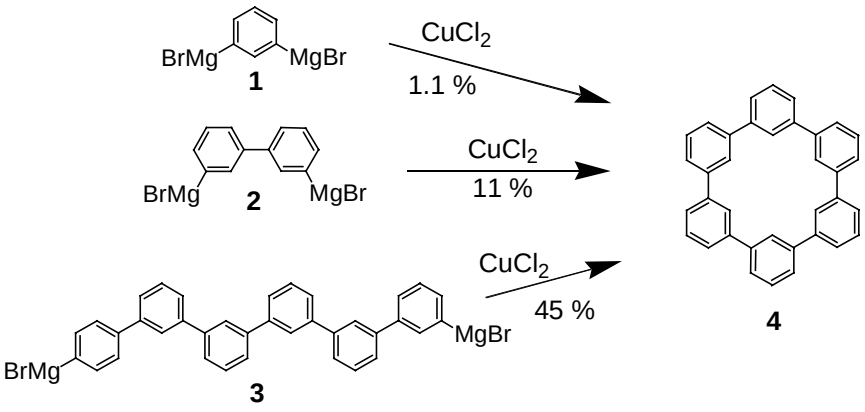
3. Literature Survey

Shape-persistency of a macrocycle sets limitations upon the chemistry of its backbone. In the class of cycles discussed here, their backbone consists only of rigid unsaturated units like aryl or ethynyl.[38,39] Other predominant classes are cyclopeptides,[40] the biologically important cyclodextrines,[41] and metallacycles.[42]

3.1 Synthetic strategies

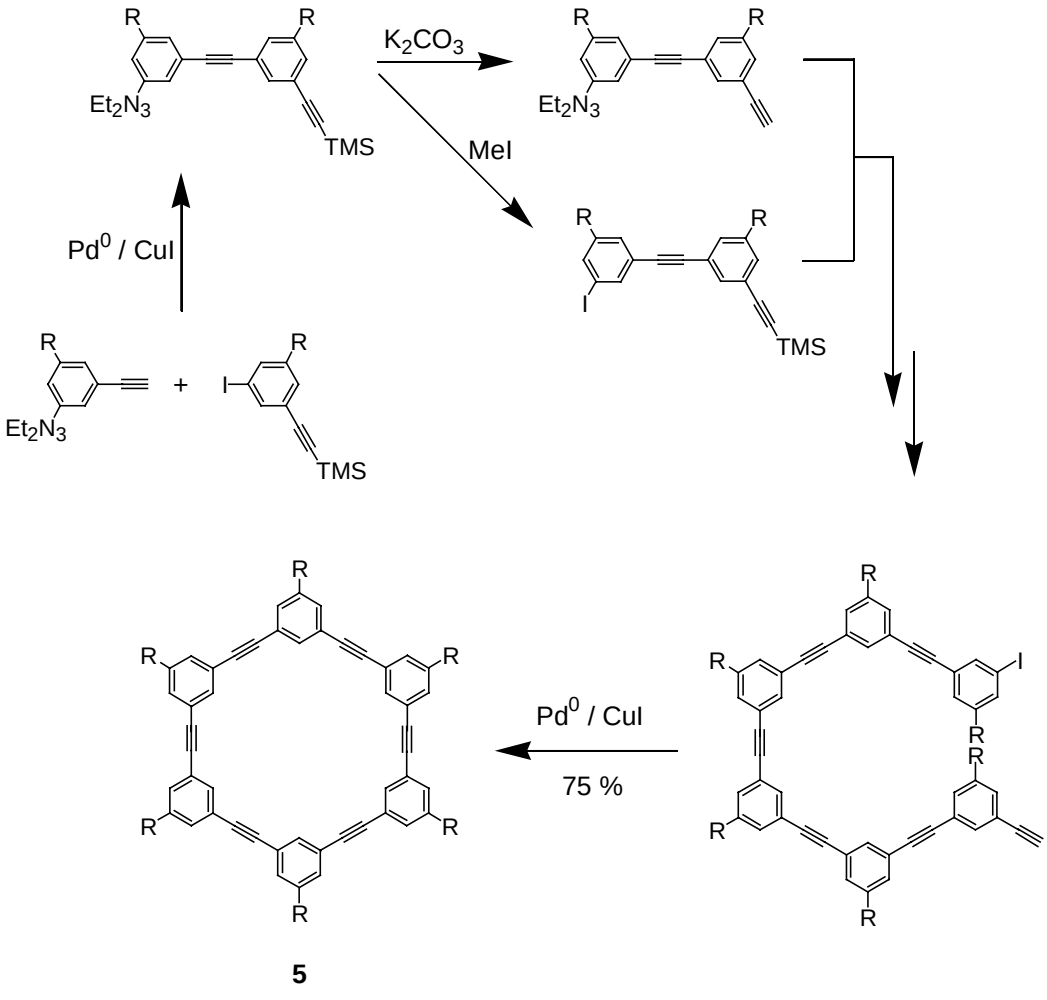
In 1967, Staab compared different strategies for the preparation of a nonfunctionalized cyclic hexa-*m*-phenylene **4** by oxidative Grignard coupling (Scheme 2).[43] While the statistic coupling of the simple monomer **1** yielded 1.1 % of the cyclic coupling product **4** next to oligomeric material, 11 % of **4** could be isolated from the reaction of a dimeric precursor **2**. The cyclization of the hexamer **3** only requires a single intramolecular coupling step, and the yield of **4** is as high as 45 %. Already from Staab's early work, one can see the problems and limitations of this research area up to even nowadays, which hampered progress for another 25 years. There is the dilemma between cyclizing simple precursors affording low (or, in worst case, no) cyclization yield connected with troublesome isolation from oligomeric side product on the one hand, and extended, but synthetically laborious precursors affording higher cyclization yield on the other. These problems obviously increase with ring size. Furthermore, there was demand for an efficient coupling chemistry which would tolerate a certain number of functionalities to open the field for more sophisticated structures.



