28th Congress of the International Society of Heterocyclic Chemistry

28 August – 2 September 2022

University of California, Santa Barbara

Conference Organizing Committee

Christopher Vanderwal, ISHC President and Conference Co-organizer
Javier Read de Alaniz and Yang Yang, Local Conference Co-organizers
Frederick Luzzio, ISHC Treasurer

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ISHC Committees

Executive Committee

President: Professor Christopher Vanderwal, UC Irvine
Immediate Past-President: Professor Masayuki Inoue, University of Tokyo
Secretary: Professor David Williams, University of Indiana
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Dr. Peter Meier, Novartis
Professor Christian Melander, Notre Dame University
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Professor Jason Smith, University of Tasmania
Professor Hidetoshi Tokuyama, Tohoku University

Welcome and On-site Information

Welcome to UC Santa Barbara!
We hope you will enjoy your time here and that you will take the opportunity to explore our campus and the local area.
If you have questions during your stay, please visit the registration desk in the University Center Corwin Pavilion Lobby or the Manzanita Village front desk (or call 805-893-6161).

REGISTRATION & INFORMATION DESK
Located in the Corwin Pavilion Lobby at the University Center.
Registration hours:

Sunday, August 28, 5:00pm - 9:00pm
Monday, August 29, 7:30am - 9:00am

Information Desk hours:

Sunday, August 28, 5:00pm - 9:00pm
Monday, August 29, 7:30am - 4:30pm
Tuesday, August 30, 8:30am - 4:30pm
Wednesday, August 31, 8:30am - 2:00pm
Thursday, September 1, 8:30am - 4:30pm
Friday, September 2, 8:30am - 12:00pm

PARKING INFORMATION

- A valid parking permit is required at ALL TIMES on campus.
- Your permit is NOT VALID in the following spaces: Vendor, Metered, Reserved (R), Restricted, Coastal Access, Gold Spaces, Faculty Permits Required at All Times, Faculty and Staff Permits Required at All Times, Handicapped Accessible (without an accompanying DMV-authorized Disabled placard).

Guests staying on campus
(i.e. accommodations in Manzanita Village or at The Club & Guest House with comped parking)

- At check-in, you will receive a parking permit from the front desk.
- Parking for the ISHC Conference is in Lot 22.
- Your Lot 22 permit is valid in Lot 3 (near the University Center) anytime on Sunday, and after 5pm on Monday and Tuesday, should you want to park closer for registration and the poster sessions.

Guests staying off campus
(i.e. accommodation off-campus or at The Club & Guest House without comped parking)

- Visitor E-Parking rates
  - $8.00/weekday
  - $4.00 after 5PM or weekends
  - E-Permits may be purchased from the pay stations in the lots, and Park Mobile is available, allowing visitors to skip the pay station and conveniently pay for parking through their phone.
- Parking for the ISHC Conference is in Lot 22.
  - Your Lot 22 permit is NOT valid in Lot 3.
  - Anytime on Sunday, and after 5pm on Monday and Tuesday, you may purchase a parking permit for Lot 3, near the University Center, if you want to park closer for registration and the poster sessions.

MEALS

Dining Commons

- Participants staying in Manzanita Village have their meals at the De La Guerra Dining Commons included.
    - Please show your room keys to gain entry.
- Participants NOT staying in Manzanita Village can purchase meals at De La Guerra Dining Commons with a credit card (Visa or Mastercard) for $12+tax/meal.

Catered Meals

Your conference registration fee includes a

- Wine and Cheese reception on Sunday evening (5:00 to 7:00 pm)
- Beach Barbeque on Thursday evening (5:30 pm start)

EXCURSIONS (Wednesday, August 31)

Harbor Cruise

If you have pre-registered and paid for the Harbor Cruise, you will receive a ticket at registration.

2:00pm - Start boarding charter bus at the Manzanita Village bus loop. Present your ticket to the driver.
2:15pm - Bus leaves promptly.
3:00pm - Cruise starts and lasts two hours.
5:15pm - Bus leaves harbor and returns to UCSB.
Please note: De La Guerra Dining Commons will be open for dinner from 6:30-7:30pm.

If you want to stay longer

- From the harbor it is about a 15-20 minute walk, or a short Uber/Lyft ride, to the Funk Zone and State Street
- The Funk Zone is about a 15 minute Uber/Lyft ride back to campus.

Downtown Santa Barbara Excursion

If you signed up for the complimentary bus from UCSB to downtown Santa Barbara:

UCSB pick-up/drop-off: Manzanita Village bus loop
2:15pm - Departs UCSB.
3:00pm - Departs UCSB

Downtown drop-off/pick-up: Near the Santa Barbara Visitor Center at 1 Cabrillo Blvd.
4:45pm - Departs downtown
5:30pm - Departs downtown
Please note: De La Guerra Dining Commons will be open for dinner from 6:30-7:30pm.
Each bus can seat 56 people.

If you miss the last pick up, the bus fills up, or you'd like to stay downtown later, you will be on your own to catch an Uber/Lyft/taxi back. UCSB is only about a 15 minute drive from downtown.

WIFI

UCSB Wireless Web

Pick "UCSB Wireless Web" from the network options and select "Guest Registration" under the credential login. You'll receive an SMS/text message with a username and password, which is enabled for a seven-day connection. For questions or issues, contact noc@ucsb.edu.

Eduroam is available.

UCSB COVID PROTOCOLS

COVID Information

In an effort to avoid viral transmission, all conference activities other than the lecture sessions will be held outdoors, including the welcome reception, refreshments between lectures, poster sessions, and the conference dinner.

Vaccination

All attendees must either be up-to-date* (including any booster doses when eligible) with a COVID vaccine that is authorized by the World Health Organization (WHO) and show proof of their vaccination status OR they must provide proof of a negative COVID test upon arrival and test regularly during their time on campus.

Vaccination status and negative COVID tests will be verified at registration.

Unvaccinated Attendees and Attendees Who are Not Up-To-Date* on their Vaccination

Unvaccinated attendees and attendees who are not up-to-date* on their vaccination must produce a negative test result upon arrival (take within 24 hours for antigen test or 72 hours for PCR test). Tests will be available at the registration desk for initial verification if needed.

Testing

Please plan to bring your own COVID tests if you'd like to be able to test during the conference in case of exposure or symptoms.

Positive COVID Test

- Attendees will not be allowed to attend the conference.
- Attendees who are staying in Manzanita Village or The Club & Guest House will need to relocate off-campus within 24 hours of testing positive.

Masking

Attendees are required to follow the current UCSB campus guidelines on masking. Effective June 13, 2022 masks are strongly recommended but no longer required in indoor spaces on campus, regardless of vaccination status. However, the ISHC Congress Organizers have decided that, in view of the high rates of local SARS-CoV-2 transmission, masks will be required during the lecture sessions for everyone except the presenter. **Please see below for the ISHC masking policy.**

Additional COVID-19 Requirements

Attendees must comply with any additional COVID-19 related procedures that may be implemented by the University, County, or State.

** A person is considered up-to-date on COVID-19 vaccinations when they have received all recommended COVID-19 vaccinations, including booster doses when eligible. People who are not up to date on their COVID-19 vaccinations include: (i) people of all ages, including children, who have not completed a series of primary vaccinations to protect against COVID-19; (ii) individuals <2 weeks after the primary vaccination series; (iii) individuals with an approved exception or deferral to UC Policy: SARS-CoV-2 (COVID-19) Vaccination Program; (iv) persons who have completed a primary vaccination series and are eligible for the booster, but have not received a booster dose*

ISHC Masking Policy

Although COVID-19 case incidences have begun to decrease in most parts of Southern California, transmission rates remain significant. To ensure the safest possible conference, and to respect the concerns of those who are at increased risk, we will require that attendees wear masks during the lectures, with the exception of the speaker. We know that people will be joining us from places with vastly different approaches to masking and other transmission mitigation efforts, so we would rather err on the side of caution to make sure that everyone is comfortable. Thank you for your cooperation.

ISHC Brief History and Past Presidents

The International Society of Heterocyclic Chemistry (ISHC) was established in August, 1968, in Albuquerque, New Mexico, in the USA by Dr. Raymond N. Castle (1916–1999). The function of the society is to promote heterocyclic chemistry, in particular by serving as the primary sponsoring agency for the ISHC Congress, a large biennial meeting attracting hundreds of participants. Further aims of the ISHC are to honor persons who have made outstanding contributions to the field with three distinguished Awards and the appointment of ISHC Fellows. The ISHC is also actively involved in the publication of "*Progress in Heterocyclic Chemistry*" (PHC) a major reference work on heterocyclic chemistry, and monthly bulletins providing updates on recent publications by ISHC members to the ISHC community.

The current president of the ISHC is Christopher D. Vanderwal, of UC Irvine (2019–2022), and the past presidents are:

1973–75 Raymond Castle (founder), Albuquerque, USA
1976–77 Edward Elslager, Warner–Lambert Parke–Davis Pharmaceuticals, USA
1978–79 Miha Tisler, University of Ljubljana, Slovenia
1980–81 Leroy Townsend, University of Michigan, USA
1982–83 Wolfgang Pfleiderer, University of Konstanz, Germany
1984–85 Stewart Schneller, University of South Florida, USA
1986–87 Henk van der Plas, University of Wageningen, Netherlands
1988–89 Yoshio Ban, Hokkaido University, Japan
1990–91 Victor Snieckus, University of Waterloo, Canada
1992–93 Jan Bergman, The Royal Institute of Technology, Sweden
1994–95 Albert Padwa, Emory University, USA
1996–97 Hal Moore, UC Irvine, USA
1998–99 Christopher Moody, University of Exeter, UK
2000–01 Yoshi Yamamoto, Tohoku University, Japan
2002–03 Steven Weinreb, Penn State, USA
2004–05 *Marco Ciufolini, University of British Columbia, Canada
2006–07 Margaret Brimble, University of Auckland, NZ
2008–09 Jeffrey Aube, Kansas University, USA
2010–11 Richard Taylor, University of York, UK
2012–13 Dawei Ma, Shanghai Institute of Organic Chemistry, China
2014–15 Daniel Comins, NCSU, Raleigh NC, USA
2016–17 Oliver Reiser, University of Regensburg, Germany
2018–19 Masayuki Inoue, The University of Tokyo, Japan

*Note: 2003, Alessandro Dondoni, University of Ferrara, Italy, was elected President–Elect but could not serve his term as President due to health problems.

Conference Schedule

The information found on the following pages can also be accessed directly on the conference website in scrollable form at: https://ishc.chem.uci.edu/schedule

Sunday 28 August

17:00 – 19:00	Conference Registration	Opening Mixer
19:00 – 21:00		

Monday 29 August

7:30 – 9:00	Conference Registration	
8:45 – 9:00	Conference Opening	Corwin West
Session Chair:	**Scott Rychnovsky**	
9:00 – 10:00	Plenary Lecture 1 **Erick Carreira**	Corwin West
10:00 – 10:30	Coffee Break	
10:30 – 11:30	Plenary Lecture 2 **Vy Dong**	Corwin West
11:30 – 12:30	Plenary Lecture 3 **Frances Arnold**	Corwin West
12:30 – 14:00	Lunch Break	

Monday 29 August (continued)

	Session Chairs: Till Opatz	Jeff Kuethe	Shuji Akai	Theo Michels
14:00 – 14:40	Invited Lecture 1 — Corwin West **David Nicewicz**	Invited Lecture 2 — Corwin East **Sabine Flitsch**	Invited Lecture 3 — Flying A **Sabine Hadida**	
14:40 – 15:20	Invited Lecture 4 — Corwin West **Corinna Schindler**	Invited Lecture 5 — Corwin East **Brett Fors**	Invited Lecture 6 — Flying A **Uttam Tambar**	
15:20 – 15:40	Oral Presentation 1 — Corwin West **David Martin**	Oral Presentation 2 — Corwin East **Yang Yang**	Oral Presentation 3 — Flying A **Arturo Orellana**	Oral Presentation 4 — State **Vincent Lindsay**
15:40 – 16:00	Oral Presentation 5 — Corwin West **Joshua Pierce**	Oral Presentation 6 — Corwin East **Allen Hong**	Oral Presentation 7 — Flying A **Thomas Livinghouse**	Oral Presentation 8 — State **Valerie Schmidt**
16:00 – 16:30	Coffee Break			
16:30 – 16:50	Oral Presentation 9 — Corwin West **Joel Smith**	Oral Presentation 10 — Corwin East **Ida Chen**	Oral Presentation 11 — Flying A **Tom Driver**	Oral Presentation 12 — State **Simon Blakey**
16:50 – 17:30	Invited Lecture 7 — Corwin West **Scott Rychnovsky**	Invited Lecture 8 — Corwin East **Todd Hyster**	Invited Lecture 9 — Flying A **Jennifer Riggs**	
17:30 – 19:00	Poster Session 1			

Tuesday 30 August

Session Chair:	**Mike Harmata**			
9:00 – 10:00	Plenary Lecture 4 Corwin West **Matthew Gaunt**			
10:00 – 10:30	Coffee Break			
10:30 – 11:30	Plenary Lecture 5 Corwin West **Masayuki Inoue**			
11:30 – 12:30	Plenary Lecture 6 Corwin West **L.-C. Campeau**			
12:30 – 14:00	Lunch Break			
Session Chairs:	**Corey Stephenson**	**Javier Read de Alaniz**	**Mike Luzzio**	**Mary Beth Daub**
14:00 – 14:40	Invited Lecture 10 Corwin West **Erik Alexanian**	Invited Lecture 11 Corwin East **Garret Miyake**	Invited Lecture 12 Flying A **Matthew Tudge**	
14:40 – 15:20	Invited Lecture 13 Corwin West **Satoshi Ichikawa**	Invited Lecture 14 Corwin East **Thomas Müller**	Invited Lecture 15 Flying A **Osvaldo Gutierrez**	
15:20 – 15:40	Oral Presentation 13 Corwin West **Andrew Lawrence**	Oral Presentation 14 Corwin East **Jolene Reid**	Oral Presentation 15 Flying A **Christian Malapit**	Oral Presentation 16 State **David Stuart**
15:40 – 16:00	Oral Presentation 17 Corwin West **Jonathan Scheerer**	Oral Presentation 18 Corwin East **Jean-Luc Ayitou**	Oral Presentation 19 Flying A **Laura Anderson**	Oral Presentation 20 State **Won-jin Chung**
16:00 – 16:30	Coffee Break			
16:30 – 17:10	Invited Lecture 16 Corwin West **Ed Anderson**	Invited Lecture 17 Corwin East **Alison Narayan**	Invited Lecture 18 Flying A **Regan Thomson**	
17:10 – 17:30	Poster Talks Corwin West TBA (2 x 10 min)	Poster Talks Corwin East TBA (2 x 10 min)		
17:30 – 19:00	Poster Session 2			

Wednesday 31 August

Session Chair: **Al Padwa**

9:00 – 10:00	Industry Award Lecture — Corwin West — **Rémy Angelaud**
10:00 – 10:30	Coffee Break
10:30 – 11:30	Katritzky Award Lecture — Corwin West — **Sarah Reisman**
11:30 – 12:30	Taylor Award Lecture — Corwin West — **Viresh Rawal**
12:30 – 14:00	Lunch Break
14:00 –	**Excursions** (no scientific program during afternoon and evening)

Thursday 1 September

Session Chairs: **Evan Horn** **Yang Yang** **Darius Vrubliauskas**

9:00 – 10:00	Plenary Lecture 7 — Corwin West — **Joseph Fox**		
10:00 – 10:30	Coffee Break		
10:30 – 11:10	Invited Lecture 19 — Corwin West — **Peter Zhang**	Invited Lecture 20 — Corwin East — **Hans Renata**	Invited Lecture 21 — Flying A — **Andrew McNally**
11:10 – 11:50	Invited Lecture 22 — Corwin West — **Mingji Dai**	Invited Lecture 23 — Corwin East — **Martin Schnermann**	Invited Lecture 24 — Flying A — **Noritaka Chida**
11:50 – 12:30	Invited Lecture 25 — Corwin West — **Erik Sorensen**	Invited Lecture 26 — Corwin East — **Rebecca Buller**	Invited Lecture 27 — Flying A — **David Lupton**
12:30 – 14:00	Lunch Break		

Thursday 1 September (continued)

	Session Chairs: **Kevin Kou**	*Session Chairs:* **Sean Feng**	*Session Chairs:* **Alan Aitken**	*Session Chairs:* **Sharon Michalak**
14:00 – 14:40	Invited Lecture 28 — Corwin West — **Andrew Evans**	Invited Lecture 29 — Corwin East — **Ellen Sletten**	Invited Lecture 30 — Flying A — **David Nagib**	
14:40 – 15:00	Oral Presentation 21 — Corwin West — **Christopher Newton**	Oral Presentation 22 — Corwin East — **Will Gutekunst**	Oral Presentation 23 — Flying A — **Till Opatz**	Oral Presentation 24 — State — **Dennis Hall**
15:00 – 15:30	Coffee Break			
15:30 – 15:50	Oral Presentation 25 — Corwin West — **Oliver Reiser**	Oral Presentation 26 — Corwin East — **Magnus Pfaffenbach**	Oral Presentation 27 — Flying A — **Aaron Aponick**	Oral Presentation 28 — State — **Jennifer Stockdill**
15:50 – 16:10	Oral Presentation 29 — Corwin West — **Mark Levin**	Oral Presentation 30 — Corwin East — **Erin Stache**	Oral Presentation 31 — Flying A — **Ramesh Giri**	Oral Presentation 32 — State — **Carl Lovely**
16:10 – 16:30	Poster Talks — Corwin West — TBA (2 x 10 min)	Poster Talks — Corwin East — TBA (2 x 10 min)		
17:30 – 19:30	**Conference Dinner** BBQ on Goleta Beach			

Friday 2 September

	Session Chair: **Frederick Luzzio**
9:00 – 10:00	Plenary Lecture 8 — Corwin West — **Marisa Kozlowski**
10:00 – 11:00	Plenary Lecture 9 — Corwin West — **Armen Zakarian**
11:00 – 11:20	Corwin West — Closing Remarks and Poster Prizes
11:30 – 13:00	Lunch and Departure

List of Posters: Monday Poster Session

Presenters please set up your poster *before the beginning of the morning session* on the board number assigned to you, as shown below.

Poster A-1: Abdelwahed, Sameh; Prairie View A&M University Prairie View *New quinoxaline-based derivatives as PARP-1 inhibitors: design, synthesis, antiproliferative, and computational studies*
Poster A-2: Andjaba, John; Massachusetts Institute of Technology *Catalytic Benzoxazine Synthesis Enabled by P(III)/P(V)=O Cycling*
Poster A-3: Barnes, Griffin; University of California, Irvine *Total Synthesis of (±)-Alstonlarsine A from (±)-Alstolucine B, F through a 1,7–Hydride shift, Mannich sequence.*
Poster A-4: Bieniek, Jessica; Department of Chemistry, Johannes Gutenberg University, Mainz, Germany *Direct Electrochemical Synthesis of N,N'-Disubstituted Indazolin-3-ones under Sustainable and Metal-Free Conditions*
Poster A-5: Burtoloso, Antonio; University of São Paulo *Asymmetric dihalogenation of sulfoxonium ylides*
Poster A-6: Čičak, Marijo; Institute of Organic Chemistry and Biochemistry of the Czech Academy of Sciences, Prague, Czech Republic *Syntheses of the ortho-polysubstituted azobenzenes*
Poster A-7: Davis, Arabella; Furman University *Development of a [2+2] Photocycloaddition of 2-Pyridones using Organic Photocatalysis*
Poster A-8: Dwulet, Natalie; University of California, Irvine *The Total Synthesis of Isoneoamphilectane*
Poster A-9: Grant, Phillip; University of Vienna *Direct stereodivergent olefination of carbonyl compounds with sulfur ylides*
Poster A-10: Häfliger, Joel; Westfälische Wilhelms-Universität Münster *Stereocontrolled Synthesis of Fluorinated Isochromans via I(I)/I(III) Catalysis*

Poster A-11: Hillman, Ashlyn; University of Delaware
Minimalist Tetrazine Carbohydrate Probe for Rapid Bioorthogonal No-Wash Live-Cell Labeling of Bacterial Peptidoglycan

Poster A-12: Iwai, Kento; Kochi University of Technology
A Safe Synthetic Equivalent of Nitroacetonitrile and Its Synthetic Uses toward 3-Cyanoisoxazoles

Poster A-13: Ji, Haofan; University of Georgia
Enantiospecific Heteroatom-Tethered 1,6-Enyne Cycloisomerizations and Their Utilization in Natural Product Total Synthesis

Poster A-14: Johnson, Lucas; University of California, Irvine
Cobalt-Catalyzed Annulation via Hydrogen Atom Transfer: Expedient Access to Arene-Fused Cycloalkanes

Poster A-15: Kikushima, Kotaro; Ritsumeikan University
Transition-metal-free functionalization of (hetero)arenes via highly reactive TMP-iodonium(III) acetates

Poster A-16: Kraina, Pavel; The Institute of Organic Chemistry and Biochemistry of the Czech Academy of Sciences
Modulators of Human and Bacterial Adenylate Cyclases Based on 7-Substituted 7-Deazapurine Analogues of Adefovir

Poster A-17: Lam, Nelson; University of Cambridge
Guidelines for Predictable Remote Directed C(sp2)–H Activation and their Application Towards Site-Selective Remote C–H Activation of Quinolines

Poster A-18: Linden, Martin; Department of Chemistry, Johannes Gutenberg-University Mainz
Electrochemical Synthesis of Pyrazoles and Pyrazolines via Iodine-mediated [3+2] Dipolar Cycloaddition

Poster A-19: Liu, Shaonan; University of California, Santa Barbara
A Stereoselective Enzymatic Mannich Reaction

Poster A-20: Luzzio, Frederick; University of Louisville
An Oxidation Study of Phthalimide-Derived Hydroxylactams and Lactams

Poster A-21: Makara, Colette; University of Delaware
Development of a High Throughput Photochemical Flow Method for the Large-Scale Synthesis of trans-Cyclooctenes

Poster A-22: Matikonda, Siddharth Sai; National Institutes of Health
Cyanine Phototruncation: From Mechanistic Analysis to Applications in Super Resolution Microscopy and Cell Tracking

Poster A-23: Michalak, Sharon; Amgen
Innovations on the Process Development of a a tri-sugar siRNA ligand

Poster A-24: Neglia, Sophia; University of Delaware
Catalytic Activation of Bioorthogonal Chemistry Using Thermal Catalysis

Poster A-25: Niman, Scott; University of California, Irvine
Efforts Towards the Synthesis of Neoamphilectane

Poster A-26: Okawa, Ryotaro; Hokkaido University
Total synthesis of pseudouridimycin

Poster A-27: Pak, Bonnie and Supantanapong, Nantamon; University of California, Irvine
Syntheses of Lissoclimide Analogues and the Investigation of Novel Halogen–π Interactions

Poster A-28: Pippel, Daniel; Janssen R&D
New Methods for Heterocycle Functionalization in the Context of Drug Discovery Programs at Janssen La Jolla

Poster A-29: Qin, Ziyang; California Institute of Technology
Intramolecular C(sp3)–H Amination to Construct Chiral N-Heterocycles Enabled by Engineered Cytochrome P450 Enzymes

Poster A-30: Ramirez, Melissa; Caltech
Origins of Endo Selectivity in Diels–Alder Reactions of Cyclic Allene Dienophiles

Poster A-31: Slough, Carly; Furman University
A [2+2] Photocycloaddition–Cyclobutane Fragmentation Approach to Annulated Pyridones

Poster A-32: Tallon, Amanda; University of Delaware
Dihydrotetrazine oxidation by a genetically encodable catalyst for rapid turn-on of bioorthogonal chemistry intracellularly

Poster A-33: Tsang, Stephanie; University of Delaware
Mechanistic Study of the Activation of Rapid Bioorthogonal Chemistry via Photocatalytic Oxidation Dihydrotetrazines to Tetrazines

Poster A-34: Vaňková, Karolína; Institute of Organic Chemistry and Biochemistry of the Czech Academy of Sciences
Novel N-branched acyclic nucleoside phosphonates as inhibitors of Plasmodium 6-oxopurine phosphoribosyltransferases

Poster A-35: Wang, Xiye; Columbia University
Electric Field Influence on Hydrocarbon Autoxidation and Amine Acylation

Poster A-36: Wienhold, Max; Westfälische Wilhelms-Universität Münster
Coumarin Synthesis by Direct Annulation: β-Borylacrylates as Ambiphilic C3-Synthons

Poster A-37: Zehnder, Troy; University of Michigan Chemistry Dept - Schindler Group
Olefination of Hydrazones and Oximes Mediated by Ruthenium Alkylidenes

List of Posters: Tuesday Poster Session

Presenters please set up your poster *before the beginning of the morning session* on the board number assigned to you, as shown below.

Poster B-1: Akai, Shuji; Osaka University *Chemo- and Regioselective Cross-dehydrogenative Coupling of 3-Hydroxycarbazoles Using a Heterogeneous Oxovanadium Catalyst*
Poster B-2: Atwood, Brian; Iktos Inc *In silico generation of heterocycle-containing drug-like small molecules: towards tools for the many different needs of drug discovery projects.*
Poster B-3: Becker, Marc; Merck & Co., Inc. *Applications of Biocatalysis in the Synthesis of PCSK9 Inhibitors*
Poster B-4: Blackner, Jake; University of Alberta *Diazaborines: Phenolic Isosteres with Hydroxy Group Exchange Capability*
Poster B-5: Capani Jr., Joseph; University of California, Irvine *An Enantioselective Synthesis of Wickerol B*
Poster B-6: Daniel, Matthieu; CEA *Synthesis and reactivity of 5-Hydrazino-3-Nitro-1,2,4-triazole (HNT) : an amphoteric energetic platform*
Poster B-7: Desai, Shrey; University of Toronto *Organoboron-Catalyzed, Regioselective Alkylation of Azoles*
Poster B-8: Fotherby, Fiona; School of Chemistry, University of St Andrews, UK *Synthesis and Evaluation of New Dihydrotetrathiafulvalene Systems for Metal Surface Adsorption and Hydrogen Bonding*
Poster B-9: Gross, Jonathan; Johannes Gutenberg-University *Computer-Aided Natural Product Structure Elucidation and Mechanochemical Synthesis of Organic Thiocyanates*
Poster B-10: Hielscher, Maximilian; Johannes Gutenberg University Mainz *The Anodic Phenol-Phenol Coupling – Optimizing Electrolysis Conditions is the Key to the Efficient Formation of Biphenols and Polycycles.*

Poster B-11: Horino, Satoshi; Osaka university
Enantiodivergent synthesis of both enantiomers by dynamic kinetic resolution with R-selective lipases

Poster B-12: Jemas, Andrew; University of Delaware
Catalytic Activation of Bioorthogonal Chemistry with Light (CABL) Enables Rapid, Spatiotemporally Controlled Labeling and No-Wash, Subcellular 3D-Patterning in Live Cells Using Long Wavelength Light

Poster B-13: Jiu, Alexander; UC Irvine
Enantioselective Addition of Pyrazoles to Dienes

Poster B-14: Kaur, Milanpreet; University of Calgary
Designing New Strategy For C-H Functionalization using a Hypervalent Iodine Reagent

Poster B-15: Kou, Kevin; UC Riverside
Strategies Towards the Synthesis of Heterocyclic Natural Products

Poster B-16: Kuethe, Jeff; Merck & Co., Inc.
Total Synthesis of a Macrocyclic PCSK9 Inhibitor

Poster B-17: Li, Yang; University of California, Santa Barbara
Lithium Enolate with a Lithium-Alkyne Interaction in the Enantioselective Construction of Quaternary Carbon Centers: Efficient Synthesis of Indole Alkaloids (+)-Goniomitine and (+)-Quebrachamine

Poster B-18: Liu, Xin; Deptartment of Chemistry, Colorado State University, Fort Collins
Diversification of C–F bonds in organofluorides and fluoropolymers by visible-light organic photoredox catalysis

Poster B-19: Lovely, Carl; UT Arlington
Progress Towards a Total Synthesis of Ceratinadin B

Poster B-20: Luzzio, Frederick; Chemistry Dept; University of Louisville
Nucleoside Antibiotic Support Studies: Synthesis of 4'-(2-oxazolyl) Uridine Scaffolds

Poster B-21: Mansour, Ali; University of Ottawa
Strategic use of gold(I)-catalysis for the concise synthesis of polycyclic indole motifs

Poster B-22: Meyer, Stephanie; Westfälische Wilhelms-Universität Münster, Germany
Fluorocyclization via I(I)/I(III) catalysis: a concise route to fluorinated oxazolines

Poster B-23: Muzikova Cechova, Lucie; IOCB, AS CR
Tunable photochemical properties in 5-phenylazopyrimidines: From solution to solid state

Poster B-24: Nguyen, Hanh; University of California, Irvine
Stereocontrolled Access to Quaternary Centers by Birch Reduction/Alkylation of Chiral Esters of Salicylic Acids

Poster B-25: Nishio, Tomoya; Graduate School of Pharmaceutical Sciences, Osaka University
Direct Nucleophilic Substitution of Alcohols Using an Immobilized Oxovanadium Catalyst

Poster B-26: Okumatsu, Daichi; Osaka University
Oxidative Amination of Enolates Utilizing (Diarylmethylene)amino Benziodoxolones

Poster B-27: Patel, Monika; University of Delhi
Versatile Chemistry of KOH-DMSO

Poster B-28: Rychnovsky, Scott; UC Irvine
Total Synthesis of (2R)-Hydroxynorneomajucin, a Norsesquiterpene from Illicium Jiadifengpi

Poster B-29: Qiu, Jiawei; Osaka University
Iridium-Catalyzed Isomerization/Cycloisomerization/Aromatization of N-Allyl-N-sulfonyl-o-(λ^1-silylethynyl)aniline Derivatives to Give Substituted Indole Derivatives

Poster B-30: Rosenberger, Julia; University of Delaware
Subcellularly-localized Photocatalysts and Far-red Light Enable Catalytic Bioorthogonal Uncaging in Live Cells

Poster B-31: withdrawn

Poster B-32: Tao, Yujia; California Institute of Technology
Synthetic Strategies Toward the Total Synthesis of (–)-enterocin

Poster B-33: Vaith, Jakub; University of Rochester
Regiodivergent synthesis of 2- and 3-substituted indolines and pyrrolidines through Pd-catalyzed heteroannulation of 1,3-dienes with bifunctional reagents

Poster B-34: Wada, Yuki; Osaka University
C-C Bond Formation between 1,4-Naphthoquinone and Ru-Carbene Complex with N-Heterocyclic Carbene (NHC) Ligand

Poster B-35: Wang, Minghao; UCI
Enantioselective Coupling of Cyclopropenes with Pyrazoles via Copper(I) Catalysis

Poster B-36: Xu, Mizhi; University of California, Santa Barbara
Resonance Promoted Ring-Opening Metathesis Polymerization of Twisted Amides

Poster B-37: Zhao, Ke; University of California Santa Barbara
Rational Design on Bifunctional Ligand in Asymmetric Gold Catalysis

Award Lecture Abstracts

Taylor Awardee Viresh Rawal

Katritzky Awardee Sarah Reisman

Industrial Awardee Rémy Angelaud

Efficient Construction and Selective Functionalization of Heterocycles in the Manufacturing of Active Pharmaceutical Ingredients

R. Angelaud

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Heterocycles are present in more than 90% of active pharmaceutical ingredients (API) and come in a very wide variety of shapes and sizes. We will present the different synthesis strategies designed and developed to access some of these heterocyclic molecules towards the manufacture of marketed pharmaceutical drugs and APIs currently in clinical development.

Progress toward members of the hapalindole family of alkaloids

V. H. Rawal,[a],*J. Xu,[a] and L. Hu[a]

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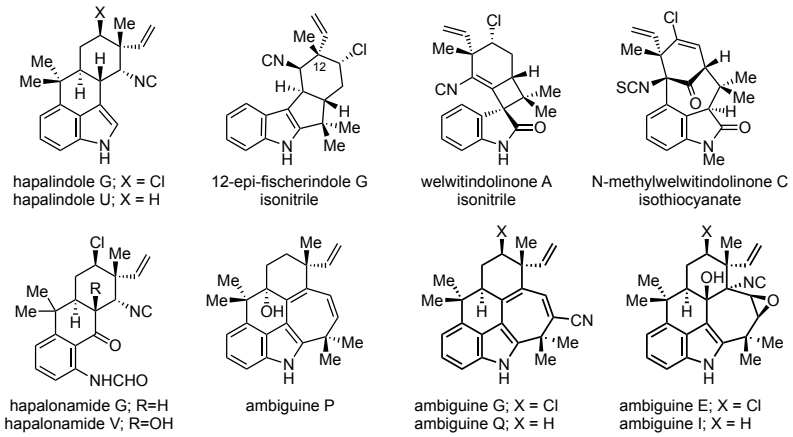
**vrawal@uchicago.edu*

Abstract: A chemical synthesis comprises a series of reactions that gradually increase the complexity of the starting material until it is finally transformed into the desired target. While the specific reactions—the tactics—chosen for each step are crucial, a successful total synthesis campaign must also be undergirded by an overall strategy that solves the crucial structural challenges inherent to a particular class of natural products. In this presentation, I will discuss the strategic and tactical considerations that went into our work on the synthesis of some cyanobacteria derived indole alkaloid metabolites, focusing in particular on the pentacyclic ambiguines group of compounds, which are a subset of the hapalindole family of alkaloids.[1-3]



Representative of Hapalindoles, Welwitindolinones, Hapalonamide, and Ambiguines

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Necessity is the Mother of Invention: Natural Products and the Chemistry They Inspire

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**reisman@caltech.edu*

The chemical synthesis of natural products provides an exciting platform from which to conduct fundamental research in chemistry and biology. Our group is currently pursuing the synthesis of several structurally complex natural products, many of which contain heterocycles at their core. The densely packed arrays of heteroatoms and stereogenic centers that constitute these polycyclic targets challenge the limits of current technology and inspire the development of new synthetic strategies and tactics. This seminar will describe the latest progress in our target-directed synthesis endeavors.

Plenary Lecture Abstracts

Innovation By Evolution: Bringing New Chemistry To Life

F. H. Arnold

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Not satisfied with biology's vast catalyst repertoire, I want to create new enzyme catalysts and expand the chemistry of life. We use the most powerful biological design process, evolution, to optimize existing enzymes and invent new ones, thereby circumventing our profound ignorance of how sequence encodes function. Evolution can innovate by exploiting the promiscuous catalytic activities of extant proteins to mold new enzymes. We are using this insight to explore chemistries that become available to enzymes in a new environment. I will illustrate with a few examples how 'carbene transferase' and 'nitrene transferase' enzymes have been generated by directed evolution of Fe-heme proteins in the presence of abiological carbene and nitrene precursors. These new-to-nature biocatalysts can exhibit remarkable selectivity for their targeted reactions, arising from macromolecular active sites that are readily tuned by evolution.

Changing the World, One Reaction at a Time

L.-C. Campeau[a]

[a]*Department of Process Research and Development, Merck Research Laboratories, Merck & Co. Inc., Rahway, New Jersey, 07065, USA*
**lc.campeau@merck.com*

Nucleoside analogues are ubiquitous in nature and are critical component of life-saving therapies used in the treatment of viral disease and cancer. Despite their widespread use and commercial value, the state-of-the-art methods for their preparation in drug discovery, drug development and eventual commercialization are lacking and remain a poorly solved problem in organic synthesis. In addition to posing synthetic challenges, custom nucleoside total synthesis presents several challenges with respect to green and sustainable chemistry, where current methods largely rely on chiral pool feedstocks and protecting group chemistry. We have developed a suite of novel methods for the synthesis and scale-up of nucleosides and cyclic dinucleotides. These efforts have culminated to an aspirational synthesis from commodity chemicals using a biocatalytic in-vitro cascade for construction of nucleosides.

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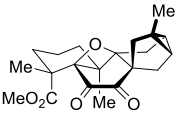
Recent Developments in Strategies and Tactics Towards Complex Secondary Metabolites

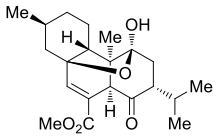
Erick M. Carreira

ETH-Zürich

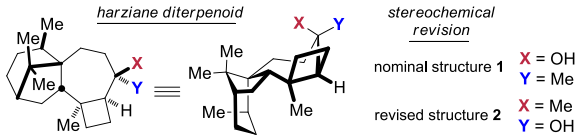
The talk will include discussion and analysis of recent natural product targets that have been synthesized in the group. It will focus on target oriented synthesis as an engine for the generation of novel methods and approaches to bioactive agents. The methods involve novel, unexpected reactivity and unusual building blocks that are fully integrated to lead to efficient routes.



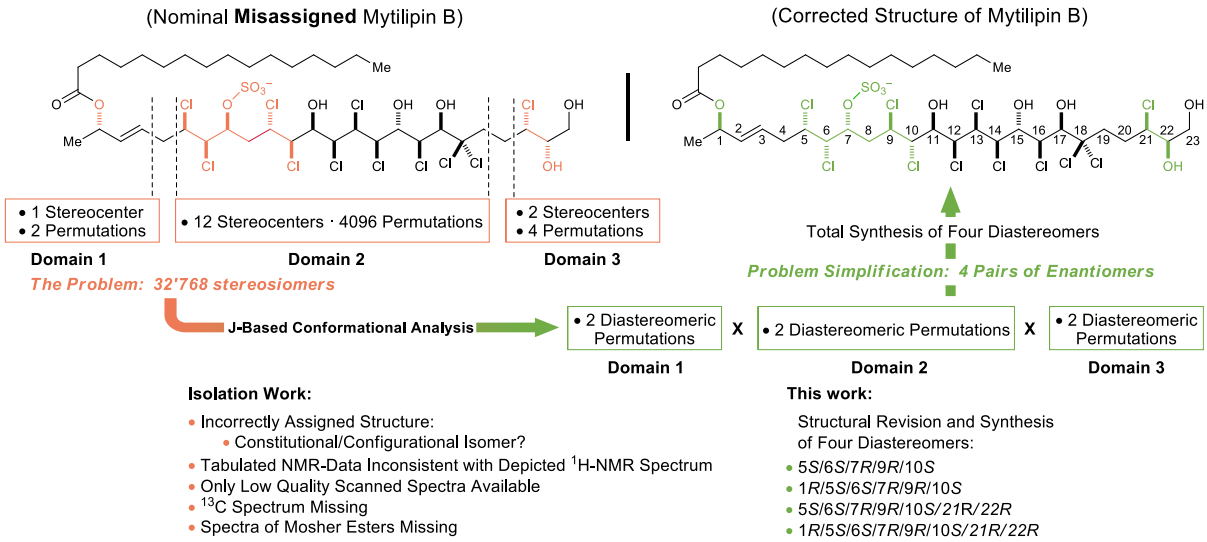
(–)-Mitrephorone A



(+)-Sarcophytin
reassigned absolute configuration



- unprecedented and highly caged 6–5–7–4 skeleton
- 6 contiguous stereocenters
- 3 quaternary carbon atoms



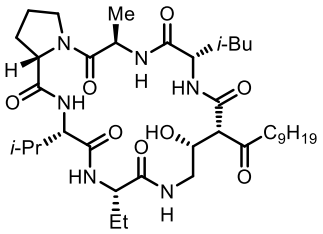
Isolation Work:

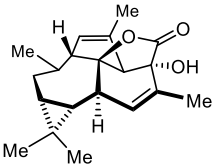
- Incorrectly Assigned Structure:
  - Constitutional/Configurational Isomer?
- Tabulated NMR-Data Inconsistent with Depicted ^{1}H-NMR Spectrum
- Only Low Quality Scanned Spectra Available
- ^{13}C Spectrum Missing
- Spectra of Mosher Esters Missing

This work:

Structural Revision and Synthesis of Four Diastereomers:

- 5*S*/6*S*/7*R*/9*R*/10*S*
- 1*R*/5*S*/6*S*/7*R*/9*R*/10*S*
- 5*S*/6*S*/7*R*/9*R*/10*S*/21*R*/22*R*
- 1*R*/5*S*/6*S*/7*R*/9*R*/10*S*/21*R*/22*R*





Euphorikanin A

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Choose Your Own Adventure in Metal-Hydride Catalysis

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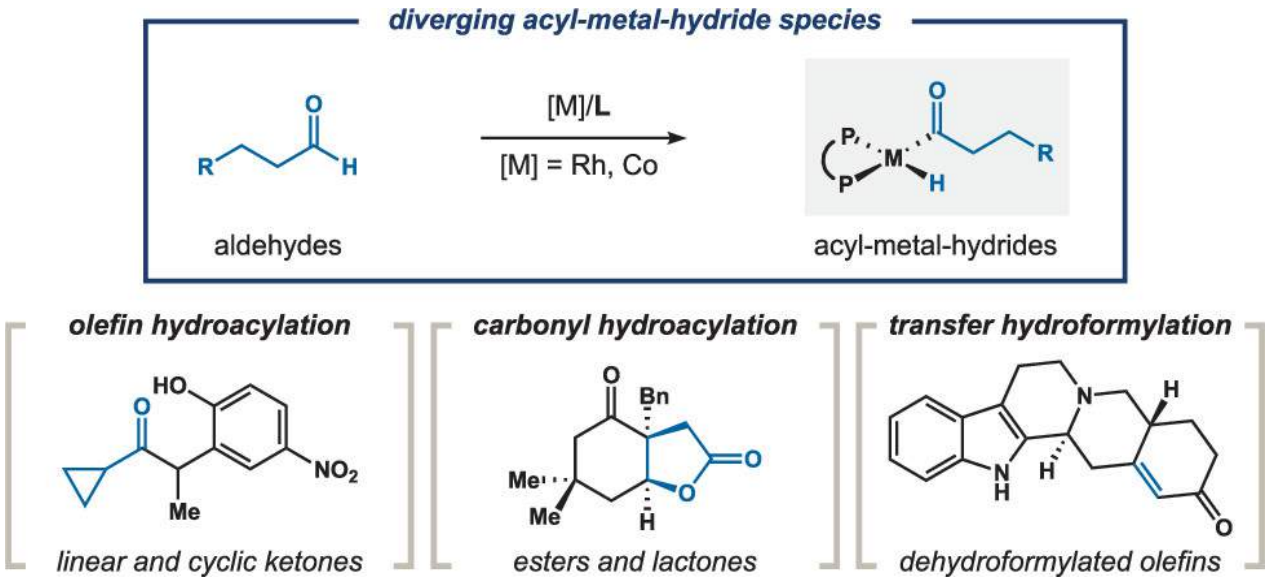
Metal hydrides promote diverse organic transformations that include both C─C bond making and C─C bond breaking processes.[1,2] This lecture will highlight the development of Rh, Co, and Cu-catalysts for use in enantioselective hydrofunctionalizations (e.g., hydroacylation, hydroamination, and hydrothiolation). A unique transfer hydroformylation will be described that allows conversion of aldehydes or alcohols to olefins. The presentation emphasizes mechanistic studies that demonstrate the role of counter-ions in controlling selectivity. Lastly, we disclose applications of these catalysts for transforming feedstocks into more complex building blocks and targets for applications in biology and medicine.



