Direct Catalytic Asymmetric Synthesis of α-Chiral Bicyclo[1.1.1]pentanes

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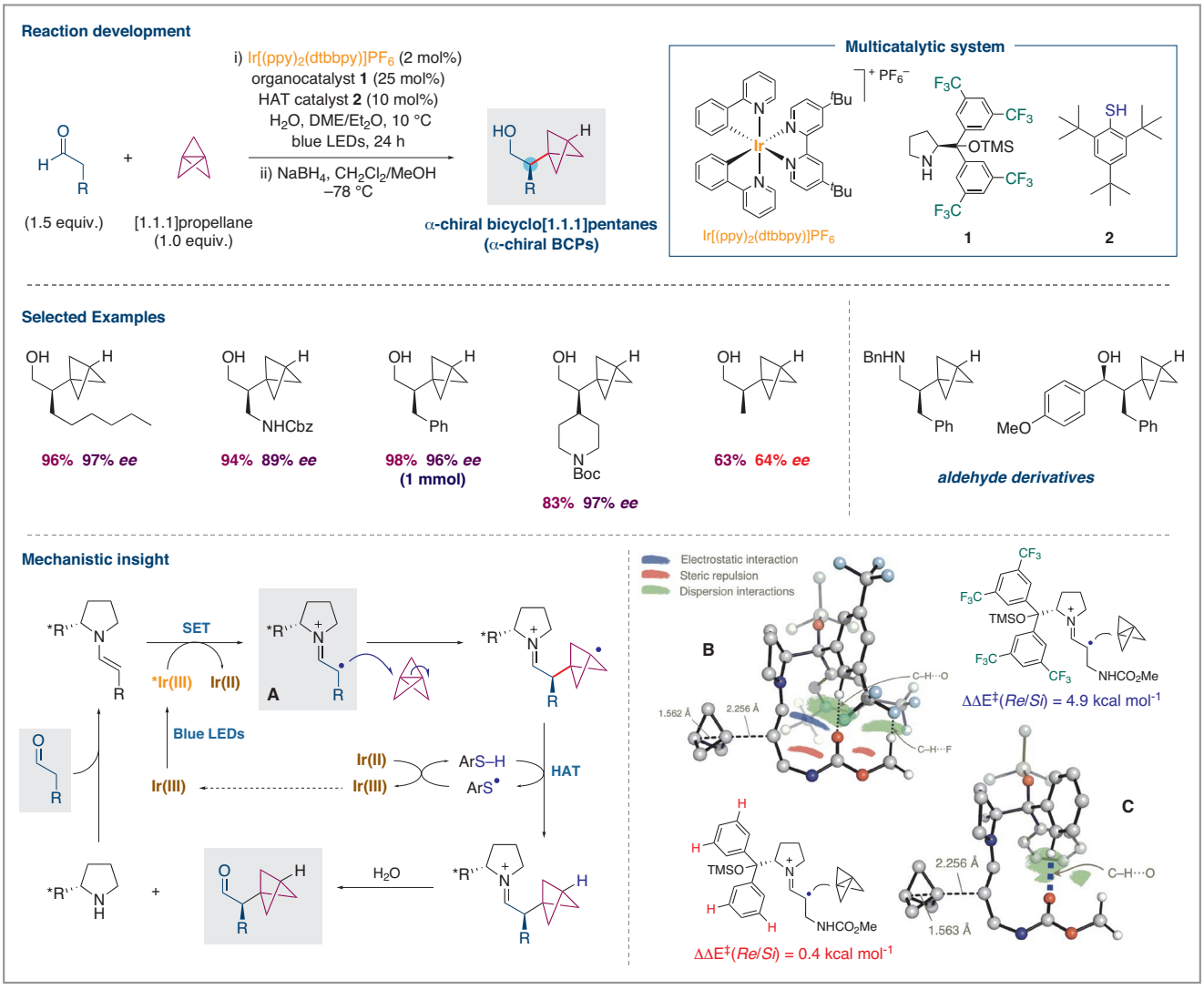
Bicyclo[1.1.1]pentanes (BCPs) have become highly attractive bioisosteres for *para*-substituted arenes and *tert*-butyl groups in medicinal chemistry, due to their advantageous pharmacokinetic properties.[1] However, the synthesis of BCPs featuring adjacent stereocentres has remained a significant challenge – these motifs would correspond to α-stereogenic benzyl groups, which are again of high importance in drug design. The group of Professor Edward A. Anderson at the University of Oxford (UK) has been studying this area for some time. "At the starting point of our work, just two catalytic methods[2,3] had been reported to install an α-stereocentre on a pre-formed BCP," said Professor Anderson. The group realised that an alternative and very attractive approach to this problem would be the direct formation of a stereogenic centre upon ring-opening of [1.1.1]propellane, the smallest tricyclic hydrocarbon and the ubiquitous precursor to BCPs. "Despite decades of work on ring-opening reactions of [1.1.1]propellane, no such direct asymmetric addition process had been described. The symmetry of this fascinating cage molecule renders an asymmetric ring opening all the more challenging," explained Professor Anderson. He went on: "From our previous work, we knew that radical-based additions proceed in high yields and under mild conditions;[4,5] however, the field of catalytic asymmetric radical reactions as a whole is rather underdeveloped and in early studies, PhD student Marie Wong indeed found that previous asymmetric radical chemistries failed when faced with [1.1.1]propellane. Nonetheless, we were aware of the pioneering work of the MacMillan group on asymmetric alkylations of aldehydes with styrenes as radical acceptors,[6] which used a three-component catalytic system comprising an organocatalyst (typically a Hayashi–Jørgensen diarylprolinol derivative), a photoredox catalyst (an iridium complex), and a hydrogen-atom-transfer catalyst (HAT catalyst, typically a thiol). The key question for Marie," continued Professor Anderson, "was whether these three catalysts could successfully operate on [1.1.1]propellane, as a number of side reactions could be envisaged, such as polymerization of the propellane, or its direct reaction with the thiol HAT catalyst."

