

# Ring Construction via Annulation

Ruben Martinez

## Background and history: What's in a name?

Annulation has no official (IUPAC) definition until 1994!

### Michael Jung clears the haze around the term:

"Annulation, derived from the Latin word *annulatus* (ringed) means "the formation of rings". In organic chemistry this term is used to describe the process of building a ring onto a pre-existing system, cyclic or non-cyclic... This broad definition includes in a general sense many reactions that are not thought of as annulation reactions, such as Diels-Alder reactions, acid catalyzed polyolefinic cyclizations, photochemical, radical and thermal cyclizations."

*Tetrahedron* **1976**, 32, 3.

### Rick Danheiser's simplified definition:

"We define as annulations those ring-forming processes in which two molecular fragments are united with the formation of two new bonds."

*J. Am. Chem. Soc.* **1982**, 104, 7670.

### Dennis Curran backs Danheiser

"Although it is used very commonly by organic chemists, the word "annulation" has yet to find a standard spelling or meaning. An authoritative review recommends the spelling "annulation", not "annelation". The latter spelling is not listed in any of the dictionaries that we consulted. We subscribe to the definition of Danheiser that an annulation is a "ring-forming process in which two molecular fragments are united with the formation of two new bonds". A ring need not be appended to a preexisting ring to qualify as an annulation."

*J. Am. Chem. Soc.* **1989**, 111, 8873.

### Gary Molander adds clarity and wisdom

"The condensation of two acyclic units through creation of two bonds in a single process is by far the most efficient means of creating cyclic molecules. Mechanistically such conversions may take place in either a concerted manner (like the Diels-Alder cycloaddition reactions) or in a sequential mode that is characteristic of many [3 + 2] annulations for five-membered ring synthesis. From a synthetic point of view, either process is sufficient so long as regiochemistry and stereochemistry can be controlled."

*Acc. Chem. Res.* **1998**, 31, 603.

## Definitions (IUPAC Recommendations 1994)

### Annulation

A transformation involving fusion of a new ring to a molecule via two new bonds. Some authors use the term "annelation" for the fusion of an additional ring to an already existing one, and "annulation" for the formation of a ring from one or several acyclic precursors, but this distinction is not made generally.

### Annelation

Alternative, but less desirable term for annulation. The term is widely used in German and French language publications.

### Cycloaddition

A reaction in which two or more unsaturated molecules (or parts of the same molecule) combine with the formation of a cyclic adduct in which there is a net reduction of the bond multiplicity.

### Cyclization

Formation of a ring compound from a chain by formation of a new bond.

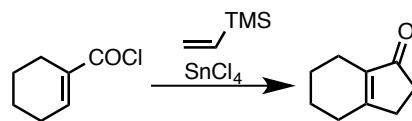
Glossary of terms used in physical organic chemistry  
*Pure Appl. Chem.* **1994**, 66, 1107.

### What to expect

The focus of this seminar will be methods for ring construction that can be used as a package (one-pot protocol) rather than a series of reactions ultimately leading to a cyclization.

## Annulation types and varieties

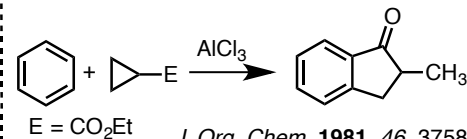
### Two Carbon Annulation



*J. Org. Chem.* **1980**, 45, 1046.

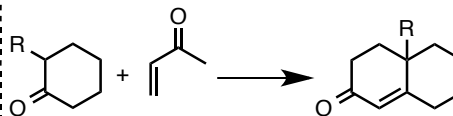
### Three Carbon Annulation

Review: *Synthesis* **1984**, 520.



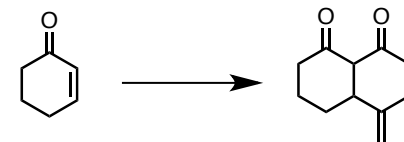
*J. Org. Chem.* **1981**, 46, 3758.

### Four Carbon Annulation (Robinson type)



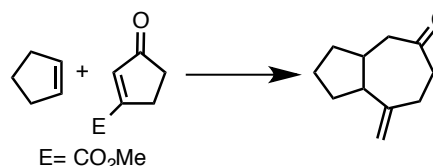
Review: *Tetrahedron* **1976**, 32, 3.

### Four Carbon Annulation (non-Robinson type)



*J. Org. Chem.* **1984**, 49, 4567.

### Five carbon annulation

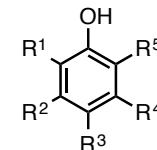


*Tetrahedron. Lett.* **1990**, 31, 5985.

### Spiroannulation



### Benzannulation



### Some well known annulations not covered

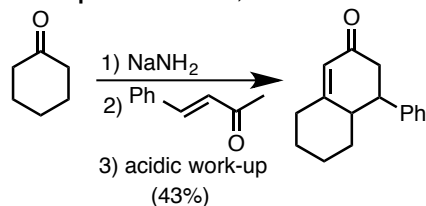
Dötz  
Pictet-Spangler  
Larock indole synthesis

These well known, powerful transformations are deserving of their own group seminar to showcase the synthetic utility and potential of each.

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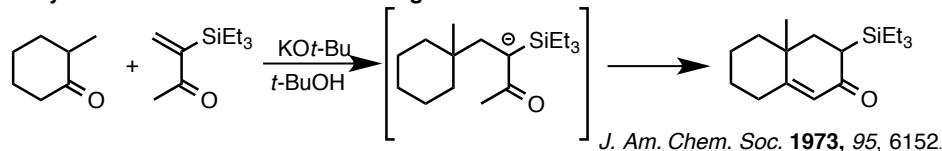
## Robinson Annulation

Initial report Robinson, *J. Chem. Soc.* **1935**, 1285-1288.

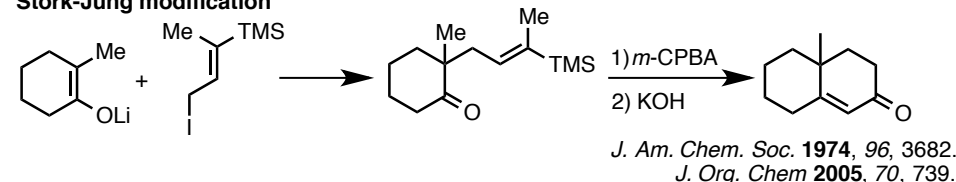
### General note

The Robinson annulation is useful only in simple cases, or where the availability of starting materials compensates for the low yield of desired product. The reaction is typically low yielding due to polymerization of Michael acceptor by strongly basic enolates.

