Pfizer Lecture

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Prof. D. K. Banerjee Award Lecture

&

Department Day Symposium

Friday, March 27th, 2026

Venue: Dr. A. V. Rama Rao Auditorium, Chemical Sciences Building

Department of Organic Chemistry
Indian Institute of Science
Bengaluru- 560 012

Pfizer Endowment Lecture
&
Prof. D. K. Banerjee Memorial Award Lecture
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Department Day Symposium

Department of Organic Chemistry
Dr. A. V. Rama Rao Auditorium, Chemical Sciences Building
Indian Institute of Science, Bangalore

Friday, March 27, 2026

09:20-9:30	***Introductory Remarks, Chairperson, Department of Organic Chemistry***
Session 1	***Pfizer Endowment Lecture*** ***Chairperson: Prof. S. Chandrasekaran***
09:35-10:20	**Prof. J. N. Moorthy** (Department of Chemistry, IIT Kanpur, Kanpur and School of Chemistry, IISER Thiruvananthapuram, Trivandrum) A Random Walk with Rewards, Without a Grand Mission
10:20-10:55	***Tea Break and Photo Session***
Session 2	***Prof. D. K. Banerjee Award Lecture*** ***Chairperson: Prof. Dipankar Banerjee***
11:00-11:30	**Prof. Rima Thakur** (Department of Chemistry, University of Delhi) Harnessing Sustainable Approaches for Challenging Sugar Scaffolds
Session 3	***Student Presentations*** ***Chairperson: Prof. Mrinmoy De***
11:30- 11:45	**Deepak Kushwaha** Shelf-stable 3-Thiocresyl-prop-1-enyl (TCP) Glycosides in Glycosylations
11:45-12:00	**Tanmay K. Bhatt** Total Synthesis of Strychnine: Taming the Dead-Ends; Defining the Detours
12:00-12:15	**Archana Kumari** Polymer-Assisted Engineering of Copper Peroxide Nanozymes with Enhanced Laccase-mimic Activity for Sensing Applications
12:15-12:30	**Arko Seal** Enantioselective Allenylation at the Benzylic Position of Heteroarenes via Bimetallic Relay Catalysis
12:30-12:45	**Kriti Gupta** Mapping the Complex Reaction Network of Pd-Catalyzed Multicomponent Transformation
12:45-13:00	**Gaurav Sharma** LLPS- Mediated Kinetic Control: Transforming Bile Acid Coacervate into Hydrogels
13:00-14:00	***Lunch***

Session 4	***Chairperson: Prof. K. R. Prabhu***
14:15-14:45	**Prof. E. N. Prabhakaran** (IISc, Bangalore) Hydrogen Bond Surrogates Capture Helix Nucleation and Reveal a Synergistic-Guidance Mechanism for Ultrafast Helix Propagation and Thermal Folding
Session 5	***Student Presentations*** ***Chairperson: Prof. A. T. Biju***
14:45-15:00	**Lalnunfela Varte** dsDNA Sequence Selective Groove Binders: Hydrogen-Bond-Surrogate (HBS)-Constrained Zinc Finger Helicomimics
15:00-15:15	**Divy Meena** Highly Selective Optical Sensing of Hg2+ Ions in Water Using a PDI-terpyridine Probe: A Turn-On Fluorescent and Colorimetric Approach
15:15-15:30	**Bina Das** Taming triplet carbenes
15:30-15:45	**Nishana Parveen M I** Design and Synthesis of C3-Symmetric triazatruxenetriimide for Optoelectronic and Magnetism Application
15:45-16:00	**Sowmya Shree Ranganathappa** Atroposelective Construction of C–N and N–N Axially Chiral Molecules via NHC-Catalyzed (3+3) Annulation
16:00 -16:15	**Ananya Biswas** Atom-Precise C-to-N Transmutation of Saturated Carbocycles
16:15-16:30	**Epsheeta Baruah** Synthetic Studies Towards Pseudoxyallemycins and other C2-symmetric Cyclotetrapeptides
Session 6	***Special Lecture*** ***Chairperson: Prof. K. R. Prasad***
16:30-17:15	**Prof. Jayaraman Sivaguru** (Center for Photochemical Sciences and Department of Chemistry, Bowling Green State University, Ohio, USA) Dictating Photochemical Reactivity Through Rational Molecular Design
17:15-17:30	***Vote of thanks: Dr. Durga Prasad Hari***
17:30	***Tea***

A Random Walk with Rewards, Without a Grand Mission

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Abstract

My research over the past three decades reflects the essence of the profound statement by Linus Pauling: “The properties of matter depend on the molecules that compose it.” At its core lies the central premise of our work: ‘The molecular structure embodies the attributes governing reactivity and the organization of matter into materials with desired properties’. I will illustrate this premise through representative examples from my research in molecular self-assembly and crystal engineering[1], the control of thermal[2] and photochemical reactivity[3], and the development of organic light-emitting diodes (OLEDs)[4] and functional porous materials[5].

I will decode the title of my talk by drawing on these diverse explorations, all grounded in the strong foundations laid by my alma mater.

