NUS National University of Singapore | Faculty of Science

Advances in Science

Volume 31 January 2026

A special issue on Manufacturing, trade and connectivity

FEATURES

Table of Contents

RESEARCH FEATURES

Advances in Science

The Faculty of Science conducts basic and applied experimental, theoretical and simulation research over a broad spectrum of science, mathematics and technology domains. We cover most of the key fields in biological sciences, chemistry, physics, pharmacy, pharmaceutical sciences, food sciences, natural history, mathematics, statistics and data science.

Advances in Science is now published online once a year. It is written for a broad scientific audience interested to keep up with some of the key areas of science pioneered by researchers at the Faculty of Science.

For further information on the research in this newsletter, please contact:

Editor: SOH Kok Hoe (kok.hoe@nus.edu.sg)
Consultants: Professor CHEN Wei (chmcw@nus.edu.sg)
Associate Professor LIOU Yih-Cherng (dbslyc@nus.edu.sg)

Dean's Office, Faculty of Science
National University of Singapore
Blk S16, Level 9, Science Drive 2
Singapore 117546

For the latest research news, please refer to:
URL: https://www.science.nus.edu.sg/blog/category/research-news/

On the cover: Manufacturing, trade and connectivity enabled by Science. Translating laboratory breakthroughs into AI-driven production, while data networks connect ships, rail, aircraft and satellites, binding materials innovation to a resilient, intelligent global supply chain. [Image generated using AI-Know, powered by OpenAI's GPT Image 1 model.]

Shedding light on the symmetry properties of solids

Advancing the understanding and control of solids through laser polarimetry

The ubiquity and importance of symmetry in crystals

Symmetry is a fundamental concept that shapes our world, from the mirror symmetry of a butterfly's wings to the rotational symmetry of a snowflake or a starfish. In the realm of solid-state materials, particularly single crystals, symmetry is not merely an aesthetic feature; it is a core principle that dictates their physical properties and functionalities.

Consider the simple concept of mirror symmetry. Your right hand is the mirror-symmetric partner of your left hand (see Figure 1A). We can apply the same test to a crystal lattice. In Figure 1B, the red and blue circles represent different atoms. If we generate its mirror image, we find it perfectly coincides with the original crystal; this is a mirror-symmetric crystal. In contrast, the crystal in Figure 1C is mirror-asymmetric. The displacement of the red atom from the centre breaks the symmetry, as the original lattice and its mirror partner are no longer identical. This fundamental difference has profound implications for the crystal's behaviour.

Why crystal symmetry is fundamental

Understanding the symmetry properties of crystals is crucial for two primary reasons.

First, symmetry provides the most precise framework for describing new phases of matter and the emergence of novel physical orders. Many modern technologies — from non-volatile memory and sensors to transducers and actuators — rely on functional materials exhibiting phases like ferroelectricity, ferromagnetism, or piezoelectricity. The onset of these phases is universally described as a symmetry-breaking transition.

Returning to our example, imagine the atoms in Figure 1B carry opposite charges. With the red atom perfectly centred within the cube of blue atoms, the positive and negative charge centres coincide, resulting in no net electric dipole moment. However, if all the red atoms in the crystal are collectively displaced from their central positions, as in Figure 1C, a macroscopic electric polarisation emerges, and the crystal becomes ferroelectric. This phase transition is marked by a reduction in symmetry. Consequently, detecting changes in symmetry is the most powerful way to identify and understand these emergent orders.

Second, symmetry enables the classification of materials. While the number of possible compounds is vast; for example, estimates suggest there are over **50,000 stable ternary compounds** alone. Symmetry arguments allow us to categorise these countless material candidates into a total of just 32 unique point groups (or crystal classes). Each class shares a common set of symmetry operations and, therefore, similar physical properties. This classification system, born from mathematical rigour, dramatically simplifies the discussion and discovery of new materials by grouping them based on their inherent symmetry rather than their chemical composition alone.

Our method: Optical probes of crystal symmetry

Our research group specializes in using advanced optical techniques to directly probe the symmetry properties of crystals. Traditional laser spectroscopy often focuses on measuring energy- or frequency-resolved responses. In contrast, detecting symmetry requires unique optical setups designed to be sensitive to the spatial and polarisation anisotropy of a material.

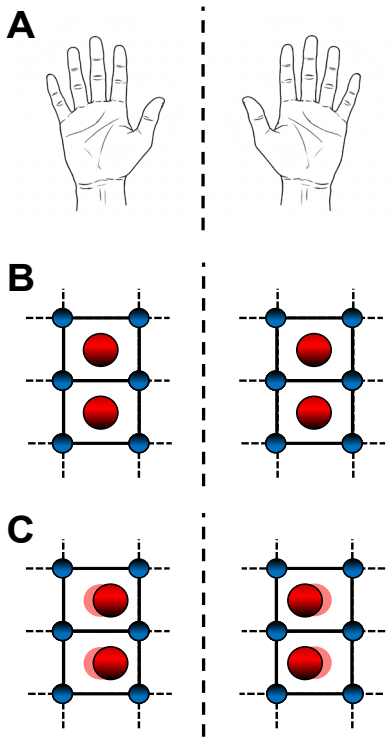


Figure 1: Conceptual diagrams illustrating mirror symmetry. (A) Right hand is the mirror-symmetric partner of left hand. (B) A mirror-symmetric crystal structure. (C) A mirror-asymmetric crystal structure.

