

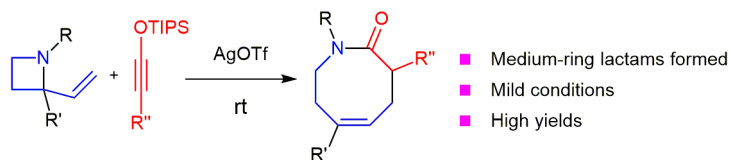
Synform

People, Trends and Views in Chemical Synthesis

2019/09

Synthesis of Eight-Membered Lactams through Formal [6+2] Cyclization of Siloxy Alkynes and Vinylazetidines

Highlighted article by A. Wu, Q. Feng, H. H. Y. Sung, I. D. Williams, J. Sun



Contact

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Dear Readers,

Today we had one of the two back-to-back University Open Days for prospective students and the campus was very busy with nearly 30,000 visitors – including guests, parents and guardians – on its premises. Although my involvement with undergraduate students is rather limited, I am trying to do my bit to help out and during one of the presentations aimed at helping students to decide whether they really want to study chemistry or else, I could not help but think of how I was at that age. Interestingly, out of about 50 prospective students, only a handful raised their hand without hesitation when asked whether they wanted to get a degree in chemistry. That kind of struck me, because I still clearly remember that it would have been unconceivable for me to study anything other than chemistry and my only goal in life at that time was to become a scientist. Thirty years on, I am still absolutely in love with chemistry and I believe I am doing the best job in the world, so I consider myself extremely lucky and privileged. I just feel a bit sorry for those students who did not raise their hands, because the passion for science – and chemistry in particular – has made my life so much better and full of satisfactions. I will always be grateful to CHEMISTRY!

And thanks a lot also to all the authors who shared their thoughts and information to make this new issue of SYNFORM possible, of course! The first article covers a novel formal [6+2] cyclization process leading to eight-membered lactams, developed by the groups of J. Sun and I.D. Williams (P.R. of China). The second contribution comes from the group of the 2018 Nobel Laureate in Chemistry, Professor Frances H. Arnold (USA), and deals with a new exciting chapter – recently published in *Science* – of the Directed Evolution of Enzymes saga that won her the top award. The third

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article covers the synthesis of tetrazole and dihydroisoquinoline compounds obtained by isocyanide-based multicomponent reactions developed by the group of X. Feng (P.R. of China). The issue is completed by a YCF interview with J. Zhao (P.R. of China) – an up-and-coming chemist who talks about his research interests at the frontier of organic synthesis and chemical biology.

Enjoy your reading!!!

Matteo Zanda

Contact

If you have any questions or wish to send feedback, please write to Matteo Zanda at: synform@outlook.com

Synthesis of Eight-Membered Lactams through Formal [6+2] Cyclization of Siloxy Alkynes and Vinylazetidines

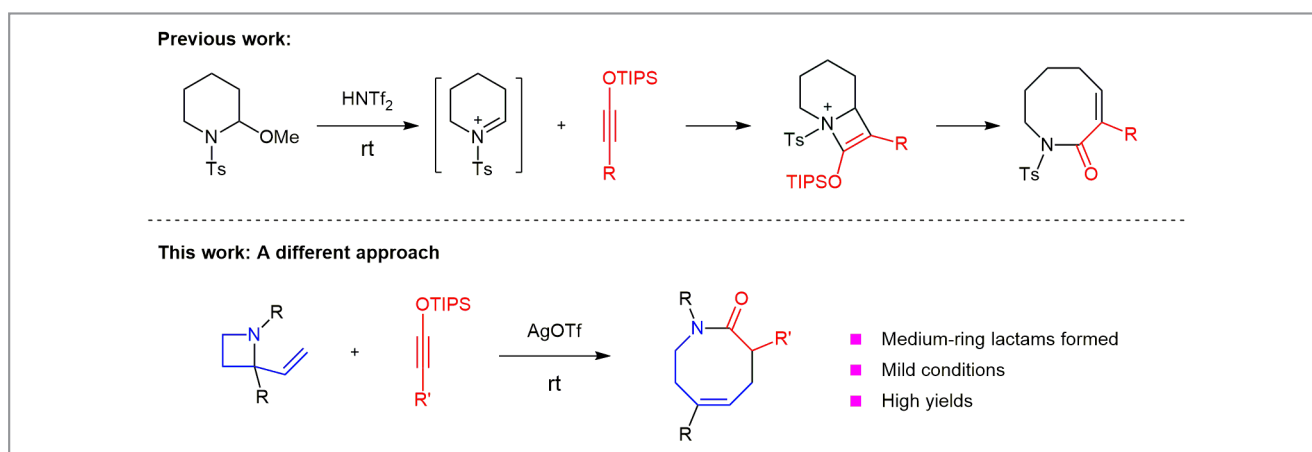
Angew. Chem. Int. Ed. **2019**, *58*, 6776–6780

Medium-sized cyclic compounds are those that typically include an 8- to 11-membered ring (7-membered rings are also sometimes regarded as medium-sized rings¹), and are widespread motifs in many kinds of natural products. They are also useful building blocks in the preparation of natural and bioactive compounds.² Due to ring strain and transannular interactions,^{1a} efficient assembly of these medium-sized compounds has remained a long-standing challenge in organic synthesis. Among the various existing approaches, the most general one is the intramolecular cyclization of an acyclic substrate. Specifically, intramolecular lactonization/lactamization from the corresponding seco-acids or amino acids and ring-closing metathesis from the corresponding dienes represent the two major strategies. However, intramolecular cyclization is known to be outcompeted by an intermolecular competitive dimerization process, since the latter does not suffer from ring strain or transannular interactions. While the desired lactone formation could be enhanced to some degree by employing a low concentration or slow addition of substrate, this improvement is not predictable or always satisfactory. Moreover, this comes at the cost of solvent convenience, operational simplicity, and scale of the synthesis.

In 2015, the laboratory of Professor Jianwei Sun at the Hong Kong University of Science and Technology (P. R. of China) reported a strategy to synthesize medium-sized lac-

tams from cyclic iminiums and siloxy alkynes in the presence of a Brønsted acid (Scheme 1).³ “In continuation of our success on this topic and in collaboration with the laboratory of Professor Ian D. Williams, we developed a new approach by further taking advantage of siloxy alkynes and strained rings (Scheme 1),” said Professor Sun. He continued: “Vinyl-substituted oxetanes or azetidines are reactive compounds due to the strained four-membered ring along with the vinyl group, which could serve as a potential six-atom unit to construct eight-membered-ring systems in a formal [6+2] cycloaddition reaction.”

