ROYAL SOCIETY OF CHEMISTRY

20-23 March 2016, University of California, Irvine, USA

Challenges in Organic Chemistry

ISACS19

#ISACS

Book of Abstracts

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ROYAL SOCIETY OF CHEMISTRY

Welcome letter

Dear Participant,

On behalf of the Royal Society of Chemistry, and the ISACS19 Scientific Organising Committee we welcome you to Irvine and the nineteenth International Symposium on Advancing the Chemical Sciences (ISACS).

This significant global symposia series supports the Royal Society of Chemistry's flagship journal *Chemical Science*. Now in its seventh volume, *Chemical Science* has already established itself as a leading journal in the field, publishing research of the most exceptional quality and impact across the chemical sciences.

With all articles in *Chemical Science* now being published Open Access, and with Article Processing Charges (APCs) being waived for at least two years from 2015, some of the very best chemistry research is now available free to publish and free to read.

The ISACS conference series continues to focus on key challenges across the broad chemistry field. In the coming years we look forward ISACS symposia to be held across multiple continents, including:

- Challenges in Organic Chemistry, 20 - 23 March 2016, Irvine, United States
- Challenges in Challenges in Nanoscience, 10 - 12 November 2016, Beijing, China
- International Symposium on Macrocyclic and Supramolecular Chemistry in conjunction with ISACS: Challenges in Organic Materials & Supramolecular Chemistry, 2 - 6 July 2017, Cambridge, UK

Each ISACS event draws together a dynamic group of internationally renowned speakers to discuss recent topical developments and challenges in their own research field.

The programme for this meeting features a single stream of plenary lectures, complemented by contributed talks. We have been delighted with the quality of the oral abstracts submitted for consideration and are certain that these shorter talks add further weight to an already impressive and exciting line-up of plenary lectures. We thank all speakers and poster presenters for their contributions and the Scientific Committee for their assistance in assembling such a high quality programme.

In addition to the excellent lecture programme, and the associated poster sessions, the conference provides a superb opportunity to meet your peers, build relationships and exchange views on recent scientific developments.

We hope you will have an interesting, challenging and informative time whilst in Irvine. Thank you for joining us in this fantastic city for this important international event; we hope you enjoy your stay and leave inspired by the presentations, posters and discussions.

Best regards,

Professor Vy Dong
University of California, Irvine
Co-Chair ISACS19

Dr May Copsey
Executive Editor, General Chemistry
Royal Society of Chemistry

Conference sessions

The main conference will run from Sunday 20 – Wednesday 23 March 2016 and will take place at the Arnold and Mabel Beckman Center of the National Academies of Sciences and Engineering

The Scientific Committee warmly invites you to take part in ISACS19 and looks forward to welcoming you to Irvine, California.

Poster sessions

Two formal poster sessions have been scheduled. We request that presenters man their poster boards for the first half an hour of each session. During the poster sessions the number displayed at the bottom of the abstract in this book correlates to the poster board where it will be displayed.

Monday 21 March
Poster Session 1: 15:35 – 17:05 Odd numbered posters

Tuesday 22 March
Poster Session 2: 15:30 – 17:00 Even numbered posters

Sponsors

We would like to thank the following for their generous sponsorship support of ISACS19

Conference information

All sessions will take place in the Auditorium and the poster sessions, refreshments and lunches will take place in the Atrium.

WiFi

Please see the registration desk for the code.

Catering

Sunday 20 March:
Arrival coffee and lunch, afternoon coffee and the welcome drinks reception with canapés. Please note that no dinner is provided on Sunday 20 March.

Monday 21 – Tuesday 22 March:
All daytime catering is provided on Monday 21 and Tuesday 22 March (refreshments and lunch) but no dinners are provided and the evenings are free for delegates to explore the surrounding area.

Wednesday 23 March:
Morning refreshments along with bagels will be provided but please note that there will be no lunch on this day.

Hotel transfer information

Accommodation is not included in your registration fee.

The conference offered preferential rates at the Wyndham Irvine Hotel and will provide coach transport to and from this hotel at the following times each day:

Sunday 20 March:
Beckman Center to Wyndham Irvine Hotel at 19:00

Monday 21 March:
Wyndham Irvine Hotel to Beckman Center at 08:30
Beckman Center to Wyndham Irvine Hotel at 18:30

Tuesday 22 March:
Wyndham Irvine Hotel to Beckman Center at 08:30
Beckman Center to Wyndham Irvine Hotel at 17:45

Wednesday 23 March:
Wyndham Irvine Hotel to Beckman Center at 08:30

(please note, all timings printed here are subject to change – please see the registration desk for the most recent timings)

Invited speaker biographies

Ashraf Brik
Technion - Israel Institute of Technology, Israel

Ashraf Brik is a Professor of Chemistry at the Schulich Faculty of Chemistry in the Technion-Israel Institute of Technology. Brik received his B.Sc. in Chemistry from the Ben-Gurion University of the Negev (1996) and his M.Sc. degree in Organic Chemistry from the Technion-Israel Institute of Technology (1998). His Ph.D. was obtained in 2001 from the Faculty of Chemistry in the Technion in Bioorganic Chemistry. From 2002 to 2006, Brik was a Research Associate in the Scripps Research Institute. In 2007, Brik joined the Department of Chemistry in the Ben-Gurion University of the Negev as an Assistant Professor and was promoted to an Associate Professor in 2011 and to a Full Professor in 2012. In 2015, Brik Joined the Schulich Faculty of Chemistry in the Technion. Brik is well known for his contributions for the development of chemical approaches to prepare posttranslationally modified proteins for biochemical, biophysical and functional analyses. Professor Brik is the recipient of the Bessel Award of the Humboldt Foundation for 2015, the 11th Hirata Award, Teva Award for Excellence in memory of Eli Hurvitz for 2013, the Tetrahedron Young Investigator Award in Bioorganic and Medicinal Chemistry for 2013 and the 2011 Israel Chemical Society prize for Outstanding Young Chemist.

Darren Dixon
University of Oxford, UK

Darren J. Dixon graduated (first class honours) and obtained his D. Phil from the University of Oxford, where he worked with Prof. S. G. Davies. In 1997 he moved to the University of Cambridge to carry out post-doctoral work with Prof. S. V. Ley FRS. He began his independent career in 2000 at Cambridge before moving in 2004 to a Senior Lecturership at The University of Manchester. In 2007 he was promoted to Reader and in 2008 he moved to his current post as Professor of Chemistry at the University of Oxford where he holds the Knowles-Williams Tutorial Fellowship in Organic Chemistry at Wadham College.

His research interests lie predominantly in the field of asymmetric catalysis where he has ongoing research programs developing practicable and synthetically powerful methodologies, based on the harnessing of new chemical reactivity or cascades of chemical reactivity, that allow the highly enantio- and diastereocontrolled formation of difficult-to-access, structural/stereochemical motifs common to biologically relevant complex natural products and pharmaceutical or agrochemical compounds.

He has received several awards including a prestigious EPSRC Leadership Fellowship (2008-2013), the AstraZeneca Research Award in Organic Chemistry (2010), the Royal Society of Chemistry's inaugural Catalysis in Organic Chemistry Award (2010), the Novartis Lectureship in Central Europe (2011), the Andrew S. Kende Distinguished Lectureship at the University of Rochester (2013), the Fred Pattison Distinguished Lectureship at Northwestern University, Ontario, Canada and the Novartis Chemistry Lectureship (2016-2017). He is a member of the scientific advisory board of AVRA laboratories (Hyderabad), serves as an Associate Editor for the Beilstein Journal of Organic Chemistry, serves on the Consulting Board of Editors of Tetrahedron/Tetrahedron Letters (2015-present) and is the PI and Director of the EPSRC Centre for Doctoral Training in 'Synthesis for Biology and Medicine' in Oxford (2014-present).

Michelle Chang
University of California, Berkeley, USA

Michelle C. Chang earned a B.Sc. in Biochemistry and in French Literature at the University of California in San Diego in 1997. This was followed by research as a National Science Foundation Predoctoral Fellow from 1997 to 2000 and as a M.I.T./ Merck Foundation Predoctoral Fellow between 2000-2002. In 2004 she obtained her Ph.D. at the Massachusetts Institute of Technology with Professor JoAnne Stubbe and Professor Daniel G. Nocera. After a Postdoctoral Fellowship at the University of California, Berkeley, she joined the faculty where she is currently an Associate Professor in the Department of Chemistry.

The Chang laboratory utilizes the approaches of mechanistic biochemistry, molecular and cell biology, metabolic engineering, and synthetic biology to address problems in energy and human health. Her group designs and creates new biosynthetic pathways in microbial hosts for in vivo production of biofuels from abundant crop feedstocks and pharmaceuticals from natural products or natural product scaffolds.

Michelle's honors and awards include Camille and Henry Dreyfus Foundation New Faculty Award (2007), Arnold and Mabel Beckman Foundation Young Investigator Award (2008), Technology Review TR35 Young Innovator Award (2008), BayBio Rising Star Award (2008), NSF, CAREER (2009), Agilent Early Career Award (2010), Hellman Foundation Faculty Award (2010), American Chemical Society-Sociedade Brasileira de Química Young Talents in Science Award (2011), NIH New Innovator Award (2011), DARPA Young Faculty Award (2012), Iota Sigma Pi Agnes Fay Morgan Award (2012), Paul Saltman Award in Bioinorganic Chemistry (2013), 3M Young Faculty Award (2013), Camille Dreyfus Teacher-Scholar Award (2013).

Seth Herzon
Yale University, USA

Seth Herzon was born in Philadelphia, Pennsylvania in 1979 and graduated from Valley Forge Military Academy (Wayne, PA) in 1997. In 1998, he began his undergraduate studies at Temple University (Philadelphia, PA). There he conducted research in the laboratories of Professor Grant R. Krow, studying the synthesis and chemistry of highly strained azabicyclohexanes [such as N-(tert-butoxycarbonyl)-2-azabicylo[2.1.1]hexane]. In 2002 he moved to Cambridge, MA to begin his graduate studies at Harvard University. Under the guidance of Professor Andrew G. Myers, he developed enantioselective syntheses of the complex antiproliferative alkaloids avrainvillamide and stephacidin B. After graduating in 2006, he moved to the University of Illinois, Urbana-Champaign, to begin postdoctoral studies with Professor John F. Hartwig. At the U of I he was engaged in the study of new transition metal-mediated C–H bond functionalization reactions and the development of new methods for reaction discovery. In 2008 he joined the Department of Chemistry at Yale University as Assistant Professor of Chemistry. He was promoted to Associate Professor of Chemistry in 2012, and in 2013 was appointed to Professor of Chemistry.

Kami Hull
University of Illinois at Urbana-Champaign, USA

Kami L. Hull received her B.A. degree in chemistry from Macalester College in 2003. She obtained her Ph.D. from the University of Michigan in 2009 under the mentorship of Prof. Melanie S. Sanford. She went on to be an NIH postdoctoral fellow at Stanford University from 2009–2012 in the laboratory of Prof. Barry M. Trost. Professor Hull joined the faculty at the University of Illinois in the fall of 2012.

Ning Jiao
Peking University, China

Ning Jiao received his PhD degree (2004) (with Prof. Shengming Ma) at Shanghai Institute of Organic Chemistry (SIOC), CAS. He spent 2004–2006 as an Alexander von Humboldt postdoctoral fellow with Prof. Manfred T. Reetz at Max Planck Institute fur Kohlenforschung. In 2007, he joined the faculty at Peking University as an Associate Professor, and was promoted to Full Professor in 2010. His current research efforts are focused on: 1) To develop green and efficient synthetic methodologies through Single Electron Transfer (SET) process; 2) Aerobic oxidation, Oxygenation and Nitrogenation reactions; 3) The first-row transition metal catalysis and the inert chemical bonds activation. Dr. Jiao has receives several awards in recognition of his scientific achievements that include: Fellow of The Royal Society of Chemistry (2015), Roche Chinese Young Investigator Award (2014), The National Science Fund for Distinguished Young Scholars (2013), Thieme Chemistry Journal Award (2013), and The Chinese Homogenous Catalysis Young Chemist Award (2013). He is currently advisory board member of *Scientific Reports, Heterocyclic Communication*, and *Natural Product against Cancer*.

Yamuna Krishnan
University of Chicago, USA

Yamuna Krishnan, is a Professor and Brain Research Foundation Fellow of Chemistry and the Grossman Institute of Neuroscience at the University of Chicago. She received a PhD from the Indian Institute of Science, Bangalore and pursued her postdoctoral studies as an 1851 Research Fellow at the University of Cambridge, UK, with Shankar Balasubramanian. She set up her group at the NCBS, Bangalore, in 2005 that focuses on intelligent DNA-based molecular devices to interrogate cellular processes. Selected honors include the Shanti Swarup Bhatnagar Award in Chemical Sciences, the Wellcome Trust Senior Fellowship, the AVRA Young Scientist Award, Associateship of the Indian Academy of Sciences, the Innovative Young Biotechnologist Award, the INSA Young Scientist Medal, the YIM Boston Young Scientist Award and most recently featured on *Cell's* 40 under 40.

James Nowick
University of California, Irvine, USA

James Nowick is a Professor of Chemistry at the University of California, Irvine. He received his A.B. (Bachelors) degree in Chemistry in 1985 from Columbia University and his Ph.D. degree in Organic Chemistry in 1990 from MIT, where he was both an NSF Graduate Fellow and an ACS Division of Organic Chemistry Graduate Fellow. After an NSF postdoctoral fellowship in supramolecular chemistry at MIT, he began his independent career as an Assistant Professor at UCI in 1991. He was promoted to Associate Professor in 1996 and Professor in 1998. His research interests include peptidomimetic chemistry, molecular recognition, and supramolecular chemistry. In recognition of his scientific contributions, he has received a Camille and Henry Dreyfus Foundation New Faculty Award, an American Cancer Society Junior Faculty Research Award, an NSF Young Investigator Award, an Arnold and Mabel Beckman Foundation Young Investigator Award, a Presidential Faculty Fellow Award, a Camille Dreyfus Teacher-Scholar Award, an Alfred P. Sloan Research Fellowship, and an American Chemical Society Arthur C. Cope Scholar Award. He is a Fellow of the American Association for the Advancement of Science. For his contributions to research and education at UCI, he has received the Award for Outstanding Faculty Contribution to Undergraduate Research, the Chancellor's Award for Excellence in Undergraduate Research, and the School of Physical Sciences Award for Outstanding Contributions to Undergraduate Education.

Kyoko Nozaki
University of Tokyo, Japan

Kyoko Nozaki (center) received her B.Sc. in 1986 and her Ph.D. in 1991 from Kyoto University under the guidance of Professor Kiitiro Utimoto. During her Ph.D. study, she joined Professor Clayton H. Heathcock's group at the University of California at Berkeley as an exchange student. In 1991, she started her research career as an instructor at Kyoto University, became an associate professor in 1999, and then moved to the University of Tokyo as an associate professor in 2002. Since 2003, she is a full professor at the University of Tokyo. Her accomplishments include the Chemical Society of Japan Award for Young Chemists (1998), the Organometallic Chemistry directed towards Organic Synthesis (OMCOS) (2003), the SPSJ Wiley Award (2004), the Japan IBM Science Award (2005), the Mukaiyama Award (2008), the Saruhashi Prize (2008), and the Mitsui Chemicals Catalysis Science Award (2009), 40th Annual G. Stafford Whitby Lecturer, The Univ of Akron (2013), The Award of the Society of Polymer Science, Japan (2013), Schlenk Lecturer, Universität Tübingen (2013), 1st Casey Lecturer, University of Wisconsin, Madison (2014), Tarrant Lecturer, University of Florida (2015), and The ACS Arthur K. Doolittle Award (2015). Her research interest is focused on development of homogeneous catalysts for organic synthesis and polymer synthesis.

Nicola Pohl
Indiana University, USA

Nicola Pohl, professor of chemistry and the Joan and Marvin Carmack Chair in Bioorganic Chemistry, received her B.A. degree from Harvard College in 1991 and her Ph.D. in chemistry from the University of Wisconsin-Madison in 1997. Following an NIH Postdoctoral Fellowship in the Department of Chemical Engineering at Stanford University, she joined the faculty at Iowa State University in the fall of 2000. She was a professor of chemistry and of chemical and biological engineering and held the Wilkinson Professor of Interdisciplinary Engineering at Iowa State University before moving to Indiana University in summer 2012. Her work has been recognized with a National Science Foundation CAREER Award, Cottrell Scholar Award, a Sloan Foundation Fellowship, and the Horace S. Isbell Award. She has served as co-chair of the Carbohydrates Gordon Research Conference and Chair of the Carbohydrate division of the American Chemical Society. She currently serves on the editorial advisory boards of *Organic Letters* and *The Journal of Organic Chemistry*.

Peter Seeberger
Max-Planck Institute of Colloids and Interfaces, Germany

Peter H. Seeberger studied chemistry in Erlangen (Germany) and completed a PhD in biochemistry in Boulder (USA). After performing research at the Sloan-Kettering Cancer Center Research in New York he built an independent research program at MIT where he was promoted to Firmenich Associate Professor of Chemistry with tenure. After six years as Professor at the ETH Zurich he assumed positions as Director at the Max-Planck Institute for Colloids and Surfaces in Potsdam and Professor at the Free University of Berlin in 2009.

Professor Seeberger's research on the chemistry and biology of carbohydrates and continuous flow synthesis spans a broad range of topics from engineering to immunology and has been documented in over 400 peer-reviewed journal articles, four books and more than 35 patents. This work was recognized with more than 25 international awards from the US (e.g. Hudson Award from the ACS), Germany (e.g. Körber Prize), Holland, Israel, Japan, Switzerland and international organizations. In 2013 he was elected to the Berlin-Brandenburg Academy of Sciences.

Peter H. Seeberger serves as the Editor-in-Chief of the *Beilstein Journal of Organic Chemistry* and is a co-founder of the *Tesfa-Ilg "Hope for Africa" Foundation*. The research in the Seeberger laboratory has given rise to several companies in the USA and Germany.

RB Sunoj
IIT Bombay, India

Raghavan B. Sunoj: Received his Ph.D. under the tutelage of Jayaraman Chandrasekhar from the Indian Institute of Science Bangalore. After a couple of years of postdoctoral research in the laboratory of Christopher Hadad at the Ohio State University, Columbus, OH, he returned to India in the year 2003 to take up an independent position as an assistant professor in the department of chemistry, Indian Institute of Technology Bombay. He was promoted to a full professor in the year 2012. He is an elected member of the board of World Association of Theoretical and Computational Chemists (WATOC) and a fellow of the Royal Society of Chemistry (London). He has won several national awards as well as the excellence in teaching award from the IIT Bombay. He has published well over hundred research papers in the area of reaction mechanism and asymmetric catalysis. His current research interests are in the domain of computational organic chemistry with emphasis on transition state modeling in asymmetric catalysis, mechanisms of multi-catalytic reactions, and computational design of catalysts.

Jin-Quan Yu
Scripps Research Institute, USA

Jin-Quan Yu received his B.Sc. in Chemistry from the East China Normal University, and completed his undergraduate thesis studies with Prof L.-X. Dai, and B.-Q. Wu at the Shanghai Institute of Organic Chemistry. He obtained his M.Sc. from the Guangzhou Institute of Chemistry with Prof X.-D. Xiao, and his Ph.D. from the University of Cambridge, with Prof. J. B. Spencer. Following a time as a Junior Research Fellow at Cambridge, he joined the laboratory of Prof. E. J. Corey at Harvard University as a postdoctoral fellow. He then began his independent career at Cambridge (2003–2004), before moving to Brandeis University (2004–2007), and finally to TSRI, where he is currently Frank and Bertha Hupp Professor of Chemistry.

Andrei Yudin
University of Toronto, Canada

Professor Andrei K. Yudin obtained his B.Sc. degree at Moscow State University and his Ph.D. degree at the University of Southern California under the direction of Professors G. K. Surya Prakash and George A. Olah. He subsequently took up a postdoctoral position in the laboratory of Professor K. Barry Sharpless at the Scripps Research Institute. In 1998, he started his independent career at the University of Toronto. He received early tenure, becoming an Associate Professor in 2002, and received an early promotion to the rank of a Full Professor in 2007. Prof. Yudin is one of the pioneers in the design of new chemical transformations.

Currently, the main focus of research in the Yudin group is to develop a bridge between basic chemistry research and drug discovery. In addition to significant fundamental discoveries, his lab is making tangible contributions to chemical industry. In 2009, Sigma-Aldrich used his method and created a wide range of reagents now known as the Yudin amino aldehydes. These powerful molecules are being used to solve some of the long-standing problems of complex molecule synthesis. Prof. Yudin and his students have made molecules that effectively mimic secondary structures such as beta turns, beta sheets, and alpha helices in various contexts.

Amongst Professor Yudin's awards are the CSC Award in Combinatorial Chemistry, the 2004 Amgen New Faculty Award, the 2010 CSC Merck-Frosst Therapeutic Center Award, the 2010 Rutherford Medal of the Royal Society of Canada, the 2011 University of Toronto Inventor of the Year Award, and the 2015 Bernard Belleau Award in Medicinal Chemistry. Professor Yudin is a Fellow of the Royal Society of Canada. He is currently the Editorial Board Chair of the Royal Society of Chemistry journal *Organic & Biomolecular Chemisty*.

Invited speaker presentations

INV01 Target-driven total synthesis
Seth Herzon
Yale University, USA

INV02 In search of biologically active compounds using the tools of chemical synthesis
Andrei K. Yudin
University of Toronto, Canada

INV03 Ligand-accelerated C-H activation reactions: Distance and geometry
Jin-Quan Yu
Scripps Research Institute, USA

INV04 New catalytic approaches for simplifying complex target synthesis
Darren Dixon
University of Oxford, UK

INV05 Synthetic biology approaches to new fluorine chemistry
Michelle Chang
University of California, Berkeley, USA

INV06 Development of new catalysts toward utilization of renewable resources
Kyoko Nozaki
University of Tokyo, Japan

INV07 Transition metal-catalyzed amination and amidation reactions
Kami Hull
University of Illinois at Urbana-Champaign, USA

INV08 From simple hydrocarbons to *N*-containing compounds through nitrogenation strategy
Ning Jiao
Peking University, China

INV09 Automated glycan assembly enables molecular glycobiology and material science
Peter Seeberger
Max-Planck Institute of Colloids and Interfaces, Germany

INV10 Challenges in oligosaccharide analysis and synthesis
Nicola Pohl
Indiana University, USA

INV11 Transition state modeling in asymmetric cooperative catalysis: Insights on mechanism and stereoselectivity
RB Sunoj
IIT Bombay, India

INV12 Organic chemistry applied to proteins: The case of ubiquitination and deubiquitination
Ashraf Brik
Technion - Israel Institute of Technology, Israel

INV13 Synthetic DNA devices quantitate protein activity in living organisms
Yamuna Krishnan
University of Chicago, USA

INV14 Unlocking the mysteries of amyloid diseases with chemical model systems
James Nowick
University of California, Irvine, USA

The Underline denotes the presenting author to whom the affiliation applies

Oral presentations

O01 **Synthetic efforts aimed at the briarane diterpenoids**
Andrew Harned
Texas Tech University, USA

O02 **Enantioselective synthesis of the steroidal core of batrachotoxin**
Jacob DeForest, Justin Hilf, Maureen Kelly, Scott Rychnovsky
University of California, Irvine, USA

O03 **Structure elucidation and total synthesis of the kalimantacin antibiotics**
Freya Bull, Iain Thistlethwaite, Christine Willis
University of Bristol, UK

O04 **The new roles of diboron in organic synthesis**
Qiuling Song
Huaqiao University, China

O05 **Palladium/phosphaadamantane catalyst enables an exclusively *trans*-selective chlorocarbamoylation of alkynes**
Christine Le, Xiao Hou, Theresa Sperger, Franziska Schoenebeck, Mark Lautens
University of Toronto, Canada

O06 **Catalytic C-H bond functionalization and access to fluorinated compounds**
Chengjian Zhu, Pan Xu, Weipeng Li, Jin Xie
Nanjing University, China

O07 **Synthesis and late-stage reducing-end modification of heparan sulfate-like oligosaccharides utilising a [2.2.2] iduronic lactone**
Robin Jeanneret, Charlotte Dalton, Jordi Bella, Gordon Jayson, John Gardiner
The University of Manchester, UK

O08 **Synthesis of labelled heparan sulfate oligosaccharides for single molecule investigation of protein binding**
Charlotte E. Dalton, Steven D. Quinn, Robin A. Jeanneret, Laura E. Baltierra-Jasso, Aidan Rafferty, Michael J. Morten, Steven W. Magennis and John M. Gardiner
The University of Manchester, UK

O09 **A light and chemically driven molecular machine imitating the arm movements of a human breaststroke swimmer**
Christoph Burkhart, Gebhard Haberhauer, Sascha Woitschetzki
University of Duisburg-Essen, Germany

O10 **Computational approach to develop phosphoramidite ligand applied to Rh-catalysed asymmetry cycloisomerization and Cu-catalysed asymmetry conjugate addition**
Qian Peng, Robert Paton
University of Oxford, UK

O11 **Dimerization of two alkyne units: Model studies, intermediate trapping experiments, and kinetic studies**
Sven Fabig, Gebhard Haberhauer, Rolf Gleiter
Universität Duisburg-Essen, Germany

O12 **Minute perturbations of glutamate 22 in Alzheimer's Aβ induce distinct aggregation profiles**
Jevgenij Raskatov, Christopher Warner, Subrata Dutta, Victoria Klein, Eefei Chen
University of California, Santa Cruz, USA

O13 **Imidazole-peptide foldamers: Switching of the driving forces within the helix**
Abdulselam Adam, Gebhard Haberhauer
Universität Duisburg-Essen, Germany

The Underline denotes the presenting author to whom the affiliation applies

Poster presentations

P01-F **α-Arylation of saturated azacycles and *N*-methylamines via palladium(II)-catalyzed C(sp^3)−H coupling**
Pritha Verma, Jillian Spangler, Yoshihisa Kobayashi, Dong-Hui Wang, Jin-Quan Yu
The Scripps Research Institute, USA

P02 **Exploring mass production of versatile catalytic reactions in continuous flow**
Li Wan, Kai Guo, Kai Qiao, Xiaoning Sun, Ning Zhu
Nanjing Tech University, China

P03 **Acetonitrile as a cyanating reagent: Cu-catalyzed cyanation of arenes**
Yamin Zhu, Zengming Shen
Shanghai Jiao Tong University, China

P04 **Synthesis of chlorins by diels-alder cycloadditions of pheophorbide a and its derivatives**
Margetic Davor, Anamarija Bris, Zelijko Marinic, Zhi-Long Chen
Rudjer Boskovic Institute, Croatia

P05 **Alteration of anti-proliferative activity of vulpinic acid in novel colloidal system vulpinic acid-treated poly (vinyl benzyl chloride)**
Mehmet Candan, Ayşegül Varol, Rukiye Karabacak, Ayşe Koparal, Mehmet Varol, Turgay Tay
Anadolu University, Turkey

P06 **Application of β-seleno-phenylalanine in additive-free one-pot ligation-deselenization chemistry**
Xiaoyi Wang, Lara Malins, Richard Payne
The University of Sydney, Australia

P07 **Targeted protein surface sensors: A new class of fluorescent probes that can track protein structural changes and binding interactions**
Yael Nissinkorn, Leila Motiei, David Margulies
Weizmann Institute of Science, Israel

P08 **Asymmetric organocatalytic addition reactions of enolisable anhydrides to maleimides: A novel approach towards the synthesis of chiral succinimides**
Bruce Lockett-Walters, Stephen Connon
Trinity College Dublin, Republic of Ireland

P09 **Asymmetric synthesis of thiohydantoins by the virtue of axial chirality**
Ilknur Dogan, Sevgi Sarigul
Bogazici University, Turkey

P10 **Challenges and opportunities in metal catalyzed C-3 functionalization of indoles with carbonyls and their surrogates**
Swapna Sarita Mohapatra, Sujit Roy
Indian Institute of Technology Bhubaneswar, India

P11 **Chemical route optimization of gamma-carboline compounds**
Denis Billen, Olivia Goethe, Denis Sobieray, Valerie Westrick
Zoetis Pharmaceutical Sciences, USA

P12 **Construction of aryl- and trifluoromethyl-substituted tertiary alcohols via aldol reactions catalyzed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)**
Dongxin Zhang, Fujie Tanaka
OIST, Japan

P13 **Cycloaddition reactions using enolisable anhydrides with imines catalysed by cinchona alkaloids**
Aaron Gutierrez Collar, Stephen Connon
Trinity College Dublin, Republic of Ireland

P14 **Dehydrophenylalanine as a traceless turn inducer**
Diane Le, Jan Riedel, Yamin Zhu, Vy Dong
University of California Irvine, USA

P15 **Design and synthesis of novel sulfonamide-containing benzoxazoles as human GST P1-1 inhibitors**
Tugba Ertan Bolelli, Yaman Musdal, Bengt Mannervik, Kayhan Bolelli, Serap Yilmaz, Ozum Ozturk, Ilkay Yildiz, Esin Aki-Yalcin, Ismail Yalcin
Ankara University, Turkey

