and direct path to their synthesis (Scheme 61).



Scheme 61

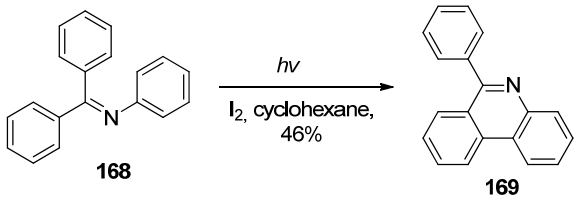
2.1.4 The Mechanism of the Photocyclization of Schiff' Bases

The mechanistic proposals for the oxidative photocyclization available in literature[21] describes the reaction as follows: Starting with protonation or coordination by a Lewis acid the Schiff' Base (**149**) is transferred to its *Z*-isomer by a following photochemical *E*-*Z*-isomerization (Scheme 62). The next step is described as a 6π electrocyclic reaction to the dihydrophenanthridine intermediate (**167**). Finally, oxidation with transfer of two hydrogen atoms to another molecule of starting material takes place to form the final product phenanthridine (**150**) accompanied by *N*-benzylaniline (**151**) as side-product.



Scheme 62

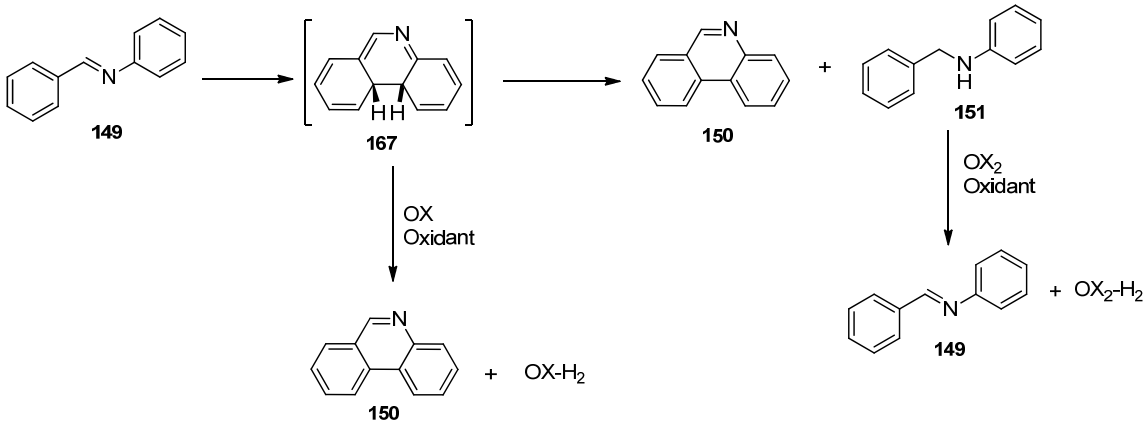
Moreover, it has been shown that the thermal *Z*-*E* isomerization of aromatic imines is extraordinarily fast, as the half life of the *Z*-isomer is about 1s at room temperature.[12] On the other hand, the *Z*-isomer of protonated Schiff' Bases is rather stable at room temperature.[21] This is supported by another experiment from Mallory *et al.*, the photocyclization of *N*-(diphenylmethylene)aniline (**168**) to 2-phenylbenzo[*3,4*]quinoline (**169**) (Scheme 63). As the molecule has a natural *E* and *Z*-configuration the photocyclization works without acid to stabilize the *Z*-isomer in 46% yield on condition that an oxidant is added. Moreover, they do not comment on the formation of reduced side-product.



Scheme 63

Interestingly, it was found by Hugelshofer and co-workers, that besides conc. sulfuric acid, also Lewis acids are possible promoters of the reaction.[22] Finally, E. Selli reported that the photogenerated *Z*-isomer undergoes a slow, thermal cyclization reaction under acidic conditions.[21]

The established mechanism in literature states dihydrophenanthridine (**167**) as intermediate.[12] This offers in principal two different approaches to suppress the side-reaction and to improve the yields of the reaction. On one hand the intermediate could be oxidized to the dihydrophenanthrene (I_2 or O_2). In the original procedure the Schiff' Base itself has an oxidizing role which now is taken over by the oxidant (OX, Scheme 64). On the other hand, another oxidant could (OX_2, Scheme 64) be an additive which itself does not interfere with photocyclization. Therefore, the hydrogen would leave the molecule like in the original reaction, but finally the amine is reoxidized by this oxidant (OX_2) to recycle the starting material. Both approaches could afford yields above 50%.



Scheme 64

2.2 Results and Discussion

2.2.1 Optimization of the Photocyclization of Schiff' Bases

2.2.1.1 Optimization of the Solvent and the Promoter[23]

Based on this mechanism, we started the optimization using *N*-benzylidineaniline (**149**) as test substrate. Due to the possibility to perform the reaction in organic media using a Lewis acid instead of the harsh conditions in concentrated sulfuric acid, we decided to investigate the influence of different organic solvents and Lewis acids. A solvent screening was performed changing parameters like temperature and concentration as well. Out of the tested solvent MeCN was found to be the most suitable.

Moreover, the influence of the concentration was investigated. As usual in photochemistry, low concentrations in our case around 18 mmol/L were found to be optimal.

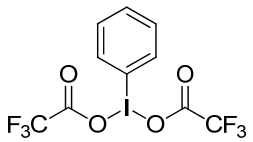
In an extensive Lewis acid screening[24] only a few are suitable for the conversion of the Schiff' Base to the phenanthridine, namely $Zn(ClO_4)_2$ and $BF_3{}^*OEt_2$. Moreover, besides concentrate sulfuric acid it was found that triflic acid also promotes the reaction. In addition to the superior yields, criteria like tolerance towards functional groups and cost were also included in our choice to use boron trifluoroetherate as Lewis acid in our further optimization attempts. A reaction performed without any acid led to the quantitative reisolation of starting material which proves the necessity of adding an acidic promoter. Finally, it is important to mention that the Schiff' Base and the Lewis acid are both sensible towards water. Therefore, the reactions were performed in dry solvents under protective atmosphere of nitrogen.

Under these standard conditions reproducible yields of phenanthridine around 48% were achieved. Moreover, the side-product *N*-benzylaniline (**151**) was formed in around 32%.

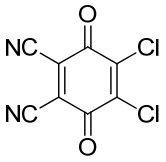
2.2.1.2 The Influence of Oxidants and Anti-Oxidants

From this starting point several additives were added to improve the yields. (Table 3) Besides the exemplary oxidants used (Entries 3-10) several other compounds[25] were examined. No oxidants could be found which increased the yield to over 48%. It is important to remark that several oxidants (Entries 3-6) seem to suppress the formation of the side-product **151**.

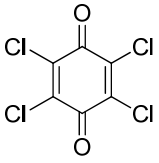
Table 3



PIFA



DDQ



Chloranil

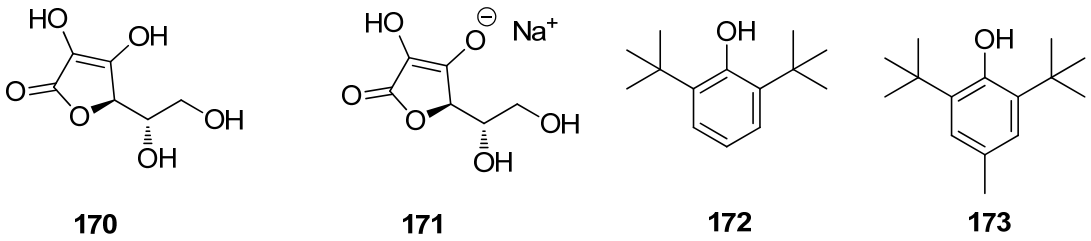
Entry	Additive	Yield **150**	Yield **151**
1	–[a)]	48	32
2	–[b)]	38	24
3	Iodine	9	0
4	Chloranil	9	0
5	MnO_2	8	0
6	DDQ	8	0
7	Oxone®	3	0
8	K_2O	23	3
9	$CuCl_2$	21	4
10	CAN	0	0
11	PIFA	2	0

a) 18 mmol/L solution of **149** in absolute MeCN with 1.1 eq BF_3*OEt_2 stirred over 12 h at 40°C in a Rayonet photochemical reactor under nitrogen atmosphere

b) conditions like above but equipped with a $CaCl_2$ drying tube without protection gas

CAN= cerium ammonium nitrate.

Moreover, it was found, that ascorbic acid (**170**), sodium ascorbate (**171**), butylhydroxy-toluene **172**, 2,6-di-tert-butylphenol (**173**), all commonly used anti-oxidants and radical scavenger, completely shut down the reaction (Figure 17).

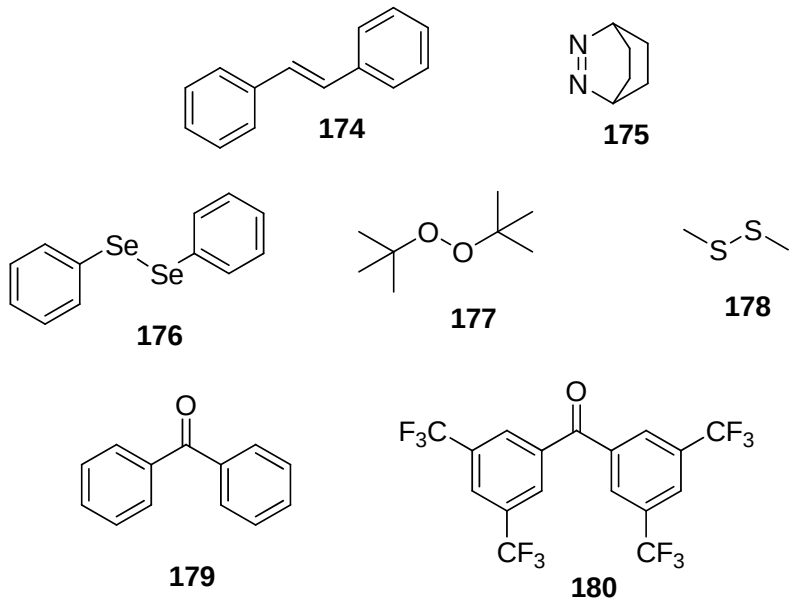


170 **171** **172** **173**

Figure 17

2.2.1.3 The Influence of Hydrogen Absorbers and Photosensitizer

As it is unknown whether the two hydrogen atoms, which are transferred during the reaction, exist as two H-radicals or leave dihydrophenanthridine (**167**) as H^+ and H^- ions, hydrogen-acceptors for all these three species were investigated.



174 **175** **176** **177** **178** **179** **180**

Figure 18

Table 4 shows a selection of hydrogen scavengers screened. Stilbene (**174**) and 2,3-diazabicyclo[2.2.2]oct-2-ene (**175**) are known to be reduced by hydrogen sources, the latter is especially active as the ring strain is significantly reduced during the reduction. Phenyldiselinide (**176**) reacts readily with sources of H^+ and H^-. Di-*tert*-butylperoxide (**177**) is cleaved under UV-irridiation to the peroxide radical which readily abstracts H-radicals to form the alcohols and is therefore a good choice if hydrogen radicals are released during the photocyclization.[26] Methyldisulfite (**178**) is as well sensitive to different sources of hydrogen due to the low bond strength of the S-S bond. When these compounds where used in the photocyclization three of them (**175, 176, 178**) showed no influence on the yields of the

product and the side-product whereas, stilbene and di-*tert*-butylperoxide led even to a decrease in yield. Furthermore, benzophenone (**179**) and the electron-poor tetra(trifluoromethyl)benzophenone **180** where used to investigate their influence on the photocyclization.

Table 4: 18 mmol/L solution of **149** in absolute MeCN with 1.1 eq additive stirred over 12 h at 40°C in a Rayonet photochemical reactor under nitrogen atmosphere

Entry	Additive	Yield **150**
1	**174**	20%
2	**175**	<50%[a)]
3	**176**	35-45% [b)]
4	**177**	6%
5	**178**	39%
6	**179**	12%
7	**180**	18%

a) qualitative HPLC analysis, without internal standard

b) HPLC analysis, not calibrated

Both molecules are known photosensitizers and the trifluoromethyl derivative **180** forms a stabile radical itself which can absorb hydrogen atoms. The yield of the phenanthridine was reduced in both reactions, showing that the sensitizer do not improve the reactions.

In the case of bis(3,5-bis(trifluoromethyl)-benzophenone (**180**) the ratio between product and side-product is even lower (1.1:1) than without additive.

As an intermediate result we found, that all our attempts to optimize the reaction conditions failed to increase the yield above 48%. This result was unexpected as the dihydrophenanthridine intermediate (**167**) described in literature is very similar to the dihydrophenanthrene (**157**) which occurs during the photocyclization of stilbene (Scheme 59). However, in our intensive screening of oxidants not a single one showed the ability to abstract the hydrogen atoms from the intermediate to increase the yield. Moreover, the hydrogen could

not be transferred to our selection of hydrogen acceptors. The best hydrogen acceptor remains the Schiff' Base itself.

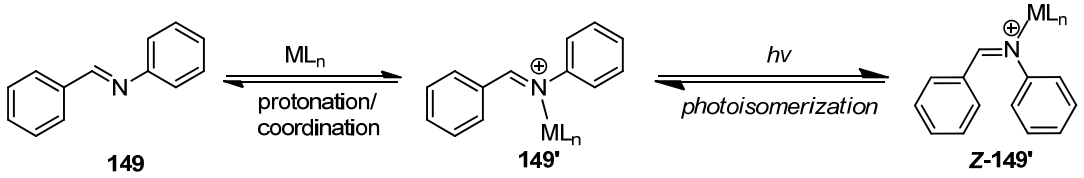
At this point we started to investigate the mechanism systematically (Scheme 62), beginning with the first steps, coordination of the Lewis acid and the *E*-*Z*-isomerization.

2.2.2 Mechanistic Investigations

Whereas, in the reaction of stilbene to phenanthrene, the singlet π,π* excited state is stable at room temperature, the singlet π,π* excited state of *N*-benzylideneaniline (**149**) interconverts quickly to the ^{1}n,π* excited state which is lower in energy. Compared to the yields above 90% for the stilbene cyclization, the reaction of *N*-benzylideneaniline (**149**) to phenanthridine (**150**) occurs at -10°C and only in a yield of about 2% under similar conditions in the same time-frame.[27] Irradiation shifts the photo-equilibrium towards the *Z*-isomer, like in the stilbene reaction. However, thermal back-isomerisation to the *E*-isomer is significantly faster for *N*-benzylideneaniline. This theory is supported by the fact that *N*-benzylideneaniline (**149**) readily cyclizes under influence of Lewis or Brønsted acids, where its nitrogen lonepair is not available. Consequently, the π,π* excited state is now the lowest in energy and phenanthridine (**150**) is formed under irradiation.

To understand the mechanism of the photocyclization in more detail we investigated all the steps of the mechanism separately:

2.2.2.1 The E-Z-Isomerisation



Scheme 65

As stated in the literature, there seems to be a consensus that the *E*-*Z*-isomerization occurs via a photochemical exited state. Under our standard conditions when we used $BF_3{}^*OEt_2$ a rapidly change of color (to yellow) occurred after the addition of the Lewis acid to the Schiff' Base

solution in acetonitrile. Moreover, they UV-spectrum was changed significantly by the addition. (Figure 19)

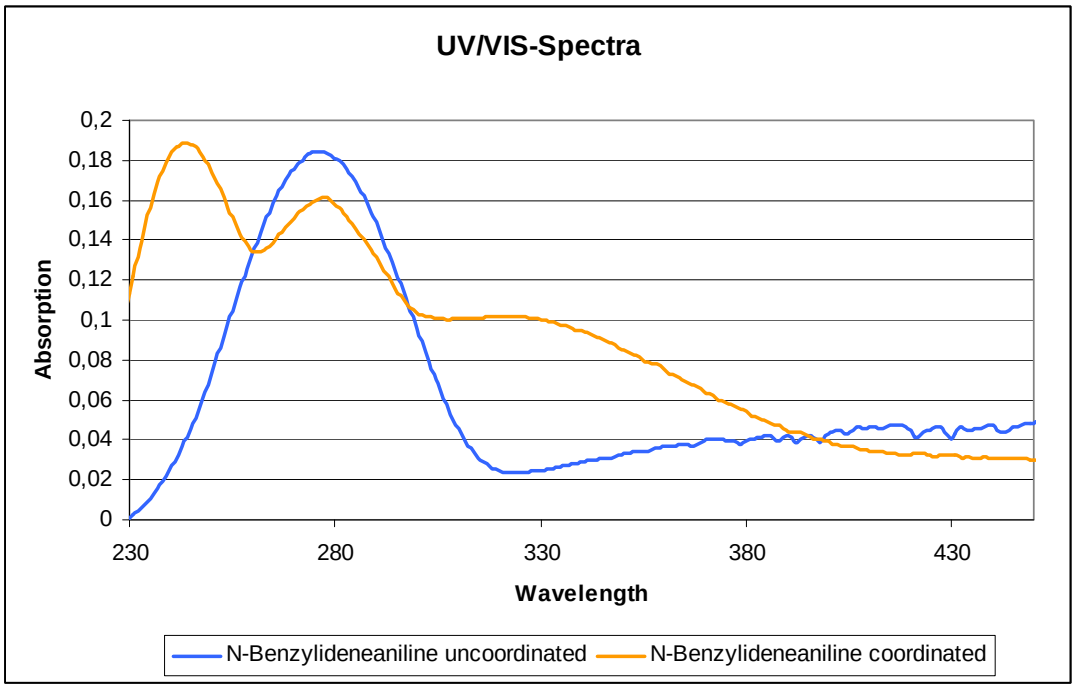
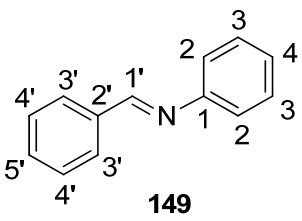


Figure 19

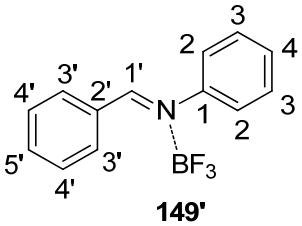
Full NMR assignment of the Schiff' Base-BF_3 complex showed significant changes in the ^{1}H and ^{13}C spectra (Table 5).

Especially the high field shift (7.82 to 7.23 ppm) of the protons in *ortho*-position (3'), which imply structural changes, was unexpected. One possible explanation was that the interconversion between the *E* and *Z*-isomer might occur and we obtain an E/Z-mixture in solution as soon as we add BF_3.

Table 5



149



149'

	Free Schiff' Base **149**		Complexed Schiff' Base **149'**	
	1H (ppm)	13C	1H (ppm)	13C
1	-	152.1	-	140.1
2	7.14	120.8	7.28	123.8
3	7.31	129.1	7.53	130.2
4	7.15	125.8	7.81	120.1
1'	8.37	160.3	8.89	168.1
2'	-	136.2	-	133.4
3'	7.82	128.7	**7.23**	133.7
4'	7.39	128.7	7.41	129.3
5'	7.39	131.3	7.61	135.6

To investigate this theory further we calculated the stabilities of the *E/Z*-isomers of the neutral Schiff' Base, the protonated Schiff' Base and the BF_3-complexed Schiff' Base via B3LYP-DFT calculations[28]. The results (Table 6) in the gas-phase show for the neutral Schiff' Base and the protonated Schiff' Base the *E*-isomer as the more stable isomer. For the BF_3-Schiff' Base complex however, the *Z*-isomer is about 6 kJ/mol more favorable. This prompted us to calculate the stabilities in acetonitrile solution as well, confirming our findings as the Z-isomer is even more stabile in solution.

Table 6: DFT Calculations

	Gas-phase			Solution
	149	H^+-**149**	BF_3-**149**	BF_3-**149**
Stability E over Z	25 kJ/mol	20 kJ/mol	-6 kJ/mol	-10 kJ/mol
Stable Isomer	*E*	*E*	*Z*	*Z*

The minimized structure of the BF_3-SB complex (**149'**) is shown in Figure 20. Since the calculated ΔG = 10 kJ/mol correspond to a equilibrium constant of K=56 one would expect to find 98% *Z*-isomer in solution. This result and our UV and NMR spectra indicate that the *E*-*Z*-isomerization occurs without the influence of irradiation.

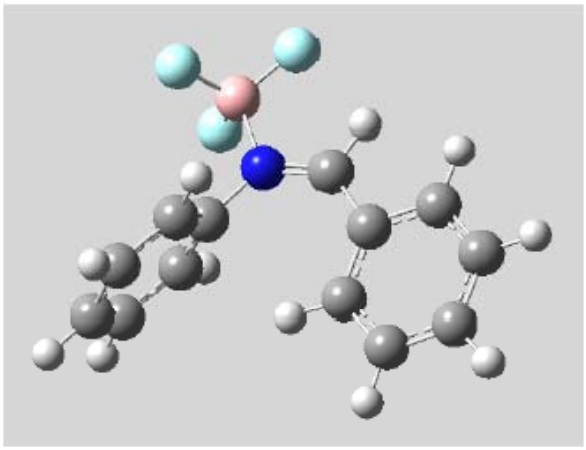
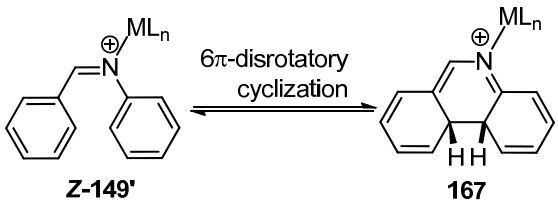


Figure 20

2.2.2.2 The Cyclization Step

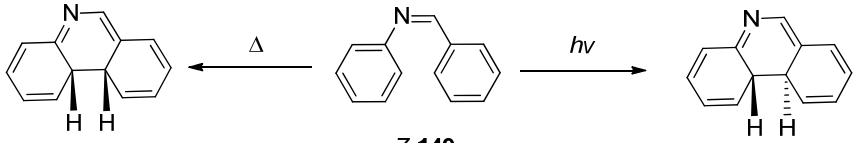


Scheme 66

Our next investigations concerned the cyclization step. As stated above it was assumed that the cyclization itself proceeds without the influence of light as a thermal process, which is

indicated by the experiments, where prior irradiated samples of the Schiff' Base in sulfuric acid, undergo a slow cyclization in the dark.[21] In principal the electrocyclic reaction from *N*-benzylideneaniline (**149**) to dihydrophenanthridine (**167**) could proceed via a photochemical (conrotatory) or thermal (disrotatory) pathway (Table 7). To investigate the possibility of a thermal cyclization several experiments were done at 140°C. First, the reaction was performed in concentrated sulfuric acid at 140°C and at 200°C in the microwave. Both attempts led to complete decomposition of the starting material and no isolation of any organic product. For the reactions with a π-acid in xylene after one night the Schiff' Base was still the mayor component of the mixture and phenanthridine could only be observed in traces.

Table 7: Schiff' Base 18 mmolar in solvent stirred at 140°C over night



167 *Z*-**149** **167'**

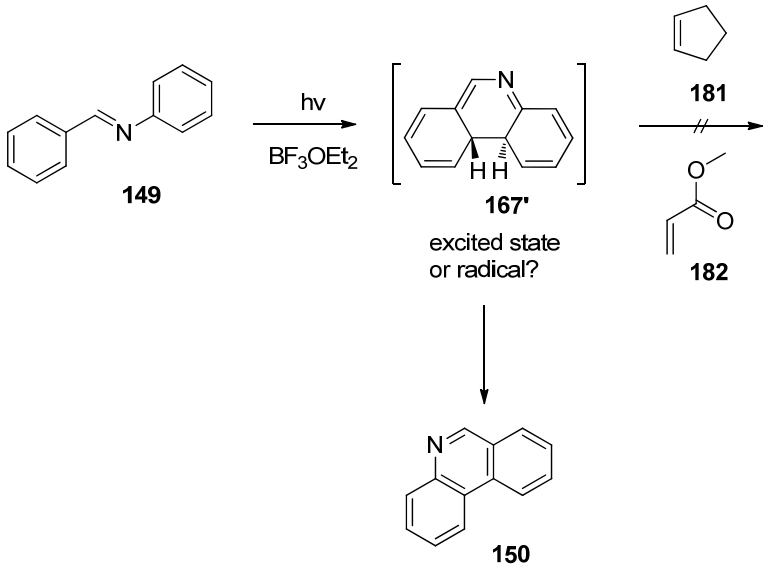
Entry	Additive 1	Additive 2	Solvent	**150**/**149** ratio
1	Microwave[a)]	-	H_2SO_4	no product
2	-	-	H_2SO_4	no product
3	-	-	Xylene	1:19
4	CuI	-	Xylene	1:12
5	$HAuCl_4$	-	Xylene	1:10
6	CuI	I_2	Xylene	1:12
7	CuI	Chloranil	Xylene	1:11
8	Microwave	$BF_3{}^*OEt_2$	MeCN	no product
9	Microwave	-	MeCN	no product
10	[b)]	-	Ph_2O	1:10

a) 200°C

b) 250°C

This ratio could be increased via the addition of several π-acids from 19:1 to 11:1. The addition of oxidants did not influence the thermal cyclization. Neither experiments in the microwave nor in boiling diphenylether (250°C) gave thermal cyclization products in synthetically useful yields (<8%). As a matter of fact, our investigations showed that a thermally allowed disrotatory cyclization is very slow compared to the photochemical reaction conditions.

As the overall reaction without UV-light only proceeds slowly and the isomerization proceeds probably Lewis acid induced, at least one of the following steps, either the cyclization or the dehydrogenation of the dihydrophenanthridine (**167**), has to be influenced by the irradiation. Another fact, supporting our theory for a photochemical cyclization mechanism is that the presence of oxygen seems to influence the reaction (Table 3, Entry 1+2). This is common for photochemical reactions, where the triplet oxygen quenches the reaction.[29] Furthermore, we performed two experiments to trap the excited state of the Schiff' Base with an alkene (Scheme 67, cyclopentene (**181**), methyl acrylate (**182**)).

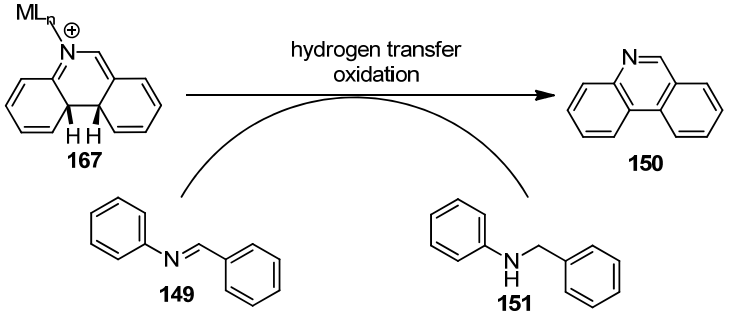


Scheme 67

The reaction with cyclopentene did not work as well as usual (12% phenanthridine, 6% phenyl-benzylamine). On the other hand, methyl acrylate seemed to have little influence on the reaction (40% phenanthridine, 34% phenyl-benzylamine). In both reactions we were unable to detect any adduct between the Schiff' Base and the alkene. As a matter of fact, the alkenes seemed to be inert toward an attack of the photoexcited Schiff' Base.

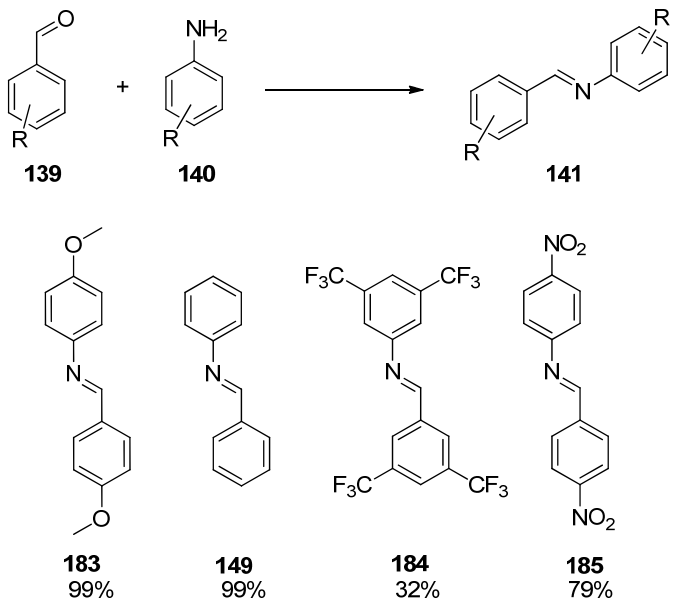
Our preliminary working mechanism at this point was the following: An *E*→*Z*-isomerization induced by the Lewis acid, followed by a photochemical conrotatory cyclization to the dihydrophenanthridine. Herein, the *Z*-isomer could be in equiblibrium with the dihydrophenanthridine. The final step the oxidation to the phenanthridine should then be irreversible and rate determining.

2.2.2.3 The Oxidation and Hydrogen Transfer Step



Scheme 68

The first experiments performed in our group to investigate this hydrogen transfer were the comparison of the reactivity of different Schiff' Bases. Therefore, we synthesized the Schiff' Bases shown in Scheme 69. Compounds **183** and **149** where synthesized with a Dean-Stark apparatus with a catalytic amount of *p*-TsOH in quantitative yields without the need for further purification. The tetra(trifluoromethyl)-Schiff' Base **184** was also synthesized in this manner with the azeotrope distillation of the formed water. Unfortunately, the reaction was not completed and the separation from the aldehyde was quite challenging. Kugelrohr distillation and recrystallization from hexane afforded the desired Schiff' Base **184** in only 32% yield. For the synthesis of the bis(nitro)-Schiff' Base **185** a new procedure by K. Moonen *et al.* was used, where $MgSO_4$ was used as drying agent.[30] After recrystallization from toluene the target compound was isolated in 79% yield.

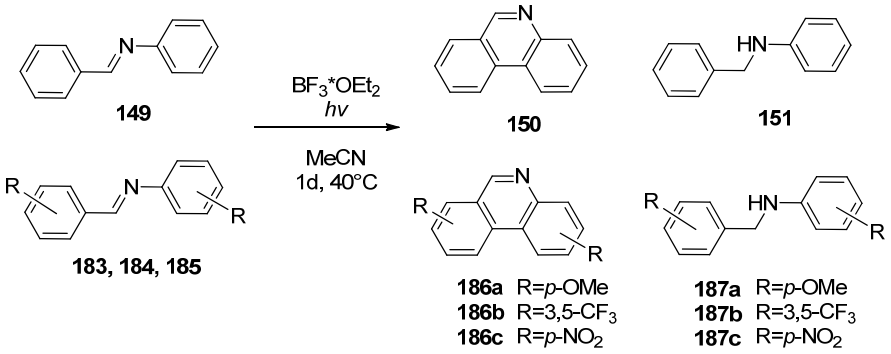


Scheme 69

We expected an influence of the electronic effect on possible cyclization reactions. The idea was to setup mixed experiments between one electron rich or deficient Schiff' Base with our standard substrate. Our expectation was, that one of the Schiff' Bases has a higher affinitiy towards the released hydrogen from the dihydro-intermediate **167** and, therefore, act as a sacrificial hydrogen absorber.