Scheme 2. Staab's approaches towards a cyclic hexaphenylene.[43]

The breakthrough for the shape-persistent macrocycles came about ten years ago with new developments in different aspects of macrocyclization. In 1992, Moore published a

strategy for the convergent, repetitive synthesis of well-defined oligomeric ring precursors.[44] The cyclization of these telechels under pseudo high-dilution conditions afforded the macrocycle **5** in 75 % yield (Scheme 3). The basic transformations involved the Pd^0 catalyzed Sonogashira coupling of aryl iodide and terminal acetylene, and an orthogonal protection/deprotection scheme for these functionalities. N,N,-dialkyltriazene served as a placeholder for iodo and could be unmasked with iodomethane. The trimethylsilyl (TMS)-protecting group for acetylene was removed in slightly basic conditions. The sequence of these deprotection/coupling steps was repeated an appropriate number of times to generate the desired linear phenylacetylene oligomer. This was then cyclized in one intramolecular coupling step by the Sonogashira cross-coupling method.

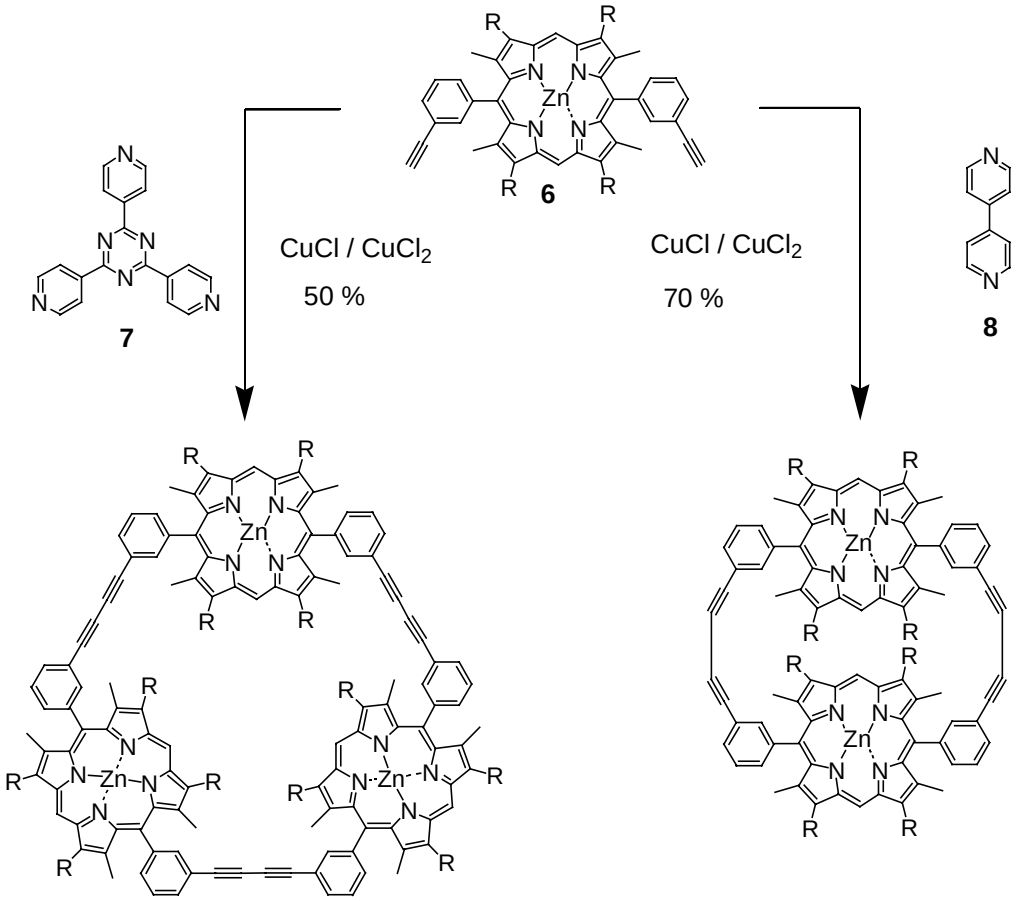


5

Scheme 3. Moore's repetitive strategy to phenylacetylene macrocycles.[44]

