Reviews:

Conformational Analysis of Cyclopentane

• In the envelope conformation, one carbon atom is positioned out of plane from the others.
• In the half-chair conformation, three atoms are co-planar.
• Interconversion between the envelope and half-chair conformations, known as a “pseudorotation,” is rapid. The two conformers differ in energy by 0.9 kcal/mol, with the envelope conformation being preferred.

Synthetic Methods For the Construction of Cyclopentanes:
• Radical Cyclizations
  • General Mechanism for Free Radical Cyclizations

Initiation
A – B \rightarrow A^* + B^*

Propagation
X
\rightarrow
\text{H}^* \text{H}
\rightarrow
\text{H–M}
\rightarrow
\text{H}^* \text{H}
\rightarrow
\text{M}^* + \text{H}^* \text{H}

5-Membered Ring Synthesis by Radical Cyclization

Baldwin’s Rules for Ring Closure:

<table>
<thead>
<tr>
<th></th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>endo-tet</td>
<td>–</td>
<td>–</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>exo-tet</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>endo-trig</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>√</td>
</tr>
<tr>
<td>exo-trig</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>endo-dig</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>exo-dig</td>
<td>x</td>
<td>x</td>
<td>√</td>
<td>√</td>
</tr>
</tbody>
</table>


For revisions and modifications to Baldwin’s rules, see:

• 5-exo-trig cyclization is kinetically favored over 6-endo-trig cyclization.
• This preference is explained by stereoelectronic effects where formation of the five-membered ring is favored because of better orbital overlap:


Alpay Dermenci, Fan Liu
Effects of non-bonded interactions on the regioselectivity of radical cyclizations:

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>ratio (exo:endo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H(\cdot)  (\cdot)</td>
<td>(\cdot)  (\cdot)</td>
<td>98 : 2</td>
</tr>
<tr>
<td>H(\cdot)  (\cdot)  (\cdot)</td>
<td>(\cdot)  (\cdot)  (\cdot)</td>
<td>40 : 60</td>
</tr>
<tr>
<td>H(\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)</td>
<td>(\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)</td>
<td>&gt;99 : 1</td>
</tr>
<tr>
<td>H(\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)</td>
<td>(\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)</td>
<td>68 : 32</td>
</tr>
<tr>
<td>H(\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)</td>
<td>(\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)</td>
<td>98 : 2</td>
</tr>
<tr>
<td>H(\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)</td>
<td>(\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)</td>
<td>55 : 45</td>
</tr>
</tbody>
</table>

Rate comparisons of 5-exo-trig free radical cyclization reactions:

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Rate ((s^{-1}))</th>
<th>(E_a) (kcal/mol)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>H(\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)</td>
<td>(\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)</td>
<td>4 x 10(^7)</td>
<td>6.2</td>
<td>(a)</td>
</tr>
<tr>
<td>H(\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)</td>
<td>(\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)</td>
<td>4 x 10(^8)</td>
<td>3.6</td>
<td>(c)</td>
</tr>
<tr>
<td>H(\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)</td>
<td>(\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)</td>
<td>2 x 10(^{-1})</td>
<td>16.3</td>
<td>(e)</td>
</tr>
<tr>
<td>H(\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)</td>
<td>(\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)  (\cdot)</td>
<td>2 x 10(^4)</td>
<td>8.3</td>
<td>(f)</td>
</tr>
</tbody>
</table>


Alpay Dermenci, Fan Liu
Stereochemistry in radical cyclizations

Chair-like exo transition states are favored, where the substituents are preferentially placed in pseudoequatorial positions. The alternative boat-like transition states are however close in energy and selectivity is often modest:

Chair-like

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{trans} \\
\text{H} & \quad \text{cis}
\end{align*}
\]

\[
\begin{align*}
64 : 36 & \\
29 : 71 & \\
33 : 67 & \\
83 : 17 & \\
100 : 0
\end{align*}
\]

Radical Initiators

The O–O bond of peroxides is weak and can be cleaved thermally or photochemically. Peroxides are commonly used as a source for radicals:

\[
\frac{\text{O} \text{O}}{\Delta \text{or} \text{hv}} \rightarrow 2 \times \text{RO}^* \]

In the following example, C–H abstraction by the t-butoxy radical gave a stabilized radical intermediate, which underwent cyclization:

Azo compounds are also commonly used to generate radicals:

\[
\frac{\text{N} \text{N}}{\Delta \text{or} \text{hv}} \rightarrow \text{R}^* + \text{N}_2 + \text{R}' \]

