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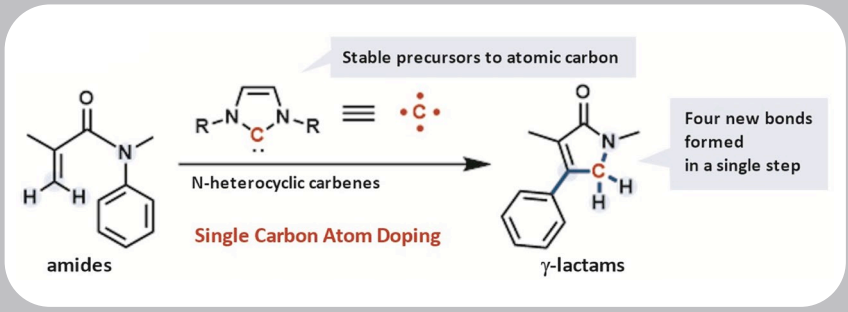
People, Trends and Views in Chemical Synthesis

2023/06

Single-Carbon-Atom Transfer to α,β-Unsaturated Amides from N-Heterocyclic Carbenes

Highlighted article by M. Kamitani, B. Nakayasu, H. Fujimoto, K. Yasui, T. Kodama, M. Tobisu



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Dear Readers,

Artificial intelligence (AI) and machine learning (ML) – which in my understanding (I am far from being a specialist in the field) is an application or subset of AI – are progressively extending their influence on the realm of chemistry, including that of organic synthesis. Some even think that AI will – at some point in a not-too-far future – replace chemists entirely, not just in the execution of organic reactions but also in their design and planning. I will leave these predictions – and related analysis on whether this is good or bad, or simply inevitable – to others who have more talent in terms of crystal ball gazing, but certainly the impact of AI and ML in the organic chemistry literature is becoming increasingly evident. One such example is featured in the closing article of this issue of SYNFORM, where I. Larrosa and co-authors (UK) in a recent *Nature* article took advantage of the opportunities offered by an ML approach to analyze a set of kinetic data to uncover the underlying reaction mechanisms, which ultimately resulted in a better understanding – and optimization – of complex organic processes. This is a very exciting development – which perhaps owes something to certain chemometric methods that were trending a few decades ago – because it is not difficult to conceive a future where similar ML or AI methods will be routine for analysing organic reactions before even trying any lab experiment. Although this piece of research is extremely visionary and exciting, there is more great science in this June issue of SYNFORM. Indeed, the first article covers a new application of photochemical catalysis, which makes use of pyridinium salts for achieving the enantioselective alkylation of enolates and enamines, as reported by U. Tambar (USA). The second article features a recent and conceptually ground-breaking Science paper by M. Tobisu (Japan) who demonstrated that *N*-heterocyclic carbenes can be used as stable synthetic precursors for the transfer of a single carbon atom to α,β-unsaturated amides. A SYNFORM issue would not be complete without an interview, this one featuring 2023 Thieme Chemistry Journal Awardee M. Tekle-Smith (USA) and her research strategies to innovate drug discovery, materials chemistry, and data science applications.

Enjoy your reading!

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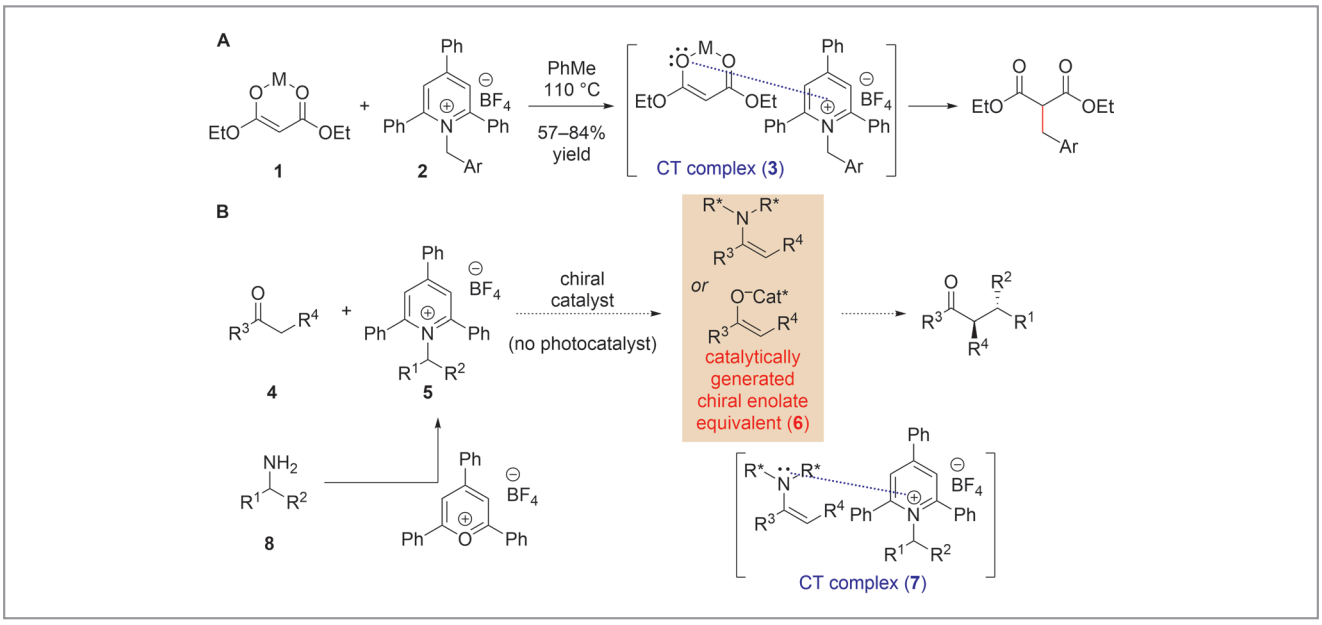
Catalytic Photochemical Enantioselective α-Alkylation with Pyridinium Salts