P16 **Design, synthesis and electronic properties of push-pull-push type dye**
Rajen Kundu
University of Colorado Boulder, USA

P17 **Desymmetrizations via rhodium-catalyzed ketone hydroacylation**
Xuesong Wu, Yubin Bai, Zhiwei Chen, Vy Dong
University of California Irvine, USA

P18 **A combined allylic azide rearrangement and Tsuji-Trost allylic substitution reaction**
Simon Kim, Robert A. Batey
University of Toronto, Canada

P19 **Efforts toward the synthesis of new CID-cleavable protein cross-linkers**
Sarah Block, Clinton Yu, Eric Novitsky, Lan Huang, Scott Rychnovsky
University of California Irvine, USA

P20 **Nickel catalyzed stereospecific cross coupling: Novel approaches to optically enriched triarylmethanes**
Luke Hanna
University of California, Irvine, USA

P21 **Hydrothiolation of alkenes and alkynes catalyzed by 3,5-dimethyl-5-vinylthiazolium and poly(3,5-dimethyl-5-vinylthiazolium)**
Young Keun Chung, Supil Chun, Jungyoung Chung, Ji Eun Park
Seoul National University, South Korea

P22 **Synthesis and characterisaiton of chlorin dimers**
Ruisheng Xiong, Anna Arkhypchuk, Daniel Kovacs, Eszter Borbas
Uppsala University, Sweden

P23 **Investigation into the formal dyotropic shift of himbert cycloadducts**
Alexander Karns, Hung Pham, Christopher Vanderwal, Kendall Houk
University of California, Irvine, USA

P24 **Ionic liquid mediated stereoselective synthesis of 2,3-disubstituted quinazoline-4(3H)-ones derived from glycine linked sulphonamide**
Taroshkumar S. Patel, Urmila H. Patel, Ritu B. Dixit, Bharat C. Dixit
V. P. & R. P. T. P Science College, India

P25 **Ionic liquid promoted application of Biginelli type reaction methodology under microwave irradiation yielding hybrid dihydropyrimidines**
Jaimin D. Bhatt, Chaitanya J. Chudasama, Kanuprasad D. Patel
V. P. & R. P. T. P. Science College, India

P26 **Kinetic resolution of azomethine imines by Brønsted acid catalyzed enantioselective reduction**
Amanda Bongers, Patrick J. Moon, André M. Beauchemin
University of Ottawa, Canada

P27 **Mechanism and origin of stereoselectivity of NHC catalyzed asymmetric reactions using transition state models**
Yernaidu Reddi, Raghavan B Sunoj
IIT Bombay, India

P28 ***N*-heterocyclic carbenes and their salts – a versatile toolbox for membrane interactions and micellar catalysis**
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P29 **Novel borylated building blocks and heterocycles in palladium & rhodium catalysis**
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P30 **On the mechanism and the role of Lewis acid additives in a palladium catalysed directed C–H functionalization reaction**
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P31 **Organocatalytic dynamic kinetic resolution of enolisable anhydrides**
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P32 **Palladium-catalyzed electrochemical oxygenation of C(sp^3)−H bonds**
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P33 **Pharmacophore identification analysis on hGST P1-1 enzyme inhibitory active benzothiazole derivatives**
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P34 **Photoredox catalyzed formation of quaternary centers via 3º oxalates**
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P35 **Preparation of nano-lignin peroxidase particles as reusable catalysts**
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P36 **Redox controlled on/off light switch**
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P37 **Rh-catalyzed enantioselective desymmetrization triggered by C-H activation**
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P38 **Rhodium-catalyzed alkyne hydrofunctionalization**
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P39 Rhodium-catalyzed tandem isomerization and hydroamination of alkynes
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P45-F Building up molecular complexity using cobalt catalysis through C-H activation and C-H functionalization
Oriol Planas, Christopher Whiteoak, Anna Company, Xavi Ribas
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P46-F Cobalt-catalyzed intramolecular hydroacylation towards an enantio-, diastereo-, and regioselective synthesis of cyclobutanones
Daniel Kim, Jan Riedel, Vy Dong
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P47-F Kinetic resolution of oxazinones to give orthogonally protected β-amino acids
Sarah Cronin, Stephen Connon
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P48-F N-heterocyclic carbenes - versatile ligands for nanoparticle stabilization
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Westfälische-Wilhelms-Universität Münster, Germany

P49-F Progress towards the total synthesis of nagelamide J
Anika Tarasewicz, Marvin Morales, Robert A. Batey
University of Toronto, Canada

P50-F Synthesis and biological evaluation of the haterumaimides
Zef Konst, Anne Szklarski, Sharon Michalak, Yvonne Schmidt, Christopher Vanderwal
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P51-F Synthesis of indole-2-carboxylate derivatives via palladium-catalyzed aerobic amination of aryl C–H bonds
Kyle Clagg, Stefan Koenig, Haiyun Hou, David Russell, Adam Weinstein, Shannon Stahl
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University of Aberdeen, UK

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Jasneet Kaur, Akshay Kumar, Swapandeep Singh Chimni
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P55 Synthesis of isocoronene
Iain Currie
Curtin University, Australia

P56 Cyclopropane synthesis via stereospecific intramolecular reductive cross-electrophile couplings
Emily Tollefson, Lucas Erickson, Elizabeth Jarvo
University of California, Irvine, USA

P57 Veratryl alcohol imprinted synthetic polymers: Catalysts for H_2O_2-dependent oxidation of veratryl alcohol to verataldeheyde
Ilker Avan, Turgay Tay, Ender Köse, Ridvan Say
Anadolu University, Turkey

P58 Catalytic activity of Mn(II) complexes on alcohol oxidation
İbrahim Kani, Yalçın Kılıç
Anadolu University, Turkey

P59 Rhodium catalyzed cyanation of chelation assisted C(sp^2)-H bonds
Chaitanya Manthena, Pazhamalai Anbarasan
Indian Institute of Technology, Madras, India

P60 "Enz-flow: Towards a novel synthesis of levomilnacipran"
Amanda Evans, Christian Ayoub, Matthew Nguyen, Roberto Pineda, Frances Arnold, Hans Renata, Jennifer Kwan
California State University Fullerton, USA

P61 Tetrahydroxydiboron-mediated palladium-catalyzed transfer hydrogenation and deuteriation reactions using water as the H or D atom donor
Steven Cummings, Thanh Le, Alyssa Jones, Lorenzo Quiambao, Gilberto Fernandez, Benjamin Stokes
UC Merced, USA

P62 Diaryl selenide-catalyzed trifluoromethylthioamination of alkenes
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Sun Yat-Sen University, China

P63 Sulfur(VI) fluoride exchange: Another good reaction for click chemistry
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P64 Remote asymmetric ullman cross-coupling using guanidinylated peptides as multi-functional ligands
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Yale university, USA

P65 A heterocyclic triphenylene designed and synthesized for sky blue phosphorescent organometallic complexes

Patrick J G Saris, Mark E Thompson
University of Southern California, USA

P66 Synthesis of high triplet energy triazole and imidazole organic host materials for white organic light emitting diode application

Muazzam Idris, Tyler Fleetham, Peter Djurovich, Mark E Thompson
University of Southern California, USA

P67 Bronsted acid-catalyzed electrophilic substitution reactions for the synthesis of chiral carbocycles

Xiao Cai, Amir Keshavaraz, Justin Omaque, Gilberto Fernandez, Benjamin Stokes
UC Merced, USA

P68 1,2-/1,3-Diamination of arenes with domino aryne precursors: A combination of experimental and theoretical study

Yang Li, Dachuan Qiu, Lu Li, Song Liu, Jiarong Shi, Jia He, Xiao Yue, Yu Lan
Chongqing University, China

P69 Novel acess to P-epi McGuigan Prodrugs

Eric Ashley, Peter Mullens, Marc Poirier, Charles Jayne, Edward Cleator
Merck Research Laboratories, USA

P70 Enantioselective synthesis of an intermediate in the preparation of a novel candidate for the treatment of HCV

Dustin Bringley, Amy M Cagulada, Johann Chan, Nolan D Griggs, Stephen P Lathrop, Kenneth S Matthews, Andrew W Waltman
Gilead Sciences, UK

P71 Highly stereoselectivity synthesis of a new class of pentasubstituted cyclopentenes

Alexander Fernández, Marco A F de Moraes Junior, Antonio L Braga, Daniel Garcia, Márcio Weber
Federal University of Santa Catarina, Brazil

P72 Total synthesis of gelsenicine via a catalyzed cycloisomerization strategy

Phil Knutson, Eric Newcomb, Blaine Pederson, Eric Ferreira
University of Georgia, Georgia

P73 An approach toward the C20-diterpenoid alkaloids cochlearenine, dictyzine, and related natural Products

Kevin Kou, Beryl Li, Richmond Sarpong
University of California, Berkeley, USA

The Underline denotes the presenting author to whom the affiliation applies

Target-driven total synthesis

Seth Herzon

Yale University, *USA*

Natural products total synthesis provides a rich and unparalleled opportunity to develop new synthetic transformations, conceive novel and general strategies to access complex structures, and study the mechanism of action of bioactive targets. We will present a unified pathway to synthesize the batzelladine alkaloids, a family of complex guanidinium alkaloids produced by various marine organisms. In addition, we have developed a general and versatile route to prepare complex diazofluorenes, an unusual functional group found in the antiproliferative metabolites known as the lomaiviticins. Applications of this chemistry towards the syntheses of lomaiviticin A and elucidation of its mechanism of action will be presented.

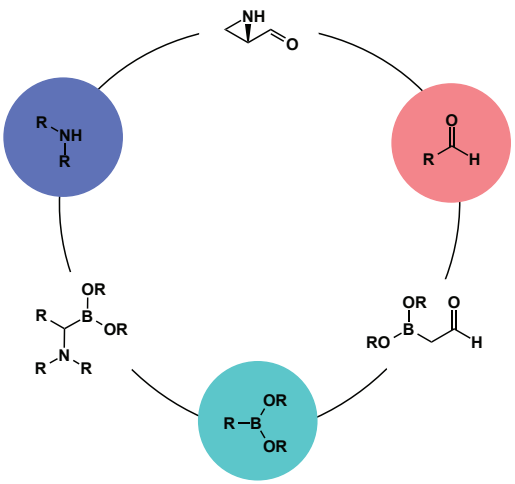
In search of biologically active compounds using the tools of chemical synthesis

Andrei K. Yudin

University of Toronto

In 2006, our studies in synthesis had led to the development of molecules that contain seemingly incompatible functional groups – an amine and an aldehyde. What started as a curiosity-driven project has turned into a sustained exploration of kinetically amphoteric molecules. As an example, the multifunctional nature of aziridine aldehydes enables them to participate in highly efficient transformations, seamlessly leading to syntheses characterized by minimal reliance on protecting groups. In this lecture, I will illuminate several key applications of aziridine aldehydes developed in our lab, including our ongoing efforts in the area of peptide macrocyclization. I will also describe our inroads in the area of boron transfer technologies. Boron-containing molecules have found a preeminent role as both the endpoints of synthesis and as synthetic intermediates that allow one to tap into the enormous potential of the carbon-boron bond. We have developed synthetically useful building blocks that contain nucleophilic carbon-boron bonds in close proximity to electrophilic centers. I will highlight the origins of this area of research and will discuss some future directions of our work in the field of synthesis enabled by organoboron compounds.

The "fateful triangle" of multifunctional reactivity



Ligand-accelerated C-H activation reactions: Distance and geometry

Jin-Quan Yu

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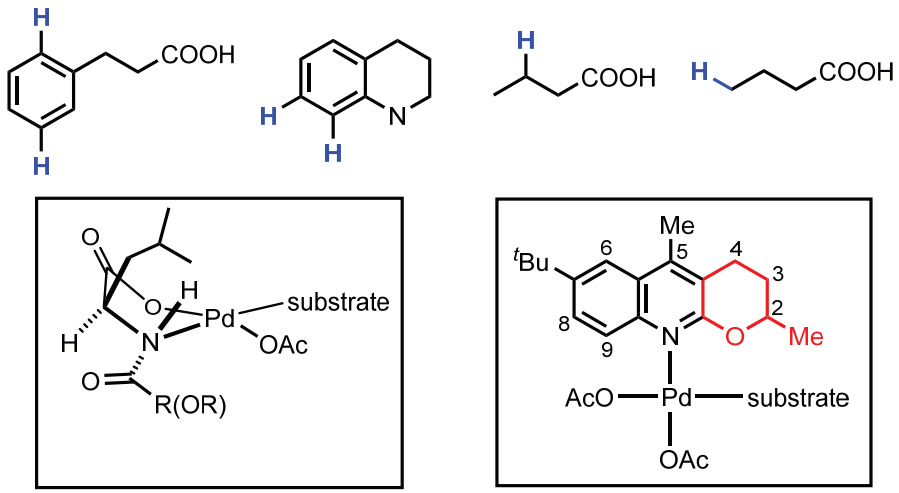
Two different classes of novel ligands are developed to drastically accelerate Pdcatalyzed C–H activation reactions. These ligands enable the activation of C–H bonds that are near or far from a functional group, demonstrating the feasibility of achieving selectivity by recognizing the distal and geometric relationship between different C–H bonds and existing functional groups. Enantioselective C–H activation reactions are also made possible by using chiral version of these ligands, providing new disconnections for asymmetric synthesis.



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New catalytic approaches for simplifying complex target synthesis

Darren J. Dixon

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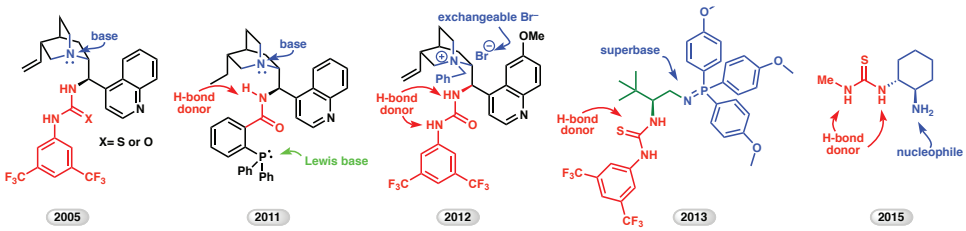
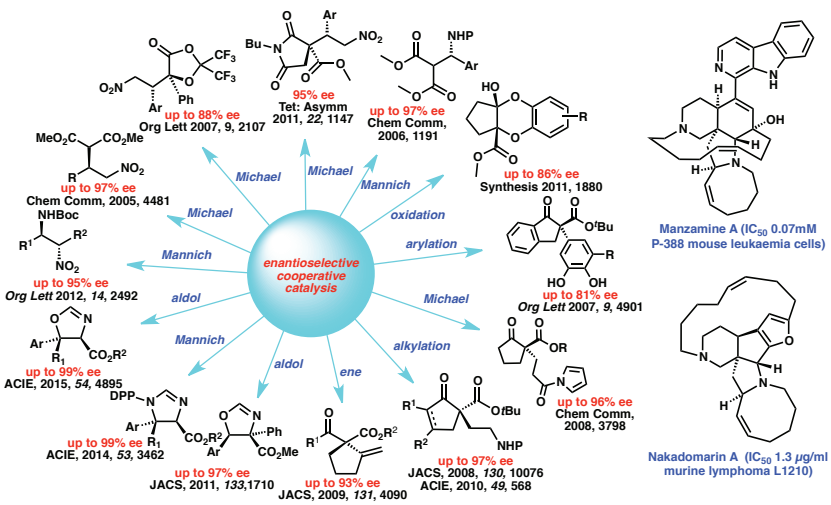
Catalysts that provide new reactivity and stereocontrol in efficient bond-forming reactions, are essential tools for converting low cost starting materials into high value, structurally complex, stereochemically defined product materials. Combining sets of such catalysts and their reactions with complexity building cascade reactions provide the perfect approach to synthesising complex target molecules as single stereoisomers in the shortest number of steps and time. In this presentation, new families of metal-free and metal-rich cooperative catalysts and their use in highly enantioselective addition reactions (Michael, Mannich, aldol) and other relevant transformations, will be described.



Their strategic application, to the discovery of new one-pot reaction cascade processes to generate novel, stereochemically defined scaffolds and architectures useful for library and target synthesis will also be discussed. Further application of selected methodologies as pivotal carbon-carbon bond forming steps in the total synthesis of a range of manzamine alkaloids will then be discussed. These syntheses serve to illustrate how complex natural product targets can be rapidly accessed when combinations of catalyst-controlled reactions, one-pot multistep procedures and powerful route-shortening cascades are designed into the overall synthetic sequence.



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Synthetic biology approaches to new fluorine chemistry

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No abstract available at time of print.

Development of new catalysts toward utilization of renewable resources

Kyoko Nozaki

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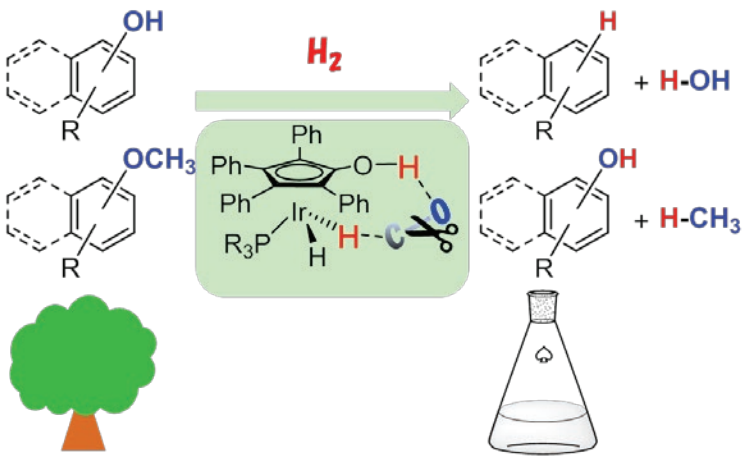
The development of mild methods for the synthesis of bulk chemicals using renewable feedstocks is a critical technological hurdle along the path to a sustainable chemical economy in the future. Carbon dioxide is one of the most attractive renewable C1 resources, which has many practical advantages such as abundance, economic efficiency, and lack of toxicity. The favorable nature as a carbon source is, however, inextricably linked to its inherent inertness. Here we report a new strategy to circumvent thermodynamic and kinetic barriers for copolymerizations of carbon dioxide and olefins by using a meta-stable lactone intermediate, 3-ethylidene-6-vinyltetrahydro-2*H*-pyran-2-one, which is formed by the palladium-catalyzed condensation of carbon dioxide and 1,3-butadiene. Subsequent free radical polymerization of the lactone intermediate afforded high-molecular-weight polymers with a carbon dioxide content of 33 mol% (29 wt%). [1]

For more than half a century, the chemical industry has mostly depended on petroleum as chemical feedstock. Because oil is hydrocarbon with low oxidation state, various selective oxidation processes have been developed for its conversion to value-added chemicals. Unlike petroleum, renewable resources, plant dry matter for example, is mostly composed of highly oxidized carbon compounds such as cellulose and lignin, which are not very amenable for deoxygenation and subsequent processing into chemical compounds on the market. Thus, the development of an efficient technology involving the chemical reduction becomes a great challenge. Here in this communication, we report direct and selective hydrogenolysis of sp^2 C–OH bonds in arenols by hydroxycyclopentadienyl dihydridoiridium catalysts. Hydrogenolysis of sp^3 C–O bonds in aryl methyl ethers were also achieved using the same catalysts. These catalyses were further applied to deoxygenation of a lignin model compound, implying the potential application for mass production of arenes from lignin or its degraded components.[2]



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Transition metal-catalyzed amination and amidation reactions

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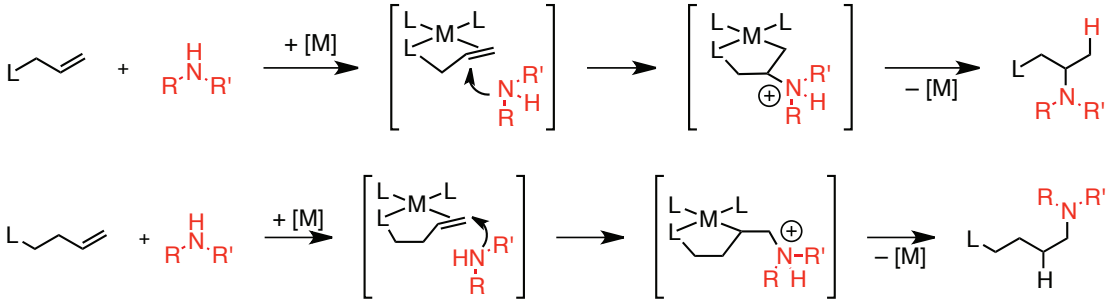
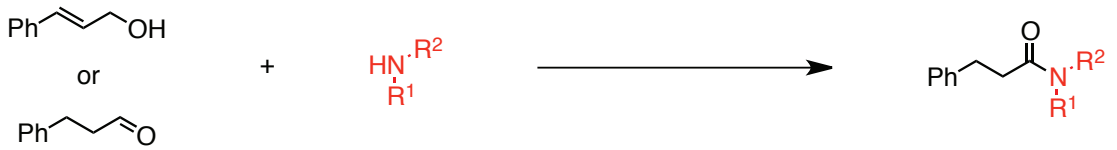
Carbon–nitrogen bonds are ubiquitous in pharmaceuticals, organic materials, and natural products. These C–N bonds are often incorporated as amines or amides. Despite their prominence, they are often formed in poor atom and step economy. One of the primary goals of the Hull Group is to develop alternative syntheses of this two important functionalities.

Hydroamination, the addition of an amine across an alkene or alkyne, couples two readily available functional groups to form new C–N and C–H bonds with 100% atom economy. Our group has demonstrated that Lewis basic groups proximal to the olefin can coordinate to a cationic rhodium catalyst and promote a regio-, chemo-, and stereoselective hydroamination reaction for the synthesis of 1,2- and 1,4-diamines. The reactions proceed selectively through five-membered metallacyclic intermediates, which is the key to the high selectivity observed.



Oxidative amidation reactions are a promising approach to the synthesis of amides; in this approach alcohols and amines are coupled directly through dehydrogenation or transfer hydrogenation processes. The Hull Group has demonstrated that allylic alcohols or aldehydes undergo a selective oxidative coupling reaction for the synthesis of amides. The reactions are highly chemoselective for reacting with the allylic alcohol or aldehyde, as other alcohols and alkenes are well tolerated under the reaction conditions. Further, primary and secondary amines as well as anilines are readily coupled to afford the corresponding amide.



From simple hydroncarbons to *N*-containing compounds through nitrogenation strategy

Ning Jiao

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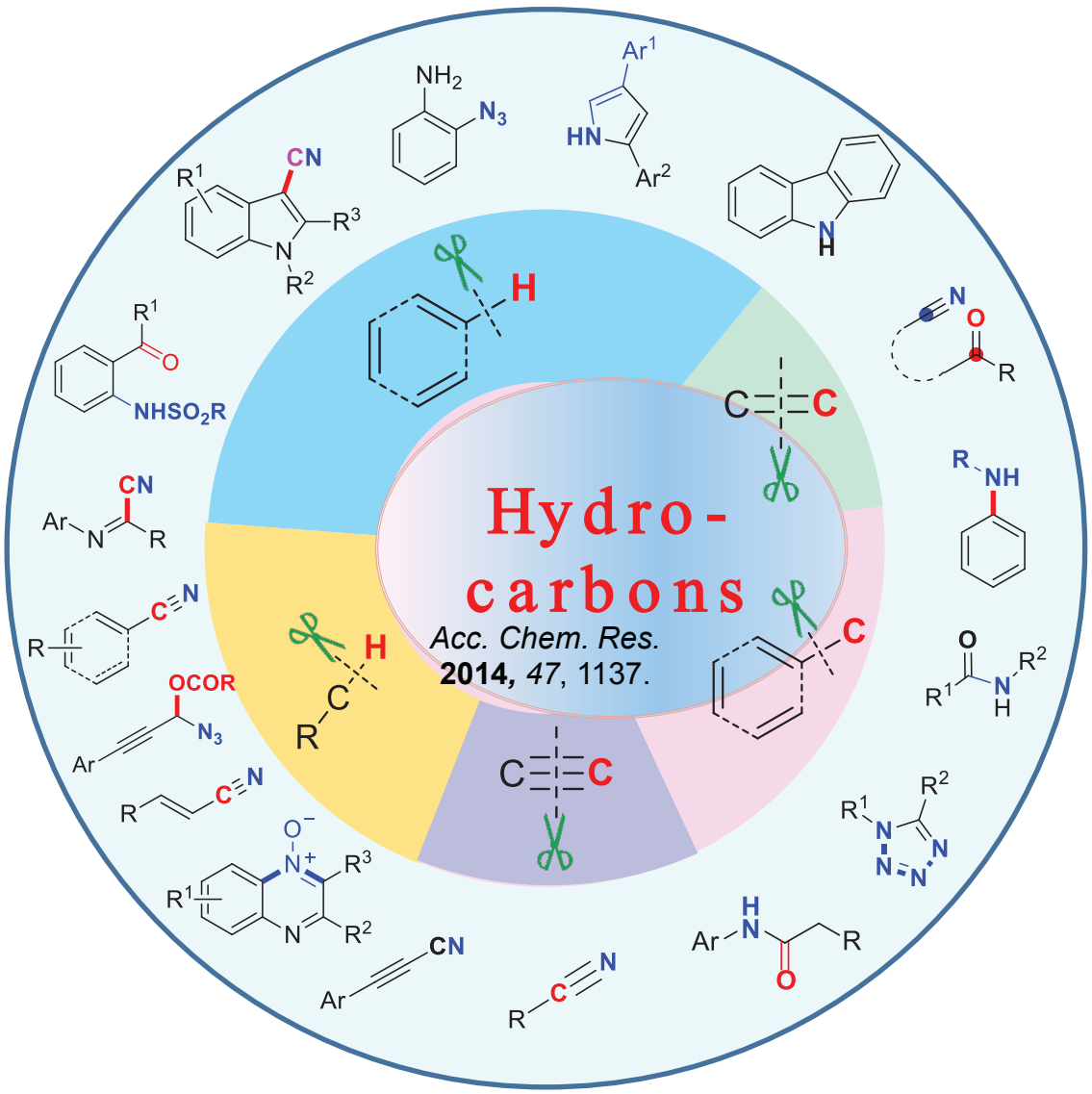
The development of novel methods for the preparation of nitrogen-containing molecules has been of long-standing interest to organic chemists due to their great importance in chemistry and biology. Recently, we have developed some direct approaches to nitrogen-containing molecules by direct nitrogenation of simple molecules at mild conditions through oxidative C-H and C-C bond cleavage strategies employing NaN_3, $TMSN_3$, or DMF as the nitrogen source (Figure 1). In this talk, the details of these direct transformations as well as the recent development will be presented.

Figure 1



Automated glycan assembly enablesmolecular glycobiology and material science

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Pure glycans are key to enable biochemical, biophysical and immunological studies aimed at understanding the role of carbohydrates. Described is the development of a fully integrated platform for automated glycan assembly (AGA) based on solid-phase oligosacharide sythesis[1] and carbohydrate arrays to address biological problems. Particular emphasis in this lecture will be placed on the new automated synthesis platform[2] that has been commercialized. [3,4] Access to defined polysaccharides as long as 50-mers enables now biological as well as materials science investigations. [5] These synthetic polysaccharides can be combined much like “molecular LEGO” to create even larger oligosaccharide assemblies. Quality control of synthetic glycans can now be garanteed using ion mobility mass spectrometry to very low levels. [6]

Carbohydrate arrays are used as diagnostics and in support of vaccine programs that are based on conjugates with synthetic oligosaccharides to screen blood sera.[7] Case studies of specific vaccines will provide an appreciation for the approach that is now advancing candidates toward clinical testing. [8,9] Fully synthetic vaccine candidates exploit iNKT cells for to induce a robust and protective immune response.[10]

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Challenges in oligosaccharide synthesis and analysis

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Many advances in understanding the role of carbohydrates in biological systems are stalled by the lack of diverse and chemically well-defined glycan structures and methods to quickly and definitively identify such structures. Because these problems of carbohydrate synthesis and analysis are interrelated, we have taken a systems approach to tackling these challenges. This talk will provide an overview of the current challenges in the development of solution-phase-based automated oligosaccharide protocols[1], including access to monosaccharide building blocks, and the development of robust de novo carbohydrate sequencing[2] workflows.

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Transition state models in asymmetric catalysis as a tool for rational catalyst design

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Computational quantum chemistry has been increasingly employed toward rationalizing the stereochemical outcome in catalytic reactions.[1] The approach typically involves the identification of kinetically significant transition states and intermediates. In our laboratory, ab initio as well as DFT methods are employed to gain insights into carbon-carbon and carbon-heteroatom bond-forming reactions of immediate practical significance.[2] The key objective of our research is to gain molecular insights on the factors responsible for stereoselectivity and to exploit such insights toward *in silico* design of novel asymmetric catalysts.[3] In other words, our research is motivated by past experiments while our results are meant to motivate future experiments.

A number of examples wherein the conventional transition state models required systematic improvements toward accounting the observed product distribution and stereochemical outcome will be presented. In general, the presentation would encompass a few contemporary themes in the domain of organocatalysis and cooperative multi-catalytic reactions.[4] Interesting interpretations/rationalizations of experimental observations besides meaningful guidelines for rational improvements in the design of asymmetric catalysts would remain the key focus of the presentation. The contents are designed to cater to a broad and diverse group of audience; hence, the chemical insights would be emphasized, rather than a labyrinth of technical details.

