Bent Molecules

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Single-Handed Towards Nanosized Organic Molecules

*Michael Mastalerz**

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Interest in purely artificial, large, but defined, discrete organic structures arises not only for academic reasons,[1] for example, to get a deeper understanding of the aromaticity of lager systems, such as kekulene or [18]-annulene,[2] but also to develop new compounds that have been predicted to have exciting materials properties, which one day might find their way into new technological products.[3] In this respect, recent efforts towards the synthesis of larger conjugated nanobelts,[4] which represent cutouts of carbon nanotubes, are quite remarkable, although the multistep reaction sequences most often contain one or two synthetic steps with low to moderate yields.

The introduction of dynamic covalent chemistry (DCC) resulted in larger, more complex structures such as Borromean rings, trefoil knots, and a quadruply interlocked giant shape-persistent cage becoming achievable in high yields.[5] Unfortunately, there are still a number of disadvantages for DCC-generated structures—often a reduced stability towards changes of environmental parameters such as temperature, solvent, concentration, and pH value.

As a consequence of their D_{3h}-symmetric shape, triptycene and related bicyclic structures are ideal units to construct covalently linked rigid macrocycles with the π-planes of the aromatic units orthogonal to the macrocyclic plane.[6] It is, therefore, not surprising that efforts have been made to use these types of bicyclic molecular building blocks for this purpose. In 2007, Chong and MacLachlan described the possibility of making large macrocycles by the formation of phenazine units through condensation of bis(*ortho*-phenylenediamines) with bis(*ortho*-quinones).[7] However, only small subunits of ring structures have been made. The inherent synthetic problem in generating a macrocycle in this case is the statistical formation of two regioisomeric phenazine intermediates in the ratio of 1:1 (Scheme 1, top); only one of those can lead to the ring. Even with the assumption that each phenazine formation occurs quantitatively, the formation of the final hexameric cyclic product can statistically reach a maximum of 3% yield. It is, therefore, not surprising that no synthesis of such a phenazine macrocycle has been reported to date.

[*] Prof. Dr. M. Mastalerz
Organisch-Chemisches Institut
Ruprecht-Karls-Universität Heidelberg
Im Neuenheimer Feld 273, 69120 Heidelberg (Germany)
E-mail: michael.mastalerz@oci.uni-heidelberg.de

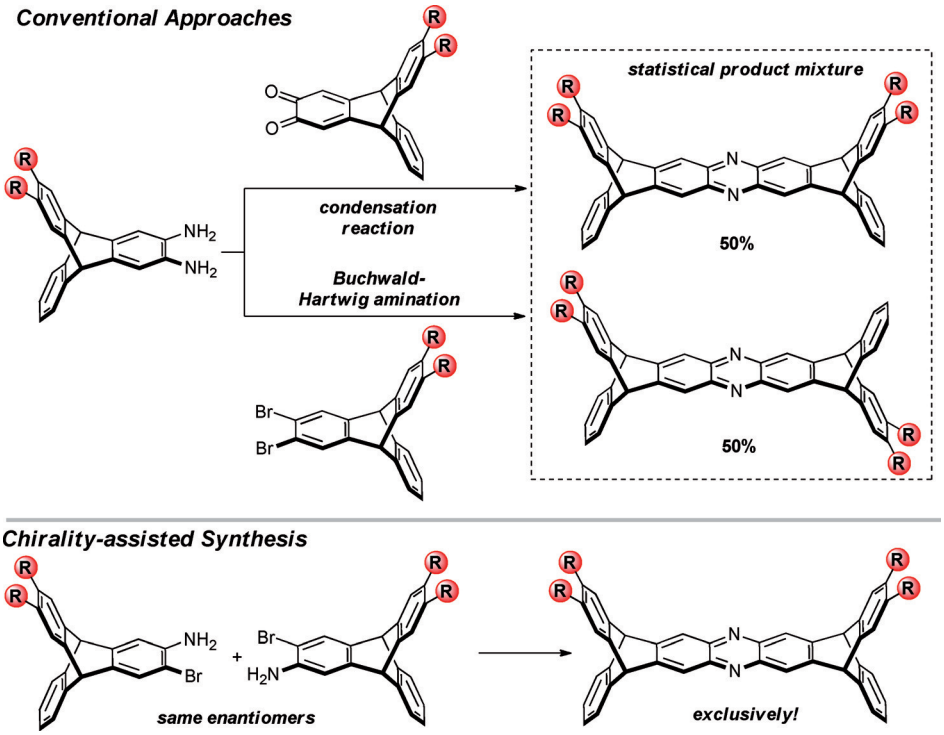
This may change with the recent contribution of Li, Schneebeli, and co-workers.[8] They presented an approach that they named "chirality-assisted synthesis". The key concept is the combination of placing the two reaction sites for Buchwald–Hartwig amination reactions—the bromo and the amino substituent—*ortho* to each other,[9] and those being part of a chiral bicyclic molecule (Scheme 1, bottom). If the enantiopure form of the bromoamine is used, the resulting reaction product can only have a curvature in one direction, thereby giving one product exclusively.

