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HETEROCYCLES IN FOCUS

Ring expansion strategy to access functionalized 2-oxazolines (microreview)

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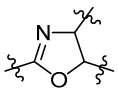

The development of innovative methods for the construction of heterocycles is an important topic in synthetic and medicinal chemistry. Ring expansion strategies, involving the cyclization of strained aza rings, have been well developed in the synthesis of diverse heterocyclic compounds. This microreview summarizes recent advances in the ring expansion reactions of aziridines, oxetanes, and azetidines to access a series of functionalized 2-oxazolines, which are versatile structural motifs in drugs and bioactive molecules.

Introduction

Oxazolines are among the most important units in medicinal chemistry, being widely found in biologically active compounds and pharmaceuticals.[1] They have also been used as the central structures in various other capacities, such as auxiliaries, ligands, and organocatalysts in asymmetric synthesis,[2] and as monomers for the preparation of polymers.[3] Considering the wide applications of oxazolines and their derivatives, remarkable progress has been achieved in the direct construction of these compounds.[4] One of the most attractive strategies for their synthesis is the ring expansion of strained rings.[5–11] Recently, ring expansion strategies have made a significant contributions to diverse fields ranging from synthetic organic chemistry to materials chemistry,[12] providing an efficient, green, and sustainable approach to the synthesis of valuable compounds. Of particular note is the cycloaddition of strained aza rings, a powerful strategy for the construction of nitrogen-containing heterocycles such as five- and six-membered azacycles, medium-sized rings, and macrocycles.[13] In this microreview, we provide an overview of recent reports on the catalytic and noncatalytic ring expansion strategy for the access to various synthetically valuable oxazolines. These achievements are categorized according to the size of the azacycle.

Leyan Liu is currently pursuing a BSc degree at the Shanghai University of Engineering Science in China. She is currently carrying out an innovative project (developing the novel cascade reactions to construct heterocycles) under the guidance of Full Professor Huangdi Feng.

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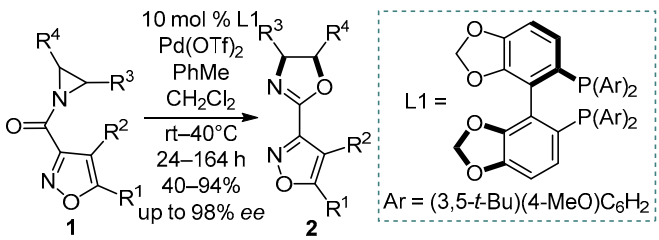
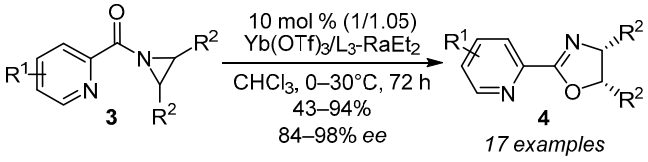
Synthesis of 2-oxazolines *via* aziridine ring expansion

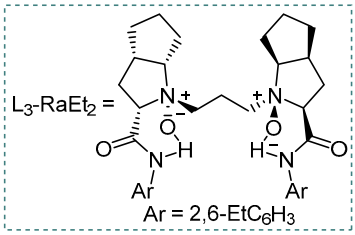
Aziridines are important building blocks in organic chemistry that readily undergo ring expansion reactions.[14] The rearrangement of *N*-acylaziridines, known as the Heine reaction, has been well developed for the synthesis of oxazolines under various catalytic systems.[15] In 2016, Morgan and coworkers reported the first enantioselective Heine reaction of *meso*-*N*-acylaziridines **1** for the synthesis of isoxazole-containing 2-oxazolines **2** using a cationic palladium(II)-diphosphine catalyst.[5] In this reaction, the 3-acylisoxazole was required as a novel directing group for the effective transformation of the substrates **1**. In addition, the R^1 and R^2 groups at the C-5 and C-4 positions of the isoxazole structure enabled tuning of the reaction yield and enantioselectivity.