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Organic chemistry applied to proteins: The case of ubiquitination and deubiquitination

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In this talk, I will present our synthetic approaches for protein ubiquitination to shed light on the various unknown aspects of the ubiquitin signal in cellular pathways. The enzymatic attachment of ubiquitin to a specific protein target is a widely utilized posttranslational modification in eukaryotes, which is involved in various aspects of cellular functions and has been implicated in several diseases. The overwhelming majority of biochemical, biophysical and structural studies in the field rely on the in vitro enzymatic reconstitution of this complex modification for the protein of interest. However, the enzymatic approaches are often challenged by the isolation of the specific ligase, the heterogeneity of the modified protein and obtaining workable quantities of the ubiquitinated conjugates. Our group is developing novel non-enzymatic methods for the efficient and site-specific protein ubiquitination to overcome the limitations of the enzymatic machinery. These approaches allowed for the semisynthesis of homogeneous ubiquitinated protein such as alpha-synuclein and histone H2B to support the ongoing efforts aiming at studying the effect of ubiquitination in these systems. We are also expanding these approaches to study and target different deubiquitinases to shed light on their role in health and disease, and ultimately, for drug development.

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Synthetic DNA devices quantitate protein activity in living organisms

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University of Chicago

Due to its nanoscale dimensions and ability to self-assemble via specific base pairing, DNA is rapidly taking on a new aspect where it is finding use as a construction element for architecture on the nanoscale.[1] Structural DNA nanotechnology has yielded architectures of exquisite complexity and functionality *in vitro*. However, till 2009, the functionality of such synthetic DNA-based devices in living organisms remained elusive. Work from my group the last few years has bridged this gap where, we have chosen architecturally simple, DNA-based molecular devices and shown their functionality in complex living environments. Using two examples, from our lab[2] where we have created DNA-based fluroescent reporters for pH and chloride, I will illustrate the potential of DNA based molecular devices as unique tools with which to interrogate living systems.

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Unlocking the mysteries of amyloid diseases with chemical model systems

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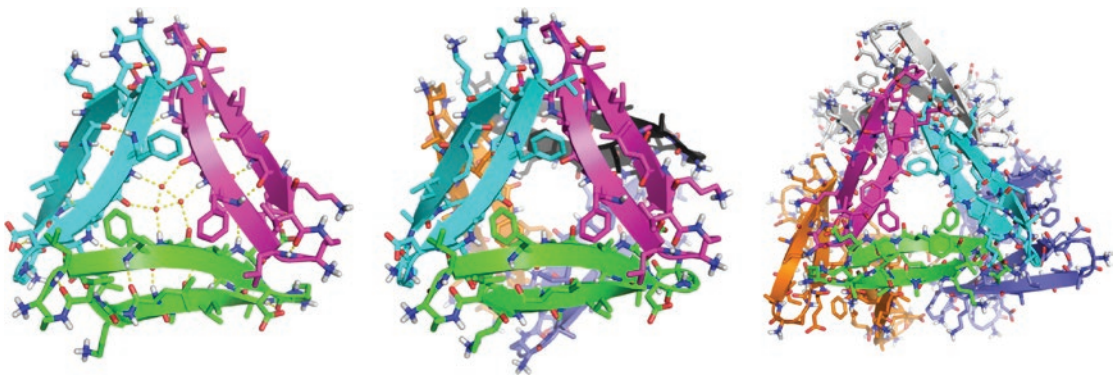
Amyloid oligomers have emerged as the key toxic species in amyloid diseases. Our laboratory is determining the structures and mechanism of action of oligomers of peptides and proteins associated with Alzheimer's disease, Parkinson's disease, frontotemporal dementias, type II diabetes, and other diseases involving protein aggregation. We are able to obtain high-resolution structures by constraining fragments of the peptides and proteins to beta-hairpins and determining the structures of the oligomers that form by X-ray crystallography. Through these studies, in conjunction with biophysical and cell biology experiments, we are gaining new insights into the molecular basis of amyloid diseases. This talk will describe some of our ongoing studies.[1-8]



X-ray crystallographic structure of oligomers of a peptide derived from $Ab_{17–36}$. Trimer (left). Hexamer — a dimer of trimers (center). Dodecamer — a tetramer of trimers (right). (PDB 4NTR)

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Synthetic efforts aimed at the briarane diterpenoids

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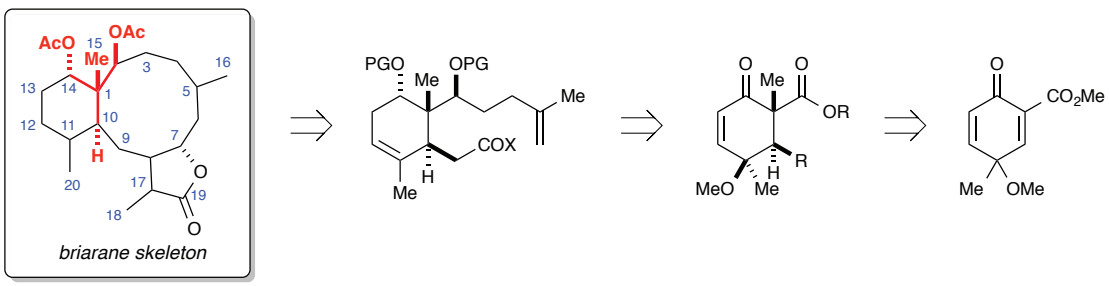
The briarane diterpenoids are a large family of gorgonian derived natural products, many of which display interesting biological activity.[1] These compounds are characterized by a *trans*-fused bicyclo[8.4.0]tetradecane ring system. A central stereotetrad comprising C1, C2, C10, and C14 is present in many of the family members. The briaranes are thought to be biosynthetically related to the eunicellin and briarellin natural products as well as the cembranoids. However, unlike these other natural product families, the briaranes have been the subject of far fewer synthetic studies, and no completed total synthesis of any briarane family member has been reported. Our efforts in this area have focused on harnessing the unique reactivity profile inherent to 2,5-cyclohexadienones and several synthetic approaches based on this scaffold will be presented.[2] In particular our efforts have focused on trying to control the relative configuration of the stereogenic quaternary carbon at C1. Through these efforts, we have learned that torsional steering in the transition state[3] is a dominant influence at this position and can be used to favorably control the stereochemical outcome of a “simple” β-ketoester alkylation reaction.



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Enantioselective synthesis of the steroidal core of batrachotoxin

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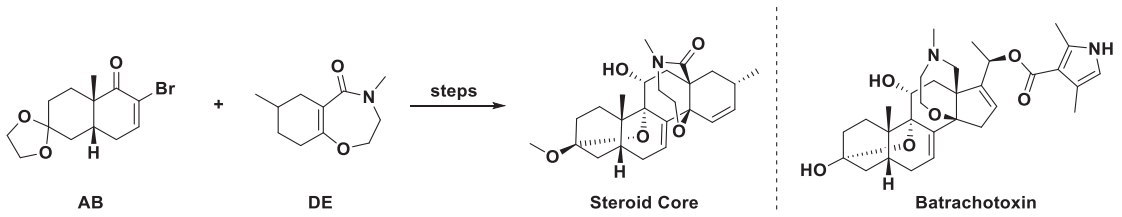
Batrachotoxin (BTX) was first isolated by Daly et al. in 1965 from the venom of the Columbian poison arrow frog, *Phyllobates aurotaenia*.[1] Its unprecedented structure contains a tetracyclic steroidal core, seven-membered oxazapane ring, and transannular hemiketal. It is the most potent small molecule agonist (LD_{50} = 1-2 μg/kg) for the voltage-gated sodium ion channel ($Na_v1.n$; n = 1-7).[2] Mutated $Na_v1.n$ channels are implicated in a variety of pain-related conditions, such as neuropathic and congenital insensitivity to pain, and have also been directly linked to the onset of epilepsy, diabetes, and erythromelalgia.[3] The development of isoform-selective agonists and antagonists of $Na_v1.n$ channels has important implications for human health. Due to the lack of sufficient natural sources, the bioactivity and binding conformation profile of BTX with sodium ion channels has yet to be completely elucidated.

While notable progress has been made towards the synthesis of BTX[4] only the Kishi group has successfully completed a total synthesis.[5] While a tremendous accomplishment, Kishi's synthetic product was racemic, and the route suffered from a longest linear sequence of 44 steps. As a result, there remains an unmet challenge to develop a concise, enantioselective synthesis of BTX. Herein we report our efforts towards the total synthesis of BTX. Our retrosynthesis focuses on a late-stage construction of the C-ring through the coupling of fully elaborated AB and DE rings. This highly convergent approach facilitates the rapid synthesis of the steroid core, and highlights the capability of the disclosed route to readily prepare significant quantities of advanced intermediates. With this strategy, we will be able to make strategically modified analogues and assess their effect on ion channel activity.



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Structure elucidation and total synthesis of the kalimantacin antibiotics

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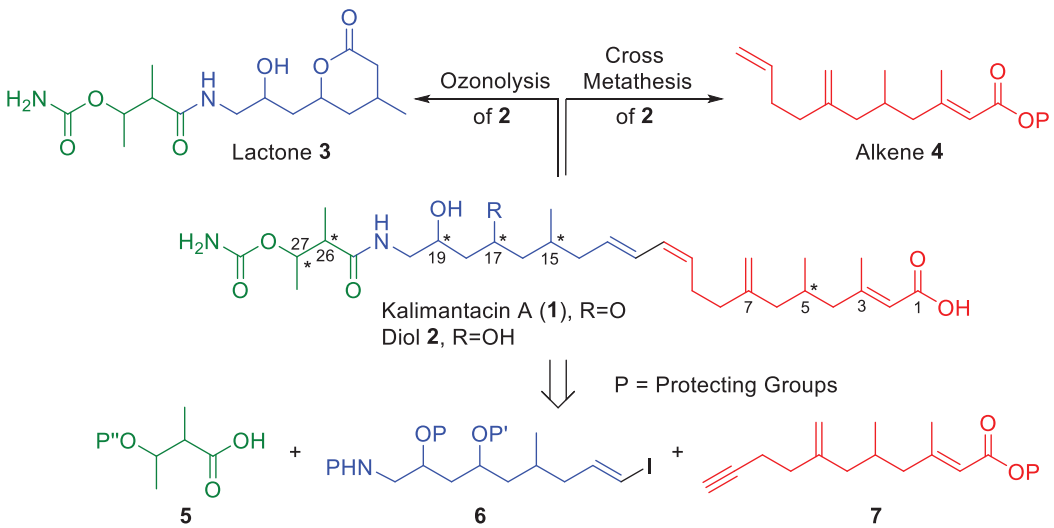
Introduction

Kalimantacin A (**1**) is a polyketide-derived natural product produced by the bacterium *Pseudomonas fluorescens*.[1-3] Further kalimantacin analogues have been isolated from rational mutations of the biosynthetic pathway, including diol **2**.[4] They are produced *via* a *trans* PKS/NRPS pathway and the presence of four β-branches (carbons 3, 5, 7 and 15) are biosynthetically intriguing. Furthermore, kalimantacin A (**1**) exhibits potent antibiotic activity against methicillin-resistant *Staphylococcus aureus* (MRSA). The structure of the kalimantacins have been investigated by spectroscopic methods, however the stereochemistry of the stereocentres (*) remained unknown.



Discussion and future work

attempts to prepare a crystalline derivative for X-ray studies have not been successful. Therefore, we have determined all of the previously unknown stereocentres, using a combination of spectroscopy, synthesis and degradation studies (diol **2** to give lactone **3** and alkene **4**).[5] To confirm the proposed structure we are currently completing the total synthesis of kalimantacin diol **2**. The enantioselective synthesis and coupling of **5**, **6** and **7** are complete, and current studies are focussed on the final steps.[5] The biosynthetic pathway will be probed to give insight into the control of β-branching and will assist with the rational design of related compounds with improved bioactivities and stability.

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The new roles of diboron compounds in organic synthesis

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Diboron compounds, especially (pinacol)diboron, are very important borylative reagents, which are widely used in organic synthesis for the preparation of a myriad of organoboron compounds, since organoboronates are prevalent building blocks in organic synthesis and pharmaceutical industries. Numerous transition-metal catalyzed cross-coupling with organoboron as coupling partners have been developed and in a word, boron chemistry is one of the long-lasting themes in organic chemistry since its birth. Despite these advancements, surprisingly and interestingly, protodeboration is underdeveloped and very few attentions have been focused on this type of reaction. In this presentation, several useful and efficient methods have been developed based on borylation/ protodeboration and thus a new role of diboron compounds is established in organic synthesis.

Palladium/phosphaadamantane catalyst enables an exclusively *trans*-selective chlorocarbamoylation of alkynes

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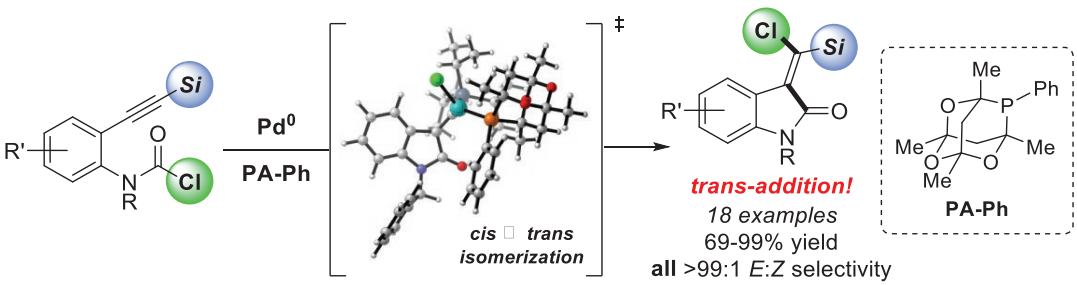
In contrast to acid chlorides and chloroformates, carbamoyl chlorides have not been frequently exploited in transition metal catalyzed alkyne addition reactions, despite their potential for accessing valuable nitrogen-containing molecules. In this study, pharmaceutically-relevant methylene oxindoles are synthesized via a palladium(0)-catalyzed intramolecular chlorocarbamoylation reaction of alkynes. A relatively underexplored class of caged phosphine ligands are uniquely suited for this transformation, enabling high levels of reactivity and exquisite *trans*-selectivity. Mechanistic studies and computations provide support for a palladium-mediated *cis*-to-*trans* isomerization process, thus demonstrating that specific substrate/catalyst combinations can override the inherent *cis*-selectivity in traditional carbometalations. This report represents the first transition-metal catalyzed atom-economical addition of a carbamoyl chloride across an alkyne.



Catalytic C-H bond functionalization and access to fluorinated compounds

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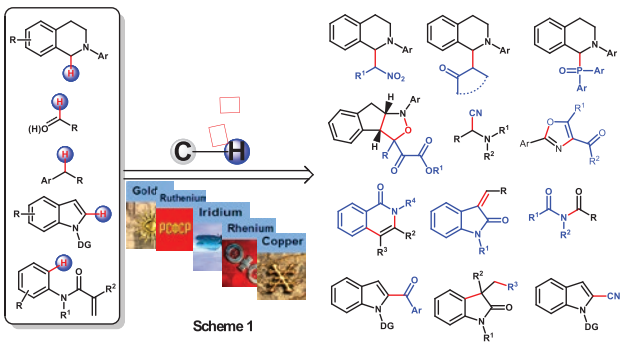
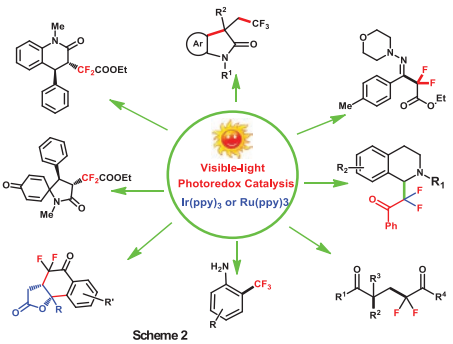
The C-H functionalization is a perennial topic of interest for organic chemists, it is a great challenging task to accomplish highly selective C-H bond functionalization under mild conditions. In the past a few years, several kind of late-transition metal-Au-Re-Ru-Ir-Cu etc.-catalyzed C-H bond functionalization reactions were developed in our laboratory, the directed alkylation, cyanation, oxidation, amination, acylation and phosphonation were realized. With those transformation methods, different kind of heterocyclic compounds were effectively constructed.[1]



Scheme 1

Fluoroalkyl containing organic compounds have attracted considerable attention from the pharmaceutical, chemical, and agrochemical industries due to their beneficial effects on the physiochemical properties and pharmacological profiles of drugs. Recently, our group achieved visible-light-induced tri- or difluromethylation with different kind of fluro reagents, several kinds of fluorinated compounds were synthesized efficiently (Scheme 2).[2]



Scheme 2

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Synthesis and late-stage reducing-end modification of heparan sulfate-like oligosaccharides utilising a [2.2.2] iduronic lactone

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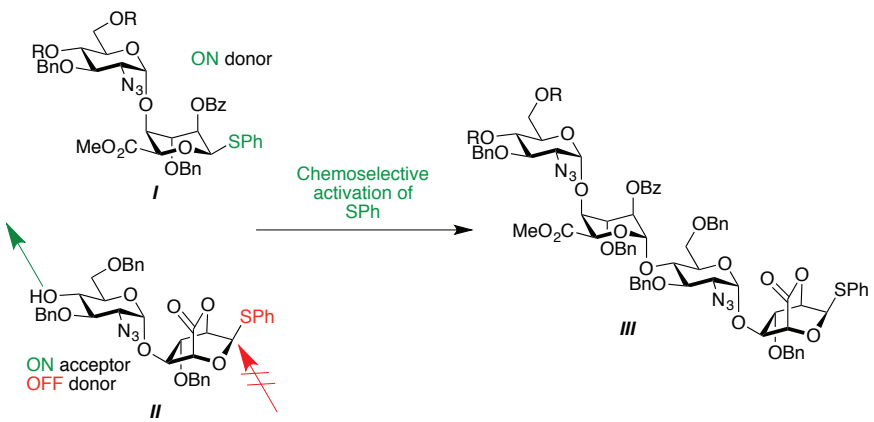
Glycosaminoglycans (GAGs) are structurally diverse carbohydrates playing essential roles in the regulation of a number of important biological functions. Heparan sulfate (HS), a GAG of particular biomedical relevance, is a cell-surface sulfated polysaccharide composed of glucosamine (GlcN) linked to a uronic acid (D-GlcA or L-IdoA). HS is capable of binding to various proteins (growth factors, chemokines) and as such is crucial in facilitating numerous cell signalling pathways and has been linked to Alzheimer's disease, oncogenesis and viral infection. HS oligosaccharides are therefore potential therapeutic agents for these conditions.[1] Due to the structural complexity and heterogeneity of native HS, the binding modes of such agents are not well-defined. Chemical synthesis allows access to HS-like sequences of variable length and with programmable sulfation patterns, which are essential to interrogate structure-specific effects on HS-protein interactions.[2] The additional conformational flexibility of the HS chain caused by the presence of iduronic acid also plays an important role in HS-protein interactions.

The synthesis of L-iduronates is one of the largest challenges in the synthesis of HS oligosaccharides. Our group has recently reported a route to novel [2.2.2] bicyclic thioglycoside iduronate lactones.[3] These bicyclic lactones are unreactive as glycosyl donors and can be used as glycosyl acceptors to provide HS disaccharides via chemoselective activation of glucoazide thioglycosides. The disaccharides can be converted via base-mediated lactone opening to monocyclic iduronate thioglycosides (*I*). Here we demonstrate the chemoselective activation of these iduronate glycosyl donors in the presence of iduronate lactone-containing disaccharides (*II*) to provide a new route to longer HS oligosaccharides (*III*). This generates HS oligosaccharides with thioglycoside capacity which can be activated post-oligomerisation and thus allows late-stage diversification (e.g protein conjugation/ labelling) via glycosylation at the reducing end.



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Synthesis of labelled heparan sulfate oligosaccharides for single molecule investigation of protein binding

Charlotte E. Dalton,[a] Steven D. Quinn,[b] Robin A. Jeanneret,[a] Laura E. Baltierra-Jasso,[a,b] Aidan Rafferty,[b] Michael J. Morten,[b] Steven W. Magennis[b] and John M. Gardiner[a]

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Heparan sulfate (HS) is a cell-surface sulfated polysaccharide that binds to multiple proteins (chemokines, growth factors) to facilitate cell proliferation/differentiation signalling pathways and has been implicated in cancer development, viral infection and Alzheimer's disease.[1] HS oligosaccharides are therefore potential therapeutic agents for these conditions. However, the structural requirements for protein binding are ill-defined due to the structural complexity of HS, in particular with regards to variable sulfation patterns and binding sequence lengths. Although digest products of native HS can be used to investigate HS properties, these are necessarily heterogeneous and thus synthetic structurally-defined HS oligosaccharides are critical to define any specific structural features related to biological activities. Synthetic HS oligosaccharides are tunable in terms of length, order of monosaccharides and sulfation pattern,[2] all of which have impact on HS-protein interactions.

Herein we present the use of a protected amine tag for the labelling of synthetic HS oligosaccharides with fluorescent dyes suitable for single molecule fluorescence studies. Single molecule methods have been utilised as powerful tools in biology/biophysics to study dynamic processes and allow observation of rare events which would be 'averaged out' in ensemble measurements.[3] Access to labelled synthetic HS fragments allows investigation of interactions with proteins at the single molecule level for the first time, and provides a method complementary to NMR studies (ensemble) and X-ray crystallography (non-dynamic). This presentation will describe the development of a methodology for use of single molecule fluorescence in HS fragment-protein interaction studies.

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A light and chemically driven molecular machine imitating the arm movements of a human breaststroke swimmer

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In recent years a significant number of molecular switches and machines could be synthesized and investigated. Such nano-apparatus do contain functional groups which perform specific structural changes when stimulated, e.g. by light irradiation, chemical energy or electron-transfer processes. Quite often macroscopic movements inspire researchers when creating a sequence of structural changes which are individually stimulated. In the literature molecular analogues to rotors[1], gears[2], clutches[3], etc. have been described.

A special challenge is to design molecular machines that can exist in different states, corresponding to different sterical conformations, where the path of leaving the first state differs from the path of returning to the starting point, because otherwise no mechanical work is performed.[4]

In our group, we synthesized a molecular machine with two different, independently switchable moieties, which can be reversibly stimulated by light irradiation and by chemical complexation, respectively. We choose azobenzene as the moiety which switches by irradiation, and bipyridine as the structural element that changes its conformation by complexation resp. decomplexation of added Copper-ions. The movement of the machine reminds of the arm motion of a human breaststroke swimmer. The unidirectionality was reached by a chiral clamb on the peptidic scaffold at which the two flexible arms are attached (see figure).

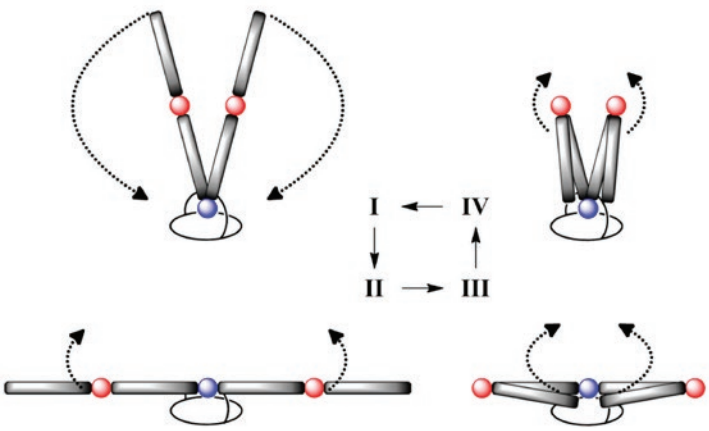

Figure: Structure, concept and principle of the nanoswimmer.[5]

The structural changes of the two units, corresponding to the movements of the swimmer, and the existence of the different states (I-IV, see figure) were investigated and proven by CD- and UV-spectroscopy and compared with calculated spectra. To verify the complexation of the bipyridine with the Copper-ions, mass spectrometry was carried out. The analytical data clearly show that we were able to synthesize a molecular machine which can be stimulated to pass through a unidirectional four-state cycle similar to the arm movements of a human breaststroke swimmer.

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Computational approach to develop phosphoramidite ligand applied to Rh-catalysed asymmetry cycloisomerization and Cu-catalysed asymmetry conjugate addition

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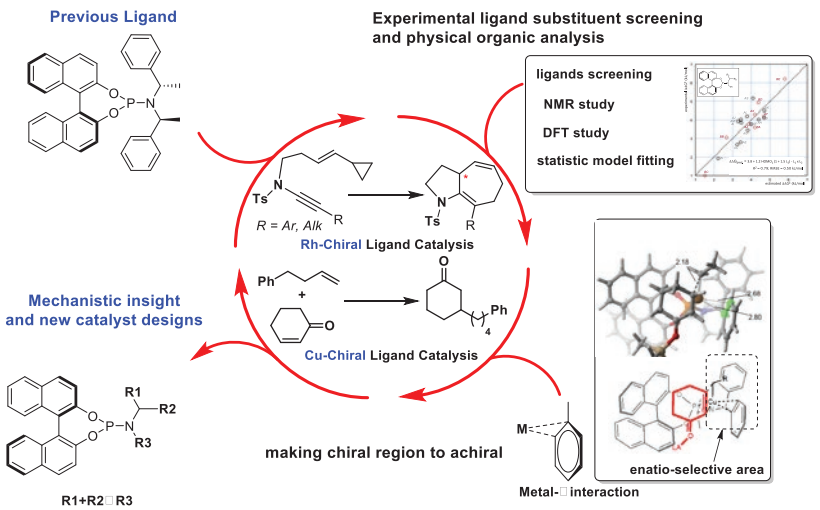
Demand for higher efficiency, economy, and selectivity in the synthesis of novel molecular scaffolds drives organic chemistry. The development of modular chiral ligands has led to the discovery of several transition metal:ligand complexes that catalyze various reactions with impressive levels of enantioselectivity. However, discovery of the appropriate chiral ligands for a desired transformation remains a formidable task. This is especially true for reactions where detailed mechanistic data are yet to be uncovered. Computational understanding of the mechanism of catalyst-control can lead to improved understanding and guide synthetic effort. Recently, Sigman and coworkers[1] have combined physical organic and quantum chemistry with modern data analysis techniques to elucidate the underlying reaction mechanism, facilitating the rational design of more effective catalysts.



Through computational quantum chemistry we have explored how the structural elements of the phosphoramidite ligand affect catalyst structure and selectivity in Rh-catalysed asymmetry cycloisomerization (with Prof. Edward Anderson)[2] and Cu-catalysed conjugate additions (with Prof. Stephen Fletcher)[3]. Elucidation of the important interactions has been achieved by studying the effects of ligand-structural variation on both the catalyst structure and resulting enantioselectivity, through a combination of experimental and theoretical techniques. These studies illustrate the ability of quantitative structure-selectivity relationships to provide both models for asymmetric induction and catalyst structural hypotheses that may be further probed by experiment and computation. Collectively, such an approach leads to the rational modification/simplification of chiral ligands for more effective catalysts.

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Dimerization of two alkyne units: Model Studies, intermediate trapping experiments, and kinetic studies

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By means of high level quantum chemical calculations (B2PLYPD and CCSD(T)), the dimerization of phenylacetylenes substituted with different groups such as F, Cl, OH, SH, NH_2, and CN to the corresponding diradicals and dicarbenes was investigated. Substituents attached to the reacting centers reduce the activation energies and the reaction energies with increasing electronegativity of the substituent (F > OH > NH_2, Cl > SH, H, CN). This effect was explained by a stabilizing hyperconjugative interaction between the σ* orbitals of the carbon-substituent bond and the occupied antibonding linear combination of the radical centers.

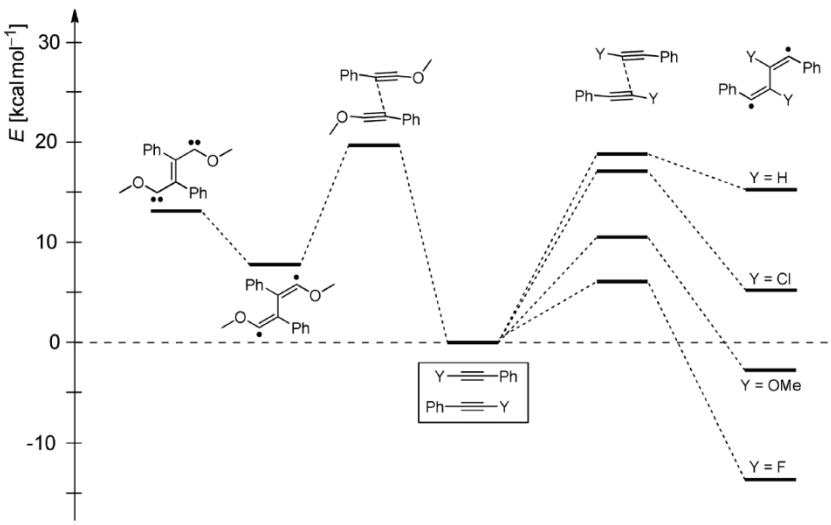

Figure 1: Energy profiles of the dimerization of substituted phenylacetylenes to diradicals as well as to a methoxysubstituted dicarbene calculated using B2PLYPD/6-31G.*

Trapping experiments of the proposed cyclobutadiene intermediates using maleic anhydride as dienophile as well as kinetic studies confirm the calculations. In the case of phenylmethoxyacetylene (Ph−C≡C−OCH_3) the good yield of the corresponding cycloaddition product makes this cyclization reaction attractive for a synthetic route to cyclohexadiene derivatives from alkynes.

