SYNTHESIS Best Paper Award 2019: Enantioselective Synthesis of *cis*- and *trans*-Borocyclopropylmethanol: Simple Building Blocks To Access Heterocycle-Substituted Cyclopropylmethanols

Synthesis **2019**, *51*, 3834–3846

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 André Charette and co-workers, from Université de Montréal, Canada, are the recipients of the SYNTHESIS Best Paper Award 2019. The authors are recognized for their stereospecific approach to alkylamines. In announcing the award, Paul Knochel, Editor-in-Chief of SYNTHESIS, indicated that the selection committee was impressed by the important methodology study on several levels, including the high synthetic interest of the products, the elegant enantioselective method, the extensive potential applications, and the engaging composition and presentation of the study.

SYNFORM spoke with Professor André Charette, 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 A. B. Charette

André B. Charette received his B.Sc. in 1983 from Université de Montréal. He then moved south of the border to the University of Rochester to continue his graduate studies. Under the supervision of Robert K. Boeckman Jr., he completed the total synthesis of the ionophore calcimycin, which earned him the degrees of M.Sc. (1985) and Ph.D. (1987). Following an NSERC postdoctoral fellowship at Harvard University with D. A. Evans, he began his academic career at Université Laval (Quebec City) in 1989 as Assistant Professor. In 1992, he joined once again his alma mater (Université de Montréal), where he has been promoted to the rank of Full Professor since 1998 and where he also serves in a variety of current functions. Among others, he is the holder of a Canada Research Chair in Stereoselective Synthesis of Bioactive Molecules (2005–2018), the Co-Director of the FRQNT Centre in Green Chemistry and Catalysis (2009–), the Co-Director of the NSERC CREATE Training Program in Continuous Flow Science, and the Director of his Department of Chemistry (2014–2020).

With a publication record that encompasses over 230 articles in international journals, 13 book chapters, and 3 patents, he has achieved worldwide recognition in the area of asymmetric processes, new synthetic methodologies in batch and under continuous flow conditions. His research lies primarily in the development of new methods for the stereoselective synthesis of organic compounds and natural products. More particularly, he has devised conceptually novel and practical approaches to the design of catalysts and reactions for the synthesis of cyclopropanes, heterocyclic derivatives and greener functional group transformations, which can find many applications in the pharmaceutical industry. More recently, his efforts have focused on preparing and using highly sensitive reagents, such as diazo reagents, under continuous flow conditions to make the process much safer to use on larger scale.

Throughout his career, he has received >20 international awards from both academic and industrial communities. Among his most prestigious honors are the CIC Medal (2018), a Doctorate Honoris Causa from INSA-Rouen (2015), the CSC Alfred Bader Award (2009), the Marie Victorin Award from the Government of Quebec (2008) and an ACS Arthur C. Cope Award (2007). He is currently the Editor-in-Chief of the Encyclopedia of Reagents for Organic Synthesis (e-EROS). As an academic leader, he has been training together >200 postdoctoral fellows, graduate students and undergraduate interns and has helped raise them to the rank of highly qualified scientists.

  • Published online: June 17, 2020 • DOI: 10.1055/s-0039-1691183

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?*

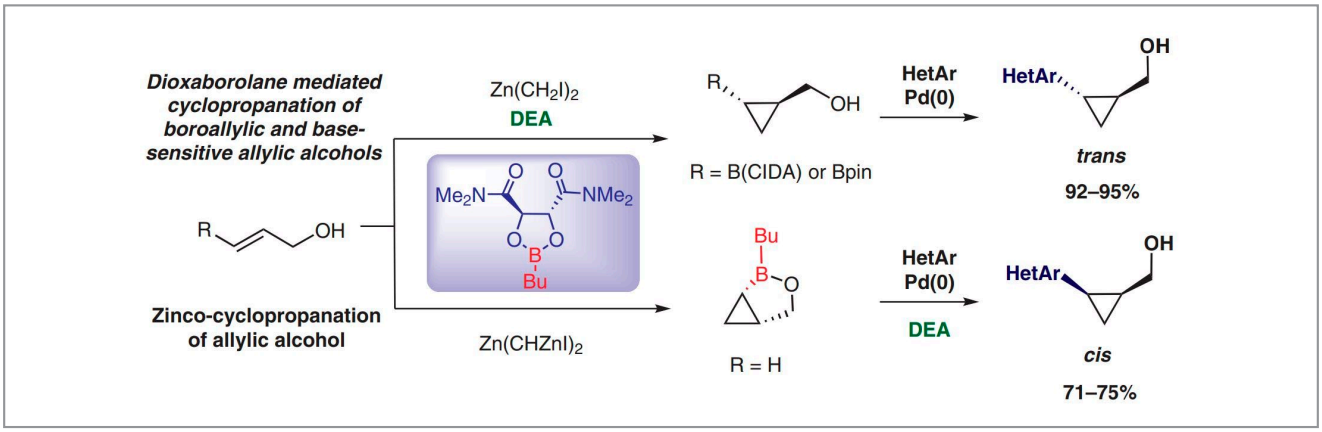
Prof. A. B. Charette Several asymmetric borocyclopropanation methodologies have emerged over the last decade. However, access to enantioenriched borocyclopropanes has remained limited and many of these borocyclopropanes are prone to decomposition through protodeboronation. We have developed a versatile zinc-mediated enantioselective cyclopropanation of a tetracoordinate boronate-bearing allylic alcohol for the preparation of enantioenriched borocyclopropane building blocks (Scheme 1). One of the challenges was to develop conditions that would be highly chemoselective, thus avoiding the traditional oxidative work-up procedure. The resulting borocyclopropylmethanol derivatives allowed us to access *N*-heterocyclic substituted cyclopropanes in very good yields with excellent diastereo- and enantiocontrol. Enantioenriched borocyclopropanes are highly valuable building blocks and can be used in various C–C bond-forming reactions. This enantioselective borocyclopropanation reaction is a significant addition to the highly versatile and robust enantioselective zinc carbenoid mediated cyclopropanation reactions which can now be extended to base-sensitive substrates.

