Reviews:

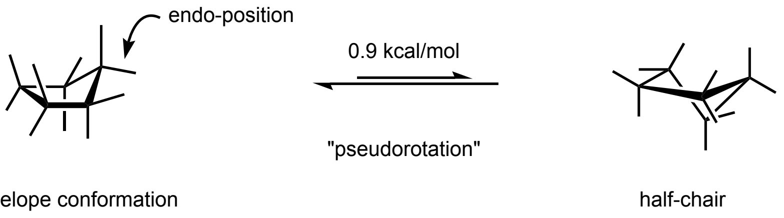
Gilmore, K.; Alabugin, I. V. *Chem. Rev.* **2011**, *111*, 6513–6556.

Albert, M.; Fensterbank, L.; Lacôte, E.; Malacria, M. *Top. Curr. Chem.* **2006**, *264*, 1–62.

Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237–1286.

Zard, S. Z. *Radical Reaction in Organic Synthesis* ; Oxford University Press: New York, 2003.

Conformational Analysis of Cyclopentane



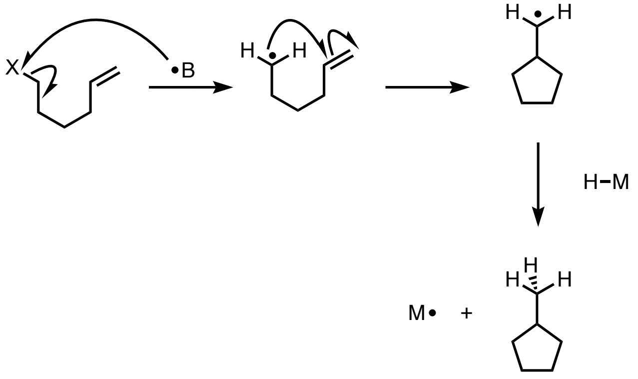
- In the envelope conformation, one carbon atom is positioned out of plane from the others.
- In the half-chair conformation, three atoms are co-planar.
- Interconversion between the envelope and half-chair conformations, known as a "pseudorotation," is rapid. The two conformers differ in energy by 0.9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

Synthetic Methods For the Construction of Cyclopentanes:

- **Radical Cyclizations**
- General Mechanism for Free Radical Cyclizations

Initiation $A{-}B \longrightarrow A\bullet + B\bullet$

Propagation



- Radicals are highly reactive intermediates and can be used for the construction of hindered or strained systems.
- Radical cascades can be used for building complex polycyclic systems.
- Controlling radical reactions remains a challenge. *Exo*-cyclizations are typically favored kinetically over *endo*-cyclizations.
- **Baldwin's Rules for Ring Closure:**

		3	4	5	6
-tet	**endo-**	–	–	x	x
	exo-	√	√	√	√
-trig	**endo-**	x	x	x	√
	exo-	√	√	√	√
-dig	**endo-**	√	√	√	√
	exo-	x	x	√	√

– = not predicted

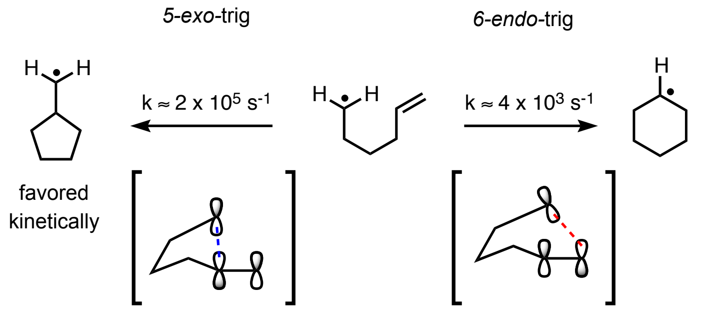
√ = favored

x = unfavored

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

For revisions and modifications to Baldwin's rules, see:
Beckwith, A. L. J.; Easton, C. J.; Serelis, A. K. *J. Chem. Soc. Chem. Comm.* **1980,** 482–483.
Gilmore, K.; Alabugin, I. V. *Chem. Rev.* **2011**, *111*, 6513–6556.

- 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:



Dewar, M. J. S.; Olivella, S. *J. Am. Chem. Soc.* **1978**, *100*, 5290–5295.
Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron,* **1985**, *41*, 3925–3941.

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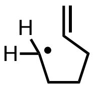
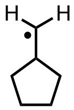
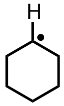
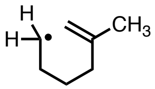
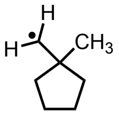
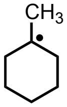
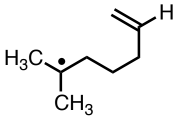
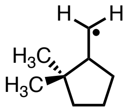
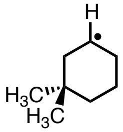
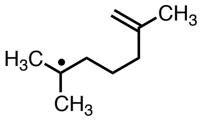
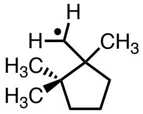
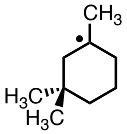
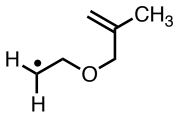
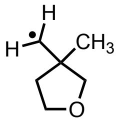
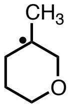
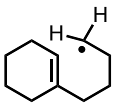
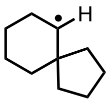
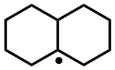
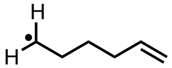
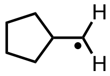
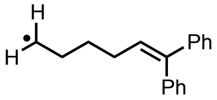
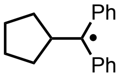
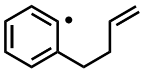
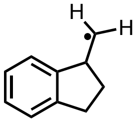
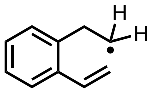
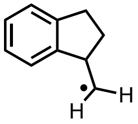
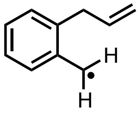
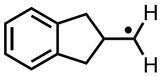
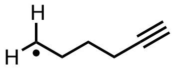
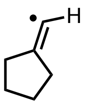
- Effects of non-bonded interactions on the regioselectivity of radical cyclizations:

Substrate	**Product** *exo*	 *endo*	**ratio** (*exo*:*endo*)
			98 : 2
			40 : 60
			>99 : 1
			68 : 32
			98 : 2
			55 : 45

Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959–974.
Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925–3941.
Bechwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073–3100.
Beckwith, A. L. J.; Lawrence, T. *J. Chem. Soc. Perkin Trans. 2* **1979**, 1535–1539.