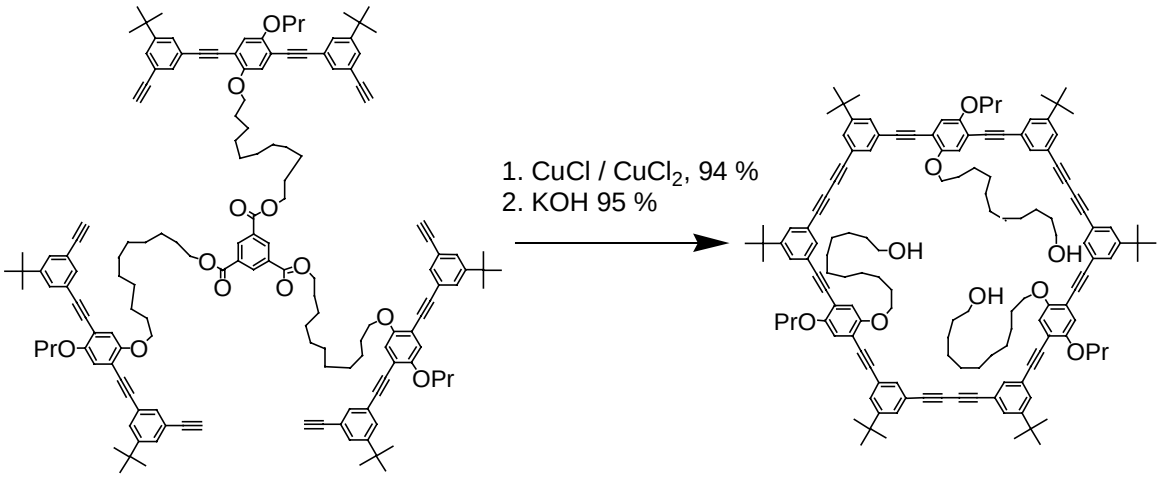
Two years earlier, Sanders had shown how the cyclization yield of smaller precursors would be improved by the template effect (Scheme 4).[45] Cyclization of bisacetylene **6** under Glaser coupling conditions afforded a mixture of macrocycles of different size. In the

presence of appropriate pyridyl templates **7** or **8**, however, cyclization could be forced into the desired direction. The reason for this selectivity is a prearrangement of the precursors around the template.



Scheme 4. Sander's strategy via a coordinatively bound template;[45] *R = $CH_2CH_2COCH_3$.*

Höger extended this approach to covalently bound templates, which were cleaved off later, and obtained macrocycles in impressive yields of 94 % under pseudo high-dilution Glaser coupling conditions (Scheme 5).[46,47] New insight into this effect was gained by detailed studies on size and flexibility of the template, which was positioned exo- or endo-cyclically. The template was either attached to the ready precursor, or the precursor built up while being bound to the template (for an overview, see lit.[39]). Höger demonstrated that not an exact prearrangement of the bisacetylenes but their high local concentration (under overall high-dilution conditions in the reaction mixture) was responsible for high product yield. If, on the other hand, the conformational freedom of the intermediate is restricted too much by the template, the desired reactions are kinetically hindered and yields will drop dramatically.[48]



Scheme 5. Höger's strategy via a covalently bound template.[46,47]

First investigations into a solid-phase protocol for the synthesis of cyclic phenylacetylenes using Moore's coupling chemistry have been reported; the desired product, however, was not isolated yet.[49]

A large variety of different shape-persistent macrocycles has been reported in the recent years. A few general trends can be drawn from literature.

In cyclization chemistry, Sonogashira (ref. Scheme 3) and Glaser type (ref. Scheme 4) couplings dominate the field, probably due to their high tolerance towards functional groups, the generally high yields, and the fact that elaborated methods to built up conveniently functionalized precursors exist. There are a few examples for Suzuki[29,50] or zirconocene couplings,[51] but earlier reported methods like Stevens-Castro,[52] oxidative Grignard[43] or lithium organyl couplings[14] were totally replaced by the new methods. There have been only two examples in the last four years of other coupling methods, one using McMurry coupling (followed by conversion of the formed double into triple bonds),[53] and the other acetylene metathesis.[54] Very recently, however, another double elimination protocol for the synthesis of phenylacetylene macrocycles via sulfoximines has been published.[55]

