Subproject C5.2

Synthesis of Functionalized Organic Nanostructures

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Introduction and Summary

The aim of this subproject is the design and synthesis of new rigid tetrahedral and pseudo-octahedral core structures for the generation of DNA hybrids that self-assemble to functionalized three dimensional nanostructures. Each core structure will hold a certain number of DNA strands in fixed spatial orientations in order to generate three dimensional architectures through the formation of DNA double helices *via* the Watson-Crick base pairing.
It was planned to use methane, adamantane and in a later stage, cubane derivatives as tetrahedral cores. Hexakis functionalized 1,4-bistritylbenzene derivatives, which are based on the rigid tetraphenylmethane scaffold, were envisioned as pseudo-octahedral cores (Figure 1). Octahedral cores (fullerenes) are synthesized in C1.06 (Bräse/Roesky). Chirality of the different core structures and subsequently of the resulting networks is a major issue of this project as it engenders novel highly interesting properties.

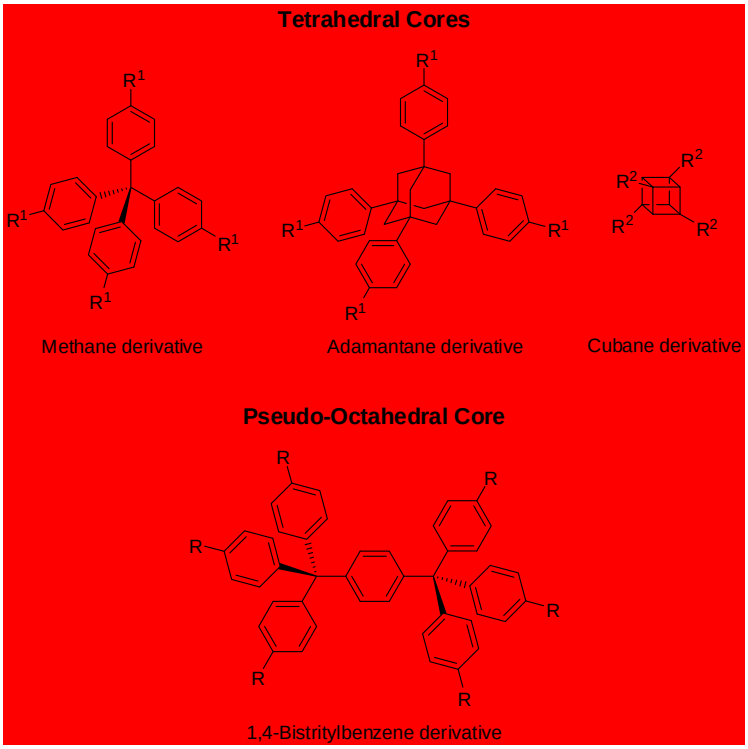
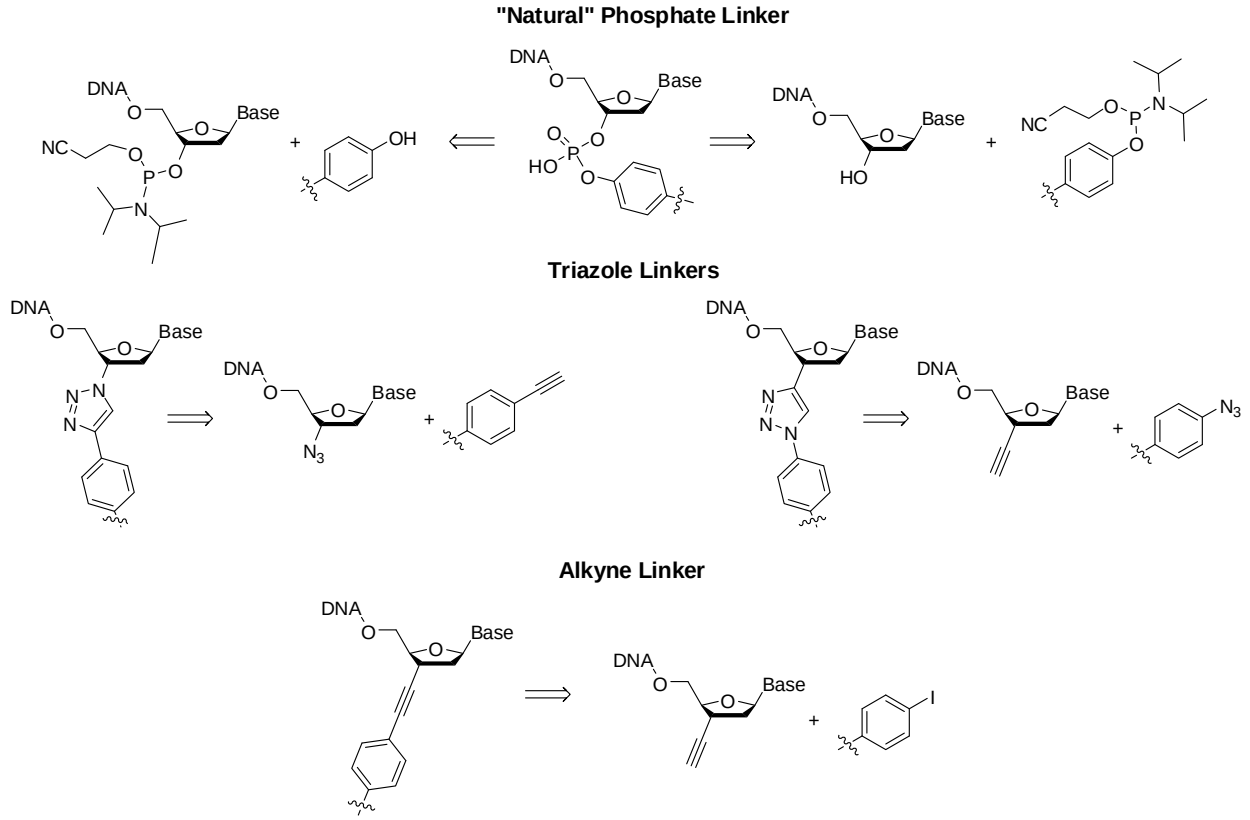


Figure 1: Envisioned tetrahedral and pseudo-octahedral core structures; for fullerene cores, see C1.06.

The task of the Bräse group consists of the synthesis of core structures bearing appropriate functionalities to allow further derivatization with DNA strands. The arms of the different core molecules are composed of rigid spacers, such as phenyl, biphenyl or acetylene bridged biphenyl groups. Different linkers, connecting the spacers to the DNA strands, have been considered. The oligonucleotides will either be attached through a phosphate group or *via* more rigid triazole or alkyne moieties (Scheme 1). For the phosphate approach, the corresponding phosphoramidite or phenol core derivatives have to be prepared, whereas the triazole linker requires azide or alkyne precursor cores respectively. The alkyne linker can be attached *via* a Sonogashira cross coupling involving either an alkyne or iodide containing core structure.
Each tetrahedral core contains four linker-spacer systems whereas the pseudo-octahedral 1,4-bistritylbenzene derivatives bear six of them. It was furthermore intended to prepare core structures

having four linker precursors, which would allow the generation of building blocks having all different DNA strands. If one could obtain these cores in enantiomerically pure form, either directly *via* asymmetric synthesis or *via* racemic resolution, the three dimensional architecture generated by such a pure enantiomer would be chiral and enclose chiral cavities and/or channels. This would enlarge the already broad application spectra of these functionalized nanostructures by properties intrinsically linked to their chirality.[1,2]



Scheme 1: Retrosynthetic analysis of three different linker systems.

