Poster 1

Progress Towards the Total Synthesis of Laingolide A

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Laingolide A is an enamide-containing secondary metabolite isolated from the Lyngbya bouillonii cyano-bacteria near the northern coast of Papua New Guinea in 1999. Progress towards the first total synthesis and determination of the naturally occurring macrocyclic stereoisomer is described. An efficient yet versatile retrosynthetic pathway was designed using three building blocks: a dibromo olefin obtained through the Corey-Fuchs reaction, an acid chloride with an azide handle, and a boronic acid-carboxylic acid sourced from Roche ester. The key step of this total synthesis is a novel Suzuki-Miyaura coupling reaction followed by a lactone to lactam ring expansion with a palladium catalyst.

Poster 2

The PMI Predictor – a Web App Enabling Green-by-Design Chemical Synthesis

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The development of sustainable processes for the synthesis of new clinical candidates is a priority for every pharmaceutical company. The ultimate efficiency of a molecule's synthesis is a combination of the strategy to assemble the molecule (route of synthesis) and the subsequent effort to design an efficient process. While multiple approaches are available to aid the development of efficient processes, far fewer methods to guide the selection of synthetic strategy – with respect to its influence on efficiency – have been described. Herein we describe a green-by-design approach to route selection and development, assisted by predictive analytics and historical data. In order to aid the selection of more efficient strategies, we created a user-friendly web application, the "PMI Prediction Calculator," to foretell the probable efficiencies of proposed synthetic routes, prior to their evaluation in the laboratory. This tool can also be used to benchmark the outcome performance of a developed process. We expect that use of this app will bring greater awareness of sustainability during the ideation phase of route design and will contribute to a reduced environmental impact of pharmaceutical production. The app can be accessed following the link:

https://acsgcipr-predictpmi.shinyapps.io/pmi_calculator/

Poster 3

Palladium-catalyzed Cross-coupling of Phenyl Esters

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Aryl esters are convenient and useful electrophiles for transition-metal catalyzed cross-coupling due to their abundance, stability, and utility as building blocks for organic synthesis. Traditionally, cross-coupling reactions utilizing aryl ester substrates required harsh reaction conditions or were not highly selective. In this presentation, mild non-decarbonylative Suzuki-Miyaura and Buchwald-Hartwig cross-coupling reactions of phenyl esters to form ketones and amides, respectively, using the recently developed (η3-1-tert-butyl-Indenyl)Pd(L)Cl precatalyst, will be described. The reaction optimization and substrate scope will be discussed, and role of rapid precatalyst activation in achieving mild reaction conditions will be emphasized. Additionally, this method has been extended to non-decarbonylative Suzuki-Miyaura coupling reactions of phenyl ester derivatives of amino acids to form aryl amino ketones. This reaction is important because there are relatively few transition-metal catalyzed methods for the functionalization of the carboxylic acid moiety on amino acids, and even fewer which preserve the carbonyl functional group.

Poster 4

Deaminative Cross-Couplings of Alkylpyridinium Salts

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Alkyl amines are inexpensive and widely abundant chemicals in organic synthesis, making them a great handle for further functionalization. Functionalization via cleavage of the carbon-nitrogen (C-N) bond has recently been discovered as a powerful transformation of these abundant, easily protected alkyl amines. Due to the prevalence of $C(sp^3)–C(sp^3)$ bonds in bioactive molecules, methods to create alkyl-alkyl bonds have become increasingly desirable. We have developed a nickel-catalyzed Suzuki cross-coupling of alkyl pyridinium salts with an alkyl boron species derived from an alkene, providing a new alkyl-alkyl forming method. The optimization, scope, and mechanistic understanding of these reactions will be presented.

Poster 5

Photoredox-catalyzed Amination for Tyrosine Bioconjugation

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Protein bioconjugation is an important tool in a wide variety of chemical biology applications, such as tracking protein distribution in cells, probing enzymatic functions, or targeted drug delivery. Photoredox catalysis, which takes advantage of the synergistic effect of high energy visible light (400–500 nm) and photocatalysts, is an especially privileged platform for protein bioconjugation because it can selectively functionalize redox-active amino acid residues under mild, biologically compatible conditions. Tyrosine residues, given their amphiphilic phenol side chains, exist in intermediate frequency on the surface of many proteins and make desirable targets for bioconjugation. While tyrosine phenols are well-known to exhibit nucleophilic reactivity, they are also very much redox-active. We aim to take advantage of the redox properties of tyrosine in endogenous proteins and bioconjugate a versatile phenoxazine coupling partner via photoredox-catalyzed amination.

Poster 6

Isohexane-Soluble Anilinium Borate Activators for Metallocene Catalysts

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Catalyst solutions in toluene are often used for solution polymerization of olefins with metallocene-based catalysts. There is a desire to develop toluene-free catalyst formulations for polyolefins. Although metallocenes have appreciable solubility in aliphatic solvents, ammonium borate-based activators do not and thus present an opportunity for improvement. We present the study of novel activators that were made to understand and improve the solubility and activity of metallocene catalyst systems. The installation of aliphatic solubilizing groups, in addition to structural modifications to affect sterics and electronics, are described herein. Through this work, soluble borate activators with comparable performance were identified.