A representative technique we employ is Second-Harmonic Generation (SHG) polarimetry [1]. As illustrated in Figure 2A, we illuminate a sample with an intense laser beam at a fundamental frequency (ω). We then carefully collect the weak, emitted light at exactly twice the frequency (2ω), known as the second harmonic. Crucially, we measure how the intensity of this second-harmonic signal varies as we rotate the crystal angle (ϕ). The physical process of SHG is inherently sensitive to symmetry; it is forbidden in centrosymmetric crystals under electric-dipole approximation and allowed in non-centrosymmetric ones.

When applied to an orthorhombic crystal, this method produces a characteristic four-lobe intensity

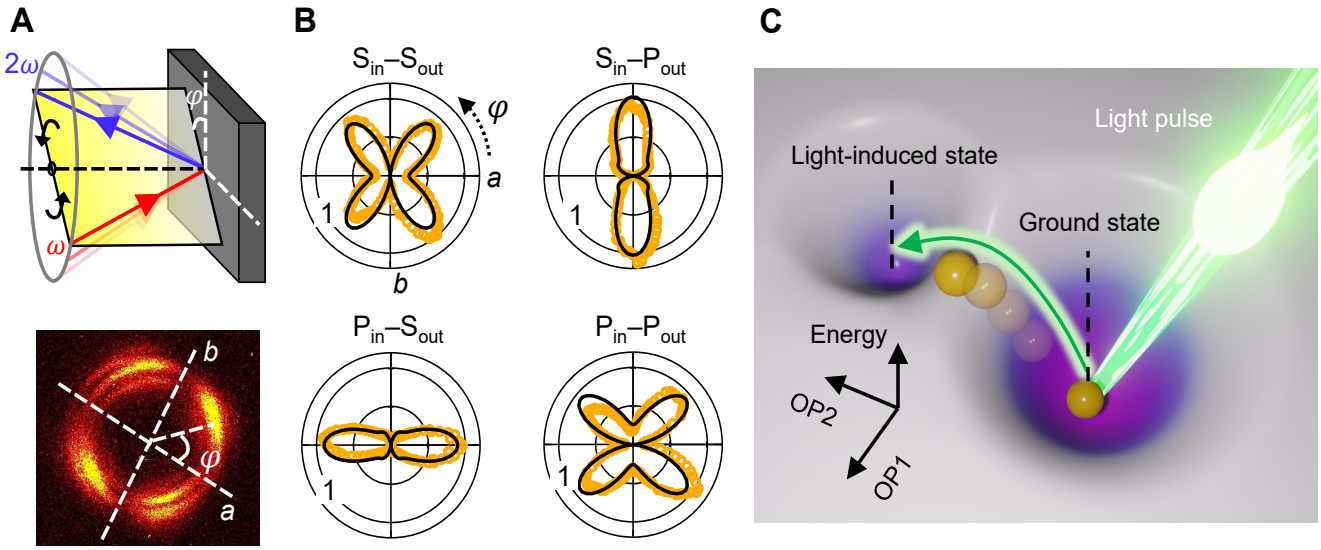


Figure 2: (A) Schematic of the Second-Harmonic Generation (SHG) polarimetry setup with a representative intensity polar plot. (B) SHG polar plots for an orthorhombic crystal under different polarisation conditions. (C) Diagram of a material being driven into a metastable state via ultrafast laser excitation.

pattern in the polar plot (lower panel of Figure 2A), which directly maps onto the two mirror axes of the crystal's structure. Figure 2B shows a series of such polar plots for different combinations of input and output laser polarisations. The resulting patterns act as a fingerprint, making the crystal's symmetry, including its major axes and mirror planes, clearly visible and directly assignable.

Our expertise lies in developing a suite of complementary optical instruments. While SHG is exquisitely sensitive to structural and electronic symmetry, other techniques like Magnetic Circular Dichroism (MCD) or the Magneto-Optical Kerr Effect (MOKE) are ideal for probing magnetic order and symmetry. Similarly, Raman polarimetry can reveal the symmetry of vibrational modes. By combining these tools, we can construct a comprehensive picture of a material's symmetry landscape across its structural, electronic, magnetic, and vibrational degrees of freedom.

Towards the full optical control of crystal symmetry

We believe the next frontier lies not only in detecting symmetry but also in actively manipulating it. Beyond our diagnostic tools, we utilise high-power femtosecond laser pulses from ultrafast amplified laser systems to build sophisticated time-resolved experiments.

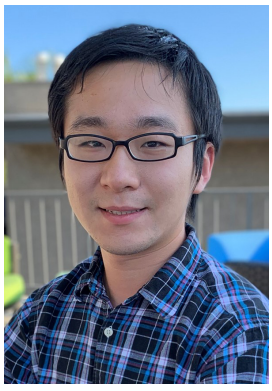
The purpose of these systems is to deliver a massive packet of energy to the sample within an incredibly short period (femtoseconds, or 10^{-15} seconds). This sudden excitation violently drives various degrees of freedom — electrons, the atomic lattice, and spins — far out of their equilibrium state. As the system subsequently relaxes, as depicted in Figure 2C, it may not simply return to its original state. Instead, it can settle into a so-called metastable state — a hidden phase of matter that is not accessible under normal equilibrium conditions because it does not represent the global free-energy minimum [1]. A laser pulse can act as a "symmetry switch," guiding the material into these novel states where it remains stable for a definitive, and often long, period.

The development of this technology for the ultrafast, arbitrary control of material phases holds immense promise. It could pave the way for next-generation information processing devices operating at unprecedented clock rates and shed new light on the fundamental properties of quantum phases in solids.

By shedding light on solids, we aim to illuminate a bright future.