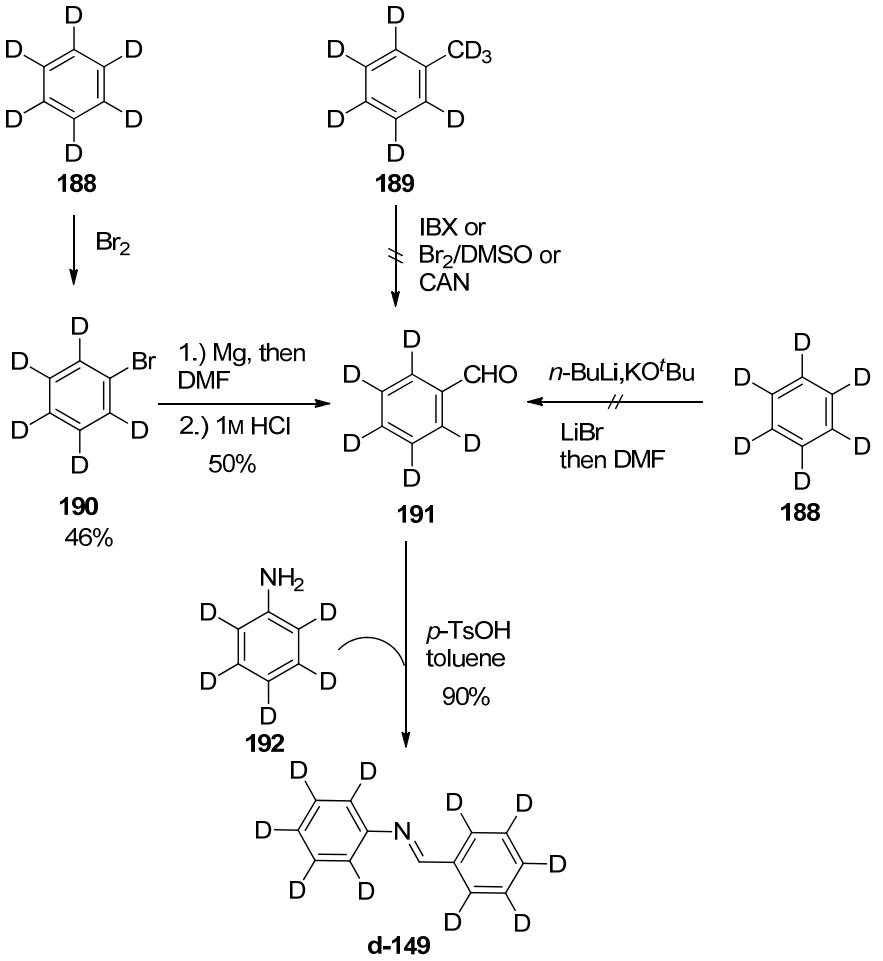
The results from these three mixed experiments are summarized in Table 8. In the mixed experiments with the electron poor Schiff' Bases (Entries 2+3) the formation of the side-product is lowered, despite that the overall yield of the phenanthridine is decreased. Furthermore, in both cases neither reaction product nor side-product from the cyclization of the electron poor Schiff' Base could be detected. In the reaction with the electron rich *p*-dimethoxy imine **183** the yield for product is the same as in the reference experiment. Whereas the yield of the side-product is slightly increased (37%). Moreover, in the cyclization product 2,9-dimethoxy-phenanthridine (**186a**) was also detected in the reaction mixture, while no traces of the reduced 4-methoxy-N-(4-methoxybenzyl)-aniline (**187a**) were found. This results are obviously also influenced by the fact, that when a 1:1 mixture of two Schiff' Bases is used, both absorb the UV light. Therefore, the reactivity is not only characterized by the affinity towards hydrogen, but also by the absorbance of different Schiff' Bases at certain wavelength.

Table 8



Entry	R=	Yield **150**	Yield **151**
1	H	48%	32%
2	*p*-OMe	27%	10%
3	3,5-CF_3	24%	0%
4	*p*-NO_2	47%	37%

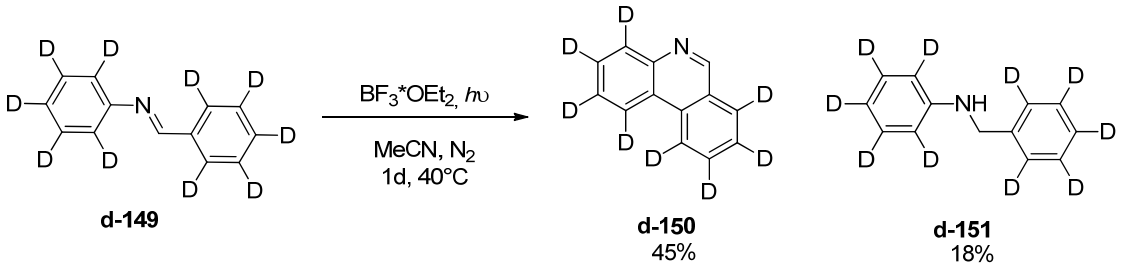
It seemed, that electronic factors have little influence on the hydrogen absorption or that their influence might be compensated by the change in UV-absorption of the reaction mixture. As a result, another way to investigate the oxidation step was proposed. If the oxidation step would be indeed rate determining, it should be possible to observe a kinetic isotope effect between the transfer of two hydrogen and two deuterium atoms. Therefore, a synthesis for the perdeuterated Schiff' Base (**d-149**) was designed. As deuterated aniline (**192**) is commercially available, we had to synthesize pentadeutero benzaldehyde (**191**, Scheme 70). First attempts starting directly from d^8-toluene (**189**), via oxidation with IBX, Br_2/DMSO or cerium ammonium nitrate failed to yield the aldehyde. In Addition, the Schlosser base type approach[31] with the direct deprotonation of d^6-benzene **(188)** did not yield the desired aldehyde. Therefore, the concept of a Grignard reaction with DMF and acidic workup was chosen starting from deuterated benzene (**188**). The bromination of d^6-benzene was attempted and yielded the d^5-bromobenzene in 46% yield.



Scheme 70

A Grignard reaction with DIBAL activation[32], was used for the halogen-magnesium exchange. Addition of this Grignard reagent to DMF and workup with 1M HCl afforded the d^5-benzaldehyde (**191**) in 50% yield. Condensation with d^5-aniline gave the desired d^{10}-Schiff' Base (**d-149**) in 90% yield.

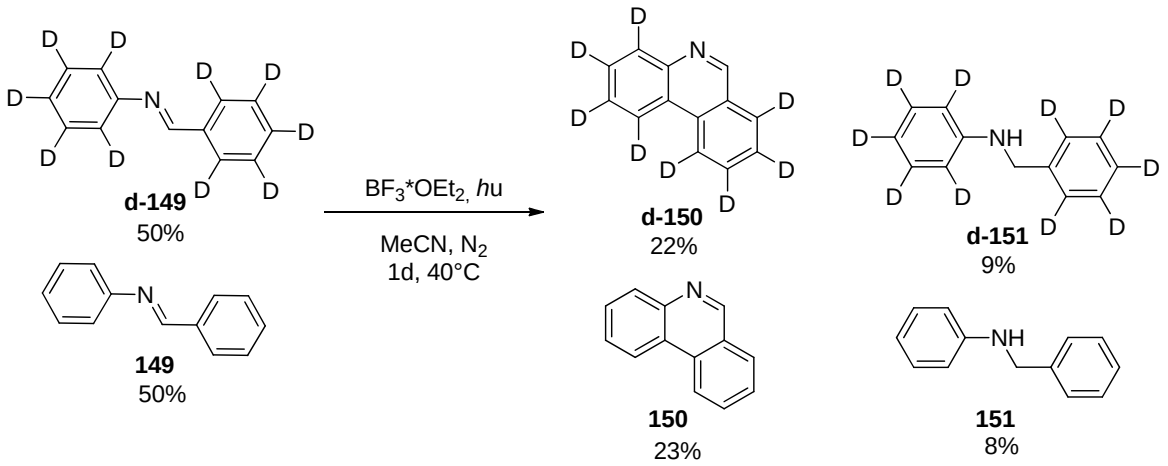
This molecule was submitted to an oxidative photocyclization under our standard conditions to yield the deuterated product (**d-150**) in 45% yield (Scheme 71).



Scheme 71

As this deuterated analoga performs similar in the reaction we then carried out a mixed experiment. A 1:1 mixture of the deuterated and non-deuterated Schiff' Bases was photocyclized under standard conditions. The result of this reaction was investigated via GC-MS and LC-MS (Scheme 72). As the peaks could be separated in the GC four signals could be analyzed in the mass spectrometer. A 1:1 mixture of phenanthridine (**150**) and d^8-phenanthridine (**d-150**) as well as a 1:1 mixture of both side-products (**151**, **d-151**) was obtained. These ratios were confirmed by LC-MS as well. Moreover, it was possible to isolate the two phenanthridines, and the two amines, **151** and **d-151**, via preperative TLC.

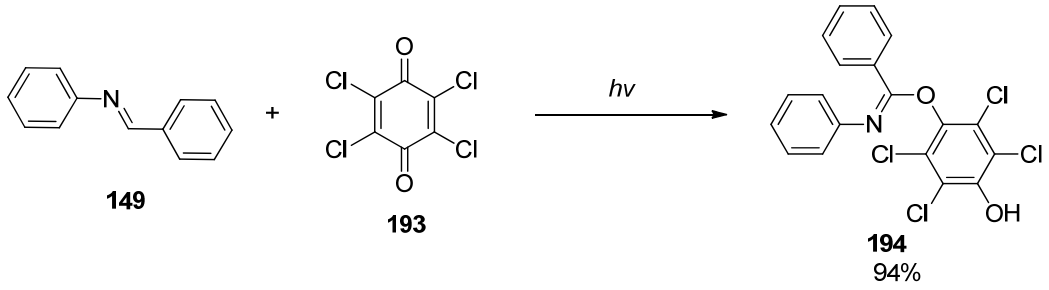
Due to the fact, that the rate of a reaction involving a C-H bond is typically 5 to 10 times faster than the corresponding C-D bond, our results showed, that the hydrogen (deuterium) atoms are not transferred in the rate determining step of the photocyclization.[33]



Scheme 72

As no oxidant or hydrogen scavenger seems to be able to suppress the side-reaction and the Schiff'Base itself seems to be the fastest hydrogen absorber we concluded that the hydrogen transfer might occur intramolecularly. As explained above, in the context of photochemistry

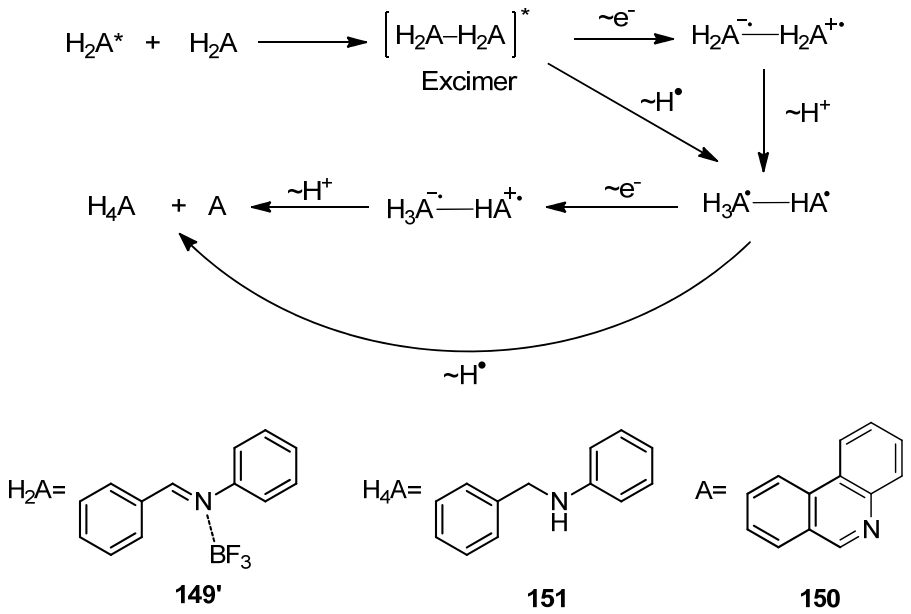
exciplex formation might be a reasonable hypothesis. The Exciplex formation for aromatic iminium salts was already reported by P. S. Mariano.[34] He stated, that the electronic excited state of iminium salts is a better one electron acceptor than its ground state. Moreover, C.-F. Chen and co-workers report the Photoinduced reaction of different Schiff' Bases with Chloranil (**193**, Scheme 73).[35] He also reported the formation of charge transfer complexes as a first reaction step.



Scheme 73

In this case, the Schiff' Base reacts as electron donor. Furthermore, they state that the hydrogen atom might be transferred in an exciplex state between the Schiff' Base (**149**) and chloranil (**193**).

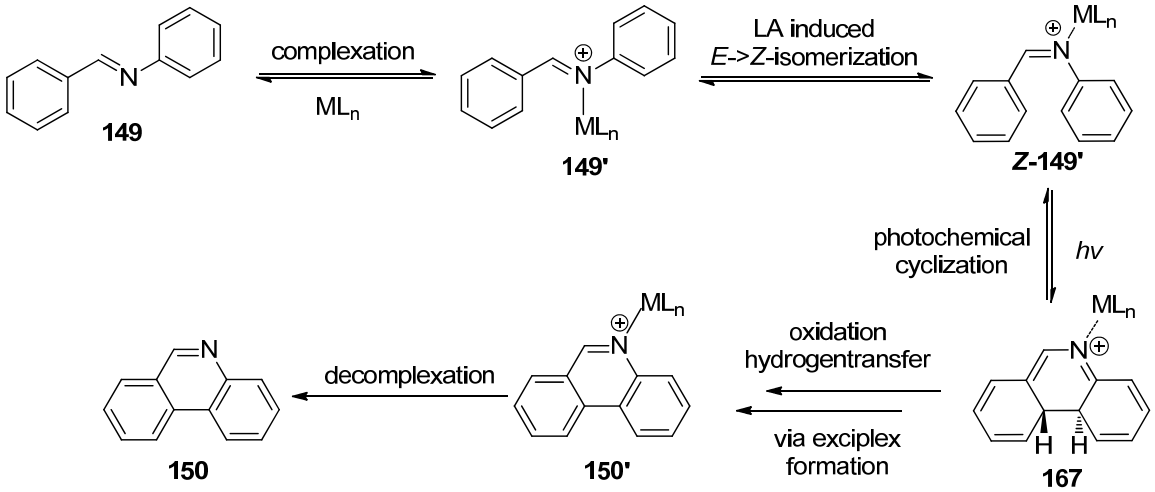
In our case one Schiff' Base-Lewis Acid complex could act as an electron donor as well and another molecule could act as the electron acceptor. The first step of this supramolecular interaction would then be the formation of an excimer. In this excimer, the transfer of electrons as well as the transfer of the two relevant hydrogen atoms would be an intramolecular transfer. The actual transmission of the two hydrogen atoms might either occur step wise (first e^- then H^+ transfer) or in one step (H-Atom transfer) (Scheme 74)



Scheme 74

This might explain why the Schiff' Base was in all cases found to be the superior hydrogen acceptor, even though a huge variety of oxidants and hydrogen absorbing molecules were investigated. As the kinetic intramolecular hydrogen transfer is in full agreement with all our experimental results the excimer formation seems like a reasonable conclusion.

All our mechanistic observations combined draw a new picture of the mechanism (Scheme 75):

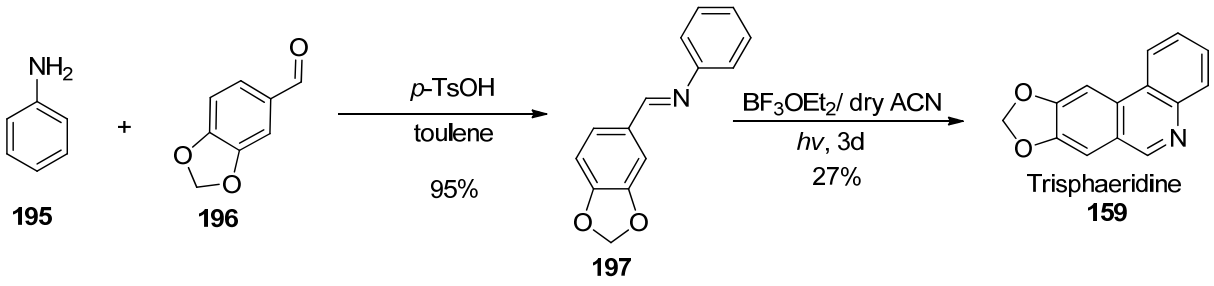


Scheme 75

Starting with a Lewis acid induced *E*→*Z*-isomerization, followed by a conrotatory photocyclization the dihydrophenanthridine (**167**) is formed. This intermediate cannot be trapped by oxidants or hydrogen scavengers but transfers the two hydrogen atoms directly to another molecule of starting material **149** to form phenanthridine (**150**) and *N*-benzylphenylamine (**151**). As stated before the photocyclization occurs probably in a pre-equilibrium and dihydrophenanthridine (**167**) is oxidized and the hydrogen atoms are transferred in a non rate-determining step. This hydrogen transfer might take place via an excimer in an intramolecular fashion.

2.2.3 Synthesis of Trisphaeridine by the improved Photocyclization procedure.

To prove the usefulness of the photocyclization we used a two step procedure[36] to Trisphaeridine (**159**, Scheme 76), a natural product of the class of the phenanthridine alkoids which have a broad range of potent pharmacological activities such as antitumor and antiviral activities and inhibition of DNA topoisomerase I.[37] Trisphaeridine was already synthesized by different groups.[44]



Scheme 76

In our approach, which was starting from the commercially available aromatic amine (**195**) and aldehyde (**196**) the Schiff' Base (**197**) was formed in 95% yield. Photocyclization under our standard conditions yielded Trisphaeridine (**159**) in 27% yield. This is to our knowledge one of the shortest syntheses of Trisphaeridine.

2.3 Conclusion

Concerning the photocyclization of Schiff' Base we did an extensive and thorough optimization study. We tested various solvents, Lewis acid promoters and concentrations to establish a reliable method. We found, that $BF_3{}^*OEt_2$ in acetonitrile at concentrations of about 18 mmol/l are the best conditions to achieve yields very close to the theoretical limit of 50%. Furthermore, we investigated the influence of several compound classes like oxidants, anti-oxidants, hydrogen absorbers and photosensitizers on the reaction.

In addition, we started to investigate each step of the mechanism of the photocyclization of Schiff' Bases. NMR studies, UV investigations and quantum chemical calculations provided new insights into the *E*-*Z*-isomerization, which was found to be not photochemically but Lewis acid induced. Moreover, we investigated the electrocyclization reaction. As all of our thermal cyclization attempts failed we concluded that the cyclization has to proceed in a photochemical 6π-conratatory fashion.

Additionally, we examined the hydrogen transfer and oxidation step. We established, that the influence of the electronics of different Schiff' Bases was not in close relationship to their reactions. Moreover, we found that the hydrogen transfer is most probable not the rate determining step, as the mixed experiments with the perdeuterated Schiff' Base resulted in a 1:1 ratio of deuterated and non-deuterated products. As all our attempts to avoid the reduction of the starting material through external oxidants or hydrogen absorbing molecules were unsuccessful an excimer formation accompanied by an intramolecular hydrogen and electron transfer is the most probable explanation for our experimental results.

Finally, we could prove the usefulness of the improved photocyclization in the two step synthesis of Trisphaeridine.

2.4 References

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[25] Tempo, Cu_2O, PIDA, Mn(OAc)3, *t*-BuOOH, *p*-benzoquinone

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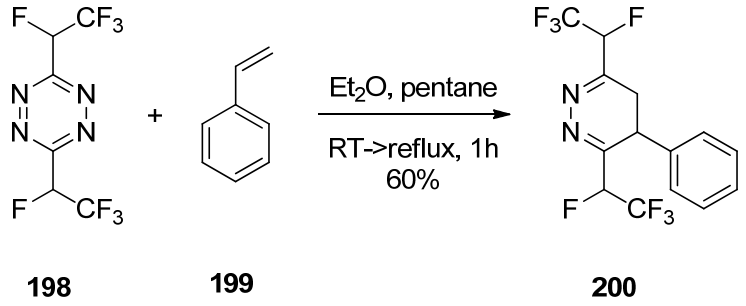
Chapter 3

Application of a Bidentate Lewis Acid to the Inverse Electron Demanding Diels-Alder Reaction of Five-Membered Heterocycles

3.1 Introduction

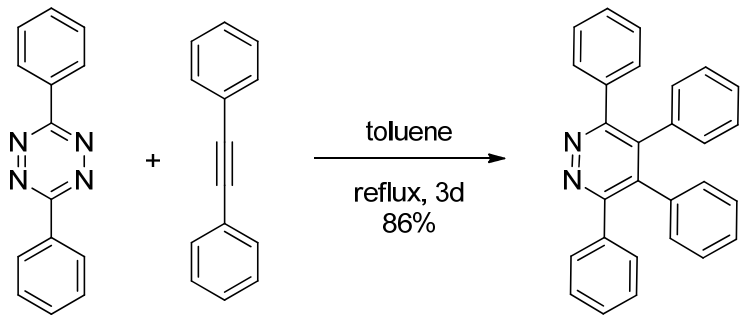
Inverse electron demanding Diels-Alder reactions were first reported by R. A. Carboni and R. V. Lindsey in 1959 when they demonstrated the reaction of electron poor tetrazines with different dienophiles.[1] As dienes they used 3,6-bis(1,2,2,2-tetrafluoroethyl)-1,2,4,5-tetrazine (**198**) and 3,6-bis(phenyl)-1,2,4,5-tetrazine (**201**). They reported reactions for several alkenes as shown in Scheme 77.



198 **199** **200**

Scheme 77

Moreover, they also used alkynes (**202**, Scheme 78) which usually required higher reaction temperatures. Interestingly, they investigated as well very reactive alkenes (e. g. tetracyanoethylene) known to react readily in Diels-Alder reactions and surprisingly found them not to react.



201 **202** **203**

Scheme 78

As for most Diels-Alder reactions known at this point, usually the diene was electron rich and the dienophile was electron poor their report was really astonishing. For their pioneer work, this reaction is also known as the Carboni-Lindsey reaction.

Nowadays with more sophisticated knowledge of molecular orbitals and their interactions the Diels-Alder reaction can be divided into three groups: The neutral, the normal and the inverse electron demanding Diels-Alder reaction (IEDDA). The frontier molecular orbital interactions of these three types of Diels-Alder reactions are shown in Figure 21.[2]

For the neutral type, the interactions between the $HOMO_{dienophile}$-$LUMO_{diene}$ and the $HOMO_{diene}$-$LUMO_{Dienophile}$ are similar. For the normal type Diels-Alder reaction the overlap of the $HOMO_{diene}$-$LUMO_{Dienophile}$ is dominating, while for the inverse case the $HOMO_{dienophile}$-$LUMO_{diene}$ is controlling the reaction. (Red arrows Figure 21) Moreover, the influence of electron donating and withdrawing groups is depicted by the blue arrows.

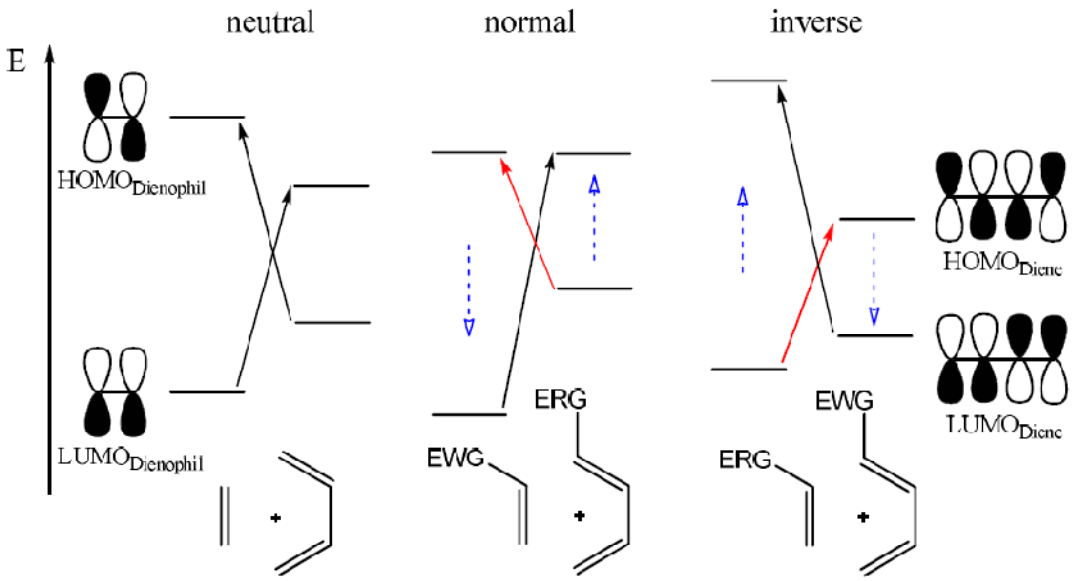
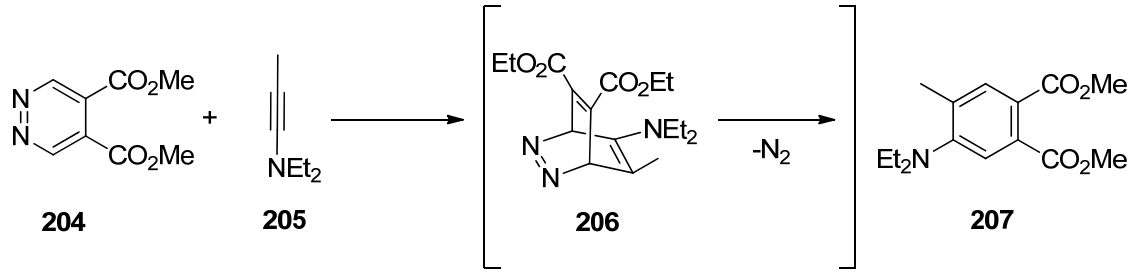


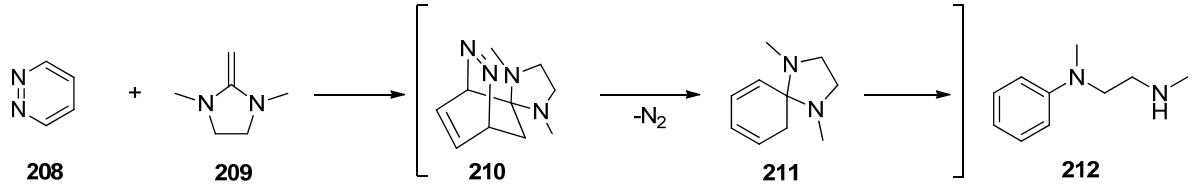
Figure 21

In recent decades the IEDDA reaction was applied to other dienes than the original 1,2,4,5-tetrazines. H. Neunhoeffer und G. Werner published the reactions of pyridazines (**204**) with electron rich alkynes (**205**).[3] (Scheme 79). They utilized the electron withdrawing effect of the two ester groups to activate this diene.



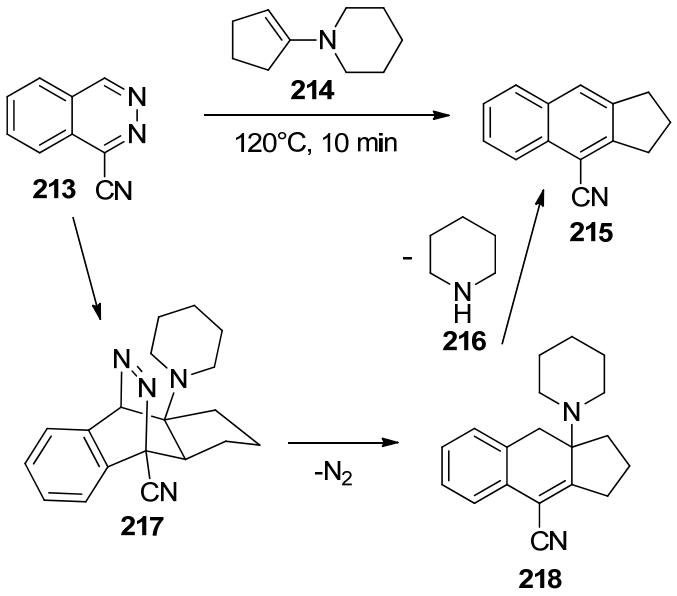
Scheme 79

As unsubstituted pyridazines were to unreactive with available dienophiles, U. Gruseck and M. Heuschmann used strongly activated dienophiles like 1,3-dimethyl-2-methyleneimidazolidine (**209**) and temperatures of about 160°C to achieve the IEDDA.[4]



Scheme 80

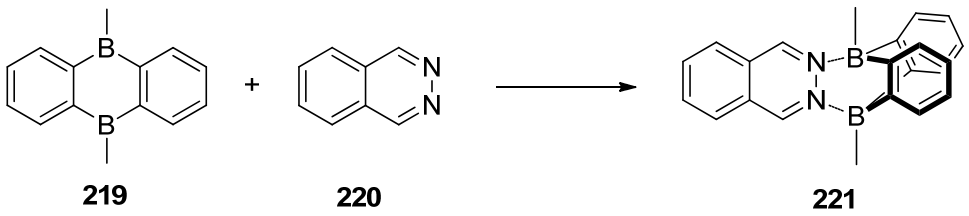
Another diene used was 4-cyanophthalazine (**213**). E. Oishi *et al.* reported the reaction of electron poor phthalazines with activated alkynes and enamines (Scheme 81).[5] Moreover they demonstrated, that unsubstituted phthalazine could react as well with enamines at temperatures around 130°C.



Scheme 81

As the reactions of all these dienes were either requiring elevated temperatures (130°C-160°C) or electron withdrawing substituents on the diene to activate it further, we became interested into the activation of those kinds of dienes using a catalyst. The role of the catalyst should be similar to the electron withdrawing substituents: It should reduce electron density of the diene system and, therefore, lower the energy of the LUMO. Such catalyst would permit IEDDA reactions with less reactive dienes and dienophiles, or at least significantly reduce the temperatures required for the already established reactions.

Since all the dienes used so far contained two nitrogen atoms, our group focused on the development of a catalyst which can coordinate to the nitrogen and thereby withdraw electron density. In previous work we found that the bidentate Lewis acid (**219**, Scheme 82) is strongly activating phthalazine (**220**) via the formation of a 1:1-complex (**221**).[6]



219 **220** **221**

Scheme 82

Moreover, we were able to predict this complexation and activation by the Lewis acid with quantum chemical calculations. Figure 22 shows the structure and frontier molecular orbitals of phthalazine and its complex with our developed catalyst.[6] A significant lowering of the LUMO orbital from -1.76 eV to -3.05 eV is observed by the Lewis acid activation.

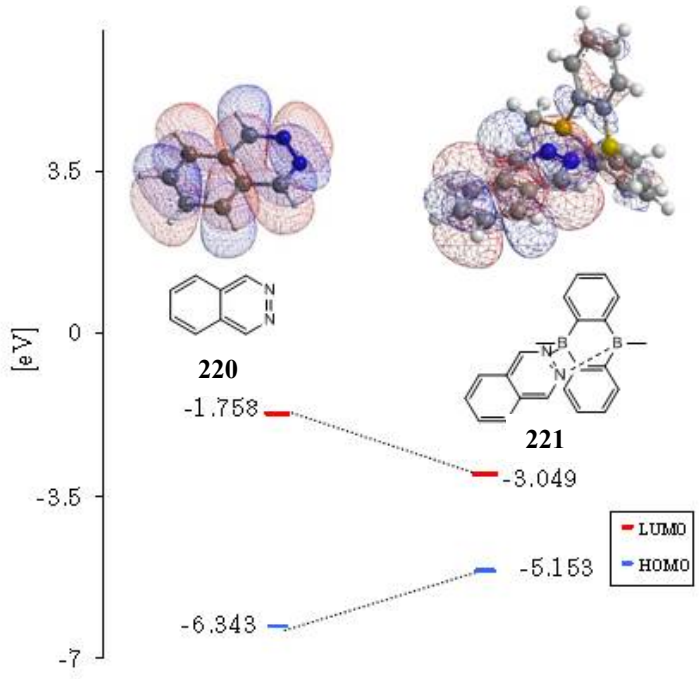


Figure 22

This complexation could also be observed in the NMR spectrum (Figure 23), where clearly the highfield shift of the Lewis acid can be seen and, correspondingly, the lowfield shift of the phthalazine signals.