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

Substrate	**Product**	**Rate** (s^{-1})	E_a (kcal/mol)	**Ref.**
		2.4×10^{5}	6.2	(a)
		4×10^{7}	N/A	(b)
		4×10^{8}	3.6	(c)
		1.5×10^{5}	7.3	(d)
		2×10^{-1}	16.3	(e)
		2.8×10^{4}	8.3	(f)

Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, *Part A: Structure and Mechanisms*, 5th ed.; Springer: New York, 2007.

(a) Beckwith, A. L. J.; Easton, C. J.; Lawrence, T.; Srelis, A. K. *Aust. J. Chem.* **1983**, *36*, 545–556.
(b) Ha, C.; Horner, J. H.; Newcomb, M.; Varick, T. R.; Arnold, B. R.; Lusztyk, J. *J. Org. Chem.* **1993**, *58*, 1194–1198., Newcomb, M.; Horner, J. H.; Filipkowski, M. A.; Ha, C.; Park, S.-U. *J. Am. Chem. Soc.* **1995**, *117*, 3674–3684.
(c) Johnson, L. J.; Lusztyk, J.; Wayner, D. D. M.; Abeywickreyma, A. N.; Beckwith, A. L. J.; Scaiano, J. C.; Ingold, K. U. *J. Am. Chem. Soc.* **1985**, *107*, 4594–4596.
(d) Franz, J. A.; Barrows, R. D.; Camaioni, D. M. *J. Am. Chem. Soc.* **1984**, *106*, 3964–3967.
(e) Franz, J. A.; Alnajjar, M. S.; Barrows, R. D.; Kaisaki, D. L.; Camaioni, D. M.; Suleman, N. K. *J. Org. Chem.* **1986**, *51*, 1446–1456.
(f) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron Lett.* **1985**, *26*, 373–376.
(g) Beckwith, A. L. J.; Hay, B. P. *J. Am. Chem. Soc.* **1989,** *111*, 230–234.

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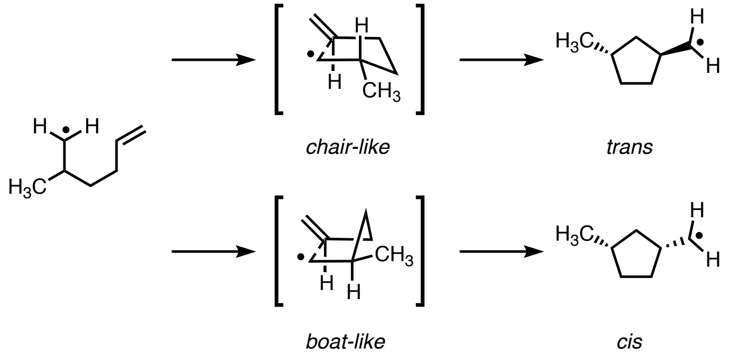
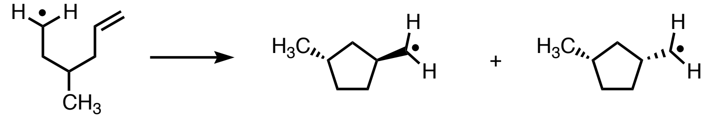
- Stereochemistry in radical cyclizations
- Chair-like *exo* transition states are favored, where the substituents are preferentially placed in pseudoequatorial positions. The alternative boat-like transition states are however close in energy and selectivity is often modest:

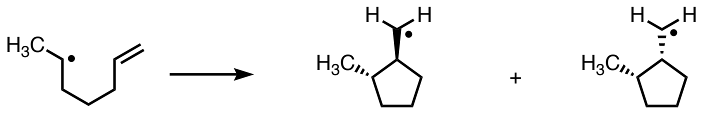
Ratio (*trans* : *cis*)



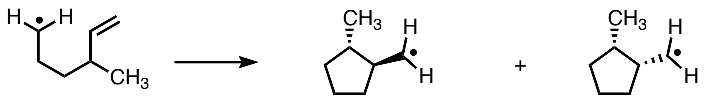
64 : 36



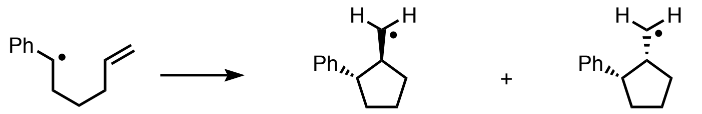
29 : 71



33 : 67



83 : 17



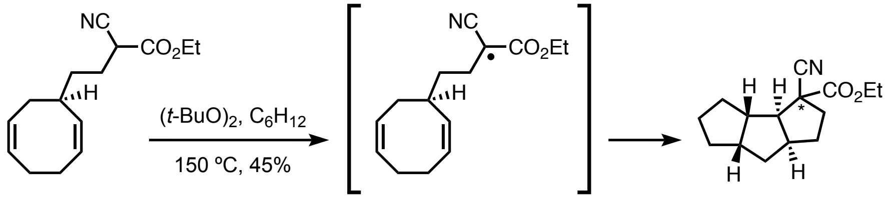
100 : 0

Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959–974.

- **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:

$$R{-}O{-}O{-}R \xrightarrow{\Delta \text{ or } h\nu} 2 \times RO\bullet$$

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



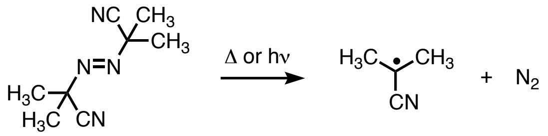
a mixture of epimers at *carbon

Winkler, J. D.; Sridar, V. *J. Am. Chem. Soc.* **1986**, *108*, 1708–1709.

- Azo compounds are also commonly used to generate radicals:

$$R{-}N{=}N{-}R' \xrightarrow{\Delta \text{ or } h\nu} R\bullet + N_2 + \bullet R'$$

- 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_6H_6, 100 ºC) = 6 h):



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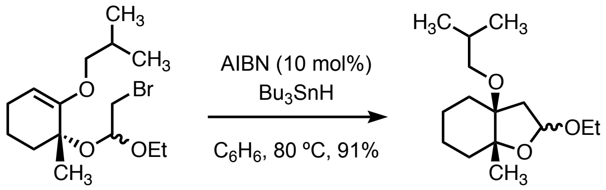
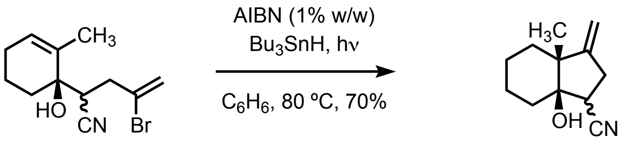
- Tin hydride reagents such as Bu_3SnH readily transfer hydrogen atoms to free-radical intermediates (bond dissociation energy of $Bu_3Sn–H$ = 78 kcal/mol):



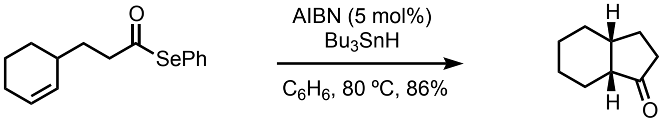
Ladlow, M.; Pattenden, G. *Tetrahedron Lett.* **1984**, *25*, 4317–4320.

