

Radicals II: Stereoselective Reactions

October 23, 2009
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Stereoselective Radical Reactions

- Radical cyclizations
 - From acyclic systems (Beckwith-Houk model)
 - From cyclic systems
- Radical additions
- Chiral auxiliary controlled radical reactions
- Catalytic enantioselective radical reactions

Selected references:

- D. P. Curran, N. A. Porter, B. Giese, *Stereochemistry of radical reactions*, VCH Verlagsgesellschaft, Weinheim, **1996**.
- *Radicals in Organic Synthesis*, P. Renaud, M. P. Sibi, Ed., Wiley-VCHD, Weinheim, **2001**, Vol. 2.
- *Radicals in Synthesis I & II*, A. Gansäuer Ed., In *Top. Curr. Chem.*, Springer-Verlag Berlin Heidelberg **2006**, Vol. 263 & 264.
- G. Bar, A. F. Parsons, *Chem. Soc. Rev.* **2003**, 32, 251–263.
- G. J. Rowlands, *Tetrahedron* **2009**, 65, 8603–8655.

Introduction

Application of radicals in synthesis

In the past (before 1980s):

- Rare examples of stereoselective radical reactions
- Outcoming selectivity not understood
- “Messy” reactions
- Unpredictable reactions
- Species too reactive

Limited potential for
synthetic chemistry

Can highly reactive intermediates be selective?

Today:

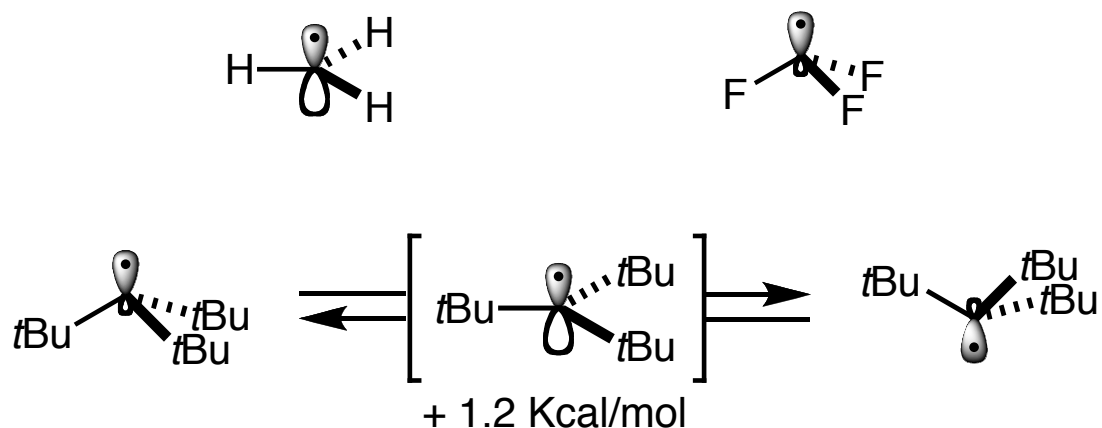
- Modulation of the reactivity (concentration, temperature,...)
- Good compatibility with several functional groups
- Mild conditions
- Chemo- and regioselective radical reaction reported
- Rationalization of the intermediates
- Importance of the relative rates for the selectivity
- Usually higher selectivity at low temperatures

Valued
intermediates in
synthetic chemistry

The Carbon Centered Radical

The carbon centered radical:

- Planar or slightly pyramidal with a small barrier to inversion.
- Electronegatives substituents and stereoelectronic effects can increase the inversion barrier energy and induce radical pyramidalization.



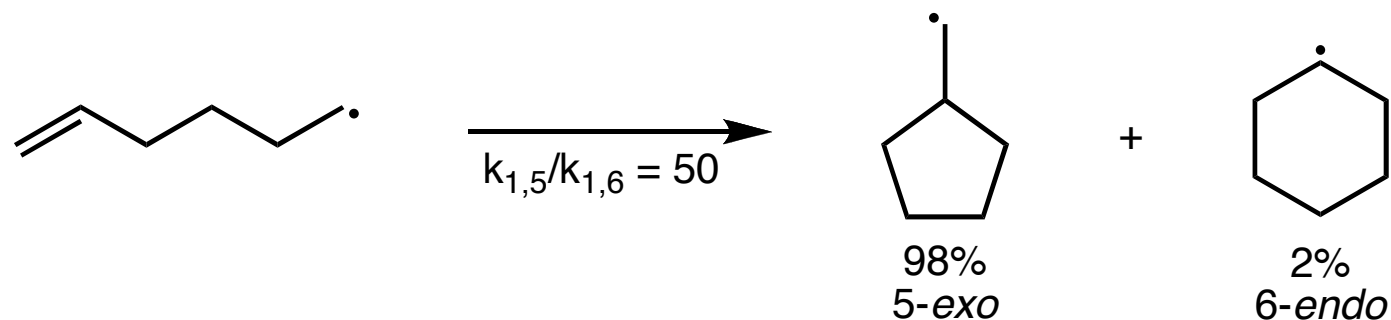
Disadvantage

Stereochemical information often lost
upon formation of the radical

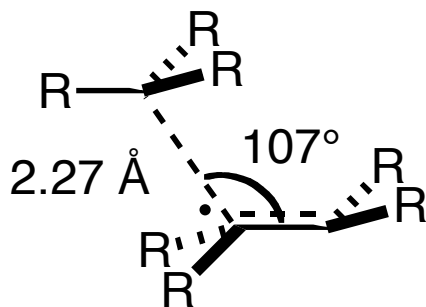
Advantage

Stereoselective preparation of the
precursor not required

The Hexenyl Radical Cyclization



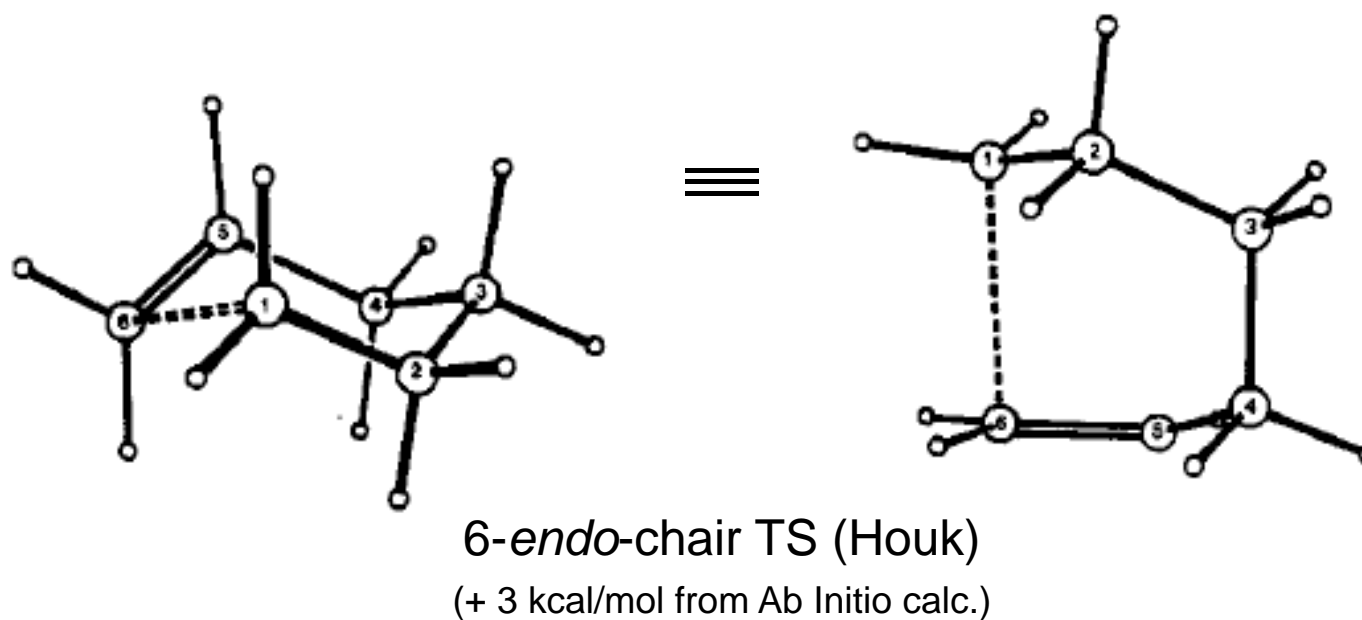
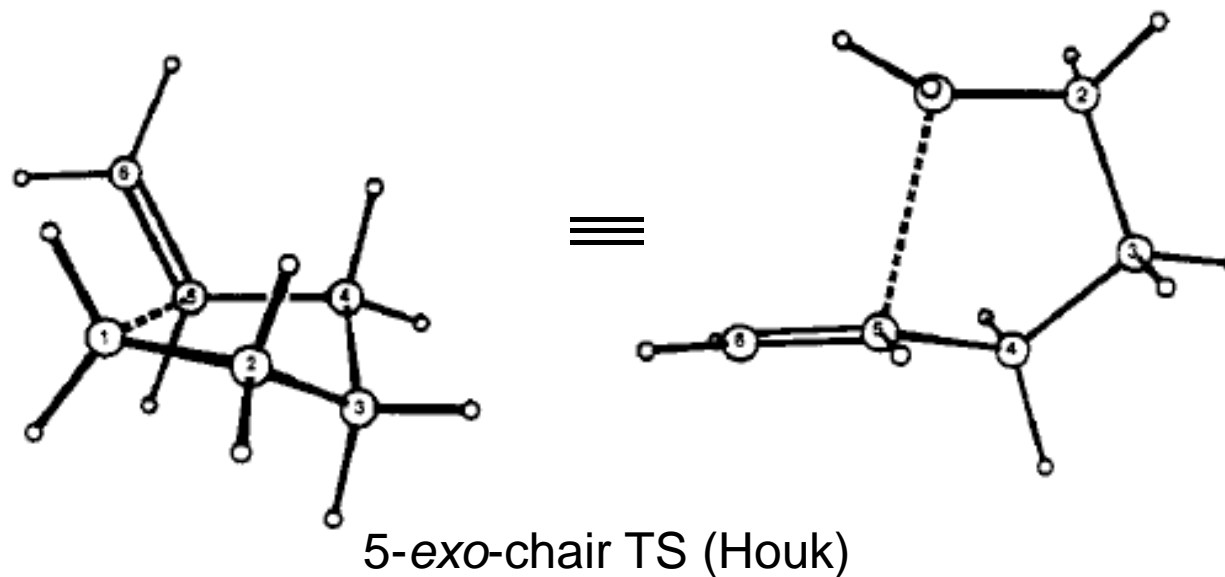
Backwith (1985) and Houk (1987): MM2 force-field based model for the prediction of the selectivity in radical cyclizations.



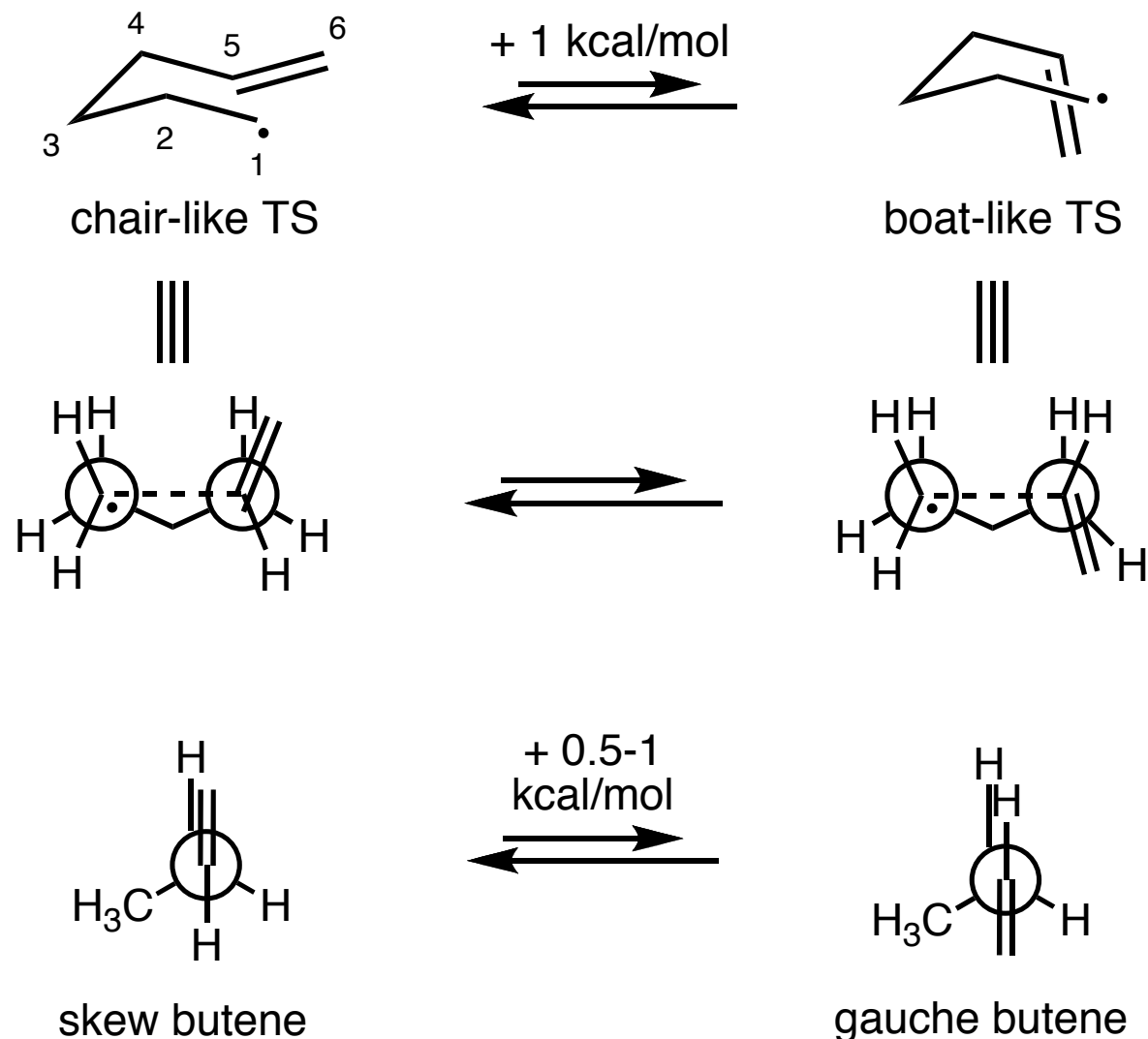
Premise:

- Early TS: forming bond fixed at 2.27 Å.
- Angle attack similar as in nucleophilic reactions.
- Reaction through a chair-like TS.