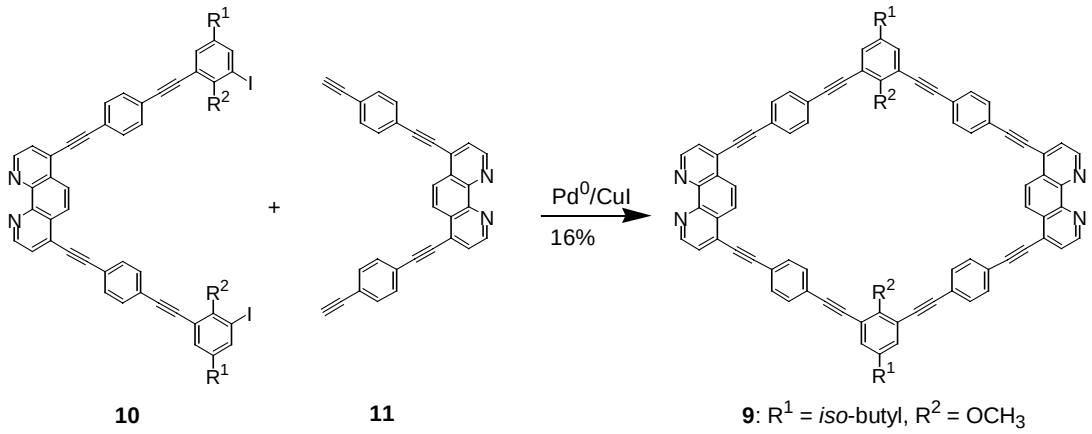
Even if covalently or complex bound templates have been shown to either significantly shorten the synthetic pathway for the precursors or to increase the yield drastically, they have not found wide application yet. A problem is surely the higher demand in synthetic design, i.e., the exact geometry for rigid complexating templates or the additional efforts in synthesis for precursors covalently bound at flexible templates.

One-pot statistical oligomerization-cyclizations are not feasible for the construction of large macrocycles; on the other hand, most groups also avoided synthesizing a single extended precursor for high-yield cyclization in one coupling step; its preparation is not only

time consuming, but in some cases even synthetically very difficult, e.g., when a symmetrically functionalized terpyridine unit has to be transformed into an unsymmetrically functionalized moiety. Often, rings are closed from 2-3 precursors, into whose synthesis even statistic reactions may be included.

3.2 Shape-persistent macrocycles with heteroatoms

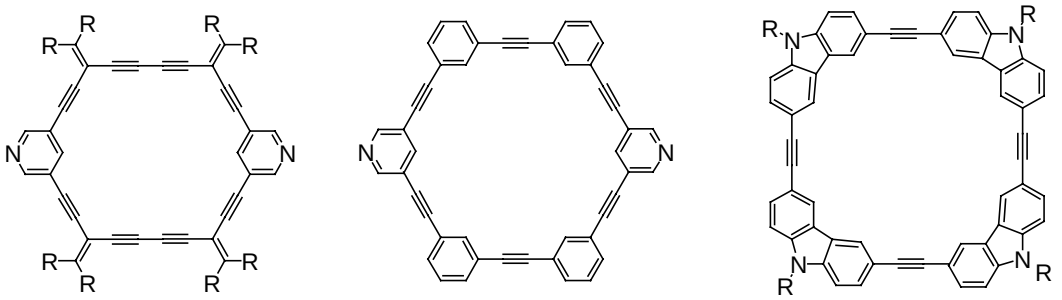
A rapidly growing number of reports deal with shape-persistent macrocycles containing heteroaromatic subunits as anchor points for metal ions. While only rather small cyclohexa-*m*-pyridines were reported[56] besides Sander's porphyrine macrocycles until four years ago,[45,57] the situation has totally changed since then.



*Scheme 6. Macrocycle **9** with two phenanthroline units by Schmittel.*[58]

Schmittel prepared a 50-membered macrocycle **9** containing two exotopic phenanthroline units in 16 % yield from the two ring precursors **10** and **11** by Sonogashira coupling (Scheme 6).[58] This type of cycle can be complexed exocyclically to serve as a building block for molecular boxes.

Other examples of cycles with exotopic ligand sites containing pyridine or carbazolyl units are shown in Figure 1. Tykwinski prepared cycles **12a-c** by cyclization from 2 precursors under Glaser type conditions.[19,20] While **12a** was not soluble and **12c** could not be isolated pure, all three cycles were complexed with Ru porphyrins and characterized as such. Lees prepared cycle **13** by Sonogashira and a similar structure (not shown) by Glaser-Hay coupling.[18] Both cycles were complexed with Re(I) tricarbonyl. Maruyama prepared **14** as cyclic dimer from two precursors; as a side product, he could also characterize the cyclic tetramer.[59]



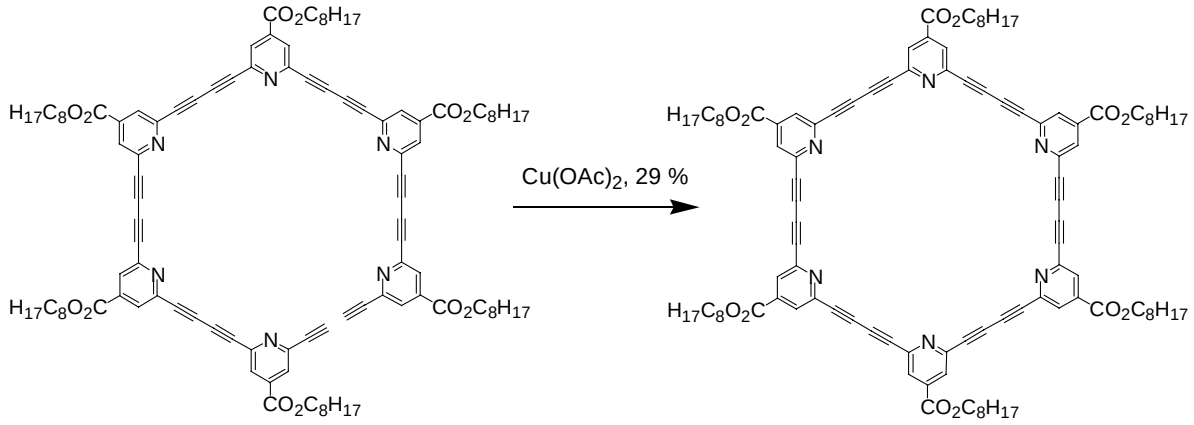
12a: R = Me
12b: R = Ph
12c: R = adamantyliden