- Whereas the bond dissociation energies of C–halogen bonds are less than 80 kcal/mol ($BDE_{C–I}$ = 57 kcal/mol, $BDE_{C–Br}$ = 67 kcal/mol, $BDE_{C–Cl}$ = 79 kcal/mol), BDEs of O–H bonds are ~110 kcal/mol. As a result, radical cyclizations can be carried out in the presence of free hydroxyl groups:



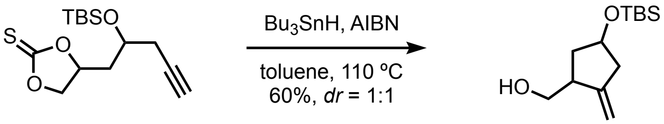
Stork, G.; Baine, N. H. *J. Am. Chem. Soc.* **1982**, *104*, 2321–2323.

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



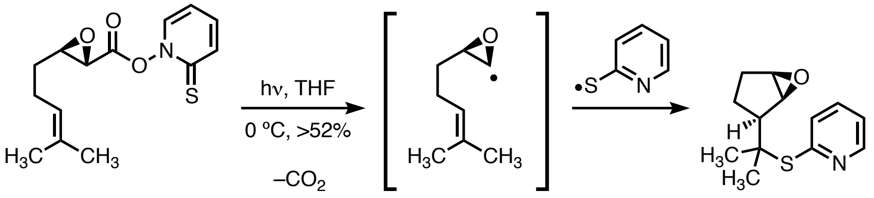
Boger, D. L.; Mathvink, R. J. *J. Org. Chem.* **1988**, *53*, 3377–3381.

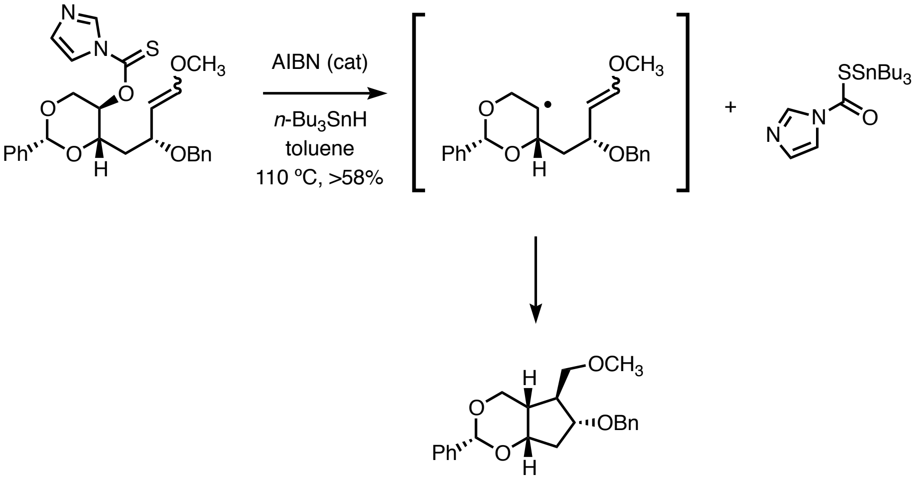
- Thionocarbonates can also be used as substrates for radical cyclization reactions:



Ziegler, F. E.; Metcalf III, C. A.; Schulte, G. *Tetradehdron Lett.* **1992**, *33*, 3117–3120.

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





Ziegler, F.; Wang, Y. *Tetrahedron Lett.* **1996**, *37*, 6299–6302.
RajanBabu, T. V. *J. Org. Chem.* **1988**, *53*, 4522–4530.

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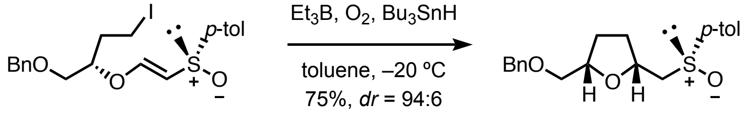
- Trialkylboranes can be used with O_2 to generate radicals. This reaction proceeds readily even at –78 ºC, making it an ideal radical cyclization initiator for functionalized substrates:

$$R_3B \quad + \quad O_2 \quad \longrightarrow \quad R_2BOO\bullet \quad + \quad R\bullet$$

Olivier, C.; Renaud, P. *Chem. Rev.* **2001**, *101*, 3415–3434.

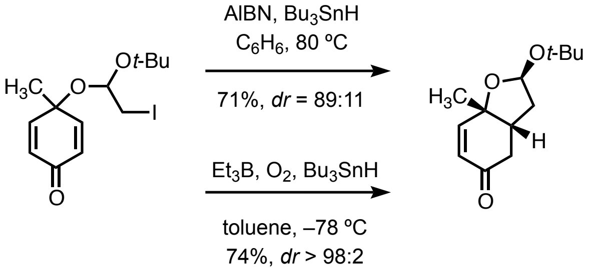
- Bu_3SnH is used as the terminal hydride donor in the following example:



single diastereomer

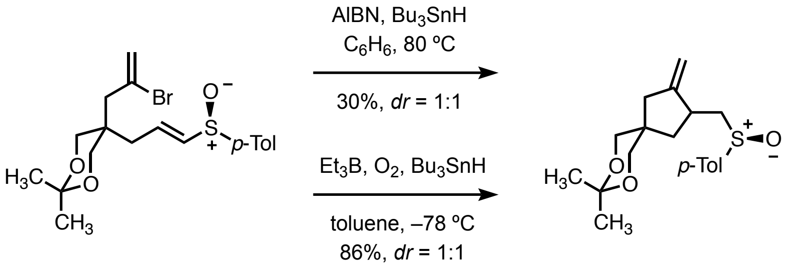
Keum, G.; Kang, S. B.; Kim, Y.; Lee, E. *Org. Lett.* **2004**, *6*, 1895–1897.

