

Baldwin's Rules

Kevin Olivier
February 27, 2009

Important References –

Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734-736

Baldwin, J. E. *et al. J. Org. Chem.* **1977**, *42*, 3846-3852

Johnson, C. D. *Acc. Chem. Res.* **1993**, *26*, 476-482

Jack Baldwin

Events in the life

- 1964 – received Ph.D. from Imperial College London
- 1967 – joined faculty at Pennsylvania State University
- 1970 – moved to Massachusetts Institute of Technology
- 1976 – published The Rules
- 1978 – moved to Oxford University, Fellow of Royal Society
- 1997 – knighted
- 2005 – retired

Current research interests

- biomimetic natural product synthesis
- synthetic methods
- biosynthesis

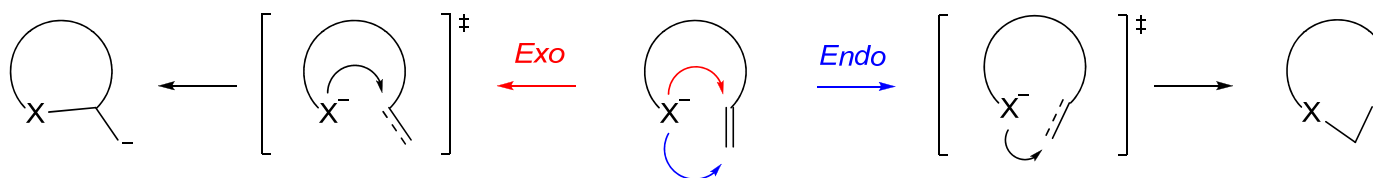
Baldwin's-Rules Nomenclature

3, 4, 5, 6, or 7

The number of atoms in the forming ring

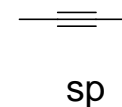
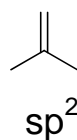
Endo or Exo

The orientation of the breaking bond relative to the smallest forming ring



Tet, Trig, or Dig

The geometry of the carbon atom participating in ring closure



Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734-736

The Rules

1. Tetrahedral Systems

3 – 7-*Exo* favored

5 & 6-*Endo* disfavored

2. Trigonal Systems

3 – 7-*Exo* favored

3 – 5-*Endo* disfavored

6 & 7-*Endo* favored

3. Digonal Systems

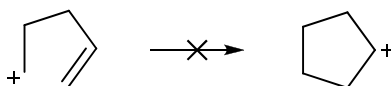
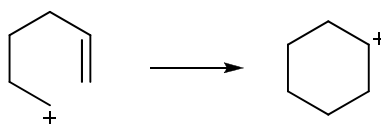
3 & 4-*Exo* disfavored

5 – 7-*Exo* favored

3 – 7-*Endo* favored

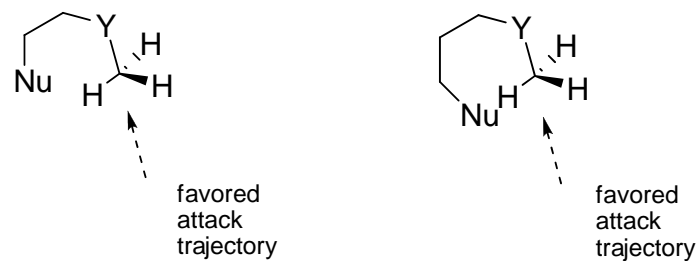
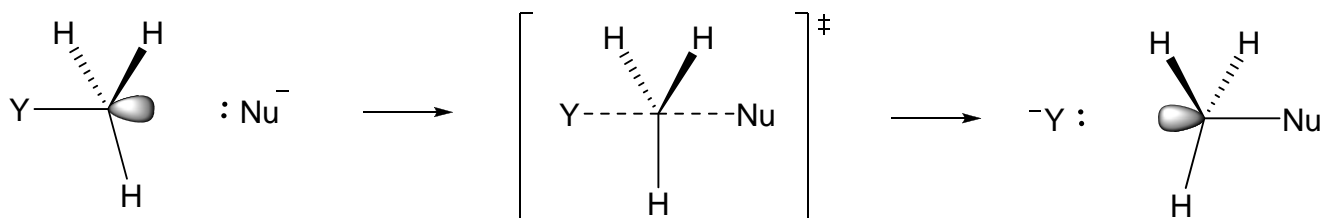
The Scope of the Rules

1. Disfavored ring closures are not impossible, just energetically more demanding than favored ring closures
2. Apply not only to anion cyclizations but also to cation and radical cyclizations