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Minute perturbations of glutamate 22 in alzheimer's Aβ induce distinct aggregation profiles

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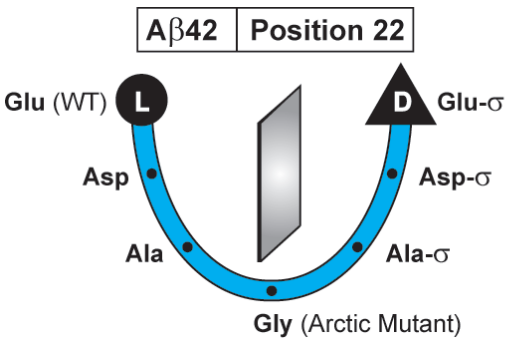
University of California, Santa Cruz

Amyloid beta 42 plays an important role in both onset and progression of Alzheimer's Disease.[1] The highly disordered polypeptide forms various aggregates of diverse sizes, shapes and toxicities.[2] To advance our understanding of the framework, novel molecular tools need to be developed. Familial AD-causing mutations can offer important insight into regions of Aβ that are critical for aggregation and toxicity.[3] Some least ten single residue variants of Aβ have been identified thus far. From those, four occupy position 22 of the polypeptide, which normally expresses glutamate. We have developed a novel stereochemical approach that probes this residue at various stages of aggregation. Minute alterations with distinct aggregation profiles were identified that could be potentially employed as molecular probes of AD mechanism. Our approach can be extended to other residues of Aβ and further amyloidogenic polypeptides.



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Imidazole-peptide foldamers: Switching of the driving forces within the helix†

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Folding is one of the most important processes in nature and provide the foundation for life. The amazing diversity of functions displayed by biomolecules is accessible with only 20 amino acids. It is inconceivable which functions are attainable by the innumerable available non-natural monomers. Therefore foldamers, non-natural folded oligomers, have aroused immense scientific interest.[1-4]

Here we show the synthesis and structural analysis of the first imidazole-pseudopeptide-based foldamer. The screw sense of the helix is determined by a single chiral imidazole unit which is attached at the N terminus of the oligomer. Circular dichroism (CD) spectroscopic investigations showed that the folding process depends on the water content of the solvent in a unique parabolic way.[5]

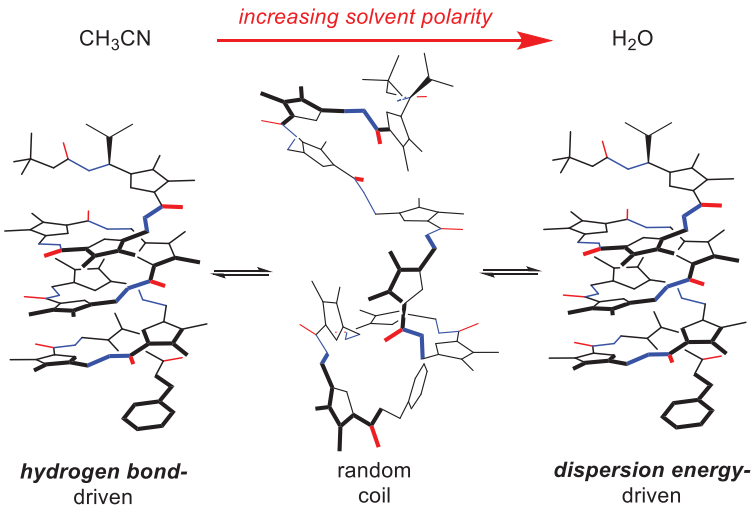

Fig. 1 Increasing water content switches the driving forces within the foldamer.

In a pure organic solvent, the helix is stabilized by hydrogen bonds between the amide hydrogen atoms and the nitrogen atoms of the azole ring. In aqueous solution, the folding process is driven by dispersion interactions. Surprisingly the formation of the helix is more pronounced in aqueous solution than in organic solvents.

Furthermore, the helical structure can be switched from the folded to the unfolded structure by varying the temperature or by addition of copper(II)triflate or cyclam, respectively.[5]

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α-Arylation of saturated azacycles and *N*-methylamines via palladium(II)-catalyzed C(sp^3)−H coupling

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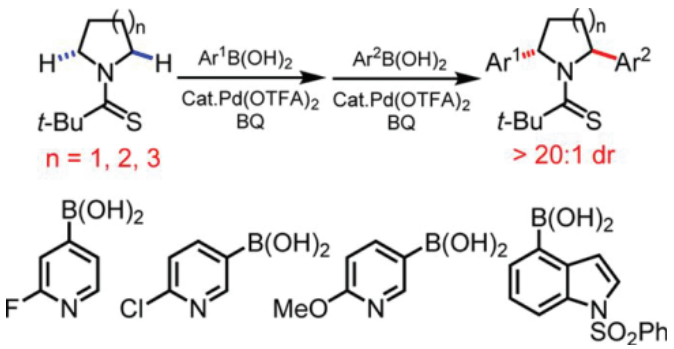
The prevalence of saturated cyclic amines in pharmaceutical compounds and bioactive natural products has led to significant interest in the functionalization of C(sp^3)−H bonds adjacent to nitrogen. Herein, we report the development of the first Pd(II)-catalyzed α-C(sp^3)−H arylation of saturated cyclic amines and *N*-methyl amines with arylboronic acids.[1] This transformation is applicable to wide arrays of pyrrolidines and boronic acids, including heteroaromatic boronic acids. The excellent monoselectivity of this reaction allows diastereoselective one-pot heterodiarylation of pyrrolidines. This transformation is also applicable to larger cyclic amines such as piperidines and azepanes. This is a rare example of the coupling of methylene C−H bonds with organometallic reagents. The enantioselective arylation and alkylation versions of this reaction is currently under development.



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Exploring mass production of versatile catalytic reactions in continuous flow

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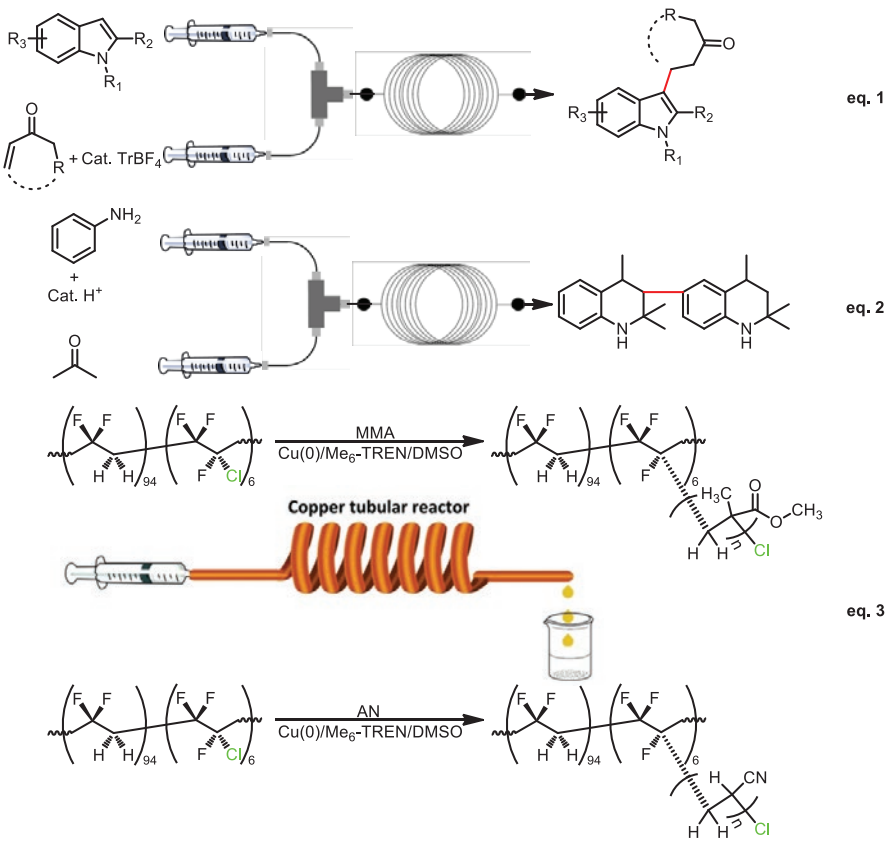
Continuous flow processing has emerged as a new tool in the academic, pharmaceutical and fine chemical production due to its favourable safety profile among other benefits, such as efficient mixing, enhanced heat and mass transfer, access to extreme reaction conditions, reproducibility and scale up, in-line workups and automated operation. Nowadays, many fabulous organic methodology have been established in organic synthesis, but mass production of desired compounds is still a big challenge. Based on this, we focused on employing micro flow system in versatile catalytic reactions to develop novel technology of mass production. Recently, we succeeded to accomplish three catalytic reactions in continuous flow. (1) C-C bond formation on C3 position of indoles catalyzed by carbocations (**eq. 1**); (2) preparation of rubber antioxidant RD catalyzed by acid (**eq. 2**); (3) graft copolymerization of methyl methacrylate (MMA) and acrylonitrile (AN) from P(VDF-*co*-CTFE) *via* SET-LRP by using copper tubing as a catalyst source (**eq. 3**). All those reactions proceeded smoothly and efficiently, also exhibited highly selectivity of corresponding products. They are easily operational without clogging and conveniently scale up without amplification effect.



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Acetonitrile as a cyanating reagent: Cu-catalyzed cyanation of arenes

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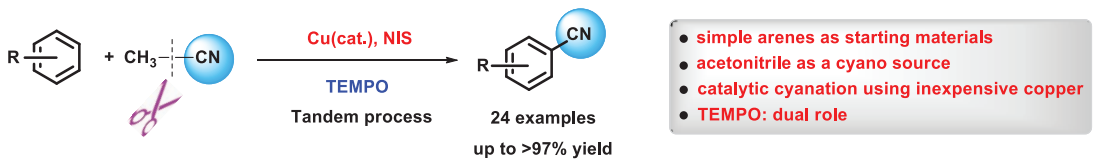
A novel approach for the Cu-catalyzed cyanation of simple arenes using acetonitrile as an attractive cyano source has been documented. The C−H functionalization of arenes without directing groups involves a sequential iodination/cyanation to give the desired aromatic nitriles in good yields. A highly efficient Cu/TEMPO system for acetonitrile C−CN bond cleavage has been discovered. TEMPO plays a significant role in promoting this cyanation transformation: 1) TEMPO, a cheap oxidant, allows the reaction to be catalytic in copper; 2) $TEMPOCH_2CN$ is formed in situ and acts as the active cyanating agent. This system represents a new avenue to break the relatively inert C–CN bond.



Synthesis of chlorins by diels-alder cycloadditions of pheophorbide a and its derivatives

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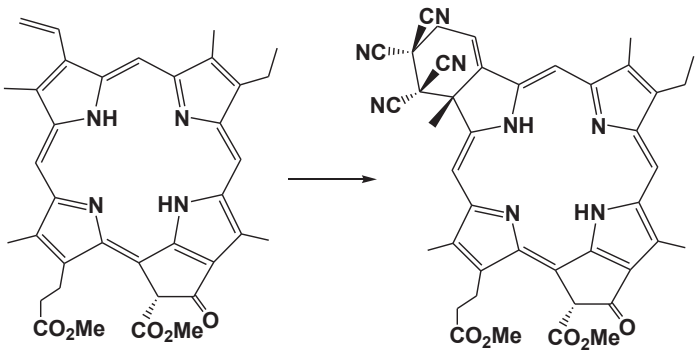
The Diels-Alder reactions were exploited in the preparation of novel long wavelength chlorin photosensitizers for photodynamic therapy[1]. Styryl group and furan carboxamide substituents were used as diene components in [4+2] cycloaddition functionalizations[2]. Pheophorbide a and chlorin e6 were effectively functionalized by cycloaddition reactions using conventional and nonconventional reaction conditions (MW irradiation[3] and extremely high pressure[4]).



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Alteration of anti-proliferative activity of vulpinic acid in novel colloidal system vulpinic acid-treated poly (vinyl benzyl chloride)

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Polymeric materials, especially polymer colloids, known as latex, draw a great attention of scientists due to their high stability and eco-friendly properties.[1] Colloidal polymers can be functionalized with various active groups such as cationic groups, which could be utilized for the attachment or bonding of the biologic molecules to improve or mask the dedicated properties of biomolecules.[1d] Vulpinic acid is an important natural molecule, isolated from lichen Letharia vulpina, displays antimicrobial, antiviral, anti-proliferative, antiangiogenic, anticancer and electrochemical properties.[2] We, therefore, aimed to develop novel polymeric colloidal system based on vulpinic acid loaded polymer colloids by utilization of chloromethyl functionality on poly(vinyl benzyl chloride) (PVBC) to determine the alteration of anti-proliferative capacity of vulpinic acid. For this purpose, PVBC colloids were treated with vulpinic acid in triethylamine as described previously,[1d, 3] and PVBC/vulpinic acid colloidal systems were obtained at two different concentrations. Vulpinic acid contents of PVBC/vulpinic acid colloidal systems were determined as 11.3% and 4.3% (w:w). Characterization of the colloids were achieved by using Fourier Transform Infrared (FTIR) spectroscopy, thermogravimetric analysis, zetasizer and Scanning Electron Microscopy (SEM). Anti-proliferative activities of the colloids were determined for 72 hour treatment on human skin keratinocyte (HaCaT) cell line by using thiazolyl blue tetrazolium bromide (MTT) cell viability assay, and the applied colloid concentrations were chosen by consideration of half maximal inhibitory concentration (IC50) of vulpinic acid (approximately 50 µg/ml).[4] The obtained data showed that vulpinic acid loaded colloidal systems showed less anti-proliferative activity than bare vulpinic acid, although applied concentrations of the colloids include IC50 of vulpinic acid. Consequently, this study reveals that anti-proliferative feature of vulpinic acid on HaCaT cells are masked and limited when vulpinic acid molecules are loaded to poly (vinyl benzyl chloride) colloids. The cytotoxic feature alteration of vulpinic acid might be useful in different application fields such as photo-protective or antimicrobial applications. Therefore, further studies with this colloid systems should be designed and performed to determine the alteration of the other activities of vulpinic acid, and identify industrial applications.

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Application of β-seleno-phenylalanine in additive-free one-pot ligation-deselenization chemistry

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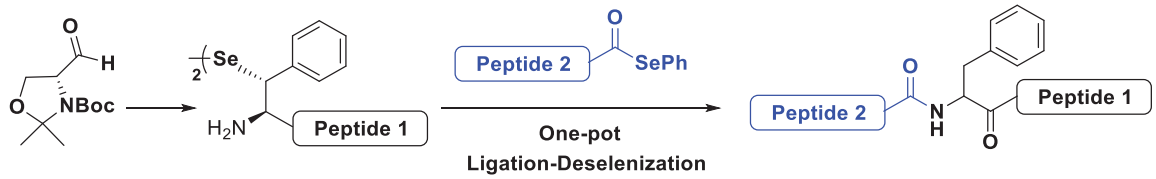
The efficient synthesis of a suitably protected β-selenophenylalanine derivative from commercially available Garner's aldehyde and the incorporation of this building block into the N-terminus of resin-bound peptides *via* Fmoc-solid phase peptide synthesis (SPPS) has been achieved.[1] Simple mixing of β-selenophenylalanine-containing peptides with peptides bearing a C-terminal selenoester functionality in aqueous buffer led to rapid ligation to afford native peptide linkages. These additive-free peptide ligation reactions were high yielding and reached completion in 10 minutes to 8 hours depending on the steric bulk at the ligation junction.[2] Following the ligation event, and without purification, an *in situ* radical deselenization reaction was employed which rapidly afforded native peptide products. Studies toward the use of this new ligation technology for the rapid one-pot assembly of proteins will also be presented.



Scheme 1. Synthetic strategy of β-Se-Phe and its application in peptide ligation.

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Targeted protein surface sensors: A new class of fluorescent probes that can track protein structural changes and binding interactions

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We have developed a novel method for tracking changes that occur on protein surfaces with fluorescent molecular sensors.[1] Although various probes that can detect proteins and follow their activity have been developed and used in analytical biosciences, such systems are generally designed to bind well-defined protein binding sites and not their surfaces. In this poster we show how the difficulty of selectively recognizing protein surfaces by using synthetic agents can be circumvented by attaching relatively non-specific synthetic receptors and a His-tag binder on the same molecular scaffold. These receptors are modified with an environmentally sensitive fluorescent probe, which enables the system to track various protein-surface modifications and binding interactions (Figure 1).

Figure 1. Targeted protein surface sensors were successfully used to track various protein-surface modifications and binding interactions.1

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Asymmetric organocatalytic addition reactions of enolisable anhydrides to maleimides: A novel approach towards the synthesis of chiral succinimides

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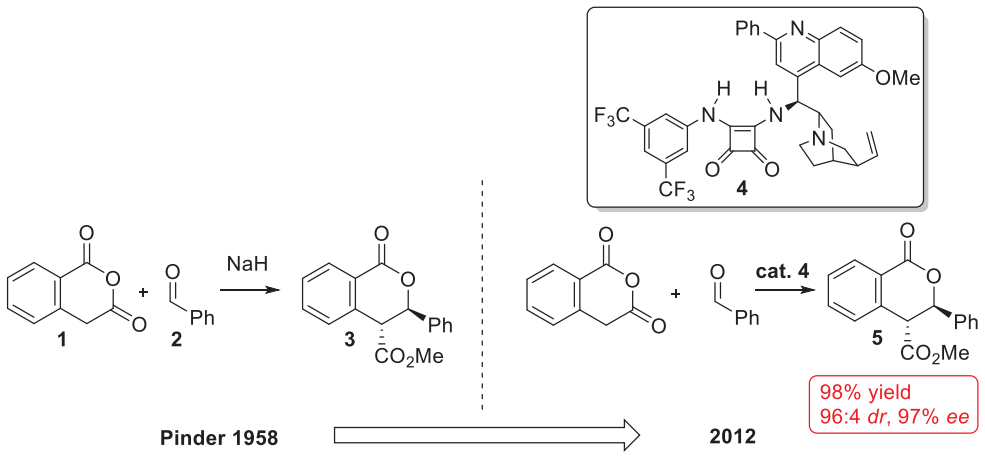
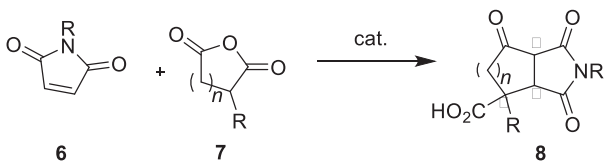
Since the beginnings of asymmetric organocatalysis, the ever expanding field has produced a diverse catalogue of robust and highly asymmetric transformations which employ a manifold of distinct substrates - providing access to a spectacular array of chiral organic building blocks.[1]

A range of classic cycloaddition reactions are particularly amenable to asymmetric induction by organocatalysis,[2] including the cycloaddition of enolisable anhydrides to a range of electrophiles[3] - exemplified by Pinder's 1958 cycloaddition of homophthalic anhydride **1** to benzaldehyde **2**. This reaction has been developed into a highly *diastereo*- and *enantio*-selective process catalysed by the modified bifunctional cinchona alkaloid **4**.[4]



In efforts to expand the scope of the electrophilic component in this reaction – we are investigating the use of maleimides as Michael acceptors[5] in these cycloaddition reactions to allow for rapid, stereo-controlled synthesis of fused bicyclic lactams of general type **8**.



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Asymmetric synthesis of thiohydantoins by the virtue of axial chirality

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Thiohydantoins are cyclic amino acid derivatives with a large variety of phamacological activities. In this work axially chiral thiohydantoins were shown to form atroposelectively as nonracemic mixtures by the reaction of *ortho*-arylisothiocyanates with amino acid esters in the presence of triethylamine (Figure 1), whereas the synthesis of nonaxially chiral derivatives returned thiohydantoins racemized at C-5 of the heterocyclic ring. The micropreparatively resolved enantiomers of nonaxially chiral derivatives were found to be optically stable under neutral conditions. Starting with **S** amino acid esters, the 5-methyl-3-aryl-thiohydantoin derivatives with bulky *ortho* substituents were found to form predominantly with *the* **S** configuration at C-5. However the corresponding 5-isopropyl thiohydantoins turned out to be more prone to racemization at C-5 during ring formation. The isomers of the synthesized axially chiral thiohydantoins have been identified through HPLC analyses with chiral stationary phases (Figure 1 insets **a** and **b**), combined with ^{1}H NMR experiments (Figure 1 insets **c** and **d**) and in all cases a high prevalence of the **P** isomers have been obtained. In addition the barriers to rotation around the $N_{(sp2)}$-$C_{(aryl)}$ chiral axis[1] have been determined.

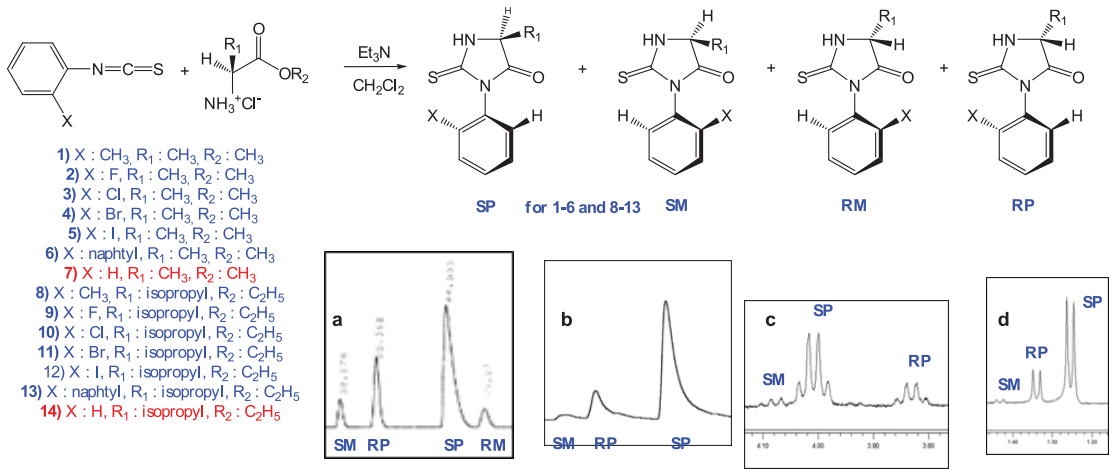

Figure 1 The synthesis of the compounds 1-14. Insets: for compound 4 a) HPLC at 60oC b) HPLC at 30oC ChiralPak IC as the stationary phase, 95:5 Hex:EtOH as the eluent c) 1H NMR quartets in the presence of (S)-(-)-2,2,2-trifluoro-1-(9-anthryl)ethanol ((S)-TFAE) d) the doublets in the presence of S-TFAE.

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Challenges and opportunities in metal catalyzed C-3 functionalization of indoles with carbonyls and their surrogates

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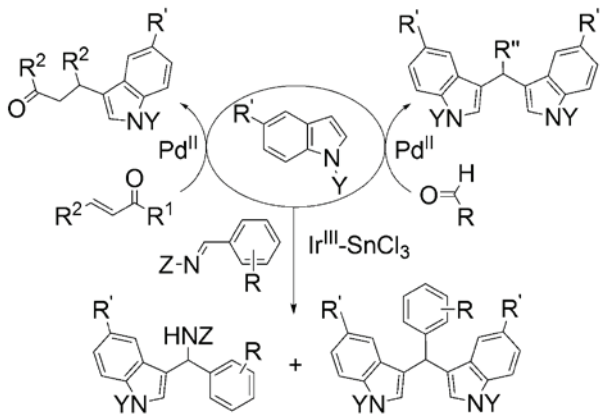
Structural motifs bearing the *'C-3 functionalized indole core'* including bisindolylmethanes are frequently found in pharmaceuticals, natural products, and other functional synthetics.[1] Development of selective, atom-economic and bench-friendly strategies for the construction of such motifs is challenging. In the present work, we report the C-3 functionalization of indoles using bimetallic Ir^{III}-$SnCl_3$ and monometallic Pd^{II} catalyst. The bimetallic catalyst $[Ir(COD)(SnCl_3)Cl(\mu\text{-}Cl)]_2$ promoted the reaction of electron-rich indoles with aldimines giving rise to functionalized amines and triheteroarylmethanes.[2,3] On the other hand, facile C-3 alkylation of indoles with electrophiles like carbonyls and enones was achieved using the monometallic catalyst $[PdCl_2(MeCN)_2]$.[4] The major advantage of such a reaction is that it does not require any co-catalyst, acid, base, additive, or external ligand and is totally insensitive to air and moisture. In this presentation, the details of optimization studies, and substrate scope in the above reactions will be highlighted.



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Chemical route optimization of gamma-carboline compounds

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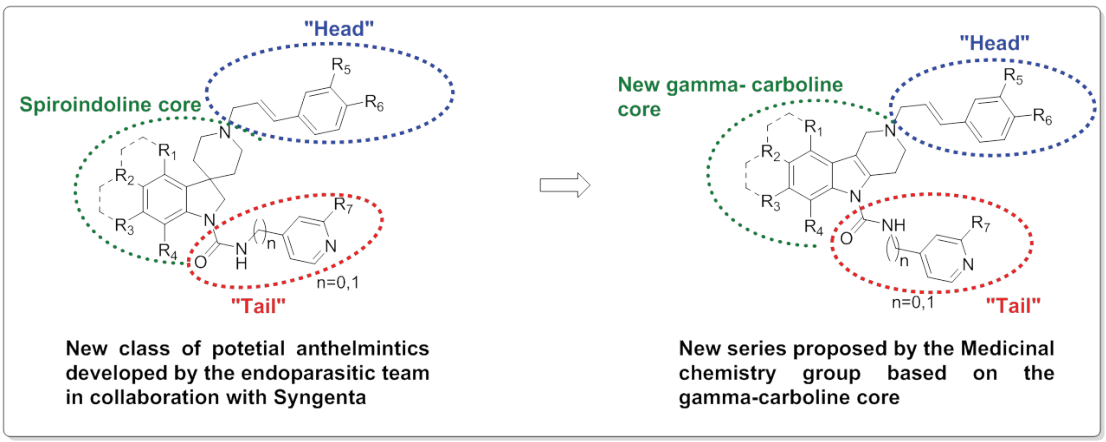
**Michigan State University*

Zoetis Medicinal Chemistry has been seeking a new series of active analogues, based on a γ-carboline motif, as a replacement of the spiro indoline motif present in the initial lead compound. As the discovery phase of the project comes to a conclusion, synthetic efforts have been started on the critical route optimization work, seeking an efficient manufacturing route.

Synthetic challenges and solutions found for the construction of the γ-carboline containing analogues are presented in this poster.



New class of potetial anthelmintics developed by the endoparasitic team in collaboration with Syngenta

New series proposed by the Medicinal chemistry group based on the gamma-carboline core

Construction of aryl- and trifluoromethyl-substituted tertiary alcohols via aldol reactions catalyzed by 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU)

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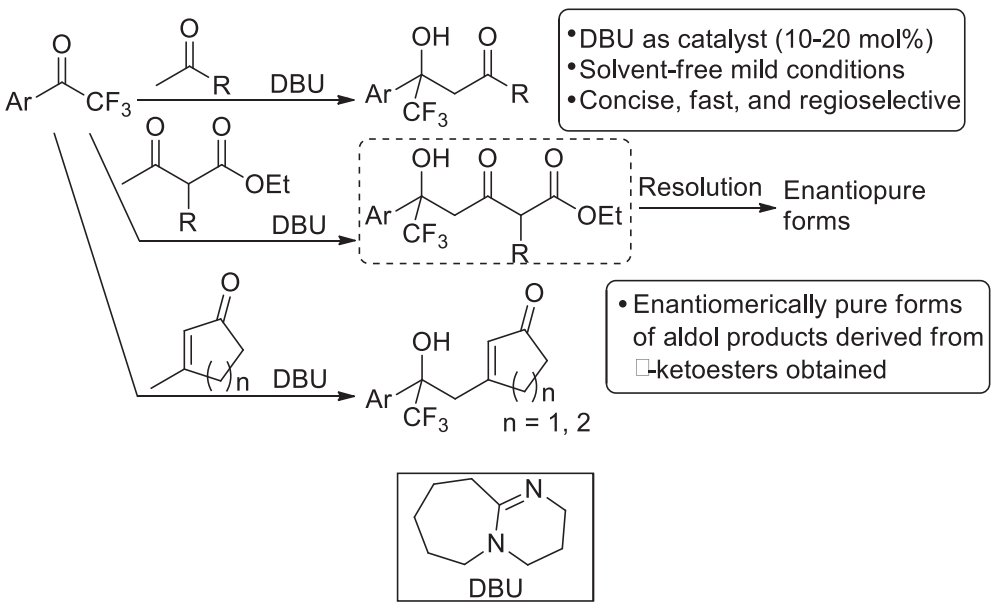
The development of the methods for the synthesis of molecules bearing aryl- and trifluoromethyl-substituted tertiary alcohol moieties is important because these molecules are used as bioactive candidates, enantiomer-discriminating reagents, and their synthons and building blocks. We have developed concise aldol reaction methods to construct these molecules.