Stereoelectronic Explanation

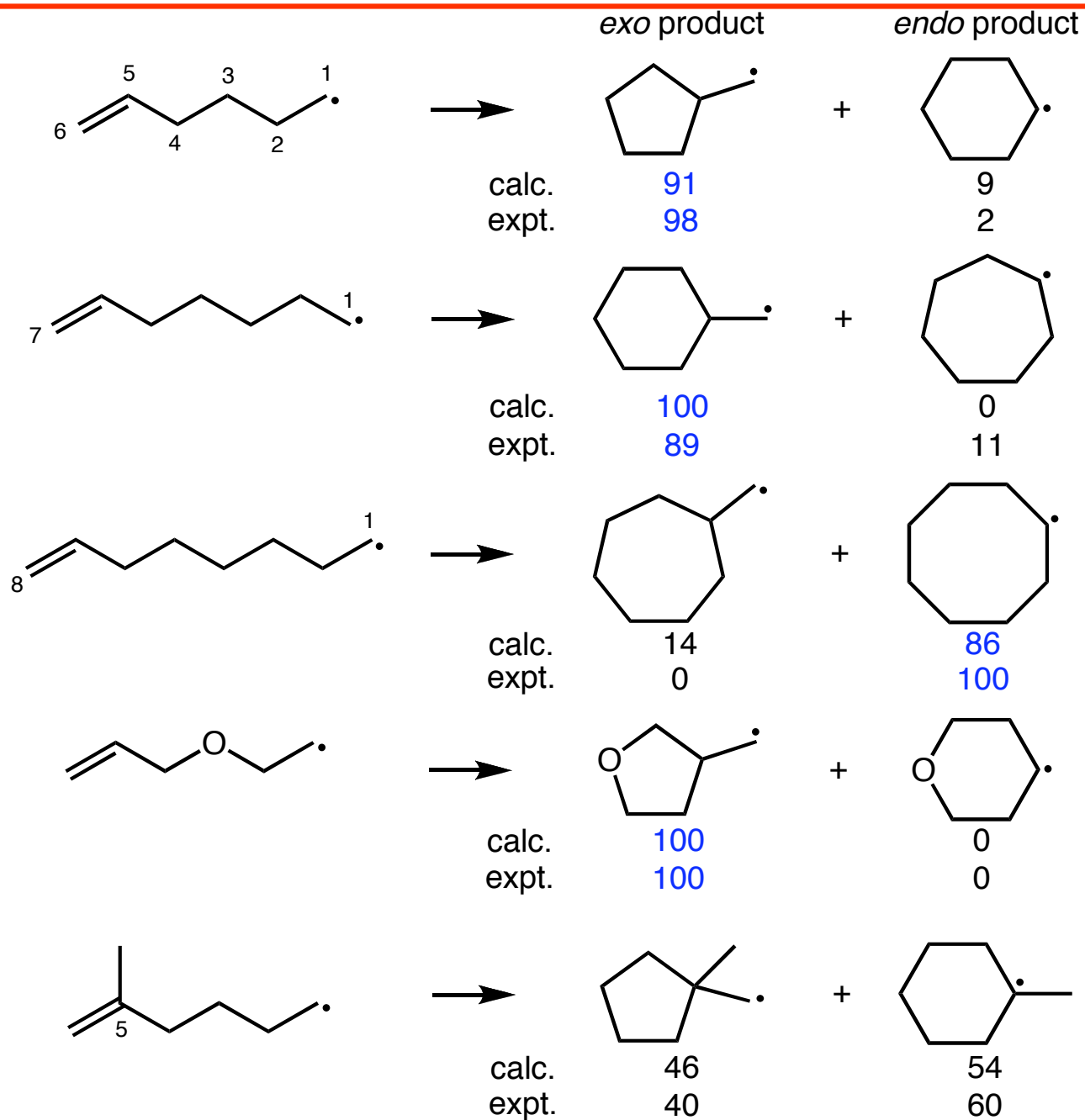


Chair or Boat?



Possible contribution of the “boat” TS in the 5-exo cyclization (Houk)

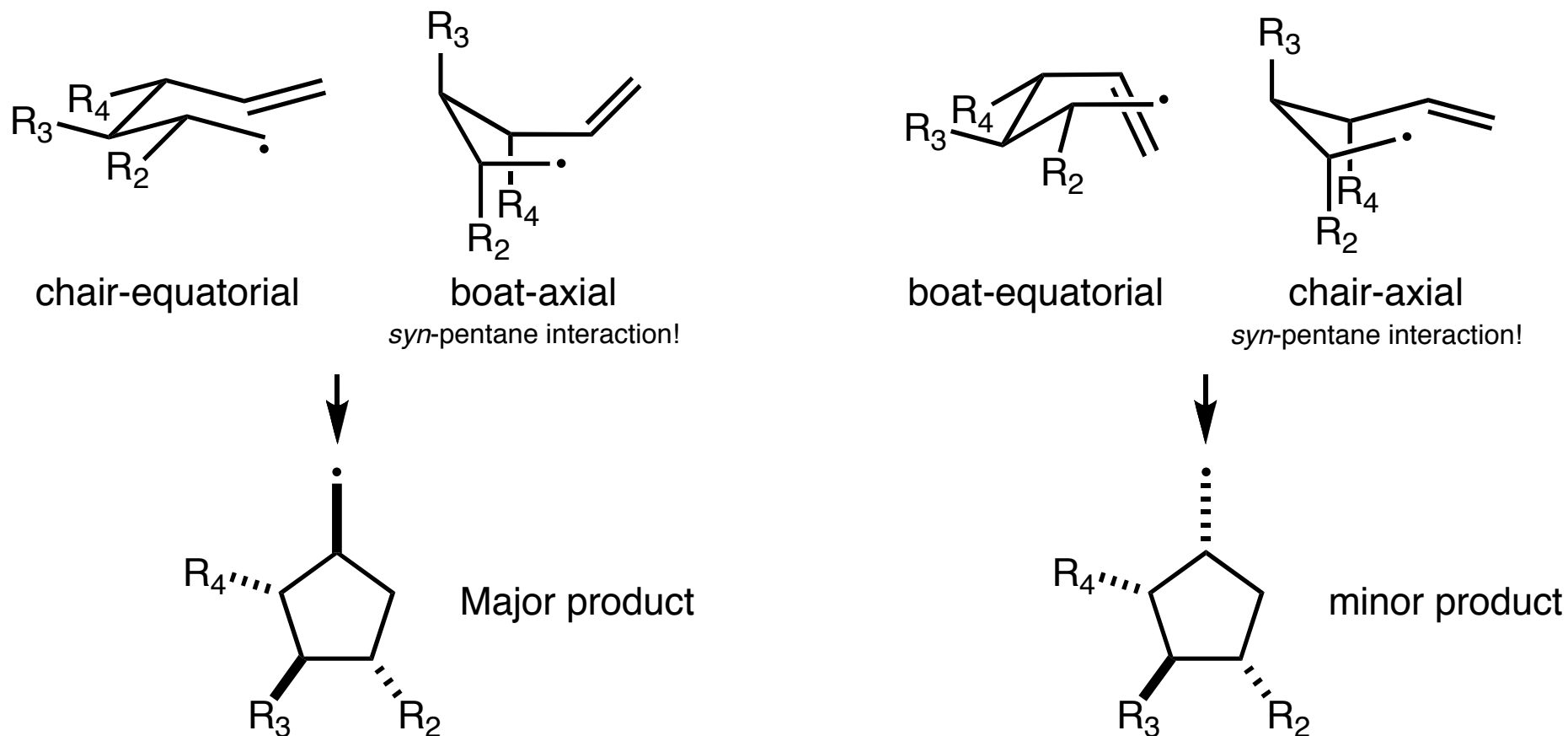
Model and Experimental Results



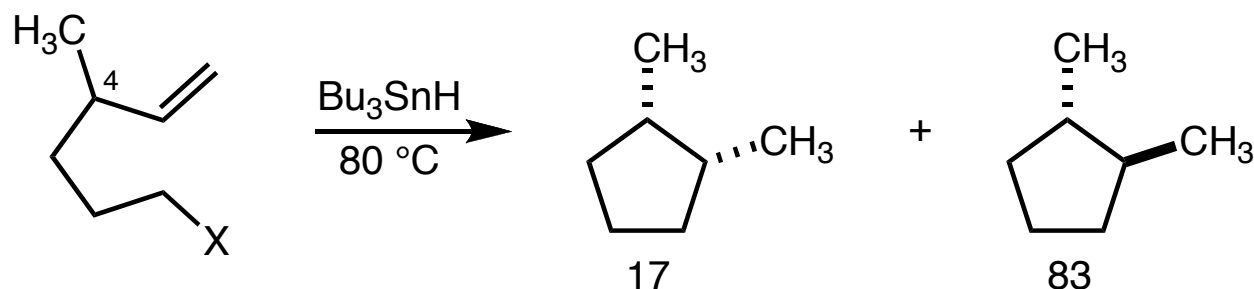
Cis/Trans Selectivities for the Hexenyl Radical Cyclization

The Beckwith-Houk rule:

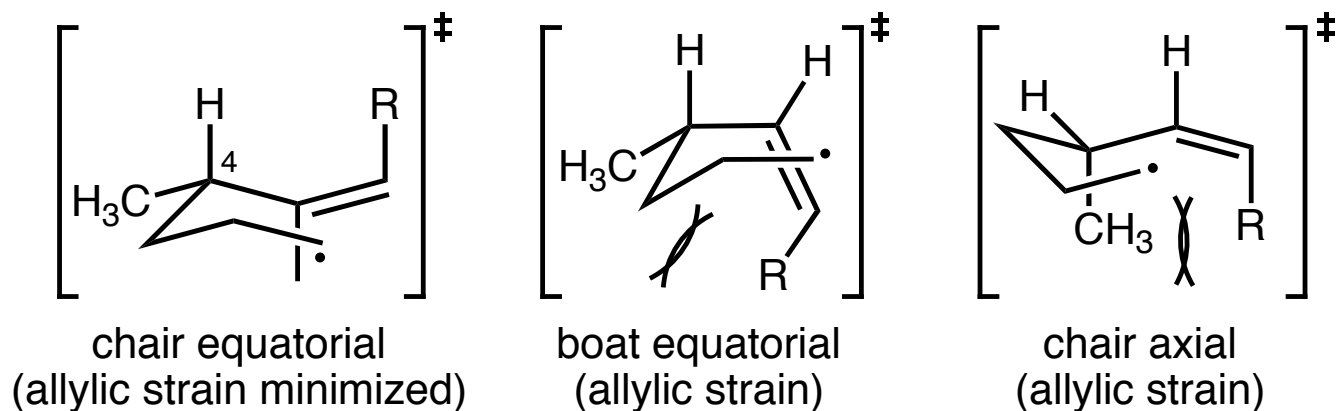
The major product arises when the substituents occupies an equatorial conformation, while the minor product arises when the substituent is axial.



Cyclization of the 4-Substituted Hexenyl Radicals



- Class with the highest selectivity (*cis/trans* ratio often $>5/95$).
- A strain plays a central role.



Rule of thumb:

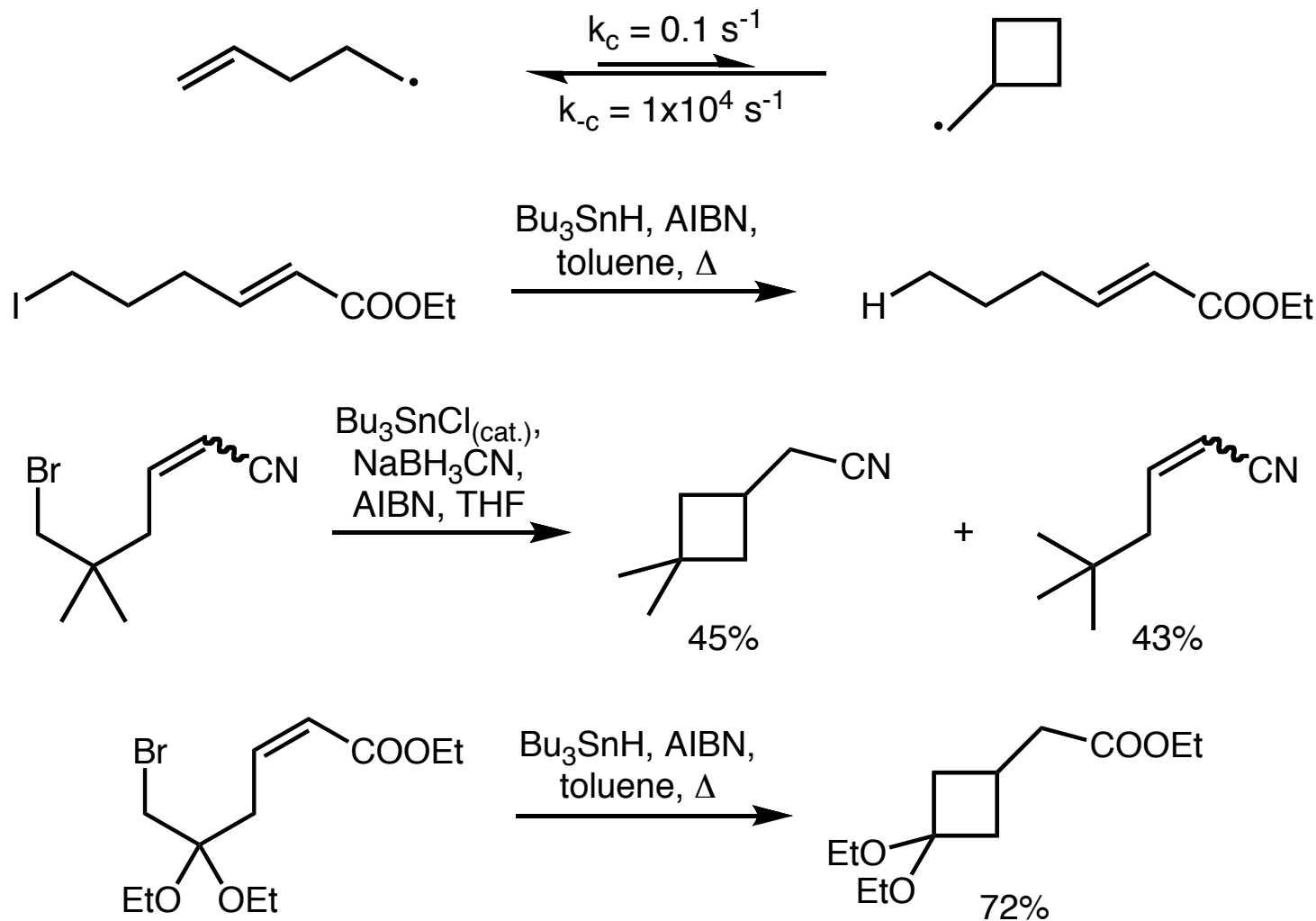
When multiple substitutions are present, the **4-substituent dominate due to A-strain.**

Multiple substitutions can afford reinforcing or non reinforcing selectivity.