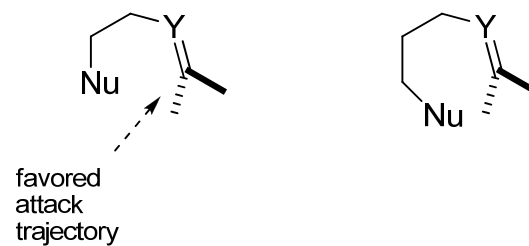
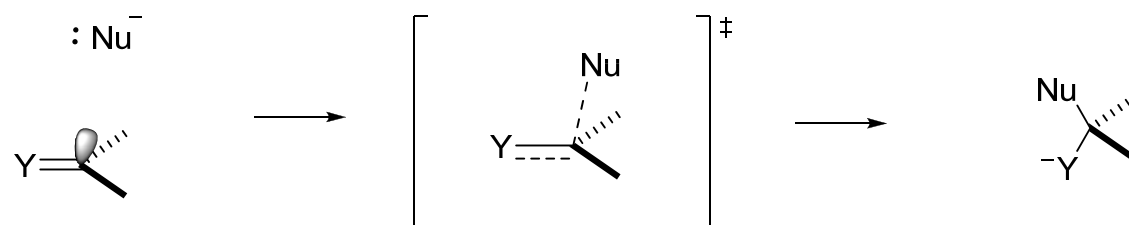
Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734-736

Rationalization: Rule 1



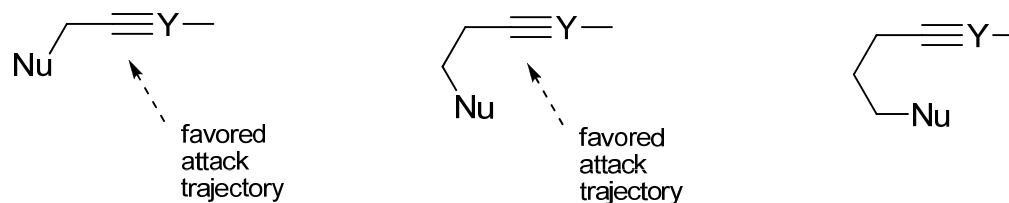
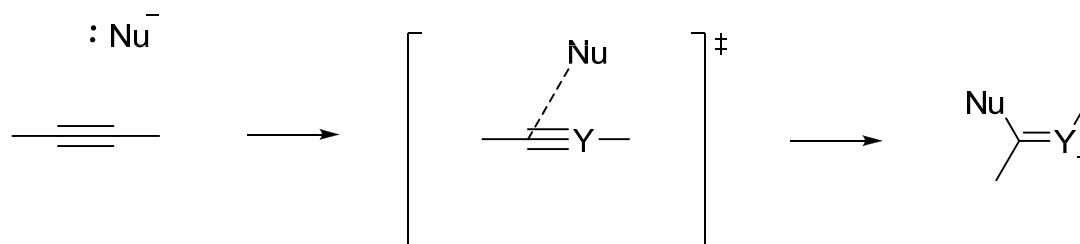
Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734-736

Rationalization: Rule 2



Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734-736
Bürgi, H. B., Dunitz, J. D., *et al. Tetrahedron*, **1974**, 30, 1563-1572