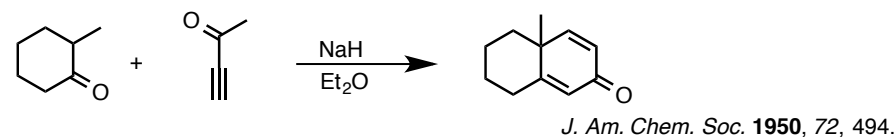
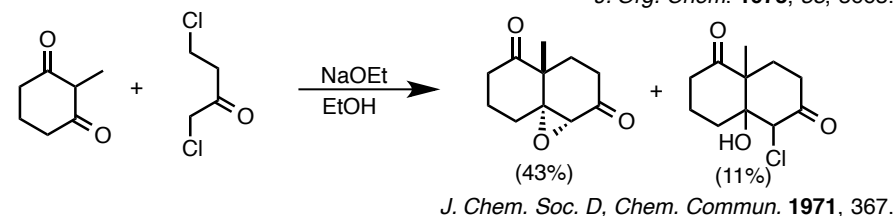
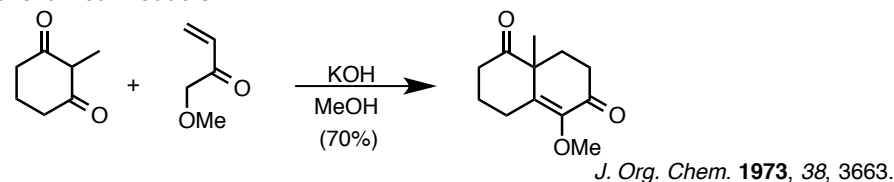
### $\alpha$ -silyl enone stabilization and shielding



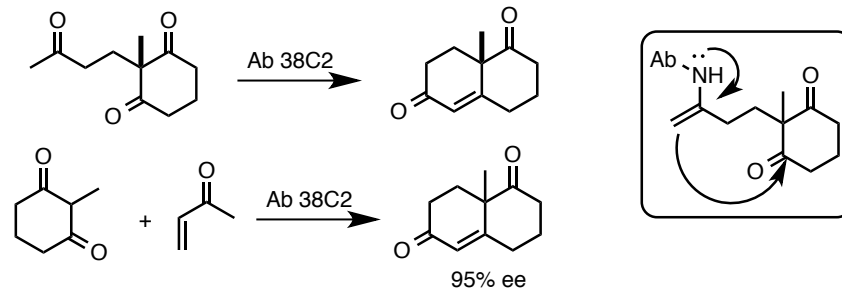
### Stork-Jung modification



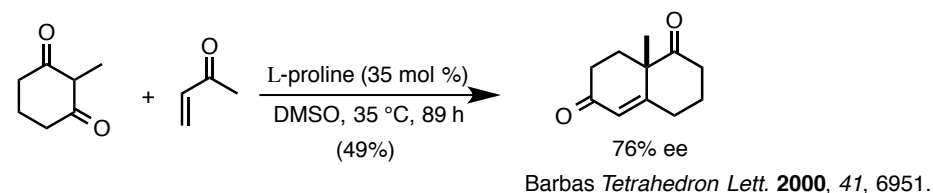
### Functionalized Products



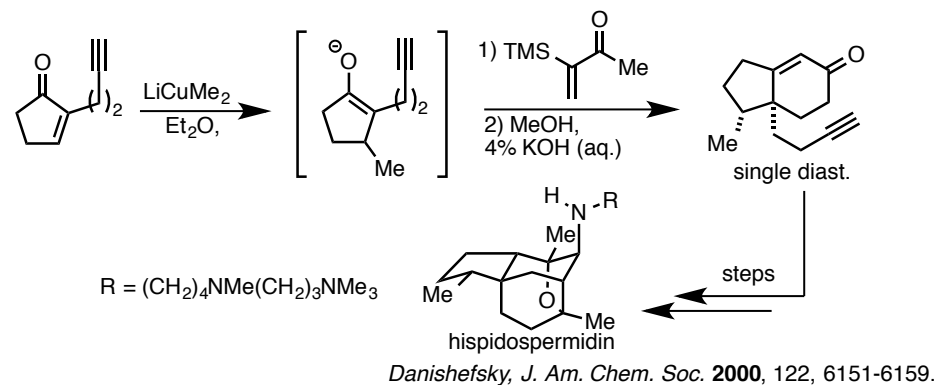
### Antibody-catalyzed enantioselective Robinson annulation



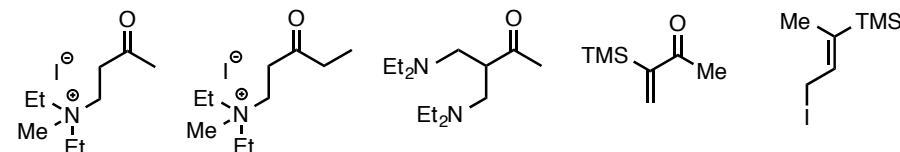
### A proline-catalyzed asymmetric Robinson annulation reaction



### Total synthesis of hispidospermidin



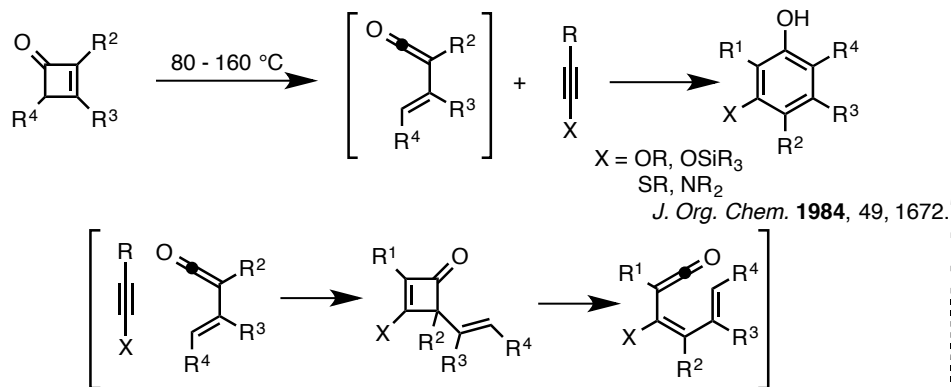
### Some important masked Michael acceptors



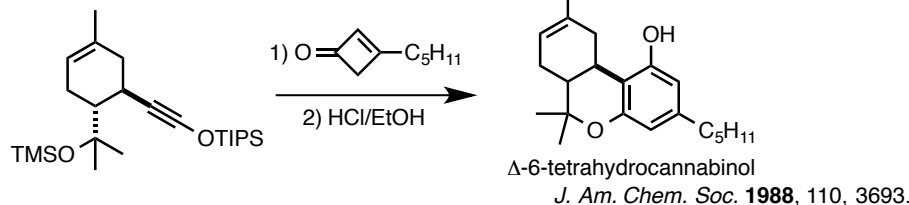
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## Danheiser benzannulation