A more straightforward approach to nanostructures with chiral cavities/channels consists in the use of peripheral chiral building blocks.[3] In this case, a given core has four or six identical DNA strands but bears a chiral group on each arm, making the whole core a chiral molecule.[4] The synthesis of such cores is easier from a synthetic point of view and has consequently also been investigated.

The specific goals of *subproject C5.2* for the last funding period were:

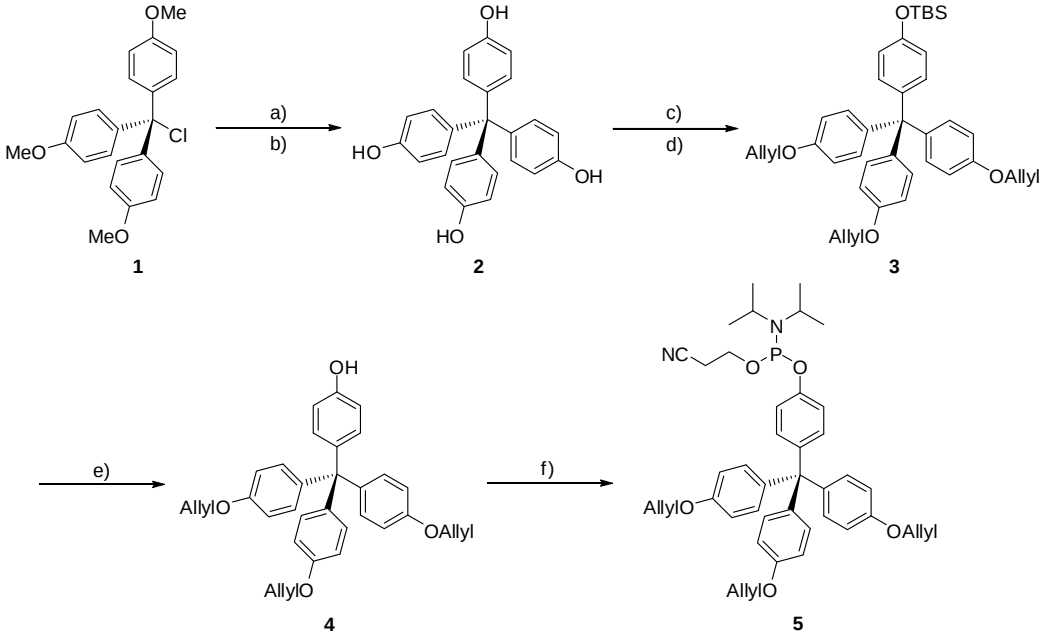
- Preparation of appropriate tetrahedral core structures in synthetically useful scales compatible with DNA solid phase synthesis.
- Development and investigation of different linker systems to attach the DNA strands.
- Asymmetric synthesis of tetrahedral core structures for the use as building blocks in functionalized nanostructures.
- Development of a method allowing the racemic resolution of central chiral tetrahedral core structures in synthetically useful quantities.
- Synthesis of different peripheral chiral tetrahedral cores.
- Use of "Click-chemistry" to effectively generate a variety of achiral or chiral tetrahedral and octahedral building blocks.
- Adaption of the protocols for the synthesis of tetrahedral core structures to generate the corresponding pseudo-octahedral analogues.

1. Synthesis of Achiral Tetrahedral Core Structures

Accesses to different methane and adamantane derivatives have been developed and will be discussed in this section.[5] Although, the respective syntheses differ somewhat, methane and adamantane cores use identical spacers, such as phenyl, biphenyl or acetylene bridged biphenyl groups, and share the same connecting groups.

1.1 Using the Phosphate Linker

Ideally, the cores should directly be used in a completely robotized solid phase DNA synthesis. In order to do so, the structures should have one free or active linker that can directly be attached to a DNA strand on solid support. The remaining ones will then be deprotected and solid phase DNA synthesis should subsequently allow the stepwise generation of the residual DNA strands.
The first compounds to be addressed were methane derivatives bearing phenyl spacers and four alcohol functionalities as identical linker precursors in a top-down synthesis (Scheme 2). Three of the four phenols of 4,4',4",4"'-methanetetrayltetraphenol (**2**) had to be protected with an DNA compatible protecting group and the fourth converted to a phosphoramidite. Tetraphenol **2** was obtained by a two step procedure developed in the Bräse group. Desilylation using TBAF and reaction of the generated free phenol function finally delivered phosphoramidite **5** which was directly handed over to the group of C. Richert in charge of the DNA synthesis.

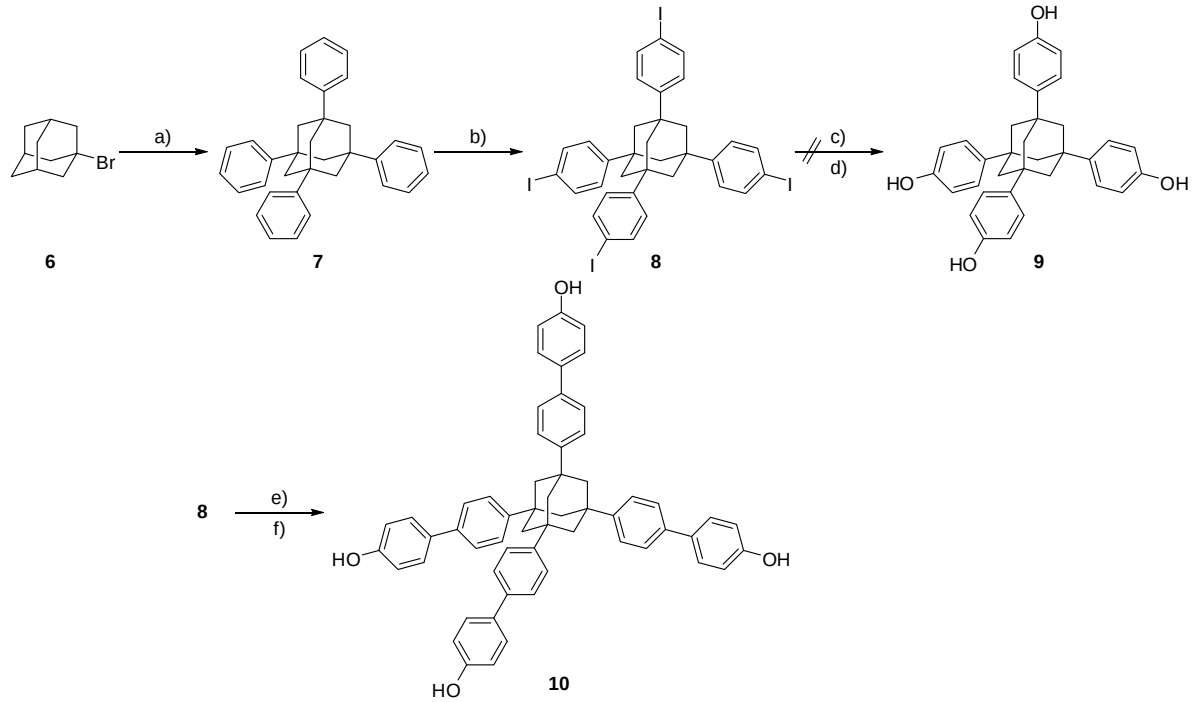


Scheme 2: Synthesis of compound **5**. Reagents and conditions: (a) Phenol, 215 °C then (b) BBr_3, CH_2Cl_2, 0 °C to r.t., **70%** (over two steps); (c) TBDMSCl, imidazole, THF, r.t., **25–40%**; (d) Allyl methyl carbonate, $Pd_2(dba)_3$, dppp, THF, r.t., **quant.**; (e) TBAF, THF, r.t., **80%**; (f) β-Cyanoethyl-*N*,*N*-diisopropylchlorophosphoramidite, $(i\text{-Pr})_2$EtN, THF, r.t., **86%**.

