

## Outline

1. Sulfenylation
  - Asymmetric variations
2. Thiocarbonyl and Thioketal Reactivity
  - Etherification (Studies Toward Brevetoxin B)
  - Eschenmoser Sulfide Contraction
  - Aza-Robinson
  - Thionium Aldol
  - Thionium Allylation
3. Olefination
  - Ramberg-Bäcklund Reaction
  - Chugaev Elimination
  - Barton Kellogg Olefination
4. Cycloadditions
  - thia-Paternò-Büchi
  - Sulfur Ylide [3+2]
5. Sigmatropic Rearrangements
  - Mislow-Evans Rearrangement
  - Sharpless-Kresze Allylic Amination
  - Zard Inversion

## What is not covered

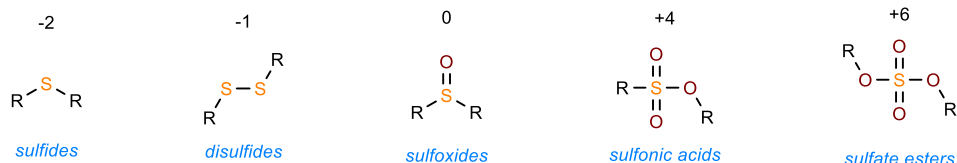
The following transformations are not covered: Corey Winter, Corey-Seebach, Corey-Chaykovsky, Julia-Kocienski, Pummerer rearrangement Barton deoxygenation, Barton decarboxylation, and thianthreniums For Pummerer Rearrangement see the MOTW prepared [https://www.sarlahgroup.com/files/ugd/f6a755\\_77dbdde20f0e4bad9ae0fe7a3c18632e.pdf](https://www.sarlahgroup.com/files/ugd/f6a755_77dbdde20f0e4bad9ae0fe7a3c18632e.pdf)

**“Sulfur is more than oxygen’s fat brother”**



## Reviews and books

1. Sulfur (IV) chemistry
  - <https://doi.org/10.1021/acs.chemrev.9b00111>
2. Sulfur rearrangements
  - <https://doi.org/10.1007/978-3-540-68100-7>
3. Unusual xanthate reactivity
  - <https://doi.org/10.1002/anie.199706721>
4. Personal account with sulfur over 50 years of work
  - <https://doi.org/10.1080/17415993.2012.717294>

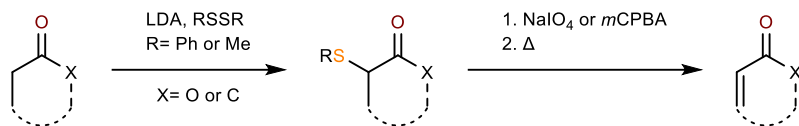


- Larger covalent radius 104.9 nm vs oxygen’s 70.2 nm
- Much more polarizable
- Weaker  $\sigma$  and  $\pi$  bonds with carbon compared to oxygen
- Polarization of C—S bond is not as significant compared to that of the C—O bond

Schaumann, E. *Sulfur—Mediated Rearrangements I*. 2007, <https://doi.org/10.1007/978-3-540-68098-7>

# Sulfenylation

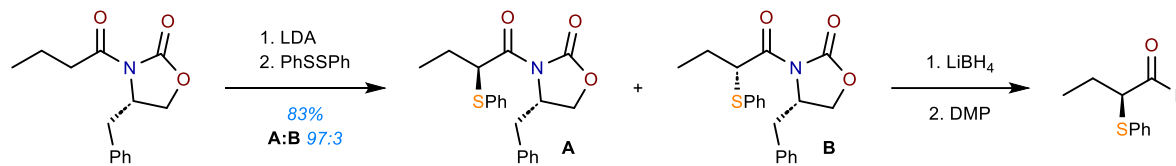
## Early Report



- Sulfenylation is typically accomplished by first formation of an enolate, followed by trapping with an electrophilic sulfur source.
- Most traditionally used to form  $\alpha,\beta$ -unsaturated carbonyls.

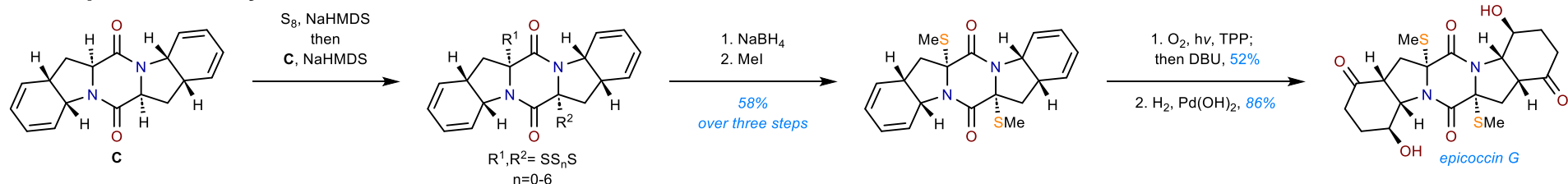
Trost, B. *J. Am. Chem. Soc.* **1973**, 95, 6840–6842. <https://doi.org/10.1021/ja00801a058>

## Chiral Auxiliary

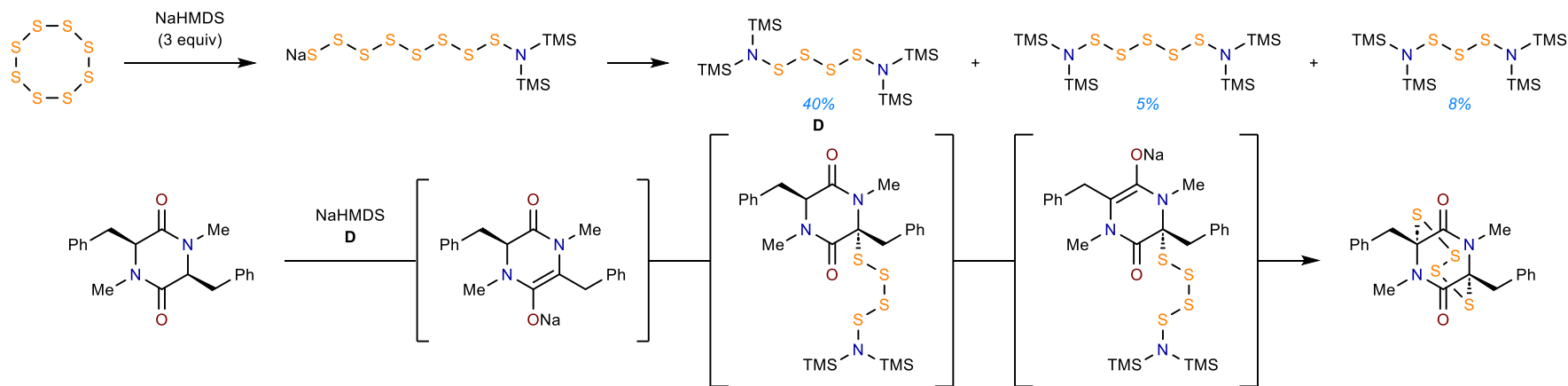


Warren, S. *Tetrahedron. Lett.* **1994**, 35, 3991–3994. [https://doi.org/10.1016/S0040-4039\(00\)76722-0](https://doi.org/10.1016/S0040-4039(00)76722-0)

## Example in Total Synthesis



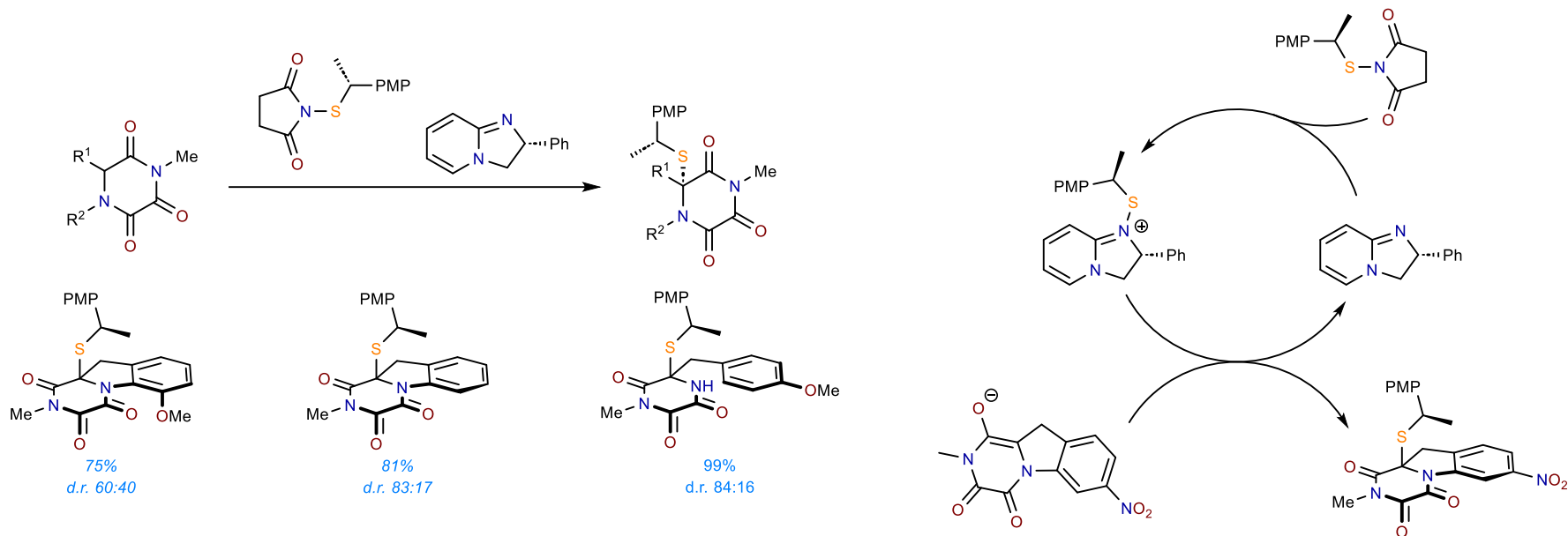
Nicolaou, K.C. *J. Am. Chem. Soc.* **2011**, 133, 8150–8153. <https://doi.org/10.1021/ja2032635>