13

14: R = n-$C_{14}H_{29}$

Figure 1. Other macrocycles with exotopic ligand sites by Tykwinski,[19,20] Lees[18] and Maruyama.[59]

Tobe cyclized a single precursor **15** under Eglinton-Glaser conditions to give 42-membered pyridinophane **16** in 29 % yield (Scheme 7).[17] Under similar conditions, he obtained a 28-membered analogue in 50 % yield (not shown). He could prove both cycles to form heteroaggregates in solution with their analogues in size which carry endocyclic cyano substituents.

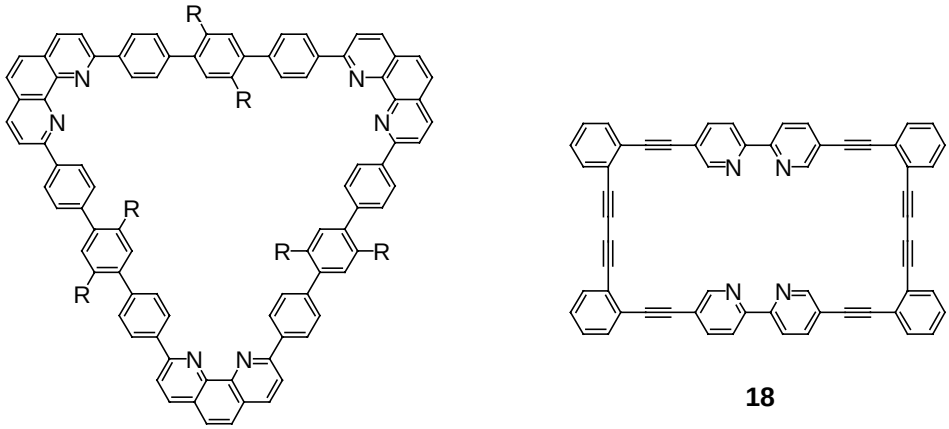


15 **16**

*Scheme 7. Macrocycle **16** with pyridine units by Tobe.[17]*

Rehahn isolated 54-membered phenylene macrocycle **17** with three endotopic phenanthroline units as a cyclotrimeric side product from a Suzuki polycondensation (Figure 2).[50] Mass spectrometric investigations showed that neither small oligomers nor rings larger than this were formed. This remarkable selectivity was attributed to the conveniently fixed angles of the 2,9-substituted phenanthroline moieties. Baxter obtained 40-membered macrocycle **18** containing two pyridine units by Hay coupling of two precursors in 34 % yield.[60] The cyclic backbone is, different from the others cited here, not planar, but twisted.

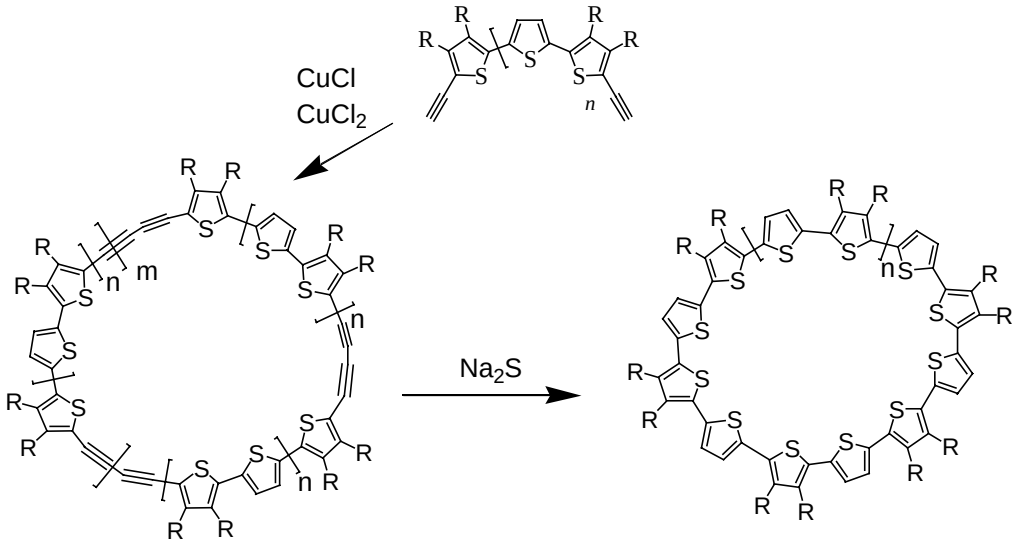
The bipyridine units can, therefore, bind metal ions in an enforced tetrahedral coordination geometry.



