Synthetic methodology

https://doi.org/10.1038/s44160-023-00455-8

Strained allenes for heterocycle difunctionalization

Courtney C. Roberts

Strained allenes in piperidines and tetrahydropyrans are used to generate highly-decorated heterocycles.

Strained cyclic intermediates, such as arynes, have been leveraged by synthetic chemists for decades to open up chemical space. This utility is a result of their potent reactivity caused by the strain contained in the cyclic component.[1,2] While arynes have proven an invaluable synthon, more recently, cyclic allenes have emerged as a compelling building block for constructing molecular complexity.[2,3] This emergence is, in part, due to the necessity of synthesizing saturated molecules for purposes such as drug development.[4] In particular, saturated heterocycles such as piperidine and tetrahydropyran are key components of pharmaceuticals.[5] Despite their prevalence, to date, there is a dearth of reports using cyclic allene intermediates to synthesize highly-functionalized piperidine and tetrahydropyran cores.

Now, writing in *Nature Synthesis*, Garg and co-workers demonstrate the facile synthesis of a precursor to an unsymmetrical azacyclic allene, as well as numerous functionalizations from this highly-reactive intermediate (Fig. 1).[6] This work is supported by computational studies showing that when a strategic tosyl protecting group is present on the nitrogen, an allenic resonance structure is favoured over a zwitterionic resonance structure which would generate an iminium and carbanion. This strained allene is primed to undergo a variety of difunctionalization reactions and sets up an interesting regioselectivity picture regarding which alkene in the allene will react.

First, a gram-scale synthesis of a strained precursor is developed that uses an epoxide in a silyl nucleophilic ring-opening reaction. The use of a common epoxide functional group enables many further derivatives to be generated from readily-available starting materials. Garg and co-workers demonstrate this ability by using the route to synthesize an unsymmetrical oxacyclic allene precursor.

With the precursor in hand, a mild fluoride activation is used to unmask the unsymmetrical azacyclic 2,3,4-allene. This allene can be coupled with a wide variety of coupling partners through cycloaddition reactions. The addition of cyclic 4-π components, such as furans and pyrroles, results in a variety of bridged cyclic enamine products that contain additional heteroatoms. Remarkably, these (4+2) cycloaddition reactions are generally very diastereo- and regioselective with an endo-selective reaction occurring at the distal alkene of the 3,4-position. In contrast, (2+2) cycloadditions give excellently regioselective reactions at the proximal 2,3-position, to generate fused cyclobutane products. Finally, (3+2) dipolar cycloadditions are showcased with a wide variety of dipolar reagents, giving fused bi- and tricyclic products. Interestingly, these (3+2) reactions are not regioselective and favour both products of reaction at the distal and proximal positions, setting up an interesting question about the mechanism of these cycloaddition reactions.

The oxacyclic allene also undergoes these cycloaddition reactions. Garg and co-workers report an exciting transition-metal-catalysed coupling reaction of the oxacyclic allene with a pyridyl coupling partner. This reaction hints at the realm of products that may be possible from the straightforward synthesis of these heterocyclic allenes. The reaction conditions are mild (30 °C) and are compatible with esters, sulfones, nitriles, halides and other functional groups.

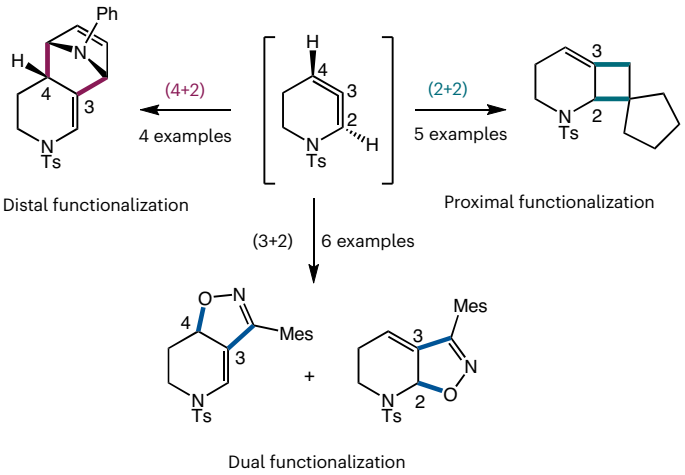

Fig. 1 | N-Heterocyclic allenes as key intermediates. A wide variety of difunctionalized products, including those resulting from (2+2), (3+2), and (4+2) cycloadditions, are reported. Ts, tosyl; Mes, mesityl.

The overall picture in terms of regioselectivity for reactions involving the azacyclic allene is high regioselectivity for the distal 3,4-alkene position in (4+2) reactions and for the proximal 2,3-alkene in (2+2) reactions, whereas the (3+2) reactions are typically unselective. This intriguing selectivity is investigated using mechanistic probes. When an inverse demand (4+2) substrate replaces a normal demand (4+2) substrate, finally reaction at the 2,3-alkene is observed in a (4+2) cycloaddition. This product indicates that the regioselectivity is governed by electronic matching of the substrates, with the 3,4-alkene being more electron poor while the 2,3-alkene is more electron rich owing to the proximal lone pair on nitrogen.

Alternatively, the thermal (2+2) reaction is likely to proceed through a diradical intermediate. This putative intermediate is interrogated through stereochemical considerations when using an isomerically pure 1,2 disubstituted styrene derivative. Finally, it is proposed the (3+2) cycloaddition reactions operate under competing concerted and stepwise radical mechanisms, which in turn yields both regioisomers because these reactions operate at similar rates. These multiple mechanistic pathways open up a wide range of potential coupling partners for future consideration. This is verified with the reaction of the unsymmetrical oxacyclic allene operating under the same regioselectivity rules.

The outlook for future work may include the development of models for how to alter regioselectivity to access other regioisomeric products. Moreover, it will be exciting to see if multicomponent difunctionalizations, other than annulations, can be developed using these now readily-available precursors. In addition, it is likely that these N-heterocyclic allenes will be used as key building blocks for the synthesis of natural products.

Courtney C. Roberts [1,2] ✉
[1]Department of Chemistry, University of Minnesota, Minneapolis, MN, USA. [2]Twitter / X: @cortnieroberts
✉e-mail: ccrob@umn.edu

Published online: 02 January 2024

References

1. Tadross, P. M. & Stoltz, B. M. *Chem. Rev.* **112**, 3550–3577 (2012).
2. Anthony, S. M., Wonilowicz, L. G., McVeigh, M. S. & Garg, N. K. *JACS Au* **1**, 897–912 (2021).
3. Spence, K. A., Meza, A. T. & Garg, N. K. *Chem Catal.* **2**, 1870–1879 (2022).
4. Vitaku, E., Smith, D. T. & Njardarson, J. T. *J. Med. Chem.* **57**, 10257–10274 (2014).
5. McGrath, N. A., Brichacek, M. & Njardarson, J. T. *J. Chem. Educ.* **87**, 1348–1349 (2010).
6. Kelleghan, A. V., Tena Meza, A. & Garg, N. K. *Nat. Synth*. https://doi.org/10.1038/s44160-023-00432-1 (2023).

Competing interests

The author declares no competing interests.