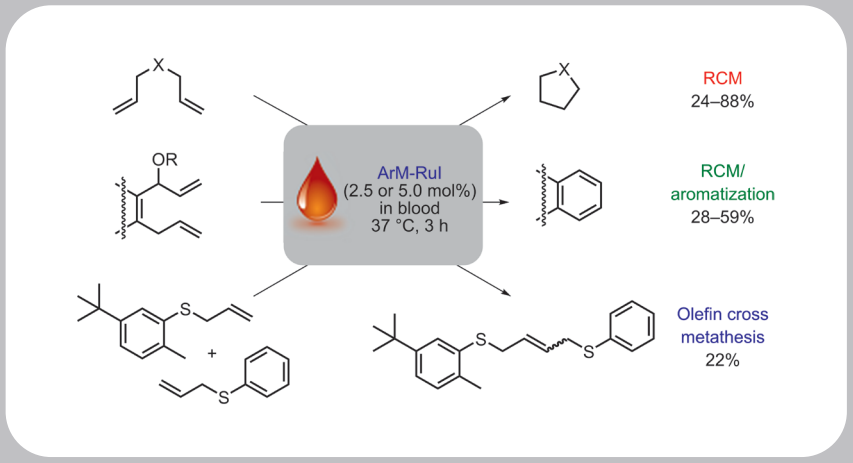
Synform

People, Trends and Views in Chemical Synthesis

2024/04

Catalytic Olefin Metathesis in Blood

Highlighted article by I. Nasibullin, H. Yoshioka, A. Mukaimine, A. Nakamura, Y. Kusakari, T.-C. Chang, K. Tanaka



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Thieme

Dear Readers,

Early in February, *Nature* published a shocking article authored by E. M. Wolkovich - an associate professor of forest and conservation sciences at the University of British Columbia in Vancouver, Canada – concerning her traumatic experience of being accused by a reviewer of using ChatGPT to write a manuscript, which ultimately led to the manuscript's rejection, despite the fact that she was able to prove beyond any doubt that in fact she had not used any Generative AI tool (DOI: 10.1038/d41586-024-00349-5). My first thought upon reading this article was that – when it comes to Generative AI – the principle that one is innocent unless otherwise proven does no longer seem to be valid. In fact, the suspicion of having committed the heinous crime of relying on the assistance of ChatGPT for writing a text is always there, creeping and lingering in the shadows, while the author has to prove their innocence even when there is no proof whatsoever to the contrary. I honestly find this situation quite depressing, and in my personal opinion ChatGPT is just one of the many and perfectly legal tools that can be used to assist the writing of manuscripts and grant applications, provided its use is duly acknowledged by the author/applicant. More importantly, this story puts further emphasis on the question of how to discern what is AI-generated and what is authentic. With the improvement of AI technology, this issue will become increasingly difficult to address, and it may well be that the only way out will be the use of "counter-AI" technology capable of ensuring a distinction between the two, something that is actually already being used for identifying manuscripts where figures are not authentic, but generated with the support of algorithms. At this point – in this maze of new information, guidelines and rules, often improvised, on the use of AI – I believe that the gatekeepers (e.g., academic institutions, international organisations, journals and editors) should do anything in their power to minimise the risk of not achieving what should be the main objective: to defend the essential values of research freedom and integrity, while embracing this new technology, which is simply unavoidable.

This April issue of SYNFORM starts with the fascinating work of K. Tanaka (Japan) at the interface between synthetic chemistry, biology and bioconjugate chemistry and their catalytic olefin metathesis performed in blood. It is followed by a Young Career Focus interview with C. R. Kennedy (USA), a Thieme Chemistry Journals Awardee for 2023. The next Literature Coverage article is a particular pleasure for us, as it stems from the group of the new Editor-in-Chief of SYNLETT, D. Maiti (India), whose group developed a strikingly original synthesis of unsaturated bicyclic lactones that overrides conventional C(sp^3)–H site selectivity. The final article of this rich issue is the Literature Coverage of a novel use of the thianthrenation reaction – developed by W. Shu (P. R. of China) – that represents a metal-free intermolecular Heck-type strategy to achieve a broad set of alkene functionalizations, such as sulfonylation, cyanation, amination, and amidation.

In this issue

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Catalytic Olefin Metathesis in Blood

Chem. Sci. **2023**, *14*, 11033–11039

The rate of success of anticancer drugs in clinical trials is dismal, and many reasons for that have been proposed, including poor pharmacokinetics and drug bioavailability, unexpected systemic toxicity, a lack of efficacy, and drug resistance. Professor Katsunori Tanaka at the Tokyo Institute of Technology (Japan) and the RIKEN Institute (Japan) believes that a straightforward method to solve these problems is to directly synthesize therapeutic drugs at cancer sites, thereby not only avoiding unwanted side effects on healthy tissues but also allowing for a direct evaluation of drug therapeutic effects toward various cancers. "To minimize the burden on the body and maximize therapeutic effects, a method that is biocompatible and exhibits robust catalytic ability to produce the necessary amounts of drugs *in vivo* is desirable," added Professor Tanaka.

Recently, various transition-metal catalysts have been widely explored for uncaging prodrugs and synthesizing bioactive drugs in biological environments because they display remarkable catalytic reactivity in a myriad of chemical transformations.[1] Nonetheless, Professor Tanaka told SYNFORM that the method is difficult to apply *in vivo*, because blood cells and different metabolites, such as glutathione (GSH), tend to deactivate transition-metal catalysts. "The majority of these *in vivo* examples have involved nanocarriers with encapsulated transition metals, because the large surface-area-per-volume ratio of nanocarriers enables the loading of greater amounts of metal catalysts, thereby enhancing the reaction rates," said Professor Tanaka. He added: "However, these nanocarriers have been used in excess rather than in catalytic quantities to produce the required amounts of desired products *in vivo*, indicating that the blood environment substantially hindered their reactivity. A method that implements truly catalytic organometallic reactions in blood has not yet been reported."