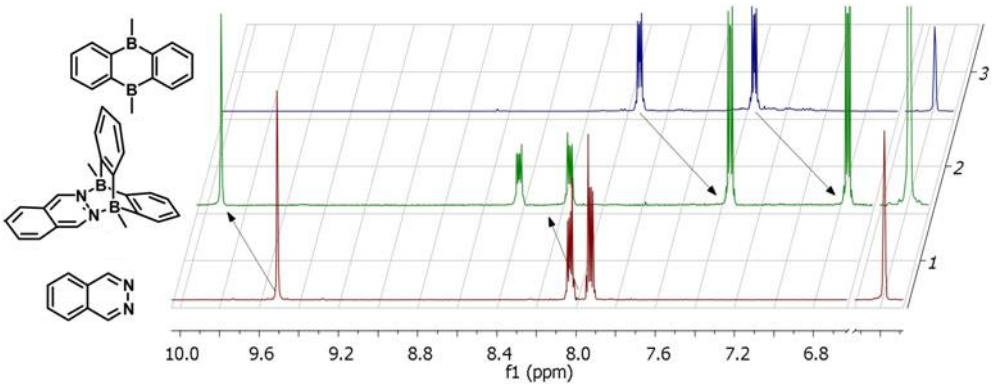
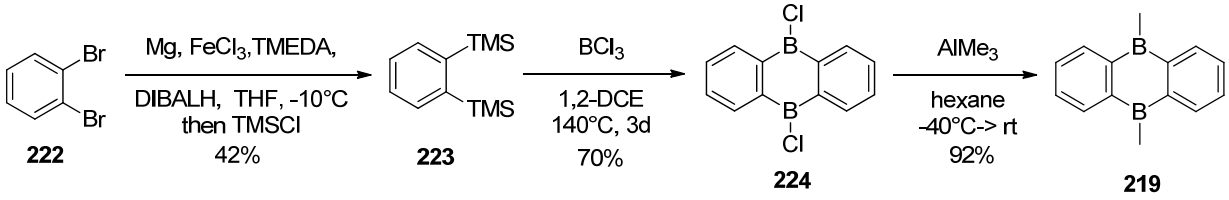


Figure 23

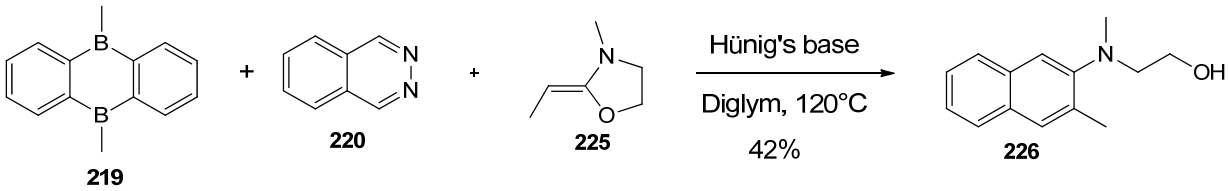
The catalyst itself can be synthesized in a three step procedure from 1,2-dibromobenzene (**222**, Scheme 83). Iron catalyzed formation of the bis-Grignard derivative and reaction with TMS-Cl afforded the 1,2-bis(trimethylsilyl)benzene (**223**) in 42% yield even on large scale (up to 30 g).[7] The next step, a silicon-boron exchange and dimerization, was performed in

70% yields in overheated 1,2-dichloroethane. The final step the alkylation with trimethyl aluminium afforded the bidentate Lewis acid catalyst **219** in 92% as a white solid. The catalyst **219** and the chloro-precursor **224** are very sensitive to oxygen, but can be stored under nitrogen atmosphere at room temperature for prolonged periods without noticeable decomposition.



Scheme 83

Moreover, the catalyst shows the ability to activate dienes and to facilitate reactions in amounts of only 2.5 mol%. Figure 24 depicts the reaction of phthalazine (**220**) with an activated dienophile **219** with and without catalyst.[6]



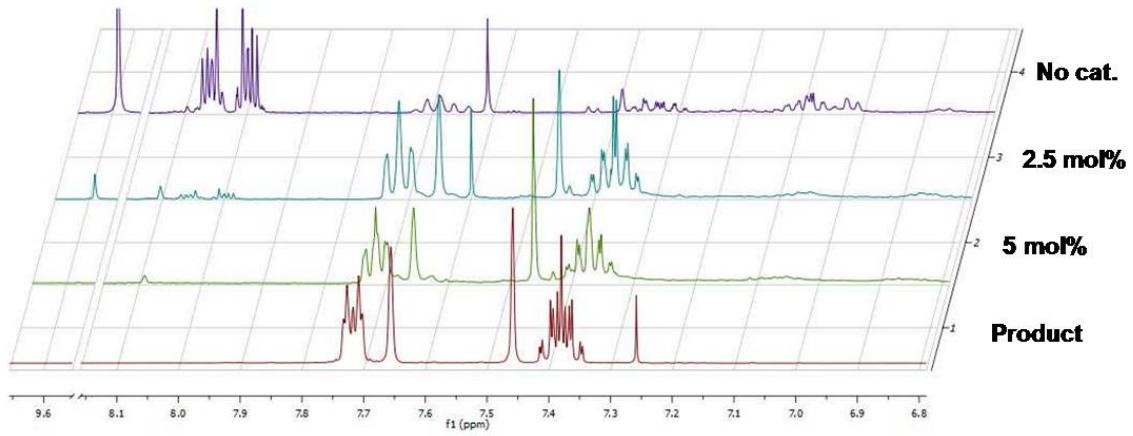
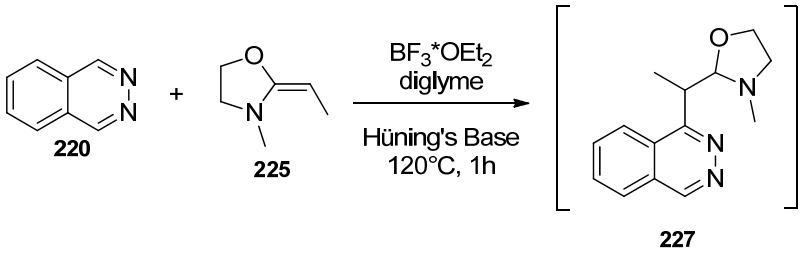


Figure 24

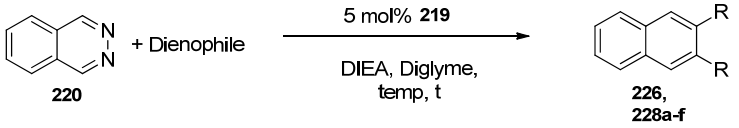
The catalyst accelerates the reaction significantly. Moreover, a control experiment with $BF_3{}^*OEt_2$ a monodentate Lewis acid led presumably to addition to the imine carbon of the phthalazine (**227**, Scheme 84). This proves that only a bidentate Lewis acid is suitable for these transformations.

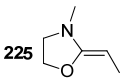
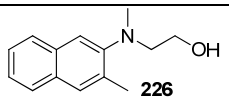
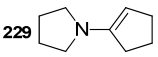
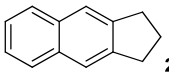
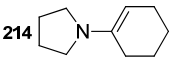
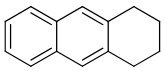
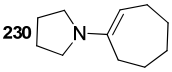
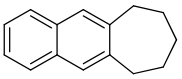
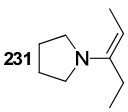
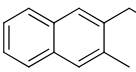
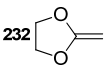
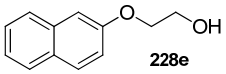
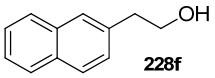


Scheme 84

After this first proof of concept, we screened different reaction with various dienophiles (Table 9).

Table 9

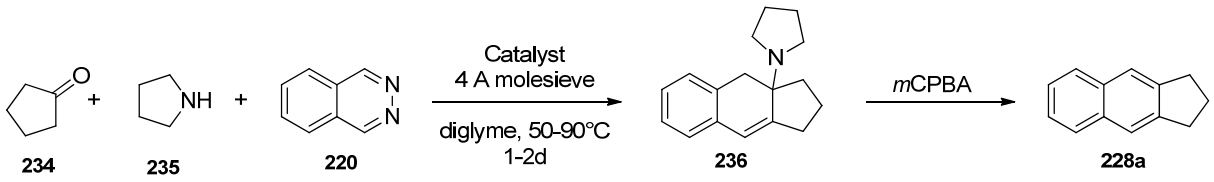


Entry	Dienophile	Temp/t	Product/yield
1		120 ºC 20 h	 **226** (42%)
2[b]		55 ºC 2.5 d	 **228a** (52%)
3		90 ºC 2.5 d	 **228b** (80%)
4[b]		80 ºC 2.5 d	 **228c** (85%)
5[b]		130 ºC 2.5 d	 **228d** (25%)
6		160 ºC 10 h	 **228e** (45%)
7		170 ºC 72 h	 **228f** (43%)

a] 5 mol % **2,** 1.5-3 equiv dienophile, 2 equiv DIEA, diglyme.

[b] Enamine was prepared in situ from the corresponding ketone and pyrrolidine.

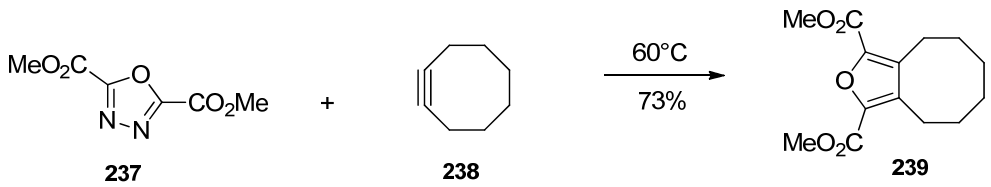
Interestingly, it was even possible to use ketones and secondary amines for the reaction to form the enamine *in situ*. The water generated in the condensation of amine and ketone does not destroy the catalyst or interferes with the IEDDA reaction (Scheme 85). In the case of an enamine as dienophiles sometimes *m*-CPBA was added to eliminate the intermediary amine (**236**) in a Cope-elimination type reaction.



Scheme 85

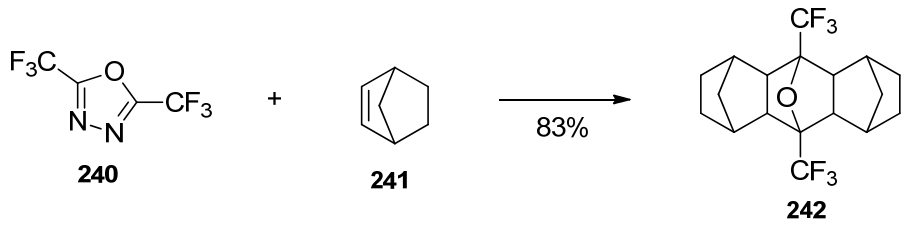
Five-membered aromatic heterocycles can be as well successfully used as dienes in IEDDA reactions when electron poor heterocycles meet reactive dienophiles.[8] Nevertheless, there are only few five-membered aromatic heterocycles who have suitable properties to participate in the IEDDA.

J. Sauer *et al.* investigated the IEDDA reaction of 1,3,4-oxadiazoles.[9] Although, they had to use very reactive dienophiles, like cyclooctyne, they achieved the reaction at 60°C in good yields. (Scheme 86)



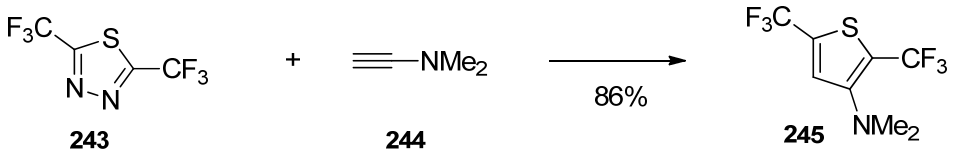
Scheme 86

Interestingly, they reported the formation of bis-adducts, when dienophiles like norbornene were used. In this case the product of the Diels-Alder reaction readily reacted with another molecule of norbornene to the hexacyclic compound **242** in good yields.



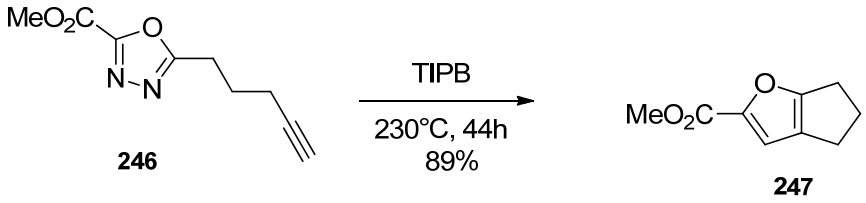
Scheme 87

Moreover, they also investigated the reaction of 1,3,4-thiadiazoles as shown in Scheme 88, where a bis(trifluoromethyl)-thiadiazole **243** reacts with an highly activated alkyne **244** to form the substituted thiophene.



Scheme 88

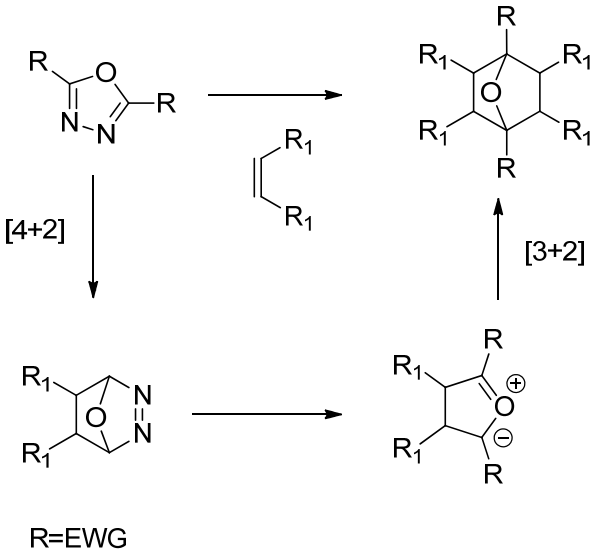
In the last decade D. L. Boger and co-workers were investigating the IEDDA reaction during their synthesis of natural products of the vinca alkaloids. They reported the intra-molecular IEDDA reaction of 1,3,4-oxadizales as depicted in Scheme 89.[10]



Scheme 89

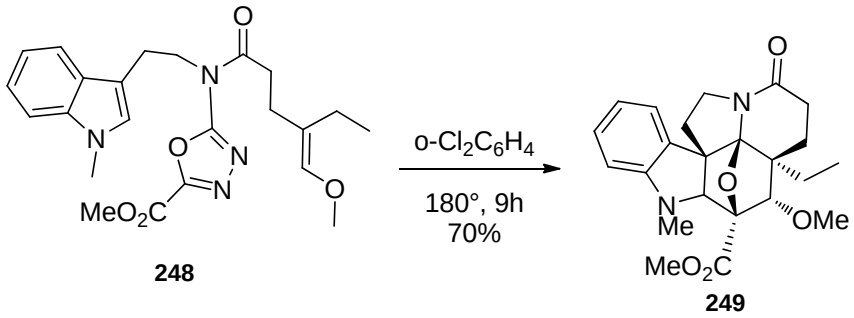
As the dienophiles, they used, are quite unreactive (terminal alkynes) they had to employ very high temperatures between 160°C-230°C to achieve good conversions within a few days. They reported that 1,2-dichlorobenzene and tri*iso*proplybenzene are suitable solvents for these high temperature reactions. Moreover, they also propose a mechanism for the formation of bis-adducts which was observed quite often during such reactions (Scheme 90). The diene reacts slowly in the [4+2]-cycloaddition and after the release of nitrogen, a 1,3-dipolar

compound is formed. This 1,3-dipol can itself react with another unsaturated compound in a fast [3+2]-cycloaddition to form the bis-adduct.



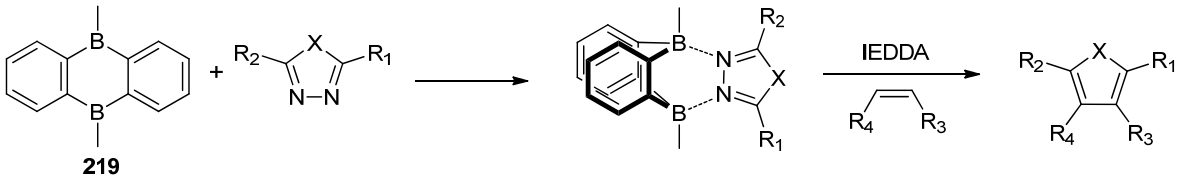
Scheme 90

Furthermore, they successfully used their developed methodology to synthesize complex molecules (Scheme 91) where both reactions, the [4+2]- and the [3+2], were intra-molecular. Here again an 1,3,4-oxadiazole is the diene and the two dienophiles were an indole and an enol ether.



Scheme 91

Since our group designed a bidentate Lewis acid catalyst **219** to activate phthalazines, we were also interested if the same Lewis acid can act as catalyst for the preparation of five-membered heterocycles.



X= O, S, NR

Scheme 92

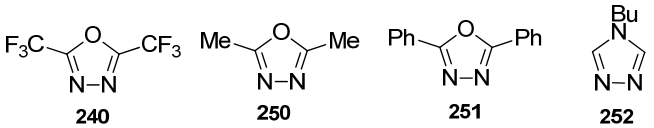
If the boron-based bidentate Lewis acid coordinates the 1,3,4-oxadiazoles on both nitrogen atoms, on one hand it should be possible to enhance the reactivity of the diene without electron withdrawing groups and on the other hand to enable the application with less activated dienophiles. This would be a very divers approach towards 2,3,4,5-substituted furans, thiophenes or pyrroles.

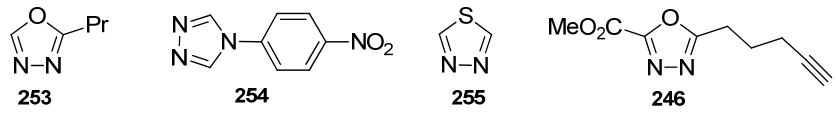
3.2 Results and Discussion

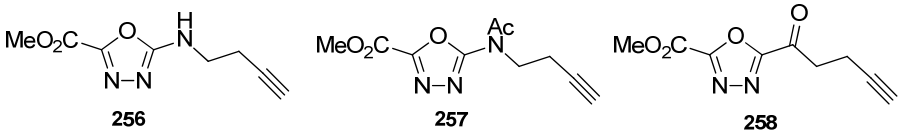
3.2.1 Quantum Chemical Calculation

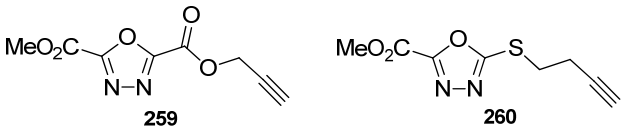
In our previous work on phthalazine we could demonstrate the usefulness of quantum chemical calculations to investigate the influence of the bidentate Lewis acid catalyst on the reactivity in particularly its activating effect on the LUMO orbital of the diene. The LUMO energy for phthalazine was lower by about 1.3 eV. Table 10 shows the results of our calculations of a selection of five-membered heterocycles.

Table 10









Diene	complex type	bond length B-N	LUMO Energy		ΔE (free diene-complex)
			diene	Lewis acid complex	
240	π-complex	3,9 Å	-2,04	-1,93 [a]	0,11 [a]
250	σ-complex	1,8 Å	-0,11	-1,76	-1,65
251	σ-complex	3,3 Å	-1,61	-1,64 [a]	0,03 [a]
252	σ-complex	1,7 Å	0,53	-1,32	-1,85
253	σ-complex	1,7 Å	-0,27	-1,96	-1,69
254	σ-complex	1,7 Å	-2,95	-3,59	-0,64
255	σ-complex	1,7 Å	-1,27	-2,81	-1,54
246	σ-complex	1,7 and 1,8 Å [b]	-1,73	-3,96	-2,23
256	σ-complex	1,7 and 1,8 Å [b]	-1,39	-2,25	-0,86
257	π-complex	3,8 Å	-1,64	-1,87 [a]	-0,23 [a]
258	π-complex	3,9 Å	-2,72	-2,67	0,05
259	π-complex	4,1 Å	-2,52	-2,53	-0,01
260	σ-complex, monodentate	3,8 Å	-1,76	-2,03	-0,27

[a] Energy from the LUMO+1 Orbital, as the LUMO itself was not located on the diene

[b] Complex was unsymmetric

In all cases the Lewis acid seemed to lower the LUMO energies significantly by between 1.5 and 2.2 eV. Exceptions were 2,5-bis(trifluoromethyl)-1,3,4-oxadiazole (**240**, raise of LUMO by +0.11 eV) 2,5-bis(phenyl)-1,3,4-oxadiazole (**251**, almost no influence on the LUMO energy) and 1-(4-nitrophenyl)-1,3,4-triazole (**254**). The reason for this could be that the first two dienes (**240**, **251**) had a different mode of complexation, whereas the triazole **254** might be already too electron poor (diene LUMO-energy of -2.95 eV) to coordinate strongly. For the Boger-type dienes only the ones with the smaller residues at the 5-position of the oxadiazole seemed to form σ-complexes. Larger substituents like acetyl, carboxyl or carbonyl groups led to calculations, where a π-complex was the lowest in energy. This explains also the minor impact of the coordination to the LUMO energy in the complex compared to the free diene. Figure 25 shows the LUMO energy of the calculated dienes and provides the trend that in general electron withdrawing groups lower the LUMO energy.

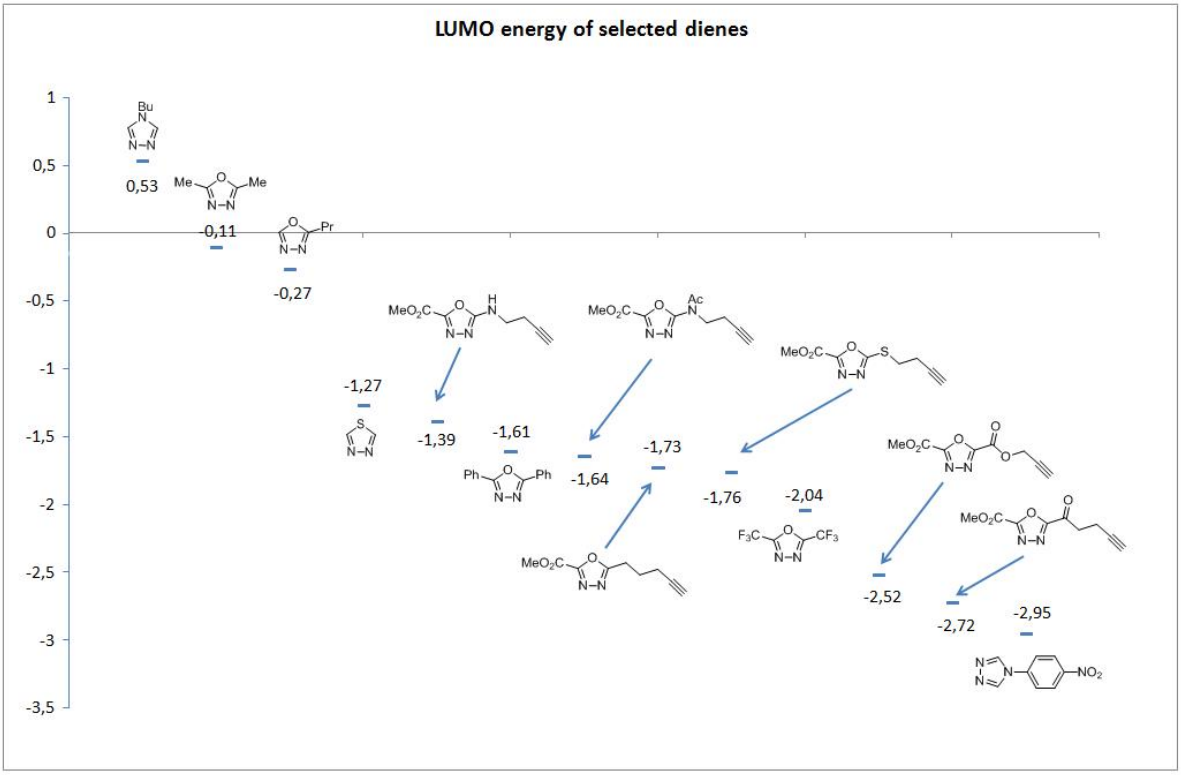


Figure 25

The optimized structures where in general similar to the 2,5-bis(methyl)-1,3,4-oxadiazole (**250**) shown in Figure 26, the average B-N bond length was around 1.75 Å. In the cases of two different substituents on the 2- and 5-position the complexes had usually slightly different

B-N bond lengths. Furthermore, in the case of the bulky 2,5-diphenyl-1,3,4-oxadiazole (**251**) this bond length increase to 3.3 Å (Figure 26). In this example the catalyst was not bended but flat. This result was in accordance to the only slight decrease of the LUMO energy as described above. Interestingly, 2,5-bis(trifluoromethyl)-1,3,4-oxadiazole (**240**) was found to form a π-complex with the Lewis acid. As mentioned before, this led to a raise of the LUMO energy, instead of a desired decrease.

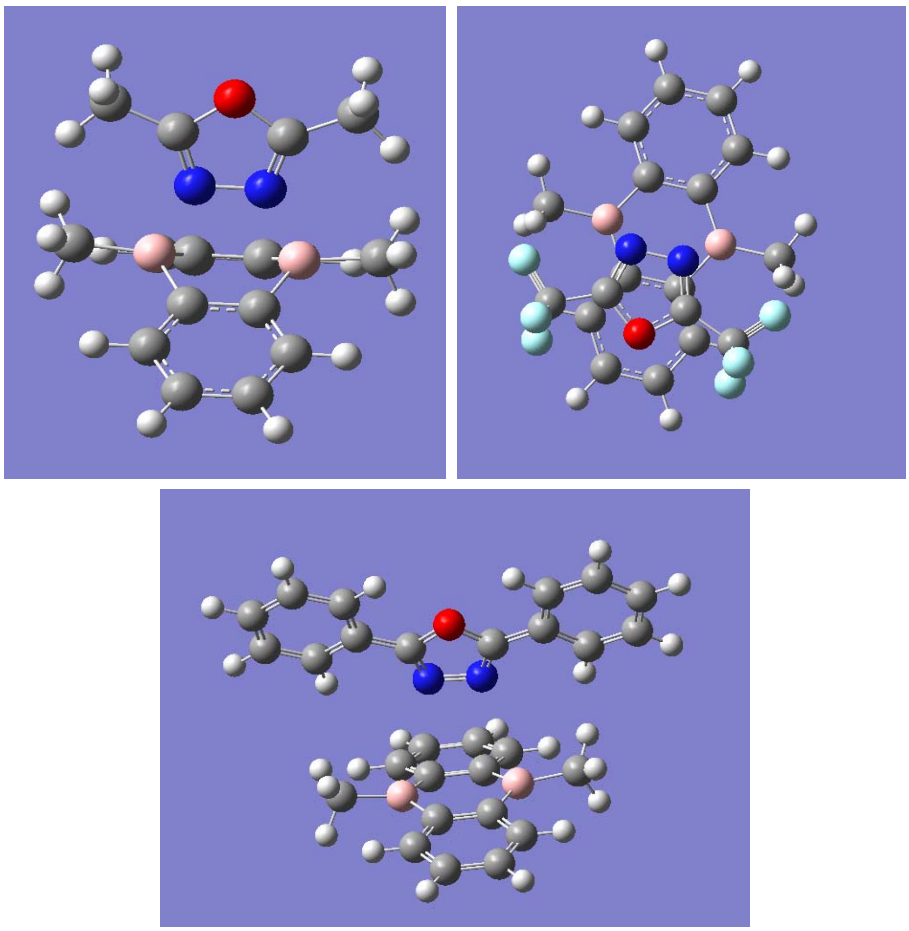


Figure 26

Moreover, the energy of the HOMO orbital of several dienophiles was calculated as well to investigate the gap between these orbitals and the LUMO orbitals of the diene (Figure 27). Several cyclic and electronically varying alkenes were investigated as most reports of IEDDA reactions with 1,3,4-oxadiazoles were performed with them. Furthermore, different alkynes were investigated, the 1,3,4-oxadiazoles investigated by D.L. Boger *et al.* where of special interest as they are suitable for intra-molecular reactions. The general knowledge, that

electron rich substituents raise the HOMO energy could be confirmed for our systems via these calculations.

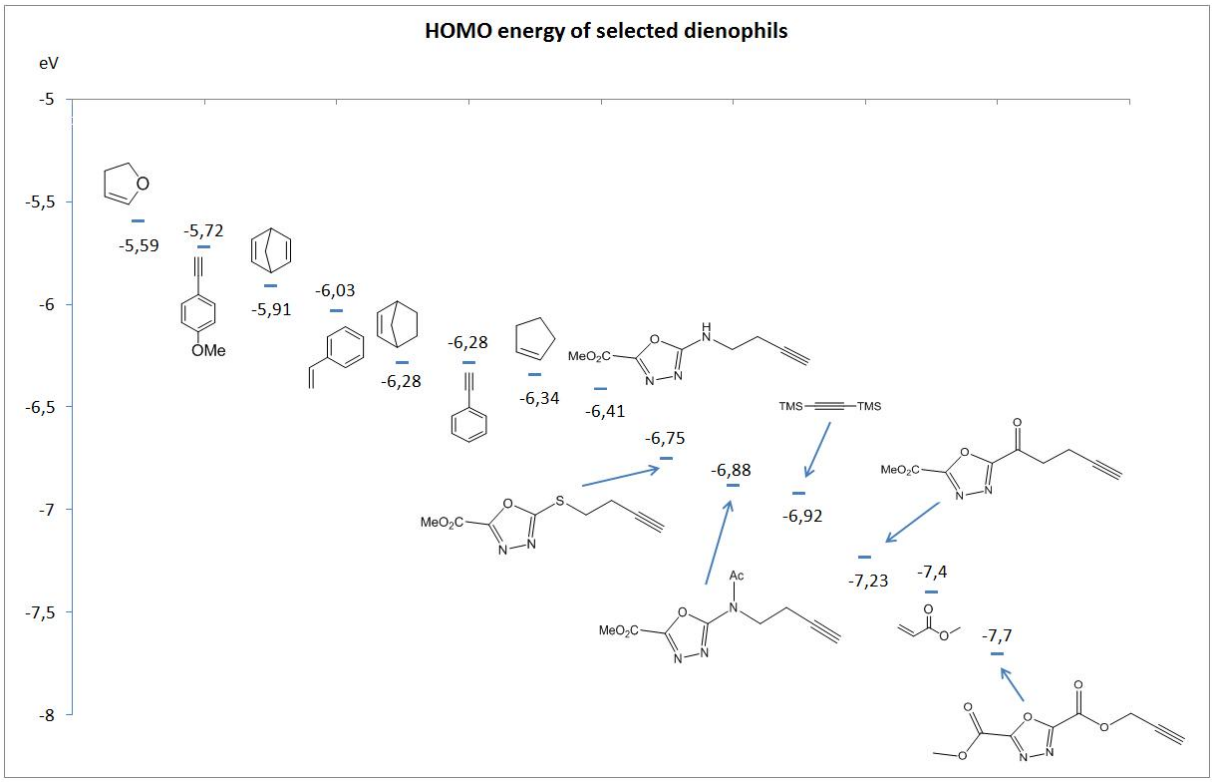


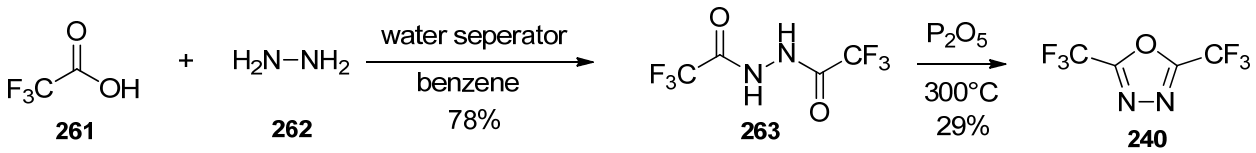
Figure 27

3.2.2 Synthetic Results

3.2.2.1 Synthesis of Dienes

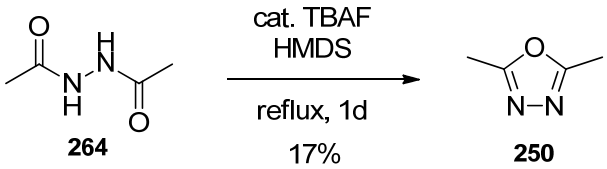
At the beginning of this project it was important to start with the synthesis of different five-membered heteroaromatic dienes, to be able to perform the complexation experiments and the inverse electron demanding Diels-Alder reaction. Therefore we prepared several dienes starting with 2,5-bis(trifluoromethyl)-1,3,4-oxadiazole (**240**), a very electron poor compound with a low boiling point of 61°C. Following a literature procedure we started from trifluoroacetic acid and hydrazine hydrate to form the bishydrazide **263** in 78% yield.[11] The following step, the dehydrative cyclization, was challenging as the low boiling point of the product made the isolation complicated. Reagents like oleum or phosphorous pentoxide and elevated temperatures were required to perform this cyclization. Following the approach by B. G. Jones *et al.*, we were able to prepare oxadiazole **240** in 29% yield by directly trapping it in

a dry ice cooled flask.[12] The 2,5-bis(trifluoromethyl)-1,3,4-oxadiazole (**240**) itself is a highly volatile colorless liquid.