17: R = C_6H_{13}

18

Figure 2. Macrocycles by Rehahn[50] and Baxter.[60]



19a: n = 1, m = 1, R = C_4H_9
19b: n = 1, m = 2, R = C_4H_9
19c: n = 2, m = 1, R = C_4H_9
19d: n = 2, m = 2, R = C_4H_9

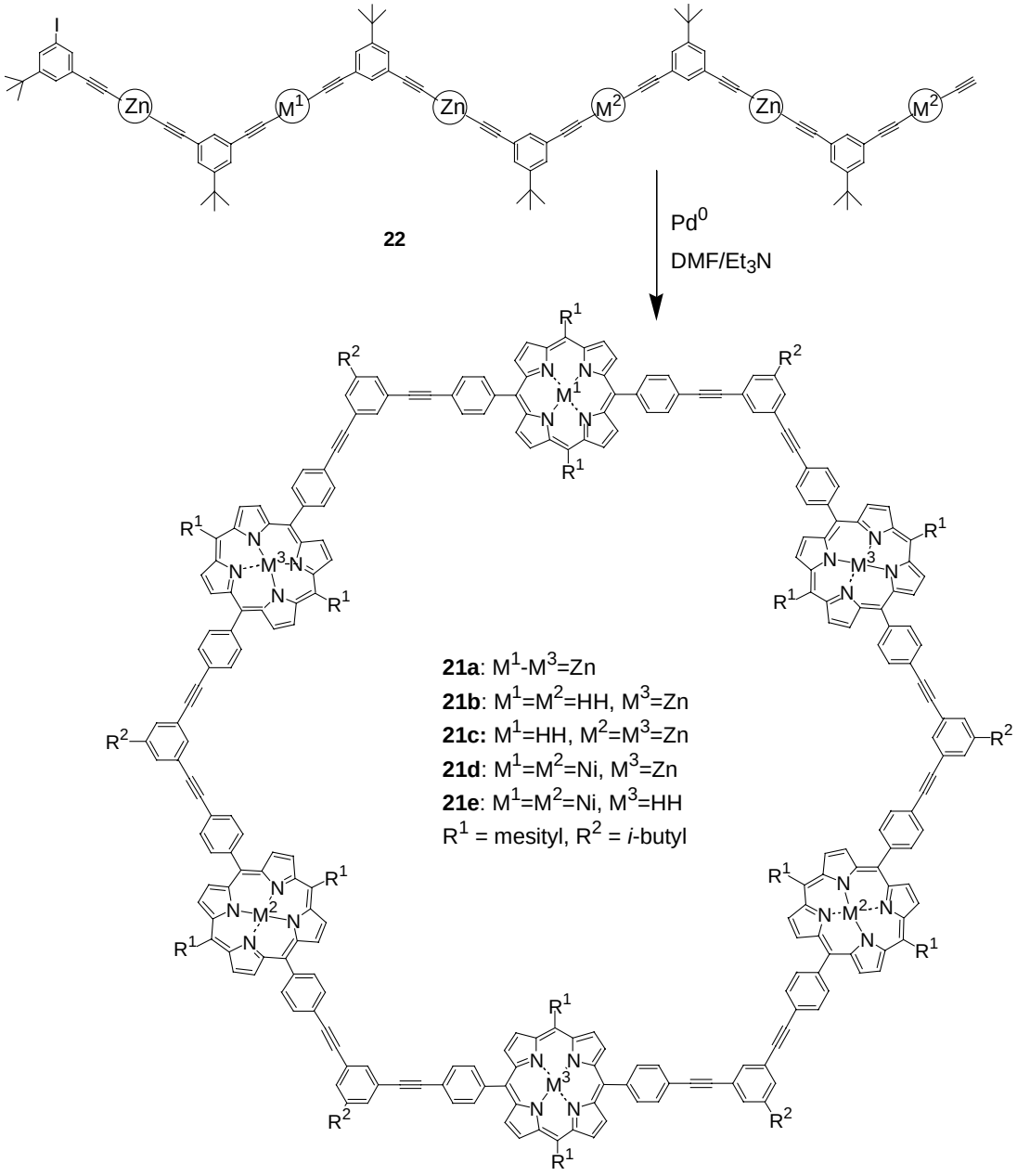
20a: n = 1, R = C_4H_9
20b: n = 3, R = C_4H_9
20c: n = 4, R = C_4H_9

R = *n*-butyl

Scheme 8. Thiophene derived macrocycles by Bäuerle.

