

4. General Part

4.1 General Strategy

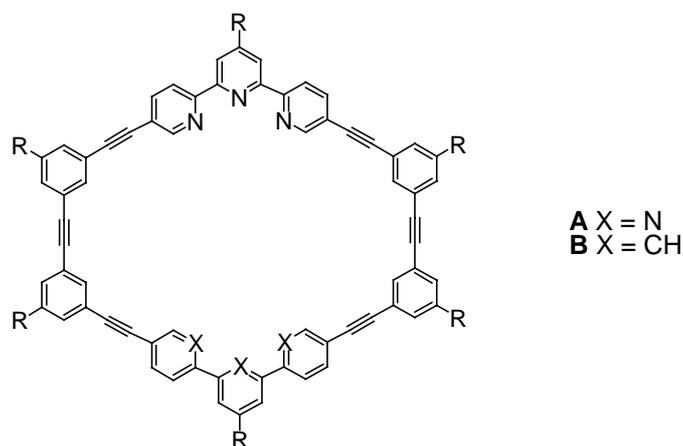


Figure 3. Structure of the envisaged macrocycle with one or two terpyridine units; R = positions for side groups.

The envisaged structure **A** (Figure 3) contains two 2,2':6',2''-terpyridine units held in a hexagonal framework. The hexagonal topology is common for nearly all planar shape-persistent macrocycles published yet (an important exception are Tilley's Zr derived triangles, ref. Scheme 10, p. 12). Six *meta*-connected aromatic building blocks form the corners of the hexagon, while acetylenes and *para*-connected aromatic units represent its sides. The replacement of one terpyridine by a terphenyl unit gives the geometrically similar macrocycle **B**. Thus, cycles with either one or two terpyridine units would allow a stepwise approach towards metal complexes.

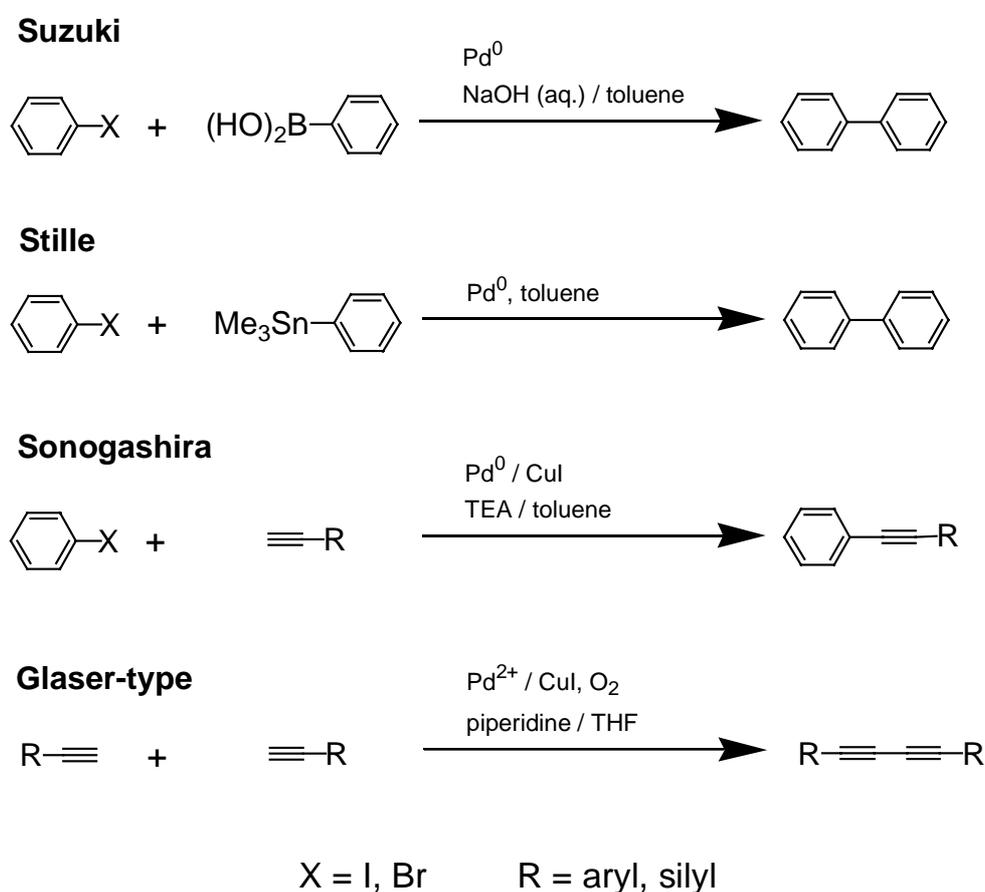
The side groups R represent long, flexible alkyl chains. These are necessary to make the rigid structure soluble.⁷⁵ Some of the groups R may also be furnished with functionalities, which allow a later modification of the macrocycle.

