1. PHD PROJECT DESCRIPTION (4000 characters max., including the aims and work plan)

Project title: Stereocontrolled Construction of Planar-Chiral Heterocycles via N-Heterocyclic Carbene Catalysis

1.1. **Project goals:** The aim of this PhD research is to develop new, stereocontrolled strategies for the construction of planar-chiral heterocyclic architectures through N-heterocyclic carbene (NHC) catalysis. The project focuses on the enantioselective synthesis of isoindole- and carbazole-based macrocyclic compounds, with special attention to atroposelective macrolactonization as a means of inducing and stabilizing planar chirality. These studies are positioned within the broader context of advancing the fundamental understanding of stereocontrol, conformational restriction, and configurational stability in macrocyclic systems, without pursuing direct applications at this stage.

1.2. **Outline:** The research will encompass:

- **Development of new NHC-catalyzed enantioselective macrolactonization protocols** to access planar-chiral macrocyclic frameworks.
- **Exploration of structure–stereochemistry relationships** in macrocycles, with emphasis on ansa chains, lariat arms, and substituent effects.
- **Synthesis of model substrates based on isoindole and carbazole scaffolds**, including the design and incorporation of novel stereogenic elements.
- **Theoretical investigations (DFT-based)** to assess rotation barriers, transition state geometries, and the effect of structural modifications on chirality transfer and configurational stability.
- **Elucidation of key factors** governing stereochemical outcome, including catalyst structure, substrate electronics, and steric interactions.

1.3. **Work plan:** Year 1: Literature review, training in organocatalysis and NHC chemistry; synthesis of model substrates

- Mastering air- and moisture-sensitive techniques
- Model studies on enantioselective annulations and acylazolium intermediates
- Establishing synthetic access to functionalized isoindole and carbazole substrates

Year 2: Method development in macrolactonization reactions and screening of NHC catalysts

- Optimization of reaction conditions for macrocyclization
- Initial evaluation of atroposelectivity and planar chirality induction
- Introduction of sterically biased elements (ansa chains, lariat arms)

Year 3: Expansion of substrate scope and mechanistic studies

- Synthesis and testing of diversified macrocyclic scaffolds
- Computational analysis of key reaction pathways
- Exploration of catalyst-substrate interactions and stereochemical models

Year 4: Finalization of synthetic platforms, evaluation of configurational stability, publication of results, and dissertation writing

1.4. Literature*:*

1. [1] a) Asymmetric Organocatalysis, Eds. List B., Maruoka K., Thieme Verlag, 2012. b) "Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications" Dalko P., Ed., Wiley-VCH, Weinheim, 2013. c) Asymmetric Organocatalysis - from Biomimetic Concepts to Applications in Asymmetric Synthesis, Eds. Berkessel A., Gröger H., Wiley-VCH, 2005. d) Asymmteric Organocatalysis in Natural Drug Synthesis, Eds Wasser M., Springer-Verlag Wien 2012.
2. 2] N-Heterocyclic Carbene in Organocatalysis, Eds Biju A., Wiley-VCH, 2018.
3. a) Kozlowski M.C., Morgan B. J., Linton E.C.,*Chem.Soc.Rev.***2009**,38,3193. b) J. Wang et.all., *ACS Med. Chem.Lett.* **2017**, *8*,299. c) J. Wencel-Delord et. all. *Chem.Soc.Rev.* **2015**, *44*, 3418. d) G. Yang, D. Guo, D. Meng, J. Wang, *Nat.Commun.* **2019**, *10*, 3062. e) S. Zhuo et. all *Angew. Chem. Int. Ed.* **2019**, *58*, 1784. f) A. T. Biju et. all. *Angew. Chem. Int. Ed.* **2021**, *60*, 12264. g) J. Wang et. all *Nat.Commun.* **2018**, *9*, 611. h) B. Tan et. all *Chem. Rev.* **2021**, *121*, 4805

3.1. Required initial knwledge and skills of the PhD candidate:

1. • Solid grounding in **organic chemistry**, including reaction mechanisms and stereochemistry
2. • Basic experience with **synthetic laboratory techniques** (e.g. chromatography, NMR, reaction optimization)
3. • Familiarity with **organocatalysis and/or catalysis in general** is an advantage
4. • Willingness to learn **computational chemistry methods (e.g. DFT)**
5. • Strong analytical thinking and attention to detail
6. • Capacity to work both independently and as part of a collaborative research team

6.1. Expected development of the PhD candidate's knowledge and skills

By the end of the project, the PhD candidate will:

- Be proficient in **advanced synthetic methodologies** in stereoselective organic synthesis and macrocycle construction
- Understand and apply **principles of asymmetric organocatalysis**, including NHC-mediated activation modes
- Be capable of independently **designing and optimizing multistep synthetic routes**
- Acquire **computational skills** for the mechanistic interpretation of catalytic processes
- Gain experience in **scientific communication**, including manuscript preparation, presentation of results at conferences, and participation in international collaborations
- Contribute original knowledge to the emerging field of planar-chiral macrocyclic chemistry