

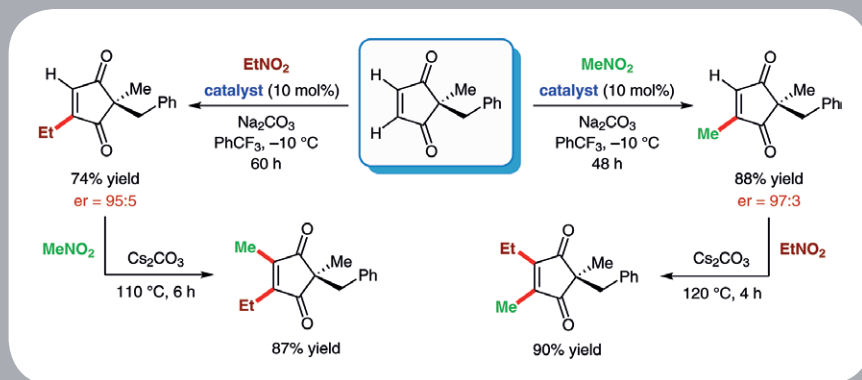
Synform

People, Trends and Views in Chemical Synthesis

2015/05

Organocatalytic Enantioselective Formal C(sp²)-H Alkylation

Highlighted article by M. S. Manna, S. Mukherjee



Contact

Your opinion about Synform is welcome,
please correspond if you like:
marketing@thieme-chemistry.com

Dear Readers,

I hope you had a chance to visit the Thieme Chemistry website (<https://www.thieme.de/en/thieme-chemistry/home-51399.htm>) recently, and had a look at the new 'News articles' which highlight some of the most important e-first articles published in SYNLETT and SYNTHESIS. If you did, you will have noticed the News on the recent SYNLETT paper published by Alan Spivey (Imperial College London, UK), and another one by Shaobin Miao (Georgia Regents University, Atlanta, USA) and Tohru Nagamitsu (Kitasato University, Tokyo, Japan) in SYNTHESIS. We believe these brief 'alerts' are an effective means for increasing both impact and visibility of your articles published in the Thieme Chemistry journals, and we hope this new online editorial feature will contribute to make it even more appealing for you to publish your cutting-edge research with us.

This May 2015 issue of SYNFORM, which is more special than ever because the layout is brand new and – in my opinion – absolutely superb, is opened by a Young Career Profile featuring J. Wulff (Canada) who answers to our usual five questions concerning his research interests and prospects. The fascinating 'phosphinoboration reaction' designed by S. Westcott (Canada, again!) comes next, followed by the elegant desymmetrization reaction introduced by S. Mukherjee (India). Last but definitely not least, the impressive catalytic enantioselective synthesis of indanes developed by M. Smith (UK).

Enjoy your reading!



In this issue

<ul style="list-style-type: none"> ■ Young Career Focus 	Professor Jeremy E. Wulff (University of Victoria, Canada) A62
<ul style="list-style-type: none"> ■ Literature Coverage 	The Phosphinoboration Reaction A64
<ul style="list-style-type: none"> ■ Literature Coverage 	Organocatalytic Enantioselective Formal C(sp²)-H Alkylation A67
<ul style="list-style-type: none"> ■ Literature Coverage 	Catalytic Enantioselective Synthesis of Indanes by a Cation-Directed 5-endo-trig Cyclization A71
	Coming soon..... A75

Contact

If you have any questions or wish to send feedback, please write to Matteo Zanda at: synform@outlook.com

Young Career Focus: Professor Jeremy Wulff (University of Victoria, Canada)

Background and Purpose. From time to time SYNFORM meets young up-and-coming researchers who are performing exceptionally well in the arena of organic chemistry and related fields of research, in order to introduce them to the readership. This Young Career Focus presents Professor Jeremy Wulff (University of Victoria, Canada).

Biographical Sketch



Prof. J. Wulff

Jeremy Wulff is originally from Vancouver Island (Canada), and completed his BSc at the University of Victoria (UVic, Canada) in 1999. He then undertook PhD studies at the University of Calgary (Canada) with Professor Thomas Back, and postdoctoral work at Harvard University (USA) with Professor Andrew Myers before returning to UVic as an independent investigator in 2007. He was promoted to Associate Professor with tenure in 2013.

Dr. Jeremy Wulff holds a Michael Smith Foundation for Health Research Career Investigator Award, as well as the Tier II Canada Research Chair in Bioactive Small Molecule Synthesis. His research program revolves around organic synthesis and medicinal chemistry.

house, and also spent a few years' worth of 'free' time making a 17-foot cedar strip kayak with a friend. The joy that comes with creating new things has always been a driving force for me.

I didn't set out to be a chemist. But in the 2nd year of my undergraduate studies, I suddenly realized that a person could **make molecules** and I was hooked for life. For the next several years, I devoted all of my energy to learning how to be a better molecule maker – participating in several undergraduate research projects in both academia and industry before finally doing a total synthesis PhD with Thomas Back at the University of Calgary.

Eventually I became just as interested in what those molecules could do. In my postdoctoral work with Andrew Myers (Harvard University) I took on a chemical biology project that required me to learn an entirely new field. I'd never done so much as a high-school biology course, but before I knew it I was culturing cancer cells, running Western blots, expressing proteins, spending days camped out in front of a flow cytometer, and even designing my own biological assays. When it was time to set up my own lab, this experience was invaluable in allowing me to craft a unique research program.

SYNFORM *What do you think about the modern role and prospects of organic synthesis?*

Prof. J. Wulff Organic synthesis has so much to offer the world! Every aspect of biology and medicine requires new molecules and synthetic techniques in order to move forward. Just think of the tremendous impact that automated peptide and polynucleotide synthesis has had upon the practice of biological science. Not to mention the impact of the polymerase chain reaction (PCR), which is really just a fancy implementation of supramolecular chemistry (annealing) and enzymatic synthesis (chain extension).

Much has been said about how the trend in the pharmaceutical industry toward the use of therapeutic antibodies or RNAi to control protein function will lead to a decrease in the importance of the traditional practice of small-molecule-

INTERVIEW

SYNFORM *What is the focus of your current research activity?*

Prof. J. Wulff My group is most excited about making interesting organic compounds that have useful biological functions. I'm fortunate that my laboratory space at the University of Victoria includes both a well-equipped synthetic lab for making complex molecules, and a class II biosafety lab for studying the biological effects of our final compounds.

SYNFORM *When did you get interested in synthesis?*

Prof. J. Wulff I've always enjoyed making things. When I'm not doing science, I build new decks and sheds around our

based medicinal chemistry. But this ignores the fact that such agents are prohibitively expensive and (for technical reasons) don't become 'generic' as easily as small-molecule drugs. For a number of reasons, small molecules will always be better drugs than antibodies. And someone will always have to know how to make them.

