Stereocontrolled 1,3-Nitrogen Migration To Access Chiral α-Amino Acids

Highlighted article by C.-X. Ye, X. Shen, S. Chen, E. Meggers

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Dear Readers,

This is one of those days when hay-fever and pollen allergy get the best of me. If you have hay-fever you know what I mean; if you don’t, you can consider yourself very lucky. Running nose, non-stop sneezing and itchy eyes are making the task of writing this editorial more challenging than climbing Mount Everest wearing diving fins. I tried an anti-histamine but the only tangible effect has been to become even more dizzy. You will therefore forgive me if on this occasion I will keep the introduction very short and go straight to the content of this October 2022 issue of SYNFORM, which is very exciting and starts with a clever and versatile strategy to access functionalized α-amino acids in a stereocontrolled manner through a 1,3-nitrogen migration, as described in a Nat. Chem. paper by E. Meggers (Germany). The second article remains in the amino acids realm, providing an overview of the innovative strategy for forming a peptide bond between sterically hindered α,α-disubstituted α-amino acids and N-alkyl cysteines developed by Y. Hayashi (Japan). The issue continues with an interesting interview with the Thieme Chemistry Journals Awardee Kevin Cariou (Chimie ParisTech, PSL University, CNRS, Institute of Chemistry for Life and Health Sciences, France) focussing on his research devoted to the synthesis of biologically important compounds and related medicinal chemistry. The closing article covers the conceptually novel approach proposed by Y. Wang (P. R. of China) for promoting the addition to alkenes through weak interactions triggered by Se···π bonding catalysis, which leads to unsaturated carbocycles and polyalkenes.

Enjoy your read… achoo!

Matteo Zanda
There is great demand for unnatural and non-proteinogenic α-amino acids, which find a number of applications both in basic and applied research. For example, unnatural amino acid side chains modulate the chemical, physical, and pharmaceutical properties of peptides, proteins and other bioactive molecules. Chiral amino acids are also used as chiral building blocks for chiral catalysts and as chiral auxiliaries. Despite the development of many powerful synthetic methods to access optically active α-amino acids, efficient catalytic enantioselective methods are still sought after and the subject continues to attract strong interest in modern organic chemistry.¹

The research group of Professor Eric Meggers at the University of Marburg (Germany), in collaboration with Professor Shuming Chen at Oberlin College (Ohio, USA), recently reported a new synthetic strategy to access chiral non-racemic α-amino acids (Scheme 1). “Our two-step method is surprisingly simple and straightforward,” said Chen-Xi Ye, who is first author of the title article, adding: “Abundant and easily accessible carboxylic acid feedstock molecules are first ligated to a nitrene precursor followed by a stereocontrolled 1,3-nitrogen shift from the carboxylic acid oxygen to the α-carbon.” According to the authors, the method displays a broad scope, providing rapid access to non-racemic α-amino acids with aryl, allyl, propargyl, and alkyl side chains, also permitting stereocontrolled late-stage amination of carboxylic acid containing drugs and natural products. The method builds on recent advances in asymmetric nitrene C(sp³)–H insertion chemistry. “While these reported examples are typically designed as intramolecular reactions to provide cyclic nitrogen-containing compounds with high regio- and stereocontrol,² our new method combines the advantages of an intramolecular nitrene insertion with the ability to access acyclic amine-containing molecules by using an unprecedented stereocontrolled 1,3-migratory nitrene C(sp³)–H insertion process,” said Professor Meggers. Professor Chen added: “Density function theory (DFT) calculations support a triplet nitrene mechanism via a hydrogen atom transfer (HAT) followed by a C–N bond formation.”

While initial experiments were performed with a chiral-at-metal ruthenium catalyst, it later turned out that a chiral iron complex serves as an equally powerful catalyst for the stereocontrolled 1,3-nitrogen migration. “There is currently great interest in the development of iron-catalyzed reactions, including asymmetric reactions,³ due to the high abundance of iron on Earth in combination with its low toxicity profile,” said Xiang Shen, the second author on this Nat. Chem. paper.

