

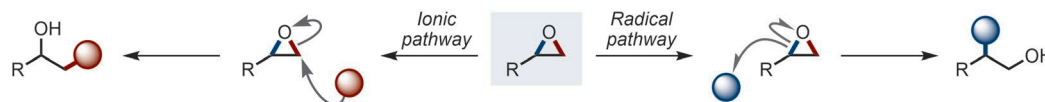
Catalytic Reductive Ring Opening of Epoxides Enabled by Zirconocene and Photoredox Catalysis

Chem 2022, 8, 1762–1774

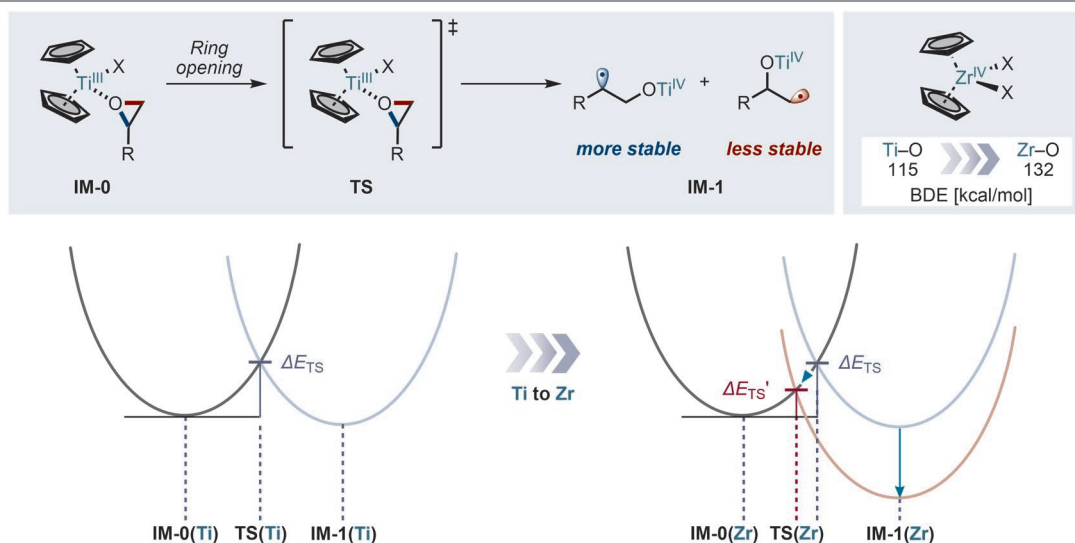
The epoxide ring is a key structural motif frequently found in biologically active compounds, natural feedstocks, and various synthetic intermediates. Generally, epoxides act as electrophiles, but C–O bond homolysis furnishes a nucleophilic carbon radical that can subsequently undergo a variety of functionalizations (Scheme 1).

“The most common catalyst for transformations related to epoxide C–O bond homolysis is titanocene(III) which has been exclusively exploited over the past 30 years by synthetic chemists,” said Professor Junichiro Yamaguchi, from Waseda University (Tokyo, Japan), who added: “The mildness of the reaction conditions has enabled this transformation to be involved in numerous natural product syntheses. With titanocene catalysis, homolysis preferably occurs at the C–O bond to give a more stable radical.” Considering the Bell–Evans–Polanyi