Having said that, it's worth acknowledging that organic synthesis has not experienced the kind of 'quantum leaps' that have occurred in other fields. People doing biochemistry or high-energy physics right now are carrying out experiments that would have been unimaginable a couple of decades ago. And that's simply not the case for us synthetic chemists (despite what one might believe from the bombastic titles of our papers). To really unlock the potential of organic synthesis will require a paradigm shift in transform predictability and synthetic efficiency.

SYNFORM Your research group is active in the areas of total synthesis and bioorganic chemistry. Could you tell us more about your research and its aims?

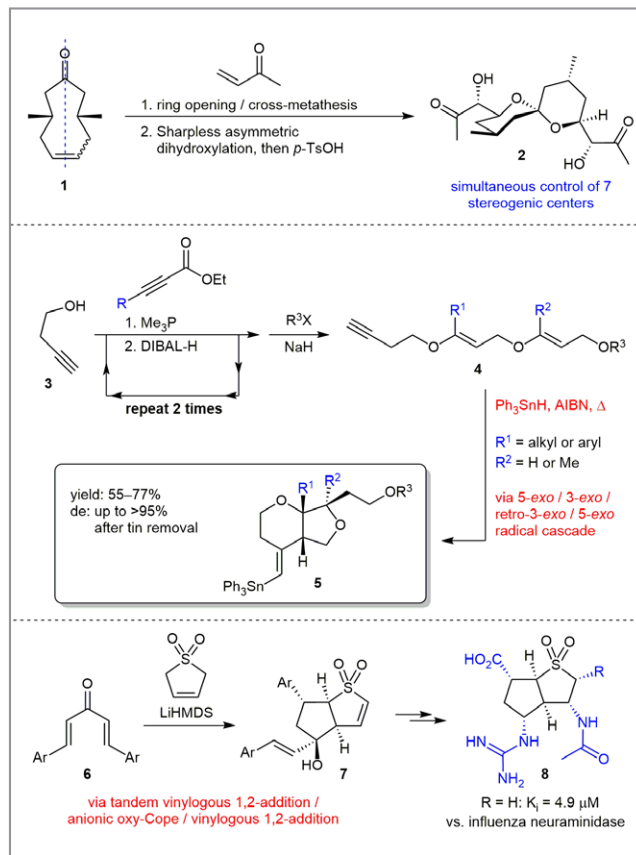
Prof. J. Wulff One of the things that architecturally complex molecules have going for them is their intrinsic molecular rigidity. I'm fascinated by the idea of exploiting this rigidity as a way to precisely control biology. We therefore look for targets where we can (1) create an efficient tandem or cascade synthesis of a complex, functionalized core of some defined molecular geometry; (2) decorate the core with functional groups necessary for engagement with a biological system; and then (3) use the resulting molecule in a medically relevant problem of biological control.

Some of our targets are natural products. For example, we recently developed a cascade to transform *meso*-cyclononene **1** (possessing no absolute stereochemistry) into the functionalized, rigid core of didemnaketol A, a molecule thought to function as a dissociative inhibitor of HIV-1 protease.¹

Other times our targets are non-natural structures that we design for specific purposes. For example, we described an iterative synthesis of oligovinyl ethers (**4**)² that we could subsequently use as substrates in a radical cascade reaction to access functionalized bicycles **5**.³ We envision that related transformations will lead to oxasteroidal molecules with a range of interesting biological properties.

SYNFORM What is your most important scientific achievement to date and why?

Prof. J. Wulff Probably the clearest example of what we're trying to do has been our sulfone-based neuraminidase in-



hibitors. These came about through our discovery of a novel tandem reaction that couples bis-vinyl ketones (**6**) and simple cyclic sulfones to provide rigid, orthogonally functionalized sulfone bicycles.⁴ These can be further decorated to achieve, among other things, molecules like **8** that mimic the enzyme-bound state of the potent antiviral agent peramivir.^{5,6}

Matthews Farnik

REFERENCES

- (1) J. A. Davy, B. Moreau, A. G. Oliver, J. E. Wulff *Tetrahedron* **2015** DOI: 10.1016/j.tet.2015.03.043.
- (2) K. A. Davies, J. E. Wulff *Org. Lett.* **2011**, *13*, 5552.
- (3) N. F. O'Rourke, K. A. Davies, J. E. Wulff *J. Org. Chem.* **2012**, *77*, 8634.
- (4) M. G. Brant, C. M. Bromba, J. E. Wulff *J. Org. Chem.* **2010**, *75*, 6312.
- (5) M. G. Brant, J. E. Wulff *Org. Lett.* **2012**, *14*, 5876.
- (6) M. R. Richards, M. G. Brant, M. J. Boulanger, C. W. Cairo, J. E. Wulff *Med. Chem. Commun.* **2014**, *5*, 1483.