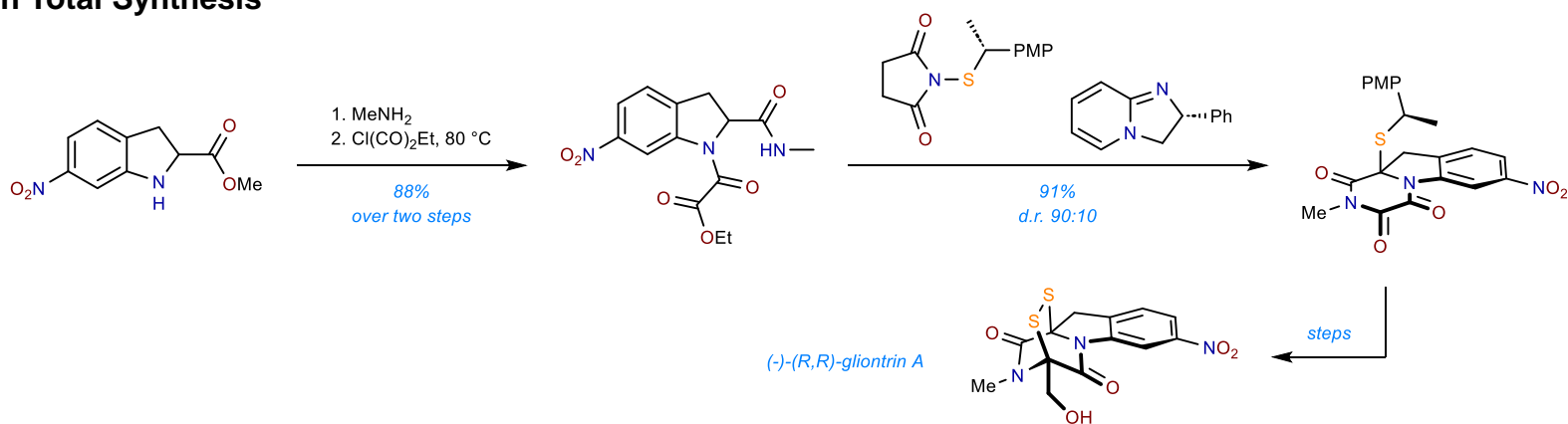
Nicolaou, K.C. *J. Am. Chem. Soc.* **2012**, 134, 17320–17332. <https://doi.org/10.1021/ja308429f>

# Sulfenylation

## Asymmetric Variation



## Example in Total Synthesis

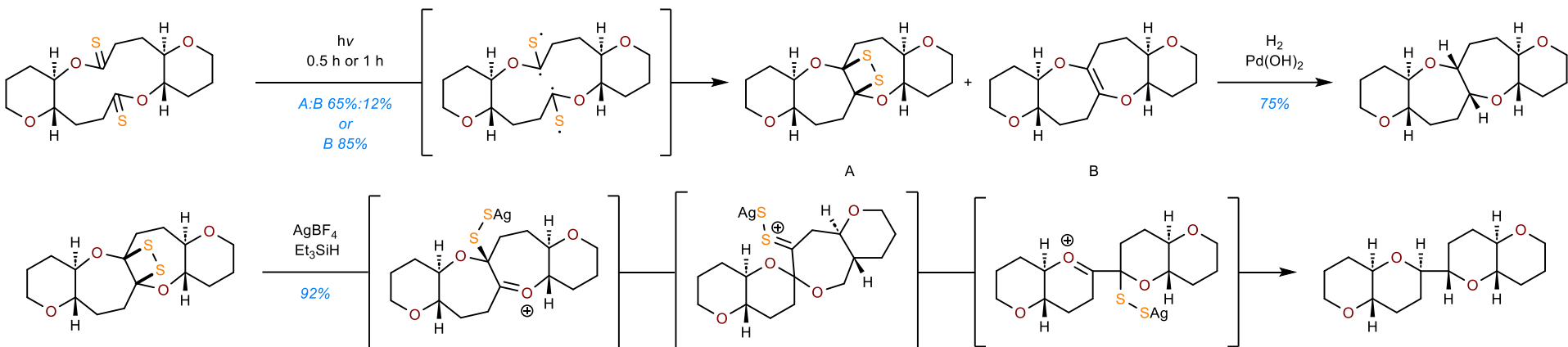


Strand, D. *J. Am. Chem. Soc.* **2021**, 143, 21218–21222. <https://doi.org/10.1021/jacs.1c10364>

Strand, D. *Angew. Chem. Int. Ed.* **2024**, 63, e202412397. <https://doi.org/10.1002/anie.202412397>

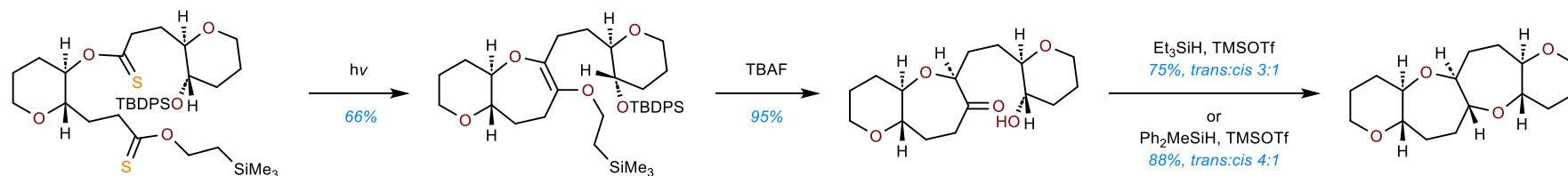
# Thiocarbonyl Reactivity

## Studies Toward Brevetoxin B

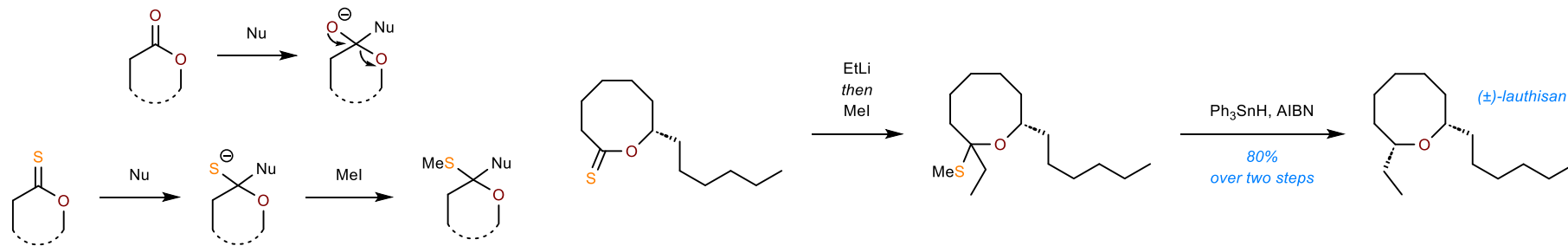


Nicolaou, K.C. *J. Am. Chem. Soc.* **1990**, 112, 3029–3039. <https://doi.org/10.1021/ja00164a025>

Nicolaou, K.C. *J. Am. Chem. Soc.* **1986**, 108, 6800–6802. <https://doi.org/10.1021/ja00281a056>



Nicolaou, K.C. *J. Am. Chem. Soc.* **1989**, 111, 4136–4137. <https://doi.org/10.1021/ja00193a076>

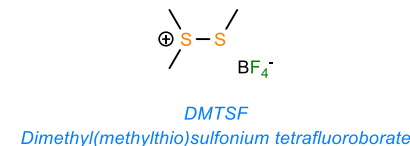
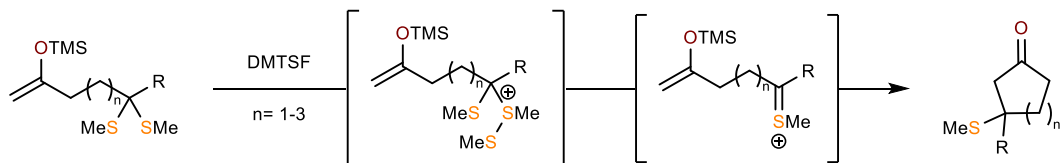


Nicolaou, K.C. *J. Am. Chem. Soc.* **1990**, 112, 6263–6276. <https://doi.org/10.1021/ja00173a013>

Nicolaou, K.C. *J. Am. Chem. Soc.* **1987**, 109, 2504–2506. <https://doi.org/10.1021/ja00242a041>

# Thioketal Reactivity

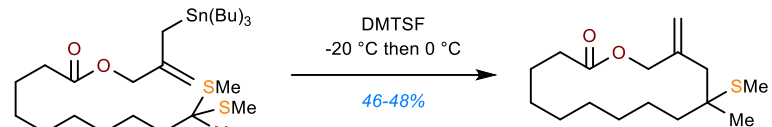
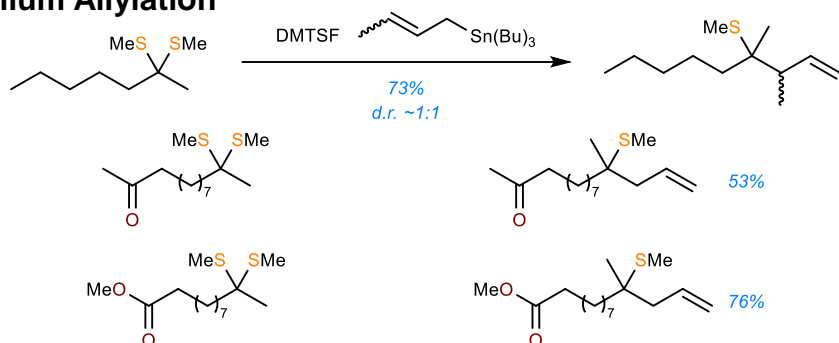
## Thionium Aldol



- DMTSF is commercially available \$119 for 1 g from TCI (at the time of preparation).
- Can be prepared by treating dimethyl disulfide with Meerwein's salt.