For more details, please visit: https://www.physics.nus.edu.sg/faculty/li-xinwei/

Xinwei LI is an Assistant Professor in the Department of Physics at the National University of Singapore, currently leading a newly established lab that focuses on experimental optical condensed matter physics. In 2014, he graduated from Fudan University with a B.Sc. in Physics. He received his Ph.D. degree in 2019 from the department of electrical and computer engineering at Rice University. From 2019 to 2023 July, he worked as a Troesh prize postdoctoral fellow of Physics at Caltech. He is a recipient of the Singapore National Research Foundation Fellowship in 2024. His research focuses on developing ultrafast optical techniques as a means for detecting symmetry-breaking phase transitions in condensed matter and for creating unusual photo-induced phases of quantum materials.



Reference

[1] Li X; Esin I; Han Y; Liu Y; Zhao H; Ning H; Barrett C; Shan J-Y; Seyler K; Cao G; Refael G; Hsieh D*, "Time-hidden magnetic order in a multi-orbital Mott insulator" Nature Physics Volume: 21 Issue: 3 Page: 451-457 DOI:10.1038/s41567-024-02752-1 Published: 2025.

Today's discards, tomorrow's shield

Dual valorization of yeast cells and pomegranate peel to enhance microbial safety and quality of salmon fillets

Introduction

Raw salmon, widely enjoyed around the world in dishes like sushi and sashimi, is both nutrient-rich and delicate. In real-world settings, its freshness and safety can deteriorate quickly, resulting in a notably short shelf life. When we talk about improving food safety, we often think of cutting-edge technologies or newly developed synthetic preservatives. In my research group, however, we began exploring something simpler, and perhaps more powerful. We have been thinking about how the by-products from common food processing industries might offer a sustainable solution to an enduring challenge: keeping ready-to-eat seafood safe and fresh. This question became the foundation of our research.

A closer look at the microbial threats from raw salmon

Raw salmon poses certain health risks in terms of microbiological safety, as it is consumed without being cooked. Its high nutrient content and abundant moisture profile create an ideal environment for microbial proliferation. This presents two types of microbial challenges: pathogenic and spoilage-causing microorganisms. Foodborne pathogens can cause serious health risks through either pre-formed toxins in foods or post-consumption infection after ingestion. Spoilage-causing microorganisms, as the name suggests, progressively degrade product quality, leading to unacceptable sensory changes and ultimately, food waste.

While we always keep in mind that refrigeration serves as a primary control method, many microorganisms demonstrate concerning resilience to cold temperatures, with some (like *Listeria monocytogenes*) capable of growing even under typical refrigeration conditions. At the same time, consumers are increasingly cautious about conventional or innovative synthetic additives, preferring clean-label, minimally processed foods. Therefore, our goal was to explore whether natural, food-grade materials, specifically those derived from by-products, could form a protective strategy to slow both microbial contamination and spoilage, helping raw salmon stay fresh and safe for longer under refrigeration conditions.

Finding value in what's left behind: Food by-products

My attention turned to two common food by-products: spent yeast and fruit peel.

The first is spent yeast. During beer production, large quantities of yeast are generated during fermentation. Once that process is complete, the yeast is typically filtered out and discarded. But under the microscope, these yeast cells have an interesting, capsule-like morphology, which makes them excellent bio-vehicle for encapsulating sensitive bioactive substances, making them particularly promising as delivery systems in foods.

The second is fruit peel. Pomegranate (*Punica granatum L.*) peel is particularly noteworthy, as it constitutes nearly 50% of the fruit's weight and is abundant in polyphenols and flavonoids. These substances have well-documented antimicrobial and antioxidant effects, meaning they can help slow bacterial growth and prevent degradation. However, the direct application of peel extracts in food systems faces several challenges, including their inherently unpleasant taste, diminished functional effects caused by interactions with food ingredients during processing or storage, and the sensitivity of bioactive compounds to light, high temperatures, and pH variations.

This led me to a simple yet powerful idea: what if we could combine these two types of by-products to create a natural antimicrobial strategy for raw salmon? In this approach, the yeast capsule could serve as a carrier for the pomegranate peel extract, protecting the bioactive compounds and allowing them to be released gradually over time.

Further enhancing the antimicrobial effect

While the basic idea was promising, our team also aimed to further enhance the effectiveness of the yeast capsule. One of the challenges in fighting bacteria is ensuring that the antimicrobial compounds come into close contact with the bacterial cells.

To support this, we modified the yeast cell particles with betaine hydrochloride, which is classified as GRAS (Generally Recognised as Safe). This modification gave the yeast cells a positive surface charge. This charge is important because most bacteria carry a naturally negative charge on their surfaces. By adding a positive charge to the yeast capsule, they can bind more readily and strongly to bacterial cells. This simple electrostatic attraction - like magnets snapping together - helped bring the antimicrobial compounds from the peel extract closer to their targeted bad microorganisms.