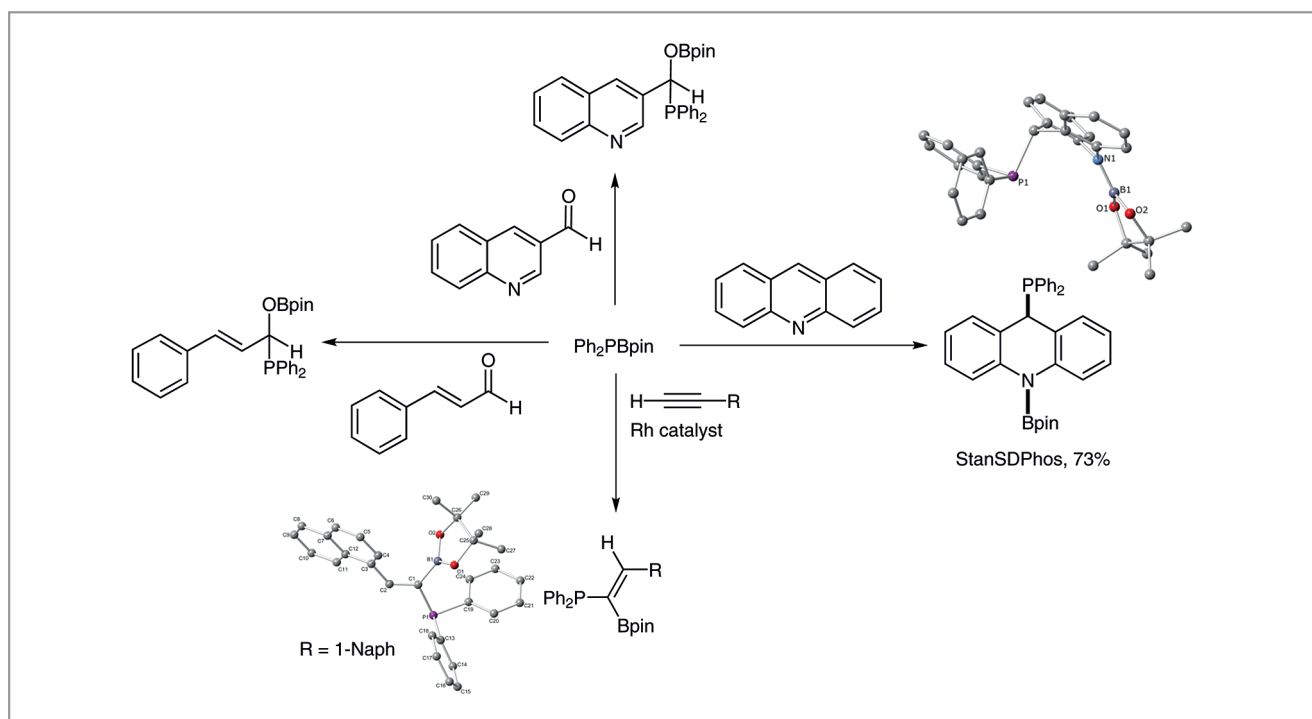
The Phosphinoboration Reaction

Angew. Chem. Int. Ed. **2015**, *54*, 2121–2125

The addition of boron–element bonds (where element = H, B, Sn, Si, Se, S) to organic substrates has become a fundamentally important reaction in organic synthesis over the past few decades. Classic examples are the hydroboration reaction (element = H) or diboration/borylation reactions (element = B), but many more reactions of this type are becoming an integral part of the arsenal of reactions available to organic chemists. Recently, the research group of Professor Stephen Westcott at Mount Allison University (New Brunswick, Canada) reported on a unique phosphinoboration reaction where compounds with a single P–B bond add readily to unsaturated bonds. Professor Westcott said: “Although research associate Chris Vogels initially made the starting phosphinoboronate esters several years ago, the project didn’t really take off until we assembled a remarkable group of people to conduct this research.” He continued: “Erika was an undergraduate student at the time and initiated the reactivity studies as part of her Honours thesis work. Chris Vogels and Dr. Steve Geier rocked this project and helped design the substrate scope, finished

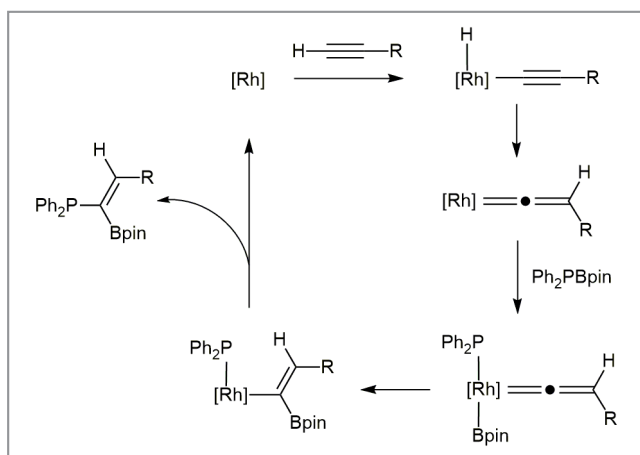
the addition reactions, isolated products and carried out the catalytic work. Dr. Andreas Decken was crucial in solving the challenging molecular structures using X-ray diffraction studies and confirming the nature of the resulting addition products, which was key to our understanding of the 1,1-addition product observed in the unusual reaction with terminal alkynes. Dr. Simon Doherty investigated the computational aspects of this project, provided fundamental insights into the chemistry and co-wrote the publication. The editor of the journal and anonymous reviewers were also exceedingly helpful. It really has been a great team effort all around and everyone played a critical role in the success of this work.”

Highlighted in Scheme 1 are some of the more remarkable reactions covered in this initial study. “Surprisingly, addition of Ph_2PBpin to acridine proceeded at room temperature to give the corresponding 1,4-addition product, named StanSDPhos here because we plan to expand this chemistry by investigating its use as an ambiphilic ligand and in Frustrated Lewis Pair (FLP) chemistry,” said Professor Westcott, who



Scheme 1 Reactions of Ph_2PBpin

continued by explaining that the reduction of pyridine derivatives with other boron agents usually requires the use of a transition metal to facilitate the addition. “Chemoselective reduction of the aldehyde group was observed in reactions with 3-quinolinecarboxaldehyde and one equivalent of Ph_2PBpin ,” he continued. Interestingly, the reaction of *trans*-cinnamaldehyde with Ph_2PBpin gave only the corresponding 1,2-addition product, even though 1,4-addition products are observed predominantly in other borylation reactions. “Finally, the first example of a metal-catalyzed phosphinoboration reaction was reported with terminal alkynes,” said Professor Westcott, “which presumably proceeds via a vinylidene-type mechanism (Scheme 2), to give unusual 1,1-addition products.”



Scheme 2 Possible mechanism for the phosphinoboration of terminal alkynes

Professor Westcott concluded: “We are excited this work has received such positive attention, especially from the groups of Doug Stephan (University of Toronto, Canada) and Elena Fernández (University Rovira i Virgili, Spain), who are now interested in helping us develop this unique reaction. We hope others will want to expand this chemistry and are looking forward to seeing what else these new phosphinoboronate esters can do!”

Matteo Fanello

About the authors



E. N. Daley

Erika N. Daley was born and raised in Halifax, Nova Scotia (Canada). She obtained her BSc (Hons) in chemistry from Mount Allison University (Canada) in 2014. Erika is currently a PhD student at the University of Toronto (Canada) under the guidance of Professor Douglas W. Stephan. She holds an Ontario Graduate Scholarship and was recently awarded the BASF Canada Graduate Student Award. Her current research focuses on investigating the synthesis and reactivity of novel Group 13 cations for hydrogenation catalysis. Erika is also an executive member of the U of T Green Chemistry Initiative and a Science Ambassador at Pueblo Science.



C. M. Vogels

Christopher M. Vogels received his BSc from Mount Allison University (Canada) in 1993 and his MS from New Mexico State University (USA) in 1996 under the supervision of Professor Michael Johnson, studying reactions between potassium ferrate and a variety of arsenic compounds. He has been working with the Wild Toads since 1997 as a Research Associate and Lab Manager and has helped

training hundreds of remarkable undergraduate students. His current research interests include the synthesis of novel transition-metal complexes and the biological activity of boron-containing compounds.