We have recently reported aldol reactions of a pyruvic aldehyde derivative with isatins catalyzed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).[1] Based on the results, we tested the DBU catalysis for the aldol reactions of ketone donors with aryl trifluoromethyl ketone acceptors. We found that the DBU-catalyzed reactions were relatively fast and provide the aldol products in good to high yields with perfect regioselectivities under mild conditions.[2] The C-C bonds of the aldol reactions formed at the methyl group of alkyl methyl ketones, at the γ-position of β-keto esters, and at the methyl group of β-methyl-substituted cyclic enones. For the aldol products from the reactions of β-keto esters, the enantiomerically pure forms were obtained by the resolution of the enamines of the aldol products with a homochiral amine.



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Cycloaddition reactions using enolisable anhydrides with imines catalysed by cinchona alkaloids

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Trinity College Dublin

The reaction between enolisable anhydrides and aldehydes has received a great deal of attention in our group[1], allowing access to optically pure lactone products. Broadening scope to other electrophiles such as Michael acceptor has been investigated successfuly[2].

Racemic cycloaddition reactions between various enolisable anhydrides and imines have long been known to be capable of exhibiting excellent diasteroselectivity[3], however, asymmetric variants of these reactions have until recently remained largely unexplored in the literature.

The challenges associated with this chemistry relate either to the propensity for the imine to behave as a nucleophile and open the cyclic anhydride[4], or conversely, for the imine to behave as a base and activate the anhydride as a nucleophile (generating an unwanted, uncontrolled background reaction)[5]. In either scenarios, a fast background, uncatalysed reaction is problematic.

In order to obtain stereocontrol using a chiral catalyst, the basic and nucleophilic characteristics of the imine must be suppressed. We propose this could be achieved by attaching electron withdrawing groups (i.e. sulfonyl groups) to the imine nitrogen. The results of our investigations along these lines will be reported.

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Dehydrophenylalanine as a traceless turn inducer

Diane N. Le*, Jan Riedel, Yamin Zhu and Vy M. Dong
University of California, Irvine

Cyclic peptides have emerged as a class of interesting molecules due to their enhanced metabolic stability and conformational rigidity. We report a method to access cyclic peptides using dehydrophenylalanine as a traceless turn inducer. Macrocyclization occurs in concentrations as high as 0.1M. Rh-catalyzed hydrogenation affords access to the cyclic peptide. Moreover, mechanistic insight into tandem enamide hydrogenations is presented.

Design and synthesis of novel sulfonamide-containing benzoxazoles as Human GST P1-1 Inhibitors

Tugba Ertan-Bolelli[a,*], Yaman Musdal[b], Bengt Mannervik[b], Kayhan Bolelli[a], Serap Yilmaz[a], Ozum Ozturk[a], Ilkay Yildiz[a], Esin Aki-Yalcin[a] and Ismail Yalcin[a]

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The glutathione *S*-transferases (GSTs) are a family of widely distributed Phase II detoxication enzymes that catalyse the conjugation of a broad variety of reactive electrophiles to the nucleophilic sulfur atom of the glutathione[1]. Human GST P1-1 (hGST P1-1) is the most prevalent isoform of the mammalian cytosolic GSTs. hGST P1-1 is frequently overexpressed in rat and human tumors, including various carcinomas. It's suggested that overexpression of hGST P1-1 by human tumor cells may play a role in resistance to cancer chemotherapy, especially if it is associated to overexpression of the cell membrane GSH conjugate transporters multidrug resistance proteins[2-4]. Hence, hGST P1-1 can be a promising target for inhibition in cancer treatment.

In this study, new sulfonamide containing benzoxazole derivatives have been designed and synthesized as hGST P1-1 enzyme inhibitors. Compounds were evaluated *in vitro* inhibitory activities on this enzyme. Most of the tested compounds has better activity than the reference drug ethacrynic acide. Docking studies were carried out on hGST P1-1 enzyme (pdb: 6GSS) by using CDocker method in Discovery Studio 3.5 software[5]. We reported that our newly synthesized compounds bound to the H site of the enzyme and they seem to act as competitive inhibitors of hGST P1-1. The compounds obtained from this research can be used as scaffolds in design of new potent hGSTP1-1 inhibitors useful in the treatment of the resistance of cancer chemotherapy.

Keywords

Antıcancer; benzoxazole; dockıng; HGST P1-1; sulfonamıde

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Design, synthesis and electronic properties of push-pull-push type dye

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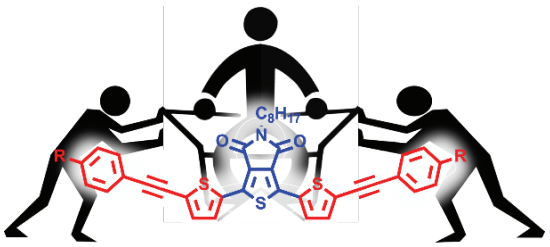

Sonogashira cross-coupling protocol was employed for the construction of a push-pull-push type dye. Ethynyl π-spacer extends the effective π-conjugation length between push and pull units without altering the planarity of the electron donor/acceptor pair. The variation of the strength of alkyne π-spacer electron push (or donor) units of these dyes has a strong effect towards the shifting of both absorption and emission maxima and thereby on the Stokes shift.

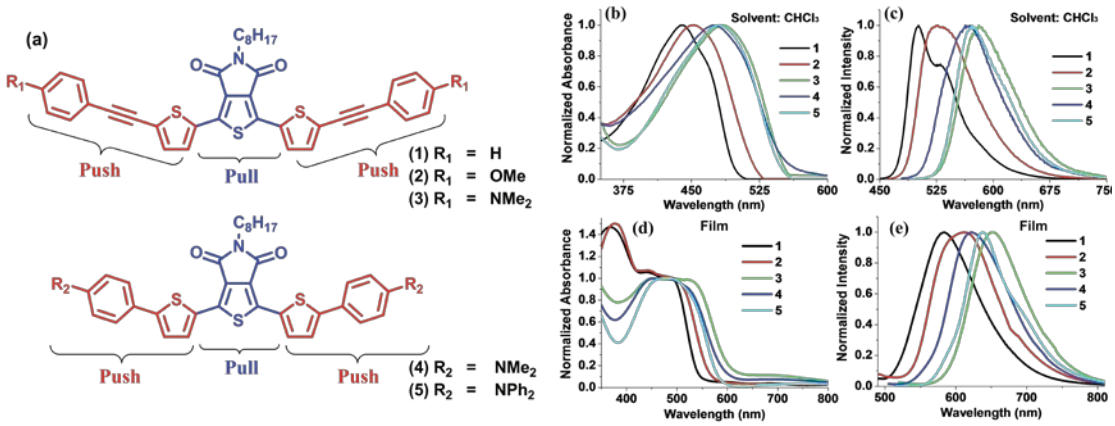

Figure 1. (a) Chemical structures of push-pull-push dye. UV-visible and fluorescence spectra of the dye 1-5 in (b-c) solution and in (d-e) film.

The dyes were solvatochromic and their solvatochromicity was highly dependent on the electron push unit (Figure 1). Strong red shifted emissions were likely to arise due to the internal charge transfer (ICT) from electron push unit to electron pull unit. Calculated energy values of HOMO→LUMO transitions are in good accordance with experimental observations. Alkyne conjugated electron push units (–C≡C–Ar; Ar = Ph, Ph-OMe, Ph-NMe_2) are more effective to increase the E_{HOMO} levels. Overall, experimental and theoretical results of the push-pull-push dyes indicate that they can be used as a promising conjugated materials with predictable electronic properties for optoelectronic devices.

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Desymmetrizations via rhodium-catalyzed ketone hydroacylation

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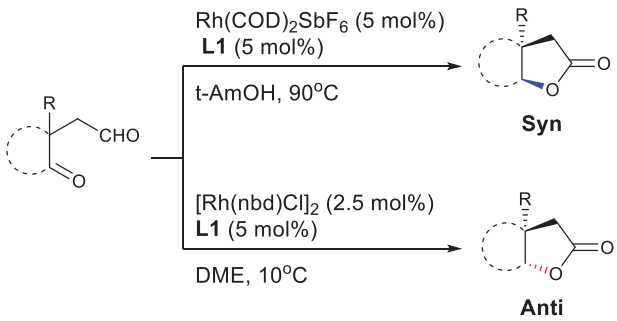
This poster describes a rhodium-catalyzed hydroacylation of aliphatic 1,4-keto aldehydes to generate lactones with high enantioselectivity. The sense of diastereoselectivity can be controlled by solvent choice and temperature. In 1,2-dimethoxyethane at 10°C, the *syn* isomer is the major bicyclic motif, whereas in tert-amyl alcohol at 90°C, the *anti* isomer is favored. Scope, limitations, and mechanistic insights will be discussed.



up to 98% yield, >20:1 dr, 99% ee

A combined allylic azide rearrangement and Tsuji-Trost allylic substitution reaction

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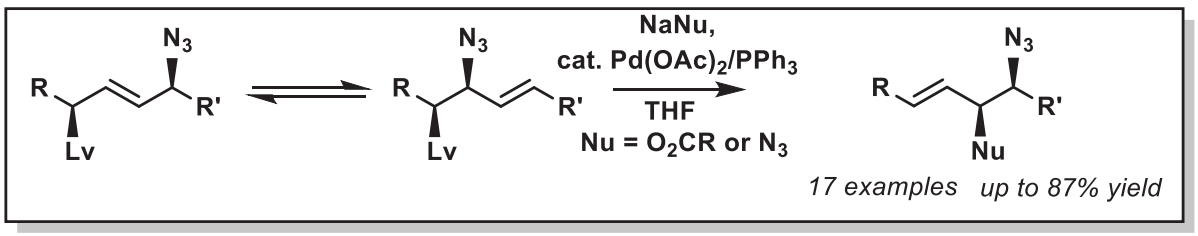

The [3,3] allylic azide rearrangement is a process which can occur at room temperature and has seen little synthetic utility in the past. Our laboratory has developed a domino reaction involving an allylic azide rearrangement followed by Tsuji-Trost allylic substitution. The reaction selectively converts synthetically problematic equilibrium mixtures into single stereoisomers. This process diastereoselectively generates densely functionalized diazides and azido-alcohols. Currently, efforts are focused towards using the aforementioned products to generate pyrrolidine azasugars.

Efforts toward the synthesis of new CID-cleavable protein cross-linkers

Sarah Block, Clinton Yu, Eric Novitsky, Lan Huang, Scott Rychnovsky
University of California Irvine, USA

Protein-protein interactions (PPIs) are the basis of cellular pathways, performing essential regulatory roles. The malfunctions of cell signaling pathways and PPIs have implications in various human disorders, including neurodegenerative diseases and cancers. Mapping of protein interactions in living systems is helpful for the identification of protein complexes that may be potential targets for drug treatment. Unfortunately, it is difficult to identify physiologically relevant PPIs for drug targets, as these interactions are often transient in nature. Chemical cross-linkers coupled with mass spectrometry analysis can be used to map protein-protein interactions and localize their interaction interfaces in living systems. Advantages of chemical cross-linkers include small sample size, tolerance for sample heterogeneity, and automated analysis. Furthermore, collision-induced dissociation (CID) cleavable protein cross-linkers simplify data analysis during cross-linking experiments. Most commercially available cross-linkers target a small subset of the 20 natural amino acids and are not designed to cleave in the mass spectrometer. We have designed and synthesized CID-cleavable protein cross-linkers that target a range of amino acid side chains in order to expand the available cross-linker toolbox.

Nickel catalyzed stereospecific cross coupling: Novel approaches to optically enriched triarylmethanes

Luke Hanna

University of California, Irvine, USA

Nickel catalyzed cross coupling reactions offer facile access to single enantiomers of known anticancer drug motifs,triarylmethanes. Stereospecific coupling of benzylic carbamates and pivalates with aryl- and heteroarylboronic esters has been developed. The reaction proceeds with selective inversion or retention at the electrophilic carbon, depending on the nature of the achiral ligand. Tricyclohexylphosphine ligand provides products with retention of configuration, while an N-heterocyclic carbene ligand provides the product with inversion.

Hydrothiolation of alkenes catalyzed by 3,5-dimethyl-5-vinylthiazolium and poly(3,5-dimethyl-5-vinylthiazolium)

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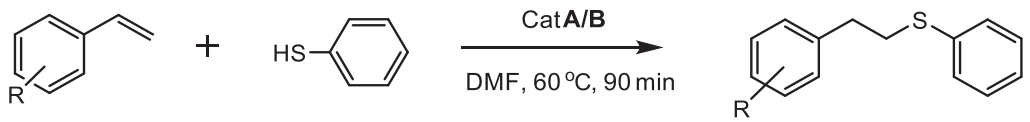
Department of Chemistry, College of Natural Sciences, Seoul National University, Seoul 08826, Korea

Organic sulfur compounds have widespread applications in materials chemistry and chemical biology.[1] Thus, the development of efficient synthetic methodologies for the incorporation of sulfur into organic frameworks is of significant interest.[2] In this context, the hydrothiolation reaction, a direct addition of the S-H bond of thiols to unsaturated carbon-carbon bonds, is a simple and atom-economical approach to the synthesis of organic sulfur compounds.[3] The development of efficient catalytic systems that can promote hydrothiolation is an important challenge for the synthetic organic chemists. However, some of the reported procedures have many disadvantages. Thus, the development of a more efficient and convenient method for the hydrothiolation of alkenes and alkynes is necessity.

Recently, we developed a polymer-based organocatalytic system, poly(4-vinyl N-heterocyclic carbene)s.[10] Continuing our work on expanding the scope of polymer-based organocatalytic systems, we screened a variety of reactions in the presence of 3,5-dimethyl-5-vinylthiazolium (**A**) and poly(3,4-dimethyl-5-vinylthiazolium)s (**B**). Interestingly, we found that **A** and **B** were highly effective catalysts for the hydrothiolation of alkenes under mild conditions. A simple and efficient protocol for the synthesis of linear thioethers via the anti-Markovnikov addition of thiols to alkenes using organic catalysts, **A** and **B** was discovered. Our catalysts were highly effective even in the presence of air and did not involve metal complexes or free radical initiators. High turnover numbers were observed in the presence of the polymeric catalyst **B**. The details will be discussed.



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Synthesis and characterisaiton of chlorin dimers

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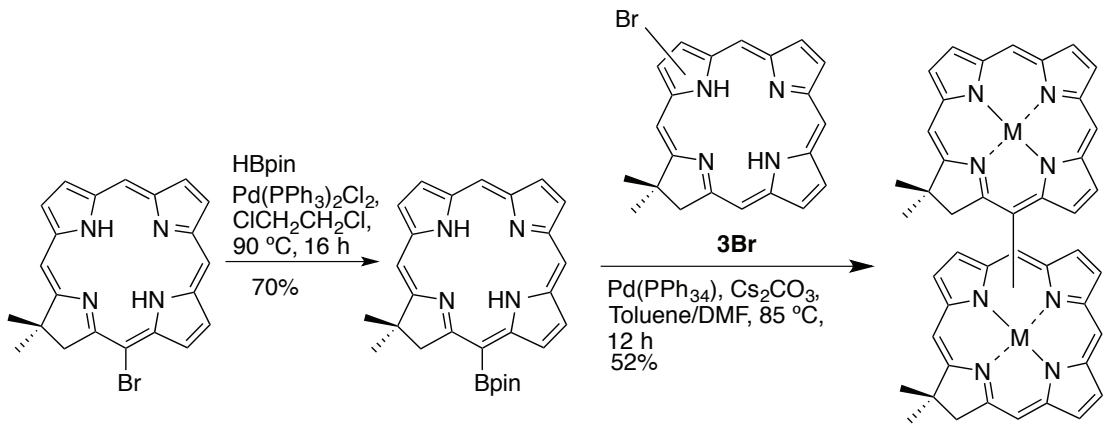
Directly linked porphyrin dimers have been investigated extensively[1]. However, their red-absorbing analogues based on hydroporphyrins (chlorins and bacteriochlorins), have gained very little attention due to the synthetic involved in preparing such structures. Borylated chlorins were synthesized through Miyaura borylation[1b, 2] of the corresponding bromochlorins.[3] With these versatile intermediates, a series of directly linked *meso*-*meso* and β-*meso* linked chlorin dimers were accessed *via* Suzuki-Muyaura couplings. Metallation with Zn- or Pd-salts afforded the corresponding metal chelates. The photophysical properties of all dimers were investigated, and compared to those of monomeric reference species.



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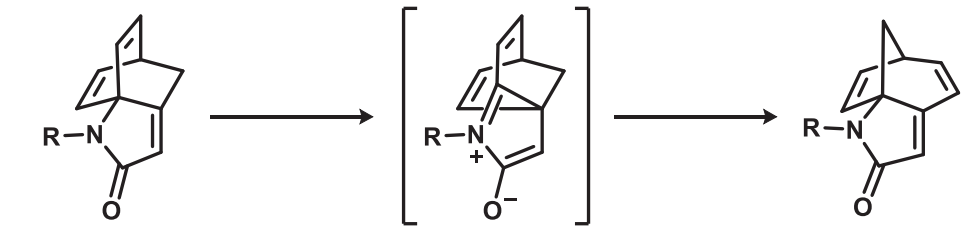
Investigation into the formal dyotropic shift of himbert cycloadducts

Alexander S. Karns*, Hung V. Pham, Christopher D. Vanderwal and Kendall N. Houk

University of California, Irvine (A.S.K. and C.D.V.) and University of California, Los Angeles (H.V.P. and K.N.H.)

A series of substituent effects and nonbonding interactions was studied in order to investigate the formal dyotropic rearrangement of select bicyclo[2.2.2]octadiene scaffolds to energetically preferred bicyclo[3.2.1]octadiene scaffolds.[1] Substrates and conditions were designed to stabilize the proposed zwitterionic intermediate through charge delocalization and to promote the formal dyotropic shift under more mild conditions. The observation of an unforeseen byproduct provides strong circumstantial support for the presence of the proposed zwitterionic intermediate in the formal dyotropic shift mechanism. Additionally, in-depth calculations by the Houk group at UCLA identify the impact of substituents and non-bonding interactions on the energetics of this transformation.



"Himbert Cycloadduct"

- General Lewis Acid Conditions for Unactivated Substrates
- Mechanistic Support for Zwitterionic Intermediate via Substituent Effects
- Further Support via "Trapped Intermediate" Isolation
- Computational Investigation of Mechanism and Substituent Effects

Reference

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Ionic liquid mediated stereoselective synthesis of 2,3-disubstituted quinazoline-4(3*H*)-ones derived from glycine linked sulphonamide

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Grimmel's method was optimized as well as modified achieving the cyclization and incorporation of glycine linked sulphonamide in 4-quinazolin-(3*H*)-ones. Further, the generation of heterocyclic motif at position-3 of 4-quinazolinones was explored by synthesis of imines, which unfortunately led to an isomeric mixture of stereoisomers. The hurdle of diastereomers encountered on the path was eminently rectified by development of new rapid and reproducible methodology involving the use of ionic liquids as solvents as well as catalyst for the synthesis of imines at position 3 leading to procurement of single *E*-isomer as the target hybrid heterocyclic molecules. The purity and presence of single isomer was also confirmed by HPLC and spectroscopic techniques. The *X*-ray crystallographic study was performed for the conformation of structure and crystal lattice of intermediate sulphonamide substituted 3-aminoquinazolinone. Further, studies along the generation of fused heterocyclic motif at position 3 are in continuation in our laboratory.

Ionic liquid promoted application of Biginelli type reaction methodology under microwave irradiation yielding hybrid dihydropyrimidines

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A novel series of hybrid diaryl pyrazole linked dihydropyrimidines containing heterocyclic amide side arm was synthesized. The Biginelli type reaction methodology was optimized under conventional as well as microwave heating conditions. Subsequently, a comparative study relating to the employment of various catalysts under different heating conditions was carried out. The use of TEAA as a mild, inexpensive, thermally stable, non-toxic as well as recyclable catalyst/reaction medium under microwave condition was established and implemented for one pot multicomponent reaction methodology with high yields and comparatively lower reaction time leading to environmentally benign reaction process. Proceedingly, the synthesized molecules were screened *in silico* and *in vitro* proving their antimalarial efficacy against plasmodium species.

Kinetic resolution of azomethine imines by Brønsted acid catalyzed enantioselective reduction

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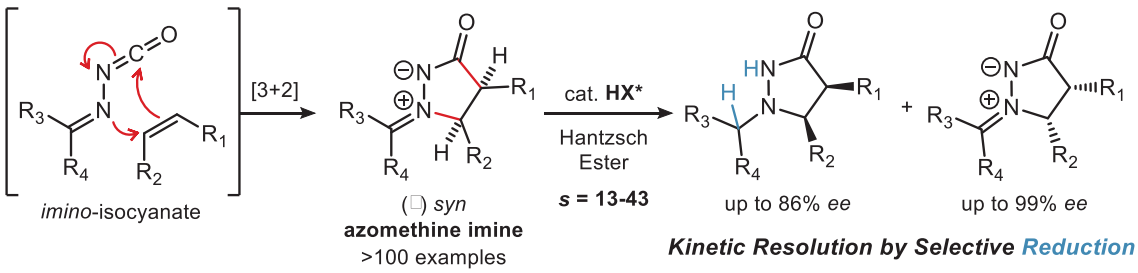
Very few methods utilize alkenes as substrates in β-amino carbonyl synthesis. Our group has developed an intermolecular alkene aminocarbonylation reaction using blocked imino-isocyanates. This concerted cycloaddition gives access to complex, racemic N,N'-cyclic azomethine imines and derivatives containing the β-amino carbonyl motif that are difficult to access by other methods.[1,2,3] With our goal to synthesize new enantioenriched β-amino carbonyls, we recently developed a kinetic resolution of azomethine imines using enantioselective Brønsted acid catalyzed reduction.[4] Both the products and recovered starting materials can be used to access both enantiomers of β-amino carbonyl derivatives. These results, including applications beyond N,N'-cyclic azomethine imines, will be discussed.



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Mechanism and origin of stereoselectivity of NHC catalyzed asymmetric reactions using transition state models

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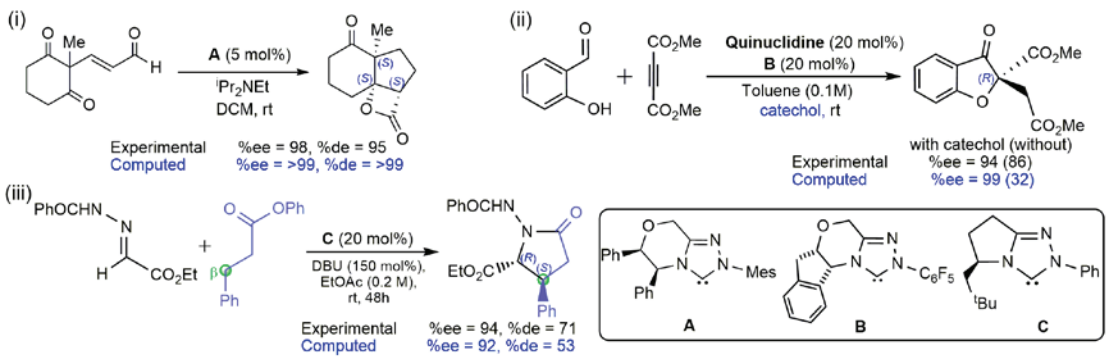
N-heterocyclic carbenes (NHCs) have been used as effective organocatalysts in asymmetric transformations.[1] NHC's ability to impart umpolung type reactivity, led to several asymmetric transformations such as benzoin, Stetter, Claisen rearrangement, annulation, cycloaddition and many other reactions.[2] In this poster, we wish to present molecular insights on three such important asymmetric reactions.[3] The first reaction involves desymmetrization of a 1,3-diketone catalyzed by chiral morpholine based triazolium NHC (**A**).[2b] In the second dual-catalytic cascade reaction, a chiral morpholine based triazolium NHC (**B**) and quinuclidine catalyze the formation of chiral benzofuranones from salicylaldehyde and dimethyl acetylenedicarboxylate (DMAD).[2c] The third reaction is an sp^3 β-C−H bond functionalization in saturated aliphatic esters catalyzed by pyrrolidine based triazolium NHC (**C**).[2d] We have investigated the mechanism and origin of stereoinduction using transition state models in all these reactions.[3] The role of additives and bases is identified. The origin of asymmetric induction stems from the differences in O−H···π, lone pair···π, C−H···O and N−H···O non-covalent interactions between the stereocontrolling transition states. These molecular insights were used in the modifications on N-aryl substituents of chiral triazolium NHCs (**B**) such that the weak non-covalent interactions in the transition states are altered. We predict improvements in the stereoselectivity for asymmetric multicatalytic cascade reaction.[3b]



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N-heterocyclic carbenes and their salts – a versatile toolbox for membrane interactions and micellar catalysis

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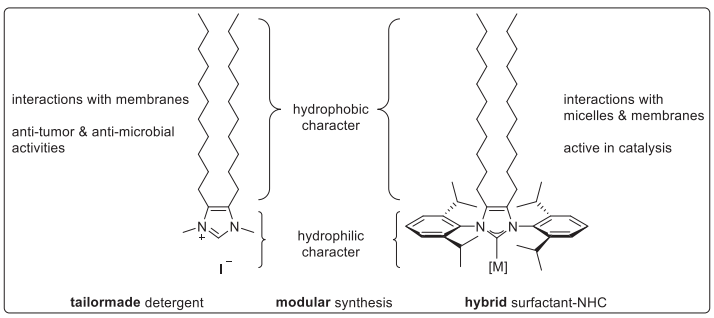
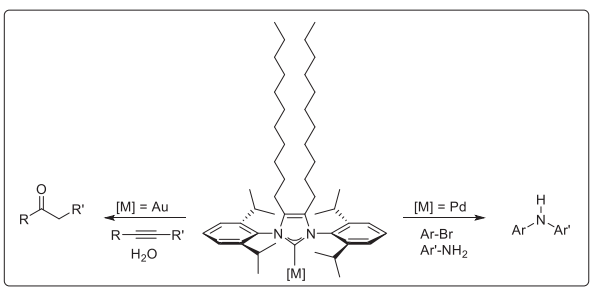
Westfälische Wilhelms-Universität Münster, Organisch-Chemisches Institut

Since the isolation of the first free *N*-heterocyclic carbene (NHC) in 1991,[1] NHCs became a versatile and frequently used tool in organic chemistry.[2] Despite the great success of NHCs, comparably little attention was paid to their salts, except for the field of ionic liquids.[3] Based on our work on stabilizing palladium nanoparticles with NHCs,[4] which contain long alkyl chains in the backbone, we realized the structural compliance with cationic surfactants and lipids. We therefore decided to systematically investigate the biological activities of our NHC salts.[5] Film balance and Quartz crystal microbalance (QCM) measurements showed an interaction of our NHC salts with DPPC membranes depending on the alkyl chain length. The strength of the interaction correlates with the critical micelle concentration (CMC) of the NHC salts. Computational investigations elucidated the mode of interaction between NHC salts and DPPC membranes.[6] Additionally, anti-tumor and anti-microbial activities, with a unique negative correlation between the CMCs and the LD50 values, were observed with a selectivity for gram-positive cell lines.



Inspired by the membrane interactions we used a derived NHC ligand for the synthesis of gold and palladium complexes for micellar and lipophilic catalysis. In case of micellar catalysis we showed the first gold catalyzed alkyne hydration in pure water and elucidated the mechanism.[7] The palladium complex was applied for C-N couplings in lipophilic media.[8]



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Novel borylated building blocks and heterocycles in palladium & rhodium catalysis

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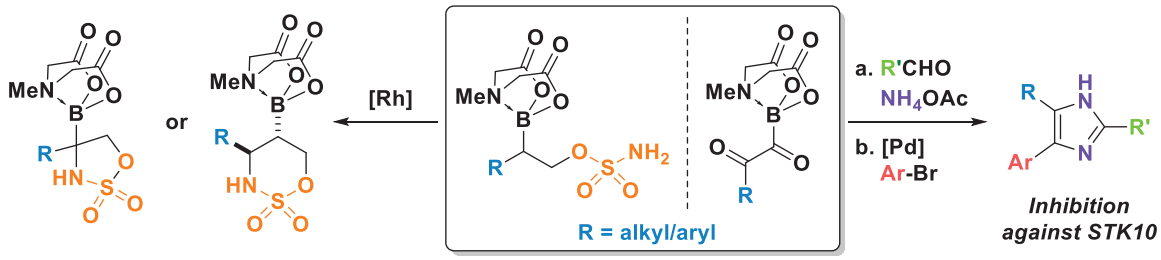
University of Toronto, Canada



With our recent developments of α-bromo boryl aldehydes,[1] α-bromo acyl boronates,[2] and 1,4-dicarbonyl boronates[3] for the synthesis of previously inaccessible borylated heterocycles well established, we have focused our attention on the development of 1,2-borylsulfamate esters and diketo-acyl boronates. The 1,2-borylsulfamate esters, synthesized from α-boryl aldehydes through a reduction/sulfamate ester formation sequence, undergo a rhodium-catalyzed chemoselective C-H amination process to afford cyclic α- and β- amino boronates.[4] These scaffolds are of particular interest due to their presence in protease inhibitors[5], namely the FDA-approved Bortezomib.[6] Furthermore, the double condensation of diketo-acyl boronates to afford uniquely substituted borylated imidazoles will also be presented. Upon further functionalization via palladium-catalyzed cross-coupling of the C-B bond yields a modular approach towards densely functionalized imidazoles, where preliminary results have shown that one of our compounds exhibits potent inhibition against serine/threonine kinase STK10.