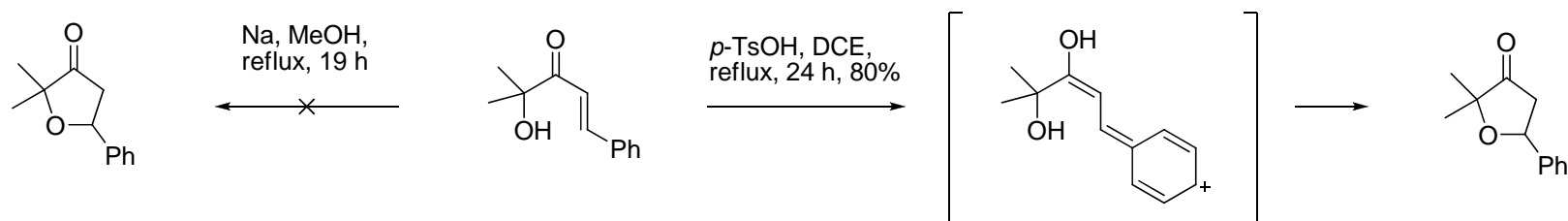
Rationalization: Rule 3



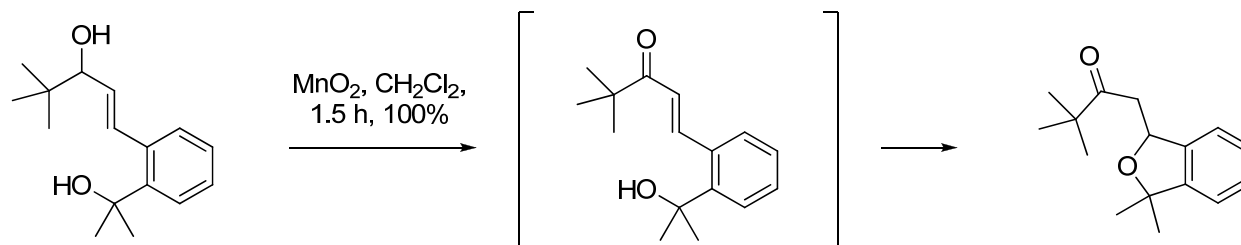
Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734-736

Experimental Investigation of the Rules

➤ 5-Endo-Trig



➤ 5-Exo-Trig



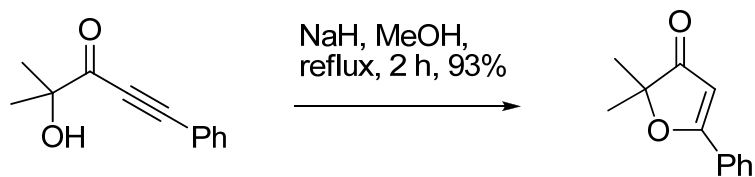
Baldwin, J. E. *et al.* *J. Org. Chem.* **1977**, *42*, 3846-3852

Nazarov, I. N. and Elizarova, A. N. *Bull. Acad. Sci. USSR Cl. Sci. Chem.* **1948**, 107.

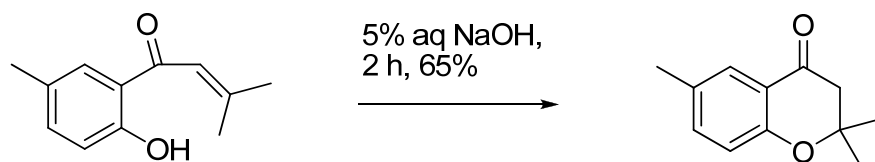
Nazarov, I. N. and Elizarova, A. N. *Chem. Abstr.* **1948**, *42*, 7737

Experimental Investigation of the Rules

➤ 5-Endo-Dig



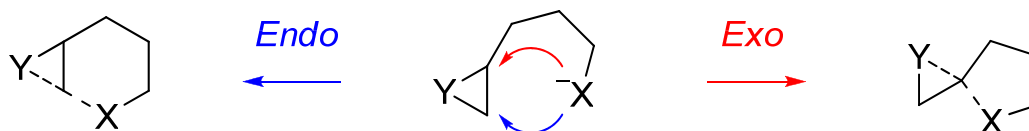
➤ 6-Endo-Trig



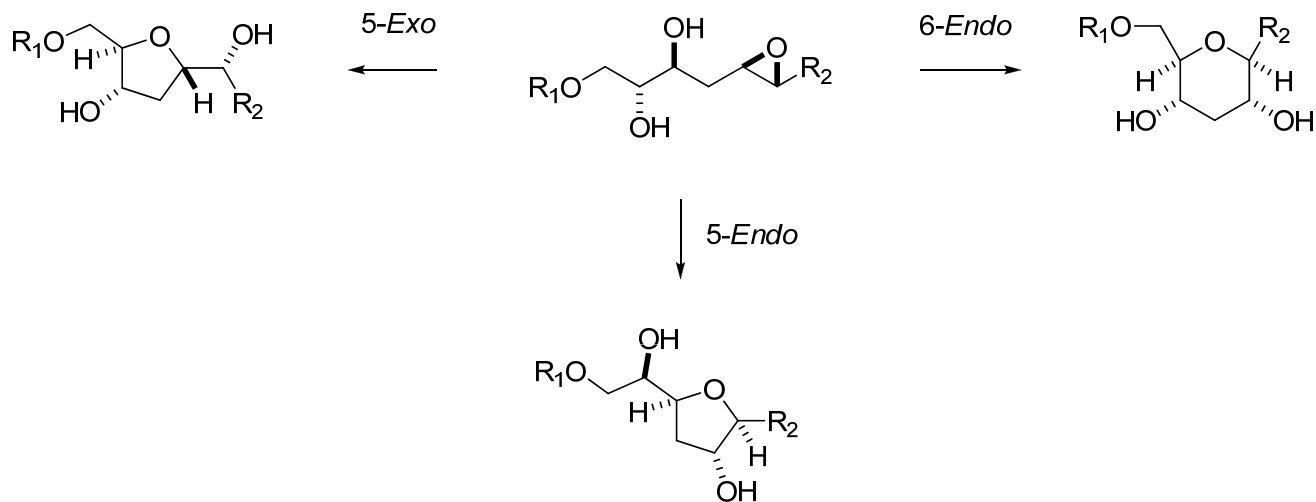
Baldwin, J. E. *et al.* *J. Org. Chem.* **1977**, *42*, 3846-3852