To confirm this interaction, we used a strain of *Salmonella* tagged with a fluorescent marker, allowing it to glow under microscopic fluorescent light. Our observations indeed revealed that the glowing *Salmonella* were clearly clustered around the modified yeast particles in high numbers (see Figure 1). This visual evidence supported our hypothesis: the modified capsules were more likely to attach to bacterial cells

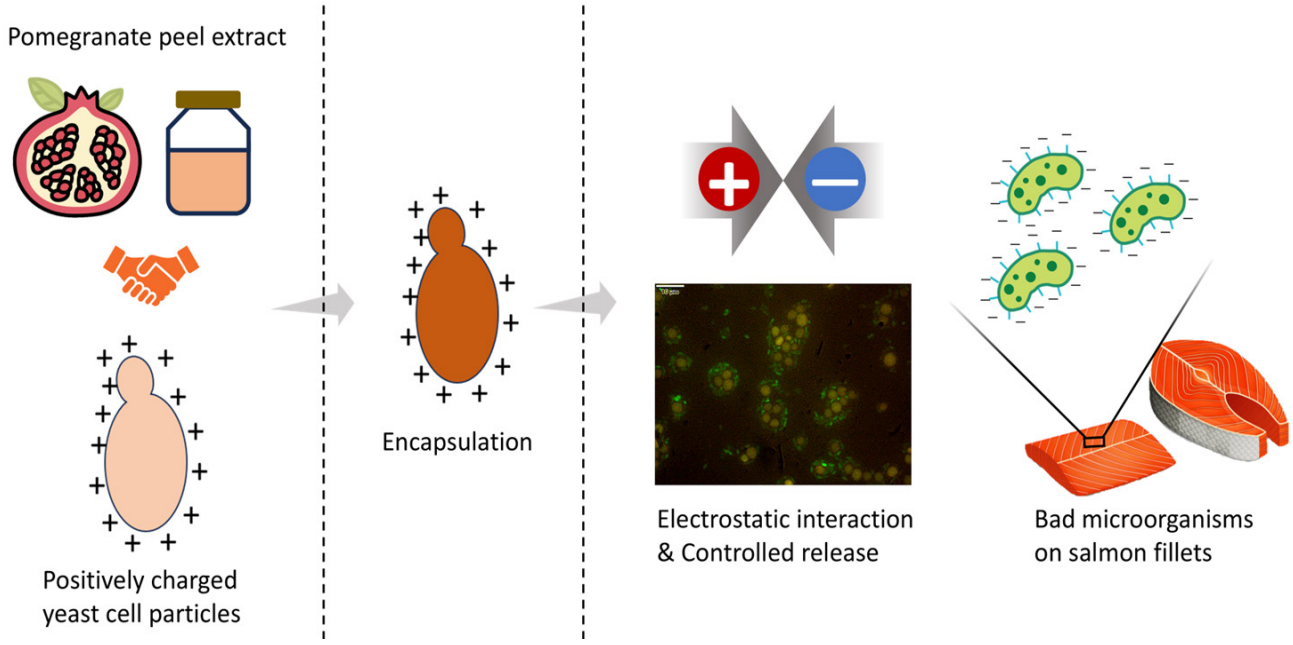


Figure 1: Schematic overview of the preparation of pomegranate peel extract encapsulated in positively charged yeast cell particles, and their interaction with harmful microorganisms on raw salmon fillets.

than their unmodified counterparts.

Application to raw salmon

With the materials prepared, we moved on to applying the strategy to real food. Salmon fillets were treated with pomegranate peel extract encapsulated within the positively charged yeast cell particles. All the fillets were stored under refrigeration conditions, just as they would be in retail settings or home refrigerators.

Microbial populations and chemical quality were tracked during storage. Pathogenic bacteria (*L. monocytogenes* and *Salmonella*) were well inhibited to stable or nearly undetectable levels within the first few days of storage. Spoilage-causing bacteria also grew at a much slower rate compared to untreated samples, which meant that the fillets maintained their microbial shelf life for a much longer period.

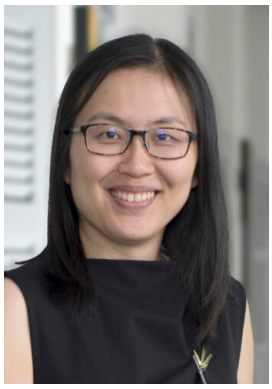
Perhaps most notably, we observed a marked reduction in the accumulation of biogenic amines, which are metabolites generated during microbial metabolic activities. These compounds are associated with edible quality of salmon, and when consumed in high amounts, can lead to adverse health effects such as headaches, nausea, or elevated blood pressure. The lower biogenic amine levels in treated samples indicated enhanced safety and edibility.

Conclusion

As food scientists, we are often encouraged to innovate and to find new materials, new methods, and new technologies. But sometimes, innovation does not come from creating something entirely new. Instead, it comes from looking again at what we already have and seeing it in a new light. This research reminded us that what we discard today might just be the solution we need tomorrow. As our global population grows and the demand for fresh, minimally processed foods increases, we need solutions that are effective, affordable, and acceptable to the public. The use of food by-products is one such solution, which allows us to close loops in the food system, turning residues into resources.

For more details, please visit: https://www.fst.nus.edu.sg/our_people/faculty-members/li-dan/

LI Dan is an Associate Professor in the Department of Food Science and Technology and Associate Director of the Research Centre on Sustainable Urban Farming (SUrF) at the National University of Singapore. She obtained her B.Sc. and M.Sc. in Food Science from Ocean University of China and earned her Ph.D. from Ghent University. Her research interests focus on the improvement of current study methods of foodborne pathogens, identification and prevention of emerging microbial threat, and development of novel and natural antimicrobial strategies.



Reference

[1] Hua Q, Liu L, Chen S & Li D, "Dual valorization of yeast cells and pomegranate peel to enhance microbial safety and quality of salmon fillets" Future Foods Volume:12 DOI: 10.1016/j.fufo.2025.100678 Published: 2025.