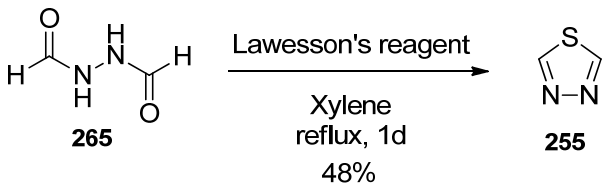
Scheme 93

Our next synthetic target was 2,5-bis(methyl)-1,3,4-oxadiazole (**250**). First, commercial available diacetylhydrazine **264** was tried to get to react with phosphorous pentoxide at temperatures of about 300°C, like mentioned above for the synthesis of the bistrifluoromethyl derivative **240**. Unfortunately, maybe due to the higher boiling point it was impossible to distill the oxadiazole **250** from the solid/solid mixture. Therefore, another procedure was followed using a one-pot silylation/condensation protocol. The diacetylhydrazine was refluxed in HMDS with a catalytic amount of TBAF. After work up it could be distilled under reduced pressure to yield 17% of the pure 2,5-bis(methyl)-1,3,4-oxadiazole (**250**).



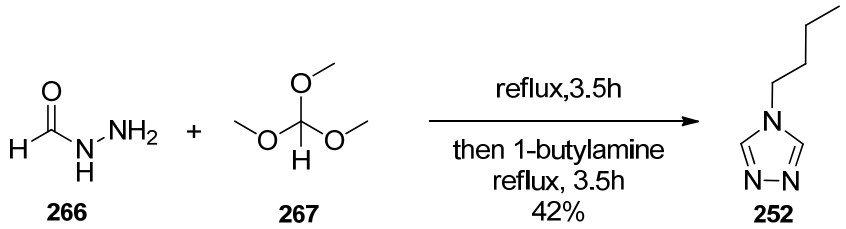
Scheme 94

The synthesis of thiadiazole **255** was as well challenging. Commercial available bisformylhydrazide (**265**) was reacted with Lawesson's reagent in refluxing xylene. The product could be separated by column chromatography by running a gradient from hexane to ether. The whole reaction mixture was directly added to a pre-packed SiO_2-column, first eluting xylene followed by 1,2,4-thiadiazole (**255**), a low melting (45°C) white solid.



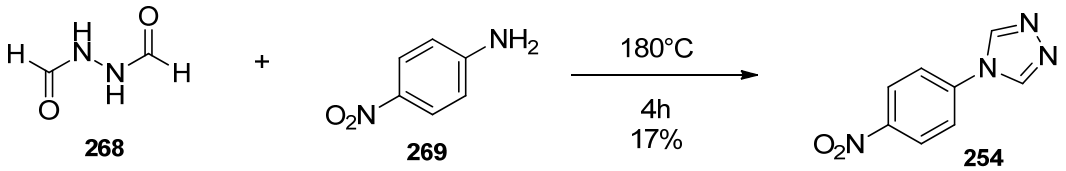
Scheme 95

Furthermore, 4-butyl-1,2,4-triazole (**252**) could be synthesized in 42% yield in a one-pot procedure. This compound was of special interest, as the protons directly on the aromatic core are very good indicators to a coordination of the two nitrogen atoms to the Lewis acid.



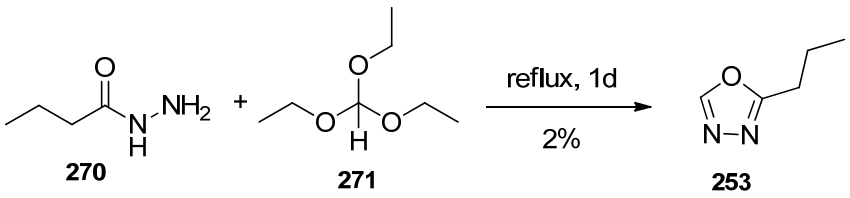
Scheme 96

Another triazole, which was chosen was 4-(4-nitrophenyl)-1,2,4-triazole (**254**). It was synthesized at 180°C from diformylhydrazide (**268**) and 4-nitroaniline (**269**) and repeated recrystallizations led to the pure triazole in 17% yield.



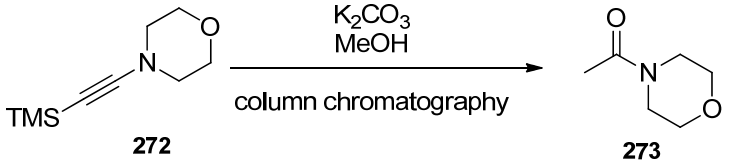
Scheme 97

In addition, 2-propyl-1,3,4-oxadiazole (**253**) could be synthesized from butyric acid hydrazide with triethyl orthoformate. Only 2% yield could be obtained as the product was hard to separate from butyric acid and three distillation steps were needed to isolate the pure compound.



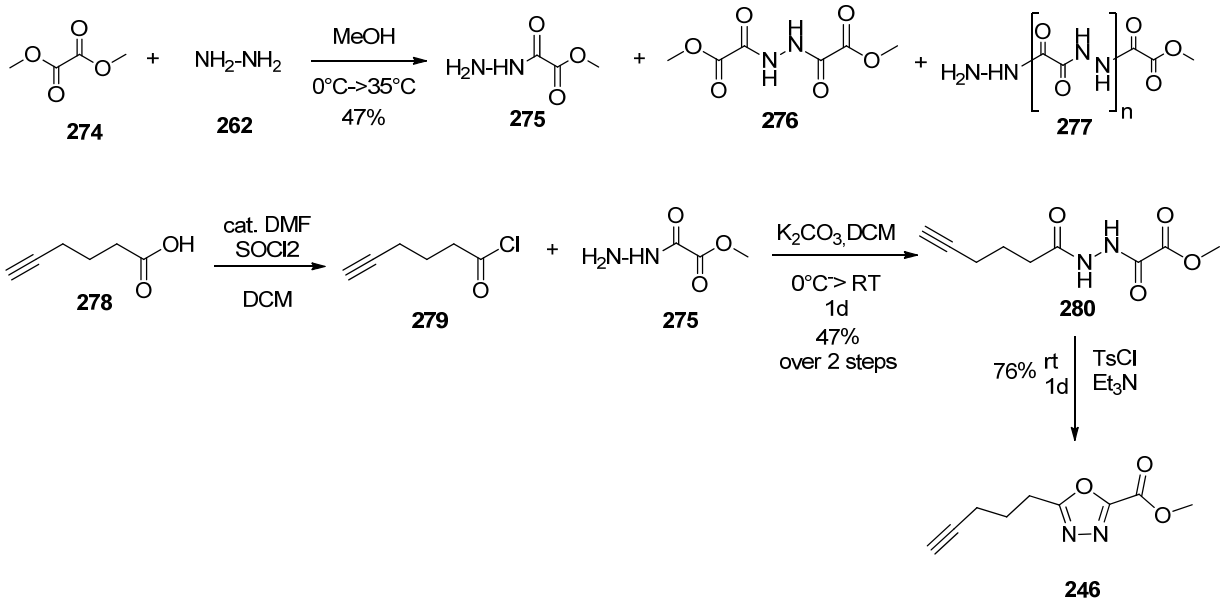
Scheme 98

Moreover, it was desired to test activated alkynes in the IEDDA reaction. The commercial available N-(2-trimethylsilyacetylene)-morpholine (**272**), had to be deprotected to synthesis the terminal alkyne (Scheme 99). Unfortunately, the procedure led to the isolation of N-(acetyl)-morpholine (**273**) after column chromatography, as hydrolysis took place.



Scheme 99

As already mentioned oxadiazoles as shown in Scheme 89 were used by D.L. Boger *et al.* in intramolecular IEDDA reactions at temperatures between 160°C and 230°C. Our aim was to synthesize oxadiazole **246** and perform a bidentate Lewis acid catalyzed reaction to investigate if an activation and therefore a temperature reduction was possible. This oxadiazole **246** was synthesized from dimethyl oxalate (**274**) and hydrazine (**262)**. In this first step the concentration of the hydrazine was critical. When a 60% hydrazine solution was used only bishydrazide **276**, starting materials **274** and oligomeric compounds **277** were isolated. Only the use of an 80% hydrazine solution led to the isolation of the monohydrazide **275** in 47% yield. This monohydrazide **275** was reacted in a second step with freshly prepared 5-hexynoic acid chloride (**279**) to form the bisamide **280** in 47 % yield. The cyclization was performed with TsCl and Et_3N to afford the desired oxadiazole **246** in 76%.



Scheme 100

3.2.2.2 NMR-Complexation Studies

As described in the introduction, the phthalazine showed a strongly coordinating behavior to the bidentate Lewis acid catalyst. The coordination was so stabile that a solid phase crystal structure was obtained. Moreover an intense coordination in the NMR was observed. It was expected, that in the case of a coordination of a Lewis acid to a Lewis base (in this case the diene), the signals of the acid in NMR are shifted highfield (as it becomes more electron rich) and the signals of the diene are shifted lowfield (due to the electron withdrawing effect of the Lewis acid). This coordination and the consequent lowering of the LUMO orbital of the diene is the key to the increase of reactivity. As we already investigated the coordination via quantum chemical calculations, the NMR experiments were now a suitable additional investigation. Table 11 gives an overview about the coordination experiments.

Table 11

Diene	Shifts ^{1}HNMR		Complexation in NMR
	Lewis Acid (Δ in ppm)	Diene (Δ in ppm)	
220	-0.6	+0.3	yes
240	No shift	No shift	not observed
250	-0.3	-0.1	not observed
251	-0.25	+0.1	Yes (weak)
252	-0.7	+0.55	yes
254	-0.15	+0.8	yes
255	- 0.75	- 0.1	Not observed
246	-0.15	+0.15	Yes (weak)

There was a clear coordinative shift found for the 4-(butyl)-triazole **252** and the 4-(4-nitrophenyl)-triazole **254**. For 2,5-bis(methyl)-1,3,4-oxadiazole (**250**) the coordination is improbable as the methyl protons where highfield shifted. On the other hand as the carbon atoms next to the nitrogen, which bind to the Lewis acid, are clearly lowfield shifted this result was unclear. No coordination in the NMR experiment was observed for 2,5-bis(trifluoromethyl)-1,3,4-oxadiazole (**240**) and 1,3,4-thiadiazole (**255**). A likely but weak coordination was the result of the experiments with 2,5-bis(phenyl)-1,3,4-oxadiazole (**251**) and Boger-oxadiazole **246**.

The absence of the coordination to the 2,5-bis(trifluoromethyl)-1,3,4-oxadiazole was in accordance to the quantum chemical calculation, where a π-complex was observed. On the other hand, the lack of coordination of 1,3,4-thiadiazole and the Boger-oxadiazoles **246** was in contrast to the calculations.

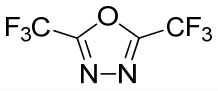
3.2.2.3 Uncatalyzed IEDDA Reactions

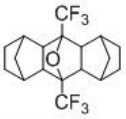
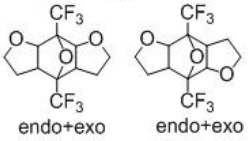
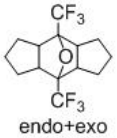
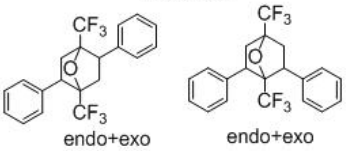
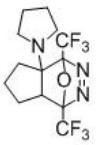
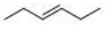
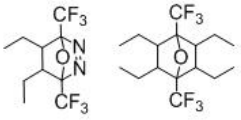
As reported in the literature 2,5-bis(trifluoromethyl)-1,3,4-oxadiazole (**240**) is very reactive as it is a very electron deficient diene. When we performed the IEDDA we wanted to start by

investigating the limits of the reaction by finding a system where the reaction just does not work anymore. Therefore, we investigated this IEDDA reaction with various dienophiles (Table 12) qualitatively by controlling the reactions via NMR and GC-MS.

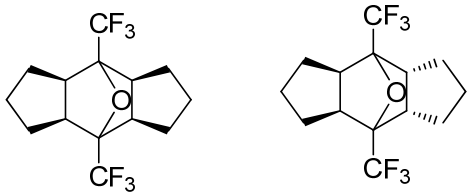
In the first few experiments we found out, that it was best to use three equivalents of the diene itself as solvent for the reaction. This facilitated the NMR-spectroscopy (the solvent has no signals in the ^{1}H-NMR) as well as the GC-MS investigations. Moreover, it was necessary to use pressure vials or pressure stable NMR-tubes as the diene had a low boiling point of 60°C and sometimes temperature of 140°C were necessary.

Table 12



Entry	Dienophil	Temperature	Solvent	Products	Reaction time	Conversion
1		140°C	Diene (3 eq.)		3 h	full conversion
2		140°C	Diene (3 eq.)	 endo+exo endo+exo	6 h-10 h	full conversion
3		140°c	Diene (3 eq.)	 endo+exo	7 d	80%
4		140°C	Diene (3 eq.)	 endo+exo endo+exo	7 d	40%
5		RT	Diene (3 eq.)		1 min	full conversion
6		140°C	Diene (3 eq.)		6 d	full conversion
7		140°C	CDCl3	no reaction	10 d	no reaction
8		140°C	Diene (3 eq.)	no reaction	14 d	no reaction
9		140°C	Diene (3 eq.)	no reaction	3 d	no reaction
10		140°C	Diene (3 eq.)	decomposition	1 d	tin-compound seems to be unstable

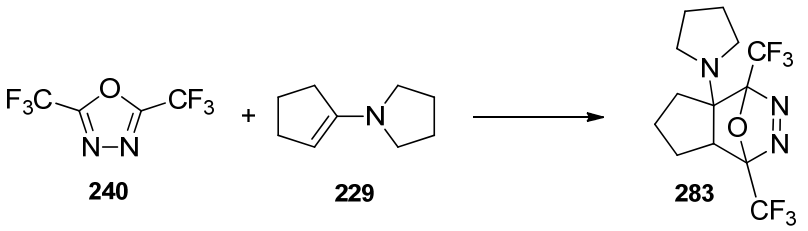
Norbornene (**241**) as dienophile led to full conversion after 3h at 140°C, and the signals in the NMR was in accordance with the report form J. Sauer *et al.* The reaction with 2,3-dihydrofuran (**233**) led to 4 isomers which could be detected in the GC-MS and in the NMR. Both regioisomers were formed and both isomers themselves were found as the *exo*- and *endo*-product. Until the full conversion of cyclopentene the reaction had to be heated for already 7d. Both *endo*- and *exo*-products were formed as well (**281**, **282**, Figure 28)



281 **282**

Figure 28

The same phenomena, the formation of 4 isomers was also observed for styrene. Even though, the reactivity of styrene was low after 7d most of the dienophile was converted. The enamine **229** reacted very rapidly with the oxadiazole **240**. Already during the addition the mixture readily started to reflux and the conversion was complete after a few min. The GC-MS showed only the mass of the cycloadduct **283**, before elimination of nitrogen (Scheme 101)



240 **229** **283**

Scheme 101

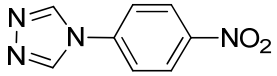
As we encountered this before, for the phthalazines, we tried several procedures to facilitate the elimination. Unfortunately, neither UV-light irradiation, addition of *m*-CPBA (Cope type elimination) nor tris(4-bromophenyl)aminium hexachloroantimonate[13] induced the elimination.

In the case of 3-hexene the reaction was finished after 6 d and afforded a mixture of the cycloadduct and the bisadduct. Furthermore, methyl acrylate was inert at our reaction

conditions, probably because of its low HOMO energy due to the electron withdrawing ester group. Moreover, different non-strained alkynes, phenylacetylene, bis(trimethylsilyl)-acetylene, bis(trimethylstannyl)acetylene were not reactive enough in the reaction. This is in accordance to literature where only strained alkynes like cyclooctyne or very electron rich alkyne like *N*,*N*-dimethylethynamine were reacting.

With these results, our first aim, to demonstrate the limits of the IEDDA, was accomplished. If our catalyst can decreased the reaction temperature significantly, or give access to reactions with dienophiles, which are not reacting without catalyst (e.g. alkynes) we can prove the activity of the catalyst for the five-membered heterocycles.

Table 13



254

Entry	Dienophil	Temp-erature	Solvent	Products
1		140°C	$CDCl_3$	no reaction[a)]
2		140°C	d^6-Acetone	no reaction[a)]
3		140°C	d^2-tertrachloroethane / d^6-DMSO	no reaction[b)]
4		140°C	d^6-DMSO	no reaction after 14 d

a) diene not soluble in solvent
b) to much solvent required, high dilution conditions

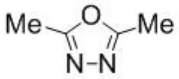
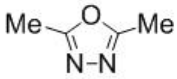
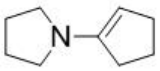
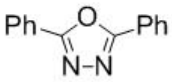
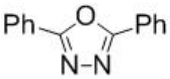
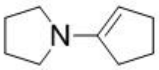
However, first we wanted to investigate the reactivity of the other synthesized heterocycles compared to 2,5-bis(trifluoromethyl)-1,3,4-oxadiazole (**240**). We started with the investigation of 4-(4-nitrophenyl)-1,2,4-triazole (**254**, Table 13), as our calculations showed that it was the diene with the energetically lowest lying LUMO orbital. The major challenge was to find a suitable solvent for the very insoluble diene. After the screening of chloroform, acetone, tetrachloroethane we found that DMSO readily dissolves the diene. As mentioned before, dilution led to slower conversion rates, so only a minimum amount of DMSO was

used. Unfortunately, no Diels-Alder product was detected even after 14d at 140°C. As the electron poor 2,5-bis(trifluoromethyl)-1,3,4-oxadiazole (**240**) reacted readily with different dienophiles we want to investigate the more electron rich 2,5-bis(methyl)-1,3,4-oxadiazole (**250**) (Table 14). Unfortunately, no reaction was observed even after heating for prolonged times (14d) at 140°C. As the LUMO of this diene is much higher in energy than the trifluoromethyl derivative **240** these experimental results were in conclusion with the quantum chemical calculations.

The next diene investigated was 2,5-bis(phenyl)-1,3,4-oxadiazole (**251**) (Table 14). As the diene itself is a solid, we could not perform the reaction under neat conditions, which were found to be superior in the trifluoromethyl-oxadiazole analoga (**240**). As well no conversion could be achieved, even after 14 d at 140°C. The reasons could either be the higher lying LUMO orbital or the steric hindrance due to the two phenyl substituents.

Finally, we also performed some reactions with 1,3,4-thiadiazole (**255**) as diene (Table 14). As it is a low melting solid (41°C) we performed neat reactions as well as reactions in solvents. The diene was found to be not reactive enough to perform reactions at temperatures below 140°C.

Table 14

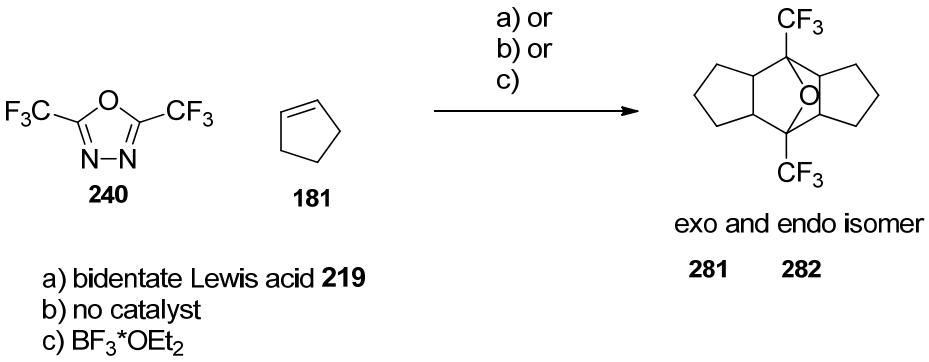
Entry	Diene	Dienophil	Temp-erature	Time	Solvent	Products
1			140°C	8 d	neat	no reaction[a)]
2			140°C	7 d	neat	no Diels-Alder product
3			140°C	14 d	$CDCl_3$	no reaction[a)]
4			140°C	7 d	$CDCl_3$	no reaction[a)]
5			140°C	7 d	d^3-MeCN	no reaction[b)]
6			140°C	3 d	$CDCl_3$	no reaction[a)]
7			rt→80 °C	2 d	neat	no reaction[b)]

a) no conversion, still both starting materials detected in GC-MS and NMR
b) decomposition

3.2.2.4 Catalyzed IEDDA Reactions

After exploring the limitations of the uncatalyzed IEDDA, we now wanted to investigate if our bidentate Lewis acid catalyst **219** could overcome these and facilitate reactions with former inert dienes and dienophiles or lower the reaction temperature significantly. First we investigated reactions with 2,5-bis(trifluoromethyl)-1,3,4-oxadiazole (**240**).

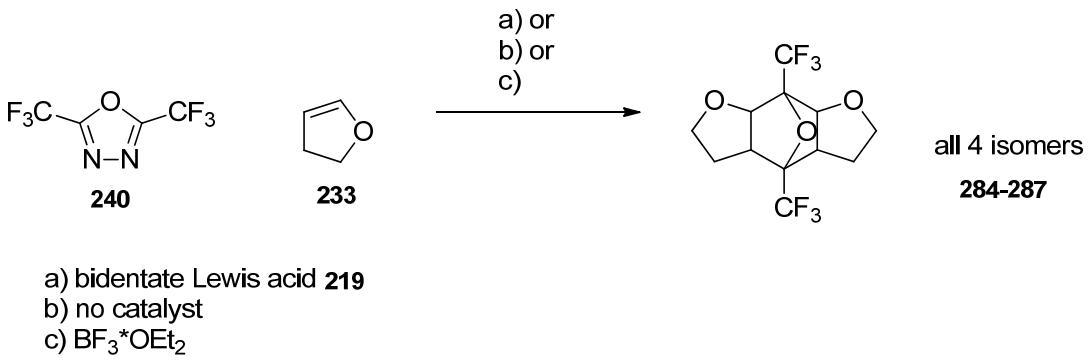
To investigate the influence of the bidentate Lewis acid on some reaction four kinetic studies were performed, comparing the reaction rate in the bidentate Lewis acid catalyzed reaction with the non-catalyzed and $BF_3{}^*OEt_2$ catalyzed reactions. The first used dienophiles was cyclopentene (**181**):



Scheme 102

The reactions were only investigated qualitatively. The ratio between starting materials and the products could not be determined in the GC-MS and partial evaporation due to the high temperature (140°C) made the quantitative comparison in the end impossible. Qualitatively, it was found that no product is formed at 50°C without Lewis acid, which shows the accelerating effect of the catalyst and $BF_3{}^*OEt_2$. When the temperature was raised to 80°C even the uncatalyzed reaction started and the product could be observed. Continued stirring of all three experiments at 80°C led to the result, that actually the reaction with the bidentate Lewis acid is the slowest at this elevated temperatures compared to the non-catalyzed and $BF_3{}^*OEt_2$ catalyzed reactions.

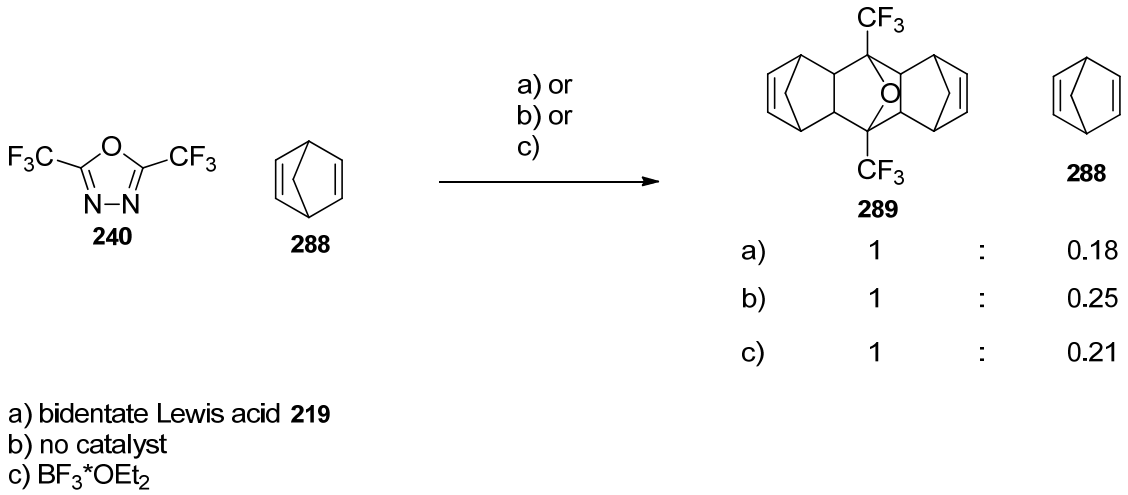
The next studies were performed with 2,3-dihydrofuran (**233**) as dienophile:



Scheme 103

For this diene both catalyzed reaction failed. For $BF_3{}^*OEt_2$ the side reaction, the cationic polymerization is known. The use of the bidentate Lewis acid unexpectedly also led to decomposition of the 2,3-dihydrofuran. This reaction was even performed again twice, but unfortunately led to a similar result. Hence, no conclusion about the reactivity of the Lewis acid could be achieved in these experiments.

Furthermore, norbornadiene (**288**) was used:



Scheme 104

For norbornene as dienophile it was found, that neither catalyst has an accelerating effect on the reaction, as after 3 days (full conversion of the diene) the ratio between product and starting material were almost the same for all three reactions (NMR spectra, Figure 29)

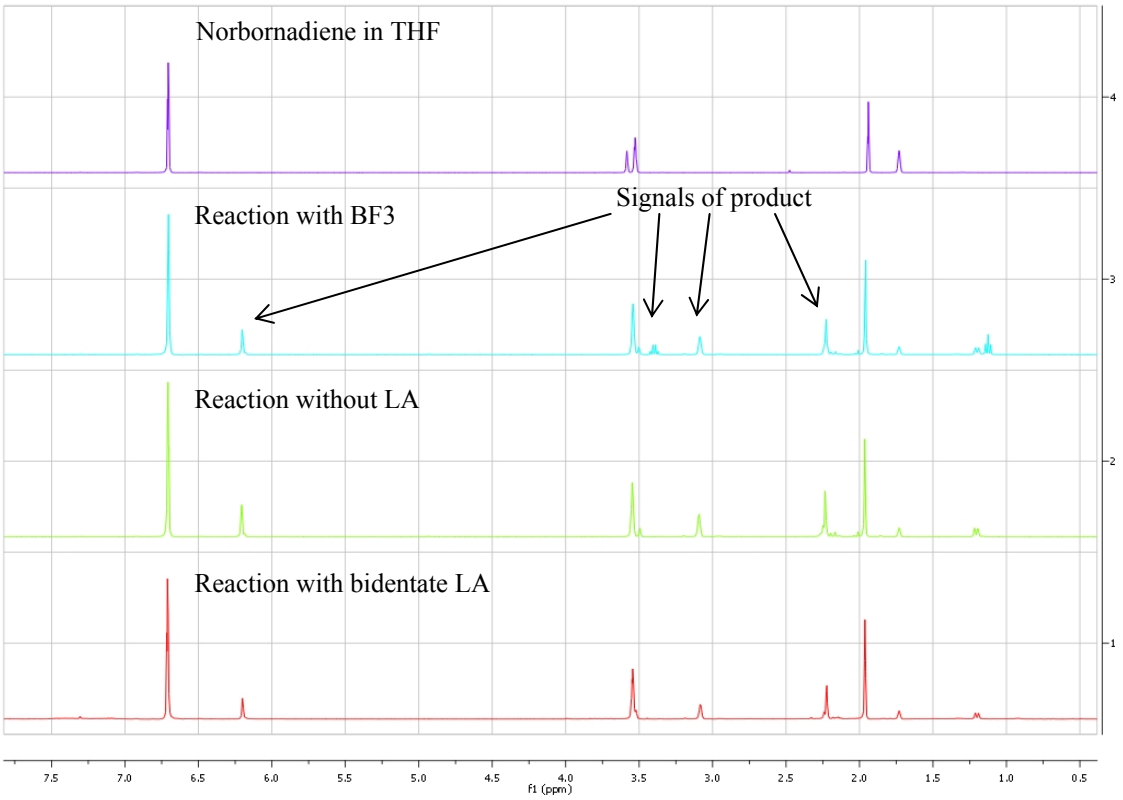
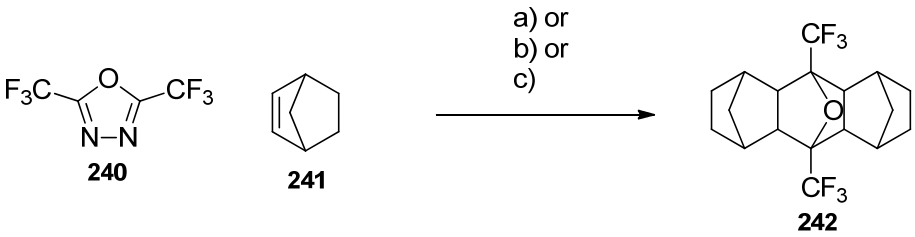


Figure 29

Finally, norbornene (**241**) was also used in another kinetic study:

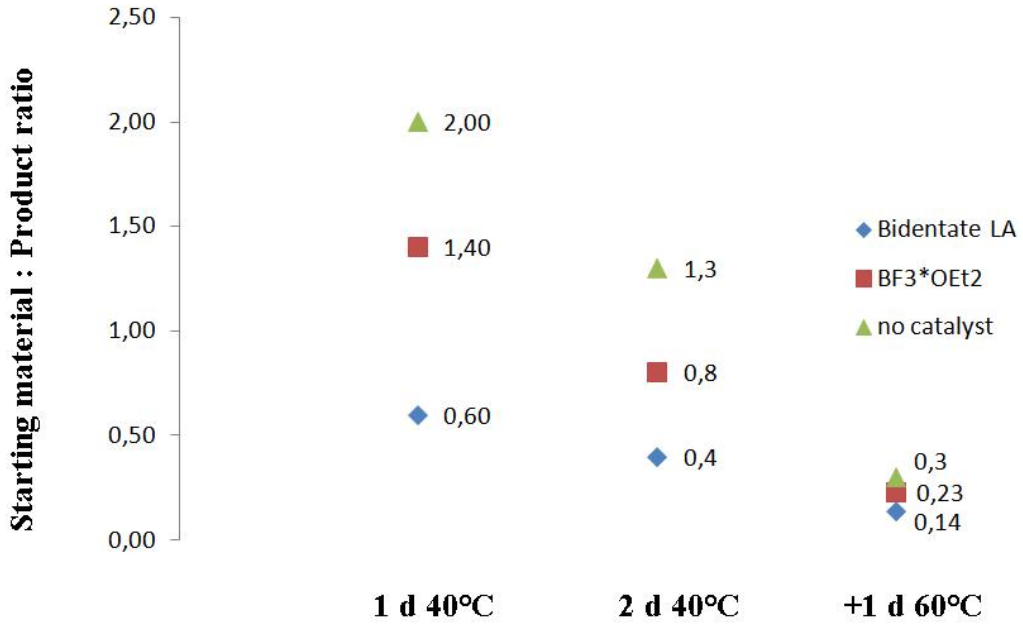


a) bidentate Lewis acid **219**
b) no catalyst
c) BF_3*OEt_2

Scheme 105

In this case the catalyst seemed to have an extraordinary strong catalytic effect (Figure 30). Already after 1d the ratio of starting material to product is almost four times better than in the uncatalyzed and still much faster than in the BF_3*OEt_2 catalyzed reaction. As a matter of fact,

the major compound after 1 d for the bidentate Lewis acid catalyzed reaction is already the product, whereas in the other two experiments the starting material is still the major component of the reaction mixture. This trend is continued and the bidentate Lewis acid catalyzed reaction shows faster conversion throughout the whole reaction time. At the end the three reactions were heated to 60°C for 3d and full conversion of the starting material was achieved for each of them.