The Fourth Rule

Cyclizations that open 3-membered rings constitute a separate class



Generally, 5-*Exo* predominates among competing modes



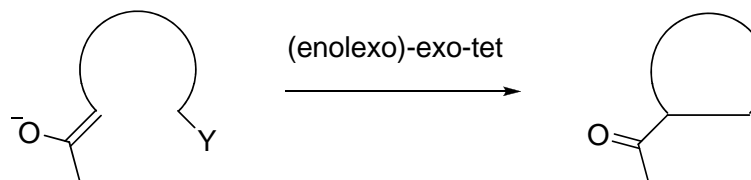
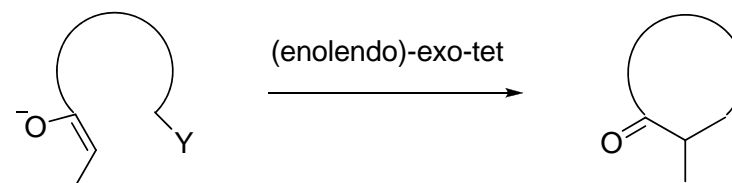
Baldwin, J. E. *et al. J. Org. Chem.* **1977**, *42*, 3846-3852

Shevlin, C. G., Janda, K. D., Lerner, R. A. *et al. J. Am. Chem. Soc.* **1993**, *115*, 8453-8454