With this hypothesis in mind, Dr. An Wu, a former graduate student in the Sun group, initially studied the reaction between vinyloxetanes and siloxy alkynes for producing eight-membered-ring lactones. However, in the presence of a variety of promoters, vinyl oxetanes were extremely easy to convert into six-membered rings. He then turned to using 1-benzyl-2-methyl-2-vinylazetidines and (hex-1-yn-1-yloxy) triisopropylsilane as the substrates and tried testing the reaction with different Lewis acids. Fortunately, the desired eight-membered lactam was observed in some cases. After optimizing the conditions, the product was eventually obtained in 89% isolated yield. “Vinylazetidines should be more stable than vinyloxetanes, which might minimize intramolecular decomposition of the former before the desired intermolecular



Scheme 1 Background and current approach

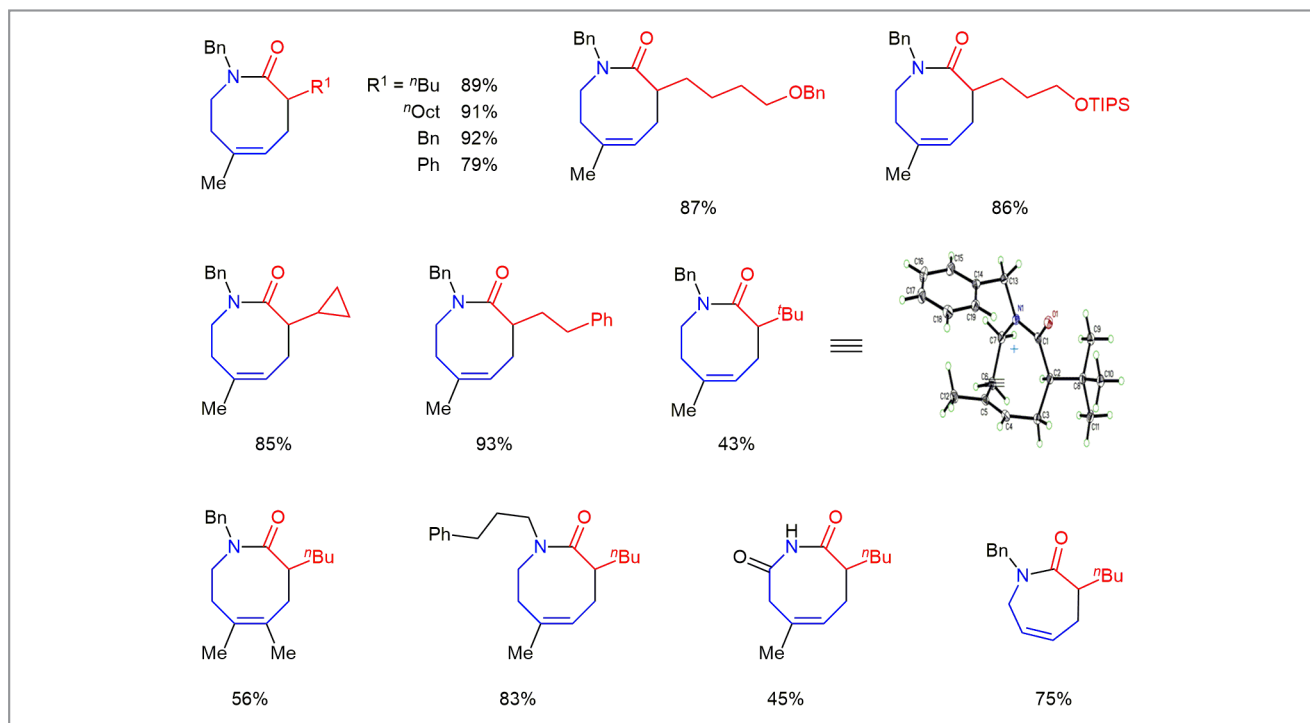


Figure 1 Selected examples

bond formation,” said co-author Professor Ian D. Williams. He continued: “Moreover, the nitrogen atom in azetidines can be more nucleophilic and thus benefit the cyclization step.”

With the optimized conditions in hand, the scope of the reaction was extended by Dr. Wu (Figure 1). Almost all the siloxy alkynes were able to react in this process to give good to excellent yields. A range of different vinylazetidines were also examined. The structure of the *tert*-butyl-substituted lactam was determined using X-ray crystallography by co-authors Dr. Herman H. Y. Sung and Professor Williams.

To explore the mechanism of the reaction, Dr. Wu carried out a range of control experiments, including chirality-transfer experiments and a deuterium-labeling test. After analyzing the results, the team proposed a pathway that includes a [3,3]-sigmatropic rearrangement from a ketene intermediate. Mr. Qiang Feng, another graduate student from the Sun group, helped synthesize the pure ketene to react with vinylazetidine in dichloromethane and he successfully obtained the desired lactam in 79% yield. This result strongly supported the proposed mechanism.

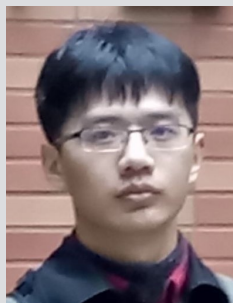
“Inspired by the possible involvement of a ketene intermediate in the mechanism, we were interested in applying other complementary conditions for ketene formation in this lactam formation,” said Prof. Sun. Tri(*p*-methoxyphenyl)phos-

phine was found to be a superior Lewis base catalyst for the same transformation. Moreover, acyl chlorides and *tert*-butyl ynoyl ethers were also demonstrated to be compatible ketene precursors to react with vinylazetidines.

“In conclusion, we have developed a new strategy for the efficient preparation of medium-ring lactams from vinylazetidines and siloxy alkynes,” said Prof. Sun, continuing: “Importantly, this reaction proceeded via an unexpected mechanism involving ketene as the key intermediate. The observation of chirality transfer provided important insights to revise the initially envisioned mechanism. This insight led to the development of further alternative Lewis base catalysis and catalyst-free conditions from other ketene precursors, thus providing complementary solutions to this important synthetic problem.”

Mattias Farnok

About the authors



A. Wu

An Wu received his B.S. degree in chemistry from Nanjing University (P. R. of China) in 2015. In 2018, he obtained his Ph.D. in organic chemistry from the Hong Kong University of Science and Technology (P. R. of China), working with Prof. Jianwei Sun. Currently, he is a postdoctoral fellow with Prof. Hisashi Yamamoto at Chubu University (Japan).