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On the mechanism and the role of Lewis acid additives in a palladium catalysed directed C–H functionalization reaction

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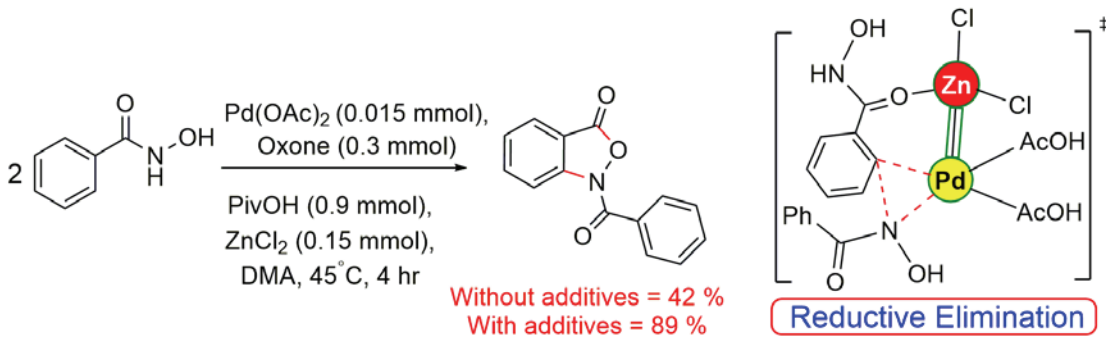
Transition metal catalysed aromatic C–H bond functionalization is an effective tool in organic synthesis.[1] Selectivity and reactivity in C–H bond functionalization have been improved by using different additives.[2] Molecular understanding of the role of additives in the catalytic cycles remains vague.[3] In a recent example, benzisoxazolones, an important biologically active compound, was synthesized from benzohydroxamic acids via C−H bond activation using palladium catalysis.[4] The reactivity was improved by the addition of both the pivalic acid and $ZnCl_2$ as the additives. Two different modes of participation of $ZnCl_2$ in the catalytic cycle is examined. Lewis acid mode of activation and through the involvement of a Pd-Zn heterobimetallic species. Mechanism of this catalytic reaction has been studied using transition state models obtained at DFT (M06) level of theory. Our calculations indicate that the Lewis acid mode of activation operates in the C–H bond activation and a Pd-Zn heterobimetallic interaction is vital in the C_{aryl}–N bond formation. The nature of ligands around the two metals and intermetallic distance is important in determining the catalytic activity of Pd-Zn heterobimetallic mode of activation. Insights obtained from our study is expected to be useful in the design and catalytic activity of multimetallic catalysis.



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Organocatalytic dynamic kinetic resolution of enolisable anhydrides

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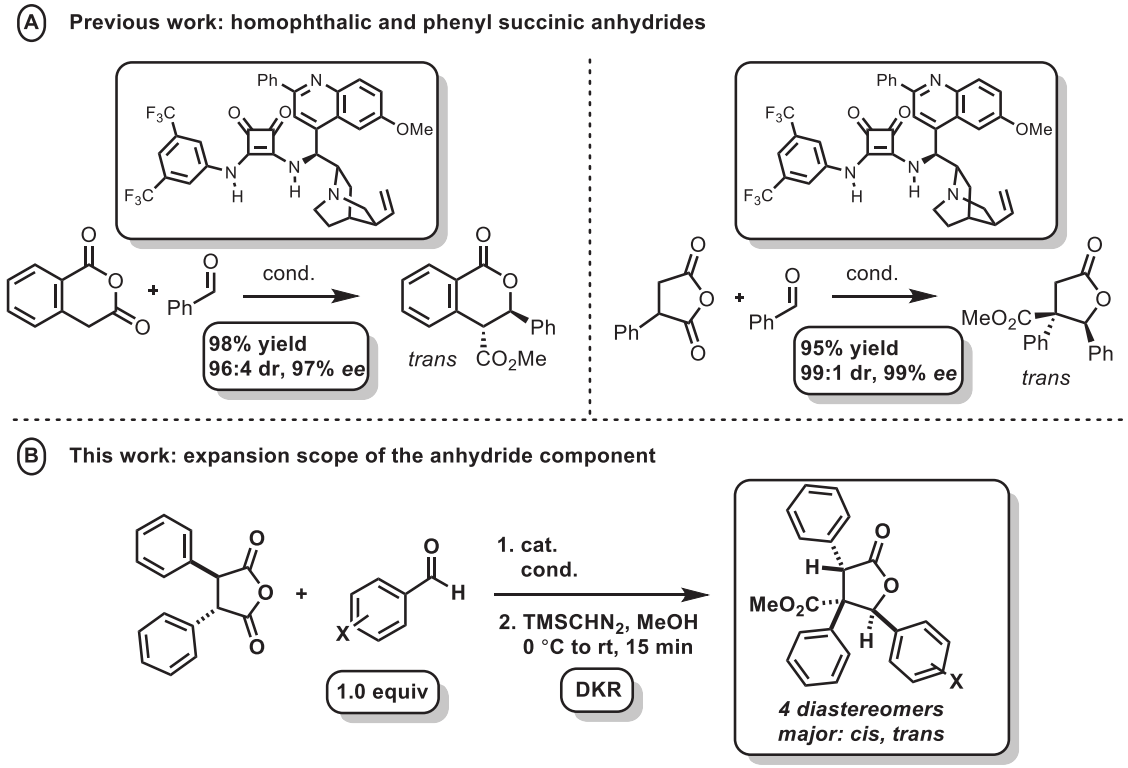
In 2012, our research group reported the first catalytic asymmetric cycloaddition reactions between homophthalic and aryl succinic anhydrides with aldehydes as electrophiles.[1, 2] In the presence of a small amount of a Cinchona based organocatalyst under mild conditions, these enolisable anhydrides were added to a range of aromatic and aliphatic aldehydes to furnish dihydroisocoumarin[1] and paraconic acid[2] (γ-butyrolactone) derivatives in excellent yields, *diastereo*- and *enantio*-selectivities (up to 99:1 dr, 99% *ee*, Figure **A**)

In this work, we now aim to expand the scope of the anhydride component in this reaction by incorporating one extra chiral centre in the core of the phenyl succinic anhydrides. The dynamic kinetic resolution of these enolisable anhydrides *via* their addition to a range of aldehydes, allows us to generate highly functionalised five-membered ring lactones containing three contiguous stereocenters (including one quaternary) in one pot. (Figure **B**)



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Palladium-catalyzed electrochemical oxygenation of C(sp^3)−H bonds

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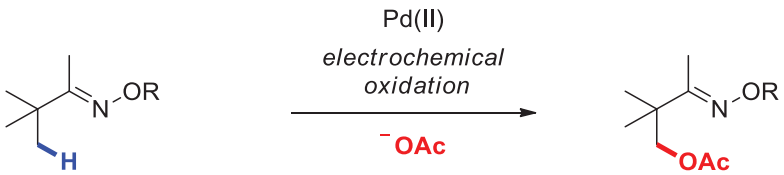

Reductive elimination from high-valent palladium species can achieve various carbon-carbon and carbon-heteroatom bond formation. Many of two-electron oxidants containing oxygen, nitrogen or halogen moieties were used to form the Pd(III) or Pd(IV) complex, which include multiple possible partners for reductive bond-forming reactions. One solution to achieve selective elimination from these high-valent metal species is the use of one electron oxidants. Electrochemical oxidation to realize the high-valent metal species could not only solve the selective bond formations problems but also provide a sustainable process. In 2009, Kakiuchi and co-workers successfully achieved Pd-catalyzed aromatic C–H halogenations under electrochemical oxidation.[1] Inspired by this seminar work, C-P, C-O bond formation has been achieved via arene C(sp^2)-H functionalization.[2] However, Pd-catalyzed C(sp^3)–H bond functionalization via electrochemical oxidation remains challenge. In this study, palladium-catalyzed oxygenation of unactivated sp^3 C–H bonds by means of electrochemical oxidation has been developed.[3] The oxygenation occurs efficiently under mild conditions over a wild rage of unactivated methyl groups.

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3. *Unpublished results*

Pharmacophore identification analysis on hGST P1-1 enzyme inhibitory active benzothiazole derivatives

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Glutathione transferases (GSTs) are multifunctional enzymes that are involved mainly in detoxification of endogenously produced and xenobiotic compounds in living organisms. GST P1-1, the most prevalent isoform in mammalian organisms, is involved in the development of resistance to anti-cancer cells towards drugs[1-2]. With increasing knowledge of GST structure and function, rational drug design strategies and mechanism-based inhibitors have been exploited successfully[3].

HipHop provides feature-based alignment of a collection of compounds without considering the activity. It matches the chemical features of a molecule, against drug candidate molecules. HipHop takes a collection of conformational models of molecules and a selection of chemical features, and produces a series of molecular alignments in a variety of standard file formats. HipHop begins by identifying configurations of features common to a set of molecules. A configuration consists of a set of relative locations in 3D space and associated feature types. A molecule matches the configurations if it possesses conformations and structural features that can be superimposed within a certain tolerance from the corresponding ideal locations. HipHop also maps partial features of molecules in the alignment set. This provision gives the option to use partial mapping during the alignment. Partial mapping allows to identify larger, more diverse, more significant hypotheses and alignment models without the risk of missing compounds that do not have to map to all of the pharmacophore features[4, 5, 6].

In this study, common feature pharmacophore identification analysis on hGST P1-1 enzyme inhibitory active new benzothiazole derivatives was carried out by using HipHop method (Discovery Studio 3.5)[6].

Keywords

Antıcancer; benzothıazole; HGST P1-1; HıpHop; pharmacophore

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Photoredox catalyzed formation of quaternary centers via 3º oxalates

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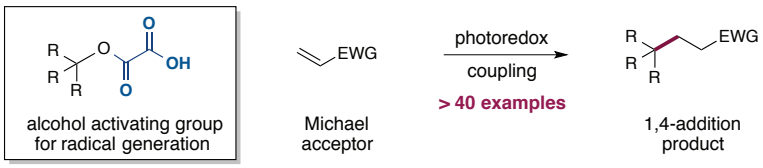
UC Irvine

Christopher Nawrat and David W. C. MacMillan
Princeton University

Alkyl oxalates are new bench-stable alcohol-activating groups for radical generation under visible light photoredox conditions. Using these precursors, the first net redox-neutral coupling of tertiary and secondary alcohols with electron-deficient alkenes is achieved.



Preparation of nano-lignin peroxidase particles as reusable catalysts

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This study describes the preparation of nanoprotein particles carrying lignin peroxidase (LiP) using a photosensitive microemulsion polymerization technique. After characterization of the prepared nanostructures with LiP photosensitive cross-linking features, the activity of the nanoparticles was assayed using tetramethylbenzidine (TMB) as the substrate. The parameters such as pH, temperature and initial enzyme concentration that affect the activity were investigated by using prepared nanoparticles and compared to free LiP. The reusability of the nanoLiP particles was also investigated and the obtained results showed that the nanoLiP particles exhibited admirable potential as a reusable catalyst.

Acknowledgements

Financial support of Anadolu University Research Projects Commission (Project No: 1001F35) is gratefully acknowledged.

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Redox controlled on/off light switch

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Switches and molecular motors represent a fascinating and challenging research field in organic chemistry. In recent years an increase in publications dealing with these topics is found. The movement of a switch is available through different external stimuli, for instance light, electrochemical processes or metal ions.[1,2]

Figure 1 shows an azobenzene and its motion. This light-induced switch undergoes an isomerization reaction from the thermodynamically stable *trans* **1a** to the *cis* **1b** isomer.

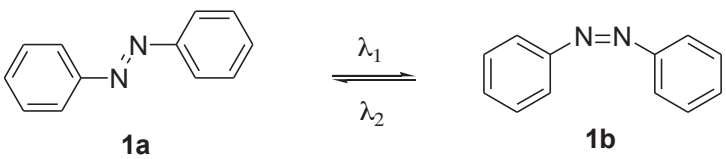

Figure 1: Motion of an azobenzene switch.

Here we show the synthesis and analysis of an azo switch, which can be turned on and off by an electrochemical process. On the one hand the switch can be stimulated by light to perform a *trans* to *cis* isomerization. On the other hand the chemical structure allows to turn the switch off, by oxidizing it. The latter is reversible, which means it is possible to turn the switch on again. To use the switch in a molecular machine the switching process must be unidirectional. This is achieved by using a cyclic imidazole clamp.[3] A combination of this system with a second light switch could lead to a molecular machine whose motion is only light-driven.

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Rh-catalyzed enantioselective desymmetrization triggered by C-H activation

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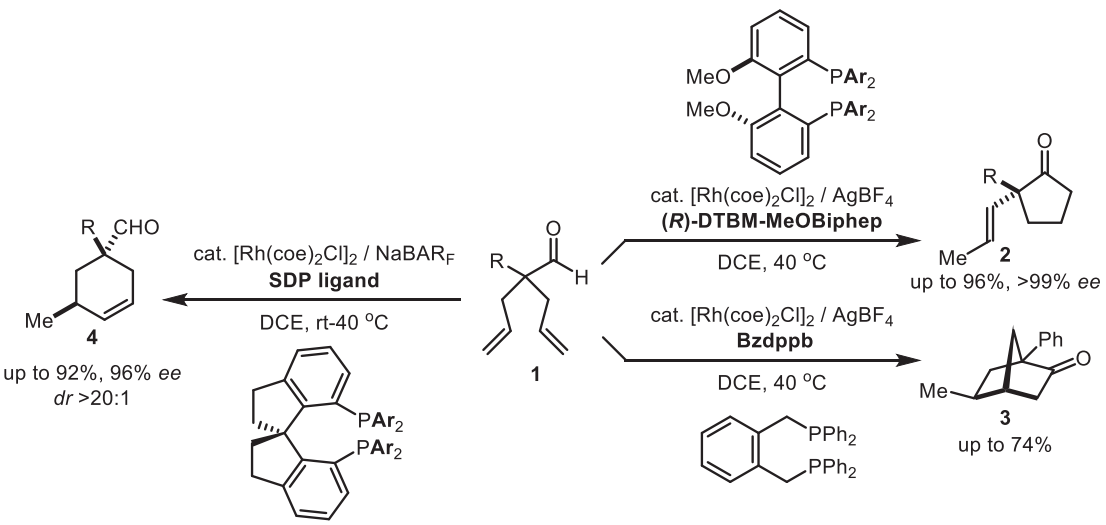
Desymmetrization has emerged as a way to access chiral quaternary-carbon motifs, which are among the most challenging stereocenters to generate with enantiocontrol.[1] Strategies involving C−H bond activation are especially promising yet rare.[2] Given this challenge, we have recently disclosed a Rh-catalyzed desymmetrization of all-carbon quaternary centers from prochiral α,α-bis(allyl)aldehyde **1** by a cascade featuring isomerization and hydroacylation.[3] A BIPHEP ligand promotes enantioselective formation of α-vinylcyclopentanones **2**. Mechanistic studies support irreversible and enantioselective olefin-isomerization followed by olefin-hydroacylation. We have also demonstrated a desymmetrization of prochiral aldehyde **1** to form scaffolds bearing quaternary centers *via* carboacylation to generate **3**. Finally, we have established a metal-catalyzed isomerization to generate cyclohexenecarboxaldehydes **4** bearing α-quaternary centers. This Rh-catalyzed method provides enantioselective access to a 3,3,5-trisubstituted cyclohexene motif that is inaccessible by the well-established Diels-Alder and therefore complements conventional cycloadditions.[4]



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Rhodium-catalyzed alkyne hydrofunctionalization

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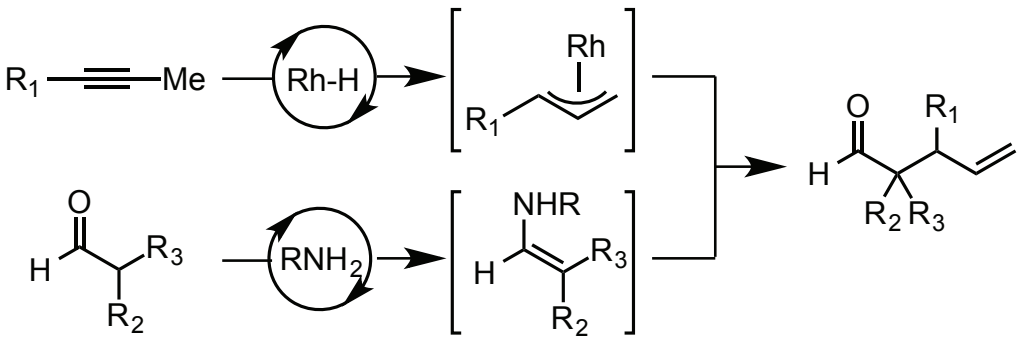
The coupling of internal alkynes with aldehydes is achieved via tandem rhodium catalysis. Combining organo- and transition metal catalysis allows for regio-, diastereo-, and enatioselective access to aldehydes with vicinal quaternary and tertiary carbon centers.



Rhodium-catalyzed tandem isomerization and hydroamination of alkynes

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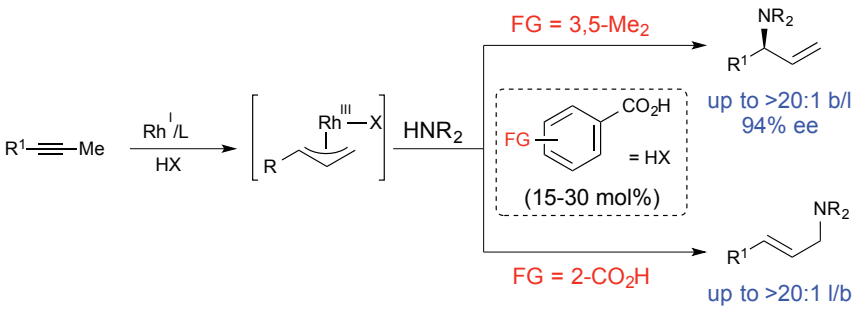
Under Rh-tandem catalysis, alkynes can be isomerized to allenes and subsequently be coupled to various nucleophiles. This strategy was successfully applied to the enantio- and regioselective hydroamination of alkynes with amine nucleophiles to afford N-allylic amines as opposed to imines and enamines, which are the products of traditional alkyne hydroamination. A carboxylic acid additive switch allows access to either the branched or linear isomer with excellent regiocontrol by an isomerization pathway.



Switchable selectivity in an NHC-catalysed dearomatizing annulation reaction

Mirco Fleige*, Chang Guo, Daniel Janssen-Müller, Constantin-Gabriel Daniliuc and Frank Glorius

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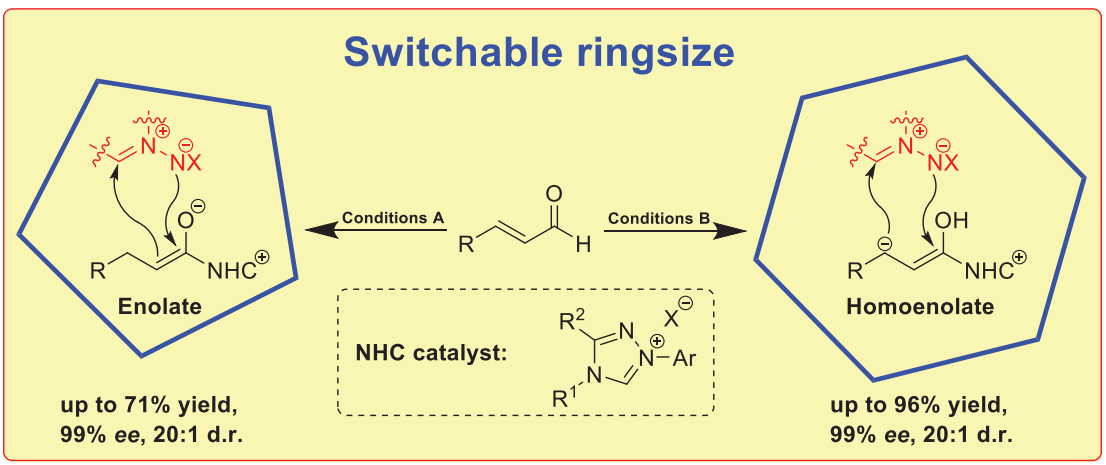
Over the last years N-heterocyclic carbene (NHC) catalysed annulation reactions have become an important and powerful tool to generate heterocycles bearing stereocenters.[1] First reports on this type of reaction were shown by Bode[2] and Glorius[3] in 2004, wherein NHC-catalysed [3+2] annulation of enals with aldehydes provided γbutyrolactones. Since then NHC-catalysed reactions involving the reactivity of acyl anions, homoenolate, acylazolium and enolate equivelants have emerged in organic catalysis.[4]

Here we achieved a NHC-catalysed regio- and enantioselective annulation reaction of enals in a switchable reaction pathway leading to 5- and 6-membered hetero-cycles.[5]



Under reaction conditions **A** the corresponding 5-membered heterocycle was formed via a reactive enolate. Employing conditions **B**, the annulation reaction proceeds via a homoenolate and gives a 6-membered ring system. These NHCcatalysed reactions provide heterocycles in high yields and generate two stereocenters in excellent enantio- and diastereoselectivity.

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Total synthesis of curvulamine

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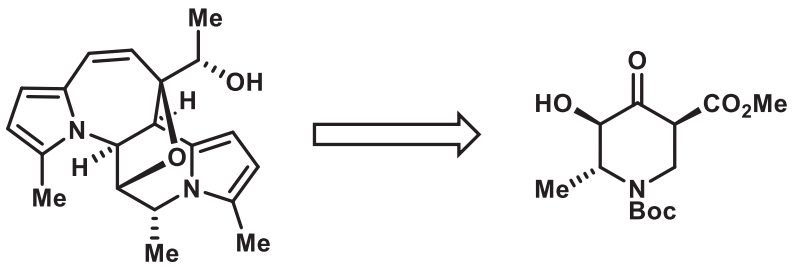
During the past ten years, international health agencies have been warning society about antimicrobial resistance and in 2014, the World Health Organization stated that “Antibiotic resistance […] is now a major threat to public health.” Despite this alarming situation, many pharmaceutical companies stopped their research programs owing to poor returns on investment. There is therefore a need to develop new molecules that possess antimicrobial activity to rise to the ever worsening challenge of drug resistant microorganisms.

Curvulamine (**1**) is biosynthesized by *Curvularia* fungus coming from the floral gut of white croaker fish and was isolated by Tan and co-workers in 2014[1]. Its structure was confirmed by X-ray analysis and it was found to exhibit potent activity against various pathogens such as *Veillonella parvula, Actinomyces israelii, Streptococcus sp., Bacteroides vulgatus, Peptostreptococcus sp*.



Curvulamine (**1**)

From a structural point of view, curvulamine possesses six contiguous stereocenters organized around a densely functionalized THF ring as well as two 1,2,5-trisubstituted pyrroles. Accessing a substantial amount of curvulamine would allow the determination of its absolute configuration and for more biological tests to be performed. Therefore, we envisaged an efficient synthesis of curvulamine using a late-stage introduction of the pyrroles and a diastereoselective ring-closure metathesis as a strategy. Our poster will report the advances made in this direction.

Keywords

Total synthesis, antimicrobial, alkaloid, natural product.

Reference

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Towards the development of small molecule kinase mimetics

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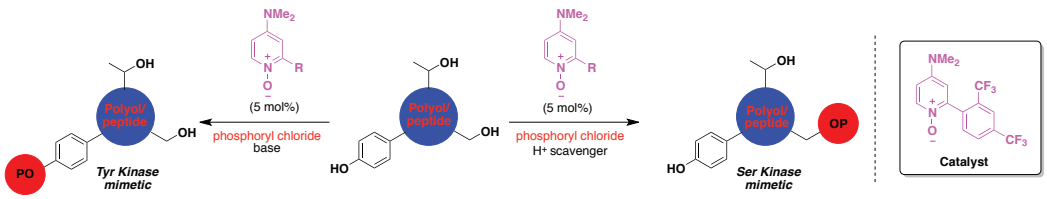
j.murray12@imperial.ac.uk

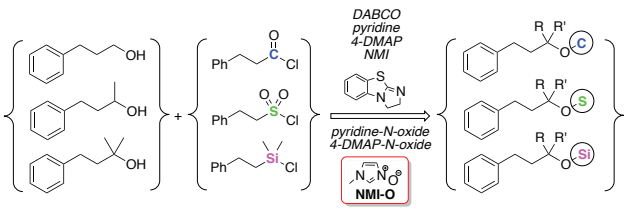
The development of selective synthetic kinase mimetics for the phosphorylation of hydroxyl containing amino acids (Ser/Thr/Tyr) would provide an efficient, late-stage method of incorporating phosphate functionalities to peptides and low MW proteins.[1–3]

Our laboratory has reported the development of novel 2-aryl-4-dimethylaminopyridine-*N*-oxide (DMAP-*N*-oxide) derived kinase mimetics for the selective phosphorylation of hydroxyl-containing amino acids, polyols and peptides (Scheme 1).[4,5] These reactions proceed in good to very good yields and high levels of chemoselectivity for primary *vs*. secondary *vs*. phenolic alcohols (Ser *vs*. Thr *vs*. Tyr) have been demonstrated in the phosphorylation of poly-alcohol containing substrates. Rate studies have been conducted on protected derivatives of these amino acids under various conditions and have revealed that reaction rates and thus substrate selectivity are highly dependent upon the choice of base. The utility of this methodology in has also been demonstrated in the site selective phosphorylation of a heptapeptide; mimicking the action of tyrosine kinases.



Scheme 1 – Selective phosphorylation of polyol containing substrates

Recently, we have been investigating the use of aryl-*N*-oxide catalysts in analogous acylation, sulfonylation and silylation processes, comparing their activity to commonly used Lewis-basic catalysts (*Scheme 2*).[6] Interestingly, we have demonstrated that whilst amine derived catalysts are more active for acylation, aryl-*N*-oxides are more efficient for the sulfonylation and silylation of alcohol derivatives.



Scheme 2 – Catalyst evaluation for acylation, sulfonylation and silylation

Importantly, we have reported the first highly efficient silylation of tertiary alcohol derivatives using 1-methylimidazole-*N*-oxide (NMI-O). Currently, we are investigating the use of aryl-*N*-oxide catalysts for the selective 'tagging' of phosphorylated amino acids to provide a chemical tool to access the phosphoproteome.

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Towards the synthesis of (−)-Vibralactone

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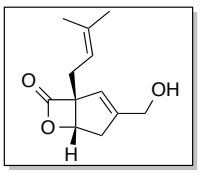
Vibralactone (**1**), first reported in 2006 from *Boreosterum Vibrans,* is a potent inhibitor of pancreatic lipase (PL), and a potential anti-obesity lead candidate.[1] Obesity has become a serious worldwide health concern due to its association with chronic diseases such as diabetes and heart disease. This rise in obesity causes economic strain due to the associated health care costs, leading to an increase in demand for obesity therapeutics. Vibralactone (**1**) is a low molecular weight molecule with a fused β-lactone ring core, which presents an interesting target for synthetic investigation.

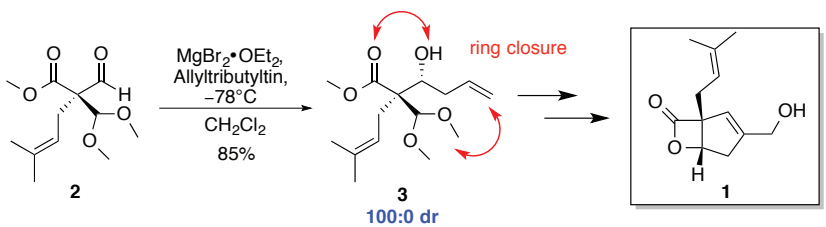


(−)–Vibralactone (**1**)

*Figure 1: Structure of (−)-Vibralactone (**1**)*

Our objective is to develop an asymmetric synthesis of vibralactone that would later be applicable to the synthesis of a range of analogues for bioactivity evaluation and SAR studies. Key challenges include the efficient stereo-controlled formation of adjacent tertiary and quaternary carbon centres within highly functionalised intermediates, which are suitable for rapid progression towards the target.

