

Empowering Women in Organic Chemistry 2020

Poster Abstract Booklet

4:00–5:00pm EDT Posters 1–41 5:00-6:00pm EDT Posters 42-82

Information for Attendees

Each poster will have an assigned Zoom room. You will receive a list of the links to these Zoom rooms separately. Please visit the posters of interest to you. You may come and go from the poster rooms as you please. In this virtual poster session format, we have encouraged presenters to use whatever format works best to present their work; in some cases, presenters may use multiple slides instead of the traditional static poster.

Posters 1-41 will be available from 4:00-5:00pm EDT. Posters 42-82 will be available from 5:00-6:00pm EDT.

Please do not photograph or record the poster presentations, unless you have the explicit permission of the presenter.

Strategies Towards the Total Synthesis of Dimeric Pyrrole-2-Aminoimidazole Natural Products Nagelamide J and Agelamadin B

Anika Tarasewicz, Marvin Morales, Robert A. Batey* University of Toronto, Toronto, Ontario a.tarasewicz@utexas.edu

Dimeric bromopyrrole alkaloids nagelamide J and agelamadin B were recently isolated from the Okinawan marine sponge Agelas species. These natural product are structurally unique because they were the first isolated members of the pyrrole-2-aminoimidazole class of alkaloids to possess a cyclopentene fused to a 2-aminoimidazole. Despite the promising antimicrobial activity against Staphylococcus aureus, further studies of these natural products have been hindered due to their low abundance. Thus, an efficient strategy to construct the core of nagelamide J and agelamadin B is essential to explore the full biological profile of these marine alkaloids.

Our approach for the total synthesis of nagelamide J and agelamadin B focuses on a divergent strategy. The cyclopentene core is formed by a Lewis acid catalyzed rearrangement. This method provides the desired trans-diamine stereochemical relationship in one-step which is challenging by other procedures. Elaboration of the core has led to the development of selective amidation and guanidinylation reactions. We have also conducted preliminary studies for the challenging connectivity between the 2-aminoimidazole and the cyclopentene ring. Herein, we will highlight the methods used to form the core and our current strategy towards the first total synthesis of nagelamide J and agelamadin B.

A Computational and Experimental Mechanistic Investigation of the Catalytic Enantioselective Minisci-type Addition to Heteroarenes

Avene C. Colgan , Kristaps Ermanis, Barbara W. Hadryś, Rupert S. J. Proctor, Jonathan M. Goodman, Robert J. Phipps * Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, CB2 1EW, United Kingdom acc83@cam.ac.uk

N-Heteroarenes are an important class of compounds found throughout nature with widespread applications in the pharmaceutical and agrochemical industries. Minisci-type reactions – involving the addition of radical nucleophiles to basic heteroarenes – offer a direct approach for structural elaboration. Recently, our group reported a dual-catalytic strategy for a Minisci-type reaction involving the addition of prochiral radicals, generated from amino acid derivatives, to pyridines and quinolines [1]. This combination of photoredox and chiral Brønsted acid catalysis provided functionalised N-heteroarene products in high yields, with excellent enantioselectivities (ees up to 97%) and complete regiocontrol (C-2 addition only), however, the precise mechanism by which this process operates, and the origins of selectivity remained unclear. In this poster we detail the collaborative effort to further investigate the mechanism through experimental investigations and comprehensive DFT calculations which probe the precise nature of the stereochemistry-determining step. DFT calculations unveiled a clear preference for an unexpected mode of internal deprotonation, involving just one molecule of catalyst, which underpins the high enantioselectivities observed. The mechanistic model was further validated by experimental supports.

References:

[1] Proctor, R. S. J.; Davis, H. J.; Phipps, R. J. Science, 2018, 360, 419-422.

Efforts Toward the Syntheses of O-linked Fucosylated Amino Acid Targets

Ashley E. DeYong, Nicola L. B. Pohl* Indiana University, Bloomington, Indiana adeyong@iu.edu

The O-linked fucose post-translational modification has been shown to play an important role in the Notch signaling pathway. Despite knowing the importance of this modification, there still remains information to be gained through chemical synthesis, in that this can allow for higher quantities of pure material. This work specifically focuses on the chemical syntheses of fucosylated amino acid building blocks, which will then be incorporated into larger biomolecular structures to probe the structure and function of these systems to gain further insight regarding the importance of these modifications. These building blocks will also be used directly in SPPS. Chemical syntheses of these targets can be challenging because of the acid-labile linkage of fucose, and a fast and effective way to synthesize these targets is yet to be determined. An automated flow chemistry approach can address the long reaction times of the previous syntheses of these targets and can also address the high commercial cost of these building blocks and make them more accessible. Automating the syntheses of these building blocks will allow for more straightforward optimization and reproducibility. Herein progress towards developing an automated flow method using minimal steps to synthesize O-linked fucosylated amino acid building blocks will be presented.

Synthesis of Cinnamo hydroxamic acid Derivatives and Evaluation of their Herbicidal Activity.

Ajay Kumar, Sushila Arya, Virendra Kasana* G. B. Pant University of Agriculture and Technology, Pantnagar, Uttarakhand. ajay.tiwari1591@gmail.com

In the present investigation, Cinnamo hydroxamic acid derivatives have been synthesized employing green chemistry principles. The compounds of Cinnamo hydroxamic acid have been tested for herbicidal activity against Radish (Raphanus sativus) seeds at 50, 100 and 200ppm concentratios and compared with standard pendimethalin. Amongst the tasted compounds, (3-nitro cinnamo hydroxamic acid, o-tolyl-(3-bromo)cinnamo hydroxamic acid and 2-Bromo-(4-chloro)cinnamo hydroxamic acid) exhibit maximum significant activities at concentration 200ppm.

Iridium-Catalyzed Asymmetric Hydrogenation of 1,3-Disubstituted Isoquinolines

Alexia N. Kim, Aurapat Ngamnithiporn, Eric R. Welin, Martin T. Daiger, Christian U. Grünanger, Michael D. Bartberger, Scott C. Virgil, Brian M. Stoltz* Caltech, Pasadena, CA akim2@caltech.edu

The development of a general method utilizing a hydroxymethyl directing group for the asymmetric hydrogenation of 1,3-disubstituted isoquinolines to provide chiral 1,2,3,4-tetrahydroisoquinolines is reported. The reaction, which utilizes [Ir(cod)Cl]2 and a commercially available chiral xyliphos ligand, proceeds in good yield with high levels of enantioselectivity and diastereoselectivity (up to 95% ee and >20:1 dr) on a range of differentially substituted isoquinolines. Directing-group studies demonstrate that the hydroxymethyl functional group at the C1 position is more efficient at enabling hydrogenation in comparison to other substituents, although high levels of enantioselectivity were conserved across a variety of polar and nonpolar functional groups. By utilization of the generated chiral β -amino alcohol as a functional handle, the synthetic utility is further highlighted via the synthesis of 1,2-fused oxazolidine, oxazolidinone, and morpholinone tetrahydroisoquinolines in one step. Additionally, a non-natural analogue of the tetrahydroprotoberberine alkaloids was successfully synthesized.

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Improved Synthesis of Biaryl Phosphorinane Ligands and Applications in Pd-Catalyzed Cross-Coupling of Hindered, Electron-Deficient Anilines with Bulky (Hetero)Aryl Halides

Alison M. Wilders, Jeremy Henle, Michael C. Haibach, Rafal Swiatowiec, Jeffrey Bien, Shashank Shekhar AbbVie alison.wilders@abbvie.com

We report a general and high yielding procedure for the synthesis of biaryl phosphorinanes (ligands) by phospha-Michael addition of primary biarylphosphines (ArPH2) to 1,4-diene-3-ones in hexafluoroisopropanol (HFIP), under relatively mild conditions (50-110 °C). HFIP as solvent significantly accelerates the phospha-Michael addition and allows the reaction to proceed with only 1-2 equivalents of dienone. Previously inaccessible ligands could now be readily prepared. Biaryl phosphorinanes derived from addition to dibenzylideneacetone are highly active ligands for Pd-catalyzed coupling of hindered, electron- deficient anilines with hindered (hetero)aryl halides (ArX), a challenging class of C–N cross-coupling reaction with few precedents. Very broad substrate scope and functional group tolerance was observed under the reaction conditions. Computational studies suggest that ligands containing aryl substituents on the phosphacycle promote coordination of hindered, electron-deficient anilines to the oxidative addition intermediate (L)Pd(II)(Ar)(X) more than the ligands containing alkyl substituents.

Disclosures:

All authors are employees of AbbVie and may own AbbVie stock. AbbVie sponsored and funded the study; contributed to the design; participated in the collection, analysis, and interpretation of data, and in writing, reviewing, and approval of the final publication.

One Pot Deracemization of Alcohols Using Two Mutants of Secondary alcohol Dehydrogenase from Thermoanaerobacter ethanolicus

Sodiq A. Nafiu, Masateru Takahashi, Samir M. Hamdan, Musa M. Musa* King Fahd University of Petroleum and Minerals, Saudi Arabia aliwowiyy@gmail.com

We developed a one-pot, two-step deracemization approach for secondary alcohols using two mutants of Thermoanaerobacter ethanolicus secondary alcohol dehydrogenase (TeSADH). This approach was implemented in deracemization of phenyl-ring-containing secondary alcohols. (S)-Configured alcohols were obtained in up to >99% enantiomeric excess using W110G and W110V TeSADHs. W110G TeSADH enables a non-stereoselective oxidation of alcohol racemates to their corresponding ketones, followed by W110V TeSADH-catalyzed enantioselective reduction of the resulted ketone intermediates to enantiopure (S)-configured alcohols. A heat treatment is needed to inactivate the enzyme used in the first step, which was eliminated by using sol-gel encapsulated W110G TeSADH mutant to oxidized racemic alcohols. We further developed this approach to a one-pot, one-step (concurrent) deracemization strategy via stereoinversion using two mutants of TeSADH that exhibit opposite stereo-preferences towards secondary alcohol substrates and achieved up to >99.5% enantiomeric excess and quantitative yields of (S)-alcohols. Stereochemical identities of the products were investigated using a chiral column equipped Gas chromatography (GC). Meanwhile, we confirmed the chemical identity using Gas chromatography-mass spectrometry (GC-MS) and nuclear magnetic resonance (¹H & ¹³C).

Nickel-Catalyzed Arylboration of Unactivated Alkenes: Scope and Mechanistic Exploration

Alison L. Lambright, Stephen R. Sardini, Grace L. Trammel, Yanyao Liu, Humair M. Omer, Peng Liu, M. Kevin Brown* Indiana University, Bloomington, IN allambri@iu.edu

Alkene difunctionalization reactions are an essential class of reactions in modern organic chemistry as a useful synthetic method to rapidly build up chemical complexity from widely available starting materials. Carboboration reactions are specifically interesting because of the high synthetic utility of the newly formed carbon-boron bond while also installing a carbon-carbon bond. With the majority of carboboration reactions only viable on activated alkenes, our lab has developed a novel nickel-catalyzed diastereoselective arylboration reaction of unactivated alkenes. In addition, reaction conditions have been optimized to include traditionally unreactive substrates such as 1,1-di- and trisubstituted alkenes to form all-carbon quaternary centers as products. Reactivity of these substrates are significant as it represents a rare example of a tertiary organometallic nucleophile, an intermediate prone to β -hydride elimination, engaging in a cross-coupling event. The mechanism of this reaction has been studied through both experimental and computational methods, uncovering a novel Ni(I/III) catalytic cycle for this transformation. Driven by mechanistic understanding, we also have developed a diastereoselective arylboration of unactivated alkenes using a distal amide moiety as a directing group.

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Catalytic α-Hydroarylation of Acrylates and Acrylamides via an Interrupted Hydrodehalogenation Reaction

Alena M. Vasquez, John A. Gurak Jr., Candice L. Joe, Emily C. Cherney, Keary M. Engle* Scripps Research, San Deigo, CA alvasquez@scripps.edu

The palladium-catalyzed, α -selective hydroarylation of acrylates and acrylamides is reported. Under optimized conditions, this method is highly tolerant of a wide range of substrates including those with base sensitive functional groups and/or multiple enolizable carbonyl groups. A detailed mechanistic study was undertaken, and the high selectivity of this transformation was shown to be enabled by the formation of a [PdII(Ar)(H)] intermediate, which performs selective hydride insertion into the β -position of α , β -unsaturated carbonyl compounds.

