

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

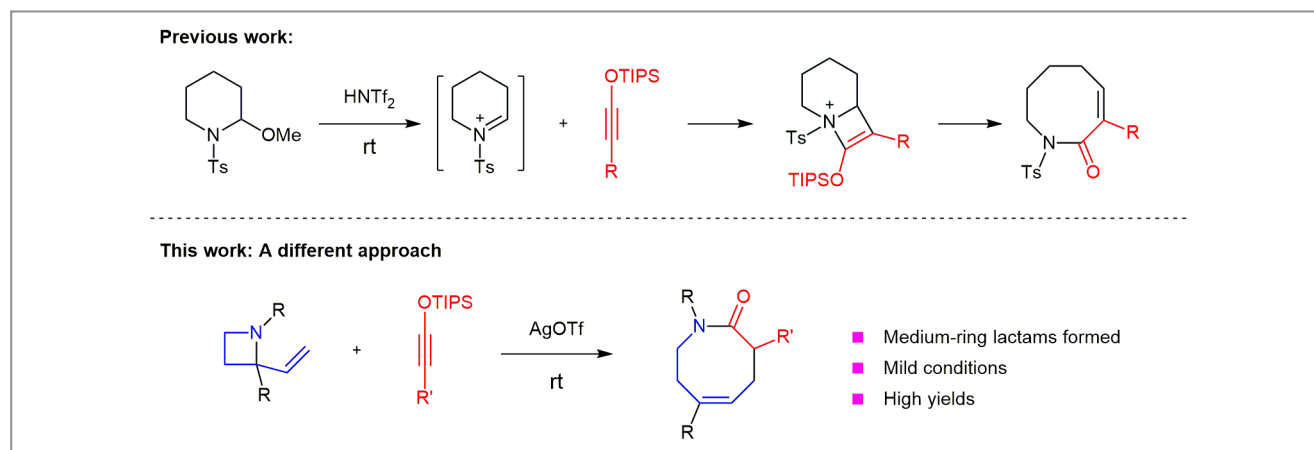
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Medium-sized cyclic compounds are those that typically include an 8- to 11-membered ring (7-membered rings are also sometimes regarded as medium-sized rings¹), and are widespread motifs in many kinds of natural products. They are also useful building 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-vinylazetidine 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

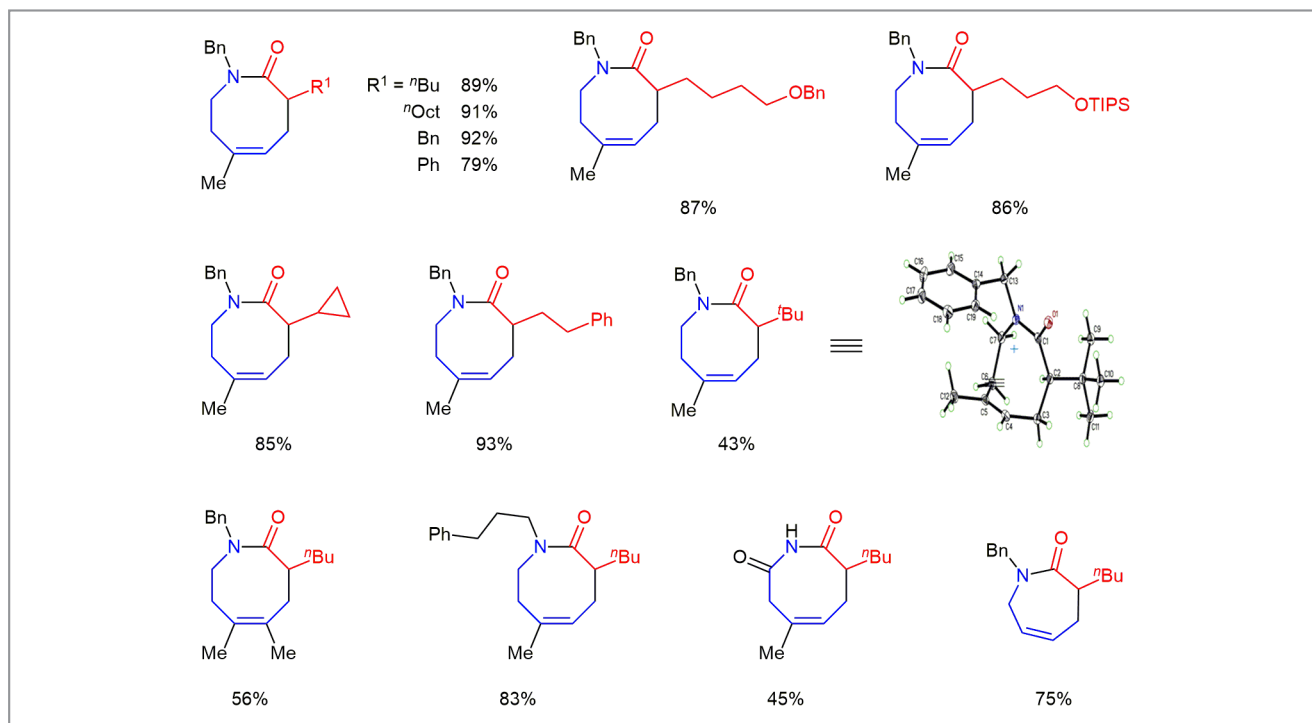


Figure 1 Selected examples

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.

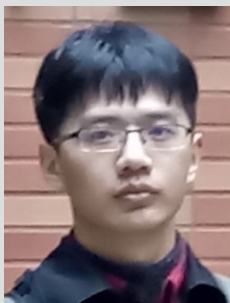
“Inspired by the possible involvement of a ketene intermediate in the mechanism, we were interested in applying other complementary conditions for ketene formation in this lactam formation,” said Prof. Sun. Tri(*p*-methoxyphenyl)phos-

phine was found to be a superior Lewis base catalyst for the same transformation. Moreover, acyl chlorides and *tert*-butyl ynol 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.”

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About the authors



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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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