Here we present our approach to the synthesis of vibralactone with the focus of closing the cyclopentene ring by an aldol cyclisation of a dialdehyde, which can be accessed via key intermediate **3** (**scheme 1**). This highly functionalised system (3) has been synthesised in good yield over four steps with complete control of the stereochemistry of the secondary alcohol. This has been achieved by a diastereoselective allylation[2] (**scheme 1**), utilising the acetal protecting group to induce facial selectivity. Generation of this chiral centre is a significant improvement on the previous synthesis of vibralactone where the best selectivity achieved was 3:2.[3] Routes to the synthesis of (±)-vibralactone (*1*) will be detailed in the poster along with current work towards the asymmetric synthesis.



*Scheme 1: Overview of the synthetic strategy including the diastereoselective allylation of aldehyde **2**.*

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X-ray crystallographic structures of a trimer, dodecamer, and annular pore formed by an $A\beta_{17–36}$ β-hairpin

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Amyloidogenic peptides and proteins form porelike assemblies of oligomers that are thought to be important in neurodegeneration.[1] The structures of these assemblies are not known at atomic resolution. The absence of high-resolution structures of these assemblies constitutes an important gap in understanding Alzheimer's disease, Parkinson's disease, and other amyloid diseases. Our research group recently elucidated the X-ray crystallographic structure of a dodecamer formed by a β-hairpin that comprises $A\beta_{17-23}$ and $A\beta_{30-36}$.[2] The dodecamer consists of a tetramer of trimers, each of which consists of three β-hairpins. In the current study we have incorporated $A\beta_{24-29}$ to create a β-hairpin comprising $A\beta_{17-36}$. Here we report the X-ray crystallographic structures of the dodecamers formed by twelve of the $A\beta_{17-36}$ β-hairpins and an annular pore formed by five of the dodecamers.

X-ray crystallographic structure of a dodecamer derived from $A\beta_{17-36}$
(PDB 4NTR, *JACS* **2014**, *136*, 5595)

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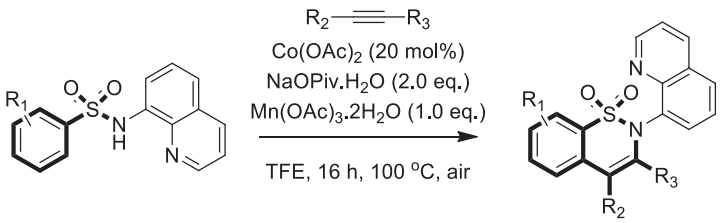
Building up molecular complexity using cobalt catalysis through C-H activation and C-H functionalization

Oriol Planas*, Christopher J. Whiteoak, Anna Company and Xavi Ribas

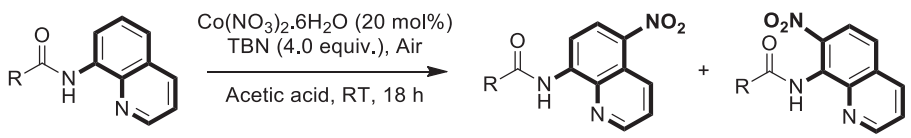
QBIS-CAT Research Group, Institut de Química Computacional i Catalisi (IQCC), Departament de Química, Universitat de Girona, Girona, Catalonia, Spain

Sulfonamide containing compounds have found application in numerous pharmaceutical drugs.[1] In particular, cyclic sulfonamides (sultams) have been applied as anti-inflammatory drugs and carbonic anhydrase/ Calpain I inhibitors. Consequently, new catalytic protocols towards the synthesis of sultams would be of significant interest. Recently, Daugulis and co-workers have shown that using a Co-catalyzed C-H activation methodology, alkynes can be coupled to aryl amides containing an 8-aminoquinoline directing-group with high regioselectivity.[2] With this precedent in mind we have developed a Co-catalyzed aryl sulfonamide coupling with alkynes for the synthesis of sultams offering improved regioselective control over a previously reported Rh-catalyzed approach.[3] The reaction shows a broad substrate scope with products obtained in good to excellent isolated yields (60-97%) and with high regioselectivities.[4]



"Sultam motif"

We have also applied Co-catalysis in a totally different mechanistic scheme for the nitration of aminoquinolines using carboxamides as auxiliary groups. Aromatic nitro compounds are important chemical intermediates and are also prevalent in dyes, pharmaceuticals, perfumes and explosives.[5] Classically, nitration of aromatic compounds has been carried out using a mixture of HNO_3 and H_2SO_4, whereby regioselective control and functional group tolerance under these harsh conditions is often challenging. Whilst developing new cobalt-catalyzed C-H activation protocols using the 8-aminoquinolone directing group, we have recently discovered a new Co-mediated nitration strategy which permits remote functionalization of the C5 and C7 positions of the aminoquinoline moiety *via* a SET mechanism using *tert*-butyl nitrite (TBN) as nitro source.[6]



Major *Minor*

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Cobalt-catalyzed intramolecular hydroacylation towards an enantio-, diastereo-, and regioselective synthesis of cyclobutanones

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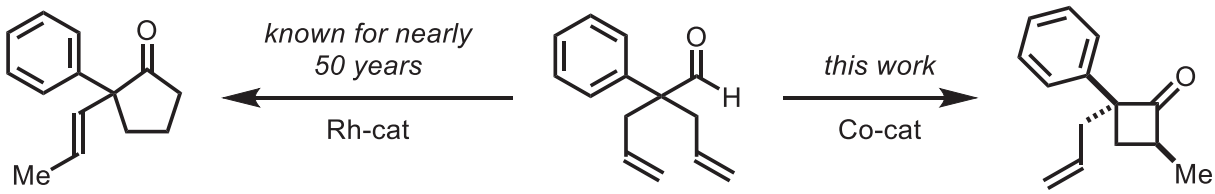
University of California at Irvine, USA



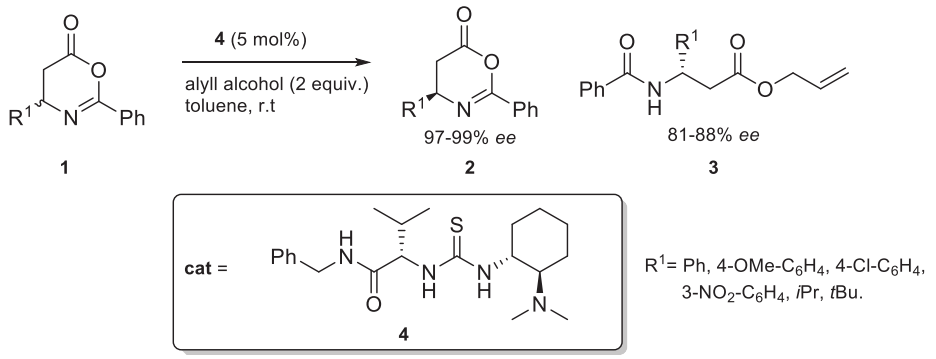
In nearly 50 years of intramolecular hydroacylation, cyclization of 4-pentenal derivatives favor formation of the 5-membered ketone product under Rh-catalysis. It has been demonstrated that cobalt-catalysis has similar reactivity to Rh-catalysis but also has the potential to develop complementary chemistry. We recently reported hydroacylation of α,α-bis(allyl)aldehydes with Rh-catalysis to synthesize cyclopentanones. However, using Co-catalysis led to formation of a 4-membered cyclobutanone product in good yield and stereocontrol.

Kinetic resolution of oxazinones to give orthogonally protected β-amino acids

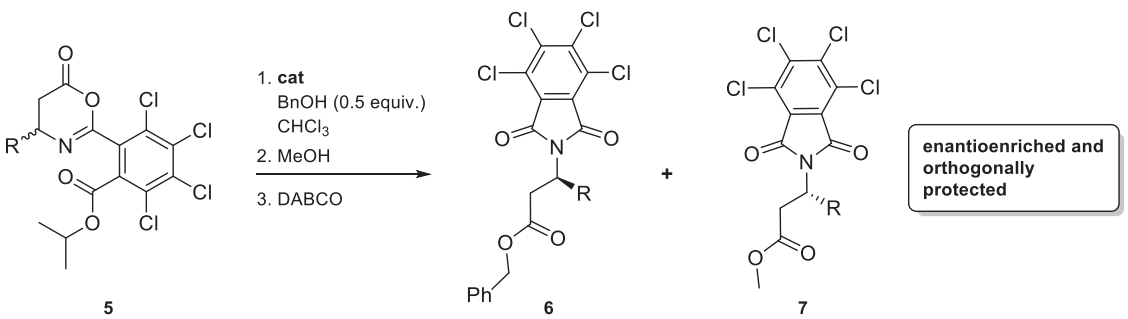
Sarah A. Cronin*, Stephen J. Connon
Trinity College Dublin

Compared to their azlactone counterparts, the organocatalytic kinetic resolution of oxazinones to yield enantioenriched amino acids is vastly underdeveloped. All current methods generate the *N*-benzoyl protected amino acid **3** upon ring opening.[1] Hydrolysis of the benzoyl amide functionality requires harsh reaction conditions which result in the simultaneous cleavage of the ester protecting group to yield the free amino acid. Selective re-protection of the amino acid is then required for further use in peptide synthesis. In this work we hope to overcome this lack of orthogonality by the preparation of TCIC-substituted oxazinones (**5**). This unit not only results in increased reactivity of the substrate, it also generates a product (after ring opening of the oxazinone) which can be converted to a phthalamide *in situ*.[2] Subsequent removal of the phthalamide protecting group can be achieved in the presence of the ester functionality and *vice versa*; the amino acids generated are thus orthogonally protected. We have described efforts to synthesise the TCIC-substituted oxazinones and our investigation into the search for optimum reaction conditions for the catalytic transformation to give a wide range of protected amino acid products.

Current methods for the KR of oxazinones:



This work:



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N-heterocyclic carbenes - versatile ligands for nanoparticle stabilization

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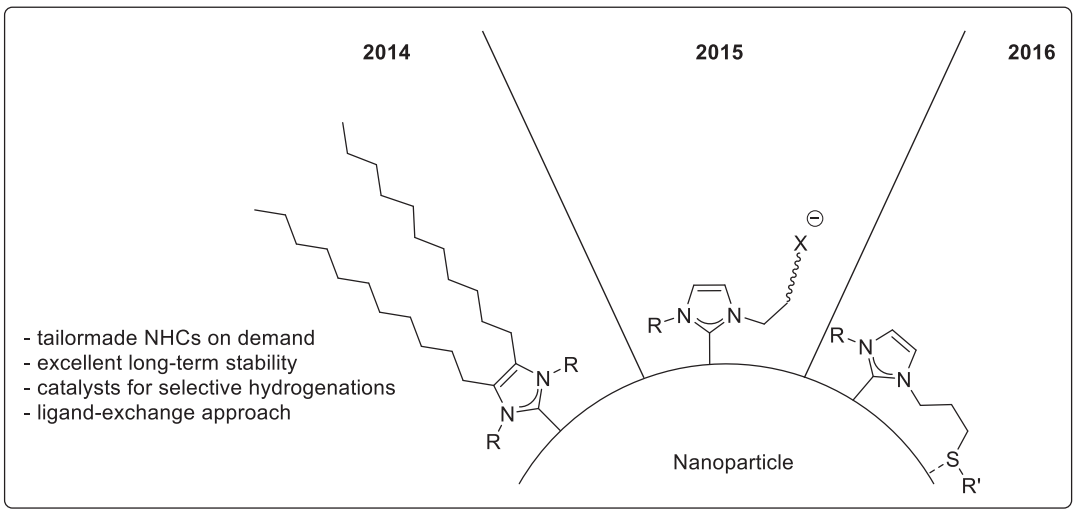
Westfälische Wilhelms-Universität Münster, Organisch-Chemisches Institut

N-heterocyclic carbenes (NHCs) are well established ligands in organometallic chemistry, which results from their electron-rich character and directed steric demand towards the metal leading to strong transition metal to carbon bonds. Additionally, the synthesis of NHCs enables a diverse structural variation and therefore adaption of the required characteristics.[1] Due to their unique properties and the vast variety NHCs have emerged as an excellent ligand class for surface stabilization and modification.[2]



During the last years, we developed a variety of NHC-ligands for the stabilization of different nanoparticles (for example palladium and gold). The NHC stabilized nanoparticles were synthesized from well-defined thioether stabilized nanoparticles *via* a powerful ligand-exchange approach. All of the fully characterized nanoparticles showed good long-term stability and promising reactivity in catalysis. Installing long alkyl chains in the backbone of the NHCs provided stable nanoparticles due to steric repulsion with the opportunity to add different substituents at the nitrogen positions on demand (2014)[3]. An alternative stabilizing motif, electrostatic repulsive, was achieved by introducing charged groups at the end of a side chain of a NHC resulting in water-soluble nanoparticles (2015)[4]. A combinatorial approach is given with a modular, bidentate NHC-thioether-hybrid system, which imparts an easy synthesis of different kinds of ligands with the required properties depending on the substituent attached to the thioether moiety (2016)[5].

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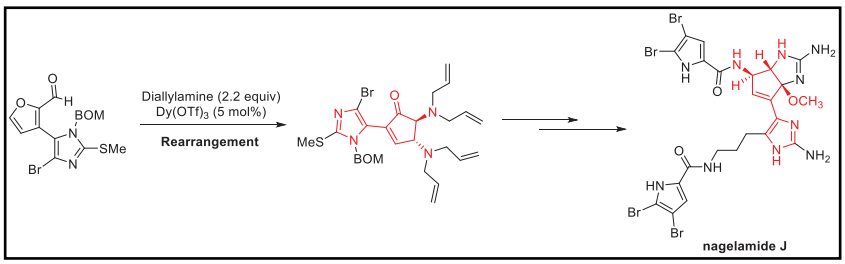
Progress towards the total synthesis of nagelamide J

Anika Tarasewicz*, Marvin Morales and Robert A. Batey
University of Toronto, Toronto, Canada

A novel dimeric bromopyrrole alkaloid, nagelamide J, was recently isolated from the Okinawan marine sponge *Agelas* species.[1] This natural product is structurally unique because it is the first isolated member of the pyrrole-2-aminoimidazoles (P2AI) class of alkaloids possessing a cyclopentane fused to a 2-aminoimidazole. Preliminary studies show that nagelamide J exhibits excellent antimicrobial activity against *Staphylococcus aureus* (MIC = 8.35 μg/mL), a bacteria that poses a major threat in health care due to drug resistance. The highly functionalized core and the promising biological activity of this natural product makes this an interesting synthetic target. Our approach focuses on using a Lewis acid catalyzed rearrangement in the formation of the nagelamide J core. Herein, we will highlight the methods used to form the core and the future strategy towards the first total synthesis of nagelamide J.



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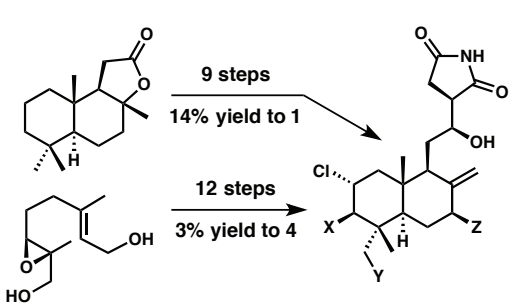
Synthesis and biological evaluation of the haterumaimides

Zef Konst, Anne Szklarski, Sharon Michalak, Yvonne Schmidt, Christopher Vanderwal
University of California, Irvine, USA



IC_{50} P388

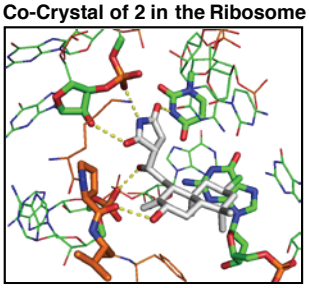
1 (X = H, Y = H, Z = OH)
chlorolissoclimide 4.4 nM

2 (X = H, Y = H, Z = OAc)
haterumaimide N 8.0 nM

3 (X = Cl, Y = H, Z = OH)
dichlorolissoclimide 2.4 nM

4 (X = Cl, Y = OH, Z = H)
haterumaimide R *untested*

Co-Crystal of 2 in the Ribosome



A rapid semi-synthetic approach from sclareolide and a fully synthetic strategy permit the synthesis of three potent antiproliferative haterumaimide natural products and numerous analogues. The semi-syntheses feature gram scale site selective C-H chlorination and a three-step sequence to furnish the βhydroxysuccinimide, salient to all haterumaimide natural products. The function oriented analogue synthesis generates haterumaimide compounds via a key polyene cyclization and utilizes unique installation of C7-hydroxy group. A number structure-activity relationships were uncovered using over 20 haterumaimide analogues with activity against three cancer cell lines. Additionally our most potent compound, (+)-chlorolissoclimide, was co-crystalized in the binding site of its cellular target in collaboration with Dr. Marat Yusupov.

Synthesis of indole-2-carboxylate derivatives via palladium-catalyzed aerobic amination of aryl C–H bonds

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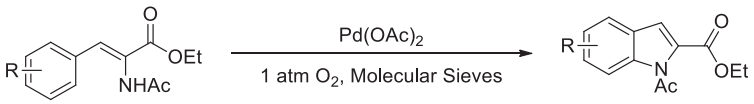
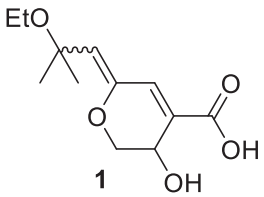
A direct, oxidative C-H amination to 1-acetyl indole-carboxylates is achieved starting from 2-acetamido-3-aryl-acrylates. Indole-2-carboxylates can be targeted with a straightforward deacetylation of the initial reaction product. The C-H amination reaction is carried out using a catalytic Pd(II) source with oxygen as the terminal oxidant. The scope and application of this chemistry is explored to demonstrate good to high yields for numerous electron-rich and electron-poor substrates. Further reaction of select products via Suzuki arylation and deacetylation provides access to highly-functionalized indole structures.



Total synthesis and structural revision of aruncin B

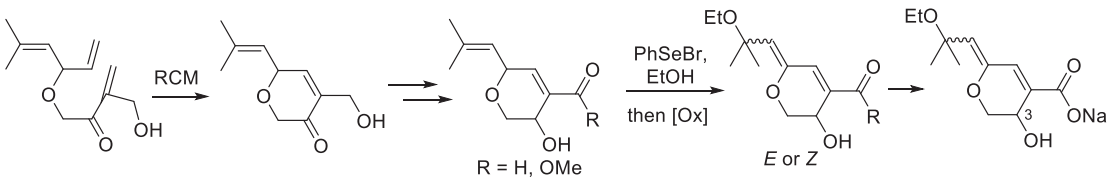
Aubert Ribaucourt* and David M. Hodgson
Chemistry Research Laboratory, 12 Mansfield Rd, Oxford OX1 3TA
University of Oxford



1

Origin and interests: Aruncin B (**1**) is a monoterpenoid recently isolated from the aerial parts of *Aruncus dioicus var. kamtschaticus* (a plant found on the Korean island Ulleung-do).[1] Preliminary biological evaluation showed potent cytotoxicity against (malignant) Jurkat T cells, involving inhibition of antiapoptotic proteins (Bcl-2 family) of these tumoral cells.[2] The structure of acid B (**1**) was assigned by spectroscopic methods (NMR and MS), with the geometry of the exocyclic double bond and absolute configuration not established. This densely functionalised monoterpenoid displays unusual structural features, dominated by a unique cross-conjugated enol ether motif on a dihydropyran core, and with a (acid-labile) tertiary allylic ether apparently co-existing with carboxylic acid functionality. To the best of our knowledge, no synthetic studies have been reported to date.

Results and discussion: In this poster, we will present divergent strategies allowing access to *E*− and *Z*-aruncin B Na-salts, as well as a regioisomeric ether of aruncin B. A ring-closing metathesis (RCM)-ethoxyselenation-elimination strategy led to both *E*− and *Z*-aruncin B Na-salts, where the precise ordering of redox steps proved crucial in determining olefin geometry. After examination of multiple mild acidification procedures, the free acid could not be obtained from these salts. Comparison of the NMR data, between the synthetic Na-salts and the reported values for the natural isolate showed several inconsistencies, and we therefore considered a structural reassignment.



Modifications to the above sequence enabled access to a regioisomeric structure, featuring the ethoxy group at C-3, but this did not match the lit. data either.

Comparison with other natural products suggested that a more profound structural revision was necessary. This poster will also present the synthesis of an alternative structure of aruncin B (**1**), for which the spectroscopic data correspond to the natural product.

Conclusion and perspectives: Syntheses of the Na-salts and a regioisomeric ether of the postulated structure of aruncin B have been achieved, but analytical data did not correspond to that reported. After structural revisions, we were able to synthesise the correct structure of aruncin B. Optimisation of the sequence and determination of the absolute configuration are in progress.

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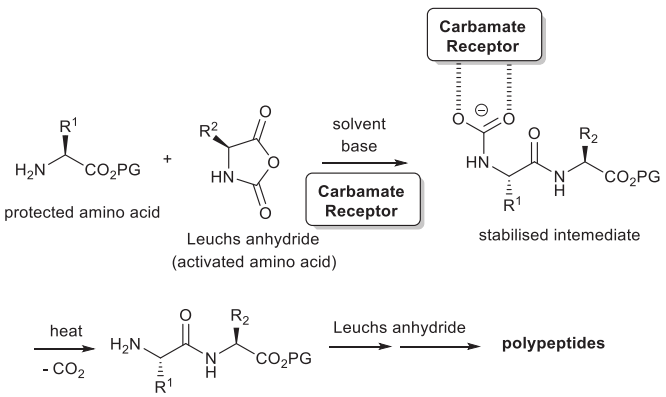
Studies on novel pepsin thesis and macrocyclisation

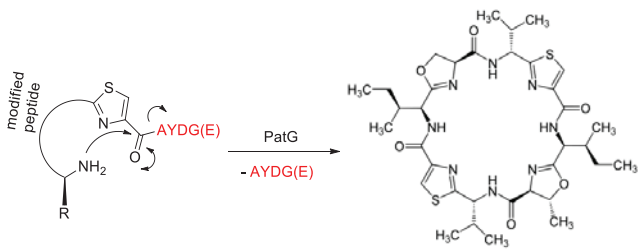
Ada Nneoyi-Egbe, Laurent Trembleau, Marcel Jaspars, Nat Smith
University of Aberdeen, UK

N-carboxy-α-amino acid anhydrides (*N*CAs) are amino acid derivatives discovered by Leuch in 1906. Ever since, they have found invaluable use in the preparation of peptide drugs and polypeptides. *N*CAs are generally synthesised using phosgene; however, due to the hazardous nature of this chemical, safer method of synthesis using protected amino acids in the presence of activating reagents such as P_2O_5, T3P, HBTU and BOP-Cl were investigated, whereby a protonated oxazolone intermediate is dealkylated to generate the corresponding amino acid *N*CA. An elegant way to prevent the decarboxylation during the synthesis of *N*CAs consists of the stabilisation of the carbamate intermediates using an appropriate receptor.



Proposed concept studied for the stepwise synthesis of peptides using NCAs.

The second part of this report, involves peptide macrocycles. Example the Patellamides, members of the cyanobactin family of cyclic compounds, made up of seven to eight amino acids, produced by *Prochloron sp*. They are synthesised by PatG macrocyclase, a subtilisin-like serine protease that cyclises linear peptides by recognizing a heterocycle (threonine and serine) present in the substrate. We also investigate the pathway by which PatGmac achieves macrocyclisation due to the recognition of the heterocycle in the natural product.



The mechanism of PatG macrocyclisation.

Enantioselective carbon-carbon bond formation using 6'-OH Cinchona alkaloids

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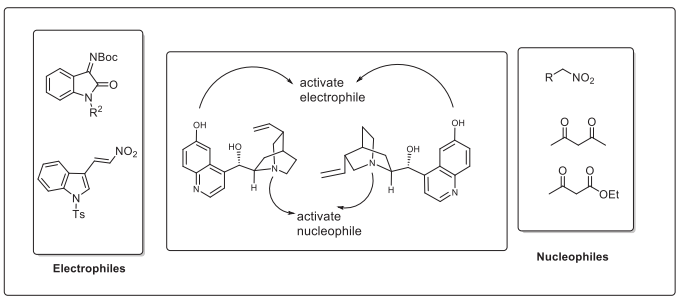
Department of Chemistry, U.G.C. Centre of Advance Studies in Chemistry, Guru Nanak Dev University, Amritsar, 143005, India

Cinchona alkaloids and their derivatives have attracted much attention in asymmetric organocatalytic reactions especially due to their unique molecular recognition ability.[1] Recently, 6'-OH Cinchona alkaloids have emerged as powerful organocatalysts for the asymmetric transformations.[2] Their most interesting feature is their availability in two pseudo-enantiomeric forms,[3] which provides easy access to both enantiomers of the product. These catalysts possess dual functionality (6'-OH and tertiary amine) for synergic activation of substrates, as well as C9-OH for further functionalization. Owing to their unique properties and efficient applications in asymmetric catalysis for enantioselective synthesis, we have been interested in their use for enantioselective carbon-carbon bond formation reactions. The organocatalyzed asymmetric reaction of isatin imine with nitroalkanes provides optically active 3-substituted-3-amino-2-oxindoles derivatives[4] in up to 89% enantiomeric excess while the reaction of indolynitroalkenes with 1,3-dicarbonyl compounds affords 3-(2-nitro-1-(1-tosyl-1H-indol-3-yl)ethyl)pentane-2,4-dione derivatives in excellent enantioselectivity up to 99%.[5]



Scheme 1: Mode of activation of nucleophile and electrophile by Cinchona alkaloids.

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Synthesis of Isocoronene

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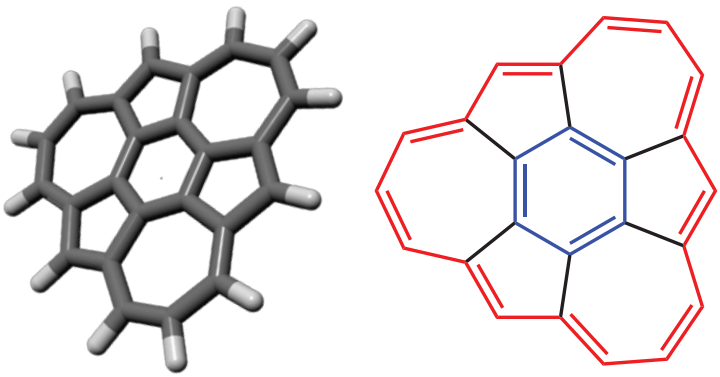
The aromaticity of corannulenes has been a subject of active discussion since the influential work by Clar on polycyclic aromatic hydrocarbons. This interest has been driven in part by the search for superaromaticity, a theoretical property of enhanced aromaticity due to extended conjugation. Previous literature has failed to find any significant superaromaticity among the vast number of known polycyclic aromatic hydrocarbons (PAH). Isocoronene (shown below) is a PAH which has not previously been synthesised. Computational studies on isocoronene have predicted a fully delocalised outer rim which would satisfy the criteria for a superaromatic system. This poster will present some approaches towards the synthesis of the isocoronene structure.
The synthesis of isocoronene will allow full characterisation and may provide the first known example of a superaromatic compound.



Cyclopropane synthesis via stereospecific intramolecular reductive cross-electrophile couplings

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University of California, Irvine, USA

An intramolecular stereospecific reductive cross-electrophile coupling reaction of 2-aryl-4-chlorotetrahydropyrans has been developed. These substrates undergo a nickel-catalyzed ring contraction to afford disubstituted cyclopropanes with excellent stereochemical fidelity at both the alkyl halide and ether bearing stereogenic centers. This new method provides access to stereochemically defined cyclopropanes in two steps from commercially available aldehydes.

Veratryl alcohol imprinted synthetic polymers: Catalysts for H_2O_2-dependent oxidation of veratryl alcohol to veratraldeheyde

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Lignin peroxidase (LiP) is an extracellular enzyme which is responsible for the biodegradation of plant cell-wall constituent, lignin. LiP has been also known to catalyze H_2O_2-dependent oxidation of veratryl alcohol (VA), to veratryl aldehyde.[1,2]

In order to mimic the catalytic activity of LP, molecularly imprinted polymers (MIP) and nonimprinted polymers (NIP) of Fe-porphyrin and amino acid monomers including histidine (His), tryptophan (Trp) and arginine (Arg) which existed in the active site of LP were prepared by emulsion polymerization technique. Artificial recognition cavities in MIP matrices were obtained by imprinting of veratryl alcohol while the polymer was being prepared. The catalytic activity of veratryl alcohol imprinted and non-imprinted polymers for the oxidation of veratryl alcohol with H_2O_2 to veratraldeheyde was investigated in various conditions including pH, temperature and substrate concentration. The synthetic lignin peroxidase-like polymers showed better catalytic activity for veratryl alcohol oxidation at lower pH levels (3–4) and higher temperatures (up to 80 °C) as comparing natural LiP.

Acknowledgments

Financial support of Anadolu University Research Projects Commission (Project No: 1001F35) is gratefully acknowledged.