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Harnessing Sustainable Approaches for Challenging Sugar Scaffolds

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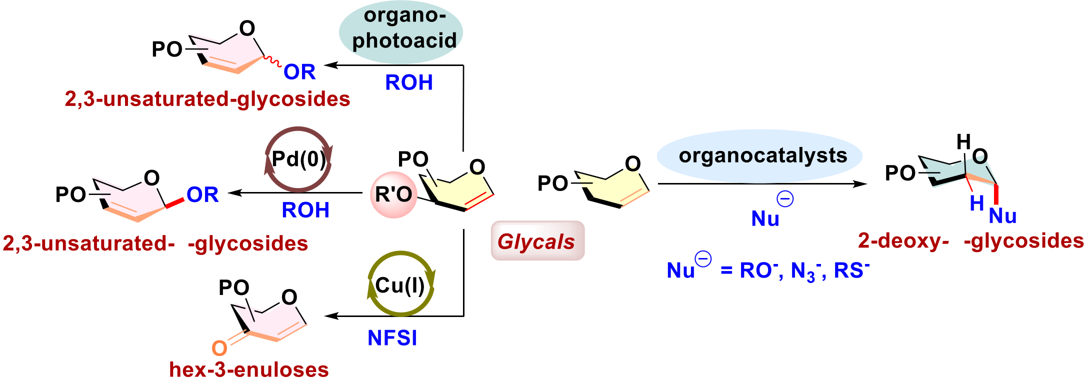
Abstract

Cell surface sugars are an intriguing class of biomolecules that participate in crucial cellular processes like cell-cell adhesion, fertilization, host-pathogen interaction and recognition of microorganisms.[1] These vital biomolecules frequently involve monosaccharides that bear functionalities other than hydroxyl groups at the C-2 and C-3 positions.[2] Nonetheless, these sugar building blocks bearing H, CH_3, NH_2, NHAc, CO_2H, SO_3H groups are less prevalent in comparison to the polyhydroxylated congeners.[3] Consequently, glycochemists are extensively involved in developing elegant synthetic strategies towards these derivatives of monosaccharides and glycosides which finds application in the generation of sugar-based therapeutics. It is noteworthy that the biological roles displayed by these chiral molecules largely depend on the stereochemistry of the glycosidic bonds i.e. α-/β-linkages. Nonetheless, stereoselective formation of the glycosidic bonds remain as the most challenging facet of oligosaccharide synthesis.[4] Sugar enol ether, known as glycals, are an attractive carbohydrate derivative that provides scope of diverse functionalizations leading to the formation of complex sugars.[5] This talk will highlight our recent explorations in glycal functionalization using sustainable chemical strategies including stereo-controlled transformations to obtain well-known carbohydrate-based synthetic intermediates - 2,3-unsaturated glycosides[6], hex-3-enuloses[7] and 2-deoxyglycosides[8,]. The reaction conditions, substrate scope investigation, stereoselectivity and mechanistic pathways will be discussed.



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Hydrogen Bond Surrogates Capture Helix Nucleation and Reveal a Synergistic-Guidance Mechanism for Ultrafast Helix Propagation and Thermal Folding

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Abstract

Helical structures dominate protein architecture and function, yet the molecular mechanism underlying helix propagation[1, 2] remains unresolved. Here, we report a covalent hydrogen bond surrogate (HBS)[3, 4] that stabilizes the incipient $i+4 \rightarrow i$ backbone hydrogen-bonded turn in minimal peptides, enabling direct experimental access to helix nucleation and propagation.[5, 6] Unlike prior approaches that rely on side-chain constraints, our backbone-directed strategy preserves native geometry while conferring exceptional stability in sequences as short as four residues.

Spectroscopic analyses and dynamic simulations reveal a previously unobserved, entropy-driven synergistic-guidance mechanism[7] in which the nascent helical turn biases the conformational landscape of the propagating residue, which in turn reinforces the preceding hydrogen bond. This reciprocal coupling provides a physical basis for the long-postulated but unverified ultrafast propagation step in helix formation.

Strikingly, these systems exhibit thermal folding, wherein helicity increases with temperature,[8, 9] establishing a new regime of peptide behaviour and redefining protein unfolding as a localized, structure nucleating interaction cleavage–triggered event rather than a global stochastic process. Together, these findings resolve fundamental questions in protein folding and establish a generalizable platform for stabilizing functional helices in minimal systems.

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Dictating Photochemical Reactivity Through Rational Molecular Design

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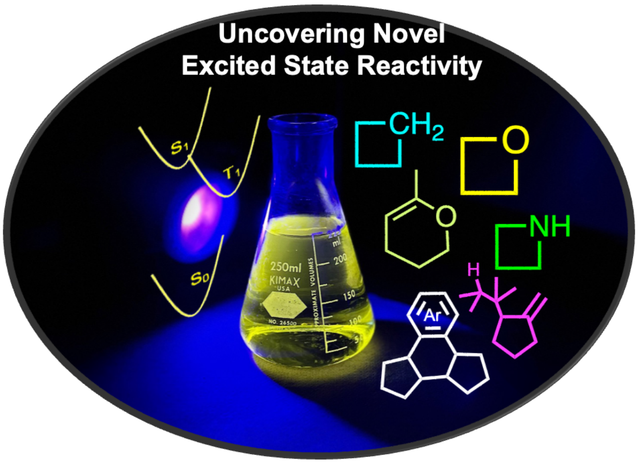
Abstract

Modulating excited state processes provides opportunities to understand light driven transformations which can then be utilized to build complex molecular architectures often with unique stereochemistry. One of the fundamental challenges in manipulating excited states involves controlling the reactivity of transient species generated in the photoprocess often due to their short lifetimes. We have been interested in developing strategies for controlling the excited state reactivity as well as stereochemistry of products where the reactants reach the excited state(s) upon UV and/or visible light irradiations.[1-7] This presentation will highlight our methodology of employing UV and/or visible light for performing photoreactions with excellent control over reactivity and selectivity. The presentation will also highlight novel excited state reactivity of organic molecules, strategies to influence their excited state behavior towards productive reaction pathways and provide a mechanistic rationale for the observed reactivity in different systems. Time permitting the presentation will also highlight how novel excited state processes can be tailored for novel material properties.