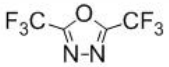
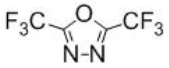
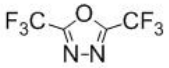
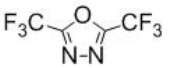
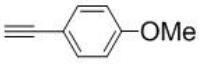
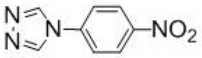
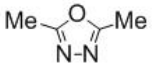
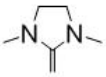
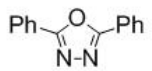
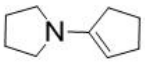
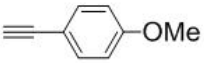
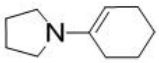
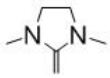
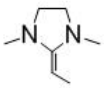


*Values for $BF_3{}^*OEt_2$ for 3d 40°C and +1 d 60°C are extrapolated.

Figure 30

As a next step several reactions with the catalyst and different dienes and dienophiles were performed. Some exemplary reactions are shown in Table 15:

Table 15

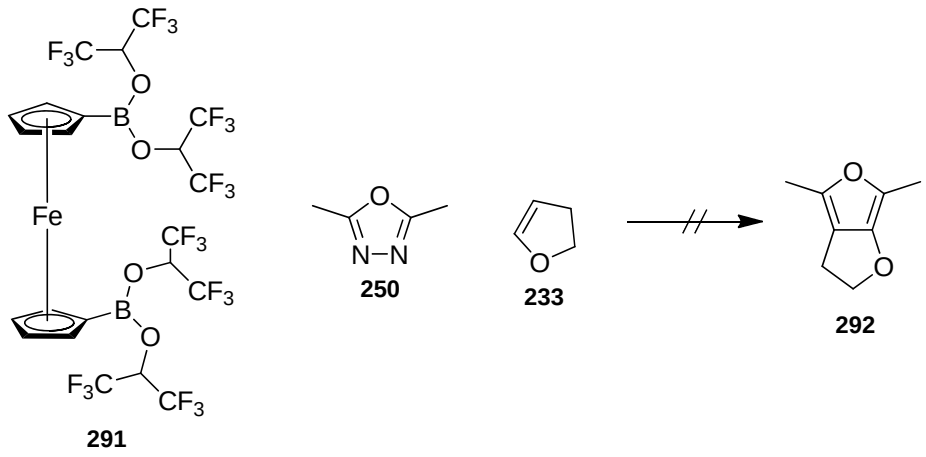
Entry	Diene	Dienophil	Bidentate LA Catalyst	Temper-ature	Solvent	Result
1			0.1 eq	140°C	dry diglyme	No reaction
2			0.1 eq	140°C	Neat	No reaction
3			0.1 eq	140°C	dry diglyme	decomposition
5			0.05 eq	70°C	dry diglyme	No reaction
6			0.1 eq	140°C	d^6-DMSO	No reaction
7			0.05 eq	150°C	dry diglyme	No reaction
8			0.1 eq	140°C	$CDCl_3$	No reaction
9			0.1 eq	140°C	d^3-MeCN/ d^6-benzene	No reaction
10			0.09 eq	40°C	Neat	decomposition
11			0.05 eq	150°C	dry diglyme	No reaction
12			0.05 eq	150°C	dry diglyme	No reaction
13			0.05 eq	150°C	dry diglyme	No reaction
14			0.05 eq	150°C	dry diglyme	No reaction

all reaction where investigated by NMR and GC-MS

The attempt to perform reactions with alkynes with the very reactive bis(trifluoromethyl)oxadiazole **240** was not successful. Bis(trimethylsilyl)acetylene was not reactive enough. Bis(trimethylstannyl)acetylene (**290**) is much more electron rich. Unfortunately, decomposition occurred at temperatures above 80°C, probably because of a reaction between the boron based catalyst and the tin compound **290**. Moreover, all reaction with 4-(*p*-nitrophenyl)-1,2,4-triazole (**254**), 2,5-bis(methyl)-1,3,4-oxadiazole (**250**) and 2,5-bis(phenyl)-1,3,4-oxadiazole (**251**) did not lead to the formation of any IEDDA product at

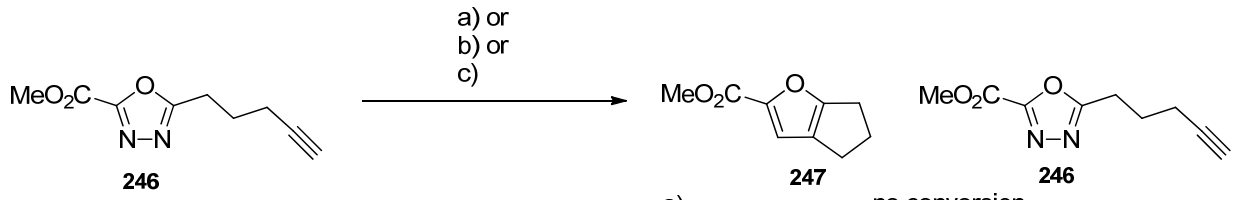
temperatures up to 140°C. The same was true for thiadiazole **255** where no reaction took place even with the very reactive 2,3-dihydrofuran (**233**) and with the enamine **229** only decomposition occurred. Finally, also the 4-(butyl)-1,2,4-triazole (**252**) was used as unreactive diene, no reaction with very reactive dienophiles even at higher temperatures (150°C) occurred.

Due to a collaboration with the Group of Ingo Crossing in Freiburg we had access to a ferrocene based bidentate Lewis acid developed in his group(Scheme 106).[14] The Lewis acid is sterically very hindered and should be suitable due to its eight activating CF_3-groups. Furthermore, in earlier studies it was found to strongly activate phthalazine. We tested this Lewis acid now with a sterically very accessible diene, 2,5-bis(methyl)-1,3,4-oxadiazole (**250**), and the reactive 2,3-dihydrofuran. Unfortunately no conversion was achieved.



Scheme 106

Finally, we wanted to test the Boger-system (**246**) with our catalyst. First, we performed a reaction at 140°C and no conversion was obtained (Scheme 107). We increased the temperature to 205°C (Boger *et al.* used 230°C) and after 3d 14% yield of the product (**247**) were achieved. Moreover, 84% of the starting material (**246**) where isolated, which showed, that the reaction was not finished and that the catalyst probably had only a slight influence on the reactivity.



a) 1,2-dichlorobenzen, 3 d, 140°C
b) 8 mol% bidentate Lewis acid catalyst, 3 d, 205°C
c) triisopropylbenzene, 44 h, 230°C

Scheme 107

3.3 Conclusion

Overall, we could investigate the five-membered heterocycles in detail. Our quantum chemical calculations showed clear trends between electronic effects and the energies of the LUMO orbitals of dienes and the HOMO orbitals of dienophiles. Moreover, several complexes between the catalyst and the dienes were calculated and most five-membered heterocycles gave complexes with the catalyst. Exceptions where the very electron poor dienes (bis(trifluoromethyl)oxadiazole **240**, and three electron poor Boger-type dienes) and dienes with sterically demanding substituents (bis(phenyl)oxadiazole) **251**. A clear correlation between this complexes and the lowering of their FMOs was established, as all σ-complexes also showed a decrease of the LUMO-orbital energies.

Moreover, we could synthesize several dienes, amongst them very challenging substances (Figure 31) due to very low boiling or melting points.

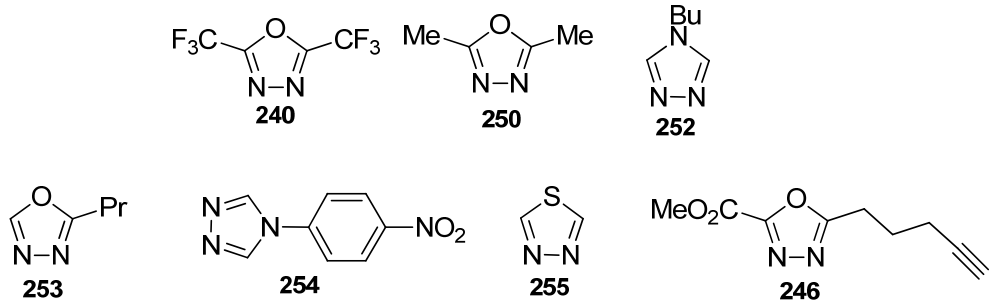


Figure 31

Furthermore, we investigated the complexation of those dienes in NMR-studies and showed that four of them (compounds **251**, **252**, **254**, **246**) led to the desired complex with our established bidentate Lewis acid.

Our investigations to determine the limits of the uncatalyzed IEDDA reaction showed clearly that only electron poor dienes were reacting and either electron rich or strained dienophiles were required to perform the reactions. Surprisingly, the very electron deficient (4-nitrophenyl)-1,2,4-triazole did not undergo any IEDDA reaction, even though the results from our calculations indicated an energetically much lower lying LUMO orbital.

In the catalyzed IEDDA reaction with the bis(trifluoromethyl)oxadiazole (**240**) no clear general activation of the Lewis acid was observed. Moreover, it was not possible to develop the reaction with alkynes at temperatures up to 140°C.

In addition, our catalyst did not activate the less reactive dienes (compound **250**, **251**, **252**, **254**, **255**) enough to perform IEDDA reactions even with very reactive dienophiles.

Finally, the fact that the reaction with the Boger-type oxadiazole could not be accelerated was in accordance with the fact, that no complex in the NMR was observed.

In conclusion, we can see that whereas our catalyst is strongly activating six-membered heterocycles (phthalazines) it seems to be not active enough to perform the same reactions with five-membered heterocycles. The difference of the reactivities can have different reasons.

First, the lone-pairs of the two nitrogen atoms, used in the complexation, have different angles in six-membered heterocycles than in five-membered heterocycles. It seems suitable to state that the six-membered heterocycles seem to have a stronger overlap of the lone pair nitrogen orbitals with the vacant orbitals of the Lewis acid.

Second, in the catalysis of phthalazine there is a difference in the transition state. Phthalazine does not lose its full aromaticity in the reaction, it only loose the contribution from one of the two aromatic rings. In our system, the aromaticity is lost completely and the energy needed to compensate this complete loss has to be higher.

To overcome these drawbacks different more reactive catalysts will be developed in our group. Electron withdrawing groups on the boron substituents might activate the catalyst further and lead to a stronger activation of the dienes. In this case even less reactive diene like 2,5-bis(methyl)-1,3,4-oxadiazole might react in IEDDA reactions in the future.

3.4 References

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Chapter 4

Experimental Part

4.1 General Information

Reagents and Solvents:

All chemicals were used as received from either: Acros, Alfa Aesar, Fluka, Fluorochem, Sigma-Aldrich or VWR without any prior purification unless otherwise noticed. Dry solvents for the reactions were purchased from Acros or Fluka, dried through standard procedures or obtained from a Pure-Solv^{TM} drying system. THF was continuously refluxed and freshly distilled from potassium benzophenone ketyl under nitrogen. Technical grade solvents for extractions and chromatography were distilled once before usage.

Sensitive reaction:

Air sensitive reactions were performed under an argon atmosphere using standard Schlenk-techniques. For water sensitive reactions heated (110°C) glass material was cooled under argon flow.

Analytics and Instruments:

^{1}H-Nuclear Magnetic Resonance (^{1}H-NMR): Bruker DPX-NMR (400 MHz) and Bruker BZH-NMR (250 MHz) instruments were used to measure the spectra. Two-dimensional spectra were recorded on a Bruker Avance 500 (500 MHz). Chemical shifts (δ) are reported in parts per million (ppm) relative to residual solvent peaks or trimethylsilane (TMS), and coupling constants (*J*) are reported in Hertz (Hz). NMR-solvents were obtained from Cambridge Isotope Laboratories, Inc. (Andover, MA, USA) or from ARMAR Ag (Döttingen, Switzerland). The measurements were done at RT . The multiplicities are written as: s=singlet, d=doublet, t=triplet, q=quartet, quin=quintet and m=multiplet. For multiplets only the chemical shift (ppm) of the center of the multiplet is reported. The abbreviation b stands for broad (e.g bs=broad singlet).

^{13}C-Nuclear Magnetic Resonance (^{13}C-NMR): A Bruker DPX-NMR (100.6 MHz) and Bruker Avance 500 (125.8 MHz) instruments were used to record the spectra. Chemical shifts (δ) are reported in parts per million (ppm) relative to residual solvent peaks. The measurements were done at RT .

Fourier-Transform Infrared Spectrometry (IR): The Spectra were recorded on a Shimadzu FTIR-8400S. The compounds were measured pure through a Specac ATR attachment.

Mass Spectrometry (MS): Mass spectra were measured by Dr. H. Nadig (Department of Chemistry, University of Basel) on a VG70-250 [electron ionization (EI)] mass spectrometer or a MAR 312 [fast atom bombardment (FAB)] mass spectrometer. FAB was preformed with 3-nitrobenzyl alcohol (NBA) or glycine (GLY) as matrix. When necessary KCl was added. An Applied Bio Systems Voyager-De™ Pro using 1,8-Dihydroxy-10H-anthracen-9-on as matrix for Matrix Assisted Laser Desorption Ionization-Time of Flight (MALDI-ToF). For the cycloparaphenylenes or macrocycles the matrix, tetracyanquinodimethane in THF with 1% silver trifluoroacetate, like described by C. Bertozzi *et. al.*, was used.[1]

High-resolution Mass Spectrometry (HR-MS): High-resolution mass spectra were recorded in the group of PD. Dr. Stefan Schürch at the University of Bern. They used a Thermo Fisher Scientific LTQ Orbitrap XL a Nanoelectrospray ion source and acetonitrile as solvent. Accurate mass determinations using electrospray ionization are performed on the QStar Pulsar instrument. Mass accuracy is better than ± 5 ppm.

Gas Chromatography-Mass Spectrometry (GC-MS): For GC/MS-analysis a Hewlett Packard 5890 Series II gas chromatography system, with a Macherey-Nagel OPTIMA 1 Me_2Si column (25 m x 0.2 mm x 0.35 m), at 1 mL/min He-flow rate (split = 20:1) with a Hewlett Packard 5971 Series mass selective detector (EI, 70 eV) was used. Moreover, a HP6890 gas chromatograph with a HP5970A detector equipped with a Machery and Nagel Optima5 5% polyphenylmethylsiloxane column (25 m x 0.2 mm id and 35 µM film thickness) was used under otherwise similar conditions.

Melting point (mp): A Will Wetzlar and a Büchi 530 apparatus were used. The measured temperatures are not corrected.

Elementary Analysis (EA): Elemental analyses were measured at the Department of Chemistry University of Basel Microanalytical Laboratory by Mr. W. Kirsch on a Leco CHN-900 analyzer.

Column Chromatography (CC): For column chromatography silica gel 60 (40 – 63 μm) from Fluka or neutral aluminium oxide from Fluka were used. The purification was performed under 0.1 – 2 bar nitrogen pressure. The eluents were technical grade and purified by distillation prior to use.

Preparative Chromatography: For preparative chromatography silica gel glass with a thickness of 2.0 mm from Analtech was used.

Thin Layer Chromatography (TLC): Silica gel 60 F_{254} glasses with a thickness of 0.25 mm from Merck or Polygram® Alox N/UV254 with a thickness of 0.2 mm from Macherey-Nagel were used. Additionally, TLC plates were obtained from Whatman (Partisil, 250 μm x 20 cm x 20 cm, florescent model K6F) and the glass was scored and plates broken into 25 x 100 mm or 50 x 100 mm size with a glass cutter. The detection was observed with a UV-lamp at 253 nm, 302 nm or 366 nm. Compounds were visualized by vanillin, $KMnO_4$, or ninhydrin in some cases.

Gel Permeation Chromatography (GPC): A Shimadzu LC-8A instrument was used to record the gel permeation chromatograms. The measurements were performed at RT with an OligoPore 300 x 7.5 mm column (particle size 6 μm) from Polymer Laboratories by eluting with toluene at a flow rate between 2–10 mL/min at λ=296 nm.

Photochemical reactor: A Rayonet Photochemical Chamber Reactor Model RPR-200, equipped with UV-lamps (300 nm and 350 nm), was used. It was combined with a Rayonet Merry-Go-Round Model-RMA-400 multi-sample rotator, where 8 samples could be irradiated together with equal radiation for each sample.

Rayonet RPR-200

Merry-go-Round

High Performance Liquid Chromatography (HPLC): All components were built by Merck Hitachi. The LaChrone series, consisting of following components was used: D-7000 interface, L-7100 pump, L-7200 auto sampler, L-7300 column oven, L-7400 UV detector and a L-7622 solvent degasser. All spectra were recorded at RT, as column a LiChrosphere® 100 RP-18 (5 µm) was utilized.

4.2 Towards the Synthesis of Carbon Nanotube Fragments[2]

The following compounds were synthesized according to literature: 2,5-diiodoterephthalic acid (**79**) [3], tetrakis(triphenylphosphine)palladium[4].

General Procedure 1 for the Protection of 1,6-Heptadiyne (**61**)

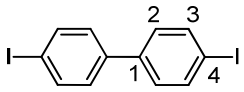
An oven dried flask was flushed with argon for 5 min. After cooling to RT, dry tetrahydrofuran was added with argon counter flow. Then, 1,6-heptadiyne (1.30 eq) was added and the mixture was cooled to 0°C. To this solution ethylmagnesium bromide (1.10 eq) was added dropwise and the reaction mixture was stirred at RT for 2.5 h. The protection reagent (1.00 eq) was slowly added. Then, the solution was allowed to warm to RT and stirred overnight. The reaction mixture was diluted with TBME and extracted with sat aq. NH_4Cl solution. After separation, the organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to afford the desired compound.

General Procedure 2 for Sonogashira Couplings Reactions:

An oven dried flask was flushed with argon for 5 min. After cooling to RT, dry tetrahydrofuran was added with argon counter flow. Then, the alkyne (1.00 eq or 2.04 eq), the aryl iodide (1.00 eq), CuI (10 mol % or 20 mol %), $Pd(PPh_3)_4$ (5 mol % or 10 mol %) and di*iso*propylamine were added under an inert atmosphere. The flask was wrapped in aluminum foil, degassed for 15 min and stirred at RT overnight. Afterwards, the solution was extracted with sat. aq. NH_4Cl solution, the two phases were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were extracted with sat. aq. NH_4Cl solution, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel.

4.2.1 First Generation Synthesis

4,4'-Diiodobiphenyl (**62**)[5]

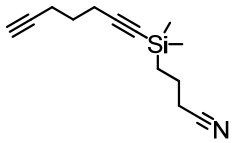


A mixture of biphenyl (**73**; 20.0 g, 130 mmol, 1.00 eq), I_2 (36.4 g, 143 mmol, 1.10 eq) and HIO_3 (16.4 g, 73.4 mmol, 0.56 eq) was stirred in AcOH (130 mL), H_2O (13 mL), conc. H_2SO_4 (13 mL) and CCl_4 (26 mL) at 80°C for 6 h. After cooling to RT, the mixture was poured into H_2O with precipitation of a solid. The remaining purple solid was extracted with a soxhlet extractor in dichloromethane overnight. The formed precipitate was collected by filtration and the mother liquor was extracted with 20% aq. Na_2SO_3. The organic layer was washed with H_2O, dried over Na_2SO_4 and filtrated. The precipitate from the mother liquor was recrystallized from $CHCl_3$. The combined precipitates were dried under high vacuum to afford the desired product (33.5 g, 82.5 mmol, 64%) as slightly yellow crystals.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.76 (m, 4H, H-2), 7.29 (m, 4H, H-3).

^{13}C-NMR (101 MHz, $CDCl_3$) δ = 140.1 (2C, C-1), 138.4 (4C, C-2), 129.0 (4C, C-3) 94.3 (2C, C-4).

CPDMS-protected bisalkyne **63**[6]



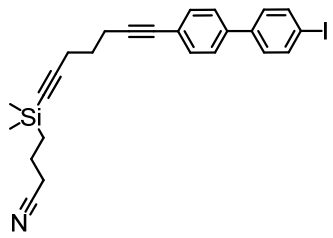
The CPDMS-monoprotected bisalkyne **63** was synthesized according to the general procedure 1 from 1,6-heptadiyne (**61**; 8.70 mL, 76.0 mmol, 1.30 eq), ethylmagnesium bromide (1M in THF 40.0 mL and 3M in Et_2O (8.50 mL, 65.5 mmol, 1.10 eq) and CPDMS-Cl (9.50 mL, 57.9 mmol, 1.00 eq) in dry THF (180 mL). After work up, the crude oil was purified by

column chromatography on silica gel (ethyl acetate/hexane 1:15 to 1:1) to yield the title compound (7.60 g, 35.0 mmol, 60%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 2.39 (t, *J*=7.0, 2H), 2.35 (t, *J*=7.1, 2H), 2.29 (td, *J*=7.1, *J*=2.4, 2H), 1.96 (td, *J*=2.6, *J*=0.6, 1H), 1.74 (m, 4H), 0.73 (m, 2H), 0.14 (s, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ = 119.9, 107.8, 83.5, 83.4, 69.1, 27.6, 20.8, 20.6, 19.1, 17.7, 16.0, –1.5.

CPDMS-monoprotected Iodobiphenylalkyne **65**



The CPDMS-monoprotected iodobiphenylalkyne **65** was synthesized according to the general procedure 2 from CPDMS-monoprotected bisalkyne **63** (2.47 g, 11.3 mmol, 1.00 eq), 4,4'-diiodobiphenyl (**62**) (4.68 g, 11.4 mmol, 1.01 eq), CuI (216 mg, 10 mol %), $Pd(PPh_3)_4$ (667 mg, 5.00 mol %) and DIPA (20 mL) in dry THF (90 mL). After work up, the crude residue was purified by column chromatography on silica gel (ethyl acetate/hexane 1:10 to 1:3 gradient) to yield the title compound **65** (2.50 g, 5.05 mmol, 45%) as a white solid and as byproduct the CPDMS-diprotected biphenylbisalkyne(1.24 g, 2.12 mmol, 19%) as an orange solid.

EA (%): calcd.: C, 60.60; H, 5.29; N, 2.83;

found: C, 60.65; H, 5.20; N, 2.62.

IR ($\tilde{\nu}$/cm^{-1}): 2952 (w), 2166 (m), 1480 (m), 1423 (w), 1388 (w), 1248 (m), 1070 (w), 1018 (m), 998 (m), 834 (m), 809 (s), 771 (m).

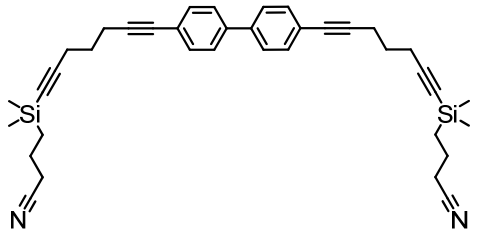
mp: 90–92°C.

MS (EI, 70 eV), *m/z*: 494 (100%) [M^+], 480, 427.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.76 (m, 2H), 7.46 (m, 4H), 7.31 (m, 2H), 2.54 (t, *J*=7.0, 2H), 2.41 (m, 4H), 1.80 (m, 4H), 0.75 (m, 2H), 0.15 (s, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ = 140.1, 139.4, 138.1, 132.2, 129.0, 126.8, 123.4, 120.0, 108.0, 93.5, 90.3, 83.4, 81.2, 27.9, 20.9, 20.7, 19.3, 18.9, 16.1, –1.4.

CPDMS-diprotected Biphenylbisalkyne **66**



The CPDMS-diprotected biphenylbisalkyne **66** was synthesized according to the general procedure 2 from CPDMS-monoprotected bisalkyne **63** (2.45 g, 11.3 mmol, 2.04 eq), 4,4'-diiodobiphenyl (**62**) (2.27 g, 5.54 mmol, 1.00 eq), CuI (213 mg, 20 mol %), $Pd(PPh_3)_4$ (662 mg, 10 mol %) and DIPA (20 mL) in dry THF (110 mL) and stirred overnight. After work up, the crude residue was purified by column chromatography on silica gel (ethyl acetate/hexane 1:3) to yield the desired product (2.54 g, 4.34 mmol, 78%) as a yellow solid.

EA (%): calcd.: C, 78.03; H, 7.58; N, 4.79;

found: C, 77.73; H, 7.61; N, 4.64.

IR ($\tilde{\nu}$/cm^{-1}): 2937 (w), 2172 (m), 1493 (m), 1426 (m), 1327 (w), 1250 (m), 1173 (m), 1020 (m), 844 (m), 819 (s), 808 (s), 763 (m), 663 (m).

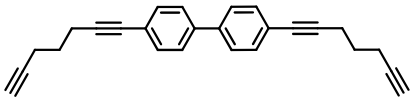
mp: 43–45°C.

MS (EI 70 eV), *m/z*: 584.4 (100%) [M^+], 516.3.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.51 (m, 4H), 7.45 (m, 4H), 2.54 (t, *J*=7.0, 4H), 2.41 (dd, *J*=7.0, *J*=15.0, 8H), 1.80 (m, 8H), 0.75 (m, 4H), 0.17 (s, 12H).

^{13}C-NMR (126 MHz, $CDCl_3$) δ = 139.8, 132.2, 126.9, 123.2, 120.0, 108.1, 90.1, 83.4, 81.3, 28.0, 20.9, 20.7, 19.3, 18.9, 16.1, –1.4.

Deprotection of the CPDMS-diprotected Biphenylbisalkyne **67**



To a solution of THF/MeOH 1:1 (120 mL) was added CPDMS-diprotected biphenylbisalkyne **66** (2.54 g, 4.34 mmol, 1.00 eq) and the mixture was divided equally into 12 vials. Then, dipotassium carbonate (0.41 g, 2.97 mmol, altogether 4.92 g, 35.6 mmol, 8.20 eq) was added to each vial and the resulting light grey mixture was stirred vigorously for 3 h. The vials were diluted with ethyl acetate (9 mL), combined, extracted with H_2O (100 mL) and washed with brine (150 mL). Drying over $MgSO_4$ and evaporation yielded a residue, which was purified by flash chromatography on silica gel (hexane/ethyl acetate 40:1) to obtain the title compound (1.20 g, 3.59 mmol, 82%) as a white solid.

EA (%): calcd.: C, 93.37; H, 6.63;

found: C, 93.26; H, 6.82.

IR ($\tilde{\nu}$/cm^{-1}): 3202 (m), 2958 (w), 2838 (w), 1500 (m), 1452 (m), 1427 (m), 1293 (m), 1004 (m), 857 (m), 822 (s), 625 (s).

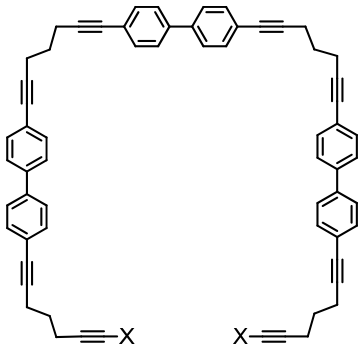
mp: 114–117°C.

MS (EI, 70 eV), *m/z*: 334.2 (100%) [M^+], 281.1.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.51 (m, 4H), 7.45 (m, 4H), 2.57 (t, *J*=7.0, 4H), 2.39 (td, *J*=7.0, *J*=2.6, 4H), 1.99 (t, *J*=2.6, 2H), 1.85 (quint, *J*=7.1, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ = 139.8, 132.2, 126.9, 123.2, 90.1, 83.8, 81.2, 69.1, 27.9, 18.8, 17.9.

CPDMS-diprotected Hexaphenylbisalkyne **68**



X= CPDMS

The CPDMS-diprotected hexaphenylbisalkyne **68** was synthesized according to the general procedure 2 from the terminal bisalkyne **67** (1.00 g, 3.00 mmol, 1.00 eq), CPDMS-protected iodobiphenylalkyne **65** (3.11 g, 6.28 mmol, 2.10 eq), $Pd(PPh_3)_4$ (369 mg, 11 mol %), CuI (116 mg, 20 mol %), DIPA (30 mL) in dry THF (90 mL) and stirred for 3 days. The residue was purified by column chromatography on silica gel (dichloromethane/hexane 1:1 with 1% ethyl acetate) to yield the title compound (3.17 g, 2.96 mmol, 99%) as a yellow solid.

EA (%): calcd.: C, 85.34; H, 6.78; N, 2.62;

found: C, 84.94; H, 6.82; N, 2.43.

IR ($\tilde{\nu}$/cm^{-1}): 2852 (w), 2934 (w) 2171 (m), 1494 (m), 1424 (w), 1249 (m), 1173 (w), 1003 (m), 816 (s).

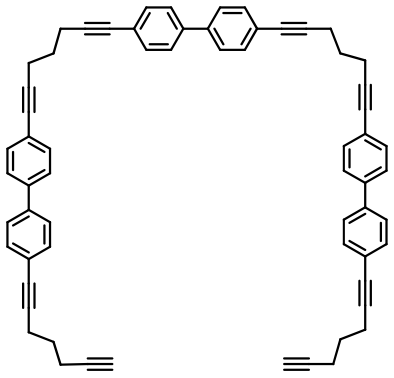
mp: 171–173°C.

MS (MADLI-ToF), *m/z* : 1068.3 (M^+).

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.51 (m, 12H), 7.46 (m, 12H), 2.54 (t, *J*=7.0, 8H), 2.54 (t, *J*=7.0, 4H), 2.42 (m, 8H) 1.80 (m, 8H), 0.75 (m, 4H), 0.16 (s, 12H).

^{13}C-NMR (126 MHz, $CDCl_3$) δ = 139.8, 132.2, 126.9, 123.2, 120.0, 108.0, 90.3, 90.1, 83.4, 81.3, 28.2, 28.0, 20.9, 20.7, 19.3, 19.0, 16.1, 0.21.

Deprotection of the CPDMS-diprotected Hexaphenylbisalkyne **69**



Dry THF (44 mL) was added to CPDMS-diprotected hexaphenylbisalkyne **68** (4.33 g, 4.05 mmol, 1.00 eq). The mixture was divided equally into 11 vials. Then, to each vial was added a solution of tetra-*n*-butylammonium fluoride (0.59 g in 4 mL dry THF, altogether 6.48 g, 24.3 mmol, 6.00 eq in 44 mL dry THF) was added. The mixture was stirred at RT overnight. Then, to each vial was added water (5 mL), the formed precipitate was collected and washed with methanol (5 mL). The precipitate was dried under high vacuum overnight to yield the desired product **69** (3.12 g, 3.86 mmol, 94%) as a grey solid.

EA (%): calcd.: C, 93.85; H, 6.15;

found: C, 90.66; H, 6.33.

IR ($\tilde{\nu}$/cm^{-1}):2934 (w), 1494 (m), 1428 (w), 1398 (w), 1003 (w), 816 (s).

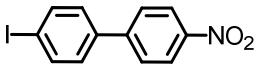
mp: over 270°C.

MS (MADLI-ToF), *m/z* : 819.1 (M^+).

^{1}H-NMR (500 MHz, $CDCl_3$) δ = 7.48 (m, 24H), 2.64 (t, *J*=7.0, 8H), 2.57 (t, *J*=7.0, 4H), 2.40 (td, *J*=7.0, *J*=2.4, 4H), 2.00 (t, *J*=2.3, 2H), 1.95 (quin, *J*=7.0, 4H), 1.85 (quin, *J*=7.0, 4H).

^{13}C-NMR (126 MHz, $CDCl_3$) δ = 139.8, 132.3, 126.9, 123.2, 90.4, 90.1, 83.8, 81.3, 69.1, 28.2, 27.9, 19.0, 18.8, 17.9, 0.21.

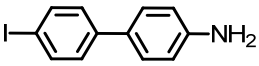
4-Nitro-4‘-iodobiphenyl **(74)**[7]



A solution of iodine (28.6 g, 113 mmol, 1.00 eq) in AcOH (130 mL) was added to biphenyl (**73,** 17.3 g, 113 mmol, 1.00 eq.) and the mixture stirred at 50°C for 15 minutes. A mixture of conc. sulfuric acid (30 mL, 563 mmol, 5.00 eq) and conc. nitric acid (21 mL, 304 mmol, 2.70 eq) was added dropwise. The reaction mixture was stirred for further 4 h at 110°C (gas-washing flask with 10% sodium thiosulfate solution was attached to the condenser). Then, KOH (600 mL, 30% solution in water) was added at 0°C with a solid precipitating. The solid was filtered dissolved in DCM (1.00 L) and the phases were separated. The aqueous phase was then extracted once with DCM (500 mL). The combined organic layers were washed with 10% aq. thiosulfate solution, dried over $MgSO_4$ and evaporated to yield an off-white solid (13.4 g, 41.3 mmol, 37 %).

