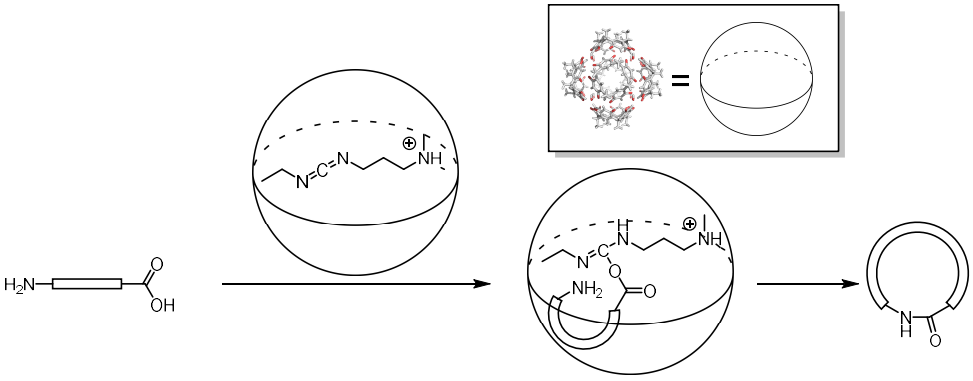
Summary

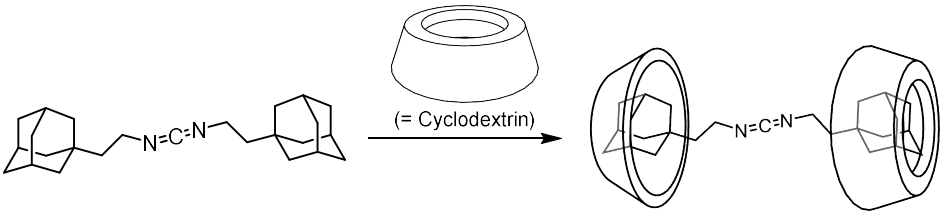
The work in this thesis describes the exploration of site-isolation strategies to facilitate difficult peptide cyclizations. In **chapter 2**, the effect of supramolecular shielding on cyclizations of difficult small peptides is investigated. Instead of covalently incorporating the peptide carboxyl group activating carbodiimide moiety in the shielding structure as in other approaches, it is held in the shielding environment by virtue of supramolecular interactions (see Scheme 1). Seven linear peptides were synthesized and reacted with resorcin[4]arene (**R[4]A**) encapsulated EDC·HCl. A sampling procedure with reproducible outcomes has been developed to allow analysis of the reaction mixture using LC-MS. However, only marginal improvements have been observed when the reactions are carried out in presence of the supramolecular capsule.



***Scheme 1**: Schematic depiction of **R[4]A**-mediated peptide cyclizations .*

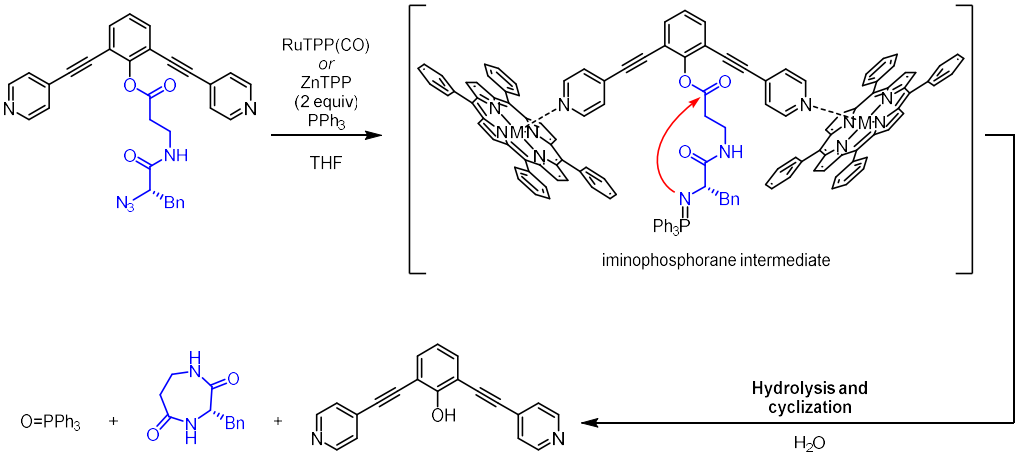
In **chapter 3**, a supramolecular approach to the previously published dendrimeric carbodiimide system is described.[1] The synthesis of two novel, di-adamantyl-functionalized carbodiimdes is explored. The function of the adamantyl groups is to enable inclusion in cyclodextrins (CDs), which are envisioned to shield the carbodiimide (and activated peptides) from the steric bulk (see Scheme 2). One of the desired carbodiimides has been successfully synthesized and studied in cyclization reactions. Although the carbodiimide functions as a coupling reagent, the addition of cyclodextrins does not lead to an increased yield of cyclic peptides. The main suspected reason is a solubility issue, which prevented the use of water, which is expected to promote a tight