Trost, B. *J. Am. Chem. Soc.* **1981**, 103, 6529–6530. <https://doi.org/10.1021/ja00411a058>

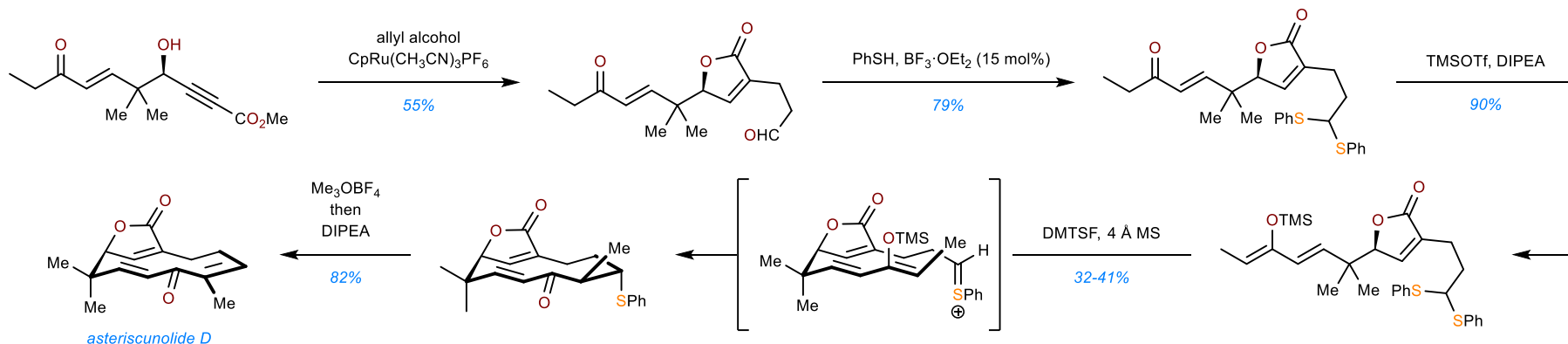
## Thionium Allylation



- Coined “super carbonyl” due to its increased reactivity over ketones and esters.
- Competent for intramolecular macrocyclization, demonstrated at 0.01 M.

Trost, B. *J. Am. Chem. Soc.* **1985**, 107, 719–721. <https://doi.org/10.1021/ja00289a043>

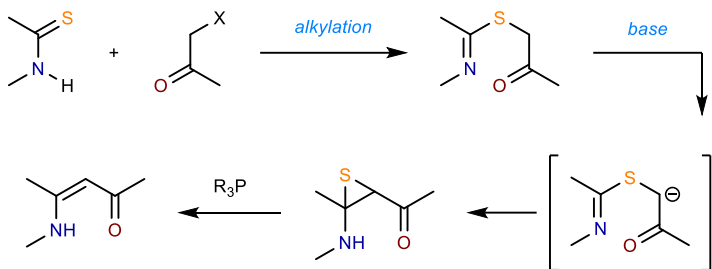
## Example in Total Synthesis



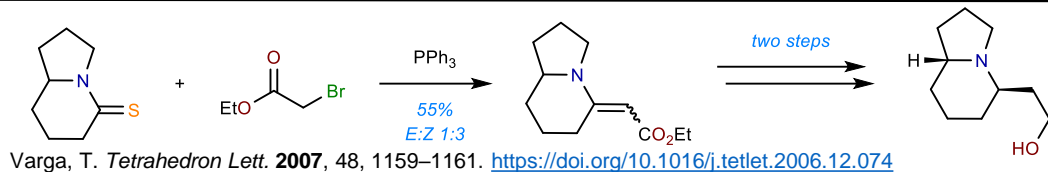
Trost, B. *J. Am. Chem. Soc.* **2012**, 134, 1474–1477. <https://doi.org/10.1021/ja210986f>

# Eschenmoser Sulfide Contraction

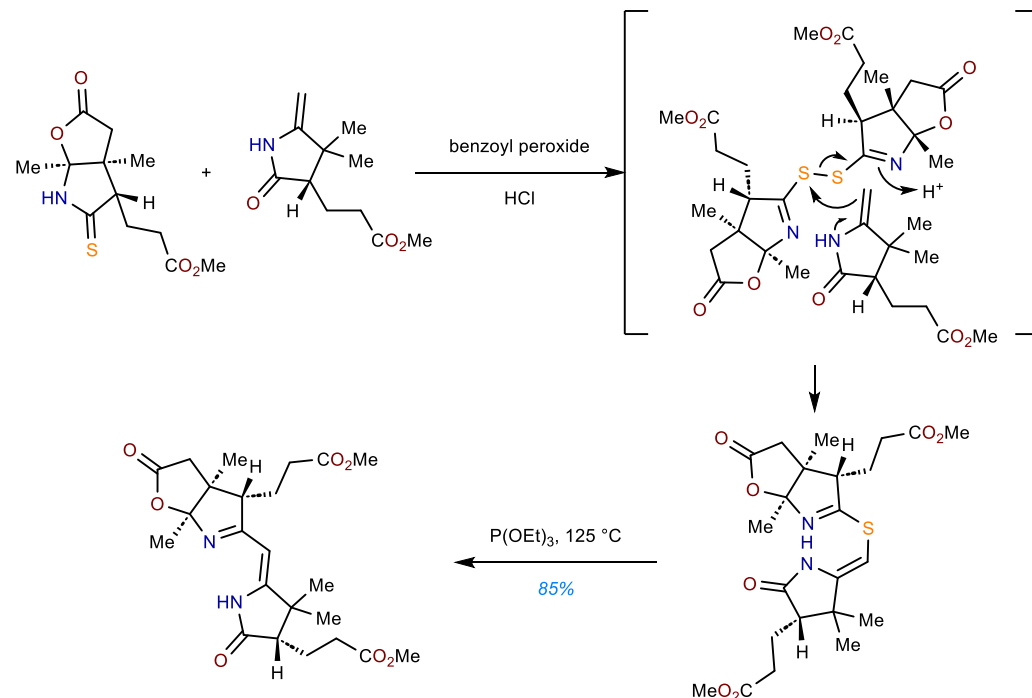
## Alkylative



Eschenmoser, A. *Helv. Chem. Acta.* **1971**, 54, 710–734.  
<https://doi.org/10.1002/hlca.19710540229>

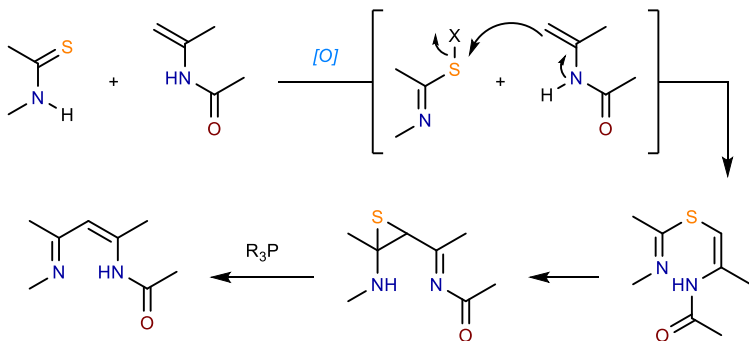


Varga, T. *Tetrahedron Lett.* **2007**, 48, 1159–1161. <https://doi.org/10.1016/j.tetlet.2006.12.074>



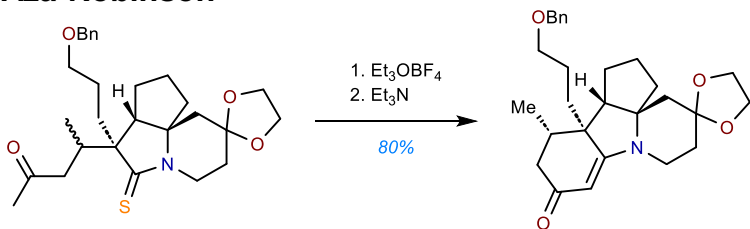
Eschenmoser, A. *Science.* **1977**, 196, 1410–1420. [10.1126/science.867037](https://doi.org/10.1126/science.867037)

## Oxidative

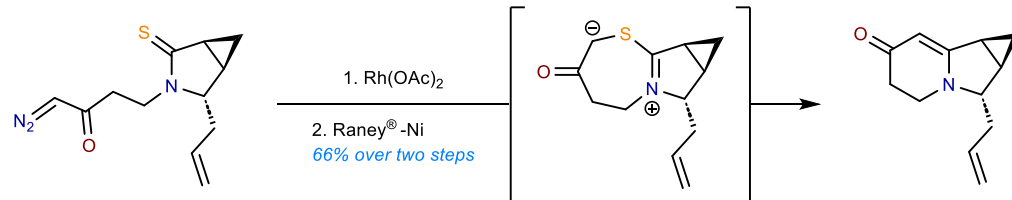


Eschenmoser, A. *Angew. Chem. Int. Ed.* **1967**, 6, 866–868.  
<https://doi.org/10.1002/anie.196708661>

## Aza-Robinson



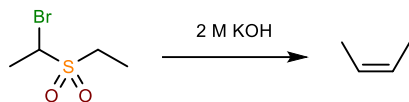
Heathcock, C. J. *J. Org. Chem.* **1992**, 57, 2531–2544.  
<https://doi.org/10.1021/jo00035a007>



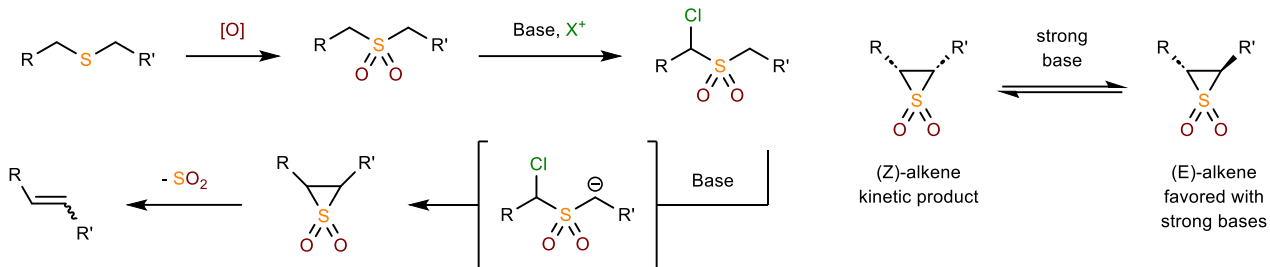
Danishefsky, S. *J. Am. Chem. Soc.* **1990**, 112, 2003–2005. <https://doi.org/10.1021/ja00161a059>

# The Ramberg-Bäcklund Reaction

## Original Report

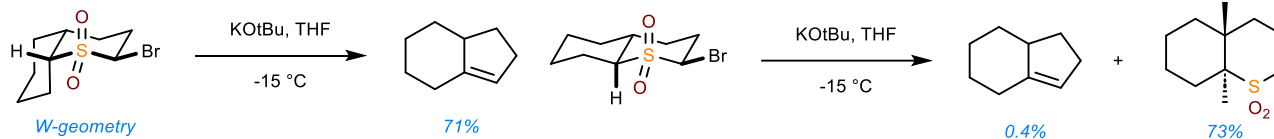


## Mechanism



Ramberg, L. *Ark. Kemi. Mineral. Geol.* **1940**, 27, 1-50.