Pentenyl Radical Cyclization and Thorpe-Ingold Effect

Pentenyl radical:

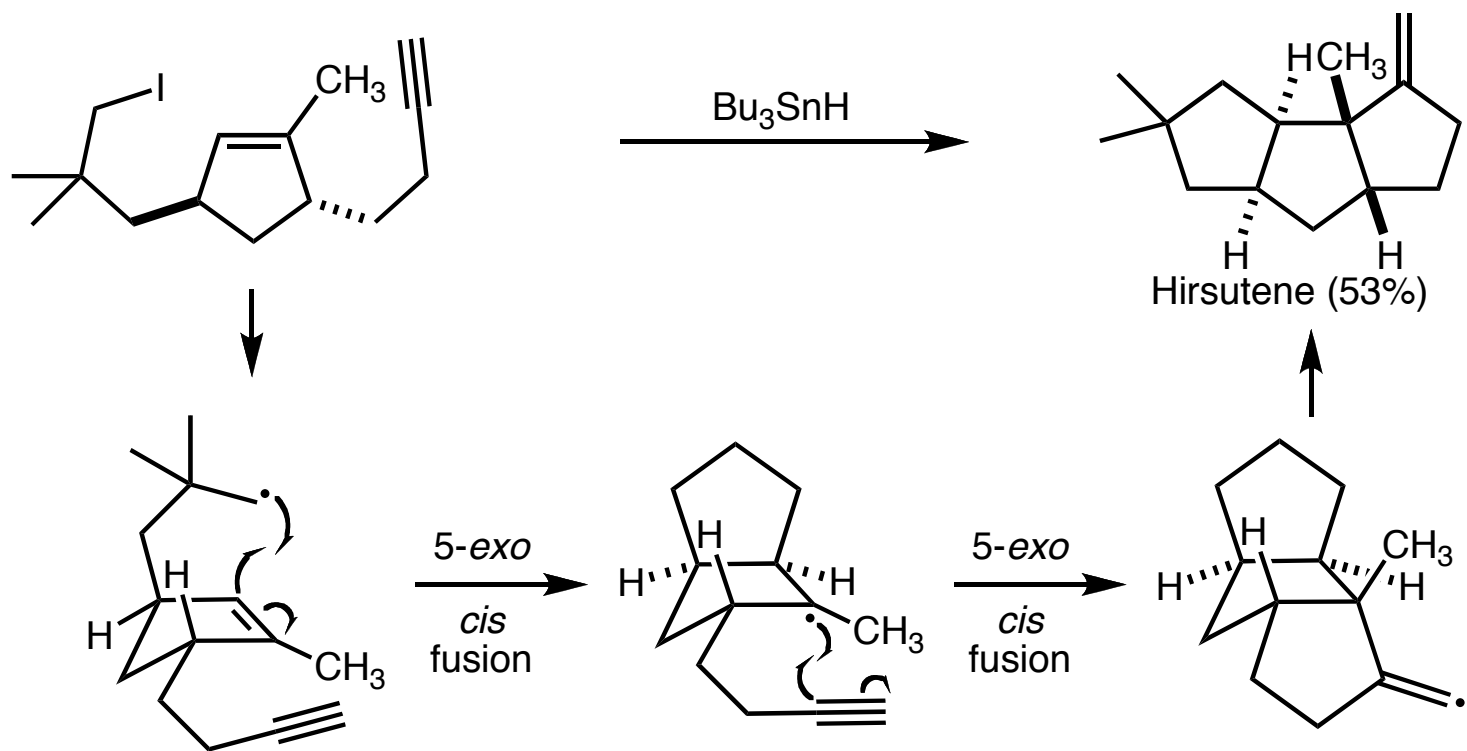
- Both 4-*exo* & 5-*endo* cyclization are disfavored, but the 4-*exo* product can be trapped.



- Cyclized product can be obtained using the right substituents.

Stereoselectivities in Cyclization from Cyclic Precursors

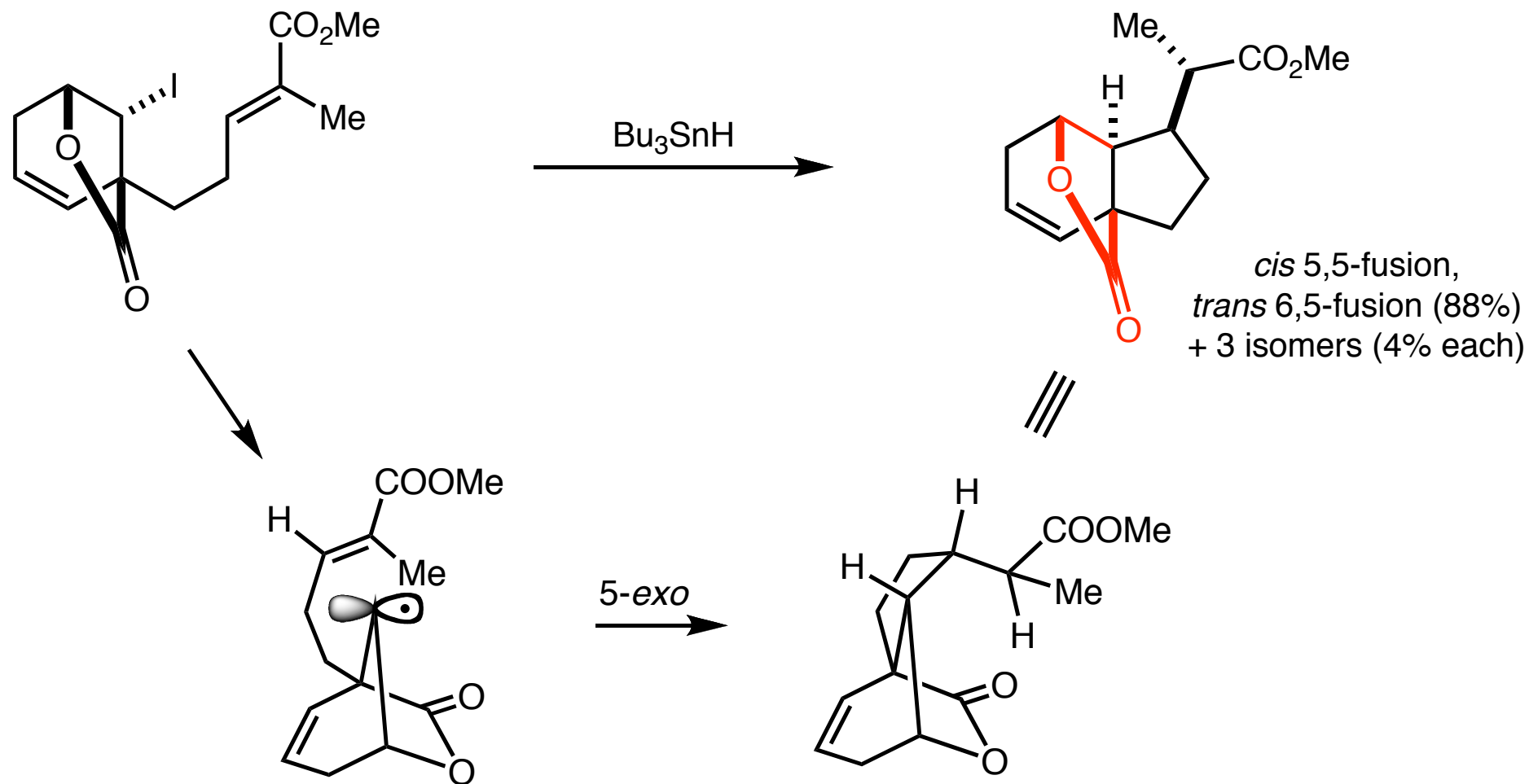
More predictable and often higher level of selectivity compared to acyclic precursors.



Rule of thumb:

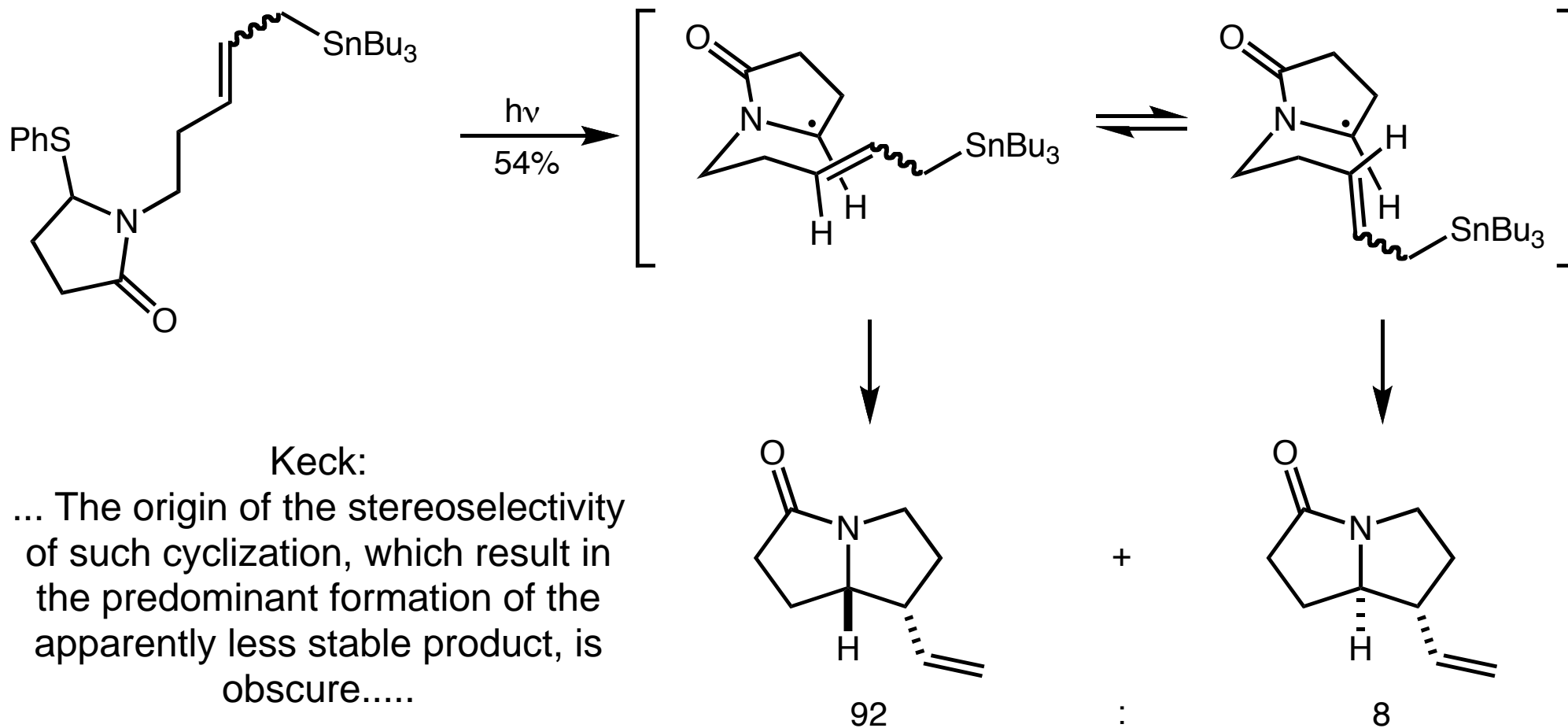
Radical cyclizations forming a ring fusion bond between two small ring (fewer than 6 atoms) give **predominantly or exclusively the *cis* product**.