A Merged Stereochemical Analysis of 1,2- and 1,3- Asymmetric Induction in Diastereoselective Nucleophilic Additions to Chiral N-Tosyl Imines

Anna Lo, Jared T. Shaw* University of California, Davis, Davis, California annlo@ucdavis.edu

A systematic investigation of the influence of inherent asymmetry of chiral N-tosyl imines on the diastereoselective outcomes of Lewis-acid mediated nucleophilic addition reactions is presented. 1,2 asymmetric induction is pronounced in α -chiral imines when nucleophilic addition is mediated by ZnBr₂ and BF₃·OEt₂, leading to either syn or anti-addition outcomes with high selectivities. The observed selectivities do not adhere to the prevailing stereoelectonic models that predict diastereomeric outcomes of nucleophilic additions to analogous α -chiral aldehydes. Experiments indicate alternative reactive intermediates are present and accessible for N-tosyl imines that are less energetically favorable for their aldehyde analogues. Nucleophilic additions to β-chiral Ntosyl imines provide an additional opportunity to explore differences in reactivity between electron-deficient imines and aldehydes. Diastereoselectivities are presented for a variety of chiral substrates and Lewis-acids, providing evidence that while inherent asymmetry can be exploited in chiral N-tosyl imines in a similar fashion to chiral aldehydes, selectivity outcomes do not strictly abide by known stereoelectronic models. A deeper understanding of the reactivity of chiral imines leads to a higher degree of stereocontrol and greater synthetic utility of imines, providing the foundation for more streamlined synthetic proposals for sought-after nitrogen containing synthetic targets.

Development of natural product-inspired tool compound leads to the identification of a novel biofilm target

Amber M. Scharnow, Amber M. Scharnow, Amy. E. Solinski, Elana Shaw, William M. Wuest* Emory University, Atlanta, Georgia ascharn@emory.edu

Biofilm-mediated diseases are particularly difficult to treat and a better understanding of the fundamental processes responsible for biofilm formation and identification of new targets is needed to enhance our ability to prevent and kill these pervasive bacterial communities. Dental caries is a biofilm-mediated disease that affects nearly 50% of children worldwide. Streptococcus mutans is the primary causative agent and has garnered interest beyond caries. It has been classified as a model organism for studying biofilm-forming Gram-positive species and has been implicated in other diseases such as infective endocarditis and more. To induce and perpetuate disease, S. mutans relies on a complex network of cellular signaling mechanisms, gene regulation and virulence traits, and polymicrobial interactions. Clarifying how these factors intersect and contribute to pathogenicity will provide a better comprehension of disease progression, polymicrobial environments, and resistance development resulting in improved treatments and preventions. To this end, we identified an improved tool compound through the diverted total synthesis of the natural product, carolacton. Subsequently we employed our tool compound in affinity-based protein profiling, chemical genetics, and confocal microscopy leading to the identification of a novel biofilm target that likely plays a critical role in cell wall biogenesis, biofilm formation, and acid tolerance.

Computational Studies of the Ligand-Controlled Regiodivergent Palladium-Catalyzed Hydrogermylation of Ynamides

Aneta Turlik, Vincent Debrauwer, Lénaic Rummler, Alessandro Prescimone, Nicolas Blanchard,* K. N. Houk,* Vincent Bizet* UCLA, Los Angeles, California aturlik@g.ucla.edu

The addition of metal hydrides, such as tin hydrides, germyl hydrides, and silyl hydrides across alkynes leads to products that are valuable building blocks for cross coupling reactions or for the synthesis of heterocycles. Blanchard and coworkers have developed a ligand-controlled palladiumcatalyzed hydrometallation of ynamides that leads to divergent regioselectivity based on the identity of the phosphine ligand used in the reaction. Using density functional theory (DFT) calculations, the role of the ligand and its effect on selectivity were investigated. In addition, various catalytic cycles were explored (e.g. germylpalladation vs. hydropalladation) in order to determine which mechanism is operative. DFT calculations support the experimental data of a hydro-palladation pathway compared to a metal palladation of the π system of the ynamide. Additionally, it was shown that the steric demands of the phosphine ligand plays a key role in reversing the regioselectivity of the reaction.

Debrauwer, V.;† Turlik, A;† Rummler, L.; Blanchard, N.; Houk, K. N.; Bizet, V. "Ligand-Controlled Regiodivergent Palladium-Catalyzed Hydrogermylation of Ynamides." *J. Am. Chem. Soc.* **2020**, *142*, 11153. DOI: 10.1021/jacs.0c03556.

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Deaminative Alkyl-Alkyl Cross-Couplings of Alkylpyridinium Salts and Alkenes

Kristen M. Baker, Diana Lucas Baca, Shane L. Plunkett, Mitchell E. Daneker, Mary. P. Watson* University of Delaware, Newark, DE bakekr@udel.edu

Alkyl amines are inexpensive and widely abundant chemicals in organic synthesis, making them attractive substrates for further functionalization. Functionalization via cleavage of the carbonnitrogen (C–N) bond has recently been discovered as a powerful transformation of these abundant, easily protected alkyl amines. Due to the prevalence of C(sp3)–C(sp3) bonds in bioactive molecules, methods to create alkyl-alkyl bonds have become increasingly desirable. By using High-Throughput Experimentation interfaced with traditional reaction optimization, we have developed a nickel-catalyzed cross-coupling of alkyl pyridinium salts with an alkyl boron species formed in situ from an alkene. The optimization, scope, and mechanistic understanding of these reactions will be presented.

Progress Towards a Unified Chemical Synthesis of Monosaccharide Building Blocks

Bethany L. Christopher, Nicola L. B. Pohl* Indiana University-Bloomington, Bloomington, IN belchris@iu.edu

Only select monosaccharides are abundant in nature, while the remaining are termed rare sugars. Rare sugars have potential applications to certain commercial industries including the food and pharmaceutical industry. To apply and study rare sugars, the scale of rare sugar synthesis must be increased. Currently, the only approach for rare sugar synthesis is through the Izumoring strategy, which uses isomerases, epimerases, and oxidoreductases to interconnect monosaccharides. Nonetheless, it is limited in scale and only permits usage of nonprotected monosaccharides. Herein, we purpose an alternative to the Izumoring strategy, the Mother of all Monosaccharides (MoM). In this strategy, semi-protected monosaccharide building blocks will be synthesized from D-fructose. Compared to the Izumoring strategy, scale can be expanded, exploration of sugar acids and deoxy sugars, in addition to investigates differing protecting groups. Once completed, aliquoted time on monosaccharide building block synthesis should be condensed, leaving time to synthesize new oligiosaccharides, to seek how differing oxidation states impacts reactivity and function, and to boldly go where no carbohydrate has gone before.

Design, Synthesis and Characterization of Self-Assembling Nucleotide Phosphoramidates

Nicole M. Bentz, Harrison T. West, Carston R. Wagner* University of Minnesota bentz106@umn.edu

Self-assembling peptides are novel biomaterials that have been widely investigated for their selfassembling properties and ability to form supramolecular structures. Non-covalent interactions that drive the assembly of the peptides typically include aromatic interactions and hydrogen bonding, which enable molecular stacking of individual monomers into highly specific and ordered structures. These high-aspect ratio structures eventually form entangled matrices that result in supramolecular hydrogels. Previous work in our lab incorporated enzymatic activity in the regulation of peptide self-assembly, where we investigated Histidine Triad Nucleotide Binding Protein 1 (hHint1) as a modulator of supramolecular self-assembly. In this work, we developed a panel of self-assembling nucleoside phosphoramidates capable of hHint1 triggered hydrogelation. A surprising observation in the development of these hHint1 responsive molecules was the spontaneous assembly of nucleoside phosphoramidate peptides into highly ordered nanofibers without enzymatic activity. To further understand the assembly properties of the self-assembling nucleoside phosphoramidates, we investigated the critical aggregation concentration of the monomers using Nile red assays and ultracentrifugation sedimentation experiments. We further employed small amplitude oscillatory rheology to investigate the gelation ability of the nanofibers without hHint1 activity, where we discovered that one of the molecules can form hydrogels due to ionic screening and G-tetrad cross-linking.

High throughput tools for continuous flow synthesis of FLT-3 inhibitor, HSN-608

Shruti A. Biyani, Qingqing Qi, Jingze Wu, Yuta Moriuchi, David H. Thompson* Purdue University biyanis@purdue.edu

Developing continuous scalable syntheses of lead compounds to support their rapid pre-clinical and clinical evaluation remains an underdeveloped area. We report an efficient telescoped continuous flow synthesis of an alkynylnaphthyridine lead compound for the treatment of FLT3 mutations in acute myeloid leukemia. Different strategies were used to develop the route, including design of experiments (DoE), high throughput experimentation (HTE), and exploitation of desorption electrospray ionization mass spectrometry (DESI-MS) to integrate, synthesize, and optimize the amidation and Sonogashira coupling. Findings from these statistical design and automation studies helped streamline our workflow to achieve a 10-fold and 5-fold reduction in catalyst and co-catalyst loadings, respectively, in the synthesis of the lead FLT3 inhibitor. The application of the continuous synthesis method enabled the safe and scalable synthesis of this lead compound using the hazardous coupling reagent, HATU, while minimizing by-product formation using a microscale flow reactor system.

Overcoming Kinetic and Thermodynamic Challenges of the Cope Rearrangement

Breanna M. Tomiczek, Ehsan Fereyduni, Ouidad Lahtigui, Michael D. Mannchen, Alexander J. Grenning* University of Florida, Gainesville, FL breanna.tomiczek@chem.ufl.edu

The classic Cope rearrangement is associated with numerous kinetic and thermodynamic issues. For instance, it is known that 3,3-dicyano-1,5-diene substrates have high kinetic barriers (requiring heating at temperatures greater than 120 °C) and typically exhibit thermodynamically unfavorable rearrangements (with low conversion to the Cope product at equilibrium). Herein, we provide two strategies for overcoming kinetic and thermodynamic challenges of previous Cope rearrangements. The first strategy employs the reductive Cope rearrangement to address thermodynamically challenging Cope rearrangements of malononitrile derived 1,5-dienes, affording full conversion to the reduced Cope product. A second strategy is a novel Cope rearrangement of highly substituted 1,5-dienes featuring Meldrum's acid at the 3-position and a 4methyl group, resulting in both kinetically and thermodynamically favorable Cope rearrangements. The Meldrum's acid moiety is a versatile functional handle capable of undergoing further functional group interconversions with ease. Building blocks generated from these Cope rearrangements are valuable as they can be applied in unique ways to complex molecule synthesis. For example, an application of this work incorporates the new Cope rearrangement into four-step sequences for accessing complex carboxylic esters and amides, utilizing Knoevenagel adducts as starting materials.

Utilization of Biophysical Assays for BPTF Reader Domain Chemical Probe Development

Caroline R. Buchholz, Huda Zahid, William C. Pomerantz* University of Minnesota, Minneapolis, Minnesota buchh112@umn.edu

In many disease states there is a dysregulation in gene expression, which can be driven by the aberrant levels or function of epigenetic protein complexes. One such epigenetic protein dysregulated in numerous cancers is the bromodomain and PHD-finger containing transcription factor (BPTF), which binds to chromatin via interactions with acetylated histone (H4K16ac) through its bromodomain and trimethylated histone (H3K4me3) through its C-terminal PHD finger to facilitate chromatin remodeling. Although evidence supports the role of the BPTF protein in disease, the relevance of its individual domains is unclear. In order to study disease function of each BPTF reader domain it will be advantageous to design selective probes for each. Currently, there are no probes for the PHD finger, but there is a reported selective small molecule for the bromodomain, AU1, and a promising new heterocycle scaffold in our lab. We have utilized Protein-Observed Fluorine (PrOF) NMR, AlphaScreen, and x-ray crystallography to rationally design and expand the heterocyclic scaffold into a potent lead series against the bromodomain. To begin to assess the ligandability of the PHD finger computational analysis has been performed, as well as development of a fragment-based screen using Car-Purcell-Meiboom-Gill (CPMG) 1H NMR, and a complementary-screening experiment using PrOF NMR.

Improving the Therapeutic Window: Synthesis of Azaborine Analogs of the Synthetic Retinoid, CD437

Cassandra L. Schrank, Brittney A. Haney, Ana V. Cheng, William M. Wuest* Emory University, Atlanta, Georgia cassandra.lynn.zaremba@emory.edu

In collaboration with Proferssor Eleftherios Mylonakis's lab at Brown University, we have demonstrated the activity of the synthetic retinoid, CD437, against methicillin-resistant Staphylococcus aureus (MRSA) as well as their membrane-targeting mechanism of action. Although CD437 and subsequent analogs have shown promising activity against gram-positive pathogens, their therapeutic viability remains an issue. Specifically, through preliminary analysis, our best performing analog, Analog 2, displayed low solubility within serum as well as high affinity for retinoid binding proteins with a concentration dependent relationship. To improve the solubility and decrease binding affinity, we have proposed a class of analogs containing an azaborine substitution for the naphthalene ring. Azaborines have a nitrogen-boron bond substituting a carbon-carbon double bond that alters the electronics of the parent scaffold. This motif has been explored successfully in both cancer and agricultural research but has yet to be applied to antibiotics. We hypothesize that this isosteric substitution may be efficient in reducing the affinity to retinoid binding proteins as well as increase its solubility thereby improving its therapeutic index.