Dr. S. J. Geier

Stephen J. Geier is a native of Sackville, New Brunswick (Canada). He completed his BSc at Mount Allison University (Canada) and went on to pursue his PhD at the University of Windsor (Canada) under the supervision of Dr. Douglas W. Stephan. His PhD work focused on Frustrated Lewis Pair (FLP) chemistry. He accompanied Dr. Stephan in his move to the University of Toronto (Canada). Following the completion of his PhD in 2010, he spent two years as an NSERC Postdoctoral Fellow in the lab of Dr. Jeffrey R. Long at the University of California, Berkeley (USA). He then returned to Sackville to help old man Westcott and has been a Research Associate with the Wild Toads at Mount Allison University since January 2013. His research interests include all things boron.

>>



Dr. A. Decken

Andreas Decken was born in Germany in 1964 and received his Diplom from the University of Duisburg (Germany) in 1989. He obtained his PhD from McMaster University (Canada) under the guidance of Michael J. McGlinchey in 1993. He continued his work at UT Austin (USA) as a Postdoctoral Fellow with Alan H. Cowley and in 1995 joined the Chemistry Department at the University of New Brunswick (Canada), Fredericton. He is currently Senior Research Associate focusing on small-molecule crystallography.



Dr. S. Doherty

Simon Doherty was awarded first class honors in Chemistry in 1987 and a PhD in 1990 with Professor A. J. Deeming at University College London (UK). He then conducted postdoctoral research with Professor Arthur J. Carty at the University of Waterloo (Canada) and with Professor Malcolm Chisholm at Indiana University (USA). In 1995, Simon was appointed as a Lecturer in Chemistry at Newcastle University (UK) and after a three-year appointment at Queens University Belfast (UK) (2000–2003) he returned to Newcastle where he is currently a

Senior Lecturer in Organometallic Chemistry and Catalysis and Director of Newcastle University Catalysis (NUCAT). His research interests are wide-ranging in organophosphorus and boron chemistry. More recent endeavors have been exploring the concept and applications of polymer-immobilized ionic-liquid-phase (PIILP) catalysis.



Prof. S. A. Westcott

Stephen A. Westcott was born in the sixties somewhere around Tecumseh and received his PhD from the University of Waterloo (Canada) under the joint supervision of Drs Todd B. Marder (now at Universität Würzburg, Germany) and R. Tom Baker (now at the University of Ottawa, Canada). He was an NSERC postdoctoral fellow, where he spent one year working with Dr. Lanny Liebeskind (Emory University, USA) and then another year working with Dr. Maurice Brookhart (University of North Carolina, USA). He has been at Mount Allison University (Canada) since 1995 and is currently a Canada Research Chair in Boron Chemistry. His research interests include catalysis and the synthesis and development of biologically active boron and transition-metal compounds. His research group is called the Wild Toads and it is best not to ask why.

Organocatalytic Enantioselective Formal C(sp²)-H Alkylation

J. Am. Chem. Soc. **2015**, *137*, 130–133

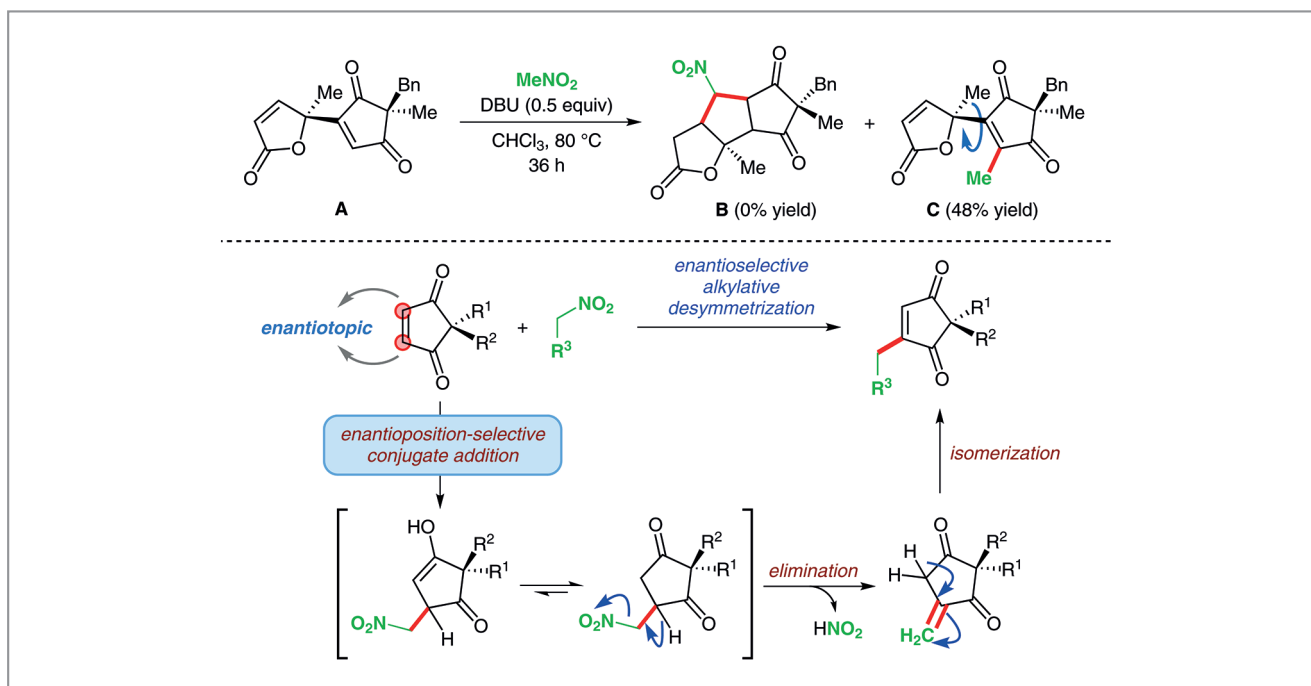
Organic compounds are characterized by the presence of various C–H bonds. Functionalization of a specific C–H bond in a molecule with a selected atom or group is among the most straightforward and desirable synthetic transformations in organic chemistry. This seemingly simple transformation is in fact a daunting challenge and often involves fancy or expensive reagents/catalysts and requires multiple synthetic steps. The present decade is witnessing a boom in direct C–H functionalization reactions. This field is dominated by transition-metal catalysts and the regioselectivity is almost always dictated by a directing group present within the same molecular framework. While the direct functionalization of C–H bonds with a functionalized alkyl group became possible through this approach, replacement of ‘H’ with a simple, non-functionalized alkyl group remained elusive.

The group of Professor Santanu Mukherjee at the Indian Institute of Science (Bangalore, India) has now developed a simple protocol for the direct alkylation of olefinic C(sp²)-H bonds, not only enantioselectively using an organocatalyst but more importantly without having to use any directing group.