Poster 7

An Alternative and Accurate Approach for Sub-Milligram Solid Dispensing for Practical High-Throughput Experimentation

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High-throughput experimentation (HTE) is a technique that aims at screening multiple reaction conditions in parallel without depleting precious starting material (scale of ≤ 1 mg) and requiring less effort per experiment. This approach can provide unbiased reaction conditions as a starting point for chemists to further investigate the transformation with minimum time investment. However, assembling a comprehensive screening set often involves the distribution of large number of reagents with diverse physical properties in small quantities. Automated solid dispensing, especially in sub-milligram scale, has long been a challenge with no practical and reliable solutions. Hence, we used our developed chemical coated beads (ChemBeads) technology, which improves flowability and content uniformity of solid reagents, to provide a universal approach to the solid handling problem. Overall, we have identified an effective automated solid dispensing platform, and a manual solid distributing technique using 3D printed calibrated scoops, to dispense sub-milligram quantities of a variety of solids. Both techniques are accurate and effective methods to dispense solid reagents at various targeted masses. The calibrated scoops would be an asset to increase applications of chemical HTE in laboratories with limited automation; it is inexpensive, easily accessible and does not require the use of analytical balances to dispense solids at sub-milligram scale.

Disclosures: All authors are employees of AbbVie. The design, study conduct, and financial support for this research were provided by AbbVie. AbbVie participated in the interpretation of data, review, and approval of the publication.

Poster 8

Total Synthesis of Cinncassin A1

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Cinncassin A1 is a phenolic, 3,4-trans-disubstitued-γ-butyrolactone isolated from twigs of the cinnamon plant, Cinnamomum cassia, with potential neuroprotective effects. In this poster we report the first total synthesis of this natural product using a Titanium-catalyzed, diastereoselective homocoupling reaction and a permanganate mediated lactonization as key steps.

Poster 9

Enantioselective Anti-Markovnikov Hydroamination of Alkenes with Sulfonamides Enabled by Proton-Coupled Electron Transfer

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Enantioselective reactions of radical intermediates remain challenging, as many mechanisms for radical generation are not coupled to chiral catalyst binding. This, in conjunction with the high intrinsic reactivity and poorly understood non-covalent interactions of open-shell intermediates, makes it challenging to design a chiral environment which can sufficiently impose stereocontrol during subsequent bond forming steps. Herein, we report an enantioselective anti-Markovnikov hydroamination of alkenes with sulfonamides, enabled by proton-coupled electron transfer (PCET). The PCET step proceeds through the simultaneous oxidation and deprotonation of a sulfonamide N–H bond by an iridium photocatalyst and chiral phosphate base, respectively. We propose that residual hydrogen bonding interactions between the resulting neutral sulfonamidyl radical and neutral conjugate chiral phosphoric acid induce asymmetry during the subsequent C–N bond formation. This reaction has been demonstrated for a variety of sulfonamides in an intramolecular cyclization reaction with selectivities up to 95% ee. These results demonstrate that neutral, open-shell hydrogen bonding interactions can be applied as a design principle for asymmetric reactions with radical intermediates.

Poster 10

Synthetic Organic and Supramolecular Strategies Toward Sequence-Controlled Polymerizations

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To date, methods to engineer polymers with precise functional group positioning generally lead to ill-defined architectures, impeding both crystallization and self-assembly. Iterative synthetic routes are promising to achieve well-defined materials, yet can be time-consuming and often require extensive product purification. Balanced cost- and time-effective strategies are needed to access novel materials. Herein, we disclose two independent methods toward obtaining sequence control: In a first route, we demonstrate the controlled synthesis of alternating copolymers prepared using ring-opening metathesis polymerization (ROMP) of a strained unsymmetrical and 'electronically-ambiguous' donor-acceptor cyclophanediene. The ROMP proceeds in wake of both steric and electronic encumbrance to afford donor-acceptor conjugated polymers. In a second separate strategy, supramolecular interactions are utilized to pre-organize and direct reactants for non-topochemical solid-state polymerizations, wherein the noncovalent interactions aid in precise C—C bond formation. Although the two approaches are different in scope, both rely retrosynthetic design to engineer 'locked-in' A-B units that are significant in a field striving to synthesize well-defined and sequence-specific materials.

Poster 11

Synthesis of γ-Boron Phosphonate Compounds

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Malaria and tuberculosis infections are the most widespread infectious diseases in the world. Certain strains of both P. falciparum and M. tuberculosis have become highly resistant to a wide variety of current drugs therefore new antimalarial and antituberculosis drugs with novel modes of action are urgently needed. The 2C-methyl-D-erythritol-4-phosphate (MEP) pathway constitutes an attractive target for the development of new anti-infective agents. This pathway is not present in humans but only in pathogens such as bacteria, fungi and protozoa. Also, it is responsible for the biosynthesis of the isoprenoid precursors isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP) which play an important role in the life cycle of many pathogens. These isoprenoids are essential for the synthesis of the cell wall in M. tuberculosis and P. falciparum. Fosmidomycin is a potent, natural product inhibitor of the MEP pathway that acts via inhibition of the enzyme 1-deoxylulose-5-phosphate reductoisomerase (IspC). Despite potent in vitro activity against IspC, fosmidomycin is highly hydrophilic and has poor bioavailability thus limiting its use as a therapeutic. For these reasons, the overall goal of this work is the design, synthesis and biological evaluation of a library of fosmidomycin analogs with increased lipophilicity to improve cellular penetration and bioavability.