**Scheme 1** Overview of the developed α-amino acid synthesis by stereocontrolled 1,3-nitrogen migration
He added: “The robust iron catalyst is easy to synthesize and stable on the benchtop. Besides the economic and environmental benefits, the iron catalyst has the additional advantage that it allows access to non-racemic α-amino acids with aliphatic side chains.”

Professor Meggers concluded: “We are convinced that this work will expedite the synthesis of unnatural α-amino acids. The developed method has several attractive features: it uses easily accessible carboxylic acid feedstock molecules; it provides chiral α-amino acids with a protecting group that can be removed under mild reaction conditions; the nitrogen shift features excellent stereocontrol, and can even be catalyzed with a robust iron catalyst; last but not least, the reaction scope is excellent, also permitting stereocontrolled late-stage aminations of carboxylic acid containing drugs and natural products.”

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About the authors

Chen-Xi Ye received his B.Sc. and M.Sc. from Xiamen University (P. R. China), where he worked in the area of (enantioselective) radical chemistry under the supervision of Prof. Xiao Zheng and Prof. Pei-Qiang Huang. Currently, he is pursuing his Ph.D. under the guidance of Prof. Eric Meggers at the University of Marburg (Germany). His current research is focused on enantioselective C(sp3)–H aminations.

Xiang Shen received his M.Sc. in organic chemistry from Xiamen University (P. R. China) and recently received his Ph.D. from the University of Marburg (Germany) under the supervision of Professor Eric Meggers, where he developed stereocontrolled iron-catalyzed C(sp3)–H aminations for the synthesis of α-amino acids.

Shuming Chen was born and raised in Hangzhou, P. R. China. After earning her B.A. from Grinnell College (USA), she carried out her Ph.D. studies under the direction of Professor Jonathan A. Ellman at Yale University (USA). She then became the Donald J. Cram Teacher-Scholar at the University of California, Los Angeles (USA), working with Professor Kendall N. Houk during the period of 2016–2020. Dr. Chen began her independent career as an Assistant Professor of Chemistry and Biochemistry at Oberlin College (USA) in 2020.

Eric Meggers studied chemistry at the University of Bonn (Germany) and received his Ph. D. from the University of Basel (Switzerland). After postdoctoral research at the Scripps Research Institute (USA) he started his independent career as Assistant Professor at the University of Pennsylvania (USA). Since 2007, Eric Meggers is Full Professor in the Department of Chemistry at the University of Marburg (Germany). The Meggers laboratory is currently focused on the design and development of chiral-at-metal complexes for applications in asymmetric catalysis.
Highly Sterically Hindered Peptide Bond Formation between α,α-Disubstituted α-Amino Acids and N-Alkyl Cysteines Using α,α-Disubstituted α-Amidonitrile

J. Am. Chem. Soc. 2022, 144, 10145–10150

α,α-Disubstituted α-amino acids can impart distinctive conformational and pharmacological properties when incorporated into peptides and proteins. However, the formation of peptide bonds is often challenging with these sterically hindered amino acids, and few efficient methods are known. The group of Professor Yujiro Hayashi at Tohoku University (Japan) has recently achieved a breakthrough in this area of research, which was reported in J. Am. Chem. Soc.

Professor Hayashi began by telling SYNFORM: “Actually, there’s a long story to tell before discussing the work in the title article. Our major interest is developing new reactions using organocatalysts and then applying these reactions to the pot-economical total synthesis of biologically active molecules (see for example Chem. Sci. 2016, 7, 866; Acc. Chem. Res. 2021, 54, 1385). The Hayashi–Jørgensen catalyst is a well-known organocatalyst, which was developed independently by our group (Angew. Chem. Int. Ed. 2005, 44, 4212) and Jørgensen’s group (Angew. Chem. Int. Ed. 2005, 44, 794). While developing the three-pot synthesis of PGE1 methyl ester (Angew. Chem. Int. Ed. 2013, 52, 3450), we found a Nef reaction with molecular oxygen in the absence of metal additives and investigated the reaction mechanism (Scheme 1) (Chem. Eur. J. 2014, 20, 15753). By having a thorough look into the reaction pathway, Mr. Jing Li – when he was a PhD student in our group (he is a PI at Xi’an Jiaotong University now) – further expanded the process into a more general and epimerization-free amide synthesis of nitroalkanes with amine nucleophiles, using molecular oxygen and iodine or N-iodosuccinimide (NIS) (Scheme 2) (Angew. Chem. Int. Ed. 2015, 54, 12986).”