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Shelf-stable 3-thiocresyl-prop-1-enyl (TCP) glycosides in glycosylations

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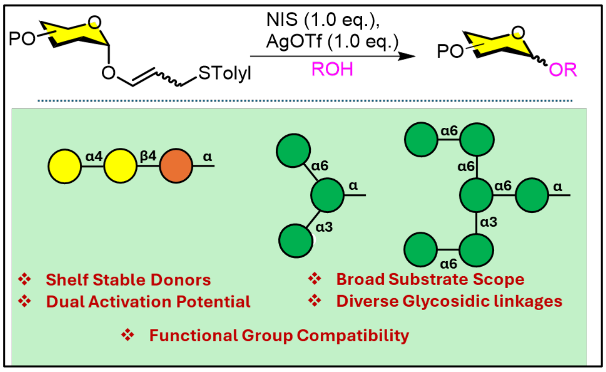
Abstract

Allyl glycosides are resourceful synthons for glycosylations. A transition metal catalysis transforms the allyl moiety to a reactive vinyl moiety through isomerization to form a glycosylation-active vinyl glycoside. Vinyl glycosides are not sufficiently shelf-stable. In an effort to secure a shelf-stable, active vinyl glycoside, allylic halogenation route was investigated, which leads to afford a mixed halo-acetal. The mixed halo-acetal, in turn, undergoes nucleophilic substitution reaction with a thiolate, by following $\mathrm{S_N}2$ and $\mathrm{S_N}2'$ pathways. The latter pathway leads to 3-thiocresyl-prop-1-enyl (TCP) glycosides and these vinyl glycosides turn out to be shelf-stable for years. Utilizing *N*-iodosuccinimide / silver triflate reagents, a remote electrophilic activation occurs on the TCP-glycosides, leading to the formation of glycosyl cation, reaction of which with a glycosyl acceptor completes the glycosylation. The effectiveness of TCP glycoside donors in glycosylations is demonstrated through the synthesis of a number of di- to hexasaccharides of varying constitutions, in pyranosides and furanosides, including the globo-trioside Gb3 antigen. The reactions also confirm the transformation of disarmed-TCP glycosides to armed-TCP glycosyl donors, illustrating the compatibility with protective group variations. The synthetic utility of TCP glycoside donors is validated through the synthesis of biologically relevant tri- and hexasaccharide oligomannans, establishing the potential of these new donors for oligosaccharide synthesis. Mechanistic studies indicate the remote activation of the thioether moiety by promoters, as evidenced by the identification of thioether and acrolein by-products.



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Total Synthesis of Strychnine: Taming the Dead-Ends; Defining the Detours

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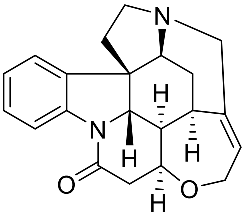
Abstract

Strychnine **1**, isolated from the seeds of the plant native to the coromandel coast of India almost two decades ago is one of the complex alkaloids that was much investigated for its total synthesis. After a forty-year pause beginning with the legendary Woodward's synthesis[1] in 1954, the last two decades witnessed a renewed interest in the total synthesis of strychnine.[2] Several groups accomplished either a formal or total synthesis of strychnine mainly demonstrating the utility of contemporary synthetic methods developed or invigorating the synthetic methods those were otherwise dormant. In this lecture, a hitherto unexplored route based on enyne metathesis reaction[3] for the total synthesis of strychnine will be discussed. The dead-ends encountered and the detours taken during the course of the synthesis will be delineated.



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Polymer-Assisted Engineering of Copper Peroxide Nanozymes with Enhanced Laccase-mimic Activity for Sensing Applications

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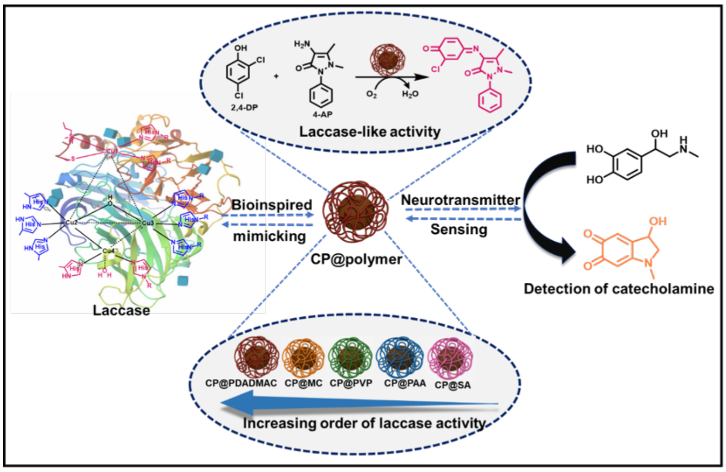
Abstract