Marie undertook a comprehensive screen of reaction conditions, including variations of all three catalysts, reactant equivalents, solvent and concentration, temperature and reaction time, and even LED lamp. Professor Anderson revealed that Marie made some curious discoveries: the enantioselectivity of the reaction appeared critically dependent not only on the nature of the chiral organocatalyst, but also, surprisingly, on the photocatalyst and the HAT catalyst. "As we initially believed the latter two would not be directly involved in the enantiodetermining step – namely, the ring opening of [1.1.1]propellane – we were intrigued to understand more about the origin (or origins) of stereoinduction," Professor Anderson remarked. He went on: "Irrespective of this, we were delighted to find that the reaction could be applied to a wide range of aldehydes, tolerating many functional groups and significant steric hindrance adjacent to the alkylation site. These products are easily transformed into other useful BCP-containing building blocks."

Working with Professor Fernanda Duarte (University of Oxford, UK), PhD student Alistair Sterling had already been establishing a theoretical reaction pathway for this asymmetric bicyclopentylation chemistry, and now took on the challenge to explain these phenomena. Professor Fernanda Duarte explained: "Alistair uncovered several key findings: firstly, that the enantioselectivity of the reaction derives not only from steric blocking of one face of the intermediate iminyl radical cation **A** (see Scheme 1) by the organocatalyst sidechain, but also from stabilizing non-covalent interactions between its trifluoromethyl groups and the aldehyde sidechain (**B**). This explained the importance of the organocatalyst substituents (**C**); and secondly, that the interconversion of the *E* and *Z* iminyl radical cations **A**, formed from oxidation of the corresponding enamines, had a higher energy barrier than their addition to propellane. Therefore, the population of these diastereomeric radical cations could also influence enantioselectivity. As this population is decided by the relative rates of oxidation of the enamine precursors, this explains why the photoredox catalyst could influence enantioselectivity, as the enamine stereoisomers could certainly possess different oxidation potentials."