Unlocking ionic interactions in catalysis

Leveraging long-range ionic interactions led to the discovery of faster, selective and general catalysts for cross-coupling reactions

Introduction

Imagine using an automated system to design and execute the chemical synthesis of various target molecules, whether for novel medicines or advanced materials. The reagents and catalysts in such a system's toolbox must be flexible enough to accommodate the diverse structures of starting materials for variable target molecules, yet precise enough to reliably deliver the desired outcome, even when the target changes. Our research aims to address the seemingly conflict between generality in substrates and specificity in reaction control: we harness electrostatic interactions between catalysts and substrates to achieve both adaptability and selectivity across a broad range of substrates for cross-coupling reactions. By leveraging the fundamental phenomenon of ionic interactions, we have uncovered principles that could be widely applicable to generality-oriented asymmetric catalysis.

Three-dimensional molecules and flatland chemical transformations

Our study has its roots in asymmetric catalysis and cross-coupling reactions, two fields that have shaped modern synthetic chemistry and have been recognised with Nobel Prizes. Through asymmetric catalysis, the three-dimensional arrangement of atoms is precisely controlled when forming new bonds, which is crucial for producing chiral molecules with the desired biological or physical properties. For example, drug molecules often function only in a specific chirality, making this precise spatial control essential for pharmaceuticals. Cross-coupling reactions join together different molecular building blocks with remarkable efficiency, so efficient that they are among the most widely used reactions in the synthesis of organic materials, and they rank second only to peptide synthesis in medicinal chemistry.

However, traditional cross-coupling reactions mainly operate on planar, aromatic molecules, essentially working in the "flatland" of chemical space, which lacks inherent three-dimensionality. This long-standing limitation has inspired us to pursue cross-coupling reactions in a three-dimensional chiral space. What strategies can we employ to introduce three-dimensionality to a transformation traditionally confined to flatland chemistry?

Engineering ionic ligands to achieve remote selectivity control

We decided to explore cross-coupling reactions on three-dimensionality molecular structures, thereby creating chirality at positions remote from the site of cross-coupling within the product. Transmitting chemical information between the cross-coupling site and the distant chiral centre presents a significant challenge. Conventional steric repulsion which depends on the sum of atomic radii becomes ineffective across such distances. Instead, we explored attractive interactions to serve as a bridge. Among the noncovalent forces, electrostatic interactions between oppositely charged species are the strongest, yet remain largely unexplored in the context of long-range asymmetric induction.

To harness electrostatic interactions at a distant position and achieve precise control over chirality, we considered how best to overcome the inherent obstacles. The dynamic nature of ionic interactions at remote sites appears at odds with the precision needed for high selectivity. Even when substrate–catalyst ionic pairing is established, the lack of directionality allows these complexes to reorganise freely. This means that the ability to pre-organise the reacting partners is less effective than with more directional interactions, such as hydrogen bonds. Moreover, ionic interactions can be disrupted by competing ionic species or polar solvent molecules, which may lead to the formation of ion clusters or hydrates and add further unpredictability.

To address these questions, we developed ionic catalysts by incorporating ionisable groups into a phosphine ligand backbone. The phosphorus atom stabilises the metal catalytic centre, while the ionisable group is positioned so that it does not coordinate with the metal. Instead, this group interacts with ionic groups on the substrate via electrostatic interactions that are distant from the cross-coupling reaction sites. Specifically, the phosphonate or carboxylate anions on the ligand engage with the carboxylate or phenolate groups of the substrate through bridging cations, akin to salt bridges commonly found in proteins.

Versatile cross-coupling reactions for diverse chiral molecules

As a rigorous test, we first evaluated their effectiveness in constructing chiral biaryls through cross-coupling reactions of substrates that contain ionizable groups. We discovered that nondirectional electrostatic interactions offer substrate adaptability unattainable through conventional means. Even when the ionic group was placed far from the reaction site, the ionic interactions between the catalyst and the substrate were preserved, and chirality induction remained highly effective. This initial success demonstrated that not only is precise control by engaging remote ionic interactions feasible, but the absence of directional constraints offers substrate adaptability. Indeed, the strategy was successfully expanded

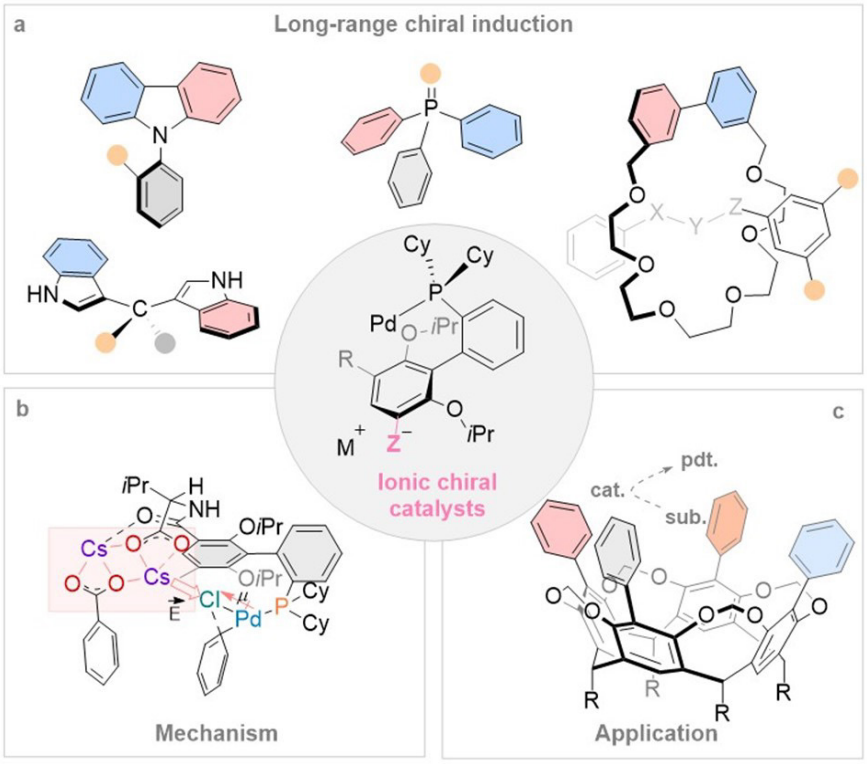


Figure 1: Ionic chiral catalysts for cross-coupling reactions. (Centre) The catalyst features various ionic groups (Z=carboxylate, phosphonate, amino acids; M=Na, K, Cs). (a) The strategy is applicable to diverse chiral molecules. (b) The electric field produced by the ionic cluster stabilises the emerging dipole moment at the Pd catalytic centre. (c) The multi-functionalised cavitand serve as artificial enzymes.

to diverse chirality elements, including carbon centres, phosphorus centres, and carbazole biaryls.