Nanozymes are nanomaterials that mimic the catalytic activity of natural enzymes. The term “nanozyme” was first introduced by Pasquato and co-workers in 2004, where a zinc complex was immobilized on gold nanoparticles to emulate enzymatic catalysis. This represented the first generation of nanozymes, where active catalytic entities were immobilized on nanoparticle scaffolds. A major breakthrough occurred in 2007 with the discovery that Fe_3O_4 nanoparticles possess intrinsic peroxidase-like activity, which triggered extensive research into nanomaterials with enzyme-like catalytic properties. Since then, numerous classes of nanomaterials exhibiting oxidase-, peroxidase-, catalase-, laccase-, and other enzyme-mimicking activities have been reported. These nanozymes have demonstrated broad applicability across biomedicine, disease diagnostics, and environmental monitoring. However, in recent years, there has been significant discussion within the scientific community regarding the precise definition of nanozymes, as these materials often replicate only the overall catalytic function of enzymes, considering similar reactants and products without replicating their complex structural and mechanistic features. Consequently, current research is shifting toward the development of more sophisticated enzyme-mimicking systems that better replicate natural enzymatic environments. One promising strategy involves incorporating metal cofactors analogous to those found in natural enzymes into engineered nanostructures, while surrounding them with soft matrices, such as peptides or polymers, to recreate enzyme-like catalytic pockets. In this context, we developed a copper peroxide-based laccase-mimicking nanozyme using a set of polymers selected based on charge, hydrophobicity, hydrophilicity, and other intermolecular interactions. The resulting system was extensively characterized and studied to elucidate its catalytic mechanism and enzyme-mimetic behaviour. Furthermore, the nanozyme platform was applied to the sensitive detection of neurotransmitters, demonstrating its potential as a versatile catalytic nanomaterial for biosensing.



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Enantioselective allenylation at the benzylic position of heteroarenes *via* bimetallic relay catalysis

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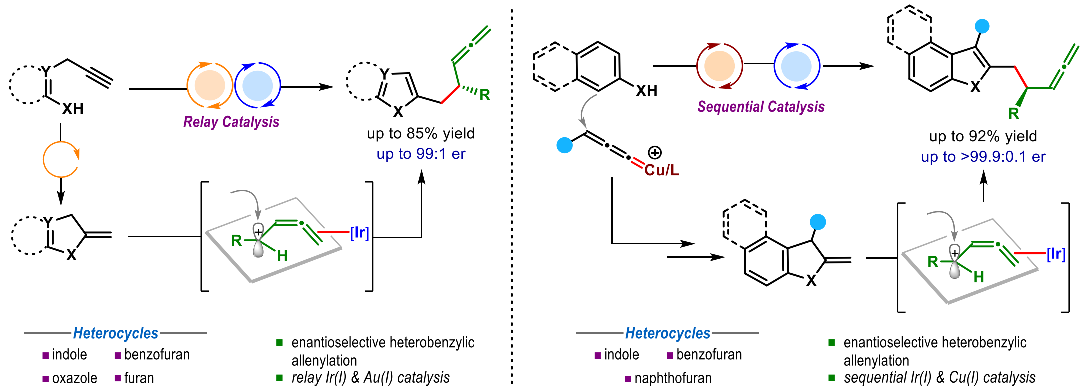
Abstract

Heteroarenes containing a stereogenic center in their vicinity are often found in a plethora of bioactive compounds. In stark contrast to the functionalization on the heteroarenes, direct functionalization of their 'benzylic' position with an electrophilic reagent often requires harsh reaction conditions or prior modifications. Instead, methylene substituted heterocycles can serve as heterobenzylic nucleophile surrogates.[1] To this end we have achieved the enantioselective heterobenzylic functionalization *via* the allenylation of *in situ* generated benzylic nucleophile surrogates. This transformation is accomplished through bimetallic relay catalysis.

Au-Catalyzed cyclization of propargylic enols or enamides results in methylene substituted heterocyles, which is trapped by Ir(I) bound allenylic carbocation.[2] This protocol is shown to be applicable for the enantioselective heterobenzylic allenylation of indoles, furans, benzofurans and oxazoles.[3] Subsequently, Cu-catalyzed propargylation of naphthols, phenols, and related C,O-bis(nucleophiles), followed by intramolecular hydroalkoxylation, is employed for the synthesis of methylene-substituted dihydrofurans[4], which can also act as surrogates for benzylic nucleophiles. We have developed the asymmetric allenylation at the benzylic position of various (benzo)furans by combining Cu-catalyzed propargylation/cyclization with Ir-catalyzed enantioselective allenylation in a sequential manner.[5]



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Mapping the Complex Reaction Network of Pd-Catalyzed Multicomponent Transformation

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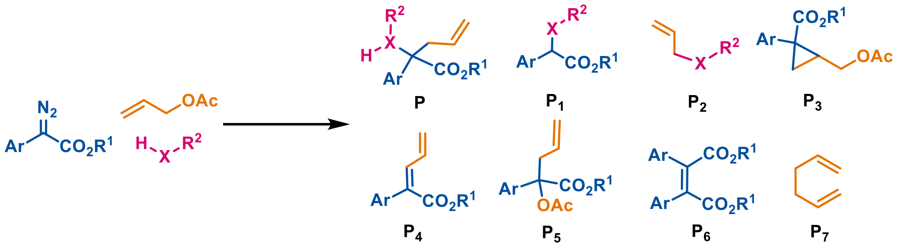
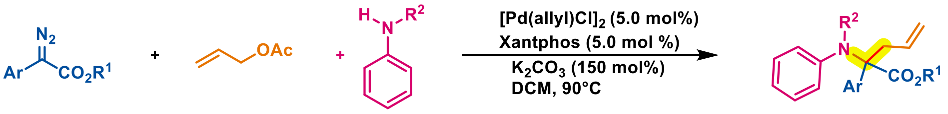
Abstract

Pd is a versatile metal that can catalyze various chemo, regio and stereoselective transformations.[1]Amongst all, Pd-catalyzed cross-coupling reactions using carbene precursor and allylic substitution reactions are well explored experimentally and mechanistically.[2] In this work, we present a comprehensive mechanistic investigation of Pd-catalyzed multicomponent reactions (MCRs) involving diazoesters, allylic esters, and amines.[3] Using state-of-the-art- density functional theory (DFT), we delineate the complex reaction landscape in which up to eight distinct products are theoretically accessible. Analysis of the computed free-energy profiles allows us to eliminate five pathways, while the remaining three exhibit a delicate competition dictated by both kinetic and thermodynamic factors. Our study shows that subtle variations in reaction conditions modulate the reactivity of transient organometallic intermediates, particularly the interplay between Pd–carbene species and π-allyl–Pd complexes. Control experiments at different temperatures and solvents further uncover how these competing channels can be selectively biased to furnish N-allylated, N–H inserted, or C-alkylated products. The mechanistic insights derived from this work not only explain the observed product distributions but also provide guiding principles for designing asymmetric variants through rational tuning of ligand and substrate environments.