Artificial metalloenzymes (ArMs) are the result of inserting transition-metal complexes into protein scaffolds of interest, which can impart enhanced biofunctionality to the anchored metal catalysts.[2] Professor Tanaka's group has recently developed a biocompatible ArM in which a Hoveyda–Grubbs complex, Ru-Cl, is anchored into a hydrophobic binding pocket of human serum albumin (HSA) (**ArM-RuCl**, Figure 1a) through the interaction of a coumarin moiety with the cavity.[3] Professor Tanaka said: "The negatively charged surface of HSA prevented the charged GSH from entering the metal-binding site, thus protecting the bound Ru catalyst even in the presence of GSH at concentrations as high as 20 mM in phosphate buffered saline (PBS) solution. However, the capacity of **ArM-RuCl** to catalyze ring-closing metathesis (RCM) was not high in blood."

Professor Tanaka emphasized that this new work showed that replacing the chloride ligands with iodide ones at the Ru catalyst of ArM dramatically improves its catalytic activity in blood (**ArM-RuI**, Figure 1a,b). "We found that just 2–5 mol% of the **ArM-RuI** could catalyze various types of olefin metathesis reactions in blood to synthesize a broad range of molecular scaffolds, including five- and six-membered carbocyclic and heterocyclic compounds, indole ring, and differently substituted naphthalenes in substantial yields (Figure 1b,c)," explained Professor Tanaka, who continued: "Furthermore, this work provided the first example of catalytic olefin cross metathesis in blood (Figure 1d). The results represent a new avenue for constructing a variety of molecules *in vivo* via olefin metathesis."

Professor Tanaka noted that the **ArM-RuI** also showed robust stability and catalytic reactivity for 24 hours in blood, adding: "In comparison with other known ArMs and metallic nanocarriers, **ArM-RuI** is the first that is shown to be able to carry out a highly efficient catalytic organometallic reaction in such a challenging biological environment. As a further demonstration (Figure 1e), we proved that the cyclic-Arg-Gly-Asp (cRGD) peptide-functionalized **ArM-RuI** with low dosages could still efficiently perform *in vivo* drug synthesis to inhibit the growth of implanted tumors in mice. This study significantly advances the field of transition-metal-catalyzed reactions, opening the door for the development of general metal-based ArMs for catalytic reactions, even in highly challenging media such as blood."

Professor Tanaka concluded: "Through combination with tailor-made drug delivery systems such as glycotargeting technology,[4] this ArM system in the future is expected to enable the synthesis of a variety of anticancer drugs only at cancer sites, for evaluation of drug efficacy and subsequent therapy in patients, without causing any side effects."

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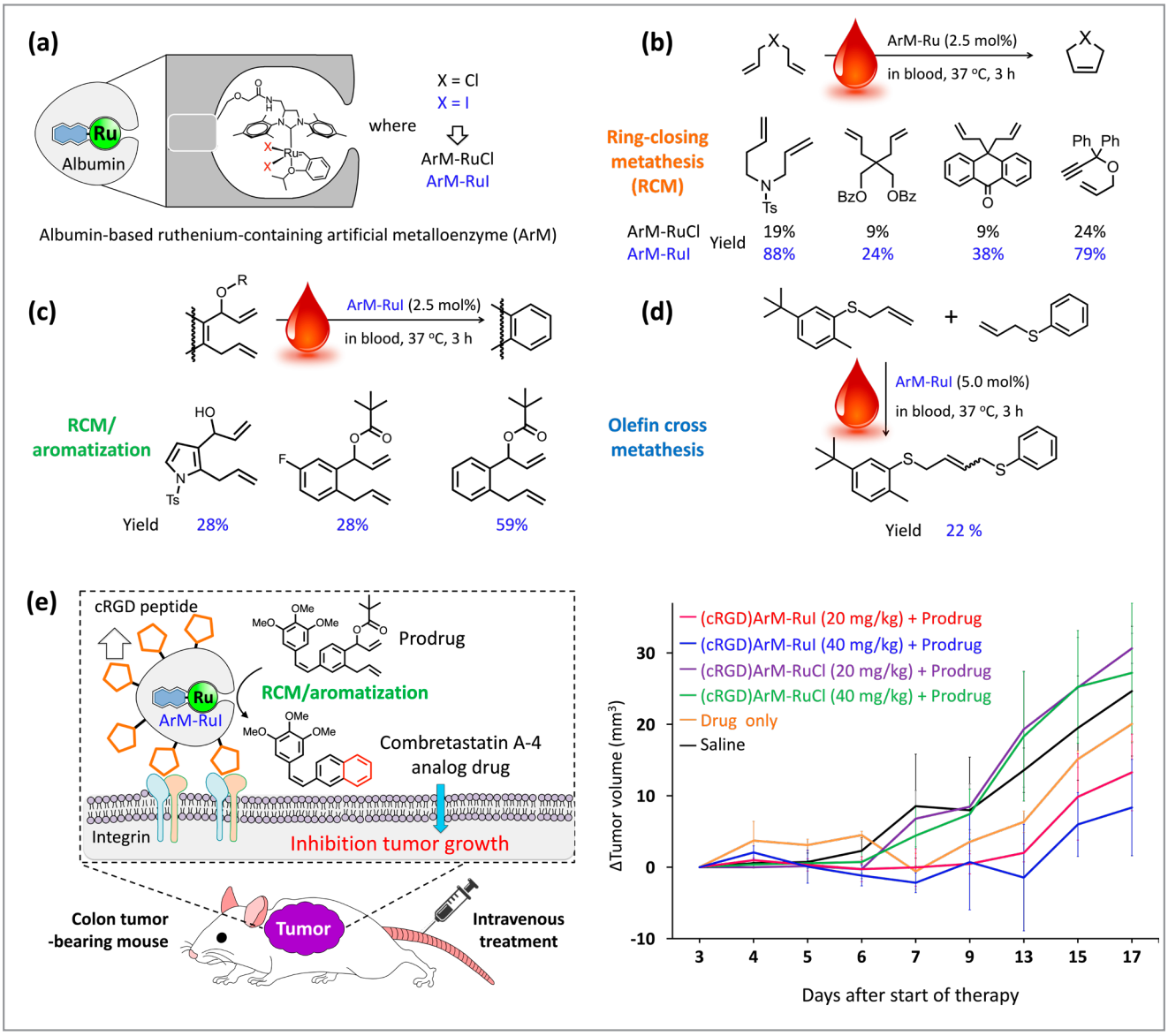