Chem. Sci. **2023**, *14*, 586–592

The research group of Professor Uttam Tambar at the UT Southwestern Medical Center in Dallas (USA) has a long-standing interest in asymmetric catalysis, with a burgeoning interest in photochemistry. "During 2020, while many labs around the world were grappling with the challenges of COVID-19, we found comfort in meeting virtually every day to talk about new research directions for our group once we could return to lab," said Professor Tambar. He continued: "Through these discussions, we started to think of ways to merge our interests in asymmetric catalysis and photochemistry. The growth of stereoselective photochemistry in recent years has been largely motivated by the significance of discovering new catalytic reactions that are environmentally benign, utilize sustainable sources of energy (such as low-energy visible light), and provide access to medicinally relevant chiral enantioenriched molecules that are not easily synthesized by other methods." [1]

As the group was contemplating its own ideas for stereoselective photochemistry, Santhi Yetra became enamored by the activation of Katritzky salts via photoinduced electron transfer. Professor Tambar explained: "We were drawn to an early paper by Professor Alan Katritzky in which he proposed a non-obvious mechanism for the alkylation of simple malonate anions by pyridinium salts (Scheme 1A).[2] While initial examination of this α-alkylation reaction would suggest a simple S_N2 mechanism, Katritzky's kinetic studies supported a non-chain radical substitution process that is initiated by a charge-transfer (CT) complex **3** between the malonate anion **1** and the Katritzky salt **2**. And then, on April 26, 2020, we asked the question that would serve as the basis for a new research direction in our lab: can we take advantage of CT complexes **7** between pyridinium salts **5** and catalytically generated electron-rich chiral enolate equivalents **6** to establish a general platform for photochemical enantioselective α-alkylations of carbonyl compounds **4** (Scheme 1B)?"

Given the prevalence of carbonyl compounds with α-stereocenters in biologically active molecules,[3] new strategies for their stereoselective synthesis have represented some of the most important developments in the group's field. "In our own graduate school curriculum at UT Southwestern, asymmetric α-alkylations are one of the first stereoselective



Scheme 1 Catalytic enantioselective α-alkylation of carbonyl compounds with pyridinium salts via charge-transfer complexes

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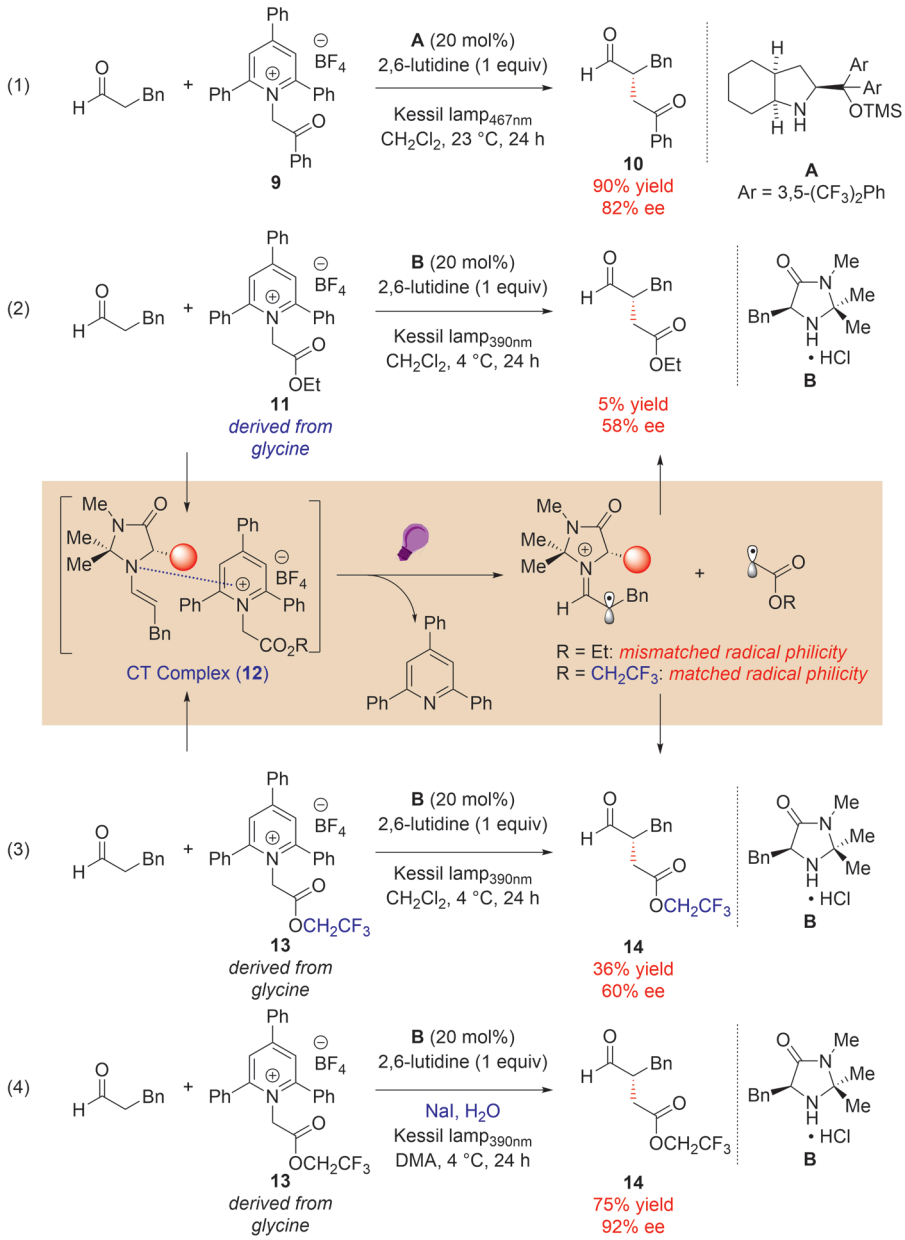
carbon–carbon bond forming reactions we teach in the advanced organic chemistry course," said Professor Tambar. He continued: "These reactions are usually categorized by the mode of catalysis and the enolate precursor, with alkyl halides and sulfonates typically utilized as the electrophiles. But the use of different classes of alkylating agents is underexplored. Our idea to couple pyridinium salts **5** with catalytically generated chiral enolate equivalents **6** would allow us to employ alkylating reagents that are ultimately derived from primary amines **8**, which have inherent advantages over traditionally used alkyl halides. For example, due to the abundance of primary amines in compound libraries and natural products, the ability to utilize them as alternatives to alkyl halides will present new opportunities in complex molecule synthesis.