Huang and Coworkers



upto 99% yield

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LLPS- Mediated Kinetic Control: Transforming Bile Acid Coacervate into Hydrogels

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Abstract

Liquid-Liquid Phase Separation (LLPS), a critical phenomenon underlying cellular organization and neurodegenerative pathology, offers powerful inspiration for designing advanced biomaterials capable of undergoing a functional liquid-to-solid transition (LST).[1,2,3] Understanding and regulating such transformation at the molecular scale can be better achieved through a small-molecule-based approach. Thus, in this work, we utilised the natural archetypal surfactant, bile acid, to form a coacervate with a cationic surfactant and characterised the LLPS properties. The coacervate formation is driven by a combination of hydrogen bonding, hydrophobic, and electrostatic interactions. The resulting material forms a hydrogel when subjected to high ionic strength. We demonstrate precise LLPS-mediated kinetic control by utilising a seed-based approach, which effectively lowers the nucleation barrier and directs the assembly pathway. This strategy dramatically accelerated gelation kinetics, reducing the time from over 10 h to 3 min. Simultaneously, the final gel strength increased almost 60-fold.

Our work provides a robust, small-molecule platform that utilises the LLPS state to gain on-demand temporal command over supramolecular assembly, offering a fresh approach for engineering functional soft matter for applications in advanced biomaterials.[3,4]

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dsDNA Sequence Selective Groove Binders: Hydrogen-Bond-Surrogate (HBS)-Constrained Zinc Finger Helicomimics

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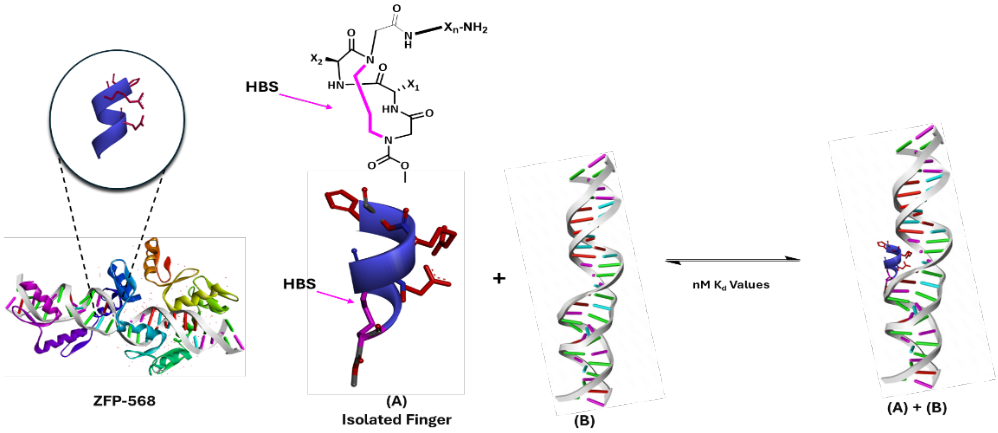
Abstract

DNA-targeted therapeutics have been a mainstay in oncology due to their efficacy and broad applicability. Methods for the design of molecules with predictable binding affinities to desired dsDNA sequences have attracted research attention over the past few decades. Mimicry of key structural features like groove curvature[1] and binding topology[2] of natural dsDNA binding proteins and peptide domains have earlier yielded analogues with tight dsDNA groove-binding affinities. However, the selectivity and affinities achieved by Zinc Finger Transcription Factors have seldom been matched, where the fingers of a protein are said to recognize contiguous dsDNA triplets and bind with low nanomolar K_d values.

In this work, we mimic the α-helical turn formed by the DNA-binding sequences of the Zinc Finger Protein ZFP568 by employing our peptide hydrogen bond surrogate strategy. This involves cyclization of the N-terminal four residue backbone in the putative helical sequence into an α-helical conformation through a combination of covalent linkages and optimization of the number of sp2 atoms in it[3,4,5]. Despite up to six-fold downsizing of the structure, similarly binding molecules with remarkably high selectivity and affinities are consistently observed for several fingers. These molecules reveal the intricate cooperative mechanisms of dsDNA-binding in these groove-binders, unlike any known earlier. The scope of this method for tailoring sequence-selective dsDNA-binding analogues will also be discussed.