Q. Feng

Qiang Feng received his B.S. degree in pharmaceutical science from Huazhong University of Science and Technology (P. R. of China) in 2011. In 2015, he obtained a Master's degree in organic chemistry from Huaqiao University (P. R. of China) under the supervision of Prof. Qiuling Song. Currently, he is a postgraduate student in the laboratory of Prof. Jianwei Sun at the Hong Kong University of Science and Technology (P. R. of China).



Dr. H. H. Y. Sung

Herman H. Y. Sung obtained his B.S. in chemistry in 1997 and Ph.D. in 2001 working with Prof. Ian D. Williams, both from the Hong Kong University of Science and Technology (HKUST, P. R. of China). He then joined the Department of Chemistry, HKUST, as a crystallographer in 2002, after a short period of postdoctoral work. He is the co-author for the work related to the single-crystal XRD experiments.



Prof. I. D. Williams

Ian D. Williams obtained his BSc and PhD in inorganic chemistry from the University of Bristol (UK) in 1986 and was a postdoctoral fellow at MIT (USA) with Prof. Stephen J. Lippard. After stints at DuPont Central (USA), Oxford (UK), Waterloo (Canada) and Penn State (USA), he joined the Department of Chemistry, HKUST (P. R. of China) as a Lecturer in 1992 and is now Full Professor and the current department head. His research interests lie in the field of crystal engineering and chiral resolution.



Prof. J. Sun

Jianwei Sun graduated with B.S. and M.S. degrees in chemistry from Nanjing University (P. R. of China) in 2001 and 2004, respectively. In 2008, he obtained his Ph.D. in organic chemistry from the University of Chicago (USA), working with Professor Sergey A. Kozmin. He then worked as a postdoctoral fellow at MIT (USA) with Prof. Gregory C. Fu. He joined the Department of Chemistry, HKUST (P. R. of China) as an Assistant Professor in 2010 and was promoted to Full Professor in 2019. He is a recipient of the Asian Core Program Lectureship Award, Hong Kong Research Grants Council Early Career Award, and the Thieme Chemistry Journals Award.

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Site-Selective Enzymatic C–H Amidation for Synthesis of Diverse Lactams

Science **2019**, *364*, 575–578

A paramount challenge in carbon–hydrogen (C–H) functionalization is to control the site selectivity of the reaction. Current methods use directing groups and/or substrate control to pick out a particular C–H bond, which limits the breadth of potential substrates. Recently, an enzymatic strategy to address this challenge was reported by Professor Frances H. Arnold and co-workers Inha Cho (PhD student) and Dr. Zhi-Jun Jia (postdoctoral fellow) from the California Institute of Technology (USA). The authors used directed evolution to tune the site selectivity of C–H amidation catalyzed by heme enzymes. Professor Arnold explained: “Enzymes offer unparalleled selectivity in an array of transformations devised first by chemists and now established in natural metalloproteins. It’s a splendid opportunity to merge human chemical ingenuity with the power of evolution to make new, synthetically useful catalysts.”

The Arnold group’s study uses an iron-heme cytochrome ‘P411’ to perform a C–H amidation transformation not found

in nature. With directed evolution, the researchers fine-tuned the site selectivity of intramolecular amidation to deliver lactam products of various sizes (Figure 1A). Four different enzyme variants, LS_{sp3} , LS_{sp2} , LS_{β} and LS_{γ} , were evolved from a single parent to target specific C–H bonds at selected sites. “Notably, the enzymes can override reactivity trends due to C–H bond strength, inductive effects, steric accessibility and/or ring strain to deliver desired lactam products with broad substrate scope, excellent regioselectivity and enantioselectivity, and as many as one million total turnovers (TTN),” said Professor Arnold. Starting from a parent enzyme with low activity, six amino acid mutations in the enzyme’s active site boosted the TTN by more than 500-fold for β -lactam synthesis (Figure 1B). This transformation can be performed on preparative scale and some products can be recovered easily by filtration from the reaction mixture (Figure 1C).

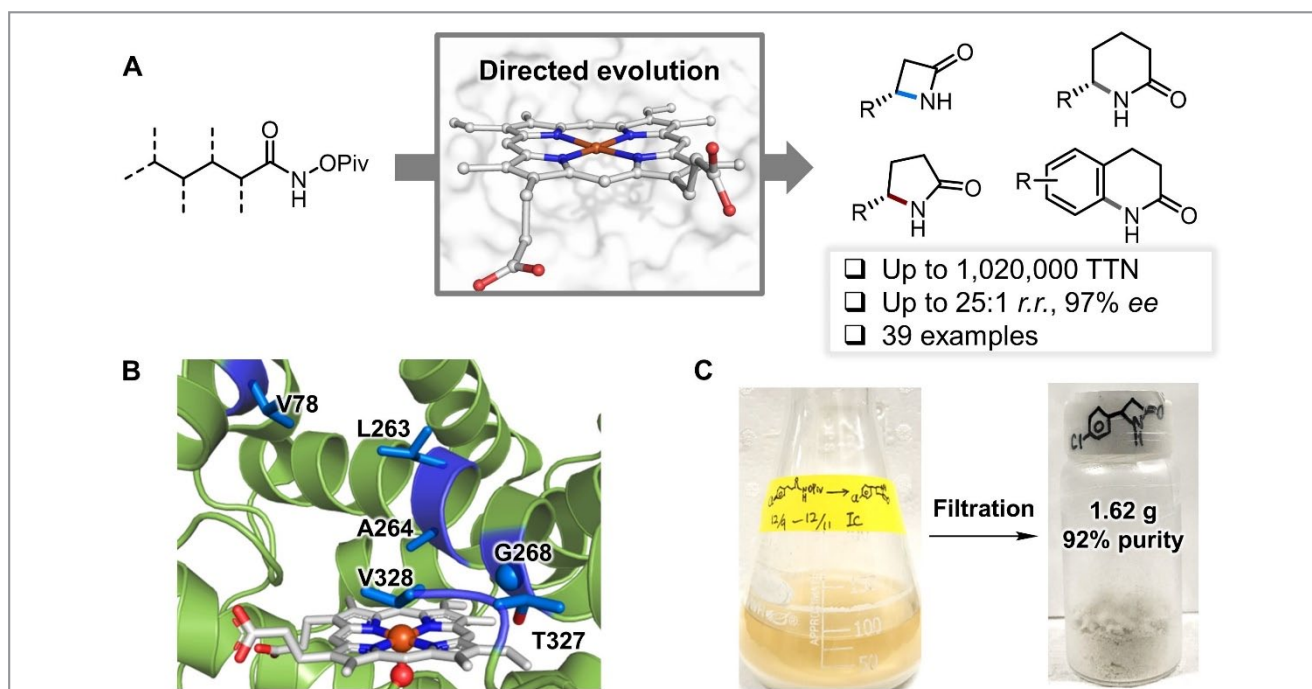


Figure 1 (A) General reaction scheme. (B) Crystal structure of a related variant (PDB ID: 5UCW), with mutated residues marked in blue (for LS_{sp3}). (C) Gram-scale synthesis.