Figure 1 Catalytic olefin metathesis in blood and its anticancer application in vivo

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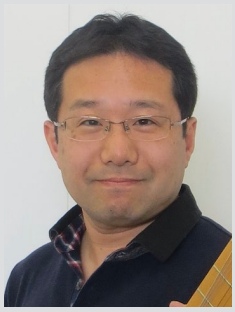
About the authors

Dr. T-C. Chang

Tsung-Che Chang received his Ph.D. (2012) in chemistry from National Tsing-Hua University (Taiwan) under the direction of Professor Chun-Cheng Lin. He joined Prof. Koichi Fukase's group at Osaka University (Japan) as a JSPS postdoctoral fellow (2013–2015) and postdoctoral researcher (2015–2017). In 2018, he joined the research group of Chief Scientist Katsunori Tanaka as a postdoctoral researcher (2018–2022). He is currently employed as a specially appointed assistant professor in Prof. Katsunori Tanaka's group at the Tokyo Institute of Technology (Japan). His research interests are in the fields of organic synthesis, synthetic carbohydrate chemistry, biocatalysis, and *in vivo* synthesis.



Prof. K. Tanaka

Katsunori Tanaka received his B.S. (1996) and Ph.D. (2002) in chemistry from Kwansei Gakuin University (Japan) under the guidance of Prof. Shigeo Katsumura. Following a postdoctoral stint with Prof. Koji Nakanishi at Columbia University (USA), he worked as an assistant professor in the group of Prof. Koichi Fukase at Osaka University (Japan). At present, he holds concurrent roles as a professor at the Tokyo Institute of Technology (Japan) and as a Chief Scientist at the RIKEN Institute (Japan). His research interests include organic synthesis, molecular imaging, *in vivo* synthesis, and natural products.

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Young Career Focus: Prof. C. Rose Kennedy (University of Rochester, USA)

Background and Purpose. SYNFORM regularly meets young up-and-coming researchers who are performing exceptionally well in the arena of organic chemistry and related fields of research, in order to introduce them to the readership. This Young Career Focus presents Prof. C. Rose Kennedy (University of Rochester, USA).

Biographical Sketch

Prof. C. R. Kennedy

C. Rose Kennedy earned her BS in chemistry in 2011 from the University of Rochester (USA) where she conducted research with Professor Kara L. Bren (bioinorganic chemistry) and Professor Alison J. Frontier (organic synthesis). She then moved to Harvard University (USA) as an NSF Graduate Research Fellow, where she worked with Professor Eric N. Jacobsen. As a PhD student, she elucidated key mechanistic features of H-bond-donor ion-pairing catalysis and developed new design principles for enantioselective catalysis through synergistic ion binding. In 2017, she moved to Princeton University (USA) as an NIH NRSA Postdoctoral Research Fellow with Professor Paul J. Chirik. As a postdoc, she leveraged mechanistic insights to develop catalytic methodology for upgrading unactivated olefins through the formation and control of metallacyclic intermediates. Rose returned to the University of Rochester in January 2020 to launch her independent career as an Assistant Professor in the Department of Chemistry. There, the Kennedy Research Group combines mechanistic elucidation with catalyst design and synthetic methodology development with an eye towards sustainability. Since starting her independent career, Rose has been recognized with the ACS PRF Doctoral New Investigator Award (2020), the Packard Fellowship in Science & Engineering (2022), the NIH Maximizing Investigators' Research Award (2023), and the Thieme Chemistry Journals Award (2023).

INTERVIEW

SYNFORM *What is the focus of your current research activity?*

Prof. C. R. Kennedy My research team is focused on mechanistic elucidation and catalyst development to achieve efficient syntheses of organic molecules, large and small. We take inspiration from the cooperative reactivity principles utilized by Nature's most efficient catalysts (enzymes) to guide our efforts. In that spirit, our projects are focused largely on using terrestrially abundant elements (including transition metals, alkali metals, and main-group elements) to access unique reactivity patterns with abundant carbon building blocks. We aspire to develop generalizable principles that enable widespread application for synthesis towards a sustainable and healthy society.

SYNFORM *When did you get interested in synthesis?*

Prof. C. R. Kennedy I first became interested by synthesis when I completed second-semester introductory organic chemistry with an outstanding instructor (and now also my colleague and mentor!), Professor Alison Frontier. I was enthralled with the molecular-level insight that an understanding of simple organic reaction mechanisms afforded in the context of biological systems. I was even more excited by the process of using those same mechanistic principles to solve synthetic "puzzles" by working through multiple possibilities to identify the best possible path to a target. The problem-solving aspect of synthesis is still what I enjoy most about the field. As I have developed more laboratory research experience, I have come to enjoy the day-to-day aspects of synthesis as well. I still find it incredibly satisfying to track a "spot-to-spot" transformation on a TLC plate, see a clean baseline in an NMR spectrum, weigh out my product as a pile of pristine white powder, or collect vividly colored blocks after a successful recrystallization.

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SYNFORM *What do you think about the modern role and prospects of organic synthesis?*

Prof. C. R. Kennedy In my opinion, organic synthesis is expanding to become a transdisciplinary tool rather than a discrete subfield. The development of efficient methods for constructing organic small molecules and macromolecules plays a critical role in progress toward addressing the grand challenges facing society. From producing and storing clean energy, to manufacturing and recycling materials, to nourishing our population through agriculture and medicine, we rely on access to organic molecules to answer cutting-edge questions and meet societal needs. Innovating in sustainable synthesis toward these varied targets thus enables ripple-effects across allied fields and society more broadly as we work toward a more sustainable future. While the day-to-day tasks and tools of the trade are continuing to evolve as automation increases, the need for ingenuity in synthesis remains! I think it's an incredibly exciting time to be a synthetic chemist!

