

Organocatalytic, Enantioselective Dichlorination of Unfunctionalized Alkenes

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The dihalogenation of alkenes is a very old reaction, one of the fundamental processes of organic chemistry that is usually taught to undergraduates in an introductory organic chemistry course. “Since the suggestion of Robert and Kimball in 1937¹ that these reactions could proceed via cyclic halonium ions (following IUPAC rules, it is better to call them ‘haliranium ions’ to indicate the three-membered ring), one might argue that the mechanism is well understood. Indeed, the mechanism involving the haliranium ion is found in most organic chemistry textbooks! It is the prime example of an electrophilic addition reaction supposed to proceed via a cyclic halonium ion, explaining the usually observed *anti*-addition of the two halogen atoms,” explained Professor Ulrich Hennecke, previously of the University of Münster (Germany) and now at Vrije Universiteit Brussel (VUB, Belgium). However, things are not always as straightforward as originally thought, and a group of researchers led by Professor Hennecke has been investigating the reaction from a novel angle.

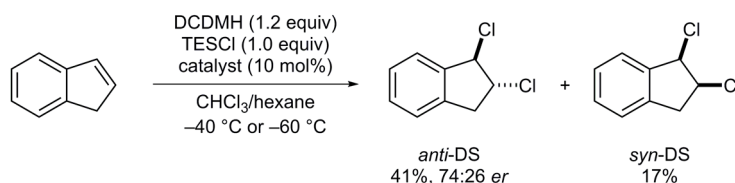
The group was surprised when they conducted their first experiments on indene and realised that the dihalogenation was not stereospecific for the *anti*-addition as it also provided the *syn*-addition product, something that cannot be explained by the formation of a haliranium ion (Scheme 1). However, they quickly learned that this fact was well known² and that the standard mechanism does not explain the experimental findings under all conditions.

Dr. Volker Wedek, one of the co-authors of the paper in Angew. Chem. Int. Ed., remarked: “It is quite surprising that for this simple reaction, which often leads to chiral molecules, only a few asymmetric methods exist that can produce one enantiomer selectively.” Prof. Hennecke continued: “There-

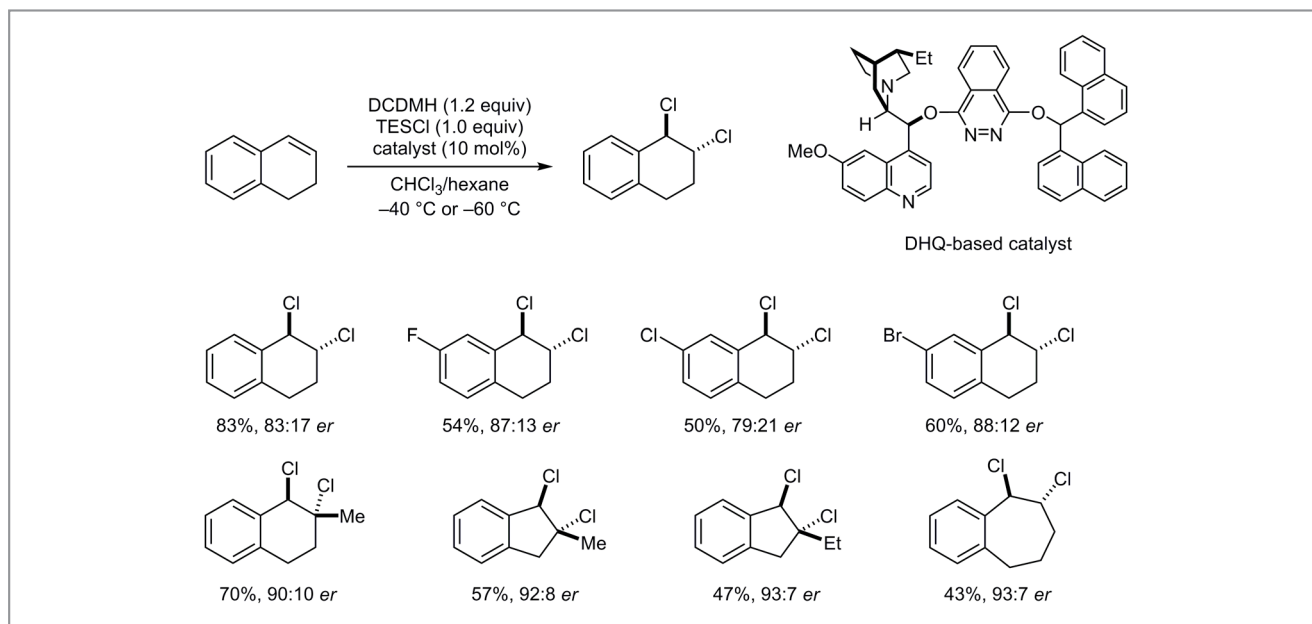
fore, we have teamed up with the group of Professor Frank De Proft, now our direct neighbour following our move to VUB, to study the reaction mechanism in more detail. Their initial calculations already showed that our dihalogenation process does not involve a symmetrical cyclic halonium ion – but rather an asymmetric, benzylic carbocation-type structure – and we hope that we will obtain a more detailed picture on the reaction mechanism in the near future.”