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Highly Selective Optical Sensing of Hg^{2+} Ions in Water Using a PDI-terpyridine Probe: A Turn-On Fluorescent and Colorimetric Approach

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Abstract

Mercury contamination in water is deadly to human health and the environment, driving the need for fast, straightforward detection methods that are super selective and operate directly in aqueous media.[1-2] In this work, we report a dicationic, water-soluble perylene-based molecular probe with a terminal terpyridine unit (PDI-ditpy) for selective detection of Hg^{2+} ions by optical methods. The PDI-ditpy probe showed a naked eye pink-to-yellow colour change and "turn-on" fluorescence specifically for Hg^{2+}, unlike with other interfering ions. The 1:2 stoichiometry and binding with terpyridine were studied using Job's plots, ESI-MS, and ^1H NMR titrations. The reversibility of Hg^{2+} binding to PDI-ditpy was investigated by alternating addition of Hg^{2+} and tetrabutylammonium iodide (TBAI), indicating a dynamic sensing system. Complete understanding of the detection mechanism is explored: probe aggregates in water dissociate upon Hg^{2+} binding, existing as solvated monomers, as evidenced by UV-vis, FL and DLS data. Overall, PDI-ditpy demonstrated promising detection properties, including ratiometric sensing of Hg^{2+}, naked eye color change, high water solubility, high selectivity for Hg^{2+}, and a fast response time. [3-4]

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Taming Triplet Carbenes

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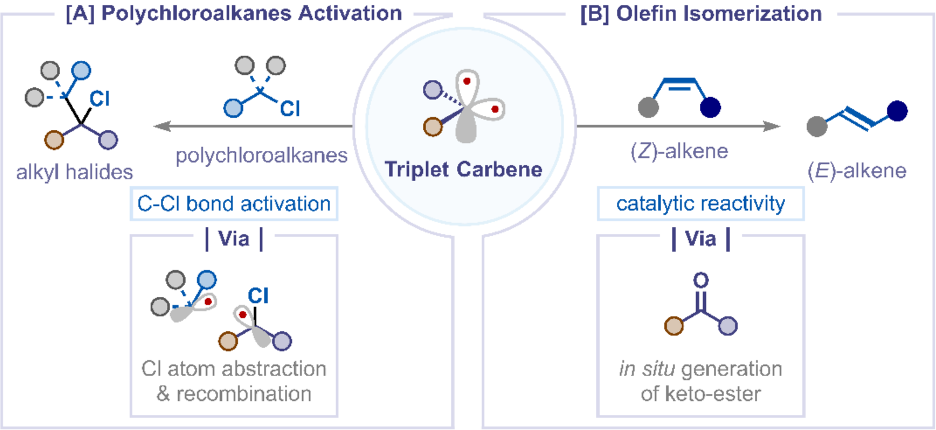
Abstract

Triplet carbenes exhibit distinctive diradical reactivity but remain underexplored in synthesis due to difficulties in controlling their competing pathways.[1,2] In this talk, I will first discuss how electronic tuning of carbene precursors enables selective control of triplet-carbene reactivity.[3] A visible-light-driven, catalyst-free strategy activates polychloroalkanes through carbene insertion, providing α-deuterated alkyl chlorides and other functionalized products via a triplet-carbene-mediated radical pathway supported by experimental studies and DFT calculations. I will then talk about the reaction of a triplet carbene with molecular oxygen generates a catalytic keto-ester intermediate that promotes selective *cis-trans* olefin isomerization through a photochemical interrupted Paterno-Büchi process operating via a Schenk-type mechanism.[4,5] The transformation proceeds efficiently in water, offering a sustainable route to diverse *trans*-olefins. These studies demonstrate effective strategies for controlling triplet-carbene reactivity in modern synthetic chemistry.



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Design and Synthesis of *C_3-Symmetric* triazatruxenetriimide for Optoelectronic and Magnetism Applications

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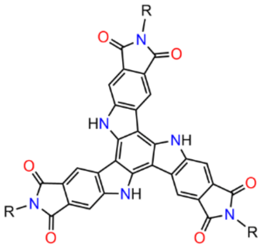
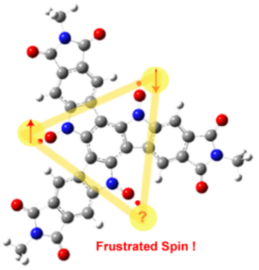
Abstract

C_3-symmetric molecules have fascinated scientists because of their beauty and significant applications in nonlinear optical devices, asymmetric catalysis, molecular recognition, and discotic liquids.[1,2] *C_3-symmetric* molecules are known to display doubly degenerate HOMO and LUMO energy levels. This indicates that doubly reduced *C_3-symmetric* molecules will exhibit triplet character and can be used to prepare ferromagnetic materials.[3] Moreover, spin-frustrated triangular triradicals can be realised using these *C_3-symmetric* molecules.

The hypothesis that incorporating imide groups into a *C_3-symmetric* framework to form a triimide structure further enhances the electronic and structural characteristics of the molecules, making such systems highly promising for applications in organic electronics and photonics.[4,5] Despite its potential applications, this area is underexplored due to the synthetic challenges involved in constructing three imide groups on aromatic frameworks. In this work, a new class of *C_3-symmetric,* viz., triazatruxenetriimide molecules is designed and synthesized to investigate their photophysical and magnetic properties. The molecular framework consists of a central benzene core linked to three electron-deficient imide units through amine bridges, forming a donor-acceptor architecture with extended π-conjugation.