A general remark concerning the graphical representation of structures in this report: The nitrogen atoms of the terpyridine unit can be expected to preferably adopt a *trans,trans* conformation, which, under complexation, can easily be forced into *cis,cis*. With respect to our concept to complex the structures at a later stage, the terpyridines are drawn *cis,cis* throughout. In literature, both ways are common. Accordingly, also the linear ring precursors are visualized in a conformation which is suggestive towards later cyclization.

4.1.1 Coupling Chemistry

The formation of shape-persistent macrocycles containing exclusively sp or sp^2 hybridized carbon atoms in their backbone affords C-C bond formations of the type (het)aryl-(het)aryl, (het)aryl-alkynyl, and/or alkynyl-alkynyl (Scheme 13).

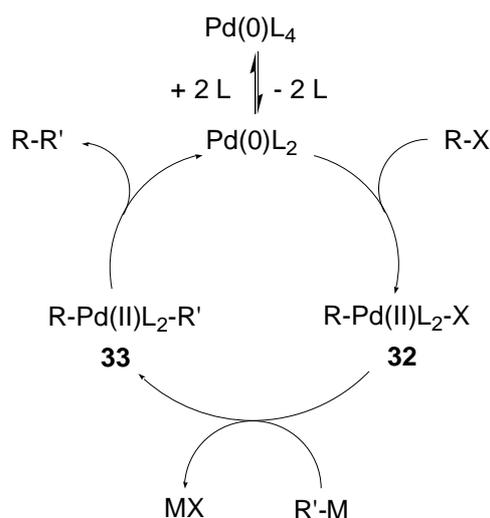
One of the most common tools for the connection of two aromatic units is the Pd^0 catalyzed cross-coupling reaction between aryl halides or triflates and a variety of organometallic reagents.^{76,77} Among these, aryl boronic acids/esters (Suzuki coupling)⁷⁸ and trialkylarylstannanes (Stille coupling)⁷⁹ have become the most important due to their high tolerance against functional groups and their stability towards air and moisture (compare with, e.g., lithium or magnesium organyls).



Scheme 13. The Pd catalyzed cross- (Suzuki-, Stille- and Sonogashira-) and homo- (Glaser-type-) coupling methods used here. Reaction conditions refer to the present work.

Both methods can be understood according to the general reaction mechanism (Scheme 14). The presence of the intermediates in this scheme is generally accepted, although further processes (including ligand exchange) are involved into the mechanism.⁷⁶ The active, coordinatively unsaturated catalyst $Pd(0)L_2$ is formed by the dissociation of two ligands from

the precursor species $\text{Pd}(0)\text{L}_4$ in solution; $\text{Pd}(\text{PPh}_3)_4$ is perhaps the most commonly used.⁷⁸ Oxidative addition of the aryl halide ArX to the complex gives **32**. The general order of reactivity $\text{ArI} > \text{ArOTf} \geq \text{ArBr} \gg \text{ArCl}$ is consistent with the strength of the C-X bond and a corresponding reactivity in this step of the catalytic cycle. This oxidative insertion is interpreted as a reversible nucleophilic attack of the palladium on the aromatic under formation of a hexadienyl intermediate, and an irreversible breaking of the bond to the leaving group.⁸⁰ It was shown that the halide leaving group may dictate which step of the catalytic cycle is rate-determining, i.e., the oxidative addition or the transmetalation.⁸¹ In this following step, complex **32** reacts as an electrophile with the nucleophilic aryl carbon atom of $\text{R}'\text{-M}$ to give **33**. For the Suzuki coupling, which generally has to be performed under basic conditions, OH^- plays a crucial role in the catalytic cycle either via ligand exchange in **32** or formation of the borate $\text{R}'\text{B}(\text{OH})_3^-$ prior to the transmetalation.⁷⁸ In the final step, reductive elimination of the desired coupling product from **33** sets free the regenerated catalyst.



Scheme 14. General catalytic cycle for Pd^0 catalyzed cross-coupling reactions.