We wondered whether the ionic catalysts could exert long-range stereocontrol on nanometre-scale molecular scaffolds. We found that the remote chirality relay for chiral rotaxanes remains effective despite the dynamic noncovalent interlocking of the molecular structure. The stepwise functionalisation of cavitands was achieved with high selectivity through fine-tuning both the ionic catalysts and the bridging alkali metals. Such a process would be impractical without selectivity control because of the low theoretical yield (<0.8%). Furthermore, in situ ion hydration turns nonselective reactions into highly selective upon adding a specific amount of water. Moreover, substrate adaptability can be achieved by simply adjusting the water/ion ratio, without the need to change the catalysts.

Looking forward

Our research has uncovered the power of remote ionic interactions in asymmetric cross-coupling reactions. The rates of these reactions can be accelerated because of attractive, long-range ionic interactions. For example, the ionic catalysts have shown significantly higher reactivity in the synthesis of an HDAC7 inhibitor in a collaborative study with Assistant Professor Derrick ONG from the Department of Physiology at the National University of Singapore. The low directionality of ionic interactions enhances substrate adaptability due to conformational flexibility, and additional tunability achieved by varying counterions and solvents adds new dimensions to the optimization of catalytic performance. These unique features of ionic catalysts have attracted the attention of scientists from commercial pharmaceutical companies in the United Kingdom and Singapore. The future development of new classes of ligands bearing nonligating ionic groups will unlock the potential of ionic interaction-directed catalysis for efficient chemical synthesis.

For more details, please visit: https://chemistry.nus.edu.sg/people/zhu-ye/

ZHU Ye is an Assistant Professor in the Department of Chemistry at the National University of Singapore. He received his Ph.D. from The University of Chicago in 2012. He was a postdoctoral fellow at Massachusetts Institute of Technology, and worked in Bristol-Myers Squibb prior to joining NUS. He is interested in developing efficient and practical methods for application in the pharmaceuticals and materials.

Reference

[1] Hong W, On IKW, Zhu Y*, “Stereoinduction without direction: the long arm of ionic chiral ligands” Trends in Chemistry Volume: 7 Pages: 263–266 Published: 2025.

DNA-based artificial enzymes

Advancing sustainable synthesis of chiral molecules by developing DNA-based artificial enzymes

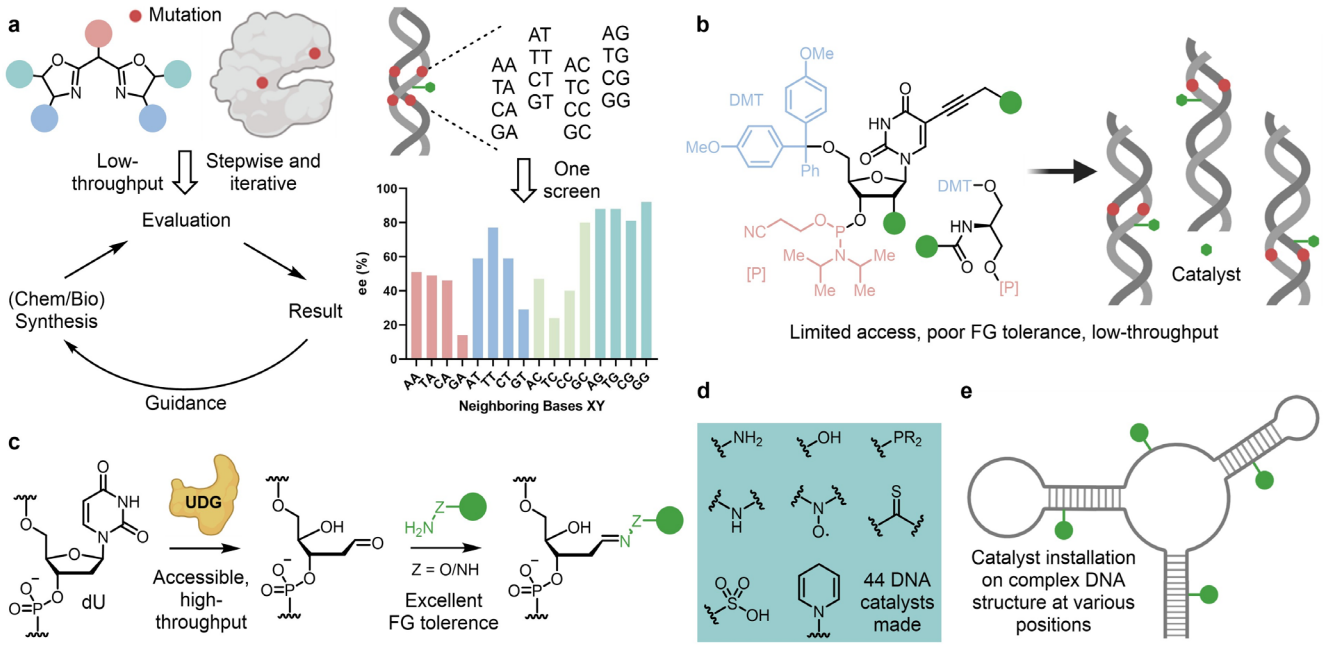


Figure 1: A chemoenzymatic conjugation method for the synthesis of DNA-small molecule catalysts.