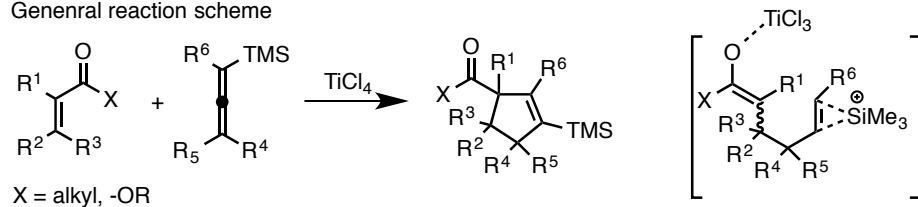


## Use of siloxyacetylenes

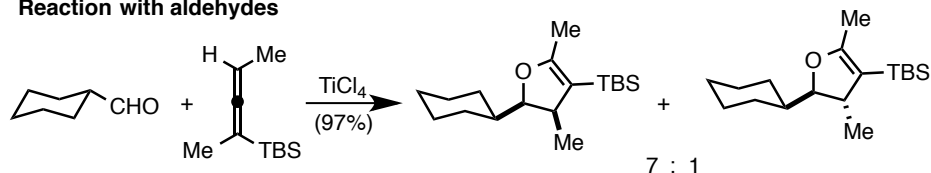


## Danheiser cyclopentene annulation

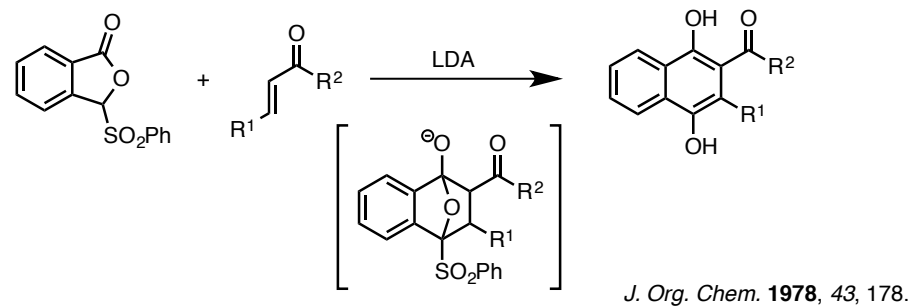
General reaction scheme



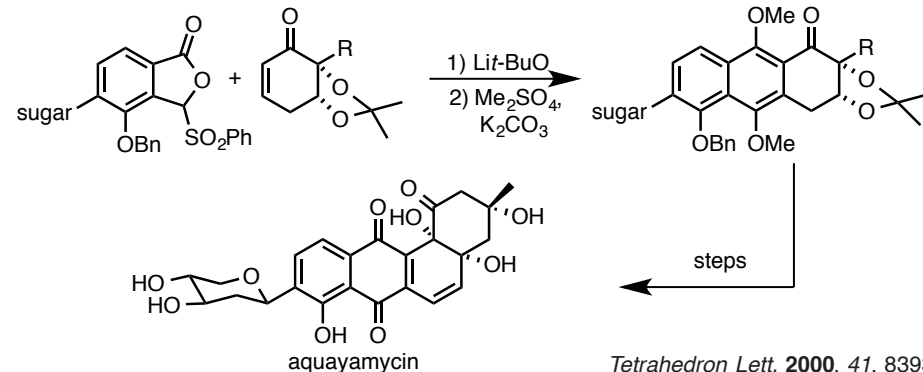
## Reaction with aldehydes



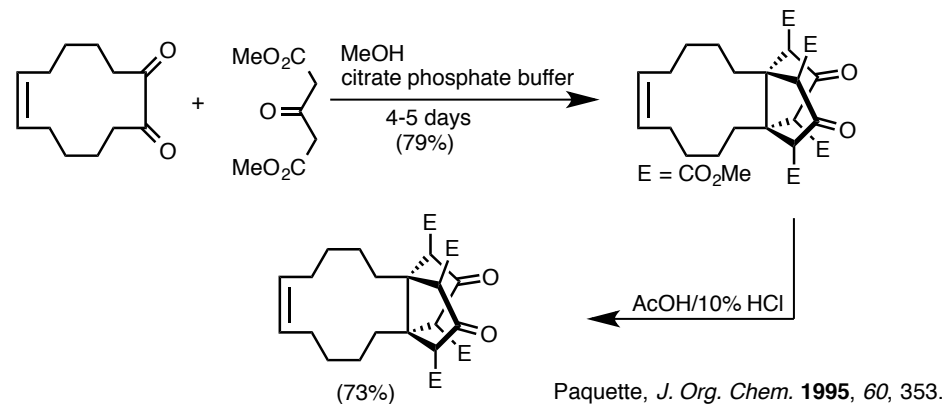
## Hauser Annulation



## Synthesis of aquayamycin



## Weiss-Cook annulation *Tetrahedron Lett.*, 1968, 4885.

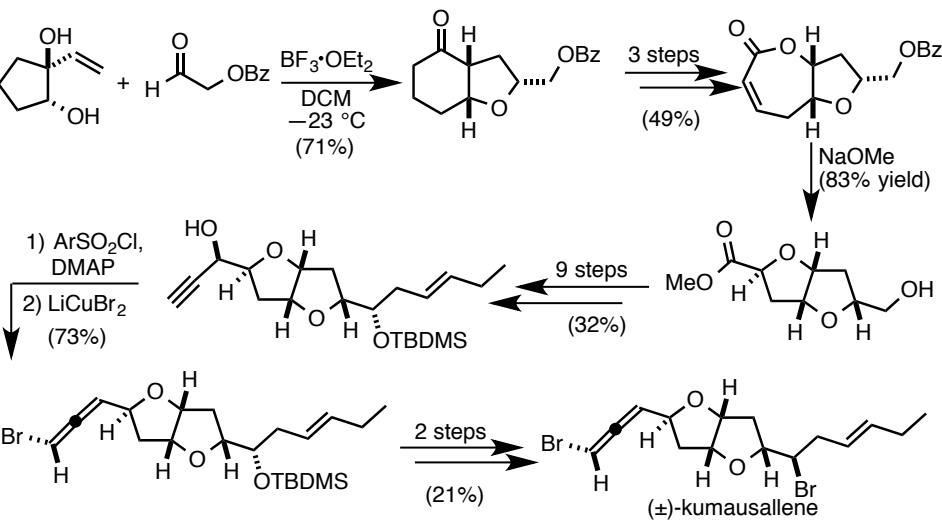


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## Prins-pinacol

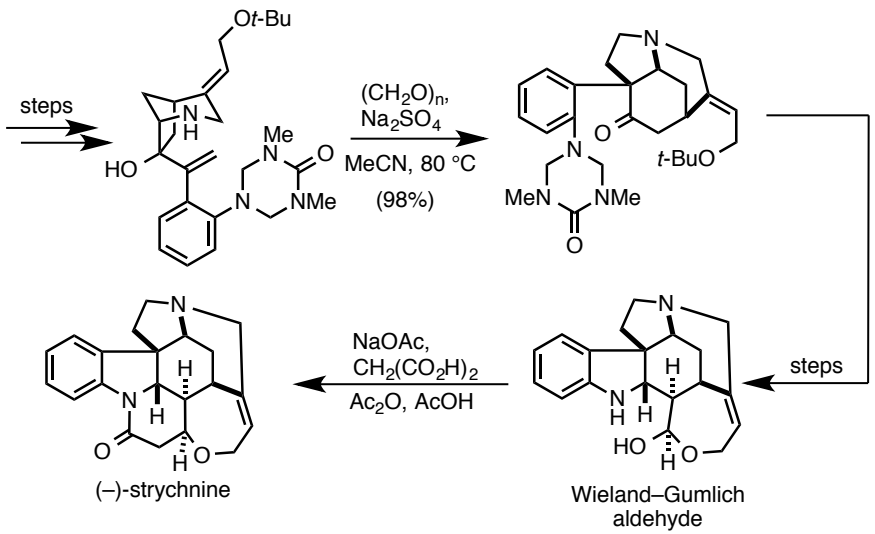
Total Synthesis of (±)-kumausallene  
Overman, *J. Am. Chem. Soc.* **1993**, *58*, 2468.