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Photocatalytically Inducible Tetrazine Ligation

A. Hillman,[a] Y. Fang,[a] A. Jemas,[a] C. Makara,[a] J. E. Pigga,[a] P. Ramaraj,[a] J. E. Rosenberger,[a] S. Scinto,[a] A. Tallon,[a] W. Trout,[a] S. Tsang,[a] C. Wang,[a] Y. Xie,[a] C. W. am Ende,[b] J. M. Fox[a,*]

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[b]*Pfizer Worldwide Research and Development, Eastern Point Road, Groton, Connecticut 06340, USA*
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This seminar will discuss recent advances in development of the tetrazine ligation– the fastest known bioorthogonal reaction.[1] Tetrazine ligation has been used broadly by the scientific community, and finds application across chemical biology, medicine, nuclear medicine, and material science. The talk will describe advances in photochemistry, flow chemistry, and cross-coupling chemistry that have enabled access to improved *trans*-cyclooctene and tetrazine reagents including a suite of tool molecules developed in collaboration between UD and Pfizer.[2–4] The talk will also discuss the catalytic activation of bioorthogonal chemistry with light, or CABL, a new method for 'turning on' rapid bioorthogonal chemistry *in vivo* and in cellular context through the photocatalyzed oxidation of dihydrotetrazines to tetrazines.[5–7] Discussed will be new tool molecules with high stability in the cellular environment in their 'off' state, and the fastest bioorthogonal reactions to date in their 'on' state. CABL photocatalysts are based on fluorescein or silarhodamine dyes with activation at 470 or 660 nm, respectively. CABL is rapid even at sub-micromolar concentrations, and CABL-photocatalysts are biocompatible due to their minimal singlet oxygen production. With single photon activation, CABL can be used to activate subcellular activation in the nucleus, mitochondria, actin, or cytoplasm and two-photon excitation promotes CABL at the suborganelle level to selectively pattern live cells under no-wash conditions. CABL can also applied to spatially resolved live-cell labeling of the low abundant protein target monoacylglycerol lipase at endogenous concentration. Kinetic studies have been used to develop a proposal explaining the fast and selective photocatalytic oxidation of dihydrotetrazines with molecular oxygen as the terminal oxidant and hydrogen peroxide as a reaction product.

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New synthetic chemistry to probe the biology of nucleic acids

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The primary code stored within RNA is displayed through the linear sequence of four nucleobases (A, C, G, U). Beyond the core information stored in the sequence of RNA, a second layer of programming exists in the form of many chemical modifications to the canonical nucleobases. By comparison, the array of modifications to the canonical nucleobases in DNA–known as the epigenetic code–is relatively limited, albeit crucial to its regulation of the gene, with methylation at C being the prevalent chemical mark. In contrast, over 140 distinct chemical variations identified in RNA, to date. These post-transcriptionally modified ribonucleotides play integral roles in the cellular control of information that is encoded in the gene. The modifications are prevalent across all RNA types and are collectively referred to as the epitranscriptome. The sheer diversity of RNA modification means that a variety of tools are needed to fully explore the epitranscriptome. Currently, most of the methods for the detection of modified RNAs use an antibody that is selective for a particular modification. Beyond the oligomeric nucleic acids, small-molecule nucleosides and nucleotides also play a crucial role in the treatment and regulation of disease. These molecules also display a plethora of structural modification compared to the native monomeric components.

This lecture will focus on developing new synthetic chemistry, based primarily on visible-light photocatalysis, that selectively modifies nucleic acids – from small molecules to genetic material – and can potentially help to unlock new lines of research in drug discovery, probe design, topology and sequencing.

Radical-Based Approach for Synthesis of Complex Natural Products

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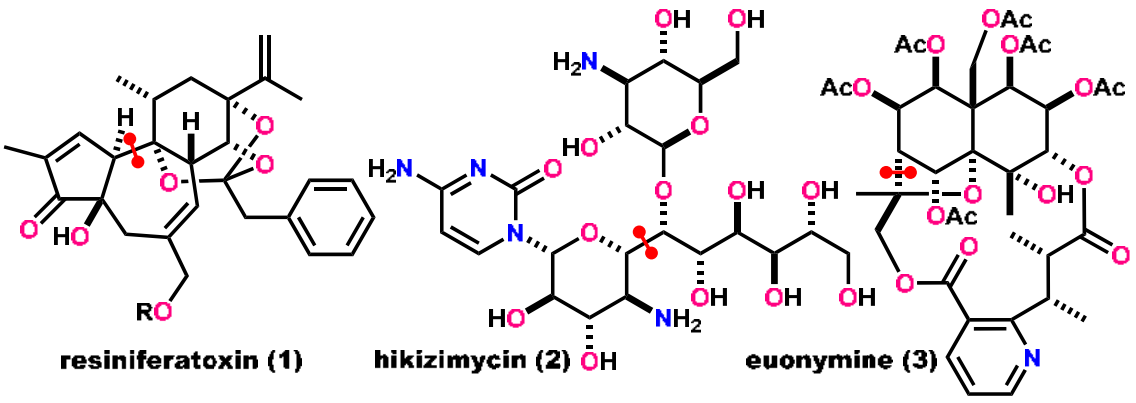
Natural products with a high ratio of sp^3-hybridized atoms and oxygen-substituted stereogenic centers represent privileged structures for the development of pharmaceuticals and chemical probes. The multiple oxygen functionalities of these natural products endow their potent and selective biological activities, although they significantly heighten the challenge of their chemical assemblies.[1] We focused on developing efficient strategies for the total syntheses of this biologically and chemically important class of molecules. Specifically, we have designed and devised radical-based strategies for assembling highly oxygenated natural products.[2,3] In this lecture, we report the development of the radical coupling reactions and the synthetic routes to resiniferatoxin (**1**),[4,5] hikizimycin (**2**),[6] and euonymine (**3**)[7] by applying the radical chemistry.



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Oxygen Driven Fragment Coupling for the Synthesis of Natural Products and Antibacterials

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Nature uses oxidative couplings to construct carbon-carbon, carbon-oxygen, and carbon-nitrogen bonds with a high degree of efficiency. Surprisingly, few laboratory equivalents are as selective or as efficient as the biological versions. The use of parallel microscale screening to discover selective and efficient catalysts for such processes using oxygen as the terminal oxidant will be discussed. The unexpected outcomes obtained highlight the value of interrogating large numbers of rationally selected variables under the umbrella of general hypothesis. The development of selective oxidative catalytic processes for phenol coupling, enol coupling, and alkyl C–H activation will be discussed. Applications in total synthesis of hypocrellin, honokiol, chaetoglobin, and pyrolaside B will be presented. Finally, studies on the mechanisms of these transformations will be described with the goal of understanding the governing principles and how they might be used to discover further new transformations.

Heterocycles in the context of natural products synthesis

Armen Zakarian

Department of Chemistry and Biochemistry, University of California, Santa Barbara

Natural products are a rich source of heterocyclic structures. Varying from aromatic, often represented in classic medicinal chemistry, to more strereochemically complex saturated nitrogen, oxygen, and other heteroatom heterocycles, they present exciting challenges for synthesis. Saturated or partially saturated heterocyclic compounds are also an emerging class of privileged targets in medicinal chemistry. In many cases, construction of heterocyclic structures is a main problem in the synthesis design. Several contributions from our group focusing on the synthesis of cylindrospermopsins, xestospongins, and other select examples will be discussed.

Invited Lecture Abstracts

New Strategies for Hydrocarbon Functionalization

Erik J. Alexanian

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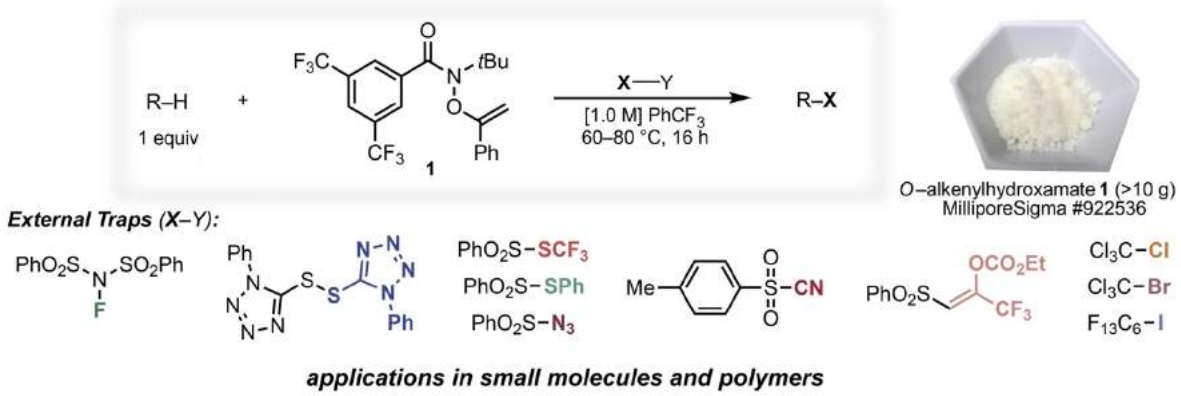
Reactions that functionalize aliphatic C–H bonds site-selectively are valuable in a range of synthetic contexts, from the sustainable synthesis of small molecules to the upcycling of post-consumer plastic waste. Our recent efforts towards the development of a general platform for intermolecular aliphatic C–H functionalization of both small molecules and polymers using heteroatom-centered radicals will be presented. The strategy features easily-accessed radical precursors to enable a diverse set of practical C–H transformations with excellent site selectivities and chemoselectivities. Applications of the reaction platform to the decarboxylative functionalization of complex molecules will also be discussed.



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Thiophene *S*,*S*-dioxides: Versatile heterocycles for natural product synthesis

Edward A. Anderson,* Kun Ho (Kenny) Park, Nils Frank, Fernanda Duarte

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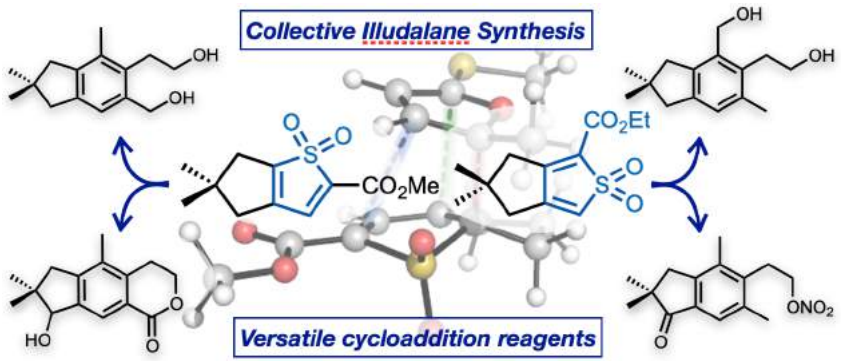
The *de novo* synthesis of polysubstituted benzene rings is an attractive strategy that avoids the need for lengthy synthetic manipulations of pre-formed arenes. One approach to such structures involves cascade Diels-Alder / retro-Diels Alder chemistry, where the extrusion of small molecules such as N_2 (from pyridazines) or CO_2 (from pyrones) can drive the cascade. A class of diene that has been largely overlooked to date in such chemistry are thiophene *S*,*S*-dioxides, derivatives of thiophenes that are easily prepared by peracid oxidation.[1] This lecture will describe recent work from our group on the first applications of thiophene *S*,*S*-dioxides as substrates for intermolecular Diels-Alder cascades in natural product total synthesis, in the context of a collective synthesis of 9 members of the illudalane family of sesquiterpenes.[2] Calculations revealed that the particular cycloaddition used in this synthesis – reaction of the thiophene *S*,*S*-dioxide with a furan – proceeds via an ambimodal transition state rather than a pure pericyclic process, with subsequent bifurcation to different (4+2) cycloadducts.[3,4] The extent of asynchronicity in this transition state is unusual in the field. Finally, recent work involving the application of thiophene *S*,*S*-dioxide cascades towards other natural product families will be described.



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Engineering Fe(II)/α-Ketoglutarate-Dependent Halogenases and Desaturases

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rebecca.buller@zhaw.ch

Late-stage functionalization of complex molecular scaffolds offers an elegant route to create novel biologically active entities. In discovery chemistry, inactivated C-H bonds are regarded as particularly promising, if challenging, points of diversification as they allow to create new analogs without resorting to *de novo* synthesis. As a prerequisite for this approach, however, the reaction procedures must be compatible with already existing functional groups in the lead structural scaffold – a task still challenging most chemical methodologies. In this context, Fe(II)/α-ketoglutarate dependent dioxygenases, enzymes which are capable of halogenating and hydroxylating sp^3 carbons with high stereo- and regiocontrol under benign conditions, have attracted increasing attention. This enzyme family's reported substrate scope, however, is often limited to natural substrates and their close analogues. By employing a combination of smart library design and machine learning assisted directed evolution, we engineered several Fe(II)/α-ketoglutarate dependent dioxygenases for the late-stage functionalization of molecules of pharmaceutical interest, ranging from non-natural amino acids to bulky macrolides, hitherto not accepted substrates.[1-4] Notably, our enzyme engineering approach allowed us to rapidly identify more active enzyme variants increasing the apparent k_{cat} and the turnover number of the enzymes by orders of magnitude. In addition, in case of the engineered soraphen halogenases, we could predict and consequently modulate the regioselectivity of soraphen halogenation allowing the targeted analysis of the small molecule's structure-function activity in biological assays.

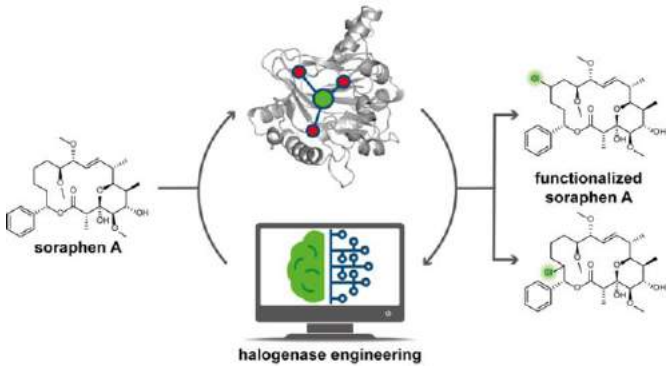

Figure: Engineering Fe(II)/α-ketoglutarate dependent halogenases for the late-stage modification of the natural product soraphen.

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Synthesis of Biologically Active Alkaloids Based on the Sequential Sigmatropic Rearrangement

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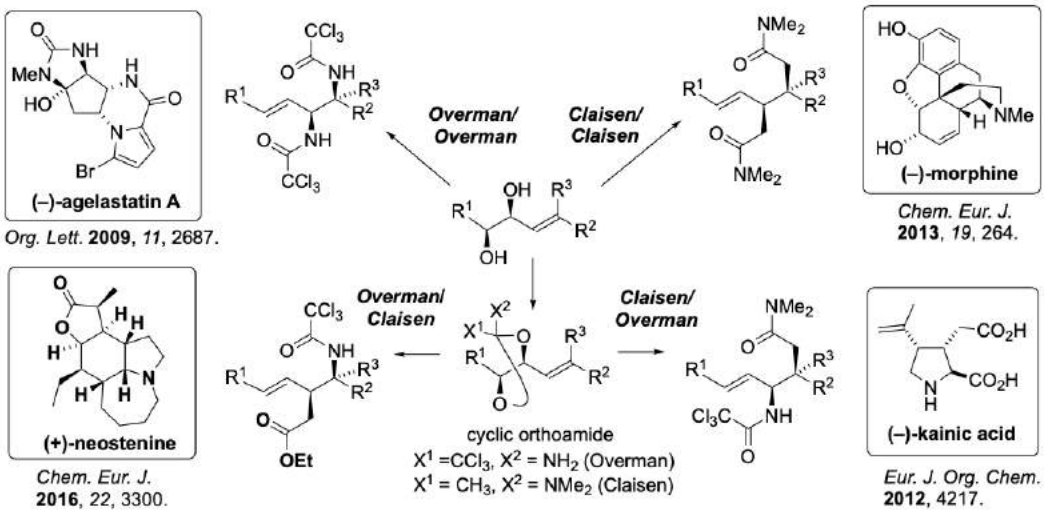
Sigmatropic rearrangement of chiral allylic alcohols is a powerful method for the chiral synthesis of natural products due to its effective chirality transfer. In this lecture, stereoselective syntheses of some biologically active alkaloids based on the methodology using the sequential sigmatropic rearrangement is presented. Treatment of a chiral allylic vicinal diol derived from sugars or tartrates with excess amount of Cl3CCN, followed by heating, afforded a product of sequential Overman/Overman rearrangement as a single diastereomer.[1] Likewise, thermal reaction of the diol in the presence of excess MeC(OEt)3 or MeC(OMe)2NMe caused the sequential Claisen/Claisen rearrangement.[2] On the other hand, reaction of the diol with stoichiometric amount of the reagent provided a cyclic orthoamide, which, upon heating, afforded the singly rearranged product. Applying the second sigmatropic rearrangement to the resulting allylic alcohol, Overman/Claisen[3] and Claisen/Overman[2b] products were obtained. By use of the sequential sigmatropic rearrangement, syntheses of several types of alkaloids have been completed.[4]



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Chemistry Innovation and Biological Discovery through Total Synthesis

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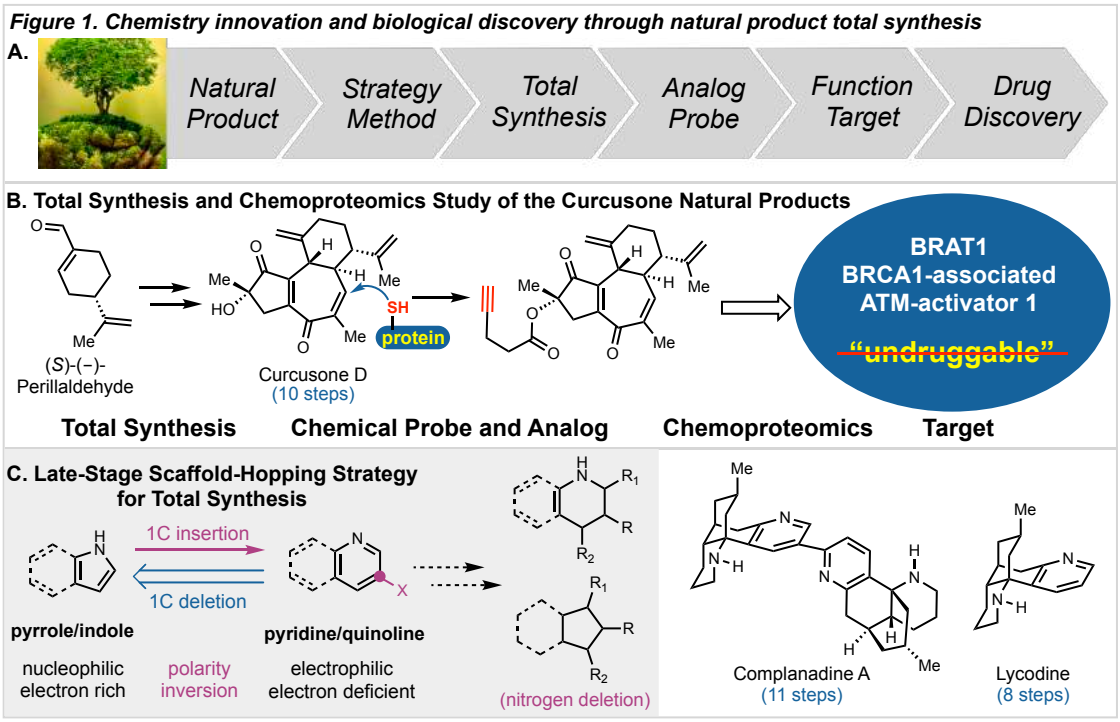
Our research focuses on innovating the strategy and methodology of organic synthesis to solve problems of biological and medicinal importance and ultimately impact human health (Figure 1A). We view the completion of a total synthesis as the beginning of a larger and deeper scholarly inquiry, which will enable us to profile the biology of the selected natural products, decipher their mode of actions, and optimize the lead compounds into novel therapeutics. This talk will highlight elements of our recent efforts in the total syntheses of the anticancer curcusone diterpenoids (Figure 1B)[1,2] and the neurotrophically active *Lycopodium* alkaloids (Figure 1C).[3] For the former, I will discuss our synthetic and chemoproteomics studies of the curcusone natural products, which culminated in the efficient total syntheses of curcusones A-D and dimericursone A for the first time and the identification and validation of BRCA1-associated ATM activator 1 (BRAT1), a master regulator of DNA damage response, as a cellular target of the curcusone natural products. For the latter, I will share how we use *Lycopodium* alkaloids complanadine A and lycodine as inspiration to develop a late-stage scaffold-hopping strategy for complex natural product total synthesis.

Figure 1. Chemistry innovation and biological discovery through natural product total synthesis



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Stereoselective Construction of Challenging C-C Bonds *via* Allylic Anions: Tetrasubstituted Alkenes and β-Stereocenters Centers

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Carbonyl olefination provides an important strategy for constructing stereodefined alkenes that are ubiquitous in important functional molecules and synthetic intermediates. Nevertheless, the difficulty associated with the stereoselective construction of alkenes tracks with the degree of substitution, in which tetrasubstituted alkenes are regarded as the most challenging and the planar equivalents of quaternary stereogenic centers. Moreover, the specific alkene geometry is often critical for conferring a specific biological or physical property, as exemplified in important pharmaceuticals and optoelectronic materials. The first part of the seminar will describe a novel dynamic kinetic resolution of polysubstituted α,β-unsaturated cyanohydrins.[1]

Polarity reversal of a conventional functional group often provides a practical advantage in synthesis, which can avoid the inherent limitations associated with a more conventional bond-forming strategy. For example, heteroatom-stabilized allylic anions constitute useful synthons for the construction of β-substituted carbonyl compounds. Nevertheless, the application of these masked homoenolate equivalents can be problematic, which can be ascribed to their ambident reactivity that often leads to the formation of regioisomeric products. Furthermore, despite the longstanding utility of allylic anions as homoenolate synthons, the *catalytic* enantioselective variant of this transformation has not been forthcoming. The seminar will also describe the catalytic enantioselective allylation of a homoenolate equivalent to provide a novel method for the construction of β-stereogenic carbonyl derivatives.[2]

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Applications of enzyme cascades in heterocycle synthesis

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Biocatalysis has become an important aspect of modern organic synthesis, both in academia and across the chemical and pharmaceutical sciences.[1,2] Its success has been largely due to a rapid expansion of the range of chemical reactions accessible, made possible by advanced tools for enzyme discovery and protein engineering. As the enzyme toolbox for biocatalysis has expanded, so has the potential for the construction of powerful enzyme cascades for efficient and selective synthesis of target molecules. The dramatic increase of biocatalysts that are now available can make design of enzyme cascades highly challenging, in particular to the non-expert.

In this talk, I will present the application of RetroBioCat,[3] a collection of tools for automated biocatalytic cascade design, that is freely available to the scientific community (https://retrobiocat.com/). I will describe its implementation in a number of *de novo* multistep biosynthetic sequences towards chiral amines, amino-polyols and heterocycles.[4]

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Development of Strong and Tough Polymers from Renewable Resources

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The development of sustainable plastics is arguably one of the most important societal challenges that need to be addressed. The current production of plastics is energy intensive, uses a significant portion of the world's petroleum supply, and leads to materials that are accumulating in our landfills and oceans.[1] On this basis, we have been focusing on making materials from dihydrofuran (DHF). DHF can be made sustainably and economically in a single step from 1,4-butanediol, which is already manufactured on a large scale from biobased resources.[2] We have developed a new cationic polymerization to yield high molar mass polyDHF, which gives a thermoplastic with high tensile strength and stiffness. This new material has properties better than, or comparable to, commercial polycarbonates and polystyrenes, enabling the use of polyDHF as a biorenewable alternative to these materials. Significantly, we have developed a new electrochemical depolymerization of polyDHF to enable chemical recycling and a circular life-cycle of this polymer.

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Recent Advances in Fe-Catalyzed Multicomponent Cross-Couplings

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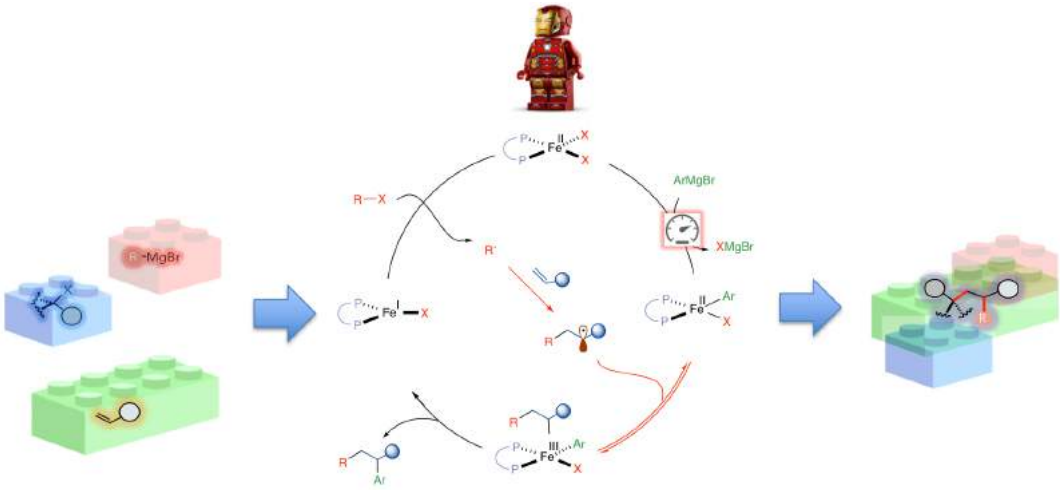
Despite advances in high-throughput screening methods leading to a surge in the discovery of catalytic reactions, our knowledge of the molecular-level interactions in the rate- and selectivity-determining steps of catalytic reactions, especially those involving highly unstable and reactive open-shell intermediates, is rudimentary. These knowledge gaps prevent control, suppression or enhancement, of competing reaction channels that can drive development of unprecedented catalytic reactions. In this talk, I will focus on our use of high-level quantum mechanical calculations, rigorously calibrated against experimental data, to interrogate the mechanisms of asymmetric iron-catalyzed C(sp2)-C(sp3) cross-coupling reactions. Then, I will focus on how our group used this combined experimental and computational approach to quickly develop a vast array of multicomponent Fe-catalyzed cross-coupling reactions.[1]



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TBA

Sabine Hadida

Vertex Pharmaceuticals, San Diego, CA

Photoenzymatic Catalysis – Using Light to Reveal New Enzyme Functions

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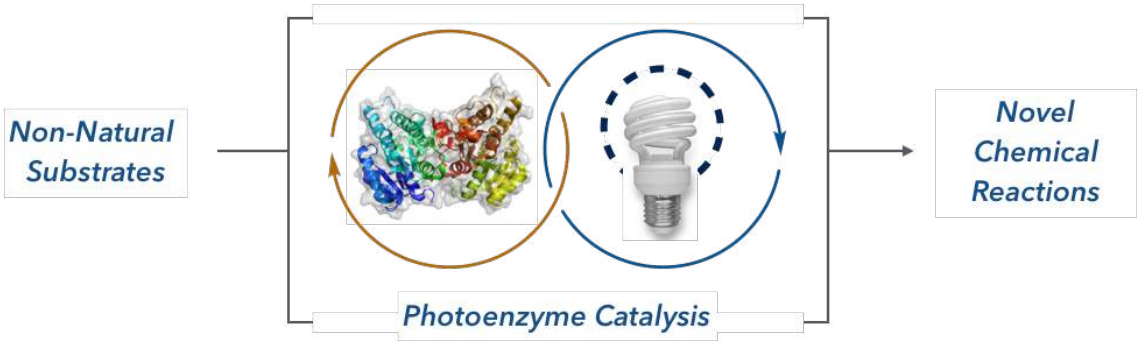
Enzymes are exquisite catalysts for chemical synthesis, capable of providing unparalleled levels of chemo-, regio-, diastereo- and enantioselectivity. Unfortunately, biocatalysts are often limited to the reactivity patterns found in nature. In this talk, I will share my groups efforts to use light to expand the reactivity profile of enzymes. In our studies, we have exploited the photoexcited state of common biological cofactors, such as NADH and FMN to facilitate electron transfer to substrates bound within enzyme active sites. In other studies, we found that enzymes will electronically activate bound substrates for electron transfer. In the presence of common photoredox catalysts, this activation can be used to direct radical formation to enzyme active sites. Using these approaches, we can develop biocatalysts to solve long-standing selectivity challenges in chemical synthesis.



Design, Synthesis and Biological Evaluation of Sphaerimicin Analogues

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The abstract Drug-resistant bacterial infections have claimed the lives of millions of people worldwide in the current status, therefore, the development of antibacterial agents with novel mechanisms of action is urgently necessary. MraY is an integral membrane enzyme, which is responsible for peptidoglycan biosynthesis. MraY is an essential enzyme for bacterial replication and an attractive target for drug-resistant bacterial drugs. Sphaerimicins are nucleoside natural products isolated from *Sphaerisporangium sp.* SANK60911.[1] Sphaerimicin A exhibits strong MraY inhibitory activity (IC_{50} 13.5 ng/mL for MraY) and promising antibacterial activity against gram-positive bacteria (MIC 1-16 μg/mL). Sphaerimicins consist of a 5'-glycyluridine, an aminoribose, a highly substituted piperidine, and a highly methyl-branched fatty acid, resulting in a complex chemical structure. The most intriguing structural feature of sphaerimicins is a macrocyclic structure fused with the aminoribose and the piperidine ring. Here I will describe the design, synthesis and biological evaluation of simplified sphaerimicin analogues.

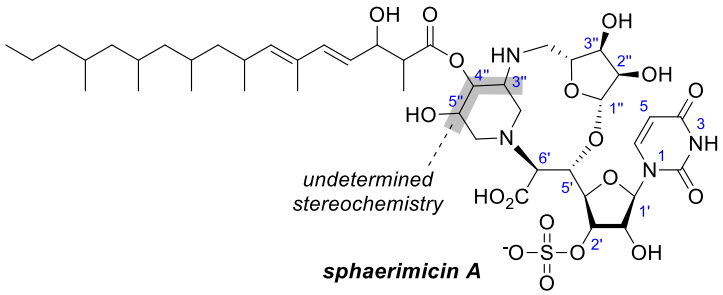

Figure 1. Structures sphaerimicin A

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Lewis base catalyzed polarity inversion of Michael acceptors

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In 1962 Price reported the hexamerization of acrylonitrile when it was exposed to phosphine catalysts in the presence of alcohols.[1] In contrast to transformations such as the Morita-Baylis-Hillman reaction it was observed that the enolate from 1,4-addition of the phosphine undergoes tautomerization to invert the polarity of the β–carbon. The related polarity inversion of Michael acceptors under NHC catalysis was observed by Fu in 2006.[2] In a series of studies from our group we have discovered and developed the polarity inversion of Michael acceptors as a valuable approach to reaction discovery.[3] In this presentation recent studies on this topic focused on enantioselectivity and reaction cascades will be discussed.[4]

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Selective Functionalization of Pyridines, Diazines and Pharmaceuticals via Unconventional Intermediates

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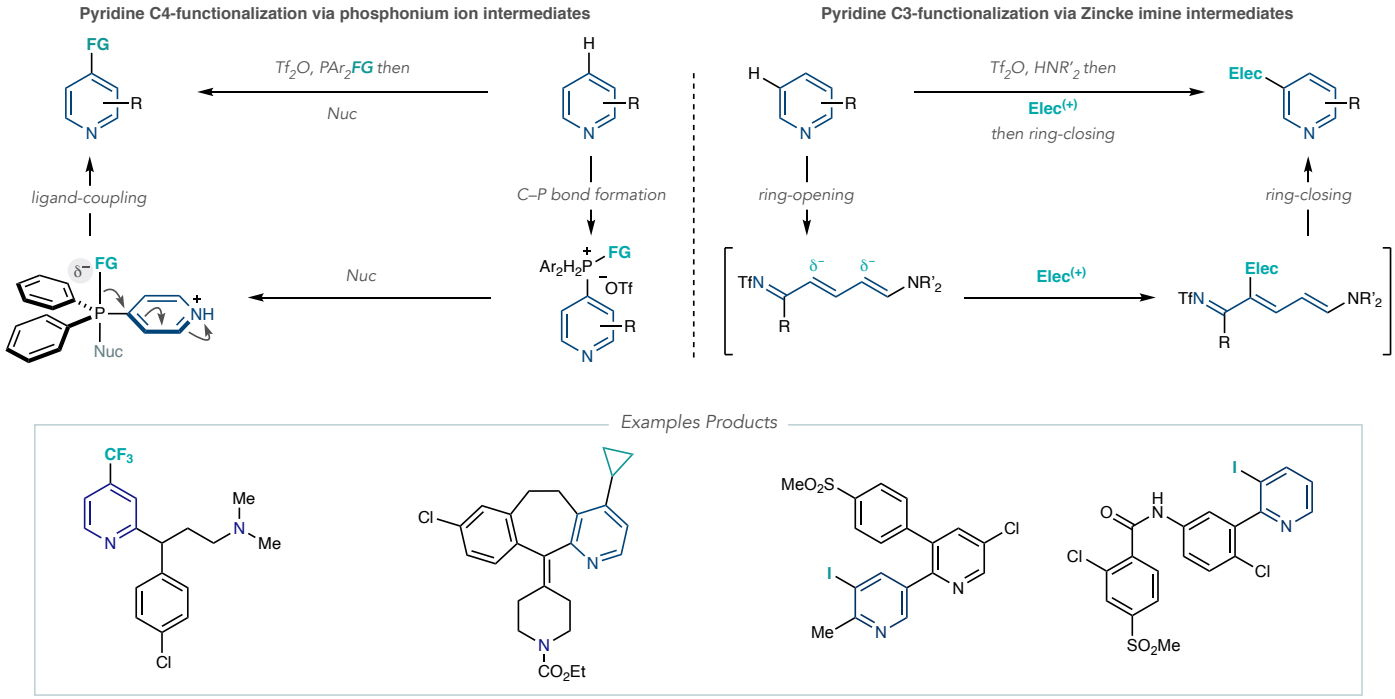
Pyridines and diazines are ubiquitous in pharmaceuticals and agrochemicals, yet there are limits in synthetic methods that can directly functionalize the C–H bonds in these structures. We will show two distinct approaches, using phosphorus and ring-opened intermediates, that enable selective functionalization of these heterocycles into a range of valuable derivatives. A range of C–C and C–Heteroatom bond formations are viable, and the chemistry functions on structures typically encountered in drug discovery programs. Our lab has also performed mechanistic and computational studies of the regioselectivity of these reactions and the phosphorus ligand-coupling processes involved.



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Strongly Reducing Organic Photoredox Catalysts

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Photoredox catalysis uses light to access electron or energy transfer pathways that can be exploited for catalysis. This presentation will focus on the design and employment of strongly reducing visible-light absorbing organic photoredox catalysts. These photoredox catalysts have been used in organocatalyzed atom transfer radical polymerization and small molecule synthesis. The developing catalyst design principles and the implications in the catalytic mechanisms will be discussed.

S,N-Ketene Acetal Merocyanines – Switchable AIEgens

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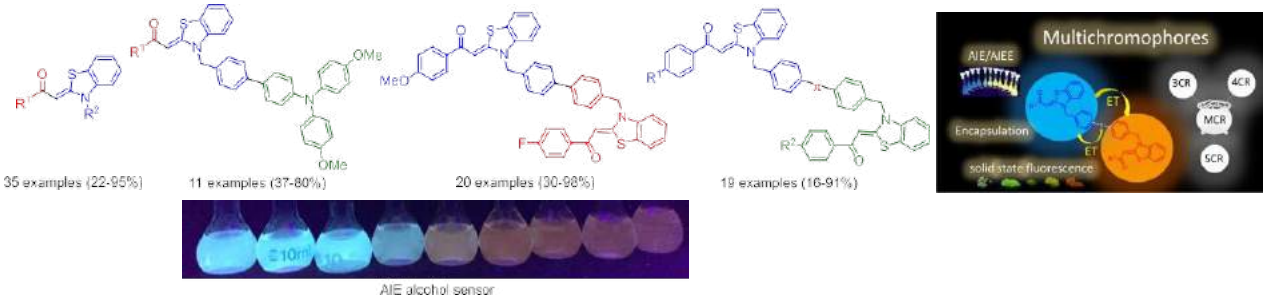
We are developing concise, efficient one-pot syntheses of functional chromophores by multi-component reactions.[1] Amongst diversity-oriented syntheses and properties of fluorophores,[2] AIE (aggregation induced emission) chromophores are particularly interesting.[3] Just recently, a modular synthesis of solid-state emissive aroyl-*S*,*N*-ketene acetals with tunable AIE characteristics could be disclosed.[4] Further expansion of the methodology gave access to aroyl-*S*,*N*-ketene acetal merocyanine based bichromophores as multifunctional AIE sensors by consecutive three-component condensation-Suzuki sequence and one-pot Masuda-Suzuki sequence,[5] and even unimolecular multichromophores with tunable AIE.[6] Bi- and multichromophore arrays are affected by the AIE of the merocyanine moieties which govern the emission readout, resulting in emission color change. The synthetic concept and AIE studies shall be discussed.



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Remote, Double, and Enantioselective C-H Functionalizations via Radical Chaperones

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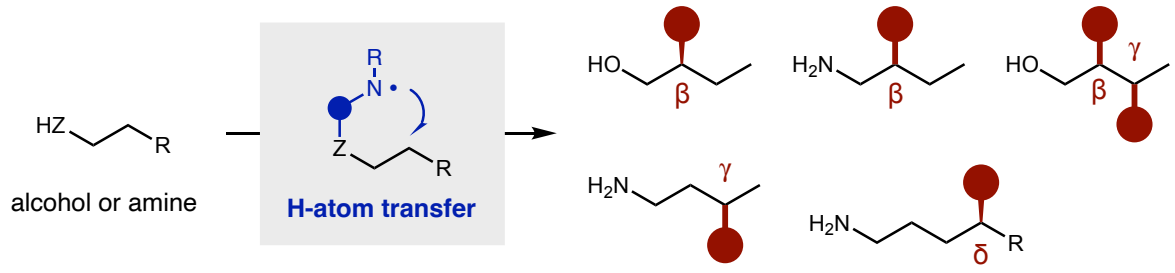
Our research is focused on developing radical chaperone strategies to harness intramolecular (1,5- or 1,6-) H-atom transfer (HAT) mechanisms to enable new modes of chemo-, regio-, and stereo- selectivity for remote, single and double C-H functionalizations of alcohols and amines. These radical chaperone tools are continually being developed to streamline the synthesis of medicinally relevant molecules and heterocycles. Key examples include: (1) enantioselective C-H amination of imidates[1] to access chiral β amino alcohols, (2) vicinal, double β,γ C-H functionalization[2] via radical-polar-crossover, (3) remote δ C-H desaturation of amines[3] for the synthesis of five- and six-membered aza-heterocycles, and (4) γ C-H functionalization of amines[4] via a triple HAT cascade. Collectively, these mechanisms merge: (*i*) either thermal or photocatalysis to generate N-centered radicals, and (*ii*) Cu or Co catalysis to selectively trap the distal radicals upon intramolecular HAT.