Poster 12

Computational Tools Facilitate the Optimization and Understanding of an Enantioselective Difluorination Reaction Catalyzed by Hypervalent Iodine Compounds

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An enantioselective transformation was developed in the Jacobsen lab which forms chiral B,B-difluoroalkylbromides from bromostyrenes, and the reaction is facilitated by a class of chiral, hypervalent iodine catalysts. Most chiral catalysts rely on a precise interplay of noncovalent interactions to induce enantioselectivity. Elucidating the mechanism of this difluorination reaction is complicated by the many noncovalent interactions likely involved, along with the heterogeneous nature of the reaction and the harsh reaction conditions. Therefore, we sought to apply the parameterization methodology developed in the Sigman lab in which computed properties of substrates and catalysts are correlated to reaction selectivity. This method has been able to reveal enantiodetermining aspects of many asymmetric, catalytic transformations without prior mechanistic information. Properties of the substrates and catalysts for this difluorination reaction were calculated, and with these results, the dependence of enantioselectivity on the structure of the substrates and catalysts was able to be expressed using only two parameters: the interaction energies of a model system and the LUMO energies of the substrates. A more selective catalyst was also predicted. Fundamental noncovalent interactions important for enantioselectivity in this transformation were revealed, contributing to our understanding of how hypervalent iodine catalysts of this type induce enantioselectivity.

Poster 13

Single-Chain Polymer Nanoparticles: A Diverse Class of Recyclable Homogeneous Catalysts

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Single-chain polymer nanoparticles (SCNPs) have emerged as a new class of intramolecularly cross-linked nanomaterials. Their polymeric nature allows complete control over solubility by incorporating solubilizing comonomers, making them attractive as nanomedicines, drug delivery vehicles, and biomimetic catalysts. The ability to incorporate solubilizing comonomers provides unique control over reaction conditions compared to small-molecule homogeneous catalysts, whose solubility is not easily changed without affecting catalytic properties. Additionally, aggregation of SCNPs in “bad” solvents enables facile purification and recovery of catalytic material. While several SCNP catalysts have been developed from commercially available monomers, rational design of ligand side chains is still in its infancy. We aim to expand the utility of SCNP catalysts by developing a diverse class of polymers containing pendant dipyrrin ligands. Facile derivatization of dipyrrin monomers will provide a user-friendly approach to optimization studies.

Poster 14

A Mechanism-Driven, High Throughput Chemistry Approach to Development of a Diastereoselective [2+2+2] Cycloaddition Reaction

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A shorter and more convergent route to a target API was conceived in a Chemical Development brainstorm after the medicinal chemistry route was found to be unsuitable for scale-up. One instrumental change during route development involved pivoting from a challenging atropselective Suzuki coupling to a late-stage atropselective [2+2+2] cycloaddition, resulting in a d.r. improvement from 13:1 (Suzuki) to 22:1 (cycloaddition). Mechanism-driven high-throughput chemistry experiments identified a matched catalyst-substrate pair and increased atropselectivity over time as key factors influencing reaction outcomes. These experiments led to the development of a mechanistic proposal and reaction protocol that greatly enhanced control of cycloaddition atropselectivity.

Poster 15

Identification of Selective APOBEC3 Ligands by Mass Spectrometry Fragment Screening

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Apolipoprotein B mRNA-editing enzyme, catalytic polypeptide-like 3 (APOBEC3) is a family of seven single-stranded (ss)DNA cytosine-to-uracil deaminase enzymes (A3A/B/C/D/F/G/H) that function as part of the innate immune defense system against foreign DNA. A3-catalyzed deamination has been associated with genomic mutation and evolution of drug resistance mutations in HIV and various cancers, signifying an important therapeutic target. Previous work by the Harki lab and collaborators has identified inhibitors of A3G that are modestly potent and cross-reactive. The goal of this project is to perform a mass spectrometry-based binding screen to identify new A3 ligands. The ligands identified from screening will be characterized and optimized leveraging medicinal chemistry, structural biology, computational chemistry, and biochemical assays to develop novel A3-specific inhibitors.

A whole protein mass spectrometry-based screen to identify ligands of A3 proteins has been developed, allowing for the identification of covalently-bound fragments identified by a shift in mass and relatively quantified as the percent of ligand bound. Early work on this project has confirmed adduction of iodoacetamide to A3G C-terminal domain (ctd), and an initial pilot screen has been performed using a small library (N=35) of fragments containing irreversible electrophiles. These results and the future directions of the project will be presented.

Poster 16

Rational Design and Facile Synthesis of Fluorescent Small Molecule Probes for Biological Studies in Live Cells

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Small-molecule fluorescent probes are powerful tools for chemical biology. Here, we introduce a highly modular quinoline-based probe called DMAQ and diazaxanthilidene-based probes called CPX and NeuroX. DMAQ contains four strategic domains that are allotted for (1) compound polarization, (2) tuning of photophysical properties, (3) click-able ligation, and (4) sensing ions. We successfully synthesized our probes in three steps from commercially available starting materials in overall yields of up to 86%. Facile probe synthesis was permitted by regioselective palladium-catalyzed cross-coupling, which enables combinatorial development of structurally diverse quinoline-based fluorophores. CPX is a clickable and photoconvertible fluorophore that enables the visualization and tracking of a specific biomolecules, complexes, and cellular compartments with precise spatiotemporal control. To demonstrate its utility, we have applied CPX to study 1) trafficking of biologically relevant synthetic vesicles and 2) intracellular processes involved in transmission of α-synuclein (αS) pathology. Lastly, NeuroX is a highly noncytotoxic and photostable nucleus staining dye for live cell and tissue imaging. We utilized NeuroX to visualize cell cycles of live neurons and for in vivo mouse brain tissue imaging.