## Geometric Requirements

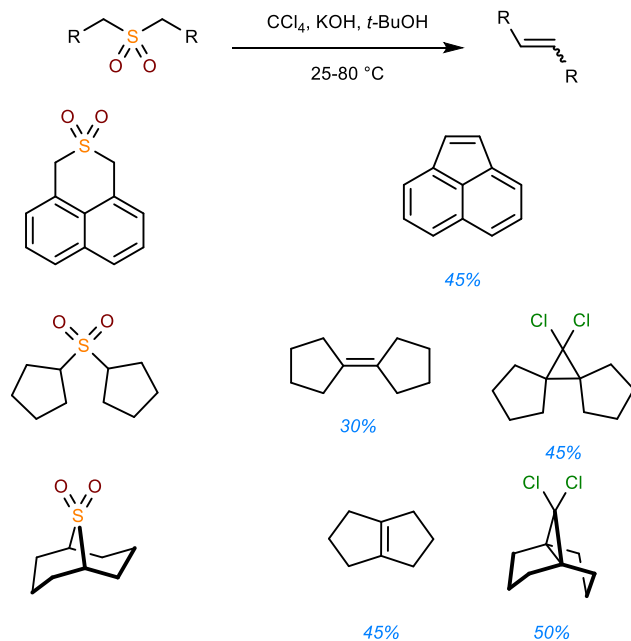


*W*-geometry

Becker, K. *Helv. Chim. Acta.* **1983**, 66, 1090–1100. <https://doi.org/10.1002/hlca.19830660412>

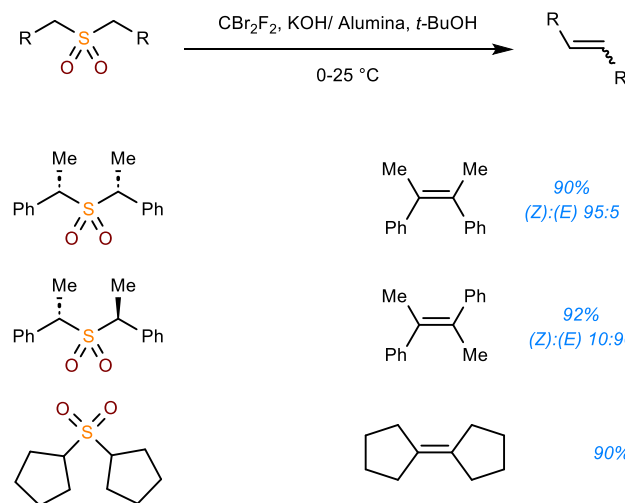
- One should expect due to the *W* geometry that is typically required the RBR should result in cis-substituents (*Z* olefin), so it is proposed epimerization of the episulfone occurs after this.
- It is of note that this is not always observed!

## Meyers Modification



Meyers, C. *J. Am. Chem. Soc.* **1969**, 91, 7510–7512. <https://doi.org/10.1021/ja01054a049>

## Chan Modification

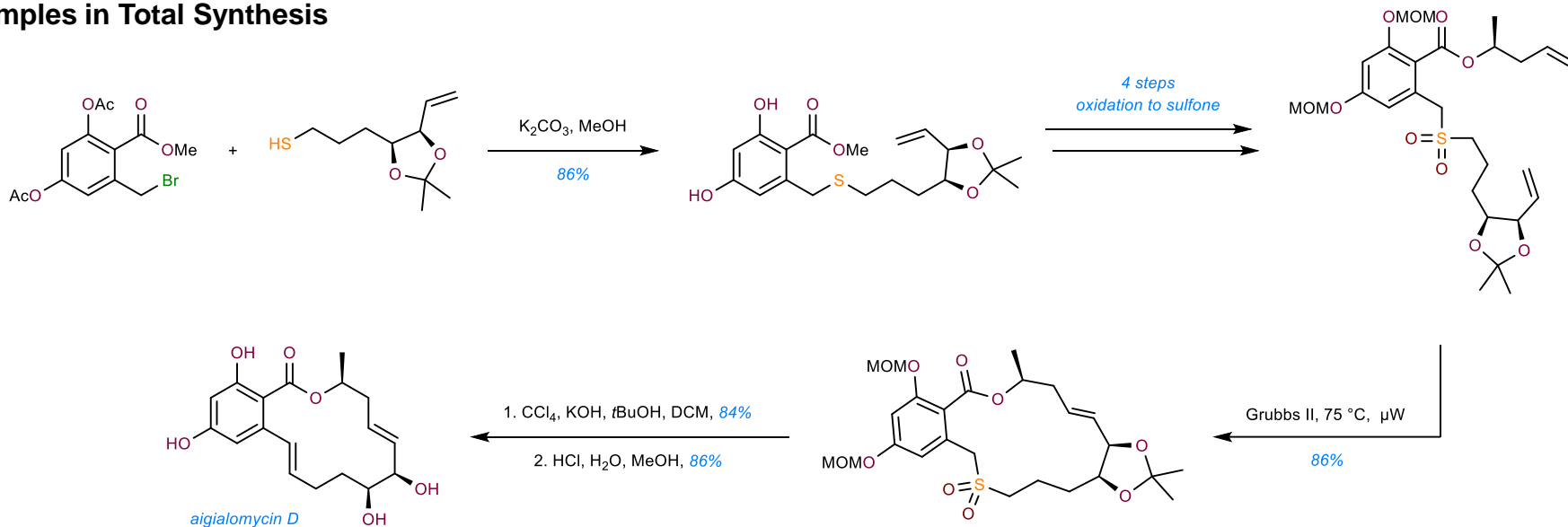


- An advantage over the Meyers protocol is that the difluoro carbene that is generated is less reactive toward olefins.

Chan, T. *Chem. Soc., Chem. Commun.* **1994**, 1771–1772. <https://doi.org/10.1021/ja00990a045>

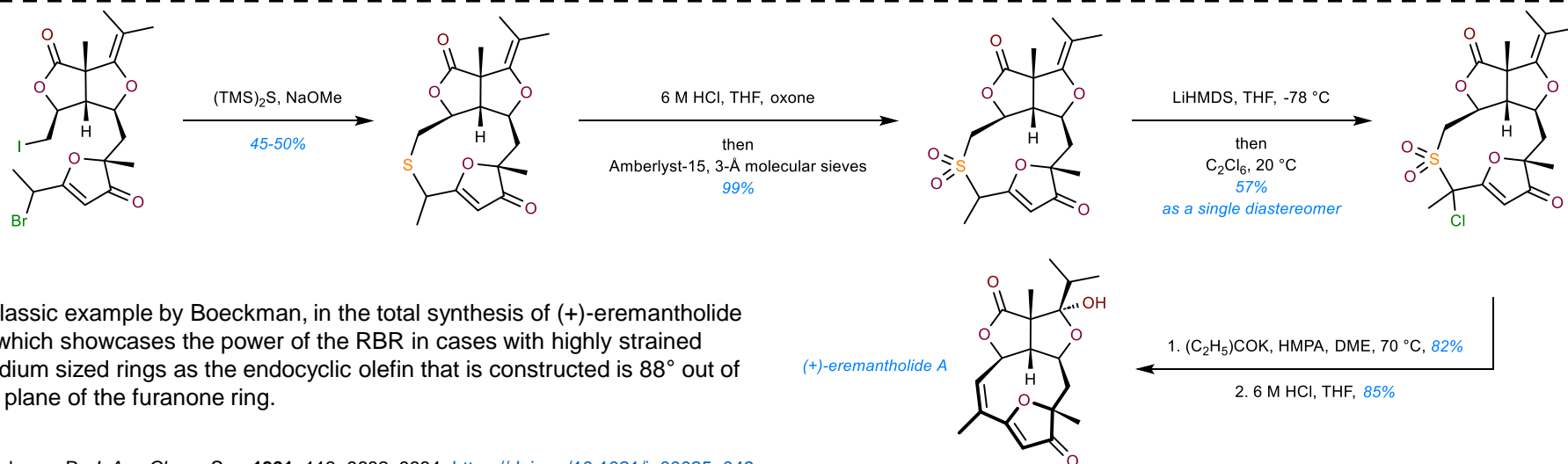
# The Ramberg-Bäcklund Reaction

## Examples in Total Synthesis



An example reported by Harvey in the total synthesis of aigialomycin D where a sulfide acts as a masked olefin.

Harvey, J. *J. Org. Chem.* **2009**, 74, 2271–2277. <https://doi.org/10.1021/jo802561s>



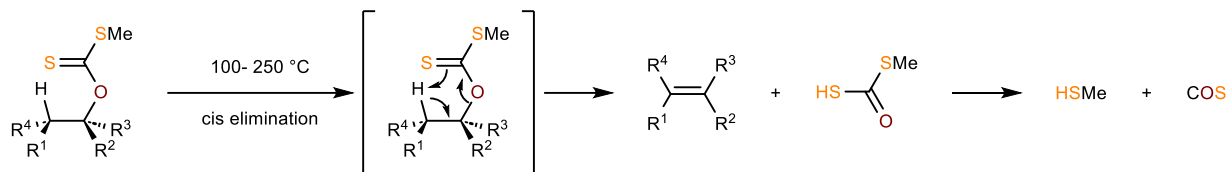
A classic example by Boeckman, in the total synthesis of (+)-eremantholide A, which showcases the power of the RBR in cases with highly strained medium sized rings as the endocyclic olefin that is constructed is 88° out of the plane of the furanone ring.

