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== Im Hause ==

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Reviewer report for the doctoral thesis of
Mr Manfred K a r r a s, MSc,
entitled

*“ Synthesis of Enantiomerically Pure Helical Aromatics Such As NHC Ligands
and Their Use in Asymmetric Catalysis “*

The present thesis, submitted by Manfred Karras, MSc, is the result of a co-tutelle project jointly supervised by Dr. Ivo Starý, Czech Academy of Science and Charles-University of Prague, and myself. The underlying, highly innovative and original research concept combines research interests from both our groups in a synergistic manner. The experimental work towards this thesis was conducted in Potsdam and in Prague, according to the co-tutelle contract between both universities. In addition, important experiments were performed in Warsaw in the group of Prof. Karol Grela during a two-month research internship.

The main idea of this project was to use enantiomerically pure helicenes as chiral inductors in transition metal catalyzed transformations. The envisaged precatalysts should be ligated to *N*-heterocyclic carbene ligands, which are well known for their high σ -donor capacity and strong metal-ligand binding properties. As a prerequisite for their synthesis, enantiopure aminohelicenes were required. Their asymmetric synthesis, conversion to the corresponding imidazolium salts, ligation to suitable Pd- and Ru-precatalysts, and eventually the evaluation of these helically chiral transition metal catalysts in asymmetric transformations were the objectives of the present thesis. I would like to state beforehand that Manfred Karras was highly successful in reaching all the objectives listed above, and that the present thesis can be considered as an important step ahead in this field of research.

The first chapter of the thesis briefly outlines historical developments of chirality phenomena in Science and then moves to a taxonomy of molecular chirality. As required for an appropriate discussion of the scientific background of this thesis, particular attention is paid to helical chirality and the substance class of helicenes. *N*-heterocyclic carbenes as ligands for transition metal catalysis are also covered appropriately, as well as the topics asymmetric catalysis, Pd-catalyzed cross coupling and olefin metathesis, which have been chosen as test reactions to prove the proposed concept. In all sub-chapters relevant literature is discussed in

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sufficient detail to place the current research into its scientific context and to lead the reader to the second chapter, which describes the objective of the present study, as summarized above.

The third and largest chapter of the thesis describes and discusses the extensive number of experimental results. In the first section (3.1), stereoselective approaches to aminohelicenes **69**, **118** and **143** are devised. These syntheses rely on elaborate sequences of Pd-catalyzed arene alkynylations and stereoselective [2+2+2]-cyclotrimerizations, which are highly diastereoselective due to allylic strain control. Aromatization can be accomplished by elimination. These syntheses are largely based on chemistry established by Starý and Stará over the past years, but have nevertheless turned out as challenging in several regards. The second section is dedicated to the conversion of aminohelicenes into the NHC-precursors, the imidazolium salts. Adaptation of established methods allowed the synthesis of symmetrical bis-helicenyl substituted imidazolium salts and unsymmetrical mono-helicenyl imidazolium salts.

Section 3.3 describes different routes to N-helicenyl substituted transition metal NHC-complexes. The NHC's were successfully ligated to Ag, Ru and Pd. In some cases, the Ag-complexes could be used to transfer the NHC ligand onto another transition metal. Unfortunately, a symmetrical bis-helicenyl substituted Ru-carbene complex remained inaccessible due to steric constraints. However, Pd-PEPPSI-complexes could be synthesized with bis-N-helicenyl substituted NHC's.

The following sections summarize the results obtained for transition metal catalyzed transformations. First, in section 3.4, an enantioselective cyclotrimerization with an in situ generated Ni-catalyst is shown. This is a nice example to demonstrate how helical chirality in the catalyst can be used to induce helical chirality in the product. The following section, 3.5, describes olefin metathesis reactions catalyzed by the helically chiral Grubbs-type catalyst. This catalyst mediates RCM reactions with a slightly lower activity than comparable achiral NHC-Ru-catalysts and with moderate enantioselectivities of up to 60% ee. Although the observed level of enantioinduction is not overwhelming at a first glance, the following discussion of the catalyst structure is highly interesting and was thoroughly performed. Mr Karras used NOE-spectroscopy and DFT calculations on an elaborate level to gain insight in the steric constraints and spatial constrictions around the metal centre. These results were not only used for calculating the %-buried volume value, but also for the preparation of a topographic steric map. These findings might serve as guidance for improving helically chiral catalysts in future investigations. The discussion is concluded by the presentation of a qualitative model for enantioinduction, which rationalizes the preferred formation of the *R*-isomer. With this discussion, an interesting analogy of the helically chiral catalyst to the more common C₂-symmetric metathesis catalysts is drawn: in both cases an out-of-plane rotation of the N-aryl substituent is responsible for the dissymmetry at the metal centre. The last section of the results-and-discussion chapter, 3.6, summarizes the – unfortunately – unsuccessful attempts at using the Pd-PEPPSI-type complexes for enantioselective Suzuki-Miyaura coupling reactions. An analysis of the buried volumes and the comparison with other chiral Pd-catalysts reveals, that the steric demand of helicenyl substituted NHC's might easily be overestimated. This might indeed be the reason for the somewhat disappointing results with regard to enantioinduction.

In chapter 4 the results are summarized and a brief outlook into future investigations is presented. Chapter 5 contains full experimental details and characterization data. Chapter 6 provides an extensive list of references. Documentation of experiments and literature citations fully meet scientific standards in every regard.

In summary, Mr Karras submits a well-written, thoroughly prepared and highly original doctoral thesis which contains numerous interesting results that were obtained in Potsdam, Prague and Warsaw. Mr Karras was not only forced to become acquainted with chemistry that is rather unusual in our group, his PhD-project was also associated with a considerable amount of travelling. This might in part explain the rather long time period of nearly 4.5 years (clearly above average) for the preparation of this thesis, starting from the beginning of the first experiments until submission of the thesis. From this thesis three publications have resulted so

far (Gay Sanchez, I.; Šámal, M.; Nejedlý, J.; Karras, M.; Klívar, J.; Rybáček, J.; Buděšínský, M.; Bednárová, L.; Seidlerová, B.; Stará, I. G.; Starý, I. Oxahelicene NHC ligands in the asymmetric synthesis of nonracemic helicenes. *Chem. Commun.* **2017**, 53, 4370-4373; Karras, M.; Holec, J.; Bednarova, L.; Pohl, R.; Schmidt, B.; Stará, I. G.; Sary, I. Asymmetric Synthesis of Nonracemic 2-Amino[6]helicenes and Their Self-Assembly into Langmuir Films. *J. Org. Chem.* **2018**, 83, 5523-5538; Karras, M.; Dąbrowski, M.; Pohl, R.; Rybáček, J.; Vacek, J.; Bednárová, L.; Grela, K.; Starý, I.; Stará, I. G.; Schmidt, B. Helicenes as chirality inducing groups in transition metal catalysis: the first helically chiral olefin metathesis catalyst. *Chem. Eur. J.* **2018**, 24, DOI: 10.1002/chem.201802786). One additional publication is in preparation and will be submitted by the end of this year.

Without hesitation and without any reservations I recommend acceptance of this thesis by the Faculties of Science of the University of Potsdam and Charles University of Prague.

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