During this study, Mr. Li observed the generation of a possible intermediate, which was confirmed as a halogen-bonded NIS-amine complex after isolation (Scheme 3b). Interestingly – recalled Prof. Hayashi – this discovery put the mechanistic basis of umpolung amide synthesis from α-bromo nitroalkane into question, which was a major advancement...
concerning the non-conventional amide synthesis reported by Johnston’s group in 2010 (Scheme 3a) (Nature 2010, 465, 1027). “These authors proposed that an in situ formed N-iodoamine acts as the key intermediate, which reacts with the α-bromo nitroalkane anion and gives the reactive tetrahedral intermediate 3′ (Scheme 3a). With Assoc. Prof. Martin Lear of our group, we thus decided to discern the reaction mechanism in our reaction system (Scheme 3b) (Chem. Eur. J. 2016, 22, 5538; Chem. Commun. 2018, 54, 6360),” remarked Professor Hayashi. He continued: “The differences we found include: 1) there was no umpolung of reactivity of amine because the NIS–amine complex 2 is the real intermediate instead of the electrophilic N-iodoamine 2′; 2) the tetrahedral intermediate 3′ was not formed; an α,α-diiodo nitro compound was formed instead; 3) the late-stage nucleophilic attack may occur through an acyl precursor (Scheme 4).”

The oxidative amide synthesis was achieved with readily available nitro compounds in a straightforward operation and highly chemoselective manner. Later, the group’s attention, with Dr Lear – now at the University of Lincoln, UK – was drawn by the challenge of performing the amidation of sterically hindered substrates in an atom-economical and mild fashion. “One day, Mr. Li presented an idea according to which the substituted malononitrile could be used as an efficient surrogate for sterically hindered amide synthesis,” explained Professor Hayashi. He continued: “The two cyano groups are not only electron-withdrawing but are good leaving groups too. A small and electrophilic acyl cyanide could be generated in the presence of oxygen under basic conditions, and then trapped by the amine nucleophile. Thereafter, the target sterically hindered amide synthesis was successfully developed, highlighting the achievement with the challenging coupling of two bulky substrates in a high-yielding manner under K₂CO₃ or Cs₂CO₃ and O₂ atmosphere in MeCN, with KCN or CsCN co-products as the only waste (Scheme 5a) (Angew. Chem. Int. Ed. 2016, 55, 9060). This work was also extended to sterically hindered esters and thioesters (Scheme 5b) (Eur. J. Org. Chem. 2019, 675).”

Since amide synthesis is closely linked to peptide synthesis, the interest of Professor Hayashi’s group in the area of atom-efficient and environmentally sustainable peptide synthesis has been growing since their first achievement in oxidative amidation. “It is clear that peptides and proteins are of exceptional importance because of their widespread occurrence in nature and their key role and prominence in biological systems and related research,” said Prof. Hayashi. He added: “Sterically hindered peptides, a key member in the peptide family, hold a special position compared to the pro-
teinogenic ones in defining peptide conformation, improving bioavailability, enhancing their stability against enzymatic degradation in vivo, and so on. α,α-Disubstituted amino acids and N-alkylated amino acids are two typical components in sterically hindered peptides.