Boeckman, R. *J. Am. Chem. Soc.* **1991**, 113, 9682–9684. <https://doi.org/10.1021/ja00025a049>



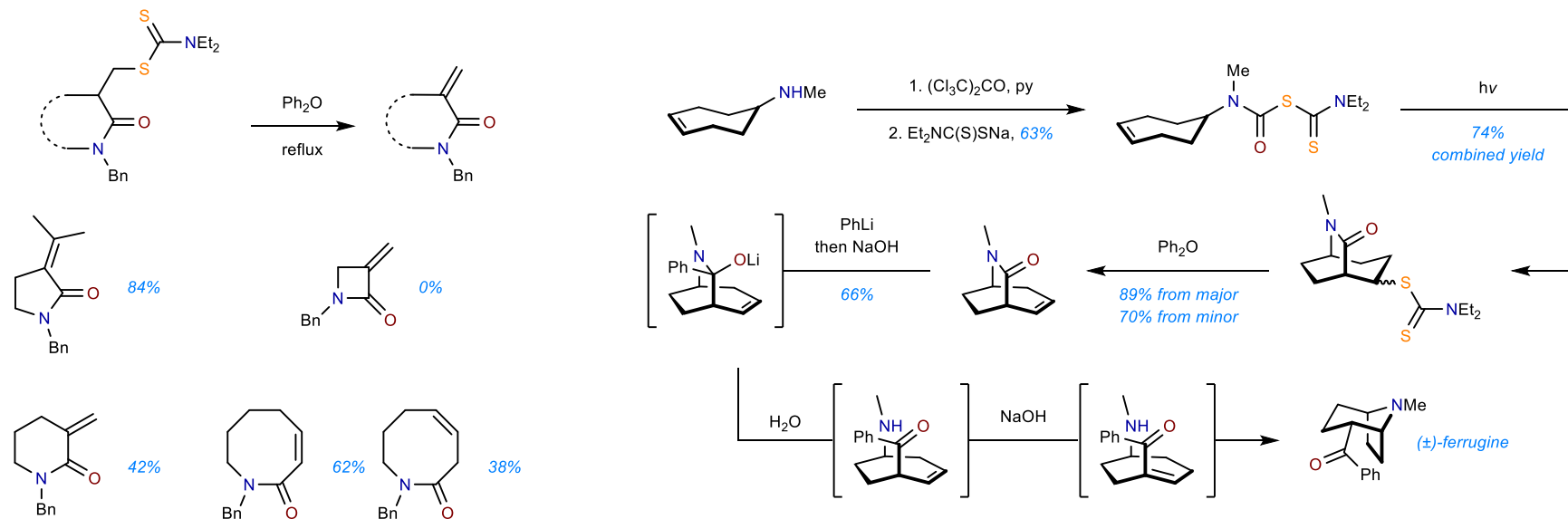
# Chugaev Elimination

## Mechanism



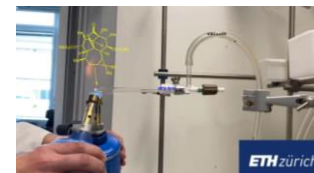
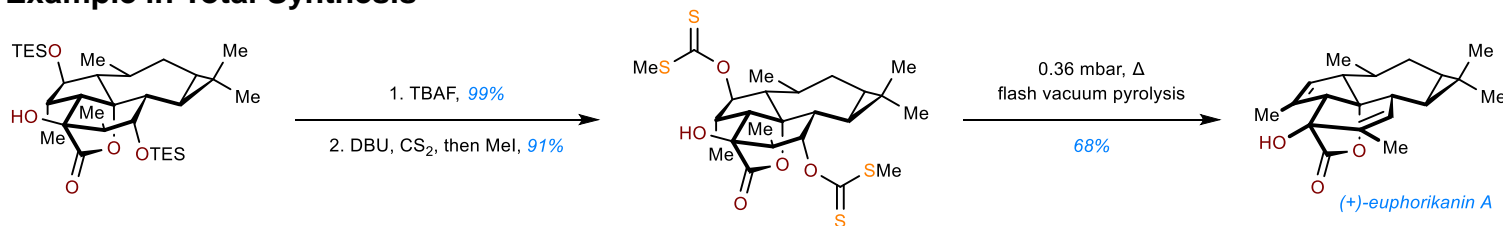
- The order of preference of H elimination follows the Saytzeff rule  $3^\circ > 2^\circ > 1^\circ$
- On occasion, this is not followed, and the more thermodynamically stable olefin is generated.

Benkeser, R. *J. Am. Chem. Soc.* **1959**, 81, 228–231. <https://doi.org/10.1021/ja01510a052>



Grainger, R. *J. Org. Chem.* **2008**, 73, 8116–8119. <https://doi.org/10.1021/jo801652x>

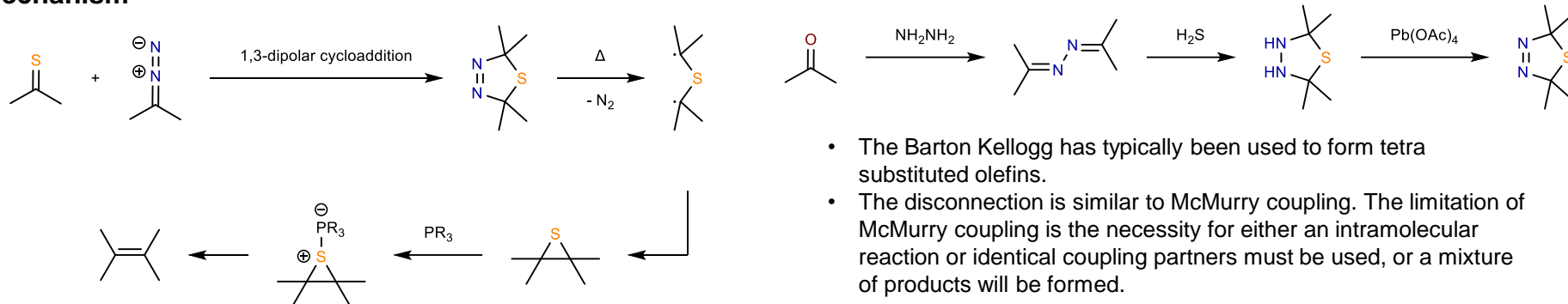
## Example in Total Synthesis



Carreira, E. *J. Am. Chem. Soc.* **2023**, 145, 27225–27229. <https://doi.org/10.1021/jacs.3c11000>

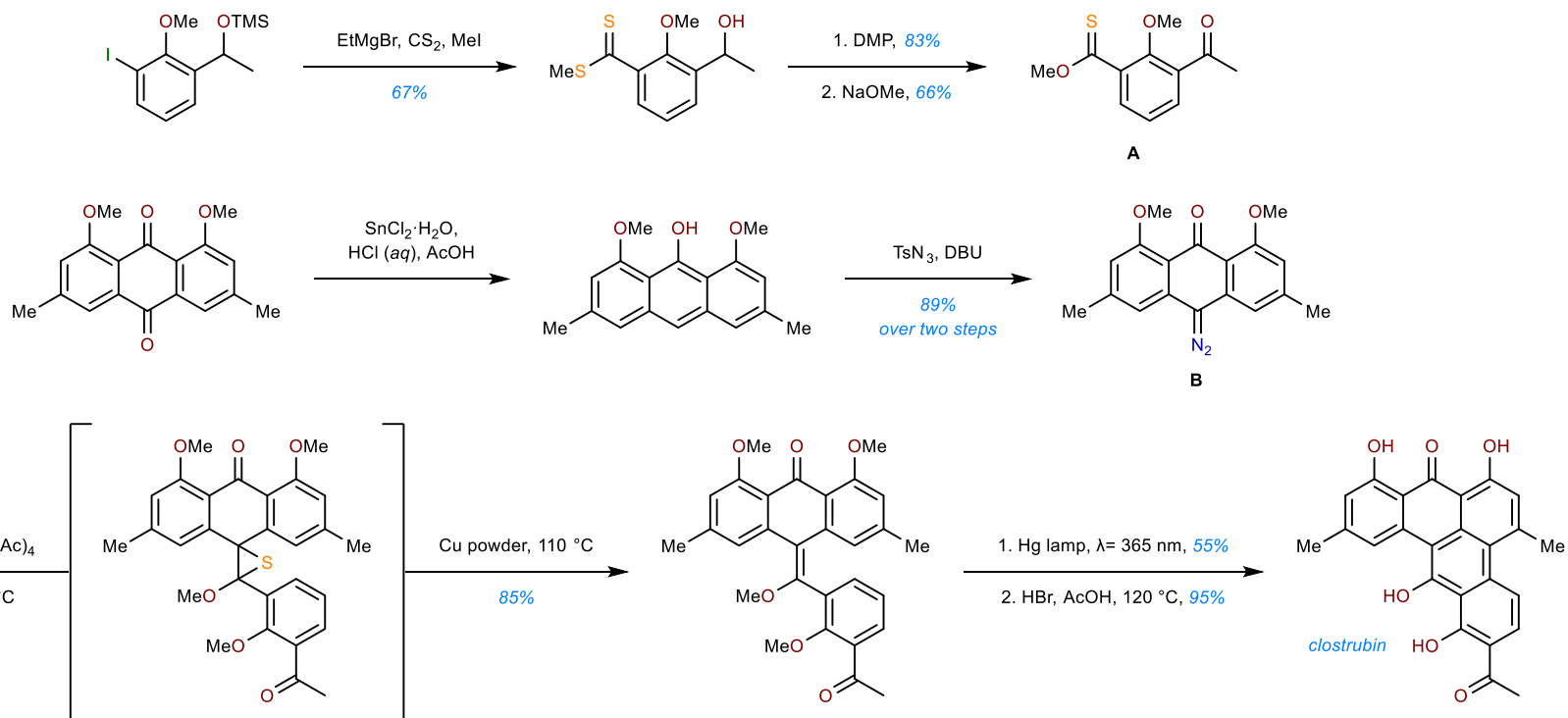
# Barton Kellogg Olefination

## Mechanism



Staudinger, H. *Helv. Chim. Acta.* **1920**, 3, 833–840. <https://doi.org/10.1002/hlca.19200030178>