Borhan, B. *et al. Org. Lett.* **2001**, *3*, 2489-2492

More Rules: Cyclizations of Enolates

enolendo or enolexo



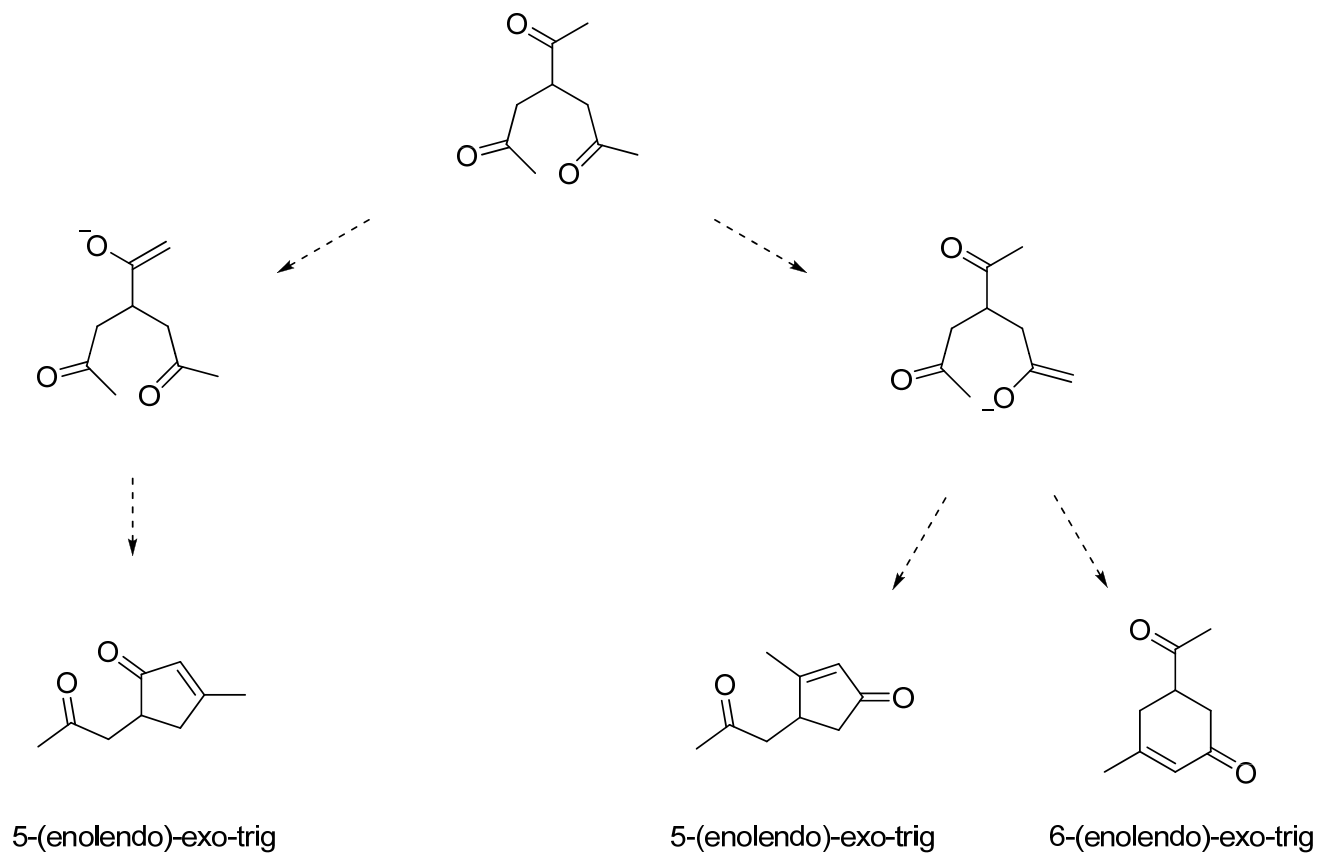
exo-tet

3 – 5 (enolendo) disfavored
6 & 7 (enolendo) favored
3 – 7 (enolexo) favored

exo-trig

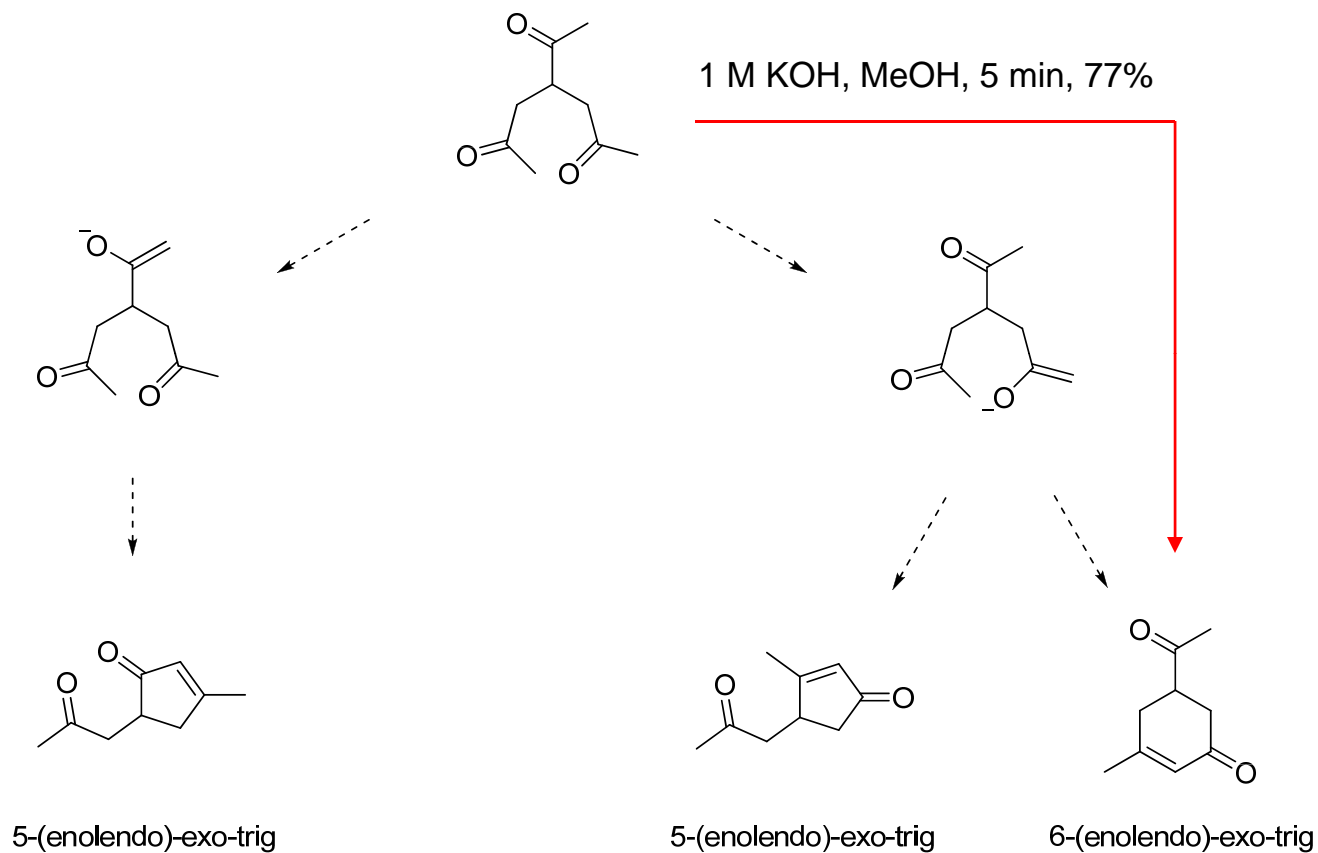
3 – 5 (enolendo) disfavored
6 & 7 (enolendo) favored
3 – 7 (enolexo) favored