Poster 17

Stereocontrolled Synthesis of Piperidines via Rh-catalyzed Ring Expansion of Aziridines

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Nitrogen-containing motifs are large structural patterns in approved drugs. Recent reviews report that 59% of FDA-approved drugs contain nitrogen piperdines. Traditional methods to synthesize piperidines often involve selective installation of functional groups prior to ring-closing. This technique can reduce efficiency and step economy as the desired target's complexity increases. This work harnesses bicyclic aziridinium ylide, generated from bicyclic cis- aziridine and vinyl electrophilic rhodium-bound carbene intermediates, to transform alkenes to >20 substituted piperidines. Asymmetric, silver-catalyzed alkene aziridination, followed by attack of the aziridine lone pair on a metal-stabilized carbene, generates the key aziridinium ylide. Subsequent [2,3]-Stevens rearrangement delivers the piperidine scaffolds in excellent diastereoselectivity. DFT calculations indicate that the reaction proceeds through vinyl aziridinium ylide. This work highlights aziridines ring expansion as a key strategy to access larger nitrogen-containing molecules.

Poster 18

Advancing Synthetic Continuous Manufacturing at Amgen

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This poster details the development of a continuous manufacturing (CM) platform for the synthesis of PR-016, a Kyprolis intermediate, including a description of successful kilo-scale demonstration, the development and impact of predictive models, implementation of integrated analytical control strategies, and plans for commercial manufacture. Overall, the convergence of development and manufacturing scales creates a platform for development that we propose will simplify and accelerate tech transfer, reduce manufacturing footprint, and broaden Amgen's network of potential commercial manufacturing sites.

Poster 19

Next Generation Catch and Release DNA Decoys with Photochemically Responsive Pyrimidine Mimics

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Transcription factors (TFs) are one of the largest classes of human proteins, stemming from over 2000 protein encoding genes. Extracellular signals activate or repress TF pathways, ultimately resulting in changes to TF-DNA occupancy and concomitant gene expression. Consequently, chemical probes that offer spatial and temporal regulation over TF-DNA binding are powerful tools for characterizing gene expression. Out of the many TF classes, the NF-κB family are master-regulators of the cellular inflammatory response and are implicated in a variety of cancers. The dynamics of NF-κB signaling are poorly understood, thus creating a need for the development of new chemical tools to elucidate its function. The Harki lab has recently reported a new class of TF-targeting DNA decoys for the study of NF-κB-DNA binding. These NF-κB-targeted Catch and Release DNA Decoys (CRDDs) utilize single-photon UV-irradiation to cleave the anomeric bond, leading to depurination between the sugar and nucleobase to achieve dissociation of the NF-κB-CRDD complex. Here, the toolbox of CRDD nucleotides was expanded with the development of novel nitro-functionalized pyrimidine mimics that can photochemically depurinate similarly to indole predecessors. This poster will report nucleoside synthesis, mechanistic studies of depurination, and the stabilities of CRDDs containing next-generation nucleotides.

Poster 20

Progress Towards the Total Syntheses of Impatien A and Ochotensimine: Utilizing a Novel Cyclization

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Impatien A, an isoindolone natural product isolated from Corydalis impatiens, and ochotensimine, a tetrahydroisoquinoline natural product isolated from Corydalis ochotensis, both possess a similar carbon scaffold featuring a spirocyclic stereogenic center. While ochotensimine and its des-methyl analog ochotensine have been shown to inhibit TNF-alpha, have been characterized as single enantiomers by optical rotation studies and by x-ray diffraction, and have been prepared via racemic syntheses, much less is known about the related impatien A. A unified approach to the preparation of the spirocyclic centers of these natural products poses a synthetic challenge both in its racemic and enantioenriched forms. We envision a metal-catalysed approach to the creation of these spirocyclic centers, which would be amenable to asymmetric induction. From readily available starting material, the southern indane half (identical to both natural products) and an appropriate northern arene half tagged with a cross-coupling handle can be synthesized with minimal chromatographic steps. Key palladium-catalysed arylation and cyclization allow for the construction of the spirocyclic framework.

Poster 21

Synthesis and Application of Methyl N,O-Hydroxylamine Muramyl Peptides

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The innate immune system's interaction with bacterial cells plays huge role in human diseases. Carbohydrates derived from bacterial cell wall, peptidoglycan (PG), are known to stimulate an immune response. To increase the chemical toolbox for studying host-PG interactions a rapid facile synthesis for PG probes is needed. To date, the field has been limited to a handful of commercially available PG probes and more recently well-defined materials that are accessible only to the skilled carbohydrate chemist (13+ chemical steps). In this study, a methodology for the modification of these critical bacterial PG fragments that is accessible to the non-specialist is developed. Using methyl N,O- hydroxylamine chemistry, two new amine functionalized linkers were established and subsequently attached to unprotected synthetic MDP at the anomeric position. This modification was shown not to affect the immunostimulatory activity of MDP. And, was proved to be applicable to larger synthetically, as well as enzymatically, generated PG fragments. Applications for these probes were also explored using Surface Plasmon Resonance (SPR), as well as by bio-conjugation with a fluorophore. Future studies include the expansion of the N,O-hydroxylamine MDP chemical tool box through the conjugation of other chemical-biology handles and further exploration of their utility.