SYNFORM *Could you tell us more about your group's areas of research and your aims?*

Prof. C. R. Kennedy Our specific projects are always evolving, but our current areas of focus include (Figure 1):

- Development and application of multi-functional ligands for complex carbon–carbon and carbon–heteroatom bond formation[1,2]
- Utilization of carboxylic acid derivatives as abundant coupling partners for fine chemical synthesis and sustainable (de)polymerization strategies[3]
- Elucidation of the selectivity controlling features of catalytic CO_x valorization
- Manipulation of electromagnetic fields for reactivity and selectivity control in organic reactions.[4]

SYNFORM *Could you tell us something about yourself outside the lab, such as your hobbies or extra-work interests?*

Prof. C. R. Kennedy I enjoy making things on a macroscopic scale, too! I invest a lot of my time outside of work on projects to restore my 103-year-old home and cultivate an organic vegetable garden. There's nothing like using a sledgehammer or power tools to relieve some stress, and it's so rewarding to finish a project and know that "I made that!"

SYNFORM *If you had not become a chemist, what other profession do you think you would have entered?*

Prof. C. R. Kennedy I was on the pre-med track before the siren's call of chemistry lured me to a research career. I was interested in becoming an infectious diseases physician because

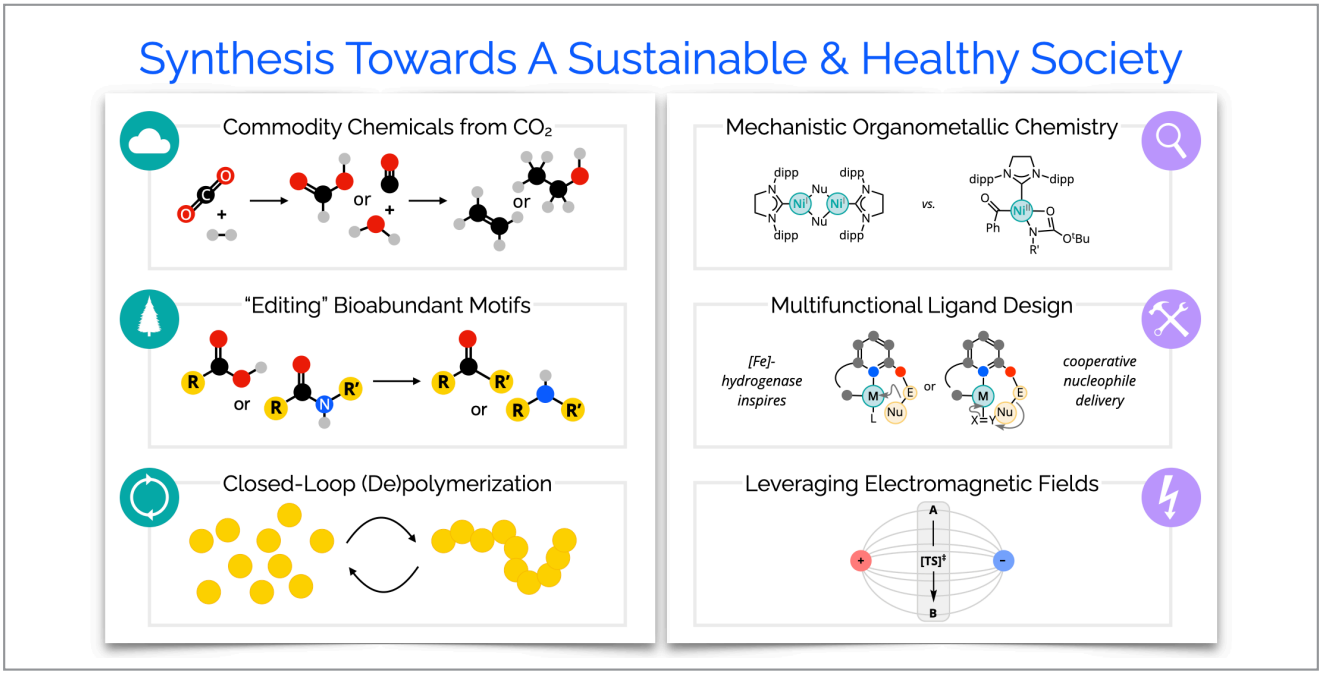

Figure 1 Synthesis towards a sustainable & healthy society

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I envisioned that I would be able to use my problem-solving skills to help people in need and contribute to the development of next-generation therapeutics. Luckily, I have found that my path in chemistry has also allowed me to impact the lives of those around me positively and contribute to pharmaceutical development in other ways!

SYNFORM *What is the most exciting aspect of your job, the one you like the most?*

Prof. C. R. Kennedy My favorited aspect of my job is working with my postdoctoral, graduate, and undergraduate mentees. In addition to the intellectual thrill of working through differential hypotheses, teasing apart complicated data, and brainstorming innovative research directions together, I find it incredibly rewarding to see my trainees grow as independent scientists. I am immensely proud of them and look forward to supporting their journeys toward their own professional aspirations. I also appreciate how they challenge me to be a better, more thoughtful scholar and mentor, so we are all growing together!

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Access to Unsaturated Bicyclic Lactones by Overriding Conventional C(sp³)–H Site Selectivity