Azoisobutyronitrile (AIBN) is frequently used as an initiator in radical reactions. The cyano substituent stabilizes the resulting radical and allows for azo decomposition under relatively mild conditions (t\(_{1/2}\) (C\(_6\)H\(_6\), 100 °C) = 6 h):

\[
\frac{\text{NC} \text{CO}_2\text{Et}}{\Delta \text{or} \text{hv}} \rightarrow \frac{\text{Ph} \text{NC} \text{CO}_2\text{Et}}{\text{Ph}}
\]


Acyl selenides can also be used to initiate radical cyclization reactions:

\[
\text{RSePh} + \text{Bu}_3\text{SnH} \rightarrow \text{RSe} + \text{Bu}_3\text{SnH}
\]

\[
\text{CH}_3 \quad \text{CH}_3 \quad \text{AIBN (10 mol%)} \quad \text{Bu}_3\text{SnH} \quad \text{C}_6\text{H}_6, 80 \degree \text{C}, 91\% \\
\text{H}_3\text{C} \quad \text{O} \quad \text{OEt} \quad \text{Br} \quad \text{CH}_3 \quad \text{CH}_3 \quad \text{AIBN (10 mol%)} \quad \text{Bu}_3\text{SnH} \quad \text{C}_6\text{H}_6, 80 \degree \text{C}, 91\% \\
\]

\[
\text{THIOCARBONATES} \quad \text{Bu}_3\text{SnH, AIBN} \quad \text{Toluene, 110 \degree \text{C}, 60\% , \text{dr}=1:1} \\
\]

Thionocarbonates can also be used as substrates for radical cyclization reactions:

\[
\]

Thionoesters can be used for radical cyclization under either photochemical conditions or in the presence of tin hydride reagents:

\[
\text{BU3SnH, AIBN} \quad \text{Tol}, 110 \degree \text{C, } >58\% \\
\]

\[
\text{BU3SnH, AIBN} \quad \text{Tol}, 110 \degree \text{C, } >58\% \\
\]

\[
\text{BU3SnH, AIBN} \quad \text{Tol}, 110 \degree \text{C, } >58\% \\
\]
Trialkylboranes can be used with O₂ to generate radicals. This reaction proceeds readily even at –78 º C, making it an ideal radical cyclization initiator for functionalized substrates:

\[ \text{R}_3\text{B} + \text{O}_2 \rightarrow \text{R}_2\text{BOO}^* + \text{R}^* \]


Bu₃SnH is used as the terminal hydride donor in the following example:

\[ \text{Et}_3\text{B}, \text{O}_2, \text{Bu}_3\text{SnH} \quad \text{toluene, –20 º C} \quad 75\%, \text{dr} = 94:6 \]


Higher diastereoselectivities can be obtained when Et₃B/O₂ is used to initiate radical formation than when AIBN is used:

\[ \text{AlBN, Bu}_3\text{SnH} \quad \text{C}_6\text{H}_6, 80 \text{ º C} \quad 71\%, \text{dr} = 89:11 \]

\[ \text{Et}_3\text{B}, \text{O}_2, \text{Bu}_3\text{SnH} \quad \text{toluene, –78 º C} \quad 74\%, \text{dr} = 98:2 \]


In the following example, higher yields were observed when Et₃B/O₂ was used:

\[ \text{AlBN, Bu}_3\text{SnH} \quad \text{C}_6\text{H}_6, 80 \text{ º C} \quad 86\%, \text{dr} = 1:1 \]

\[ \text{Et}_3\text{B}, \text{O}_2, \text{Bu}_3\text{SnH} \quad \text{toluene, –78 º C} \quad 30\%, \text{dr} = 1:1 \]


The choice of reagents can have a dramatic influence on the stereoselectivity of a reaction:

\[ \begin{align*}
\text{Bu}_3\text{SnH}, \text{AlBN} & \rightarrow \text{Bu}_3\text{SnH}, (\text{TMS})_3\text{SiH} \\
\text{82%} & \quad E/Z = 98:2
\end{align*} \]

\[ \begin{align*}
\text{B(C}_2\text{H}_3)_3, \text{O}_2 & \rightarrow \text{B(C}_2\text{H}_3)_3, (\text{TMS})_3\text{SiH} \\
\text{85%} & \quad E/Z = 11:89
\end{align*} \]

The rate of alkenyl radical inversion is faster than that of atom transfer even at –78 º C (Curran, D. P.; Chen, M. H.; Kim, D. J. Am. Chem. Soc. 1989, 111, 6265–6276.