Li, Schneebeli, and co-workers have demonstrated the strength of their concept with the high-yielding synthesis of two large molecular clefts. One of these syntheses is depicted in Scheme 2: A palladium-catalyzed coupling of two molecules of the chiral bromoamine **1** gave the C_{2v}-symmetric phenazine **2** in 89% yield as the exclusive product. Cleavage of the Boc protecting groups, reprotecting one site with $(Boc)_2O$, and subsequent bromination of the free amino group in the *ortho* position gave C_1-symmetric chiral phenazine **3** in 26% yield. A subsequent cross-coupling reaction gave molecular tweezer **4** in 56% yield; again as a single cross-coupling product.

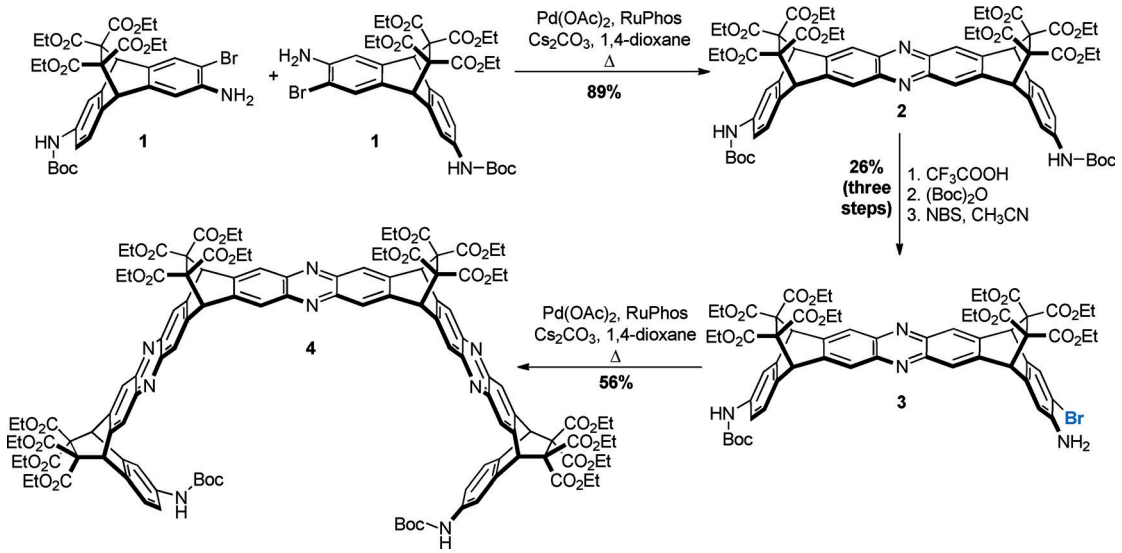
Besides the appealing synthetic aspect reported within this publication, the synthesized compounds have been studied as molecular tweezers. Tweezer **4** and its smaller congener (not depicted) act as host molecules for the binding of pillar[5]arene through π-π stacking interactions, and the binding constants increase by orders of magnitudes as the number of phenazine units increases.

The strength of the concept might not be necessarily obvious at first sight: For the synthesis of **2** from enantiopure **1**, one could argue that if one takes the racemic mixture for this reaction, one would end up with the same overall amount of final product. However, this is indeed true, but the other pure enantiomer of **1** could also be applied in the same reaction to give the same final (achiral) macrocyclic compound. So, prior separation of the enantiomers is the key to this new approach and it might not always be easy to pursue, especially for larger molecules with only a few stereogenic centers. As a consequence, enantioselective reactions will play an unexpected role in furnishing the efficient synthesis of achiral organic molecules in the nanometer regime.

I am convinced that this new approach will open another avenue towards the efficient synthesis of discrete covalent organic structures in the nanosized regime. If cyclo-oligomerization reactions of chiral precursors are successful there will be no doubt that this new method will have an impact similar



Scheme 1. Comparison of conventional approaches and the chirality-assisted synthesis for the virtual synthesis of bis(triptycenylene)phenazines.



Scheme 2. Chirality-assisted synthesis of molecular tweezer **4.**

to the introduction of templated synthesis or the concept of dynamic covalent chemistry.[10,11]

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