Scheme 2 Development of chiral amine catalyzed photochemical enantioselective α-alkylation of aldehydes with pyridinium salts

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In addition, pyridinium salts **5** are synthesized from primary amines **8** in one step and are air- and moisture-stable solids that can be easily purified and stored for long periods of time, unlike the more reactive alkyl halides."

To develop their proposed reaction, the group had to define two important parameters: the choice of catalyst and the choice of pyridinium substrate. For the catalyst, Prof. Tambar and co-workers chose to activate aldehydes with chiral amine catalysts popularized by Professors David MacMillan and Benjamin List.[4] "We were heavily influenced by early physical chemistry papers on CT complexes by Mulliken, Marcus, and Kochi,[5] as well as recent reviews on the use of CT complexation in reaction design,[6]" explained Professor Tambar. He continued: "The most influential organic chemist in this field is Professor Paolo Melchiorre, who pioneered the use of α-bromoketones and benzylic bromides as alkylating agents via light-activated CT complexation with chiral enamines formed from the *in situ* condensation of aldehydes and chiral amine catalysts.[7]"

Professor Tambar told us that their initial choice of pyridinium substrate focused on Katritzky salts derived from α-aminoketones (**9**, Scheme 2, equation 1). He explained: "The carbonyl group next to the primary amine was necessary for both formation of the CT complex with the catalytically generated chiral enamine and subsequent carbon–carbon bond formation. We quickly optimized the formation of α-alkylation products **10** from simple aldehydes and α-aminoketone-based pyridinium salts to 90% yield and 82% ee."

At this point, the group recognized the unique opportunity to use pyridinium salts derived from α-amino acids, which represent renewable and sustainable sources of alkylating reagents. In addition, the use of enantiopure natural amino acids in a reaction that proceeds through a radical intermediate would allow for catalyst-controlled stereoconvergency. "Unfortunately, with α-amino acid derived substrate **11**, we were plagued by low yields and enantioselectivities for several weeks (Scheme 2, equation 2)," said Professor Tambar. He went on: "We were confident that we were forming CT complexes **12** with catalytically generated chiral enamines, as we observed the liberation of 2,4,6-triphenylpyridine under the reaction conditions. But the desired carbon–carbon bond formation was inefficient. These experiments taught us an important lesson in the development of radical-mediated reactions: the formation of reactive radical intermediates is not sufficient for the formation of new bonds via radical intermediates. Through Dr. Eric Welin's recent review on radical philicity, we learned of the importance of matching the reactivity of radical intermediates.[8] Our first major breakthrough was the use of the electron-deficient pyridinium salt derived from the 2,2,2-trifluoroethyl ester (**13**), which resulted in an enhanced yield (Scheme 2, equation 3)."

Although the Tambar lab had experience in developing enantioselective reactions, this was their first attempt to develop a photochemical enantioselective process, which presents unique experimental challenges. Most importantly, precise control of low temperatures for long times becomes challenging when a lamp is used to irradiate a reaction mix-

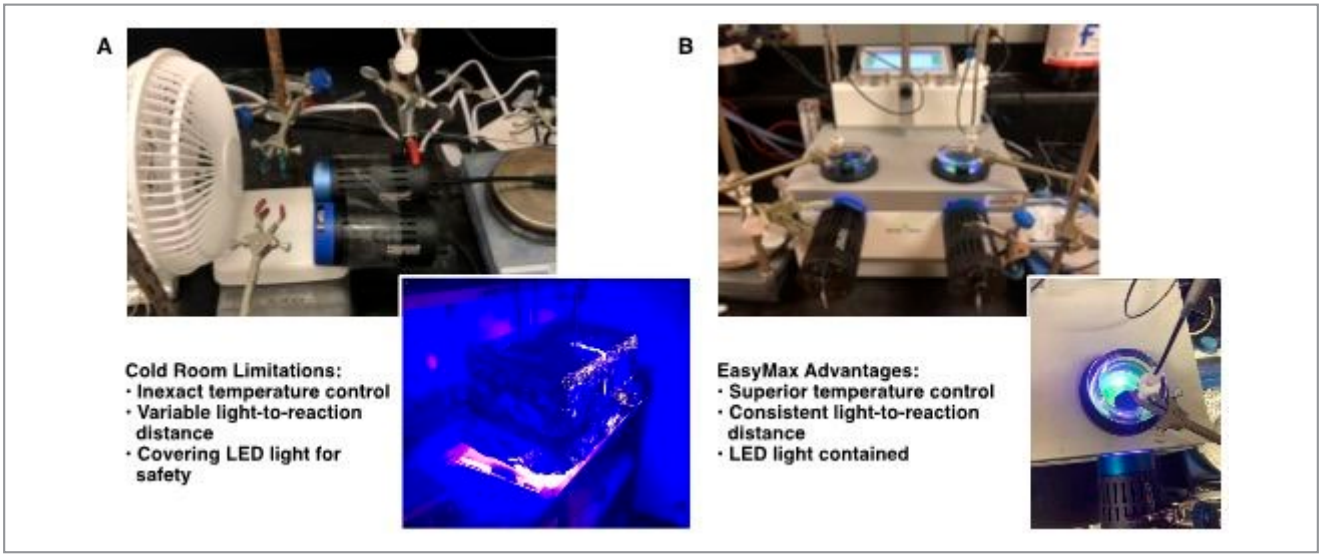

Figure 1 Control of low temperatures for long times in stereoselective photochemical reactions