The enzymes use carbonyl nitrenes – previously thought ineffective for C–H amidation due to their instability – for this reaction. The inspiration for evolving heme proteins to utilize carbonyl nitrenes came from earlier work. PhD student Inha Cho explained: “Previously we used *O*-pivaloylhydroxylamine as nitrene precursors for hemoprotein-catalyzed aminohydroxylation of olefins. The pivaloyl leaving group was highly effective for enhancing the yield and enantioselectivity of enzyme-catalyzed nitrene transfer. In 2017, Tsutsumi and co-workers (see the original paper for references) reported an intramolecular aziridination catalyzed by wild-type cytochrome P450s that use acyl-protected hydroxylamines as natural nitrene precursors in natural product biosynthesis. We reasoned that our P41s might accommodate acyl-protected hydroxamates to generate nitrene intermediates for C–H amidation.” Upon screening a collection of more than 200 enzymes, Cho found an engineered variant of P450_{BM3} that made a small amount of lactam product from a pivaloyl-protected hydroxamate precursor. She used this enzyme as a starting point for evolution of a ‘lactam synthase’.

“During mutagenesis and screening, we found some enzymes that delivered mixtures of different lactams from the same substrate, presumably due to non-optimal control of regioselectivity. We believed that these enzymes could be engineered to form lactams of specific sizes, exclusively,” explained Dr. Zhi-Jun Jia. They eventually evolved four lactam synthases, LS_{sp3}, LS_{sp2}, LS_β and LS_γ, which target different C–H bonds in the same substrate. LS_{sp3} and LS_{sp2} catalyze C(sp³)–H amidation and C(sp²)–H amidation, respectively, and enable efficient and selective β-lactam and δ-lactam synthesis (Figure 2A). The reactivity and selectivity profiles of LS_β and LS_γ on substrates with benzylic and homobenzylic C–H bonds (Figure 2B) demonstrate the tunability of enzyme-catalyzed C–H amidation. Finally, from a substrate with three sets of reactive C(sp³)–H bonds (Figure 2C), LS_β, LS_γ and LS_{sp3} afforded β-, γ- and δ-lactams, respectively.

The ‘lactam synthases’ were used to prepare a range of β-lactams (Figure 3). “Their unique structural features and *in vivo* reactivity make β-lactams versatile chemical building blocks as well as medicinal agents with antibacterial activity.

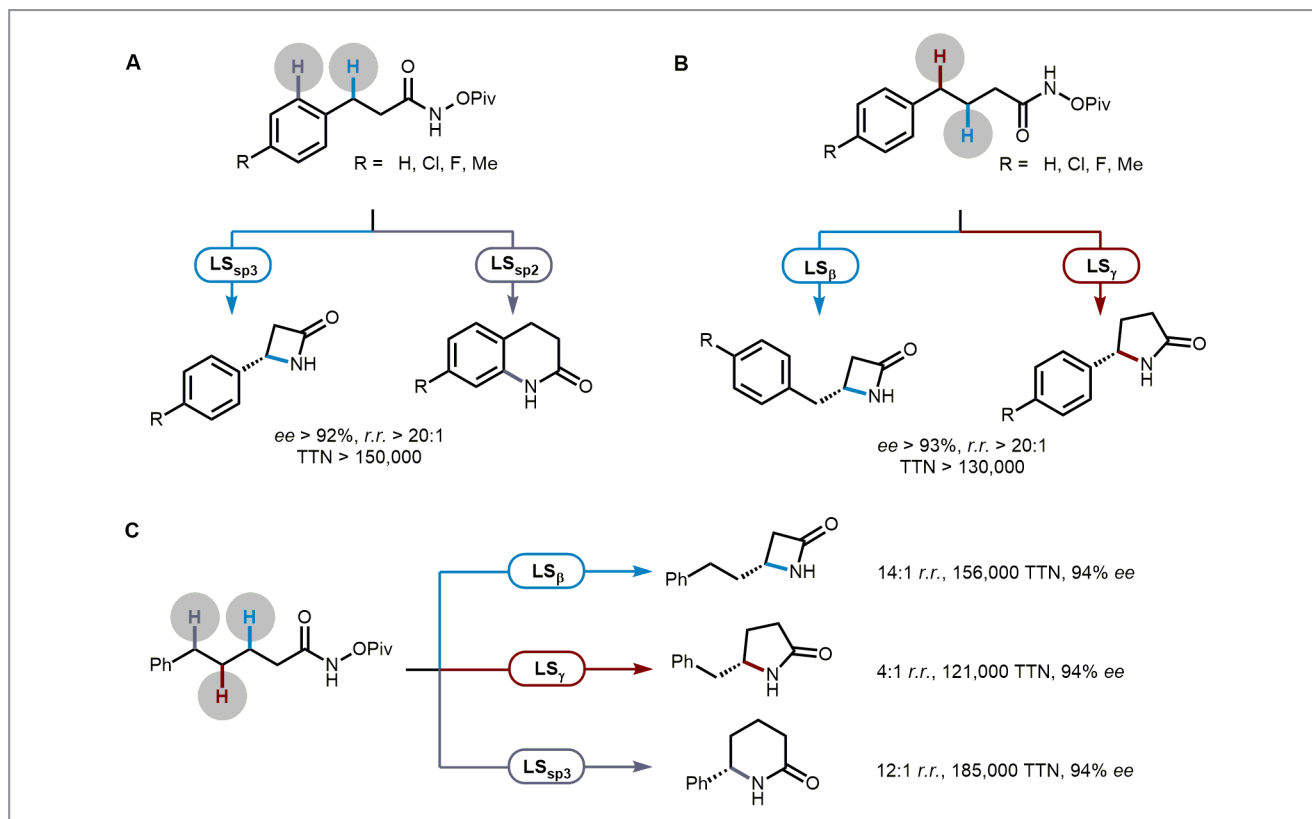


Figure 2 (A) Selectivity and scope of LS_{sp2} and LS_{sp3}-catalyzed intramolecular C–H amidation. (B) Selectivity and scope of LS_β and LS_γ. (C) Regiodivergent amidation of C(sp³)–H bonds catalyzed by LS_β, LS_γ, and LS_{sp3}.