A Complex Example of Cyclization

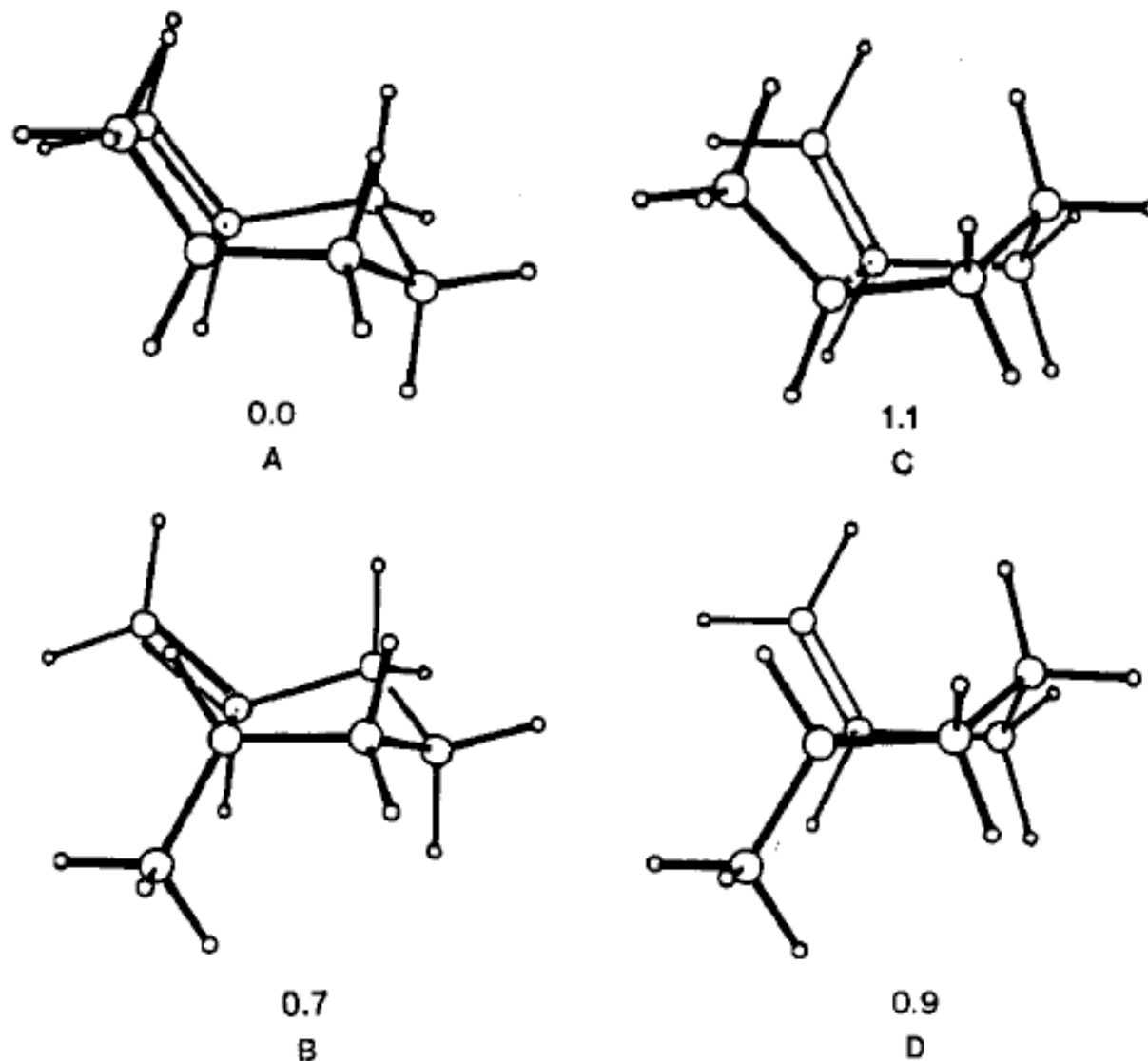


Higher preference for a 5,5 *cis*-fusion compared to the 6,5 *cis*-fusion.

Sterics?

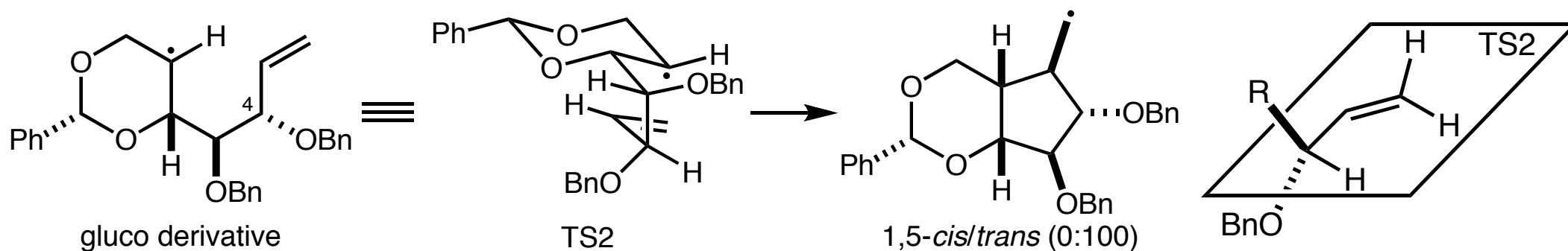
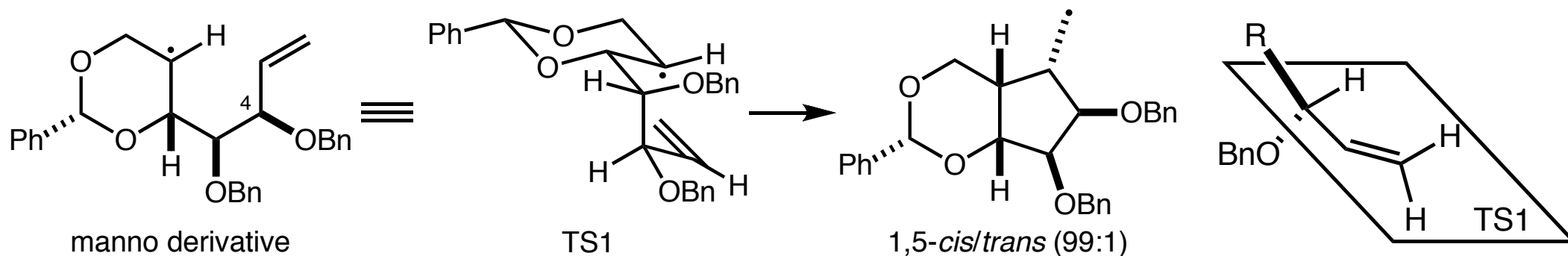
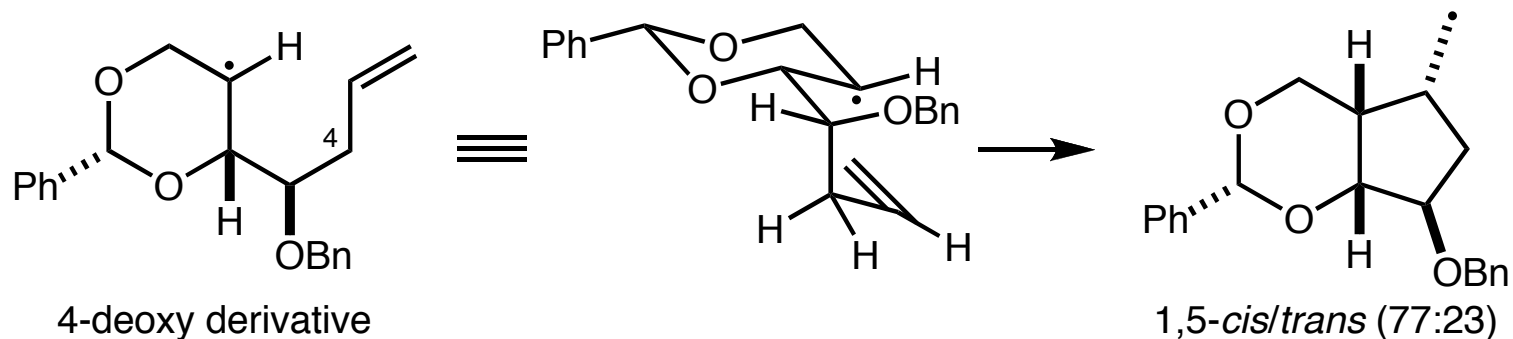


Van der Waals Attraction?



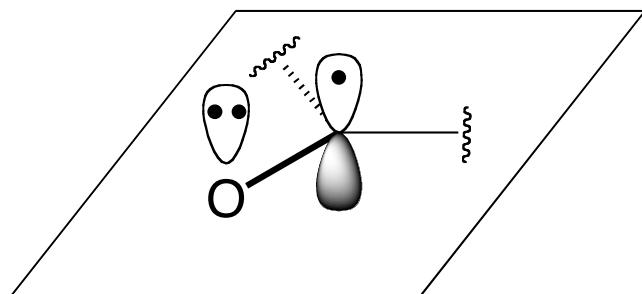
Houk:Nevertheless, there is some electronic preference for the transition states A and C relative to B and D. It is probably the result of a Van der Waals attraction, since it appears only upon inclusion of electron correlation....

Allylic Strain Directed Radicals Cyclizations

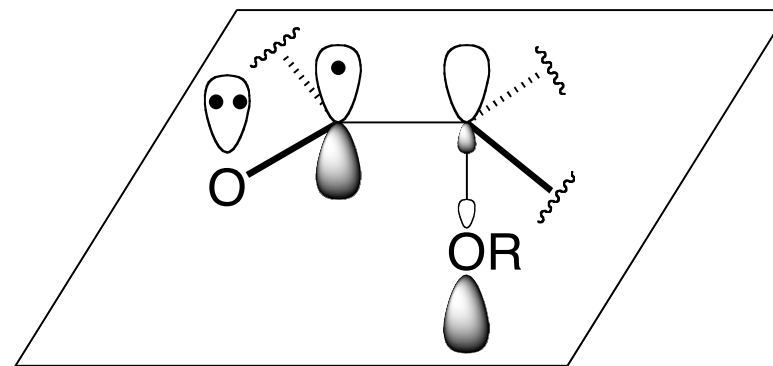


- Allylic strain makes the boat conformation lower in energy compared to the chair.
- Substituent at C4 dictates the outgoing stereochemistry.

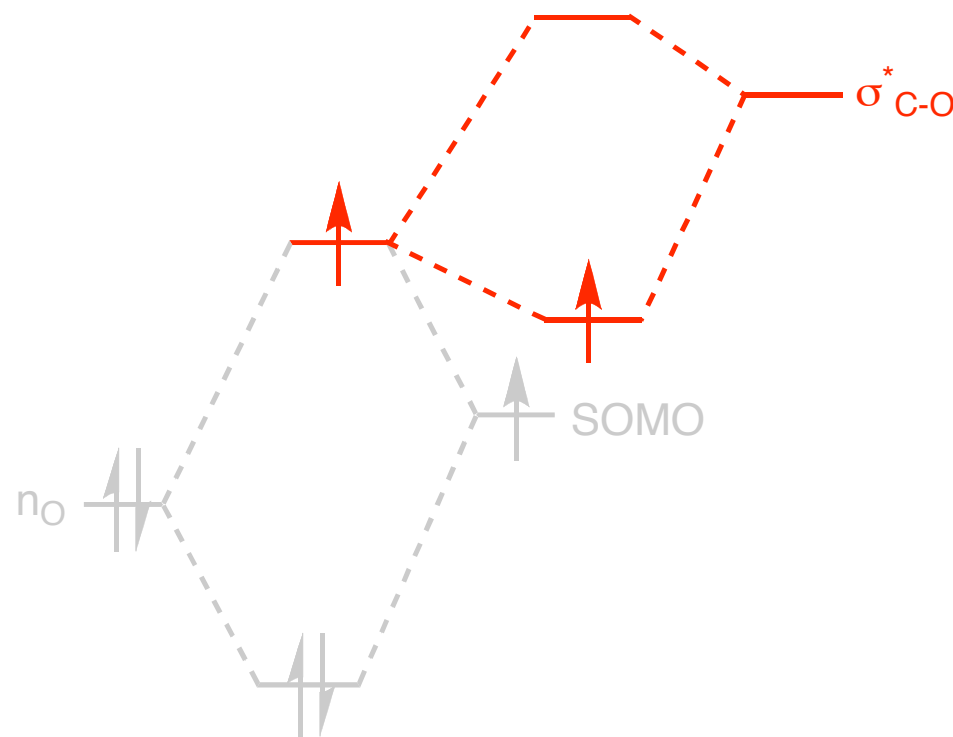
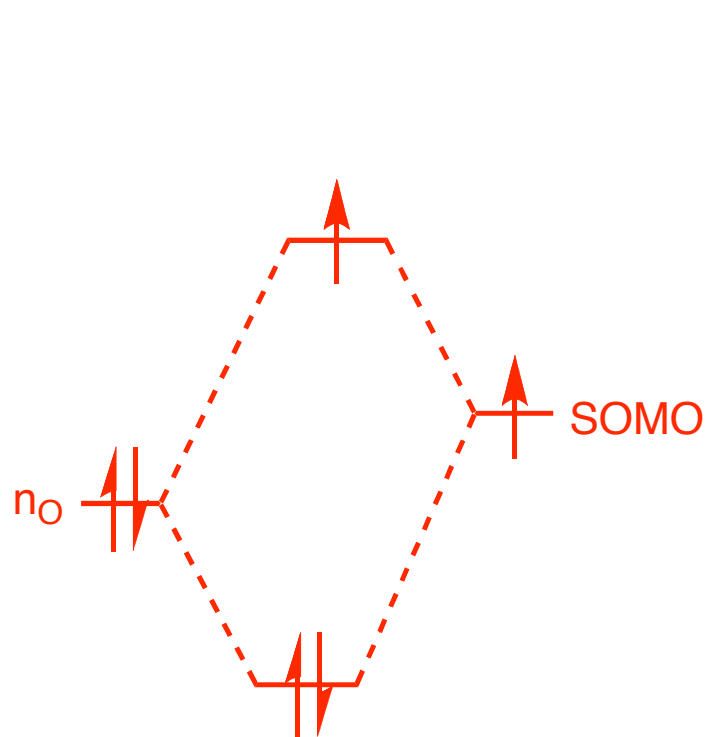
The Anomeric Effect in Radicals



