SYNTHESIS Best Paper Award 2022: Asymmetric Synthesis of Fused Tetrahydroquinolines via Intramolecular Aza-Diels–Alder Reaction of *ortho*-Quinone Methide Imines

Synthesis **2022**, *54*, 1055–1080

Background. Thieme Chemistry and the Editors of SYNTHESIS and SYNLETT present the 'SYNTHESIS/SYNLETT Best Paper Awards'. These annual awards honor the authors of the best original research papers in each of the journals, considering their immediate impact on the field of chemical synthesis.

Professor Christoph Schneider, together with Fabian Hofmann, Cornelius Gärtner and Martin Kretzschmar from the University of Leipzig, Germany, are the recipients of the SYNTHESIS Best Paper Award 2022. The authors are recognized for their thorough examination of the title reaction. Mark Lautens, Editor-in-Chief of SYNTHESIS, stated: "The Schneider lab has reported on intramolecular aza-Diels–Alder reactions of *ortho*-quinone methide imines, giving access to biologically relevant tetrahydroquinolines. Key to their success was the use of chiral BINOL phosphoric amides as Bronsted acids. This comprehensive study presents successes and limitations, as well as proposes possible transition states to explain the results. The continuing importance of the Diels–Alder reaction, and its many variants, remains a topic of intense interest 70 years after the award of the Nobel Prize in Chemistry to Diels and Alder."

SYNFORM spoke with Professor Christoph Schneider, who was happy to share some background information regarding the prize-winning paper as well as current research activities ongoing in his group.

Biographical Sketch

Professor C. Schneider (right) and co-authors Dr. Fabian Hofmann (left), Cornelius Gärtner (second from left), and Dr. Martin Kretzschmar (second from right)

Christoph Schneider received his chemical education at the University of Göttingen (Germany) and obtained a Ph.D. with Prof. Lutz F. Tietze working in the area of natural product synthesis. Subsequently, he was a postdoctoral fellow with Prof. David A. Evans at Harvard University (USA) before returning to Germany to perform independent studies towards his habilitation in Göttingen from 1994 to 1998. Thereafter he was invited for visiting professorships in Szeged (Hungary), Toronto (Canada), and Saarbrücken (Germany). In 2003 he moved to his current position as Full Professor at the University of Leipzig (Germany) where he has remained ever since. Since 2016 he has been an elected member of the review board for organic molecular chemistry within the Deutsche Forschungsgemeinschaft. His research interests are in the area of stereoselective organic synthesis with a focus on catalytic enantioselective transformations and their application towards natural product synthesis.

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INTERVIEW

SYNFORM *Could you highlight the value of your award-winning paper with respect to the state-of-the-art, as well as the potential or actual applications?*

Professor C. Schneider Nitrogen-containing heterocycles are integral constituents of many natural products, in particular within alkaloids, which display a vast array of biological activities, making them ideal candidates for the pharmaceutical industry. However, while natural products have always been an enormous source of inspiration for the development of pharmaceutically active molecules, their exact chemical structure has to be carefully modulated in order to meet the stringent requirements for medicinal applications. In this respect, chemical synthesis continues to be an indispensible tool and state-of-the-art technology to assemble the optimized target compounds with defined properties and the correct three-dimensional configuration.

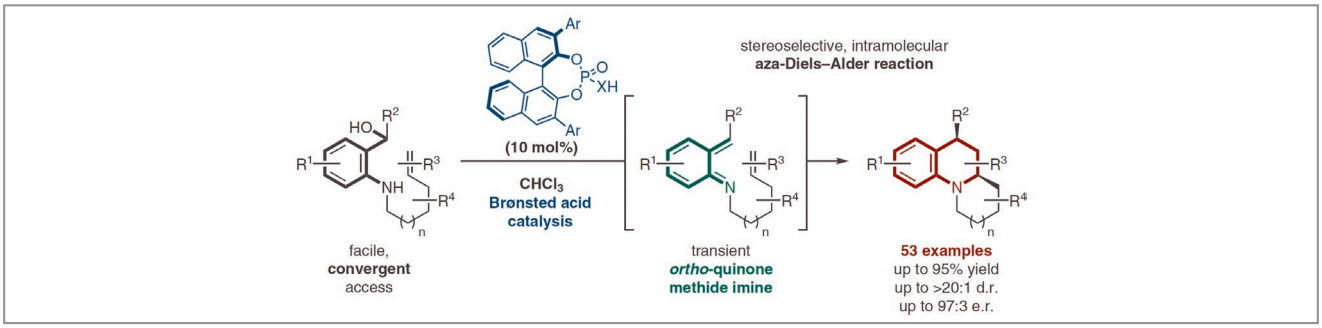
In the present manuscript we have developed the first enantioselective synthesis of benzannulated quinolizidines pursuing a highly straightforward strategy. This structural motif is present in a number of biologically very active compounds. Subjecting readily available *ortho*-amino benzyl alcohols tethered via the nitrogen atom to a suitable dienophile to chiral Brønsted acid catalysis furnishes *ortho*-quinone methide imines as transient 1-azadienes which directly engage the dienophiles in an intramolecular aza-Diels–Alder reaction. Controlled by the chiral phosphoramide catalyst, this cycloaddition proceeds with good yields and good to excellent diastereo- and enantioselectivities. A broad range of substituted quinolizidine products with rather interesting additional pharmacophore motifs embedded into the molecules (such as indoles) have been made available in just a single step. This strategy will likely be of significant value for modern medicinal chemistry as well.