Bäuerle obtained a set of 39-, 52-, 57-, and 76-membered thiophene derived macrocycles **19a-c** (Scheme 8).[61] Iodinated ter- and quinquethiophenes were furnished with an acetylene functionality by Sonogashira coupling and reacted in a statistic cyclization under

Breslow-Glaser conditions, after different coupling conditions had been evaluated. By MALDI, cyclic structures from a dimer up to a heptamer were detected; tri- and tetrameric macrocycles **19a-d** were isolated. By reaction with sodium sulfide, the butadiyne units could be transformed into thiophenes **20a-c** in yields of 23 % and 27 % for **19a** and **19b**, and 7 % for **19c** with its four butadiyne units. The cycles form regular 2-D monolayers on graphite. Interactions with fullerenes as guests inside the macrocyclic hosts will be studied in the future.[62]

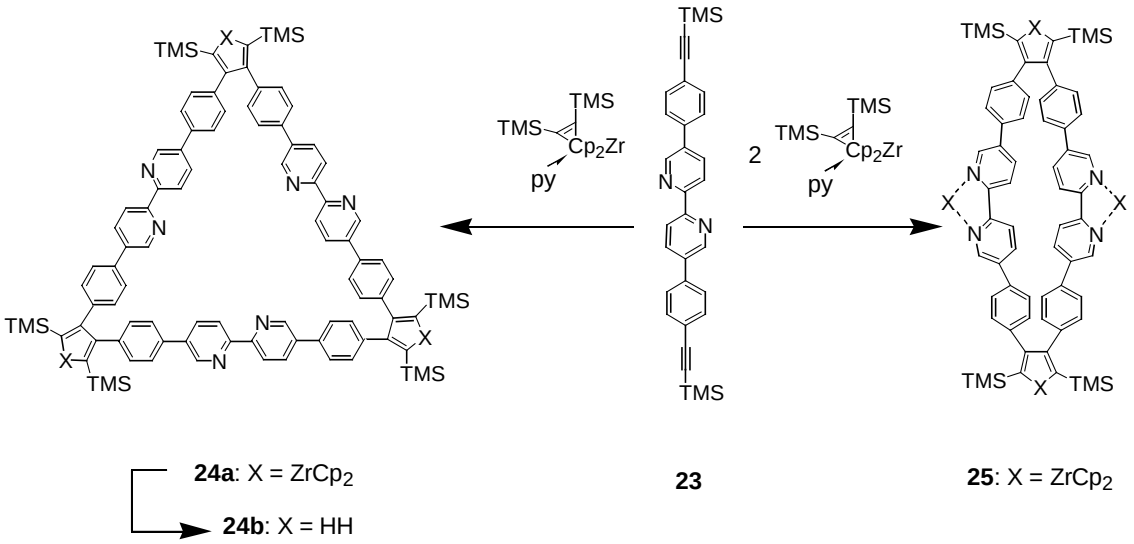


Scheme 9. Porphyrin derived macrocycle by Gossauer.[63]

A case for itself are the porphyrine macrocycles, i.e., large macrocycles containing a set of smaller macrocyclic systems. The hexameric porphyrine macrocycle **21** was prepared by Gossauer following Moore's repetitive strategy (Scheme 9).[63] From the impressive precursor **22** he gained macrocycle **21** in a yield of 20-30 %, with 144 ring members the largest shape-persistent macrocycle reported by now. The high synthetic effort is reflected by the prepared amount of 0.4 – 6 mg. By MALDI-MS and NMR techniques, he could show that **21** forms host-guest aggregates in solution with a star-shaped guest molecule.[64]

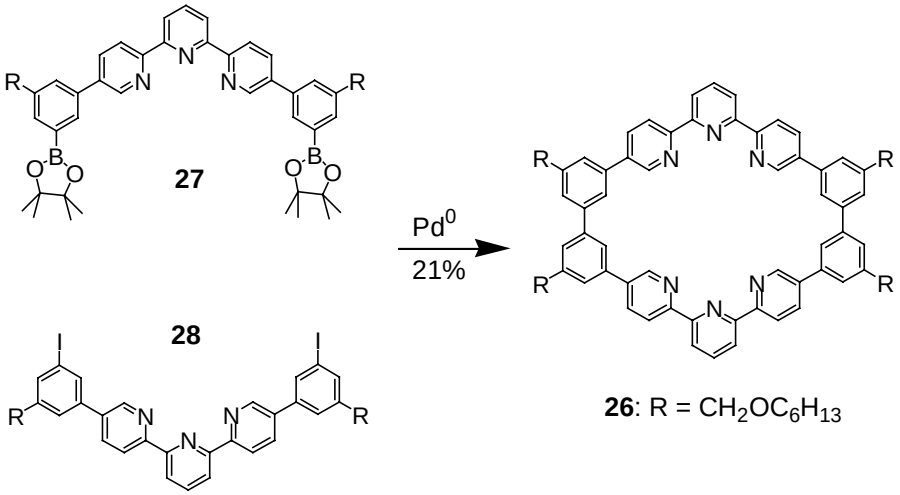
Lindsey described a different approach to 108-membered porphyrine containing macrocycles by a template directed cyclization from up to six precursors in 5.5 % isolated yield following Sander's strategy (not shown).[65]

Tilley extended his set of macrocycles by zirconocene coupling[66] by a variety of new members.[51] The big advantage of this method lies in the fact that the carbon-carbon bond formation is reversible and therefore strictly thermodynamically controlled. Yields are accordingly very high, but the method is, due to the geometry of the zirconacyclopentadiene unit, yet restricted to either triangular or "rectangular" shapes, the latter having practically no inner lumen. An example is given in Scheme 10. Diyne **23** reacts thermodynamically controlled with 1 equ. of $ZrCp_2$ to trimeric macrocycle **24**.[51c] A higher ratio of $ZrCp_2$ leads to complexation of the bipyridine unit, which is bent to an angle suitable to form thermodynamically the dimeric macrocycle **25**.[51a] The cycles can be demetalated under acid conditions.