Introduction

Enzymes are known to catalyse a wide range of highly selective reactions in our cells. To broaden the scope of reaction types to fulfil various needs, scientists modify natural enzymes through protein engineering to create unnatural enzymes, also known as artificial enzymes. The impact of protein engineering and its applications in artificial enzyme-catalysed, new-to-nature organic reactions has been recognised by the 2018 Nobel Prize in Chemistry. The development of artificial enzymes has undergone exponential growth over the past few years. Although Deoxyribonucleic acid (DNA) and Ribonucleic acid (RNA) typically do not have catalytic function in our cells, scientists are able to mimic the natural evolutionary process in laboratories to identify specific DNA or RNA sequence that is able to catalyse specific reaction, thereby giving DNA or RNA catalytic function, known as DNAzyme or ribozyme. These types of nucleic acid catalysts are normally used to modify nucleic acid substrates through partially complementary Watson-Crick base pairing between catalyst and substrate and are rarely used to convert small-molecule substrates. To design modular DNA-based artificial enzymes by bridging a chiral DNA scaffold with a wide range of small-molecule catalysts for small-molecule substrates, Feriga and Roelfes reported the first proof-of-concept study of asymmetric DNA catalysis. In this study, a metal-binding ligand was integrated with a DNA-binding ligand to yield a bi-functional small-molecule, which bridges DNA and small-molecule substrates and transfers chirality from DNA to the product. This approach relies on non-specific, non-covalent interactions between DNA and substrate, making it challenging to rationalise the stereocontrol process and to gain insight for future catalyst development. Additionally, the requirement of a DNA-binding ligand limits the types of small-molecule catalysts which can be incorporated to engage with DNA. To solve this problem, scientists employed phosphoramidite-based solid-phase synthesis to introduce small-molecule catalysts into DNA at specific sites. This approach brings two new challenges for widespread adoption. First, access to solid-phase synthesis instrument and skills is limited for non-nucleic acid chemists. Second, phosphoramidite chemistry is highly sensitive, significantly limiting the functional group diversity.

How we started?

We realised that both protein engineering and DNA synthesis are technically challenging for organic chemists, who are the major players in developing organic reactions. We saw the potential of DNA-based artificial enzymes, but due to the high technical barriers outlined above for non-specialists, there had been limited progress in the past two decades. Therefore, our first goal was to develop a general and accessible method for DNA-small molecule conjugation (see Figure 1). DNA glycosylase is a type of