## aza-Cope-Mannich

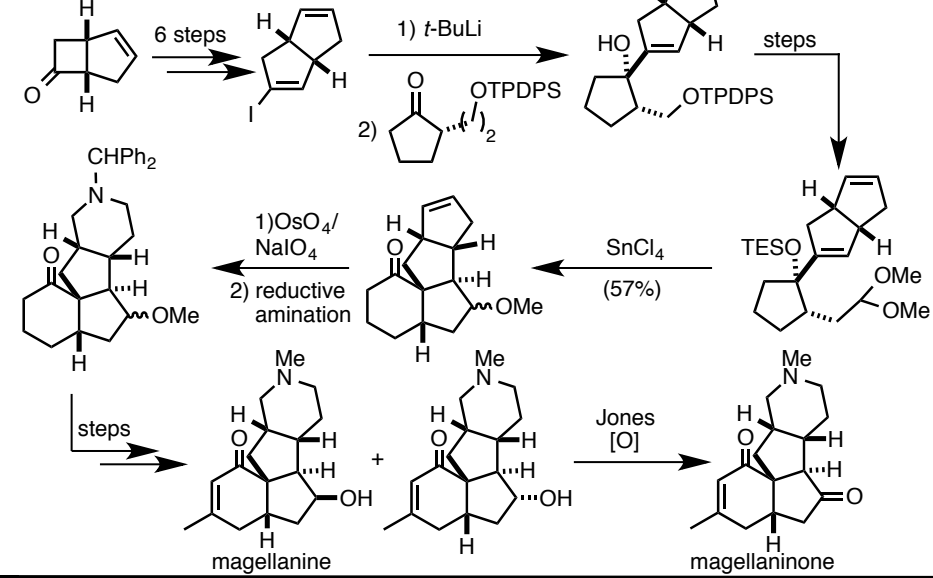
Total synthesis of (-)-strychnine

*J. Am. Chem. Soc.* **1993**, *115*, 9293.  
*J. Am. Chem. Soc.* **1995**, *117*, 5776.



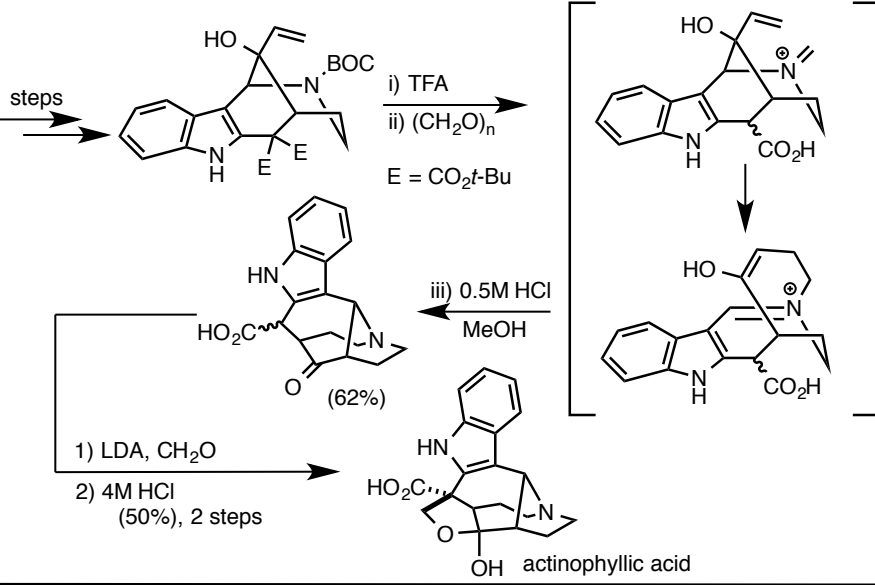
## Total Synthesis of (-)-magellanine and (+)-magellaninone

*J. Am. Chem. Soc.* **1993**, *115*, 2992.



## Total synthesis of (±)-actinophyllic acid

*J. Am. Chem. Soc.* **2008**, *130*, 7568.



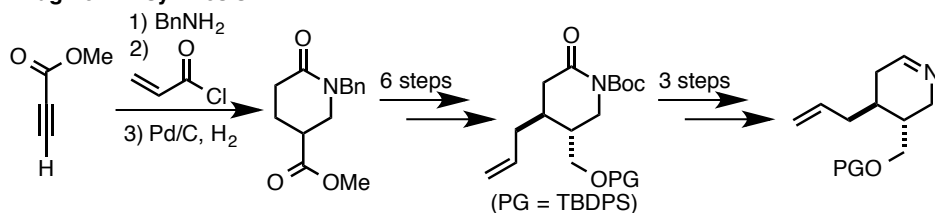
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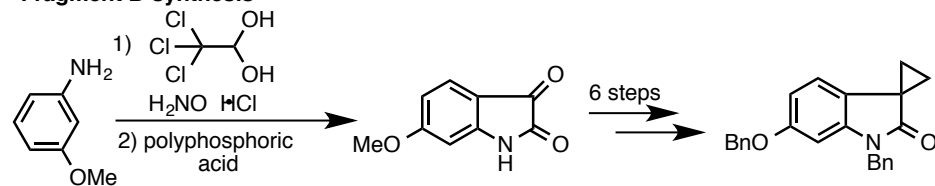
## Aza-Annulation in Total Synthesis

Synthesis of (±)-Strychnofoline *Chem. Eur. J.* 2006, 12, 8208.

