Catalytic Enantioselective Synthesis of Indanes by a Cation-Directed 5-endo-trig Cyclization


Stereocontrolled cyclization reactions represent formidable tools for constructing complex structural scaffolds of natural and biologically active molecules and the development of new cyclization methodologies continues to attract enormous interest in organic chemistry. Martin Smith’s group at the University of Oxford (UK) has been interested in the application of asymmetric phase-transfer catalysis to new reaction manifolds – particularly cyclizations – for some time. “We reasoned that chiral ammonium salts could potentially discriminate between the π-faces of a delocalized anion, which could offer...

Scheme 1

Highly enantioselective indane synthesis; dr determined by 1H NMR analysis of the crude reaction mixture; er determined by chiral HPLC analysis; yields are for isolated material. 

- a Reaction solvent was toluene–CHCl₃ (9:1).
- b (S,S)-1 was used as catalyst.
- c No DMSO was added.
- d n-Bu₄NBr was added instead of DMSO.
an approach to asymmetric electrocyclic reactions,” explained Professor Smith. This turned out to be an effective strategy, leading to the generation of complex indolines with high levels of diastereo- and enantioselectivity (Angew. Chem. Int. Ed. 2009, 48, 9979; Chem. Sci. 2012, 3, 537). Professor Smith continued: “We were keen to extend this chemistry to the synthesis of indanes but recognized that an alternative cyclization through a Dieckman-type process could compete – so the scene was set for a competition between an electrocyclic/5-endo-trig manifold and a 5-exo-trig alternative (Scheme 1).

DPhil student Craig Johnston was focused on optimization of this chemistry. “We found that whatever base-mediated conditions we used with a malonate-derived nucleophile, the 5-endo-trig manifold dominated,” he said. After a wide-ranging catalyst screen, it was found that application of a chiral dibenzazepine salt 1 disclosed by Maruoka and co-workers (Angew. Chem. Int. Ed. 2005, 44, 1549) to a cascade cyclization–alkylation led to enantioenriched indanes in up to 99:1 er as a single diastereoisomer. However, Professor Smith and Dr. Johnston were puzzled to observe that a similar reaction with an ester-derived nucleophile led exclusively to cyclization via the 5-exo-trig mode. At this stage, Professor Smith and his co-workers were interested in probing the mechanism of the reaction and turned to quantum computation. Professor Rob Paton and his group in Oxford (UK) performed a suite of calculations that demonstrated that the reaction was unlikely to be electrocyclic and was better described as an intramolecular Michael addition (Scheme 2). “These calculations enabled us to suggest a model for stereoinduction, which shows that a range of non-covalent interactions are responsible for the observed sense of enantioinduction. The divergent ring-closing behavior of the two closely related nucleophiles all stems from markedly different ground-state conformations,” explained Professor Paton. The Oxford computational group teamed up with visiting academic Professor Sergiy Okovytyy and PhD student Tetiana Sergeieva from Oles Honchar Dnipropetrovsk National University (Ukraine) to show the malonate nucleophile rotates completely out of the plane, leading to a reaction

**Scheme 2** Mechanistic possibilities and stereochemical model: (a) There are two feasible mechanistic extremes for the reaction: an anionic 5-endo-trig reaction and a suprafacial 6π electrocyclization. (b) The mode of cyclization is dictated by substitution on the nucleophilic component of the reaction: an ester leads exclusively to 5-exo-trig cyclization whilst a malonate leads exclusively to 5-endo-trig cyclization. (c) Docking of the transition state for the cyclization reaction with the catalyst indicates that non-covalent interactions including C–H···O hydrogen bonds and C–H···π interactions are responsible for the observed enantioselectivity. This correctly predicts the absolute sense of enantioselectivity observed in the reaction.
path that follows a nucleophilic 5-endo-trig trajectory devoid of any electrocyclic character. Professor Paton further explained: “Trajectory is of course important for ring-closing reactions, but the generally observed 5-exo bias is not absolute and can be overcome by sufficient perturbation of the reactant away from an electrocyclic manifold.”

“Overall this study showcases the ease with which complex indanes can be generated with high enantioselectivity using phase-transfer catalysis,” concluded Professor Smith. “It also demonstrates that geometric restrictions are not always decisive in kinetically controlled ring-closing reactions.”

About the authors

Craig Johnston was born in Broxburn (UK) in 1987. He obtained his Master’s degree in chemistry from the University of St Andrews (UK) in 2009 where he worked with Andrew Smith. He then joined Martin Smith’s research group at the University of Oxford (UK) to investigate new applications of phase-transfer catalysis in challenging asymmetric synthetic transformations. After completing his DPhil at the University of Oxford in 2014 he joined David MacMillan’s group at Princeton University as a Marie Curie International Outgoing Fellow.

Kelvin Jackson was born in 1989 in London (UK), growing up in Singapore. He attended the University of Oxford for undergraduate studies, and received an MChem in 2012 under the supervision of Professor Robert Paton. He is currently in his third year of graduate studies in Robert Paton’s group. His research focuses on the computational study of organocatalytic mechanisms and on the development of new methods to accurately compute flexible catalytic pathways and selectivities.

Abhishek Kothari studied pharmacy at Nagpur University, India (BPharm, 2003) and the National Institute of Pharmaceutical Education and Research, Mohali, India (M Tech, 2005). He was subsequently awarded the Dharam Hinduja Scholarship at the University of Cambridge (UK), where he completed his PhD (2010) in Martin Smith’s group, working on foldamers and asymmetric electrocyclization reactions. He has subsequently worked as a Research Investigator at Syngene Intl. Ltd. (Bangalore, India) with a brief stint at Intonation Research Laboratories (Hyderabad, India). His research interests are solid- and solution-phase peptide synthesis with fluorescent dyes, combinatorial chemistry and asymmetric catalysis.

Prof. S. I. Okovytyy

Sergiy I. Okovytyy is Head of the Department of Organic Chemistry and Deputy Dean of the School of Chemistry at Oles Honchar Dnipropetrovsk National University (Ukraine) and Adjunct Graduate Faculty Member at Jackson State University (USA). He received his BS (1992), MS (1993), PhD (1996), and DS (habilitated, 2006) degrees in Chemistry at Oles Honchar Dnipropetrovsk National University. In 2014 he carried out an internship at the University of Oxford where he performed collaborative research with Robert Paton. His main research goals are the investigation of organic reaction mechanisms and the development of new approaches and basis sets for the theoretical study of second-order electric and magnetic molecular properties.

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Robert Paton is an Associate Professor in Organic Chemistry at the University of Oxford. Paton’s group uses theory and computation to solve problems in organic and bio-organic chemistry. Following graduate studies with Jonathan Goodman at the University of Cambridge, and a Fulbright-AstraZeneca Postdoctoral Fellowship with Kendall Houk at UCLA (USA), Rob was appointed to a University Lectureship and Tutorial Fellowship at Oxford in 2010. Recent accolades include the MGMS Silver Jubilee Prize 2014 and a Thieme Chemistry Journal Award in 2015.

Martin Smith is an Associate Professor in Organic Chemistry and Director of the EPSRC Center for Doctoral Training in Synthesis for Biology & Medicine at the University of Oxford. He worked with Professor George Fleet at the University of Oxford for his DPhil, before moving to the University of Cambridge as the Draper’s Company Research Fellow, working with Professor Steve Ley. He started his independent career in Cambridge after the award of a Royal Society University Research Fellowship and moved to his current position in Oxford in 2008. His group is focused on synthesis, structure, and asymmetric catalysis.

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