Poster 22

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

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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.[1] The peptide antagonists Agouti Signaling Protein (ASP) and Agouti-Related Protein (AgRP) both contain the putative sequence Arg-Phe-Phe in the carboxyl terminal region, which is hypothesized to be responsible for both receptor affinity and antagonist activity.[2] This sequence is located on an exposed ß-hairpin loop, which can be mimicked in a smaller amenable scaffold.

This study focused on exploring four SNPs that were deposited into the NIH Variation Viewer[3], which result in missense mutations in the proposed active loop of AgRP.[4] It was hypothesized that the SNPs would alter AgRP signaling in the MC4R cascade, which may have physiological consequences in humans. The SNPs were incorporated into macrocyclic peptide scaffolds c[Pro-Arg-Phe-Phe-Asn-Ala-Phe-DPro] and c[Pro-Arg-Phe-Phe-Dap-Ala-Phe-DPro] which were previously reported to have nanomolar potency at the MC4R.[5]

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Poster 23

Route Optimization of a Novel CD73 Benzothiadiazine Inhibitor Containing a C5-Pyrazole

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The human ecto-5'-nucleotidase (CD73), which catalyzes the conversion of extracellular AMP to adenosine, is over-expressed in many types of cancer. Increased adenosine levels due to upregulated CD73 cause an immunosuppressive local environment, allowing tumors to escape immune surveillance. High-throughput screening identified a series of benzothiadiazine-containing compounds as potent inhibitors of CD73. The initial hit in this series featured a C5-hydroxyl group which was thought to be critical for high potency; however, a later discovery showed that replacement with a heteroaryl was tolerated. In order to expand on this finding, an optimized synthetic route to the C5-heteroaryls was sought, as the benzothiadiazine core proved to be a capricious substrate for the Suzuki cross-coupling reaction necessary to access these inhibitors. In collaboration with GSK's Chemical Catalysis & Novel Methods group, Suzuki reaction screening plates were run and analyzed, and optimized reaction conditions were identified. The experimental design and results of this methodology screen will be presented.

Poster 24

Copper (II) Catalyzed Homocoupling and Heterocoupling of Terminal Alkynes

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There are numerous bioactive compounds that have been discovered to contain 1,3-diynes, which are found in nature and widely applied in organic synthesis. Through experimentation, we have discovered the efficient synthesis of unsymmetrical and symmetrical 1,3-diynes. We have developed an efficient copper (II) triflate catalyzed homocoupling and heterocoupling reactions of a variety of terminal alkyne substrates in high yields under mild conditions. These optimal conditions were applied successfully to 14 homocoupling and 6 heterocoupling reactions of a variety of terminal alkyne substrates, an overall scope of 20 substrates.

Poster 25

Photoredox-Catalyzed Site-Selective Functionalization of Primary Amine Derivatives

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Using visible-light photoredox catalysis, the judicious choice of nitrogen protecting group allows for the site-selective functionalization of alkyl primary amine derivatives. Under basic, oxidative reaction conditions, both trifluoroacetamides and trifluoromethanesulfonamides undergo full deprotonation and further oxidation to form nitrogen-centered radicals. The fine-tuning of protecting group, and consequently resulting nitrogen radical stability allows for the differentiation in mechanistic pathways and selective alpha vs. delta functionalization. Trifluoroacetamides have been shown to remotely activate delta-C(sp3)-H through intramolecular [1,5]-hydrogen atom transfer events to produce delta-centered carbon radicals. A pivot in reactivity is observed with trifluoromethanesulfonamides by selectively forming alpha-amino radicals through intermolecular HAT processes. By coupling these radicals with electron deficient olefins, C-C bonds are selectively formed either alpha or delta. Additionally, the use of oxime ethers and isonitriles as coupling partners leads to formal aminomethylation and cyanation functionalization.

Poster 26

The Biomimetic Total Synthesis of Microansamycin A

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Ansamycins are a family of bacterial secondary metabolites that can exhibit antioxidant and antitumor bioactivities. A recently identified series of nine novel microansamycins (e.g., microansamycin A) feature a structurally intriguing and rare pentaketide backbone deriving from post-PKS modifications. The metabolites of this family share a cyclohexenone or phenol core with a bridging macrolactam containing four stereocenters, one of which is often quaternary. This densely functionalized skeleton presents a synthetic challenge and has yet to be explored. Lu et al. propose a biosynthesis from "promicroansamycin" to yield the tetracyclic parent family member, microansamycin A. Variations in this pathway could generate the other metabolites. We intend to develop a modular biomimetic route to access microansamycin A and test the feasibility of the biosynthetic proposal, particularly final cyclization. Through this synthetic endeavor, we will develop new strategies for complex polyketide synthesis and probe the unprecedented late-stage biosynthetic transformations.

Poster 27

11-Step Catalytic Asymmetric Synthesis of (–)-Bilobalide

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The Ginkgo biloba metabolite bilobalide (BB) antagonizes gamma-aminobutyric acid A receptors (GABAAR) and rescues cognitive dysfunction in Ts65Dn mice, models of Down syndrome in which GABAergic inhibition is overactive. However, BB decomposes in weakly basic media, obstructing its derivatization; and structure modification by total synthesis is frustrated by its stereochemically-rich and congested architecture. Here, we report an 11-step synthesis of (–)-bilobalide that relies on the pseudosymmetry of its core. Stereochemistry is relayed from an unusual Reformatsky reaction to a solvent-dependent radical hydration and a stereoselective oxetane acetalization. Facile skeletal rearrangement enables a late-stage 'inside-out' oxidation of a deep C-H bond. Rapid access to BB provides the opportunity to stabilize the core while maintaining its unique GABAAR antagonist profile.