Successful synthetic methods to access a sterically hindered peptide bond involving either an α,α-disubstituted amino acid or an N-alkyl amino acid have been reported. These are mostly based on the modification of the traditional coupling reagent-initiated amide synthesis, “However, the sterically hindered amide bond synthesis by direct coupling of these two components, which generates an α,α-disubstituted N-alkyl amide bond, remains extremely difficult because of the dramatically increased steric hindrance,” Professor Hayashi commented, adding: “Indeed, to our knowledge, there are only two reports of this type of bond formation: one involves the use of acyl fluoride (J. Am. Chem. Soc. 2008, 130, 14382) and the second involves thiocarboxylic acid and t-BuNC (J. Am. Chem. Soc. 2009, 131, 12924).” In both approaches, according to Prof. Hayashi, acid anhydride is formed as an intermediate, and the process proceeds through an intramolecular O,N-acyl transfer reaction. “There are only 2-aminoisobutyric (Aib) and 1-aminocycloalkane-1-carboxylic (Ac,c) acids – with a total of six examples – in the former case, and Aib with one example in the latter. As a free carboxylic acid is involved in the reaction, the nucleophile is restricted to an N-methyl mono amino acid, and only dipeptides are approachable. A peptide composed of several amino acids cannot be employed as a nucleophile in this context. Thus, the extremely sterically hindered peptide bond formation between α,α-disubstituted α-amino acids and a peptide with N-alkyl amino acids is essentially an unmet challenge, and the biological and physical functions of such peptides have not yet been explored,” said Prof. Hayashi.

Encouraged by the success of the highly hindered amide synthesis (Scheme 5a), the group became interested in expanding the oxidative amide synthesis to the synthesis of oligo-
peptides. “This study was done by PhD student Xiaoling Wang, and eventually we managed to synthesize tripeptides, tetrapeptides and pentapeptides from 2-(aminomethyl)malononitrile terminated peptide with the formation of a glycine amide bond (Scheme 6a),” said Professor Hayashi. He added: “During the generality study performed using the unprotected cysteine methyl ester, we were expecting that the acyl cyanide intermediate could be trapped by the thiol moiety, giving a thiol ester which can undergo intramolecular replacement by an amine, as in the native chemical ligation.” However, Ms. Wang observed a quick vanishing of the starting material and isolated a thiazolidine derivative in 90% yield (Scheme 6b). The authors were delighted to observe such a quick and clean transformation, subsequently coming up with the idea that there could be a chance for an α,α-disubstituted α-amido nitrile to react with N-methyl cysteine to give an active N-methylthiazolium, which can then hydrolyze to generate an α,α-disubstituted N-methyl amide bond (Scheme 6c). “Gratifyingly, this idea worked well using various α,α-disubstituted substituents and different amino acid side chains, as well as N-methyl/ethyl nucleophiles. We were pleased to observe that a decapeptide could be synthesized with just a minor decrease in the chemical yield by applying two pentapeptides as the starting materials,” said Prof. Hayashi. “Notably, the starting material is easily synthesized by Strecker’s method followed by a general coupling (Scheme 7) or prepared from a commercially available carboxylic acid followed by amidation, followed by general coupling and dehydration (Scheme 8).”

Although there is not yet evidence that such a type of extremely sterically hindered peptides has the power to change the world of peptides, the authors believe that the prospect of a near breakthrough in revealing the great potential of sterically hindered peptides will be opened by the ease of manufacturing the extremely hindered peptides described in the title article. Professor Hayashi concluded: “One can imagine that the study of conformation and pharmacological modification of therapeutic peptides by introduction of the highly hindered peptide moiety would be of great interest, given the growing interest in this area of research. The accomplishment of synthesizing such sterically hindered peptides is expected to open new avenues for investigating their conformation as well as their physical and biological properties, which may have a great impact in various research fields.”

![Scheme 7 Synthesis of starting material](image)

![Scheme 8 Synthesis of starting material](image)
About the authors

**Xiaoling Wang** was born in Anhui, China. She is now a PhD student at the Department of Chemistry, Graduate School of Science, Tohoku University, Japan. She completed her B.Sc. from Shenyang Pharmaceutical University, studying pharmaceutical preparation. In 2017, she joined Prof. Yuziro Hayashi’s group as a master student and focused on organocatalytic reactions. Her current research interests are in peptide synthesis.