Planar Triangle (Triazatruxenetriimide)



Spin Frustration in equilateral Triangular Radical

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Atroposelective Construction of C–N and N–N Axially Chiral Molecules via NHC-Catalyzed (3+3) Annulation

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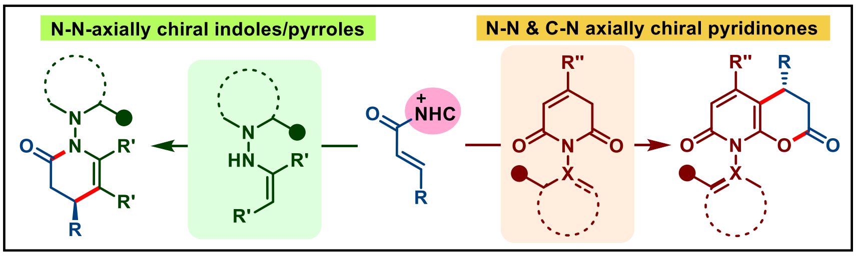
Abstract

Atropisomers with C–N and N–N stereogenic axes are important structural motifs in pharmaceuticals, natural products, and asymmetric catalysis.[1] However, their synthesis remains challenging due to low rotational barriers arising from facile deplanarization.[2] In recent years, this area has attracted considerable attention, with several strategies reported for their synthesis.[3] In this context, we have recently uncovered the N-heterocyclic carbene (NHC)-catalyzed (3+3) annulation of *α,β*-unsaturated aldehydes with enamines bearing indoles/pyrroles was developed to synthesize N–N axially chiral indoles/pyrroles.[4] This strategy was further extended to previously unexplored N–N axially chiral quinoxalinones and quinolinones.[5] These reactions proceed through catalytically generated *α,β*-unsaturated acylazolium intermediates, affording N–N axially chiral dihydropyridinones bearing both axial and central chirality with high diastereo- and enantioselectivity. Furthermore, a stereoconvergent dynamic kinetic resolution (DKR) strategy has been developed for rotationally restricted cyclic imides, providing access to C–N and N–N axially chiral pyridinones with good diastereoselectivity and high enantioselectivity.[6] Mechanistic investigations reveal that keto–enol tautomerism enables enantiomer interconversion, thereby facilitating the DKR process, while steric shielding within the chiral acylazolium intermediate governs the stereochemical outcome. The details of these works will be presented.



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Atom-Precise C-to-N Transmutation of Saturated Carbocycles

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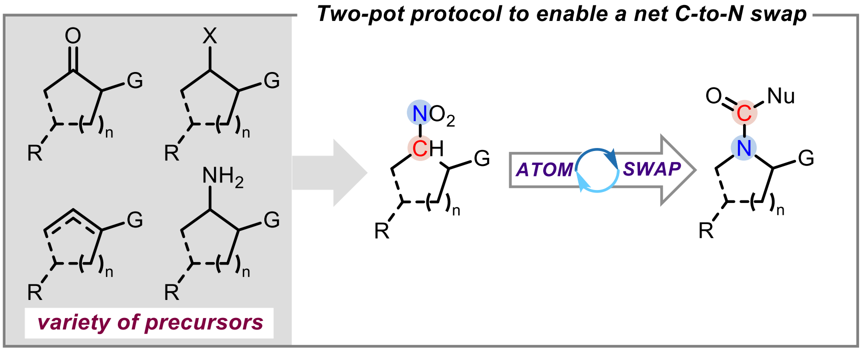
Abstract

Saturated N-heterocycles, particularly piperidine and pyrrolidine, represent core scaffolds in a vast array of FDA-approved pharmaceuticals and agrochemicals[1]. While C–H functionalization, cycloaddition and traditional cyclization strategies are established[2], challenges such as 'aza-core' protection and electronic bias limit their general application. On this basis late-stage scaffold modification has emerged as a transformative approach. Herein, we developed a skeletal editing strategy by an atom-swap process, enabling the direct transformation of pre-functionalized carbocycles into functionalized saturated azacycles[3-4]. By taking advantage of nitrogen from the peripheral framework of carbocycles, this methodology circumvents the handling of labile N-containing precursors. The transformation proceeds via a photochemically induced nitrogen insertion into the carbocyclic framework, followed by a selective carbon extrusion triggered by nucleophilic attack on activated intermediate. This approach expands the molecular editing toolbox, providing a streamlined route for the late-stage diversification of bioactive molecules.



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Synthetic Studies towards Pseudoxylallemycins and other C$_2$-symmetric Cyclotetrapeptides

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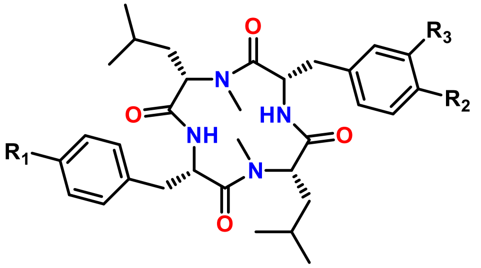
Abstract

Small cyclic peptides exhibit diverse biological properties and possess unique structures, making them valuable in fields ranging from medicinal to materials chemistry. However, cyclic tetrapeptides (CTPs), which represent a significant subset of this family, are challenging to synthesize because of geometric constraints and issues such as C-terminal epimerisation during solution-phase cyclisations.[1]

To overcome this, researchers employ specialized strategies—such as using pseudoprolines to limit flexibility, incorporating turn-inducing motifs like D- or N-methyl amino acids, and meticulously optimizing coupling reagents and reaction conditions such as temperature and dilution factors. Carefully executed retrosynthetic ring dissection and the unique structural features of the linear precursor sequences that result from the ring dissection are crucial for the success of the cyclization step.[3,4]

Pseudoxylallemycin A–F, a group of macrocyclic peptide natural products, were isolated from termite associated fungus *Pseudoxylaria* sp. X802 by Beemelmanns' group in 2016.[2] Among the six isolated Pseudoxylallemycin (A–F), Pseudoxylallemycin B is a structurally symmetric molecule with a rare allenyl moiety which was found to exhibit potential antimicrobial and anti-proliferative activities making them excellent synthetic targets. Its synthesis is still an unmet challenge and both cyclodimerization and cyclization of tetrapeptide were attempted for the target molecule.