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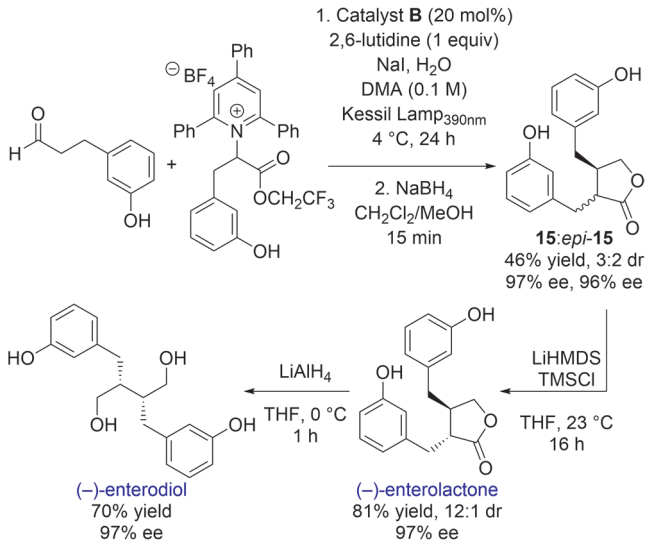
ture from a close distance. Professor Tambar remarked: "For months we were plagued with inconsistencies in ee, which we attributed to the difficulty of maintaining the reaction temperatures. Initially we ran the reactions in a 4 °C cold room utilized by biochemists (Figure 1A). Santhi Yetra and Nathan Schmitt could be seen shivering late at night through the little window of the cold room. We also used an elaborate web of clamps to maintain a constant distance between the lamp, the reaction vials, and the fan that was used for additional cooling of the mixture. As inconsistencies persisted, we finally purchased the EasyMax 102 Advanced Thermostat system from Mettler-Toledo AutoChem, Inc. (Figure 1B). This turned out to be the most important purchase for the success of the project. Although the EasyMax had never been used for photochemical reactions, we identified two key features of this instrument. First, it enables the maintenance of a constant low reaction temperature for long times. Second, the instrument has a clear window into the reaction chamber, which is typically used to view into the reaction, but we identified this as an opportunity to shine light from a lamp at a controlled distance without impacting the reaction temperature. To our delight, the EasyMax provided a new level of consistency in our results."

Professor Tambar revealed that as this was the lab's first foray into charge-transfer complexes, they had to learn a whole new set of concepts and experimental techniques. UV-Vis absorption turned out to be an essential tool for reaction optimization, but none of the synthetic chemistry labs at UT Southwestern had a UV-Vis spectrometer. "Fortunately, this is an essential instrument for biochemists in our medical center," said Professor Tambar. He continued: "Through UV-Vis studies, we quickly learned of the subtle effect of reaction components on the formation of CT complexes. For example, distinct classes of chiral amine catalysts and reaction solvents displayed different λ_{max} values for the characteristic CT band. In the presence of MacMillan's amine catalyst **B** and with DMA as the reaction medium, we formed the desired product **14** in greater than 90% ee, but the yield was still low. The next breakthrough in optimization came from Nathan Schmitt's observation in the literature of the effect of iodide salts on CT complexation.[9] We added NaI and a small amount of water to solubilize the inorganic salt, which resulted in the optimized reaction conditions (Scheme 2, equation 4)."

Once the reaction was developed, the group was motivated to apply the method to synthesize complex target molecules. "During Nathan Schmitt's yearly thesis committee meeting, Professor Myles Smith suggested that we examine the lignan natural products as possible targets," said Professor Tambar. He went on: "Unfortunately, our method inherently displayed low diastereoselectivity with pyridinium salts derived from substituted α-amino acids. Although the diastereomeric products **15** were obtained in high ee and poor dr, we recognized the potential to epimerize the mixture in the presence of base for the synthesis of the desired products with high diastereoselectivity. We utilized this approach to synthesize the lignan natural products (–)-enterolactone and (–)-entero-



Scheme 3 Synthesis of lignan natural products

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diol in high diastereoselectivity and enantioselectivity (Scheme 3)."

The group is now thinking about future directions for this project. Professor Tambar said: "We think back to our initial thoughts in April 2020 to take advantage of CT complexes between pyridinium salts and catalytically generated electron-rich chiral enolate equivalents to establish a general platform for enantioselective α-alkylations of carbonyl compounds. We plan to examine other modes of activation besides organocatalysis to forge new carbon–carbon bonds via this mechanistically interesting photochemical activation of pyridinium salts." He concluded: "We also believe CT complexes may find broader use in other areas of synthetic chemistry beyond asymmetric catalysis."

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Santhivardhana Reddy Yetra received his BSc in chemistry at the Acharya Nagarjuna University, Guntur (India), in 2008 and his MSc from Andhra University (India) in 2010. He completed his PhD at the CSIR-National Chemical Laboratory, Pune (India), under the supervision of Professor A. T. Biju. Subsequently, he was a postdoctoral fellow with Professor Lutz Ackermann at Georg-August-Universität Göttingen, Germany. Currently, he is a postdoctoral researcher in the lab of Professor Uttam Tambar at University of Texas Southwestern Medical Center (USA). His research interests include asymmetric catalysis, transition-metal catalysis and photochemistry.

N. Schmitt

Nathan Schmitt received his B.Sc. in chemistry from Texas Christian University (USA) in 2020. He then moved to the University of Texas Southwestern Medical Center (USA) and joined the lab of Professor Uttam Tambar, where he is pursuing his Ph.D. in organic chemistry. He is currently working on photochemical methodology and complex natural product synthesis.