- Higher diastereoselectivities can be obtained when Et_3B/O_2 is used to initiate radical formation than when AIBN is used:



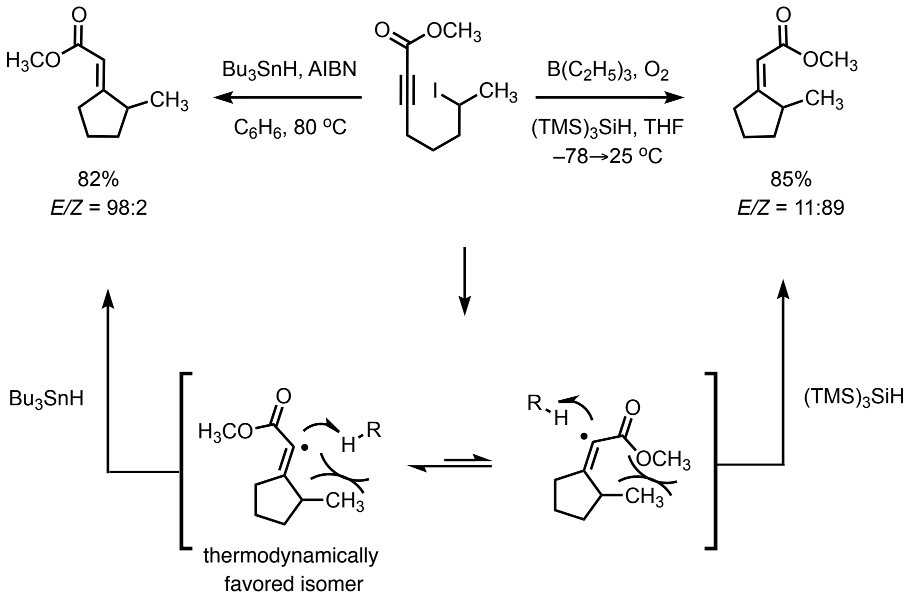
Villar, F.; Equey, O.; Renaud, P. *Org. Lett.* **2000**, *2*, 1061–1064.

- In the following example, higher yields were observed when Et_3B/O_2 was used:



Lacote, E.; Malacria, M. *C. R. Acad. Sci. Paris. T. 1. Serie IIc* **1998**, 191–194.

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

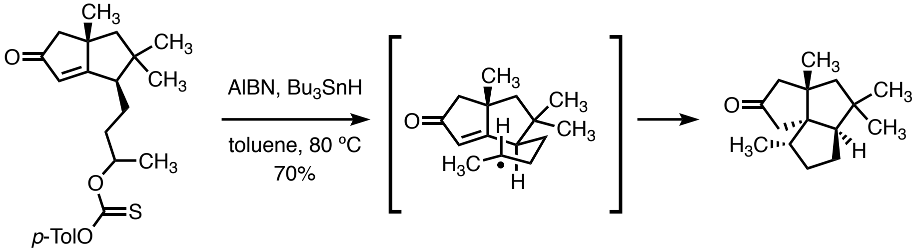


- The rate of alkenyl radical inversion is faster than that of atom transfer even at –78 ºC (Curran, D. P.; Chen, M. H.; Kim, D. *J. Am. Chem. Soc.* **1989**, *111*, 6265–6276.

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

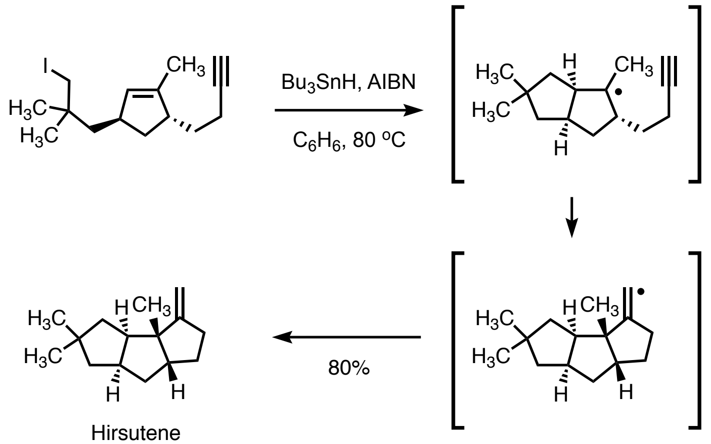
Lowinger, T. B.; Weiler, L. *J. Org. Chem.* **1992**, *57*, 6099–6101.

- **Examples of Cyclopentane Synthesis via Radical cyclization in Synthesis**
- Synthesis of silphinene:



Rao, Y. K.; Nagarajan, M. *Tetrahedron Lett.* **1988**, *29*, 107–108.

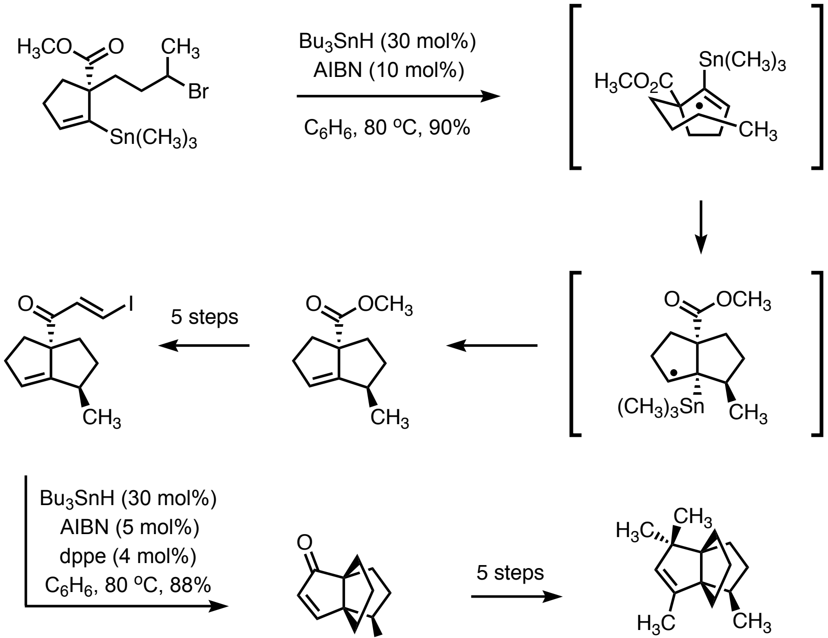
- Curran has shown that a tandem radical cyclization strategy can be used as a general approach to the triquinanes, such as hirsutene:



Hirsutene

Curran, D. P.; Rakiewicz, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 1448–1449.