^{1}HNMR (400*,* $CDCl_3$) δ = 8.30 (m, 2H), 7.84 (m, 2H), 7.71 (m, 2H), 7.36 (m, 2H).

4-Amino-4‘-iodobiphenyl (**75**)[7]



Procedure 1

Solid 4-nitro-4‘-iodobiphenyl (**74**, 4.88 g, 15.0 mmol, 1.00 eq) was suspended in EtOH (50 mL). After the addition of conc. hydrochloric acid (2.25 mL) the mixture was mechanically stirred at reflux for 10 min and then zinc powder (3.80 g, 58.1 mmol, 3.87 eq) was added in small portions. The mixture was stirred for 3.5 hours and cooled to RT . Then, 30 g potassium hydroxide in 400 mL H_2O were added. The aqueous solution was extracted with DCM (3 x 333 mL), the organic phase was dried over $MgSO_4$ and evaporated. The crude residue (4 spots on TLC) was recrystallized from EtOH and Chloroform (some insoluble solid was collected and discarded). After cooling the precipitate was collected added to chloroform and some *iso*-propanol and conc. HCl were added and the suspension was extracted with water. Then, the aqueous layer was basified with 10% NaOH extracted with $CHCl_3$, the organic phase was dried over $MgSO_4$ and evaporated. Then, the residue was again dissolved in DCM, filtered

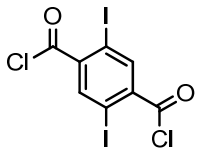
and some *iso*-propanol was added. Afterwards, conc. HCl was added, the mixture was filtrated and the mother liquor was extracted with water and this aqueous phase was combined with the precipitate. Basifying (10% NaOH) and two extractions with DCM, drying over $MgSO_4$ and evaporation yielded the title compound as a yellowish solid (956 mg, 3.24 mmol, 22 %).

Procedure 2

Solid 4-nitro-4‘-iodobiphenyl (**74**, 1.30 g, 4.00 mmol, 1.00 eq) was suspended in a EtOH/THF mixture (1:1, 60 mL) and $SnCl_2{}^*2H_2O$ (4.51 g, 20.0 mmol, 5.00 eq) was added. The mixture was refluxed until the TLC showed full conversion (4.5 h). Then, water and DCM were added until a separation of the phase occurred. The aqueous phase was extracted three times with DCM, the combined organic layers were reextracted with brine, dried over $MgSO_4$ and evaporated to afford the title compound (1.09 g, 3.70 mmol, 93%) as a yellow solid.

^{1}HNMR (400*,* $CDCl_3$) δ = 7.70 (d, *J* = 8.2*,* 2H), 7.37 (d, *J* = 8.2*,* 2H), 7.27 (d, *J* = 7.3*,* 2H), 6.75 (d, *J* = 8.21*,* 2H), 3.76 (bs, 2H).

2,5-Diiodo-1,4-dibenzoyl chloride (**80**)[3]



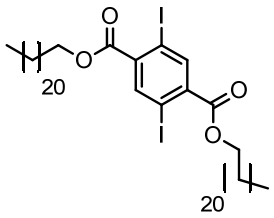
In a flask 2,5-diiodo-1,4-dibenzoic acid (**79**) (1.59 g, 3.80 mmol, 1.00 eq) and thionyl chloride (3.10 mL, 42.5 mmol, 5.60 eq) were combined and refluxed for 4 h, after which no more HCl gas evolved. The excess $SOCl_2$ was removed in vacuo, and the residue was dissolved in hot hexane. The hot, clear hexane solution was decanted into another flask and cooled, whereupon colorless crystals were obtained. Recrystallization from hexane led to crude product (673 mg, 1.48 mmol, 39%) which was used without further purification.

MS (EI, 70 eV) m/z: 453 (4%) [M^+], 418, 327, 292 (100%), 264, 228.

^{1}HNMR (400 MHz, $CDCl_3$) δ = 8.42 (s, 2H).

^{13}CNMR (101 MHz, $CDCl_3$) δ = 165.5 (2C), 143.8 (2C) 143.5 (2C), 91.8 (2C).

2,5-Diiodo-1,4-didocosanol ester (**81**)



The freshly prepared 2,5-diiodo-1,4-dibenzoyl chloride (**80**) (537 mg, 1.18 mmol, 1.00 eq) was added to a solution of docosanol (826 mg, 2.48 mmol, 2.10 eq) in DCM (minimal amount to dissolve the alcohol). Then, triethylamine (1.02 mL, 7.32 mmol, 6.20 eq) was added and the mixture was stirred overnight at reflux. The reaction was quenched with water, extracted with DCM and washed with sat. aqueous ammonium chloride, dried over $MgSO_4$, evaporated and recrystallized from hexane to yield the title compound (611 mg, 590 µmol, 43 %) as colorless crystals.

EA (%): calcd.: C, 60.34; H, 8.96;

found: C, 62.08; H, 8.95;

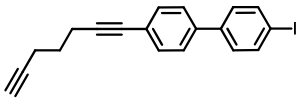
IR ($\tilde{\nu}$ /cm^{-1}): 2914 (s), 2892 (w), 2849 (m), 1728 (m), 1471 (m), 1283 (w), 1240 (m), 1234 (w), 1126 (w), 1114 (w), 1044 (m), 953 (w), 906 (w), 717 (m).

mp: 59-61°C.

MS (EI, 70 eV) m/z: 1034.5 (31%) [M^+], 908.6, 727.2, 601.3, 417.7, 292.9 (100%).

^{1}HNMR (400 MHz, $CDCl_3$) δ = 8.27 (s, 2H), 4.34 (m, 4H), 1.82 – 1.72 (m, 4H), 1.34 (m, 76H), 0.88 (t, *J*=6.9, 6H).

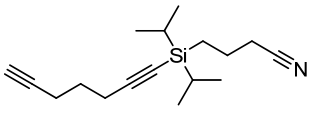
Alkenyl iodobiphenyl **82**



Monoprotected alkyne **65** (149 mg, 300 µmol, 1.00 eq) was dissolved in 6 mL THF/MeOH (1:1) and potassium carbonate (174 mg, 1.26 mmol, 4.10 eq) was added. The suspension was stirred at RT for 4 h. Then, water was added and the aqueous phase was extracted three times with ether. The combined organic layers were dried over magnesium sulfate and the solvent was evaporated. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate 20:1) to afford the title compound **82** (39.0 mg, 105 mmol, 35%) as a slightly yellowish oil. As the complete compound was directly used in the next step no further analytical data was recorded.

MS (EI, 70 eV) m/z: 370 (100%) [M^+], 243, 152, 91.

CPDIPS-monoprotected Bisalkyne **83**



The CPDIPS-monoprotected bisalkyne 83 was synthesized according to the general procedure 1 from 1,6-heptadiyne (**61**; 1.52 g, 16.5 mmol, 1.02 eq), ethylmagnesium bromide (3M in Et_2O, 5.5 mL, 16.5 mmol, 1.02 eq) and CPDIPS-Cl (3.52 g, 16.2 mmol, 1.00 eq) in dry THF (60 mL). After the work up, the crude product was purified by column chromatography on silica gel (ethyl acetate/hexane 1:15 to 1:1) to obtain the title compound (2.01 g, 7.35 mmol, 45%) as a colorless oil.

EA (%): calcd.: C, 74.66; H, 9.95; N, 5.12;

found: C, 74.66; H, 9.76; N, 5.17.

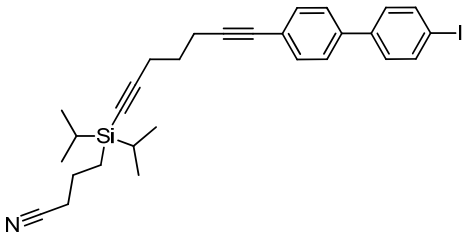
IR ($\tilde{\nu}$ /cm^{-1}): 3307 (w), 2940 (s), 2890 (w), 2864 (s), 2170 (s), 1462 (m), 126 (m), 1175 (w), 1043 (m), 881 (s), 725 (m), 697 (m), 652 (s).

MS (FAB), *m/z*: 274.2 (17%) [M$^+$+H], 230.1, 182.2 (100%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 2.36 (m, 6H), 1.97 (t, *J*=2.7, 1H), 1.78 (m, 4H), 0.99 (m, 14H), 0.72 (m, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ = 120.0, 109.0, 83.6, 80.4, 69.1, 27.8, 21.5, 21.0, 19.1, 18.4, 18.1, 17.7, 11.9, 9.9.

CPDIPS-monoprotected Iodobiphenylalkyne **84**



The CPDIPS-monoprotected iodobiphenylalkyne **84** was synthesized according to the general procedure 2 from CPDIPS-monoprotected bisalkyne **83** (1.50 g, 5.48 mmol, 1.00 eq), 4,4'-diiodobiphenyl (**62**; 2.78 g, 5.56 mmol, 1.01 eq), CuI (104 mg, 10 mol %), $Pd(PPh_3)_4$ (320 mg, 5.0 mol %) and DIPA (18 mL) in dry THF (40 mL). After one day the reaction was worked up and the crude residue was purified by column chromatography on silica gel (ethyl acetate/hexane 1:10) to obtain the title compound (1.52 g, 2.18 mmol, 40%) as a white solid and as a byproduct the diprotected biphenylbisalkyne (695 mg, 1.26 mmol, 23%) as a brown solid.

EA(%): calcd.: C, 63.15; H, 6.21; N, 2.54;

found: C, 63.20; H, 6.26; N, 2.67.

IR ($\tilde{\nu}$ /cm^{-1}): 2943 (m), 2862 (m), 2173 (w), 1478 (m), 1466 (w), 1442 (w), 1385 (w), 1176 (w), 998 (s), 882 (m), 809 (s), 729 (m), 690 (m), 672 (m).

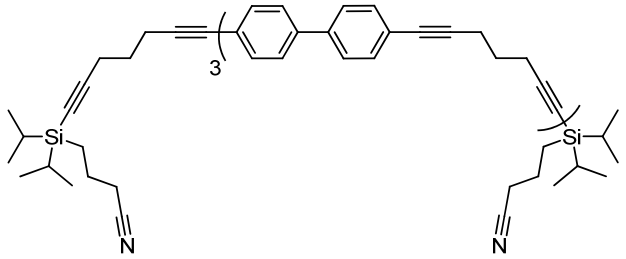
mp: 44–46°C.

MS (FAB), *m/z*: 552.1 (100%) [M^++H], 508.1, 466.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.76 (m, 2H), 7.47 (m, 4H), 7.32 (m, 2H), 2.57 (t, *J*=7.0, 2H), 2.43 (m, 4H), 1.83 (m, 4H), 1.03 (m, 14H), 0.74 (m, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ = 140.3, 139.6, 138.3, 132.5, 129.2, 127.0, 123.6, 120.2, 109.4, 93.7, 90.5, 81.4, 80.6, 28.3, 21.7, 21.2, 19.5, 19.0, 18.6, 18.3, 12.1, 10.1, 0.4.

CPDIPS-diprotected Hexaphenylbisalkyne **85**



The CPDIPS-diprotected hexaphenylbisalkyne **87** was synthesized according to the general procedure 2 from the terminal bisalkyne **67** (292 mg, 0.873 mmol, 1.00 eq), CPDIPS-monoprotected iodobiphenylalkyne **84** (1.00 g, 1.82 mmol, 2.10 eq), $Pd(PPh_3)_4$ (106 mg, 10 mol %), CuI (35 mg, 22 mol%), DIPA (10 mL) in dry THF (60 mL). After stirring for 3 days, the solution was poured into sat. aq. NH_4Cl solution (90 mL) and the organic phase was separated. The aqueous layer was extracted with ethyl acetate (3 x 100 mL), the organic layers were combined and extracted with sat. aq. NH_4Cl solution (2 x 130 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (dichloromethane/hexane 1:1 with 1% ethyl acetate) to afford the title compound (528 mg, 0.447 mmol, 51%) as a yellow solid.

EA (%): calcd.: C, 85.37; H, 7.51; N, 2.37;

found: C, 83.44; H, 7.55; N, 2.39.

IR ($\tilde{\nu}$ /cm^{-1}): 2932 (m), 2863 (m), 2168 (m), 1492 (m), 1462 (w), 1425 (w), 1003 (m), 881 (m), 821 (s), 694 (m).

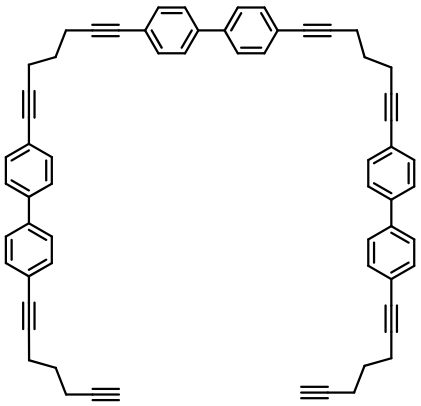
mp: 115–118°C.

MS (MADLI-ToF), *m/z* : 1180.52 (M^+).

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.49 (m, 24H), 2.64 (t, *J*=7.0*,* 8H), 2.57 (t, *J*=7.0*,* 4H), 2.43 (m, 8H) 1.95 (quin, *J*=7.0*,* 4H), 1.80 (m, 8H), 1.01 (m, 28H), 0.74 (m, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ = 139.8, 132.5, 132.4, 132.3, 132.2, 131.8, 128.8, 128.7, 126.9, 123.2, 120.0, 109.2, 90.4, 90.1, 28.2, 28.1, 21.5, 21.0, 19.3, 19.0, 18.8, 18.4, 18.2, 11.9, 9.9.

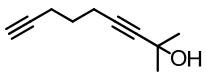
Deprotection of the CPDIPS-diprotected Hexaphenylbisalkyne **69**



Dry THF (19 mL) was added to CPDIPS-diprotected hexaphenylbisalkyne **85** (384 mg, 325 µmol, 1.00 eq). Then, a solution of tetra-*n*-butylammonium fluoride (519 mg, 1.94 mmol, 6.00 eq, in 1 mL dry THF) was added. The mixture was stirred at RT overnight. Then, water was added and the formed precipitate was collected, washed with methanol (5 mL) and dried under high vacuum to yield the desired product (255 mg, 311 µmol, 96%) as a grey solid.

Analytical data was identical with the synthesized samples from the CPDMS-strategy (*vide supra*).

DMH-monoprotected Bisalkyne **87**[8]

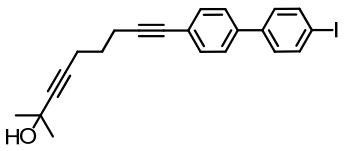


The DMH-monoprotected bisalkyne 87 was synthesized according to the general procedure 1 from 1,6-heptadiyne (**61**; 1.99 g, 21.6 mmol, 1.00 eq), ethylmagnesium bromide (3M in Et_2O 7.5 mL, 22.5 mmol, 1.04 eq) and acetone (1.60 mL, 21.7 mmol, 1.00 eq) in dry THF (25 mL). After stirring overnight the workup was performed and the crude product was purified by column chromatography on silica gel (TBME/hexane, 1:2) to afford the desired product (1.82 g, 12.1 mmol, 56%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 2.29 (m, 4H), 2.00 (bs, 1H), 1.95 (t, *J*=2.7, 1H), 1.70 (quint, *J*=7.1, 2H), 1.46 (s, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ = 86.0, 83.8, 81.4, 69.0, 65.4, 31.9, 27.7, 17.8, 17.7.

DMH-monoprotected Iodobiphenylalkyne **88**



The DMH-monoprotected iodobiphenylalkyne **88** was synthesized according to the general procedure 2 from DMH-monoprotected bisalkyne **87** (652 mg, 4.34 mmol, 1.00 eq), 4,4'-diiodobiphenyl (**62**; 1.78 g, 4.35 mmol, 1.00 eq), CuI (41 mg, 5.0 mol %) and $[Pd(PPh_3)_2Cl_2]$ (99 mg, 3.3 mol %) in dry TEA (60 mL). After stirring overnight, the solution was diluted with sat. aq. NH_4Cl solution (60 mL) and ethyl acetate (100 mL). The aqueous layer was separated and the organic phase was extracted with sat. aq. NH_4Cl solution (2 x 70 mL). The organic phase was washed with brine (90 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (ethyl acetate/hexane 1:3 to 1:2) to afford the desired product (652 mg, 1.52 mmol, 35%) as a yellow solid.

EA (%): calcd.: C, 61.69; H, 4.94;

found: C, 60.80; H, 5.04.

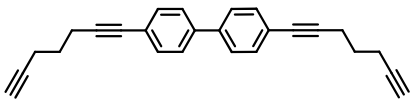
IR ($\tilde{\nu}$/cm^{-1}): 1478 (m), 1363 (m), 1238 (m), 1165 (m), 1141 (m), 1067 (m), 998 (m), 810 (s).

mp: 137–139°C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.75 (m, 2H), 7.47 (m, 4H), 7.32 (m, 2H), 2.53 (t, *J*=7.1, 2H), 2.38 (t, *J*=7.1, 2H), 1.81 (m, 3H), 1.51 (s, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ = 140.1, 139.3, 138.0, 132.2, 128.9, 126.8, 123.4, 93.4, 90.4, 86.0, 81.6, 81.0, 65.4, 31.9, 28.0, 18.8, 18.0.

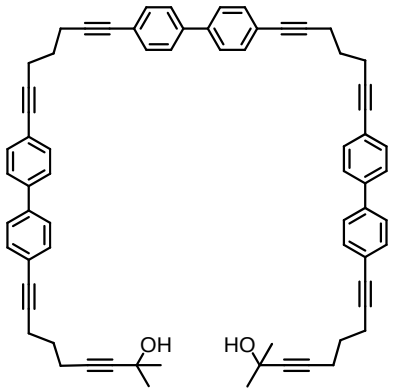
Deprotection of the DMH-diprotected Biphenylbisalkyne **67**



A mixture of DMH-diprotected arylbisalkyne **89** (268 mg, 594 µmol, 1.00 eq) and KOH (146 mg, 2.60 mmol, 4.41 eq) was stirred in toluene (27 mL) and refluxed for 10 min. After cooling to RT, the solvent was removed from the reaction mixture under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate/*hexane* 1:40) to afford the desired product (183 mg, 0.55 mmol, 92%) as a pale yellow solid.

Analytical data was identical with the synthesized samples from the CPDMS-strategy (*vide supra*).

DMH-diprotected Hexaphenylbisalkyne **90**



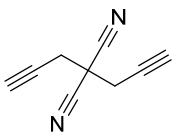
The DMH-diprotected hexaphenylbisalkyne **90** was synthesized according to the general procedure 2 from the terminal bisalkyne **67** (106 mg, 317 µmol, 1.00 eq), DMH-monoprotected iodobiphenylalkyne **88** (278 mg, 649 µmol, 2.05 eq), $Pd(PPh_3)_4$ (37 mg, 10 mol %), CuI (13 mg, 22 mol %), DIPA (6 mL) in dry THF (15 mL) and stirred for 3 days. Then, the reaction was worked up and the residue was purified by column chromatography on silica gel (TBME/hexane 1:3) to obtain the desired product (159 mg, 170 µmol, 54%) as a yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.49 (m, 24H), 2.64 (t, *J*=7.0*,* 8H), 2.54 (t, *J*=7.0*,* 4H), 2.38 (t, *J*=7.1*,* 4H), 1.94 (quin, *J*=7.0*,* 4H), 1.82 (m, 6H), 1.51 (s, 12H).

The missing analytical data is under investigation.

4.2.2 Second Generation Synthesis

2,2-Di(2-propynyl)malononitrile **93**[9]



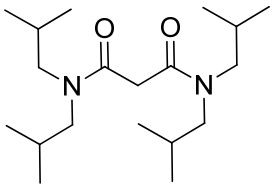
In a two-necked flask malononitrile (**91**, 1.00 g, 15.0 mmol, 1.00 eq), TBAB (200 mg, 600 µmol, 0.04 eq) and propargyl bromide (**92**, 3.58 mL, 33.2 mmol, 2.20 eq) were added to 10

mL THF and the mixture was stirred for 30 min. Then, potassium carbonate was added and the mixture was stirred overnight at RT (until TLC showed full conversion). Then, the mixture was carefully evaporated and purified by column chromatography (SiO_2, hexane/DCM 3:2) to yield the title compound (1.87 g, 13.2 mmol, 87%) as yellow solid.

MS (EI, 70 eV) m/z: 141 (13%) (M^+-1), 115, 103, 64, 39 (100%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 3.07 (d, *J*=2.6, 4H), 2.42 (t, *J*=2.6, 2H).

Tetra-*iso*butylmalonamide **95**[10]

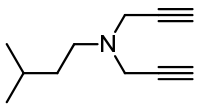


Malonyl dichloride (**94**, 1.00 g, 6.88 mmol, 1.00 eq) was added to 15 mL toluene, then di-*iso*butylamine (4.80 mL, 27.5 mmol, 4.00 eq) was added and the mixture was refluxed overnight (white precipitate formed made the mixture unstirrable). Then, the solvent was evaporated and the mixture was recrystallized from EtOAc (few drops of MeOH). The crystals formed (the amine hydrochloride) were filtered off and the mother liquor was evaporated to yield a yellow residue. Column chromatography on silica (R_f=0.29, hexane/ethyl acetate, 3:2) yielded the amide (925 mg, 2.83 mmol, 41 %) as yellow oil.

MS (EI, 70 eV) m/z: 326 (7%) (M^+), 283, 271, 215, 198, 156, 128 (100%), 57.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 3.51 (s, 2H), 3.20 (m, 8H), 2.18 (m, 4H), 0.92 (m, 3H), 0.90 (m, 3H), 0.87 (m, 3H), 0.85 (m, 3H).

Dipropargyl-isoamyl amine **102**



Isoamyl amine (**101**, 4.70 mL, 40 mmol, 1.00 eq) was added to a suspension of potassium carbonate (12.2 g, 88.0 mmol, 2.20 eq) in DMF (120 mL). After 5 min propargyl bromide (**92**, 80% in toluene, 12.5 g, 84.0 mmol, 2.10 eq) was added and the suspension was refluxed for 3 h. Then, water was added (120 mL) and the solution was extracted several times with Et_2O. The combined organic layers were dried over $MgSO_4$ and carefully evaporated (500 mbar at 40°C). Distillation (82°C, 12 mbar) of the residue yielded the desired tertiary amine (3.90 g, 23.9 mmol, 60%) as a colorless liquid.

EA (%): calcd.: C, 80.93; H, 10.49; N, 8.58;

found: C, 80.60; H, 10.56; N, 8.61.

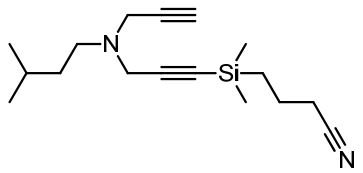
IR ($\tilde{\nu}$ /cm^{-1}): 3306 (s), 2953 (s), 2921 (m), 2874 (w), 2813 (w), 1462 (m), 1433 (m), 1325 (m), 1169 (w), 1135 (w), 1115 (m), 1085 (m), 900 (m), 854 (w).

MS (EI 70 eV) m/z: 163 (0.4%) [M^+], 106 (100%), 77, 39.

^{1}HNMR (400 MHz, $CDCl_3$) δ = 3.46 (d, *J*=2.4, 4H), 2.60 – 2.52 (m, 2H), 2.24 (t, *J*=2.4, 2H), 1.70 – 1.57 (m, 1H), 1.43 – 1.33 (m, 2H), 0.93 (d, *J*=6.6, 6H).

^{13}CNMR (126 MHz, $CDCl_3$) δ = 79.1, 73.1, 51.3, 42.3, 36.6, 26.5, 22.8.

CPDMS-dipropargyl-*isoamyl* amine **103**



Dipropargyl-isoamylamine **102** (2.32 g, 142 mmol, 1.00 eq) was dissolved in 100 mL dry THF and ethylmagnesium bromide (3M in Et_2O, 4.17 mL, 12.5 mmol, 0.88 eq) was added dropwise at 0°C. The mixture was stirred for 30 min at 0°C and 1h at RT, then CPDMS-Cl (1.91 g, 11.8 mmol, 0.83 eq) was added dropwise at 0°C. After 1 d at RT the solution was slowly quenched with water and diluted with EtOAc. The organic layer was washed twice with NH_4Cl, the aqueous layer was re-extracted with TBME and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and evaporated. The crude mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate, 4:1) to obtain the monoprotected alkyne as a colorless liquid (2.01 g, 6.97 mmol, 59%).

EA (%): calcd.: C, 70.77; H, 9.78; N, 9.71;

found: C, 70.69; H, 9.92; N, 9.71.

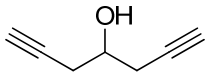
IR ($\tilde{\nu}$ /cm^{-1}): 3330 (w), 2953 (w), 2868 (w), 1464 (w), 1426 (w), 1361 (w), 1317 (w), 1250 (w), 1171 (w), 1139 (w), 1116 (w), 1088 (w), 975 (w), 831 (m), 818 (m), 816 (m), 811 (m), 794 (m), 774 (m).

MS (FAB) m/z: 289 (2%) [M^++1], 231, 154, 126 (100%), 98, 43.

^{1}HNMR (400 MHz, $CDCl_3$) δ = 3.45 (s, 1H), 3.44 (d, *J*=2.4, 1H), 2.58 – 2.53 (m, 1H), 2.42 (t, *J*=7.0, 1H), 2.24 (t, *J*=2.4, 1H), 1.84 – 1.74 (m, 1H), 1.69 – 1.59 (m, 1H), 1.38 (dd, *J*=15.1, 7.1, 1H), 0.93 (d, *J*=6.6, 3H), 0.83 – 0.75 (m, 1H), 0.19 (s, 3H).

^{13}CNMR (126 MHz, $CDCl_3$) δ = 119.9, 102.9, 87.8, 79.0, 73.2, 51.2, 43.5, 42.5, 36.5, 26.5, 22.9, 20.8, 20.7, 16.0, 0.2.

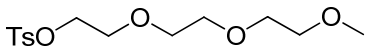
Hepta-1,6-diyn-4-ol (**105**)[11]



In a dry three-neck flask equipped with a reflux condenser, thermometer and a dropping funnel magnesium turnings (3.68 g, 152 mmol, 3.03 eq), mercury chloride (204 mg, 750 µmol, 0.500 mol %) and a crystal of iodine were stirred for 10 min under argon. Then, 100 mL of dry diethylether and propargyl bromide (**92**, 80% in toluene, pre-dried overnight with 4Å molesieve, 1.6 mL out of altogether 16.2 mL, 150 mmol, 3.00 eq) were added. After 4 min the yellow color was gone and gentle heating with a heat gun started the reaction which sustained the reflux itself. After 5 min the mixture was cooled to 10°C and the rest of the propargyl bromide (in 50 mL ether) was added in such a rate to maintain the internal temperature between 0°C and 10 °C (ice-salt bath) over 2.5 h. After complete addition the reaction was stirred for another 2 h at RT. This suspension was carefully transfered via a cannula to an overhead stirred solution of ethyl formate (**104**, pre-dried for 24 h over 4Å molesieve, 4.04 mL, 50.0 mmol, 1.00 eq) in dry ether (100 mL) at 0°C (precipitate formed). After the addition the mixture was stirred for 1 h at RT, then sat. aq. NH_4Cl solution was added. After separation the organic layer was washed with NH_4Cl and brine, the combined aqueous layers were extracted with EtOAc and dried over $MgSO_4$. Evaporation afforded a dark oil (3.8 g) which was purified via column chromatography (SiO_2, hexane/ethyl acetate, 5:1) to yield the title compound (1.93 g, 17.8 mmol, 36%) as a yellow liquid.

^{1}HNMR (400 MHz, $CDCl_3$) δ = 3.94 (dt, *J* = 11.8, 5.9, 1H), 2.58 – 2.45 (m, 4H), 2.26 (d, *J* = 5.4, 1H), 2.07 (t, *J* = 2.7, 1H).

Triethylenemethylglycol tosylate **106**[12]

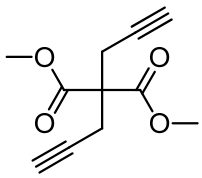


Triethylamine (16.0 mL, 115 mmol, 1.35 eq) and 2-[2-(2-methoxyethoxy)ethoxy]-ethanol (**107**, 13.3 mL, 85.0 mmol. 1.00 eq) were dissolved in 200 mL DCM under argon and tosyl chloride (19.4 g, 102 mmol, 1.20 eq) in DCM (30 mL) was added. The mixture was stirred at RT overnight (TLC showed full conversion of the alcohol). Then, the mixture was washed

twice with aqueous sodium bicarbonate solution and once with sodium carbonate. After drying over $MgSO_4$ and evaporation the crude residue (still TsCl in the mixture) was again dissolved in DCM. Washing twice with 1M HCl, once with sodium carbonate solution, drying over magnesium sulfate and evaporation yielded still a mixture of the title compound and tosyl chloride. The residue was suspended in hexane and poured on a silica plug. Elution with hexane (1.5 L) and later 5:1 hexane/ether afforded the contaminant as first fraction and later the desired product(18.6 g, 58.4 mmol, 69 %) as a colorless oil.

^{1}HNMR (400 MHz, $CDCl_3$) δ = 7.82 – 7.75 (m, 2H), 7.33 (m, 2H), 4.15 (m, 2H), 3.71 – 3.65 (m, 2H), 3.63 – 3.56 (m, 6H), 3.52 (m, 2H), 3.36 (s, 3H), 2.43 (s, 3H).

Dipropargyl methylmalonate (**110**)[13]

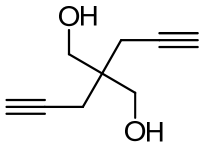


Under an inert atmosphere of argon NaH (2.86 g, 71.5 mmol, 1.10 eq., 60 wt.% in mineral oil) was added portion wise at 0°C to a solution of dimethyl malonate (**109,** 7.43 mL, 65.0 mmol, 1.00 eq) in 150 mL anhydrous THF. The mixture was allowed to warm to RT (over 30 min), whereas the mixture became cloudy. Then, propargyl bromide (7.70 mL, 71.5 mmol, 1.10 eq.) was slowly added and the mixture turned brown. The mixture was stirred for 2.5 h at RT . Then, the solution was cooled down to 0°C and NaH (2.86 g, 71.5 mmol, 1.10 eq., 60 wt.% in mineral oil) was added portion wise. The mixture was warmed and propargyl bromide (7.70 mL, 71.5 mmol, 1.10 eq.) was slowly added. The mixture was stirred for 5 h, quenched with water and extracted twice with TBME. The combined organic layers were washed with brine and the combined aqueous layers were reextracted with TBME. The organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was recrystallized from hexane and to obtain the dipropargylester as a yellowish solid (9.65 g, 46.3 mmol, 71%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 3.74 (s, 6H); 2.97 (d, *J* = 2.6, 4H); 2.01 (t, *J* = 2.6, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ = 169.3 (2C), 78.6 (2C), 72.0 (2C), 56.6, 53.5, (2C), 23.0 (2C).

Bis(homopropargyl)dialcohol **111**



Dipropargylester (**110**, 3.00 g, 14.4 mmol, 0.95 eq) was dissolved in 60 mL dry THF and cooled to –10°C - –20°C (gas bubbler attached). Then, $LiALH_4$ (1.76 g, 45.0 mmol, 3.00 eq) was added over 1h at this temperature. The mixture was allowed to warm to RT and stirred overnight. Afterwards, it was carefully quenched with water and 6% NaOH was added. Then, the suspension was acidified with 1M HCl, extracted three times with TBME, and the organic layer was dried over $MgSO_4$ and evaporated. Recrystallization from hexane and ethyl acetate yielded the title compound as white needles. (1.83 g, 12.0 mmol, 84%)

EA (%): calcd.: C, 71.03; H, 7.95;

found: C, 70.96; H, 8.04.

IR ($\tilde{\nu}$ /cm^{-1}): 3333 (w), 3277 (s), 3264 (w), 3257 (w), 3245 (w), 3243 (w), 3211 (w), 3207 (w), 3203 (w), 3200 (w), 3194 (w), 3187 (w), 3133 (w), 2938 (w), 2886 (w), 2885 (w), 1467 (w), 1460 (w), 1428 (w), 1372 (w), 1367 (w), 1313 (w), 1127, (w) 1106 (w), 1024 (s), 1003 (w), 979 (w), 965 (w), 881 (w), 960 (w), 678 (w), 668 (m), 632 (s), 629 (s), 626 (s), 613 (s), 603 (s), 600 (s).