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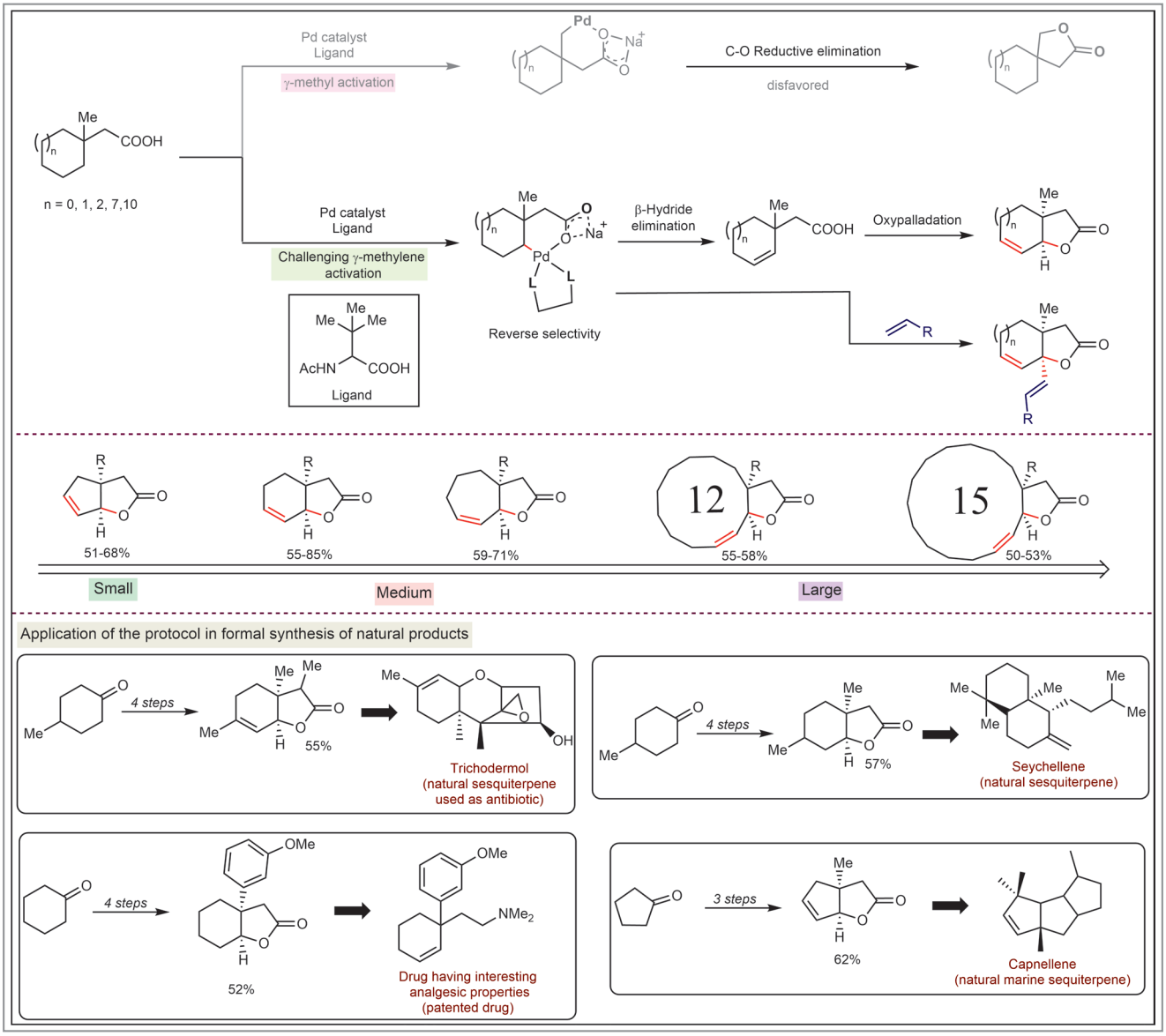
Bicyclic lactones are a privileged class of compounds that are ubiquitous in natural products and pharmacoactive molecules. The art of synthesizing such lactones in the most efficient ways has intrigued chemists for decades. Some of the popular methods utilized over the years are iodolactonization, intramolecular cyclization of hydroxy acids, and many more. In spite of the popularity and success of these reactions, they are perhaps not the most effective strategies



Scheme 1 Formation of unsaturated bicyclic lactone via γ-methylene C–H activation

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for making lactones or bicyclic lactones. "With our experience in C(sp^3)–H activation, one of our long-standing goals was to simplify the synthesis of lactones or bicyclic lactones from aliphatic carboxylic acids in a single step," stated Professor Debabrata Maiti, from the Indian Institute of Technology Bombay (India), who is also Editor-in-Chief of SYNLETT. He further elaborated: "While exploring aliphatic acids for C–H activation, we found a perfectly suitable class of substrates, namely cyclohexane-3-methyl acetic acids, that can form bicyclic lactones in a single step. However, we had to activate a methylene group in the molecule to get the fused lactone. The substrate has equally accessible methyl and methylene groups at the γ-positions that can be activated through carboxylate assisted C–H activation. Conventionally, methyl group activation is easier than methylene. Our challenge was to find suitable conditions that can reverse this site-selectivity." Indeed, a bulky amino acid like *N*-acetyl-*tert*-leucine as ligand in combination with palladium acetate as catalyst and other reagents can achieve this reversed site-selectivity and form bicyclic lactones in a single step (Scheme 1). "We were quite surprised to discover the results. The activation of the methyl group in the substrate to form a spirocyclic lactone would not have been surprising. But the spirocyclic lactone did not form at all. The rationale for this was found once we started digging out the reaction mechanism," said Professor Maiti. A collaboration with Dr. Xinglong Zhang from the Institute of High-Performance Computing (Singapore) unraveled the reason for the reverse selectivity in this reaction. Professor Maiti further stated: "Our findings are really intriguing. Apparently, methyl activation is easier than methylene in our system, which is expected. Things become interesting after the activation. Due to the lack of β-hydride in the C(methyl)–H activated complex, the subsequent step must be C–O reductive elimination. However, this elementary step has an unfavorably high barrier under our conditions. DFT calculations showed a requirement of almost 45.3 kcal/mol for this step, which is unlikely to happen. So, the methyl-activated substrate goes back to the starting material. Now, although C(methylene)–H activation has a higher barrier than C(methyl)–H activation, this pathway gives the option of a β-hydride elimination (10.3 kcal/mol and favorable under the reaction conditions) to form an alkenoic acid, followed by cyclization to form an unsaturated bicyclic acid (Figure 1)."

At a glance the reaction looks captivating: start with a carboxylic acid and, end up with bicyclic lactone containing a double bond. "The ability to synthesize bicyclic lactones in this simpler manner provided us a great opportunity to apply our protocol in complex molecule synthesis," explained Pro-