Unfortunately, it turned out that the allyl group was not compatible with DNA synthesis as it could not be deprotected without decomposition of the starting material. Similar problems occurred when Alloc was used as protecting group. Trityl or dimethoxytrityl protecting groups routinely employed during DNA synthesis, could not be used in this particular case. All attempts to form these trityl ethers resulted only in recovery of the starting material. Probably these groups are sterically too demanding to react with three phenols on the same molecule.

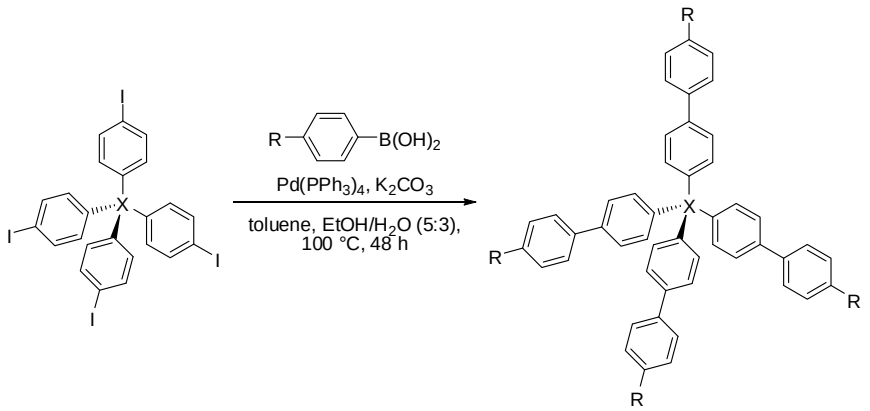
Thus, the group of C. Richert used tetraphenol **2**. This implies the minor disadvantage of generating the phosphoramide on the DNA strand attached to the solid support, which requires an additional manual step but still allowed to obtain the first DNA hybrids.

1,3,5,7-Tetrakis(4-phenyl)adamantane derivatives bearing four identical arms were also addressed in the phosphoramidite strategy. Starting with commercially available 1-bromoadamantane **6**, 1,3,5,7-tetrakis(4-phenyl)adamantane (**7**) was obtained in a Friedel-Crafts type reaction in good yield and was then converted to tetraiodo derivative **8** (Scheme 3).



Scheme 3: Synthesis of compound **10**. Reagents and conditions: (a) $AlCl_3$, *t*-BuBr, benzene, reflux, **67%**; (b) I_2, [bis(trifluoroacetoxy)iodo]benzene, r.t., $CHCl_3$, **46%**; (c) *n*-BuLi, THF, –78 °C then $B(OMe)_3$, –78 °C then (d) 3 M NaOH, 30% H_2O_2, reflux; (e) 4-Methoxyphenylboronic acid, K_2CO_3, $Pd(PPh_3)_4$, toluene, EtOH:H_2O 5:3, **65–80%**; (f) BBr_3, CH_2Cl_2, 0 °C to r.t., **77%**.

The latter did unfortunately not generate tetraphenol **9** under the conditions depicted in Scheme 3. Currently, a lot of efforts are being mobilized in the Bräse group to obtain tetraphenol **9**. However, tetraiodo **8** did react when performing a fourfold Suzuki cross coupling reaction with 4-methoxyphenylboronic acid followed by demethylation which delivered tetrabiphenol **10** in 50–60% yield over two steps. As before, compound **10** was as before handed over to the group of C. Richert in order to generate DNA hybrids and the corresponding networks. An optimization of the reaction conditions was carried out, in order to obtain better yields for compound **10**. The optimized reaction conditions for the fourfold Suzuki cross coupling reaction using the tetraiodo **8** or tetrakis(4-iodophenyl)methane (**11**) are shown in Scheme 4.



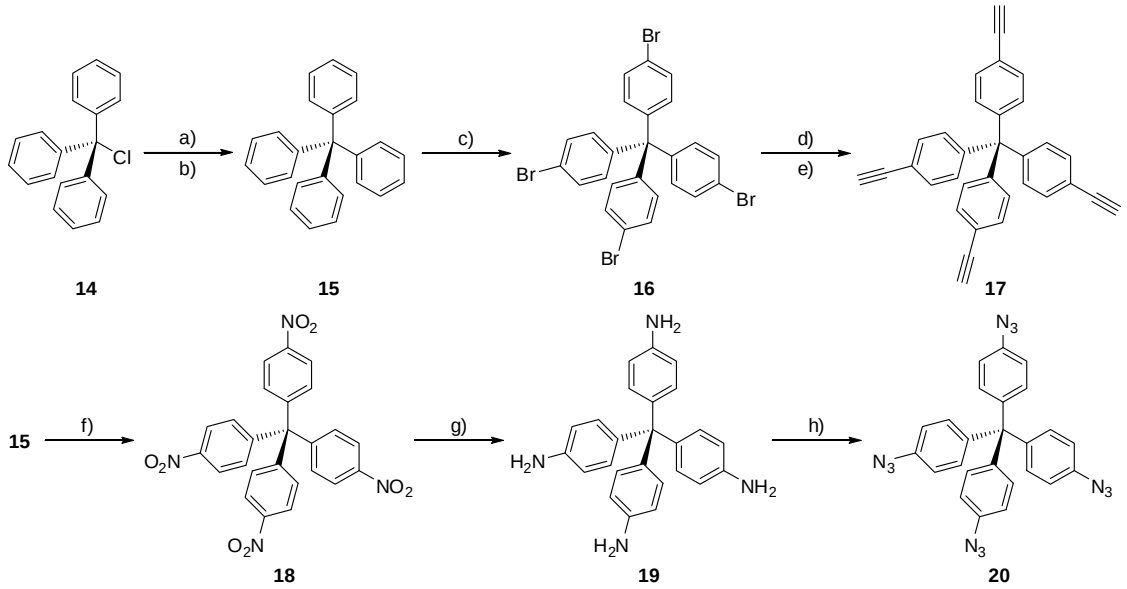
8 (X = adamantyl-1,3,5,7-tetrayl) **12** (X = 1,3,5,7-adamantyl)
11 (X = C) **13** (X = C)

Scheme 4: Optimized reaction conditions for the fourfold Suzuki cross coupling reaction.