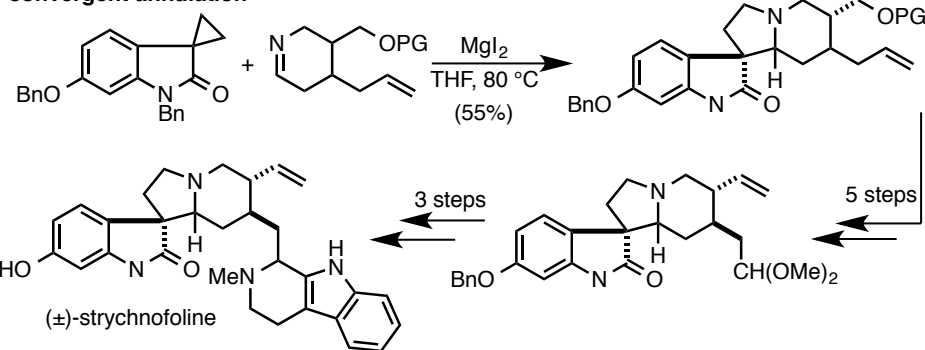
### Fragment A synthesis



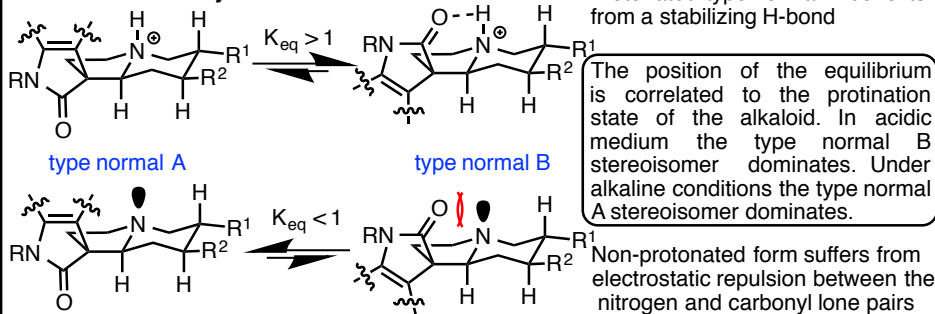
### Fragment B synthesis



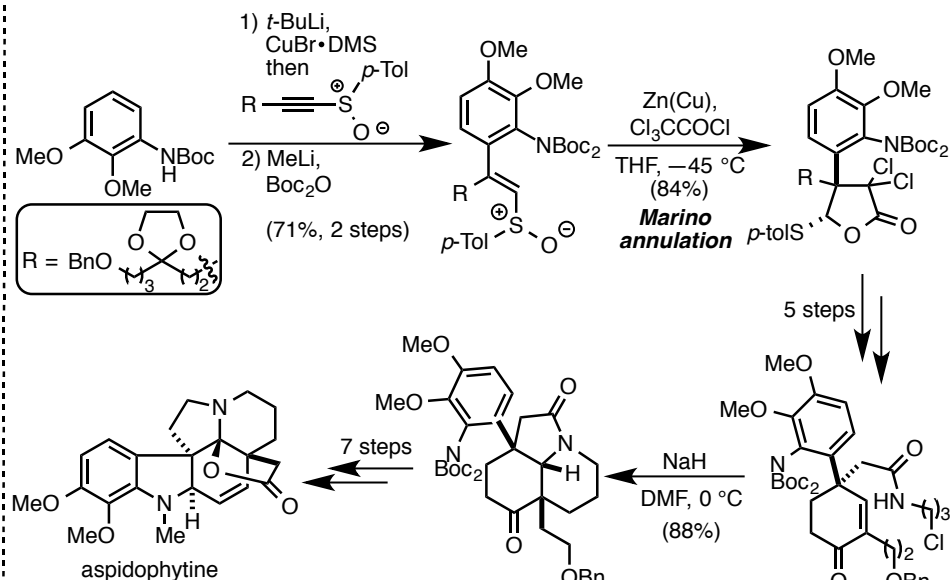
### convergent annulation



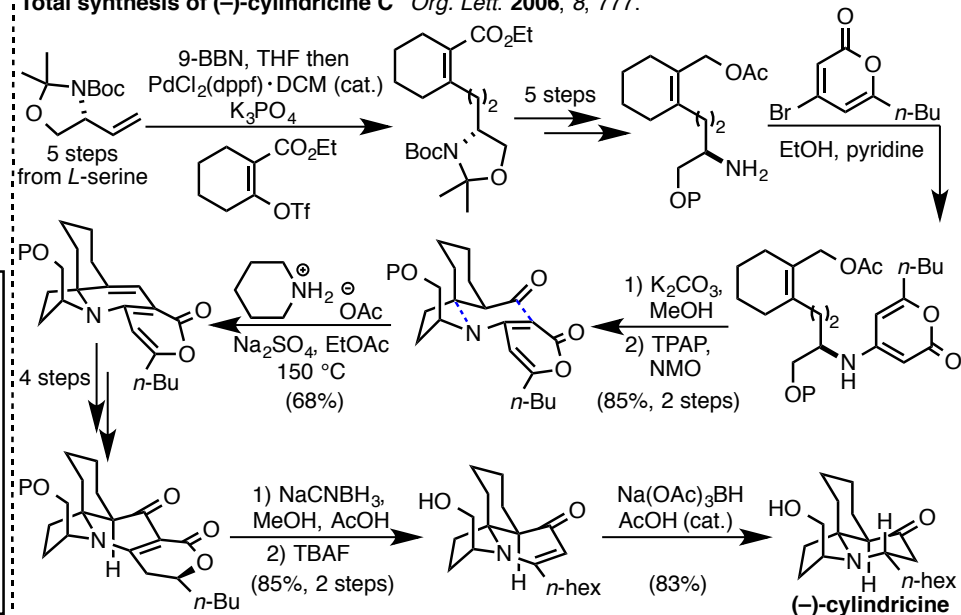
### Diastereoselectivity



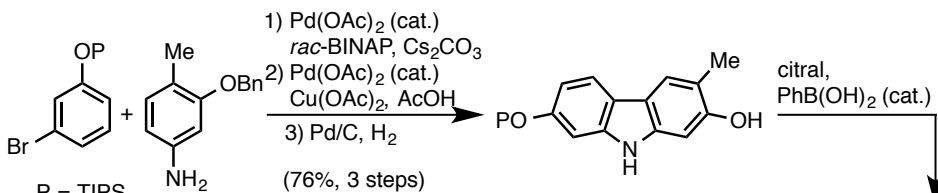
## Total synthesis of aspidophytine *Tetrahedron Lett.* 2006, 47, 7711.



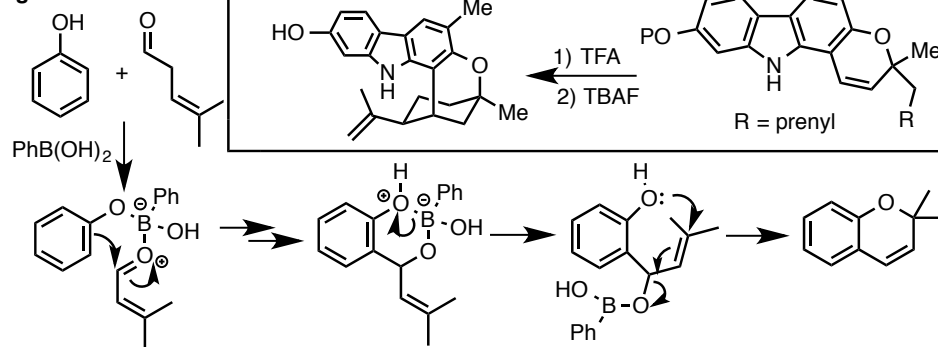
## Total synthesis of (-)-cylindricine C *Org. Lett.* 2006, 8, 777.



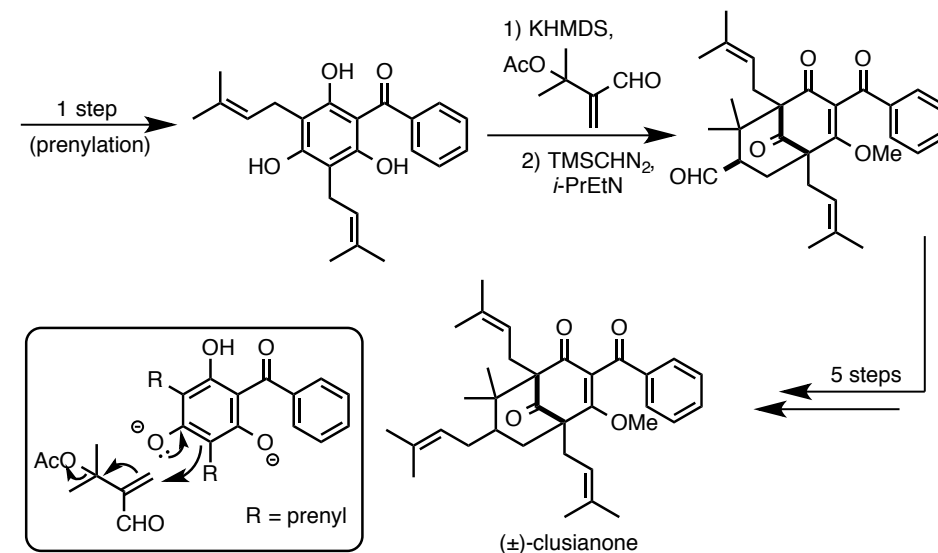
**Total synthesis of murrayamine-D** *Chem. Eur. J.* **2014**, *20*, 8536.