Experimental Investigation: Cyclizations of Enolates



Baldwin, J. E. *et al. Tetrahedron* **1982**, 38, 2939-2947

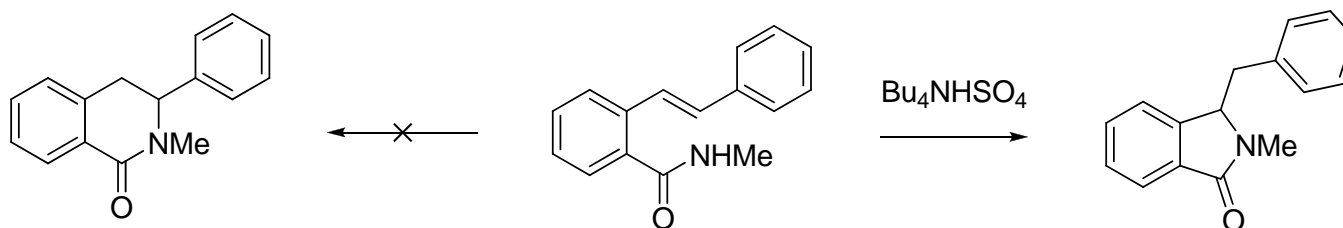
Experimental Investigation: Cyclizations of Enolates