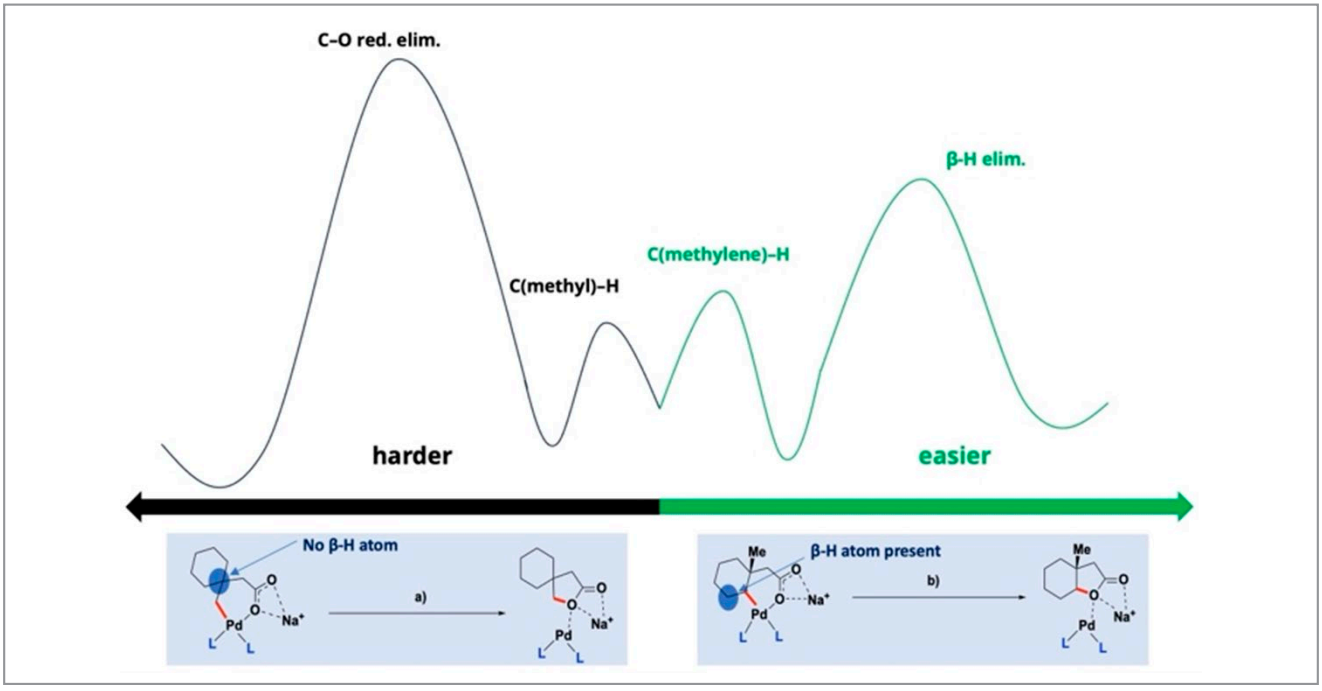

Figure 1 Illustrative energy profile showing reversed selectivity for C(methylene)–H activation product over C(methyl)–H activation product

fessor Maiti. Formal synthesis of various natural products like trichodiene, seychellene, capnellene, mesembrane, and some other bioactive molecules was demonstrated in this work utilizing the novel C–H activation method. What's more, the reaction could be performed in an intermolecular fashion where an added coupling partner like an acrylate or an allyl alcohol end up adding to the γ-methylene site without affecting the unsaturated lactone formation. "We knew the lactone formation proceeded via a C–H activated intermediate, the idea was to explore various coupling partners that can be added to the bicyclic lactone, hence enhancing the complexity and diversity of the formed products. We found acrylates and allyl alcohols can be added, but there are many yet to be explored. The beauty of this method is the formation of a quaternary center in the product, in a single step, from a methylene site in the starting material," said Professor Maiti, who thinks that native functional group assisted C(sp^3)–H functionalization is redefining the most efficient routes for high-value aliphatic compound synthesis. "In the last 5 years, this field has grown exponentially", said Professor Maiti, concluding: "Research in this area is still in its infancy. Considering the cascade effect a simple weak coordination of carboxylate can provide, there are enormous opportunities to develop complex products from simpler starting materials via native functional group assisted C–H functionalization."

About the authors

Dr. J. Das

Jayabrata Das received his Master's degree from the University of North Bengal (India) in 2016. Then he moved to the Indian Institute of Technology Bombay (India) to pursue his Ph.D. in the group of Debabrata Maiti, where he worked on transition-metal-catalyzed remote activation of aliphatic substrates. He received his Ph.D. degree in 2022. Currently, he is a post-doctoral fellow with Prof. Timothy Cernak at the University of Michigan (USA). His work revolves around the interface of chemical synthesis and computer science.

A. Ghosh

Animesh Ghosh was born and brought up in Jhargram, West Bengal (India). After graduating from Midnapore College (Autonomous), India, in 2017, he went to IIT Guwahati (India) where he received his Master's degree in 2019. Subsequently, he joined Prof. Maiti's group at IIT Bombay (India) as a Junior Research Fellow. Currently, he is working on transition-metal-catalyzed asymmetric C–H bond functionalizations.

Dr. W. Ali

Wajid Ali received his M.Sc. degree in organic chemistry from Aligarh Muslim University (India) and Ph.D. from the Indian Institute of Technology Guwahati (India) in 2018. He worked as post-doctoral fellow in UNIST South Korea under Prof. Cheol-Min Park from April 2018 to May 2019. After returning to India, he joined Prof. Maiti's group at IIT Bombay for his second post-doctorate and worked there until December 2023. His area of research interest was transition-metal-catalyzed distal sp^2 and sp^3 C–H functionalization. Currently, he is working in the Process Research Department of Syngenta Bioscience Pvt. Ltd. as a Senior Research Scientist.

T. Pal

Tanay Pal obtained his B.Sc. in chemistry from Midnapore College (Autonomous), India, in 2018. After completing his M.Sc. in chemistry from the Indian Institute of Technology (ISM) Dhanbad (India) in 2020, he joined Prof. Debabrata Maiti's group at IIT Bombay (India). Presently, he is pursuing his Ph.D. on transition-metal-catalyzed C–H activation of aliphatic motifs.

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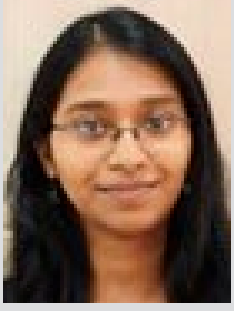
Dr. A. Mandal

Astam Mandal obtained his BSc in chemistry from Krishnath College, University of Kalyani (India), in 2016, followed by the completion of his MSc in chemistry from the University of Kalyani in 2018. He then enrolled in the Department of Chemistry at IIT Bombay (India), to pursue his Ph.D. under the guidance of Prof. Debabrata Maiti. Currently, he is actively involved in studying transition-metal-mediated distal C–H functionalization of arenes and heteroarenes.