Scheme 10. Template directed zirconocene coupling by Tilley.[51a,c]

In our group, Hensel and Lützow developed strategies to construct phenylene macrocycles in a repetitive way using the Suzuki cross coupling.[67-74] These cycles were furnished with chloro functionalities to allow further construction, e.g., their connection to 2-D networks.

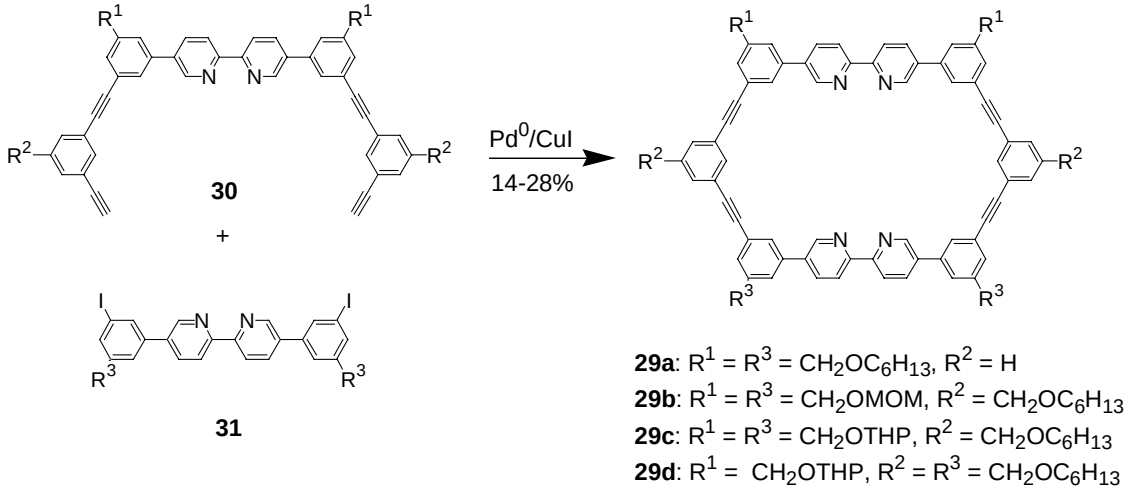


Scheme 11. Lehmann's terpyridine containing macrocycle by Suzuki coupling.[29]

In the area of heteroaromatic macrocycles, Lehmann and Henze later contributed with two different structures. Lehmann isolated the 34-membered phenylene macrocycle **26** with two opposing endotopic terpyridines from the Suzuki coupling of precursors **27** and **28** in 20 % yield (Scheme 11).[29] The precursors were built up by a sequence of Stille type cross-couplings using its high selectivity of iodo over bromo functionalized carbons and trimethylstannyl over boronic acid ester groups. This strategy involved a new synthetic route for 2,2':6',2"-terpyridines functionalized in 5,5"-position.[27] From a cyclization reaction between analogous iodo and stannyl functionalized precursors under Stille coupling conditions, no cyclic product was obtained.[28]

A set of 42-membered phenylacetylene macrocycles **29** containing two opposing bipyridine units was obtained in optimized yields of 25-30 % from two precursors **30** and **31** (Scheme 12).[32,33] Attempts to couple a bromoaryl instead of the iodoaryl under the same conditions failed.[31] The cyclizations were carried out in a sealed vessel in highly diluted reaction mixtures; the application of pseudo high-dilution conditions by using a syringe pump gave unsatisfying results. The tetraaryl building blocks were generated by Stille cross coupling; by this, a new synthetic route to 5,5'-substituted 2,2'-bipyridines had been opened.[30] Iodination of **31** had to follow a nucleophilic stannylation/de-iodo-stannylation sequence due

to the sensitivity of the bipyridine unit to BuLi, which in other cases successfully was applied in a lithiation/iodination sequence.



29a: $R^1 = R^3 = CH_2OC_6H_{13}$, $R^2 = H$
29b: $R^1 = R^3 = CH_2OMOM$, $R^2 = CH_2OC_6H_{13}$
29c: $R^1 = R^3 = CH_2OTHP$, $R^2 = CH_2OC_6H_{13}$
29d: $R^1 = CH_2OTHP$, $R^2 = R^3 = CH_2OC_6H_{13}$

Scheme 12. Henze's bipyridine derived macrocycles by Sonogashira coupling.[32,33]