

## Boron-Enabled Geometric Isomerization of Alkenes via Selective Energy-Transfer Catalysis

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Simple alkene fragments are important constituent building blocks in many biological processes where geometry often underpins function. Retinal (vitamin A) is an excellent example where the geometric isomerization is the basis of the one-zero switch in human vision. Achieving spatiotemporal control over alkene geometry in a laboratory paradigm represents a fundamental yet significant challenge for the group of Professor Ryan Gilmour at the Westfälische Wilhelms-Universität Münster (Germany). “There are numerous methods to generate stereo-defined alkene fragments for complex polyene synthesis, but these reactions often suffer from poor selectivity, and typically require independent synthesis of both isomers. An isomerization strategy (Figure 1) would be advantageous,” said Professor Gilmour.

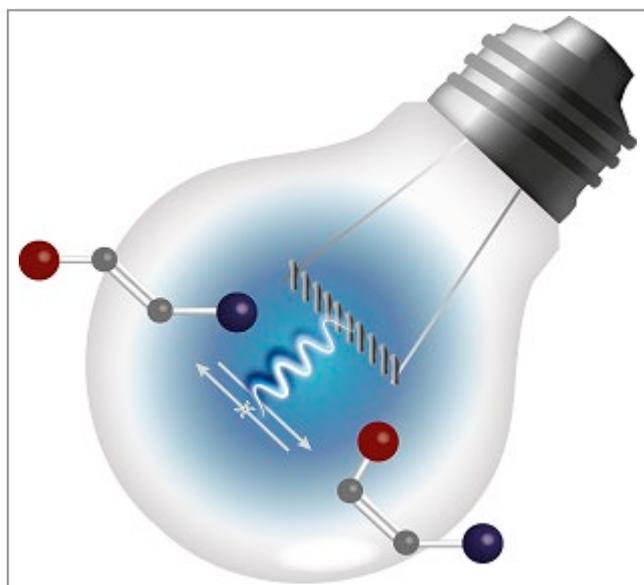
Professor Gilmour’s group has been exploring energy transfer catalysis, which provides a potentially expansive solution to this fundamental problem in enabling readily accessible *E*-alkenes to be isomerised to their more challenging *Z*-forms (for references see the original article). However, Professor Gilmour noted: “These approaches come with some notable limitations, including the need for a bulky styrenyl

chromophore to achieve efficient, selective energy transfer from an excited state photosensitizer to the substrate.”

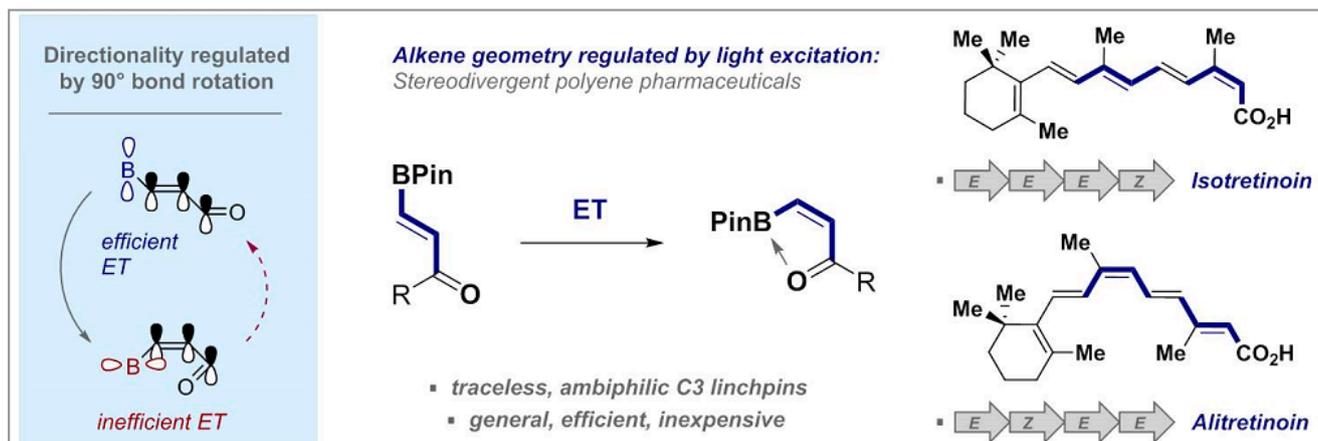
Similarly, the group found that substituents were required to achieve high levels of stereoselectivity due to the generation of 1,3-allylic strain. “Stereo-defined polyenes are common in bio-active small molecules and serve as potent therapeutics such as alitretinoin and isotretinoin, which are themselves attractive synthetic targets,” explained Professor Gilmour. He continued: “However, polyenes typically lack styrenyl chromophores and bulky  $\alpha$ -substituents. As site-selective geometric isomerisation of polyenes by energy-transfer catalysis is underdeveloped, developing simple alkene fragments that readily undergo photocatalytic isomerization would provide a solution. A key consideration was identifying amphiphilic systems to enable iterative coupling for the programmable synthesis of geometrically defined polyenes.”