“The C(sp²)-H alkylation itself does not generate any stereocenter at the reaction site, so an enantioselective alkylation must rely on a desymmetrization approach,” said Professor Mukherjee. “Prochiral 2,2-disubstituted cyclopentene-1,3-diones were chosen as the substrate, considering the wide abundance of chiral cyclopentane derivatives in many natural and non-natural bioactive molecules.”

Professor Mukherjee explained: “Desymmetrization has this unique advantage of setting up stereocenters away from the reaction site.” While choosing this class of substrates, Professor Mukherjee and graduate student Madhu Sudan Manna realized that an enantioselective C–H alkylation would represent an ideal desymmetrization – one where no additional stereocenter would be generated and the existing functionalities would remain intact.

Such reactions are conventionally carried out following a two-step sequence consisting of an asymmetric conjugate addition and oxidation, and require expensive and air-sensitive metalloalkyl reagents. The group’s aim was to achieve this transformation in a single step using an easily accessible,



Scheme 1 Discovery of nitroalkane as the alkyl source and the mechanistic hypothesis of the alkylative desymmetrization

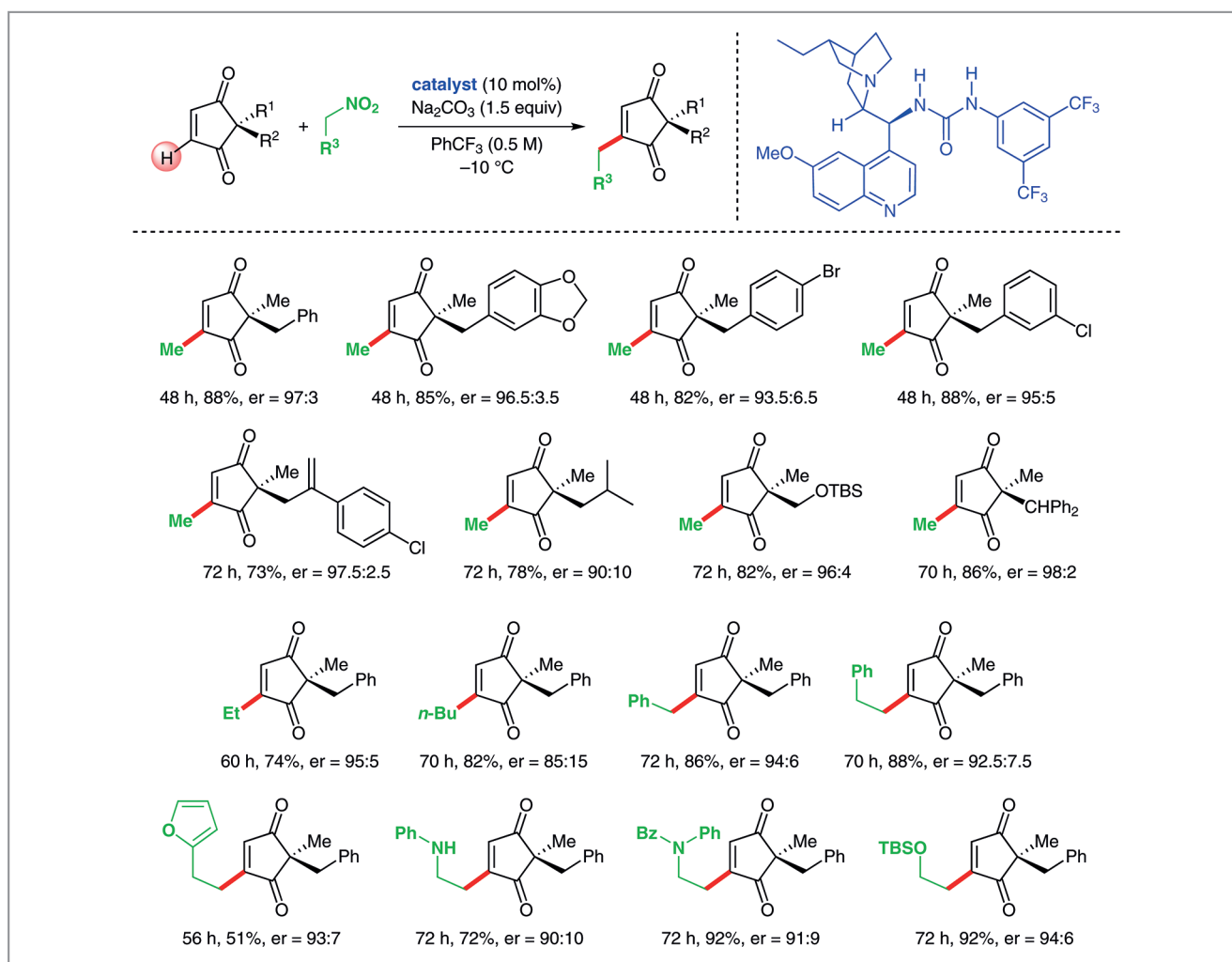
inexpensive and air-stable alkyl source. This was obviously not a trivial task.

Professor Mukherjee explained: “In a somewhat different context, our attempt to synthesize the tricyclic compound **B** from **A** through the double Michael addition of nitromethane under DBU failed and led to the formation of ‘something else’ as ‘1:1 mixture’ according to NMR (Scheme 1). Luckily, my PhD student Mr. Madhu Sudan Manna took some time to figure out the structure of this ‘undesired’ product and found it to be the C(sp²)-H-methylated product **C** as a mixture of two atropisomers.” Clearly, nitromethane was acting as the source of the methyl group in this reaction. Even though this was surprising at first glance, the leaving group ability of nitro functions is well documented in the literature. This ‘failed’ experiment laid the foundation for the present work.