**general mechanism**

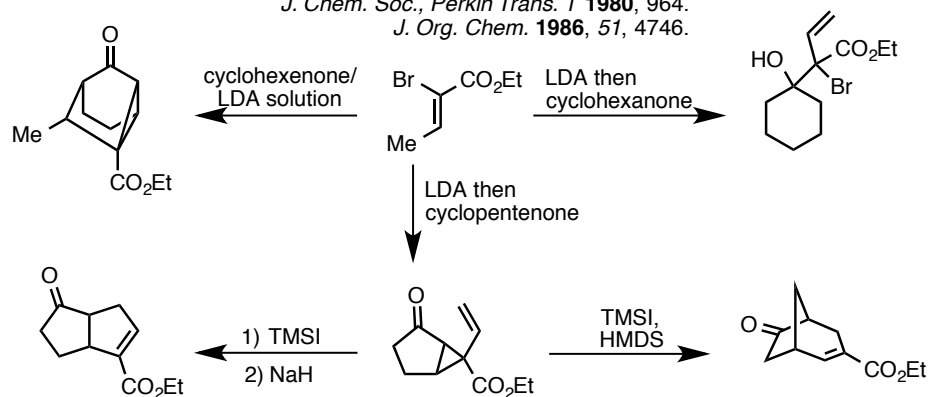


**Total synthesis of (±)-clusianone** *J. Am. Chem. Soc.* **2007**, *129*, 12682.

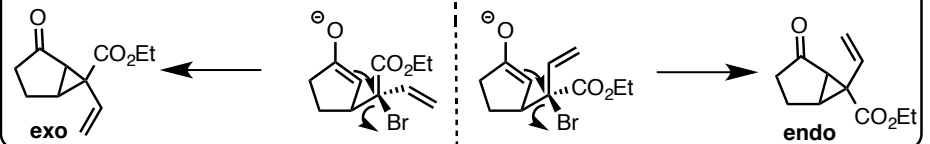


**Hagiwara annulation reagent: vinylcyclopropanation and beyond**

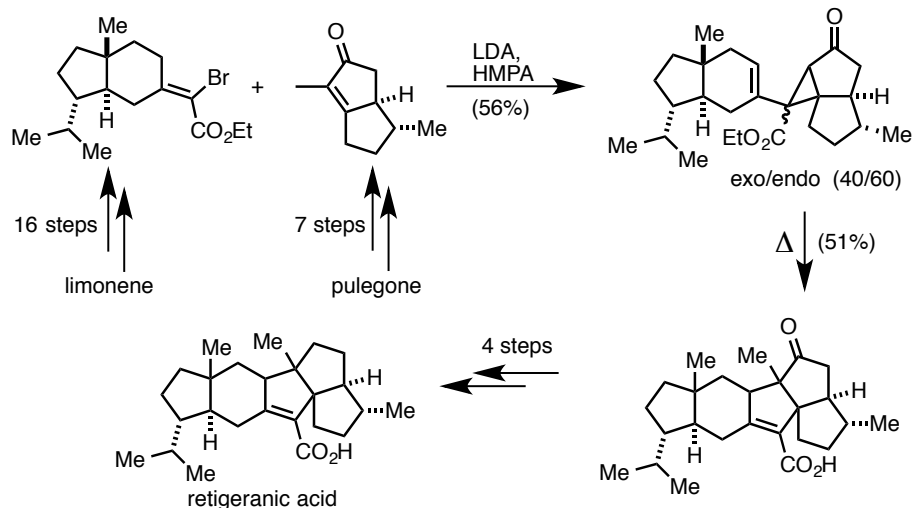
*J. Chem. Soc., Perkin Trans. 1* **1980**, 964.  
*J. Org. Chem.* **1986**, *51*, 4746.



**exo vs endo**



**Synthesis of retigeranic acid** *J. Am. Chem. Soc.* **1989**, *111*, 6691.



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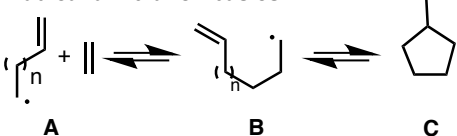
## Radical-Mediated Annulations

### Radical annulation defined:

"A radical annulation involves an intermolecular addition onto a radical acceptor, followed by intramolecular trapping of the radical intermediate onto another radical acceptor functionality present on the initial radical-bearing molecule."

*Synthesis* **2003**, *6*, 803.

### Radical annulation basics



### Once formed, radical intermediate C can:

- 1) React with initial rad. precursor
- 2) React with H atom source
- 3)  $\beta$ -fragmentation (requires design)
- 4) Add to another equiv. of rad. acceptor

### Rates matter

Radical annulation is a highly complex reaction that requires careful planning and consideration of all of the rates of each of the steps involved in order to design a viable annulation strategy.

*Synthesis* **2003**, *6*, 803.

See J. Lo H-atom transfer GM

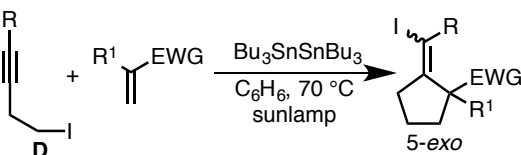
### Curran's logic for radical reaction design

When designing a radical annulation sequence, it is advantageous to permit long lifetimes for the intermediate radicals so that desired reactions can occur. The chain transfer step should be as rapid as possible to prevent diversion of the final radical along undesired pathways.

*J. Am. Chem. Soc.* **1987**, *109*, 6658

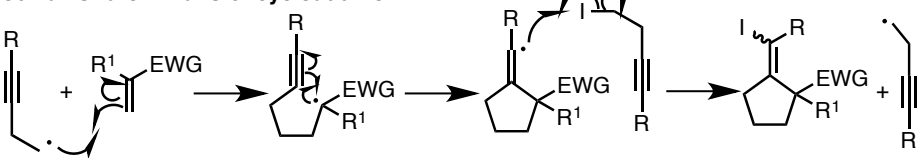
### Atom transfer radical annulation

Curran, *J. Am. Chem. Soc.* **1987**, *109*, 6658.

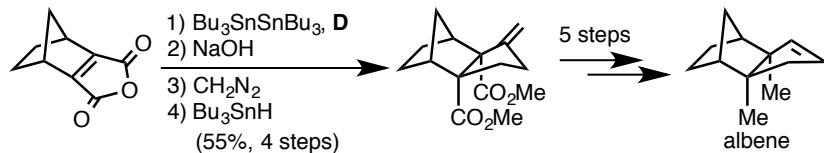


The term "atom transfer" emphasizes the method of control of the radical reaction. In the tin hydride method, the chain is transferred by H atom abstraction from the reagent. In the atom transfer method the chain is transferred by halogen atom abstraction from the starting halide.