In extensive mechanistic studies, the effects of different catalytic systems and reagents have been examined,⁸² modified, and more detailed catalytic cycles were proposed.⁸³ A large variety of studies in optimizing reaction conditions have been reported; two trends seem noteworthy here. The one is the exploration of catalytic systems which facilitate the oxidative addition of aryl chlorides, e.g., by using electron rich, sterically demanding⁸⁴ or bidentate ligands.⁸⁵ Pd -catalyzed cross coupling reactions of aryl chlorides are usually inefficient if the aryl halide does not contain electron-withdrawing substituents.⁸⁶ Another range of studies deals with the facilitation of the transmetalation step in Stille coupling.⁸⁷ The beneficial

effect of CuI as additive is explained by its ability to scavenge free ligand, which is inhibitory to transmetallation.⁸⁸

The Sonogashira coupling⁸⁹ between aryl halides and terminal acetylenes can be understood by the same catalytic cycle, if one assumes that the cocatalyst CuI functions to generate a copper acetylide, i.e., $M-R' = Cu^+CCR$ (Scheme 14). Also for the Sonogashira coupling, a large number of studies have appeared in recent years which described the optimization of the reaction conditions, i.e., by the use of additives,⁹⁰ variation of the solvent^{91,92} or the catalyst.⁹³⁻⁹⁵ This has been mostly on a descriptive level; mechanistic studies are rare.

Both the Sonogashira and the Suzuki coupling have been used to generate shape-persistent macrocycles, and for both methods, repetitive synthetic procedures including protection/deprotection schemes for the coupling functionalities have been developed (ref. Scheme 3, p. 5, lit^{67,70}). The Stille reaction is slower, and side reactions like homocouplings are observed.⁹⁶ For the cyclization step, which has to be performed under high dilution conditions to compete with oligomerization, this is a severe drawback; in the literature in recent years not a single shape-persistent macrocycle could be found which was cyclized via Stille coupling,⁹⁷ but reports about unsuccessful attempts are numerous.^{28,31,60} For the construction of appropriately functionalized terpyridine building blocks, however, the Stille cross-coupling has been proven an effective method,²⁷ which makes its application useful in this work despite the high toxicity of organostannanes.

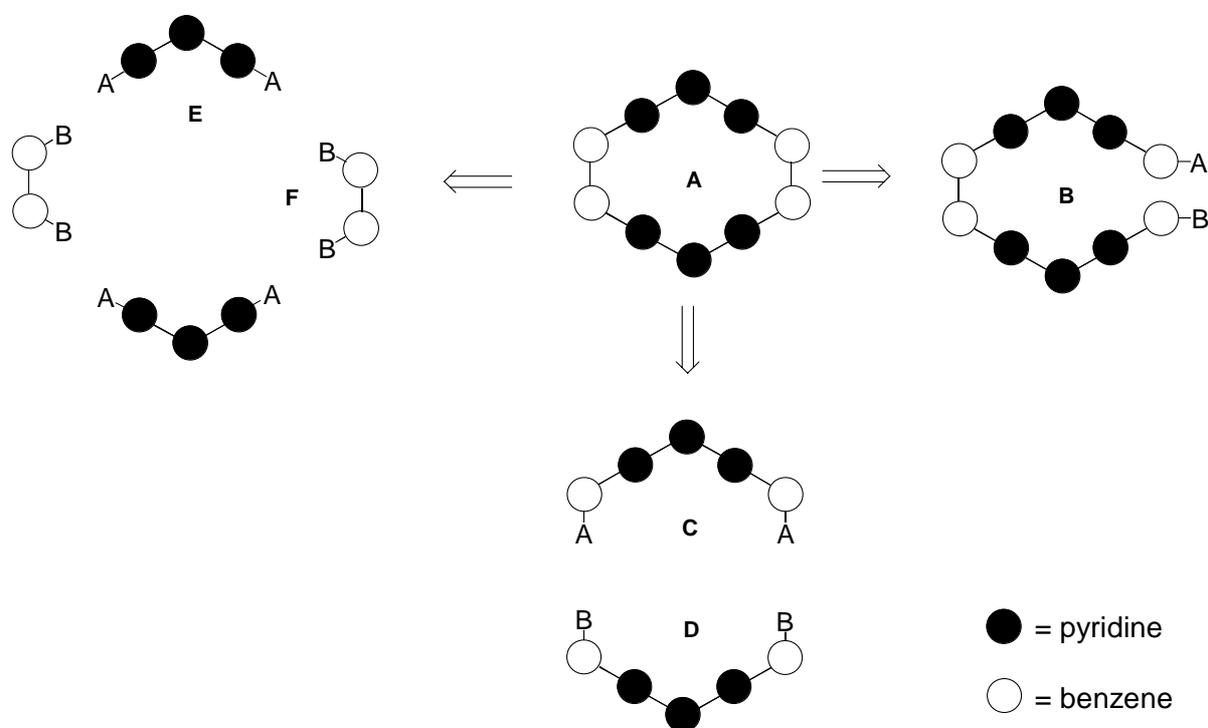
To cyclize macrocycles from equal precursors, i.e., generally two half rings, the oxidative alkynyl-alkynyl coupling has been established as a convenient homocoupling procedure.^{98,99} This method dates back to experiments by Glaser (1869),¹⁰⁰ and a large variety of different coupling conditions have been developed since then, most of which are grouped under the expression "Glaser coupling", and some have even been attributed with proper names. Practically all variations use copper catalysts. The Eglinton-Galbraith method, which is performed with an excess of $Cu(OAc)_2$ in MeOH/pyridine, has been widely used to close macrocyclic systems under high dilution conditions.¹⁰¹ The Hay method uses catalytic amounts of CuCl and TMEDA under O_2 .¹⁰² Its advantage lies in the generally better solubility of the reactive intermediates. The Breslow variation uses $Cu(OAc)_2/CuI$ in pyridine.¹⁰³ There are a few examples in literature for Pd^{2+} catalyzed oxidative alkynyl-alkynyl coupling reactions.^{104,105}