Baldwin, J. E. *et al. Tetrahedron* **1982**, 38, 2939-2947

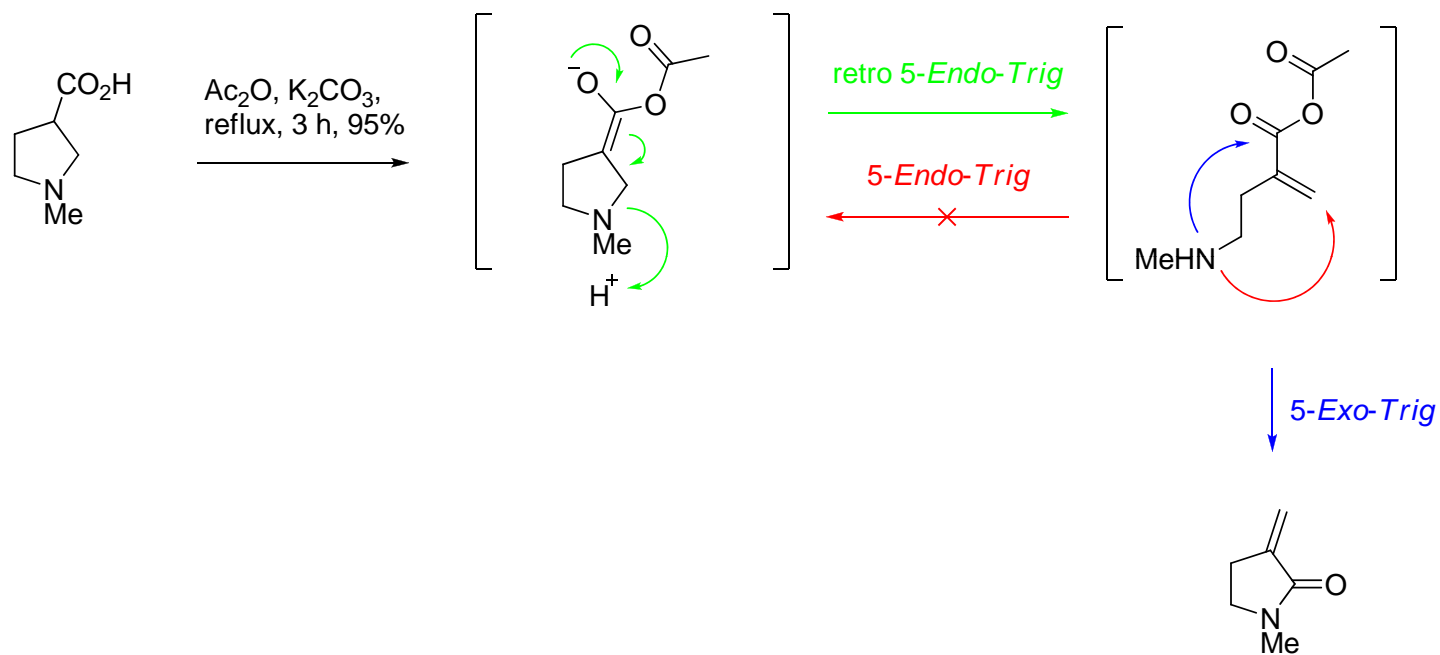
Graded Favorability

- Some favored ring closures are more favored than others
- For example, 5-*Exo-Trig* is more favored than 6-*Endo-Trig*



Napolitano, E. *et al. Tetr. Lett.* **1983**, 24, 1319-1320

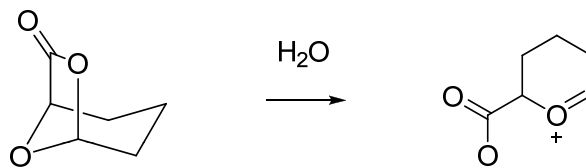
Exceptions to the Rules



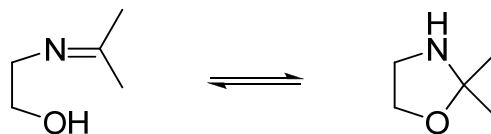
Rapoport, H. *et al. J. Org. Chem.* **1974**, 39, 893-902

Exceptions to the Rules

- Relief-of-strain driven disfavored retro *5-Endo-Trig*

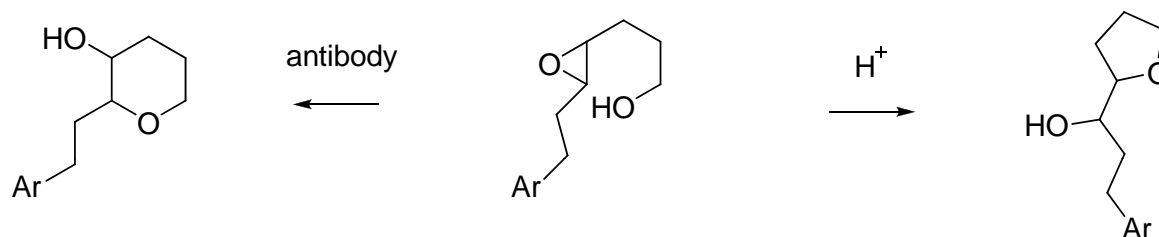


- *5-Endo-Trig* cyclic *N,O*-ketal formation



Johnson, C. D. *Acc. Chem. Res.* **1993**, 26, 476-482
Fife, T. H. *et al. J. Org. Chem.* **1992**, 57, 1295-1298
Johnson, C. D. *Tetrahedron* **1985**, 41, 5919-5928