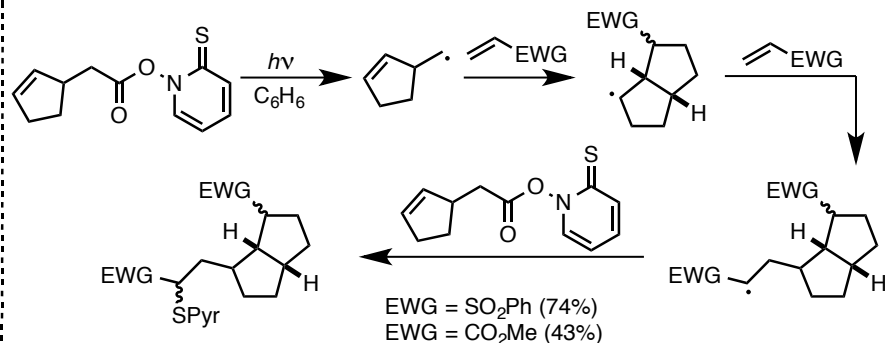
### Curran's "atom transfer cycloaddition"



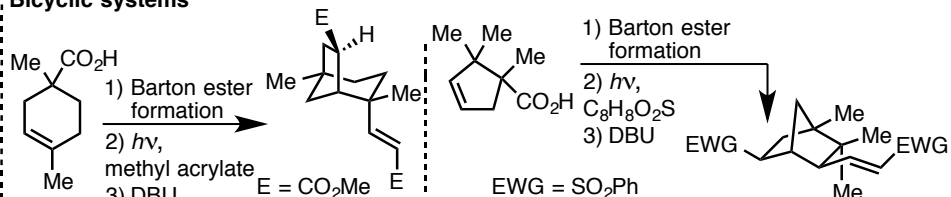
### Application of method to synthesis of albene



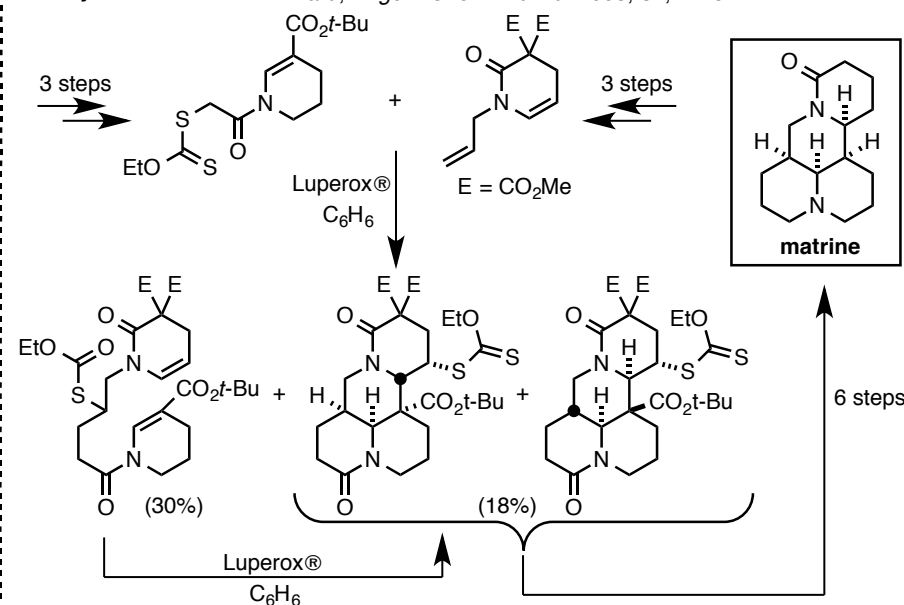
### [3+2] radical annulation strategy Barton, Zard, *J. Chem. Soc., Chem. Commun.* **1988**, 285.



### Bicyclic systems



### Total synthesis of matrine Zard, *Angew. Chem. Int. Ed.* **1998**, *37*, 1128.

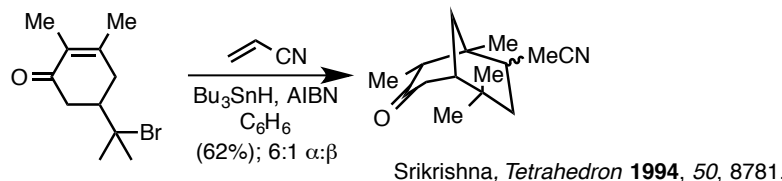


# Ring Construction via Annulation

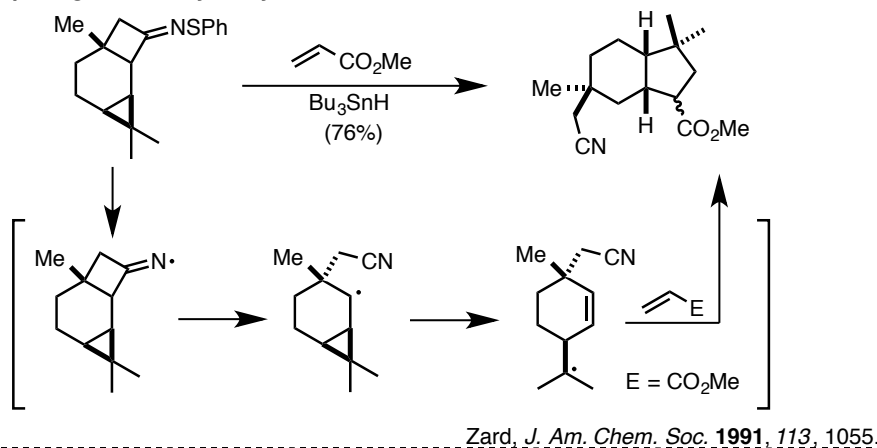
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## Radical annulation cont.

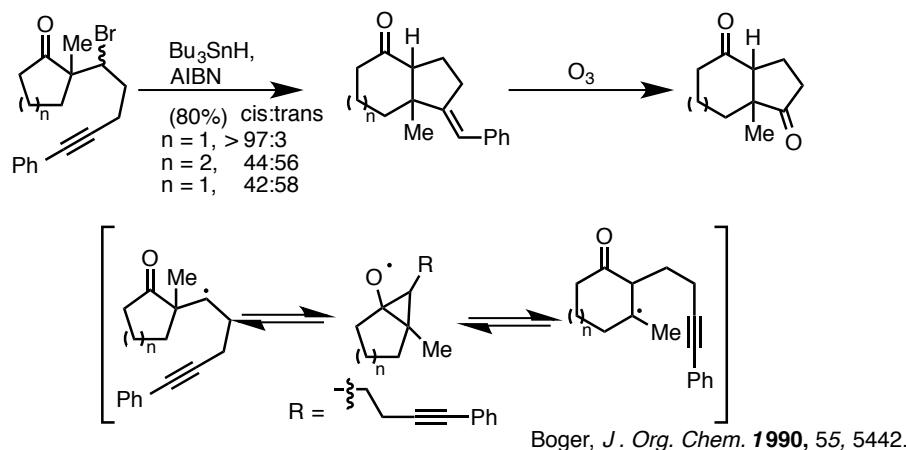
Radical annulation strategy to bicyclo[3.3.1]nonanes