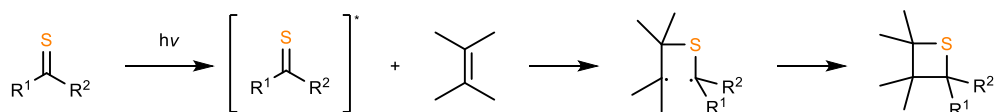
## Example in Total Synthesis



Li, A. *Nat. Commun.* **2015**, 6, 6445. <https://doi.org/10.1038/ncomms7445>

# thia-Paternò–Büchi

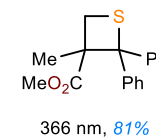
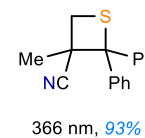
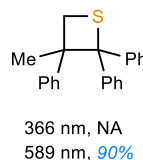
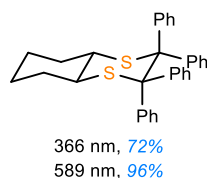
## Mechanism



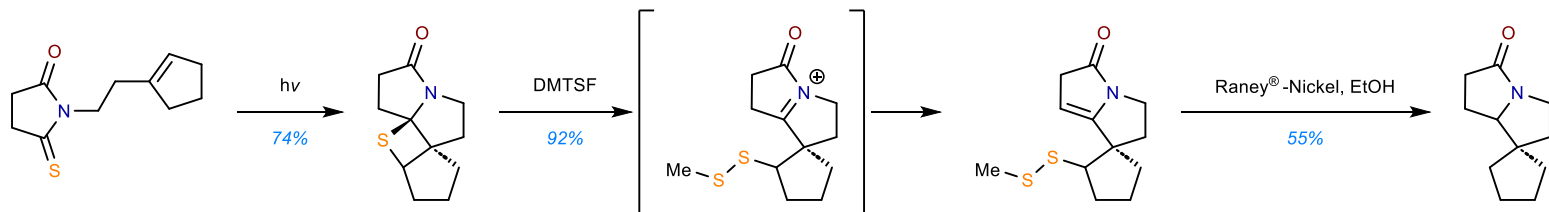
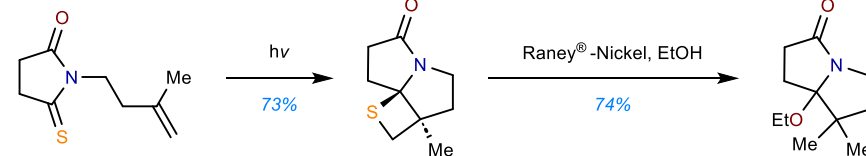
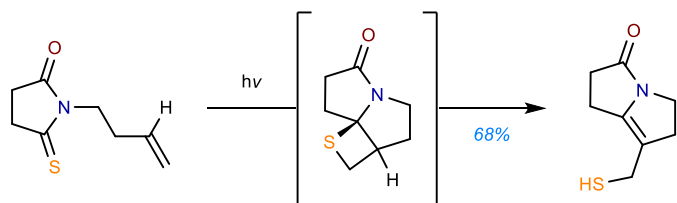
- Similar in mechanism to the Paternò–Büchi
- After excitation of the thiocarbonyl a diradical like intermediate is formed with then undergoes [2+2] with an olefin.

Boddaert, T. *Angew. Chem. Int. Ed.* **2024**, 89, e202412602. <https://doi.org/10.1002/anie.202412602>

## First Reports

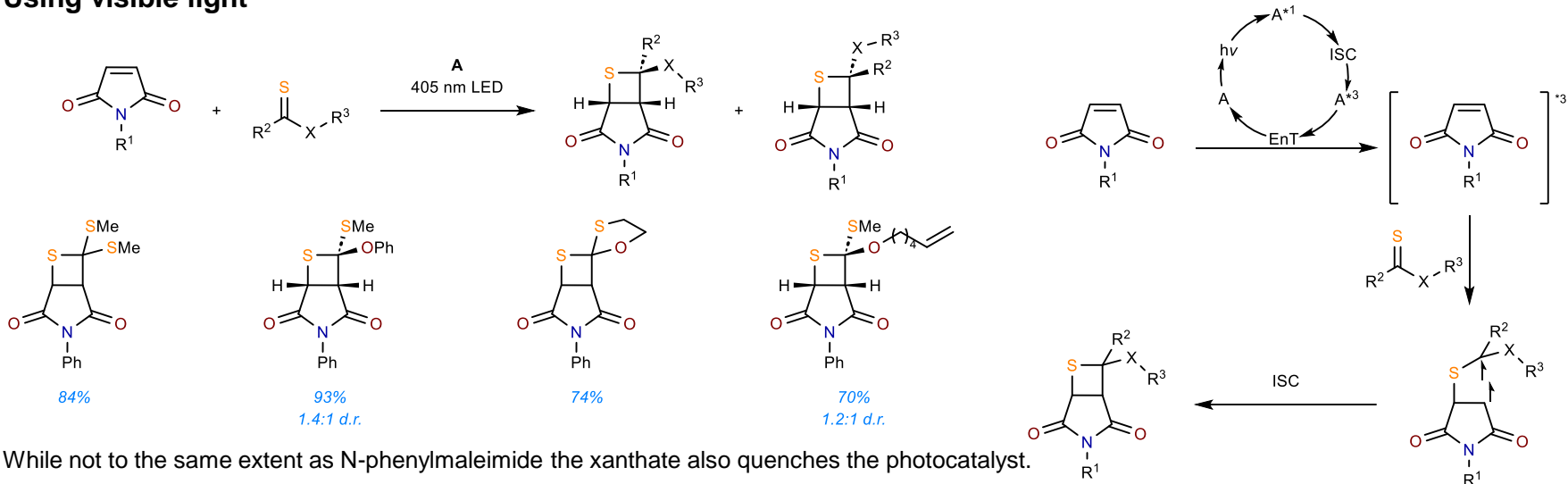


Ohno, A. *J. Am. Chem. Soc.* **1969**, 91, 5038–5045.  
<https://doi.org/10.1021/ja01046a018>



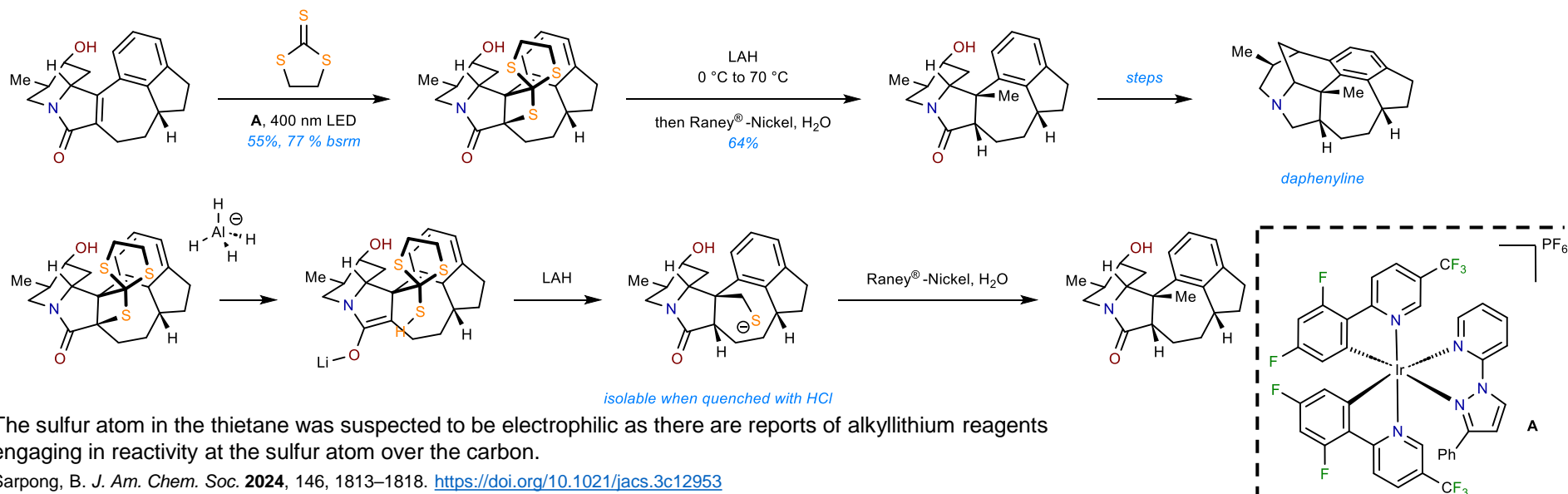
Padwa, A. *J. Org. Chem.* **2004**, 69, 33–45. <https://doi.org/10.1021/jo035127w>

## Using visible light



Liu, Q. *ACS Catal.* **2021**, 11, 446–455. <https://doi.org/10.1021/acscatal.0c05005>

## Example in Total Synthesis

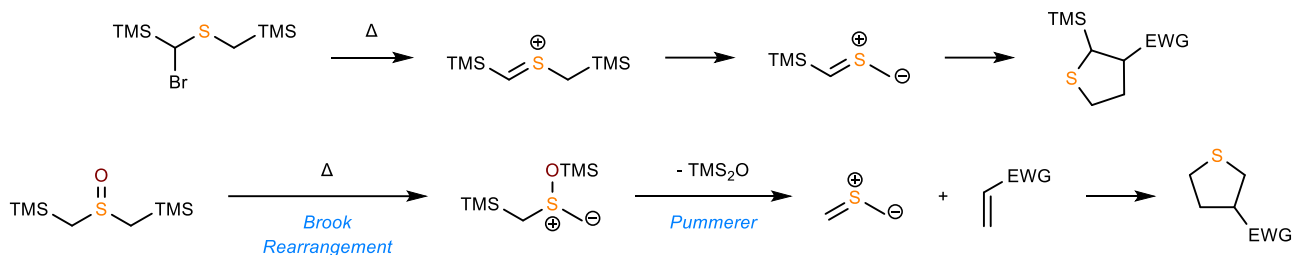


The sulfur atom in the thietane was suspected to be electrophilic as there are reports of alkyllithium reagents engaging in reactivity at the sulfur atom over the carbon.