Poster 28

Site Selective Piperazine Alkylation via Alkylation of α-Carbamyl Radicals

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Piperazine-containing compounds serve as one of the most important classes of compounds throughout all fields of chemistry. Their prevalence in naturally-occurring complexes and pharmaceuticals makes piperazines one of the most attractive motifs for synthetic chemists. To date, synthesis of highly decorated piperazine cores has been met with extreme difficulty using current synthetic methods. In a collaboration between chemistry groups at GlaxoSmithKline and the University of North Carolina, we present a site-selective approach to the functionalization of existing piperazine compounds using acridinium-based photoredox catalysis. This manifold relies on the differentiation electronically-distinct nitrogen centers within the piperazine framework to gain access to C-alkylated variants of the starting piperazines. The reaction has been designed to proceed efficiently under mild conditions without the need for exogenous additives, redox mediators or substrate-prefunctionalzation.

Poster 29

Nickel-Catalyzed Cross-Couplings of Alkyl Amine Derivatives Via C-N Bond Activation

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Primary alkyl amines are important building blocks for the synthesis of nitrogen-containing molecules. However, strategies for functionalization via cleavage of the carbon-nitrogen (C-N) bond are underdeveloped. We have recently developed a strategy to convert primary alkyl amines into alkyl arenes via nickel-catalyzed cross-coupling of Katritzky pyridinium salts. This poster will include our nickel-catalyzed Suzuki–Miyaura cross-coupling of pyridinium salts derived from α-amino acids and peptides. This method provides a broad scope including synthesis of propionic acids. We have also developed a nickel-catalyzed reductive cross-electrophile coupling of primary and secondary alkyl pyridinium salts with aryl bromides. The optimization and scope, as well as future work, of these reactions will be presented.

Poster 30

Intensification of Photoredox Reactions: from Rapid Optimization in batch to a Highly Efficient Continuous Flow Process

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Visible-light photoredox catalysis has recently emerged as an innovative and powerful strategy for the development of a wide range of currently unknown or previously inaccessible transformations in the field of organic chemistry.

Photoredox reactions has traditionally been performed in batch; recently, continuous flow methodologies have gained much attention even in this area of chemistry. Although both techniques are very useful and have been rapidly developed and adopted by the organic chemistry community, there are not an efficient method to translate the reaction in batch to corresponding continuous process due to their difference regarding the photon exposure.
In this work, we show the development of a new methodology to optimize a known or unknown reaction in microscale and move directly to continuous systems using homogeneous reaction conditions, reducing drastically the reaction times and minimize solvent waste with excellent results. This methodology will allow scale the photoredox reactions in flow systems with a high efficiency.

Poster 31

Vinyl Cations as Cyclopentenone Precursors via C-H Insertion and Alkene Addition Reactions

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We recently reported that β-hydroxy-α-diazo ketones react with Lewis acids to give fused bicyclic cyclopentenone products. This reaction occurs through the formation of a destabilized linear vinyl cation that rearranges via a 1,2-shift to provide a more stable cyclic vinyl cation, which then inserts into an unactivated C-H bond to provide the cyclopentenone product. We have since expanded our studies to include unsymmetric systems (R≠R'), and in this presentation we report our results detailing the migratory aptitude of different groups in the 1,2-shift event. We have also been exploring the use of the vinyl cation intermediates in intramolecular reactions other than C-H insertion. For example, we recently reported that the vinyl cation intermediates could be captured by pendent aromatic rings to give tricyclic 1-indenone products. We have since expanded these studies to include alkenes as the nucleophilic capturing agent, and our results from these studies will be reported as well.

Poster 32

Silyl Radical-Mediated Arylation of Heterocyclic N-Nucleophiles via Copper Metallaphotoredox Catalysis

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In this work, the coupling of N-heterocyclic nucleophiles and (hetero)aryl bromides is achieved via the merger of copper metallaphotoredox catalysis and silyl radical-mediated halogen atom abstraction. This carbon-nitrogen coupling is enabled by a photocatalytically-generated silyl radical, which abstracts bromine from the (hetero)aryl bromide, thus generating a high-energy aryl radical intermediate. Capture of the aryl radical at near diffusion rates by a copper catalyst provides an alternative mechanistic pathway to the traditional yet sluggish direct oxidative addition of aryl halides to copper. Multiple classes of heterocyclic nucleophiles—including pyrazoles, indazoles, triazoles, and 7-azaindoles—are effectively coupled under mild conditions to a wide range of pharmaceutically-relevant aryl and heteroaryl bromide partners.

Poster 33

Covering Our Bases: Development of Homogeneous Conditions for Scalable and Reproducible Cross-Coupling Reactions

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Pd-catalyzed C-N coupling reactions are ubiquitous in the syntheses of active pharmaceutical ingredients (APIs). The development of robust and scalable reaction processes is essential in order for these transformations to be suitable for large-scale manufacturing. The use of traditional weak inorganic base reaction conditions enable the desired transformation to proceed with broad functional group tolerance, but the reaction profile is scale-dependent and contingent on the inorganic base particle size. The development of dual-base homogeneous reaction conditions that enable readily scalable processes will be presented along with mechanistic experiments to develop an understanding of the role of each component of the reaction.