The more sterically demanding silane has a slower rate of hydrogen abstraction and is too encumbered to transfer hydride to the thermodynamically favored isomer.


Examples of Cyclopentane Synthesis via Radical cyclization in Synthesis

Synthesis of silphinene:

\[ \begin{align*}
\text{AlBN, Bu}_3\text{SnH} & \rightarrow \text{AlBN, Bu}_3\text{SnH} \\
\text{70%} & \quad \text{dr} = 1:1
\end{align*} \]


Fan Liu, Alpay Dermenci
Curran has shown that a tandem radical cyclization strategy can be used as a general approach to the triquinanes, such as hirsutene:

\[
\begin{align*}
\text{Hirsutene} & \xrightarrow{\text{Bu}_3\text{SnH, AIBN, } C_6H_6, 80^\circ C} \text{Hirsutene} \\
\end{align*}
\]

80%


- Synthesis of modhephene:

\[
\begin{align*}
\text{Bu}_3\text{SnH (30 mol\%)} & \xrightarrow{\text{AlIBN (10 mol\%)} , C_6H_6, 80^\circ C} \text{Modhephene} \\
\end{align*}
\]

90%

5 steps


- Double radical cyclization for the synthesis of a butenolide:

\[
\begin{align*}
\text{Stork, G.; Mook, R. J. Am. Chem. Soc.} & \text{1983, 105, 3720–3722.} \\
\end{align*}
\]

75%

88%

- Radical spirocyclization:

\[
\begin{align*}
\end{align*}
\]

- 5-Membered Ring Synthesis by Radical Cyclization

*Alpay Dermenci, Fan Liu*
Alpay Dermenci, Fan Liu

**Synthesis of merrilactone A:**

In the example below, the radical cyclization cascade was initiated by addition of $n$-Bu$_3$Sn radical to the alkyne, followed by 5-exo-trig cyclization, a procedure originally developed by Stork. Protodestannylation then provided the observed product:

- Synthesis of 7,8-epoxy-4-basmen-6-one by a transannular radical cyclization: in this example, irradiation of a $m$-(trifluoromethyl)benzoate ester in the presence of $N$-methylcarbazole, an electron-donor sensitizer, led to radical generation and expulsion of $m$-(trifluoromethyl)benzoic acid (method of Saito et al., reference below):

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5-Membered Ring Synthesis by Radical Cyclization

**Synthesis of estrone using a radical macrocyclization/transannular cyclization cascade:**


**Vinyl radicals can undergo 1,5-hydrogen abstraction followed by cyclization:**

- Dénès, F.; Beaufils, F.; Renaud, P. *Synlett*, 2008, 2389 - 2399.


In an approach to triquinanes, a series of 5-exo cyclizations was used to generate the triquinane structure from a linear precursor:

- In the presence of Sml₂, 1,5-dicarbonyls undergo reductive coupling to give cyclopentanediols. Cis stereochemistry is generally favored because of chelation to Sm³⁺:

- The intermediate ketyl radical can undergo 5-exo cyclizations:


5-Membered Ring Synthesis by Radical Cyclization

Examples of SmI₂-Mediated Reductive Cyclizations in Synthesis

- A tandem cyclization and acyl transfer provided 5,5-bicyclic systems: alkyl halides are reduced in an order which parallels their reduction potentials (I > Br > Cl):

![Example Reaction]


- Synthesis of bridged nine-membered rings, en route to eunicellin:

![Example Reaction]


- Synthesis of muscone:

![Example Reaction]

Multiple $\text{SmI}_2$-mediated cyclizations were used in the synthesis of (-)-grayanotoxin III:

- In the synthesis of patchoulenone, thiophenol was used as a terminal hydride donor:

  $\text{SmI}_2$, HMPA
  THF, –78 → 0 °C
  86%
  single diastereomer

  $\text{SmI}_2$, HMPA
  THF, –78 º C
  78%
  single diastereomer

- A 6-endo/5-exo cyclization cascade was used to construct the core structure of maecrystal Z:

  $\text{SmI}_2$, LiBr
  THF, –78 º C, 54%

  $\text{SmI}_2$, HMPA
  THF, –78 º C
  54%
  single diastereomer


In the synthesis of patchoulenone, thiophenol was used as a terminal hydride donor:

$\text{SmI}_2$, HMPA
PhSH, THF
0 º C, 74%

(-)-patchoulenone


$\text{SmI}_2$, HMPA
THF, –78 → 23 °C
64%, $dr = 93:7$

caryose