Sarpong, B. *J. Am. Chem. Soc.* **2024**, 146, 1813–1818. <https://doi.org/10.1021/jacs.3c12953>

# Sulfur Ylide [3+2]

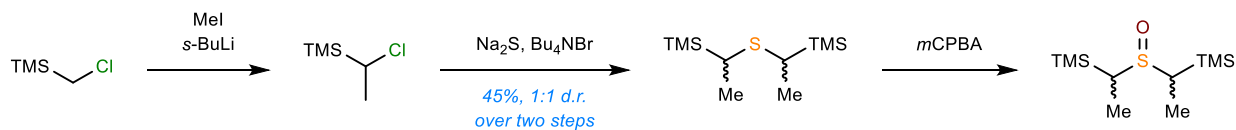
## Mechanism



Achiwa, K. *Chem. Pharm. Bull.* **1987**, 35, 1734–1740. <https://doi.org/10.1248/cpb.35.1734>

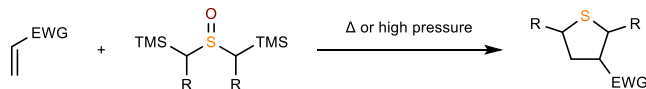
Brook, A. *Can. J. Chem.* **1968**, 46, 2115–2118. <https://doi.org/10.1139/v68-345>

## Preparation

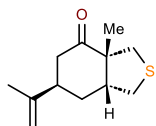


Trauner, D. *J. Am. Chem. Soc.* **2017**, 139, 11706–11709. <https://doi.org/10.1021/jacs.7b06815>

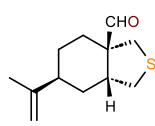
## Thermal vs. High Pressure



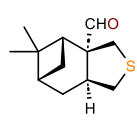
*α,β-unsaturated*



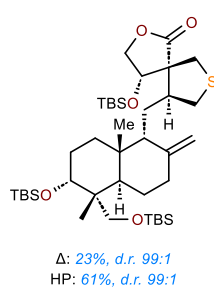
$\Delta$ : 16%, d.r. 1.3:1  
HP: 62%, d.r. 1:1



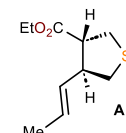
$\Delta$ : 8%, d.r. 99:1  
HP: 52%, d.r. 99:1



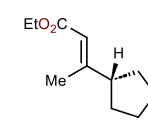
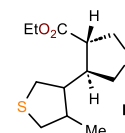
$\Delta$ : 35%, d.r. 99:1  
HP: 60%, d.r. 99:1



1,4 vs 1,6

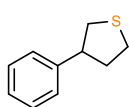


$\Delta$ : 21%, A:B 99:1  
HP: 53%, A:B 3.4:1

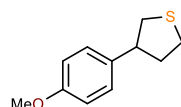


$\Delta$ : 63%  
HP: 89%

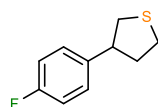
*Styrene*



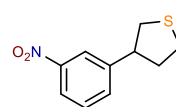
$\Delta$ : 22%  
HP: 44%



$\Delta$ : 5%  
HP: 56%

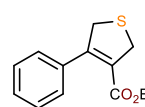


$\Delta$ : 16%  
HP: 53%

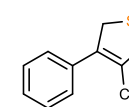


$\Delta$ : 44%  
HP: 81%

*Alkyne*

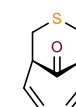


$\Delta$ : 21%  
HP: 49%



$\Delta$ : 34%  
HP: 63%

[6+3]

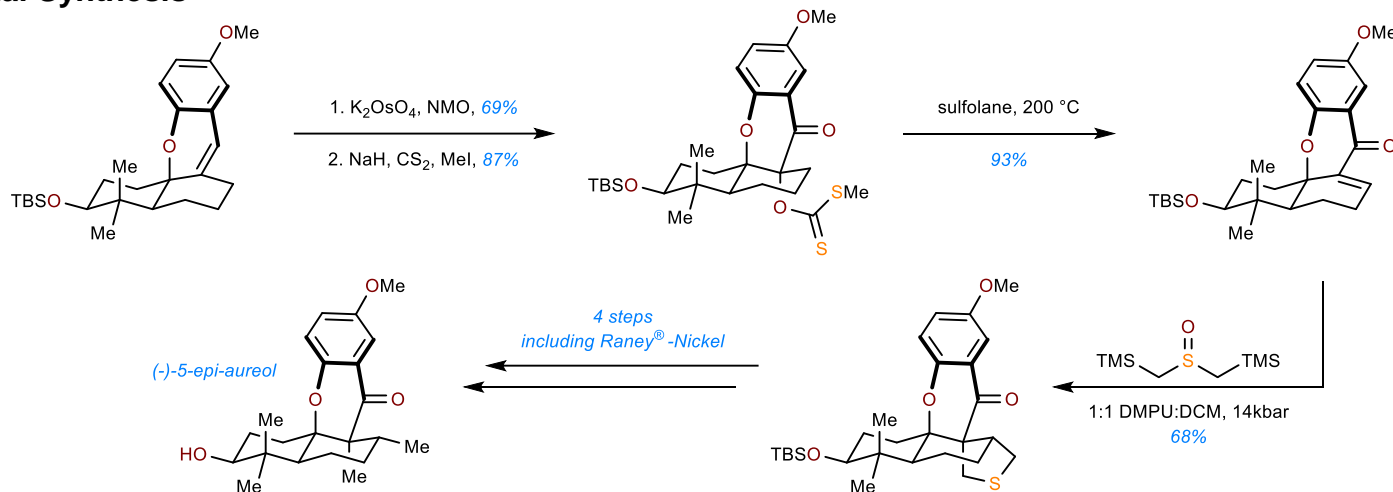


$\Delta$ : 28%  
HP: 53%

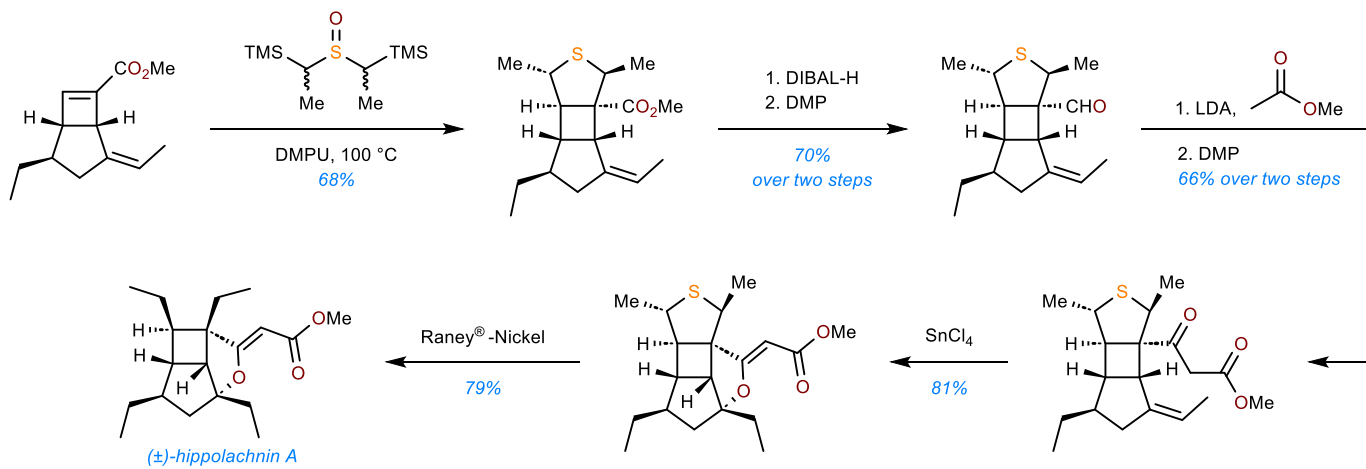
Magauer, T. *J. Am. Chem. Soc.* **2019**, 141, 13352–13357. <https://doi.org/10.1021/jacs.9b07729>

# Sulfur Ylide [3+2]

## Examples in Total Synthesis



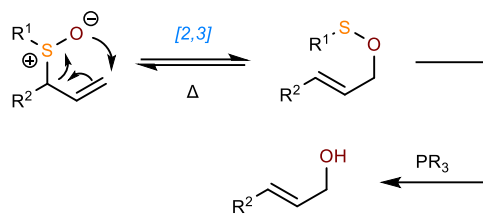
Magauer, T. *Chem. Eur. J.* **2017**, 23, 1157–1165. <https://doi.org/10.1002/chem.201605029>



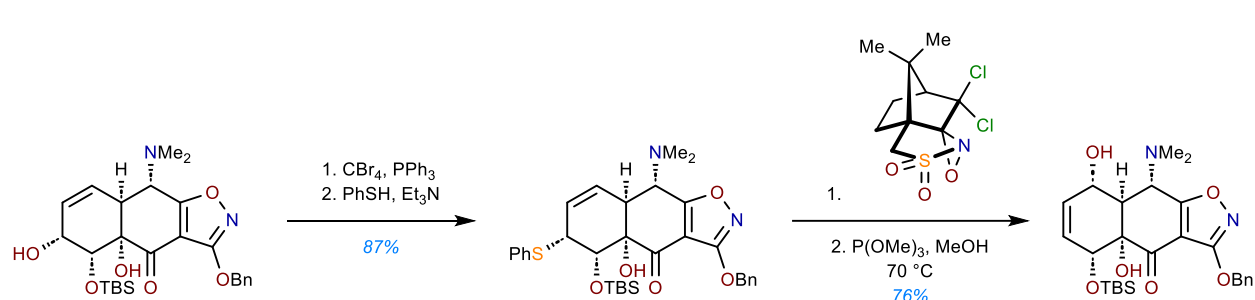
Trauner, D. *J. Am. Chem. Soc.* **2017**, 139, 11706–11709. <https://doi.org/10.1021/jacs.7b06815>