Prof. U. K. Tambar

Uttam K. Tambar moved from India to New York City (USA) in 1982. He received his A.B. degree from Harvard University (USA) in 2000, where he conducted research with Professors Cynthia Friend and Stuart Schreiber. He obtained his Ph.D. from the California Institute of Technology (USA) in 2006 under the guidance of Professor Brian Stoltz. After he completed his NIH Postdoctoral Fellowship at Columbia University (USA) with Professor James Leighton in 2009, Uttam began his independent research career at UT Southwestern Medical Center in Dallas (USA). The Tambar lab is interested in asymmetric catalysis, natural product synthesis, chemical biology, and medicinal chemistry. Uttam is currently the Bonnie Bell Harding Professor in Biochemistry, Director of Diversity for Biochemistry, Director of the Organic Chemistry Graduate Program, and Co-Leader of the Simmons Cancer Center's Chemistry and Cancer Program.

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Single-Carbon-Atom Transfer to α,β-Unsaturated Amides from N-Heterocyclic Carbenes

Science **2023**, *379*, 484–488

The issue of how to improve efficiency in increasing structural complexity of molecules is a major focus in organic chemistry. The group of Professor Mamoru Tobisu at Osaka University (Japan) has been working on the problem and this paper in Science describes their recently developed method, which allows for the four chemical bonds to be formed at a carbon center in a single step, thereby shortening the chemical processes that are traditionally used in classical methods for constructing more elaborate structures.

Professor Tobisu said: "Our findings (Figure 1) show that a simple thermal reaction between α,β-unsaturated amides and N-heterocyclic carbenes (NHCs) results in the formation of homologated γ-lactams. In this reaction, NHC serves as an atomic carbon equivalent. This means that four new chemical bonds are formed at a single carbon center in a single process. These findings are important from a fundamental point of view because an atomic carbon is too unstable to be used in organic synthesis. This reaction successfully employs stable precursors to an atomic carbon, thus providing a practical method for single-carbon-atom doping reactions." The synthetic scope of the method is shown in Scheme 1.

Professor Tobisu revealed some background to their work. He told SYNFORM: "We were originally investigating a reaction using NHC as a catalyst (*Org. Lett.* **2021**, *23*, 1572–1576). During the course of that study we isolated a byproduct, the molecular weight of which was larger than that of the starting material by 12, suggesting incorporation of a single carbon atom. This was completely unexpected and was a great surprise for us."

Starting from that serendipitous finding, the methodology was subsequently developed and optimized, while also investigating the mechanism of the process. To that end, the group