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

Prof. A. B. Charette Our group has previously published a diastereoselective borocyclopropanation using a boromethylzinc carbenoid to access borocyclopropanes in racemic form. In this work, we developed an enantioselective borocyclopropanation version of the zinc carbenoid cyclopropanation in the presence of a chiral dioxaborolane ligand that has been one of the trademarks of our research group for many years. We hoped to synthesize borocyclopropanes bearing tetracoordinate borocyclopropanes to access bench-stable borocyclopropylmethanol derivatives. To do so, we strategically planned to overcome the insolubility of existing tetracoordinate boronate derivatives by synthesizing *N*-cyclohexyliminodiacetic acid (CIDA) boronate bearing allylic alcohols instead and targeted an alternative to the oxidative conditions used for the removal of the dioxaborolane ligand. A major contribution to this methodology was the discovery that diethanolamine can be used to cleave dioxaborolane bound to the desired cyclopropane. With these borocyclopropanes in hand, we then used these building blocks in C–C bond coupling reactions to access *N*-heterocycle substituted cyclopropanes. This class of compounds is rather difficult to prepare in enantio- and diastereo-enriched form using known methodologies.

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

Prof. A. B. Charette Our laboratory focuses on the stereoselective synthesis of organic compounds, the development of new tools for synthetic organic chemists (amide bond formation, amide bond cleavage, synthetic methodologies that take advantage of continuous flow synthesis such as safe preparation and use of highly reactive diazo reagents), as well as the synthesis of biologically relevant compounds. In the specific area of borocyclopropanes, we developed the borocyclopropanation of allylic ethers using a boromethylzinc reagent as well as a UV light mediated borocyclopropanation of styrenes



Scheme 1

using continuous flow technology. Our group has broadly studied new reagents leading to cyclopropanes with better chemoselectivities, higher enantiocontrol, and milder reaction conditions. We have characterized zinc carbenoid reagents and explored gem-dizinc carbenoids to access trisubstituted cyclopropanes.

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

Prof. A. B. Charette Organic synthesis plays a fundamental role in medicinal chemistry, in the agrochemical industry, as well as in materials science and energy-related areas to name a few. The modern role of organic chemistry is to address the continuous demand of making molecules faster, safer, easier, and under environmentally benign conditions. Researchers are often faced with relatively simple synthetic blockades despite the development of numerous methodologies available and therefore any contribution that addresses functional group compatibility or an in depth understanding of fundamental concepts of organic chemistry should be embraced. You never know whether the next reaction that you are developing will constitute a breakthrough to synthesize the next life-saving drug. In the field of research, it is difficult to predict which novel methodologies could be the next standard for bond forming or breaking chemistry or for which applications it could play a major role. As a scientist, it is important to keep an open mindset and embrace new perspectives while also continuing to obtain a better understanding of the fundamentals of organic chemistry. This is the beauty about doing fundamental research. My philosophy about productive research goes far beyond the publishing rate of scientists; research should really focus on the quality of science that is being done and the level of impact it has on society.

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

Prof. A. B. Charette The objective of the paper was to overcome a fundamental limitation of the enantioselective cyclopropanation reaction using zinc carbenoids in a manner that would further broaden its scope and motivate synthetic chemists to embrace this approach to make heterocycle-substituted cyclopropanes. The SYNTHESIS Best Paper Award recognized our paper for studying the enantioselective cyclopropanation reaction of boroalkenes and it impacts us on several levels. This award encourages us to continue our research to produce novel synthetic methodologies and push the boundaries of organic synthesis. It is also a major motivation boost for the students and postdoctoral researchers who are working in synthesis to have their work widely recognized.

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