**Jing Li** was born and grew up in Hunan (China). He received his PhD in 2016 from Tohoku University (Japan) under the supervision of Prof. Yuziro Hayashi. In 2016, he joined Prof. Nuno Maulide’s group at the University of Vienna (Austria) as a postdoctoral fellow. In 2019, he moved to Prof. Yuziro Hayashi’s group at Tohoku University (Japan) as an assistant professor. In 2021, he started his independent group in Xi’an Jiaotong University (China). His research is currently focused on thioamide and thiopeptide chemistry.

**Yujiro Hayashi** was born in 1962 in Gunma, Japan, and received his BSc (1984), MSc (1986) (Prof. T. Mukaiyama) and PhD (1992, Prof. K. Narasaka) degrees from The University of Tokyo (Japan). He was appointed as an assistant professor at The University of Tokyo in 1987, then moved to Tokyo University of Science (Japan) as an associate professor (1998), where he was promoted to full professor (2006), before moving to Tohoku University (Japan) in 2012. He undertook postdoctoral studies at Harvard University (USA) with Prof. E. J. Corey in 1994–1996. He is an associate editor of Chemistry Letters (2010 to present). His current interests focus mainly on the development of new synthetic reactions in the field of organocatalysis, and the total synthesis of biologically active natural products.
Young Career Focus: Dr. Kevin Cariou
(Chimie ParisTech, PSL University, CNRS, Institute of Chemistry for Life and Health Sciences, France)

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 Dr. Kevin Cariou (Chimie ParisTech, PSL University, CNRS, Institute of Chemistry for Life and Health Sciences, France).

INTERVIEW

SYNFORM What is the focus of your current research activity?

Dr. K. Cariou My research lies at the interface of developing new synthetic methods and the development of biologically active molecules. In terms of methodology, we focus on iodine(III) reagents, ynamides and organometallic compounds to try to access original scaffolds. For medicinal chemistry, our interest mostly lies in the development of anti-infectious molecules.

SYNFORM When did you get interested in synthesis?

Dr. K. Cariou I know it sounds clichéd but as a very small kid, I already liked chemistry, probably without knowing it was actually chemistry. Both my parents are pharmacists and there were some chemicals in the garage. I vividly remember a small flask with a drop of mercury inside, heavy and metallic yet liquid; that was fascinating. I also remember permanganate crystals, which could transform clear water into a beautiful purple solution. (Note: parents, do not let your children play with chemicals without adequate supervision!).

Kevin listens to a lot of music (often with loud guitars) and enjoys spending time outside, preferably near the ocean (if possible, in the waves), two passions he tries to share with his two kids.
Young Career Focus

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

Dr. K. Cariou For a while, it seemed that organic chemistry was passé, an old discipline where the last important discoveries dated from the 1970s (the Mirozoki–Heck coupling for example) and everything done since was merely dusting up old reactions. I obviously beg to differ, as there have been tremendous accomplishments recently. These accomplishments are not just “we are able to do it faster in a more eco-compatible fashion” or ‘trendy’ as one might have considered CH-activation or photoredox catalysis at first sight. New reactivities have been uncovered, which enable access to uncharted synthetic routes and chemical space. I strongly believe that we need new reactions to make new molecules that will prove useful for medicinal purposes, energy storage or even information transfer. This is undoubtedly impossible without organic synthesis and organic chemists will have a key role to play to make unforeseen reactions tangible.

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

Dr. K. Cariou As I mentioned, we are interested in anti-infectious molecules. Research in the field of antibiotics and antifungals has been mostly left aside by industry, while resistances have become extremely worrisome. This led to the current situation where the WHO has issued a list of bacteria for which new antibiotics are urgently needed and will soon publish an analogous list for pathogenic fungi. This places the burden of risk on the shoulders of academics and fragile start-ups. Our goal is to use our knowledge and expertise in molecular synthesis to propose new options for treating resistant strains. The ideal aim is to both overcome resistances and avoid the apparition of new ones. For that we not only use the great toolbox of organic synthesis but, in the meantime, also strive to expand that toolbox.