- Synthesis of modhephene:

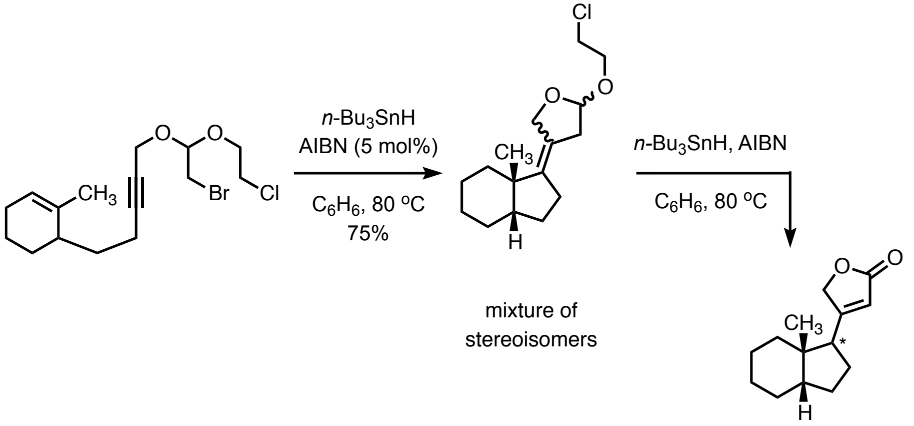


Modhephene

- Dppe was used to sequester residual Pd metal from the previous synthetic step.

Jasperse, C. P.; Curran, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 5601–5609.

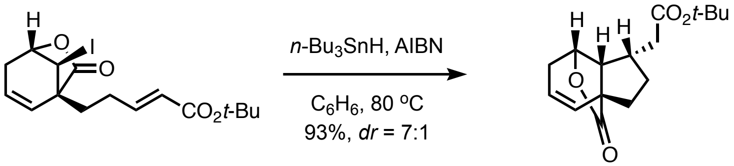
- Double radical cyclization for the synthesis of a butenolide:



mixture of stereoisomers

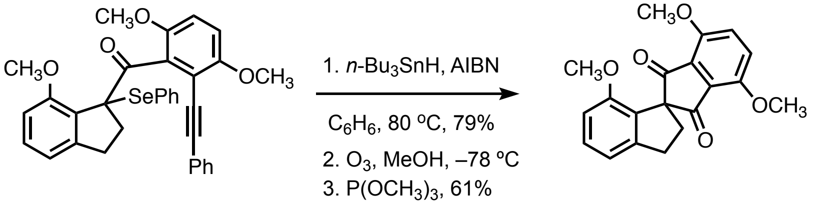
single diastereomer (*stereochemistry not assigned)

Stork, G.; Mook, R. *J. Am. Chem. Soc.* **1983**, *105*, 3720–3722.



Hart, D. J.; Chuang, C.-P. *J. Org. Chem.* **1983**, *48*, 1782–1784.

- Radical spirocyclization:



Clive, D. L. J.; Angoh, A. G.; Bennett, S. M. *J. Org. Chem.* **1987**, *52*, 1339–1342.

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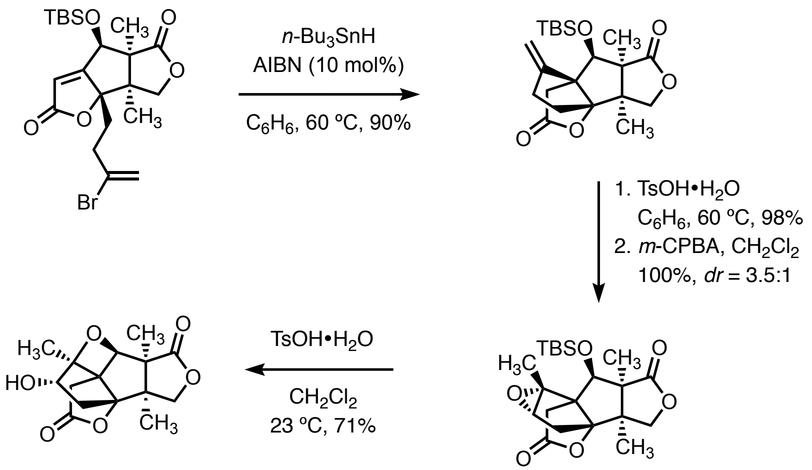
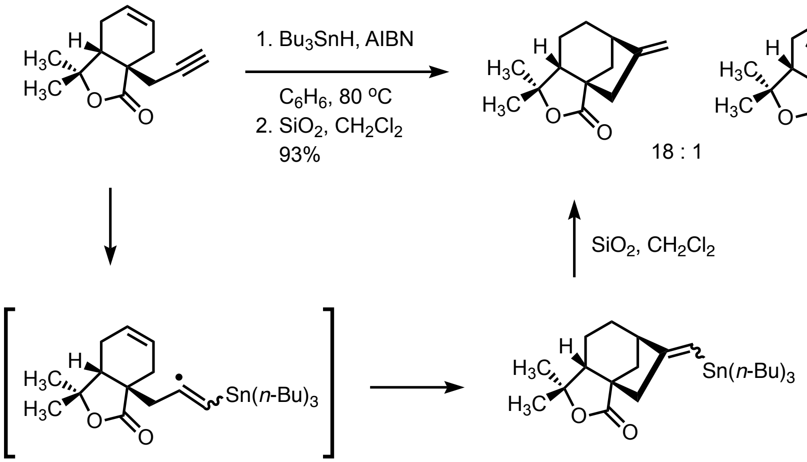
- Synthesis of merrilactone A:



(±)-merrilactone A

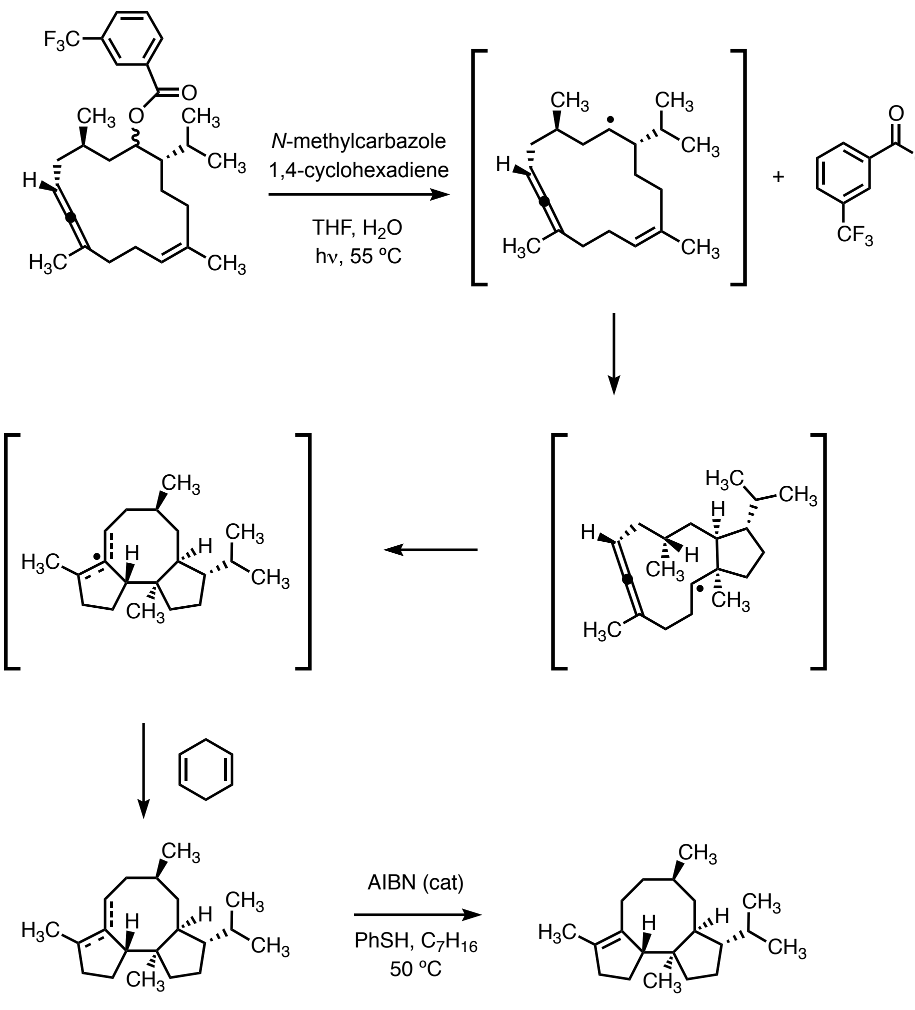
Birman, V. B.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2002,** *124,* 2080–2081.

- In the example below, the radical cyclization cascade was initiated by addition of n-Bu_3Sn radical to the alkyne, followed by by 5-*exo*-trig cyclization, a procedure originally developed by Stork. Protodestannylation then provided the observed product:



Toyota, M.; Yokota, M.; Ihara, M. *J. Am. Chem. Soc.* **2001**, *123*, 1856–1861.
Stork, G.; Mook, R., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 2829.

- 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):

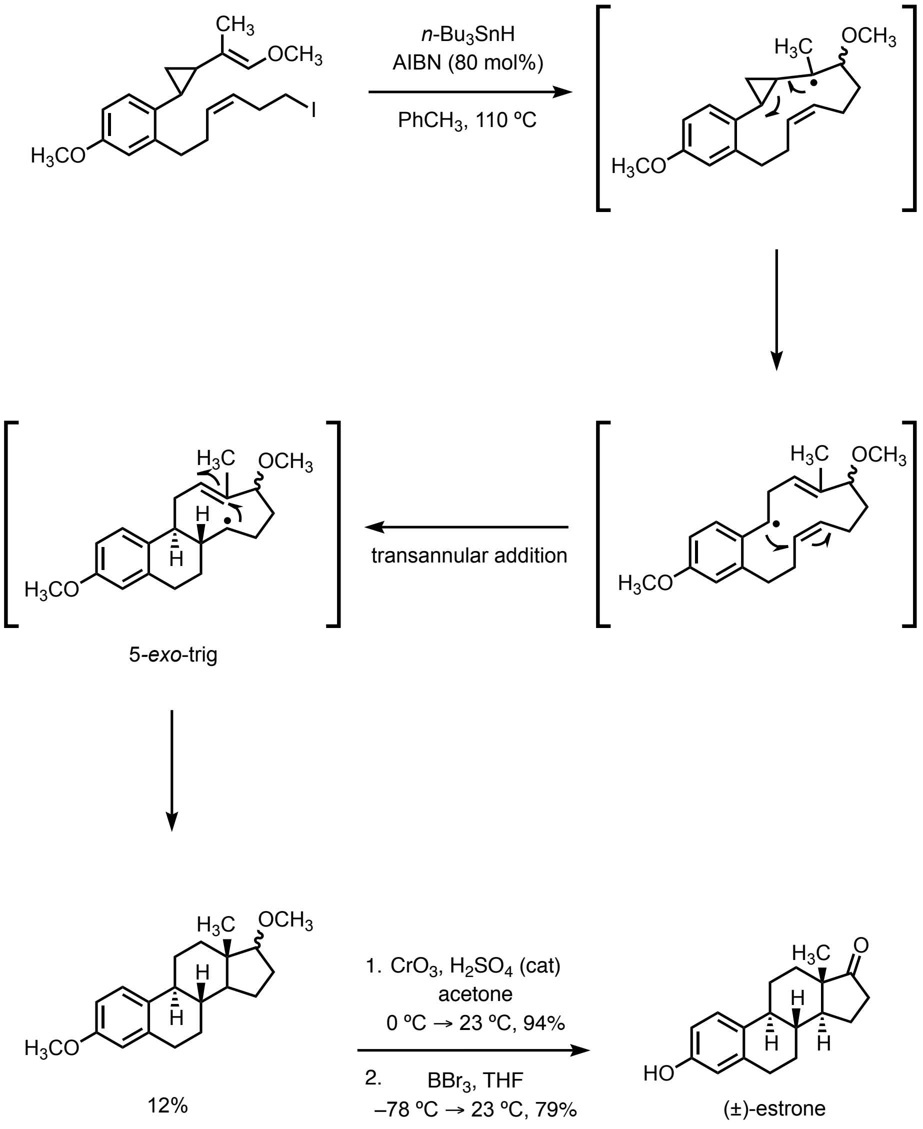


51%
mixture of isomers

91%
a single isomer

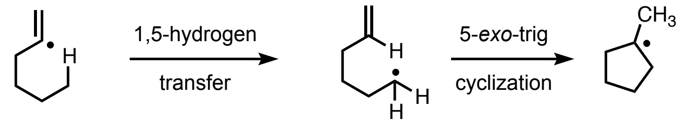
Myers, A. G.; Condroski, K. R. *J. Am. Chem. Soc.* **1993**, *115*, 7926–7927.
Myers, A. G.; Condroski, K. R. *J. Am. Chem. Soc.* **1995**, *117*, 3057–3083.
Saito, I.; Ikehira, H.; Kasatani, R.; Watanabe, M.; Matsuura, T.; *J. Am. Chem. Soc.* **1986**, *108*, 3115–3117.