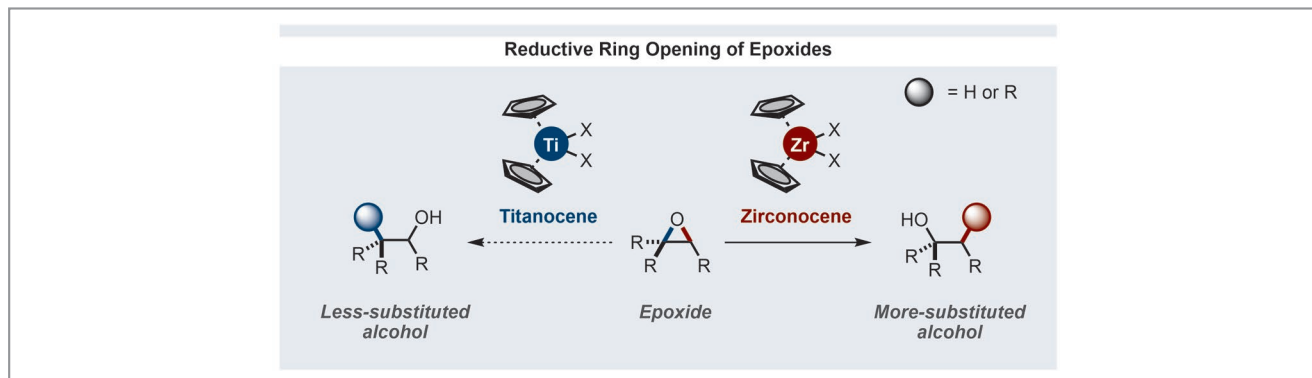
principle, activation energy decreases if the ring-opening step becomes more exothermic. Likewise, the transition state would shift earlier and become more similar to the starting material. According to the Hammond postulate, in an earlier transition state the contribution of the stability of the resulting radicals to regioselectivity would diminish. Intrigued by the higher oxophilicity of zirconium compared to titanium, Professor Yamaguchi’s group became interested in using zirconocene for the ring opening of epoxides (Scheme 2). Assistant Professor Eisuke Ota, a co-author on the paper, said: “We reasoned that the stronger oxophilicity of zirconium relative to titanium should render the ring opening exothermic. On this basis, we envisioned that the use of zirconocene would impact the conventional regioselectivity in the ring opening of epoxides.”



Scheme 1 Ring opening of epoxides



Scheme 2 Titanocene-catalyzed ring opening of epoxides and shifting transition state using zirconocene



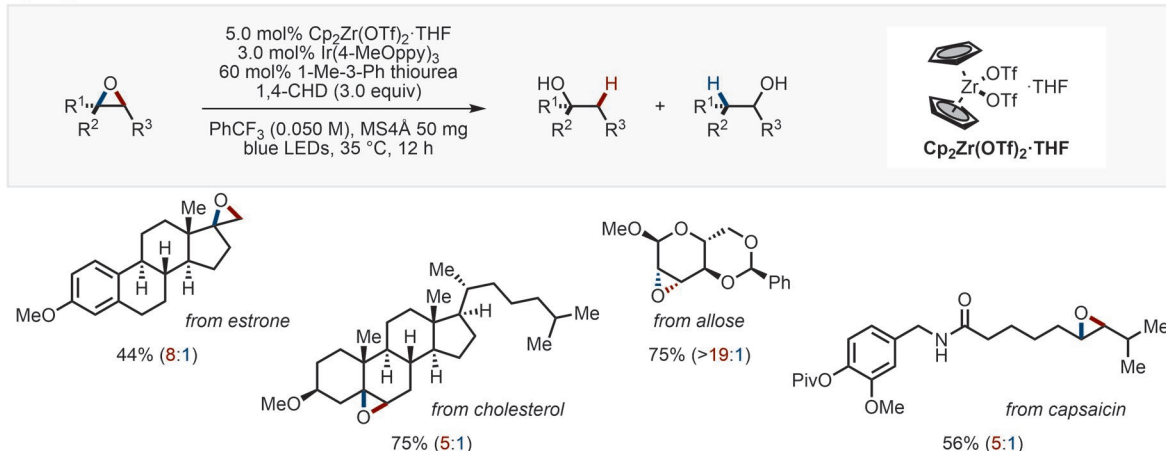
Scheme 3 Complementary regioselectivity in the reductive ring opening of epoxide between titanocene and zirconocene catalysis