$n_O \rightarrow \text{SOMO}$

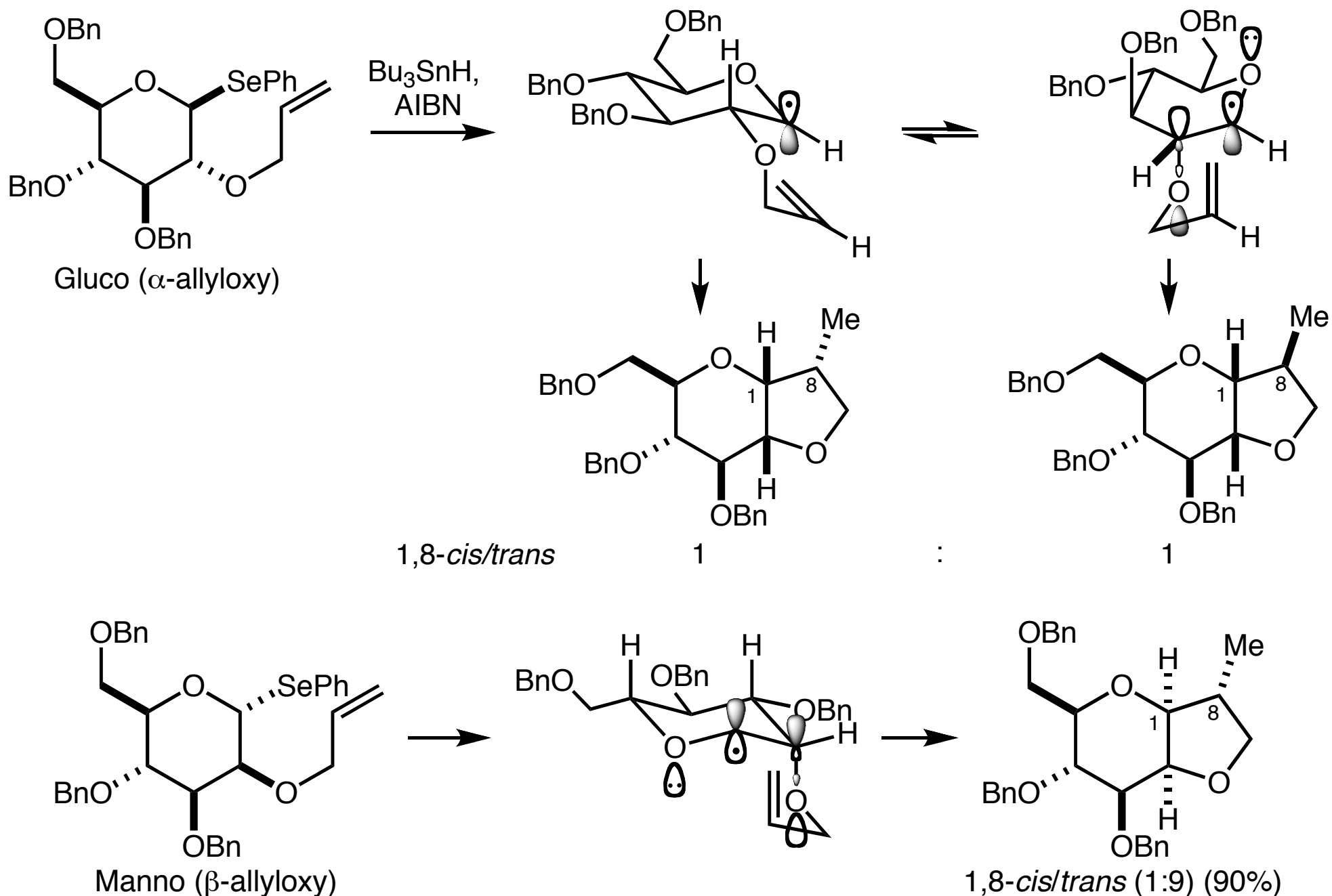


$n_O \rightarrow \text{SOMO} \rightarrow \sigma^*_{C-O}$



This stabilization does not exist in compound that lack the α -EWG group!

The Anomeric Effect in Sugar Derived Radicals

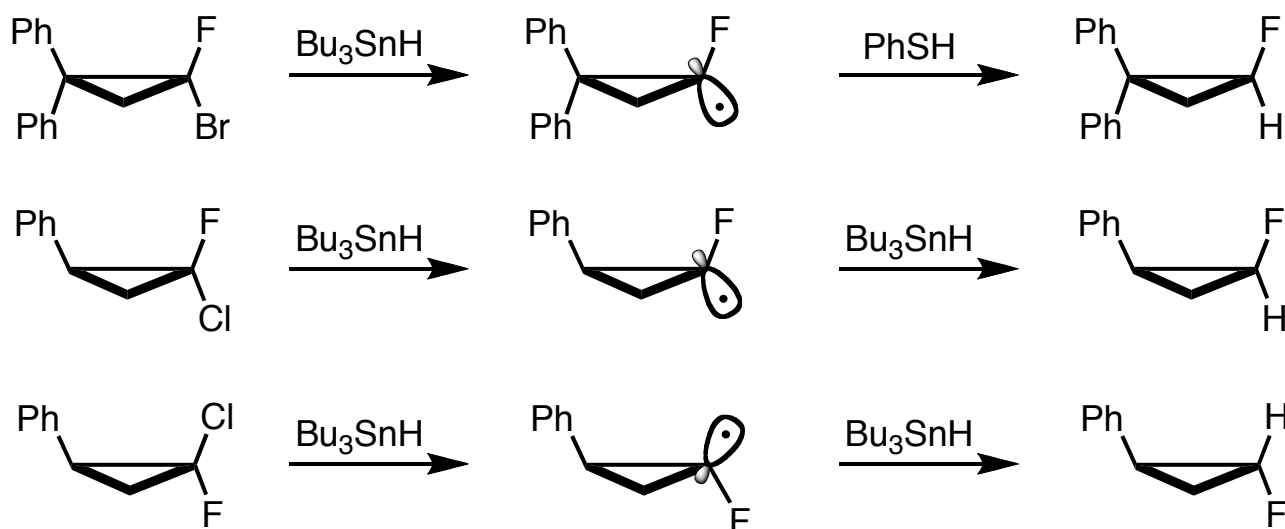


Conclusion for Cyclic Radical Cyclizations

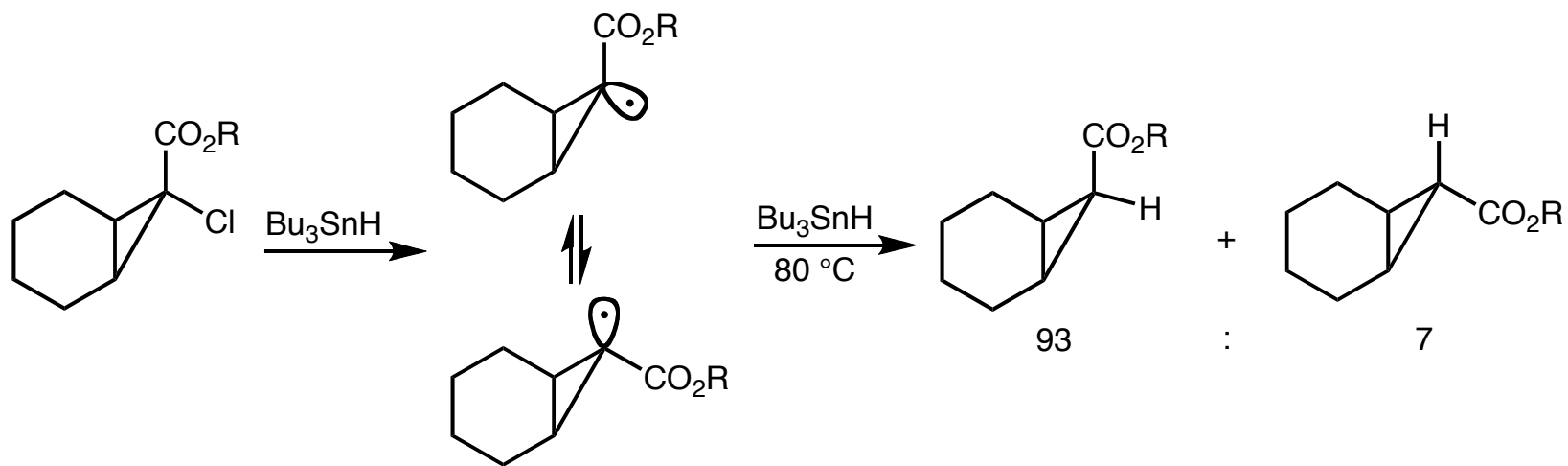
- Beckwith-Houk model
 - The major product arises when the substituents occupies an equatorial conformation

- Stereoelectronic effects influencing radical cyclizations
 - A-strain control (substituent in position 4 dominates)
 - Thorpe-Ingold effect
 - Anomeric effect

Diastereoselectivity in β -Substituted Cyclopropyl Radicals



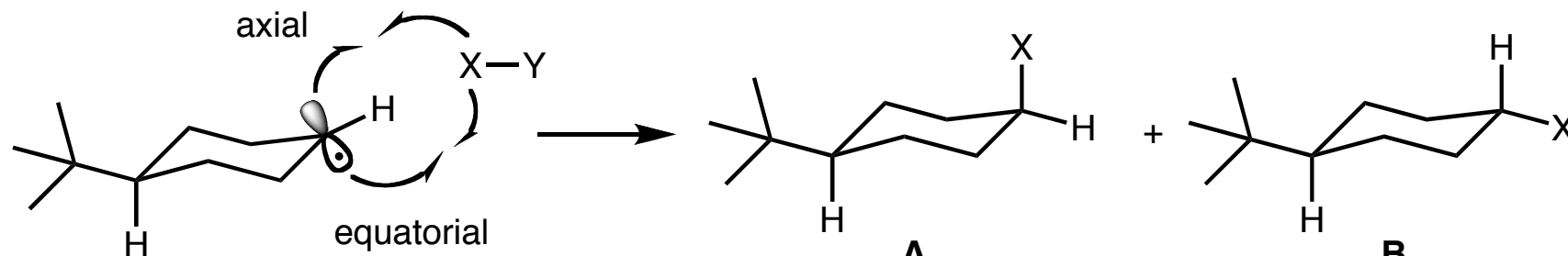
T. Ando, H. Yamanaka, F. Namigata, W. Funasaka, *J. Org. Chem.* **1970**, 35, 33; K. Gawronska, J. Gawronski, H. M. Walborsky, *J. Org. Chem.* **1991**, 56.



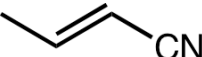
Thermal equilibration of the radical & preferential convex face attack.

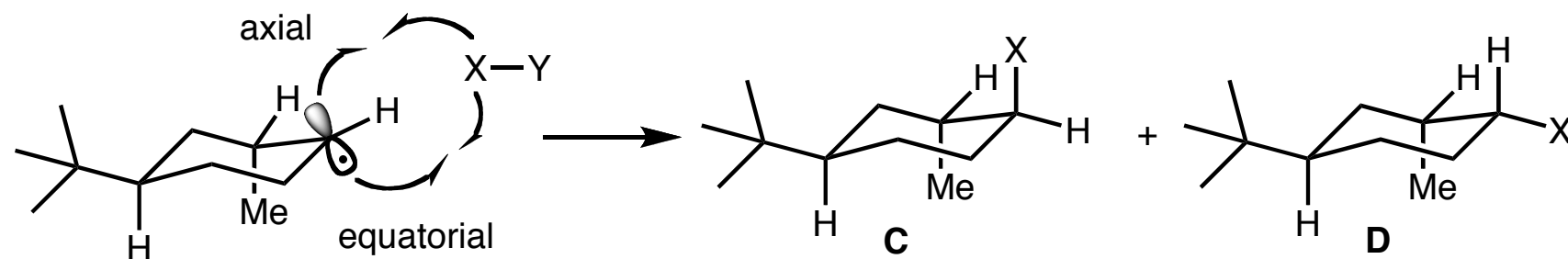
T. Ishihara, K. Hayashi, T. Ando, *J. Org. Chem.* **1975**, 40, 3264.

Selectivities for the Six-Member Ring Radicals

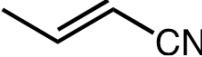


Similar selectivities as for
the ionic reductions

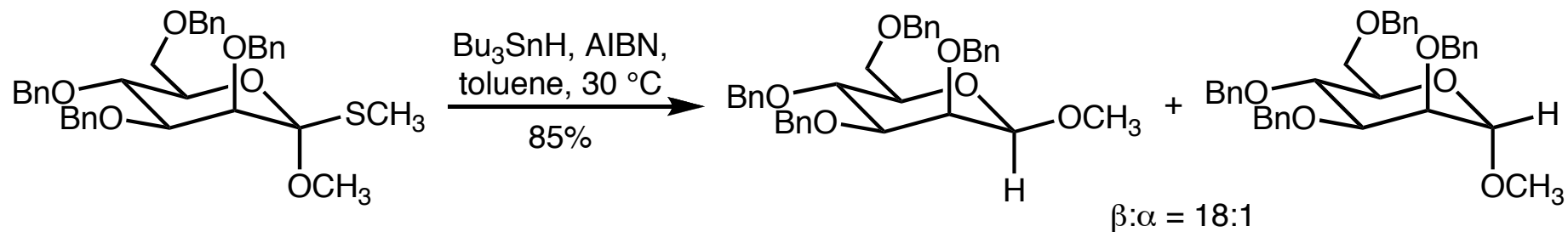
RCO ₂ -OH	80	:	20
Cl ₃ C-Cl	77	:	23
Bu ₃ Sn-D	70	:	30
Cl ₃ C-Br	69	:	31
	26	:	74



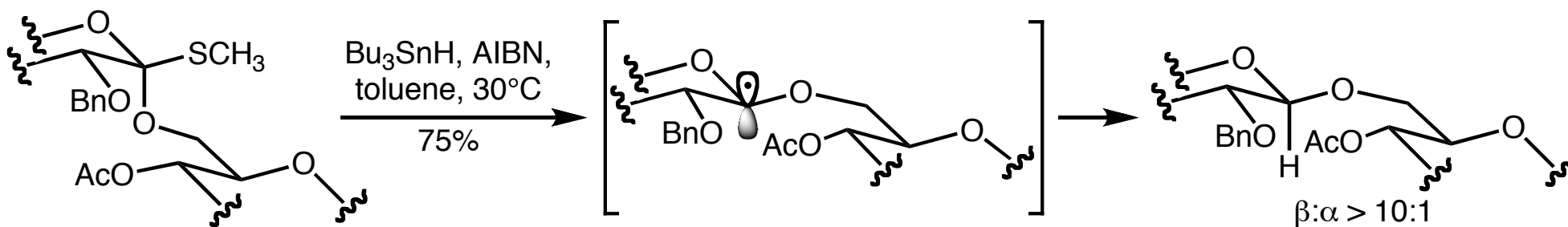
Axial β -Me-substituent
increases the axial attack

RCO ₂ -OH	90	:	10
Cl ₃ C-Cl	85	:	15
Cl ₃ C-Br	85	:	15
	83	:	17

The Anomeric Effect Again



- The **radical is attacked from the axial position** rather than the expected equatorial!