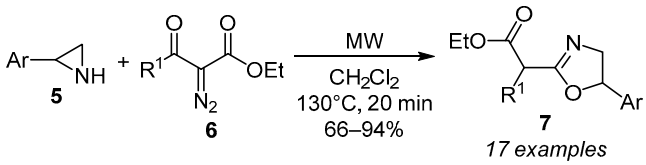
Synthesis of 2-oxazolines *via* aziridine ring expansion (continued)

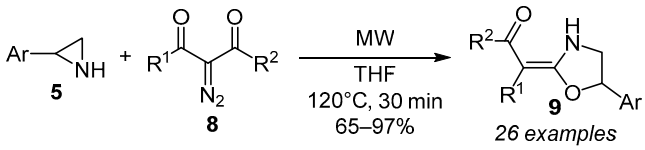
Chiral pyridine-oxazoline ligands have been widely employed in catalytic asymmetric reactions in recent years. In 2022, an asymmetric Heine reaction of *meso*-*N*-(2-picolinoyl)aziridines **3** was established by the group of Feng.[6] Using chiral ytterbium(III)-*N*,*N*'-dioxide complex as a catalyst, a variety of pyridine-containing oxazolines **4** were obtained in 43–94% yields with good enantioselectivities. Notably, the pyridine-oxazoline products also showed potential applications as both Lewis base catalysts and ligands in asymmetric reactions.





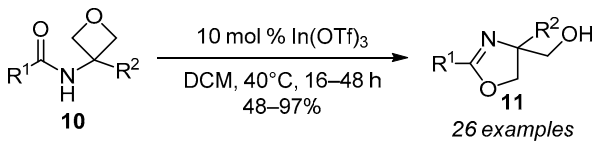
Ring expansion of aziridines by intermolecular cycloaddition serves to introduce new heterocycles. In 2022, Xu and coworkers disclosed an efficient strategy for the synthesis of oxazoline derivatives **7** from aziridines **5** and diazo esters **6**.[7a] This microwave-assisted reaction performed by ethoxycarbonylketene-induced electrophilic ring expansion of aziridines, afforded the target products in good to excellent yields under catalyst-free conditions. Meanwhile, the same group reported a similar work using 2-diazo-1,3-diketones **8** as the substrates and THF as a solvent, which produced 1,3-oxazolidine derivatives **9** in 65–97% yields.[7b]

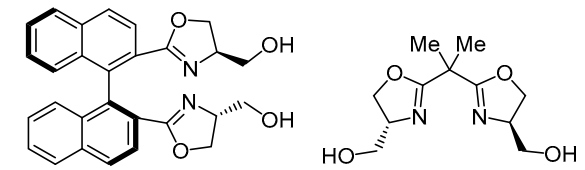


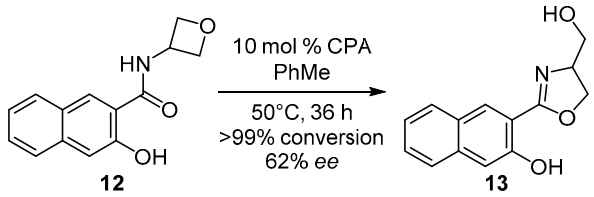


Synthesis of 2-oxazolines *via* oxetane ring expansion

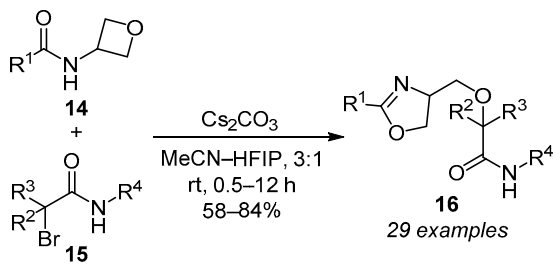
Oxetanes as synthetic building blocks have played an important role in organic synthesis. In 2019, an $In(OTf)_3$-catalyzed synthesis of oxazolines **11** from 3-amidooxetanes **10** was developed by the group of Sun,[8a] complementing the conventional oxazoline synthesis. A wide range of readily available 3-amidooxetanes could be subjected to a facile intramolecular cyclization to generate the corresponding 2-oxazolines in good to excellent yields. Additionally, this strategy has also been employed to rapidly synthesize several valuable oxazoline-based bidentate ligands, natural products, and antibacterial compounds. In 2021, the same group studied the desymmetrization reaction of naphthol-containing oxetane **12** by intramolecular cyclization using chiral phosphoric acid (CPA) as catalyst, resulting in the formation of chiral oxazoline **13**.[8b]