Professor Anderson concluded: "Overall, this chemistry should provide an efficient and general way to synthesize valuable α-chiral bicyclopentanes for medicinal chemistry research. Our groups are keen to continue exploring both the experimental and theoretical consequences of the concepts we have developed, which we hope should extend beyond BCPs."



Scheme 1 Multicatalytic synthesis of α-chiral bicyclo[1.1.1]pentanes by asymmetric addition of aldehydes to [1.1.1]propellane

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About the authors

Dr. M. L. J. Wong

Marie Wong is from Cameron Highlands, Malaysia, and received her MChem degree from the University of Oxford (UK) in 2016. During this time, she conducted research with Prof. Edward Anderson (University of Oxford), Prof. John Hartwig (UC Berkeley, USA) and Prof. Scott Miller (Yale University, USA). She then joined the EPSRC Synthesis for Biology and Medicine Centre for Doctoral Training (SBM CDT) at the University of Oxford. She completed her PhD studies in 2021 on the synthesis and functionalization of α-chiral bicyclo[1.1.1]pentanes under the supervision of Prof. Edward Anderson.

A. J. Sterling

Alistair Sterling received his MChem degree in 2017 from the University of Oxford (UK). During his studies, he spent a semester in the group of Prof. Erick Carreira (ETH Zürich, Switzerland), before returning to Oxford to study total synthesis under the supervision of Prof. Edward Anderson. He subsequently received an Oxford-Radcliffe scholarship to undertake doctoral studies at the University of Oxford, and after briefly working on carbon-rich nanoring synthesis under Prof. Harry Anderson, he joined the groups of Profs. Fernanda Duarte and Edward Anderson. His doctoral research focuses on the development of physical organic models to explain the reactivity of strained organic molecules, using computational techniques to aid the development of new reactions.

Dr. J. J. Mousseau

James J. Mousseau was born in Montréal, Quebec, Canada. Upon completing his B.Sc. in Honors Biochemistry in 2004 at Concordia University (Canada), he continued his M.Sc. studies at Concordia under the supervision of Professor Louis Cuccia and was involved in the synthesis of novel crescent-shaped urea-linked heterocyclic foldamers. In 2011 he completed his Ph.D. studies under Professor André Charette at Université de Montréal (Canada) studying arene direct functionalization processes. After completing an NSERC Postdoctoral Fellowship at the Massachusetts Institute of Technology (USA) under Professor Tim Jamison, he joined Pfizer in 2013 in Groton, CT (USA) as a medicinal chemist working in the area of inflammation and immunology. He is a co-author on ~40 publications and recent synthetic interest has been around developing new methodologies to provide chemists with tools to 'escape the flatland'.

Professor F. Duarte

Fernanda Duarte is an Associate Professor in Chemistry at the University of Oxford (UK). Her current position commenced in 2018, following appointments at the University of Edinburgh (UK; Chancellor's Fellow), the University of Oxford (Newton Fellow) and Uppsala University (Sweden; PDRA). She leads a diverse team of researchers working at the interface of organic chemistry, supramolecular catalysis, and computational chemistry. Her main research interests centre on the prediction of chemical reactivity in the condensed phase, combining classical, quantum and machine-learning approaches. Her group has also developed a series of computational software to facilitate molecular design and reaction mechanism exploration. She has published over 50 peer-reviewed scientific publications and received several awards, including most recently the 2020 MGMS Frank Blaney Award from the Molecular Graphics and Modelling Society.

Professor E. A. Anderson

Edward A. Anderson is Professor of Organic Chemistry at the University of Oxford (UK). He began his independent career as an EPSRC Advanced Research Fellow in 2007, during which he was appointed as Associate Professor at Jesus College, Oxford in 2009, and then as Professor in 2016. His research interests encompass a wide range of synthetic organic chemistry, including natural product total synthesis, transition-metal catalysis and mechanistic study, bicyclo[1.1.1]pentanes and related small rings, antiparasitic natural products, the chemistry of ynamides and yndiamides, and EPR spectroscopy in nucleic acids. He is a recent recipient of the Novartis Chemistry Lectureship (2018), and RSC Bader Award (2020).

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