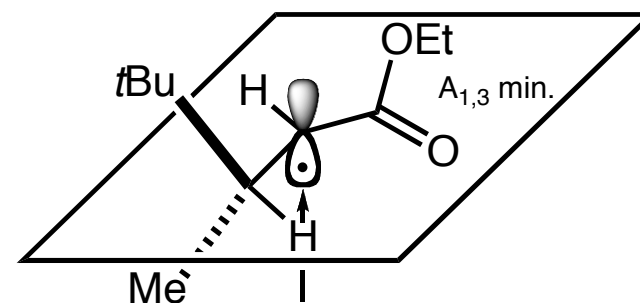
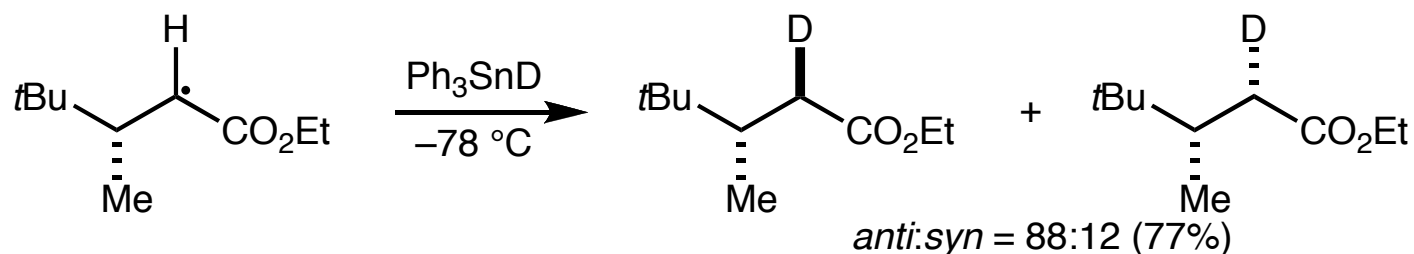
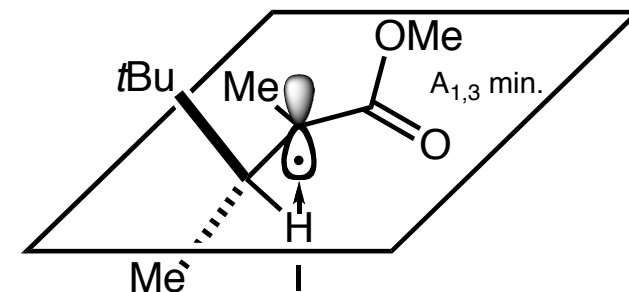
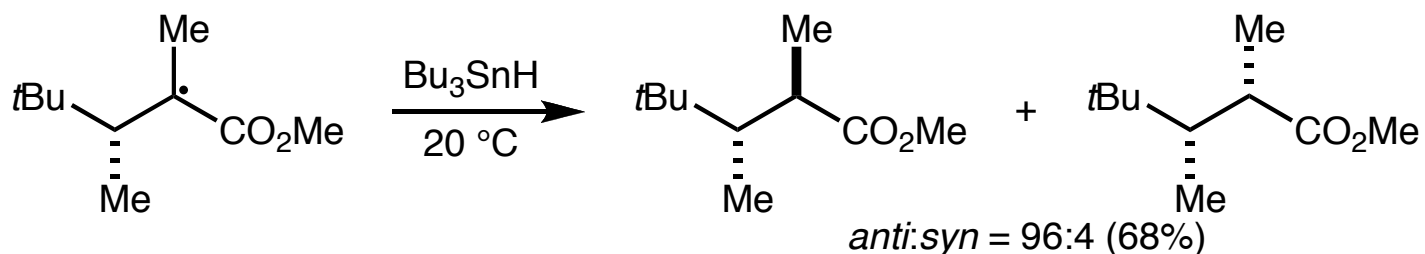


- Application for the preparation of β -glycosides.

Control Effects for the Addition to Acyclic Radicals

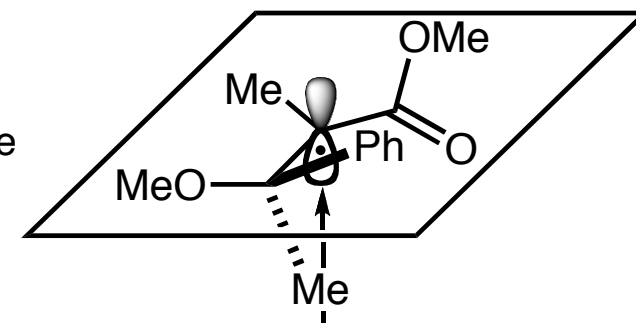
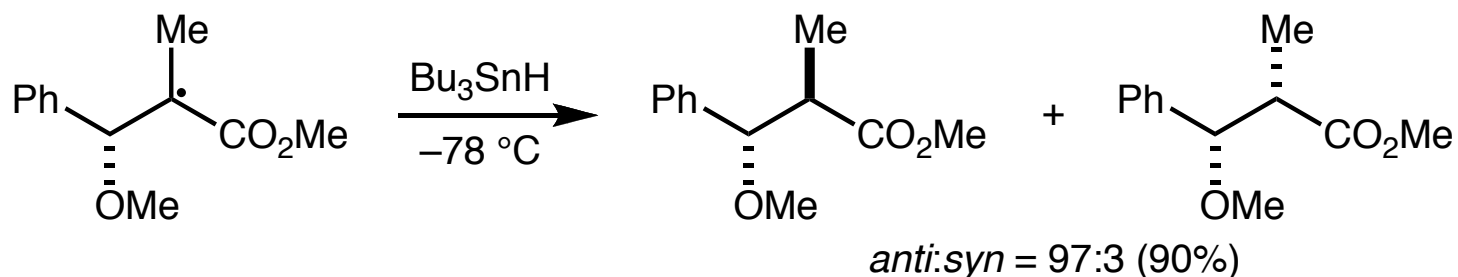
Because the low activation energy and the early TS for radical reactions, often the major product afford from the lowest energy ground conformer (see also Hammond's postulate).

Allylic strain effects



B. Giese, W. Damm, F. Wellerich, H.-G. Zeitz, *Tetrahedron Lett.* **1992**, 33, 1863; D. J. Hart, R. Krishnamurthy, *J. Org. Chem.* **1992**, 57, 4457.

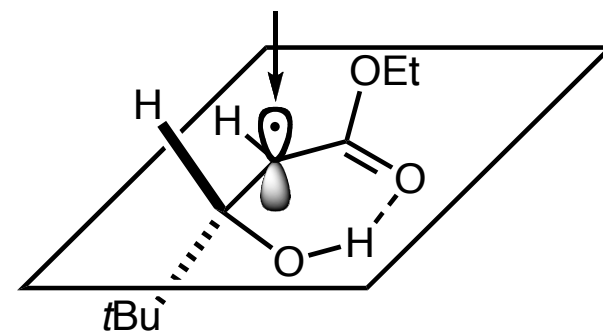
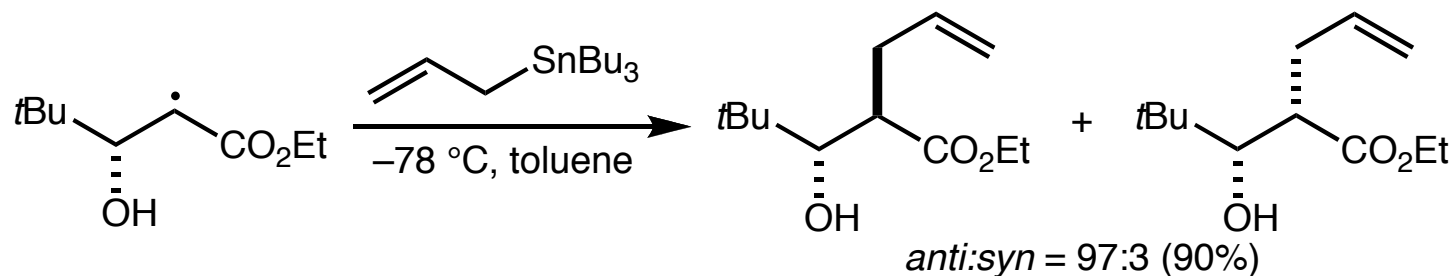
Polar substituents effects



Y. Guindon, C. Yoakim, R. Lemieux, L. Boisvert, D. Delorme, J.-F. Lavallée, *Tetrahedron Lett.* **1990**, 31, 2845.

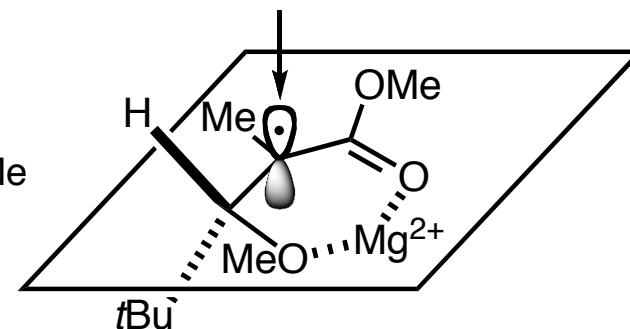
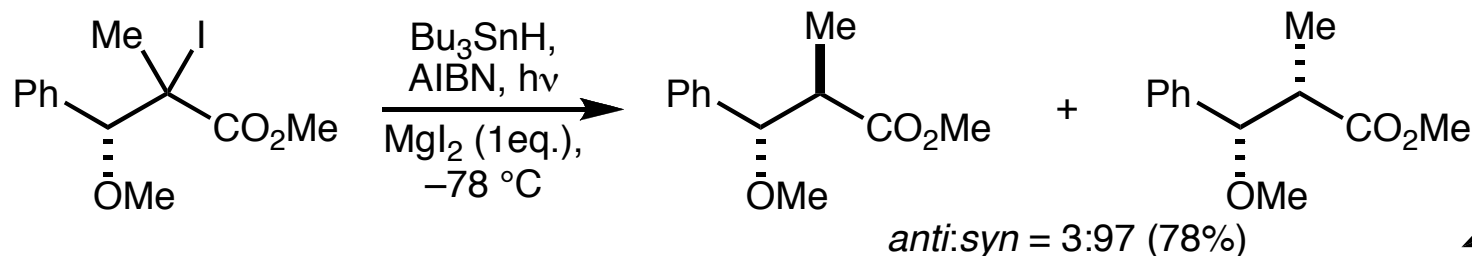
Control Effects for the Addition to Acyclic Radicals

Hydrogen bond effect



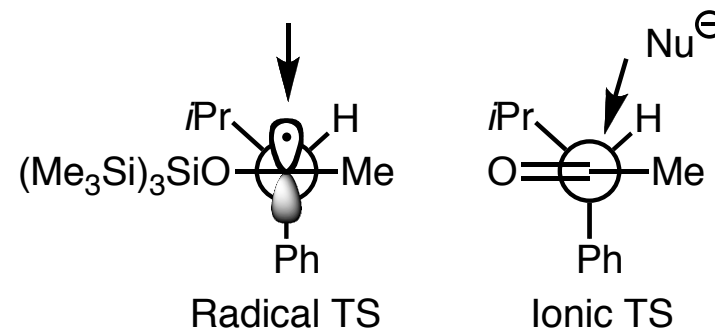
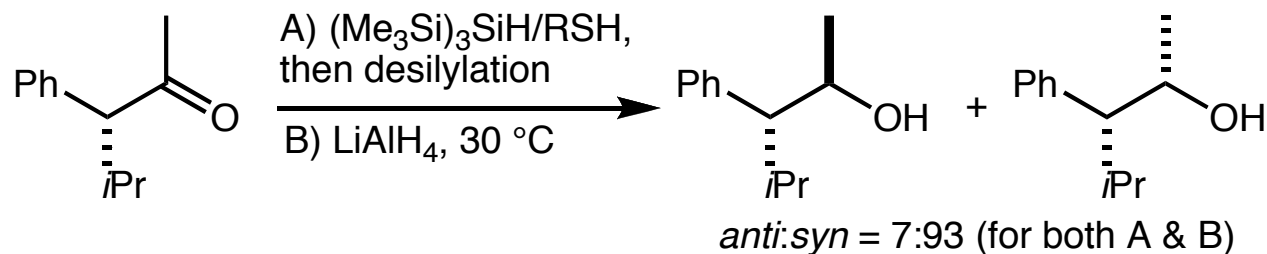
D. J. Hart, R. Krishnamurthy, *J. Org. Chem.* **1992**, 57, 4457.