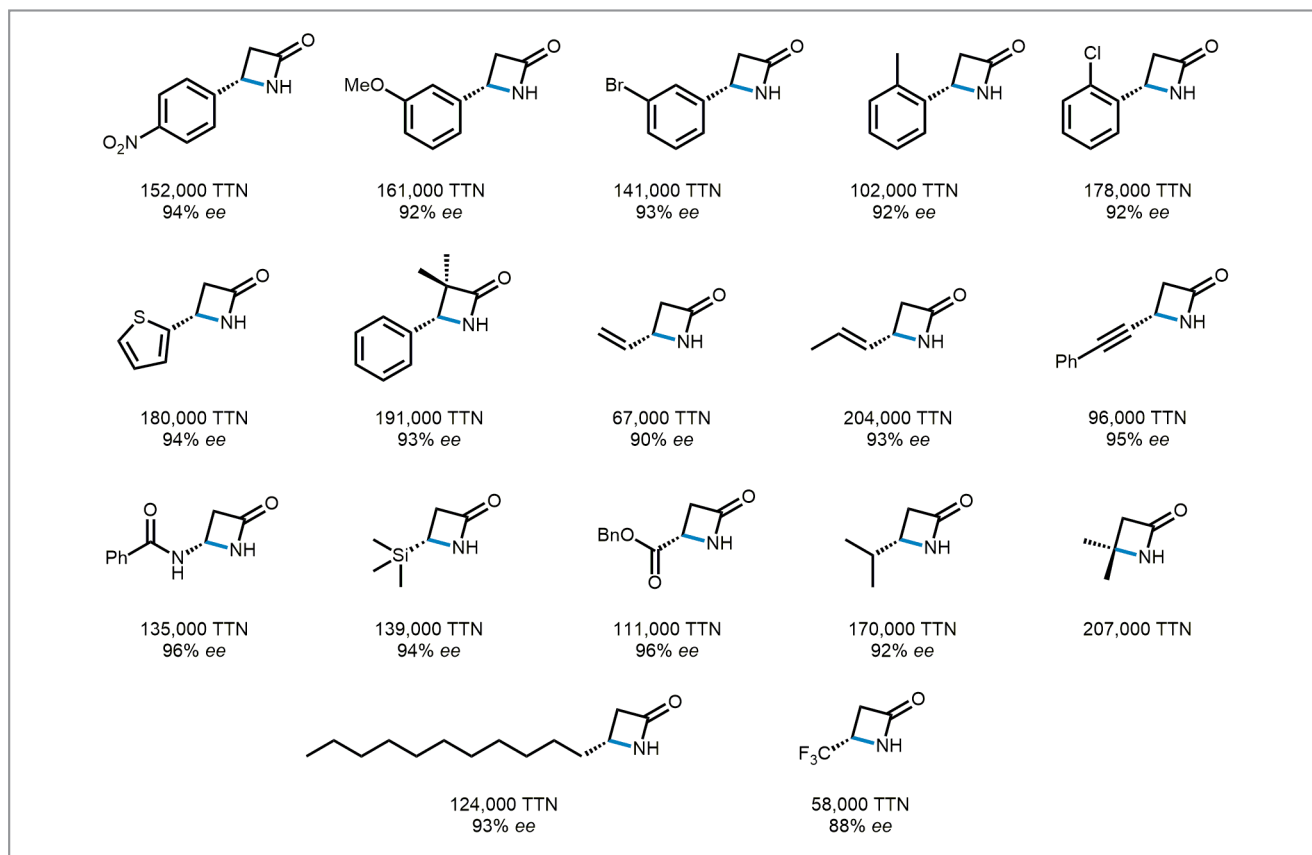


Figure 3 Range of β -lactam products synthesized with this method.

Since the discovery of penicillin in 1929, extensive use of antibiotics has led to the emergence of antibiotic resistance and significantly limited future therapeutic options,” explained the authors of this study. “To feed new β -lactam antibiotics to the pipeline, a general synthetic platform is desirable. We hope that this work could provide a modular, sustainable and scalable method to efficiently construct diverse libraries of chiral β -lactams for drug development. Additionally, the enzymes are easy to prepare in *E. coli*, and the enzymatic reaction is robust.” They concluded: “We hope that chemists will be able to use enzymes for synthesis in the same way we use small-molecule catalysts today.”

Professor David O’Hagan from St. Andrews University (UK), who is an expert on the use of enzymes in organic synthesis, commented: “This report in *Science* is particularly exciting as the enzyme is induced to generate nitrenes, intermediates we rarely associate with enzymology due to their high reactivity, and then various reaction modes are channeled by evolving and selecting for different outcomes. Direct methods to form C–N bonds have had a major impact in modern organic and

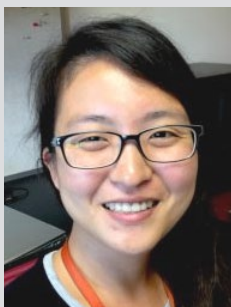
medicinal chemistry, so engineering this group of biocatalysts is particularly impressive and raises the bar. It shows that protein engineering has the power to harness catalysts for any reaction we are prepared to focus on, even those we would not normally associate with enzymes.”

Matthew Fenske

About the authors

*Prof. F. H. Arnold*

Frances H. Arnold earned a Bachelor's degree in mechanical and aerospace engineering from Princeton University (USA) and a doctorate in chemical engineering from the University of California at Berkeley (USA). She is the Linus Pauling Professor of Chemical Engineering, Bioengineering, and Biochemistry at the California Institute of Technology (USA). In 2018, she was awarded the Nobel Prize in Chemistry for her work on directed evolution of enzymes.

*I. Cho*

Inha Cho then joined Dr. Frances H. Arnold's group at the California Institute of Technology (USA) as a graduate student in biochemistry and molecular biophysics. Her main research focus is to engineer iron hemoproteins for abiological nitrene transfer chemistry.