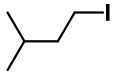
mp: 61-62°C

MS (FBA): 153 m/z (100%) [M^++H], 137 m/z, 91 m/z, 43 m/z.

^{1}HNMR (400 MHz, $CDCl_3$) δ = 3.77 (d, *J*=5.7, 1H), 2.40 (d, *J*=2.7, 1H), 2.13 (t, *J*=5.7, 1H), 2.07 (t, *J*=2.7, 1H).

^{13}CNMR (101 MHz, $CDCl_3$) δ = 80.4, 71.4, 66.7, 42.2, 21.9.

Isoamyl iodide[14]



Procedure 1:

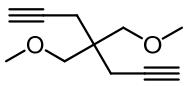
Imidazole (25.8 mL, 390 mmol, 2.60 eq), triphenylphosphine (51.1 g, 195 mmol, 1.30 eq) and isoamyl alcohol (16.5 mL, 150 mmol, 1.00 eq) were stirred at 0°C in 400 mL MeCN/EtO2 (1:3) and iodine (49.5 g, 195 mmol, 1.30 eq) was added portion wise. The suspension was stirred at RT until TLC showed full conversion (1.5h). Then, sat. thiosulfat solution was added, the organic phase was washed with 1M HCl and NH_4Cl solution. Drying over $MgSO_4$ and evaporation yielded a white slightly wet solid. Hexane was added and the suspensions was put on a silica plug and eluted with hexane (1 L). Evaporation yielded the iodide (5.38 g, 27.2 mmol, 18%) as a colorless liquid.

Procedure 2:

Sodium iodide (34.5 g, 230 mmol, 1.16 eq) was dissolved in acetone (200 mL) and isoamyl bromide (30.0 g, 199 mmol, 1.00 eq) was added. The mixture was refluxed for 1.5 h, then 2/3 of the solvent was carefully evaporated, the residue was poured on water and the organic phase was separated. The organic phase was washed with aqueous sodium thiosulfate solution, distilled under reduced pressure (100°C) to yield the title compound (35.2 g, 178 mmol, 89%) as a colorless liquid.

^{1}HNMR (400 MHz, $CDCl_3$) δ = 3.23 – 3.18 (m, 1H), 1.76 – 1.63 (m, 2H), 0.93 – 0.86 (m, 3H).

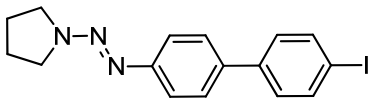
4,4-Bis(methoxymethyl)hepta-1,6-diyne **117**[15]



A solution of the diol **111** (4.90 g, 32.2 mmol. 0.976 eq) and iodomethane (8.1 mL, 129 mmol, 3.90 eq) in dry THF (100 mL) was added dropwise at 0°C to a suspension of sodium hydride (60% in oil, 3.63 g, 90.8 mmol) in THF (100 mL). The mixture was stirred for 1 h at RT, diluted with Et_2O and slowly quenched with water. Then, a few milliliters of a saturated solution of NH_4Cl were added, the organic layer was washed twice with NH_4Cl solution and brine, dried over $MgSO_4$, filtered and concentrated. The crude mixture was purified by distillation under reduced pressure (85°C, 5 mbar) to furnish the title compound as a colorless liquid (4.84 g, 26.9 mmol, 78%).

^{1}HNMR (400 MHz, $CDCl_3$) δ = 3.35 (d, *J*=3.4, 4H), 3.34 (s,6H), 2.35 (d, *J*=2.7, 4H), 1.98 (t, *J*=2.7, 2H).

Triazene **118**



Procedure 1:

A solution of 4-amino-4‘-iodobiphenyl (**75**, 502 mg, 1.70 mmol, 1.00 eq) in 0.68 mL of conc. HCl was cooled in an ice bath while a solution of $NaNO_2$ (126 mg, 1.78 mmol, 1.05 eq) in cold water (3.75 mL) was added dropwise. The resulting solution of the diazonium salt was stirred at 0 °C for 30 min and then added at once to a solution of pyrrolidine (0.28 mL, 3.40 mmol, 2.00 eq) and K_2CO_3 (1.18 g, 8.50 mmol, 5.00 eq) in 1:2 acetonitrile/water (2.4 mL). The reaction mixture was allowed to warm to RT and stirred for 30 min. The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was washed twice with brine, dried ($MgSO_4$), filtered, and concentrated by evaporation. Then, the crude product was stirred with

1M HCl (5 mL) and DCM (150 mL), water was added and separation, drying ($MgSO_4$) and evaporation yielded the triazene as a red solid. (128 mg, 340 µmol, 20%)

Procedure 2:

A solution of 4-amino-4‘-iodobiphenyl (**75**, 1.00 g, 3.40 mmol, 1.00 eq) was dissolved in 30 mL THF and cooled to -40°C. Then, BF_3*OEt_2 (1.93 g, 13.6 mmol, 4.00 eq) was added dropwise (slightly yellowish solution), followed by ^{t}Bu-ONO (1.43 mL, 11.9 mmol, 3.50 eq). The mixture was warmed to RT, ether was added, the precipitate was collected and washed with ether and dissolved in MeCN (50 mL). Then, a solution of pyrrolidine (0.49 mL, 5.95 mmol, 1.75 eq) and K_2CO_3 (1.22 g, 8.84 mmol, 2.60 eq) in water (10 mL) was added at 0°C and the mixture was allowed to warm to RT over 4 h. Afterwards, DCM was added, the organic phase was separated and the aqueous layer was again extracted with DCM. The combined organic phases were washed with 1M HCl and NH_4Cl, dried over $MgSO_4$ and evaporated to yield the triazene as a red solid. (903 mg, 2.40 mmol, 71%)

EA (%): calcd.: C, 50.94; H, 4.27; N, 11.14;

found: C, 50.88; H, 4.26; N, 10.87.

IR ($\tilde{\nu}$ /cm^{-1}): 2970 (w), 2868 (w), 1472 (m), 1426 (m), 1394 (m), 1379 (m), 1338 (m), 1316 (m), 1257 (w), 1221 (w), 1208 (w), 1154 (w), 1102 (w), 1057 (w), 996 (m), 978 (w), 850 (m), 827 (m), 808 (s), 735 (m).

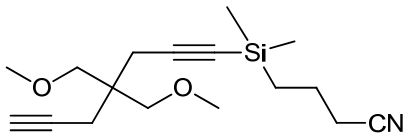
mp: 162-164°C.

MS (EI, 70 eV) m/z: 377 (29%) [M^+], 306, 279, 152 (100%), 76.

^{1}HNMR (400 MHz, CDCl3) δ = 7.76 – 7.71 (m, 2H), 7.55 – 7.50 (m, 2H), 7.50 – 7.45 (m, 2H), 7.37 – 7.32 (m, 2H), 3.81 (bs, 4H), 2.04 (m, 4H).

^{13}CNMR (101 MHz, $CDCl_3$) δ = 1513, 140.7, 137.9, 136.7, 128.9, 127.5, 121.0, 92.6, 24.0.

CPDMS-4,4-bis(methoxymethyl)hepta-1,6-diyne **119**



Dialkyne **117** (3.72 g, 20.0 mmol, 1.00 eq) was dissolved in 100 mL dry THF and ethylmagnesium bromide (3 mol/l in Et_2O, 5.87 mL, 17.6 mmol, 0.880 eq) was added dropwise at 0°C. The mixture was stirred for 30 min at 0°C and 1 h at RT, then CPDMS-Cl (2.71 g, 16.6 mmol, 0.830 eq) was added dropwise at 0°C. After 2 d at RT the solution was diluted with ether and slowly quenched with water. The organic layer was washed twice with NH_4Cl, the aqueous layer was re-extracted with TBME and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and evaporated. The crude mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate, 6:1) to obtain the monoprotected alkyne as a colorless liquid (2.94 g, 9.62 mmol, 58%).

EA (%): calcd.: C, 66.84; H, 8.91; N, 4.59;

found: C, 66.00; H, 8.78; N, 4.49.

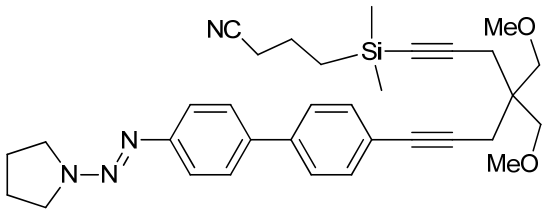
IR ($\tilde{\nu}$/cm^{-1}): 3291 (w), 2926 (w), 2887 (w), 2812 (w), 2177 (w), 1733 (w), 1477 (w), 1455 (w), 1428 (w), 1250 (m), 1195 (w), 1174 (w), 1101 (s), 1031 (m), 964 (w), 955 (w), 834 (s), 828 (s).

MS (FAB) m/z: 306 (100%) [M^++H], 126, 98, 45.

^{1}HNMR (500 MHz, $CDCl_3$) δ = 3.17 (s, 10H), 2.25 (t, *J*=7.0, 2H), 2.21 (s, 2H), 2.16 (d, *J*=2.7, 2H), 1.82 (t, *J*=2.6, 1H), 1.62 (ddd, *J*=19.0, 9.5, 6.3, 2H), 0.64 – 0.55 (m, 2H).

^{13}CNMR (126 MHz, $CDCl_3$) δ = 121.4, 106.7, 86.5, 82.2, 75.2, 72.1, 61.1, 43.4, 24.9, 23.6, 22.3, 22.1, 17.5, 1.6 (2C).

CPDMS-4-alkenyl-4'-pyrrolidintriazenyl-biphenyl **120**



To a dry 100 mL three-neck flask was added 4-iodo-4'-(pyrrolidinetriazene)-biphenyl **118** (3.09 g, 8.20 mmol, 1.00 eq), tetrakis(triphenylphosphine)palladium (479 mg, 410 µmol, 5.00 mol%) and copper iodide (156 mg, 820 µmol, 10.0 mol%) in argon counter flow. Then, CPDMS-4,4-bis(methoxymethyl)hepta-1,6-diyne **119** (2.51 g, 8.20 mmol, 1.00 eq), di*iso*propylamine (10 mL) and absolute THF (60 mL) were added via syringe. The mixture was degassed by bubbling argon through for 15 min and continuously stirred at RT overnight. Afterwards, the mixture was diluted with EtOAc, washed with NH_4Cl solution (3x) and brine, dried over $MgSO_4$ and evaporated. The remaining crude product was purified by column chromatography (SiO_2, hexane/ethyl acetate, 2:1) to obtain the title compound (3.71 g, 6.69 mmol, 82%) as a yellow oil which solidified after a few hours.

EA (%): calcd.: C, 71.44; H, 7.63; N, 10.10;

found: C, 71.18; H, 7.84; N, 10.16.

IR ($\tilde{\nu}$ /cm^{-1}): 2924 (w), 2869 (w), 2183 (w), 1487 (m), 1426 (m), 1340 (m), 1318 (m), 1253 (m), 1244 (m), 1221 (m), 1198 (m), 1153 (m), 1130 (m), 1099 (s), 1040 (m), 959 (m), 828 (s), 819 (s).

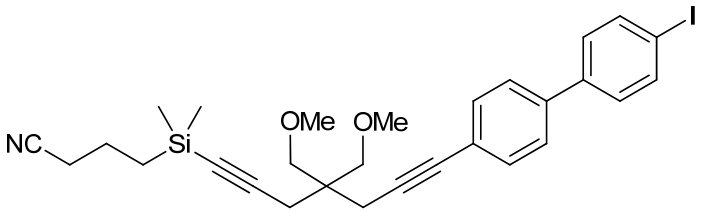
mp: 78-80°C.

MS (EI 70 eV) m/z: 554 (100%) [M^+], 456, 411, 379, 203, 126, 98, 45.

^{1}HNMR (500 MHz, $CDCl_3$) δ = 7.55 (dd, *J*=8.2, 6.4, 1H), 7.46 (dd, *J*=14.0, 8.4, 1H), 3.81 (s, 1H), 3.42 (s, 1H), 3.38 (s, 2H), 2.56 (s, 1H), 2.45 (s, 1H), 2.39 (t, *J*=7.0, 1H), 1.82 – 1.74 (m, 1H), 0.78 – 0.73 (m, 1H), 0.17 (d, *J*=5.6, 1H).

^{13}CNMR (101 MHz, $CDCl_3$) δ = 151.2, 140.5, 137.2, 132.2 (2C), 127.6 (2C), 126.8 (2C), 122.5, 121.0 (2C), 105.5, 87.1, 85.1, 82.9, 74.1, 59.7 (2C), 42.6 (2C), 24.0 (2C), 23.8, 23.3 (2C), 20.9 (2C), 20.7 (2C), 16.1 (2C), 0.2(2C).

CPDMS-4-alkenyl-4'-iodo-biphenyl **121**



CPDMS-4-alkenyl-4'-pyrrolidintriazenyl-biphenyl **120** (200 mg, 360 µmol, 1.00 eq) was dissolved in 1-iodobutane (4.00 mL, 35.0 mmol, 9.72 eq) and stirred at 135°C overnight. The black solution was evaporated and the residue was purified by column chromatography (SiO_2, hexane/ethyl acetate, 5:1) to obtain the iodo-compound (139 mg, 240 µmol, 66%) as a yellow oil.

EA (%): calcd.: C, 59.69; H, 5.287; N, 2.40;

found: C, 65.09; H, 5.91; N, 2.72.

IR ($\tilde{\nu}$/cm^{-1}): 2932 (w), 2874 (w), 2808 (w), 2178 (w), 1479 (w), 1421 (m), 1383 (w), 1249 (w), 1195 (w), 1173 (w), 1097 (m), 1030 (w), 999 (s), 957 (w), 833 (s), 809 (m), 791 (m), 782 (m), 773 (m), 763 (m).

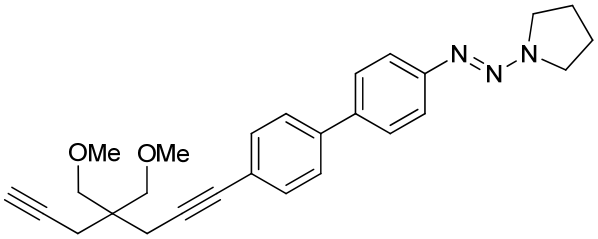
mp: 168-170°C.

MS (EI, 70 eV) m/z: 583 (14%) [M^+], 538 (100%), 506, 329, 189, 126, 98, 45.

^{1}**HNMR** (400 MHz, $CDCl_3$) δ = 7.79 (d, *J*=8.6, 1H), 7.53 – 7.47 (m, 2H), 7.34 (d, *J*=8.6, 1H), 3.43 (s, 2H), 3.40 (d, *J*=0.8, 3H), 2.58 (s, 1H), 2.46 (s, 1H), 2.42 (t, *J*=7.0, 1H), 1.86 – 1.75 (m, 1H), 0.81 – 0.75 (m, 1H), 0.20 (d, *J*=0.8, 3H).

^{13}CNMR (101 MHz, $CDCl_3$) δ = 151.3, 140.8, 138.0, 136.7, 128.9 127.5, 126.9, 121.0, 92.6 (2C), 91.6, 77.4, 70.9, 47.6, 35.0 29.9, 29.6 (2C), 24.0, 20.0, 19.5 (2C), 19.0, 13.9, 0.27 (2C).

Deprotection: 4-alkenyl-4'-pyrrolidintriazenyl-biphenyl **122**



CPDMS-4-alkenyl-4'-pyrrolidintriazenyl-biphenyl **120** (200 mg, 0.36 mmol, 1.00 eq) was dissolved in 12 mL THF/MeOH (7:5) and potassium carbonate (199 mg, 1.44 mmol, 4.00 eq) was added. The mixture was stirred for 2.5 h at RT, diluted with EtOAc and washed with water (2x) and brine. Drying over $MgSO_4$ and evaporation yielded an oil which was further purified by column chromatography (SiO_2, hexane/ethyl acetate, 5:1) to afford the title compound (126 mg, 290 µmol, 82%) as a yellow solid.

EA (%): calcd.: C, 75.50; H, 7.27; N, 9.78;

found: C, 75.45; H, 7.16; N, 9.77.

IR ($\tilde{\nu}$ /cm^{-1}): 2965 (w), 2924 (w), 2854 (w), 2711 (w), 1476 (m), 1426 (m), 1398 (m), 1335 (w), 1316 (m), 1260 (w), 1222 (w), 1159 (w), 1122 (w), 1104 (w), 1056 (w), 1024 (w), 997, 813 (s), 693 (m).

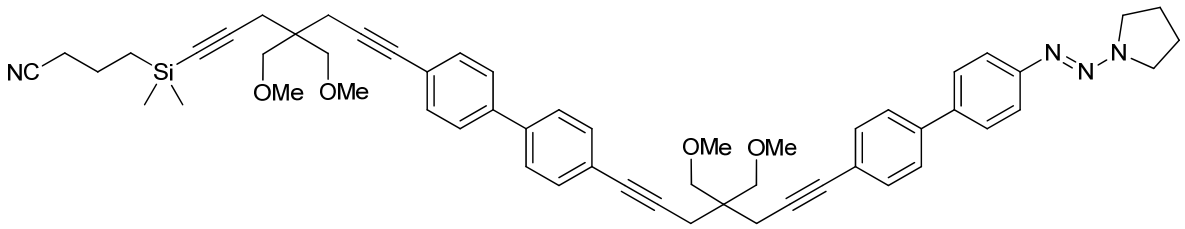
mp: 138-140°C.

MS (EI, 70 eV) m/z: 429 (100%) (M^+), 331, 299, 286, 254, 203, 189, 152, 70, 45.

^{1}HNMR (400 MHz, $CDCl_3$) δ = 7.61 – 7.54 (m, 1H), 7.53 – 7.45 (m, 1H), 3.84 (s, 1H), 3.46 (s, 1H), 3.40 (s, 1H), 2.61 (s, 1H), 2.45 (d, *J*=2.7, 1H), 2.09 – 2.04 (m, *J*=6.8, 1H), 2.04 (t, *J*=2.7, 1H).

^{13}CNMR (101 MHz, $CDCl_3$) δ = 151.1, 140.5, 137.2, 132.2, 127.6, 126.7, 122.5, 121.0, 87.1, 82.9, 81.1, 74.0 (2C), 70.6 (2C), 59.7 (2C), 42.4, 24.0, 23.2, 22.3.

CPDMS-4-alkenyl-4'-pyrrolidintriazenyl-bis(biphenyl) **123**



To a dry 50 mL three-neck flask was added 4-alkenyl-4'-pyrrolidintriazenyl-biphenyl **122** (85.9 mg, 200 µmol, 1.00 eq), a solution of CPDMS-4-alkenyl-4'-iodo-biphenyl **121** (117 mg, 200 µmol, 1.00 eq) in 2 mL diethylether, tetrakis(triphenylphosphine)palladium (11.8 mg, 10.0 µmol, 5.00 mol%) and copper iodide (3.81 mg, 20.0 µmol, 10.0 mol%) in argon counter flow. Then, di*iso*propylamine (1 mL) and absolute THF (20 mL) were added via syringe. The mixture was degassed, by bubbling argon through for 15 min, and continuously stirred at 45°C overnight (TLC still showed both starting materials). Therefore, stirring was continued for another 2 d at 45°C. Afterwards, the mixture was diluted with EtOAc, washed with NH_4Cl solution (3x) and brine, dried over $MgSO_4$ and evaporated. The remaining crude product was purified by column chromatography (SiO_2, hexane/ethyl acetate, 2:1) to obtain the desired product (87.0 mg, 98.3 µmol, 68%) as yellow wax.

EA (%): calcd.: C, 75.90; H, 7.39; N, 6.32;

found: C, 73.95; H, 7.36; N, 5.23.

IR ($\tilde{\nu}$/cm^{-1}): 2925 (w), 2874 (w), 1487 (w), 1426 (w), 1405 (w), 1336 (w), 1316 (w), 1260 (w), 1224 (w), 1194 (w), 1098 (m), 1033 (w), 955 (w), 821 (s).

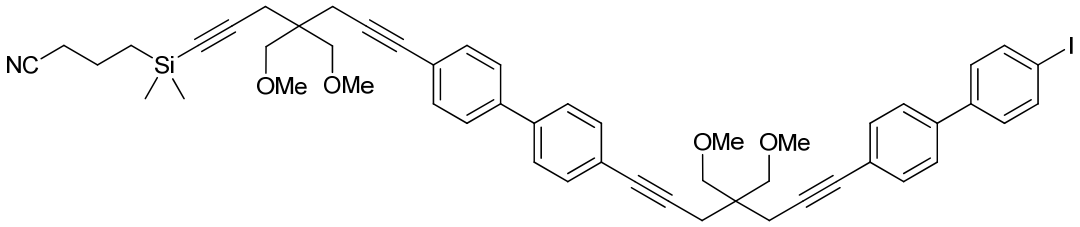
MS (FAB) m/z: 885 (33%) [M^++1 9, 786, 710, 494, 444, 289, 190, 154, 126, 98 (100%), 45.

^{1}HNMR (500 MHz, $CDCl_3$) δ = 7.55 (m, 4H), 7.48 (m, 3H), 3.82 (s, 1H), 3.51 (s, 1H), 3.41 (s, 4H), 3.37 (s, 2H), 2.66 (s, 1H), 2.55 (s, 1H), 2.44 (s, 1H), 2.40 (t, *J*=7.0, 1H), 2.05 (s, 2H), 1.82 – 1.73 (m, 1H), 0.79 – 0.73 (m, 1H), 0.17 (s, 3H).

^{13}CNMR (126 MHz, $CDCl_3$) δ = 151.1, 140.4, 139.9 139.8, 137.2, 132.3, 132.3, 132.3, 132.2, 128.8, 128.7, 127.6, 127.0, 126.9, 126.7, 121.0, 105.4, 87.9, 87.6, 87.3, 85.1, 82.9, 82.7, 74.3,

74.1, 68.3, 59.8, 59.7, 53.7, 43.0, 42.5, 38.9, 30.6, 29.9, 24.0, 23.8, 23.4, 23.3, 20.9, 20.7, 16.1, 14.3, 11.2, 0.22 (2C).

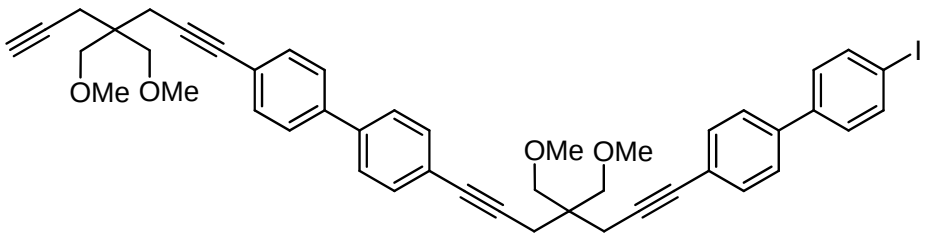
CPDMS-4-alkenyl-4'-iodo-bis(biphenyl) **123b**



CPDMS-4-alkenyl-4'-pyrrolidintriazenyl-bis(biphenyl) **123** (87.0 mg, 83.5 µmol, 1.00 eq) was dissolved in 1-iodobutane (1.00 mL, 8.75 mmol, 105 eq) and refluxed for 12 h. Afterwards, the solution was evaporated and the residue was purified via column chromatography (SiO_2, hexane/ethyl acetate, 4:1) to yield the title compound (61.0 mg, 60.1 µmol, 72%) as semi-solid.

^{1}HNMR (500 MHz, $CDCl_3$) δ = 7.81 (d, *J*=8.5, 2H), 7.58 – 7.49 (m, 12H), 7.36 (d, *J*=8.5, 2H), 3.55 (s, 2H), 3.46 (s, 4H), 3.42 (s, 3H), 2.70 (s, 2H), 2.61 (s, 1H), 2.49 (s, 1H), 2.44 (t, *J*=7.0, 1H), 1.86 – 1.78 (m, 1H), 0.84 – 0.78 (m, 1H), 0.22 (s, *J*=6.4, 3H).

Deprotection: 4-alkenyl-4'-iodo-bis(biphenyl) **124**



CPDMS-4-alkenyl-4'-iodo-bis(biphenyl) (**123b**, 56.0 mg, 61.3 µmol, 1.00 eq) was dissolved in a 1:1 THF/MeOH mixture (2 mL) and potassium carbonate (34.0 mg, 245 µmol, 4.00 eq) was added. The mixture was stirred at RT for 2.5 h, diluted with EtOAc and washed with

water (2x) and brine. Drying over $MgSO_4$ and evaporation yielded an oil which was further purified by column chromatography (SiO_2, hexane/ethyl acetate, 6:1) to afford the title compound (36.0 mg, 45.6 µmol, 75%) as a yellow oil.

EA (%): calcd.: C, 70.05; H, 5.75;

found: C, 96.35; H, 6.36.

IR ($\tilde{\nu}$ /cm^{-1}): 3287 (w), 2924 (w), 2872 (w), 2808 (w), 1492 (w), 1478 (m), 1288 (w), 1194 (w), 1099 (s), 1097 (s), 1064 (m), 1062 (m), 1000 (m), 955 (w), 821 (s), 810 (s).

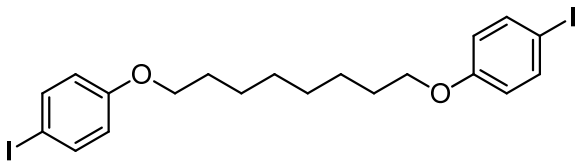
MS (EI 70 eV) m/z: 788 (100%) [M^+], 743, 711, 662, 585, 443, 317, 253, 228, 45.

^{1}HNMR (400 MHz, $CDCl_3$) δ = 7.76 (d, *J*=7.0, 1H), 7.53 – 7.44 (m, 5H), 7.31 (d, *J*=7.3, 1H), 3.50 (s, 2H), 3.43 (s, 2H), 3.41 (d, *J*=1.2, 3H), 3.38 (d, *J*=1.2, 3H), 2.65 (s, 2H), 2.58 (s, 1H), 2.42 (s, 1H), 2.01 (s, 1H).

^{13}CNMR (101 MHz, CH_3CN+D_2O) δ = 140.2 (2C), 139.8 (2C), 139.4 (2C), 138.1 (4C), 132.3 (4C), 129.0 (4C), 126.9 (4C), 123.3 (2C), 93.5, 87.8, 82.7, 81.1, 77.6, 77.2, 76.9, 74.30, 74.0, 70.7, 68.2, 59.8 (2C), 59.7 (2C), 43.0, 42.4, 25.8 (2C), 23.5 (2C), 23.2, 22.3.

4.2.3 Further Experiments

1,8-bis(4-iodophenoxy)octane (**130**)



To 25 mL *n*-butanol were added 1,8-dibromooctane (1.86 mL, 10.0 mmol, 1.00 eq), 4-iodophenol (4.51 g, 20.5 mmol, 2.05 eq) and potassium hydroxide (1.16 g, 20.6 mmol, 2.06 eq) and the mixture was refluxed overnight. Then, water and DCM were added until the formed precipitate was dissolved. Then, the organic layer was extracted 3 times with 0.5M NaOH, once with brine and dried over $MgSO_4$. The crude residue was recrystallized from hot acetone yielding title compound (2.96 g, 5.38 mmol, 54%) as a colorless solid

EA (%): calcd.: C, 43.66; H, 4.40;

found: C, 43.73; H, 4.30.

IR ($\tilde{\nu}$/cm^{-1}): 2936 (w), 2903 (w), 1585, (w) 1569 (w), 1484 (m), 1471 (m), 1284 (m), 1239 (m), 1226 (w), 1173 (w), 1100 (w), 1029 (w), 988 (w), 828 (m), 809 (m), 806 (m), 723 (w).

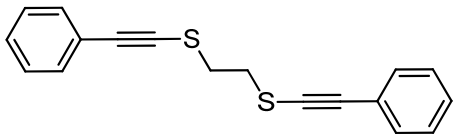
mp: 103-105°C.

MS (EI, 70 eV) m/z: 550 (100%) [M^+], 330, 219, 69.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.56 (m, 4H), 6.69 (m, 4H), 3.93 (t, *J*=6.5, 4H), 1.79 (m, 4H), 1.43 (m, 8H).

^{13}CNMR (126 MHz, $CDCl_3$) δ = 159.2, 138.4, 117.1, 82.6, 68.2, 29.5, 29.3, 26.1.

1,2-Bis(phenylethynylthio)ethane (**135**)[16]



Phenylacetylene (**133**, 449 mg, 4.40 mmol, 2.20 eq) was dissolved in 40 mL dry THF and cooled to –78°C under argon. Then, *n*-butyllithium (2.5M in hexane, 1.76 mL, 2.20 eq) was added and the mixture was stirred for 60 min at this temperature. Afterwards, ethylene dithiocyanate (**134**, 288 mg, 2.00 mmol, 1.00 eq) was added in argon counterflow at −78°C and the mixture was slowly warmed to RT and stirred overnight. Then, saturated ammonium chloride and EtOAc were added, the organic layer was separated, washed with brine and the combined aqueous phases were re-extracted with EtOAc. The combined organic layers were dried over magnesium sulfate, evaporated and the residue was purified by column chromatography (SiO_2, hexane) yielding crude product. Recrystallization from hexane yielded title compound (272 mg, 924 µmol, 46%) as yellow crystals.

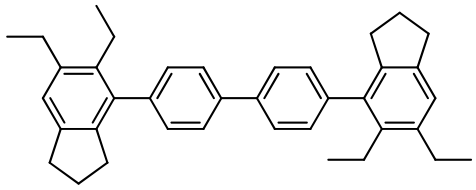
MALDI-MS: 294 [M^+] m/z.

MS (EI, 70 eV, m/z): 294 (M^+), 266, 234, 190, 133, 121, 89.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.40 (m, 4H), 7.29 (m, 5H), 3.19 (s, 4H).

^{13}C-NMR (101 MHz, $CDCl_3$/d^6-Acetone) δ = 131.8 (4C), 128.6 (2C), 128.5 (4C), 123.2 (4C), 94.4 (2C), 78.0 (2C), 35.3 (2C).

4,4'-Bis(5,6-diethyl-2,3-dihydro-1H-inden-4-yl)-1,1'-biphenyl **(138)**



The terminal bisalkyne **67** (110 mg, 329 µmol, 1.10 eq) and 3-hexyne (**137**, 747 mg, 9.00 mmol, 30.0 eq) were dissolved in anhydrous 2-propanol (10 mL) and dry THF (10 mL) under argon in a microwave vessel. The mixture was degassed with argon, then Wilkinson's catalyst was added (28.0 mg, 30.0 µmol, 0.10 eq) and the flask was sealed. The suspension was heated for 6 h at 100°C in a microwave oven. Then, the volatiles were evaporated under reduced pressure and the crude residue was purified by column chromatography (SiO_2, ethyl acetate/hexane 1:4) to obtain the pure product (90 mg, 180 µmol, 55%) as a yellowish oil.

^{1}HNMR (400 MHz, $CDCl_3$) δ = 7.73 (d, *J*=8.3, 4H), 7.31 (d, *J*=8.2, 4H), 7.14 (s, 1H), 2.96 (t, *J*=7.4, 4H), 2.72 (q, *J*=7.6, 4H), 2.55 (m, *J*=24.8, 7.4, 8H), 2.04 – 1.93 (m, 4H), 1.30 (t, *J*=7.5, 6H), 0.98 (t, *J*=7.5, 6H).

MALDI-MS: 498 m/z [M^+].

The missing analytical data is currently under investigation.

4.3 Mechanistic Investigation of the Photocyclization of Schiff' Bases

N-benzylphenylamine (**151**) and phenanthridine (**150**) were commercial available from Acros and used without further purification. D^5-aniline was bought from Armar Chemicals Switzerland.

General Procedure 1: Photocyclization of Schiff' Bases

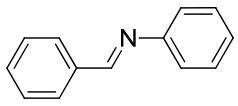
The Schiff' Base (276 mmol, 1.00 eq) was dissolved in dry acetonitrile (15 mL) in a quartz-tube. The mixture was degassed with argon for 10 min, then $BF_3{}^*OEt_2$ (304 mmol, 1.10 eq) was added under argon counterstream. The reaction was then stirred in a Rayonet photochemical reactor overnight and monitored via HPLC to achieve full conversion (usually after 12-16 h). The solution was evaporated and the residue was purified by column chromatography or preperative TLC.