Under the optimized reaction conditions, a whole range of novel tetrabiphenyl derivatives were synthesized *via* the fourfold Suzuki cross coupling reaction.[6]

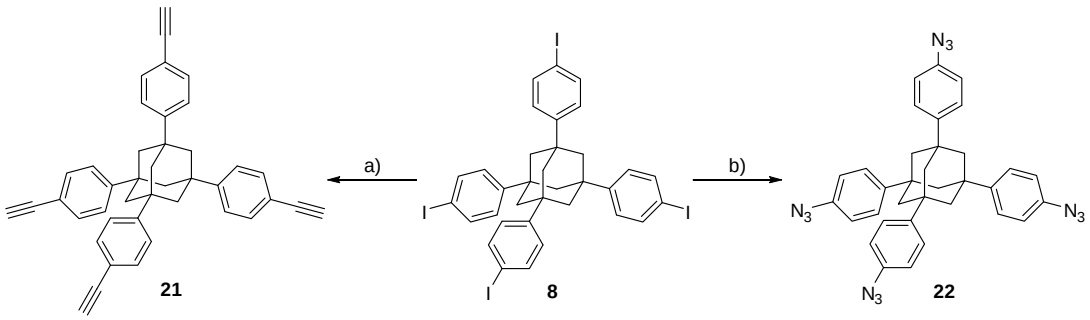
1.2 Using the Triazole Linker

The triazole moiety has been chosen as second linker because it is more rigid than the phosphate group present in naturally occurring DNA strands. This should lead to reinforced three dimensional predispositions for the attached DNA strands and consequently improve the chance to obtain periodic networks *via* self-assembly. One has however to bear in mind that the triazole group is an angular linker which might be unfavorable for the crystallization process.
These linkers can be obtained in a straightforward manner using the so-called "Click-chemistry". Triazoles can indeed be prepared in a generally high yielding copper(I)-catalyzed 1,3-dipolar cycloaddition reaction of azides and alkynes. As depicted in Scheme 1, the "Click-reaction" can be performed with an azide on the core structure and an alkyne containing deoxyribose derivative or the other way around. As a consequence, synthetic accesses to both, the tetraazide and the tetraalkyne cores, have been developed.
Tetraalkyne **17** was obtained in a straightforward manner starting from trityl chloride **14** (Scheme 5). First, literature known tetrabromo derivative **16** was prepared.[7] A fourfold Sonogashira cross coupling followed by a desilylation step finally delivered compound **17** in excellent overall yield.
The synthesis of tetraazide **20** turned out to be more complicated than expected as direct formation from the tetrabromo or tetraiodo derivatives, which gave non reproducible results. Thus, an alternative route starting from tetraphenylmethane **15** [8] was developed converting the latter into tetraamino compound **19** *via* nitro derivative **18** (Scheme 4).[7a] Target compound **20** was obtained through diazotization and subsequent addition of sodium azide in very good yields.



Scheme 5: Synthesis of compounds **17** and **20**. Reagents and conditions: (a) Aniline, Δ then (b) H_2SO_4, isoamyl nitrite, H_3PO_2, **93%**; (c) Br_2, **90%**; (d) Ethynyltrimethylsilane, NEt_3, $PdCl_2(PPh_3)_2$, CuBr, benzene, 80 °C then; (e) TBAF, benzene/MeCN, r.t., **77%** (over two steps); (f) HNO_3, AcOH, Ac_2O, –10 °C, **72%**; (g) H_2, Pd/C, MeOH, r.t., **quant.**, (h) HCl, $NaNO_2$, NaN_3, H_2O, –5 °C to r.t., **75%**.

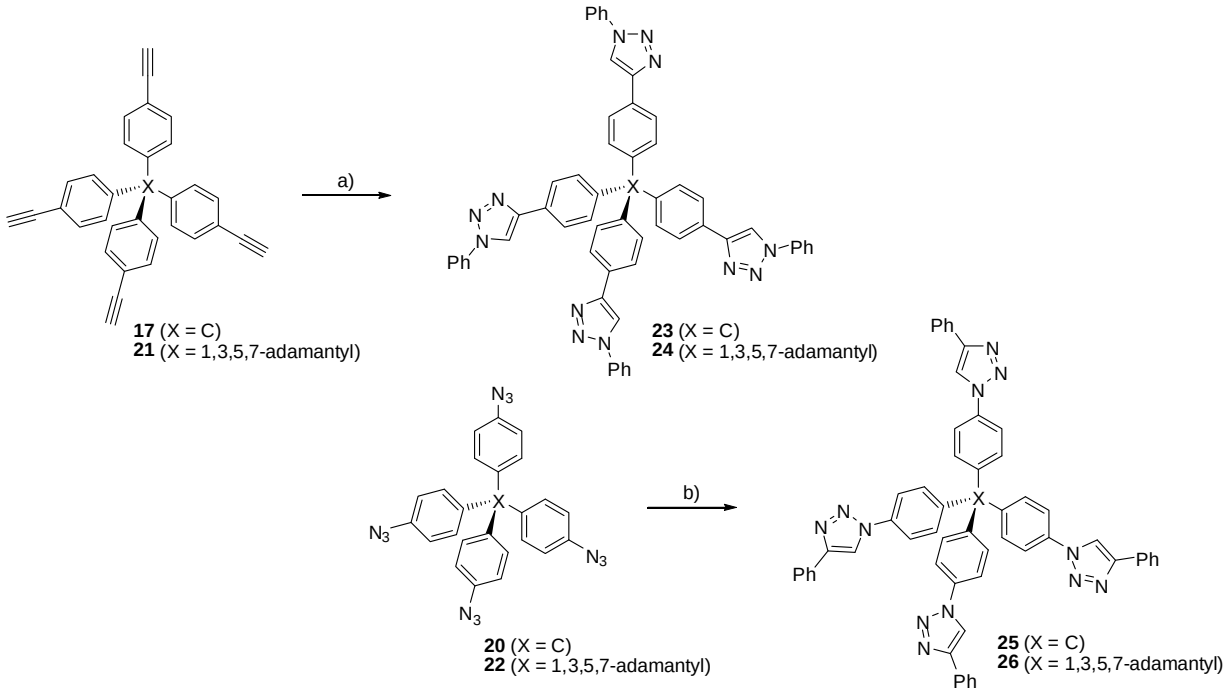
1,3,5,7-Tetrakis(4-phenyl)adamantane alkyne and azide derivatives have also been prepared. As for its methane analog, tetraalkyne **21** was obtained *via* a fourfold Sonogashira cross coupling reaction followed by a desilylation step (Scheme 6). Tetraazide **22** on the other hand could, unlike its methane analog, be generated directly from tetraiodo **8** in moderate yield. The alternative route *via* diazotization and addition of sodium azide, starting from 1,3,5,7-tetrakis(4-nitrophenyl)adamantane, could also be applied successfully.



Scheme 6: Synthesis of compounds **21** and **22**. Reagents and conditions: (a) Ethynyltrimethylsilane, NEt_3, $PdCl_2(PPh_3)_2$, CuI, THF, 90 °C; then TBAF, benzene/MeCN, r.t., **42%** (over two steps); (b) NaN_3, *N*,*N'*-dimethylethylenediamine, CuI, sodium ascorbate, DMSO/ H_2O (10:1), 100 °C, **34%**.

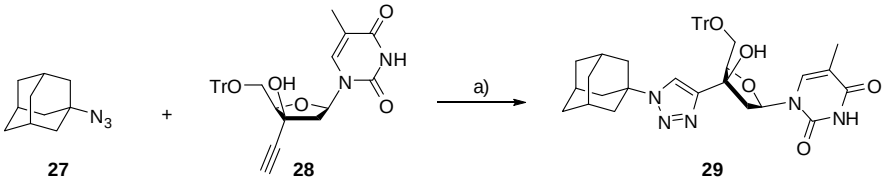
With all the different azide and alkyne derivatives in hand, the copper(I)-catalyzed 1,3-dipolar cycloaddition was investigated.[9] Conditions for a fourfold "Click-reaction" were first optimized with phenylazide and phenylacetylene respectively (Scheme 7). For both, methane and adamantane cores, excellent results were obtained performing the fourfold "Click-reaction" with the tetraazides as well as with the tetraalkynes.