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Biocatalysis and Complex Molecule Synthesis

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Natural sources, such as plants, fungi and microbes, have historically provided compounds with potent pharmaceutical properties. While it can be challenging to build complex natural products in a lab using existing chemistry methods, Nature has perfected these biosynthetic pathways. The work described leverages the power of Nature's tools for building complex molecules to synthesize novel molecules with therapeutic potential. The reactivity and selectivity of enzymes from natural product pathways are often unparalleled in existing chemical methods. Enzymes with potential synthetic utility are used as a starting point for engineering biocatalysts with (1) broad substrate scope, (2) high catalytic efficiency, and (3) exquisite site- and stereoselectivity. These biocatalytic methods are employed to efficiently synthesize biologically active complex molecules.

New Avenues in Synthesis via Organic Photoredox Catalysis

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Single electron pathways are common in the biological realm and are integral to photosynthesis and physiological processes in humans. As synthetic chemists, we seek to harness the power of single electron mediated pathways to more efficiently make the pharmaceuticals, agrochemicals and materials that the modern world requires. My group seeks to use organic salts as excited state catalysts to mediate single electron processes in the development of new chemical transformations. This lecture will give a brief background to organic photoredox catalysis and cover some of the reactivity from my group including C-H functionalization chemistry and applications to radiolabeling technology. Lastly, this lecture will describe how acridinium photooxidants can be transformed to excited state super reductants via two-photon absorption.

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Combining Synthetic Chemistry and Biology for Streamlining Access to Complex Molecules

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By virtue of their unrivaled selectivity profiles, enzymes possess remarkable potential to address unsolved challenges in chemical synthesis. The realization of this potential, however, has only recently gained traction. Recent advances in enzyme engineering and genome mining have provided a powerful platform for identifying and optimizing enzymatic transformations for synthetic applications and allowed us to begin formulating novel synthetic strategies and disconnections. This talk will describe our recent efforts in developing a new design language in chemical synthesis that centers on the incorporation of biocatalytic approaches in contemporary synthetic logic. Case studies will focus on the use of this platform in the chemoenzymatic syntheses of complex natural products and also highlight how this platform could serve as a starting point to enable further biological and medicinal chemistry discoveries.

Molecular glues co-opting cereblon: Discovery of CC-99282 and future opportunities to target the undruggable proteome

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Considerable advances in the protein degradation field have opened further opportunities to target the "undruggable" proteome. Molecular glue molecules co-opting cereblon and leading to cellular protein degradation of transcriptional regulators are clinically approved. A number of next-generation cereblon E3 ligase modulators, CELMoDs®, are currently advancing to the clinic or are already undergoing clinical assessment. CC-99282 was specifically designed to address the unmet needs of patients with relapsed or refractory (R/R) lymphomas, who tend to have a poor prognosis and life expectancy. The medicinal chemistry optimization campaign culminating in strong in vivo xenograft efficacy and clinical responses will be described. Additionally, historical learnings and applications from molecular glue protein degradation programs and key scientific aspects from ongoing drug discovery programs will be discussed.

Synthesis and Structure Assignment of Natural Products

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Natural product synthesis forces us to develop strategies and methods to overcome synthetic challenges, and it can be used to establish structure and to provide material for testing. I will present recent syntheses of a sesquiterpene, illisimonin A, and a macrolide, strasseriolide B, that illustrate challenges we encountered and how they were overcome. Strasseriolide B shows anti-malarial activity, which is unusual for a macrolide natural product. The structure of illisimonin A was revised through synthesis, and the new method developed during the structure assignment will be discussed.

Azetidines, Azetines, and Oxetanes: New Cycloadditions of Imines and Carbonyls

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Four-membered nitrogen heterocycles such as azetidines possess unique properties that make them desirable for drug discovery and synthesis applications. However, synthesis of these compounds is challenging, limiting their applicability. While oxetanes and cyclobutanes are commonly synthesized by highly atom-economical light-mediated [2+2] reactions, this powerful methodology remains limited for the synthesis of azetidines via the aza Paternò-Büchi reaction. Herein we report the development of visible-light mediated intermolecular aza Paternò-Buchi reactions,[1,2,3] harnessing the triplet state of unique cyclic oximes, specifically 2-isoxazoline-3-carboxylates, as imine equivalents for the synthesis of unique azetidine and azetine products. Following energy transfer from an iridium photocatalyst, these cyclic oximes initiate [2+2] reactions with unactivated alkenes and alkynes, allowing access to a broad range of azetidines and azetines with excellent yield. This method is mild, operationally simple, and broadly applicable. Importantly, these products can be easily converted to free monocyclic azetidines, offering a new approach to these desirable targets.

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Harnessing Cyanine Chemistry to Learn the Rules of Antibody-Drug Conjugate Targeting

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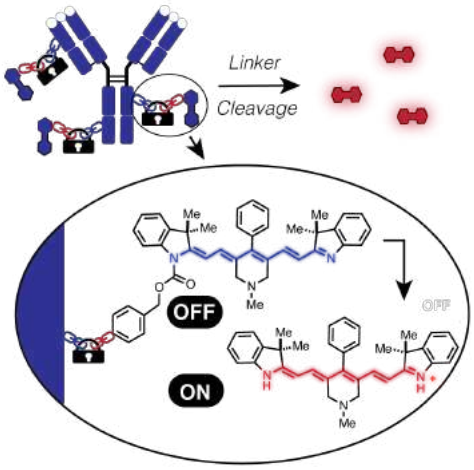

Recent progress in the translation of antibody-drug conjugates (ADCs) has validated the potential of ligand-targeted drug delivery strategies. However, the clinical application of these strategies has encountered significant, often unanticipated, toxicity. Critically, many of these toxicities do not result from monoclonal antibody (mAb) binding to its cognate target, but rather from deleterious effects of the hydrophobic small molecule/linker combination on *in vivo* targeting of the mAb. Novel experimental approaches are needed to assess targeting early in the design, synthesis, and testing process. We hypothesize that *in vivo* optical imaging is uniquely poised to assess the role of payloads and linkers on ADC properties. This is because optical probes are small molecules of similar molecular weight and physical properties to drug payloads. We first set out to address the role of payload properties. By developing synthetic methods that enable the rapid synthesis of chemically varied heptamethine cyanines, we have assembled and quantitatively compared the targeting of a series of substituted variants.[1,2] These efforts suggest that highly polar, and specifically zwitterionic, substituents dramatically improve the *in vivo* properties of mAb conjugates. To examine the role of ADC linkers, conventional always-ON probes are not suitable to study the site and extent of bond cleavage. To address this, we have created a new class of fluorogenic probes in the near-infrared (NIR) range that result from modification of heptamethine norcyanines with stimuli-responsive carbamate linkers. These nor*cy*anine car*bam*ates (CyBams) exhibit exceptional turn-ON ratios and can be activated by a range of enzymatic and chemical triggers. [3,4] By optimizing the cellular uptake and retention of these probes, we have created mAb-targeted variants that allow us to quantitatively study linker chemistry in animal models. Overall, our goal is to develop and ultimately apply an "imaging-first" workflow for the design and testing of well-tolerated targeted drug delivery agents.

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Chromenylium fluorophores for *in vivo* imaging

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Fluorescence imaging is a central tool for visualizing complex biological systems, yet the contrast and resolution attainable *in vivo* is limited due to autofluorescence and light scattering at visible and near infrared (NIR) wavelengths. Recently, the shortwave infrared region of the electromagnetic spectrum (SWIR, 1000 – 2000 nm) has emerged as an optimal region for *in vivo* fluorescence imaging due to few endogenous SWIR chromophores and minimized scattering of light by tissue. While the SWIR demonstrates great promise, suitable materials are needed with emission at these low energies for the development of optical contrast agents. Namely, non-toxic organic small molecules with bright emission > 1000 nm are necessary to expand both the basic science and clinical applications of fluorescence imaging. Our group has developed biocompatible polymethine fluorophores with shortwave infrared emission. We discovered that chromenylium heterocycles condensed with a polymethine linker yield bright SWIR-emissive fluorophores. Heterocycle modification has provided a suite of fluorophores that can be used in concert with each other for multiplexed imaging.

Pleurotin: highlights of its history and synthesis

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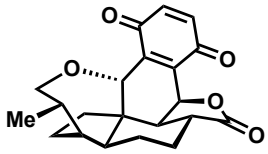
Abstract: Over a period spanning 75 years, research on pleurotin has revealed its antibiotic properties, intricate molecular structure, and potential as an anticancer agent. The discovery that pleurotin inhibits the thioredoxin-thioredoxin reductase system and transcription of cancer-related genes triggered improvements to its production by fermentation methods. Thirty-four years ago, the Hart laboratory demonstrated that this metabolite is also accessible by the concepts and methods of organic synthesis.



Pleurotin

This lecture will address these achievements and give an emphasis to our recently described 8-step formal synthesis of pleurotin.[1] This project challenged our assumptions about Diels-Alder chemistry and ultimately gave us an opportunity to probe a unique strategy for inverting the configuration of an unactivated hydrogen-bearing stereocenter.

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Stereoselective Reactions with Feedstock Chemicals

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For several decades, chemists have developed new approaches to valuable materials that are economically efficient and environmentally benign. To this end, synthetic chemists have developed new synthetic strategies to access complex molecules from simple, inexpensive, and abundant feedstock chemicals. Our research group is motivated to develop new methods in this area. We present recent examples from our laboratory of stereoselective reactions with feedstock chemicals as starting materials. First, we discuss our approach to the stereoselective functionalization of unsaturated hydrocarbons through catalytic pericyclic reactions with chalcogen-based reagents. For example, we have developed enantioselective allylic functionalizations of terminal and internal alkenes. Second, we describe our approach to the enantioselective α-alkylation of aldehydes with amino acid derived alkylating reagents. We have devised a strategy for the activation of pyridinium salts derived from amino acids through the formation of light-activated charge transfer complexes with catalytically generated electron rich chiral enamines derived from aldehyde substrates and a chiral amine catalyst.

Natural Products in the Atmosphere

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Volatile terpenes emitted from the world's forests play a significant role in the formation of atmospheric aerosol particles, which in turn influence climate, air quality, and human health through a variety of direct and indirect mechanisms. Despite the importance of these aerosol particles, they remain poorly understood and continue to contribute the largest uncertainty to estimates of total radiative forcing. This lecture will describe efforts within my lab towards the synthesis of putative biogenic terpene-derived constituents of atmospheric aerosol particles, including isoprene-derived epoxides, in order to investigate their climate relevant physical properties. Recent advances in the synthesis of isotopically-labeled pinene derivatives that are driving collaborative investigations into the complex oxidation pathways of terpenes in the atmosphere will also be presented.

Driving Efficiencies in Drug Discovery via the Tactical Application of High-throughput Chemistry Solutions

Matthew Tudge

Medicinal Chemistry, Glaxo SmithKline, King of Prussia, PA

High-throughput chemistry platforms are increasingly becoming a part of modern Medicinal Chemistry departments due to the strategic advantages they offer in terms of improving drug discovery efficiencies. Herein, we will introduce our recent work on merging synthetic chemistry experiments and biological assays - a concept that we term direct-to-biology (D2B) - through the disclosure of several case studies that highlight the effectiveness of this approach in the rapid discovery of novel Proteolysis Targeting Chimeras (PROTACSs) and other small molecule modalities.

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Metalloradical Catalysis for Stereoselective Radical Reactions

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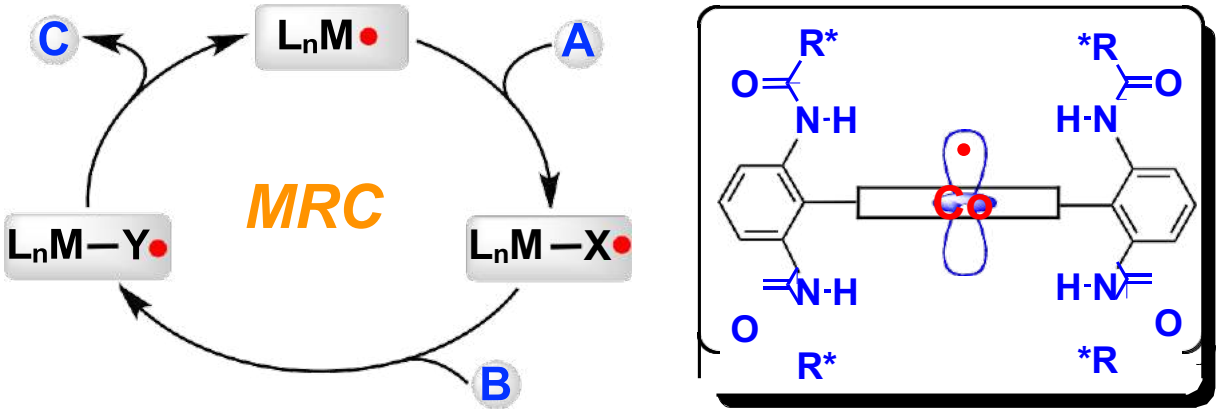
Organic synthesis has been dominated by the development of chemical reactions that are based on two-electron heterolytic ionic processes, either stoichiometrically or in catalytic fashion. While one-electron homolytic radical chemistry is equally rich and has been demonstrated with a number of unique features, its application for practical synthesis of organic molecules has been hampered by several enduring challenges. Over the past two decades, my laboratory has been in the process of formulating metalloradical catalysis (MRC) as a general concept to guide the development of fundamentally new approaches for controlling both reactivity and stereoselectivity of radical reactions. In essence, metalloradical catalysis aims for the development of metalloradical-based systems for catalytic generation of carbon- and nitrogen-centered radicals from common organic compounds without the need of radical initiators or the use of light. The subsequent reactions of the resulting organic radical intermediates, which remain covalently bonded or closely associated with the metal center, can be effectively controlled by the catalyst. For achieving enantioselective radical reactions via MRC, we have developed a family of unique chiral metalloradical catalysts based on structurally well-defined Co(II) complexes of D_2-symmetric chiral porphyrins with tunable electronic, steric, and chiral environments. These Co(II)-based metalloradical catalysts have been shown to be highly effective for a wide range of stereoselective organic reactions, including C=C cyclopropanation, C=C aziridination, C–H alkylation, and C–H amination. Due to their distinctive stepwise radical mechanisms that involve unprecedented α-metalloalkyl and α-metalloaminyl radical intermediates, the Co(II)-based metalloradical systems enable addressing some long-standing problems in these important organic transformations while offering ample opportunity for invention of new synthetic tools.



Short Talk Abstracts

Substituent and Solvent Effects on 4π-Electrocyclizations of *N*-Alkenylnitrones

Laura L. Anderson,[a]* Laura Alonso,[a] Michael Shevlin[a,b]

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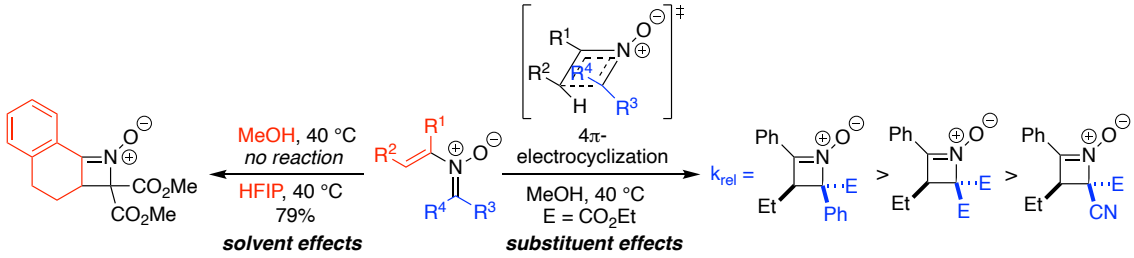
The role of substituent and solvent effects in promoting the 4π-electrocyclization of *N*-alkenylnitrones to give azetidine nitrones have been investigated by experimental examination of relative rates, reversibility, and alternative reaction pathways. These transformations favor formation of a strained heterocyclic ring and can be combined with a Chan-Lam-Evans reaction to provide modular access to *N*-alkenylnitrones from simple starting materials.[1] In-depth analysis of these reactions was undertaken to facilitate the development of azetidine nitrones as versatile precursors for the synthesis of densely-substituted azetidines.[1] Mechanistic investigations, including solvent-dependent Hammett and Eyring studies, provide insight into the stereoelectronic effects that control these electrocyclizations and identify trends that can be used to expand the synthetic utility of the method for the rapid and facile synthesis of stereodefined azetidines.



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Making Chiral Heterocycles Using Chiral Heterocycles as Ligands

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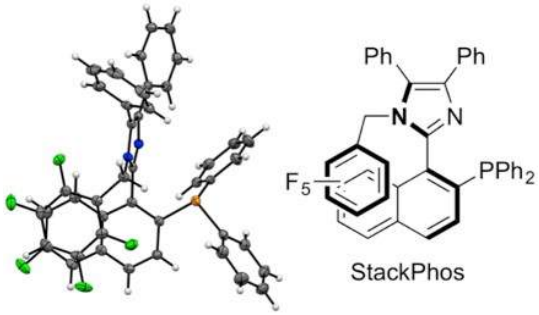
Enantioselective catalysis has been a mainstay of contemporary organic chemistry and, as such, the development of new ligands for transition metal catalysis is an important and active area of research. Finding new ligand archetypes enables the development of new reactions and new synthetic strategies. In this vein, we introduced imidazole-based chiral biaryl *P,N*-ligands[1,2] where the axial chirality is enabled by stabilizing pi-pi interactions. These ligands have proven to be excellent promoters for Cu- and Pd-catalyzed reactions and recent results in this area from our laboratory will be presented.[3-5]



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Pro-Aromaticity Induced Triplet Photochemistry in Acene-quinodimethyl Thioamides: Synthesis, Mechanism, and Photophysics

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Molecular systems containing pro-aromatic units such as *ortho*– or *para*–quinodimethyl ring are often presented to exist as a mixture of resonant species *viz.* closed– and open–shell structures. Recently, a number of strategies have been employed to isolate/stabilize either one of the resonant species/forms of quinodimethyl based molecules. Yet, there are still queries regarding the ground and excited states aromaticity of these exotic systems. To this end, our group developed a new reaction that allowed to synthesize novel acene-quinodimethyl thioamides starting from readily available acene diimides.[1,2] Expectedly, upon photo-excitation ($S_0 \rightarrow S_1 \rightarrow T_1$), the acene-quinodimethyl thioamides of our interest will undergo aromaticity reversal in their lowest triplet excited state following the Baird rule of aromaticity. To afford the acene-quinodimethyl thioamides, we established a novel [2 + 4] cycloaddition reaction followed by reductive desulfurization. Furthermore, we employed computational tools to map out the reaction trajectory as well as evaluate discrete aromaticity and global/total aromaticity of the quinoidal based systems.[3]

The presentation will describe a rationale design and execution of the new quinodization reaction involving acene diimides. I will also discuss the mechanistic rationale which is based on computational modelings of the reaction trajectory and reactive intermediates. The discussion will also cover the aromaticity and photophysical properties of the new quinoidal chromophores.

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Planar Chiral Rhodium Complexes for Enantioselective Catalysis

Simon B. Blakey

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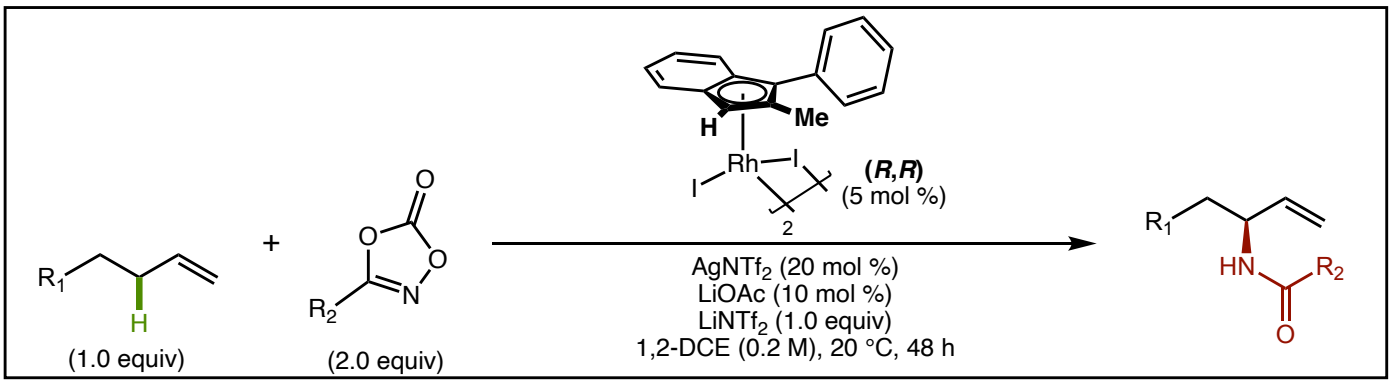
The development of new reactions and catalysts for the oxidative cross-coupling of C-H bonds with C-H, N-H and O-H bonds will be discussed. Strategically, these reactions allow for the synthesis of complex molecules from their constituent components, minimizing the need for functional group activation and manipulation. A novel planar chiral catalyst platform for enantioselective reactions will be presented. Illustrative examples of emergent applications will be provided.



Cyclic Amines: from Production to Application

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Cyclic amines are either secondary or tertiary amines. Examples of cyclic amines include aziridine, piperidine, piperazine etc. In this talk, commercial process to produce cyclic amines will be discussed and new application of these amines will also be included. In addition, challenges in the cyclic amine area will also be proposed.

Synthesis of *cis*-Thiiranes as Diastereoselective Access to Epoxide Congeners via 4π-Electrocyclization of Thiocarbonyl Ylides

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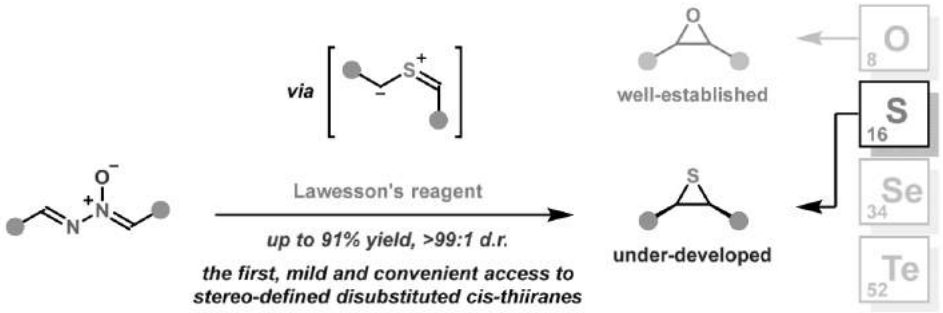
Organochalcogen heterocycles are ubiquitously present and widely utilized in various fields. Among them, oxirane has been extensively studied, and all of the stereoisomeric forms are readily available. In contrast, synthetic studies on thiirane were rarely reported, and thus the useful sulfur-congener of oxirane has been difficult to access in a stereodefined form.[1] In this research, a general stereoselective synthesis of *cis*-thiiranes is accomplished by taking advantage of stereospecific electrocyclization of *trans*-thiocarbonyl ylides, which are generated in situ from readily available *E*,*E*-aldazine *N*-oxides upon treatment with Lawesson's reagent.[2] This newly developed practical method provides a variety of *cis*-1,2-diarylthiiranes as essentially single diastereomers in high yields under mild reaction conditions. The intermediacy of *trans*- thiocarbonyl yilde is confirmed by mechanistic experiments, and the excellent stereocontrol is rationalized by DFT calculation.



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The Development of Single Electron Transfer Reductive Processes to Construct *N*-Heterocycles from Nitroarenes via Radical Anion Intermediates

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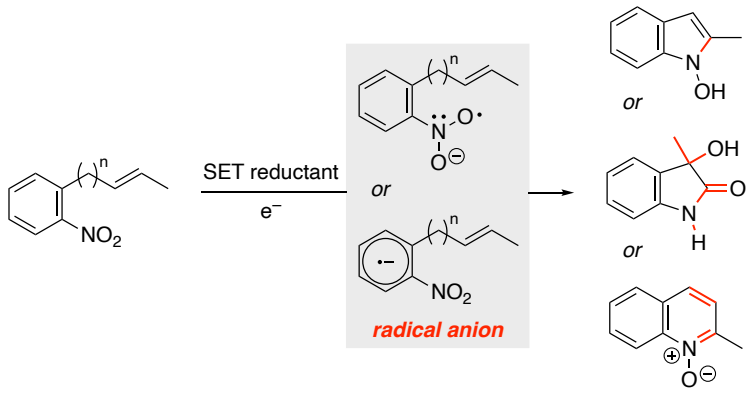

Our research program is centered on the development of new methods to construct *N*-heterocycles by leveraging the reactivity embedded in aryl azides, nitroarenes, or aryl amines. While our previous efforts have focused on generating electrophilic *N*-aryl nitrogen reactive species using transition metal catalysts, we were curious if we could access radical intermediates through the single electron reduction of nitroarenes. We found that these species could be accessed at room temperature using *tert*-butoxide as the reductant and that the resulting radical anions exhibit unique reactivity to enable the formation of C–NAr and/or C–O and C–C bonds in the construction of five- or six-membered *N*-heterocycles.[1]

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Alkene Dicarbofunctionalization with C(sp^3) Carbon Sources

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Alkenes are important feedstock for organic synthesis with two vicinal sites for bond formation. Simultaneous construction of two carbon-carbon bonds across these vicinal positions is a most powerful strategy to generate complex products from simple starting materials. This process is highly significant from a synthetic perspective due to its ability to reduce a multistep process to a one-step endeavor. However, developing such a process is a challenging feat due to the intrinsic nature of unactivated alkenes to undergo migratory insertion with kinetics slower than cross-coupling, and alkylmetal intermediates to undergo β-H elimination with kinetics faster than transmetalation/reductive elimination, both of which are detrimental to alkene difunctionalization. This process is even more challenging when C(sp^3) (alkyl) coupling partners are used as carbon sources. In this talk, we will discuss and present our strategies to difunctionalize unactivated and mildly activated alkenes with two carbon sources with particular focus on the use of C(sp^3) (alkyl) coupling partners.[1] Mechanistic pathways pertaining to these new reactions devised based on radical probes, competition experiments and quantitative kinetic studies will also be discussed.

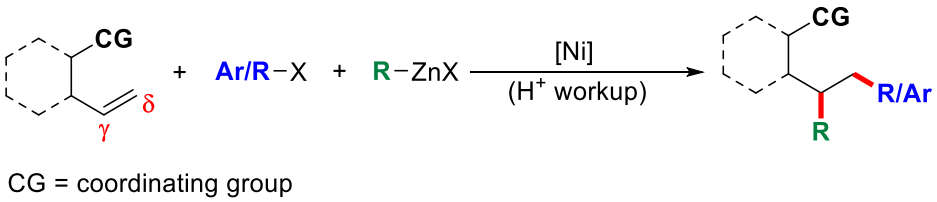

Figure 1. Alkene dicarbofunctionalization with C(sp^3) carbon sources.

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New Opportunities in Polymer Synthesis Using Twisted Amides

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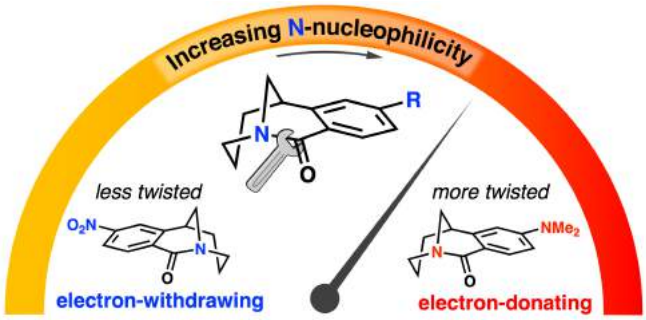
While most amide bonds are regarded as robust linkages in chemical environments due to significant resonance stabilization from the nitrogen atom, twisted amides are at odds with this paradigm due to their unique geometric constraints. Removal or weakening of this key stabilizing interaction results in heightened reactivity that provides an opportunity for the development of new directions in polymer science. This presentation will highlight how twisted amides have been leveraged to produce a new class of living polymerization that is promoted through a halide-rebound cascade process.[1] Through remote functionalization, the rates of polymerization can be tuned over multiple orders of magnitude and change the rate limiting step of propagation.[2] During the presentation, the effect of geometric distortion on polymerization behavior will be highlighted to provide a rational framework for the development of future twisted amide systems.



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From Drug Discovery to Catalysis:

Design, Properties, and Application of Hemiboronic Heterocycles

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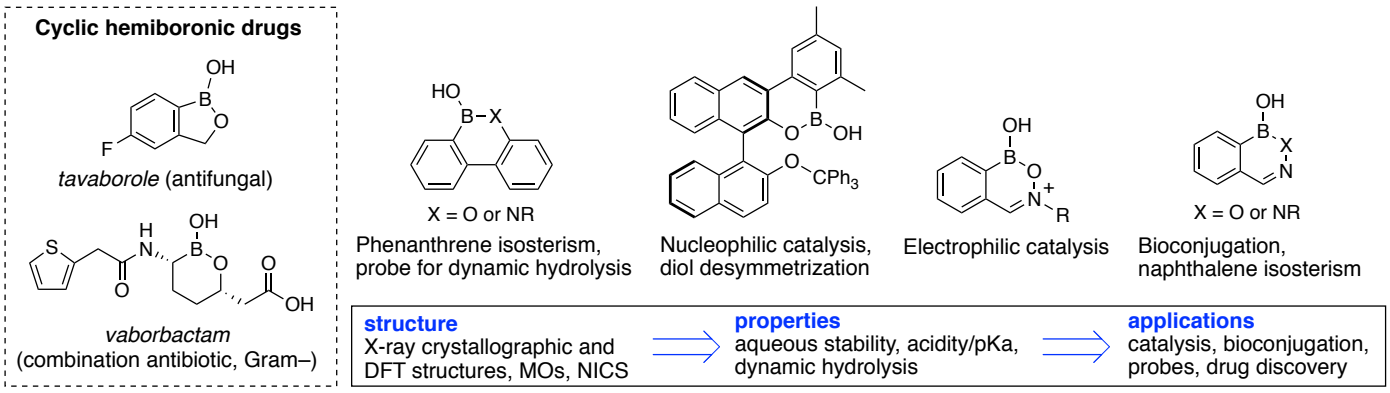
The successful development and commercialization of the benzoxaborole drugs tavaborole and crisaborole has initiated a renaissance surrounding heterocycles derived from boronic acids in organic and medicinal chemistry. These new drugs, along with other cyclic hemiboronic acids, demonstrate a wide range of biological properties such as antifungal, antibacterial, and anti-inflammatory activity. Despite the success of these boroheterocycles, many questions remain unanswered regarding the desirable physical properties and the dynamic behavior of boranol (BOH)-containing heterocycles in aqueous media. Likewise, a precise knowledge of the acidic nature (Lewis *vs* Brønsted) of the boranol unit of these hemiboronic heterocycles is crucial toward tailoring their uses.

In the past few years, this laboratory has investigated several classes of hemiboronic heterocycles providing a comprehensive evaluation of their structure, stability, chemical and physical properties.[1-2] To resolve decades of conflicting views on the acidic and aromatic characteristics of pseudoaromatic hemiboronic acids, a multipronged experimental and computational approach was employed. These fundamental studies can help guide a systematic application of select boroheterocycles as enantioselective reaction catalysts,[3] in bioconjugation, and as new drug chemotypes and bioisosteres of pharmaceutically important classes of heterocycles. In recent work, hemiboronic heterocycles were identified as modular scaffolds enabling both nucleophilic and electrophilic activation of alcohols, which was exemplified in the monophosphorylation of diols, and the reduction of pi-activated alcohols and ketones with silanes under ambient conditions, respectively.



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Stereocontrolled synthesis of arylomycin-based gram-negative antibiotic GDC-5338

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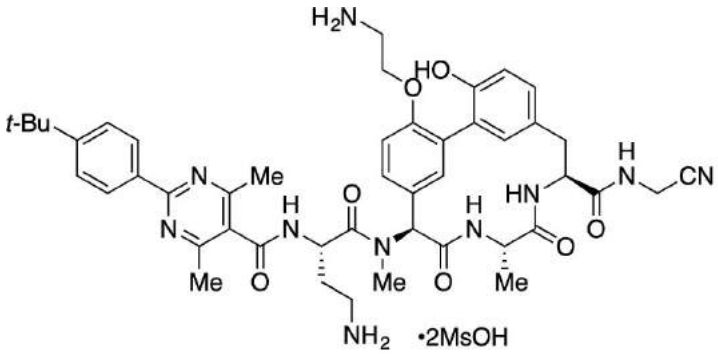
We report an efficient, stereocontrolled, and chromatography-free synthesis of the novel broad spectrum antibiotic GDC-5338.[1] The route features the construction of a functionalized tripeptide backbone, a high-yielding macrocyclization via a Pd-catalyzed Suzuki–Miyaura reaction, and the late-stage elaboration of key amide bonds with minimal stereochemical erosion.



GDC-5338 (1)

- 17 steps longest linear sequence, 15% overall yield
- High yielding Suzuki-Miyaura macrocyclization in 88% yield
- High stereochemical integrity (>99:1 dr)
- High overall purity >99 A % HPLC

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Exploring New Strategies in Asymmetric Synthesis

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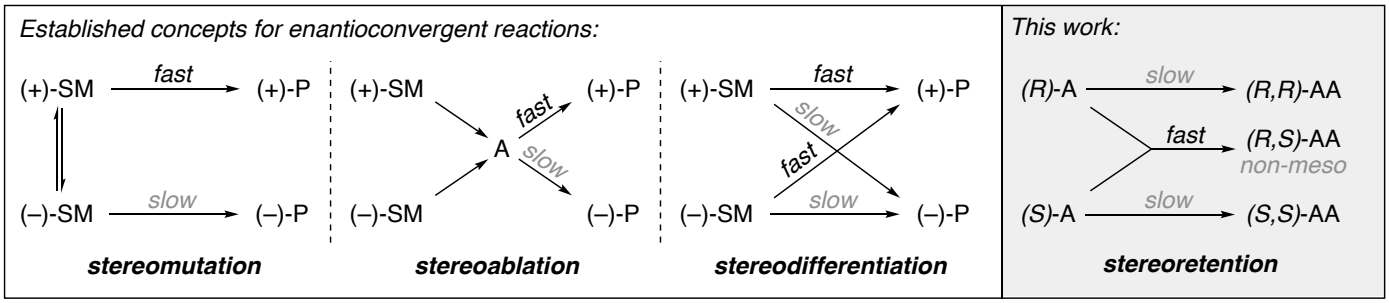
The ability to synthesise chiral molecules in enantioenriched form is vitally important; it underpins many fields of pure and applied science. [1] The utilisation of racemic substrates in asymmetric synthesis is relatively challenging and complex. Resolution reactions give a maximum yield of 50% and necessitate the separation of remaining starting material from product. Enantioconvergent reactions, on the other hand, can convert 100% of a racemic starting material into a single enantioenriched product.[2] Three conceptual approaches have been exploited in the literature to achieve enantioconvergent reactions; *stereomutation*, *stereoablation*, and *stereodifferentiation*. These three established concepts all suffer from common limitations in their potential substrate scope. First, the stereogenic element of the starting material needs to be labile, towards mutation, ablation, or inversion. Second, substrates containing multiple stereogenic elements are not readily amenable. In this presentation, a fundamentally different approach to enantioconvergent reactions will be presented, which proceeds with retention of configuration. This *stereoretention* approach has the potential to enable the design of enantioconvergent reactions that utilize racemic substrates with robust and/or multiple stereogenic elements.



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Single Atom Logic for Skeletal Editing

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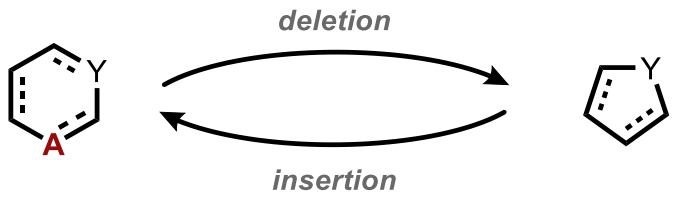
Reactions which can manipulate the connectivity of the molecular skeleton are underexplored as tools for late-stage functionalization, in part because their implementation has been hindered by their often nonintuitive retrosynthetic logic. This presentation will cover transformations discovered in our laboratory which address this challenge by enabling single-atom changes to aliphatic and aromatic systems through the insertion and deletion of single heavy atoms (C,N,O, etc.), as well as more complex manipulations leveraging combinations of these elementary transformations.[1] Our approach to this problem is modality-agnostic, drawing from a wide range of reactive species and synthetic disciplines (organometallic chemistry[2], reagent design[3-5] photochemistry[6]). Applications to late-stage functionalization and diversification of complex pharmaceutically relevant compounds as well as unique opportunities for synthesis will be presented alongside mechanistic findings.



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Reactivity of Sulfonylcyclopropanols as Precursors of Amide Homoenolates for the Synthesis of Fused Heterocycles

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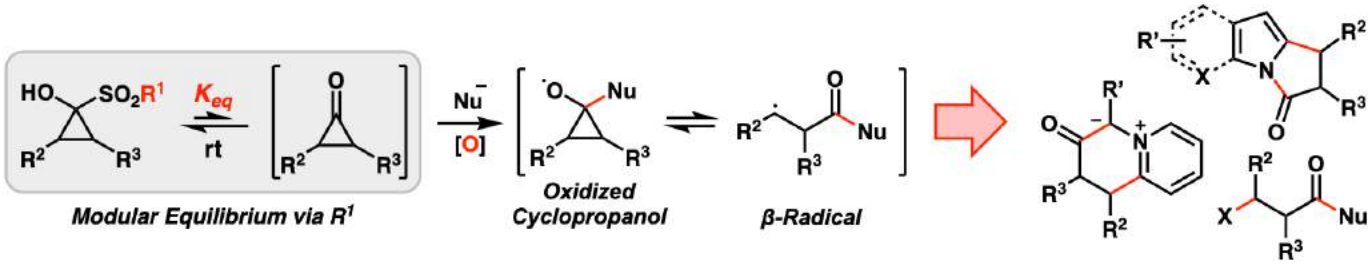
Our research group recently reported on the use of readily accessible 1-sulfonylcyclopropanols as versatile cyclopropanone equivalents in a range of new synthetic disconnections.[1] When these same species are treated with nitrogen nucleophiles such as *N*-heterocycles, the resulting transient hemiaminal adducts are reported here to act as effective amide β-radical equivalents in the presence of silver or iron catalysts, leading to fused heterocycles or β-halogenated amides difficult to access otherwise. The strategy was also extended to the use of pyridinium ylides as initial nucleophiles in the presence of manganese salts, affording fused dihydropyridine motifs highly relevant to medicinal chemistry and to the total synthesis of alkaloids.



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Chelate Forming Antimicrobial Conjugates for the Control of Biofilm-Forming Bacteria

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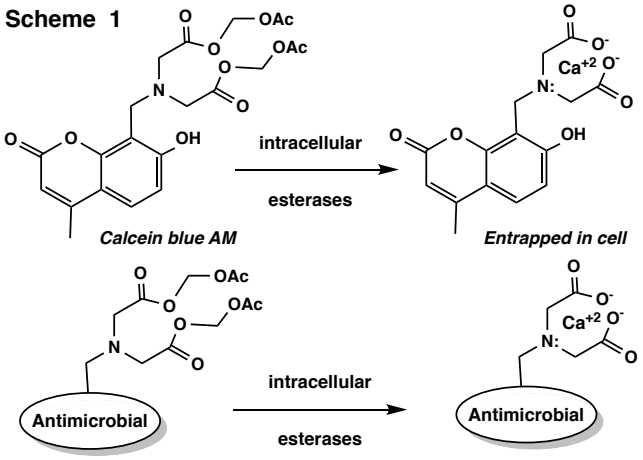
Abstract: The discovery of new, highly potent antimicrobial agents for the control of biofilm-forming bacteria remains an enduring objective of the chemical and biological sciences. Over the years, the attainment of this goal has remained relatively elusive due to the pronounced ability of colonized bacteria to resist antibiotics by a variety of mechanisms, including efficient cellular efflux clearing. Since most pathogenic bacteria can exist as biofilm communities, the discovery of novel antimicrobial conjugates capable of eradicating established biofilms has the potential to markedly enhance the efficacy of antibiotics that are otherwise ineffective. Such therapeutic entities should have a significant impact on human medicine. Importantly, bacterial biofilms also underlie the persistent colonization of hospital facilities, both driving and sustaining nosocomial infections.