Chelation effect



Y. Guindon, J.-F. Lavallée, G. Homer, J. Rancourt, *J. Am. Chem. Soc.* **1991**, 113, 9701.

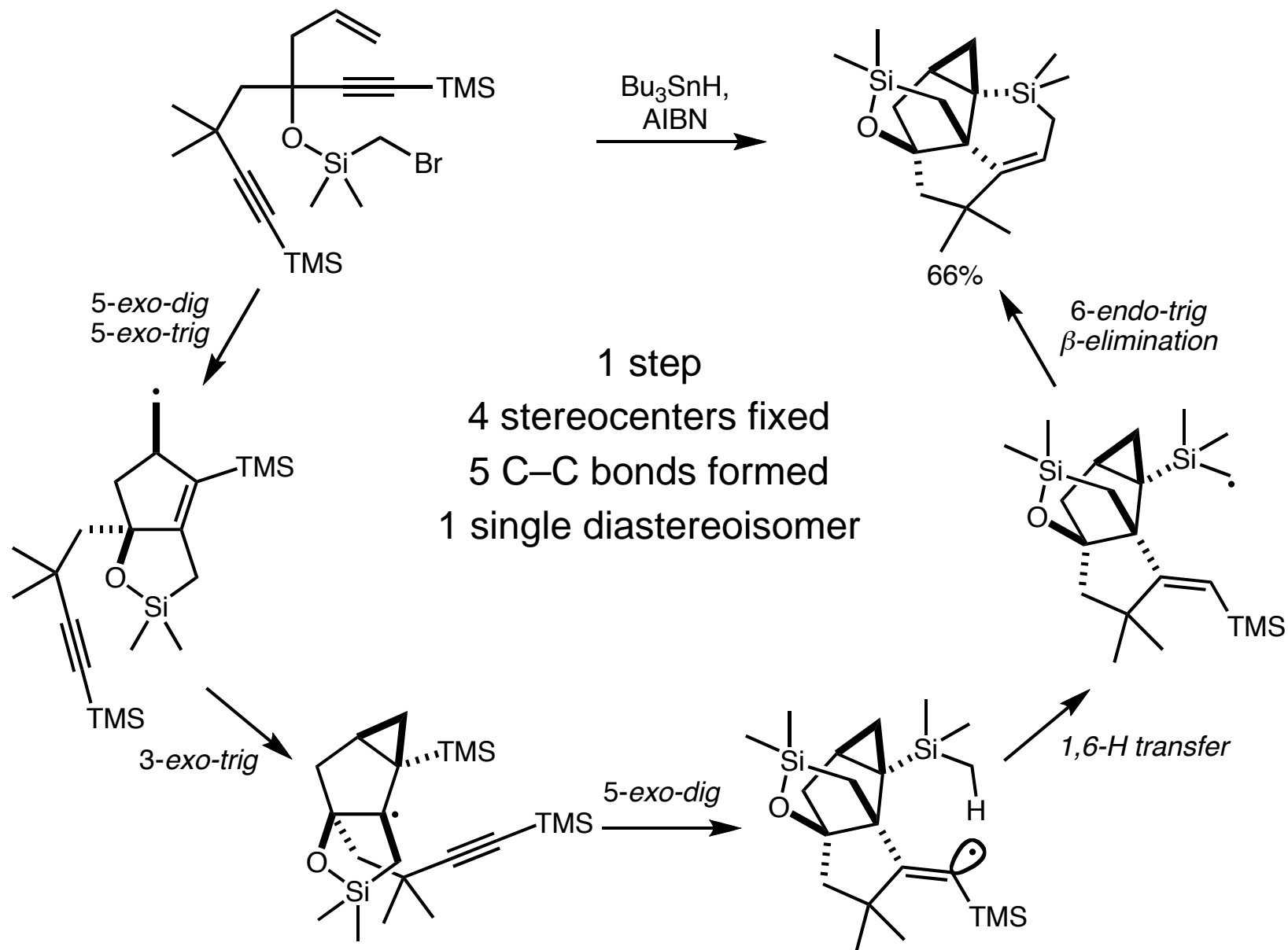
The Felkin-Anh rule for radicals



B. Giese, W. Damm, J. Dickhaut, F. Wetterich, *Tetrahedron Lett.* **1991**, 32, 6097.

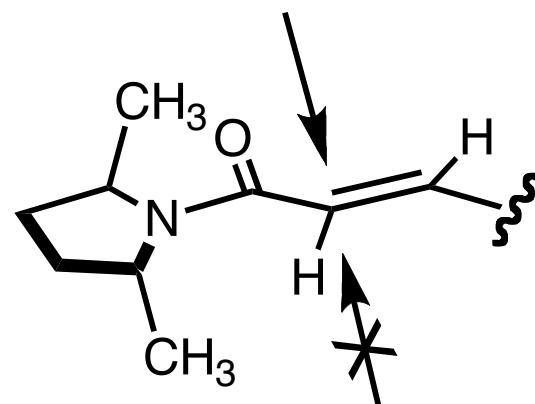
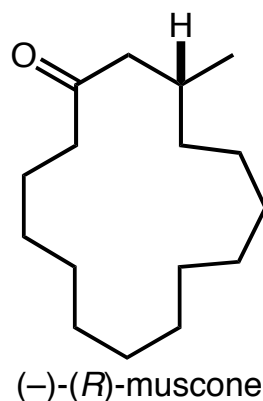
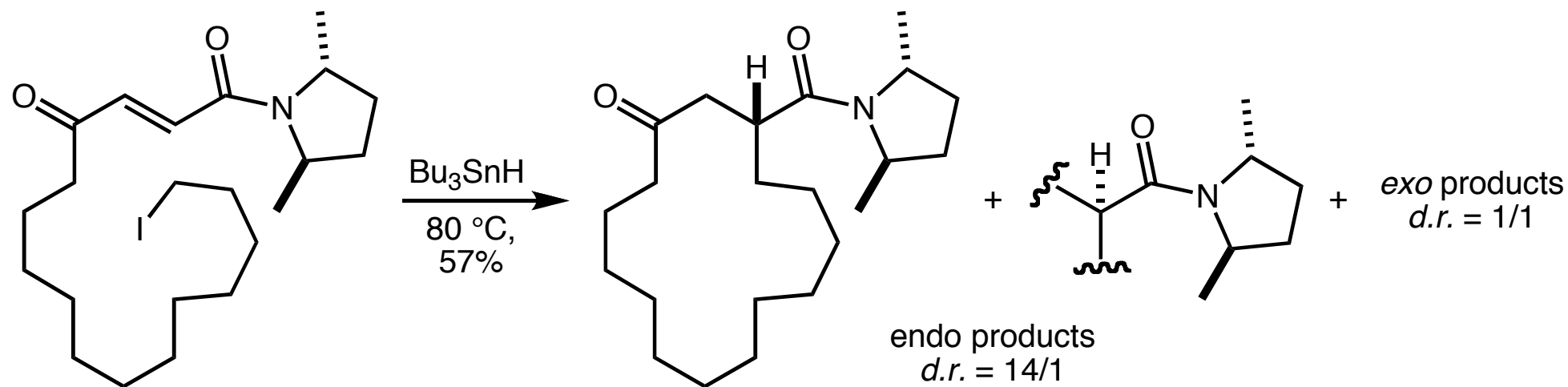
A Cascade Radical Reaction

Radical cascade during the synthesis for the preparation of triquinane skeleton



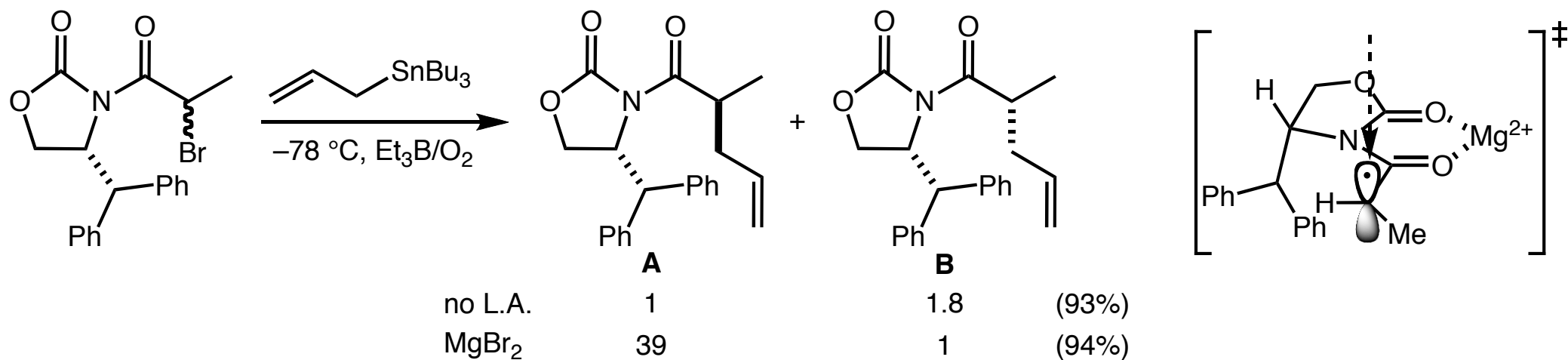
Chiral Auxiliary Control

First applications of chiral auxiliary in radical chemistry (2,5-dimethylpyrrolidine amide)

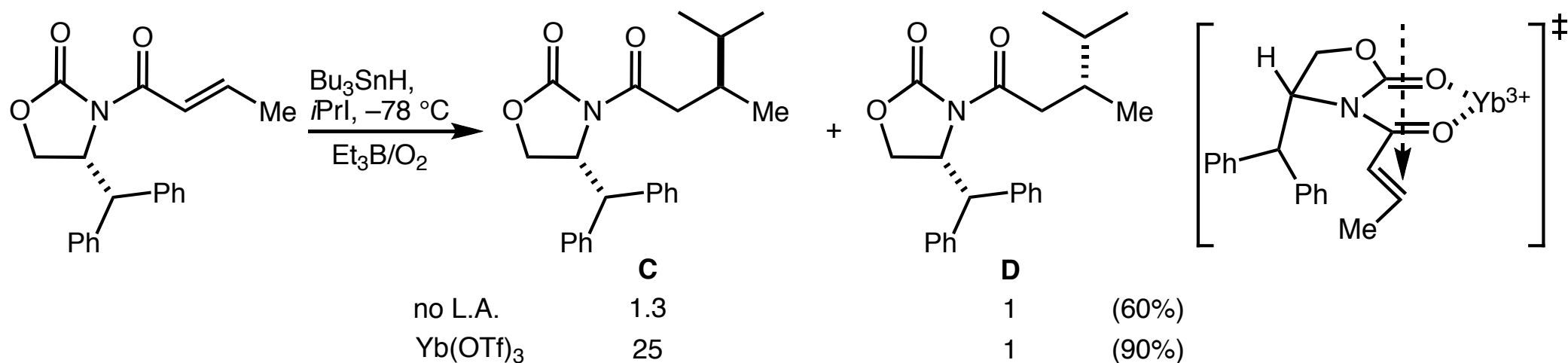


- Selectivity observed when the radical adds to the α position of the amide; no selectivity when attack occurs at the β position.

The Evans Oxazolidinone in Radical Chemistry

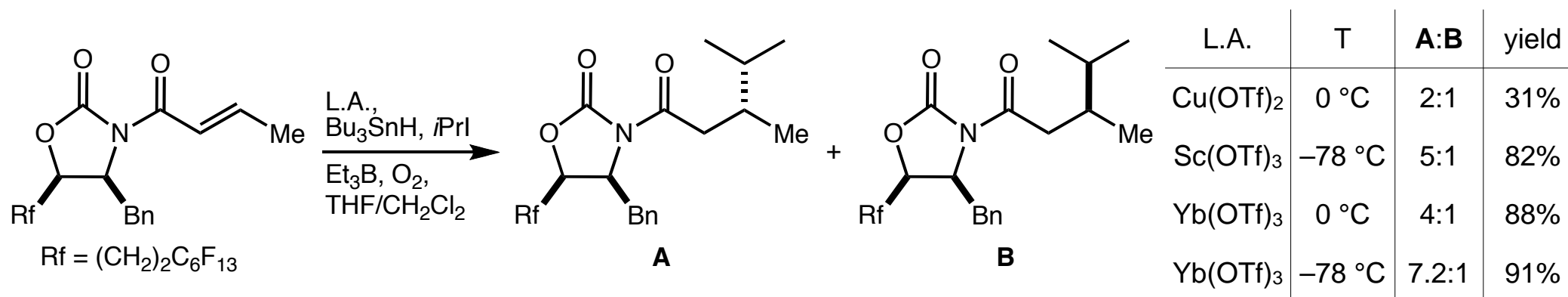


Conjugate radical reaction

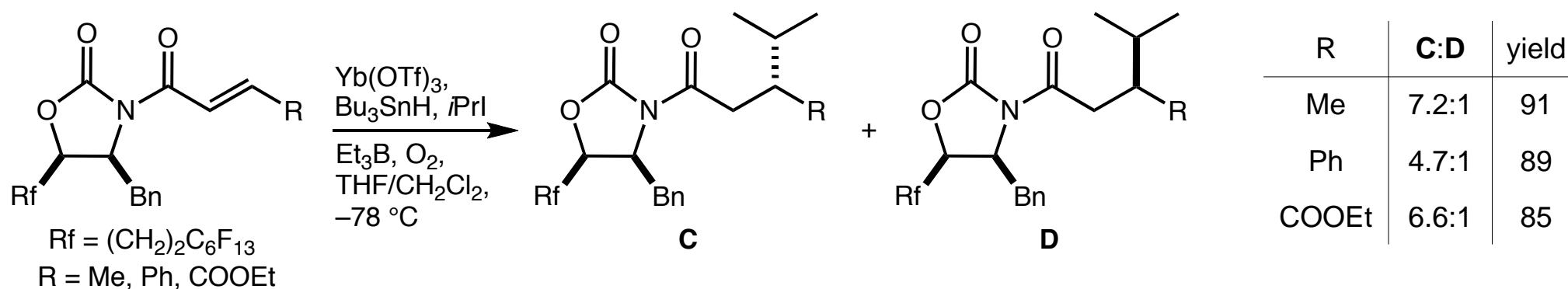


- High selectivity only under chelation control, scarce selectivity if only dipole minimization.

