SYNTHESIS Best Paper Award 2017: Asymmetric Synthesis of 2,3,4-Trisubstituted Piperidines

Synthesis **2017**, *49*, 604–614

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.
Tõnis Kanger and his co-workers from the Tallinn University of Technology (Estonia) are the recipients of the SYNTHESIS Best Paper Award 2017. The authors are recognized for their work on the asymmetric synthesis of 2,3,4-trisubstituted piperidines. Paul Knochel, Editor-in-Chief of SYNTHESIS, commented: "The paper describes an asymmetric synthesis of substituted piperidines, which are indeed very important pharmaceutical targets, and this new piperidine synthesis uses two impressive organocatalytic cascades. The selection committee noted not only the scientific value of the paper, but also its presentation. It is a wonderful contribution that we are proud to have published in SYNTHESIS."
SYNFORM spoke with Tõnis Kanger 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

Prof. T. Kanger

Tõnis Kanger received his BSc in 1982 from Tartu University (Estonia) and his PhD in 1990 from the Estonian Academy of Sciences. After postdoctoral studies at the Pierre et Marie Curie University, Paris (France), with Professor Alexandre Alexakis, he returned to Estonia, where he is currently Professor at the Tallinn University of Technology. His research interests are focused on methodology of organic synthesis, asymmetric synthesis and organocatalysis.

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?*

Prof. Tõnis Kanger The article deals with the synthesis of substituted piperidines. Piperidine is a very important scaffold in medicinal chemistry, being the third most prevalent ring system in small-molecule drugs. There is a huge range of variety in the biological properties of its derivatives: from the very poisonous coniine isolated from poison hemlock, that was used for the execution of ancient philosopher Socrates, to highly active compounds used in modern medicine. Therefore, it is not surprising that the synthesis of substituted piperidines has been studied thoroughly. It is known that properties of the piperidine derivatives depend on the substitution pattern of the ring. Although the synthesis of fully or densely substituted piperidines is well described, there are few examples of the synthesis of 2,3,4-trisubstituted piperidines. Another important point is stereoselectivity of the substitution. Not only relative stereochemistry but also absolute configuration of the stereocenters is of importance for biological activity. We disclosed a stereoselective method affording 2,3,4-trisubstituted piperidines in high diastereomeric and enantiomeric purities. Obtained derivatives are important intermediates for

  • Published online: May 17, 2018 • DOI: 10.1055/s-0036-1591478

the synthesis of various biologically active compounds. Reactive substituents (ester, formyl, or nitro groups) at the piperidine ring can be further converted into other functionalities, adding extra value to the described method.

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

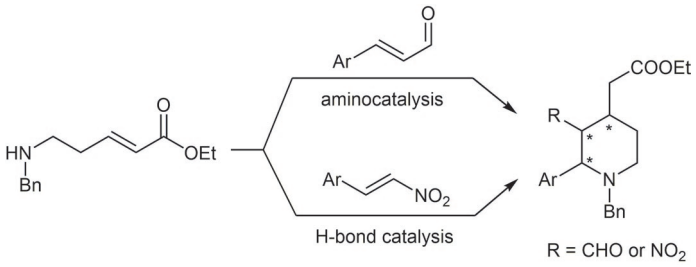
Prof. Tõnis Kanger My group has been dealing with asymmetric organocatalysis for several years. The main focus has addressed the efficiency of the reactions. From a synthetic point of view, cascade reactions where several chemical bonds are formed consecutively in one step are the most preferred to increase it. One of the most useful technologies for cascade cyclization reactions is the Michael addition mediated ring closure. To conduct the cascade reaction, multifunctional starting compounds are needed. By choosing a properly substituted Michael donor and acceptor, a variety of cyclic products can be obtained. Planning the first step of the cascade as an aza-Michael reaction provides a platform for the synthesis of heterocycles. We conducted the reaction of *N*-benzyl-5-aminopentenoate with different Michael acceptors (Scheme 1). Depending on the structure of the first Michael acceptor, different activation modes can be used. α,β-Unsaturated carbonyl compounds can be activated via the formation of iminium ions in aminocatalysis, and unsaturated nitro compounds via H-bonding catalysis. In both cases, the first step of the cascade is an aza-Michael addition followed by the second intramolecular conjugated addition. Three stereogenic centers are generated in the course of the reaction. The main goal of our strategy to be addressed was obtaining a single enantiomerically pure stereoisomer. Highly stereodefined reactions must be used for that task. Fortunately, both activation methods are well described in the literature and our experience in this field provided hints for the fast and efficient selection of catalysts.

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

Prof. Tõnis Kanger For now, my group is continuously dealing with the problem of efficiency in asymmetric organocatalysis. We have published a triple cascade leading to a pentacyclic product with two quaternary and one tertiary stereocenter in one step in high enantiomeric and diastereomeric purity (*Synthesis* **2018**, *50*, 314). When catalysis is applied in a rearrangement reaction with 100% atom efficiency, it leads to a highly efficient process. We have used this approach for the asymmetric Wittig rearrangement on cyclic and acyclic allyl ethers and these studies are ongoing. Also, we are looking for novel activation methods in catalysis. When a halogen atom is connected to a more electron-withdrawing moiety it becomes electron-deficient, interacting with atoms donating a lone pair. This attractive interaction is called a halogen bond and it is widely exploited in crystal engineering to construct supramolecular complexes and networks. The application of the halogen bond in solution is more challenging. Recently, halogen bond catalysis has received more attention. We have designed and synthesized chiral triazole-based catalysts with easily tunable properties and presently investigate their potential in asymmetric organocatalysis.

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

Prof. Tõnis Kanger Synthetic organic chemistry is and will continue to be a cornerstone for the pharmaceutical industry. Organic synthesis is not a solved problem and many challenges concerning selectivity, efficiency and sustainability remain. Although more processes will be automated, synthetic chemists are needed to elaborate novel sustainable methods for selective transformations. We have to learn from Nature.



Scheme 1

It is amazing how efficiently biological machinery works. The development of biomimetic methods and working together with scientists dealing with synthetic biology is one solution to achieve higher efficiency and sustainability in organic synthesis. Today, organic synthesis is a cross-disciplinary research area. Its achievements have impact on materials science, biology, physics, etc. and, on the other hand, these subjects influence the development of organic synthesis. Collaboration and co-operation between universities and industry is essential to facilitate the progress of organic synthesis and tackle scientific challenges.

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