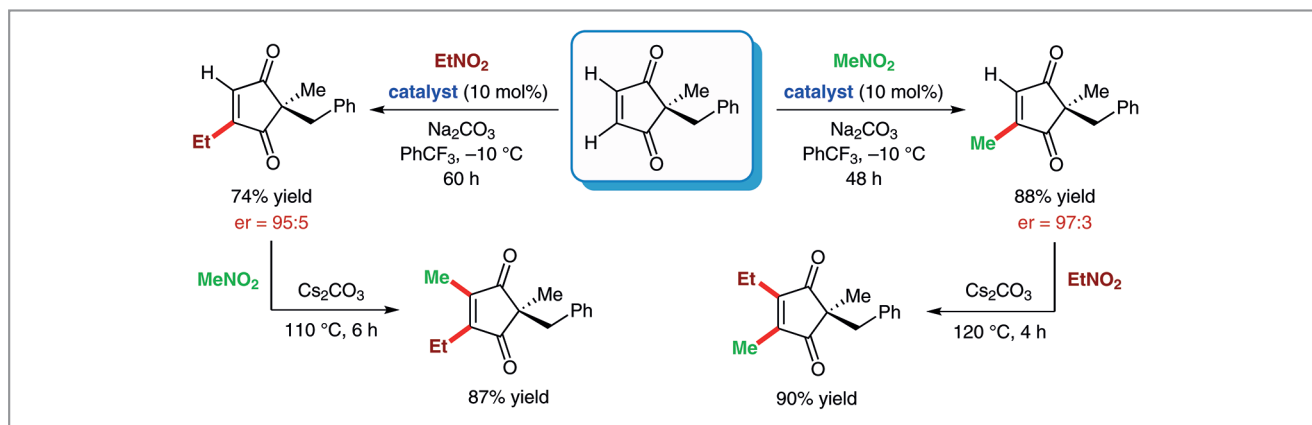
“Once we deciphered the mechanism of this reaction,” said Professor Mukherjee, “its potential became clear to us.”

“We immediately realized that an enantioselective conjugate addition to prochiral 2,2-disubstituted cyclopentene-1,3-diones is all that is required to achieve an alkylative desymmetrization,” he continued. “We were convinced, based on our previous experience, that bifunctional tertiary amino(thio)urea derivatives could do this job.” The choice of this catalyst candidate, however, gave rise to another issue. Since nitrous acid is a byproduct of this reaction, effective catalyst turnover would require the presence of a terminal base – one which would not catalyze the (non-selective) conjugate addition.

A rigorous yet systematic optimization study then established dihydroquinine-derived urea as the optimum catalyst and Na₂CO₃ as the terminal base. Finally, the organocatalytic



Scheme 2 Organocatalytic enantioselective C(sp²)-H alkylation: representative examples



Scheme 3 Synthesis of unsymmetrical tetrasubstituted olefins by double C(sp²)-H alkylation

enantioselective C(sp²)-H alkylation was achieved, showing broad substrate scope in terms of both the prochiral electrophiles and the nitroalkanes (Scheme). Functionalized nitroalkanes could also be used for introducing functionalized alkyl groups. In almost all cases, the products were obtained in high yield.

“An advantage of our C(sp²)-H alkylation protocol is that the desymmetrized products can be further alkylated,” said Professor Mukherjee. Using a different nitroalkane under elevated temperature, unsymmetrical tetrasubstituted olefins were obtained. “An even more remarkable feature is that, simply by changing the sequence of nitroalkanes, both the product enantiomers can be obtained under the influence of a single catalyst antipode (Scheme 3),” said Professor Mukherjee. “These compounds would be very difficult to synthesize by other means. To demonstrate the usefulness of this double alkylation protocol, the core structure of an antibiotic natural product (+)-madindoline B was synthesized.”

“To summarize, a highly enantioselective organocatalytic olefinic C(sp²)-H alkylation has been developed in our labs,” said Professor Mukherjee. “This alkylative desymmetrization of prochiral 2,2-disubstituted cyclopentene-1,3-diones makes use of inexpensive, easily accessible and air-stable nitroalkanes as the alkyl source, and generates synthetically useful five-membered carbocycles containing an all-carbon quaternary stereogenic center remote from the reaction site. This, to the best of our knowledge, is the first example of the use of nitroalkane as the alkyl source in an enantioselective transformation. We believe this work will inspire the development of other alkylative and related transformations including desymmetrizations,” concluded Professor Mukherjee.

Professor Erick M. Carreira (ETH Zurich, Switzerland), a SYNTHESIS and SYNFACTS Editorial Board member, com-

mented: “Mukherjee has managed to brilliantly amalgamate various concepts to generate a valuable synthetic transformation, and one that promises to impact the synthesis of complex structures at the level of both tactics and strategy. An optically active urea organocatalyst is employed to effect an enantioselective desymmetrization reaction of an achiral Michael acceptor bearing a quaternary prostereogenic center with nitroalkanes. But that is just the beginning: Mukherjee relies on the unique aspects of the nitro group as a ‘chemical chameleon’, in which it serves to enable the generation of a nucleophile and subsequently, having done its job marvelously, itself serves as a leaving group, or electrofuge. The end result of the reaction is the generation of optically active products that are not otherwise easily prepared. It is truly spectacular... I wish I had thought of it myself!”

Madhu Manna

About the authors



M. S. Manna

Madhu Sudan Manna received his B.Sc. (Chemistry Hons.) from Bajkul Milani Mahavidyalaya, West Bengal (India) in 2008, and his M.Sc. (Chemistry) from the Indian Institute of Technology, Guwahati (India) in 2010. He is currently pursuing his Ph.D. at the Indian Institute of Science, Bangalore (India) under the supervision of Professor Mukherjee. His research interests include the application of asymmetric organo-

>>

catalysis for studying vinylogous nucleophilic reactivity including asymmetric desymmetrization reactions.



Prof. S. Mukherjee

After receiving his M.Sc. from Indian Institute of Technology, Kanpur (India) in 2000, **Santanu Mukherjee** earned his Ph.D. (*summa cum laude*) in 2006 working with Professor Albrecht Berkessel at the Universität zu Köln (Germany). He worked as a Postdoctoral Fellow with Professor Benjamin List at the Max-Planck Institut für Kohlenforschung in Mülheim an der Ruhr (Germany) during 2006–2008 and with Professor E. J. Corey at Har-