Poster 34

Chemoselective Cyclic Alcohol Oxidation with N-Ligated 3-Iodanes

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The chemoselective functionalization of alcohols in complex polyols remains a fundamental synthetic challenge. While significant advancements have been made in the selective derivatization at the oxygen center, chemoselective oxidation to the corresponding carbonyls is less developed. In cyclic systems, while selective oxidation of axial alcohols is well known, a complimentary equatorial selective process has not yet been re-ported. Herein, we report the utility of nitrogen-ligated (bis)cationic iodanes (III) (N-HVIs) for alcohol oxidation and their unprecedented levels of selectivity for the oxidation of equatorial over axial alcohols. The conditions are mild and the simple pyridine-ligated reagent is readily synthesized from commercial PhI(OAc)2 and can be either isolated or generated in situ. Conformational selectivity is demonstrated in both flexible 1,2-substituted cyclohexanols and rigid polyol scaffolds, providing chemists with a novel tool for chemoselective oxidation.

Poster 35

Chemical Synthesis and Nanoscale Characterization of Silk-Mimetic Segmented Copolymer

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Spider dragline silk is one of the nature's high-performance materials, as it exhibits comparable tensile strength to steel at a fraction of the density with toughness surpassing that of Kevlar and Nylon. This remarkable mechanical property results from its primary sequence, resembling segmented copolymer with hydrophobic block, rich in alanine, and hydrophilic block, rich in glycine. Chemically synthetic polymers mimicking silk structure and properties are desirable for applications, including biomedical scaffolds, tissue regeneration, bioelectronics, and biosensors due to its ability to interface with living tissues and robust mechanical properties. Here we are demonstrating a facile and robust synthetic strategy of silk-mimetic segmented multiblock copolymer via solid phase peptide synthesis (SPS) followed by step-growth polymerization of poly(alanine) and α,ω-bis{2-[(3-carboxy-1-oxopropyl)amino]ethyl}polyethylene glycol. The resultant polymers were analyzed using mass spectrometry and gel permeation chromatography. The effect of poly(alanine) chain lengths (n = 3-10) in the polymer self-assembly was studied in detail by wide-angle X-ray scattering (WAXS) that suggests oligopeptide segments could aggregate into β-sheet structure with parallel or antiparallel symmetry and may result into variable mechanical properties.

Poster 36

Towards Molecular Complexity: Alkene Carboboration via Cu/Pd Synergistic Catalysis

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Alkene difunctionalization constitutes a powerful approach for rapidly attaining complex molecular scaffolds from simpler and more widely available compounds. Cu/Pd synergistic catalysis is an effective method for alkene difunctionalization, as it simultaneously establishes a carbon-carbon bond and versatile carbon-boron bond through a nucleophilic alkyl-Cu species that is generated in situ. Previously, our group has demonstrated the utility of this system through the development of diastereoselective and enantioselective variants with styrene derivatives. This work extends the approach to the 1,1- and 1,2-carboboration of α-methylstyrene derivatives, which presents the unique challenge of not only successfully cross-coupling a tertiary alkyl-Cu species, but also selectively accessing regioisomeric products through distinct Pd ligand environments. Furthermore, this process can be done enantioselectively, which is significant due to the inherent complexity of the system. Additionally, progress on the alkenylboration of vinylsilanes and vinylboronic esters is highlighted, including scope and synthetic applications.

Poster 37

Selective Radical C-H Functionalization of Amines and Alcohols

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The selective functionalization of C-H bonds serves as a platform to streamline the synthesis of versatile molecular entities from simple feedstocks. In this study, the C-H functionalization of abundantly available amines and alcohols has been realized through catalytic, radical-mediated pathways. Specifically, C-H arylation of amines has been achieved via a copper catalyst and aryl boronic acids, where C-C coupling is preceded by a 1,5-hydrogen atom transfer. Furthermore, this reactivity has been applied to the selective desaturation of unbiased amines to introduce a distal alkene under a Cu and Ir dual catalytic system. Finally, radical chaperone-mediated amination of alcohols has been rendered catalytic and studied mechanistically. It is anticipated that these methodologies will lead to further development of novel C-H functionalization strategies, with the intention of advancing the material and pharmaceutical industries.

Poster 38

Process Development at Corteva Agriscience™

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An increasing and often mobile global population demands a higher production of food to feed the additional two billion people expected on this planet by 2050 . Controlling insects, pathogens, and weeds that negatively impact crop productivity remains an ongoing and essential undertaking. The ability to synthesize complex molecules has allowed for the development of a multitude of organic compounds as active ingredients in the crop protection industry. Corteva Agriscience, as one of the world leading agriculture companies, has developed numerous novel products which increase the sustainability of food production. For example, Rinskor™ active, a new rice herbicide developed by Corteva Agriscience, was recently awarded our sixth Green Chemistry Challenge award.

We emphasize the Principles of Green Chemistry in our active ingredient process R&D, and one key Green Principle necessitated by the scale of our operations is to minimize the risk of accidents. A multitude of synthetic methods in organic chemistry have recently been introduced towards new synthetic strategies. However, information regarding compatibility and robustness of the reaction conditions on multikilogram scale is usually omitted. Detailed studies are therefore needed to utilize such strategies on larger scales. The process chemistry group at Corteva Agriscience works towards the successful development of practical, safe and cost-effective processes for the synthesis of compounds from kg to hundreds of tons. Optimization of reaction conditions, cost reduction, safety concerns and waste minimization are key goals of our group.