An Efficient Room Temperature Cobalt Catalyst for Nitrile Dihydroboration

Chandrani Ghosh,[†] Suyeon Kim, Matthew R Mena, Jun-Hyeong Kim, Raja Pal, Christopher L. Rock, Thomas L. Groy, Mu-Hyun Baik,* Ryan J. Trovitch* Arizona State University, Tempe, Arizona [†] Current Affiliation: New York University, New York, New York cg162@nyu.edu

Nitrile reduction to primary amines is a widely employed synthetic strategy in pharmaceutical, agrochemical, and specialty chemical industries. Common reducing methods are often challenged by poor product selectivity, cost, and process safety. In contrast, catalytic dihydroboration is an attractive, greener, and atom efficient approach. It also offers the selective preparation of primary amine derivatives (N,N-diboryl amine), which are extensively used in organic synthesis. However, due to high bond dissociation energy of nitriles, transition metal catalysts are scarcely reported. Moreover, most of the known catalysts are either precious metals or require heating and high catalyst loadings. This presentation describes the use of an efficient Earth abundant cobalt catalyst that enables nitrile dihydroboration at room temperature. Dihydroboration of 14 substrates featured good tolerance to functional groups including halides, ethers and heterocycles. Mechanistic analysis using control experiments and DFT calculations revealed a novel and comprehensive mechanism involving ligand-assisted borylation. Furthermore, N,N-diboryl amine products have been successfully utilized in amide synthesis without any catalyst or activating agent. To the best of our knowledge, this is the first report for cobalt catalyzed nitrile dihydroboration at room temperature with a TOF of up to 380 h-1.

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Dearomative Synthetic Entry into the Altemicidin Alkaloids

Claire S. Harmange Magnani, Thomas J. Maimone* University of California, Berkeley claire magnani@berkeley.edu

Altemicidin and related monoterpene alkaloids possess dense, highly polar azaindane cores and demonstrate potent cytotoxicity and tRNA synthetase inhibition. Reports that tRNA synthetase inhibitors serve as excellent candidates for antibiotic and antimalarial drug development and speculations that the rare primary sulfonamide sidechain–pervasive throughout the altemicidin alkaloids–effectively imitates natural aminoacyl AMP substrates have motivated us to synthesize altemicidin family members for systematic study of this biological activity.

Nonetheless, the congested alpha-amino acid motif decorating an iridoid-like core has rendered the altemicidin alkaloids both a synthetic challenge and biosynthetic mystery to date. Herein we report a distinct and concise synthetic entry into the altemicidin alkaloids. Key chemical findings include: the exploitation of a dearomative pyridinium addition reaction, a [3+2] cycloaddition to stereospecifically install the quaternary amine moiety, and a novel molybdenum-mediated double reduction to establish the fully functionalized azaindane with minimal redox manipulations. This work addresses several chemoselectivity challenges and uses abundant feedstock chemicals to produce altemicidin with scalability and convergence enabling future research into its medicinal properties.

Mannich-type Reactions of Cyclic Nitrones: Effective Methods for the Enantioselective Synthesis of Piperidine Alkaloids

Tessa Lynch-Colameta, Vladislav G. Lisnyak, Scott A. Snyder* University of Chicago, Chicago, IL colameta@uchicago.edu

Although there are dozens of biologically active 2- substituted and 2,6-disubstituted piperidines, only a limited number of approaches exist for their synthesis. Herein is described two Mannich-type additions to nitrones, one using β -ketoacids under catalyst-free conditions and another using methyl ketones in the presence of chiral thioureas, which can generate a broad array of such 2-substituted materials, as well as other ring variants, in the form of β -N-hydroxy-aminoketones. Both processes have broad scope, with the latter providing products with high enantioselectivity (up to 98%). The combination of these methods, along with other critical steps, has enabled 8-step total syntheses of the 2,6-disubstituted piperidine alkaloids (–)-lobeline and (–)-sedinone.

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Synthesis and thermophysical properties of agmatine-based ionic liquids and salts bearing biorelevant anions: Old drugs towards one direction biocompatibility

Dajana S. Lazarevic, Milan B. Vranes, Jovana J. Panic, Prof. dr Milan Vranes* Faculty of Sciences, Novi Sad, Republic of Serbia dajanna.lazarevic@gmail.com

For the first time, dicationic biological molecule agmatine in the synthesis of three novel ionic liquids, agmatine ibuprofenate, agmatine salicylate and agmatine nicotinate, as well as of six salts, agmatine citrate, agmatine ascorbate, agmatine glutamate, agmatine m-hydroxybenzoate, agmatine nitrate, and agmatine chloride was used. Agmatine is an endogenous polycationic amine derived from L-arginine through enzymatic decarboxylation from amino acid L-arginine. It is present in plasma and widely distributed in mammalian tissues. In the central nervous system, agmatine is considered to have the role of a neurotransmitter. The synthesis was conducted by neutralization of agmatine hydroxide solution with relevant acids and then characterized by IR, NMR, TG and DSC measurements. Cytotoxicity study of these compounds has been performed on the human non-tumor cell line (normal fetal lung fibroblasts, MRC-5) and human caucasian colon adenocarcinoma (HT-29). Thus, the obtained biocompatible ionic liquids and salts may be potentially beneficial for stabilizing bioactive compounds by improving solubility in aqueous media and biodistribution to target sites. This can cause easier and better dissociation of the ionic liquids and hence greater biological availability of both cation and anion in the organism.

Programmed Sequential Additions to Dihalogenated Muconitriles

Elsa M. Hinds, Adam J. Zahara, Sidney M. Wilkerson-Hill* University of North Carolina, Chapel Hill, NC ehinds@email.unc.edu

A variety of dihalogenated mucononitriles were synthesized and their reactivity were explored to assess their ability to function as linchpin reagents. Bis(2-chloroacrylonitrile) and bis(2-bromoacrylonitrile) were synthesized in 2-3 steps from commercially available materials and were shown to undergo conjugate addition reactions with both nitrogen and carbon nucleophiles in good to excellent yields, and the sequence of the addition could be controlled. The multicomponent coupling products could then be diversified to access tetrahydronaphthalene motifs in very good yield.

Setting up a Discovery Process Research Group at Janssen

Elizabeth C. Swift, Daniel Pippel, Jaume Balsells Janssen R&D, San Diego, CA eswift1@its.jnj.com

The transition from Discovery to Development is an exciting time in a compound's journey from an idea to its commercial launch. The Discovery Process Research group at Janssen was created to impact this critical project space in a number of ways. The group's main goals are to use chemistry problem-solving to contribute to program strategy and execution, enable and inspire broad structure–activity relationship studies, deliver bulk intermediates, and define the synthetic route for transition to preclinical development. This poster will present the ideas behind the creation of the group and demonstrate our plans for impact on the drug discovery process.

Synthesis of Azetidines via Visible Light-Mediated Intermolecular [2+2] Photocycloadditions

Emily R. Wearing, Marc R. Becker, Corinna S. Schindler* University of Michigan, Ann Arbor, Michigan ewearing@umich.edu

Strained, four-membered nitrogen heterocycles such as azetidines are highly desirable compounds for drug discovery and development, however, these compounds can pose synthetic challenges limiting their applicability. While intermolecular [2+2] photocycloadditions are commonly employed to enable the synthesis of 4-membered cyclobutanes and oxetanes, this powerful methodology remains underdeveloped for the synthesis of azetidines through the aza Paterno-Buchi reaction. Herein we report the development of a visible-light mediated aza Paterno-Buchi reaction that utilizes the unique triplet state reactivity of cyclic oximes, specifically 2-isoxazoline-3-carboxylates. The reactivity of these oximes can be harnessed by triplet energy transfer from an iridium photocatalyst, allowing for cycloaddition with a broad range of alkenes. This approach is characterized by its operational simplicity, broad scope, and mild conditions, enabling the synthesis of highly functionalized azetidines from readily available precursors. These azetidine products can be converted to unprotected, free azetidines, offering a new approach to these highly desirable synthetic targets.

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Exploiting Unique Features of the Casp2 Active Site to Generate Selective Probes for the Study of Tau-related Neurodegeneration

Jessica L. Fuller, Kathy Nelson, Bill McCue, Michael Walters, Barry Finzel* University of Minnesota fulle395@umn.edu

Down-regulating or genetically deleting caspase-2 (Casp2) protects neurons from excitotoxicity and oxidative stress, and repairs synaptic and cognitive deficits that cause tauopathies. Casp2 cleaves tau protein at D314 to generate the cleavage product Δ tau314. This results in tau mislocalization to the dendritic spines, which leads to synaptic dysfunction and impaired cognition. Based on these findings, our hypothesis is that Casp2 inhibition will restore cognitive function in tauopathies. To demonstrate that inhibiting Casp2 activity can prevent neurodegenerative abnormalities, we are seeking to develop a selective Casp2 inhibitor to serve as a chemical probe. Structural differences between the active sites of Casp2 and caspase-3 (Casp3), include (1) Casp2 preference for pentapeptides as opposed to tetrapeptides, (2) differences in the shape and properties of the S2 pocket, and (3) the presence of an acidic amino acid (glutamic acid, E52) in the Casp2 active site. Exploiting these differences, as well as others observed upon comparison of protein-inhibitor structures at Casp2 and Casp3, will aid the generation of selective Casp2 probes that will be used to elucidate the role of Casp2 in tau-related neurodegeneration. A look at the structural biology work to date on this project will be presented.

Double-headed nanosystems for oral drug delivery

Gagandeep Kaur, Meenakshi Arora, Raghu Ganugula, M. N. V. Ravi Kumar Texas A&M University, College Station gkaur@tamu.edu

Ligand-receptor stoichiometry plays an important role in receptor-medicated targeted delivery. We demonstrate a novel strategy to engineer double-headed nanosystems by chemical modification of the carboxyl terminal polyester with a linker that offers tripodal arrangement of ligands on the particle surfaces. The in vivo results suggest that the bioavailability of encapsulated curcumin is proportional to the ligand density rendered by double-headed nanosystems.

Ni-Catalyzed Dearomative Arylboration of Indoles

Grace Trammel, M. Kevin Brown* Indiana University gneathe@iu.edu

Arylboration of alkenes is a synthetically valuable alkene functionalization strategy in which C(sp3)-B and C(sp3)-C(sp2) bonds are formed in a single transformation, resulting in netdifunctionalization after derivatization of the C-B bond. Our group recently discovered a Nicatalyzed arylboration of challenging unactivated alkene substrates, including 1,1- and 1,2disubstituted, and trisubstituted alkenes.

In this work, Ni-catalyzed dearomative arylboration of N-Boc-indoles has been developed. Methods for transition metal catalyzed, intermolecular dearomatization of indoles are rare and limited. This method accomplishes dearomatization of a variety of substituted indoles in good yield, high regioselectivity, and >20:1 dr. The indoline products contain a versatile boronic ester handle that may be functionalized to access diverse and medicinally-interesting molecules.

Poster 29

Rational design, synthesis and fluoride sensing studies using urea-receptor functionalized push-pull chromophores for equipment-Free, low-cost, visual detection system in water

Gowri Jayamurugan, Sachin Jalwal and Arif Hassan Dar, Govindasamy Jayamurugan* Institute of Nano Science and Technology, Mohali-160062, Punjab, India gowri.rp221842@inst.ac.in

Among the contaminants fluoride is unique as its presence in water both low and high is dangerous and would lead to skeletal and non-skeletal fluorosis-disorders. UNICEF reports that fluorosis is endemic in at least 25 countries across the globe due to fluoride rich belt. Currently available, solution based commercial kits demand instrument based analytical methods. Some colorimetric receptors are exist but they suffer low-sensitivity and handling issues like work only with pH=1, use of metals, chemical-treated paper etc. The main challenge in H-bonding mediated fluoride recognition is its reversibility under aqueous conditions. Hence, no single receptor works under environmental conditions. To overcome this, our approach is to combine the urea receptor with non-planar push-pull chromophores whose charge-transfer properties can be greatly altered upon binding fluoride. The successful demonstration visual detection in water was achieved by judicious choice of substitution on the urea-receptor functionalized chromophores. Thus, enabling to exhibit enhanced colorimetric color change. The developed receptors provide multiway outputs like UV/Vis, fluorescence, NMR, and more importantly visual detection in both solution- and solidphases. In summary, the patented technology describes the rationally developed non-obvious chromophore and simple untreated paper kit to test the fluoride content upto 3 ppm in aqueous conditions is presented.

Cell type-specific lysosome targeting chimeras (LYTACs) promote membrane protein degradation

Green Ahn, Steven M. Banik, Caitlyn L. Miller, Carolyn Bertozzi* Stanford University, Stanford, CA greenahn@stanford.edu

Targeted protein degradation (TPD) has become an effective strategy to modulate components of proteome that are canonically challenging to drug. Several TPD platforms including PROTACs rely on the cytosolic ubiquitin proteasome system to induce degradation, restricting their targets to proteins with accessible cytosolic domains. In order to expand the scope of TPD to broader targets, we have developed lysosome targeting chimeras (LYTACs) for targeting extracellular and membrane proteins for degradation. Our strategy bridges the target protein with an endogenous surface receptors such as the cation-independent mannose-6-phosphate receptors (CI-M6PR) that traffic proteins to the lysosome for degradation.

LYTAC's reliance on an internalizing receptor enables targeting distinct cell types with precision, based on their complement of internalizing receptors. Here we developed LYTAC for targeting membrane proteins in a cell type-specific manner by hijacking a surface receptor exclusively expressed on hepatocytes. Our strategy induced selective degradation of membrane targets in hepatocytes, and resulted in substantial functional effect.