Drug-conjugate strategies have been effectively used to modify a wide array of structurally diverse pharmaceuticals to improve their physicochemical, pharmacokinetic, solubility and biopharmaceutical properties. This can be achieved through the incorporation of bio-reversible functional groups, which will be cleaved enzymatically upon delivery of the drug to the desired site. *To target a biofilm, an ideal drug-conjugate would partition from the bulk aqueous phase into the biofilm, where it would be concentrated and retained*. A chemical strategy that illustrates this principle involves the concentration of fluorescent dyes within living cells. This mechanism should allow a small amount of antimicrobial agent to be added to the bulk medium and effectively deploy to biofilm-impacted surfaces *and undergo intracellular concentration therein*. Reactive esters have been employed to enhance membrane permeability and are used in fluorogenic cell viability stains (e.g., Calcein blue AM). This labile (acetoxy)methyl coumarin derivative passively crosses the cell membrane of viable cells where it is then converted into Calcein blue by esterase cleavage, which is retained within the cell as its Ca^{+2} chelate, without compromising the cell membrane (Scheme 1). *Importantly, the intensity of intracellular fluorescence* ***increases*** *over time as the cleaved dye becomes concentrated within cells of the biofilm*. We have recently shown the validity of this mechanism for the delivery and retention of antimicrobial cargos into *S. epidermidis and P. aeruginosa* biofilms.[1] Significant enhancements of antibacterial activities were observed in both the planktonic (MIC) and biofilm (MBEC) states.

Scheme 1



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Total Synthesis of the Nagelamides

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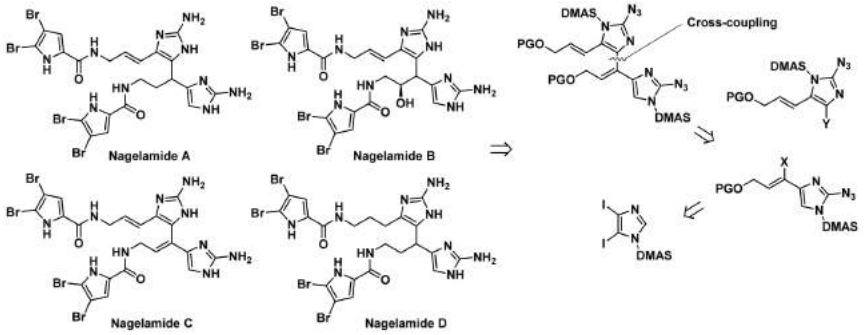
The nagelamides are small group, ca. 30 members, of pyrrole-aminoimidazole alkaloids belonging to the larger oroidin family of marine natural products. These compounds, first reported by the Kobayashi lab in 2004,[1] are considered to be acyclic oroidin dimers and may serve biosynthetically as precursors to other family members.[2] While the biological activities of these molecules have been reported to include antibiotic and anti-proliferative activity, their broadscale investigation remains to be accomplished. As part of a broader effort towards the oroidin alkaloids, we have been interested in developing approaches to the nagelamides as they not only serve as interesting targets themselves but they also may function as intermediates to other, more complex, family members. Initial studies have been directed towards family members with a C10-C15' link between the two oroidin fragments, specifically nagelamides A-D.



Our approach is predicated on a disconnection between the two imidazole containing fragments, specifically through the use of a cross-coupling reaction. Late-stage introduction of the imidazole 2-amino moieties via metalation and electrophilic trapping and incorporation of the pyrrole carboxamides through a novel application of the Mitsunobu reaction. The cross-coupling fragments would emerge from the derivatization of diiodoimidazole via sequential functionalization. This approach resulted in a total synthesis of the reported structure of nagelamide D.[3] Recent efforts have focused on nagelamide A and nagelamide C for which the core frameworks were readily constructed,[4,5] however, use of the same Mitsunobu strategy to incorporate the pyrrole carboxamides was thwarted by allylic transposition. Finding conditions to mitigate allylic transposition was challenging until it was discovered that azide could be incorporated; this gave tetra azides as late-stage intermediates. Once accomplished, our attention turned to incorporation of the pyrrole carboxamides and it was realized that opportunities existed for telescoping the sequence if the azides could be elaborated chemoselectively and a direct method for the incorporation of the amides could be developed. This presentation will report the construction of the cross-coupling building blocks and application to assembly of the nagelamide frameworks, in addition the discovery of pyrrole thio carboxylic acids as a means to convert azides into the corresponding amides will be discussed. Unexpected issues with thio acid oxidative coupling to form bisulfides will be described along with methods for mitigation. Applications of these new thio acids to the synthesis of oroidin analogs and as a means to complete the total synthesis of nagelamides A and C will be presented.

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Development of *P*- and *N*-heterocycles as high-energy anolytes for organic-based redox flow batteries

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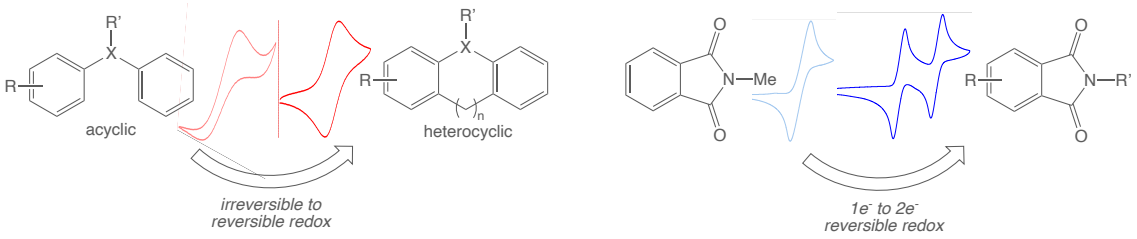

Redox flow batteries (RFBs) integrate renewable energy sources into grid-scale electricity production because their configuration enables decoupling of power and capacity. Non-aqueous RFBs offer the possibility of accessing higher energy densities than their aqueous analogues due to the larger electrochemical potential windows of organic solvents where the redox active molecules operate.[1] However, to fill in this chemical space, redox-active organic molecules as energy storage materials (anolytes and catholytes) are needed with a unique combination of properties, including highly reversible extreme redox potentials and/or multi-redox processes, high solubility in nonaqueous media, and stability to prolonged electrochemical charge–discharge cycling.[2,3] In this presentation, we report the discovery and development of two types of organic-based (phosphorous and nitrogen-containing heterocycles) redox active molecules that possess extreme redox potentials and their ability for multi-redox process. The design and synthesis of a library of target heterocyclic compounds, and the investigation of their electrochemical properties as anolytes in RFBs will be discussed.

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Synthesis of Neuroprotective Limonoid Natural Products

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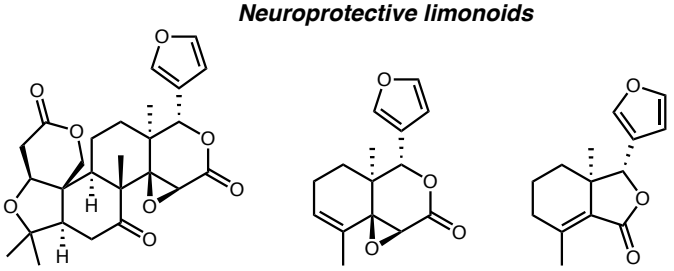
Limonoids are polycyclic terpenes with diverse structures and myriad biological activity that have attracted the attention of synthetic chemists since their discovery in the 1960s.[1] A subset of the limonoids has been reported to have neuroprotective properties against glutamate toxicity, but details about their mechanism of action and structure-activity relationship studies are lacking.[2] We have developed an asymmetric synthesis of one class of degraded limonoids and investigated their neuroprotective effects in cell culture studies. Our results on the synthesis of analogs and probe molecules for the investigation of neuroprotective properties will be discussed.

Neuroprotective limonoids



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Bisketene Equivalents as Diels–Alder Dienes in Complex Natural Product Synthesis

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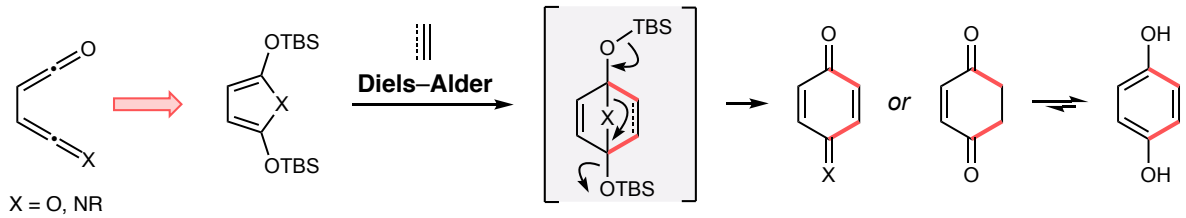
The *para*-(hydro)quinone motif features within a large number of biologically active natural products. Complex derivatives can often only be prepared in small quantities via lengthy multi-step sequences, impeding efforts to leverage targets in applied settings. We have recently developed a one-pot Diels–Alder methodology for accessing highly substituted *para*-quinones in a highly convergent manner. Central to realizing the transformation was the development of a bisketene equivalent that is sufficiently stable to be handled without specialized techniques, while also remaining primed for a facile ring-opening event. The generality of the approach was demonstrated through the preparation of several *para*-hydro-, benzo-, and imino-quinones, including a gram-scale synthesis of a neuroprotective para-hydroquinone-containing natural product. Ongoing studies concerning the application of this chemistry in the collective synthesis of several complex meroterpenoid natural products will also be discussed.



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Electrochemical Amide Coupling and Photochemical Bond Activations

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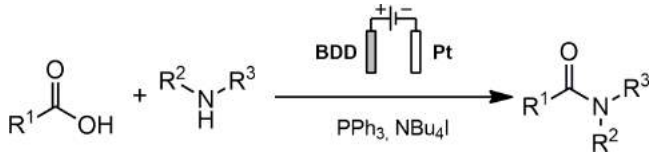
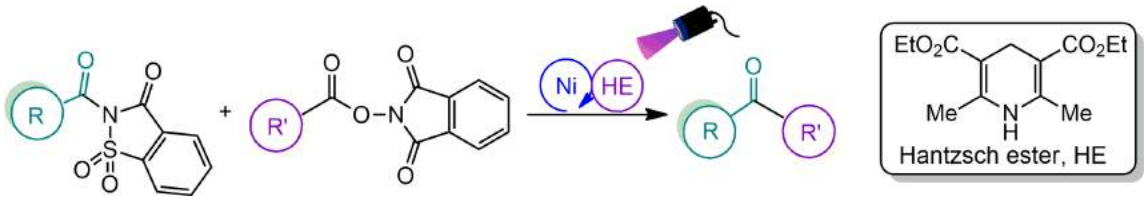
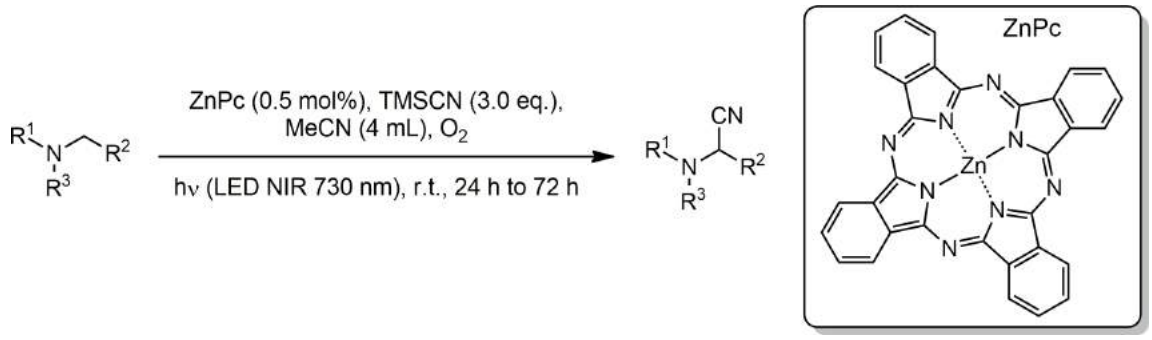
The formation of amides from amines and carboxylic acids is a key process employed in many areas of chemistry. While redox coupling approaches using stoichiometric amounts of oxidants and reductants are well established, electrochemical strategies are still scarce. Here, we present an anodic amide coupling protocol using PPh_3 and iodide which has a broad substrate scope. The stoichiometric co-product Ph_3PO can be recycled using known strategies. Even challenging couplings can be achieved in moderate to high yields while reagents posing safety risks are entirely avoided.[1]



A second topic of the presentation will be new bond formations using photochemical activation. Here, a dual nickel photoredox-catalytic synthesis of ketones and photoredox-catalytic transformations using infrared light will be presented.[2,3]





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Mining the Reactivity of Dearomatized 4-Alkylpyridines

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[b]*Roche Innovation Center, F. Hoffmann – La Roche, Basel, Switzerland*
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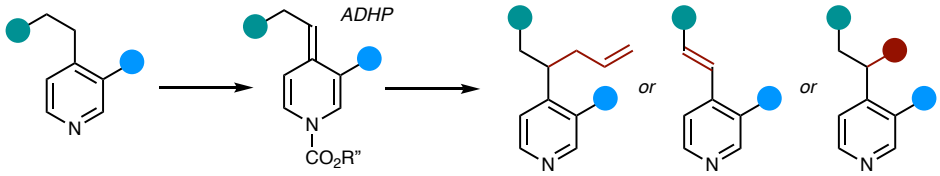
4-Alkylpyridines can be dearomatized using a 'soft enolization' approach to generate alkylidene dihydropyridines (or ADHPs). These semi-stable intermediates present many opportunities for diversification of 4-alkylpyridines, providing access to attractive building blocks for discovery chemistry. Using ADHPs we have recently developed palladium-catalyzed allylation[1] and dehydrogenation[2] of 4-alkylpyridines. Through this work we also learned that ADHPs can behave as soft nucleophiles that undergo conjugate addition[3] to unsaturated ketones. These reactions tolerate a broad range of sensitive functional groups and activated positions, and display pyridylic selectivity. In this presentation I will provide an overview of our recent progress in this area.



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Efficient synthesis of *N*-substituted 3-amino-2-pyridones

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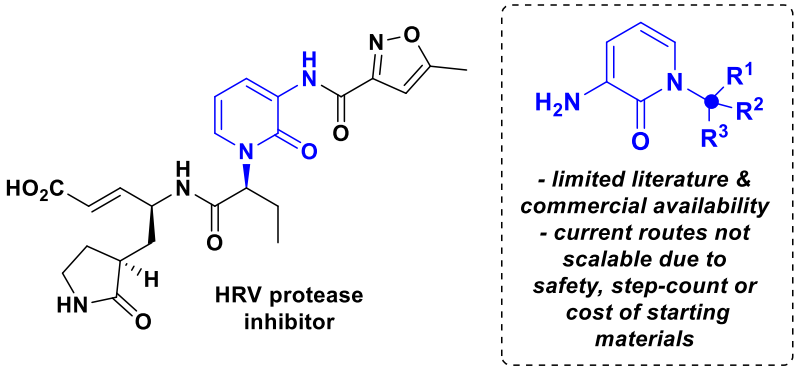
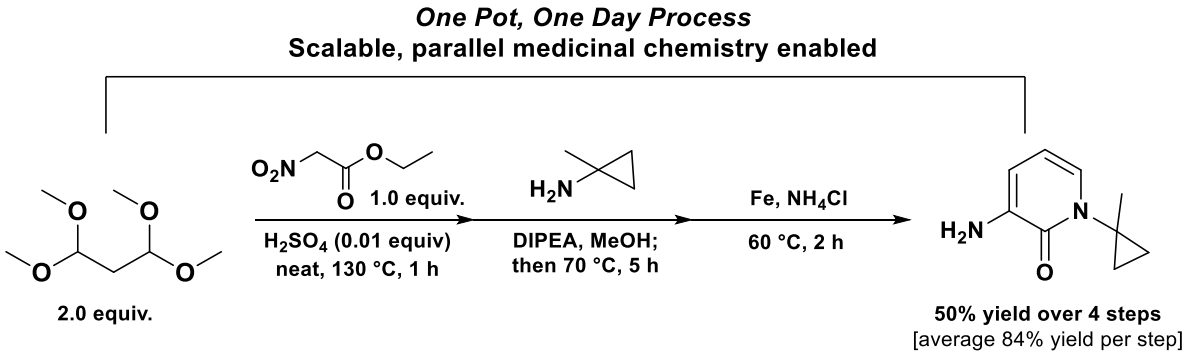
Pyridones have found extensive applications as versatile building blocks in organic synthesis and as privileged scaffold in drug discovery. This heterocycle is frequently applied in medicinal chemistry projects because it can serve both as a hydrogen bond acceptor and/or donor, act as a bioisostere for amides, phenyls, and pyridines, and impact a target drug molecule's lipophilicity, aqueous solubility and metabolic stability.[1,2] The *N*-substituted 3-amino-2-pyridone motif is precedented in a variety of compounds which exhibit interesting biological activities such as Jarin-1 inhibitor, interleukin-1B inhibitor and human leukocyte elastase inhibitor.



Multiple synthetic strategies have been developed to access this scaffold. However, 3-amino-2-pyridones bearing a quaternary carbon, cyclopropyl or heterocycle off the pyridone nitrogen atom remain challenging to prepare since they cannot be accessed via nucleophilic substitution reaction. Herein, we describe the efficient one-pot synthesis of a large variety of *N*-substituted 3-amino-2-pyridones from ethyl nitroacetate which is scalable and parallel medicinal chemistry (PMC) enabled.



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Adventures in the Synthesis of Bioactive Natural Products

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Marine natural products often have complex structures and potent biological activities; however, little is understood regarding how their molecular structure correlates with function or what biological targets or pathways are involved. Through rapid and efficient chemical syntheses of bioactive marine natural products we are able prepare ample quantities of material to explore both structure-activity relationships as well as target identification studies. In all our efforts, a key focus is the development of short, scalable and selective synthetic approaches, accomplished by new reaction development and strategic synthetic planning. This talk will focus on our efforts to develop novel approaches to prepare heterocycles in the context of marine natural products, particularly our efforts toward the bipolamine, curvulamine and related polypyrrole families of natural products.

Quantitative Modeling Tools for Prediction in Synthesis and Catalysis

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When faced with unfamiliar reaction space, synthetic chemists typically apply the reported conditions (reagents, catalyst, solvent, and additives) of a successful reaction to a desired, closely related reaction using a new substrate type. Unfortunately, this approach often fails owing to subtle differences in reaction requirements. Consequently, an important goal in synthetic chemistry is the ability to transfer chemical observations from one reaction to another. Therefore, we have aimed to develop a program that assists the rapid analysis of the general interactions that impart asymmetric induction allowing the quantitative transfer of this stereochemical information to new reaction components and mechanisms. This talk will describe our recent efforts in developing this quantitative modeling workflow to assist in synthesis planning,[1] reaction optimization,[2,3] and selectivity prediction.[4]

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Photocatalyzed ATRA reactions as key step towards the synthesis of heterocycles

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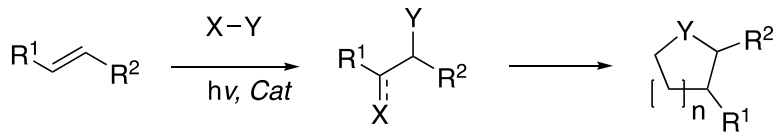
Photocatalyzed ATRA reactions provide a powerful tool for the difunctionalization of alkenes, which can be subsequently exploited for the synthesis of heterocyclic scaffolds. Representative examples from our group to illustrate this approach will be presented.



X = Hal, O; Y = SO_2R, NHR, CH_2NO_2, CHNHR

Leading References:

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Preparation and Application of 1,4-Oxazinone Precursors in the Construction of Pyridine Derivatives

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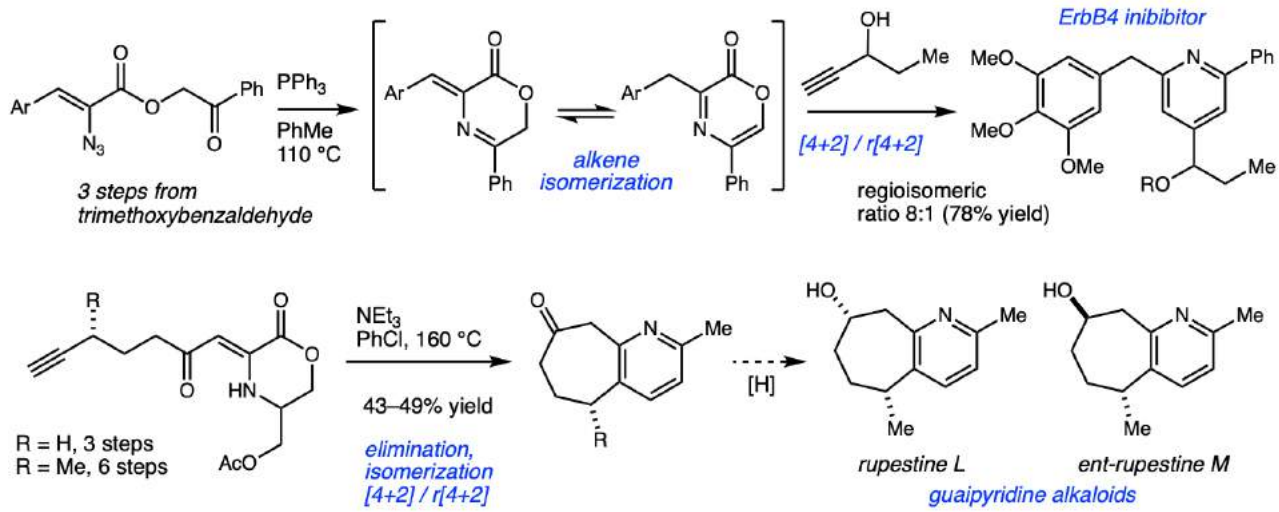
**jrscheerer@wm.edu*

1,4-Oxazinones are the most reactive precursors for cycloaddition / cycloreversion sequences leading to the formation of pyridines. Our recent efforts have revealed new methods for the preparation of oxazinones. Application of oxazinones in tandem cycloaddition / cycloreversion sequences has enhanced our understanding of the reactivity and selectivity of this reaction sequence. Several case studies in the preparation of polysubstituted pyridine structures of interest will be described, including the synthesis of (1) a bioactive trisubstituted pyridine[1] that shows ErbB4 enzyme inhibition and (2) studies directed toward rupestine L and *ent*-M, representative guaipyridine alkaloid natural products.[2]



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Accessing 4-Membered Heterocycles Through Metal-Ligand Cooperation Strategies

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Recent developments for the construction of 4-memebered heterocycles via 2+2 carbonyl-olefin and imine-olefin photocycloadditions will be presented. Advancing these fundamental processes has been enabled by selective activation of non-conjugated, cyclic alkenes through a coordination-metal-ligand cooperation. Efforts in methods development will be presented alongside mechanistic investigations through a combination of experimental spectroscopes and computational studies.

Dearomative Alkaloid Synthesis

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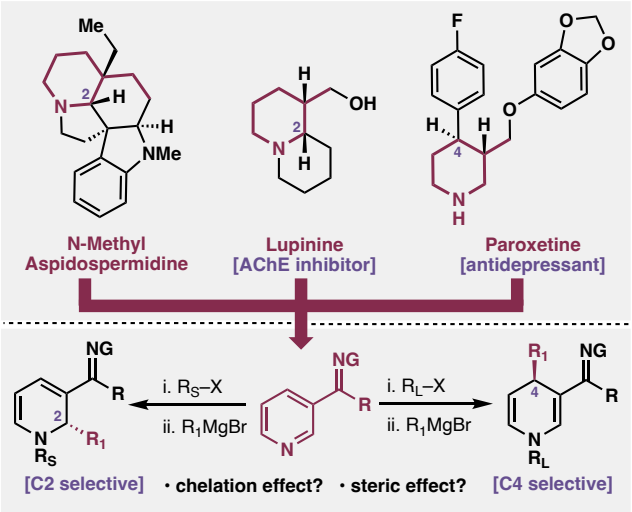
Alkaloid natural products are structurally diverse secondary metabolites that have served both as pharmaceutical leads and inspiration for the invention of novel chemical transformations. Substituted piperidine rings, a common motif found both in pharmaceutical ingredients and alkaloids alike, have continued to demand concise syntheses to allow for facile access to varied substitution patterns and privileged biologically active scaffolds. Our work has concerned the redox-economic construction of these alkaloids starting from readily available pyridine starting materials.[1] This discussion will first concern the innate regiochemical preference of organometallic nucleophiles to substituted pyridiniums,[2] followed by investigations into their controlled regioselective and stereoselective dearomatization as a platform for concise total synthesis.[3] Importantly, controlled regiodivergent asymmetric additions to pyridiniums have been achieved, enabling synthetic divergence to structurally distal targets that are natural and/or pharmaceutically relevant.[4] Discussion of mechanism and translational synthetic applications will also be highlighted.



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4. Unpublished results.

Photon-driven strategies for challenging bond activations

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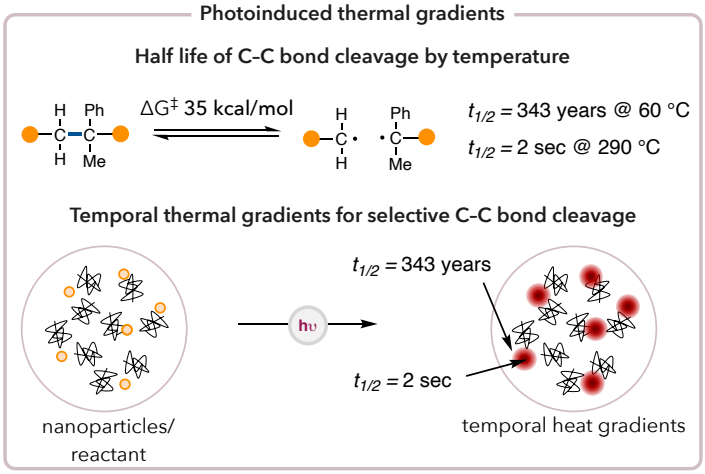
Photon-driven processes have emerged as a powerful tool for achieving challenging bond cleavages and bond formations.[1] Photocatalysis offers the benefit of temporal and spatial control with low energy light, which has been widely advantageous in polymers and materials to access sequence control or 3D structure. The judicious choice of photocatalyst enables a precision of reactivity not amenable to other strategies. We will demonstrate how photocatalyst identification can be leveraged for selective C–H abstraction for tunable product distributions, and applied in a scalable photo-flow process.[2] Additionally, I will discuss using visible light irradiation to enable temporal heating for generating and confining highly reactive intermediates for selective C–C bond cleavages.



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Synthesis of heterocyclic peptide secondary metabolites from cyanobacteria harmful algal blooms (cHABs)

J. L. Stockdill,[a]* J. A. Westrick,[a] R. M. I. Morsy,[a] B. S. Ramakrishna,[a] Z. Harris,[a] S. Kasmer,[a] D. C. Szlag[b]

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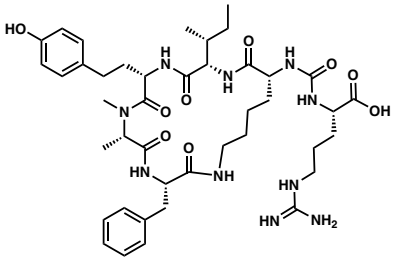
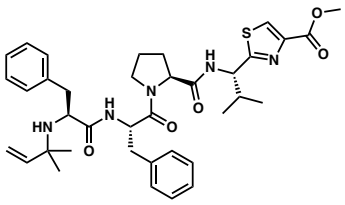
Cyanobacteria harmful algal blooms occur in freshwater, estuaries, and marine waters across the world and are a direct and increasing threat to human health via contamination of drinking water, recreational water, and freshwater and coastal seafood. Cyanobacteria thrive in warm, high-nutrient waters and produce heterocyclic peptide secondary metabolites that cause liver, neurological, dermal, gastrointestinal, and kidney diseases and cancer as well as antimicrobial and antiproliferative activities. This seminar will present synthetic approaches to selected heterocyclic cyanopeptides.



Anabaenopeptin F



Aeruginosamide C

Aryne formation via formal dehydrogenation of simple arenes

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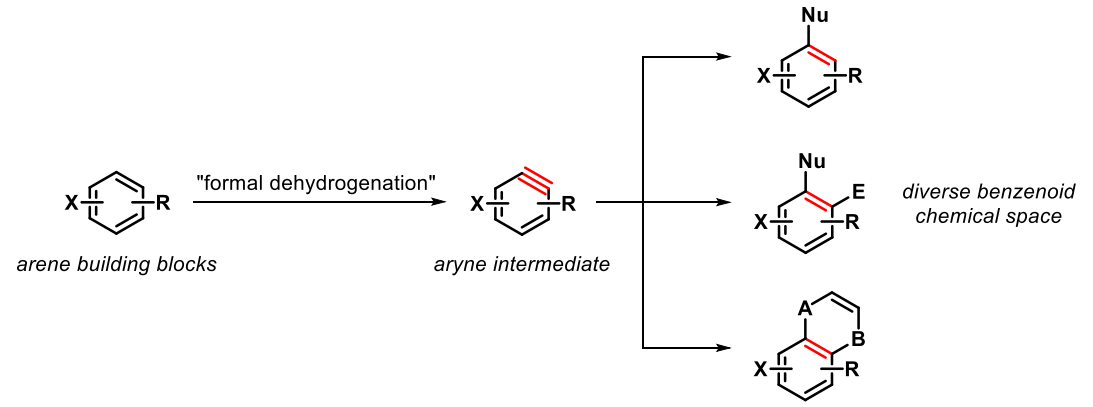
Arynes are novel intermediates for organic synthesis as they engage a diverse set of coupling partners. Consequently arynes are capable of generating a wide range of benzenoid chemical space. Despite a wide reactivity profile, major hurdles to using aryne chemistry are lengthy synthesis of the aryne precursor or harsh conditions to generate aryne intermediates themselves. Here, we describe a method to generate arynes that is both efficient and mild via a formal dehydrogenation of simple arenes. The method is so mild that all other halides are tolerated and therefore is a way to derivatize highly valuable aryl halide building blocks. Moreover, the method may be used for late-stage derivatization of advanced intermediates.



New-to-Nature Metalloredox Biocatalysis for Stereoselective Radical Transformations

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Abstract: Bringing new catalytic functions to naturally occurring enzymes can dramatically expand the repertoire of enzymology and generate novel biocatalysts. Inspired by the innate redox properties of first-row transition-metal cofactor, our group has recently begun to repurpose metalloproteins to catalyze stereoselective radical reactions triggered by single electron transfer. Due to the lack of exploitable stereocontrol elements in synthetic systems, steering the absolute and relative stereochemistry of these free radical processes is notoriously difficult in asymmetric catalysis. We engineered a set of metalloenzymes to impose excellent stereocontrol over the bond forming events in these unnatural processes, allowing stereodivergent radical catalysis to be easily carried out. These metalloenzymes are fully genetically encoded and function in bacterial cells, displaying excellent activities at room temperature. Collectively, this evolvable metalloenzyme platform represents a promising solution to tame fleeting radical intermediates for asymmetric catalysis.

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Poster Abstracts

New quinoxaline-based derivatives as PARP-1 inhibitors: design, synthesis, antiproliferative, and computational studies

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[b] *Institute for Computational Molecular Science and Department of Chemistry, Temple University, Philadelphia, Pennsylvania 19122, USA.*
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Abstract: Herein, the 2,3-dioxo-1,2,3,4-tetrahydroquinoxaline[1] was used as a bio-isosteric scaffold to the phthalazinone motif of the standard drug Olaparib[2] to design and synthesize new derivatives of potential PARP-1[3] inhibitory activity using the 6-sulfonohydrazide analog **3** as the key intermediate. Although the new compounds represented PARP-1 suppression impact of IC_{50} values in the nanomolar range, compounds **8a**, **5** were the most promising suppressors producing IC_{50} values of 2.31 and 3.05 nM compared to Olaparib of IC_{50}: 4.40 nM. Compounds **4**, **10b**, and **11b** showed a mild decrease in the potency of the IC_{50} range: 6.35-8.73 nM. Furthermore, compounds **4**, **5**, **8a**, **10b**, **11b** were evaluated as in vitro antiproliferative agents against the mutant BRCA1 (MDA-MB-436, breast cancer) compared to Olaparib as a positive control. Compound **5** exhibited the most significant potency of IC_{50}: 2.57 μM, whereas the IC_{50} value of Olaparib[2] was 8.90 μM. In addition, the examined derivatives displayed a promising safety profile against the normal WI-38 cell line. Cell cycle, apoptosis, and autophagy analyses were carried out in the MDA-MB-436 cell line for compound **5** which exhibited cell growth arrest at the G2/M phase, in addition to induction of programmed apoptosis and an increase in the autophagic process. Molecular docking of the compounds **4**, **5**, **8a**, **10b**, **11b** into the active site of PARP-1 was carried out to find out their modes of interaction. In addition, in silico ADMET study was performed. The results evidenced that compound **5** could serve as a new framework for discovering new potent anticancer agents targeting the PARP-1 enzyme.

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Chemo- and Regioselective Cross-dehydrogenative Coupling of 3-Hydroxycarbazoles Using a Heterogeneous Oxovanadium Catalyst

Shuji Akai,[a,*] Kengo Kasama,[a] Yuuya Hinami,[a] Karin Mizuno,[a] Kyohei Kanomata[a]

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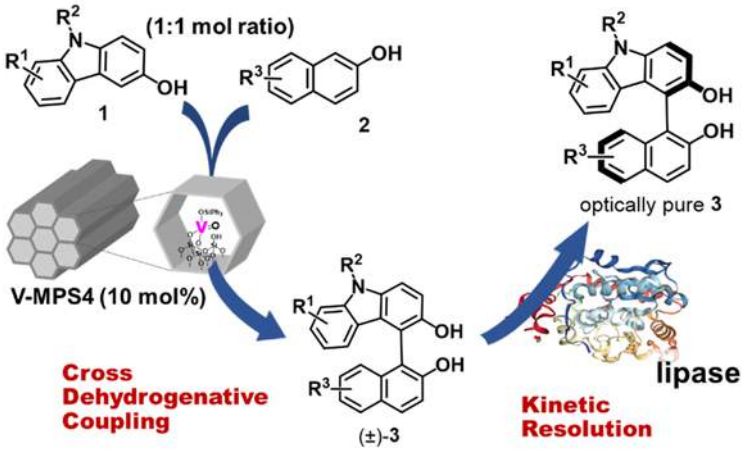
Background and objective: The direct oxidative coupling of the C-H bonds of two aromatic compounds is a powerful and atom-economical method for biaryl formation without requiring pre-functionalization of the substrates. While various transition metal catalysts have been successfully used for homo-coupling reactions, oxidative cross-coupling of two different aromatic compounds, i.e., cross dehydrogenative coupling (CDC), still remains challenging because of the need to supress the homo-coupling and to control the reaction position precisely. We have invented a unique catalyst, V-MPS4, in which an oxovanadium(V) moiety is immobilized on the inner surface of mesoporous silica with a pore size of 4 nm, and used it as a racemization catalyst in lipase-catalyzed dynamic kinetic resolution of secondary alcohols.[1] In this study, we have aimed to develop a new CDC reaction using V-MPS4 to produce heterobiaryls having 3-hydroxycarbazole moieties and also to combine it with lipase-catalyzed kinetic resolution (KR) to obtain optically pure heterobiaryls (Figure).

Results and discussion: As a result of intensive studies, CDC of 3-hydroxycarbazole **1** and an equal amount of 2-naphthol **2** using 10 mol% V-MPS4 under ambient pressure of molecular oxygen was successfully established to obtain the desired cross-coupling product (±)-**3** in high yield and with excellent chemo- and regioselectivity. The reaction showed a wide substrate scope, including *N*-substituted 3-hydroxycarbazoles **1**. Particularly noteworthy is the fact that the heterogeneous V-MPS4 catalyst has a much higher activity than a homogeneous catalyst, $VO(OSiPh_3)_3$, even though the oxovanadium structures of both reagents are almost identical. Furthermore, V-MPS4 was reused three times without a significant decrease in product yield.[2] These results are noteworthy because homogeneous oxovanadium catalysts have been mainly investigated for the homo- and cross-coupling reactions of hydroxycarbazoles so far.

We also found that a commercially available *Pseudomonas* sp. lipase was suitable for KR of (±)-**3**. In particular, KR was highly efficient for (±)-**3** with substituents on the carbazole nitrogen atom producing (*R*)-**3** and (*S*)-**3** with high optical purity (98% *ee*).[3]



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Catalytic Benzoxazine Synthesis Enabled by P^{III}/P^{V}=O Cycling

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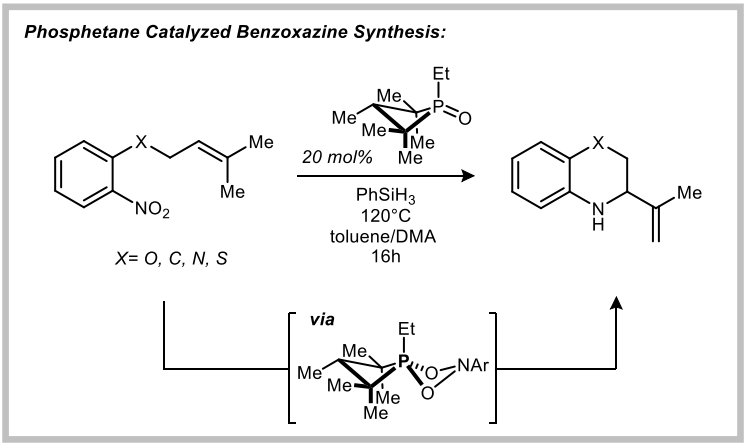
Nitrogen containing heterocycles are commonly displayed in a wide array of commercially attractive molecules, including, pharmaceuticals, dyes, conjugated polymers and polymer resins. An attractive method to access nitrogen containing heterocycles is through the generation of nitrene or nitrenoid equivalents to induce group transfer reactions, such as aziridination, or bond insertion strategies, such as C–H aminations. Recently, biphillic phosphorous catalysts have been identified towards accessing carbazole and indole derivatives via nitroarene deoxygenation followed by C–H bond insertion[1]. Here, we expand this work utilizing a P^{III}/P^{V}=O platform to catalytically access benzoxazine derivatives from nitro deoxygenation and subsequent nitroso-ene reactivity.



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In silico generation of heterocycle-containing drug-like small molecules: towards tools for the many different needs of drug discovery projects.

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Using heterocyclic scaffolds in drugs and drug-like small molecules is a fundamental pillar in small molecule drug discovery. There are many reasons for heterocycles appearing in so many small molecule drugs and the topic has been well discussed in the literature.[1-5] Our focus for this work is on heterocycles 1) utility as bioisosteres, 2) well-defined structure scaffolding and conformational properties, 3) tunable physiochemical and ADME properties, and 4) synthetic challenges and opportunities. These properties of heterocycles can be computed and encapsulated by computational representations and used in modern artificial intelligence (AI) and machine learning (ML) applications.[6-10]

Iktos is a chemistry AI company. We develop AI/ML tools to aid our drug discovery collaboration projects and to provide as a SaaS application to computational and medicinal chemists.[11] The primary tools from Iktos are Makya for *de novo* generative compound design and Spaya for data-driven retrosynthesis prediction. We have developed a variety of approaches generate virtual molecules within Makya and to direct these generations to converge towards an optimal *in silico* profile of properties.[12-13] The target profiles of virtually generated compounds can encompass a range of goals including QSAR-modellable properties, predicted binding with docking or free-energy perturbation, and synthesizability. We will discuss technology improvements directed towards use of heterocycle properties during molecule optimization, exploration of diverse heterocyclic scaffolds, and integration of heterocycle synthesis strategies to guide generations. We have implemented scaffold hopping algorithms, synthesis-based forward generation algorithms, and new molecular fingerprints and have made comparisons with some of the tools, techniques, and algorithms from the scientific literature. We have evaluated the performance of these newly implemented tools, techniques, and algorithms, in a virtual drug discovery project focused on identifying novel inhibitors of VEGFR2 with desirable physiochemical and predicted ADME properties and present the results through multiple rounds of design and evaluation with a discussion of improving the outcomes of the AI/ML tools for a practical drug discovery project.