Dr. C. Teja

Chitrala Teja was born in Chittoor, Andhra Pradesh, India. He received his M.Sc. (2015) in organic chemistry from Sri Venkateswara University, Tirupati (India). Then he joined Dr. Khan's research group at Vellore Institute of Technology (India) for pursuing doctoral studies. He worked on sp^2, sp^3 C–H functionalizations, 1,3-dipolar cycloadditions and mechanistic investigations. He received his Ph.D. in 2021. Currently, he is working as a post-doctoral fellow under Prof. Debabrata Maiti at IIT Bombay (India). His current research focuses on palladium-catalyzed nondirected sp^2 C–H functionalizations.



S. Dutta

Suparna Dutta received her Master's degree in chemistry from the Indian Institute of Technology Kharagpur (India) in 2020. Then she joined Prof. Debabrata Maiti's group at the IIT Bombay (India) and is currently pursuing her Ph.D. on transition-metal-catalyzed remote C–H bond activation of aliphatic substrates.

Dr. R. Pothikumar

Rajagopal Pothikumar received his Ph.D in SRM Institute of Science and Technology Chennai (India) in 2021. He then joined Prof. Debabrata Maiti's group where he worked on transition-metal-catalyzed remote activation of aliphatic substrates and photocatalysis. Currently, he is a post-doctoral fellow funded by a NRBC research program with Prof. Grégory Pieters and Prof. Edmond Gravel at the Commissariat à l'énergie atomique et aux énergies alternatives (CEA Paris-Saclay, France). His research involves the synthesis of chiral π-conjugated molecules including heterohelicenes, TADF emitters and the encapsulation of such emitters into micelles to develop fluorescent nanodots.

Dr. H. Ge

Haibo Ge received his PhD in medicinal chemistry from The University of Kansas (USA) in 2006, and then moved to The Scripps Research Institute (USA) for postdoctoral studies. In 2009, he began his independent academic career at the Indiana University – Purdue University Indianapolis (USA) and relocated to Texas Tech University (USA) in 2020. Research by his group is mainly focused on the development of novel methods for carbon–carbon and carbon–heteroatom bond formation through transition-metal-catalyzed C–H functionalization.

Dr. X. Zhang

Xinglong Zhang received his MSc (2016) and DPhil (2019) at the University of Oxford, UK. After a brief postdoctoral stint at the California Institute of Technology, USA, he joined the Institute of High Performance Computing (IHPC), A*STAR, Singapore as a research scientist in 2020. His research interests include computational catalysis in transition-metal-catalyzed C–H functionalization and asymmetric organocatalysis (https://xinglong-zhang.github.io).

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Prof. D. Maiti

Debabrata Maiti obtained his Ph.D. in 2003 from Johns Hopkins University, USA with Prof. Kenneth D. Karlin. Later he moved to Massachusetts Institute of Technology, USA to pursue post-doctoral studies with Prof. Steve Buchwald. In 2011, he joined IIT Bombay (India) as an assistant professor. He is now a full professor at IIT Bombay (India). His research area revolves around catalysis for metal-catalyzed C–H activation of arenes, heteroarenes, aliphatic compounds, photocatalysis, electrocatalysis, and artificial metalloenzymes, among others.

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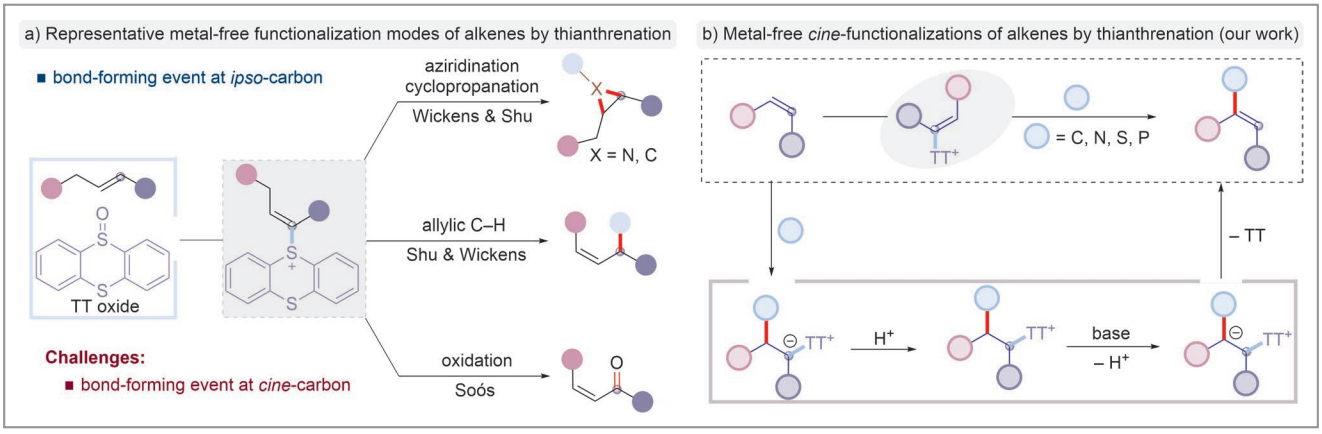
Unified Metal-Free Intermolecular Heck-type Sulfonylation, Cyanation, Amination, Amidation of Alkenes by Thianthrenation

Nat. Commun. **2024**, *15*, 529

Carbon–carbon double bonds are ubiquitous in organic molecules and are among the most valuable functional groups for orthogonal derivatization in organic synthesis. Given the synthetic versatility of alkenes, their functionalization represents a highly important research topic. "In this area, the Heck reaction is one of the most prominent and effective methods for direct functionalization of the C–H bond of alkenes," said Professor Wei Shu [Southern University of Science and Technology (SUSTech), P. R. of China], adding: "Typically, Heck reactions give access to functionalized alkenes by adding a substituent at the less substituted position of alkenes. Comparably, Heck-type substitution at more substituted position of alkenes is less investigated and remains challenging."