Based on these results, a mono "Click-reaction" was attempted between azido adamantane **27** and alkyne nucleoside **28,** which has been provided by the group of C. Richert (Scheme 8).



Scheme 7: Synthesis of compounds **23** and **25** (X = C). Reagents and conditions: (a) Phenylazide, $CuSO_4 \cdot 5H_2O$, sodium ascorbate, *t*-BuOH/H_2O, 70 °C, **99%**; (b) Phenylacetylene, $CuSO_4 \cdot 5H_2O$, sodium ascorbate, *t*-BuOH/H_2O, 70 °C, **77%**. Synthesis of compounds **24** and **26** (X = 1,3,5,7-adamantyl). Reagents and conditions: (a) Phenylazide, $CuSO_4 \cdot 5H_2O$, sodium ascorbate, DMSO/H_2O, 80 °C, **80%**; (b) Phenylacetylene, $CuSO_4 \cdot 5H_2O$, sodium ascorbate, DMSO/H_2O, 80 °C, **quant**.

Under the previously optimized conditions, the corresponding triazole nucleoside **28** could be obtained in 65% yield.



Scheme 8: Synthesis of compound **29**. Reagents and conditions: (a) $CuSO_4 \cdot 5H_2O$, sodium ascorbate, DMSO/H_2O, 100 °C, **65%**.

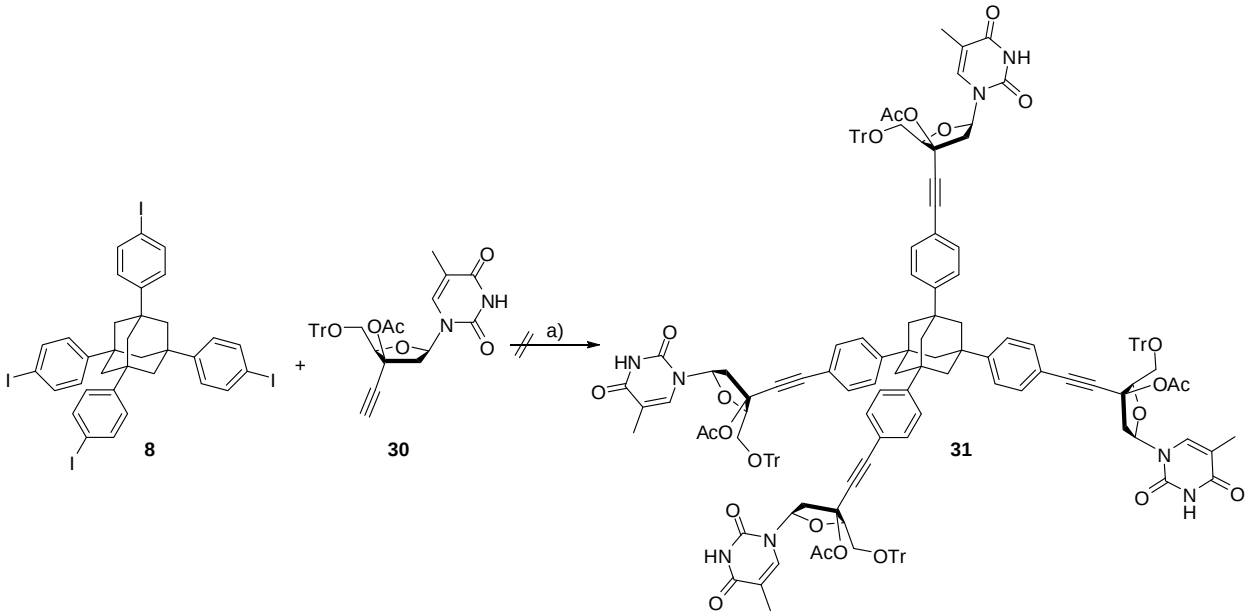
However, when the reaction was however with tetraazido adamantane **22** and nucleoside **28** (data not shown), no fourfold "Click-product" could be detected using optimized reaction conditions. While these reaction conditions worked extremely well for a broad variety of organic substrates, the nucleoside **28** showed no reactivity. In the meantime, the reaction was performed successfully in close collaboration with the group of C. Richert, using slightly different reaction conditions. Even the attachment of further nucleosides to the tetrahedral "Click-core" could be achieved. This approach will be intensified as soon as we dispose of more of the given nucleosides or novel nucleosides.

1.3 Using the Alkyne Linker

The last linker to be tested is an alkyne bridge between the phenyl spacer and the deoxyribose skeleton, which can be readily addressed *via* Sonogashira cross coupling reactions. As for the triazole moiety, this linkage is more rigid than the naturally occurring phosphate group. In contrast to the triazole, it is a linear linker, which should not negatively influence the molecular crystallization.

The first model reactions were performed on tetraiodide **8** and either nucleoside **28** or **30** (both provided by the group of C. Richert) (Scheme 9). Target compound **31** could not be detected by

MALDI-TOF, only its fourfold detritylated form, probably accompanied by partially detritylated coupling products was detected after complete deprotection. All attempts to avoid detritylation, *e.g.* running the reaction at room temperature, were not successful.



Scheme 9: Synthesis of compound **31**. Reagents and conditions: (a) $PdCl_2(PPh_3)_2$, CuI, Et_3N, THF, 50 °C.

There are ongoing studies to perform a detritylation on the crude mixture, without affecting the acetyl protection group, in order to obtain a pure coupling product, that bears only four free primary alcohols.

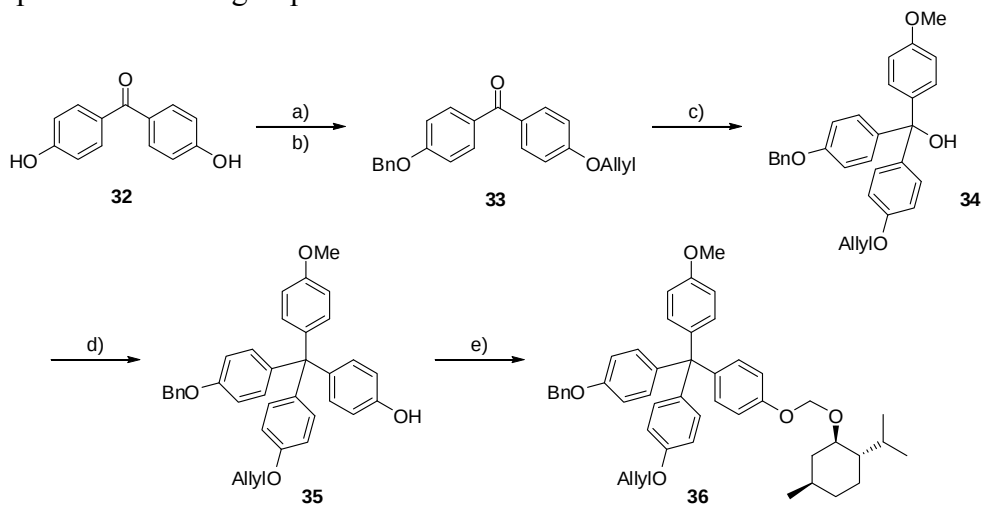
2. Synthesis of Chiral Tetrahedral Core Structures

As already mentioned before, synthesizing chiral core structures that will generate networks with chiral pores and/or channels through self-assembly is one of the major issues of this subproject. In order to reach that goal, two different strategies have been employed. One consists of preparing central chiral structures [10] whereas the other concentrates on the preparation of peripheral chiral molecules.