*Dr. Z.-J. Jia*

Zhi-Jun Jia was born in Sichuan, P. R. of China. He received his B.S. in biology as well as marketing from Sichuan University (P. R. of China), and his M.S. degree in medicinal chemistry at the same university in 2012 under the guidance of Prof. Ying-Chun Chen. In 2016, he earned his Ph.D. in chemical biology under the supervision of Prof. Dr. Herbert Waldmann at the Max-Planck Institute for Molecular Physiology (Germany), working in biology-oriented synthesis. After one year of postdoctoral research in the same group, he joined Prof. Dr. Frances H. Arnold's lab as a DFG (Deutsche Forschungsgemeinschaft) postdoctoral fellow in 2018, where he is repurposing natural metalloenzymes for abiotic transformations through directed evolution.

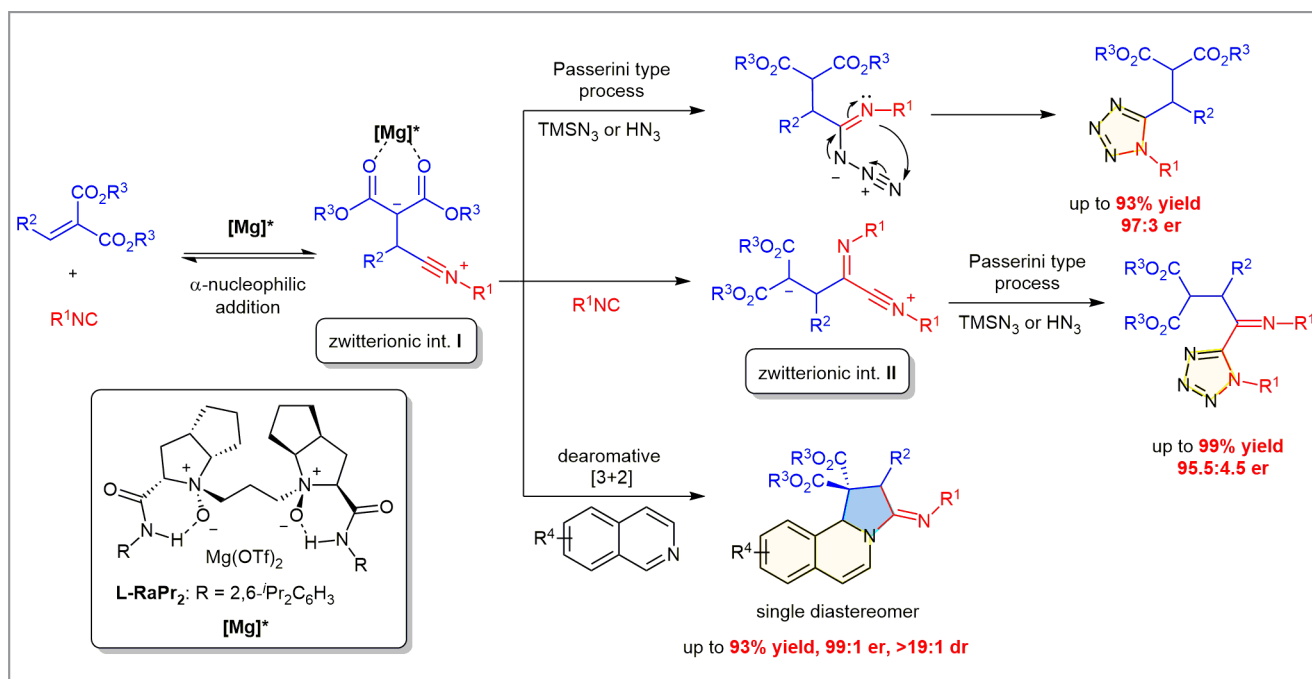
Asymmetric Synthesis of Tetrazole and Dihydroisoquinoline Derivatives by Isocyanide-Based Multicomponent Reactions

Nat. Commun. **2019**, *10*, 2116

Isocyanide-based multicomponent reactions (IMCRs), which enable the diversity- and complexity-oriented synthesis of collections of compounds taking advantage of the unique reactivity of the isocyanide functionality, have attracted great interest in the past several decades. In particular, the Passerini and Ugi reactions, and their variants, provide facile and powerful methods for the rapid construction of α -acyloxy carboxamides and α -acetamido carboxamides, as well as many heterocycles. Professor Xiaoming Feng at Sichuan University (P. R. of China) pointed out that enantioselective versions of these types of reactions, which are seemingly simple and yet challenging, have been recently achieved by several research groups after extensive studies.¹ “Mechanistically, the stereochemistry-determining step involved in Passerini and Ugi reactions is a nucleophilic addition of isocyanides to C=X bonds (X = O, or NR’). Based on this working hypothesis, it is reasonable to postulate that a similar zwitterionic intermediate could be readily generated through the enantioselective

addition of simple isocyanides to a C=C bond and subsequently could be trapped by an intra- or intermolecular nucleophile to afford cyclic or acyclic chiral compounds (Scheme 1),” explained Professor Feng, who added: “Moreover, the nucleophilic addition of isocyanides to C=X or C=C bonds results in the generation of zwitterionic intermediates I, which are potentially used as 1,3-dipoles in cycloaddition reactions. To the best of our knowledge, only sporadic racemic syntheses were reported, and asymmetric IMCRs triggered by the addition of simple isocyanides to a C=C bond remain elusive.”

A chiral C₂-symmetric N,N'-dioxide-based Lewis acid catalyst, designed and developed by the group of Professor Feng, exhibited excellent efficiency and selectivity in a number of organic transformations.² Professor Feng remarked: “Based on our previous work regarding functionalized isocyanides, Qian Xiong, a first-year graduate student in my group, approached this challenge. Initially, the reaction of dimethyl 2-(cyclohexylmethylene) malonate, 2-naphthyl isocyanide and TMSN₃



was conducted in the presence of chiral *N,N'*-dioxide–metal complex. Surprisingly, the central metal played a vital role and only $\text{Mg}(\text{OTf})_2$ afforded the desired product. At the same time, tetrazoles arising from a four-component reaction were isolated as the major products. How to control the chemoselectivity of this reaction was the next objective. As I often say, organic transformations are easy and the key to them is whether you can find a proper point (conditions) to work!” Professor Feng revealed that it took Qian Xiong several months to find this point. Eventually, with an excess amount of metal salt ($\text{Mg}^{\text{II}}/\text{L-RaPr}_2 = 1.4:1.0$) and at 30 °C, the process afforded the four-component tetrazole as the only product. “Comparatively lower temperature and an excessive amount of ligand ($\text{Mg}^{\text{II}}/\text{L-RaPr}_2 = 1.0:1.5$) is of benefit to the three-component pathway,” said Professor Feng.