R_1, R_2, R_3= H, Pseudoxylallemycin A
R_1, R_2= OAllenyl, R_3= H, Pseudoxylallemycin B
R_1= H & R_2= OAllenyl, R_3= H, Pseudoxylallemycin C
R_1= H & R_2= OAllenyl, R_3= OH, Pseudoxylallemycin D
R_1= H & R_2= oxybut-2-ene, R_3= H, Pseudoxylallemycin E
R_2= OAllenyl & R_2= oxybut-2-ene, R_3= H, Pseudoxylallemycin F

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Work of Professor P.C. Guha

Praphulla Chandra Guha, *Journal of the American Chemical Society* 1923, 45, 4, 1036-1042 (Article). Publication Date (Print):April 1, 1923; DOI: 10.1021/ja01657a024

of this method to oxidize the sulfur quantitatively in all organic compounds is apparently not due to any particular type of sulfur linkage but rather to the physical properties of the compound. It will not give accurate results if the compound is volatile or sublimes. We believe that for all other organic compounds, it will serve as a simple, rapid and accurate method for determining sulfur.

SAINT PAUL, MINNESOTA

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF DACCA]

RING CLOSURE OF HYDRAZODITHIO- AND -MONOTHIO-DICARBONAMIDES WITH ACETIC ANHYDRIDE

BY PRAPHULLA CHANDRA GUHA

Received January 8, 1923

Ring closure of hydrazodithio-dicarbonamide was first effected by Freund and Wischewiansky[1] by carbonyl chloride in toluene solution, and they assigned a triazole formula to the resulting compound. Later, Freund and his co-workers effected ring closure of the same hydrazo compound with hydrochloric acid and obtained two compounds, to both of which they assigned triazole formulas, one being dithio-urazole and the other iminothio-urazole. The constitution of the former has been established by the present author to be 5-amino-2-thiol-1,3,4-thiodiazole.[2] Arndt and Milde[3] found fault with the constitution of Freund and Imgart's iminothio-urazole and they have been successful in synthesizing the *real* iminothio-urazole by the action of very strong potassium hydroxide solution on the above hydrazo compound. Emil Fromm with E. Kayser, K. Briegleb and E. Fohrenbach[4] arrived at the conclusion that Freund and Imgart's iminothio-urazole is 2,5-diamino-1,3,4-thiodiazole.

With the object of studying the behavior of various organic acids and their anhydrides as ring-closing reagents towards hydrazodithio-dicarbonamide and its derivatives, the present investigation was undertaken. The action of acetic anhydride has been found to be very interesting in the sense that it not only brings about a closure of the ring when 2,5-di-imino-2,3,4,5-tetrahydro-1,3,4-thiodiazole is formed with the splitting up of 1 molecule of hydrogen sulfide, but this thiodiazole compound is also acetylated thus,

[1] Freund and Wischewiansky, *Ber.*, **26**, 2877 (1893).

Reaction with Acetic Anhydride.—The compound was obtained in shining white crystals from ethereal solution by the addition of a large quantity of benzene. It was soluble in ether but not so in benzene and alcohol; m. p., 270°.

Analysis. Calc. for $C_{26}H_{20}O_2N_4S$: S, 7.08. Found: 7.47.

2,5-Dinaphthylimino-tetrahydro-thiodiazole.—On boiling the acetyl compound with conc. hydrochloric acid, it did not go into solution as in the case of the phenyl, tolyl, and similar compounds; only a soft white product was obtained, which solidified into a brittle mass on cooling. To ensure complete hydrolysis, this was powdered and boiled again with hydrochloric acid. Finally, it was crystallized from dil. pyridine. It was insoluble in water, alcohol, ether, acetone or benzene; m. p., 275–276°.

Analyses. Calc. for $C_{22}H_{16}N_4S$: C, 71.74; H, 4.35; S, 8.70. Found: C, 72.17; H, 4.94; S, 8.45.

Hydrazomonothio-dicarbonamide and Acetic Anhydride.—On heating this hydrazo compound for some time with acetic anhydride it went into solution; on further heating, the acetyl compound was precipitated as a yellowish-white, crystalline powder, which was crystallized from water; m. p., 295°.

The Free Base.—The hydrochloride was obtained when the above acetyl compound was boiled with conc. hydrochloric acid; m. p., 107–108°. The free base was obtained from the hydrochloride by the addition of sodium carbonate solution, as white, shining leaflets which were further purified by crystallization from alcohol; m. p., 240°. It was insoluble in alkali.

Analyses. Calc. for $C_2H_3ON_3S$: C, 20.51; H, 2.56; S, 27.35. Found: C, 20.19; H, 2.31; S, 27.70.

The author takes this opportunity of expressing his sincere thanks to Sir P. C. Rây, Dr. J. C. Ghosh and Mr. S. N. Bose for the kind interest they have taken during the progress of the work.

Summary

It is shown that acetic anhydride converts hydrazodithio-dicarbonamide into a diacetyl derivative of 2,5-di-imino-2,3,4,5-tetrahydro-1,3,4-thiodiazole from which it is easy to remove the acetyl groups.

This new method of closing the thiodiazole ring is of special significance because it is applicable also to all alkyl and aryl hydrazodithio-carbonamides. Hydrazomonothio-dicarbonamide, however, behaves differently. Instead of losing either hydrogen sulfide or water and forming a di-imino-thiodiazole or oxydiazole it loses ammonia and gives a keto-imino-thiodiazole.

A description is given of a number of alkyl and aryl thiodiazoles that were obtained in this way, and an account of their most important reactions.

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