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Total Synthesis of (±)-Alstonlarsine A from (±)-Alstolucines B or F through a 1,7-Hydride Shift/Mannich Cascade

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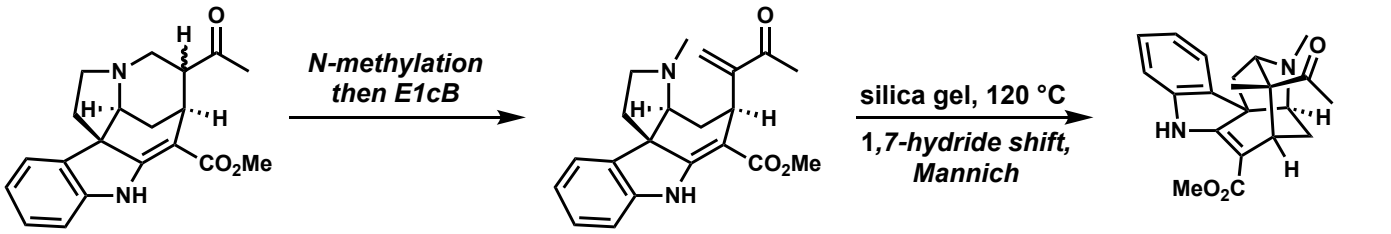

26% yield, 11 steps from PMB-tryptamine

A total synthesis of (±)-alstonlarsine A is described. *N*-Methylammonium derivatives of alstolucines B or F (**1**) were transformed to enone **2** through an E1cB reaction. This intermediate was converted to alstonlarsine A (**3**) after adsorption onto silica gel and heating. This sequence supports the chemical feasibility of an intramolecular hydride shift/Mannich cascade as the biosynthetic origin of alstonlarsine A. Both starting materials, alstolucine B and F, were previously synthesized in our lab as intermediates in a synthesis of alsmaphorazine B.[1]

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Applications of Biocatalysis in the Synthesis of PCSK9 Inhibitors

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Inhibition of Proprotein Convertase Subtilisin/Kexin type-9 (PCSK9) improves cardiovascular outcomes in patients requiring additional low-density lipoprotein cholesterol reduction on top of statins, but there has been limited uptake of the two commercialized PCSK9 antibody inhibitors due in part to cost and route of administration. The protein-protein interaction between PCSK9 and the low-density lipoprotein receptor which is targeted by these therapies is a large, flat surface, which has made the discovery of orally bioavailable small molecule inhibitors highly challenging. This poster will introduce the use of macrocyclic peptides to interrupt such protein-protein interactions and describe the early chemistry development of such a PCSK9 inhibitor. These compounds feature several unnatural amino acids as well as a complex, multicyclic architecture, presenting challenges in their chemical synthesis. New biocatalytic tools are presented that rely on engineered enzyme to address the challenging synthesis of these unnatural amino acids.

Direct Electrochemical Synthesis of *N*,*N'*-Disubstituted Indazolin-3-ones under Sustainable and Metal-Free Conditions

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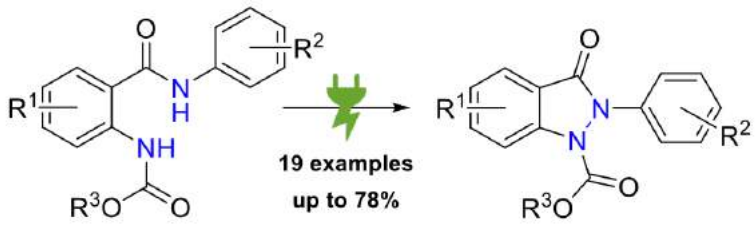

Indazolin-3-ones represent an important class of N-heterocycles due to their broad range of biological activity.[1] Conventional indazolin-3-one syntheses often involve harsh reaction conditions, the use of toxic reagents in stoichiometric amounts or transition metal catalysts, leading to large amounts of reagent waste, high costs and safety hazards.[2] In contrast, electrochemical methods have proven to provide a sustainable and broadly applicable synthetic tool for the synthesis of various N-heterocycles. By applying current as a traceless oxidant, reagent waste can be diminished, work safety increased and costs can be lowered.[3]

Recently, we developed the first broadly applicable and sustainable electrochemical synthesis of *N*,*N'*-disubstituted inda- zolin-3-ones via an intramolecular anodic dehydrogenative N-N coupling reaction.[4] This method features mild reaction conditions, an easy experimental setup, sustainable and inexpensive electrode materials and a low supporting electrolyte concentration, providing access to various indazolin-3-one derivatives in very good yields up to 78%. Additionally, the excellent scalability of the reaction was demonstrated. Cyclic voltammetry experiments were conducted to get insights into the mechanism. Currently, selected indazolin-3-one derivatives are investigated regarding their antifungal properties.

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Diazaborines: Phenolic Isosteres with Hydroxy Group Exchange Capability

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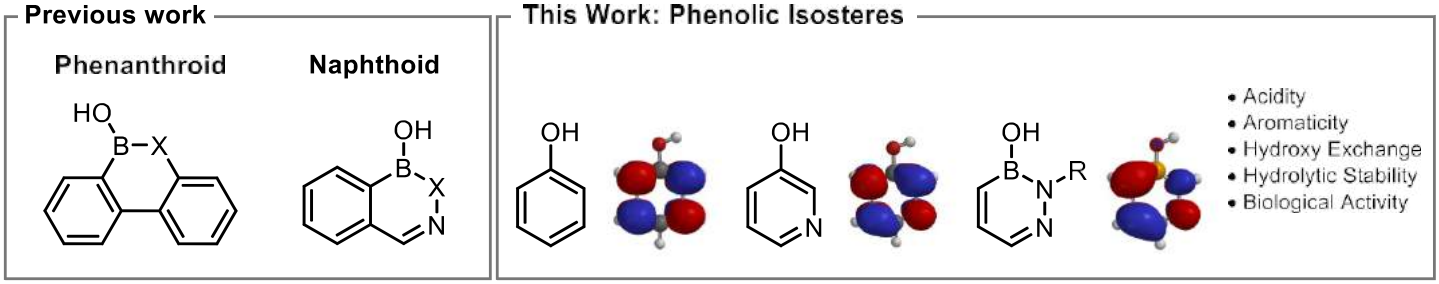
Heterocyclic organic molecules have a diverse range of applications, such as ligands in catalysis, integral components of functional materials, and as important substructures in medicinal chemistry.[1-3] The design and preparation of therapeutics that contain boronic acids and their derivatives has recently gained a significant amount of attention due to a large variety of possible molecular interactions and the relatively non-toxic nature of boron.[4] The potential of these heterocycles is exemplified by the success of the benzoxaborole ring system as a pharmacophore, which is present in the FDA approved pharmaceuticals Tavaborole (Kerydin®) and Crisaborole (Eucrisa®). As such, there exists an opportunity to design boron heterocycles as novel chemotypes that could provide solutions to previously unmet problems in medicine and human health.

Our laboratory has recently rectified some long-convoluted questions regarding the acidic and aromatic nature of boranol- containing (B-OH) naphthoid and phenanthroid isosteres.[5,6] Understanding these fundamental properties is essential for guiding the application of boroheterocyclic compounds in catalysis, materials, and medicinal chemistry. These previous studies on naphthoid and phenanthroid analogs motivated us to explore the parent benzenoid diazaborines, a novel class of boranol-containing phenolic isosteres that are free of influence from a fused aromatic ring. In order to gain a better understanding of this new chemotype, their acidic and aromatic properties have been interrogated through a combination of experimental, spectroscopic, and computational studies. The preparation of these compounds and the evaluation of their physical properties will allow for the synthesis of derivatives tailor-made for specific applications in catalysis, materials, and medicinal chemistry.



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Asymmetric dihalogenation of sulfoxonium ylides

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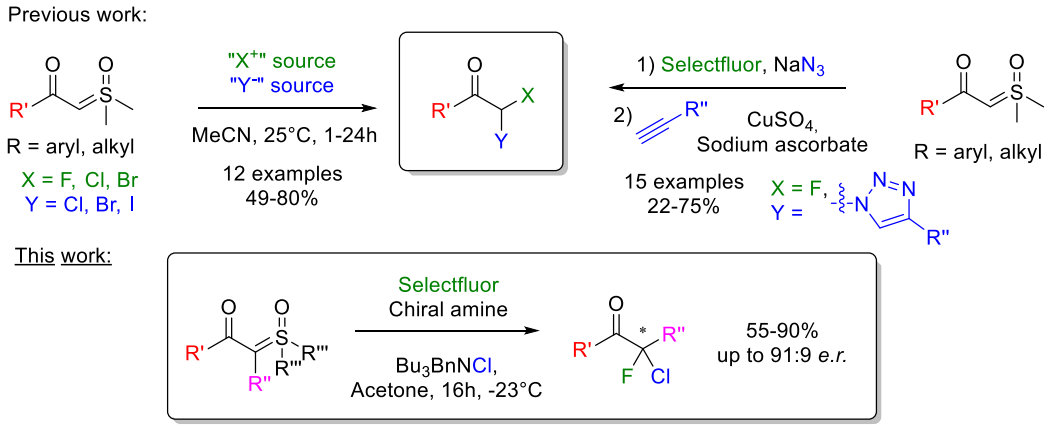
Introduction of fluorine substituents can alter the pKa of neighboring groups, dipole moments, and other molecular properties such as metabolic stability, lipophilicity and bioavailability, which makes organoflourine compounds ubiquitous in agrochemicals and medicinal compounds.[1-3] In contrast to the number of studies involving asymmetric α-mono-flourination[4] and asymmetric α-mono-chlorination of carbonyl compounds, there are only a few studies involving asymmetric formation of α,α-dihalogenated carbonyl compounds.[5-7] In every case, the halogens are installed in different steps, with the two C-X bonds being formed in subsequent reactions.

Utilizing the ability of sulfur ylides in promoting both nucleophilic and electrophilic reactions, our group recently reported methodologies allowing access to a variety of α,α-difunctionalized carbonyl compounds, in racemic fashion (Scheme 1).[8,9] Inspired by these contributions, we envisioned that using a chiral source of electrophilic halogen would enable access to enantioenriched α-chloro-α-fluor carbonyl compounds. Herein we report the first example of asymmetric dihalogenation in which both C-X are formed in the same reaction step. Up to this point we were able to prepare 5 examples of enantioenriched α-chloro-α-fluor carbonyl compounds in 55-90% yields and up to 91:9 *e.r.*



Scheme 1. Difunctionalization of sulfoxonium ylides: previous racemic works and novel asymmetric methodology.

Studies are underway to explore the scope and limitations of this methodology and to increase the enantioselectivity.

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An Enantioselective Synthesis of Wickerol B

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We report the total synthesis of antiviral diterpenoid wickerol B. Our strategy relied upon early installation of a tertiary alcohol stereogenic center followed by sequential C–C bond forming events for construction of the planar 6- 6-5 tricyclic core through stereochemical relay. Elaboration to the strained tetracyclic core was achieved through a late- stage Prins cyclization that could lead to several unusual and undesired products formed by strain-induced rearrangements. Throughout this campaign, desired stereoselectivity and reactivity outcomes proved challenging to attain. Consequently, numerous detours were taken while accessing key structural features, including enoate ester installation via a cerium-mediated 1,2 alkynylation/Meyer–Schuster rearrangement and formal aldehyde α-methylation via a Claisen rearrangement/deoxygenation sequence. Investigation of substrate-controlled C–C bond formation led to the development of conditions providing complementary stereochemical outcomes and diverse carbocyclic frameworks. Discoveries enabled by this endeavor may translate to the synthesis of other complex targets.

Syntheses of the *ortho*-polysubstituted azobenzenes

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Azobenzenes are a subclass of reversible light-switchable molecules due to their ability to undergo photoisomerization.[1] The basic structure of the azobenzenes is represented by two benzene rings connected by an azo bond. Reversible photoisomerization is observed as *trans*-*cis* isomerization around the azo bond. As the *trans* isomer is more stable in most of the cases, the thermal stability of the *cis* isomer is studied in order to investigate the physico-chemical properties of the azobenzene systems. The thermal stability (measured as half-life $t_{1/2}$) of *cis* isomer can be tuned by the character (electron-donor/acceptor, spatial demands) and position of substituents on benzene rings (e.g., fluoro substituents in *ortho* positions substantially extend the half-life of the *cis* isomer).[2,3]

The goal of this study was to develop a synthetic approach for the derivatization of 2,6-dichloroazobenzene as well as 2,6-dichloro-2',6'-difluoroazobenzene using the Suzuki reaction, and subsequently investigate the effect of the aryl and fluorine substituents on the photoisomerization and half-life of new *ortho*-polysubstituted azobenzenes.

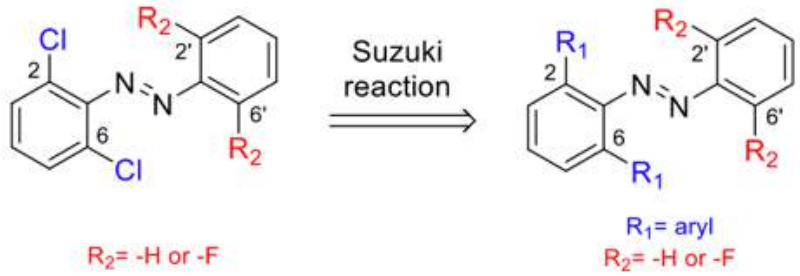

Figure 1. Unsymmetrically substituted azobenzenes

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Synthesis and Reactivity of 5-Hydrazino-3-nitro-1,2,4-triazole (HNT): an Amphoteric Energetic Platform

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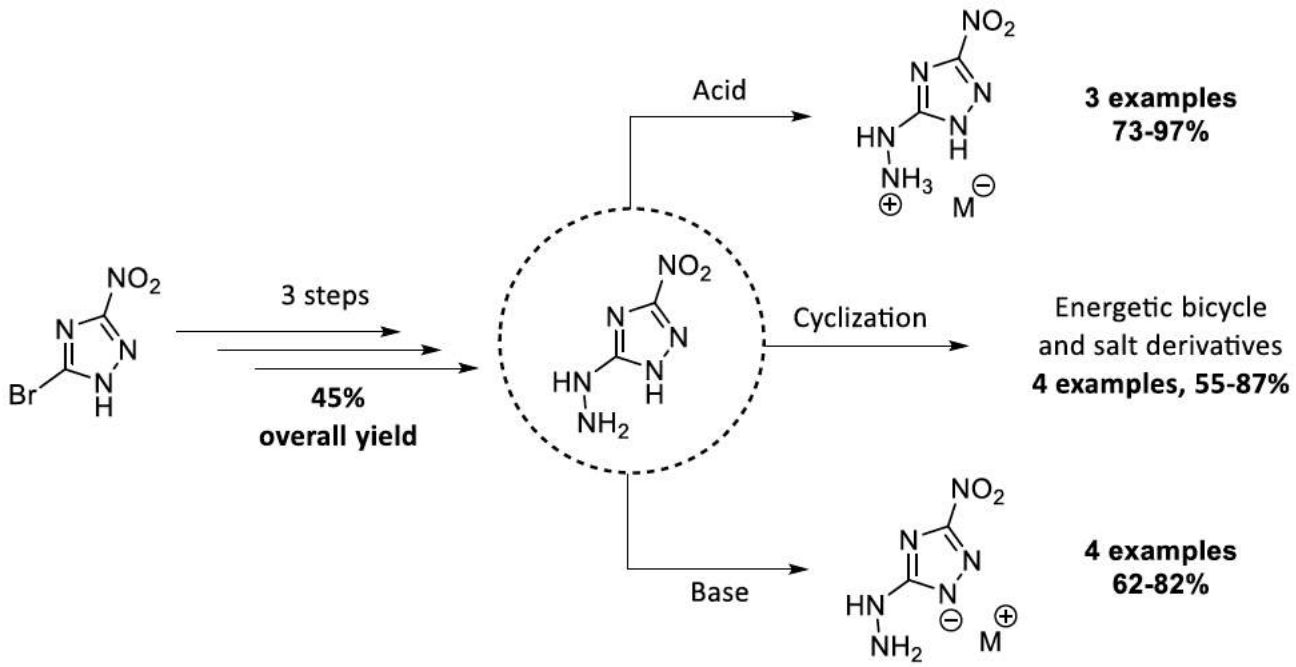
Triazoles are a major class of heterocyclic compounds, widely used in pharmaceutical and energetic applications due to their high nitrogen content coupled with the presence of explosophoric groups like nitro, hydrazino or azido.

Although some hydrazino-1,2,4-triazoles have been described lately,[1] HNT is still surprisingly missing, making it doubtful as a free base, as only hydrochloride and sulfate salts were reported.[2,3]

Herein, the first synthesis of HNT is described from 5-bromo-3-nitro-1,2,4-triazole (BNT) in three steps, as well as other energetic compounds derived from it, including salts, thus demonstrating that HNT is not only a feasible, stable molecule, but also a valuable platform towards powerful and thermally stable energetic compounds.



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Development of a [2+2] Photocycloaddition of 2-Pyridones using Organic Photocatalysis

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Pyridones are important heterocycles owing to their applications in medicinal chemistry and their use as building blocks in organic synthesis. In particular, photochemical reactions of pyridones provide access to diverse molecular scaffolds that would otherwise be challenging to make. We are developing a two-step synthesis of annulated 2-pyridones using visible light photocatalysis that features a [2+2] photocycloaddition followed by cyclobutane fragmentation. While [2+2] photocycloadditions of 2-pyridones have been well documented in the literature, these methods have relied on triplet sensitizers that absorb UV light. We have been investigating both transition metal and organic photosensitizers that absorb visible light to improve reaction efficiency and functional group compatibility. We have identified two photocatalysts capable of catalyzing the intramolecular [2+2] reaction of *N*-alkylated 2-pyridones, which will enable the development of an oxidative cyclobutane fragmentation toward annulated pyridones.

Organoboron-Catalyzed, Regioselective Alkylation of Azoles

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Aromatic nitrogen heterocycles, or azoles, are found in around 59% of FDA-approved small molecule drugs.[1,2] These rings are a subset of molecular fragments that have the capacity to alter pharmacological profiles of drugs through key descriptors such as lipophilicity, polarity, molecular weight, and hydrogen bonding. Typically comprised of five- and six-membered aromatic rings, a common modification of azoles in druglike molecules is the incorporation of an N atom in place of a CH group which often improves molecular properties such as potency.[3] A route towards this modification is through substitution reactions of commercially available nitrogenous rings. The simplest of these reactions is N-alkylation which involves replacing a hydrogen atom with an alkyl species on the NH group of a ring.

N-alkylation of unsubstituted heterocycles such as triazoles, tetrazoles, indazoles and purines is of great interest due to their aforementioned medicinal applications. However, a challenge with using these species as nucleophiles is that they can react at two or more different nitrogen atoms, giving rise to mixtures of isomeric products. Organoboron catalysis provides a means of inducing *N*-selectivity in alkylations of azoles through epoxy alcohol ring-openings and conjugate additions of enones.[4] This work discusses two sets of electrophiles used in alkylating azoles in a regioselective manner (**Figure 1**).[5,6] With 2,3- and 3,4- epoxy alcohols, organoboron acids can coordinate to the primary alcohol tether and deliver the azole intramolecularly to provide high ring-opening- and *N*-selectivity. When using enones, an amine additive is required to activate the electrophile via an iminium intermediate. A range of diazoles, triazoles, and tetrazoles are explored in both studies, including the nucleobase purine.

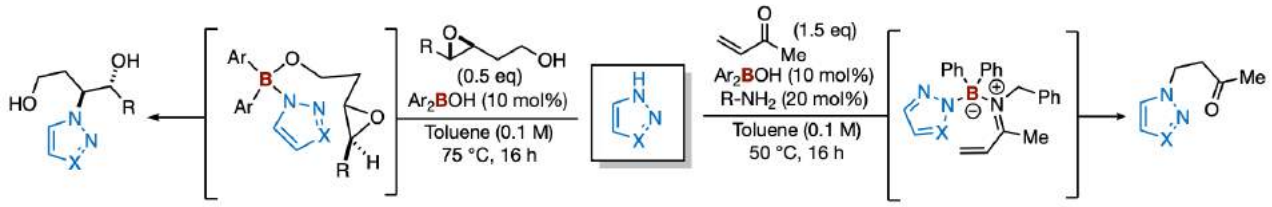

Figure 1. Organoboron-catalyzed, regioselective alkylation of azoles via epoxy alcohol ring-opening and *aza*-Michael additions.

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The Total Synthesis of Isoneoamphilectane

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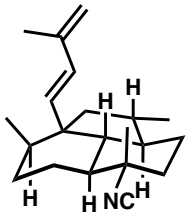
We report the first total synthesis of the rare isocyanoterpene natural product, isoneoamphilectane, in 23 steps from known materials. The core of the unique 6/6/5 ring system is generated in a concise sequence involving a Mukaiyama–Michael addition and sequential intramolecular alkylation reactions. The completion of the synthesis hinged on a challenging contrathermodynamic *cis*-to-*trans* decalone epimerization; we investigated multiple epimerization strategies and discovered a cyclic sulfite-based pinacol-like rearrangement to install the strained ring system. Additional key steps in our route include an intramolecular alkoxide-directed elimination and an HAT-mediated alkene hydroazidation.

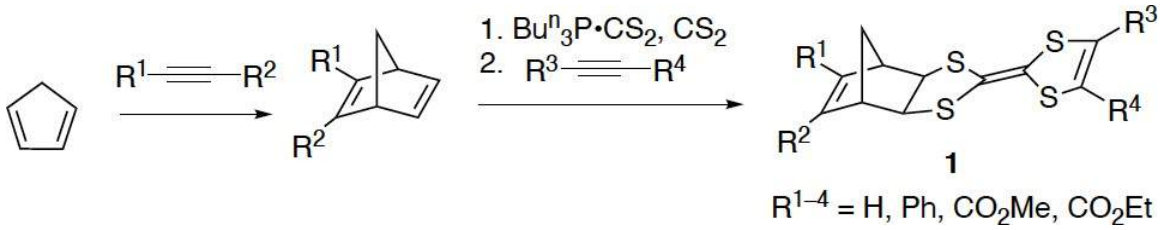


Synthesis and Evaluation of New Dihydrotetrathiafulvalene Systems for Metal Surface Adsorption and Hydrogen Bonding

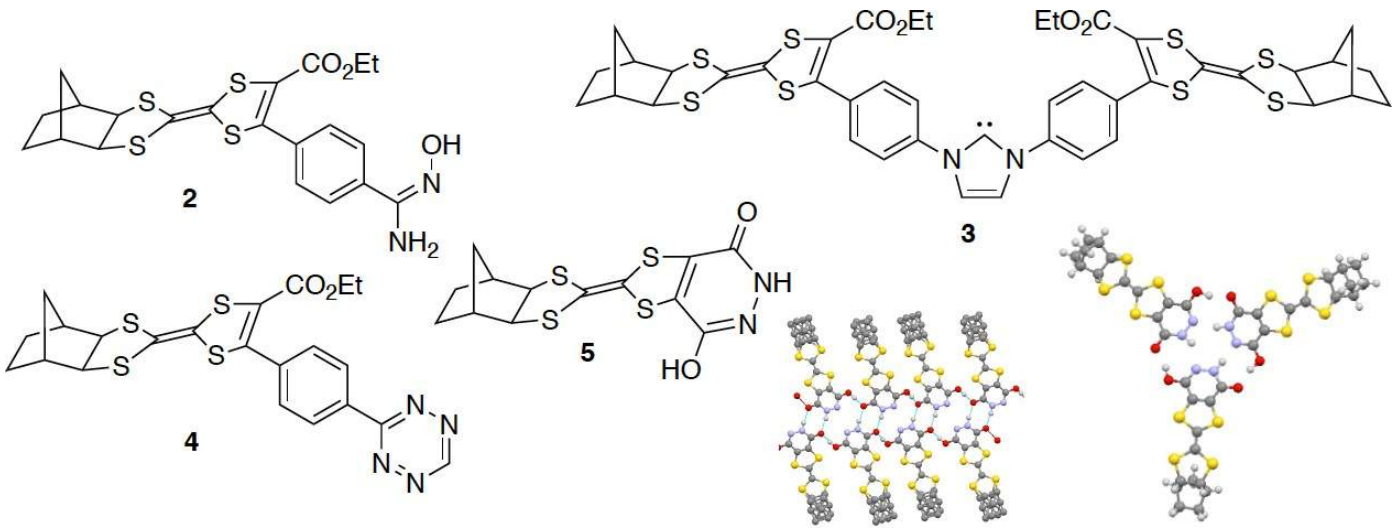
Fiona M. Fotherby and R. Alan Aitken*

EaStCHEM School of Chemistry, University of St Andrews, St Andrews, UK

Some years ago we described a new direct method to prepare norbornane-fused dihydro-TTF compounds **1**.[1,2] Although yields are only moderate, the method allows modular construction of a wide range of substituted examples and structural and electronic properties of a range of these will be presented.



We have already shown that a tetrakis(thiol-functionalised) analogue is efficiently adsorbed on a gold surface,[3] and current work towards new functionalised dihydro-TTFs capable of metal binding and self-association through hydrogen bonding will be described. In particular the amidoxime-compound **2** is designed to bind strongly to copper, the NHC **3** should show metal binding, the target tetrazine donor acceptor compound **4** is of interest.



The pyridazinedione compound **5** forms several different hydrogen bonded crystal forms including a cyclic trimer and a linear ribbon structure depending on the solvent of recrystallisation.

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Direct stereodivergent olefination of carbonyl compounds with sulfur ylides

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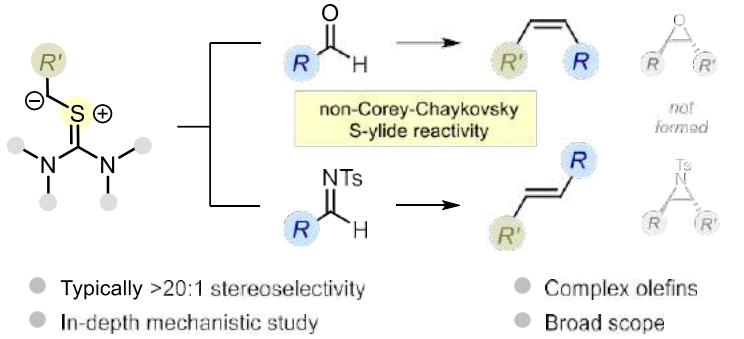
The reactivity of phosphorus and sulfur ylides toward carbonyl compounds constitutes a well-known dichotomy that is a common educational device in organic chemistry—the former gives olefins, while the latter gives epoxides.[1-3] Herein, we report a stereodivergent carbonyl olefination which challenges this dichotomy, showcasing thiouronium ylides as valuable olefination reagents. With this method, aldehydes are converted to *Z*-alkenes with high stereoselectivity and broad substrate scope, while N-tosylimines provide a similarly proficient entry to *E*-alkenes. In-depth computational and experimental studies clarified the mechanistic details of this unusual reactivity.



Revisiting the dichotomy of sulfur and phosphorus ylide reactivity

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Computer-Aided Natural Product Structure Elucidation and Mechanochemical Synthesis of Organic Thiocyanates

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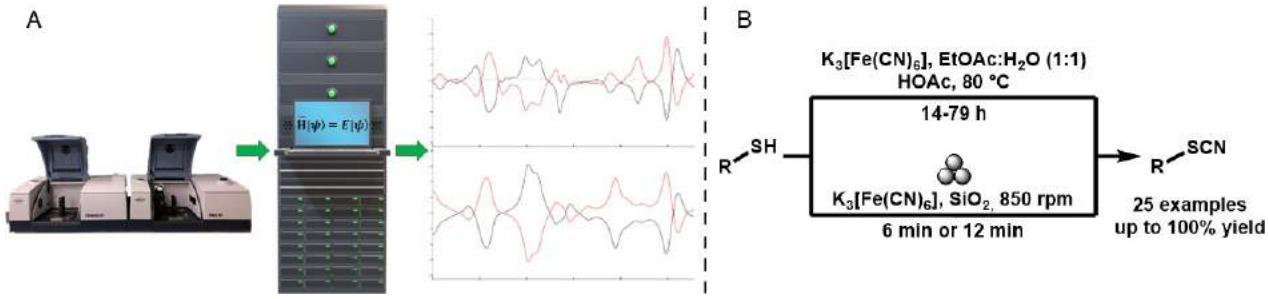
A well-established approach in drug discovery is the identification of pharmacologically active compounds from natural sources (plants, sponges, fungi, etc.), some of which have been known for their biological activity for centuries. An important part of this workflow is the elucidation of the correct structure of unknown secondary metabolites.

By combining spectroscopic methods with quantum mechanical calculations on the DFT-level, the capability to predict and confirm the exact chemical structure of several small molecules of such examples arose, using NMR- and CD-spectroscopy as well as polarimetry as standard working tools.[1,2]



Organic thiocyanates are a very versatile compound class not only with interesting biological activities but also as potential new drug motifs that could bypass increasing drug resistances.

In another project, a method development in the sense of the green chemistry principles is demonstrated by the preparation of thiocyanates using a biphasic reaction mixture or a ball-milling approach in combination with a non-toxic cyanide source. The optimized approach proofed to be widely applicable to a variety of commercially available thiols and disulfides.[3]

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Stereocontrolled Synthesis of Fluorinated Isochromans via I(I)/I(III) Catalysis[1]

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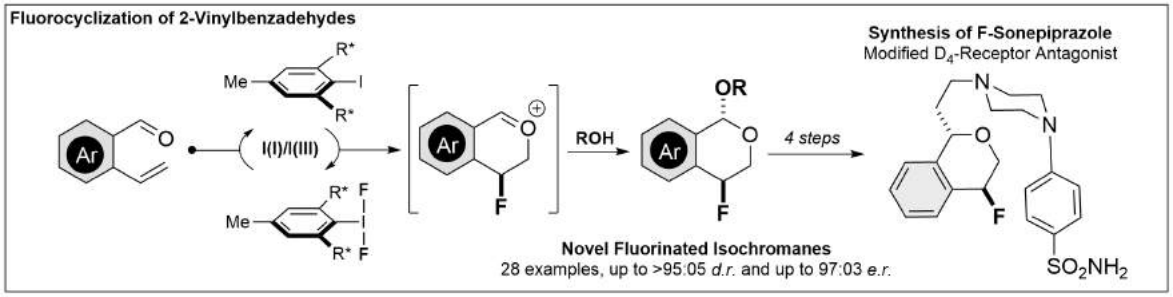
Abstract: Fluorinated, heterocyclic compounds play a highly important role in modern drug discovery.[2,3] Novel fluorinated isochromane building blocks were designed, enabling the expansion of the organofluorine chemical space from 2 to 3 dimensions.[4] For the synthesis of the desired products, a fluorocyclization/acetalization cascade was considered. It was found, that simple 2-vinylbenzaldehydes undergo a fluorocyclization mediated by an aryl iodide organocatalyst (20 mol%). Selectfluor® was used as a terminal oxidant and a HF•Pyridine mixture as a nucleophilic fluoride source in $CHCl_3$ as a solvent. In the presence of an additional alcohol to trap the intermediate oxocarbenium ion (see Scheme below), the desired 4-fluoro-1-alkoxyisochromanes were obtained with high stereoselectivities (up to 95:05 *d.r.* and up to 97:03 *e.r.*) and good yields. To show the synthetic utibility and possible applications of the obtained products, synthetic manipulations of the acetal functionality were demonstrated, including the multi-step synthesis of a fluorinated version of sonepiprazole, a highly potent D_4-receptor antagonist.[5] Structural analysis using single crystal X-Ray diffraction revealed stereoelectronic aspects such as $\pi \rightarrow \sigma^*_{C\text{-}F}$,[2b] suggesting the [$CH_2$-CHF] unit to act as a stereoelectronic mimic of the [O-CH(OR)] acetal motif.



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The Anodic Phenol-Phenol Coupling – Optimizing Electrolysis Conditions is the Key to the Efficient Formation of Biphenols and Polycycles.

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The anodic C,C–coupling represents a sustainable and efficient synthetic pathway for the formation of symmetrical or non-symmetrical biaryls and for the construction of a series of polycyclic scaffolds. In contrast to established approaches such as reductive coupling reactions the generation of reagent waste can be completely avoided, since there is no need for leaving groups and transition-metal catalysts.[1] Recently, our group developed a wide range of synthesis protocols for various biaryl systems using neutral or acidic electrolytes,[2] and polycyclic scaffolds using basic electrolytes.[3] Nevertheless, the optimization of the numerous reaction parameters, such as current density, supporting electrolyte, choice of electrode material, poses a challenge, as these parameters usually correlate with each other. Classical optimization approaches such as the one-factor-at-a-time method (OFAT) often fail to quantify the relevant correlations between the individual parameters and fail to address the global optimum of yield or selectivity.[4] Using design of experiments (DoE), we optimized the protocol for the phenol arene cross-coupling, enabling high current densities and increased cell loadings of up to 5 mmol for *ortho* as well as *para* coupling reactions in 25 mL beaker-type cells.[5] When the reaction is transferred from the batch cell to an electrochemical flow cell, additional parameters such as the flow rate increase the complexity of the parameter space even further.[4–6] Using a fractional factorial design, we optimized multiple reaction parameters in a flow electrolyzer at once by means of 35 experiments, resulting in highly efficient reaction condition with an almost threefold increase in space-time yield in contrast to time-consuming linear OFAT optimization.[6]

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Minimalist Tetrazine Carbohydrate Probe for Rapid Bioorthogonal No-Wash Live-Cell Labeling of Bacterial Peptidoglycan

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Bacterial peptidoglycans (PG) are recognized by immune cells and broken down into fragments that are used as signaling molecules for further immune system activation.[1] Misrecognition of different bacterial fragments has been implicated in different inflammatory and autoimmune conditions.[2] As a result, bioorthogonal carbohydrate probes have been utilized as important tools for monitoring PG biosynthesis and breakdown. PG is composed of two carbohydrate subunits, *N*-acetylglucosamine (NAG) and *N*-acetylmuramic acid (NAM). Commonly used bioorthogonal NAM probes typically contain alkyne or azide groups, due to their small size and increased incorporation into bacterial PG.[3] However, copper-catalyzed alkyne-azide cycloaddition reactions are not compatible with live cells, and strain promoted alkyne-azide cycloaddition reaction rates are modest and therefore not as desirable for live-cell labeling. Alternatively, the tetrazine-transcyclooctene ligation, which is the fastest known bioorthogonal reaction and not cytotoxic, allows for rapid live-cell labeling of PG at biologically relevant concentrations.[4] Previous work to increase reaction kinetics by using tetrazines probes was limited due to low incorporation of the probe because of its size.[5] In this work, we have utilized new synthetic approaches to making asymmetric tetrazines to construct a tetrazine NAM probe with a minimized linker. This minimalist tetrazine carbohydrate probe has been successfully incorporated into Gram-negative and Gram-positive bacterial PG. Fixed and rapid live-cell, no-wash labeling was successful in both free bacteria and bacteria that had invaded macrophages. Overall, this probe allows for rapid, efficient, no-wash labeling of bacterial PG which will prove to be an exceptional tool for monitoring PG biosynthesis and investigating fragment production and subsequent immune signaling cascades.

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Enantiodivergent synthesis of both enantiomers by dynamic kinetic resolution with *R*-selective lipases

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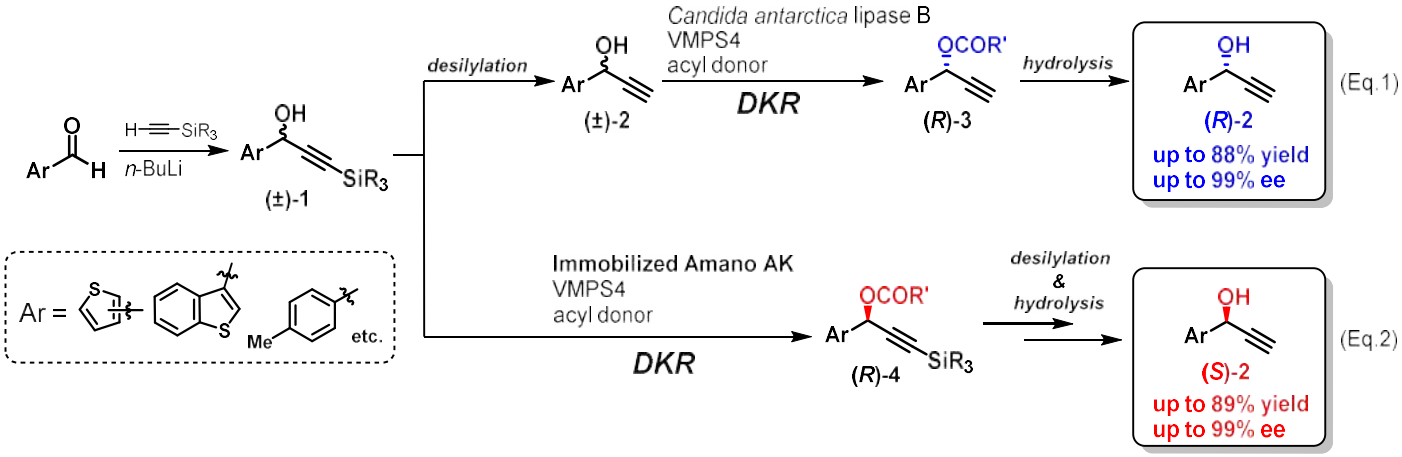
Background and Purpose: Natural lipases tend to recognize the size differences of substituents near the carbinol moiety and selectively esterify (*R*)-alcohols. Although kinetic resolution utilizing this property has been widely reported, each enantiomer are obtained in a maximum 50% yield. Recently, we have developed a dynamic kinetic resolution (DKR) method for the quantitative conversion of racemic alcohols to optically active compounds by the combined use of our original racemization catalyst, VMPS4, in which oxovanadium species are immobilized within mesoporous silica (MPS) pores, and commercial lipases[1]. Furthermore, we reported that secondary propargylic alcohol (±)-**2** can be converted to (*R*)-**3** in excellent yield and optical purity using this method (Eq. 1)[2]. On the other hand, (*S*)-selective hydrolase has been rarely used for DKR due to their low catalytic activity and stability[3]. Therefore, we investigated another DKR method for the synthesis of (*S*)-alcohols (*S*)-**2** to using (*R*)-selective lipases by introducing a bulky trialkylsilyl group on ethynyl terminal carbon of **2** to temporarily invert the size relationship of the substituents near the carbinol moiety.

Results: After screening of lipases applicable to the substrate (±)-**1**, *Pseudomonas fluorescence* lipase (commercial name, Amano AK) was found to be optimal. Then, by combining lipase AK immobilized on Celite and VMPS4, DKR of (±)-**1** afforded (*R*)-**4** in high yield and high optical purity (Eq. 2). Thus, the choice of either (±)-**1** or **2** has achieved the enantiodivergent synthesis of both enantiomers of propargylic alcohols **2**.



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A Safe Synthetic Equivalent of Nitroacetonitrile and Its Synthetic Uses toward 3-Cyanoisoxazoles

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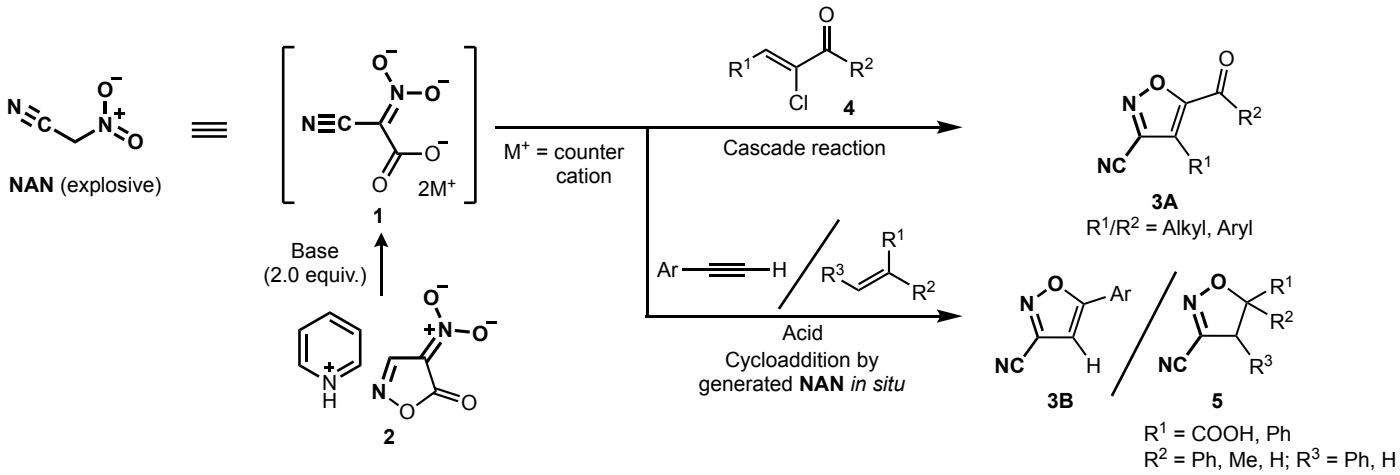
The active methylene compounds are essential building block in organic synthesis. Among them, nitroacetnitrile (**NAN**) has fascinating cyano and nitro groups which facilitate further chemical conversion. However, **NAN** should be handled as an explosive compound, thus, its synthetic uses have been limited. Based on these background, cyano-*aci*-nitroacetate **1**, safe synthetic equivalent of **NAN**, has been investigated in our group.[1] Dianion **1** can be generated from pyridinium salt of 4-nitrooxazol-5-one **2** upon treatment with two equivalents of base. Reagents **1** and **2** were easy to handle, and soluble in common organic solvents when organic amine was used as a base. Besides, the safety of **1** and **2** was confirmed by differential scanning calorimetry (DSC) measurement. In this poster, we will introduce two synthetic pathways towards 3-cyanoisoxazoles **3** using **2**. The first method is a cascade reaction with α-chloro-α,β-unsaturated ketones **4**, in which Michael addition of **1** to **4**, subsequent intramolecular substitution and dehydrative aromatization furnishes 5-acyl-3-cyanoisoxazoles **3A**. Acyl and cyano groups of **3A** exhibited high electrophilicity due to their electron-withdrawing effect through the isoxazole ring, thus, **3A** readily underwent the click reaction with organic azide and annulation between 5-acyl and 4-aryl units. The second synthetic method was performed by cycloaddition with alkynes or alkenes to afford corresponding isoxazoles **3B** and isoxazolines **5**, respectively, in which protonated **NAN** serves as a 1,3-dipole. Thus, **NAN** can be used as a synthetic equivalent of the cyanonitrile oxide which requires several limitations in the generation and handling. Since synthetic routes for 3-cyanoisoxazoles **3** and 3-cyanoisoxazolines **5** were limited to date despite high chemical convertibility of the cyano group, these synthetic methods are valuable to construct a library of isoxazoles and isooxazolines.