Another important issue to be elucidated concerned the exact structure of the four-component product. Initially, the authors thought a mixture of diastereomers of four-component products was formed in the process, based on primary analysis of ^1H NMR spectra. “However, several phenomena suggested that this hypothesis may have not been correct, for example the fact that only two peaks were clearly identifiable by CSP-HPLC analysis of this hypothetical diastereomeric mixture,” explained Professor Feng. He continued: “Furthermore, the diastereomeric ratio of the four-component reaction products did not change after recrystallization. These were among the observations that suggested to us that there might instead be an equilibrium between these two compounds. Therefore, variable-temperature and solvent NMR studies, as well as careful analysis of 2D NMR, were carried out and the outcomes obtained collectively supported the conclusion that rotamers existed in our system.” The utility of the current synthetic strategy was further highlighted by using the key zwitterionic intermediate **1** as a 1,3-dipole in the first example of enantioselective dearomative [3+2] annulation reaction of isoquinolines. Chiral fused polycyclic 1,2-dihydroisoquinoline-based amidine derivatives were obtained with good to excellent results. “Although isoquinoline is the only substrate to participate in the reaction so far, we believe that other substrates may also be capable of capturing such active intermediates to construct important chiral molecules,” said Professor Feng confidently. As Prof. Michael P. Doyle (University of Texas at San Antonio, USA) commented: “This manuscript has used the authors’ well-known catalysts, the increasingly common concept of multicomponent reactions, and mildly reactive and easily handled materials to formulate complex chemical processes that are intrinsically dependent on the alkylidene malonate, the isocyanide, and the catalyst as the foundation for new chemical syntheses. The feature of this manuscript that is

most significant is the potential of the isocyanide–alkylidene adduct for transformations beyond those reported in this manuscript, and with the discovery that the magnesium(II)–*N,N'*-dioxide ligand is appropriate for high enantiocontrol, this manuscript can be expected to stimulate further research in the area. I can envision successful outcomes from reactions with indole, with diazo compounds, including cycloaddition reactions, and, perhaps, even with vinyl ether.”

Professor Feng concluded: “All in all, the attractive features of IMCRs along with the unique reactivity of the isocyanide functionality will offer huge potential in discovering new, concise and efficient methods for the synthesis of highly valuable chiral compounds. We hope that the current research can stimulate other researchers to join us in exploring the underdeveloped area together.”

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About the authors



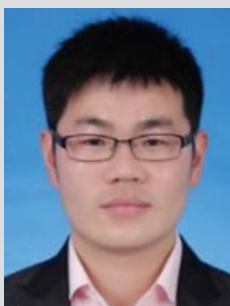
Q. Xiong

Qian Xiong received his BS from Sichuan University (P. R. of China) in 2016. He is currently a PhD student in the College of Chemistry, Sichuan University, under the supervision of Prof. Xiaoming Feng. His focus is on asymmetric isocyanide-based multi-component reactions.



Prof. X. Liu

Xiaohua Liu received her BS (2000) from Hubei Normal University (P. R. of China) and her MS (2003) and PhD (2006) from Sichuan University (P. R. of China). She joined the faculty of Prof. Feng's group at Sichuan University where she was appointed a Professor in 2010. Her current research interests include the asymmetric catalysis of chiral guanidines and organic synthesis.



Dr. S. Dong

Shunxi Dong received his BS (2008) and PhD (2013) from Sichuan University (P. R. of China). He joined RWTH Aachen University (Germany) as a Humboldt postdoctoral fellow with Prof. Carsten Bolm in 2013. After postdoctoral studies (2016–2017) at the University of Münster (Germany) with Prof. Gerhard Erker, he joined the faculty of Prof. Feng's group at Sichuan University. His interests include the design of chiral catalysts and their utility in new asymmetric transformations.



Prof. X. Feng

Xiaoming Feng received his BS (1985) and MS (1988) from Lanzhou University (P. R. of China). Then he worked at Southwest Normal University (P. R. of China, 1988–1993) and became an Associate Professor in 1991. In 1996, he received his PhD from the Institute of Chemistry, Chinese Academy of Sciences (CAS) under the supervision of Prof. Zhitang Huang and Prof. Yaozhong Jiang. He went to the Chengdu Institute of Organic Chemistry, CAS (P. R. of China, 1996–2000) and was appointed a Professor in 1997. He did postdoctoral research at Colorado State University (USA, 1998–1999) with Prof. Yian Shi. In 2000, he moved to Sichuan University (P. R. of China). He was selected as an Academician of the Chinese Academy of Sciences in 2013. He focuses on the design of chiral catalysts, the development of new synthetic methods and the synthesis of bioactive compounds.



Y. Chen

Yushuang Chen received her BS from Sichuan University (P. R. of China) in 2015. Now, she is a PhD student in the College of Chemistry, Sichuan University, under the supervision of Prof. Xiaoming Feng. Her research interests focus on asymmetric reactions involving bimetallic relay catalysis.

Young Career Focus: Dr. Junfeng Zhao (Jiangxi Normal University, P. R. of China)

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. Junfeng Zhao (Jiangxi Normal University, P. R. of China).

Biographical Sketch



Dr. J. Zhao

Junfeng Zhao obtained his Bachelor's degree and M.Sc. degree from Beijing Normal University (P. R. of China, 2001) and Central China Normal University (P. R. of China, 2005, with Professor Mingwu Ding), respectively. He then pursued his PhD studies with Professor Liuzhu Gong at Chengdu Institute of Organic Chemistry, CAS (P. R. of China) for one year before moving to Singapore, where he received his PhD in 2010 under the guidance of Professor Teckpeng Loh at Nanyang Technological University. After postdoctoral research at Nanyang Technological University, University of Bonn (Germany) and University of Münster (Germany) from 2010 to 2013, with Professor Chuanfa Liu, Professor Michael Famulok and Professor Armido Studer, respectively, he moved to The University of Hong Kong (P. R. of China), where he worked as a research assistant professor in Professor Dan Yang's group. In 2014 he started his independent career at Jiangxi Normal University (P. R. of China) as a full professor. He received awards including the Chinese Government Award for Outstanding Self-financed Students Abroad (2009), the research fellowship from the Alexander von Humboldt Foundation (2010), the Reaxys PhD Prize Finalist (2011), the Thieme Chemistry Journals Award (2018), and the Distinguished Lectureship Award of The Chemical Society of Japan (2019). His research interests include the development of novel synthetic methodologies and chemical biology of peptides and proteins.