Professor Ota remarked: “Fortunately, we succeeded in developing a catalytic protocol for the ring opening of epoxides using zirconocene and photocatalysis, even though zirconocene(III) has been scarcely utilized in organic synthesis. Compared to the well-established ring opening methods with titanocene, the present protocol exhibited reversed regioselectivity to afford the more-substituted alcohols (Scheme 3).” He continued: “This reaction is remarkably general, as it smoothly cleaves C–O bonds of epoxides in the presence of a variety of functional groups (Scheme 4). Natural-product-derived epoxides are also tolerated. Not only hydrogenation, but also radical cyclization was achieved with electron-deficient alkenes. Furthermore, the ring opening of benzyl ethers afforded a series of benzylidene acetals.”

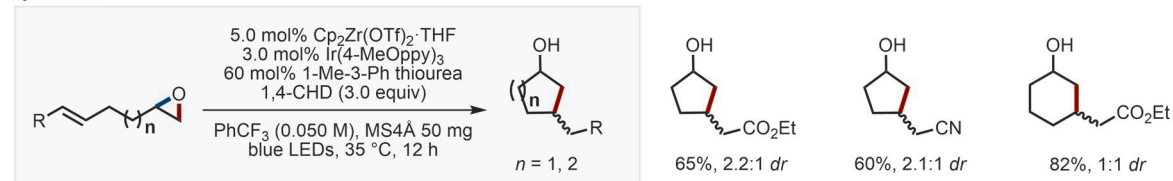
Professor Ota concluded: “The contrasting regioselectivity renders our catalytic protocol complementary to conventional methods using titanocene. We believe that this method for reductive opening will become a strategically important transformation of epoxides in synthetic chemistry, that may lead to revisiting the potential of zirconocene chemistry.”