General Procedure 2: Thermal Cyclization of Schiff' Bases

The Schiff' Base (276 mmol, 1.00 eq) was dissolved in either 15 mL xylene, acetonitrile, diphenylether or sulfuric acid (98%) in a pressure tube and thoroughly degassed with argon. Then, the π-acids and oxidants were added and the mixture was stirred at 140°C-250°C overnight. The crude mixture is cooled, monitored by HPLC, evaporated and column chromatography afforded the products.

In case of sulfuric acid as solvent, the mixture was carefully poured on ice (500 g) and neutralized via addition of sodium carbonate (until pH=7-9). Then, the mixture was extracted three times with EtOAc, dried over $MgSO_4$ and the volatiles were removed under reduced pressure. The residue was purified by column chromatography or preperative TLC.

(E)-*N*-Benzylideneaniline (**149**) [17]



Benzaldehyde (5.00 mL, 49.5 mmol, 1.00 eq) and aniline (**195**, 4.51 mL, 49.5 mmol, 1.00 eq) were dissolved in toluene (150 mL) in a flask equipped with a Dean-Stark apparatus, to

remove the formed water via azeotrope distillation. One crystal of *p*-TsOH was added and the mixture was refluxed overnight. Then, the solvent was evaporated and the crude product was purified by recrystallization from ethyl acetate to yield the title compound (8.88g, 49.0 mmol, 99%) as slightly yellow crystals.

IR ($\tilde{\nu}$/cm^{-1})**:** 3059 (w), 3028 (w), 2885 (w), 1695 (w), 1626 (m), 1589 (m), 1576 (m), 1483 (s), 1450 (m).

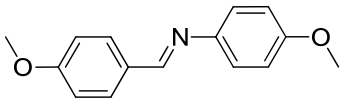
UV/VIS (MeCN) λ_{max}= 270 nm.

MS (EI 70 eV) m/z: 181 (93%) [M^{+}], 180 (100%), 104, 77, 51.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.47 (s, 1H), 7.93 (m, 2H), 7.49 (m, 3H), 7.41 (t, *J*= 7.7, 2H), 7.25 (m, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ = 160.4, 152.1, 136.2, 131.4, 129.1, 128.8, 128.7, 125.9, 120.8.

(*E*)-*N*-(*p*-Methoxybenzylidene)-*p*-methoxyaniline (**183**)[18]



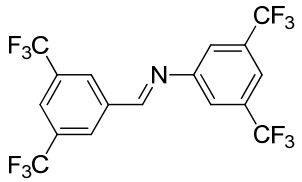
p-Anisaldehyde (2.00 mL, 16.1 mmol, 1.00 eq) and 4-methoxyaniline (1.90 mL, 16.2 mmol, 1.00 eq), were dissolved in 150 mL toluene in a 250 mL flask equipped with a Dean-Stark apparatus. Few crystals of *p*-TsOH were added and the mixture was refluxed overnight. Then, the reaction was allowed to cool to RT and the solvent was removed under reduced pressure to yield green crystals of the title compound (3.88 g, 16.1 mmol, 99%).

UV/VIS (MeCN) λ_{max}= 279 nm, 329 nm.

mp: 145°C.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.41 (s, 1H), 7.84 (d, *J*=8.7, 1H), 7.21 (dd, *J*=9.4, 2.8, 1H), 6.98 (d, *J*=8.7, 1H), 6.93 (d, *J*=8.9, 1H), 3.87 (s, 1H), 3.83 (s, 1H).

(*E*)-*N*-[3,5-Bis(trifluoromethyl)benzylidene]-3,5-bis(trifluoromethyl)aniline (**184**)



A crystal of p-TsOH was added to a solution of 3,5-bis(trifluoromethyl)benzaldehyde (736 mg, 3.04 mmol, 1.00 eq) and 3,5-bis(trifluoromethyl)aniline (697 mg, 3.04 mmol, 1.00 eq.) in 150 mL of toluene. The solution was refluxed overnight, whereby, the water formed was removed via azeotrope distillation. The mixture was allowed to cool to RT and the solvent was removed under reduced pressure to afford a mixture of the product and the aldehyde. The mixture was purified by bulb to bulb distillation (50°C, 1.7 mbar) and recrystallized from hexane to afford the Schiff' Base (436 mg, 961 μmol, 32%), as a white solid.

EA (%): calcd.: C, 45.05; H, 1.56; N, 3.09;

found: C, 44.98; H, 1.67; N, 3.09.

UV/VIS (MeCN) λ_{max}=265 nm.

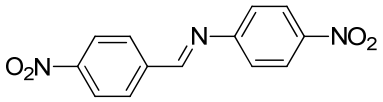
mp: 85-87°C.

MS (EI, 70 eV) m/z: 453 (100%) [M^+], 434 m/z, 240 m/z, 213 m/z, 163 m/z.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.61 (s, 1H), 8.41 (s, 2H), 8.05 (s, 1H), 7.81 (s, 1H), 7.67 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 159.8, 152.1, 137.3 (2C), 133.0 (4 C), 129.2 (2C), 125.7, 124.3, 122.1, 121.4 (2C), 120.5 (2C).

(*E*)-*N*-(*p*-Nitrobenzylidene)-*p*-nitroaniline (**185**)[17]



p-Nitrobenzaldehyde (421 mg, 2.70 mmol, 1.00 eq), *p*-nitroaniline (**269**, 377 mg, 2.70 mmol, 1.00 eq) and $MgSO_4$ (0.5 g) were suspended in dry DCM (5mL) and stirred for 3 d at RT . Then, the suspension was extracted with water and the organic layer was evaporated. The formed dark yellowish amorphous solid was recrystallized from toluene to yield (*E*)-*N*-(*p*-nitrobenzylidene)-*p*-nitroaniline (578 mg, 2.13 mmol, 79%) as a yellow solid.

mp: 195-198°C.

UV/VIS (MeCN) λ_{max}= 299 nm, 323 nm.

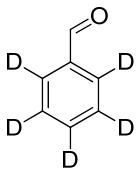
IR (ν/cm^{-1})**:** 3103 (w), 3080 (w), 2918 (w), 2835 (w), 1628 (w), 1597 (m), 1582 (m), 1508 (s, $\nu_{C=N}$), 1508 (m), 1414 (w).

MS (EI 70 eV): 271 (100%) [M^+], 241, 224, 195, 178, 151, 103, 76, 50.

^{1}H-NMR (400 MHz, d^6-DMSO): 8.83 (s, 1H, H_{imine}), 8.38 (d, J= 8.7, 2H), 8.30 (d, J= 8.9, 2H), 8.21 (d, J= 8.7, 2H), 7.50 (d, J= 8.9, 1H).

^{13}C-NMR (101 MHz, d^6-DMSO): 162.3, 156.6, 149.3, 145.4, 140.7, 130.2 (2C), 125.0 (2C), 124.1 (2C), 122.1 (2C).

d^5-Benzaldehyde (**191**)[19]



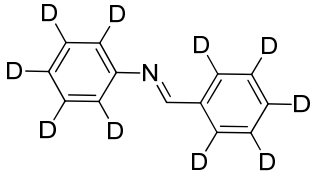
Magnesium turnings (729 mg, 30.0 mmol. 1.54 eq) and DIBALH (122 µl, 600 µmol, 30.0 meq) in 5 mL THF were stirred and d^5-bromobenzene (2.00 mL, 19.5 mmol, 1.00 eq) in 5 mL THF was added dropwise (reaction started after 10-15 drops) The drop rate was adjusted so

that the mixture refluxed gently (The reaction was controlled via GC-MS). Then, the Grignard reagent was cannulated to DMF (2.32 mL, 30.0 mmol, 1.54 eq) which was cooled to 0°C. Afterwards, the mixture was poured on 1M HCl (30 mL), filtered (filter cake rinsed with TBME) and the phases were separated. The HCl-phase was extracted three times with TBME and the combined organic layers were dried over $MgSO_4$, filtered and carefully evaporated (only 200 mbar, 40°C). The crude mixture was purified by kugelrohr distillation (73°C, 30 mbar) to yield the pure product (1.04 g, 9.83 mmol, 50 %) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 10.02 (s, 1H).

^{13}C-NMR (126 MHz, CDCl3) δ = 192.6, 136.4, 134.2, 129.4 (2C), 128.8 (2C).

d^{10}-*(E)*-*N*-Benzylideneaniline (**d-149**)



d^5-Benzaldehyde (**191**, 387 µl, 2.70 mmol, 1.00 eq), d^5-aniline (**192**, 246 µl, 2.70 mmol, 1.00 eq) and a crystal of *p*-TsOH were dissolved in 75 mL toluene. The solution was refluxed overnight, whereby, the water formed was removed via azeotrope distillation. The mixture was allowed to cool to RT and the solvent was removed under reduced pressure. The oil was solidified in the freezer and the crude yellow product was dissolved in hot EtOAc, precipitated by addition of hexane, collected and rinsed with cold hexane. A following recrystallization from ether yielded title compound (465 mg, 2.43 mmol, 90%) as a white solid.

HR-MS (ESI, MeCN): calcd.: 191.1592 m/z (M^++H);

found: 192.1592 m/z (M^++H).

UV/VIS (MeCN) λ_{max}= 272 nm.

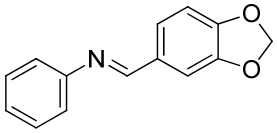
mp: 47–48°C.

MS (ESI): 192 [M^++1].

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.48 (s, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ = 160.6, 152.2, 136.3, 131.1, 129.1 (2C), 128.7 (2C), 128.3 (2C), 125.5, 120.7 (2C).

E)-*N*-(Benzo[1,3]dioxol-5-methylene)-aniline (**197**)[20]



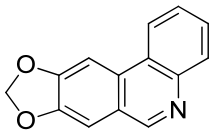
Piperonal (**196**, 452 mg, 3.00 mmol, 1.00 eq), aniline (**195,** 274 µl, 3.00 mmol, 1.00 eq) and 0.9 g silica gel were added to 5 mL EtOH and the suspension was sonicated in an ultrasound bath for 15 min at RT . The mixture was filtered over celite®, the filter cake was washed with 10 mL EtOH and the filtrate was evaporated to yield the crude product, which was purified by kugelrohr distillation (250°C, 10 mbar) to yield (*E*)-*N*-(benzo[1,3]dioxol-5-methylene)-aniline (478 mg, 2.12 mmol, 71%) as green-yellow crystals.

mp: 69°C

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.34 (s, 1H, H_{imine}), 7.54 (m, 1H), 7.38 (m, 2H), 7.23 (m, 4H), 6.89 (dt, *J* = 7.8, *J* = 2.1, 1H), 6.04 (s, 2H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ = 159.6, 152.3, 150.7, 148.7, 131.4, 129.3 (2C), 126.0 (2C), 121.1 (2C), 108.4, 107.1, 101.8.

Trisphaeridine (**159**)



(*E*)-*N*-(Benzo[1,3]dioxol-5-methylene)-aniline (**197**) (33.9 mg, 150 µmol, 1.00 eq) was dissolved in 0.5 mL deuterated ACN and $BF_3{}^*OEt_2$ (50.0 µl, 260 µmol, 1.73 eq) was added. The reaction mixture was irradiated for 3 days in a Rayonet RPR-200 photochemical reactor. The suspension was filtered, the filter cake was washed with hexane and discarded. Then, the mother liquor was cooled (–18°C) and the precipitate was collected to yield trisphaeridine (9.4 mg 41.0 µmol, 27%). Moreover the other regioisomer [1,3]dioxolo[4,5-k]phenanthridine (8.37 mg, 37.5 µmol, 23%) was also afforded.

HR-MS (ESI, MeCN): calcd.: 224.0706 m/z (M^++H);

found: 224.0708 m/z (M^++H).

MS (ESI) m/z: 224 [M^++1].

GC-MS: 223 m/z.

1H NMR (500 MHz, CDCl3): δ = 9.10 (s, 1H), 8.37 (d, *J* = 8.42, 1H), 8.15 (d, *J* = 8.4, 1H), 7.90 (s, 1 H), 7.68 (m, 1H), 7.62 (m, 1H), 7.33 (s, 1H), 6.17 (s, 2 H).

^{13}C NMR (126 MHz, CDCl3): δ = 151.9, 151.5, 148.2 144.0, 130.2 129.8, 128.0, 127.1, 124.3, 123.0 122.0, 105.4, 101.9, 99.8

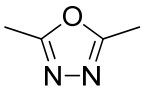
4.4 Application of a Bidentate Lewis Acid to the Inverse Electron Demanding Diels-Alder Reaction of 5-Membered Heterocycles

1,2-bis(trimethylsily)-benzene (**223**) was synthesized according to the procedure from S. N. Kessler *et al.*[21]

4.4.1 Synthesis of Dienes

2,5-Diphenyl-1,3,4-oxadiazole (**251**) was commercial available from Acros and was used without further purification.

2,5-Dimethyl-1,3,4-oxadiazole (**250**)[22]



Commercial available diacetylhydrazine (**264**, 2.32 g, 20.0 mmol, 1.00 eq) and TBAF hydrate (20.0 mg, 71.6 µmol, 3.50 mol%) were stirred in hexamethyldisilazane (3.87 g, 24.0 mmol, 1.20 eq) at reflux under argon overnight. Then, methanol was added and the mixture was evaporated. Distillation (70°C, 20 mbar) yielded the pure product (330 mg, 3.36 mmol, 17%) as a colorless liquid.

GC-MS: 98 m/z [M^+], 56 m/z, 43 m/z.

^{1}HNMR (500 MHz, $CDCl_3$) δ = 2.47 (s, 1H).

^{13}C-NMR (500 MHz, $CDCl_3$) δ = 163.5, 10.8.

1,3,4-Thiadiazole (**255**)[23]

To a suspension of 1,2-diacylhydrazine (**265**, 1.82 g, 20.0 mmol, 1.00 eq) in 50 mL xylene was added Lawesson's reagent (8.09 g, 20.0 mmol, 1.00 eq). The suspension was refluxed overnight and added while still hot to a prepacked alumina column (pentane as eluent). The xylene was eluted with pentane and the solvent was gradually shifted to diethyl ether to eluate

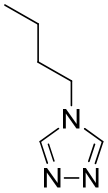
the product. After removal of the solvents the residue was recrystallized (pentane/diethyl ether) to obtain thiadiazole (822 mg, 9.55 mmol, 48%) as a white solid.

mp: 38-41°C

^{1}HNMR (400 MHz, $CDCl_3$) δ = 9.24 (s, 2H).

^{13}C-NMR (500 MHz, $CDCl_3$) δ = 151.3.

4-Butyl-1,2,4-triazole (**252**)[24]

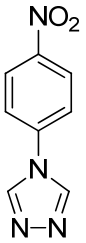


Trimethyl *ortho*formate (**267**, 12.9 g, 120 mmol, 1.50 eq) and formyl hydrazide (**266**, 4.80 g, 80.0 mmol, 1.00 eq) were refluxed in dry methanol (32 mL) for 3.5 h. The mixture was cooled to RT and *n*-butylamine (7.91 mL, 80 mmol, 1.00 eq) was added over 15 min. The mixture was again heated at reflux for another 3.5 h. The reaction mixture was then directly distilled under reduced pressure with a vigreux column (134°C, 2 mbar) to afford the triazole (4.20 g, 33.6 mmol, 42%) as colorless liquid.

^{1}HNMR (400 MHz, $CDCl_3$) δ = 8.13 (s, 2H), 4.01 (t, *J*=7.2, 2H), 1.83 – 1.73 (m, 2H), 1.34 (m, 2H), 0.94 (t, *J*=7.4, 3H).

^{13}C-NMR (500 MHz, THF) δ = 140.4, 42.2, 31.0, 17.7, 11.0.

4-(*p*-Nitrobenzyl)-1,2,4-triazole (**254**)[25]



A mixture of diformylhydrazine (**268**, 908 mg, 10 mmol, 1.00 eq) and 4-nitroaniline (**269**, 1.40 g, 10 mmol, 1.00 eq) was heated in an open beaker at 180°C for 4 h. Both substances are solids but started melting during the heating to form a sticky liquid. Moreover, during the heating time water was formed and evaporated. After cooling the crude material was recrystallized from ethyl acetate and then toluene to afford the title compound as a yellow solid (325 mg, 1.71 mmol, 17%).

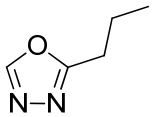
mp: >250°C.

MS (EI 70 eV) m/z: 190 (100%) [M^+], 160, 133, 105, 90, 39.

^{1}**HNMR** (400 MHz, DMSO) δ = 9.33 (s, 2H), 8.47 – 8.40 (m, 2H), 8.08 – 7.99 (m, 2H).

^{13}**C-NMR** (500 MHz, THF) δ = 145.0, 138.4, 137.7, 123.5, 119.5.

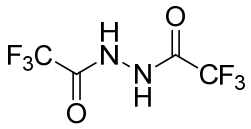
2-Propyl-1,3,4-oxadiazole (**253**)[26]



A mixture of butyric acid hydrazide (**270**, 2.50 g, 24.5 mmol, 1.00 eq) and triethyl *ortho*formate (**271**, 12.5 mL, 73.6 mmol, 3.00 eq) was refluxed overnight. Then, the mixture was cooled and distilled from reduced pressure to obtain a mixture of products and a malodorous side-product. The distillation (85°C, 10 mbar) had to be repeated twice until the pure oxadiazole (60 mg, 540 µmol, 2%) could be isolated as colorless liquid.

^{1}**HNMR** (400 MHz, $CDCl_3$) δ = 8.33 (s, 1H), 2.86 (t, *J*=7.5, 2H), 1.90 – 1.74 (m, 2H), 1.01 (t, *J*=7.4, 3H).

1,2-Bis(trifluoroacetyl)hydrazine (**263**)[27]



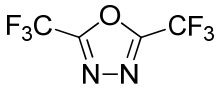
Hydrazine hydrate (**262**, 25.4 mL, 419 mmol, 1.00 eq) was added through the condenser to a stirred solution of trifluoroactetic acid (**261**, 38.0 mL, 512 mol, 1.22 eq) in benzene (300 mL). During the exothermic addition there was fog formation in the flask. The hydrazine hydrate was rinsed from the condenser with 50 mL benzene and the mixture was heated under reflux for 2 h. A Dean-Stark trap was fitted to the flask and the heating (100°C) was continued for 3.5 h. Then, more trifluoroacetic acid (38.0 mL, 512 mol, 1.22 eq) was added and the reflux was continued in the absence of the Dean-Stark trap for 2 h. Again the flask was fitted with a Dean Stark condenser and the mixture was refluxed overnight. The resulting white solid was collected by filtration, dried under reduced pressure to afford 1,2-bis(trifluoroacetyl)hydrazine (73.3 g, 327 mmol, 78%).

mp: 173°C

^{1}HNMR (400 MHz, $CDCl_3$) δ = 5.99 (s, 1H).

^{19}F NMR (376 MHz, $CDCl_3$) δ = -65.03 (s).

2,5-Bis(trifluoromethyl) -1,3,4-oxadiazole (**240**)[28]



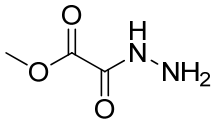
In a 250 mL flask 1,2-bis(trifluoroacetyl)hydrazine (**263**) (14.5 g, 64.8 mmol, 1.00 eq) was thoroughly mixed with phosphorus pentoxide (35 g) and the mixture was covered with another layer of phosphorus pentoxide (17 g). The flask was connected to a water cooled distillation bridge, which itself was connected to a receiving flask, which was cooled with dry ice and acetone to -78°C. The mixture was now heated with a heatgun to 300-350 °C until no more liquid was distilled of. The distillate was collected as solid in the dry ice/acetone cooled flask and melted readily when the cooling was removed to afford a colorless liquid. The crude

product was distilled (63-65°C) from calcium hydride to obtain the pure title compound (3.81 g, 18.5 mmol, 29%) as a highly volatile liquid.

GC-MS: 206 m/z [M^+], 136 m/z, 69 m/z.

^{19}F NMR (376 MHz, $CDCl_3$) δ = -64.9.

2-(Hydrazinyl)-methyl malonate (**275**)[29]



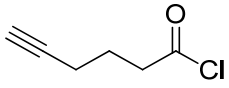
Dimethyl malonate (**274**, 23.6 g, 200 mmol, 1.00 eq) was dissolved in 200 mL methanol and cooled to -40°C (acetonitrile/dry ice). Then, a 80% (the reaction failed with 60% solution) hydrazine hydrate solution (**262**, 9.00 g, 180 mmol, 0.90 eq) in 40 mL methanol was added slowly and the mixture was stirred between -40°C and -20°C for 1h. The mixture was gently heated in an oil bath (35°C) and a white solid (bishydrazide **276**) was filtered off and discarded. The residue was evaporated until only about 35 mL remained in the flask. After cooling in an ice bath another precipitate was formed and collected to afford the monohydrazide (9.92 g, 84.0 mmol, 47%) as colorless crystals.

ESI-MS: 119 m/z [M^++1].

^{1}HNMR (400 MHz, DMSO) δ = 10.2 (bs, 1H), 4.64 (bs, 2H), 3.75 (s, 3H).

^{13}CNMR (101 MHz, DMSO) δ = 160.83, 155.34, 52.65.

5-Hexynoyl Chloride (**279**)

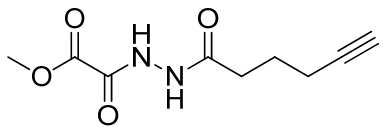


5-Hexynoic acid (**278**, 1.90 g, 16.9 mmol, 1.00 eq) was dissolved in 10 mL of $CDCl_3$, and a catalytic amount of DMF (0.1 mL) was added. The solution was cooled to -40°C

(acetonitrile/dry ice) and oxalyl chloride (1.59 mL, 16.9 mmol, 1.00 eq) was added dropwise under argon atmosphere. The solution was stirred at ambient temperature and monitored by NMR (α-proton shifted from 2.3 to 3.1). When NMR indicated complete conversion (3 h), the solution of hexynoyl chloride was used immediately in the next step without purification.

^{1}HNMR (400 MHz, $CDCl_3$) δ = 3.11 (m, 2H), 2.31 (m, 2H), 2.05 (m, 1H) 1.93 (m, 2H).

2-[(2-Hex-5-ynoyl)hydrazinyl]-methyl malonate (**280**)[30]

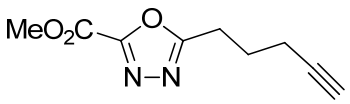


2-(Hydrazinyl)-methyl malonate (**275**, 3.59 g, 16.9 mmol, 1.00 eq) and potassium carbonate (2.34 g, 16.9 mmol, 1.00 eq) were suspended in 50 mL dry dioxane under argon and cooled to 0°C. Then, the solution of 5-heynoyl chloride (**279**, 16.9 mmol in 10 mL $CDCl_3$) was added dropwise. The mixture was stirred at RT overnight. Then, the reaction was concentrated under reduced pressure. Column chromatography (SiO_2, ethyl acetate/hexane 2:1->4:1 gradient) afforded the title compound (2.10 g, 9.87 mmol, 58.4 %) as a white solid.

mp: 65-66°C.

^{1}HNMR (500 MHz, DMSO) δ = 10.71 (s, 1H), 10.00 (s, 1H), 3.81 (s, 3H), 2.24 (t, *J*=7.4, 2H), 2.19 (td, *J*=7.2, 2.6, 2H), 1.99 (s, 1H), 1.69 (p, *J*=7.3, 2H).

Methyl 5-(Pent-4-ynyl)-1,3,4-oxadiazole-2-carboxylate (**246**)[30]



p-Toluenesulfonyl chloride (900 mg, 4.70 mmol, 1.18 eq) and 2-[(2-hex-5-ynoyl)hydrazinyl]-methyl malonate (**280**, 849 mg, 4.00 mmol, 1.00 eq) were dissolved in 40 mL DCM under

argon. Then, triethylamine (600 µL, 4.70 mmol, 1.18 eq) was added and the solution was stirred overnight at RT. Then, the solvent was evaporated and the residue was purified by column chromatography (SiO_2, ethyl acetate/hexane, 1:3 -> 1:1 gradient) to obtain the oxadiazole (591 mg, 3.04 mmol, 76%) as a colorless liquid.

^{1}HNMR (400 MHz, $CDCl_3$) δ = 4.05 (s, 3H), 3.10 (t, *J*=7.5, 2H), 2.37 (td, *J*=6.8, 2.6, 2H), 2.13 – 2.04 (m, 2H), 2.00 (t, *J*=2.6, 1H).

^{13}CNMR (101 MHz, $CDCl_3$) δ = 168.9, 156.9, 155.0, 82.4, 70.2, 54.0, 25.1, 24.4, 18.0.

4.4.2 Inverse Electron demanding Diels-Alder reactions

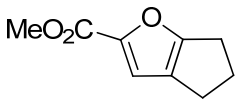
General procedure for the uncatalyzed Diels-Alder reactions:

The diene was dissolved in a suitable dry solvent (in some cases the diene was used in excess as solvent) and the dienophil was added. Then, the solution was stirred at temperatures up to 140°C for up to 14 d. The reaction mixture was cooled to RT and then investigated via NMR and GC-MS.

General procedure for the Lewis Acid catalyzed Diels-Alder reactions:

The diene was dissolved in a suitable dry solvent (in some cases the diene was used in excess as solvent) and the dienophil was added. The mixture was degassed via 5 freeze-pump-thaw cycles and introduced into a glove box. There 5-10 mol% of the bidentate Lewis acid catalyst **219** were added and to solution was stirred at temperatures up to 140°C for up to 14 d. The reaction mixture was cooled to RT and then investigated via NMR and GC-MS.

Methyl 5,6-Dihydro-4*H*-cyclopenta[*b*]furan-2-carboxylate (**247**)[30]



Methyl 5-(Pent-4-ynyl)-1,3,4-oxadiazole-2-carboxylate (**246**, 24.0 mg, 124 µmol, 1.00 eq) was dissolved in 1,2-dichlorobenzene (20 mL). The solution was degassed via 5 freeze-pump-thaw cycles and introduced into a glove box. There, the bidentate Lewis acid catalyst **219** (2.0 mg, 9.81 µmol, 8 mol%) was added. The mixture was stirred in a sealed pressure tube for 3 d at 205°C. Then, it was cooled to RT and directly added to a prepacked silica gel column which was equilibrated in hexane. The 1,2-dichlorobenzene was eluated with pure hexane, then a gradient to 1:1 ethyl acetate/hexane was applied. The two eluated fraction where the starting material **246** (20.0 mg, 103 µmol, 84%) and the title compound (3.0 mg, 18.1 µmol, 14%) as a slightly yellowish semi-solid.

^{1}HNMR (400 MHz, $CDCl_3$) δ = 6.96 (s, 1H), 3.80 (s, 3H), 2.68 (m, 2H), 2.52 (m, 2H), 2.41 (m, 2H).

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Appendix

Abbreviations

Å	Ångström
Ac	Acyl
Ar	Aromatic
AcOH	Acetic acid
Alox	Aluminium oxide
bp	Boiling point
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
calc.	Calculated
cat.	Catalytic
CC	Column chromatography
CNT	Carbon nanotube
COD	Cyclooctadiene
CPDMS	3-Cyanopropyldimethylsilyl
CPDIPS	3-Cyanopropyldi*iso*propylsilyl
CVD	Chemical vapor deposition
d	Days
d	Doublet
DA	Diels-Alder
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DDQ	2,3-Dichloror-5,6-dicyano-1,4-benzoquinone
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamid
DMH	Dimethylhydroxy
DMSO	Dimethylsulfoxide
dppf	1,1'Bis-(diphenyl-phosphino)-ferrocene
EA	Elementary analysis
EI	Electron impact
eq	Equivalents
Et	Ethyl
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
ESI	Electron spray ionisation
eV	Electron volt
FAB	Fast atom bombardement
FT	Fourier transformation
GC	Gas chromatography
GPC	Gel permeation chromatography
h	Hours
HOMO	Highest occupied molecular orbital
HOTf	Trifluoromethanesulfonic acid
HPLC	High performance liquid chromatography
IEDDA	Inverse electron demanding Diels-Alder
*i*Pr	*iso*-Propyl
IR	Infrared spectroscopy
J	Coupling constant
k	Rate constant
kJ	Kilojoule
LDA	Lithiumdi*iso*propylamine
LUMO	Lowest unoccupied molecular orbital
M	Molarity
MALDI	Matrix-assisted laser desorption ionisation

Me	Methyl
MeCN	Acetonitrile
m	Multiplet (NMR), medium (IR)
min	Minutes
MOM	Methoxymethyl
mp	Melting point
MS	Mass spectrometry
MWNT	Multi-walled nanotubes
m/z	Mass charge ratio
NBS	*N*-Bromosuccinimide
NMR	Nuclear magnetic resonance
PG	Protecting group
pin	Pinacol
ppm	Parts per million
p-TsOH	*para*-Toluenesulfonic acid
q	Quartet
quint	Quintet
RT	Room temperature
s	Singlet (NMR), strong (IR)
SB	Schiff' Base
SM	Starting material
SP	Side-product
SWNT	Single-walled nanotubes
t	Triplet
TBAF	Tetra-*n*-butylammonium fluoride
TBME	*tert*-Butylmethyl ether
T/C value	The elongated survival of mice treated with a drug divided through the survival of control mice
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TEA	Triethylamine
TOF	Time of flight
UV/VIS	Ultra violet ─ visible light absorption
w	Weak (IR)

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Education and Research Experience:

University of Basel, Switzerland

2008-Mai 2011	**PhD candidate** in organic Chemistry, Ph.D. advisor: Prof. Dr. Andreas Pfaltz, Supervisor: Dr. Hermann A. Wegner.
2007-2008	**Master of Science** in Chemistry, Advisor: Dr. Hermann Wegner
2003-2007	**Bachelor of Science** in Chemistry,

Hans-Thoma-Gymnasium Loerrach, Germany

2002	**Abitur** (Grade 1.7).

Teaching Experience:

2008-2010	Taught and administered Organic Chemistry course.
Since 2008	Supervised and trained master and visiting students.

Honors:

2010	Awarded a Travel-Fellowship of the Karl-Ziegler-Foundation to visit the 3rd European Chemistry Congress.
2010	Awarded PhD-Fellowship of the Novartis University Relations Program in Organic Chemistry.
2008	Awarded two year PhD-Fellowship of the “Fonds der Deutschen chemischen Industrie”.
2002	Awarded the Chemistry-Prize of the Hans-Thoma-Gymnasium Loerrach for graduating top of class.

Talks and Publications:

Talks:

- *Towards a Selective Chemical synthesis of Carbon Nanotubes*, Fellowship meeting of the "Fond der deutschen chemischen Industrie", October **2009**, Frankfurt am Main, Germany.

Poster:

- *Towards the Synthesis of Cycloparaphenylenes*, Fall meeting of the Swiss Chemical Society, September **2010**, Zurich, Switzerland.
- *Towards the Synthesis of Cycloparaphenylenes*, 3rd EUCheMS congress, August **2010**, Nuremberg, Germany.
- *Approach Towards a Rational Synthesis of Carbon Nanotubes*, 29th Regio Symposium, November **2009**, Rheinfelden, Germany.
- *Development of a Scavenger Assisted Oxidative Photocyclization*, CUSO Summer School 'Quo vadis electrons', September **2008**, Villars-sur-Ollon, Switzerland.

Publications:

- *Mechanistic Investigations of the Photocylization of Schiff' Bases*, manuscript in preparation.

Basel, May 5th, 2011

Eidesstattliche Erklärung

Hiermit erkläre ich an Eides statt, dass ich meine Dissertation mit dem Titel *Method Development, Synthesis and Mechanistic Investigations of Heteroaromatic Compounds* selbständig und nur mit den darin angegebenen Hilfsmitteln verfasst habe. Ich erkläre ausserdem, dass ich diese Dissertation bei keiner anderen Universität und keiner anderen Fakultät der Universität Basel eingereicht habe.

Basel den 05.05.2011

Jonathan Basler