SYNFORM *Can you explain the origin, motivations and strategy used for conducting the award-winning research?*

Professor C. Schneider We have a long-standing interest in asymmetric Brønsted acid catalyzed reactions going all the way back to our discovery of the first enantioselective, vinylogous Mannich reaction in 2008 which evolved into a platform strategy for alkaloid total synthesis over the last decade. More recently, we have been interested in chiral Brønsted acid catalyzed cycloadditions of transient *ortho*-quinone methides, an extremely powerful synthetic strategy for the assembly of benzannulated oxygen heterocycles. From there it was only a small step to extend this concept to the corresponding anilines and the formation and cycloaddition of transient *ortho*-quinone methide imines and the synthesis of nitrogen heterocycles. In a preceding manuscript, we established the first enantioselective intermolecular aza-Diels–Alder reaction. Due to the trivalent nature of the nitrogen atom, and different from the oxygen analogues, we could attach the dienophile directly onto the diene here and conceptualize an intramolecular Diels–Alder reaction. A first report from the Corey group in 1999 demonstrated the general concept in a base-mediated, racemic reaction, while our SYNTHESIS paper established the first catalytic, enantioselective process.

SYNFORM *What is the focus of your current research activity, both related to the award paper and in general?*

Professor C. Schneider Our research continues to focus on novel reaction development and the application of these methods in the context of natural product synthesis. In my opinion this is an ideal training exercise to demonstrate the power and versatility of newly invented methodology. We have just completed a biomimetic, enantioselective total syn-



Scheme 1 Enantioselective synthesis of benzannulated quinolizidines

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thesis of tetrahydrocannabinoids and are currently in the final stages of a total synthesis of the nuphar alkaloids thiobinupharidine and thionuphlutine which display significant cytotoxic activity. Both syntheses utilize our own methodology in their central steps.

In the area of reaction development, we have extended the methodology described in the award paper to cycloadditions of indole and pyrrole methides giving rise to complex nitrogen heterocycles in enantiomerically highly enriched form. In addition, we focus on other Brønsted acid catalyzed, enantioselective transformations which are currently underdeveloped, for example novel Piancatelli and Nazarov cyclizations. Moreover, we strive to attach chiral Brønsted acids onto solid support and thus employ heterogeneous chiral catalysts under continuous flow conditions for the large-scale production of valuable fine chemicals.

SYNFORM *What do you think about the modern role, major challenges and prospects of organic synthesis?*

Professor C. Schneider Organic synthesis continues to be a central discipline within the chemical sciences. Among the major challenges ahead of us, I see difficult carbon–carbon bond-forming reactions effected by chiral catalysts, especially between quaternary chiral centers and within highly functionalized molecules. The prospect of utilizing modified enzymes as chiral catalysts obtained by directed evolution has only recently begun to play a role in organic synthesis. Moreover, protecting-group-free or at least protecting-group-reduced total synthesis is an ambitious, yet worthwhile, goal and would increase the atom economy of a given synthesis. Finally, artificial intelligence and machine learning are just beginning to change the way we execute organic synthesis and will not only affect chemistry, but most certainly revolutionize all branches of sciences.

SYNFORM *What does this award mean to you/your group?*

Professor C. Schneider This award is a wonderful recognition of our group's work and likewise a strong inspiration and encouragement, especially for the PhD students who performed the actual experiments.

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