2.1 Central Chiral Tetrahedral Cores

Central chiral core structures with four orthogonal linker precursors are particularly interesting, as they allow the attachment of four different DNA strands. These cores should generate networks, which could be used for various highly interesting applications. Such cores could even lead to anisotropic crystalline structures. One should indeed be able to control the direction in which a given crystal is growing by adding the adapted central chiral DNA hybrid cores.
To start with, a racemic bottom-up synthesis of a central chiral tetraphenylmethane derivative has been investigated. 4,4'-Dihydroxybenzophenone (**32**) was first monobenzylated followed by allylation of the second phenol function (Scheme 10). Grignard addition to benzophenone **33** gave then trityl alcohol **34** in good yield. A Friedel-Crafts reaction finally delivered racemic tetraphenylmethane derivative **35**.
Different approaches to separate the two enantiomers have then been investigated. One consisted in the reaction of the free phenol function with an enantiomerically pure protecting group and the separation of the two diastereomers **36** (Scheme 10). Unfortunately, both presented identical retention fractions during silica column chromatography and could not be separated. Currently, a

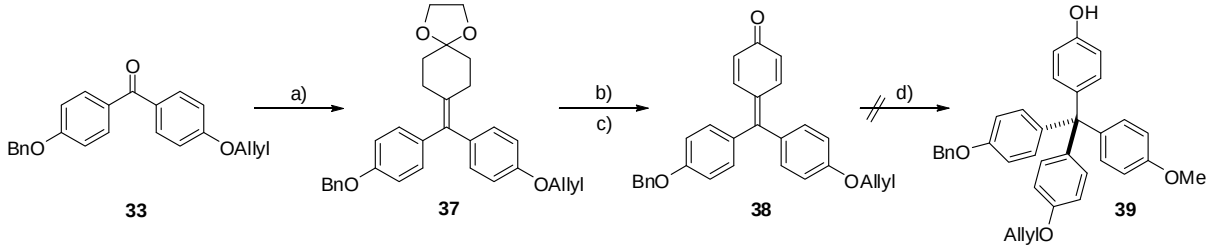
procedure for the separation of enantiomers **35** and diastereomers **36** respectively on chiral HPLC is being developed in the Bräse group.



Scheme 10: Synthesis of compound **36**. Reagents and conditions: (a) BnBr, NaH, DMF, r.t. then (b) AllylBr, NaH, DMF, r.t., **39%** (over two steps); (c) 4-Bromoanisole, Mg(0), THF, reflux, **70%**; (d) Phenol, 100 °C, **57%**; (e) (1*S*,2*R*,4*R*)-2-(Chloromethoxy)-1-isopropyl-4-methylcyclohexane, NaH, DMF, 0 °C to r.t., **96%**.

In parallel, there are ongoing synthetic trials to selectively convert each protected phenol function of **35** and **36** into one of the three previously described linker systems (chapter 1.1 - 1.3).

In a second approach, a central chiral structure should be generated through asymmetric synthesis. To do so, benzophenone derivative **33** was submitted to a McMurry cross coupling reaction in the presence of 1,4-dioxaspiro[4.5]decan-8-one to obtain alkene **37** (Scheme 11). The latter was converted to rosolic acid derivative **38** during a two step procedure. Finally, an asymmetric 1,6-addition using a novel Rh-catalyst should generate the enantiomerically pure tetrahedral core **39**.



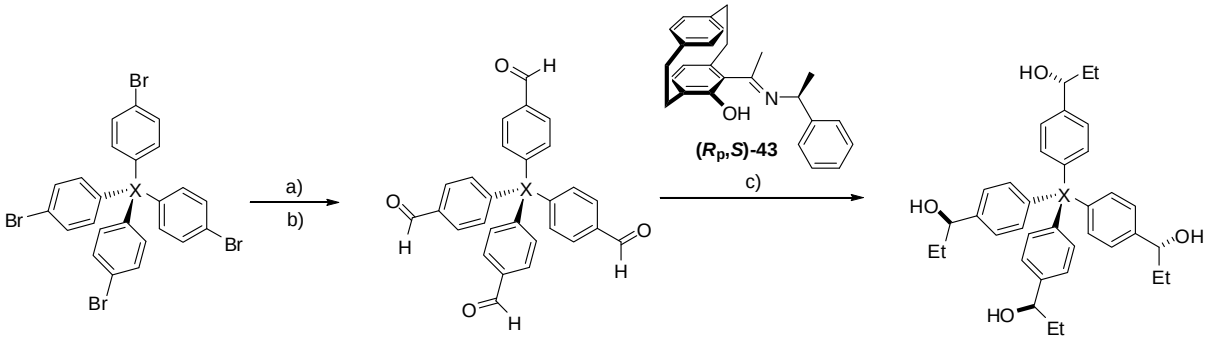
Scheme 11: Synthesis of compound **39**. Reagents and conditions: (a) 1,4-Dioxaspiro[4.5]decan-8-one, $TiCl_4$, Zn(0), THF, 75 °C, **75%**; (b) HCl, H_2O/THF, 100 °C then (c) MnO_2, $CHCl_3$, **25%**; (d) (4-Methoxyphenyl)zinc(II) chloride, $[RhCl((S)\text{-Binap})]_2$, TMSCl, THF, r.t.

A first attempt did not result in the formation of the desired product, a mixture of compounds was obtained instead which has not yet been separated. Further efforts will be made to change the protecting groups to ensure that they cannot react with the organometallic reagent and cause byproducts during the addition reaction. In order to optimize this crucial step, a collaboration with the theoretical chemistry group of W. Klopper has been established to predict the aptitude of various nucleophiles, for either an 1,2- or 1,4- or 1,6-addition reaction on the previously mentioned system **38**. First results showed, that the 1,6-addition is energetically favored over all other addition pathways. In parallel, an unfunctionalized test system (fuchsone) was employed to verify the theoretical results. These test reactions showed that the size of the attacking nucleophile is responsible for the type of addition. When methyl was used as nucleophile only the 1,6-addition product was observed. Unfortunately no 1,6-addition took place by using unsubstituted or substituted phenyl nucleophiles. At this stage, efforts are made to solve this problem. A promising

possibility would be the use of sterically less demanding phenyl precursors, which could be transformed into substituted phenyl rings after the 1,6-addition.

2.2 Peripheral Chiral Tetrahedral Cores

Peripheral chiral core structures bearing four identical arms consisting stereogenic centers, also constitute very interesting target structures as they allow the generation of chiral networks. Besides, they are generally easier to prepare and their synthesis should be much shorter than that of the central chiral cores.
The Bräse group has only recently started to address these kind of structures. So most of the results presented below are only preliminary ones and need further optimization.
In the series of the methane derivatives, a first peripheral chiral core could be prepared starting with tetrabromo derivative **16** which was converted to the corresponding tetraaldehyde **41** (Scheme 12). The latter was then submitted to an asymmetric 1,2-addition reaction using diethylzinc and paracyclophane ligand **43**.[11] This process, which has been largely investigated in the Bräse group, allowed to obtain tetraalcohol **44** in 30% yield. By using the Mosher ester strategy, we were able to determine the global ratio and absolute stereochemistry of the formed stereogenic centers for compound **44**.[12] A ratio of 4.8:1 was determined reflecting a *global enantiomeric ratio* (er_{global}).[13] Efforts are being made to enhance the yields of the process and the stereoselectivity.