In addition, the heterogenous nature of both the polymer ligand and conjugation chemistry in our first implementation of LYTACs prevented rigorous structure-function studies. We are now using site-specific chemistry to conjugate a homogeneous ligand to the antibody to elucidate the structure-function relationships of LYTACs. Site-specific conjugation also demonstrated that the structure of LYTACs has a powerful effect on the pharmacokinetic profile in vivo.

A Lewis Acid Catalyzed Deoxyfluorination of Alcohols Mediated by a Phosphorus Reagent

Hye Won Moon, Alexander T. Radosevich* MIT, Cambridge, MA hmoon@mit.edu

Deoxyfluorination of alcohols is an attractive method to access organofluorine compounds from naturally abundant and readily available alcohol-containing precursors. Current methods typically proceed under basic reaction conditions, which often results in a significant amount of elimination side products. An excess amount of the fluoride source is also commonly used. By contrast, we have developed a novel base-free deoxyfluorination reaction that uses tritylfluoride as a stoichiometric fluoride source. The reaction is initiated by phosphine-mediated activation of the substrate alcohol through O–H oxidative addition, followed by Lewis acid-catalyzed fluoride shuttling to afford the target deoxyfluorination product. By tuning the fluoride ion affinity (FIA) of the triarylborane Lewis acid, the reaction condition is optimized to enable the deoxyfluorination of a variety of aliphatic alcohols, including secondary and tertiary alcohols with stereoinversion. Given that these substrates are relatively challenging for other methods that typically undergo C–F bond formation via $S_N 2$ substitution, this method will potentially complement existing deoxyfluorination methods.

Progress in the total synthesis of nagelamide M

Grace E. Hubbell, Jetze J. Tepe* Michigan State University, East Lansing, Michigan hubbel30@chemistry.msu.edu

Nagelamide M is an oroidin alkaloid first isolated from the Agelas sp. marine sponge in 2008 which contains a synthetically challenging tetrahydro-pyrrolo imidazol-ol ring system and has yet to succumb to total synthesis. This molecule shares several important structural features with the oroidin alkaloids palau'amine and dibromophakellin, which our group have previously identified as biologically active molecules towards an intracellular target used in the treatment of certain cancers. Previous syntheses of the tetrahydro-pyrrolo imidazol-ol ring in total syntheses of other oroidin alkaloids such as dibromoagelaspongin and the axinellamines have involved oxidative cyclization upon the 2-aminoimidazole by a nitrogen nucleophile. We propose that the nucleophilic attack of guanidine upon a reactive α -iminoketone be utilized to facilitate the construction of the tetrahydro-pyrrolo imidazol-ol ring system. This presentation will highlight the synthetic progress towards the α -iminoketone moiety to achieve the first total synthesis of nagelamide M.

Interrupted Carbonyl-Olefin Metathesis of Cyclic, Aliphatic Ketones

Hannah L. Vonesh, Haley Albright, Corinna S. Schindler* University of Michigan hvonesh@umich.edu

Functionalized pentalenes, indenes, naphthalenes and azulenes represent common structural motifs in many compounds of biological importance. We herein describe a new iron-catalyzed synthetic strategy that enables access to these central scaffolds in two steps from commercial material. This method complements established transformations between carbonyl and olefin moieties, such as carbonyl-ene, Prins and carbonyl-olefin metathesis (COM) reactions as a fourth reactivity mode. Experimental and theoretical investigations support a mechanism that interrupts the carbonyl-olefin metath-esis reaction pathway through the distinct fragmentation of intermediate oxetanes resulting in the direct formation of functionalized pentalenes, indenes, naphtalenes, and azulenes. The scope of this new iron-catalyzed transformation between carbonyl and olefin functionalities is demonstrated with 19 examples proceeding in up to 99% yield.

No Sprout Left Behind: An ode to peniciaculin A and its derivatives

Ingrid K. Wilt, Adrian R. Demeritte, Alex T. Kim, William M. Wuest* Emory University, Atlanta, GA ingrid.kristin.wilt@emory.edu

Alternaria brassicae causes premature wilting and leaf spots in brassica plants, such as Brussels sprouts and cabbage, leading to devastating crop depletion and economic loss. Inhibitors of A. brassicae, referred to as quinone outside inhibitors (QOIs), bind to the quinone outside site of the Cyt bc1 complex of the electron transport chain, acting as ubiquinone mimics and stalling ATP production. Peniciaculin A, isolated from marine sediment, demonstrates potent activity against the fungal pathogen A. brassicae (MIC = $0.5 \mu g/mL$). Due to aryl chemotype similarities with known QOI azoxystrobin and preliminary binding site modeling, the phenol core of peniciaculin A is proposed to interact with key Phe128 residue in the Cyt bc1 and the biaryl fragment with Phe274, Phe276, and Tyr278, while the alkyl side chain may access an unexplored hydrophobic binding pocket, increasing potency against A. brassicae. The diverted synthetic route to peniciaculin A utilizes a pivotal Grignard addition into a chiral auxiliary to install the tetrasubstituted benzylic stereocenter and nucleophilic substitution to join the phenol core to the biaryl fragment. Biological evaluation of peniciaculin A and key derivatives will be investigated to determine if this class of molecules is inhibiting fungal growth as QOIs.
Synthetic modular approach for fully degradable imine-based p-type and ntype polymer semiconductors

Jerika A. Chiong, Helen Tran, Shayla Nikzad, Nathaniel J. Schuster, Amnahir E. Peña-Alcántara, Kathy Liu, Vivian R. Feig, Sara R. A. Ruth, Zhenan Bao* Stanford University, Stanford, CA jachiong@stanford.edu

Skin-inspired electronics show promise for use in health applications and eco-friendly consumer products. As we continue to rely increasingly on consumer electronics, there is a need to render these products transient. Devices that are biodegradable open avenues for use in implantable electronics. Polymers are an attractive platform for electronics due to their scalability and ability to be rationally tuned by synthetic design. Previously, our group has designed a fully degradable semiconductor based on the seminal use of imine bonds to make acid-labile polymers. However, the development of these semiconductors requires the synthesis of new monomers for each new polymer design, and the resulting charge carrier mobility does not meet current standards. Herein, we present a synthetic modular approach for the rapid preparation of degradable imine-based donor-acceptor polymers with established (often commercially available) monomers, leading to improved charge carrier properties and the first demonstration of a fully degradable n-type semiconductor. We show characterization by UV-Vis spectroscopy and GIWAXS as well as the performance of these polymer semiconductors in field-effect transistors. This approach for fully degradable semiconductors is crucial toward advancing the field of skin-inspired electronics and addressing unmet challenges in health and the environment.

Probing Noncovalent Interactions in Asymmetric Catalysis Using Computational Chemistry and Data Science

Jacquelyne A. Read, Matthew S. Sigman,* Eric N. Jacobsen* University of Utah, Salt Lake City, UT jacquelyne.read@utah.edu

Noncovalent interactions are often key features of enantioinduction in asymmetric catalysis, from organocatalytic systems to transition-metal catalysis. Repulsive interactions arising from the steric properties of molecules are frequently invoked when rationalizing stereochemical outcomes of transformations, yet attractive noncovalent interactions can be just as important for enantioinduction. Correlating molecular properties to the selectivity of a transformation can reveal selectivity-determining features. This approach was employed for several different transformations. Symmetry-adapted perturbation theory (SAPT) was used to compute noncovalent interaction energies of model systems at relatively low-cost and reasonably high accuracy. These interaction energies proved essential for interpreting enantioinduction in a number of asymmetric, catalytic transformations. The enantioselectivity of a fluorinative bromonium rearrangement was discovered to be dependent upon both a CH-pi interaction and a pi-pi interaction. Multiple asymmetric, hydrogen-bond-donor catalyzed transformations were also studied using the library of computed SAPT interaction energies, as well as molecular properties derived from density functional theory (DFT). These properties were used to build statistical models for selectivity, and correlating these molecular features to enantioselectivity data for multiple transformations revealed specific noncovalent interactions as stereocontrolling factors.

Ketone Reductase Biocatalysis in the Synthesis of Chiral Intermediates Toward Generic Active Pharmaceutical Ingredients

Joanne B. Sampson, Marina Y. Raynbird, Dan A. Smith, Siân M. Forsyth, Jonathan D. Moseley and Andrew S. Wells CatSci Ltd, Cardiff, Wales jo.sampson@catsci.com

For some time, biocatalysis has been recognised as a viable technology in the scale-up and manufacture of valuable chiral intermediates in the chemical industry. Not only do enzymes often afford greater stereoselectivity than traditional chemical transformations, but many biocatalytic processes are highly efficient and require less energy, resulting in highly sustainable manufacturing processes. Consequently, the use of biocatalysis in the synthesis of high-value products, such as active pharmaceutical ingredients (APIs), is gaining momentum. In this work, a range of generic APIs and key intermediates were examined for potential chiral alcohol motifs. For seven APIs, eight precursor ketones were acquired and then subjected to reduction by >400 commercially available ketone reductases. Positive screening results were achieved for five ketones screened, with multiple ketone reductases available for each successful ketone. Selectivity was typically >99.5% ee, including for the opposite enantiomer. The three best examples were optimised and quickly scaled up to 1 L scale in high conversion and isolated yield while retaining selectivity of >99.5% ee for the desired alcohol enantiomer. This work illustrates that where a wide range of enzymes are available, productive enzymes to give either alcohol enantiomer can be readily identified and rapidly scaled up to produce chiral alcohols.

Total Synthesis of Nortopsentine D

Katarina L. Keel, Jetze J. Tepe* Michigan State University, East Lansing, MI keelkata@msu.edu

Nortopsentine D was first isolated in 1996 from the axinellid sponge Dragmacidon sp. and is part of a family of imidazolediylbis(indole) alkaloids. While the majority of this family is comprised of imidazole-linked indoles, Nortopsentine D contains a 4H-imidazol-4-one as its core heterocycle. This natural product was tested for its cytotoxicity against KB tumor cells and proved to be highly cytotoxic when methylated, with an EC50 of $0.014 \mu g/mL$, or 18 nM. To synthesize Nortopsentine D, the 4H-imidazol-4-one was divided into two key intermediates, an indole-3-carboxamidine and a 1-indole-2-imidazopyrimidine-ethane-1,2-dione. The carboxamidine was produced through a series of transformations, starting from 6-bromoindole. The dione was produced through a Sonogashira coupling of 3-ethynylindole and 2-iodo-3-methylimidazopyrimidine. The internal alkyne was then oxidized to a dione via a gold-catalyzed nucleophilic oxidation using 2chloropyridine N-oxide. Cyclization of the carboxamidine and dione under basic conditions, followed by the deprotection of imidazopyrimidine to 2-aminoimidazole, completes the first total synthesis of Nortopsentine D.

Photoredox-Mediated Dearomative Hydrofunctionalization

Kelly A. McDaniel, Autumn R. Flynn, Anna R. Blood, Meredith E. Hughes, David B. Vogt, Nathan T. Jui* Emory University, Atlanta, Georgia kelly.anne.mcdaniel@emory.edu

Inspired by previous olefin hydroarylation methods, a photocatalytic system for dearomative indole hydroarylation has been developed for the synthesis of C2-arylindoline scaffolds. Aryl radical addition followed by a second reduction event prevents oxidation and aromatization to the indole product. In a similar way, the dearomative hydroarylation of benzene derivatives has been achieved. This process operates through a reductive radical-polar crossover mechanism where aryl halide reduction triggers a regioselective cyclization event, giving rise to drug-like spirocyclic cyclohexadienes. A protocol for the dearomative synthesis of related spirocyclic lactam/cyclohexadiene scaffolds through the cyclization of α -acyl radicals has additionally been developed. A crucial mechanistic component of this reductive radical-polar crossover system is that the first reduction must be more difficult than the second. These light-driven systems function under mild conditions without the need for precious metal-based catalysts or reagents and are tolerant of a wide range of functional groups.

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Expanding Catch and Release DNA Decoy Technology with 2-Nitropyrrole and 2-Nitroimidazole Pyrimidine Mimics

Samantha A. Kennelly, Ruben Silva Otera, Ramkumar Moorthy, Daniel A. Harki* University of Minnesota, Minneapolis, MN kenne848@umn.edu

NF- κ B is a transcription factor (TF) that regulates the expression of genes involved in key physiological processes including inflammation, cell survival, proliferation, and the immune response. NF-kB proteins continuously cycle in cells by altering their distribution between the cytoplasm and nucleus, and this dynamic activity is not fully understood. Therefore, characterizing NF-kB activity through the development of chemical tools are key to understanding its cellular functions. The Harki lab has reported that 7-nitroindole (7-NI)-containing DNA decoys designed to bind the NF-kB p50-p65 heterodimer can confer a new chemical tool to study NF-kB-DNA interactions. These NF-kB-targeted Catch and Release DNA Decoys (CRDDs) utilize singlephoton UV-irradiation to cleave the anomeric bond, leading to depurination between the sugar and nucleobase to achieve dissociation of the NF-kB-CRDD complex, yielding temporal control of the binding event. Here, photochemically responsive pyrimidine mimics based on 2-nitroimidazole (2-NI), 2-nitrobenzene (2-NB), 2-nitropyrrole (2-NP) and 3-nitropyrrole (3-NP) were explored as prospective CRDDs. Characterization studies of the pyrimidine analogues revealed that 2-NI and 2-NP can serve as CRDDs, thus expanding the chemical toolbox of CRDD nucleotides to both purine and pyrimidine mimics. This poster will report novel nucleoside synthesis, mechanistic studies of depurination, and the stabilities of CRDDs containing next-generation nucleotides.