Addressing this challenge, the operationally simple isomerization of small amphiphilic  $\beta$ -boryl acrylates was realized by the Gilmour group with excellent selectivity using thioxanthone as an inexpensive organic photocatalyst (Scheme 1). “We believed introduction of the boronic ester motif would enable a boron-gating mechanism in which the boron *p*-orbital plays a pivotal role in modulating energy transfer,” explained Dr John Molloy, who is the first author of the study. He told SYNFORM: “In conjugation, energy transfer is efficient; however, after a 90° rotation the *p*-orbital is perpendicular, and this enables directionality. Due to the popularity of organoborons and carbonyl compounds in synthetic chemistry, these geometrically defined fragments are versatile.”

Concerning the applications and future perspectives of this groundbreaking methodology, Professor Gilmour noted that it lends itself to programmable polyene synthesis. “We demonstrated that with expedient access to both isomers, a modular synthesis of stereodefined polyene therapeutics such as alitretinoin and isotretinoin could be realized. By extension, this chemistry could be further incorporated into the synthesis of various natural and unnatural polyenes,” said Professor Gilmour. He continued: “In addition, the traceless boron motif provides a synthetic handle for downstream stereospecific manipulations and so I believe that these densely functionalized, geometrically defined alkene fragments will



**Figure 1** *E* → *Z* photoisomerization of simple alkenes



**Scheme 1** An overview of the photocatalytic isomerisation of ambiphilic  $\beta$ -borylacrylates for the programmed construction of complex polyenes

serve as useful synthons in organic synthesis. Similarly, isomerization-enabled stereodivergence serves as a platform to branch into new 3D chemical space as demonstrated in the Diels–Alder reaction.” The Gilmour group believes that expedient, operationally simple access to both fragments will lead to more stereodivergent transformations with application in synthetic sequences.

Professor Gilmour concluded: “From the perspective of stereospecific alkene functionalization, this platform is attractive in enabling stereo-divergence from common building blocks, thereby circumventing the current need to prepare both alkene isomers independently.”

*Mattias Fanck*

## About the authors



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**John J. Molloy** was born in Glasgow where he obtained his Master’s degree under the supervision of Dr. Allan Watson at the University of Strathclyde (UK, 2014). This included a research stay at the Beatson Institute for Cancer Research (UK). He continued his doctoral studies with Dr. Watson at Strathclyde (2018), which included a short secondment with Prof. Ryan Gilmour at the Westfälische Wilhelms-Universität Münster (Germany). After a short research stay at the University of St Andrews (UK), John returned to WWU as an Alexander von Humboldt Post-doctoral research fellow in the group of Prof. Gilmour (2018).



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**Michael Schäfer** was born in Stadlohn, Germany. He obtained a B.Sc. degree from the Westfälische Wilhelms-Universität Münster (Germany) under the supervision of Prof. Andrea Rentmeister (2016). After a short research stay at the University of California Irvine (USA) under the supervision of Prof. Chris Vanderwal, he obtained his M.Sc. degree at the WWU in the group of Prof. Ryan Gilmour (2018) where he is currently a second year doctoral student.

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**Tobias Morack** was born in Berlin (Germany) and attended Humboldt-Universität zu Berlin (Germany). He received his B.Sc. degree in 2015 after completing his thesis work under the supervision of Prof. Stefan Hecht. He then moved to the Westfälische Wilhelms-Universität Münster (Germany) to complete his Master's degree (2017) including a research stay at the University of Cambridge (UK) working with Prof. Steven V. Ley FRS and an industrial stay at Bayer AG in Wuppertal (Germany). Tobias is currently a third-year doctoral student at the WWU Münster working with Prof. Gilmour.

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**Constantin G. Daniliuc** was born in Romania and received his Diploma in 2002 at the University 'Al. I. Cuza' Iasi (Romania). He moved to the Technical University of Braunschweig/ Institute of Inorganic and Analytical Chemistry (Germany) for his Master's studies as a beneficiary of an Erasmus/Socrates Scholarship and received his Ph.D. from the same university in 2008 under the supervision of Professor W.-W. du Mont. Since 2012, he has been Head of the Crystallographic Laboratory of Organic Chemistry Institute at WWU University of Münster (Germany), where is associated with several projects in Prof. Gilmour's research group.

*Prof. R. Gilmour*

**Ryan Gilmour** was born in Ayrshire, Scotland (UK, 1980) and was educated at the universities of St Andrews and Cambridge (both in the UK). He held research fellowships at the Max-Planck-Institut für Kohlenforschung (Germany, with A. Fürstner) and the ETH Zürich (Switzerland, with P. H. Seeberger) before being appointed as Alfred-Werner-Assistant-Professor of synthetic organic chemistry at the ETH Zürich (2008-2012). In 2013 he moved to the WWU Münster (Germany) where he is Chair of Organic Chemistry and CiMIC Professor of Chemical Biology. He is the recipient of several awards including the Ruzicka Prize, ERC Starter (2013) and Consolidator Grants (2019), and the current holder of the Prof. David Ginsburg Lecturership at the Technion (2020-2021).