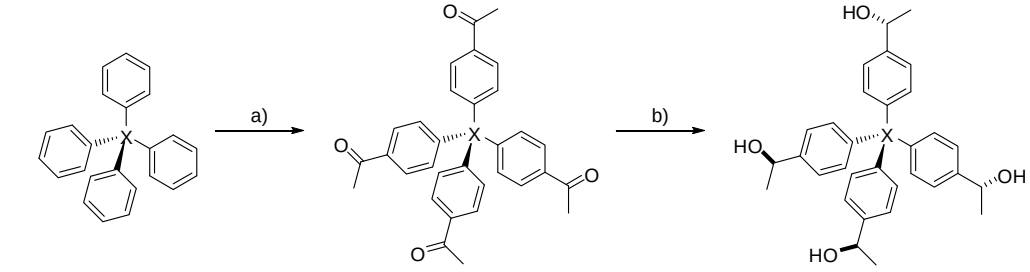
16 (X = C)
40 (X = 1,3,5,7-adamantyl)

41 (X = C)
42 (X = 1,3,5,7-adamantyl)

44 (X = C)
45 (X = 1,3,5,7-adamantyl)

Scheme 12: Synthesis of compound **44** (X = C). Reagents and conditions: (a) BuLi, THF, –78 °C then (b) DMF, –78 °C to r.t., **35%**; (c) Et_2Zn, toluene, 0 °C to r.t., **30%**. Synthesis of compound **45** (X = 1,3,5,7-adamantyl). Reagents and conditions: (a) BuLi, THF, –78 °C then (b) DMF, –78 °C to r.t.; (c) Et_2Zn, toluene, 0 °C.

The same reaction sequence has also been employed in the adamantane series and delivered target compound **45** (Scheme 12). In this particular case, purification procedures still have to be optimized.
Finally, the Bräse group also succeeded in preparing another peripheral chiral tetraalcohol in the methane and adamantane series starting from tetraphenylmethane **15** or 1,3,5,7-tetraphenyladamantane **7** respectively (Scheme 13).



15 (X = C)
7 (X = 1,3,5,7-adamantyl)

46 (X = C)
47 (X = 1,3,5,7-adamantyl)

48 (X = C)
49 (X = 1,3,5,7-adamantyl)

Scheme 13: Synthesis of compound **48** (X = C). Reagents and conditions: (a) AcCl, $AlCl_3$, CS_2, reflux, **65%**; (b) (R)-Me-CBS, BH_3·THF, THF, 0 °C to r.t., **50%**. Synthesis of compound 49 (X = 1,3,5,7-adamantyl). Reagents and conditions: (a) AcCl, $AlCl_3$, CS_2, 0 °C to r.t., **89%**; (b) CBS, BH_3·THF, THF, 0 °C to r.t., **93%**.

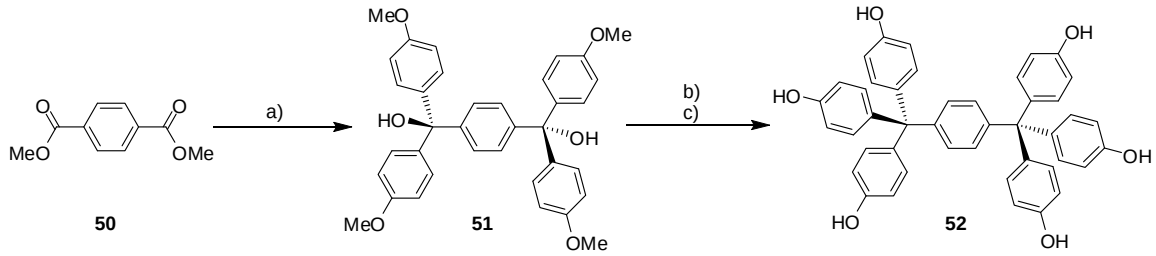
A Friedel-Crafts acylation leads to tetraketone **46** or **47** which is stereoselectively reduced to compound **48** or **49** under CBS-reaction conditions. Also in this case, the absolute configuration of the generated stereogenic centers could be determined and quantified by using the Mosher ester strategy. A global enantiomeric ratio of 10.5:1 and 12:1 were measured for compound **48** and **49**.

A third method to synthesize peripheral chiral tetraamines was established by using chiral sulfur auxiliaries. Starting from tetraaldehydes and enantiomerically pure *tert*-butylsulfinamide (Ellman-sulfinamide)[14], the peripheral chiral tetraamines were obtained in three steps (data not shown).

Many efforts are being made at the moment by the Bräse group to separate the formed stereoisomers by chiral HPLC methods.

3. Synthesis of Pseudo-Octahedral Core Structures

The synthesis of pseudo-octahedral core structures have also been investigated, namely 1,4-bistritylbenzene derivatives. In the literature only the synthesis of the unsubstituted 1,4-bistritylbenzene and the synthesis of the hexaalcohol derivative is published, but there were no further descriptions about the three-dimensional topology of these class of compounds given.
The Bräse group developed a slightly modified synthesis of 1,4-bis(tris(4-hydroxyphenyl)methyl)benzene (**52**) which allowed to obtain the product in larger scale. The synthesis starting from dimethylterephthalate (**50**) is shown in scheme 14. The first step was an addition of 4-methoxyphenyllithium to the methyl ester, the resulting tertiary alcohol was submitted to a double Friedel-Crafts alkylation with phenol. The final step was the deprotection of the methoxy protected alcohol groups to yield the desired product in 29% overall yield.



Scheme 14: Synthesis of compound **52**: Reagents and conditions: a) 4-Methoxyphenylbromide, BuLi, THF, –78 °C – r.t., **77%**; b) phenol, 200 °C, 1 h; c) boron tribromide, CH_2Cl_2, 0 °C – r.t., **37% over two steps**.

For the first time, single crystals of the compound were obtained and the threedimensional topology of the hexaalcohol **52** could be solved *via* x-ray diffraction. (see figure 2)

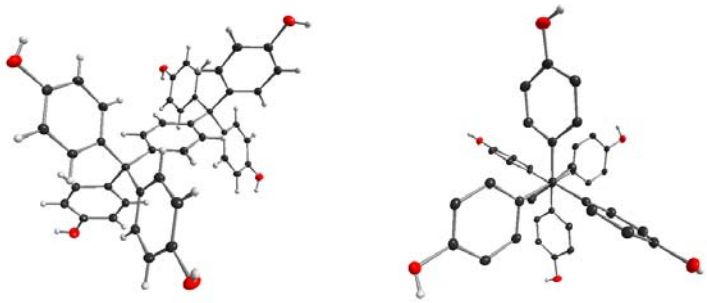
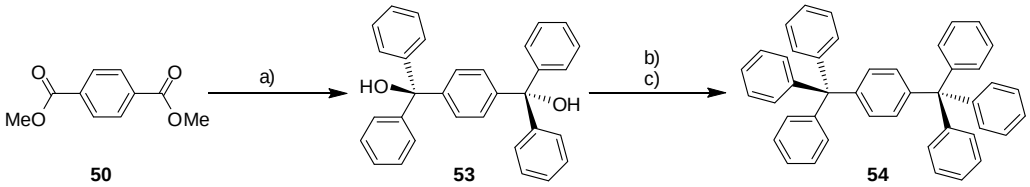