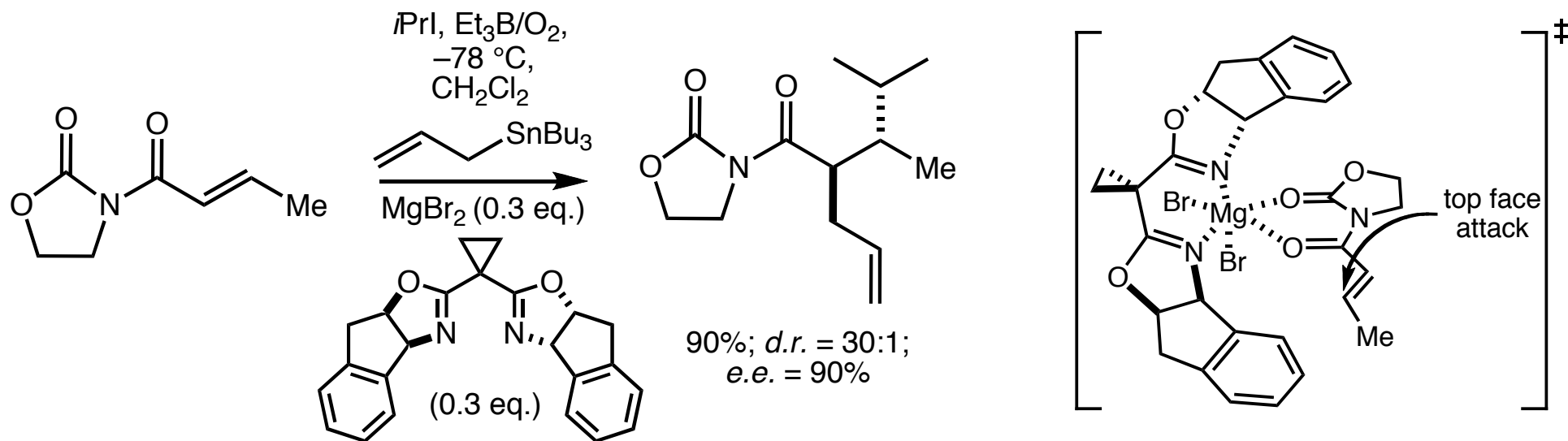
Modified Oxazolidinone Auxiliary



- Rf group to make the purification easier by fluorous solid phase extraction (FSPE).

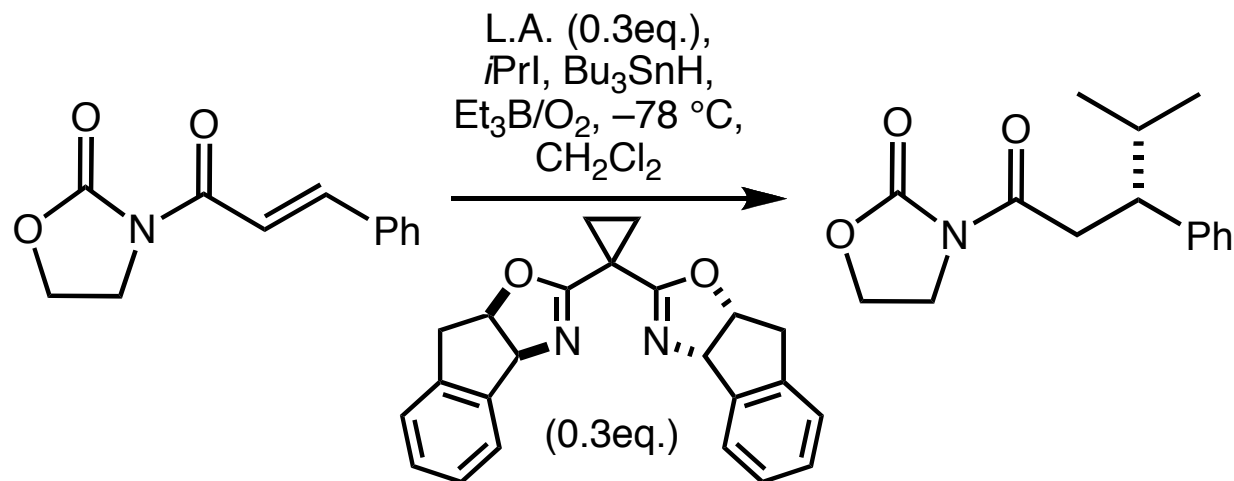


Bisoxazoline in Radical Chemistry



M. P. Sibi, J. Chen, *J. Am. Chem. Soc.* **2001**, 123, 9472.

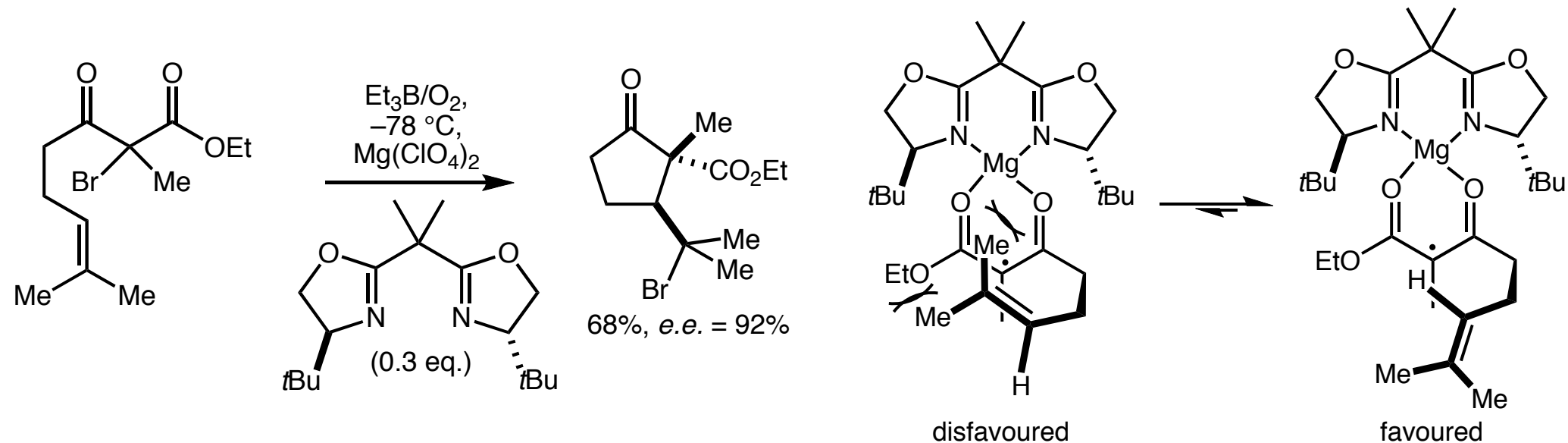
Investigation of triflimides metal salts for the radical conjugate addition



L.A.	e.e.	yield
$\text{Sc}(\text{NTf}_2)_3$	3	30%
$\text{Zn}(\text{NTf}_2)_2$	12	68%
$\text{Fe}(\text{NTf}_2)_2$	98	95%
$\text{Mg}(\text{NTf}_2)_2$	98	99%

M. P. Sibi, G. Petrovic, *Tetrahedron: Asymmetry* **2003**, 14, 2879.

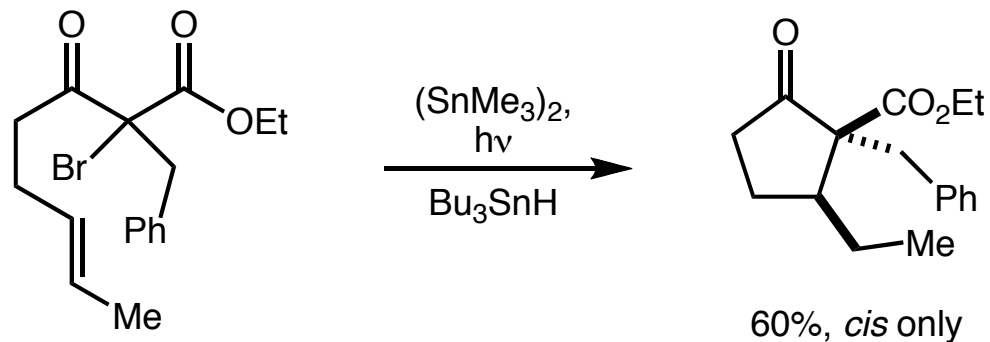
Enantioselective Radical Cyclization



- Only the 2-ester group *trans* to the 3-alkyl group could be obtained.

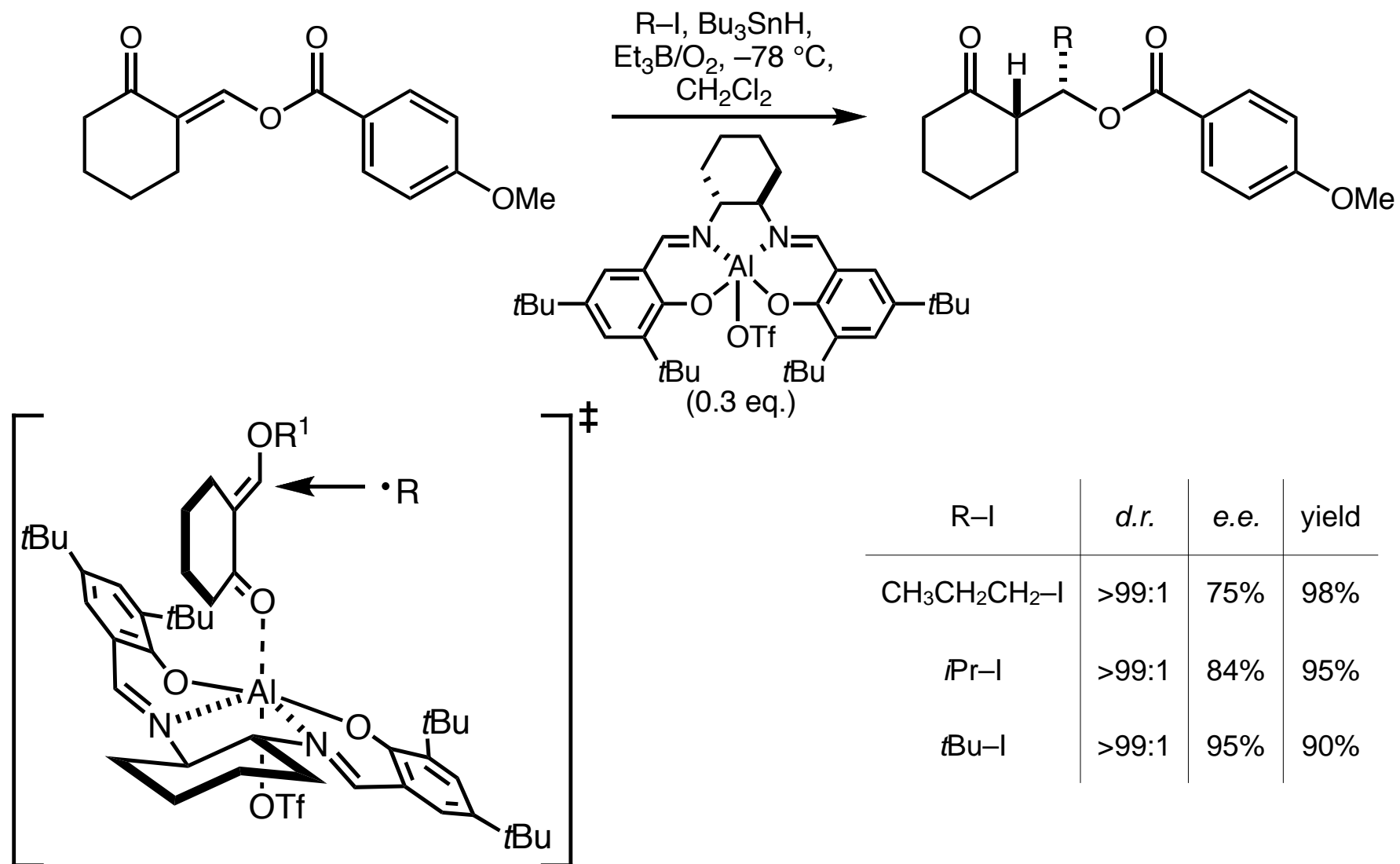
D. Yang, S. Gu, Y.-L. Yan, N.-Y. Zhu, K.-K. Cheung, *J. Am. Chem. Soc.* **2001**, *123*, 8612.

- But without chiral catalyst only the *cis* compound was formed!



D. P. Curran, T. M. Morgan, C. E. Schwartz, B. B. Snider, M. A. Dombroskin, *J. Am. Chem. Soc.* **1991**, *113*, 6607.

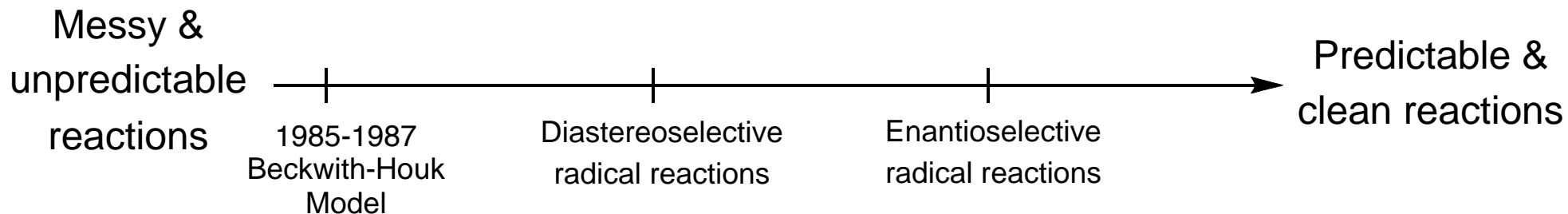
Radical Addition to Cyclic Ketones



- Hydrogen transfer from the opposite face of the •R attack.

Conclusion

30 years of radical chemistry chemistry



- Important tool in organic synthesis:
 - Mild conditions and good compatibility with several functional groups.
 - Access to complex molecular architecture.
- Efforts for a “green” radical chemistry (tin-free radical reactions).
- Field in development.

“I didn’t think that radical chemistry could be so mild and selective”