The Involvement of Halogen Atoms as Neighboring-Group Participants on Nucleophilic Substitution Reactions of Acetals

Krystyna M. Demkiw, K. A. Woerpel* New York University, New York, NY kmd481@nyu.edu

The highly diastereoselective reactions of 2-halopyrans with various nucleophiles outline the powerful influence of C2 participating halogen atoms on guiding the stereoselectivity of nucleophilic substitution reactions of acetals. Variations in the C2 halogen atom and the ring size of the substrates were studied to determine the mode of participation by the halogen atom. The observed trend of higher trans selectivity as the size of the C2 halogen atom increases is consistent with addition to the oxocarbenium ion intermediate stabilized by hyperconjugative effects. The use of carbon and oxygen nucleophiles follow this trend. To explore the possibility of a halonium ion intermediate, halogen-containing exocyclic acetal substrates were synthesized. These substrates could evoke a halonium ion intermediate though a less strained 5-membered ring, and the halogen atom would not be able to participate in hyperconjugation. The diastereoselectivity trends observed supported participation of halogen atoms by through-space electrostatic stabilization. Accelerated hydrolysis rates of these halogen-containing substrates are also consistent with the proposed electrostatic model. Regardless of ring size, the observed selectivity can be rationalized without the need to evoke a halonium ion intermediate. Thus, indicating that participating halogen atoms guide the selectivity of reactions by hyperconjugative interactions when possible, and electrostatic interactions otherwise.

Incorporation of Agouti-Related Protein (AgRP) Human Single Nucleotide Polymorphisms (SNPs) in the AGRP-Derived Macrocyclic Scaffold c[Pro-Arg-Phe-Phe-Asn-Ala-Phe-DPro] Decreases Melanocortin-4 Receptor Antagonist Potency and Results in the Discovery of Melanocortin-5 Receptor Antagonists

Zoe M. Koerperich , Mark D. Ericson, Katie T. Freeman, Robert C. Speth, Irina D. Pogozheva, Henry I. Mosberg, Carrie Haskell-Luevano* University of Minnesota, Minneapolis, MN koerp005@umn.edu

The melanocortin receptors belong to the family of G protein-coupled receptors (GPCRs). Five melanocortin receptors have been discovered to date, which respond to both endogenous agonists and antagonists, and are known to be involved in numerous biological pathways. However, the potential roles of the MC5R have not been clearly elucidated in humans. Agouti-Related Protein (AgRP), an MC3R/MC4R antagonist and MC4R inverse agonist, contains an exposed β-hairpin loop composed of six residues (Arg-Phe-Phe-Asn-Ala-Phe) that is imperative for binding and function.

This study focused on exploring four SNPs that were deposited into the NIH Variation Viewer3, which result in missense mutations in the proposed active loop of AgRP. It was hypothesized that the polymorphisms would alter AgRP signaling in the MC4R cascade, which may have physiological consequences in humans. These polymorphisms, Arg111Cys, Arg111His, Phe112Tyr, and Ala115Val (AgRP full-length numbering) were incorporated into the peptide macrocycles c[Pro1-Arg2-Phe3-Phe4-Xaa5-Ala6-Phe7-DPro8], where Xaa was Dap5 or Asn5, to explore the functional effects of these naturally-occurring substitutions in a simplified AgRP scaffold, that had previously been shown to have potent MC4R activity. All peptides lowered potency at least 10-fold in a cAMP accumulation assay compared to the parent sequences at the MC4Rs. Compounds MDE 6-82-3c, ZMK 2-82, MDE 6-82-1c, ZMK 2-85, and ZMK 2-112 are also the first AgRP-based chemotypes that antagonize the MC5R.

Organic Photoredox-Catalyzed Oxidative Reactions Under Homogeneous Single-Chain Polymer Confinement

Lauren E. Chamberlain, Ashley C. Hoover, Jacob J. Piane, Lucas T. Alameda, Elizabeth Elacqua* Penn State lec5399@psu.edu

Single-chain polymer nanoparticles (SCNPs) have emerged as a versatile catalytic platform that provide excellent control over solubility. The confined nature of SCNPs has been shown to improve the rate of catalytic transformations. While significant headway has been made in transition metal catalysis with SCNPs, light-activated SCNP catalysts have comparatively received little attention. We have developed triarylpyrylium tetrafluoroborate-functionalized SCNPs as oxidative photocatalysts. Our approach realizes the use of styrylpyrene as both a covalent cross-linker and an electron relay catalyst in photoredox-catalyzed reactions. These metal-free homogeneous single-chain photocatalysts enabled the oxidation of benzyl alcohols. The oxidation was further extended to the amidation of 4-bromobenzaldehyde, proceeding through a transient aminal generated in situ. The SCNPs proved versatile with the photocatlyzed-dimerization of substituted styrenes. In the case of [2+2]cycloadditions, we observed increased activity and low catalyst loading with respect to traditional methods, including utilizing monocatalytic polymers with small-molecule additives. Our approach realizes a dual-catalytic single-chain polymer that provides enhanced reactivity under confinement, presenting a further approach for diffusion-limited-photoredox catalysis.

Synthesis of Benzylic Alcohols by C-H Oxidation

Lalita tanwar, Jonas Börgel, Tobias Ritter Max Planck Für Kohlenforschung ltanwar@mpi-muelheim.mpg.de

Selective methylene C–H oxidation for the synthesis of alcohols with a broad scope and functional group tolerance is challenging due to the high proclivity for further oxidation of alcohols to ketones. A while ago, we reported a novel methodology for oxidative C(sp2)–O bond formation of complex arenes and heteroarenes. Recently, we report the selective synthesis of benzylic alcohols employing bis(methanesulfonyl)peroxide as an oxidant. We attempt to provide a rationale for the selectivity for monooxygenation, which is distinct from previous work; a proton-coupled electron transfer mechanism (PCET) may account for the difference in reactivity.

Poster 45

[3+2] Cycloaddition of O-isocyanates: Novel hydroxylamine-based 1,3-dipole equivalents

Meredith A. Allen, Ryan. A. Ivanovich, André M. Beauchemin* University of Ottawa, Ottawa, Canada malle100@uottawa.ca

The weak N-O bond in hydroxylamines has been exploited productively in many contexts within organic synthesis. Hydroxylamine derivatives have been used as aminating agents employing radical, free nitrene, and metal-catalyzed approaches among others. The dual nucleophilic/electronegative character of the nitrogen and oxygen of hydroxylamines is less frequently exploited. Cycloaddition reactivity analogous to the dipolar cycloaddition of nitrones can be realized using hydroxylamine-containing isocyanates - O-isocyanates. Despite the decades of reports on [3+2] cycloadditions, related reactions with uncharged 1,3-dipole equivalents remain underdeveloped.(1) The novel cycloaddition reactivity of O-isocyanates leads to a zwitterionic cycloadduct, an oxazolium ylide. This cycloadduct can undergo several reaction pathways. forming a variety of heterocycles. Divergent intermolecular cycloaddition reactivity will be presented, forming oxazinanones, β -lactams, and isoxazolidinones.

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Mechanistic Studies of Pd(II)-Catalyzed E/Z Isomerization of Unactivated Alkenes

Rei Matsuura, Malkanthi K. Karunananda, Nhi Nguyen, Keary M. Engle,* Donna G. Blackmond* Scripps Research, La Jolla, California matsuura@scripps.edu

Palladium(II)-catalyzed E/Z alkene isomerization is a common—yet surprisingly uncharacterized— process, particularly for non-conjugated alkenes. In this work, the mechanism of Pd(II)-catalyzed E/Z isomerization of unactivated olefins containing an aminoquinoline-based amide directing group is probed using in situ kinetic analysis, spectroscopic studies, kinetic modeling and DFT calculations. The directing group allows for stabilization and monitoring of previously undetectable intermediates.

'Sacrificial' Supramolecular Assembly and Pressure-Induced Polymerization: Toward Sequence-Defined Functionalized Nanothreads

Margaret C. Gerthoffer, Sikai Wu, Bo Chen, Tao Wang, Steven Huss, Shalisa M. Oburn, Vincent H. Crespi, John V. Badding, Elizabeth Elacqua* Penn State University mcg45@psu.edu

Limited supramolecular strategies have been utilized to synthesize sequence-defined polymers, despite the prominence of noncovalent interactions in materials design. Herein, we illustrate the utility of 'sacrificial' aryl-perfluoroaryl supramolecular synthons to synthesize sp3-hybridized nanothreads from sp2-enriched reactants. Our strategy features A-B reactant pairs in the form a phenol:pentafluorophenol co-crystal that is preorganized for an electronically-biased and sequence-defined polymerization. The polymerization, initiated at 12 GPa, affords an alternating copolymer featuring exogenous –OH functionalities. The external substitution is confirmed through IR spectroscopy. Importantly, the inclusion of the functional unit provides the first experimental glimpse at reaction mechanism: keto-enol tautomerization that can only occur during cycloaddition is also observed through IR spectroscopy. Our approach realizes the first example of a functionalized nanothread and attains sequence definition through sacrificial supramolecular preorganization and presents a further approach for de novo design of complex nanothreads.

Charge-Transfer Character in Excimers of Perylenediimides Self-Assembled on Anodic Aluminum Oxide Membranes

Michele S. Myong, Jiawang Zhou, Ryan M. Young, Prof. Michael Wasielewski* Northwestern University, Evanston, IL michelemyong2016@u.northwestern.edu

Chromophore aggregation strongly impacts the efficiency of organic photovoltaics (OPVs). Perylene-3,4:9,10-bis(dicarboximide) (PDI)-based electron acceptors have been shown to be excellent alternatives to fullerenes in OPVs, provided their supramolecular assemblies do not form excimers. In order to study this phenomenon in a controlled fashion, we have prepared two PDI derivatives that were incorporated into an anodic aluminum oxide (AAO) membrane. In one system, the PDI molecule has an n-propyl silatrane attached to one of its imide nitrogens, while a 12-tricosanyl group is attached to the other imide nitrogen. The silatrane reacts with the AAO surface to covalently bind the PDI. The other PDI has 12-tricosanyl groups on both imide nitrogens, which intercalate with n-octadecylsilane chains covalently bound to an AAO membrane. Since aluminum oxide is a wide bandgap semiconductor, photoexcitation of PDI does not result in charge injection into the AAO membrane; thus, the intrinsic electronic properties of the aggregated PDI molecules within the membrane can be studied. Both PDI derivatives form excimers with and without solvent in the AAO membrane pores and display increasing charge transfer character with increasing solvent polarity. Since the AAO membrane allows for any choice of solvent to be infiltrated into its pores, the PDI photophysics can be modulated over an arbitrary range irrespective of whether PDI is soluble in a particular solvent. The results presented here show how to tune the intermolecular interactions of PDI and related rylene dyes attached to walls of the AAO pores to understand the intermediate regime between solution and the solid state.

On the Mechanism of Aldehyde-Promoted Aerobic Oxidation of Aryl Iodides

Sung-Min Hyun, Asim Maity, Mingbin Yuan, Osvaldo Gutierrez, David C. Powers* Texas A&M University min6539@tamu.edu

Selective O₂ utilization remains a substantial challenge in synthetic chemistry. Biological smallmolecule oxidation reactions often utilize aerobically generated high-valent catalyst intermediates to effect substrate oxidation. Available synthetic methods for aerobic oxidation catalysis are largely limited to substrate functionalization chemistry by low-valent catalyst intermediates (i.e. aerobically generated Pd(II) intermediates). Motivated by the need for new chemical platforms for aerobic oxidation catalysis, we have recently developed aerobic hypervalent iodine chemistry. Here, we report that in contrast to canonical two-electron oxidation mechanisms for the oxidation of organoiodides, the developed aerobic hypervalent iodine chemistry proceeds via a radical chain mechanism initiated by addition of aerobically generated acetoxy radicals to aryl iodides. Despite the radical chain mechanism, aerobic hypervalent iodine chemistry displays similar substrate tolerance observed with traditional terminal oxidants, such as peracids. We anticipate these insights will enable new sustainable oxidation chemistry via hypervalent iodine intermediates.