On the other hand, according to Professor Shu, the use of alkenyl thianthrenium salts has been recognized as an effective umpolung strategy for further chemical transformation of alkenes, pioneered by Shine.[1] "Recently, Ritter[2] developed the practical and scalable synthesis of alkenyl thianthrenium salts from alkenes, opening a new avenue for the derivatization of alkenes. In particular, metal-free functionalizations of alkenyl thianthrenium salts offer opportunities to explore new chemical space for derivatizing alkenes under mild conditions. In 2021, elegant examples of electrochemical aziridination of alkenes with primary amines were demonstrated with or without thianthrene,[3]" explained Professor Shu, who added that the generation of dicationic intermediates also offers potential opportunities for *ipso*- and *cine*-substitution reactions. In 2022, the group of Professor Shu developed a unified metal-free intermolecular aziridination and cyclopropanation of alkenes by thianthrenation (Scheme 1a, top).[4] "Sulfonamides, carbamates, amides, primary amines, and methylenes with acidic protons were all successfully employed as nucleophiles," said Professor Shu. He continued: "In 2021, the Wickens and Shu groups independently reported the allylic functionalizations of alkenes via thianthrenation[5] to C–N, C–C, C–O, and C–S bonds in the presence of nucleophiles (Scheme 1a, middle), and the Soós group[6] recently developed an ene-type Kornblum–Ganem oxidation of alkenes by thianthrenation to access various α,β-unsaturated carbonyls (Scheme 1a, bottom). In general, metal-free transformations of alkenes by thianthrenation led to bond formation at the *ipso*-carbon of alkenyl thianthrenium salts. We questioned the possibility of realizing a general and new bond-formation mode of alkenyl thianthrenium salts to achieve functionalization at the *cine*-carbon of alkenes under metal-free conditions," said Professor Shu.

"In this work we effectively and successfully developed a unified protocol for metal-free *cine*-functionalizations of alkenes by thianthrenation (Scheme 1b)," said Professor Shu. He continued: "The reaction exploits the reactivity of alkenyl thianthrenium salts to form a new chemical bond at the *cine*-position instead of the *ipso*-position, allowing for the site-



Scheme 1 Metal-free functionalizations of alkenes by thianthrenation

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selective C–H functionalization of alkenes at the more substituted position to forge C–S, C–N, C–P and C–C bonds with diverse nucleophiles." Professor Shu explained: "Notably, the reaction tolerates a wide range of nucleophiles with different nucleophilic atoms. A wide range of alkenes with diverse electronic and steric properties are suitable substrates for this reaction (Figure 1). Aliphatic terminal-alkene-based thianthrenium salts are all compatible in this reaction. Moreover, alkenes with pendant amides, bromides, esters and other functional groups are compatible in the reaction. Impressively, both symmetric and nonsymmetric internal alkenes are also tolerated in this reaction. In addition, styrenes could also be efficiently reacted."

Professor Shu emphasized that the reaction represents a new metal-free reaction mode to functionalize the *cine*-carbon of alkenyl thianthrenium salts, which is complementary to previous functionalization at the *ipso*-carbon. "Mechanistic investigations revealed that the reaction takes place through site-selective nucleophilic addition followed by proton shift and regioselective elimination to afford the formal Heck product of alkenes, originating synthetically useful synthons which are difficult to access otherwise," said Professor Shu, adding that the process should be considered as a new and practical alternative for the synthesis of internal heteroatom-substituted alkenes.

"Moving forward, we will explore the boundaries of metal-free functionalizations of alkenes by thianthrenation," said Professor Shu, who concluded: "Likewise, we are studying and tuning the activity difference of diverse sites of alkenyl thianthrenium salts and the possibility of intercepting the intermediates through different mechanisms."

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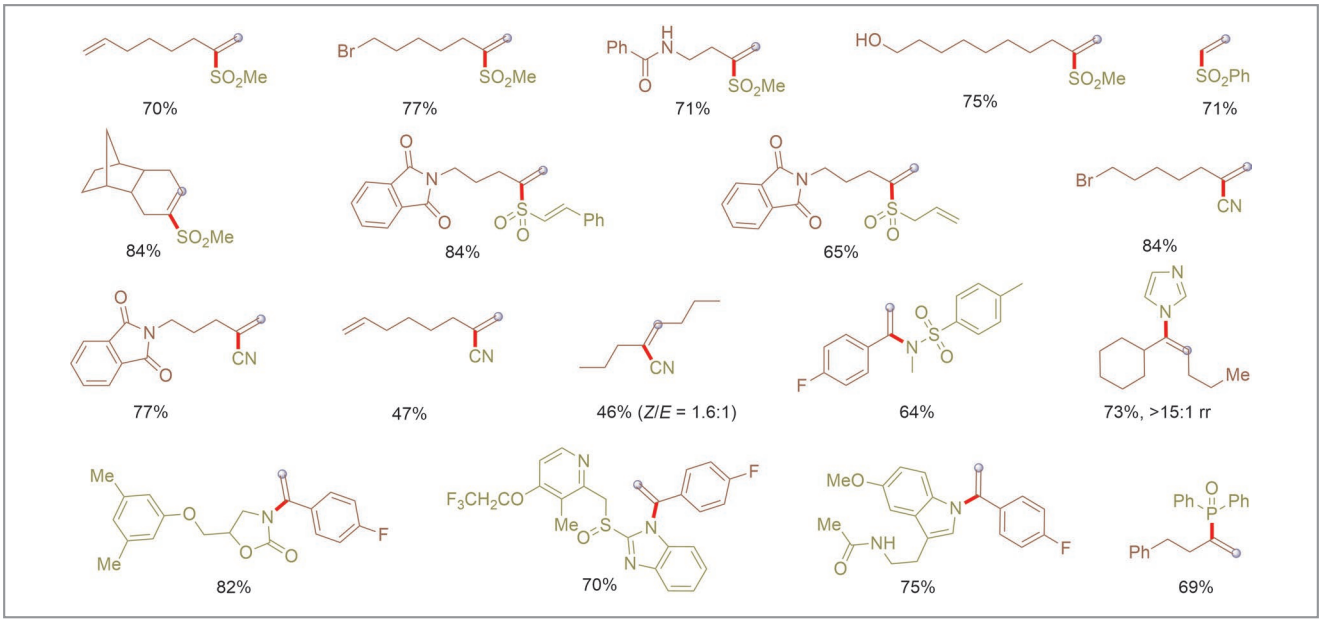

Figure 1 Selected examples of *cine*-substitution of alkenyl thianthrenium salts

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