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Catalytic Activation of Bioorthogonal Chemistry with Light (CABL) Enables Rapid, Spatiotemporally Controlled Labeling and No-Wash, Subcellular 3D-Patterning in Live Cells Using Long Wavelength Light

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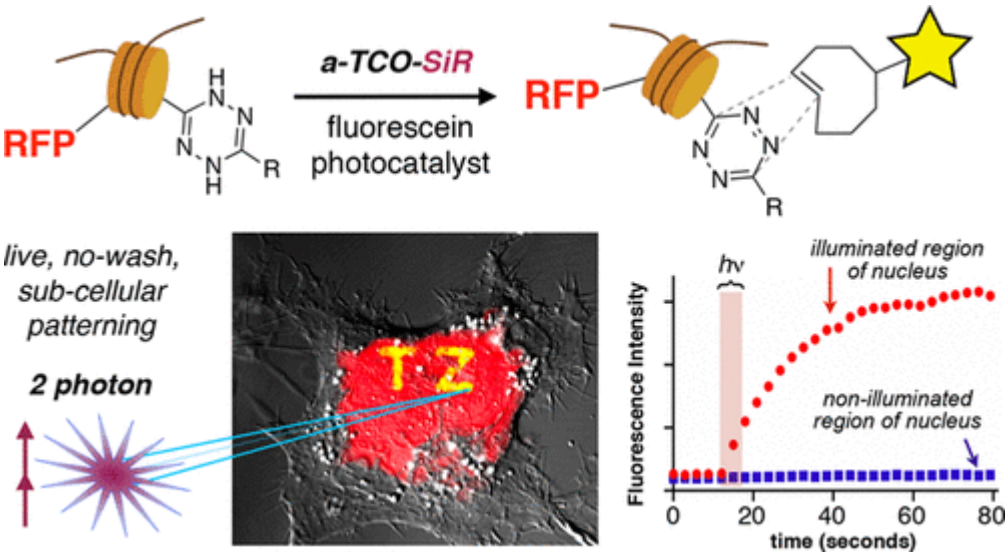
Described is the spatiotemporally controlled labeling and patterning of biomolecules in live cells through the catalytic activation of bioorthogonal chemistry with light, referred to as "CABL". Here, an unreactive dihydrotetrazine (DHTz) is photocatalytically oxidized in the intracellular environment by ambient O2 to produce a tetrazine that immediately reacts with a trans-cyclooctene (TCO) dienophile. 6-(2-Pyridyl)- dihydrotetrazine-3-carboxamides were developed as stable, cell permeable DHTz reagents that upon oxidation produce the most reactive tetrazines ever used in live cells with Diels−Alder kinetics exceeding k^2 of 10^6 M^{-1} s^{-1} . CABL photocatalysts are based on fluorescein or silarhodamine dyes with activation at 470 or 660 nm. Strategies for limiting extracellular production of singlet oxygen are described that increase the cytocompatibility of photocatalysis. The HaloTag self-labeling platform was used to introduce DHTz tags to proteins localized in the nucleus, mitochondria, actin, or cytoplasm, and high-yielding subcellular activation and labeling with a TCO-fluorophore were demonstrated. CABL is light-dose dependent, and two-photon excitation promotes CABL at the suborganelle level to selectively pattern live cells under no-wash conditions. CABL was also applied to spatially resolved live-cell labeling of an endogenous protein target by using TIRF microscopy to selectively activate intracellular monoacylglycerol lipase tagged with DHTz-labeled small molecule covalent inhibitor. Beyond spatiotemporally controlled labeling, CABL also improves the efficiency of "ordinary" tetrazine ligations by rescuing the reactivity of commonly used 3-aryl-6-methyltetrazine reporters that become partially reduced to DHTzs inside cells. The spatiotemporal control and fast rates of photoactivation and labeling of CABL should enable a range of biomolecular labeling applications in living systems.



Enantiospecific Heteroatom-Tethered 1,6-Enyne Cycloisomerizations and Their Utilization in Natural Product Total Synthesis

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Cycloisomerizations of 1,n-enynes catalyzed by electrophilic π-acid metal complexes provide a powerful method of carbon–carbon bond formation, and a unique platform for studying reactivity and mechanism.[1] Our previous report on the total synthesis of (±)-gelsenicine took advantage of a cycloisomerization/rearrangement strategy to access the central bridging bicyclic structure of the compound (Figure 1).[2] Continuing our interest in the gelsenicine total synthesis and enyne cycloisomerization, we began to formulate our own strategy toward an asymmetric variant of our route.

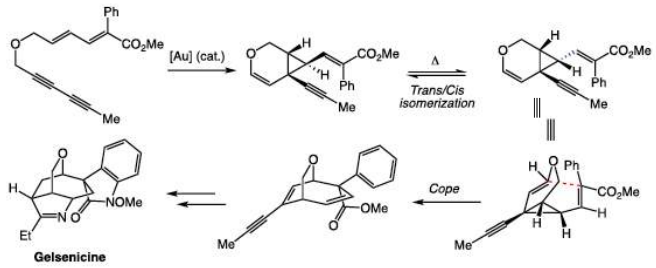


Figure 1. Our cycloisomerization/Cope rearrangement approach to gelsenicine.

In developing our asymmetric synthetic strategy based on chirality transfer, we had demonstrated enantiospecific cycloisomerizations of chiral ethereal 1,6-enynes (Figure 2).[3] This process requires a propargylic stereocenter in the substrates; although this stereocenter is destroyed in the transformation, its stereogenicity transfers in the cycloisomerization process. The substituent that dictates enantiospecificity ends up incorporated at the bridgehead position after the Cope rearrangement (Figure 2B). Therefore, we would need a removable group after the cycloisomerization/rearrangement process. Select entries from our investigation of the cycloisomerization under several Au- and Pt-catalyzed conditions are illustrated in Table 1.

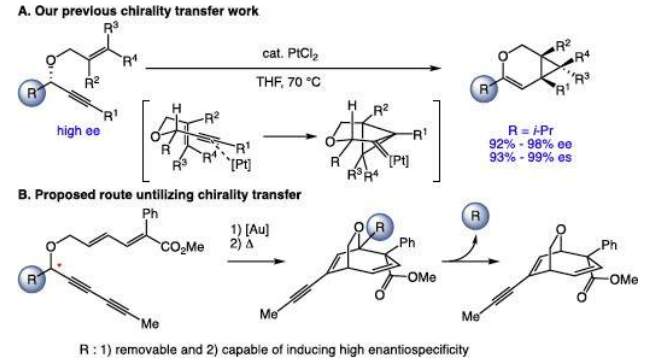
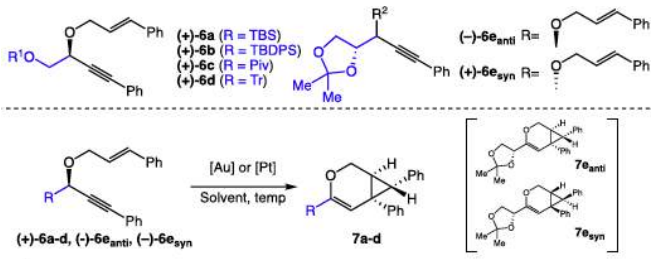


Figure 2. Chirality transfer – application to gelsenicine synthesis.

Table 1. Chirality transfer cycloisomerization with oxygenated substituents.



Entry	Substrate	Catalyst[a]	Solvent, temp (°C)	Yield (%)	ee(%)	dr[b]
1	(+)-6a	Pt-1	PhMe, 23	35	~74	
2	(+)-6a	Au	CH_2Cl_2, 23	66	82	
3	(+)-6b	Au	PhMe, 23	77	86	
4	(+)-6b	Pt-2	THF, 70	15	ND[c]	
5	(+)-6c	Au	CH_2Cl_2, 23	71	86	
6	(+)-6d	Pt-1	THF, 23	75	79	
7	(+)-6d	Au	PhMe, 23	<5	ND[c]	
8	(–)-6eanti	Au	CH_2Cl_2, 23	35		87 : 13
9	(+)-6esyn	Au	CH_2Cl_2, 23	26		18 : 82

[a] Catalyst: Au: JohnPhosAu(MeCN)SbF_6, Pt-1: $[(C_2H_4)PtCl_2]_2$, Pt-2: $PtCl_2$. [b] Anti/syn ratio, determined by ^1H NMR. [c] ND: Not determined.

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Enantioselective Addition of Pyrazoles to Dienes

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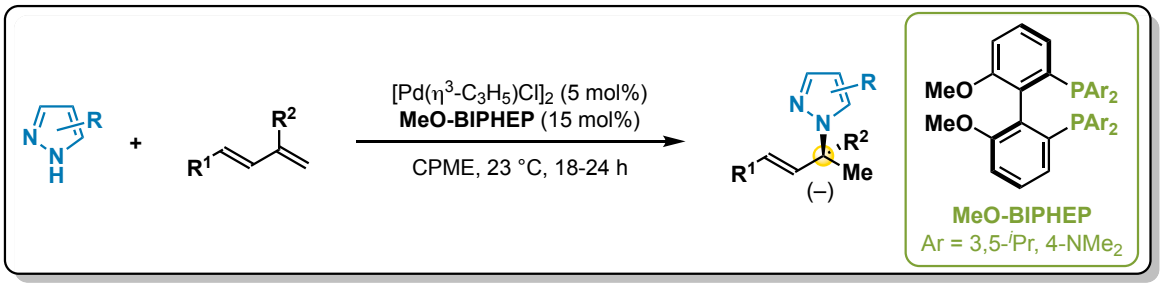
dongv@uci.edu



Nitrogen-containing heterocycles, such as pyrazoles, represent valuable scaffolds for drug discovery and thus remain an inspiration for synthetic methods. The direct addition of a pyrazole to an olefin represents an attractive and atom-economical approach for forging C–N bonds. We report the first enantioselective addition of pyrazoles to 1,3-dienes. Secondary and tertiary allylic pyrazoles can be generated with excellent regioselectivity. Mechanistic studies support a Pd(0)-catalyzed ligand-to-ligand hydrogen transfer (LLHT), distinct from previous hydroaminations. This transformation tolerates a wide range of functional groups and advances the hydrofunctionalization of dienes.

Jiu, A. Y.; Slocumb, H. S.; Yeung, C. S.; Yang, X.-H.; Dong, V. M. *Angew. Chem. Int. Ed.* **2021**, 60, 19660–19664.

Cobalt-Catalyzed Annulation via Hydrogen Atom Transfer: Expedient Access to Arene-Fused Cycloalkanes

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An annulation between allyl-substituted arenes and electron-deficient alkenes is described. Cobalt-catalyzed hydrogen atom transfer (HAT) facilitates tandem radical C–C bond formation and generates six-membered benzocyclic products that contain useful functional handles for downstream derivatization. The fate of the nascent alkyl radical depends on catalyst structure. The reaction proceeds under mild conditions, tolerates various functional groups, and provides interesting diastereoselectivity in some cases.

Designing New Strategy For C-H Functionalization using a Hypervalent Iodine Reagent

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Research in the field of C–H functionalization has modified the way chemists approach the synthesis of natural products and medicinally relevant molecules, leading to rapid and efficient derivatization. In particular, the transformation of the C-H bond into a C-X bond (where X= carbon, oxygen, or nitrogen) in heterocycles has gained interest due to their presence in medicinal chemistry.[1-3] However, despite recent advancements, various approaches for the hydroxylation of C–H bonds are carried in the presence of a transition metal.[4-6] Our research group is working on addressing this challenge by developing a novel C-H Hydroxylation strategy using a metal free reaction. We focus on using a hypervalent iodine reagent that should possess the ability to not only selectively break the benzylic C-H bond adjacent to azaheterocycle but can also favor C-H functionalization in heterocyclic substrates with multiple reactive positions. The current research efforts that will be presented focus on exploring substrate scope under this strategy.

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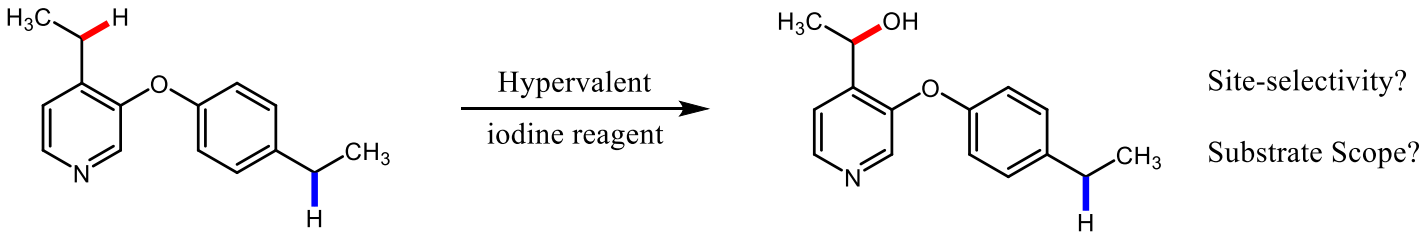

Transition-Metal-Free Functionalization of (Hetero)arenes via Highly Reactive TMP-iodonium(III) Acetates

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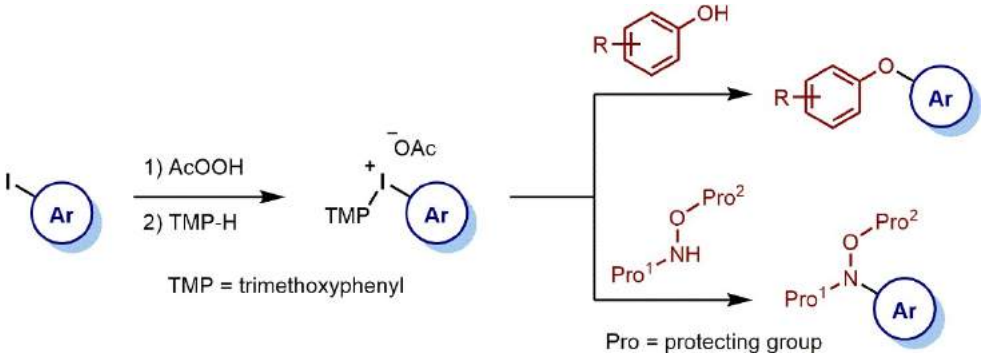
Diaryliodonium salts ($Ar^1Ar^2I^+X^-$) are hypervalent iodine(III) compounds, which are generally stable salts that serve as versatile arylating agents.[1] Various aryl-heteroatom and aryl-carbon bonds can be constructed under transition-metal- free conditions using the combination of diaryliodonium salts with the corresponding nucleophiles, such as alcohols, carboxylic acids, amines, amides, fluoride, and various carbon nucleophiles. Trimethoxyphenyl (TMP)- iodonium(III) salts, which contain a TMP group as one aryl group, lead to unified selective bond formation with another aryl group.[2] Our group recently established the efficient synthesis of TMP-iodonium acetates ($Ar(TMP)I^+AcO^-$) involving the generation of aryliodine diacetate using peracetic acid followed by condensation with 1,3,5-trimethoxybenzene.[3] Various phenol derivatives underwent arylation in the presence of TMP-iodonium acetate to afford the corresponding diaryl ethers in high yields.[4] Protected amines, such as *N*-methoxy sulfonamide derivatives, were also successfully arylated by using TMP-iodonium acetate with high reactivity. The present aryl- heteroatom bond formations were highly compatible with a wide variety of functional groups and would offer practical functionalization of (hetero)arenes.



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Strategies Towards the Synthesis of Heterocyclic Natural Products

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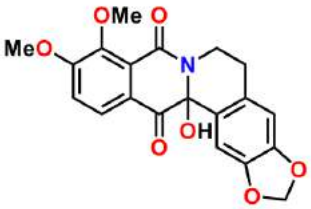
The strategic use of electron-rich substrates, such as silyl enol ethers and furans, to streamline the synthesis of isoquinoline and lycopodium alkaloids, as well as terpenoid lactones is presented. Electron-rich alkenes such as silyl enol ethers have tremendously impacted synthetic organic chemistry through the Mukaiyama aldol, Rubottom, Saegusa–Ito, and metal- catalyzed α-arylation reactions. Their use in C–H bond functionalization, however, is underexplored. Through oxidative Rh(III)/(IV)/(II)-catalysis, we implement silyl enol ethers in C–H functionalization, applying it to the concise syntheses of bioactive isoquinoline natural products. Our approaches to strained ring systems within sesquiterpene lactones and lycopodium alkaloids will also be described.



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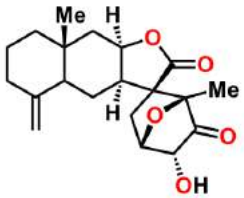
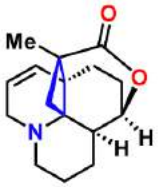


spiroalanfurantone

annotinolide A



annotinolide B

Modulators of Human and Bacterial Adenylate Cyclases Based on 7-Substituted 7- Deazapurine Analogues of Adefovir

Pavel Kraina,[a] Michal Česnek,[a] Eva Tloušťová,[a] Helena Mertlíková-Kaiserová,[a] Val J. Watts,[b]* Zlatko Janeba[a]*

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Acyclic nucleoside phosphonates (ANPs) possess a large spectrum of biological activities, however the most pronounced are their antiviral properties[1,2]. It was found, that bisamidate prodrugs of 7-halogenated 7-deazapurine analogues of adefovir exhibit a sub-micromolar activity against *Bordetella pertussis* adenylate cyclase toxin (ACT) in macrophage cell-based assays, and are able to selectively modulate some human adenylate cyclases (ACs)[3].

A number of over twenty new 7-substituted 7-deazapurine analogues of adefovir as bisamidate prodrugs were synthesised, and evaluated for their biological properties, as a continuation of an ongoing SAR study (Fig. 1). Moreover, two other types of prodrugs of the most potent derivative were prepared, to compare the prodrug masking group effects on the activity. Also, for evaluation on enzymatic assays, three most active compounds were prepared in their active metabolite form as phosphonodiphosphates.

Biological evaluation in macrophage cell-based assays revealed fourteen single-digit micromolar inhibitors of *B. pertussis* ACT. Many compounds also possessed low micromolar cytotoxic effects on some human carcinoma cells while being non-toxic for normal dermal fibroblasts. Tests on human adenylate cyclases revealed some selective modulators of AC1 and AC5 or of AC2.

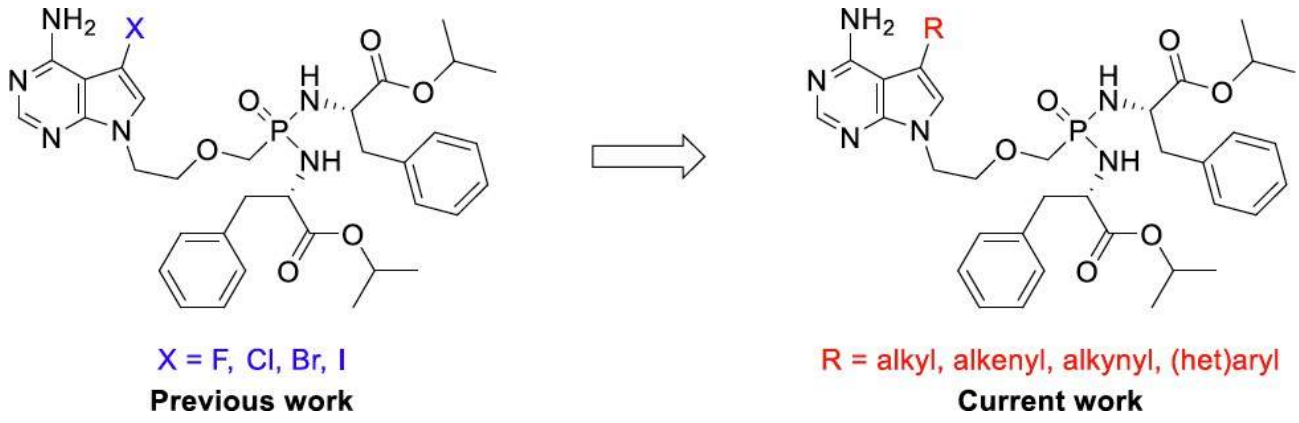

Figure 1. Overview of this work.

Acknowledgment: This work was supported by the Ministry of Education, Youth and Sports (MŠMT in Czech) in the program INTER-EXCELLENCE (project LTAUSA18086).

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Total Synthesis of a Macrocyclic PCSK9 Inhibitor

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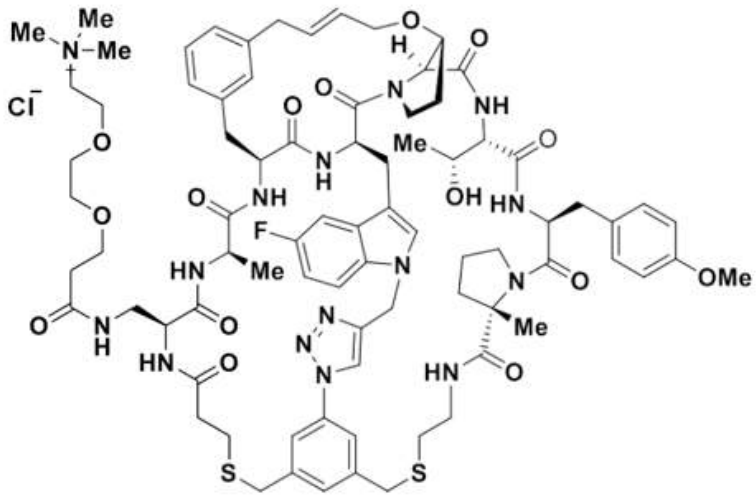
The discovery of the extremely potent, orally bioavailable proprotein convertase subtilisin-like type 9 (PCSK9) inhibitor **1** for the regulation of plasm LDL-chloesterol necessitated the need for further scaleup of this highly complex molecule. The initial synthesis involved solid phase peptide synthesis (SPPS) followed by cleavage and subsequent solution-based steps to arrive at milligram quantities of compound **1**. Recognizing that this approach would not deliver multiple gram quantities, a fully solution-based approach was required. Key aspects of these synthetic efforts leading to the gram-scale synthesis of compound **1** will be highlighted.



Guidelines for Predictable Remote Directed C(sp^2)–H Activation and their Application Towards Site-Selective Remote C–H Activation of Quinolines

Nelson Y. S. Lam, Zhoulong Fan, Kevin Wu, Keita Tanaka, Han Seul Park, Su Yong Shim, Daniel A. Strassfeld, Jin-Quan Yu*
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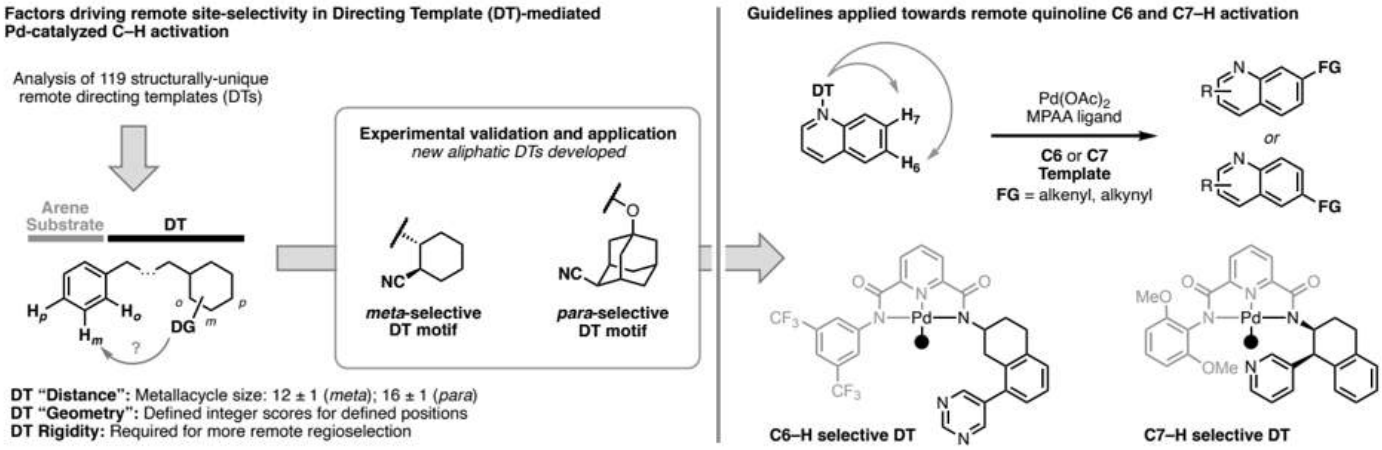
The ability to differentiate and selectively activate remote C–H bonds represents a perennial challenge in the field of Pd- catalyzed C–H activation. To this end, a "directing template" (DT) strategy has proven particularly promising, where selectivity is thought to be determined by the optimal spatial positioning of a reactive catalyst to a target C–H bond *via* a macrocyclophane-like transition state.[1] Despite its seemingly algorithmic origins, however, a systematic study on its requisite factors remain unelucidated. Here, we present an in-depth analysis of 119 structurally unique published DTs, revealing DT "distance", "geometry" and rigidity as key variables that determine selectivity at defined aryl positions. These findings are experimentally corroborated through the development of new aliphatic *meta* and *para*-selective DTs for electronically unbiased arenes.[2] Through judicious consideration of DT "distance", "geometry" and rigidity, further applications of these guidelines also facilitated the development of site-selective C–H activation and diverse functionalization at previously inaccessible C6 and C7 positions on quinolines and related heteroarenes. In doing so, this method now fully establishes a unified late-stage "molecular C–H editing" strategy to modify these pharmaceutically- relevant heterocycles at any given site and order.[3]



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3 Fan, Z.*; Chen, X.; Tanaka, K.; Park, H. S.; Lam, N. Y. S.; Wong, J.; Houk, K. N.; Yu, J.-Q. *Submitted*

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Lithium Enolate with a Lithium-Alkyne Interaction in the Enantioselective Construction of Quaternary Carbon Centers: Efficient Synthesis of Indole Alkaloids (+)-Goniomitine and (+)-Quebrachamine

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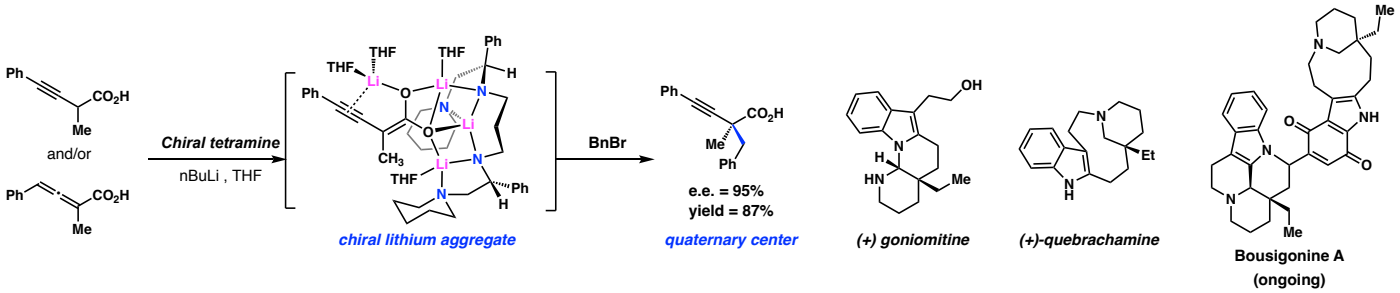
All-carbon quaternary stereocenters, a structural feature that can impart significant chemical and biological impact to a molecule, are critical to many synthetic and medicinal application. Consequently, catalytic and enantioselective approaches for constructing all-carbon quaternary centers, especially functionalized stereocenters, are highly desirable. On the other hand, the alkynyl group is an important building block in organic synthesis. Construction of alkyne substituted quaternary carbon stereocenters, coupled with subsequent functionalization of the alkyne group, would enable access to various functionalized quaternary stereocenters. A highly enantioselective, practical, and scalable technique for the assembly of alkyne-substituted quaternary centers from easy starting materials are highly desirable.

We report a method for direct enantioselective alkylation of 3-alkynoic and 2,3-alkendioic acids that form quaternary stereogenic centers using chiral lithium amide as noncovalent stereodirecting auxiliaries. The methods were effective in the alkylation of both 3-alkynoic acids, 2,3-alkendioic acids substrates with a broad range of heterocyclic and functionalized alkyl group substituents. Accompanying crystallographic studies provide mechanistic insight into the structure of well-defined chiral aggregates, highlighting cation-pi interactions between lithium and alkyne groups. The synthetic utility of this method was further demonstrated in the enantioselective total synthesis of (+)-goniomitine and formal synthesis of (+)-quebrachamine. Further application of this methodology in the context of bisindole alkaloid total synthesis (bousigonine A) is under investigation.



Electrochemical Synthesis of Pyrazoles and Pyrazolines via Iodine-mediated [3+2] Dipolar Cycloaddition

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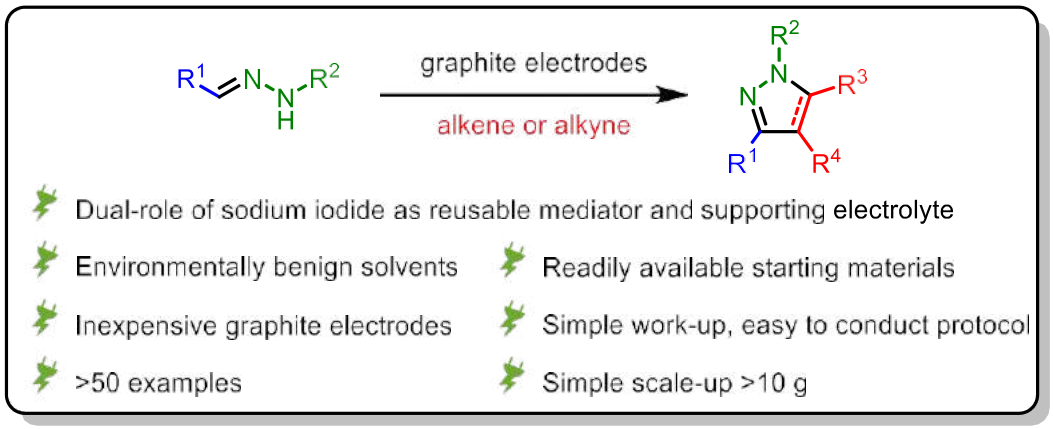

Highly biologically active pyrazole and pyrazoline derivatives are widely featured in pharmaceuticals as well as agricultural chemistry as pesticides, anti-cancerogenics or anti-microbiotics.[1] Conventionally, pyrazoles and pyrazolines can be accessed via [3+2] dipolar cycloaddition of nitril imines and dipolarophiles, requiring hydrazonoyl halo-genides as starting material, which are synthesized from hydrazones using hazardous chemicals like hypochlorite or NCS.[2] The electrochemical generation of 1,3-dipoles was established in our group for oxidation of aldoximes to the corresponding nitrile oxides, recently even for highly lipophilic betulin aldoxime.[3,4] We now developed a sustainable protocol for the electro-organic synthesis of 1,3,5-substituted pyrazoles and pyrazolines from readily available hydrazones and alkenes or alkynes. The reaction employs inexpensive sodium iodide as electrolyte as well as mediator, allowing for in situ formation of nitrile imines. Operating the reaction in a biphasic system using environmentally benign solvents allows for application of even highly sensitive alkenes such as styrene as dipolarophiles that would usually undergo side reactions or polymerization under electrolytic conditions. Thus, we herein present a protocol allowing for synthesis of pyrazolines from lab scale to 15-fold scale-up >10 g without any loss in yield.

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A Stereoselective Enzymatic Mannich Reaction

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Abstract

The Mannich reaction is widely used to construct C-C bonds in organic chemistry, but enzymatic Mannich reactions are rarely reported and there is no PLP-dependent enzyme known to catalyze Mannich reactions. Here, we report the discovery of the first example of a PLP-dependent Mannichase, LolT, catalyzing intramolecular Mannich reaction. LolT's cyclization and annulation activities allow us to access a variety of heterocyclic α,α-disubstituted α-amino acids, including pyrrolidine, piperidine, pyrrolizidine, indolizidine, quinolizidine, and azepane.

Diversification of C−F bonds in organofluorides and fluoropolymers by visible-light organic photoredox catalysis

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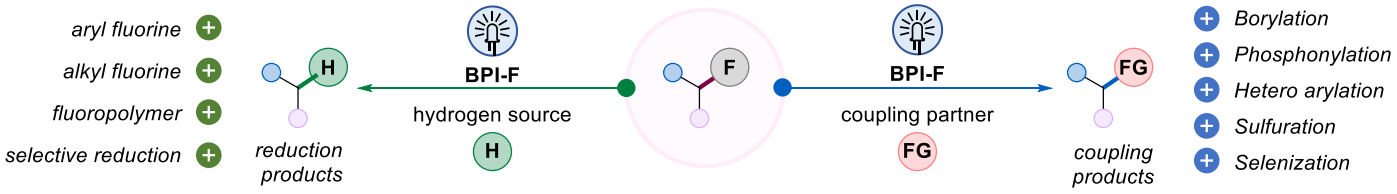
Organohalides are among the most fundamental and important building blocks in chemical synthesis because the halide serves as a versatile functional group for elimination, substitution and cross-coupling reactions. However, although organofluorides are the most commercially abundant organohalides, they are largely underutilized in chemical synthesis because the strong C−F bond severely limits reactivity. Here, we demonstrate that a strongly reducing visible-light absorbing organic photoredox catalyst can efficiently reduce C−F bonds to generate carbon centered radicals that can be intercepted for hydro-defluoronation and cross-coupling reactions. This system now enables use of organofluorides in chemical synthesis under mild reaction conditions through low loading of an organic photoredox catalyst.



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Progress Towards a Total Synthesis of Ceratinadin B

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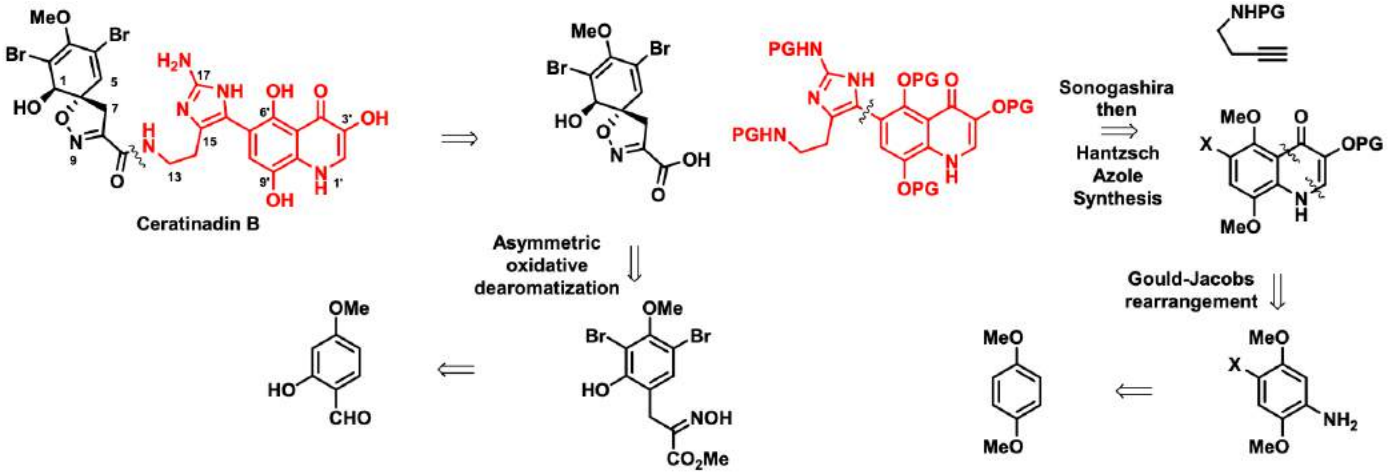
Ceratinadin B is tyrosine derived secondary metabolite isolated from marine invertebrates initially by the Bewley lab (*Oceanapia sp*. in an NIH sample repository)[1] and subsequently the enantiopode was reported by Kobayashi and co-workers (*Pseudoceratina sp*. (SS-214)).[2] This natural product is intriguing from two different perspectives. Structurally, it contains three different heterocyclic domains, including the spiro isooxazoline common to the tyrosine natural products and the unusual imidazolyl quinolone framework in an apparent fusion of two different marine alkaloids. The (1S,6R) natural product enantiomer has been demonstrated to possess potent activity as an inhibitor of mycothiol amidase, an enzyme found in mycobacteria, including the causative agent of tuberculosis. Mycothiol is used to detoxify cells very much in the same type of vein as glutathione is used in eukaryotes and is recycled through the action of mycothiol amidase. As a result, this molecule then may be potentially useful as adjuvant in the treatment of tuberculosis. The enantiomeric congener was shown to possess anti-fungal activity.



Our initial synthetic approach involved cross-coupling chemistry to construct the bis heterocycle but this was largely unsuccessful and so our approach evolved into one utilizing a Hantzsch-like synthesis of the aminoimidazole via the α-haloketone. The quinolone moiety is derived from the Gould-Jacobs rearrangement of the Meldrum's acid derivative. Disconnecting back to a haloarene and the corresponding known alkyne concludes the formation of the imidazolyl-quinolone. The spiro isooxaline is known and can be constructed via dearomatization processes which ultimately afford this fragment as a racemic mixture. While this moiety can be obtained as a single enantiomer, to date no catalytic process exists for its synthesis. Preliminary studies in our lab directed to a transition metal catalyzed asymmetric dearomatization suggest that this may provide a solution. This poster will describe the evolution of our approach to this molecule and the synthesis of advanced intermediates.

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Nucleoside Antibiotic Support Studies: Synthesis of 4'-(2-oxazolyl) Uridine Scaffolds

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The synthesis of new nucleoside-based antibiotics should benefit from the design of scaffolds which can bear the critical active components, but possess simpler molecular architecture as compared to that of the natural product. In efforts directed toward the synthesis of simplified analogues of phosphoglycosyl transferases (PGT's), a series of uridine-based compounds homologated at C-4' with an aryl-substituted oxazole ring were prepared. Conversion of 2', 3'-cyclopentylidene uridine to the corresponding 4'-carboxylate followed by Steglich ester coupling with a series of azidoalcohols gave the corresponding 4'-uridyl-derived azidoesters. The azido esters were cyclized to the substituted oxazolines using the Staudinger/aza-Wittig reaction and were directly carried on to the trisubstituted C-4'-uridyl oxazoles by treatment with DDQ or freshly-prepared nickel peroxide. The cyclopentylidine protecting group was easily removed in all cases by treatment with aqueous trifluoroacetic acid.

An Oxidation Study of Phthalimide-Derived Hydroxylactams and Lactams

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The oxidation of both *N*-substituted hydroxylactams and isoindolinones (phthalimidines) to the corresponding phthalimides using a catalytic iron/*tert*-butylhydroperoxide (TBHP) reagent system is detailed. The 2-substituted-3-hydroxyisoindolin-1-one (hydroxylactam) oxidation constitutes a rather straightforward hydroxyl→carbonyl group conversion while the latter process is a methylene→carbonyl transformation. The iron oxidant, prepared by the treatment of iron (III) chloride with trifluoroacetic acid, is used catalytically (10 mol%) in conjunction with TBHP which is the stoichiometric oxidant. For the hydroxylactam substrates, the oxidation system was effective in providing the corresponding phthalimides in isolated yields ranging from 41 to 88% within a reaction time of 24h. For the N-substituted isoindolinone to phthalimide conversions, the imide products were obtained in 76 to 96% isolated yield using the same catalyst/oxidant system. Comparisons were made with a recently-reported hydroxylactam oxidation system using nickel peroxide (NiO_2).[1] Substrates are included in the discussion which will demonstrate selectivity and protecting group tolerance.

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Development of a High Throughput Photochemical Flow Method for the Large-Scale Synthesis of *trans*-Cyclooctenes

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The synthesis of functionalized *trans*-cyclooctenes has been a major area of interest since the introduction of tetrazine ligation with *trans*-cyclooctenes in 2008.[1] *trans*-Cyclooctenes have become prominent in the field of biorthogonal chemistry due to their exceptional reaction kinetics with tetrazines.[2] Due to their widespread application in the fields of chemical biology, nuclear medicine, and material science[3], there has been a major drive to improve the throughput of the synthesis of *trans*-cyclooctenes. This work describes the photochemical isomerization of *trans*-cyclooctenes from *cis*-cyclooctenes using a high throughput photochemical flow method employing a custom reactor for the large-scale synthesis *trans*-cyclooctenes derivatives, as well as improved workup protocols. The custom flow reactor implements fluorinated ethylene propylene (FEP) tubing as an irradiation vessel in place of the previously utilized quartz flask, as well as an improved photocatalyst for Z-to-E isomerization. The ability to produce various *trans*-cyclooctenes faster, more efficiently, and on larger scale will greatly improve the efficiency and accessibility of these compounds.