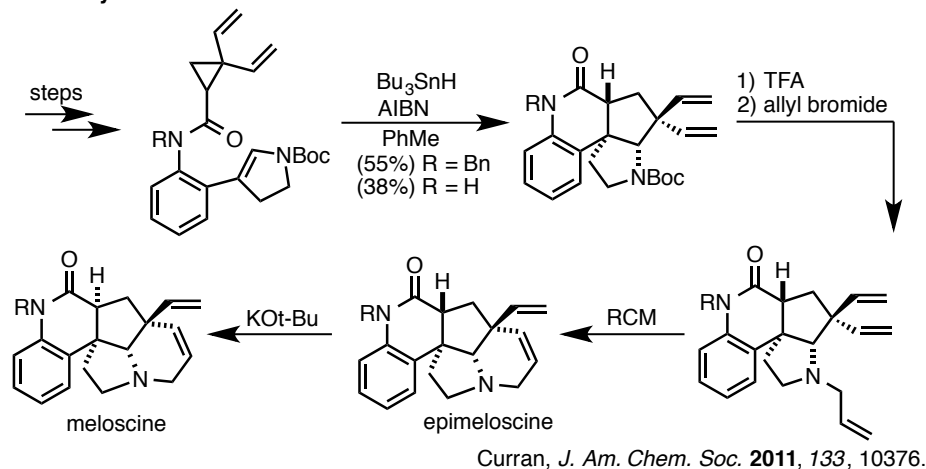
## Ring Opening Induced by Iminyl Radicals



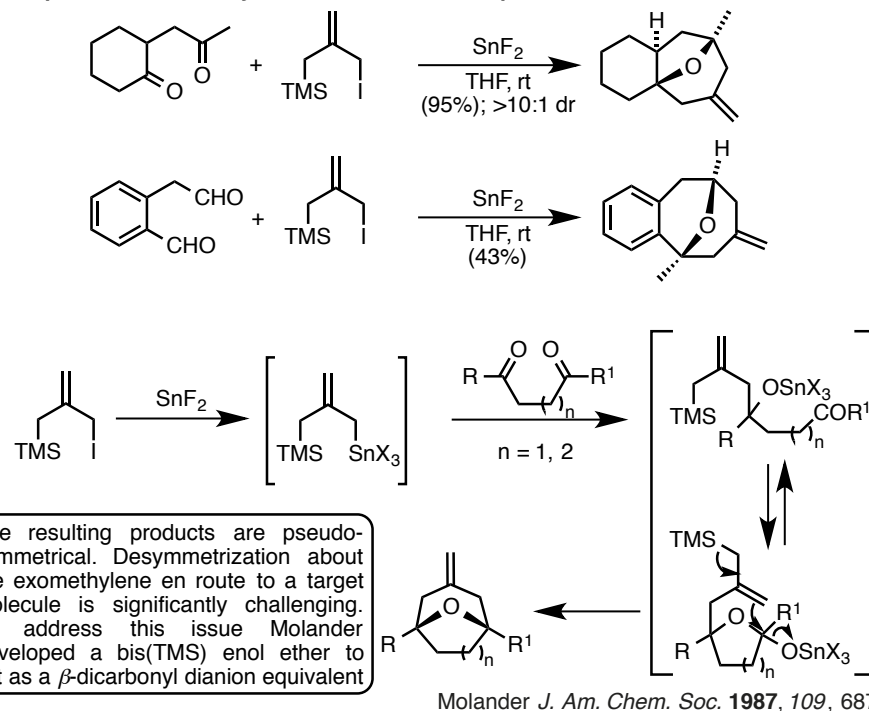
## Radical ring expansion approach to fused carbocycles



## Total synthesis of epimeloscine and meloscine enabled by a cascade radical annulation



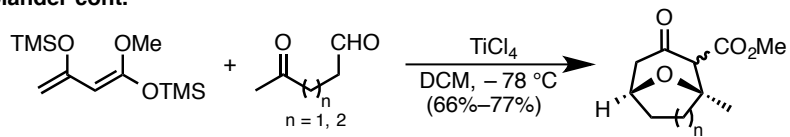
## Development of a trimethylenemethane dianion equivalent





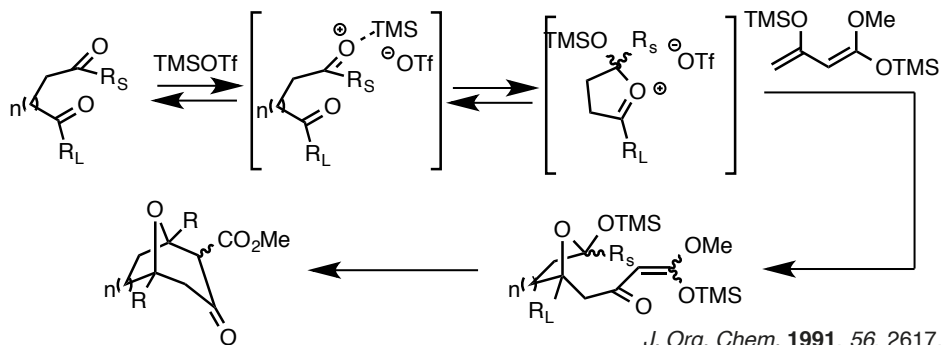
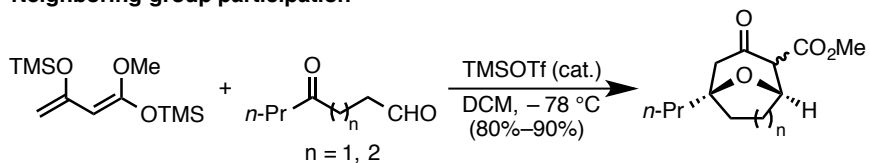
## Ring Construction via Annulation

## Molander cont.



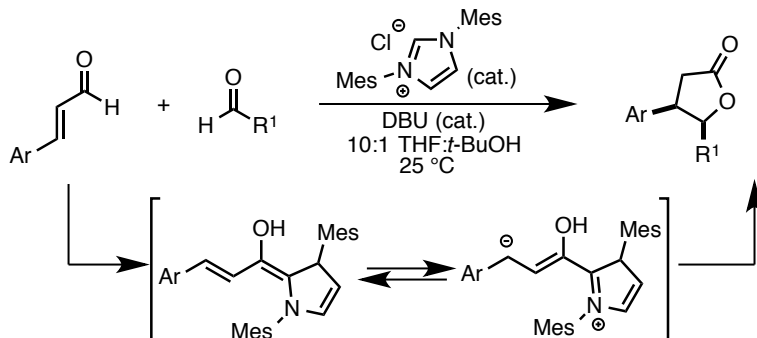
*Tetrahedron Lett.* **1989**, 30, 2351.

## Neighboring group participation



*J. Org. Chem.* **1991**, 56, 2617.  
*J. Am. Chem. Soc.* **1993**, 115, 830.

## NHC-catalyzed annulation of enals and aldehydes



Bode, *J. Am. Chem. Soc.* **2004**, 126, 14370.