The complex mechanism of the copper-mediated Glaser coupling reactions strongly depends on the concrete reaction conditions, and a generally accepted mechanism is not

available yet.⁹⁹ For the Pd-mediated couplings, a reaction cycle has been proposed via the activation of the alkynyls by Cu(I) analogously to the Sonogashira reaction (i.e. by forming a Cu(I) acetylide or by π -complexation), the formation of a dialkynyl palladium intermediate, and reductive elimination of the butadiyne coupling product.^{105,106} Detailed mechanistic studies, however, have not been reported yet.

4.1.2 Retrosynthetic Concept

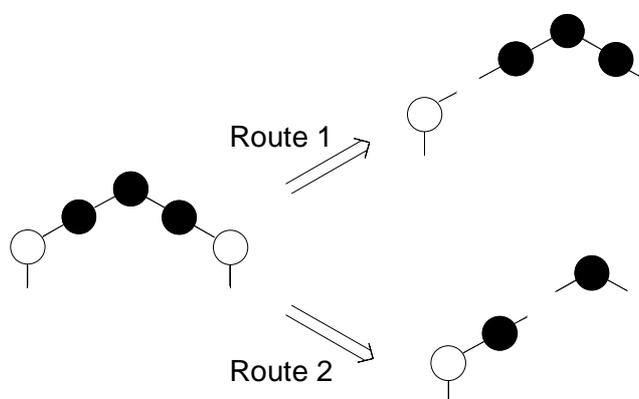
The established strategies to build up a hexagonal shape-persistent macrocycle differ principally in the complexity of ring precursor molecules on the one side and cyclization yield on the other.



Scheme 15. Retrosynthetic pathways to a hexagonal macrocycle with two terpyridine units (ethynylene units and side chains not shown).

In the extreme case, macrocycle A is cyclized from a single precursor B in one intramolecular coupling step (Scheme 15). While high synthetic effort has to be put into the synthesis of precursor B, cyclization yields as high as 75 % have been reported for this strategy.¹⁰⁷ It was systematically described by Moore (ref. Scheme 3, p. 5), and in his case, the precursor molecule was accessible by a repetitive strategy of exponential growth. The incorporation of heteroaromatics in the present case, however, leads to a decrease in symmetry of the structure to D_{2h} ; the smallest repeating unit is therefore not the single

aromatic, but the half ring (C, D) itself, which makes the repetitive strategy not feasible here. Furthermore, this strategy would afford the synthesis of unsymmetrically functionalized terpyridine units – this, up to now, has remained a synthetic challenge.^{108,109} Therefore a strategy has to be envisaged which starts from symmetrically functionalized terpyridines, i.e., from the precursors C and D, or E and F. While the former cyclization reaction via C and D affords one inter- and one intramolecular coupling step to give the cycle, the latter strategy seems less promising as it requires three inter- and one intramolecular coupling step, by which the probability of oligomeric side products increases dramatically and the expected yield in cycle accordingly decreases.



Scheme 16. Retrosynthetic pathways to half ring C/D (ethylene units, functionalities and side groups not shown).

The half ring is accessible by principally two different ways: Either, it is built up on an existing terpyridine unit (Scheme 16, Route 1), or, the side pyridines of the terpyridine unit are first extended by the ring corner aromatic, and then fused with a central pyridine in a twofold coupling reaction to give the terpyridine in the last step (Route 2). Even if this classification seems somewhat artificial at this point, its significance lies in synthetic aspects; the different coupling chemistry for the construction of the terpyridine unit (Stille) and the connection with the corner aromatic (Sonogashira) plays as well a role here as the difficulty to purify terpyridines by column chromatography. Both methods have been examined.

The cycles with only one terpyridine unit can be synthesized following the same way, by replacing the terpyridine by the geometrically similar terphenyl. One can describe this as a construction kit strategy, where, using the same coupling chemistry, different building blocks are coupled, i.e., terphenyls or terpyridines with a set of differently functionalized aromatic corner molecules.