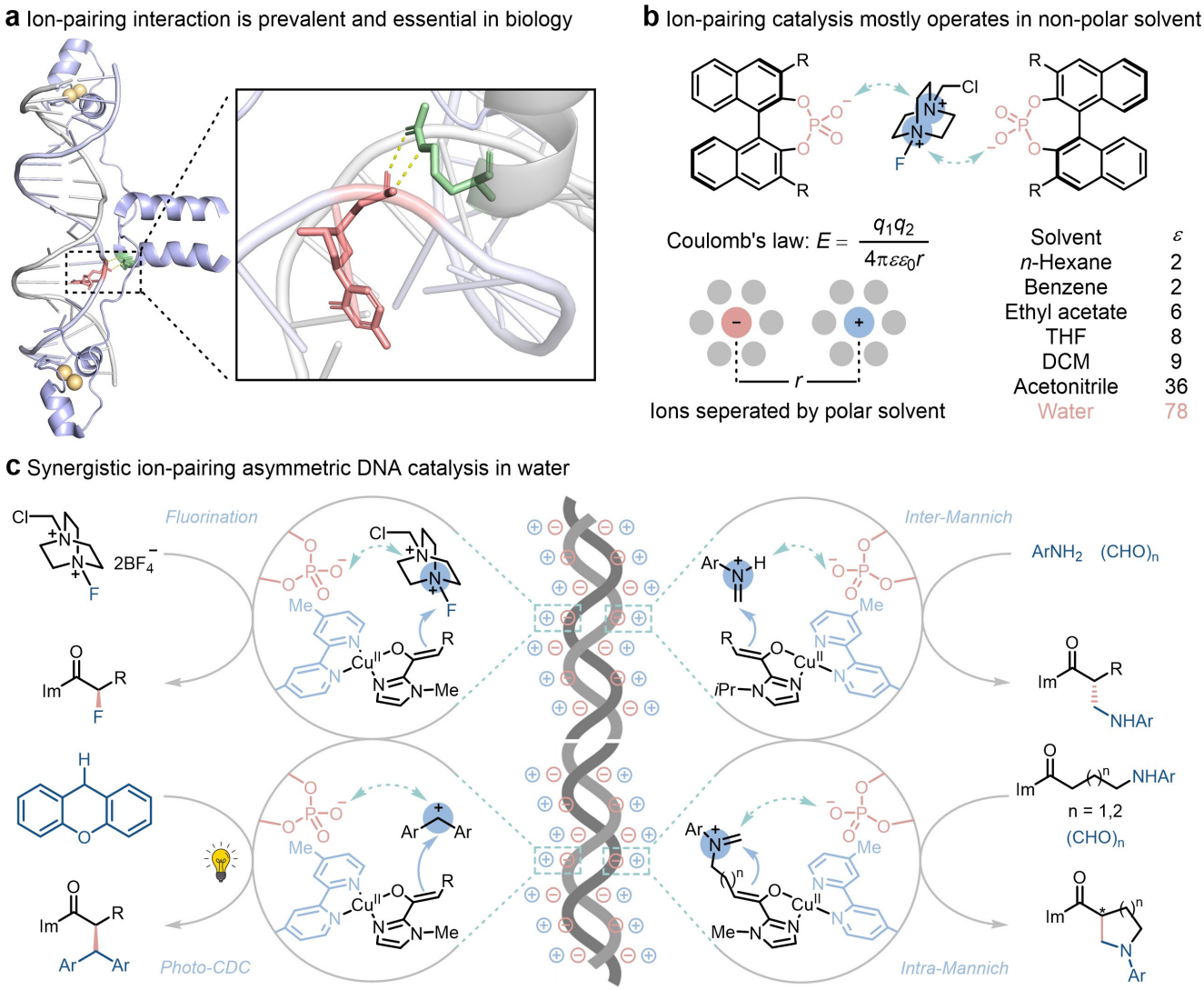


Figure 2: Ion-pairing DNA catalysis.

DNA repair enzyme that hydrolyses a damaged DNA base to an abasic site (or AP site), which equilibrates between a hemiacetal and an aldehyde. The latter can easily condense with an oxyamine to form a stable oxime with high efficiency under mild conditions. We chose uracil DNA glycosylase (UDG) and deoxyuridine (dU)-containing DNA for conjugation because of the robustness of UDG and low cost of both enzyme and dU-DNA. With this chemoenzymatic conjugation method, we can prepare dozens or even hundreds of DNA-small molecule catalysts in one day, enabling high-throughput sequence screening. In addition, the mild conjugation conditions allow the exceptional tolerance of diverse functional groups to be introduced to DNA. Notably, none of these groups needs protection or deprotection. Finally, simple ethanol precipitation provides pure DNA-small molecule catalysts ready for testing. In this study, we also demonstrated the first atroposelective DNA catalysis. We believe more people will be attracted to this field as we remove the technical barriers for conducting DNA catalysis.

Where are we now?

DNA has many unique structural features such as abundant phosphates and a helical scaffold. We aim to harness these unique features for asymmetric catalysis. Intrigued by the ubiquitous ionic interactions between negatively charged DNA phosphates and positively charged amino acids in proteins, we wondered whether we could employ DNA phosphates to interact with certain cations to induce stereocontrol (see Figure 2). Although chiral phosphates are widely used in asymmetric catalysis via ionic interactions in non-polar organic solvents, it is challenging to preserve such interactions in water. In a recently accepted study, we demonstrated that DNA phosphates can mediate a range of asymmetric transformations likely to occur within relatively hydrophobic environments. We employed experimental and computational methods to pinpoint which phosphates are directly involved in the stereoinduction step. In several other unpublished studies, we harnessed hydrogen bonding, pi-pi stacking, tunable bimetallic DNA catalysts, as well as DNA dimerization, to realize otherwise difficult reactivity and selectivity.

What is next?

More reaction types. Moving forward, we plan to apply DNA catalysis to radical processes to control their

stereoselectivity, which has always been a major challenge in asymmetric catalysis. Many transition-metal-based, redox-active reactions are also worth pursuing, particularly those requiring complicated chiral ligands.

More DNA structures. We have been focusing on a simple 17-nt hairpin DNA which does not have complicated structure. We plan to explore enzyme-like DNA aptamers as well as DNA origami (a type of nanostructure) for more sophisticated applications.

Scalable DNA production. Currently, we directly purchase DNA from commercial vendors in small quantities. To prepare for large scale (e.g. kilogram scale), we will need to significantly increase DNA production. It is not economically viable to use solid-phase synthesis to produce large amounts of DNA. Recently, an enzymatic method tailored for the synthesis of short DNA was published in the journal Science that could potentially be used to make large scale dU-DNA needed for DNA catalysis. In the long term, we will need to find a way to amplify DNA inside living organisms and perhaps perform DNA catalysis *in vivo*.

For more details, please visit: https://rzhulab.com

Ru-Yi ZHU is an Assistant Professor with the Department of Chemistry at the National University of Singapore. He obtained his B.S. with honours and distinction in Chemistry from Peking University (China) in 2013. He earned his Ph.D. at the Scripps Research Institute in 2018 with Jin-Quan YU and undertook postdoctoral studies at Stanford University with Eric T. KOOL. He started his independent career as an Assistant Professor at NUS in late 2021. The Zhu lab develops new concepts in DNA catalysis and new strategies for RNA biomedicine. He is a recipient of the ACP Lectureship Awards (from China, Korea, and Japan), and the NUS Presidential Young Professorship, among others.

References

[1] Sheng J; Li Z; Koh KKY; Shi Q; Foo A; Tan PMLT; Kha TK; Wang X; Fang L; Zhu RY*, "Merging DNA Repair with Bioorthogonal Conjugation Enables Accessible and Versatile Asymmetric DNA Catalysis" Journal of the American Chemical Society Volume: 146 Issue: 24 Pages: 16531–16539 Published: 2024.

[2] Li Z; Zheng Y*; Zhao Q; Li Y; Yap A; Zhang X*; Zhu RY*, "DNA Phosphates Are Effective Catalysts for Asymmetric Ion-Pairing Catalysis in Water" Nature Catalysis Volume: 8 Pages: 1220–1231 Published: 2025.


NUS
National University
of Singapore
Faculty of
Science