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Strategic Use of Gold(I)-Catalysis for the Concise Synthesis of Polycyclic Indole Motifs

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Catalysis by electrophilic gold complexes represents an increasingly specific and powerful tool for the generation of molecular complexity and diversity.[1] The Lewis acidic and electron donating properties of electrophilic gold complexes provide an excellent opportunity for the efficient functionalization of carbon π-systems, particularly for alkynes and allenes by π-acid catalysis.[1-3] This reactivity mode is highlighted in the formal transfer of nitrene species onto gold(I)-activated carbon π-systems, where a key α-imino gold carbene intermediate is generated. Owing to the high reactivity of the α-imino gold carbene, the addition of nucleophiles to trap this species has been thoroughly studied.[4] We leverage this unique mode of reactivity by demonstrating the efficient and rapid access to polycyclic indole motifs that can be derived into structures relevant to natural products by the intermediate α-imino gold carbene (Figure 1). In this presentation, the total synthesis of brevianamide A and an approach to the synthesis of mitragynine pseudoindoxyl will be discussed.

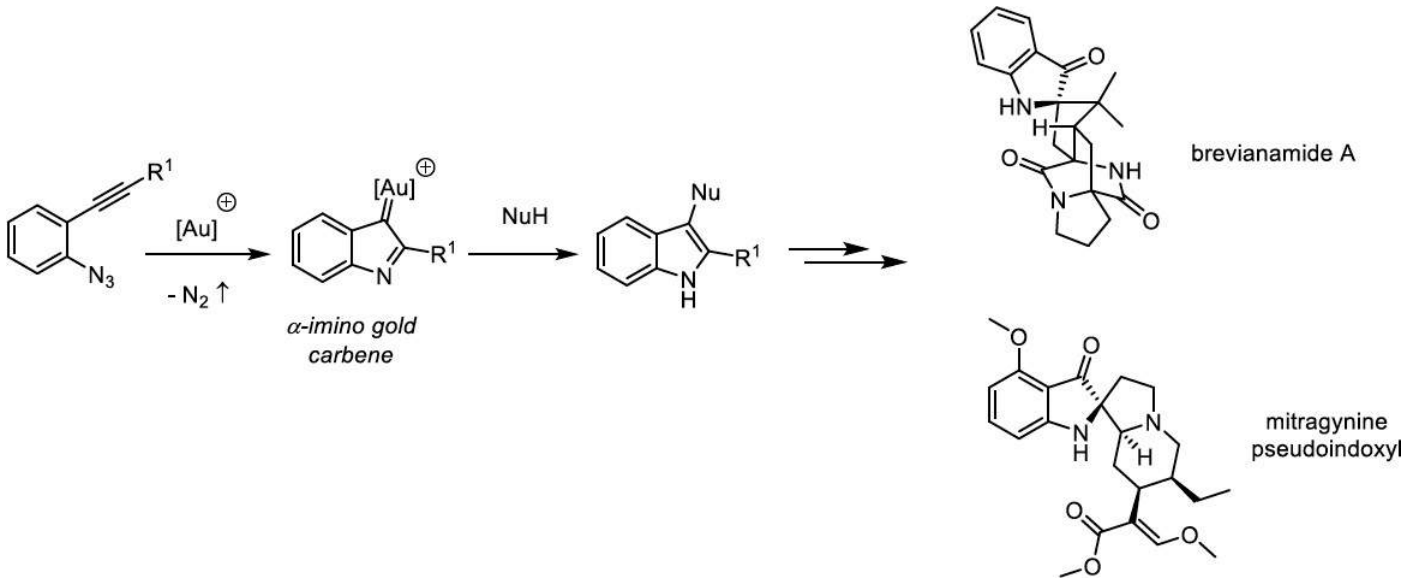

Figure 1. Synthesis of indole scaffolds utilizing gold(I)-catalysis

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Cyanine Phototruncation: From Mechanistic Analysis to Applications in Super Resolution Microscopy and Cell Tracking

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Certain fluorophores undergo photoconversion to a blue-shifted fluorescent molecule – a phenomenon known as photobluing. While broadly used cyanine dyes had been reported to provide photoblued products during certain microscopy experiments, the underlying chemical basis was not well understood. We examined the chemistry of cyanine photobluing and found that a product of pentamethine cyanine irradiation was the corresponding trimethine cyanine.[1] This is cyanine phototruncation reaction had little chemical precedent and involves the net excision of ethene diradical from the cyanine polymethine.

We first addressed the mechanistic question: are these products derived from intermolecular derivatization of previously reported photooxidative cleavage reactions or an unprecedented intramolecular rearrangement reaction? Our deuterium-labeling studies conclusively demonstrate that cyanine phototruncation is a fully intramolecular process. We also developed a detailed mechanistic framework to understand the multi-step sequence which was strongly supported by DFT calculations. Taking note of the critical role of electrophilic trapping in our mechanism, we conducted an extensive screen of over 300 conditions. These efforts identified a nucleophilic additive that improves the yield of conversion by 15-fold. We then applied phototruncation for in vitro DNA-PAINT (DNA-based points accumulation for imaging nanoscale topography) experiments that benefit from increased imager-strand concentration and, consequently, reduced acquisition time.[2]

Our recent efforts are aimed at optimizing the cyanine structure to improve phototruncation yield and enhance its utility under physiological conditions. An extensive screen of different cyanines has identified a substrate (3'-OMe-substitution on the polymethine chain) that dramatically improved the phototruncation yield by over 8-fold. Enabled by efforts that significantly improve the yield of cyanine phototruncation, we apply this chemistry to cell-tracking applications and employ it to examine immune cell migration from the tumor to the tumor draining lymph nodes (TDLNs). These studies provide a quantitative means for the temporal characterization of the tumor-derived immune-cell population in the TDLN.[3] Further efforts are currently underway to develop antibody-targeted variants of the 3'-OMe-substituted probes to characterize other dynamic migration processes in an antigen-specific manner.

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Fluorocyclization via I(I)/I(III) catalysis: a concise route to fluorinated oxazolines[1]

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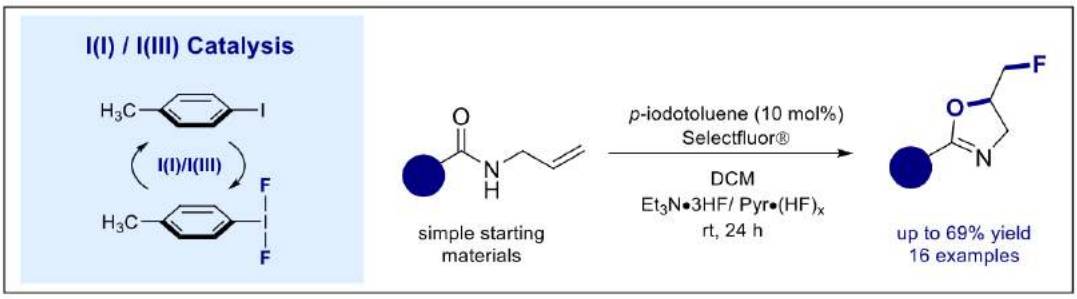

Given the importance of heterocycles in drug design,[2] efficient routes to access fluorinated scaffolds would be strategically advantageous to provide a rapid entry into important bioisostere classes and benefit from the unique physicochemical properties induced by fluorine incorporation.[3] This study reports the fluorocyclization of readily accessible *N*- allylcarboxamides enabled by iodine (I)/(III) catalysis to construct 2-oxazolines, a heterocycle prevalent within natural products[4] augmented with a fluoromethyl group. This serves to expand the current portfolio of fluorinated drug modules for drug discovery through the application of a catalytic system that offers mild conditions and features a broad substrate tolerance. The incorporation of several aryl groups containing electron rich, disubstituted or aliphatic motifs is presented, as well as the hydrolysis of the oxazolines products to the corresponding fluorohydrin. Crystallographic analysis reveals a highly preorganised structure with a *synclinal* relationship between the C(sp^3)–F bond and the C(sp^3)–O bond of the ring, demonstrating the presence of the stereoelectronic fluorine *gauche* effect.

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Innovations on the Process Development of a Tri-Sugar siRNA Ligand

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Olpasiran is a small interfering RNA (siRNA) in Amgen's hybrid modality portfolio that lowers lipoprotein(a), also known as Lp(a). It is being investigated for the treatment of atherosclerotic cardiovascular disease currently under Phase 2 clinical trials. The drug substance is an siRNA duplex (~15 kDa) conjugated to a small molecule targeting ligand, the ligand is a tri-antennary N-acetylgalactosamine molecule (tri-GalNac, ~2 kDA). The synthetic strategy and process development of intermediates in this challenging tri-GalNAc synthesis is the topic of this poster abstract.

An efficient three-step synthesis of a key intermediate in the tri-GalNac route will be presented, along with challenges associated with a triple glycosylation reaction and early investigations into leveraging biocatalysis for triple aminolysis. Additionally, the process development of an amide coupling reaction to install a C8-PEG-fragment will be detailed. Kinetics analysis was performed to characterize the mechanism for a key impurity formation which led to the engineering design of a controlled continuous-pumped slurry addition. A highly optimized aqueous extraction protocol was developed, taking advantage of this late-stage intermediate's orthogonal aqueous solubility, to purge a critical impurity.

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Tunable photochemical properties in 5-phenylazopyrimidines: From solution to solid state

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Heteroaryl azo compounds consist of heteroaromatic and benzene moieties connected with the azo group. Benzothiazoles, pyrazoles, pyridines or pyrimidines can serve as the heterocyclic part of the azo molecule. Such derivatives undergo reversible *trans-cis* isomerization upon illumination by light. The formed metastable *cis* isomer is characterized by nonplanar structure and different physicochemical properties (e.g. dipole moment), compared to the *trans* isomer. Stability of the *cis* isomer is significantly dependent on ambient conditions. Moreover, big structural change can make more difficult photoisomerization in the solid state, due to lack of free space between arranged molecules.

We prepared three classes of novel 5-phenylazopyrimidines, differing in a number of hydrogen bond donors in the neighbouring position to the azo moiety, which leads to a formation of strong intramolecular hydrogen bonds (IMHBs). We used a unique combination of advanced experimental and theoretical methods to study their photochemical and physicochemical behavior, namely 1) NMR with *in situ* irradiation, 2) optical spectroscopy, 3) scanning electron microscopy, and 4) DFT calculations. We were able to tune thermal relaxation rate and irradiation wavelength by an introduction of suitable substituents, where IMHBs as well as "push-pull" character destabilize the *cis* isomer significantly (**Fig. 1**)[1,2]. In compounds with two different hydrogen bond donors, unique photoswitchable IMHBs were discovered[3]. Such derivatives can form two stable rotamers (A/B, both as *trans* photoisomers). Furthermore, we were able to prove that 5-phenylazopyrimidines undergo photoisomerization in the solid state[4].

5-Phenylazopyrimidines represent versatile photoswitches with a wide range of tunability of their photochemical properties, which makes them eligible candidates for application in many fields, e.g. as smart materials, as a storage of data or as a tool in photobiology.

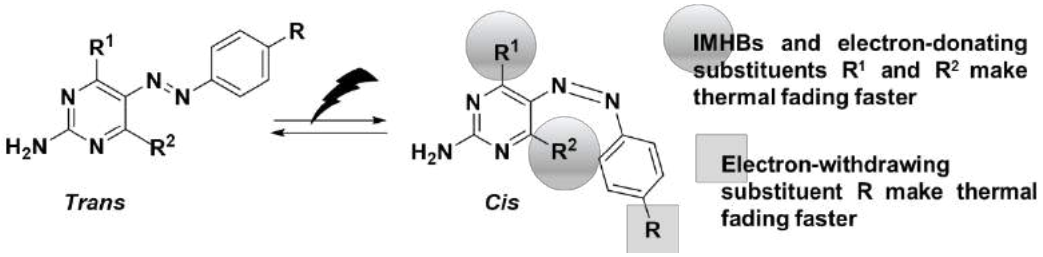

Fig. 1

This work was supported by the IOCB CAS (RVO 61388963).

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Catalytic Activation of Biorthogonal Chemistry Using Thermal Catalysis

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Rapid bioorthogonal reactions are a useful tool for drug delivery and assembly. Previously our group has established small molecule photocatalysts that can be used to promote the oxidation of dihydrotetrazines to tetrazines which subsequently participate in rapid bioorthogonal chemistry. In the absence of light, peroxidase enzymes can also be used to catalyze oxidation. This work explores the first small molecule thermal catalyst that can activate a bioorthogonal reaction with temporal control. The catalyst is able to oxidize an unreactive dihydrotetrazine to a reactive tetrazine which can conjugate to an electron rich dienophile in an inverse electron demand Diels Alder mechanism. These reactions are successful in conjugation for a protein substrate in vitro. Further, the thermal catalytic activation of dihydrotetrazine can label on the cell surface of mammalian cells. The stepwise assembly is advantageous for cell permeability and has the potential to create multivalent molecules with spatial control at the organism level.

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Stereocontrolled Access to Quaternary Centers by Birch Reduction/Alkylation of Chiral Esters of Salicylic Acids

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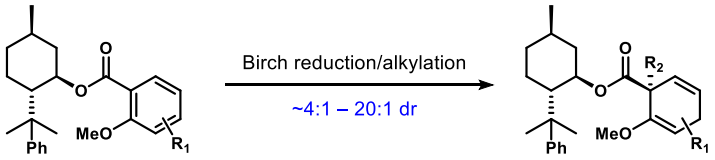

Herein is described a diastereoselective Birch reduction/alkylation using (–)-8-phenylmenthol as a chiral auxiliary to establish quaternary centers on salicylic acid derivatives. The method is compatible with a variety of alkyl electrophiles and provides synthetically useful chiral cyclohexadienes. Investigation of sterically and electronically demanding substrates provided an insight into the scope of this transformation. The chiral auxiliary can be removed via reduction with $LiAlH_4$ and recycled in subsequent reactions. The resulting products contain multiple functional handles which allow further derivations to synthetically challenging targets.

Efforts Towards the Synthesis of Neoamphilectane

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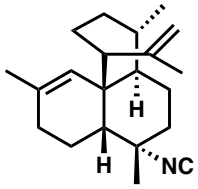
Our efforts towards the synthesis of neoamphilectane, a rare isocyanoterpene natural product, involve a concise synthesis of the spirocyclic core using a Robinson annulation and an acyl radical cyclization. Other key reactions in our sequence include a reductive deoxygenation of an oxalate and an enolate mediated epoxide-opening cyclization. Additionally, we have observed numerous counterproductive bicyclization reactions whose products lend themselves to interesting isocyanide containing analogs. Current work is focused on a key carbon–carbon bond fragmentation which will serve as a platform for the exploration of a late-stage isocyanation to complete a synthesis of neoamphilectane.



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Direct Nucleophilic Substitution of Alcohols Using an Immobilized Oxovanadium Catalyst

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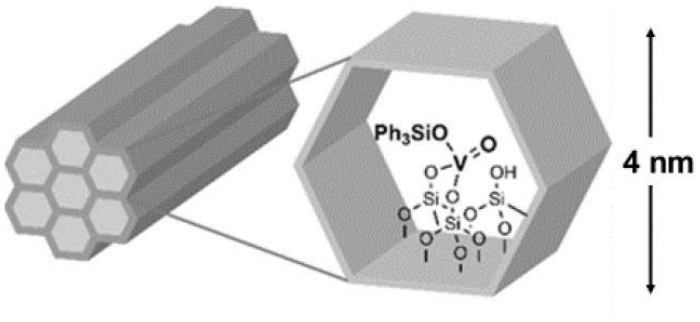
[Background & Aim]

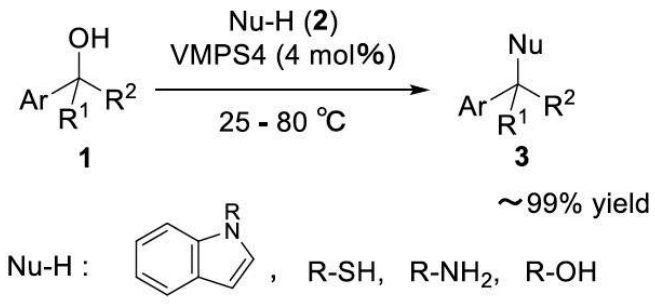
Direct substitution of alcohols is considered as one of the most important challenges for the development of green engineering in pharmaceutical and chemical industries and has been mainly studied using Brønsted acids, Lewis acids, and transition metal catalysts. However, the strong Lewis acidity of these catalysts often results in poor functional group tolerance. We recently reported a mesoporous silica-supported oxovanadium catalyst (VMPS4) in which oxovanadium was covalently bound on the surface of the mesoporous silica pore of 4-nm inner diameter (Figure 1).[1] VMPS4 catalyzes racemization via a cationic intermediate generated by the C−O bond cleavage in the substrate alcohols. Considering this, we have applied VMPS4 to the direct nucleophilic substitution of alcohols .

[Results]

The reaction of alcohols **1** and nucleophiles **2** effectively proceeded in the presence of 4 mol% VMPS4 under an argon atmosphere at room temperature to 80 ºC to give the desired compounds **3** in up to 99% yield (Scheme 1). Under the optimal conditions, VMPS4 exhibited highly chemoselective activation of alcohol **1** in the presence of an acetoxy group, which has been hardly attained by the known catalysts for the direct substitution of alcohols. Also, VMPS4 was recovered by simple centrifugation and reused over six cycles with maintaining its catalytic activity. [2]

Figure 1, The structure of VMPS4





Shceme1, Direct nucleophilic substitution of alcohols.

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Total synthesis of pseudouridimycin

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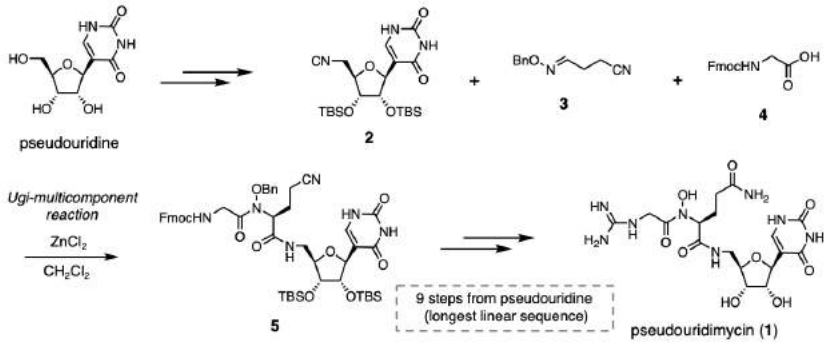
Pseudouridimycin (**1**), which is a nucleoside antibiotic isolated from *Streptomyces* species[1], possesses potent antibacterial activity against both gram-positive and gram-negative bacteria including drug-resistant strains. Biochemical and structural analysis showed that **1** selectively inhibits bacterial RNAP and binds within the active site of the polymerase, which is distinct from the rifamycin allosteric site. In addition, it exhibits no cross-resistance with the rifamycins and displays no cytotoxicity. Collectively, these properties indicate that **1** is a promising lead for antibacterial drug development.

We have accomplished the total synthesis of **1** featuring an unusual oxime Ugi-type multicomponent condensation[2] to simultaneously construct the dipeptide moiety of **1**. This key multicomponent reaction with **2**, which was easily prepared from pseudouridine in five steps, **3**, and **4** was successfully achieved in the presence of ZnCl2 in CH2Cl2. This strategy produces the non-proteinogenic *N*-hydroxyamino acid residue *in situ* from simple building blocks with simultaneous linking to substituents at the *C*- and *N*-termini in a single step. The application of this key reaction allowed us to synthesize **1** in the longest linear sequence of nine synthetic steps from pseudouridine. It is the shortest synthesis compared to the previous reports[3,4]. Additional two steps to modify the dipeptide moiety in the late stage enable us to facilitate the derivatization of **1**, followed by the global deprotection process. This short-step strategy can be applied to prepare a variety of pseudouridimycin analogs.



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Oxidative Amination of Enolates Utilizing (Diarylmethylene)amino Benziodoxolones

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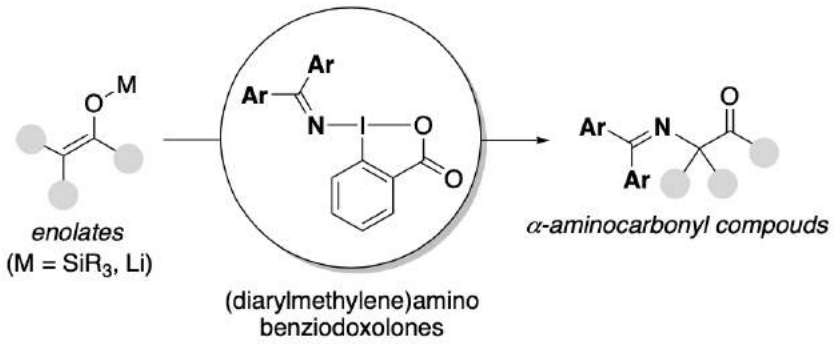
α-Amino carbonyl compounds are ubiquitous in natural products, pharmaceuticals, and agrochemicals. α-Amination of carbonyl compounds is one of the most straightforward approaches for the synthesis of such valuable molecules, and commonly used methods involve the electrophilic amination of enolates and enamines with azodicarboxylates, nitrosoarenes, and iminoiodanes, etc. as an aminating reagent. Despite great advances in this type of reaction, a general problem is that the deprotection process for accessing the target α-amino carbonyl compounds requires multistep reactions and relatively harsh conditions.

Benzophenone imine derivatives are attractive compounds in organic synthesis because they undergo facile hydrolysis and hydride reduction, providing primary amines and diarylmethylamines. On the basis of this background, we envisioned that hypervalent iodine reagents containing (diarylmethylene)amino groups would offer a promising tool for oxidative amination to deliver modifiable amine products. Herein, we report the syntheis of (diarylmethylene)amino benziodoxolones, and their use in the oxidative amination of enolates such as silyl ketene acetals[1] and lithium enolates. This new protocol can provide various easily modifiable α-amino carbonyl compounds from esters, amides, and ketones. Mechanistic investigations indicate that the oxidative amination proceeds in a radical pathway through the formation of a nitrogen-centered radical generated through a single-electron transfer between an enolate and the hypervalent iodine reagent. The developed amination reaction features transition-metal-free conditions and simple operation.



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Syntheses of Lissoclimide Analogues and the Investigation of Novel Halogen–π Interactions

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Lissoclimides are succinimide-bearing labdane diterpenoids that exhibit potent cytotoxic activity against several cancer cell lines, which are attributed to their ability to inhibit translation. Herein, we report our successful efforts towards the semi-syntheses of lissoclimide analogues to gain a deeper understanding of the structural basis for their translation inhibition via interaction with the ribosome. The analogues are designed to probe a novel halogen–π interaction that was discovered through collaborative structural biology studies of chlorolissoclimide. Featuring a highly selective C–H functionalization of sclareolide and Evans-aldol-based succinimide introduction, we generated multiple lissoclimide analogues for collaborative studies, including X-ray co-crystallography with the 80s eukaryotic ribosome. Through this work, we anticipate learning more about the novel halogen–π interaction with neighboring guanine residues in the ribosome E-site, in the hope of finding other applications for this attractive force.

Versatile Chemistry of KOH-DMSO

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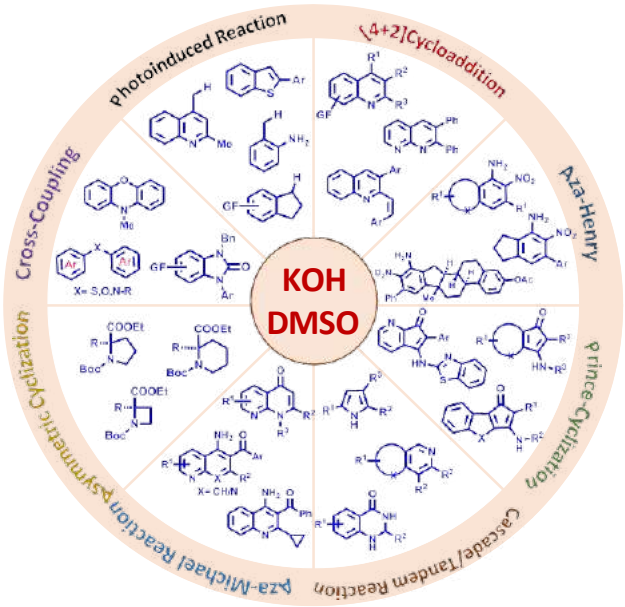

Hetero-atom containing small organic molecules have gained significant attention because of their presence in natural products, drug molecules, pharmaceuticals, agricultural chemicals, pesticides, organic materials, and solar cells. The KOH-DMSO mediated organic transformations[1] are the paradigm of contemporary, sustainable, green chemistry as it is an inexpensive, economical, non-toxic, waste-free, and environmentally benign process of fundamental simplicity. As an exemplar of green solvents along with the combination of alkali base, KOH-DMSO amalgamation revealed extraordinary basicity of about *pKa* 30–32 that was suggested to result from a synergism of two bases. This distinct property of the reagent makes it superior to the other available methods that involve the use of transition-metal catalysts. The KOH/DMSO permutation is a robust catalytic system that has witnessed significant progress in achieving nucleophilic addition/substitution, Diels Alder, [4+2] cycloaddition,[2] Aza-Henry,[3] prince cyclization,[4] cascade/tandem, aza-Michael, asymmetric cyclizations; coupling, and photoinduced reactions. This extraordinary chemistry is expected to find a versatile application in organic synthesis [5-7] and can fulfill an important role in the assembly of a useful class of interesting organic compounds.

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New Methods for Heterocycle Functionalization in the Context of Drug Discovery Programs at Janssen La Jolla

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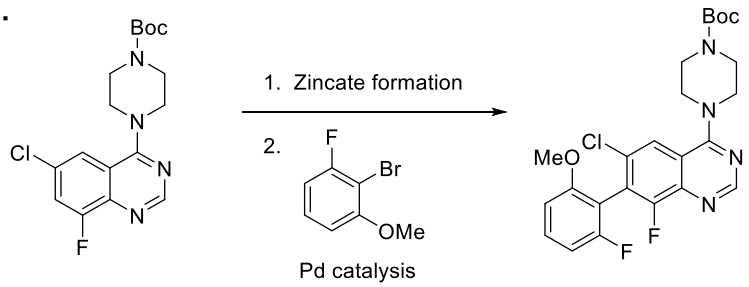
Janssen's "Discovery Process Research" team exists at the interface between Medicinal Chemistry and Process Chemistry. In addition to traditional roles of route development and API delivery to support early-stage toxicological profiling, the group is also charged with developing new synthetic approaches in the lead-optimization space to accelerate the design-make-test cycle. The selective functionalization of heterocyclic molecules in the presence of other potentially reactive moieties has been a recurring area of interest. Three recently developed methods will be presented: (**a**) selective metalation of functionalized quinazolines, (**b**) radical alkylation of heteroaryl halides, and (**c**) diastereoselective radical addition to heteroaryl sulfinimines.

a.



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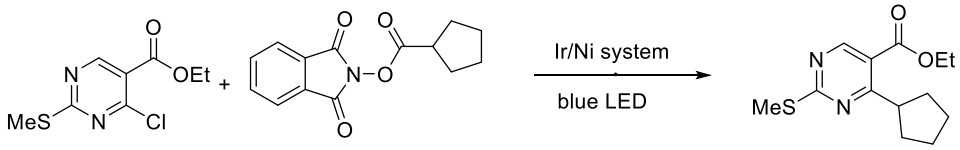

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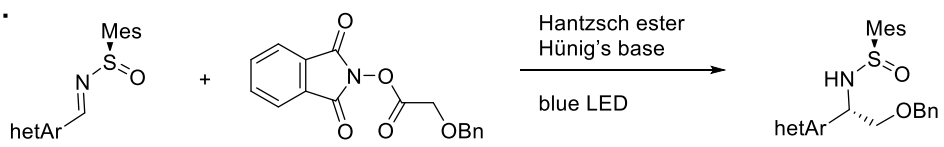

Intramolecular C(sp^3)–H Amination to Construct Chiral *N*-Heterocycles Enabled by Engineered Cytochrome P450 Enzymes

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Novel biocatalytic transformations are ideal for re-inventing traditional synthetic routes due to their high efficiency, selectivity, and sustainability. The rapid development of biotechnology in the past decades has led to the blooming of biocatalysis where enzymes are engineered for various useful and facile biocatalytic reactions. However, natural functions of enzyme are merely the tip of the iceberg. Due to demand for versatile transformations in chemical industry, one long-standing goal in biocatalysis is to develop new-to-nature enzymatic functions.

N-heterocycles are among the most significant structural components of pharmaceuticals reflecting their vital role in modern drug discovery and design. One attractive method to prepare *N*-heterocycles is intramolecular nitrene C(sp3)–H insertion. However, achieving these reactions with good regio- and enantioselective control has proven to be challenging. Herein, we report an enzymatic platform for enantioselective intramolecular C(sp3)–H amination with access to chiral pyrrolidines and indolines using alkyl and aryl azides as nitrene precursors. This biocatalytic process can aminate both benzylic and aliphatic C(sp3)–H bonds affording *N*-heterocycles with good activity and selectivity (up to 2280 total turnover number (TTN) and 97:3 *e.r.*) and can be performed on preparative scale. Enzymatic cascade reactions based on *N*-heterocyclic products is also identified demonstrating enzymes' outstanding capability to construct molecules in high complexity.

Iridium-Catalyzed Isomerization/Cycloisomerization/Aromatization of *N*-Allyl-*N*-sulfonyl-*o*-(λ^1-silylethynyl)aniline Derivatives to Give Substituted Indole Derivatives

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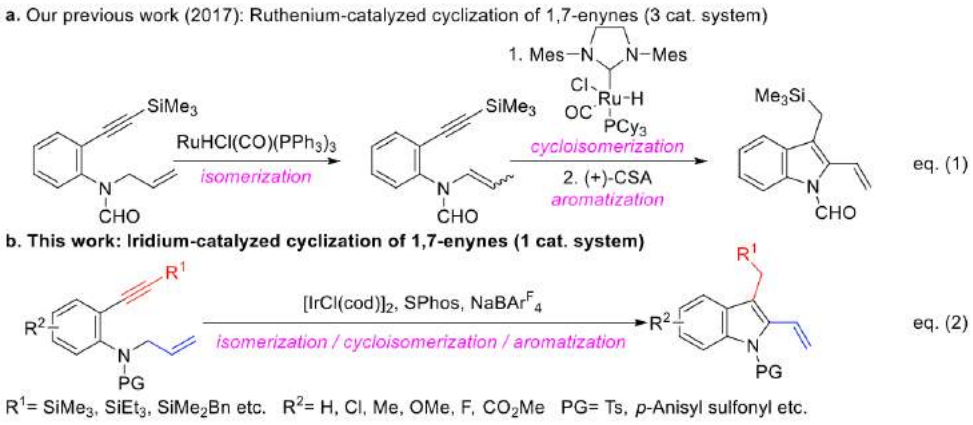
The substituted indole structure is a widespread heterocyclic skeleton in natural products, optoelectronic materials, and pharmaceutical agents. Recently we have reported Ru-catalyzed cyclization of 1,7-enynes involving an enamide and a silyl alkyne **[eq. (1)]**.[1] Although it is an atom-economical and efficient method to yield 2-vinyl-3-(silylmethyl)indoles, which have chemical transferability, two kinds of Ru catalysts and one more extra camphorsulfonic acid for aromatization are necessary. To solve these problems, we developed a one-iridium-catalyst system that transforms *N*-allyl-*N*-sulfonyl-*o*-(λ^1-silylethynyl)aniline derivatives to the corresponding substituted indole derivatives via isomerization/cycloisomerization/aromatization. This strategy provides a straightforward synthetic approach to a series of valuable indoles having vinyl and silylmethyl groups at the 2- and 3-positions **[eq. (2)]**.[2]



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Origins of *Endo* Selectivity in Diels–Alder Reactions of Cyclic Allene Dienophiles

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Strained cyclic allenes, first discovered in 1966 by Wittig and co-workers,[1] have recently emerged as valuable synthetic building blocks.[2] A diverse range of stereochemically-rich, heteroatom-containing products can be accessed via highly *endo* selective Diels–Alder cycloadditions to strained cyclic allenes. Previous experimental investigations, and computations reported here, demonstrate that the Diels–Alder reactions of furans and pyrroles with 1,2-cyclohexadiene and oxa- and azaheterocyclic analogs proceed with *endo* selectivity. This *endo* selectivity gives the adduct with the allylic saturated carbon of the cyclic allene *endo* to the diene carbons. The selectivity is very general and useful in synthetic applications. Our computational study establishes the origins of this *endo* selectivity.[3] We analyze the helical frontier molecular orbitals of strained cyclic allenes and show how secondary orbital and electrostatic effects influence stereoselectivity. The LUMO of carbon-3 of the allene (C-3 is not involved in primary orbital interactions) interacts in a stabilizing fashion with the HOMO of the diene in such a way that the carbon of the cyclic allene attached to C-1 favors the *endo* position in the transition state. The furan LUMO, allene HOMO interaction reinforces this preference. These mechanistic studies are expected to prompt the further use of long-avoided strained cyclic allenes in chemical synthesis.

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Subcellularly-Localized Photocatalysts and Far-Red Light Enable Catalytic Bioorthogonal Uncaging in Live Cells

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Bioorthogonal catalysis is an emerging field with applications in drug delivery and protein target identification. Most systems involve the expression of a non-native enzyme for the catalytic generation of biologically relevant compounds. However, targeted small molecule bioorthogonal catalysts would avoid the need for non-native expression. Furthermore, far-red photocatalysts allow for the use of long wavelength light as an external trigger. This work describes the localization of small molecule far-red photocatalysts for targeted uncaging of a biologically active compound. A dihydrotetrazine (DHTz) conjugated to a vinyl ether was used as a stable photocage for the tubulin disrupting compound nCA4. Once oxidized to tetrazine via far-red photocatalysis, an intramolecular Diels- Alder reaction occurs leading to uncaging of nCA4. In cellular studies, photocatalysts were localized to the nucleus or tubulin to observe uncaging. Cells treated with the DHTz photocage without photocatalyst or light demonstrated organized and elongated tubulin structures similar to the vehicle, whereas in the presence of both photocatalyst and light, cells exhibited disorganized tubulin structures similar to the free nCA4 control. Localized uncaging was further confirmed using ascorbate as a tool to quench extracellular photocatalysis. Overall, this work demonstrates the first photocatalytic reaction for directed uncaging at the organelle level in cells.

Total Synthesis of (2*R*)-Hydroxynorneomajucin, a Norsesquiterpene from *Illicium Jiadifengpi*

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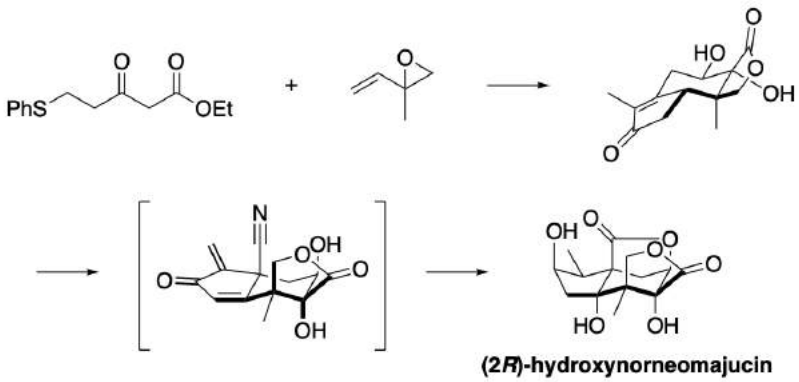
Illicium sesquiterpenes have garnered significant interest from synthetic chemists owing to their highly oxidized structures and intriguing biological activity. We will discuss the total synthesis of (2*R*)- hydroxynorneomajucin (HNNM), a norsesquiterpene derived from the *Illicium Jiadifengpi* plant.[1] This natural product displays neurotrophic activity. Small molecule neurotrophins are of interest because they have potential as therapeutic agents in neurodegenerative diseases. Key steps of our synthesis include a Tsuji–Trost asymmetric allylic alkylation, a Pauson–Khand cyclization, a Nagata hydrocyanation, and an unusual palladium-promoted oxidation. A simple sequence of reductions and a Mukaiyama hydration introduce the A-ring substituents with the correct configurations. The chemical synthesis we will present provides access to this unusual norsesquiterpene natural product.



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A [2+2] Photocycloaddition–Cyclobutane Fragmentation Approach to Annulated Pyridones

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Pyridones compose the core of several biologically active nature products and pharmaceuticals. Annulated pyridones have been underexplored in medicinal chemistry as the direct functionalization of pyridones remains a synthetic challenge. We have been developing an oxidative cyclobutane fragmentation initiated by *N*-acyliminium formation as a new strategy toward annulated pyridones. The requisite cyclobutanes are easily accessible in two steps from 2-hydroxypyridine *via N*-alkylation and triplet sensitized [2+2] cycloaddition using visible light. We have validated our approach with the successful generation of *N*-acyliminium ions using an organic photocatalyst along with an oxidant. Progress towards the cyclobutane fragmentation will be discussed.

Gas-phase Approaches to Generation of 1,4-Thiazine

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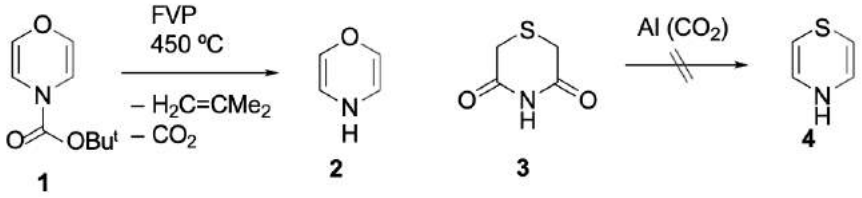
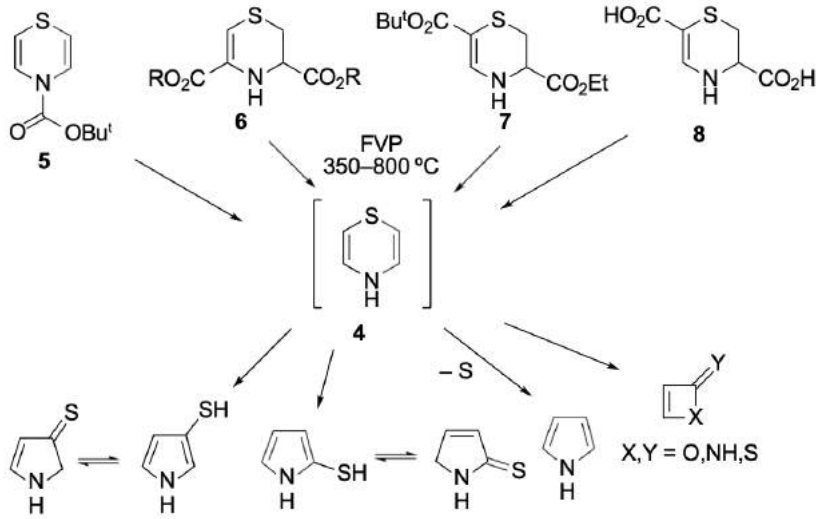
Some years ago we described formation and spectroscopic characterisation of the parent 1,4-oxazine **2** by flash vacuum pyrolysis (FVP) of precursor **1** at 450 °C.[1] Among all the possible isomeric parent 6-membered ring fully unsaturated heterocycles with one group 15 and one group 16 atom, this is so far the only example. An early report[2] of generation of 1,4-thiazine **4** by gas-phase deoxygenation of imide **3** over aluminium powder in a flow of CO_2 has never been reproduced and we believe it to be erroneous.



We now describe new attempts to generate **4** from FVP of a range of precursors including **5**, **6**, **7** and **8**. The latest evidence for the formation of **4** will be presented as well as identification of other heterocyclic products thought to be formed by its isomerisation or fragmentation.



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Dihydrotetrazine oxidation by a genetically encodable catalyst for rapid turn-on of bioorthogonal chemistry intracellularly

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The tetrazine-*trans*-cyclooctene ligation is the fastest bioorthogonal reaction to date with a second order rate constant up to $k_2 = 10^6\ M^{-1}s^{-1}$ with strained *trans*-cyclooctene (s-TCO) derivatives, far surpassing other biorthogonal reaction kinetics[1]. While electron-deficient tetrazines increase the rate of the tetrazine-TCO ligation, they are only suitable as chemical probes instead of reporters. DHT is a stable precursor to tetrazine with a longer half-life in aqueous conditions. The Fox group developed a system to induce the catalytic oxidation of DHT to tetrazine in situ, enzymatically by horseradish peroxidase (HRP) or by photooxidation in the presence of a photocatalyst and light for subsequent biorthogonal chemistry with TCO[2]. While HRP can enzymatically activate tetrazines, HRP is inactive when expressed in the reducing, calcium scarce mammalian cytosol which limits applications of this enzymatic system to mammalian endoplasmic reticulum and in vitro environments. APEX2 is an engineered ascorbate peroxidase that is active in reducing environments such as the mammalian cytosol and can oxidize a variety of aromatic molecules when H_2O_2 is present[3].We have developed a new enzymatic system that oxidizes DHT to tetrazine by utilizing an engineered ascorbate peroxidase (APEX2). We have shown that APEX2 can oxidize a wide range of DHT substrates, have elucidated the hydrogen peroxide independent enzymatic mechanism, and have conducted site-directed mutagenesis to afford an APEX2 variant that is more active towards DHT oxidation. We have also shown that APEX2 can oxidize a series of DHT prodrug scaffolds where upon oxidation, an intramolecular inverse-electron demand Diels-Alder (IEDDA) reaction occurs to release a cytotoxic drug. This prodrug scaffold has been adapted to develop a fluorogenic DHT where upon oxidation by APEX2, a free fluorophore is released resulting in the turn-on of fluorescence. We plan to utilize APEX2 to catalytically induce spatially controlled biorthogonal chemistry for imaging of proteins and cellular compartments and decaging of prodrugs for drug delivery in different areas of the mammalian cell.