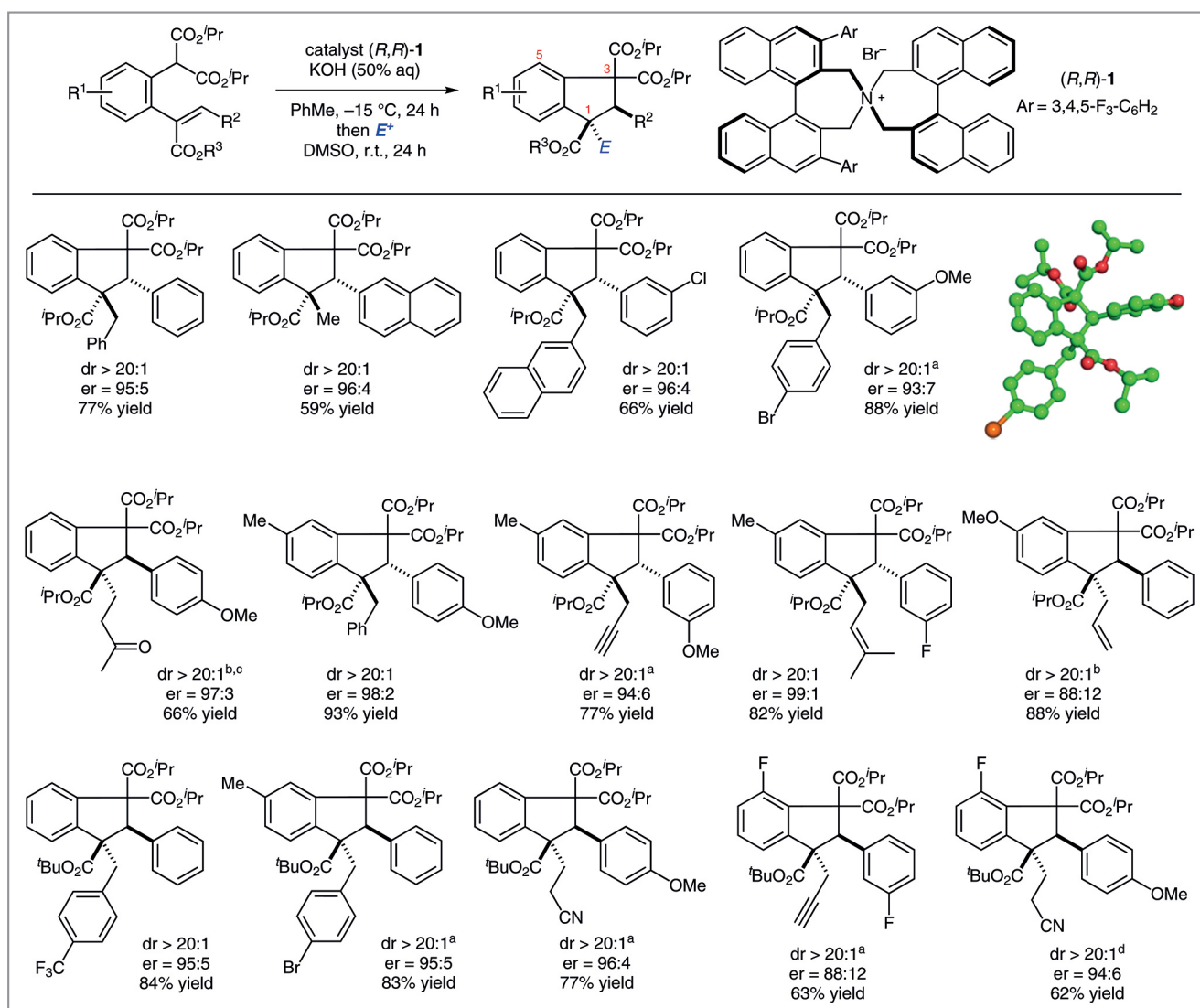
vard University (USA) during 2008–2010. In 2010, he joined the Department of Organic Chemistry at Indian Institute of Science, Bangalore (India) as an Assistant Professor. His research interests revolve around various aspects of asymmetric catalysis. He is a recipient of the Thieme Chemistry Journals Award (2011) and the Indian National Science Academy (INSA) Medal for Young Scientists (2014).

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

Nature Chem. **2015**, *7*, 171–177

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 Uni-

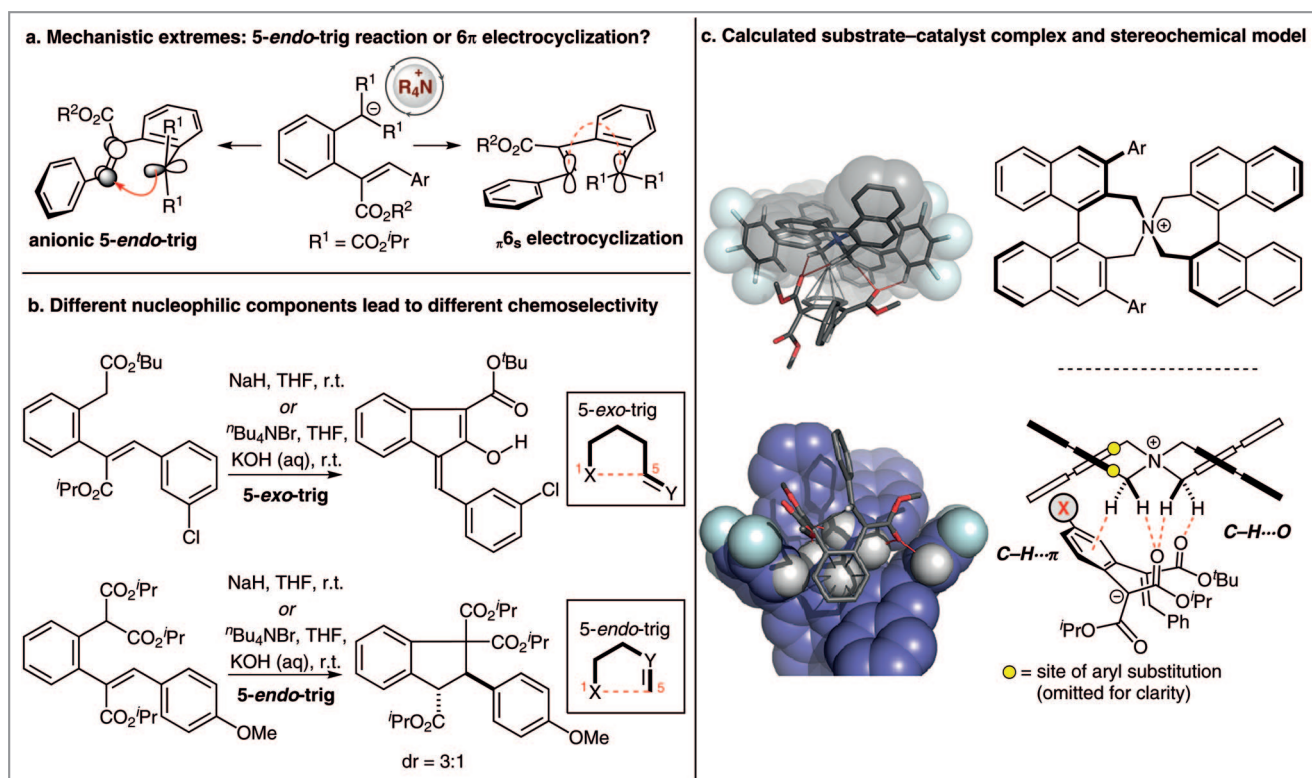
versity of Oxford (UK) has been interested in the application of asymmetric phase-transfer catalysis to new reaction manifolds – particularly cyclizations – for some time. “We reasoned that chiral ammonium salts could potentially discriminate between the π -faces of a delocalized anion, which could offer



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 6 π 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."