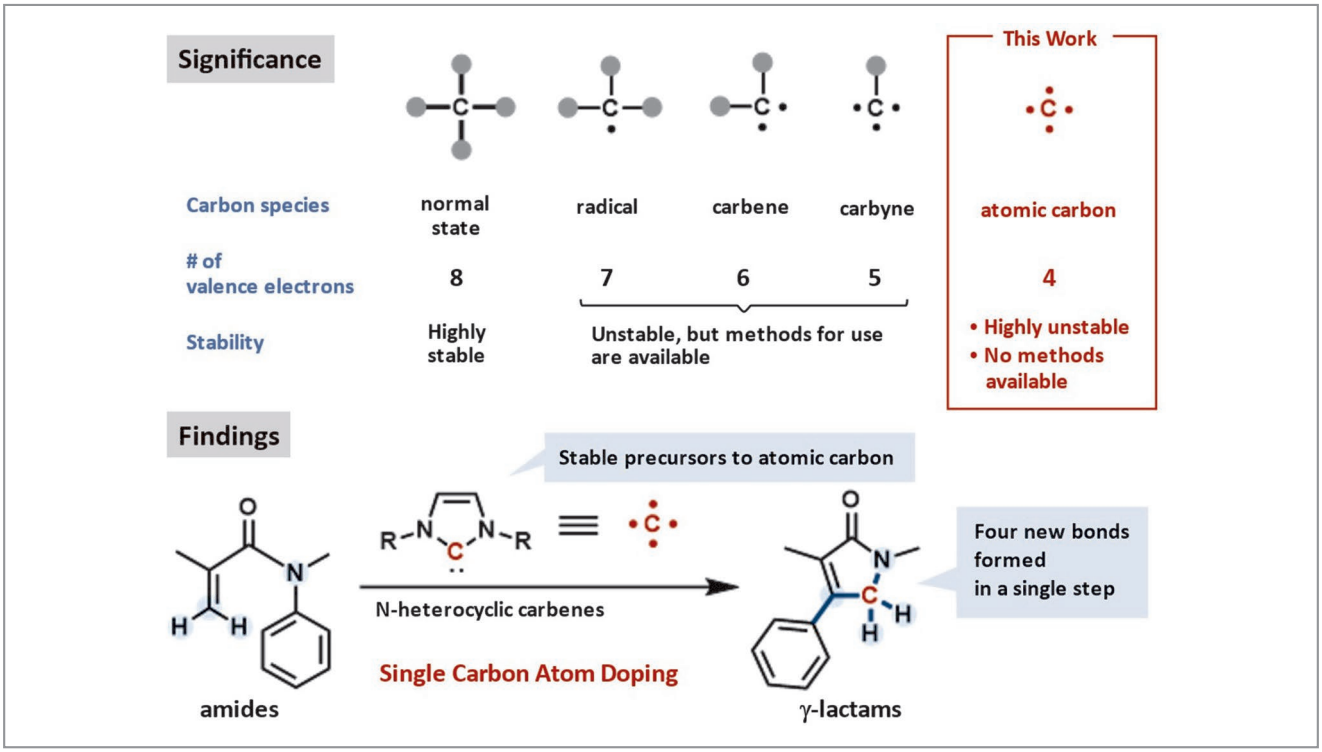

Figure 1 The single-carbon-atom doping reaction

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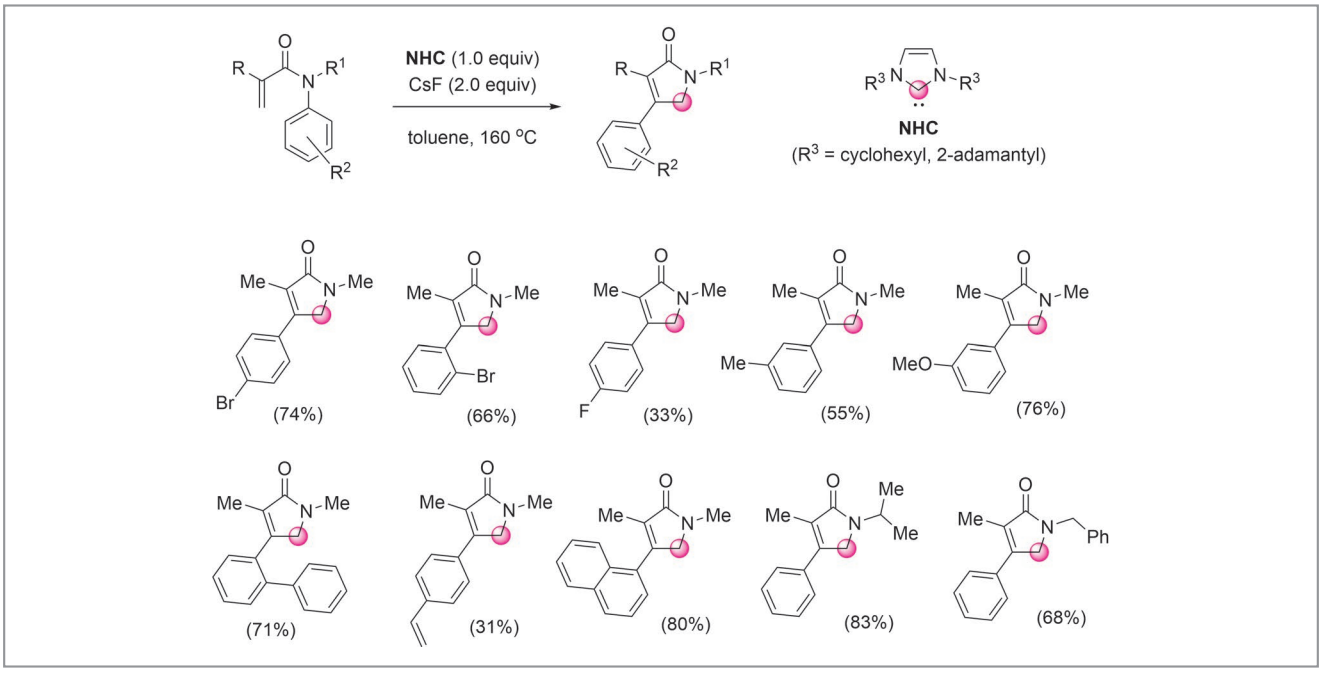

Scheme 1 Scope and applications of the methodology

performed a number of experiments, such as using an NHC labelled at the C2 position with ^{13}C, which resulted in the formation of the corresponding γ-lactam incorporating ^{13}C at the C5 position. Furthermore, deuterium labelling experiments and preparation/reaction of the intermediate imidazolium salt further confirmed the proposed mechanistic pathway.

To further demonstrate the synthetic potential of the methodology, the γ-lactam primary products were subjected to a series of transformations – such as hydrogenation, dehydrogenation and further homologations – which led to an array of functionalized pyrrole, pyrroline and pyrrolidine derivatives.

Professor Tobisu concluded: "Our next goal is to extend the concept of the carbon-atom doping reactions to be a general tool in organic synthesis by developing diverse types of transformations."

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About the authors

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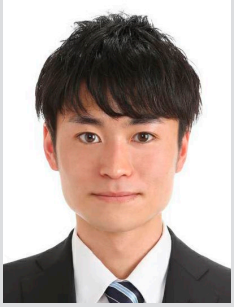
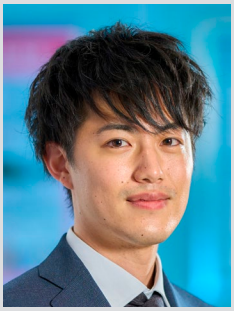
Miharu Kamitani received her MS degree from Osaka University (Japan) under the direction of Prof. Mamoru Tobisu (2021). She is currently working for DAIKIN INDUSTRIES, LTD (Japan).



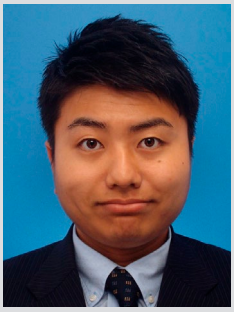
B. Nakayasu

Bunta Nakayasu received his B.S. degree from Osaka University (Japan) under the direction of Associate Professor Toru Amaya (2021). He then started his MS degree studies at the same university, under the direction of Prof. Mamoru Tobisu. His research interests include the development of new synthetic methods using N-heterocyclic carbenes.



Prof. H. Fujimoto

Hayato Fujimoto received his B.Sc. degree from Osaka University (Japan) under the supervision of Prof. Toshiyuki Moriuchi and Prof. Toru Amaya (2017). He obtained his M.Sc. (2017) and Ph.D. (2022) degrees from the same university under the supervision of Prof. Mamoru Tobisu. In 2022, he joined Prof. Tobisu's group as an assistant professor at Osaka University. His research interests focus on the development of new catalytic reactions and synthetic methods.



Prof. K. Yasui

Kosuke Yasui received his B.Sc. (2015) and M.Sc. (2017) degrees from Osaka University (Japan) under the supervision of Prof. Naoto Chatani, and Ph.D. (2020) degree from the same university under the supervision of Prof. Mamoru Tobisu. In 2018, he joined the group of Prof. Phil S. Baran in Scripps Research, USA, as a visiting student for 6 months. In 2020, he started his academic career as a program-specific assistant professor in the group of Prof. Aiko Fukazawa in Kyoto University (Japan). He then moved to Prof. Koji Hirano's group at Osaka University as an assistant professor in 2023. His research interests include the development of new catalytic reactions and novel π-conjugated systems.