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Synthetic Strategies Toward the Total Synthesis of (–)-Enterocin

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With the increasing emergence of drug-resistant bacteria, new antibiotics are in urgent demand. As part of a broader program aimed at the synthesis of antibiotic natural products, we initiated a chemical synthesis of the natural polyketide (–)-enterocin, which is bacteriostatic against both gram-positive and gram-negative bacteria. A strategy featuring a radical-polar crossover reaction as an annulation step to quickly construct the [3.2.1] bicyclic core of enterocin is detailed. Initial studies have validated the feasibility of the two key C–C bond forming steps in a sequential fashion, and will guide the future development of the radical-polar crossover cyclization. The development of an efficient and general approach will allow a comprehensive evaluation of the potential for caged polyketides to serve as potent antibiotics.

Mechanistic Study of the Activation of Rapid Bioorthogonal Chemistry via Photocatalytic Oxidation of Dihydrotetrazines to Tetrazines

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Bioorthogonal reactions are rapid and selective chemical reactions that can occur efficiently without interfering with endogenous biological activity. The fastest known bioorthogonal reaction is the tetrazine ligation, an inverse electron demand Diels-Alder reaction between the electron-poor tetrazine and electron-rich dienophile trans- cyclooctenes (TCO). A series of photocatalysts have been shown to promote the oxidation of dihydrotetrazine (DHTz) to tetrazine products, providing a biologically compatible method for activation of the tetrazine (Tz) ligation with spatiotemporal control. This photocatalytically inducible version of tetrazine ligation has been carried out in live mice and in live cells with suborganelle level spatial control. While several dyes have been developed as photocatalyts, the mechanism of photocatalysis is not well understood. This work examines the mechanism of DHTz oxidation using Silicon-rhodamine (SiR) and fluorescein dyes, which have been repurposed for photocatalysis from their traditional role as biological fluorophores. Computational and kinetic studies reveal that SiR and fluorescein dyes are able to form a ground state complexes with DHTz substrates, and the kinetic studies show that photocatalytic DHTz oxidation follows saturation kinetics. The elucidation of the mechanism is contributing to the design of more efficient photocatalysts.

Regiodivergent Synthesis of 2- and 3-Substituted Indolines and Pyrrolidines through Pd-Catalyzed Heteroannulation of 1,3-Dienes with Bifunctional Reagents

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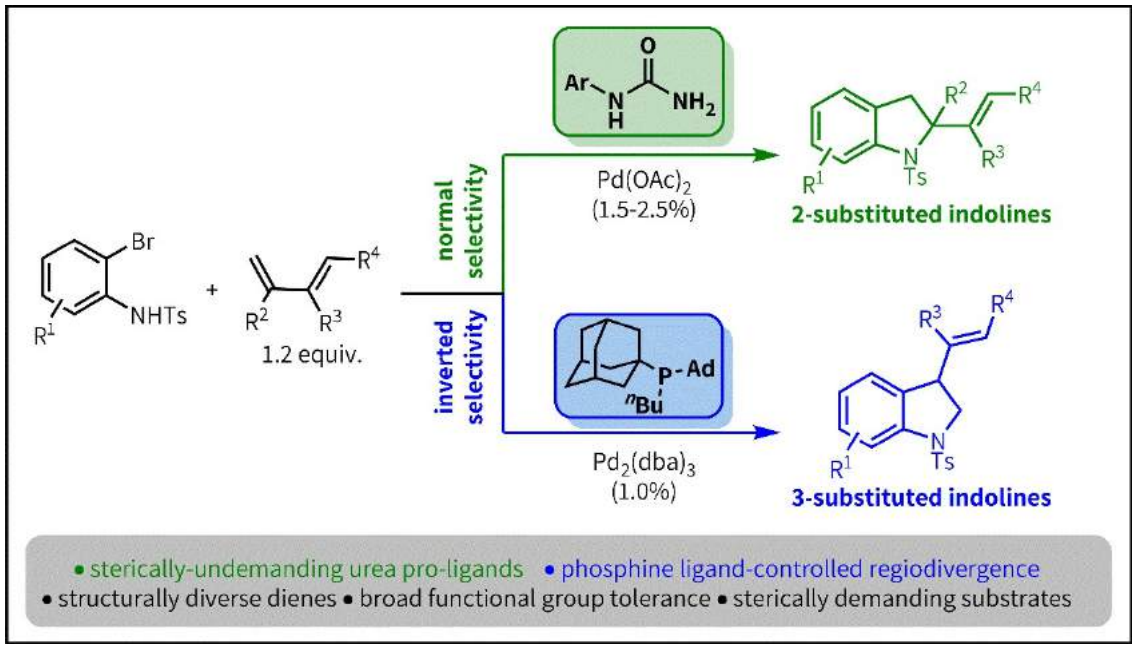
The development of two atypical ligand platforms that enable palladium-mediated regiodivergent heteroannulation of 1,3- dienes with *o*-haloanilines and related bifunctional reagents will be presented. While this class of reactions represents a convergent approach to synthesis of five-membered and larger stereocentre-containing azaheterocycles, its scope has remained limited to iodoanilines and primarily mono-substituted linear 1,3-dienes for the last four decades.[1] Our hypothesis is that this arises from the incompatibility of established ligands with the steric congestion of the Pd complexes in this transformation. We have found that ureates are an effective sterically undemanding ligand platform for palladium catalysis able to overcome the limitations of traditional ligands for late transition metals in this transformation.[2] While the ureate ligand-enabled method provides access to 2-substituted indolines and pyrrolidines, we have found that the synthesis of the complementary 3-substituted azaheterocycles can be achieved by using sterically atypical phosphine ligands that invert the selectivity of the 1,3-diene migratory insertion step. The preliminary parametrization of the phosphine ligands that induce this unusual regiodivergence will be presented.



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Novel *N*-Branched Acyclic Nucleoside Phosphonates as Inhibitors of *Plasmodium* 6-Oxopurine Phosphoribosyltransferases

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The production of nucleoside monophosphates is essential for the synthesis of DNA/RNA in all living organisms. Purine nucleotides can be provided *via* two metabolic pathways: *de novo* synthesis or less energetically demanding purine salvage pathway. Human cells utilize both pathways. However, some protozoan parasites, such as *Plasmodium* spp., rely on the synthesis of nucleotides only through the purine salvage pathway. The key enzyme in this pathway is hypoxanthine-guanine-(xanthine) phosphoribosyltransferase (HG(X)PRT), responsible for ribophosphorylation of 6-oxopurine nucleobases (**Fig.1A**). Thus, inhibition of the enzyme activity should result in the cessation of *Plasmodium* growth and reproduction.[1] In the last decade, acyclic nucleoside phosphonates (ANPs) and bisphosphonates were revealed as potent inhibitors of HG(X)PRT.[2-4] The present goal is to design even more potent inhibitors with a view to the development of effective chemotherapeutics against such infectious diseases. Using the chemical structure of the substrates/products of the enzymatic reaction and previously discovered inhibitors as the platform, a series of novel *N*-branched ANPs (**Fig.1B**) were designed and synthesized.

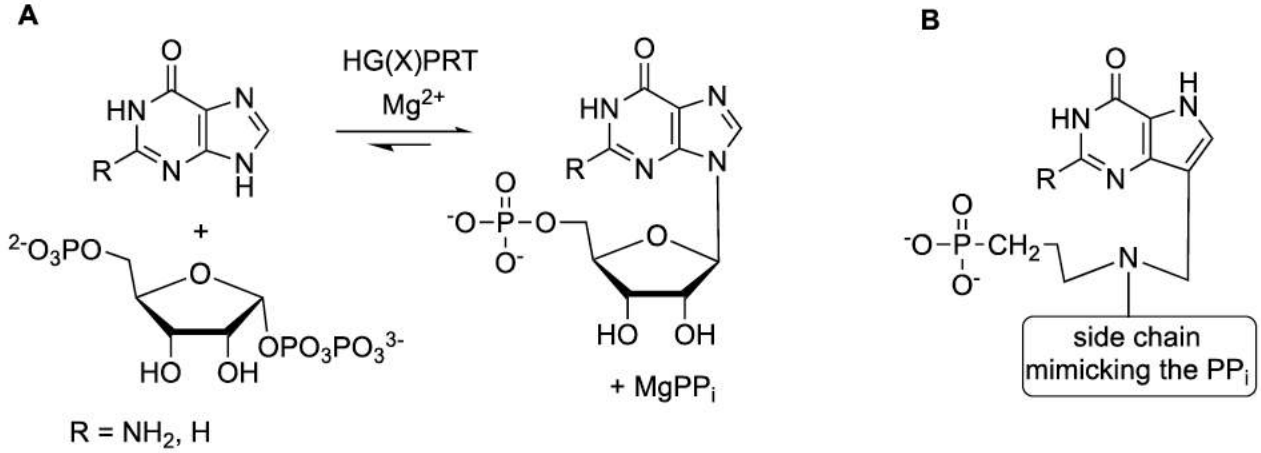

Fig.1 (A) The reaction catalyzed by HG(X)PRT. (B) Design of novel ANPs

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Carbon-Carbon Bond Formation between 1,4-Naphthoquinone and Ru-Carbene Complex with *N*-Heterocyclic Carbene (NHC) Ligand *via* Carbon(sp^3)-Hydrogen Bond Activation

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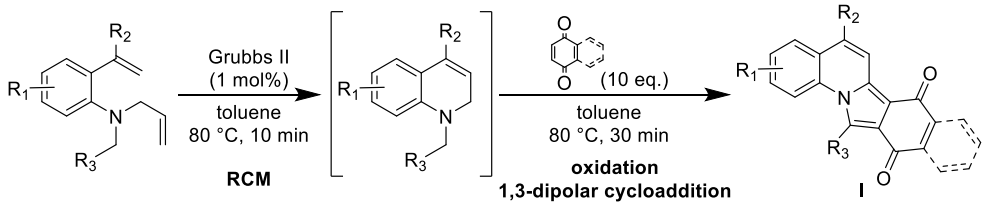
N-heterocyclic carbenes (NHC) are widely used as metal-catalysts' ligands or ionic liquids. It is well known that metathesis catalysts with NHC ligands are one of the most powerful catalysts in many fields of synthetic chemistry. The ruthenium carbene catalyst has an NHC ligand, which is known as Grubbs catalyst 2nd generation, and is widely used as an olefin metathesis catalyst, and nowadays, there are a lot of publications for other reactivities of this catalyst other than metathesis reactions.

Near Infrared (NIR) dyes, which have their maximum absorption wavelengths in the NIR region, are commonly applied in CD-R, organic Els, bioimaging, and even in photodynamic therapy. The basic structures of these dyes, however, have been limited.

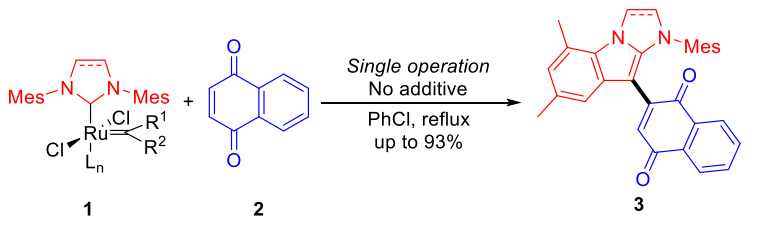
We previously developed a one-pot ring-closing metathesis (RCM)/oxidation/1,3-dipolar cycloaddition protocol[1], and we established a new skeleton, isoindolo[2,1-*a*]quinoline (**I**) (**Scheme 1**)[2]. In this project, we found a novel reaction between the NHC ligands on ruthenium carbene complexes (**1**) and 1,4-naphthoquinone (**2**), and synthesized new NIR dyes (**3**), which have blue color (λmax = 700.5 nm) (**Scheme 2**)[3]. In this poster session, we are going to show the optimization of this reaction with Box-Behnken design, substrate scope, and optical features of compounds **3**.



Ia (R_1 = 3-Me, R_2 = Me, R_3 = Ph, λ_{max} = 736 nm)
Ib (R_1 = H, R_2 = Ph, R_3 = H, σ_{978} = 50 GM)

R_1= Cl, Br, Me, OMe
R_2= Ph, Me
R_3= Ar (C_6H_4-4-NO_2, C_6H_4-4-F, C_6H_4-4-OMe), H

Scheme 1. One-pot RCM/oxidation/1,3-dipolar cycloaddition and photoproperties of compounds **I**



λ_{max} = 700.5 nm

Scheme 2. Tandem C-H activation/C-C bonds formation between NHCs and 1,4-naphthoquinone

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Enantioselective Coupling of Cyclopropenes with Pyrazoles via Copper(I) Catalysis

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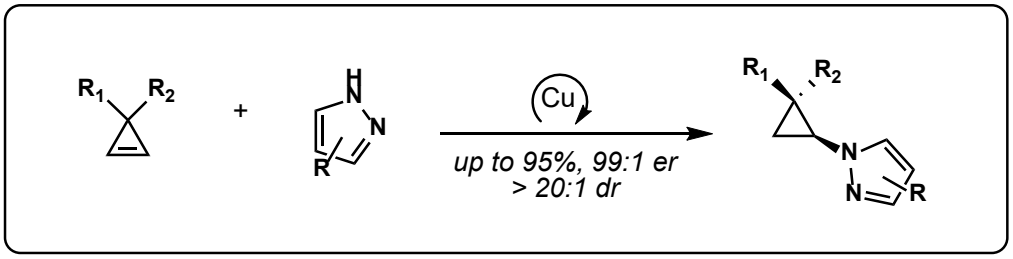
Cyclopropene hydrofunctionlization provides an efficient approach to construct molecular complexity[1]. With the increased interest in methods that incorporate nitrogen- containing heterocycles[2], we're investigating an asymmetric coupling of pyrazoles and cyclopropenes using copper catalysis. Our approach is the first enantioselective "copper-amido" hydroamination, affording high enantio- and diastereoselectivity, with wide functional group tolerance. Preliminary findings indicate the necessity of using bulky bisphosphine ligands to increase reactivity and inhibit the potential ring-opening pathway.



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Electric Field Influence on Hydrocarbon Autoxidation and Amine Acylation

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An external electric field, generated by the scanning tunneling microscopy-break junction (STM-BJ) technique, activates hydrocarbon autoxidation products to acylate amines. This novel mode of alkyl peroxide activation to generate acyl equivalents, and the subsequent intermolecular coupling can be monitored *in situ* by the conductance measurement in the STM-BJ and quantitatively characterized *ex situ* by mass spectrometry. The acylation is found to be influenced by the magnitude of the applied bias, indicating an electric field influence on thermodynamic parameters of this bulk reaction.

Coumarin Synthesis by Direct Annulation: β-Borylacrylates as Ambiphilic C_3-Synthons[1]

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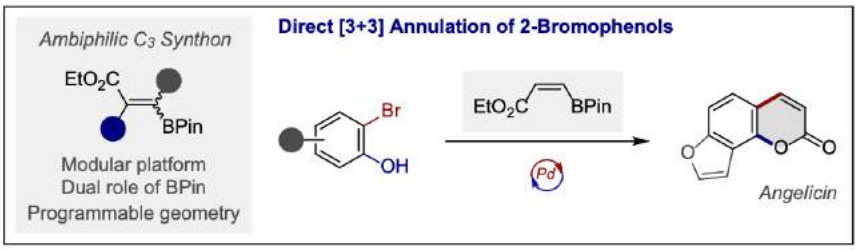

The long-standing importance of the coumarin scaffold in pharmaceuticals, natural products and functional materials is evident from the early works of Perkin[2] and Pechmann.[3] Since these benchmark reports, synthetic methods for the generation of this bicyclic framework have been complemented by transition metal,[4] photochemical[5] and modified Knoevenagel condensation approaches.[6] To further extend the synthesis repertoire, a direct [3+3] annulation approach was envisaged. In this study, modular β-borylacrylates have been utilized as small molecule synthons in the Pd-catalysed annulation reaction with 2-bromophenols to generate coumarin scaffolds. Key to the success of this methodology is the bifunctional BPin moiety: It enables the C(sp^2)-C(sp^2) Suzuki-Miyaura cross coupling between the respective 2-bromophenol and β-borylacrylate that starts the reaction cascade leading to the formation of the coumarin core. Additionally, the BPin unit extends the chromophore of the synthon, enabling selective energy transfer catalysed alkene isomerisation, leading to the critical *Z*-geometry required for cyclisation. The synthetic utility of the protocol was demonstrated through the synthesis of several coumarins differing in electronic and steric properties, such as the natural product *angelicin*. It was also possible to extend the π-system of several bioactive molecules to modulate their photophysical properties. As these compounds exhibit characteristic absorption in UV/vis-analysis, the application of this simple annulation strategy could also lead to the development of new tools for molecular imaging.

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Resonance Promoted Ring-Opening Metathesis Polymerization of Twisted Amides

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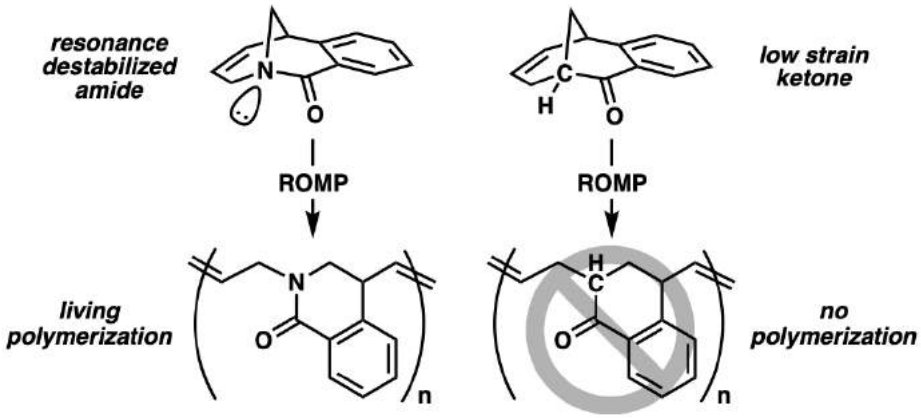
The living ring-opening metathesis polymerization (ROMP)[1,2] of an unsaturated twisted amide using the third generation Grubbs initiator is described.[3] Unlike prior examples of ROMP monomers that rely on angular or steric strain for propagation, this system is driven by resonance destabilization of the amide that arises from geometric constraints of the bicyclic framework. Upon ring-opening, the amide can rotate and rehybridize to give a stabilized and planar conjugated system that promotes living propagation. The absence of other strain elements in the twisted amide is supported by the inability of a carbon analogue of the monomer to polymerize and computational studies that find resonance destabilization accounts for 11.3 kcal•mol^{-1} of the overall 12.0 kcal•mol^{-1} ring strain. The twisted amide polymerization is capable of preparing high molecular weight polymers rapidly at room temperature, and post-polymerization modification combined with 2D NMR spectroscopy confirms a regioirregular polymer microstructure.



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Olefination of Hydrazones and Oximes Mediated by Ruthenium Alkylidenes

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Access to highly functionalized alkenes found in chemical feedstocks, pharmaceuticals, and natural products provides a desirable focus for the development of new carbon-carbon bond forming reactions. Previous approaches to imine-olefin metathesis have shown great potential for functionalized alkene synthesis but remain limited by stochiometric formation of catalytically inert metal imide products. We hypothesized that tuning the polarity of the C=N π-bond with electron withdrawing groups (NR_2, OR) would facilitate olefination reactivity with weakly electrophilic ruthenium alkylidenes to unlock a new olefination reaction. Herein, we report the use of air-stable commercially available ruthenium alkylidenes for oxime/hydrazone olefination[1], progress towards understanding the mechanism of this transformation, and potential for catalysis through a reducible ruthenium nitride intermediate.

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Rational Design on Bifunctional Ligand in Asymmetric Gold Catalysis

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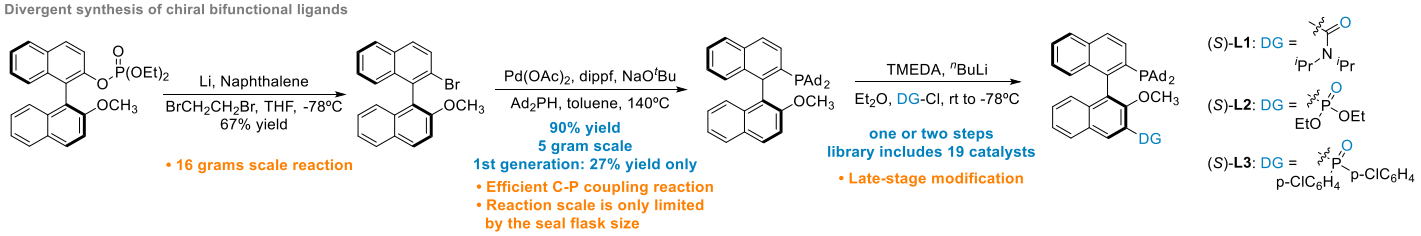
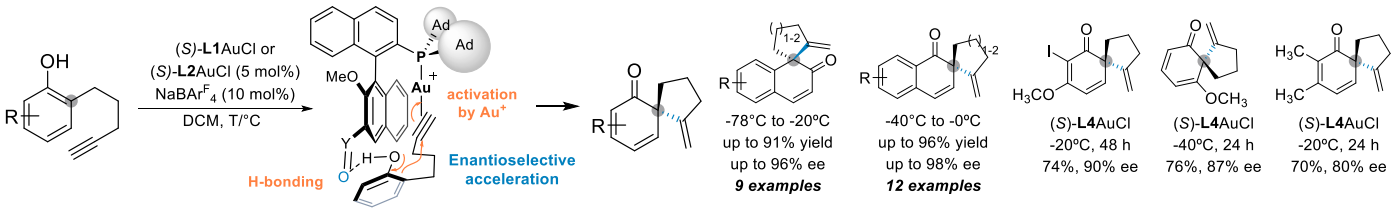
In past one decade, the cooperative asymmetric gold catalysis has attracted organic chemists' attention and was applied into various types of reaction, including isomerization of alkynes[1] and asymmetrical cyclization of allenols[2]. Herein, we reported a late-stage divergent synthesis of chiral bifunctional ligands (Scheme 1).



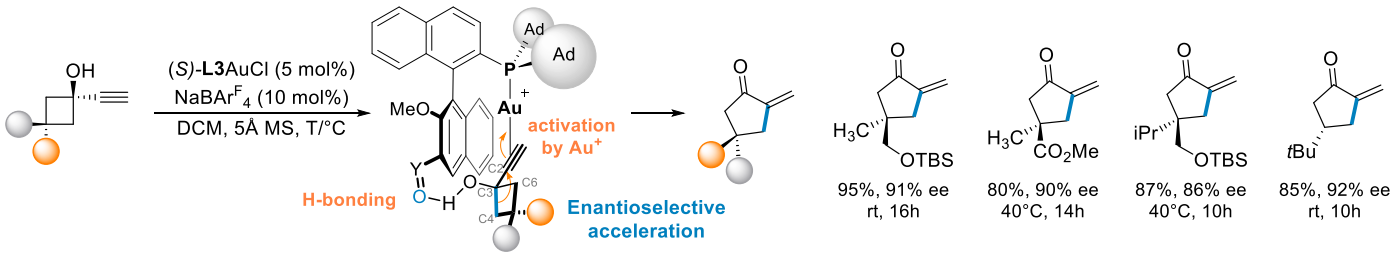
Scheme 1. Late-stage divergent synthesis of chiral bifunctional ligands.

With our new chiral bifunctional ligands, we realized a highly enantioselective dearomative cyclization, which is enabled by gold-ligand cooperative catalysis (Scheme 2). The alkyne moiety is activated by cationic gold coordination. At the same time, the basic directing group on ligand forms a hydrogen bond with hydroxy group on phenol, which accelerates one of spirocyclic enantiomers formation. The later scope study indicated that 2-naphthol, 1-naphthol and even phenol substrates can give dearomatization products in good to excellent enantioselectivity.



Scheme 2. Asymmetrical dearomatization enabled by cooperative gold catalysis

Later, we applied our chiral bifunctional ligands into desymmetrization of alkynylcyclobutanol to synthesis chiral β'-substituted cyclopentenones via conformation control (Scheme 3). The scope study indicates that chiral quaternary center and chiral tertiary center can be stablished in good enantioselectivity.



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List of Presenters and Attendees

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Prof Alan Aitken
University of St Andrews
ISHC Publicity Chair/Session Chair

Prof Shuji Akai
Osaka University
Poster Presenter/Session Chair

Dr Philip Alabi
Vividion Therapeutics
Attendee

Prof Erik Alexanian
University of North Carolina
Invited Speaker

Prof Edward Anderson
University of Oxford
Invited Speaker

Prof Laura Anderson
University of Illinois at Chicago
Short Talk

Dr John Andjaba
Massachusetts Institute of Technology
Poster Presenter

Dr Remy Angelaud
Genentech
Award Lecturer

Dr Angie Angeles
Gilead
Attendee

Prof Aaron Aponick
University of Florida
Short Talk

Prof Frances Arnold
California Institute of Technology (Caltech)
Plenary Speaker

Prof A. Jean-Luc Ayitou
University of Illinois Chicago
Short Talk

Seth Azevedo
Sanofi
Attendee

Griffin Barnes
University of California, Irvine
Poster Presenter

Dr Marc Becker
Merck & Co., Inc.
Poster Presenter

Mrs Jessica Bieniek
Johannes Gutenberg University Mainz
Poster Presenter

Mr Jake Blackner
University of Alberta
Poster Presenter

Prof Simon Blakey
Emory University
ISHC Advisory Board/Short Talk

Prof Dr Rebecca Buller
Zurich University of Applied Sciences
Invited Speaker

Prof Antonio Burtoloso
University of São Paolo
ISHC Advisory Board/Poster Presenter

Dr Chiara Cabrele
University of Regensburg
Attendee

Dr LC Campeau
Merck & Co., Inc.
Plenary Speaker

Mr Joseph Capani Jr.
UC Irvine
Poster Presenter

Prof Erick Carreira
ETH-Zurich
Plenary Speaker

Mr Antonin Cech
Attendee

Dr Ida (Xue) Chen
The Dow Chemical Company
Short Talk

Prof Noritaka Chida
Keio University
Invited Speaker

Prof Won-jin Chung
Gwangju Institute of Science and Technology
Short Talk

Ing Marijo Cicak
IOCB AS CR
Poster Presenter

Dr Ishay Columbus
Attendee

Prof James Cook
University of Wisconsin-Milwaukee
Attendee

Prof Mingji Dai
Emory University
Invited Speaker

M. Matthieu Daniel
CEA
Poster Presenter

Prof Mary Beth Daub
Furman University
Poster Presenter/Session Chair

Arabella Davis
Furman University
Poster Presenter

Prof Vy Dong
UC Irvine
Plenary Speaker

Prof Tom Driver
University of Illinois at Chicago
Short Talk

Matthew Duong
UC Irvine
Attendee

Natalie Dwulet
UC Irvine
Poster Presenter

Prof P. Andrew Evans
Queen's University
Invited Speaker

Dr Sean Feng
Gilead Sciences Inc.
Session Chair

Prof Sabine Flitsch
The University of Manchester
Invited Speaker

Prof Brett Fors
Cornell University
Invited Speaker

Miss Fiona Fotherby
University of St Andrews
Poster Presenter

Prof Joseph Fox
University of Delaware
Plenary Speaker

Prof Matthew Gaunt
University of Cambridge
Plenary Speaker

Prof Dr Ryan Gilmour
WWU Münster

Prof Ramesh Giri
Pennsylvania State University
Short Talk

Dr Phillip Grant
University of Vienna
Poster Presenter

Jonathan Gross
Johannes Gutenberg-University
Poster Presenter

Prof Will Gutekunst
Georgia Tech
Short Talk

Prof Osvaldo Gutierrez
Texas A&M University
Invited Speaker

Dr Sabine Hadida
Vertex Pharmaceuticals
Invited Speaker

Joel Häfliger
Westfälische Wilhelms-Universität Münster
Poster Presenter

Prof Dennis Hall
University of Alberta
Short Talk

Ms Gabrielle Hammersley
Vividion Therapeutics
Attendee

Prof Michael Harmata
University of Missouri-Columbia
Poster Presenter/Session Chair

Dr Aaron Herrmann
Treeline Biosciences
Attendee

Mr Maximilian Hielscher
JG|U Mainz
Poster Presenter

Ashlyn Hillman
University of Delaware
Poster Presenter

Dr Allen Hong
Genentech
Short Talk

MA Satoshi Horino
Osaka University
Poster Presenter

Dr Evan Horn
Treeline Biosciences
Session Chair

Evelyn Hosner
Thieme Chemistry
Exhibitor

Banruo Huang
UC Santa Barbara
Attendee

Prof Todd Hyster
Cornell University
Invited Speaker

Prof Satoshi Ichikawa
Hokkaido University
Invited Speaker

Prof Masayuki Inoue
The University of Tokyo
ISHC Executive—Past-President/Plenary Speaker

Kento Iwai
Kochi University of Technology
Poster Presenter

Mr Andrew Jemas
University of Delaware
Poster Presenter

Haofan Ji
University of Georgia
Poster Presenter

Alexander Jiu
UC Irvine
Poster Presenter

Mr Lucas Johnson
University of California, Irvine
Poster Presenter

Mr Narender Reddy Katta
University of Regensburg
Poster Presenter

Miss Milanpreet Kaur
University of Calgary
Poster Presenter

Dr Kotaro Kikushima
Ritsumeikan University
Poster Presenter

Prof Kevin Kou
University of California, Riverside
Poster Presenter/Session Chair

Prof Marisa Kozlowski
University of Pennsylvania
Plenary Speaker

Bc Pavel Kraina
IOCB AS CR
Poster Presenter

Dr Jeffrey Kuethe
Merck & Co., Inc. MSD
ISHC Advisory Board/Poster Presenter/Session Chair

Dr Jonathan Lam
Takeda
Attendee

Dr Nelson Lam
University of Cambridge
Poster Presenter

Prof Andrew Lawrence
University of Edinburgh
Short Talk

Mr Philip Lechner
UC Irvine
Attendee

Prof Mark Levin
University of Chicago
Short Talk

Bryant Lim
University of California-Irvine
Attendee

Mr Martin Linden
Johannes Gutenberg-University Mainz
Poster Presenter

Prof Vincent Lindsay
North Carolina State University
Short Talk

Dr Shaonan Liu
UC Santa Barbara
Poster Presenter

Dr Xin Liu
Colorado State University
Poster Presenter

Prof Tom Livinghouse
Montana State University
Short Talk

Dr Carl Lovely
UT Arlington
Short Talk/Poster Presenter

Dr Erika Lucas
Gilead
Attendee

Adam Luo
ChemScene LLC
Attendee

Tom Luong
Eikon Therapeutics
Attendee

Prof David Lupton
Monash University
Invited Speaker

Dr Michael Luzzio
Skyhawk Therapeutics
Attendee/Session Chair

Prof Frederick Luzzio
University of Louisville
ISHC Treasurer/Session Chair

Xinyi Lyu
University of Delaware
Poster Presenter

Dr Rajat Maji
UC Los Angeles
Poster Presenter

Colette Makara
University of Delaware
Poster Presenter

Prof Christian Malapit
Northwestern University
Short Talk

Mr Ali Mansour
University of Ottawa
Poster Presenter

Prof Dave Martin
University of Iowa
Short Talk

Dr Siddharth Matikonda
NIH/NCI
Poster Presenter

Prof Andy McNally
Colorado State University
Invited Speaker

Stephanie Meyer
University of Münster
Poster Presenter

Dr Sharon Michalak
Amgen Inc
Poster Presenter/Session Chair

Dr Theo Michels
Belharra Therapeutics
Session Chair

Prof Garret Miyake
Colorado State University
Invited Speaker

B.Sc. Lukas D. H. Müller
Universität Düsseldorf
Guest

Prof Dr Thomas J. J. Müller
Heinrich-Heine-Universität Düsseldorf
Invited Speaker

Ing Lucie Muzikova Cechova
IOCB AS CR
Poster Presenter

Prof David Nagib
The Ohio State University
Invited Speaker

Prof Alison Narayan
The University of Michigan
Invited Speaker

Sophia Neglia
University of Delaware
Poster Presenter

Prof Christopher Newton
University of Georgia
Short Talk

Hanh Nguyen
University of California, Irvine
Poster Presenter

Prof David Nicewicz
University of North Carolina at Chapel Hill
Invited Speaker

Dr Andrei Nikolaev
UC Santa Barbara
Attendee

Scott Niman
UC Irvine
Poster Presenter

MA Tomoya Nishio
Osaka University
Poster Presenter

Ryotaro Okawa
Hokkaido University
Poster Presenter

Mr Daichi Okumatsu
Poster Presenter

Mr Shohei Ono
Yale University
Attendee

Prof Dr Till Opatz
Johannes Gutenberg Univ. Mainz
ISHC Advisory Board/Short Talk/Session Chair

Prof Art Orellana
York University
Short Talk

Prof Albert Padwa
Emory University
ISHC Senior Fellow/Session Chair

Bonnie Pak
University of California, Irvine
Poster Presenter

Bonnie Park
UC Irvine
Poster Presenter

Dr Monika Patel
University of Delhi
Poster Presenter

Jessica Pazienza
University of California, Irvine
Attendee

Dr Magnus Pfaffenbach
Biogen
Short Talk

Prof Joshua Pierce
NC State University
Short Talk

Mr Ziyang Qin
California Institute of Technology
Poster Presenter

Mr Jiawei Qiu
Osaka University
Poster Presenter

Dr Melissa Ramirez
Caltech
Poster Presenter

Prof Viresh Rawal
University of Chicago
Award Lecturer

Prof Jolene Reid
University of British Columbia
Short Talk

Prof Oliver Reiser
University of Regensburg
Short Talk

Prof Sarah Reisman
California Institute of Technnology
Award Lecturer

Prof Hans Renata
The Scripps Research Institute
Invited Speaker

Dr Omkar Revu
zamboni chem solutions Inc.
Attendee

Dr Jennifer Riggs
Bristol Myers Squibb
Invited Speaker

Prof Nathan Romero
University of California San Diego
Attendee

Julia Rosenberger
University of Delaware
Poster Presenter

Prof Scott Rychnovsky
UC Irvine
Invited Speaker/Session Chair

Oscar M Saavedra
Attendee

Dr Jade Sainz
Guest

Sirajis Salekin
Unversity of Delaware
Attendee

Adrian Samkian
Caltech
Attendee

Prof Jonathan Scheerer
William & Mary
Short Talk

Prof Corinna Schindler
University of Michigan
Invited Speaker

Prof Valerie Schmidt
University of California San Diego
Short Talk

Dr Martin Schnermann
National Cancer Institute
Invited Speaker

Dr Marta Serafini
University of Oxford
Attendee

Dr Grant Shibuya
RAPT Therapeutics
Attendee

Emily Shimizu
UC Irvine
Attendee

Dr Fiona Shortt de Hernandez
Thieme Group (Georg Thieme Verlag KG)
Exhibitor

Prof Ellen Sletten
UC Los Angeles
Invited Speaker

Carly Slough
Furman University
Poster Presenter

Prof Joel Smith
Florida State University
Short Talk

Dr Danielle Soenen
UC Irvine
Organizer

Prof Erik Sorensen
Princeton University
Invited Speaker

Prof Erin Stache
Cornell University
Short Talk

Prof Corey Stephenson
University of Michigan
Session Chair

Prof Jenn Stockdill
Wayne State University
Short Talk

Prof David Stuart
Portland State University
Short Talk

Nantamon Supantanapong
UC Irvine
Poster Presenter

Amanda Tallon
University of Delaware
Poster Presenter

Prof Uttam Tambar
UT Southwestern Medical Center
Invited Speaker

Dr Yu Tang
FMC Stine research center
Attendee

Yujia Tao
Poster Presenter

Dr Pallavi Thakur
Zamboni Chem Solutions
Attendee

Ms Jordan Thompson
UC Irvine
Poster Presenter

Prof Regan Thomson
Northwestern University
Invited Speaker

Stephanie Tsang
University of Delaware
Poster Presenter

Dr Matthew Tudge
Glaxo SmithKline
Invited Speaker

Jakub Vaith
University of Rochester
Poster Presenter

Prof Chris Vanderwal
UC Irvine
ISHC President

Ing Karolina Vankova
IOCB AS CR
Poster Presenter

PhD Darius Vrubliauskas
Incyte Corporation
Session Chair

Mr Yuki Wada
Osaka University
Poster Presenter

Xiye (Adam) Wang
Columbia University
Poster Presenter

Minghao Wang
UC Irvine
Poster Presenter

Mr Max Wienhold
WWU Münster
Poster Presenter

Prof Sidney Wilkerson-Hill
University of North Carolina at Chapel Hill
Short Talk

Mizhi Xu
UC Santa Barbara
Poster Presenter

Prof Armen Zakarian
UC Santa Barbara
Plenary Speaker

Mr Troy Zehnder
University of Michigan
Poster Presenter

Prof Peter Zhang
Boston College
Invited Speaker

Professor Javier Read de Alaniz
UC Santa Barbara
Conference Co-organizer

Professor Yang Yang
UC Santa Barbara
Conference Co-organizer

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The 28th ISHC CONGRESS

Aug 28 - Sep 2, 2022

University of California, Santa Barbara

International Society of Heterocyclic Chemistry

Facilities Management
Environmental Health & Safety
Caesar Uyesaka Stadium
Softball Stadium
Lacrosse Field
Recreation Center
Pool
Recreation Center Fields
Pauley Track
Robertson Gym
Intercollegiate Athletics
El Colegio Road
Ocean Road
Mesa Road
Lagoon Road
Stadium Road
Student Health
Student Affairs & Admin. Services
Cheadle Hall
Coral Tree Café
North Hall
Campbell Hall
Phelps Hall
Mosher Alumni House
Henley Hall (future construction)
Ellison Hall
Buchanan Hall
Physical Sciences North
Physical Sciences South
Chemistry
Engineering Science
Elings Hall
Engr II
Kohn Hall
Courtyard Café
Henley Gate
Steck Circle
To US 101
Kerr Hall
UCSB Library
Broida Hall
MRL
Harold Frank Hall
Webb Hall
Bren Hall
Bio-Engineering
Noble Hall
Life Science
Bio II
Marine Science Research
Ocean Science Education
Psych
Music
Lotte Lehmann Concert Hall
Storke Tower
Music Library
Arts
Art Museum
University Center
Corwin Pavilion
MCC
Girvetz Hall
South Hall
Counseling & Career Services
Humanities and Social Sciences
Theater and Dance East
Events Center
Education
Social Sciences and Media Studies
Pollock Theater
Bus Loop
Student Resource
Auditorium
Theater and Dance West
The Club & Guest House
Commencement Green
Loma Pelona
San Rafael Hall
Carrillo
Manzanita Village
Ortega
San Miguel Hall
San Nicolas Hall
Santa Rosa Hall
De La Guerra
Anacapa Hall
Santa Cruz Hall
University House
Channel Islands Road
UCEN Road
Lagoon
Marine Biotechnology
Office of Technology & Industry Alliances
Marine Operations Facility
REEF/Aquarium
RESTRICTED AREA
RESTRICTED AT ALL TIMES

Points of INTEREST

A. Santa Barbara Airport
B. Recreation Center
C. Isla Vista
D. UCSB Lagoon

Conference FACILITIES

1. Corwin Pavilion
Registration in Corwin Lobby
Session location

2. Lagoon Plaza
Sunday evening reception
Refreshment breaks and poster sessions

3. University Center (UCen)
Flying A session location
Starbucks, Subway, Panda Express, Root Burger, and other eateries

4. Multicultural Center (MCC)
Session location
Exhibitors

5. Manzanita Village
On-campus accommodations

6. DeAnza Resource Center
Manzanita Village front desk

7. Manzanita Bus Loop
Wednesday excursion pick-up/drop-off location

8. Parking Structure 22
Long-term parking
(permit required)

9. Parking Lot 3
Only after 5pm parking on Sunday for evening event
(permit required)

10. Goleta Beach
Wednesday catered BBQ
Follow path along the bluffs

11. De La Guerra Dining Commons
Dining Commons for participants staying on campus
Other attendees may pay with a credit card at the entrance

12. The Club & Guest House

UC SANTA BARBARA