Review on Mgr. Angelina Andronova's PhD thesis:

"Diastereoselective synthesis of helically chiral compounds for enantioselective catalysis"

The development of new effective catalysts and ligands for enantioselective catalyis is one of the most important long-term goals of organic/organometallic chemistry for the sustainable access to chemical entities important for society. Mgr. Angelina Andronova took the challenge to provide an asymmetric access to chiral helicene and helicene-like compounds as ligands in asymmetric catalysis and to test their efficiency in selected organic transformations.

The thesis is well organized. In the Introduction the existing approaches to helicenes are summarized. They are divided in racemic and asymmetric methods to synthesize helicenes and related compounds. A subsequent part deals with the existing applications of helicene derivatives as ligands in metal catalysis and organocatalysts.

In the next chapter the goals of the experimental work for the thesis are outlined. The proposed strategy consists of an approach to two basic helicene-like frameworks having a dihydrooxepine or dihydropyran subunit by a [2+2+2] cyclotrimerization reaction and subsequent introduction of the ligating functionalities, such as phosphines or phosphites. Another main goal was the synthesis of a helically chiral 4-(dimethylamino)pyridine derivative as a new class of organocatalysts. Finally, the [2+2+2] cyclotrimerization strategy should be extended to a thiophene-containing [9]helicene skeleton. Selected synthesized compounds are proposed to be applied in nickel-catalyzed cyclotrimerization and gold-catalyzed cycloisomerization reactions.

In the major Results and discussion part the realization of the goals is reported. After a short introduction to the factors that govern the thermodynamic stability of chiral dihydrooxepine-containing helicene-like molecules, the preparation of several helicene-like dihydrooxepine structural motifs is outlined. Central steps are the construction of benzylic propargylic ethers by a Williamson etherification and the subsequent construction of the respective central diarylethyne units by a Sonogashira coupling reaction. The target heterocyclic helicene-like skeleton was obtained by cobalt- or rhodium-mediated [2+2+2] cyclotrimerization reactions. The cyclotrimerization conditions were optimized for each substrate. Photochemically promoted and thermal methodologies were exploited and compared. In some instances a continuous flow methodology proved to be advantageous. The for catalysis important phosphine and phosphite ligating units were introduced mostly by substitution reaction at phosphorus. Most of the target ligands were obtained in reasonable yields as single enantiomers, whereby terminal disubstituted (S,S)-triynes provided (P)-helicenes, while the corresponding terminal unsubstituted precursors furnished the corresponding (M)-configurated products. The structurally similar pyran-type helicene-like molecules were obtained similarly.

The techniques to assign the helicity of the products are outlined subsequently. A combination of NMR and CD-spectroscopy and X-ray crystallography allowed the unequivocal assignment of the absolute and relative configuration of the products.

The final part of the results and discussion section describes the application of the synthesized helicene-like molecules in asymmetric catalysis. The tested reactions were asymmetric [2+2+2] cyclotrimerization reactions of triynes to facilitate the asymmetric synthesis of carbohelicenes and the gold-catalyzed cyclization of 1,5-enynes to methylenecyclopentane derivatives.

In the experimental part the preparation of all new compounds is described in detail and they are characterized by NMR spectroscopy, IR spectroscopy, mass spectrometric techniques and optical rotation.

The thesis is technically well prepared. The language is concise and without serious mistakes. A few that should be corrected concern the name Bednarova in the Acknowledgements, and Vollhardt (p.34). The graphics are clearly organized; reaction conditions can be derived easily. The results are mostly clearly presented.

Nonetheless, some issues must be addressed. While the results are presented clearly, a discussion placing the results in a more general context is not very much elaborated. The thesis doesn't almost completely present any mechanistic support of the results, especially of the cyclotrimerization reactions. The thermodynamic energy differences of the products presented in the beginning of the results section (3.1.1) do not say anything about the energy of the transition states, which determine the course of the cyclotrimerization reactions.

Moreover, in almost all tables detailing the cyclotrimerizations light (hν) is stated as a "Heating mode". Looking at the procedures, this does not seem to be correct.

Several questions should be addressed:

1.) The Rh-catalyzed cyclotrimerization of **156** provides a higher atropisomeric ratio than comparable cobalt-mediated cyclizations or the photochemically triggered cyclotrimerization (Table 3.3). How can this be explained? Moreover the ca 60:40 ratio (Table 3.3) is not 2:1 (p.51).

2.) On page 59 is stated that "…the products are rendered unstable, e.g. cyano or nitro derivatives…" Has it been proven that the product is unstable, or are the reaction conditions rather interfering with the starting materials or intermediates?

3.) Does the conclusion really hold that the Co-mediated cyclotrimerization of **224** is more effective than the Ni-catalyzed process (p.66, Table 3.5)? First, the latter is catalytic and also milder, while the yield based on conversion is as high as 90%. Would mild heating improve the conversion? Was the reaction stopped after 65% conversion or did catalyst deactivation occur during the process?

4.) What is the ratio of the atropisomers of **106** at room temperature (p.68), and did crystallization give only one atropisomer?

5.) Even that it is not particularly high no rationalization for the observed asymmetric induction is provided for the cyclotrimerization of **233** catalyzed by Ni(0)/**127** or **143**. How does the reaction proceed stereochemically and what helicity has product **234**?

6.) In the experimental section the display of carbon atom resonances is not very consistent and leads to information losses. In compound **128** non-fitting numbers of aromatic singlets and dublets (12/18 vs. required 13/17) are provided, or in others aromatic resonances are apparently missing (29 of 30 in **142**, **167**, **168**, **201** or **202**, 31 of 32 in **153**, 16 of 17 in **193**, 27 of 30 in **103**, 36 of 38 in **239**. Surprisingly the number of quaternary carbons is correct, but the number of CH not.). A more clear representation of 13C NMR data is required. Compound **167** is incorrectly presented as a symmetrical diol, while it should be a monophenol based on the name. In the IR of **218** the band at 3061 cm(-1) shows up twice.

Overall Mgr. Andronova fulfilled the aims of her work and provided a valuable thesis, which fulfills the requirements. The results were published in three papers. Therefore I recommend the acceptance of the thesis and the further proceeding to the defense to earn the degree of a PhD.

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