Automated Solution-Phase Synthesis of S-Glycosides Using Highly Reactive Glycosyl Donors

Mallory K. Kern, Nicola L. B. Pohl* Indiana University, Bloomington, IN mkkern@iu.edu

Thioglycosides are S-linked glycoside analogs more resistant to chemical and enzymatic hydrolysis than their O-linked counterparts that thereby make attractive targets for carbohydratebased therapeutic development. Herein, we report the first development of methods for the siteselective incorporation of S-linkages into automated solution-phase oligosaccharide protocols. Highly glycosyl donors were used for the automated syntheses, with limited side product formation. The protocols were also shown to be compatible with the subsequent formation of Sor O-glycosides in the context of the first synthesis of mannopyranoside trimers that incorporate both S- and O-linkages to allow selective incorporation of an S-glycoside at various stages in an automated oligosaccharide synthesis program

NMR Quantification of H-Bond Donating Ability of Drugs, Bioactive Functional Groups, and Isosteres

Mira Milic, Julia J. Jennings, Karina Targos, Annaliese K. Franz* University of California Davis, Davis, CA mmilic@ucdavis.edu

Hydrogen-bonding interactions are a key feature of a pharmaceutical agent's ability to interact with biological targets. Utilizing a rapid and simple 31P NMR method in which commercially available, inexpensive triethylphosphine oxide (TEPO) was used to probe H-bond donating ability, the H-bond donating abilities of 127 compounds belonging to diverse bioactive functional groups, drugs, and isosteres were quantified utilizing 31P NMR spectroscopy. To probe H-bond donating ability, the 31P NMR chemical shift, in ppm, of a TEPO external standard was subtracted from the downfield chemical shift, in ppm, of an H-bond donor bound to TEPO. Generally, the lower the pKa of a compound or functional group class, the better its hydrogen-bond donating ability; however, the overall correlation between pKa, a value frequently used to predict acidity and indirectly H-bond donating ability, was moderate. When $\Delta\delta(31P)$ NMR measurements of H- bond donating ability were studied as a function of physiochemical properties (LogP, LogD, and plasma protein binding) and equilibrium constants (Log KHA and pKa), correlations were significantly higher. We expect our endeavors to quantify H-bond donating ability will increase the understanding of hydrogen bonding in drug molecules and contribute a directed approach to drug design.

Development of Green Solvent Processable Organic Semiconductors for Printed Electronics

Madison Mooney, Simon Rondeau-Gagne* University of Windsor moone114@uwindsor.ca

Organic-based electronics have recently become an exciting and rapidly evolving area of research due to their low manufacturing costs and improved mechanical properties compared to traditional silicon-based electronics. Printed Electronics (PE) involve the conversion of organic materials with strong electronic properties into functional inks that can be used to print a large variety of electronic devices. With the potential to be cheaper than current electronics, and the capability to be conformable and even bio-compatible, PE have an enormous potential for enabling novel technologies in a broad range of applications. However, with the ever-increasing pace of technological advancements, the cost of these new PE to the environment needs to be considered since electronic manufacturing generates millions of tons of waste each year. To address this important environmental challenge, our research aims to minimize the impact of PE processing by using eco-friendly solvents. Using polymer side-chain engineering, we have developed a series of organic semiconductors with novel green synthetic and processing characteristics. These materials demonstrate tunable solubility for greener processing and use in electronic device printing.

Rational Design of Chiral Tetradentate N4-Iron Catalysts for C(sp3)-H Oxidations

Madeline E. Rotella, Jun Zhou, Peter Zavalij, Fu Chen, Osvaldo Gutierrez* University of Maryland, College Park, MD mrotella@umd.edu

Iron is one of the most attractive targets in the search for inexpensive and nontoxic alternatives to precious metals for catalysis of commercially relevant reactions such as C(sp3)-H oxidations. Que, White, Costas and others have used tetradentate amine ligand scaffolds capable of binding to iron to promote site-selective aliphatic C-H oxidations. However, the role of spin state in these reactions and the ability to tune the spin state of the iron center is not well-defined. Herein, a computational method for the prediction of geometry and spin state of a series of known N4-tetradentate iron complexes is described. Quantum-mechanical calculations were undertaken on this library of compounds to identify a predictive method for determining spin state and geometry of such iron complexes. The ability of this model to predict the geometry and spin state of a series of new chiral diamine tetradentate iron complexes was tested. Applications of these complexes in $C(sp^3)$ -H oxidation chemistry were explored.

Efforts Towards the Synthesis of O-linked Mannose Glycopeptide Targets

Meredith L. Rudich, Nicola L. B. Pohl* Indiana University Bloomington mrudich@iu.edu

The O-linked mannosyl post-translational modification was discovered in mammalian proteins over 30 years ago, in enriched brain lysate. One of the most prevalent and widely studied O-linked mannosylated proteins is alpha-dystroglycan (α -DG). Recently, studies have focused on α -DG due to the serious diseases that are associated with its improper glycosylation, such as cancer metastasis, arenavirus entry, and multiple forms of congenital muscular dystrophy. Although now more widely understood, there still exists work to be done in the synthesis of O- linked mannosylated building blocks. These building blocks have applications in SPPS as well as in larger biomolecular structures. Chemical synthesis of these building blocks has been limited by the unreactive nature of mannose as well as long reaction times. A flow chemistry approach was taken in this synthesis, which alleviates the long reaction times by providing a more efficient heat transfer and better surface area to volume ratio. Flow chemistry also allows for a more easily scalable reaction than previous batch syntheses. Automating these reactions would make these building blocks more accessible and allow for better optimization and reproducibility of results. Herein, we present the efforts towards developing a synthesis of O-linked mannosylated amino acid building blocks from commercial reagents.

Novel Approach to Aryl Ether Synthesis Enabled by N-HVI Reagents

Myriam Mikhael, Sarah E. Wengryniuk* Temple University, Philadelphia, PA myriam.mikhael@temple.edu

Cyclic aryl ethers are common structural motifs in bioactive natural products. Herein, we describe a novel metal-free strategy for an aryl ether synthesis enabled by Nitrogen-ligated (poly)cationic hypervalent iodine reagents (N-HVIs) that, unlike prior methods, does not require prior activation or electron rich aromatics. N-HVIs are novel, abundant, and environmentally benign reagents that have excellent leaving group ability making them ideal for this novel transformation. Our approach is based on an electrophilic activation of the pendant alcohol by N-HVI reagents leading to a C-O bond formation after the aryl ring attack. This oxidative cyclization is followed by a fast generation of an iodonium salt species, providing us with an excellent functional handle for further functionalization at the aryl ring. Mechanistic investigations were performed to prove this novel Umpolung strategy, and the synthetic importance of this methodology is demonstrated in the total synthesis of bioactive complex molecules. This work represents complimentary reactivity to current methods and has the potential to greatly expand the scope of this type of transformation.

Versatile photocatalytic methods for functionalisation of electron-deficient alkenes

Natalia A. Larionova, Jun Miyatake Ondozabal, Emily G. Smith, Xacobe C. Cambeiro Queen Mary University of London n.larionova@qmul.ac.uk

Olefins are among the most abundant and widely available chemical feedstock, indispensable for both the synthetic and biological communities due to their unique reactivity profile. Thus, hydrogenation and hydrofunctionalisation of C-C double bonds are important transformations to access pharmaceutical and chemical compounds that are produced at an industrial scale. We have developed wide-scope, efficient protocols using Ir-based photocatalysts for the reduction and regioselective hydroaminoalkylation of electron-deficient alkenes.

The photocatalytic reduction opens a path for the development of greener and safer hydrogenation methodologies, avoiding the use of high-energy, strong reductants as well as the use of pressure equipment.

Radical addition to α,β -unsaturated carbonyl compounds has been widely investigated as a useful method for functionalisation at the β -position. The α -aminoalkyl radicals formed by photocatalytic oxidation are highly nucleophilic and consequently prone to attack electron deficient alkenes at β -position via Giese-type reaction. There are examples of stereoselectivity control for this reaction, but regioselectivity is completely predetermined by the nature of the substrate. As a result of our research we were able to direct radical addition to the α -position of α,β -unsaturated esters to produce potentially valuable β 2-amino acids. Importantly, our method overcomes relevant scope limitations of alternative approaches to these products, such as Mannich-type reactions.

Mechanistic Insight into Additions of Allylic Grignard Reagents to Carbonyl Compounds

Nicole D. Bartolo, K. A. Woerpel* New York University, New York, NY ndb294@nyu.edu

Allylic Grignard reagents exhibit high reactivity and low selectivity in additions to carbonyl compounds. The low selectivity observed in reactions of allylic magnesium reagents is due to reaction at rates approaching the diffusion limit. Two mechanistic explanations for this unusual behavior were explored: a concerted, six-membered transition state with allylic transposition and single-electron transfer. Using prenylmagnesium chloride as a mechanistic probe, the addition generally proceeds through a six-membered transition state with allylic transposition. Additions of allylic Grignard reagents to radical clocks bearing carbonyl groups, provides evidence against a mechanism involving single-electron transfer.

The Effect of Base and Nucleophile on the Nucleophilic Substitution of Methoxytropone Derivatives: Steric strategy to synthesize 4-and 5-Substituted Multifunctional Azulenes

Neha R. Kumar, Abhijeet R. Agrawal, Aditya Choudhury, Prof. Sanjio S. Zade* Indian Institute of Science Education and Research Kolkata, West Bengal, India nrk14rs020@iiserkol.ac.in

Azulene is a non-alternant non-benzenoid aromatic system, and in turn, it possesses unusual photophysical properties. Azulene based conjugated systems have received increasing interest in recent years as optoelectronic materials. Despite the routes available for the preparation of substituted azulene derivatives, there remain few methods that allow regioselective substitution on the seven-membered ring of azulenes due to the subtle reactivity difference among the various positions. This work explores the reactivity of substituted tropolones as the azulene precursors and provides a method to create 4- and 5-substituted multifunctional azulenes in regioselective manner. The nucleophilic substitution on 3-substituted 2-methoxytropones to form azulenes is dependant on the nucleophile and base employed. With bulkier nucleophiles (ethyl/methyl cyanoacetate), the reaction proceeds with the abnormal nucleophilic substitution (attack at C-7) irrespective of the base and with smaller nucleophiles (malononitrile), the reaction follows base-dependant normal and abnormal nucleophilic substitution. Based on these observations and DFT calculations a new synthetic strategy is devised for the regioselective synthesis of 4- and 5-substituted multifunctional azulenes.

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Development of New Strategies of Umpolung with Cyclic Hypervalent Iodine Reagents

Paola Caramenti, Nina Declas, Raj K. Nandi, Erwann S. Grenet, Jerome Waser* Ecole Polytechnique Fédérale de Lausanne pcaramen@its.jnj.com

Enamines are amongst the most exploited nucleophiles in organic synthesis. They can be formed via condensation over carbonyls, stabilized as enamides or embedded in aromatic frameworks. In particular, electron-rich azoles are perhaps the most ubiquitous "aromatic enamines". Furthermore, the subclass of mixed bi-(hetero)arenes is encountered in top selling drugs and natural bioactive compounds. Even if many methods for the formation of the (hetero)arene-indole or -pyrrole bond have been reported, low regioselectivity, homo-coupling and polymerization are common limitations. To overcome these drawbacks, a "umpolung" approach can be considered to allow new synthetic disconnections. Hypervalent iodine reagents are known to invert the reactivity of various nucleophiles, but have been only rarely used in the case of electron-rich heteroarenes; moreover, the Umpolung of enamides had never been reported. We present herein the synthesis of novel electrophilic azole, enamide and enol ether benziodoxolone reagents. These new reagents are bench stable, highly functionalizable and their synthesis is facile and scalable. They can be applied in metal-catalyzed C-H activation transformations, cross couplings, photoredox fragmentations and nucleophilic substitutions. In all methods the desired products were obtained with high regioselectivity and could not be synthesized using previously reported metal catalyzed C-H functionalization processes.

LRH-1 PROTAC as a potential breast cancer therapeutic and access to spiropiperidine pharmaceutical scaffolds via photoredox.

Racheal M. Spurlin, Michael L. Cato, Amber L. Harris, Cameron J. Pratt, Jeffery L. Cornelison, Emma H. D'Agostino, Eric A. Ortlund, Nathan T. Jui* Emory University racheal.marie.spurlin@emory.edu

One in eight women develop invasive breast cancer during their lifetime. The down-regulation of Liver Receptor Homologue-1 (LRH-1) is a promising method for estrogen-receptor-positive (ER+) breast cancer treatments, the most common subtype, due to LRH-1's role in metathesis. With the use of an LRH-1 proteolysis targeting chimera (PROTAC), we have shown a decrease of LRH-1 in cancerous cell lines due to protein's degradation. Additionally, we have sought out new methods to form pharmaceutical scaffolds using photoredox catalysis. Piperidines are the most common heterocycle in pharmaceutical drugs. Therefore, we have developed a system for the formation of spiropiperidines by hydroarylation of a vinyl piperidine with a tethered aryl halide. This light-driven system functions under mild conditions without the need for a metal-based catalyst and produces benign ammonium iodide as the only byproduct.