# Sigmatropic Rearrangements

## Mislow–Evans Rearrangement

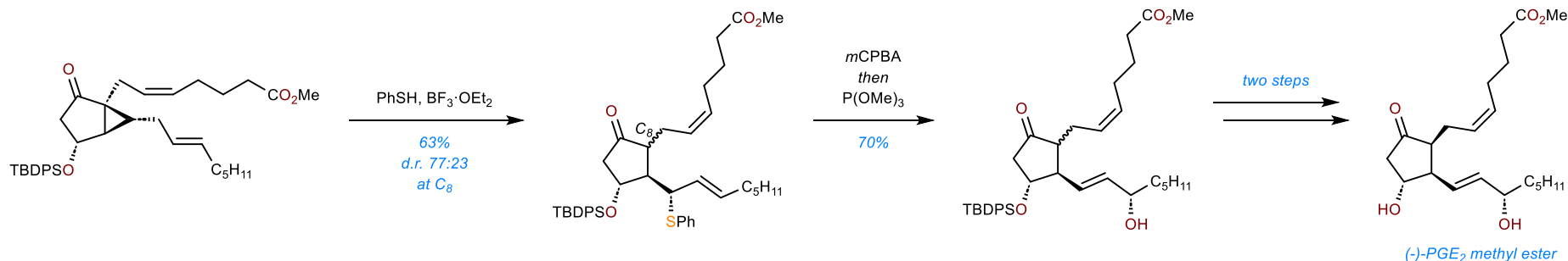


- The [2,3] is highly reversible.
- Can be pushed toward the allylic alcohol when a thiophile is used.
- E olefins are predominately favored.

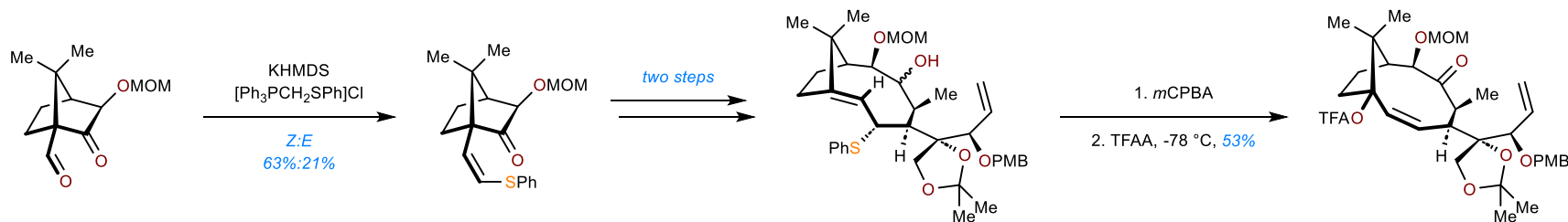


Myers, A. *Science*. **2005**, 308, 395–398. [10.1126/science.1109755](https://doi.org/10.1126/science.1109755)

## Examples in Total Synthesis



Taber, D. *J. Org. Chem.* **1992**, 57, 441–447. <https://doi.org/10.1021/jo00028a012>

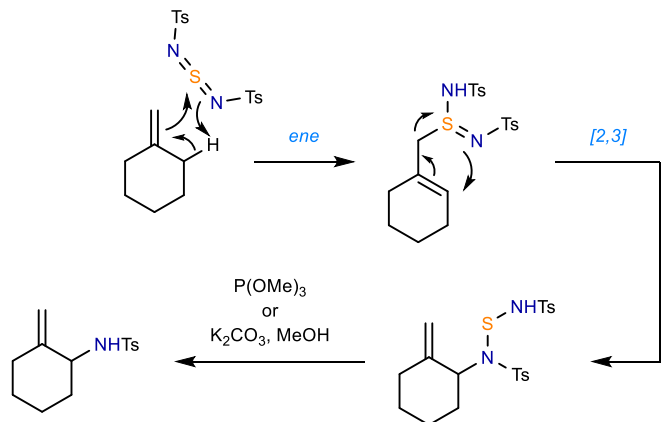


Potentially a formal Mislow–Evans rearrangement, proceeding through an  $\text{S}_{\text{N}}2'$  type pathway.

Paquette, L. *J. Org. Chem.* **1998**, 63, 129–136. <https://doi.org/10.1021/jo971591n>

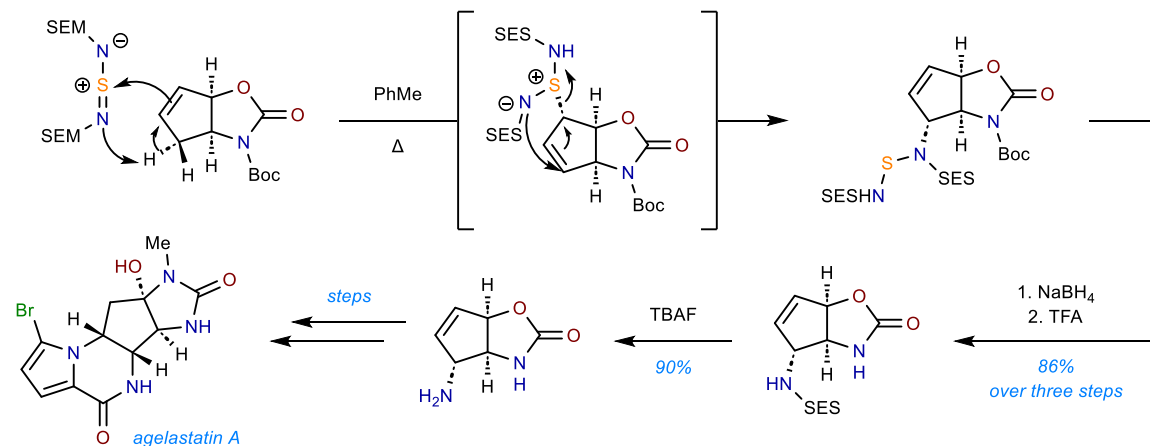
# Sigmatropic Rearrangements

## Sharpless–Kresze Allylic Amination



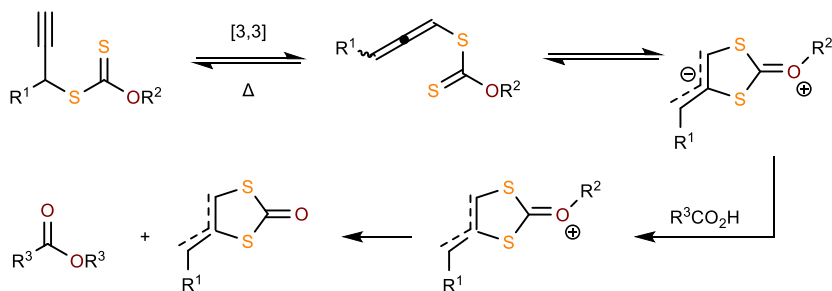
Sharpless, K.B. *J. Org. Chem.* **1999**, 41, 176–177.  
<https://doi.org/10.1021/jo00863a051>

## Application in Total Synthesis

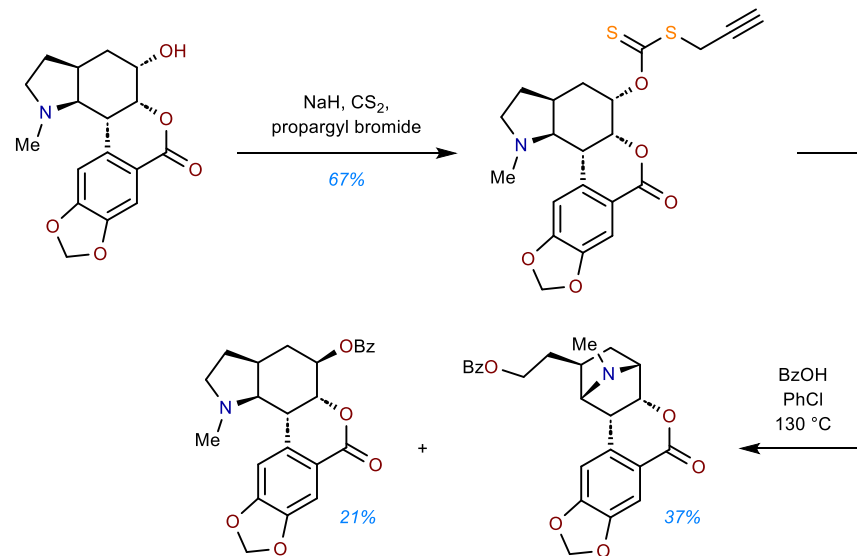


Weinreb, S. *J. Am. Chem. Soc.* **1999**, 121, 9574–9579. <https://doi.org/10.1021/ja9924871>

## Zard Inversion



## Application in Total Synthesis



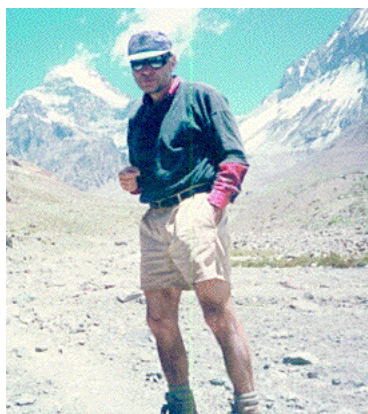
Banwell, M. *J. Org. Chem.* **2011**, 76, 8560–8563. <https://doi.org/10.1021/jo2016899>

Zard, S. *J. Am. Chem. Soc.* **1994**, 116, 9739–9740. <https://doi.org/10.1021/ja00100a045>





**Richard  
Taylor**



**Albert  
Padwa**

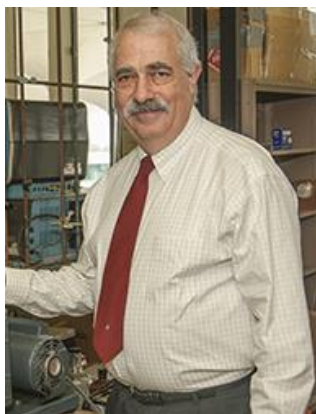


**Leo  
Paquette**



**Barry  
Trost**

**Eric  
Block**



**Samir  
Zard**



**Sir. Derek  
Barton**



**K.C.  
Nicolaou**