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

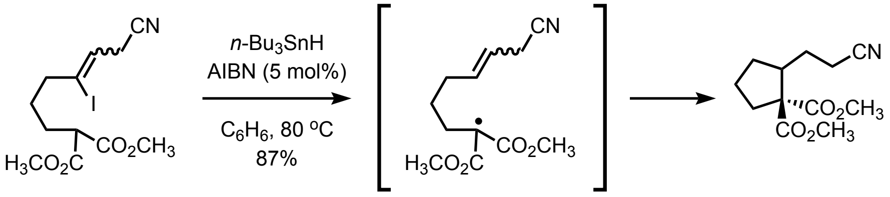


Pattenden, G.; Gonzalez, M. A.; McCulloch, Walter, A.; Woodhead, S. J. *Proc. Nat. Acad. Sci.* **2004**, *101*, 12024–12029.

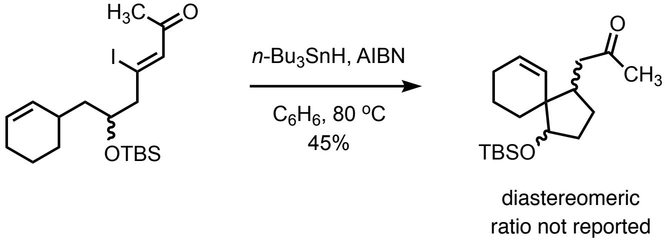
- Vinyl radicals can undergo 1,5-hydrogen abstraction followed by cyclization:



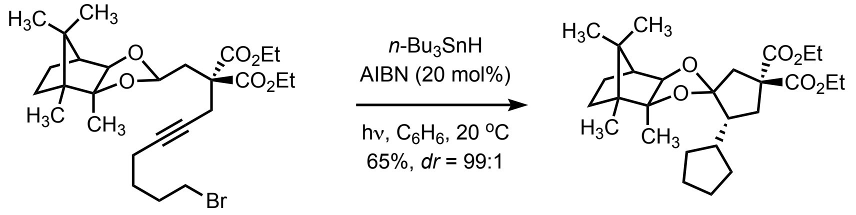
Dénès, F.; Beaufils, F.; Renaud, P. *Synlett,* **2008**, 2389 - 2399.



Curran, D. P.; Kim, D.; Liu, H. T.; Shen, W. *J. Am. Chem. Soc.* **1988**, *110*, 5900–5902.



Borthwick, A. D.; Caddick, S.; Parsons, P. J. *Tetrahedron Lett.* **1990**, *31*, 6911–6914.



Stien, D.; Crich, D.; Bertrand, M. P. *Tetrahedron* **1998**, *54*, 10779–10788.

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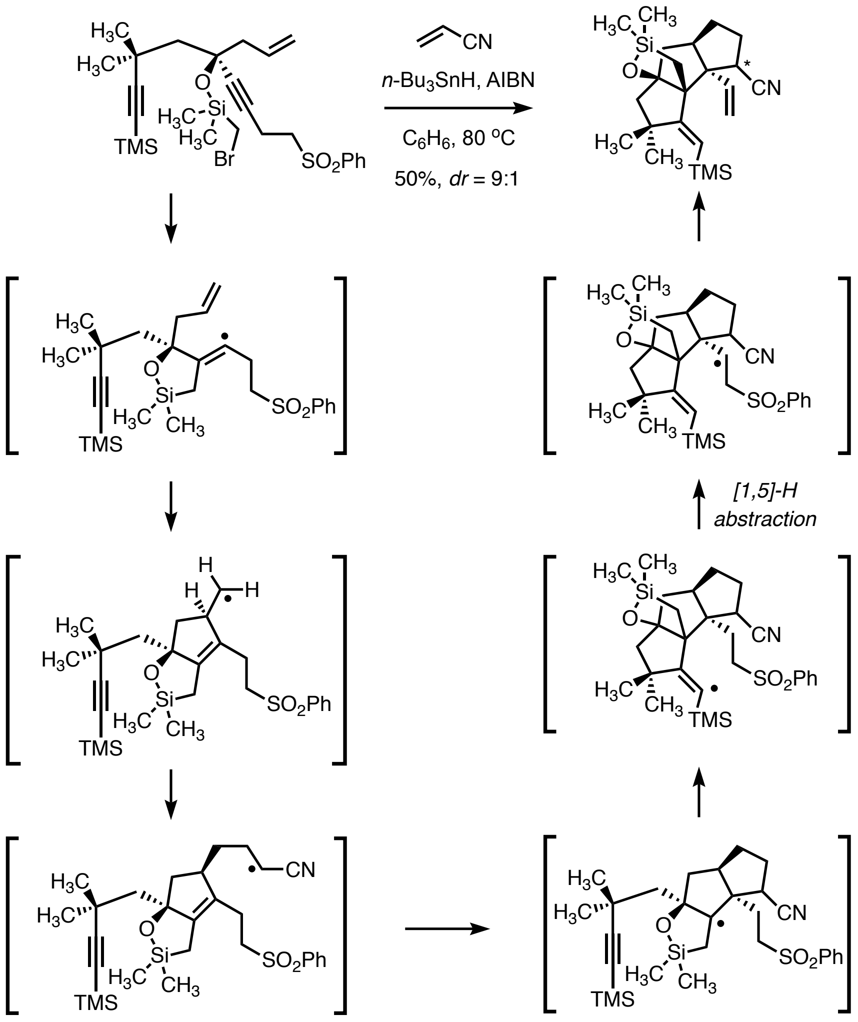
- In an approach to triquinanes, a series of 5-*exo* cyclizations was used to generate the triquinane structure from a linear precursor:



Devin, P.; Fensterbank, L.; Malacria, M. *J. Org. Chem.* **1998**, *63*, 6764–6765.

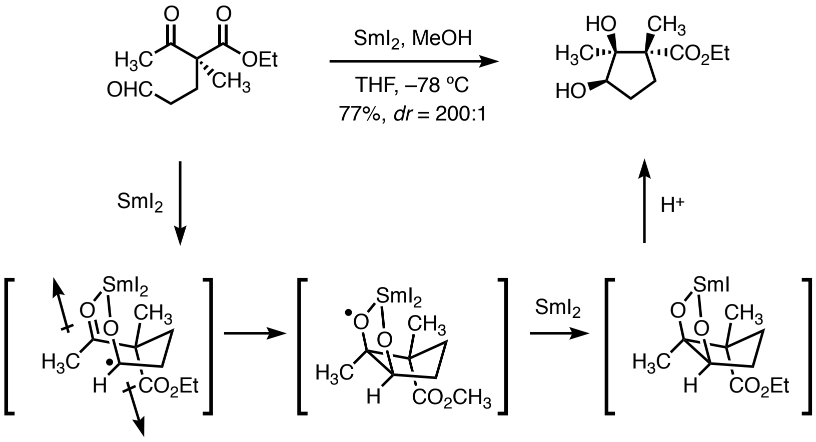
- **SmI$_2$-Mediated Reductive Cyclizations**

Edmonds, D. J.; Johnston, D.; Procter, D. J. *Chem. Rev.* **2004**, *104*, 3371–3403.