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

Dr. K. Cariou I would say it is the aerobic ididoarene catalysis system that we recently developed using a catalytic photoredox mediator. When you work in the field of hypervalent

Scheme 1 Synthetic development using iodine(III) reagents (A) and ynamides (C), examples of original bioactive compounds developed (B) and dual catalysis concept (D) in the last 10 years.
iodine(III) chemistry you are bound to think about how to make it catalytic and a lot of people have brought clever solutions to that issue. I have had the idea of an aerobic iodoarene for a while, but it was (and still is) hard to convince funders of the validity of this concept. Even after the breakthrough made simultaneously by Powers (Nat. Chem. 2018, 10, 200) and Ochiai and Miyamoto (Chem. Commun. 2017, 53, 9781) in 2017, the idea to render this aerobic process photocatalytic seemed too crazy for funding. Eventually the CNRS granted me a one-year postdoctoral fellowship in 2019 and I was lucky to hire a talented young doctor (Loïc Habert). We were then able to validate the concept and publish our results (Angew. Chem. Int. Ed. 2021, 60, 171) in about a year. Although it is still imperfect, devising an artificial oxidative transformation in which the only stoichiometric reagents are dioxygen and photons felt like a real step forward. We got great feedback from the community and, on a very personal level, I would probably not be answering these questions without this study and Loïc’s hard work.

Mirette Freude
A Selenide Catalyst for the Activation of Alkenes through Se···π Bonding

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Professor Yao Wang’s research group at Shandong University (P. R. of China) focuses on the development of innovative catalytic processes mediated by non-classical weak interactions. “We have the ambition to expand the boundaries of supramolecular catalysis,” said Professor Wang, adding: “Catalysis with weak interactions provides a fundamental platform to carry out chemical reactions; however, for this particular catalysis discipline, the use of heteroatom-participating reactants was required since the donation of electrons from these heteroatoms is necessary to generate catalytic activity. Taking a step forward, we reckoned that the activation of hydrocarbons by weak interactions and harnessing the potential of this process in catalysis are unresolved problems faced by the scientific community.”

A typical case, as pointed out Professor Wang, is the activation of alkenes by weak interactions, which has long been considered as an unfavorable approach in organic synthesis, although alkenes have been thoroughly used as raw materials for a range of transformations. “Conventionally, the activation of alkenes has been achieved by action of transition metals or strong Lewis acids. It is generally considered that weak interactions with alkenes make it difficult to generate sufficient reactivity to drive chemical reactions. Furthermore, it appears less likely that a weak interaction with an alkene substrate could give a unique reactivity that is beyond what can be achieved with a metal or a strong Lewis acid,” explained Professor Wang. He continued: “Perhaps owing to these viewpoints, e.g. the lack of reactivity and the perceived lack of urgency to pursue this strategy, the exploration on the activation of alkenes by weak interactions is almost uncharted territory in supramolecular catalysis. Thus, we became interested in this topic and had a strong wish to discover unprecedented capabilities of weak interactions on alkene substrates.”

Divalent chalcogenides have been conventionally used as Lewis base catalysts via covalent catalysis. Recent research has shown that divalent chalcogenides could be used as chalcogen bonding catalysts to activate electron donors (Scheme 1). Before starting this project, Professor Wang’s team had extensively investigated the concept of chalcogen bonding catalysis, developing a class of efficient phosphonium chalcogenide catalysts, which have subsequently found applications in diverse reaction processes. “However, these catalysts showed no catalytic activity in the activation of alkenes, even using a stoichiometric amount of catalyst. We realized that the development of new catalysts was the key to success,” remarked Professor Wang. By using a rationally designed catalyst, the team was recently able to establish a Se···π bonding catalysis approach to the activation of alkenes (Scheme 2). For proof-of-concept studies, the authors investigated alkene cyclization reactions as well as ene-type reactions: the Se···π bonding catalysis approach enabled these reactions to take place smoothly, thus demonstrating the feasibility of this catalysis method.