Prof. T. Kodama

Takuya Kodama received his Ph.D. from Osaka University (Japan) under the supervision of Prof. Takashi Kubo (2018). During his Ph.D. studies, he also worked with Prof. Masayoshi Nakano for three months (2013) at Osaka University and Prof. Michael M. Haley at the University of Oregon, USA (2017) for three months as a visiting student. He started his academic career at Osaka University in 2018 as an assistant professor with Prof. Mamoru Tobisu. His research interests include structural and physical organic chemistry, in particular, syntheses, properties, and reactivities of new organic and organometallic compounds with unprecedented electronic structures.

Prof. M. Tobisu

Mamoru Tobisu received his Ph.D. from Osaka University (Japan) under the direction of Prof. Shinji Murai (2001). During his Ph.D. studies, he also worked with Prof. Gregory C. Fu as a visiting scientist for five months at the Massachusetts Institute of Technology, USA (1999). Following a period as a scientist at the Takeda Pharmaceutical Company, Japan (2001–2005), he started his academic career at Osaka University in 2005 as an assistant professor with Prof. Naoto Chatani. He was then appointed as an associate professor at the same university in 2011 and was promoted to full professor there in 2017. Since 2020, he has also served as a director of Innovative Catalysis Science Division of the Institute for Open and Transdisciplinary Research Initiatives at Osaka University. His research interests center on synthetic organic chemistry and homogeneous catalysis.

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Young Career Focus: Professor Makeda Tekle-Smith (Columbia University, 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 Professor Makeda Tekle-Smith (Columbia University, USA).

Biographical Sketch

Prof. M. Tekle-Smith

Makeda Tekle-Smith was born and raised in Santa Barbara, California (USA). She obtained her B.A. in chemistry at Pomona College (USA) in 2014. As an undergraduate, she investigated new anti-malarial compounds with Prof. Cynthia Selassie. She then obtained her Ph.D. with Prof. James Leighton at Columbia University (USA) in 2019. There she developed new methods to construct asymmetric C(sp^3)–C(sp^3) bonds and applied these technologies to the total synthesis of non-aromatic polyketide natural products. Makeda then went on to conduct her postdoctoral research with Prof. Abigail Doyle first at Princeton University (USA) and then at the University of California Los Angeles (USA). Makeda's postdoctoral work focused on generating and harnessing reactive radical intermediates through photoredox catalysis to unveil new reactivity platforms. Makeda began her independent career at Columbia University in 2022.

INTERVIEW

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

Prof. M. Tekle-Smith My research program is working to develop novel and practical strategies for controlling selectivity in chemical reactions. Specifically, we propose the design of new asymmetric reagents and the discovery of new mechanistic platforms using photoredox catalysis and non-covalent interactions. The goals of this program are to create enantiopure substances, harness the reactivity of unconventional chiral motifs, and grow the fundamental understanding of chiral structural effects. The interdisciplinary nature of my research program offers opportunities to innovate in drug discovery, materials chemistry, and data science applications (Figure 1).

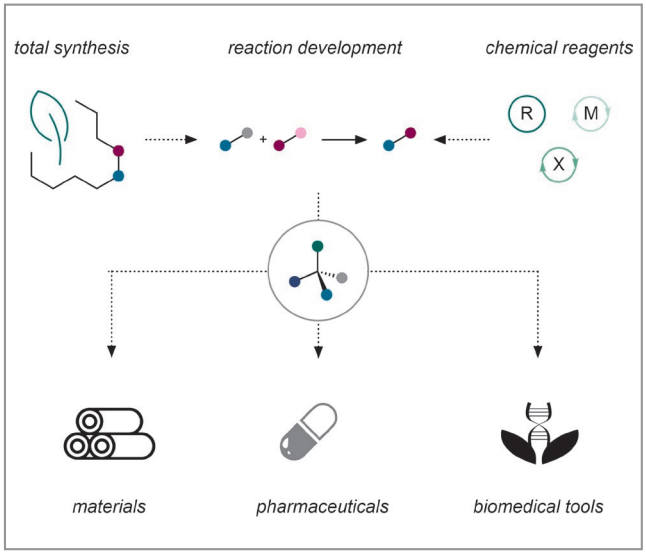

Figure 1 Research interests in the Tekle-Smith lab

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SYNFORM *When did you get interested in synthesis?*

Prof. M. Tekle-Smith I've had an affinity for chemistry since high school, but I was drawn to synthesis in particular once I took organic chemistry in college. I had incredible professors, including Prof. Cynthia Selassie and Prof. Daniel O'Leary, who showed me how organic chemistry is the world around us. The idea that you could draw a structure on paper in the morning and go make it with your own hands in the afternoon blew me away. I don't think I will ever get over the feeling of successfully making something new in the lab. One of the things that always has and will continue to drive me is the goal of making new materials and technologies that make the world better.

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

Prof. M. Tekle-Smith One of the modern roles of organic chemistry I'm most excited about is generating new chemical matter that diverges from what we see commonly in nature. With synthetic methods rapidly advancing, we now have the ability to stretch our creativity in terms of what chemical structures we can access and new potential chemical motifs we can come up with. My hope is that, especially now with the types of data science tools at our disposal, organic chemists can accurately evaluate what chemical space we have currently explored and start targeting new structural architectures.

SYNFORM *What is your most important scientific achievement to date and why?*

Prof. M. Tekle-Smith My most important achievement to date is definitely the people I have mentored and I know that will be true in the future as well. Helping colleagues find their right career paths and creating inclusive environments where creativity and diversity can thrive and flourish will always be my top priorities and greatest achievements.

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

Prof. M. Tekle-Smith If I had not become a chemist, I would have liked to be an artist. I was in an art-based academy in high school, which interwove art and design into all classes. Before deciding to go to Pomona College to study chemistry, I was seriously considering attending art school. Now I consider myself more of a molecular artist with fine art (especially portraiture) as a hobby.

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

Prof. M. Tekle-Smith Outside of the lab, I love being outside. Growing up in Santa Barbara, California, I love everything about the beach and try to get there as often as I can. I also have been playing soccer since before I can remember. I got a soccer ball for my 1-year-old birthday and have been playing ever since.