binding of the adamantyl moiety in the CD cavity. Only a dipeptide carrying a solubilizing group on its central nitrogen atom was compatible with THF and found to undergo a reaction. The presence of this group already increases the cyclization to such an extent that site-isolation provides no added benefit.



***Scheme 2**: Schematic depiction of a CD-shielded carbodiimide.*

Chapter 4 describes the synthesis of pre-activated dipeptides which are able to coordinate to metallo-porphyrins by virtue of a dipyridine featuring backbone. The metallo-porphyrins were envisioned to sterically shield the peptide (see Scheme 3). Performing the Staudinger-mediated cyclization in presence of ZnTPP increased the yield of cyclic dipeptide from 16% to 40%. The binding of ZnTPP to the dipyridine backbone was studied using NMR titrations and modelling. The results indicate that only a single ZnTPP binds to the cyclization precursor and is responsible for this beneficial effect.



***Scheme 3**: Schematic depiction a metallo-porphyrin flanked cyclization.*

In **chapter 5**, the synthesis of a novel covalent cage based on a two identical fluorene containing moieties is explored (see Figure 1). The synthesis of the anilinic version was unsuccessful, due to the lack of nucleophilicity of anilines. The route towards the benzylic amine analogue was more successful. The

synthesis of the fluorene-based cage starting from a Friedel-Crafts acylation, followed by a Suzuki-Miyaura coupling was hampered by the difficulties which prevented the installation of the halogens necessary for the subsequent Sonogashira coupling. Reversing the order and introducing the iodines first allowed the installation of the amine-bearing sidearms. After this, the core of the fluorene could be expanded by a Suzuki-Miyaura coupling. The final cage formation was attempted, but the final coupling of the two identical halves is yet to be achieved.

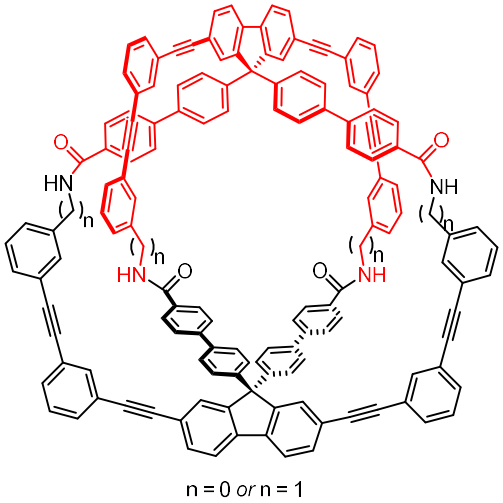


***Figure 1**: Representation of the envisioned cage structures.*

This thesis showcases several approaches that have been explored to facilitate and enhance dipeptide cyclizations. It provides a basis on which further research can expand.

References

[1] A. Amore, R. Van Heerbeek, N. Zeep, J. Van Esch, J. N. H. Reek, H. Hiemstra, J. H. Van Maarseveen, *J. Org. Chem.* **2006**, *71*, 1851–1860.