While intramolecular enyne cyclizations have been extensively investigated by using a variety of transition metals such as gold, palladium, and rhodium for decades, transition-metal-catalyzed intermolecular enyne cyclizations are rare,” said Professor Wang, who continued: “Specifically, for intermolecular [3+2] enyne cyclizations, only one reaction promoted by Rh catalysis has been reported so far, and this reaction was achieved at an elevated temperature (80 °C). Our recent work showed that Se···π bonding interactions can
activate alkenes to enable intermolecular enyne cyclizations taking place at room temperature, while these reactions could be complete within few hours (Scheme 2).” Professor Wang believes that this Se···π bonding catalysis approach to intermolecular enyne cyclizations demonstrates that it is possible to shift from transition-metal-catalysis mode to weak-interaction catalysis for achieving activation of alkenes, and this can even result in an increase of efficiency. “This capability provides a distinctive platform to study alkene chemistry,” remarked Professor Wang.

To further demonstrate the potential of Se···π bonding catalysis, the controlled cross coupling of triple alkenes was studied next. According to Professor Wang, literature reports indicated that only two-component coupling of alkenes could take place, even using an optimized Lewis acid such as In(OTf)3 coupled with carrying out these reactions under harsh conditions (120 °C) (Scheme 3). “The inertness of this type of reaction is determined by the strength of the Lewis acid required for substrate activation, since the in situ generated carbanion would strongly coordinate to a Lewis acid to form a relatively inactive complex. The latter complex not only loses reactivity when involved in a next coupling reaction with the alkene, but it requires harsh reaction conditions to release the catalyst. Therefore, it is not surprising that the controlled cross coupling of triple alkenes remains a significantly unresolved problem in organic synthesis,” remarked Professor Wang. He continued: “However, weak interactions have distinct chemical properties in contrast to strong Lewis acids, thus providing an improved option to solve such problems, which are hard to tackle by conventional approaches.”

The authors showed that this Se···π bonding catalysis approach has indeed the potential to achieve the controlled cross coupling of triple alkenes. “To realize this transformation, a range of notable problems had to be resolved. The first issue was controlling the chemoselectivity in the initial coupling step, which potentially could proceed through three distinct reaction pathways involving hetero or homo coupling of two alkenes. Once the coupling reaction had occurred, the management of the reactivity of the transient intermediate arises as a new issue, since this catalyst-stabilized species must be reactive enough to engage in a further coupling reaction to avoid stopping at a bimolecular coupling stage. Next, the chemoselectivity issue was met again, this time regarding the candidate of the second coupling reaction. Finally, the reaction must precisely stop at a triple-alkene coupling stage to avoid alkene polymerization,” explained Professor Wang.
Professor Wang concluded: “This Se–π bonding catalysis approach tells an unprecedented story, e.g. that weak interactions can catalyze chemical reactions that strong Lewis acids cannot. This new capability will change some common notions, potentially opening up promising opportunities for catalysis. We anticipate that this novel catalysis approach would serve as a new platform to develop reactions involving various π-systems such as alkenes, alkynes and aromatics.”

About the authors

**Xinglong Yuan** received his BSc degree in chemistry from Liaocheng University (P. R. of China) in 2016. He obtained his Master’s degree in chemical engineering from Lanzhou University (P. R. of China) in 2019. He then moved to Shandong University (P. R. of China) and is currently pursuing his PhD in the School of Chemistry and Chemical Engineering under the supervision of Professor Yao Wang. His research interest is focused on chalcogen bonding catalysis.

**Yao Wang** is a professor in the School of Chemistry and Chemical Engineering at Shandong University (P. R. of China). He received his BSc degree from Lanzhou University (P. R. of China) in 2006 and his PhD from the same university in 2012. Then he carried out postdoctoral research with an Alexander von Humboldt fellowship at the Max Planck Institute of Molecular Physiology (Germany). In September 2015, he began his independent career as a professor at Shandong University. He received a Thieme Chemistry Journals Award in 2019, and the National Natural Science Fund for Excellent Young Scholars in 2020. His research interests are focused on the development of new methodologies in supramolecular catalysis and the application of these methods in materials chemistry.