Enzymatic Exception



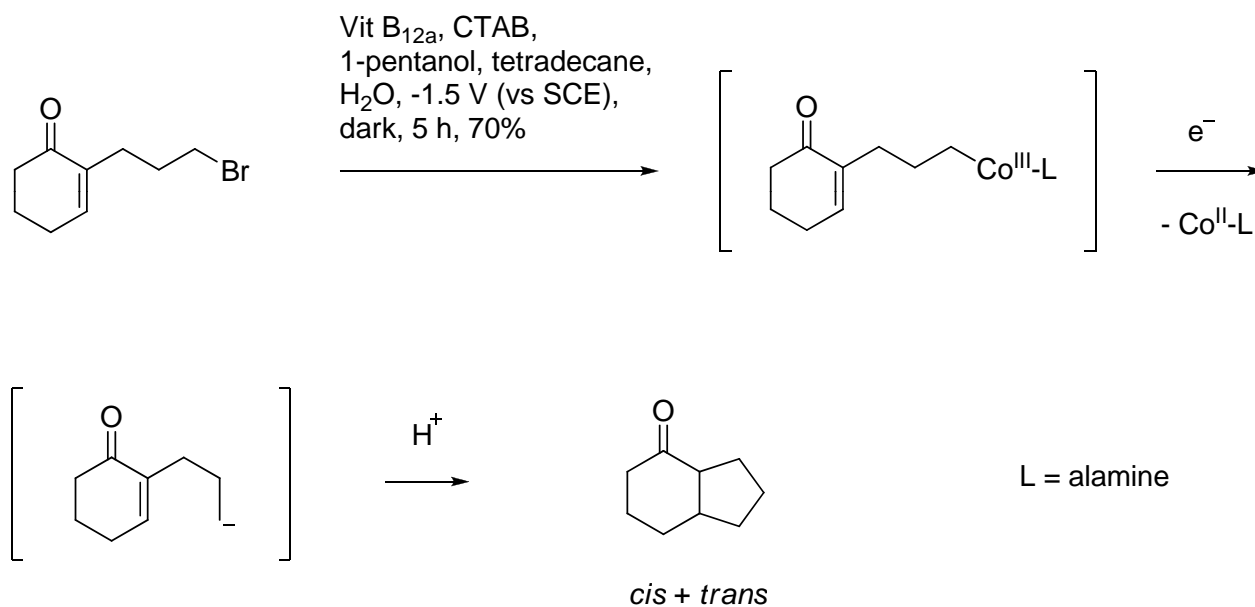
- calculations predict 5-*Exo* pathway favored by 1.8 kcal/mol
- designed antibody catalyzes 6-*Endo* pathway with high selectivity

Janda, K. D., Shevlin, C. G., Lerner, R. A. *Science* **1993**, 259, 490

Shevlin, C. G., Janda, K. D., Lerner, R. A. *et al. J. Am. Chem. Soc.* **1993**, 115, 8453-8454

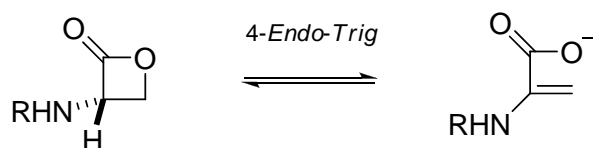
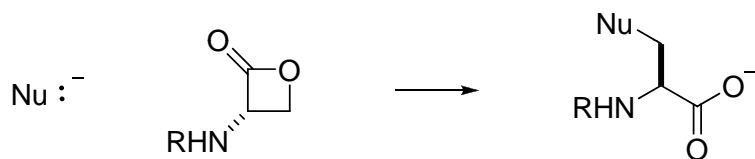
Electrochemical Exception

Electrochemical 5-*Endo-Trig* in a Microemulsion



Serine β -Lactone

- A method for β -substitution of amino acids
- The elimination side reaction is not observed
- It requires retro 4-*Endo-Trig* ring opening



Entry	R	Nu	Yield (%)
1	Boc	NH_3^+	79
2	H_2^+TsO^-	N_3	96
3	Cbz	OAc	97
4	$\text{H}_2^+\text{CF}_3\text{CO}_2^-$	L-Cys	93
5	Cbz	Me	47
6	Cbz	<i>t</i> -Bu	48
7	Cbz	Ph	55

Vedera, J. C. *et al.* *J. Am. Chem. Soc.*, **1985**, *107*, 7105-7109

Vedera, J. C. *et al.* *J. Am. Chem. Soc.*, **1987**, *109*, 4649-4659

Vedera, J. C. *et al.* *J. Am. Chem. Soc.*, **1988**, *110*, 2237-2241

Williams, R. M. *Synthesis of Optically Active α -Amino Acids* Pergamon Press, 1989, 134, 136.

Summary

Insights from Baldwin's rules

- ❑ Ease of ring formation depends on more than ring size
- ❑ Cyclizations of small rings may be impeded by the inability of the reacting termini to achieve proper orbital alignment
- ❑ Baldwin's rules are rules of thumb meant to aid in synthetic planning

Exceptions to Baldwin's rules

- ❑ Even within the stated limits of the rules, exceptions can be found
 - ❑ A Baldwin's-rules disfavored process can be driven forward under special conditions
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