Matthew Tanaka

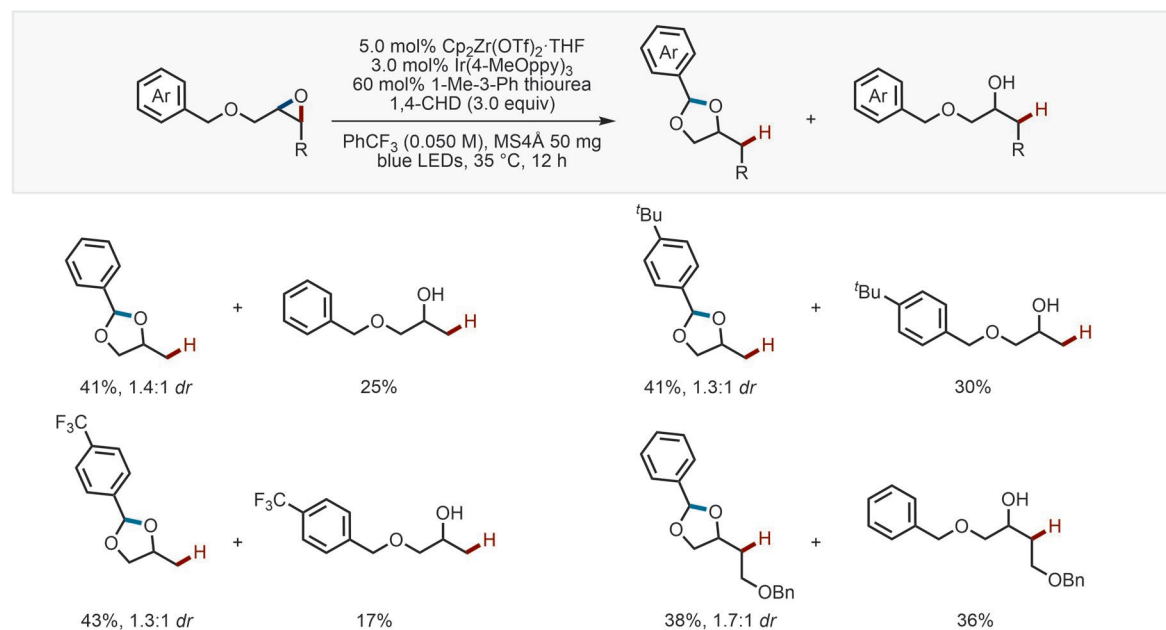
Hydrogenation



Cyclization

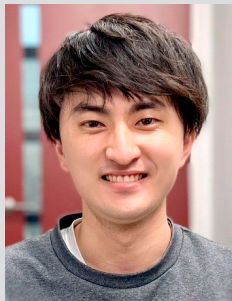


Acetal Formation



Scheme 4 Selected examples of reductive ring opening

About the authors



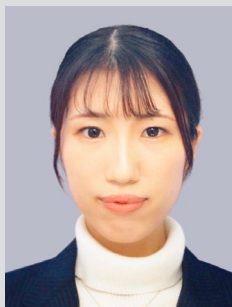
K. Aida

Kazuhiro Aida was born in Tokyo, Japan in 1997. He received his B.Sc. (2020) and M.Sc. (2022) degrees from Waseda University (Japan). Currently, he is a Ph.D. candidate in the group of Junichiro Yamaguchi at Waseda University. His research has focused on the development of inactive bond cleavage reactions using photoredox catalysis.



M. Hirao

Marina Hirao was raised in Tokyo, Japan. She received her B.Sc. degree (2021) from Waseda University, Japan. She is currently pursuing her M.Sc. degree at Waseda University in Prof. Junichiro Yamaguchi's group, where she has been carrying out research work focusing on the ring-opening functionalization of heterocyclic compounds using photoredox catalysis.



A. Funabashi

Aiko Funabashi was born in Tokyo, Japan, in 1997. She received her B.Sc. (2020) and M.Sc. (2022) degrees from Waseda University (Japan) under the guidance of Prof. Junichiro Yamaguchi. Since the spring of 2022, she has been an industrial researcher. Her research interests are the development of photoredox-catalyzed reactions.



Dr. N. Sugimura

Natsuhiko Sugimura received his B.Sc. degree from Shibaura Institute of Technology (Japan) in 1999 and his M.Sc. degree from Tokyo Institute of Technology (Japan) in 2001. After working as a researcher at the Olympus Corporation for nine years, he moved to Waseda University (Japan) as an analytical chemistry engineer in 2010. During his tenure, he obtained his Ph.D. from Tokyo University of

Technology (Japan) in 2017. His main research fields are NMR, MS, and computational chemistry.



Prof. E. Ota

Eisuke Ota was born in Chiba in 1987 and raised in Tokyo, Japan. He received his B.Sc. (2010) and M.Sc. (2012) degrees from Keio University (Japan) under the guidance of Prof. Shigeru Nishiyama. He then joined the group of Prof. Mikiko Sodeoka at RIKEN (Japan), where he completed his Ph.D. in 2016. After working as a postdoctoral researcher for one year at the same place, he became a JSPS Overseas Research Fellow in the lab of Robert Knowles at Princeton University (USA). Since the fall of 2018, he has been an assistant professor at Waseda University (Japan) working with Prof. Junichiro Yamaguchi. His research interests are the development of photochemical bond cleavage methods for organic synthesis and chemical biology.



Prof. J. Yamaguchi

Junichiro Yamaguchi was born in Tokyo, Japan, in 1979. He received his Ph.D. in 2007 from the Tokyo University of Science (Japan) under the supervision of Prof. Yujiro Hayashi. From 2007 to 2008, he was a postdoctoral fellow in the group of Prof. Phil S. Baran at The Scripps Research Institute (USA; JSPS postdoctoral fellowship for research abroad). In 2008, he became an assistant professor at Nagoya University (Japan) working with Prof. Kenichiro Itami and was promoted to associate professor in 2012. He then moved to Waseda University (Japan) as an associate professor (principal investigator) in 2016 and was promoted to full professor in 2018. His research interests include the total synthesis of natural products and the innovation of synthetic methods.