Oxalohydrazide Ligands for Copper-catalyzed C-O and C-N Coupling Reactions with High Turnover Numbers

Ritwika Ray, John F. Hartwig* University of California, Berkeley, CA, USA rayritwika@gmail.com

The development of nitrogen- and oxygen-based ligands for copper-catalyzed coupling reactions lags behind that of phosphines for analogous palladium-catalyzed coupling reactions. In particular, ligands that generate copper catalysts that react with lifetimes resembling those of palladium catalysts have been lacking. Here, we report a class of ligand based on oxalohydrazides containing N-amino pyrrole and N-amino indole groups that generates long-lived copper catalysts for couplings to form C-O bonds in biaryl ethers. Copper-catalyzed coupling of phenols with aryl bromides occurred with 8000 turnovers, which is nearly two orders of magnitude higher than prior couplings to form biaryl ethers and nearly an order of magnitude higher than those of any prior copper-catalyzed coupling. This ligand also led to copper systems that catalyzed the coupling of aryl chlorides with phenols and the coupling of aryl bromides and iodides with primary benzylic and aliphatic alcohols. In the presence of the oxalohydrazides, catalytic C-N coupling of aryl bromides with aqueous ammonia and, primary aliphatic and benzylic amines occurred with turnover numbers (TON) approaching 2000. Most notable is the C-N coupling of aryl bromides with free hydrazine with a TON of 1500, without unwanted dehydrohalogenated byproduct formation or polyarylation.

Carbon nanohoop-based polymers with sequence-dependent properties

Ruth L. Maust, Penghao Li, Brian Sun, Ramesh Jasti* University of Oregon, Eugene, OR rmaust@uoregon.edu

Carbon-based materials—such as graphene nanoribbons, fullerenes, and carbon nanotubes—have elicited significant excitement due to their wide-ranging properties and many possible applications. Efforts toward defining structure-property relationships and developing new carbon materials with unique combinations of optical, electronic, and physical properties have been hindered, however, by a lack of methods for precise synthesis, functionalization, and assembly of these materials. To overcome this challenge, we employed the tools of organic chemistry and controlled polymer synthesis to prepare complex carbon materials with a high degree of structural control. Cycloparaphenylenes (CPPs), a family of macrocycles that map onto armchair carbon nanotubes of varying diameters, can be prepared via a bottom-up approach, and derivatives of these molecules can serve as building blocks for larger structures. In particular, we have designed norbornene-functionalized CPPs which undergo controlled ring-opening metathesis polymerization. With this approach, we can access well-defined homopolymers as well as block and statistical copolymers constructed from "carbon nanohoops." These sp2-carbon-dense materials are well-soluble and exhibit fluorescence spectra and responses to guest molecules that can be tuned based on polymer composition and sequence. This work represents an important advance toward bridging the gap between small molecules and functional carbon-based materials.

Designing a Low-Cost User-Friendly High Throughput Experimentation Laboratory

Rosaura Padilla-Salinas, Jaume Balsells Janssen Research & Development LLC

rpadill1@its.jnj.com

High-throughput experimentation (HTE) is a powerful philosophy for reaction discovery and rapid optimization. Technologies originally developed for biological applications have been repurposed to allow chemists to systematically and simultaneously evaluate numerous reaction parameters on microscale. Parameter selection is guided by the prior art and chemical intuition. Automated equipment and dedicated teams for leveraging HTE to reaction discovery have become mainstays in the pharmaceutical sector. Investing in HTE infrastructure has proven itself a valuable, albeit costly, investment; it dramatically accelerates the drug discovery process and yields access to novel chemical space. Universities have also recognized the potential of HTE technologies to accelerate innovation, and through partnerships with industry, have built HTE centers as a centralized resource for their Departments. Even with these partnerships, the investment required for centers can be significant and often will intimidate organizations from adopting HTE. But a lean approach to HTE is possible; herein, we outline the key concepts and basic components for successfully building an HTE laboratory on a limited budget. We also highlight the user-friendly features of HTE that make it accessible to all labs conducting research without automated equipment. An overview of data analysis and strategies for cultivating an HTE mindset is included.

ULTRASOUND-ASSISTED GREEN ONE-POT SYNTHESIS OF LINKED BIS-HETEROCYCLIC PEPTIDOMIMETICS VIA I-MCR/POST-TRANSFORMATION STRATEGY

Sandra Cecilia Ramírez López, Bhavna Kaveti, Ma. Rocio Gámez Montaño University of Guanajuato, Guanajuato sandiiramirez22@gmail.com

A serie of linked bis-heterocyclic privileged peptidomimetic scaffolds are synthesized via a green one-pot strategy based IMCR/post-transformation/tandem. This is the first one-pot synthesis of a 2,5-diketopiperazine linked to a 1,4-disubstituted 1,2,3-triazole. The sequence used in the present work Ugi-4CR/lactamization/click is facile, mild, atom-economical, and green. Furthermore, this work contributes to the synthesis of bis-heterocycle peptidomimetics and design of new bioactive molecules with the use of two eco-friendly and powerful tools resulted in the rapid generation of molecular complexity in target molecules.

Silyl Radical-Mediated Activation of Sulfamoyl Chlorides Enables Direct Access to Aliphatic Sulfonamides from Alkenes

Sandrine M. Hell, C. F. Meyer, G. Laudadio, A. Misale, M. C. Willis, T. Noël, A. A. Trabanco, Véronique Gouverneur* University of Oxford, Oxford, United-Kingdom sandrine.hell@chem.ox.ac.uk

Due to their unique biological properties, sulfonamides can be found in many biologically active molecules for the treatment of several diseases such as cancer, CNS disorder, diabetes, dementia, HIV and others. Since many decades, the development of novel routes for the synthesis of those motifs has attracted many interests to both academia and the pharmaceutical industry. Whilst a plethora of reports has been reported for the synthesis of (hetero)arylsulfonamides, only few procedures focused on their aliphatic analogues. In the context of our collaboration with Janssen, we focused on the development of an operationally simple and cost-effective protocol for the late-stage hydrosulfamoylation of electron-deficient alkenes using sulfamoyl chlorides as radical precursors. The success of this transformation relies on the generation of a sulfamoyl radical by direct Cl-atom abstraction by a silyl radical. This metal-free protocol uses commercially available reagents as well as blue light irradiation as a green and traceless activation source. The robustness of this transformation has been demonstrated by the broad functional group tolerance and the multigram-synthesis of a building block. Furthermore, this method allowed access to unprecedented sulfonamide containing cyclobutyl spirooxindoles and found application to the late-stage functionalization of biologically active molecules.

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Interpretable Deep Learning to Design Nuclear-Targeting Abiotic Miniproteins

Carly K. Schissel, Somesh Mohapatra, Justin M. Wolfe, Colin M. Fadzen, Kamela Bellovoda, Chia-Ling Wu, Jenna A. Wood, Annika B. Malmberg, Andrei Loas, Rafael Gomez-Bombarelli, Bradley L. Pentelute* Massachusetts Institute of Technology, Cambridge MA schissel@mit.edu

There are more amino acid permutations within a 40-residue sequence than atoms on Earth. This vast chemical search space hinders the use of human learning to design functional polymers. Here we show how machine learning enables de novo design of abiotic nuclear-targeting miniproteins to traffic antisense oligomers to the nucleus of cells. We combined high-throughput experimentation with a directed evolution-inspired deep learning approach in which the molecular structures of natural and unnatural residues are represented as topological fingerprints to drive the discovery of high-activity, novel sequences. The model simultaneously deciphers and visualizes sequence-activity predictions. The predicted miniproteins, termed "Mach" and reaching 10 kDa average mass, are more effective than any previously known peptide-based delivery vehicle, nontoxic, and effective in mice, while also shuttling proteins into the cytosol. Our results demonstrate that deep learning can decipher design principles to generate highly active sequences not achievable by any other method. The approach is application agnostic and can be used to design functional polymers of any structure or activity, with implications for the chemical, biological, and medical sciences.

Diastereo- and Enantioselective C–H Insertion Reactions of Donor/Donor Carbenes with Chiral Ethers

Sarah N. Dishman, Croix J. Laconsay, James C. Fettinger, Dean J. Tantillo,* Jared T. Shaw* University of California, Davis sdishman@ucdavis.edu

C–H insertions with donor/donor rhodium carbenes exhibit some of the highest stereoselectivities reported for intramolecular C–H insertion systems. Here we report the expansion of this donor/donor system to chiral, tertiary C–H insertion centers enabling the stereoselective synthesis of highly substituted benzodihydrofuran cores in a single step. Donor/donor rhodium carbenes have been hypothesized to proceed through a stepwise mechanism, yet the factors governing their high stereoselectivity remained elusive until now. In the proposed stepwise mechanism, first the hydride transfers with high stereochemical fidelity determining the enantioselectivity. The diastereomeric ratio (dr) is dependent on the steric bulk and electronics at the C–H insertion center and can be controlled by the enantiomer of Rh2(R/S-PTAD)4. Sterically bulky, highly activated C–H insertion centers exhibit high substrate control yielding a single diastereomer and single enantiomer of product. Less bulky, less activated C–H insertion centers exhibit catalyst control over the dr wherein a single enantiomer of each diastereomer is observed. Ongoing comprehensive DFT calculations of this novel system aim to determine how Rh2(R/S-PTAD)4 controls the dr for less bulky, less activated insertion centers.

Investigation of olefin metathesis on bicyclic tetraenes towards the synthesis of 5-6-5 isoryanodane and 7-5-5 hydroazulene scaffolds

Evgeniya Semenova, Sarah K. Scott, Ouidad Lahtigui, Matthew Albritton, Ion Ghiviriga, Alexander J. Grenning* University of Florida semenovae@chem.ufl.edu

We originally aimed for the synthesis of 5-6-5 isoryanodane core by examining the olefin metathesis reactivity of bridged bicyclic tetraenes, but in the process discovered a novel rearrangement leading to the synthesis of 7-5-5 ring systems. We were also able to manipulate this method to achieve our original goal of isoryanodane core synthesis.

Pressure-induced 1D polymerization of aromatic compounds

Shalisa M. Oburn, Steven Huss, Margaret C. Gerthoffer, Sikai Wu, Vincent H. Crespi, John V. Badding, Elizabeth A. Elacqua, * Elizabeth A. Elacqua Shalisaoburn@psu.edu

Recent synthesis of extended sp3-hybridized 1D carbon-architectures called nanothreads (e.g. polytwistane, similar to higher diamondoids) provide a new avenue attaining small-diameter (ca. 0.4 nm), rigid carbon-based structures. (1) Achieved solely in the solid state through mechanochemical compression of aromatic compounds, nanothreads exhibit the potential for promising thermal properties with comparable tensile strength to diamond. Polymerization of aromatic molecules are initiated though a pressure-induced [4+2] Diels-Alder reaction upon slow compression up to 20 GPa (2). The exceedingly high pressure required for synthesis limits sample size and scalability for gram-sized quantities. One aim to increase sample size is geared towards reducing the pressure required for polymerization. Here we present emerging methodology aimed at decreasing the maximum pressure required for nanothread synthesis.

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Discovery and mechanistic characterization of a structurally-unique membrane active peptide

Shivani Bansal, Wan-Chih Sub, Madhu Budamagunta, Wenwu Xiao, Yousif Ajena, Ruiwu Liu, John C. Voss, Randy P. Carney, Atul N. Parikh, Kit S. Lam* University of California, Davis shivanibansal2002@gmail.com

Membrane active peptides (MAPs) have gained wide interest due to their far reaching applications in drug discovery and drug delivery. The search for new MAPs, however, has been largely skewed with bias selecting for physicochemical parameters believed to be important for membrane activity, such as alpha helicity, cationicity and hydrophobicity. Here we carry out a search-and-find strategy to screen a 100,000-membered one-bead-one-compound (OBOC) combinatorial peptide library for lead compounds, agnostic of those physicochemical constraints. Such a synthetic strategy also permits expansion of our peptide repertoire to include unnatural amino acids. Using this approach, we discovered a structurally unique lead peptide LBF14, a linear 14-mer peptide, that induces gross morphological disruption of membranes, irrespective of membrane composition. Further, we demonstrate that the unique insertion mechanism of the peptide, visualized by spinning disc confocal microscopy and further analyzed by electron paramagnetic resonance measurements, may be the cause of this large scale membrane deformation. We also demonstrate the robustness, reproducibility, and potential application of this technique to discover and characterize new membrane active peptides that display activity by local insertion and subsequent allosteric effects leading to global membrane disruption.
From Vinyl to Allyl: Alkenylboration of Vinylboron Derivatives Enables Facile and Modular Access to Bimetallic Double-Allylation Reagents

Stanna K. Dorn, Annika E. Tharp, M. Kevin Brown* Indiana University-Bloomington (Bloomington, Indiana) skdorn@iu.edu

Double-allylation reagents allow for the rapid construction of highly complex molecules in an expedient fashion. We have developed an efficient and modular approach towards the access of these types of reagents through Cu/Pd-catalyzed alkenylboration of alkenylboron substrates. Notable aspects of the strategy include 1) a broad alkenylboration substrate scope that includes di-, tri-, and tetra-substituted vinylhalide electrophiles; 2) novel use of an allylBdan directly in a stereocontrolled allylation without initial deprotection to the boronic ester; 3) a stereocontrolled second allylation to access complex 1,4-diol motifs; and 4) application to synthetically relevant molecules. Overall, the modularity of this approach and the ease in which complex structural motifs can be accessed in a rapid manner signify the importance and utility of this method.