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Catalytic activity of Mn(II) complexes on alcohol oxidation*

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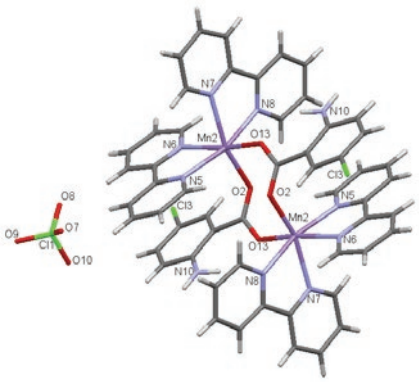
Conversion of alcohols to carbonyl compounds with oxidation reactions is one of the most important reactions of synthesis of fine chemicals [1]. Very few studies have been found in literature with binuclear Mn(II) complexes for catalytic oxidation of alcohols. In this work, we synthesized two Mn(II) complexes, $[Mn_2(\mu\text{-}4\text{-}Cl\text{-}2\text{-}NH_2C_6H_3COO)_2(phen)_4]\cdot 2(ClO_4)(CH_3OH)$ (**1**) and $[Mn_2(\mu\text{-}5\text{-}Cl\text{-}2\text{-}NH_2C_6H_3COO)_2(bipy)_4]\cdot 2(ClO_4)$ (**2**) and characterized through X-ray crystallography, for oxidations of various alcohols (cyclohexanol, cinnamyl alcohol, benzyl alcohol, 1-octanol and 1-heptanol). Catalytic activities of Mn(II) catalysts on oxidations of different alcohols were performed in acetonitrile with *t*-BuOOH as the source of oxygen. The complete conversion was obtained for oxidation of cinnamyl alcohol in 30 min. (TOF = 532 h^{-1}) for both complexes with main products, benzaldehyde (38% and 44% selectivity) and cinnamyl aldehyde (27% and 34% selectivity), respectively for **1** and **2.**



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Rhodium catalyzed cyanation of chelation assisted C(sp^2)-H bonds

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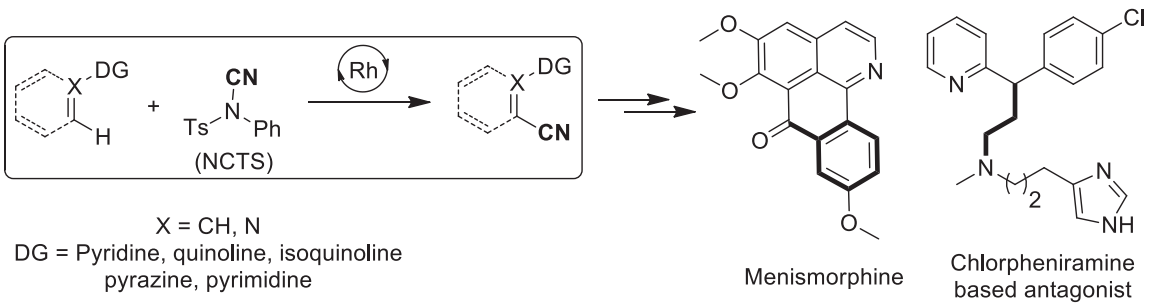
(Hetero)Aryl nitriles and acrylonitriles are the ubiquitous subunits present in various natural products, pharmaceuticals, agrochemicals, herbicides and dyes.[1] In organic synthesis, cyano group serves as valuable intermediate that can be readily transformed to various functionalized groups, such as acids, amines, aldehydes, amides, heterocycles, etc. Due to the high importance of aryl nitriles, during the last few decades, numerous methodologies were developed for the cyanation of aryl halides employing transition metal catalyst and nucleophilic cyanating reagents.[2] However, the direct cyanation of highly abundant C-H bonds utilizing non-toxic cyanating reagents are rather limited. Hence, herein we disclose the general rhodium catalyzed cyanation of various chelation assisted C(sp^2)-H bonds of arenes, heteroarenes and alkenes employing *N*-cyano-*N*-phenyl-*p*-methylbenzenesulfonamide (NCTS), as an efficient user-friendly cyanating reagent.[3] In addition, the developed methodologies were successfully utilized in the formal synthesis of menisporphine, an isoquinoline alkaloid, and chlorpheniramine-based antagonist.



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“Enz-flow: Towards a novel synthesis of levomilnacipran”

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California State University Fullerton, USA

The union of continuous flow technology and engineered enzyme catalysis is here applied towards a novel five step synthesis of an active pharmaceutical ingredient (API), levomilnacipran. This drug is currently prescribed to treat the symptoms of both major depressive disorder (MDD) and fibromyalgia syndrome (FMS).

Levomilnacipran, the single-enantiomer form of milnacipran, is a selective serotonin- and norepinephrine-reuptake inhibitor (SNRI) recently approved for treatment of patients with MDD and FMS. However, the published batch syntheses of this drug require at least nine days to perform and have not been renovated for over a decade as synthetic techniques have evolved. Chirally-pure formulations of the levo-isomer of milnacipran have been demonstrated to increase SNRI activity: a critical component of this synthesis therefore involves the enantioselective formation of the central cyclopropane ring, a common scaffold found in many bioactive molecules.

The work presented here demonstrates the utility of applying continuous processing and bioprocessing technologies to showcase a novel five step continuous synthesis of levomilnacipran. Biochemical catalytic strategies are deployed to enantioselectively install the central cyclopropane ring while utilizing efficient and sustainable reaction conditions throughout API synthesis. The advantages of flow chemistry include higher yields, faster reaction times, reduced waste, sustainable practices and access to chemistry previously considered impossible under batch protocols. By incorporating continuous bioprocessing as well as continuous processing into innovating API synthesis, a new technological platform for the use of continuous synthesis of key APIs can be developed.

Tetrahydroxydiboron-mediated palladium-catalyzed transfer hydrogenation and deuteriation reactions using water as the H or D atom donor

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Hydrogenation methods that transfer hydrogen atoms directly from water are rare and often inefficient, but are highly appealing because they need not employ H_2 gas or other H atom surrogates. We have developed an efficient method to catalytically transfer H (or D) atoms from water, through the action of diboron reagents, to hydrogenate alkenes, alkynes, and carbonyls. The reaction is amenable to complete deuterium incorporation from D_2O. A large hydrogen kinetic isotope is observed, and is taken as evidence of a rate-determining sigma bond metathesis event that generates a metal hydride intermediate.

Diaryl selenide-catalyzed trifluoromethylthioamination of alkenes

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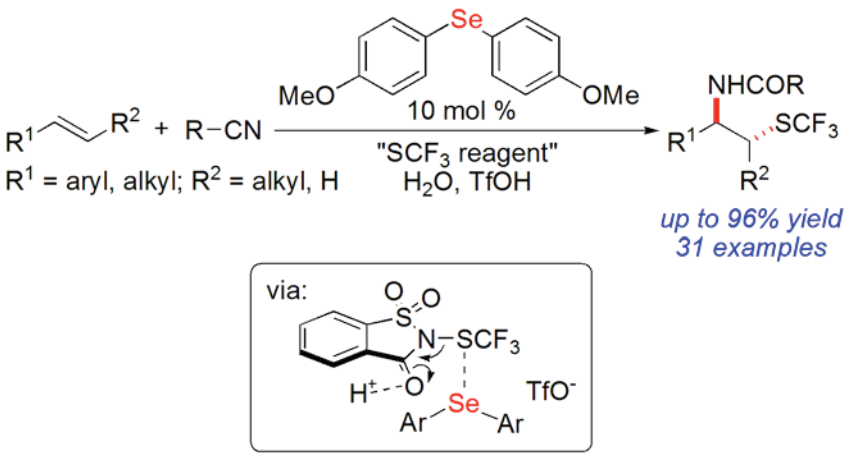
School of Chemistry and Chemical Engineering, Sun Yat-Sen University, Guangzhou 510275, P. R. China

The incorporation of trifluoromethylthio group (–SCF_3) into organic molecules can lead to an increase in their bioavailability, which is of great interest to the field of agrochemicals and pharmaceuticals. In the past several years, much effort has been dedicated to the development of efficient approaches to the SCF_3-functionalization of parent substrates, especially with SCF_3 reagents. The difunctionalization of alkenes is an efficient strategy for constructing valuable molecules. When SCF_3 and another group are added onto alkenes simultaneously by multicomponent coupling, SCF_3-containing drug candidates might be easily generated, which could provide a great opportunity for medicinal chemists.[1] We discovered that chalcogenides as the Lewis bases can activate N–SCF_3 bond[2] and have developed an efficient approach to vicinal trifluoromethylthioamination of alkenes catalyzed by electron-rich diaryl selenide. This intermolecular amination strategy was successfully applied to SCF_3-esterification of alkenes using weak acids as nucleophiles.[3]



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Sulfur(VI) fluoride exchange: Another good reaction for click chemistry

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It has been 15 years since the Cu(I)-catalyzed azide-alkyne cyclization (CuAAC) was introduced as a premier example of click chemistry, which conceptually descibes a few good reactions making stable covalent connections between small units. Recently, another good reaction for click chemistry, sulfur(VI) fluoride exchange (SuFEx) was developed in our labrotary, which consists of three near-perfect recipes.

First, treating with saturated aqueous KFHF solution was identified as a general method for converting a sulfonyl chloride to the corresponding sulfonyl fluoride, which is stable on-standing while robust in presence of catalysts as a pivotal precursor to many functional types. Second, aryl fluorosulfates were synthesized from phenols and gas SO_2F_2, a commercial fumigant insecticide known as Vikane. Aryl fluorosulfates could be further activated affording stable -$OS(O)_2O$- connection, which has been proven extremely efficient in polysulfate preparation. Third, ethenesulfonyl fluoride (ESF) as a versatile reagent was reinvestigated after it kept unknown in the wider chemical community for more than 40 years since its discovery by industry. We especially appreciate the stageable biselectrophilic feature of ESF, saving a replaceble S-F bond after Michael reaction for a later arriving nucleophile.

The SuFEx click chemistry was developed as a powerful toolkit en route to the wide applications in biology and functional materials, while chemical insights are expediting this journey. In this poster, we will present latest progress we have made in, 1) identifying more powerful catalysts for SuFEx-enabled polysulfate preparation, 2) synthesizing sulfonate dendrimer efficiently with a poly-sulfonyl-fluoride periphery using Michael addition/SuFEx iteration.

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3. unpublished results

Remote asymmetric ullman cross-coupling using guanidinylated peptides as multi-functional ligands

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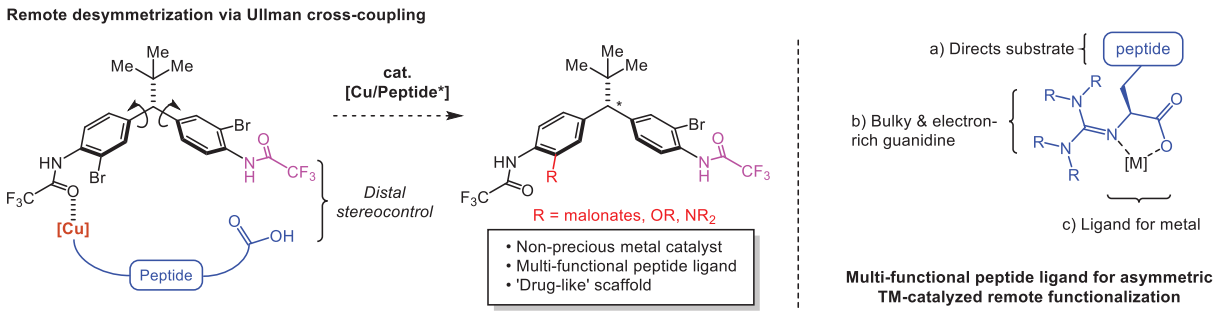
Distal asymmetric induction using catalytic methods are challenging tasks and often require macromolecular catalysts[1] or enzymes[2]. In particular, symmetry-breaking processes of meso-compounds via functionalization of remote enantiomeric sites are intriguing challenges. To date, only a few examples of using small molecule catalysts[3] are reported and employment of transition-metal catalysis remain unexplored. In this poster, we report a new class of peptide-based ligands for remote desymmetrization of diarylmethanes via Ullman cross-coupling[4]. The peptides are designed to serve multiple functions in the remote desymmetrization. N-terminus of the peptides contain bulky and electron-rich guanidines that coordinate to a copper center to facilitate the reactivity of the cross-coupling. Through our mechanistic studies, we discovered a relatively unexplored non-covalent interaction between C-terminus of the peptide and substrate that is essential for controlling the distal stereoselectivity. The new copper/peptide catalysts were able to achieve up to 93:7 *e.r.* using malonates as nucleophiles in the challenging remote desymmetrization. Currently we are exploring other Ullman-type nucleophiles for this desymmetrization.



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A heterocyclic triphenylene designed and synthesized for sky blue phosphorescent organometallic complexes

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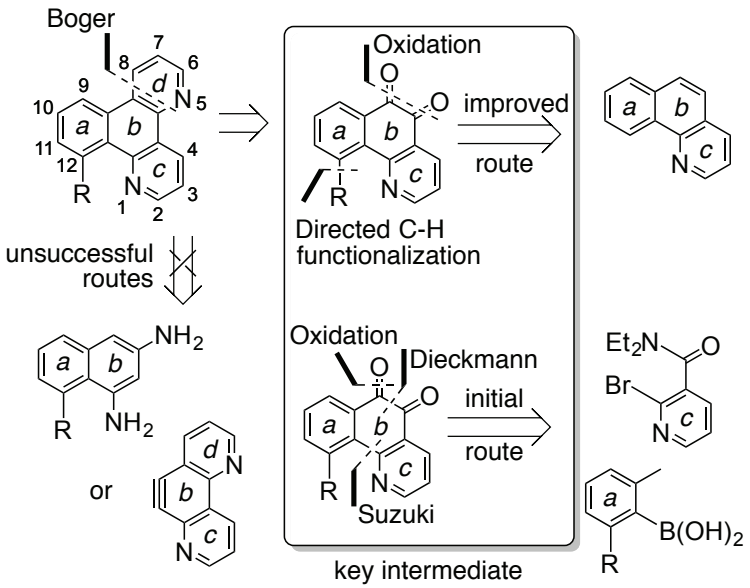
Luminescent organometallic complexes of Ir and Pt are integral to the operation of the highest efficiency organic light emitting diodes (OLEDs) and have rapidly gained increased interest for their ability to catalyze photoredox reactions in organic synthesis. The nature of the lowest lying excited state responsible for luminescence and photoredox activity can be tuned from red to blue and from oxidizing to reducing depending on the structures of the organic ligands. The most common blue emitting and photo-oxidizing ligand systems are fluorinated phenylpyridines. These suffer from chemical degradation through loss of fluoride and from non-radiative deactivation of the excited state through rotation of the phenyl-pyridine bond. Our work to address these issues in the development of a sky blue component for white phosphorescent OLEDs has lead us to design ligands from triphenylene, a rigid tetracyclic aromatic hydrocarbon with a triplet state energy comparable to phenylpyridine. By judicious choice of azasubstitution pattern, a heterotriphenylene (Bzp) has been designed to replace the well-known difluorophenylpyridine (F_2ppy).



A four-step gram scale synthetic preparation of Bzp will be presented, with emphasis on its retrosynthetic logic and versatility for producing other functional heterotriphenylene derivatives. The rational design of Bzp is validated by comparison of its platinum complex to the analogous F_2ppy complex, which exhibit the same sky blue phosphorescence (466 nm) at room temperature.

Synthesis of high triplet energy triazole and imidazole organic host materials for white organic light emitting diode application

Muazzam Idris, Tyler Fleetham, Peter Djurovich, Mark E Thompson
University of Southern California, USA

A new class of wide bandgap host materials are developed as a replacement for current carbazole-based hosts to potentially enhance the operational stability of organic light emitting diodes. In this work, a series of phenantherene derivatives incorporating triazole or imidazole rings are synthesized and their photophysical and electrochemical properties are investigated. Phenanthrene, and its triazole and imidazole substituted analogs, have high triplet energies despite their large aromatic rings making them ideal candidates as host materials for their dual benefits of high triplet energies and favorable charge transport characteristics. However, the triplet energy of these materials in the solid state are significantly reduced due to pi stacking. For this reason bulky substituent groups were added to different positions of triazole/imidazole host materials. In particular, addition of phenyl or tolyl group on the 4' position of 2-methyl-2H-phenanthro[9,10-d][1,2,3]triazole decreases pi stacking and hence enhances the triplet in solid. Similarly, changing substituent group from less bulky phenyl group in 1-phenyl-1H-phenanthro[9,10-d][1,2,3]triazole to more bulky mesityl group in 1-mesityl-1H-phenanthro[9,10-d][1,2,3]triazole enhances the triplet in solid. Similar enhancement in the solid state triplet is observed in the imidazole analogs.

Bronsted acid-catalyzed electrophilic substitution reactions for the synthesis of chiral carbocycles

Xiao Cai,* Amir Keshavarz,* Justin Omaque,* Gilberto E. Fernandez* and Benjamin J. Stokes

School of Natural Sciences, University of California, Merced, 5200 N. Lake Road, Merced, CA 95343 USA

The preparation of carbocycles using catalytic electrophilic aromatic substitution reactions is often surprisingly challenging. We are developing catalytic Thorpe–Ingold-assisted strategies to access a wide variety of functionalized carbocycles from readily available starting materials. One approach involves the construction of chiral carbocycles via intramolecular Thorpe–Ingold-assisted acid-catalyzed electrophilic aromatic substitution reactions. Alternatively, we can prepare chiral carbocycles through Thorpe–Ingold-assisted electrophilic dimerization reactions. The influence of the nature of the acid catalyst on reaction outcomes is discussed. In addition to showcasing the substrate scope permitted under our conditions, efforts towards diastereo- and enenatioselective carbocycle syntheses are also presented.

1,2-/1,3-Diamination of arenes with domino aryne precursors: A combination of experimental and theoretical study

Yang Li, Dachuan Qiu, Lu Li, Song Liu, Jiarong Shi, Jia He, Xiao Yue, Yu Lan
Chongqing University, China

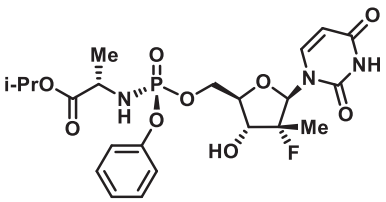
Diaminobenzenes are privileged substructures in many biologically active molecules as well as medicines, which can be assembled from our domino aryne precursors. The reaction of these aryne precursors with sulfamides and sulfonamides efficiently afforded 1,2- and 1,3-diaminobenzenes, respectively. Trisubstituted 1,3-diaminobenzenes were also obtained via an intramolecular sulfonyl group migration to the 2-position. During our study, we disclosed that potassium carbonate could act as an effective and environmentally friendly aryne-generating reagent under fluoride-free condition, which was also confirmed by DFT calculation. The relatively high activation barrier for carbonate activation allows smoother aryne-releasing process. Both experimental study and theoretical calculation were able to support the formation of two transient aryne intermediates involved in a domino double-aryne pathway, and the energy flow of the transition states has a cascade sequence. The study on the regioselectivity of the unsymmetrical aryne precursors reveals that the electronic effect could influent the preferential generation of one of the aryne intermediates, whereas steric effect between methyl and isopropyl group does not make distinct change on the product ratio.

Novel acess to P-epi McGuigan prodrugs

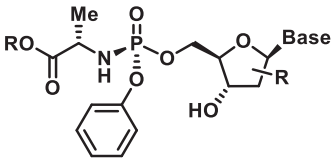
Eric Ashley*, Petere Mullens, Marc Poirier, Charles Jayne and Edward Cleator
Merck Research Laboratories, Kenilworth, NJ, USA and Hoddesdon, Hertfordshire, UK

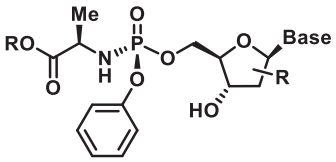
Inhibition of the hepatitis C virus (HCV) NS5b polymerase with nucleoside derivatives is an important approach for HCV therapy. Inhibition of NS5b offers advantages over other pharmacological targets within the viral genome due to the high barrier to resistance and pan-genotypic efficacy profile. Clinically validated pharmaceutical agents, including Sofosbuvir, commonly contain a ribose derivative with a McGuigan-type phosphoramidate prodrug. These phosphoramidates are converted in the liver to an active triphosphate which then act as a chain terminator of the viral replication process.

The efficacy and safety profiles of nucleoside phosphoramidates are influenced not only by the moieties attached to the phosphorus center but also by the relative stereochemistry between the various units. The current work describes a novel approach to the previously challenging D-alanine-S_P and L-alanine-R_P phosphoramidates and the application of this approach to a range of nucleoside polymerase inhibitors.



Sofosbuvir (L-alanine-S_P)





"P-epi" L-alanine-R_P and D-alanine-S_P Nucleoside Phosphoramidates

Enantioselective synthesis of an Intermediate in the preparation of a novel candidate for the treatment of HCV

Dustin Bringley, Amy M Cagulada, Johann Chan, Nolan D Griggs, Stephen P Lathrop, Kenneth S Matthews, Andrew W Waltman

Gilead Sciences, UK

An enantioselective, multistep route to an intermediate in the synthesis of an experimental HCV inhibitor is described. Process optimization of this route allowed for the development of a robust process that was successfully performed on multi-kilogram scale.

Highly stereoselectivity synthesis of a new class of pentasubstituted cyclopentenes

Alexander F. de la Torre [*a,b], Marco A. F de Moraes Junior [a], Antonio L. Braga [b], Daniel G. Rivera [a,c], and Márcio W. Paixão[a]

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The asymmetric synthesis of cyclic compounds in special 5-membered carbocyclic ring systems are of grand important, once this scaffold is widely found in numerous medicinal and biological active compounds.[1] For this porpoise, metal transition catalyst is extensively used; however, the organocatalytic-multicomponent approach version has been an unexplored area. So, in this work, a sequential asymmetric organocatalytic tandem conjugated addition [3] followed by a multicomponent reaction was done. The reaction between *n*-propanal and (*E*)-2-(2-nitrovinyl)phenols was catalyzed by Jørgensen-Hayashi organocatalyst to produce the not isolated bifunctional chiral intermediate, which was reacted in presence of amines and isocyanides components by a Ugi MW procedure. Unexpected enatio- and diastereoselective fully substituted cyclopentenes in yield range of 55-70% (Figure 1) were obtained.

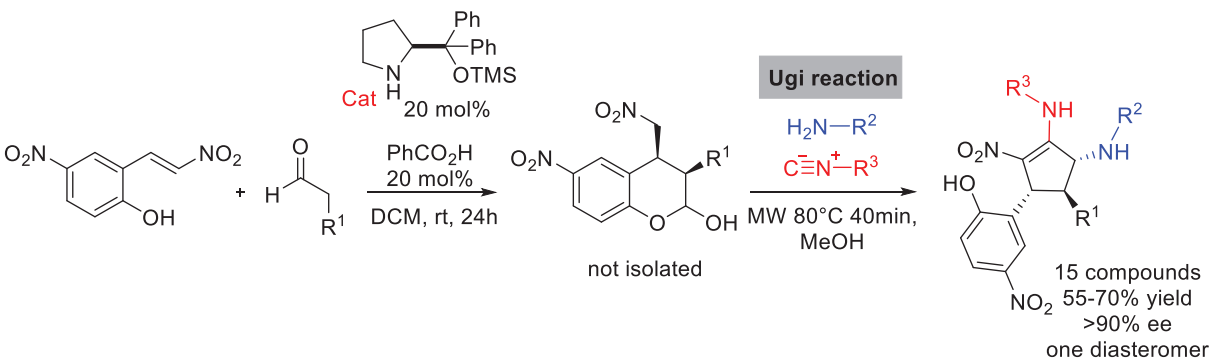

Figure 1: Organocatalytic-multicomponent sequence to the synthesis of pentasubstituted cyclopentenes

Keywords

organocatalysis, multicomponent reactions, cyclopentenes

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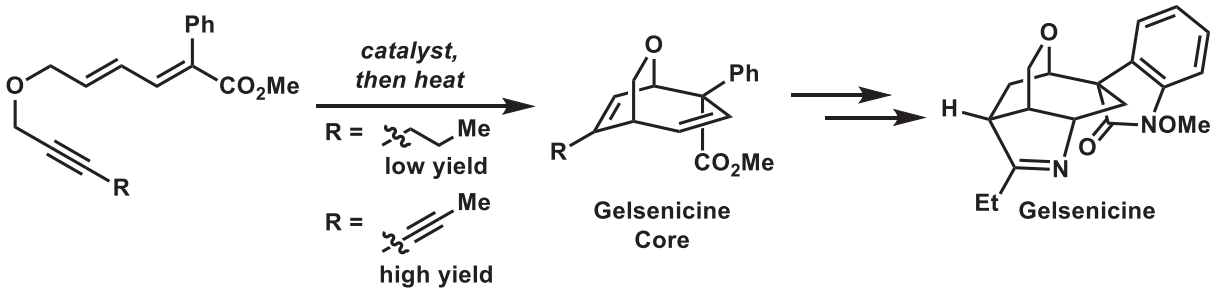
Total synthesis of gelsenicine via a catalyzed cycloisomerization strategy

Phil C. Knutson*, Eric T. Newcomb, Blaine A. Pedersen, and Eric M. Ferreira

Department of Chemistry, University of Georgia, Athens, Georgia



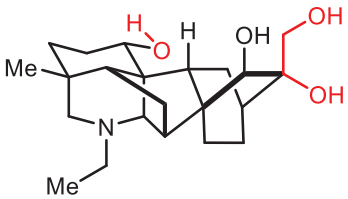
Department of Chemistry, University of Georgia, Athens, Georgia

The Gelsemium alkaloids represent a structurally diverse group of biologically active molecules. These monoterpenoid indole alkaloids possess highly compact, caged architectures that have presented synthetic difficulty to chemists for decades. We employ a metal-catalyzed cycloisomerization/Cope rearrangement strategy to efficiently generate the core structure of the family. Obstacles we encountered in the synthesis of the gelsenicine core provided platforms for creative implementation of various strategies. Circumventing a hydride shift in the Cope rearrangement pushed us to develop a new plan of attack, a diyne substrate that disallowed the hydride shift. A platinum-catalyzed cycloisomerization/Cope rearrangement cascade of our diyne could be achieved albeit in moderate yields. Ultimately, we found that a stepwise approach, utilizing a cationic gold catalyst system, afforded our desired bicycle with significantly higher yields. This highly efficient process allowed us to synthesize gelsenicine in 13 steps, the shortest total synthesis of a Gelsemium alkaloid to date. We envision that further strategic diversification of the gelsemium core will allow access to a number of members within the family.

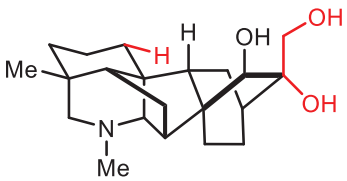
An approach toward the C20-diterpenoid alkaloids cochlearenine, dictyzine, and related natural products

Kevin GM Kou*, Beryl Li and Prof. Richmond Sarpong

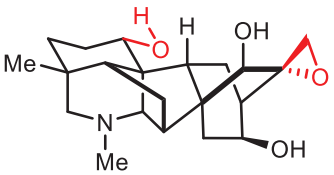
University of California, Berkeley, USA



cochlearenine



dictyzine



gomandonine

Deterpenoid alkaloids are a class of natural products featuring highly-caged, polycyclic architectures. These complex natural products are often noted for their potential to modulate Na^+ and/or K^+ ion channels.[1] There is even some evidence to suggest that these molecules are subtype-specific, which would allow specific targeting of the ion channel subtype implicated in disease, and thus provide new opportunities for better side-effect profiles. Although >1000 diterpenoid alkaloids have been isolated, only a few have been studied in detail with respect to biological function (e.g., aconitine and lappaconitine) due to difficulties in gaining access. Our group has recently reported on the total syntheses of C18- and C19-diterpenoid alkaloids.[3] Herein, we describe an approach that would allow access to the C20-family of molecules, namely cochlearenine, dictyzine, and related natural products bearing the denudatine-type framework. With a unified synthesis strategy encompassing all of the C18-, C19-, and C20 structures, we intend to probe their potential to act as isoform-specific ligands for Na^+ and K^+ ion channels.

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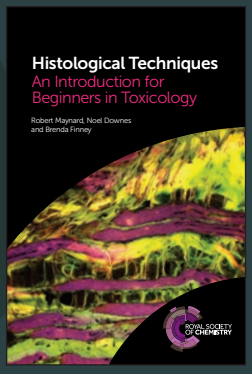

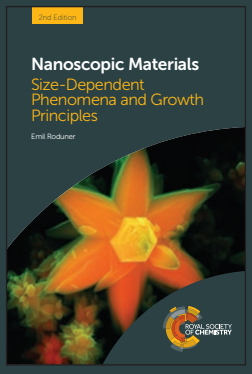

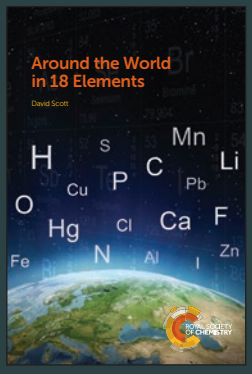

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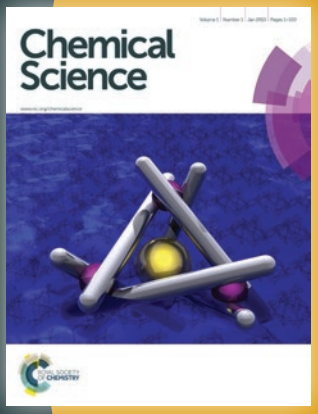

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