Mattes Fank

About the authors



Dr. C. Johnston

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.



Dr. A. Kothari

Abhishek Kothari studied pharmacy at Nagpur University, India (BPharm, 2003) and the National Institute of Pharmaceutical Education and Research, Mohali, India (MTech, 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 electrocyclic 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.



K. Jackson

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.



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.

>>

*T. Sergeieva*

Tetiana Sergeieva completed a Bachelor's degree (2008) at Kirovohrad State Pedagogical University (Ukraine), and an MSc degree in chemistry (2009) from Oles Honchar Dnipropetrovsk National University. She is currently a PhD student in the collaborative double PhD program established by Oles Honchar Dnipropetrovsk National University and Jackson State University. In 2014, Tetiana was awarded a scholarship to the University of Oxford, where she worked in Robert Paton's group. Her research interests are focused on quantum-chemical investigations of ring-formation and transformation mechanisms.

*Prof. R. Paton*

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.

*Prof. M. Smith*

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.

Coming soon

— Literature Coverage

Difluorohomologation of Ketones

— Literature Coverage

Organocatalysis Meets Visible Light Meets Carbon Monoxide

— Literature Coverage

4-Trimethylsilyl-5-iodo-1,2,3-triazole: A Key Precursor for the Divergent Syntheses of 1,5-Disubstituted 1,2,3-Triazoles

Further highlights

Synthesis **Review: Recent Advances in the N-Heterocyclic Carbene (NHC)-Organocatalyzed Stetter Reaction and Related Chemistry**

(by A. T. Biju et al.)

Synlett **Account: In Vitro Reconstitution of Metabolic Pathways: Insights into Nature's Chemical Logic**

(by C. Khosla)

Synfacts **Synfact of the Month in category "Organocatalysis": Facile Access to β^2 -Amino Esters via NHC-Catalysis**

For current SYNFORM articles, please visit www.thieme-chemistry.com
 SYNFORM issue 2015/06 is available from May 18, 2015
 at www.thieme-connect.com/ejournals

Editor

Matteo Zanda, NRP Chair in Medical Technologies, Institute of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen, AB25 2ZD, UK and
 C.N.R. – Istituto di Chimica del Riconoscimento Molecolare
 Via Mancinelli, 7, 20131 Milano, Italy
 Editorial Assistant: Alison M. Sage
synform@outlook.com; fax: +39 02 23993080

Editorial Office

— Managing Editor: Susanne Haak,
susanne.haak@thieme.de, phone: +49 711 8931 786
 — Scientific Editor: Selena Boothroyd,
selena.boothroyd@thieme.de
 — Scientific Editor: Stefanie Baumann,
stefanie.baumann@thieme.de, phone: +49 711 8931 776
 — Scientific Editor: Michael Binanzer,
michael.binanzer@thieme.de, phone: +49 711 8931 788
 — Assistant Scientific Editor: Christiane Kemper,
christiane.kemper@thieme.de, phone: +49 711 8931 785
 — Senior Production Editor: Thomas Loop,
thomas.loop@thieme.de, phone: +49 711 8931 778
 — Production Editor: Helene Ott,
helene.ott@thieme.de, phone: +49 711 8931 929
 — Production Editor: Thorsten Schön,
thorsten.schoen@thieme.de, phone: +49 711 8931 781
 — Editorial Assistant: Sabine Heller,
sabine.heller@thieme.de, phone: +49 711 8931 744
 — Marketing Manager: Julia Stötzner,
julia.stoetznern@thieme.de, phone: +49 711 8931 771
 — Postal Address: Synthesis/Synlett/Synfacts, Editorial Office, Georg Thieme Verlag KG,
 Rüdigerstraße 14, 70469 Stuttgart, Germany,
 — Homepage: www.thieme-chemistry.com

Publication Information

Synform will be published 12 times in 2015 by Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany, and is an additional online service for Synthesis, Synlett and Synfacts.

Publication Policy

Product names which are in fact registered trademarks may not have been specifically designated as such in every case. Thus, in those cases where a product has been referred to by its registered trademark it cannot be concluded that the name used is public domain. The same applies as regards patents or registered designs.

Ordering Information for Print Subscriptions to Synthesis, Synlett and Synfacts

The Americas: Thieme Publishers New York, Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA.

Via e-mail: customerservice@thieme.com

Via website: www.thieme-chemistry.com

Phone: +1 212 760 0888; Fax: +1 212 947 1112

Order toll-free within the USA: +1 800 782 3488

Europe, Africa, Asia, and Australia: Thieme Publishers Stuttgart, Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany.

Via e-mail: customerservice@thieme.de

Via website: www.thieme-chemistry.com

Phone: +49 711 8931 421; Fax: +49 711 8931 410

Current list prices are available through www.thieme-chemistry.com.

Online Access

The online versions of Synform as well Synthesis, Synlett and Synfacts are available through www.thiemeconnect.com/products/ejournals/journals where it is also possible to register for a free trial account. For information on multi-site licenses and pricing for corporate customers as well as backfiles, please contact our regional offices:

The Americas: esales@thieme.com, phone: +1 212 584 4695

Europe, Africa, Asia, and Australia: eproducts@thieme.de, phone: +49 711 8931 407

India: eproducts@thieme.in, phone +91 120 45 56 600

Japan: brhosoya@poplar.ocn.ne.jp, phone +81 3 3358 0692

Manuscript Submission to Synthesis and Synlett

Manuscript submissions will be processed exclusively online via <http://mc.manuscriptcentral.com/synthesis> and <http://mc.manuscriptcentral.com/synlett>, respectively. Please consult the Instructions for Authors before compiling a new manuscript. The current version and the Word template for manuscript preparation are available for download at www.thieme-chemistry.com.

Copyright

This publication, including all individual contributions and illustrations published therein, is legally protected by copyright for the duration of the copyright period. Any use, exploitation or commercialization outside the narrow limits set by copyright legislation, without the publisher's consent, is illegal and liable to criminal prosecution. This applies to translating, copying and reproduction in printed or electronic media forms (databases, online network systems, Internet, broadcasting, telecasting, CD-ROM, hard disk storage, microcopy edition, photomechanical and other reproduction methods) as well as making the material accessible to users of such media (e.g., as online or offline backfiles).

Copyright Permission for Users in the USA

Authorization to photocopy items for internal or personal use, or the internal or personal use of specific clients, is granted by Georg Thieme Verlag KG Stuttgart · New York for libraries and other users registered with the Copyright Clearance Center (CCC) Transactional Reporting Service, provided that the base fee of US\$ 25.00 per copy of each article is paid directly to CCC, 22 Rosewood Drive, Danvers, MA 01923, USA, 0341-0501/02.