Organic solvent and ionic liquid based electrolyte for lithium-ion batteries

Snezana M. Papovic, Dajana S. Lazarevic, Milan Vranes* Faculty of Sciences, Novi Sad, Republic of Serbia snezana.papovic@dh.uns.ac.rs

The ionic liquids (ILs) are considered as electrolytes for next generation of lithium-ion batteries (LIBs). They posses low flammability, thermal stability, high conductivity and wide electrochemical stability window. In order to decrease viscosity and further increase conductivity, ILs are usually combined with some organic solvent (cosolvent) for LIBs applications. In this work the 0.5 M solution of LiTFSI salt in low viscosity ionic liquid 1,3-diethylimidazolium bis(trifluoromethylsulfonyl)imide, (C2C2imTFSI), without cosolvent, was tested as electrolyte for LIBs by using robust anatase TiO2 nanotube arrays (NTAs) electrode. The galvanostatic (GS) testing was performed at different current rates and also at different temperatures, 25-55oC, at current rate 3C. Capacity of TiO2 NTAs is due to both bulk and surface storage of Li+-ion, and significantly increases with temperature increase. GS experiments demonstrated excellent capacity retention with improved Coulombic efficiency during final cycling at current rate ~3 C, but with the decrease in capacity of TiO2 NTAs comparing to values before temperature raise or change of current rate. The decomposition of electrolyte was observed by detecting the change of colour of electrolyte in bottle type cell during experiments at elevated temperatures.

Total Synthesis of the Reported Structure of Cahuitamycin A

Savannah J. Post, Justin A. Shapiro, William M. Wuest* Emory University, Atlanta, GA spjorda@emory.edu

In 2016, the cahuitamycins, a new group of natural products, were discovered through a screen of natural product extracts. These molecules were shown to selectively inhibit biofilm growth in Acinetobacter baumannii, a Gram-negative ESKAPE pathogen, with minimal effect on planktonic growth. The active compounds contain canonical siderophore iron-chelating moieties, including a phenolate-oxazoline and a hydroxamate. They also contain an unusual piperazate residue that has rarely been observed in other natural products. We have recently completed the first total synthesis of the reported parent compound, cahuitamycin A, along with a synthetic analog replacing the piperazate with a proline, a known bioisostere. Biological evaluation and extensive NMR analysis revealed key differences between the synthetic cahuitamycin A and the authentic sample. Based on these findings, we have proposed a new structure for the natural product, which is a structural isomer of that which was reported. Ongoing efforts include the synthesis of the proposed structure, as well as the other reported natural products, in order to further confirm our findings and use this class of molecules to investigate the interplay between iron homeostasis and biofilm formation.

Increased degradation of A53T mutant alpha-synuclein mediated by small molecule activated 20S proteasome.

Sophia D. Staerz , Corey J. Jones, Jetze J. Tepe* Michigan State University, East Lansing, MI staerzso@msu.edu

Currently, there are no available therapeutics to prevent or slow down the progression of neurodegenerative diseases, such as Alzheimer's and Parkinson's. Aggregates of disordered proteins are a common pathological feature of these neurodegenerative diseases. The human 20S proteasome mediates the clearance of the aggregate-prone intrinsically disordered proteins (IDPs). Recently, there has been promising evidence that by enhancing the activity of the 20S proteasome offers a possible therapeutic pathway to combat the toxicity associated with these IDP aggregates. Chlorpromazine, an anti-psychotic medication, was identified as a 20S proteasome activator. Through the development of Chlorpromazine analogs, potent 20S proteasome activators have been identified that increases the degradation of pathologically relevant IDPs, such as the pathogenic A53T mutated alpha-synuclein in mammalian cell lines.

Anti-Markovnikov Oxyalkynylation of Ene-carbamates and Enol-ethers under Photoredox Catalysis

Stephanie G. E. Amos, Stefano Nicolai, Jerome Waser* Ecole Polytechnique Federale de Lausanne, Lausanne, Switzerland stephanie.amos@epfl.ch

Atom economy constitutes a key point of interest for new synthetic methodologies. Alkene difunctionalisation is, in this context, an excellent example. It allows a rapid increase of molecular complexity, in particular in radical transformations.[1] Over the past decades, photocatalysis has emerged as a selective and efficient way to generate reactive radical intermediates.[2] In recent years, an alkene radical cation apporach to hydrofucntionalisation has been explored with unactivated alkenes.[3]

Alkynes have broad applications and are useful platforms for subsequent transformations. The development of new alkynylation strategies has become a major research topic in our group. Herein, we present a new metal-free photocatalytic method for the selective difunctionalisation of ene-carbamates and enol-ethers passing through an alkene radical cation intermediate. This methodology exploits the somophilic and nucleophilic character of the EthynylBenziodoXolone (EBX) reagents to allow the atom economical oxyalkynylation of alkenes providing 1-alkynyl-1,2-aminoalcohols and 1,2-diols.[4]

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On the Mechanism of the Castagnoli-Cushman Reaction and its Related Multi-Component Reactions

Sara Y. Howard, Michael J. Di Maso, Noah P. Burlow, Darlene Q. Tan, James C. Fettinger, Tom C. Malig, Jason E. Hein, Jared T. Shaw* University of California, Davis syhoward@ucdavis.edu

The Castagnoli-Cushman reaction (CCR) and its related 3- and 4-component reactions are powerful methods for the synthesis of densely-substituted lactam products. Computational mechanistic evidence has shown that the CCR proceeds through a Mannich-like mechanism involving a key proton transfer to form an anhydride enolate and iminium ion. To further our mechanistic understanding of the CCR, we sought to determine the relationship between the enolizability of the reacting anhydride and the rate of the reaction. Furthermore, a series of experiments were conducted to probe the structure and reactivity of known amide-acid intermediates for the 3- and 4-component variants of the CCR. The pKE values of anhydrides commonly employed in the CCR were calculated and in situ reaction monitoring with infrared spectroscopy was used to measure reaction rates. Amide-exchange experiments align with a unique mechanism in which the amine attacks the anhydride to form an amide-acid intermediate which reversibly forms free amine and anhydride. This mechanistic investigation has led to the development of a novel method for the 3-component reaction of homophthalic anhydride, amines, and aldehydes in the absence of catalysts or additives to form δ -lactams in good yields and excellent diastereoselectivity.

A Unified Metallaphotoredox Strategy for Alpha-Arylation

Tiffany Q. Chen, David W. C. MacMillan* Princeton University, Princeton, NJ tqc@princeton.edu

The alpha-aryl carbonyl moiety is an important motif found in a broad range of pharmaceuticals and naturally occurring bioactive molecules. However, challenges remain in the synthesis of alphaaryl carbonyl compounds, as classical alpha-arylation strategies are frequently limited by the need for strong bases to generate enolates or enolate equivalents. Here, we leverage an open-shell alphaacyl radical intermediate as a novel enolate surrogate, which is accessible through silvl radicalmediated halogen atom abstraction. Employing this key alpha-acyl open-shell intermediate in a metallaphotoredox cross-electrophile coupling platform, we enable the coupling of a wide diversity of activated alkyl chlorides (including alpha-chloroketones, -amides, -esters, and carboxylic acids) and aryl halides under a common and exceptionally functional group-tolerant set of conditions - providing a powerful unified methodology orthogonal to classical methods for alpha-arylation. Remarkably, using an in situ silvl masking protocol, we can directly access diverse arylacetic acid products from simple chloroacetic acid starting materials in a single step – a highly desirable yet classically challenging transformation. These resulting arylacetic acid products are modular synthetic handles, a property that we showcase using three different two-step protocols for the construction of valuable building blocks in medicinal chemistry, including aryldifluoromethyl and diarylmethane motifs.

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Ni(COD)(DQ): An Air-Stable 18-Electron Nickel(0)-Olefin Precatalyst

Van T. Tran, Zi-Qi Li, Omar Apolinar, Joseph Derosa, Matthew V. Joannou, Steven R. Wisniewski, Martin D. Eastgate, Keary M. Engle* The Scripps Research Institute, La Jolla, CA tranvan@scripps.edu

We report that Ni(COD)(DQ) (COD = 1,5-cyclooctadiene, DQ = duroquinone), an air-stable 18electron complex originally described by Schrauzer in 1962, is a competent precatalyst for a variety of nickel-catalyzed synthetic methods from the literature. Due to its apparent stability, use of Ni(COD)(DQ) as a precatalyst allows reactions to be conveniently performed without use of an inert-atmosphere glovebox, as demonstrated across several case studies.

Perovskite Catalyst for Heterogeneous Aerobic C-H Oxidation Reactions

Yeşim Şahin, Abel T. SIKA-NARTEY, Kerem E. ERCAN, Yusuf KOÇAK, Sinem ŞENOL, Emrah ÖZENSOY, Yunus E. TÜRKMEN* Bilkent University, Ankara, Turkey yesim.sahin@bilkent.edu.tr

C–H activation has become a powerful tool in molecular synthesis in recent years. Although there are extensive developments, catalytic oxidation of C-H bonds is usually accomplished by using precious noble metals and thus the need for cost effective catalysts emerged. Lately, the search for alternative ways that use less expensive and toxic first row transition metals such as manganese to replace these expensive metal catalysts still endures. Also, typical oxidation processes use excess amounts of toxic organic/inorganic reagents, hence developing a new method that employs molecular oxygen as the oxidant will have the potential to be beneficial in environmental and economical contexts. As an oxidant, molecular oxygen is green, cheap and readily available in nature. However, it is relatively unreactive toward the strong C–H bonds unless it is activated by highly efficient catalysts.

In this work, we have developed a pretreatment system to increase the activity of LaMnO3 perovskites in order to achieve catalytic aerobic C-H oxidation reactions of numerous compounds in mild conditions. The fact that this catalyst is heterogeneous provides easy separation. Besides, the low cost and high stability of the LaMnO3 perovskite make it a valuable candidate for the catalytic oxidation of unactivated C-H bonds.

Synthesis of Functional Tetrazines from Carboxylic Ester Precursors & Photocatalytic Bioorthogonal Chemistry for On-Demand Protein Labeling and Pretargeted Uncaging

Yixin Xie, Andrew Jemas, Julia Rosenberger, Yinzhi Fang, Joseph M. Fox* University of Delaware, Newark, DE yxxie@udel.edu

The bioorthogonal reaction between tetrazine and trans-cyclooctene is the most rapid bioorthogonal reaction and has become a widespread tool for studying biomolecules in living systems. Firstly, this presentation is about one-pot synthesis of thiomethyltetrazines from carboxylic ester precursors, and subsequent synthesis of unsymmetrical tetrazine via Pd-catalyzed Liebeskind coupling and 3-monosubstituted tetrazine via catalytic thioether reduction. This enables the direct installation minimal tetrazine fragments into APIs, fluorophores, affinity tags and other complex molecules. Secondly, I will present the first dihydrotetrazine/tetrazine pair that is capable of catalytic activation in living cells, since the dihydrotetrazine shows great stability towards background oxidation in living cells and the corresponding tetrazine shows the fastest kinetics among all biorthogonal reactions to date. Meanwhile, I will present a conceptually new method of pretargeted photocatalytic uncaging. The photocages consist of dihydrotetrazine core and vinylether linked bioactive phenol drug. The design is to localize antibody-photocatalyst conjugate to sites of disease, and to 'turn on' tetrazine reactivity through photocatalysis with farred light, the advantage for which is to amplify the effectiveness of antibody-directed small molecule drug delivery. The success of uncaging was confirmed by in situ kinetic monitoring, and cellular uncaging results.

Progress in the Development of Diels-Alder Reactions of Organoboron Compounds

Natalia Labadie, Noelia S. Medrán, Federico Dezotti, Juan M. Ramos Marchena and Silvina C. Pellegrinet* Instituto de Química Rosario (CONICET), Facultad de Ciencias Bioquímicas y Farmacéuticas,

Universidad Nacional de Rosario, Suipacha 531, Rosario, Argentina nlabadie@iquir-conicet.gov.ar, pellegrinet@iquir-conicet.gov.ar

The Diels-Alder reaction (DA) is unquestionably one of the most prominent reactions of organic chemistry, offering synthetic access to a wide variety of six-membered ring structures with well-defined stereochemistry. The DA reactions of boron-substituted substrates have great potential due to their intriguing mechanistic features, the accessibility of diverse unsaturated organoboron compounds and the possibility of subsequent functional group transformations. Our group has studied and described the reactivity of varied boron-substituted alkenes and alkynes as dienophiles. Later on, we began exploring the use of boron-substituted heterocycles as dienes. Herein, we present the most recent advances in our research. We were able to expand the range of DA reactions of boron-substituted dienes. The DA reactions of several boron-substituted furans at C-2 and C-3 with N-phenylmaleimide were investigated, resulting in the generation of stable adducts with excellent yields and exo diastereoselectivities. In addition, we report the novel use of a boron-substituted allene as a DA dienophile. The reactivity of allenylboronic acid pinacol ester with cyclopentadiene was studied experimentally and the mechanisms for the competing pathways were explored theoretically. Currently, we are investigating the DA reactions with other reaction partners as well as the further functionalization of the cycloadducts.