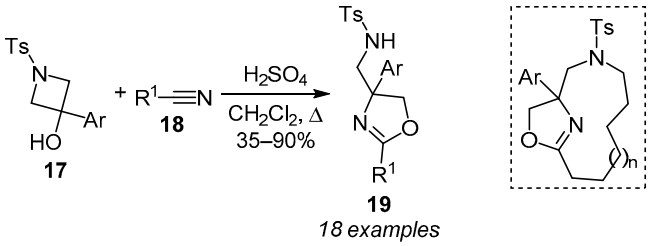


In the same year, Banerjee and coworkers described a very facile method for the synthesis of congested oxazoline amide ethers **16** from 3-amidooxetanes **14** and α-bromoamide **15** under transition-metal- and oxidant-free conditions.[9] In this reaction, the aza-oxyallyl cation *in situ* formed from compound **15**, which was used as a transient electrophilic activating and an alkylating agent, conducted the 3-amido oxetanes rearrangement to access the desired 2-oxazolines in mediate to good yields. In addition, this novel protocol had the characteristics of being mild and simple and exhibited a wide substrate scope.

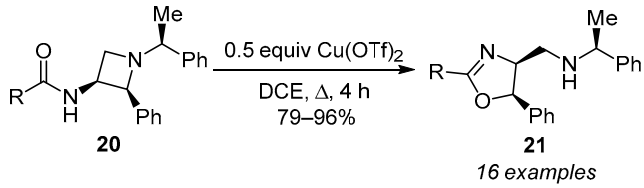


Synthesis of 2-oxazolines *via* azetidine ring expansion

As is well known, the ring expansion of azetidines has been reported for the construction of N-heterocycles.[16] In 2020, Baxendale and coworkers developed a novel condensation of 3-hydroxyazetidine **17** and nitriles **18** to give highly substituted 2-oxazolines **19** in moderate to excellent yields.[10] The reaction involved a cascade sequence initiated by a standard Ritter reaction followed by ring-opening rearrangement to give the target products. Further intramolecular cyclization of the derived products was also carried out, providing a new class of macrocycles.



Subsequently, in 2021, Zhang and coworkers reported an efficient method for the generation of 2-oxazolines **21** in excellent yields by the stereospecific isomerization of 3-amido-2-phenylazetidines **20**.[11] Using $Cu(OTf)_2$ as a promoter and DCE as a solvent, the desired products were obtained in a completely highly regio- and stereoselective isomerization manner.



Conclusions

Ring expansion strategies have been in constant evolution in the last few years. Their ability to increase molecular complexity has placed these methods in an important position among the tools for the synthesis of valuable heterocyclic compounds. As presented here, several ring expansion reactions of strained aza rings have been developed to prepare functionalized 2-oxazolines using catalytic and noncatalytic systems. We believe that the future development and application of ring expansion strategies will focus on the use of more environmentally friendly and sustainable reaction conditions.