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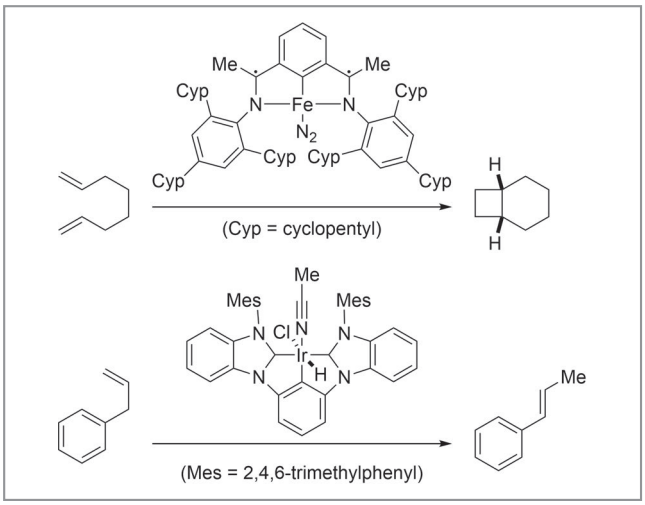
Organic Reaction Mechanism Classification Using Machine Learning

Nature **2022**, *613*, 689–695

Mechanistic studies are a type of mathematical inverse problem in which chemists analyze a set of observations (kinetic data) to uncover the underlying causes (reaction mechanisms). According to Professor Igor Larrosa, from the University of Manchester (UK), a modern approach to solving these problems involves training deep neural networks with known data. He told SYNFORM: "This can be compared to exposing the human brain to a large quantity of kinetic data generated by each mechanism, allowing it to learn the intrinsic patterns and develop the ability to deduce the reaction mechanism from previously unseen kinetic data." Professor Larrosa and Dr. Jordi Burés, also from the University of Manchester, strongly believe in the potential of using mechanistic insights to enhance the discovery and improvement of catalytic reactions. Dr. Burés said: "Our inspiration dates back to the ground-breaking work of Professor Blackmond and the benefits of open-source modelling programs like COPASI. Since then, we have been driven to explore innovative approaches to extract more comprehensive information from reaction kinetics. With the AI revolution transforming various scientific fields with remarkable outcomes, it was only natural for us to investigate its potential in the area of reaction mechanism elucidation."

During the initial exploratory experiments testing various neural network structures, the researchers achieved promising results early on. "While it took significant effort to ultimately develop a robust model, our initial success confirmed the viability of our idea and motivated us to push hard in developing it, ultimately leading to the publication of the final model," explained Professor Larrosa.



Scheme 1 Two case studies with kinetic data investigated in this work

The researchers found that interpreting the model's performance, however, was sometimes challenging due to the human limitations in understanding large neural networks and predicting the kinetic behaviour of complex chemical reactions. "Midway through the project, we were surprised by the model confusing certain reaction mechanisms, but after further consideration, we realized that it was actually a positive outcome," revealed Dr. Burés. He continued: "The model was revealing that certain mechanisms can produce the same kinetic data in certain conditions. To enhance the model's capabilities, we added the ability for it to provide multiple answers when necessary. This feature greatly improved the model's accuracy in situations where the data were insufficient to differentiate between mechanisms, due to either noise or a limited amount of data."

"We are thrilled with the outcome of this proof-of-concept article as it has opened numerous exciting opportunities in the field of kinetic analysis," said Professor Larrosa. He continued: "Our goal is to create more sophisticated models that address specific mechanistic issues and are tailored to specific experimental data. Additionally, we aim to gain a deeper understanding of how the AI model operates in order to potentially uncover new kinetic features such as reaction orders or induction periods. Furthermore, we are also investigating more ambitious applications, but it may take some time before we are ready to share."

Professor Larrosa concluded by saying: "We are at a unique turning-point in the development of artificial intelligence tools for chemistry. The next years are going to offer lots of exciting opportunities for enthusiastic students seeking to embrace new technologies; we need them!"

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About the authors

Prof. I. Larrosa

Igor Larrosa graduated with a master's in chemistry from the University of Barcelona (Spain) in 2000. He also completed a PhD degree in Barcelona (2004) with Profs. Felix Urpi and Pere Romea, including a research period in Prof. Erick M. Carreira's laboratories at ETH (Zurich). Igor then moved as a postdoctoral researcher to Imperial College London (UK) to work in Prof. Anthony G. M. Barrett's group. In 2007 he started his independent career as a Lecturer at Queen Mary University of London. Since 2014, Igor holds a Chair in Organic Chemistry at the University of Manchester. Igor has held a European Research Council Starting Grant and currently holds an ERC Advanced Grant. Igor's research interests lie in the development of new catalytic processes inspired by mechanistic understanding, with particular emphasis on transition-metal-catalysed C–H and C–C activation.

Dr. J. Burés

Jordi Burés gained his undergraduate degree in chemistry at the University of Barcelona (Spain) in 2003. He then pursued his studies for an MRes and PhD with an FPU studentship in the group of Prof. Jaume Vilarrasa. In 2010, he was awarded a postdoctoral fellowship to join the group of Prof. Donna Blackmond at The Scripps Research Institute, in California (USA). In 2013, he started his independent career at Imperial College London (UK) with an IC Junior Research Fellowship. In 2016, he was appointed Lecturer in Organic Chemistry at The University of Manchester (UK) and promoted to Senior Lecturer in 2020 and to Reader in 2022. Jordi has received the 2018 Thieme Chemistry Journals Award, the 2019 Young Researcher Award from the Spanish Royal Society of Chemistry (RSEQ), and the 2020 Hickinbottom Award from the Royal Society of Chemistry (RSC). The Burés research group develops physical organic chemistry tools to gain a deeper understanding of reaction mechanisms, allowing for the advancement of organic synthesis techniques in a rational, informed manner.

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