INTERVIEW

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

Dr. J. Zhao The research interest of my group focuses on scientific problems at the interface between chemistry and biology. In particular, we focus on the development of novel synthetic methodologies for chemical synthesis and modification of peptides, proteins and complex polycyclic compounds with important biological activities.

SYNFORM *When did you get interested in synthesis?*

Dr. J. Zhao I became interested in synthesis when I started to study organic chemistry as a sophomore. I was fascinated by the magic ability of organic synthesis to offer new compounds and new reactions just by tuning the reaction conditions or employing different catalysts. I am always curious about any unexpected experimental result because it provides opportunities for discovering new reactions.

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

Dr. J. Zhao As far as I am concerned, organic synthesis is a science not only in itself but also an important tool for other science fields. It plays a central role in drug discovery, materials science, polymer science, chemical biology and other science fields related to chemistry because it can offer various compounds with special properties as well as novel methods to solve the problems of chemical biology and materials science.

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

Dr. J. Zhao Projects in my group are designed to expose the students to the frontiers of modern organic synthesis and chemical biology, in particular the chemical synthesis and precise modification of peptides and proteins. Although most of the peptides and proteins could be prepared by employing recombinant expression technology, chemical synthesis offers advantages of introducing non-natural amino acids and other post-translational modifications in a flexible way. As a consequence, a broad range of synthetic methods have been developed for amide bond formation, the fundamental chemistry of peptide and protein synthesis, over the last century. Despite this, 'amide formation avoiding poor atom economy reagents' is still one of the top challenges for organic chemistry.¹ The situation is more serious for solid-phase peptide synthesis (SPPS) because its heterogeneous reaction conditions always require a large excess of coupling reagents, additives and N-protected amino acids to guarantee a satisfactory coupling yield. Peptide chemical synthesis has witnessed a renaissance since the beginning of the 21st century because of the discovery of therapeutic peptides and potent peptide natural products. However, the chemical synthesis of large peptides and proteins, which relies on SPPS and peptide segment condensation still remains as a formidable challenge. There are several ligation strategies including native chemical ligation,² serine/threonine ligation,³ α -ketoacid-hydroxyamine ligation⁴ and enzyme-catalyzed ligation⁵ that have been developed to join two peptide segments via a native peptide bond to offer large peptides. However, each method has its own intrinsic limitations. Thus, novel orthogonal reactions to join two unprotected peptide segments via a native peptide bond are still highly in demand. We focus on novel amide bond formation

strategies as well as ligation strategies by taking advantage of the new methods, new reagents and new reactions developed by organic chemists. My dream is to develop a kind of catalyst that can act like enzymes to facilitate the peptide bond formation by employing unprotected amino acids as the building blocks.

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

Dr. J. Zhao My most important scientific achievement to date is that we disclosed that ynamide can be used as a kind of novel coupling reagent.⁶ The notorious racemization issue associated with the activation of carboxylic acids containing an α -chiral center can be avoided completely by employing ynamide coupling reagent. Thus, the ynamide coupling reagents not only work well for simple amides but also can be used for peptide bond formation. Ynamide-mediated amide bond formation involves two-step reactions, the hydroacyloxylation of ynamide to offer an active ester and the subsequent aminolysis of such active ester. We also accomplished the ynamide-mediated thiopeptide synthesis by taking advantage of the selective hydrothioacyloxylation of ynamide with monothioamino acids to furnish α -thioacyloxyenamides as the major product, which proved to be effective thioacylating reagents to offer thioamides in quantitative yield upon treatment with the second amino ester.⁷ Similar to the formation of canonical peptide bond, no racemization was observed in either the formation or the aminolysis of the α -thioacyloxyenamides. The modular nature of this racemization/epimerization-free strategy enables us to site-specifically incorporate a thioamide bond to a peptide backbone in both solution and solid phase. In addition, ynamide coupling reagents proved to be effective for peptide segment conden-

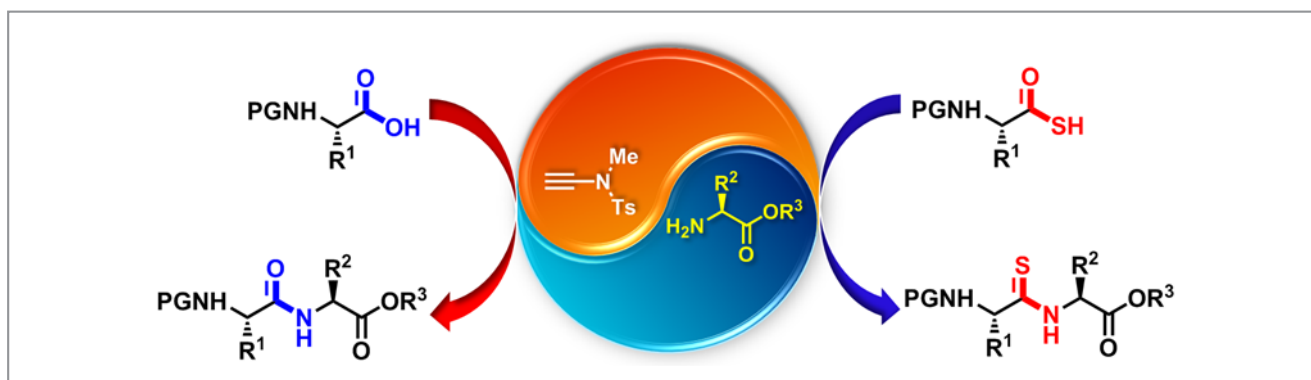


Figure 1 Ynamide-mediated peptide and thiopeptide synthesis

sation and peptide cyclization, intermolecular esterification and macrolactonization. These results demonstrated that the ynamide coupling reagent is a promising general coupling reagent for both amide and ester bond formation. It is foreseeable that the ynamide coupling reagent will find broad applications in both academia and industry. To prepare ynamide coupling reagents at a reasonable cost, we developed novel synthetic strategies with commercially available cheap chemicals as the starting materials.⁸ These methods paved the way to use ynamide coupling reagents as competitive powerful coupling reagents.



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