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References

1. (a) Wiley, R. H.; Bennett, L. L. *Chem. Rev.* **1949**, *44*, 447. (b) Moraski, G. C.; Chang, M.; Villegas-Estrada, A.; Franzblau, S. G.; Mollmann, U.; Miller, M. J. *Eur. J. Med. Chem.* **2010**, *45*, 1703.
2. (a) Cannon, J. S.; Overman, L. E. *Acc. Chem. Res.* **2016**, *49*, 2220. (b) Chen, J.; Xi, T.; Lu, Z. *Org. Chem. Front.* **2018**, *5*, 247.
3. Zhou, M.; Qian, Y.; Xie, J.; Zhang, W.; Jiang, W.; Xiao, X.; Chen, S.; Dai, C.; Cong, Z.; Ji, Z.; Shao, N.; Liu, L.; Wu, Y.; Liu, R. *Angew. Chem., Int. Ed.* **2020**, *59*, 6412.
4. (a) Ibrahim, K. T.; Neetha, M.; Anilkumar, G. *Monatsh. Chem.* **2022**, *153*, 837. (b) Zhong, L.; Shi, R.; Huang, L.; Huang, J.; Feng, H. *Tetrahedron Lett.* **2024**, *134*, 154882. (c) Vchislo, N. V.; Verochkina, E. A.; Fedoseeva, V. G. *Chem. Heterocycl. Compd.* **2023**, *59*, 537.
5. Punk, M.; Merkley, C.; Kennedy, K.; Morgan, J. B. *ACS Catal.* **2016**, *6*, 4694.
6. Li, Y.; Li, W.-Y.; Tang, X.; Liu, X.; Feng, X. *Org. Chem. Front.* **2022**, *9*, 1531.
7. (a) Lei, Y.; Xu, J. *Beilstein J. Org. Chem.* **2022**, *18*, 70. (b) Chen, X.; Huang, Z.; Xu, J. *Adv. Synth. Catal.* **2021**, *363*, 3098.
8. (a) Huang, H.; Yang, W.; Chen, Z.; Lai, Z.; Sun, J. *Chem. Sci.* **2019**, *10*, 9586. (b) Zhang, R.; Ge, S.; Sun, J. *J. Am. Chem. Soc.* **2021**, *143*, 12445.
9. Taily, I. M.; Saha, D.; Banerjee, P. *J. Org. Chem.* **2022**, *87*, 2155.
10. Ruggeri, M.; Dombrowski, A. W.; Djuric, S. W.; Baxendale, I. R. *J. Org. Chem.* **2020**, *85*, 7276.
11. Zhou, X.; Mao, B.; Zhang, Z. *Molecules* **2021**, *26*, 857.
12. (a) Yang, Z. Z.; Zalessky, I.; Epton, R. G.; Whitwood, A. C.; Lynam, J. M.; Unsworth, W. P. *Angew. Chem., Int. Ed.* **2023**, *62*, e202217178. (b) Zhang, T.; Feng, H. *Chem. Rec.* **2024**, *24*, e202400024. (c) Sun, F.; Van der Eycken, E. V.; Feng, H. *Adv. Synth. Catal.* **2021**, *363*, 5168.
13. (a) Li, R.; Li, B.; Zhang, H.; Ju, C.-W.; Qin, Y.; Xue, X.-S.; Zhao, D. *Nat. Chem.* **2021**, *13*, 1006. (b) Jung, J.-W.; Kim, S.-H.; Suh, Y.-G. *Asian J. Org. Chem.* **2017**, *6*, 1117. (c) Xu, X.; Zhong, L.; Feng, H.; Van der Eycken, E. V. *Chem. Rec.* **2023**, *23*, e202300101.
14. (a) Akhtar, R.; Naqvi, S. A. R.; Zahoor, A. F; Saleem, S. *Mol. Diversity* **2018**, *22*, 447. (b) Sabir, S.; Kumar, G.; Verma, V. P.; Jat, J. L. *ChemistrySelect* **2018**, *3*, 3702.
15. Martin, A.; Casto, K.; Morris, W.; Morgan, J. B. *Org. Lett.* **2011**, *13*, 5444.
16. (a) Mughal, H.; Szostak, M. *Org. Biomol. Chem.* **2021**, *19*, 3274. (b) Reidl, T. W.; Anderson, L. L. *Asian J. Org. Chem.* **2019**, *8*, 931.