The development of an organocatalytic enantioselective process was the next goal for the group (Scheme 2). “(DHQD)₂PHAL, originally introduced by Sharpless as a superior ligand for his bishydroxylation reaction, is a fascinating molecule with rather rigid conformations defined by the cinchona alkaloid moieties,” said Professor Hennecke. “Borhan introduced this compound as an organocatalyst to asymmetric chorolactonisation in 2010³ and since then its application in asymmetric halogenation has grown rapidly. In 2016, we prepared a new generation of unsymmetrical derivatives of (DHQD)₂PHAL and quickly realised that those organocatalysts will be suitable for alkene dihalogenation.⁴ However, optimising the reaction conditions to achieve high yields and very good enantioselectivities took much longer than expected. We are pretty happy now that the catalysts are applicable to the dichlorination of alkene without a directing group.”

Professor Hennecke remarked on the curious coincidence of his new location: “One thing that I find very interesting/remarkable is that we are now, after our move to VUB, studying the stereochemical aspects of the dihalogenation in Brussels, just around the corner from Ghent University, where August Kekulé started all of this. As far as I know, Kekulé was the first to study stereochemical aspects of alkene dibromination



Scheme 1 Stereochemical outcome of the dichlorination of indene



Scheme 2 The organocatalytic dichlorination of alkenes

when he realised that bromination of maleic acid and fumaric acid resulted in isomeric 2,3-dibromo succinic acids.⁵ This discovery is even more remarkable when considering that Kekulé was carrying out these experiments around 1860, when the modern bonding theory of carbon was just in its infancy,” concluded Prof Hennecke.

Prof Hennecke

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About the authors



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Constantin G. Daniliuc obtained his Diploma at the 'Alexandru Ioan Cuza' University of Iași (Romania) in 2002. As a beneficiary of an Erasmus Scholarship, he completed in 2003 his Master's thesis at the Technical University of Braunschweig, Institute of Inorganic and Analytical Chemistry (Germany) and received his Ph.D. from the same university in 2008 under the supervision of Professor W.-W. du Mont. Since 2012, he has

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Prof. F. De Proft

Frank De Proft (1969) obtained his PhD in sciences from the Vrije Universiteit Brussel (VUB) in 1995 and is currently full professor at this institution. His main research interests involve the development, implementation and use of chemical concepts from quantum mechanics, with special attention to the concepts introduced within the framework of the so-called "Conceptual Density Functional Theory". Applications he has investigated

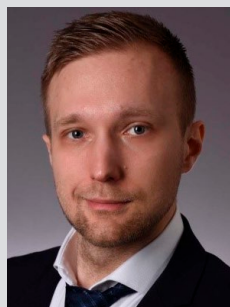
concern the reactivity of organic, inorganic, biochemical and solid-state compounds, catalysis and the *in silico* design of new compounds with optimal chemical properties and reactivity.



R. Van Lommel

Ruben Van Lommel obtained his Master's degree in chemistry at the KU Leuven (Belgium) in 2018. During his Master's studies he worked on the topic of supramolecular gels in the group of Prof. Wim De Borggraeve. His PhD continues this work and is a combination of experiments and computational chemistry, co-supervised by Prof. Frank De Proft and Prof. Mercedes Alonso at the Vrije Universiteit Brussel (VUB, Belgium). Besides

supramolecular gels, his current research interests lie in the study of reaction mechanisms by means of density functional theory and *ab initio* molecular dynamics.



Dr. V. Wedek

Volker Wedek received his BSc (2013) and MSc degrees (2015) in organic chemistry from The University of Münster (Germany) working on the synthesis of polychlorinated natural products. For his PhD studies he has stayed in the Hennecke group, where his research focuses on the development of new organocatalytic methods for the enantioselective dihalogenation of alkenes.



Prof. U. Hennecke

Ulrich Hennecke studied chemistry at the University of Marburg (Germany) before joining the group of Prof. Thomas Carell for his PhD studies on nucleic acid chemistry (PhD 2007, LMU Munich, Germany). After a postdoctoral stay with Prof. Jonathan Clayden (University of Manchester, UK), he joined the Organic Chemistry Institute of the University of Münster as junior group leader (2008). In 2018, he moved to the Vrije Universiteit Brussel (Belgium). His research interests involve synthetic organic as well as bioorganic chemistry with a special focus on halogenated organic compounds and their synthesis by new catalytic, enantioselective methods.