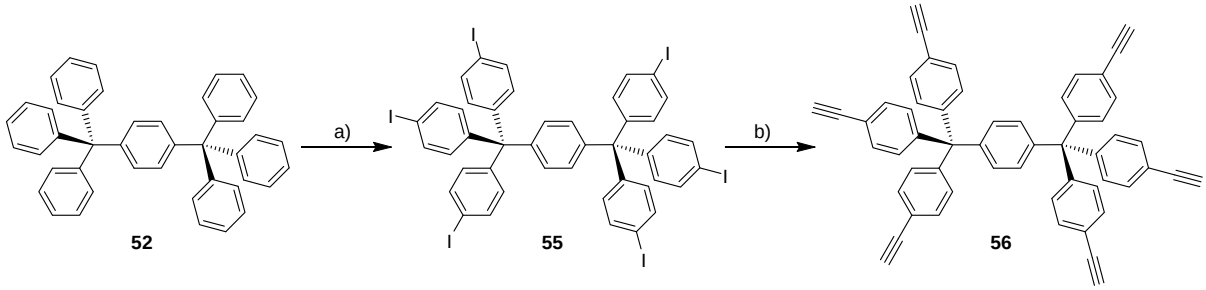
Figure 2: Crystal structure of hexaalcohol **52**; right: view along the phenylene axis to show the pseudo-octahedral topology of the six aryl moieties.

The crystal structure clearly shows the expected pseudo-octahedral topology of the six aromatic rings attached to the central benzene moiety. It should be mentioned that the symmetry of the molecule differs largely from an octahedral symmetry, which could be only achieved by hexakis substituted fullerenes, in case of organic molecules. It is much better to describe these molecules as two tetraphenylmethane scaffolds (tetrahedral shape) linked across one corner.
As soon as we had obtained hexaalcohol **52** in pure form, it was handed over to the group of C. Richert.[15]
In parallel, the Bräse group developed a novel synthesis for the generation of unsubstituted 1,4-bistritylbenzene (**54**). The three step synthesis, shown in Scheme 15, could be carried out in large scales and the product **54** was obtained in high yields and good purity.



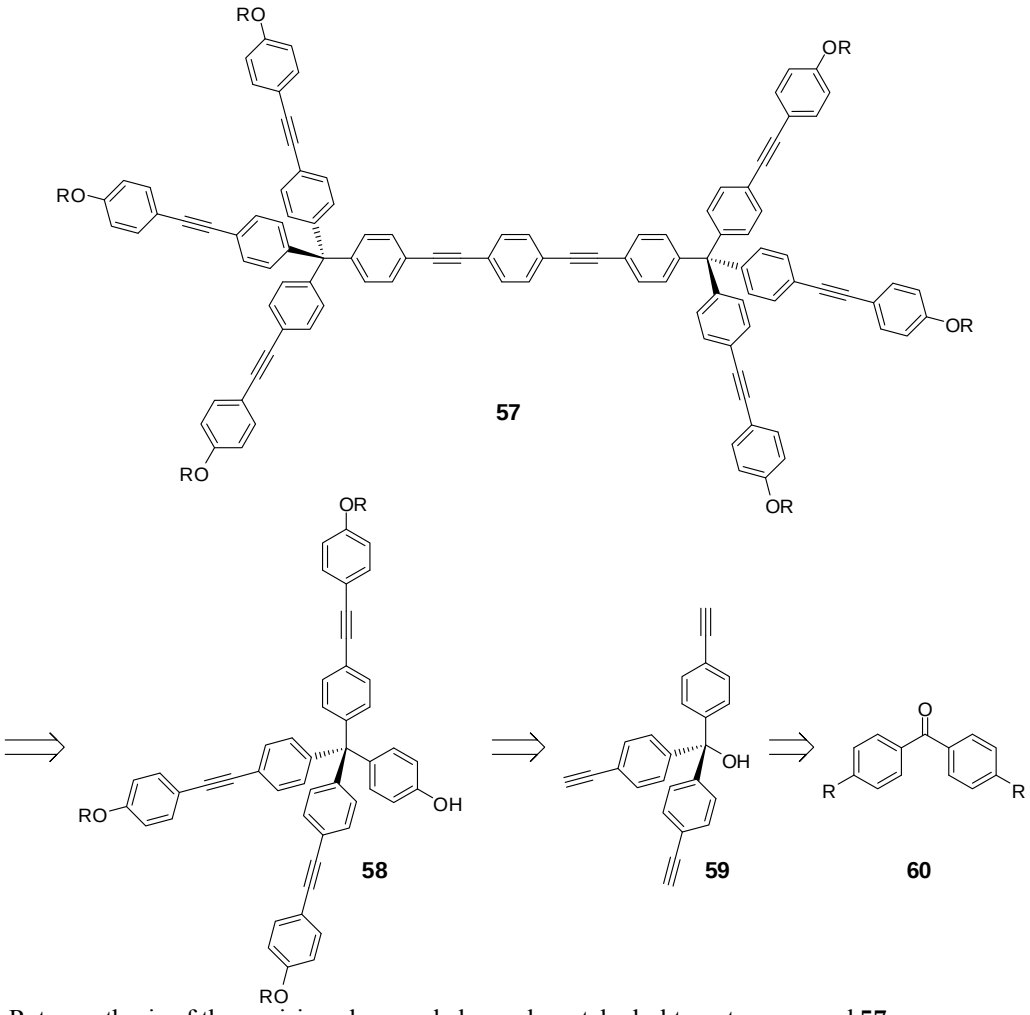
Scheme 15: Synthesis of compound **54**: Reagents and conditions: a) Phenyllithium, THF, –78 °C – r.t, **88%**; b) aniline; acetic acid; HCl, 140 °C, **77%**; c) $NaNO_2$, H_3PO_2, acetic acid, r.t., **96%**.

With compound **54** in hand, the first experiments for the hexakis functionalizations of the 1,4-bistritylbenzene derivatives, in analog to tetraphenylmethane derivatives, were performed. At this early stage, some key compounds for further usage as linker systems as described above for the tetrahedral compounds, like hexaiodide **55** and hexaacetylene **56,** could be synthesized (see scheme 16). At the moment, many efforts are made by the Bräse group to optimize the reaction conditions and to synthesize the hexaazido derivative. The synthesis of the hexanitro compound was done successfully, but further reduction to the hexaamine derivative is still a challenging problem.



Scheme 16: Synthesis of compound **56**: Reagents and conditions: a) I_2, PIFA, CCl_4, reflux, **14%**; Reagents and conditions: b) trimethylsilylacetylene, $PdCl_2(PPh_3)_2$, CuI, NEt_3, THF, 90 °C, then: TBAF, benzene, acetonitrile, r.t., **65% over two steps**.

In the near future, the synthesis of an extended hexaalcohol derivative based on the 1,4-bistritylbenzene structure motif is envisioned. The extension of the center phenyl group as well as the extension of the six arms will lead to more space for each of the six oligonucleotides which will be attached. A retrosynthesis of the envisioned extended pseudo-octahedral target compound is given in scheme 17.



Scheme 17: Retrosynthesis of the envisioned expanded pseudo-octahedral target compound **57**.

A synthetic route was developed and the first experimental results were positive. The Bräse group will intensify their efforts to synthesize the envisioned target compound **57**. As soon as we dispose some of the expanded hexaalcohol **57**, we will deliver it to the Richert group for continuative research.

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