

Synthetic Applications of Transient Strained Cyclic Alkynes and Allenes

Reported by Seth Klaine

February 28th, 2023

INTRODUCTION

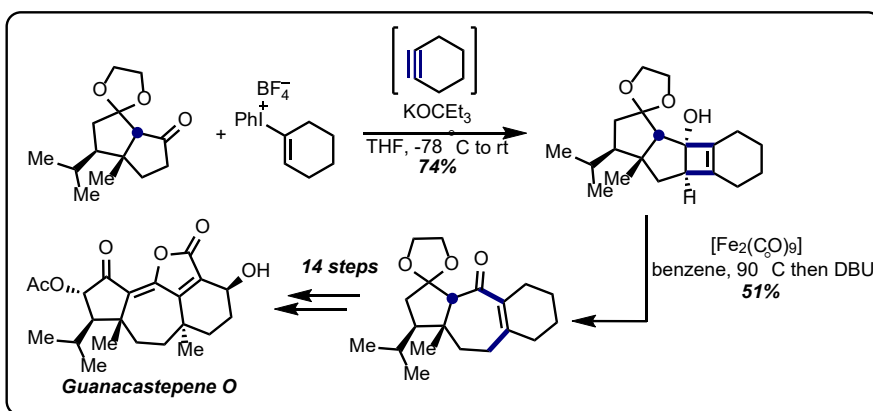
Lower-membered cyclic systems containing conventional linear moieties exhibit substantial ring strain as a result of their bent nature. Although these species are short-lived and exhibit exceptionally high strained energies, the synthetic community has recently learned how to tame these reactive intermediates in an array of various chemical transformations. During the 1960s, seminal works from J.D. Roberts and G. Wittig provided some of the first experimental evidence for the existence of cyclohexyne and 1,2-cyclohexadiene, respectively.¹ In the literature, cyclic alkyne and allene intermediates have been underutilized as synthetic building blocks due to misapprehensions concerning their reactivity and overall safety. However, the development of silyl triflate and other related precursors has allowed for exceptionally mild and practical reaction conditions to access these fleeting species. This lecture will discuss how these strained and unusual intermediates have been implemented in methods to synthesize complex, medically relevant scaffolds as well as natural products.

CYCLIC ALKYNES

The development of novel methods to rapidly access annulated *N*- and *O*-containing heterocycles from simple precursors is desirable in medicinal chemistry. In 2014, Danheiser and coworkers developed an efficient route to access 2,3-

piperidynes and showed a series of synthetically interesting cycloaddition trapping reactions.¹ In 2015 and 2016, Garg and colleagues disclosed syntheses to access 2,4-piperdyne and 3,4-oxacyclohexyne; with these intermediates in hand, the authors then showed an assortment

Scheme 1. Cycloinsertion in Total Synthesis of Guanacastepene O



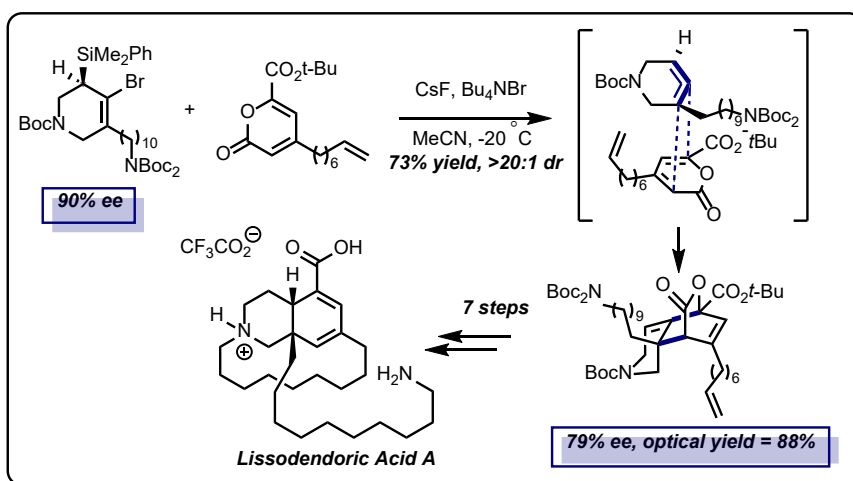
of functionalized heterocyclic scaffolds that can be obtained.¹ Carreira and Gampe disclosed a method for a direct cyclohexyne cycloinsertion into cyclic ketones to furnish fused, medium-sized rings.² The authors then applied this cycloinsertion reaction in the total synthesis of Guanacastepene O (Scheme 1).²

CYCLIC ALLENES

Over the last several decades, investigations involving small membered cyclic allene systems have been predominately occupied by theoretical studies of allene electronic structure and chirality.³ Garg and coworkers reported syntheses of silyl triflate precursors to access azacyclic allene species, and these intermediates were then subsequently trapped using cycloaddition reactions.¹ The authors showed how stereochemical information can be transmitted from an enantioenriched precursor to the cycloadducts, and DFT computational studies were also used to account for the experimentally observed selectivities. Later, Schreiber and colleagues implemented azacyclic allenes in strain-promoted cycloadditions in DNA-encoded library synthesis.⁴ In 2020, Garg and coworkers also reported intercepting transient racemic cyclic allene intermediates using an asymmetric nickel-catalyzed reaction. Absolute stereochemistry was controlled by two different mechanisms: kinetic resolution of the allene enantiomer and subsequent desymmetrization of a π -allylnickel complex intermediate.¹ The authors also included computational studies, probing the mechanism of stereochemical transmission. Inspired by their previous work on azacyclic allenes, Garg and colleagues recently reported the total synthesis of manzamine alkaloid lissodendoric acid A which involves the regioselective and stereospecific cycloaddition of a transient azacyclic allene to access the

[2.2.2]-bicyclic azadecalin core (Scheme 2).⁵ Cyclic alkynes and allenes are a valuable addition to the synthetic chemist's toolbox. The use of these species in the construction of complex molecular scaffolds and their potential application in biorthogonal chemistry warrants future investigations.

Scheme 2. Cycloaddition in Total Synthesis of Lissodendoric Acid A



REFERENCES

- (1) Garg, N. K. et al. *JACS Au* **2021**, *1*, 897–912.
- (2) Gampe, C. M.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2012**, *51*, 3766–3778.
- (3) Johnson, R. P. et al. *J. Org. Chem.* **2006**, *71*, 5708–5714.
- (4) Schreiber, S. L. et al. *J. Am. Chem. Soc.* **2020**, *142*, 7776–7782.
- (5) Garg, N. K. et al. *Science* **2023**, *379*, 261–265.