Poster 39

Synthesis and Analysis of Post-metallizable Sulfonamide-based Azo Dyes to Discern their Potential as Sustainable Hair Dyes

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Commercial hair dyes are classified as temporary, semipermanent, and permanent, the latter of which dominate the multibillion-dollar global market due to their high wash resistance. Permanent hair dyes are formed inside hair upon the oxidative coupling of aromatic precursors that give rise to oligomeric indo dyes that become physically entrapped. Unfortunately, some of the precursors used to develop these dyes are strong/extreme skin sensitizers (e.g., p-phenylenediamine). Therefore, there was an interest in identifying hair dyes with reduced toxicological effects. To fulfill this vision, prospective dyes based on monoarylide, arylazopyrazolone, and arylazonaphthol dye chemistry were synthesized. The target dyes displayed affinity toward human hair fibers, with the arylazonaphthol dye displaying the best dye uptake and little color loss on washed fibers. This dye was classified as category 3 and 1 of GHS, respectively for acute and chronic aquatic toxicity and was deemed non-mutagenic (Ames test). To mimic permanent dye formation in hair, the arylazonapthol dye was metallized inside hair using Al3+ and Fe3+ salts under mild conditions (i.e., 40oC). Unmetallized and metallized forms of the arylazonapthol dye were more wash resistant than a prototype permanent hair dye. Thus, the results from this study highlight the potential of post-metallizable azo dyes as permanent hair dye alternatives following dimerization.

Poster 40

Organosilane Antibiotics

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There is an urgent need for the development of new antibiotics because of growing resistance. Despite great effort to identify or invent new antibiotics, bacteria often evolve resistance shortly introduction of a new drug. Natural products have often been the source of novel antibiotics. Modification of known antibiotics has been instrumental to devising new effective variants but in most cases the modifications are based on peripheral decoration of the basic antibiotic core. Deep seated modifications are rare. The silicon–carbon switch approach to pharmaceutical invention has seen little application in antibiotic research. Silicon is the element most similar to carbon, is the second most abundant element in the earth's crust and has no intrinsic toxicity. Notably, naturally occurring silicon–carbon bonds are unknown. We are exploring the replacement of a tertiary alcohol in macrolide antibiotics with silanols. An example is sila-albocycline, a.k.a. alboSicline. Replacement of an alcohol with a silanol yields a slightly larger, slightly more acidic unit. A number of approaches to this new antibiotic species will be described, based in part on the Andrade synthesis of the natural product.

Poster 41

Pursuing Challenging Fluorinated Motifs with Photoredox Catalysis

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By shifting the focus of chemical reactivity from two-electron chemistry to odd-electron reactivity, accessibility to diverse chemical space is radically expanded. In addition to enabling new disconnections, the mild reaction conditions and higher functional-group tolerance of radical chemistry allows for facile late-stage modification of pharmaceutical compounds. Like radical chemistry, another field that has dramatically shaped medicinal chemistry is organofluorine chemistry. That said, the scarcity of naturally occurring fluorinated compounds coupled with the challenge of selective methods for fluorine incorporation make this field ripe for methods development. First described is a process for the radical defluorinative alkylation of α–trifluoromethyl alkenes to generate disubstituted gem-difluoro alkenes. Currently under development is a method for the arylation of trifluoromethyl alkenes, which is fills an important synthetic gap in the previous study. In parallel to these projects, an α-trifluoromethyl organotrifluoroborate reagent was invented, which allows for one-step access to a library of fluorinated alkene structures. This project was also conducted and published alongside an orthogonal method for the diversification of β-silyl, α-trifluoromethyl alcohols, which are effectively “masked” trifluoromethyl alkenes. Finally, the asymmetric hydrogenation of perfluoroalkenes is underway as a collaborative effort with BrightSpec using Molecular Rotational Resonance spectroscopy.

Poster 42

Application of DNA-Encoded Library Technology (ELT): From Libraries to Clinical Candidates

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DNA-Encoded Library Technology (ELT) is a powerful tool for hit identification and target validation. It has been broadly applied in drug discovery both in pharmaceutical industry and academia. In this presentation we will provide an overview of the ELT platform and examples of its application to the identification of highly potent hits/leads for soluble epoxide hydrolase (sEH) and RIP1 kinase that both have successfully led to drug candidates.

Poster 43

Kinetic Selectivity in Silyl Radical-Mediated Fluorination of Alkyl Bromides

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The unique properties imparted by fluorine atoms on organic frameworks have been exploited in the areas of pharmaceuticals, agrochemicals, and materials. Given the increasing interest in fluorinated motifs, the development of general methods for C–F bond formation is an important synthetic goal. In this work, a novel radical strategy for the fluorination of alkyl bromides via the merger of silyl radical activation and benzophenone photosensitization is presented. This transition metal-free protocol tolerates a broad range of substrates including those bearing unprotected alcohols, ketones, and aldehydes, demonstrating the complementary nature of this strategy to existing fluorination methods. Furthermore, the system was extended to the generation of gem-difluorinated motifs, which are commonly found in medicinal agents. Preliminary mechanistic and DFT studies suggest that a radical chain mechanism is operative with excellent kinetic selectivity for the desired alkyl fluoride over the thermodynamically favored Si–F bond.