- First introduced by Kagan, SmI$_2$ is a powerful single electron reducing agent.

Kagan, H. B.; *Nouv. J. Chim.* **1977**, 5.

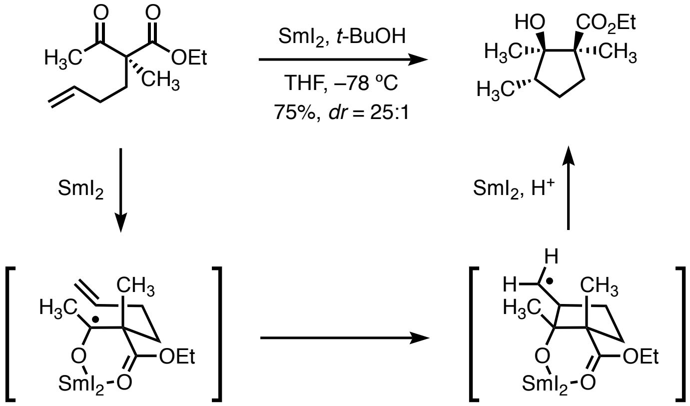
- In the presence of SmI$_2$, 1,5-dicarbonyls undergo reductive coupling to give cyclopentanediols. *Cis* stereochemistry is generally favored because of chelation to Sm^{III}:



- In the example above, dipole minimization was proposed to rationalize the relative stereochemistry between the hydroxyl and the ethyl ester.

Molander, G. A.; Kenny, C. *J. Org. Chem.* **1988**, *53*, 2132–2134.

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



Molander, G. A.; Kenny, C. *J. Am. Chem. Soc.* **1989**, *111*, 8236.

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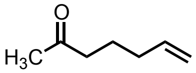
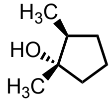
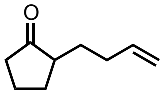
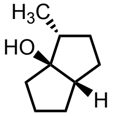
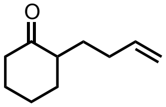
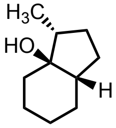
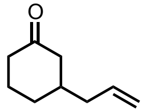
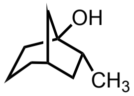
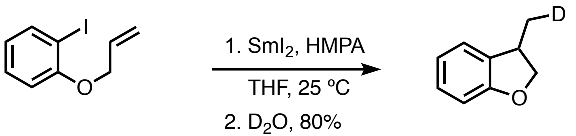
- Examples

Substrate	Product	Yield (%)	*d.r.*
		86	150 : 1
		90	150 : 1
		89	150 : 1
		88	17 : 1

Conditions: SmI_2, HMPA, THF, *t*-BuOH, 23 ºC

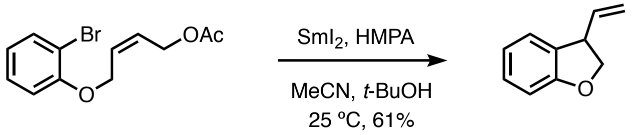
Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1992**, *57*, 3132–3139.

- Halides can also be reduced by SmI_2 in the presence of HMPA. The addition of HMPA increases the reduction potential of SmI_2:



90% deuterium incoporation

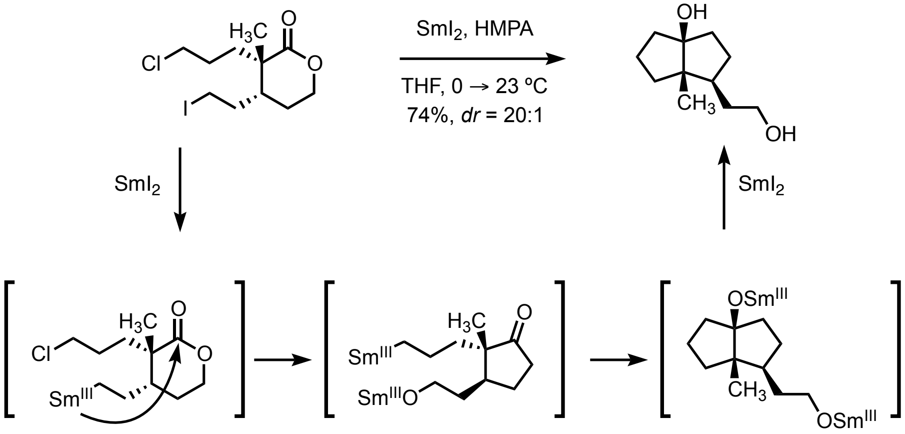
Curran, D. P.; Fevig, T. L.; Totleben, M. J. *Synlett*, **1990**, 773–774.



Inanaga, J.; Ujikawa, O.; Yamaguchi, M. *Tetrahedron Lett.* **1991**, *32,* 1737–1740.

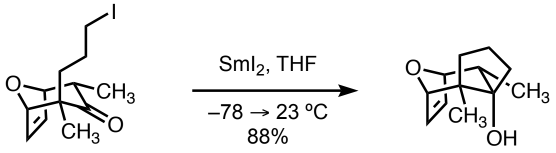
- **Examples of SmI_2-Mediated Reductive Cyclizations in Synthesis**

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



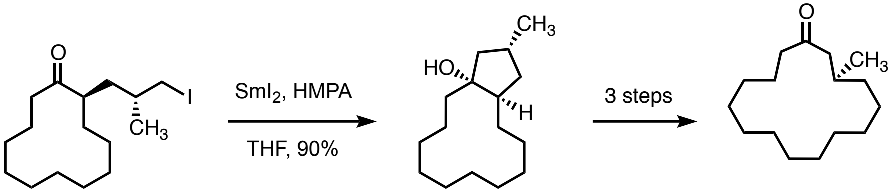
Molander, G. A.; Harris, C. R. *J. Am. Chem. Soc.* **1995**, *117*, 3705–3716.

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



Nowakowski, M.; Hoffmann, H. M. R. *Tetrahedron* **1997**, *53*, 4331–4338.

- Synthesis of muscone:



muscone

Suginome, H.; Yamada, S. *Tetrahedron Lett.* **1987**, *28*, 3963–3966.

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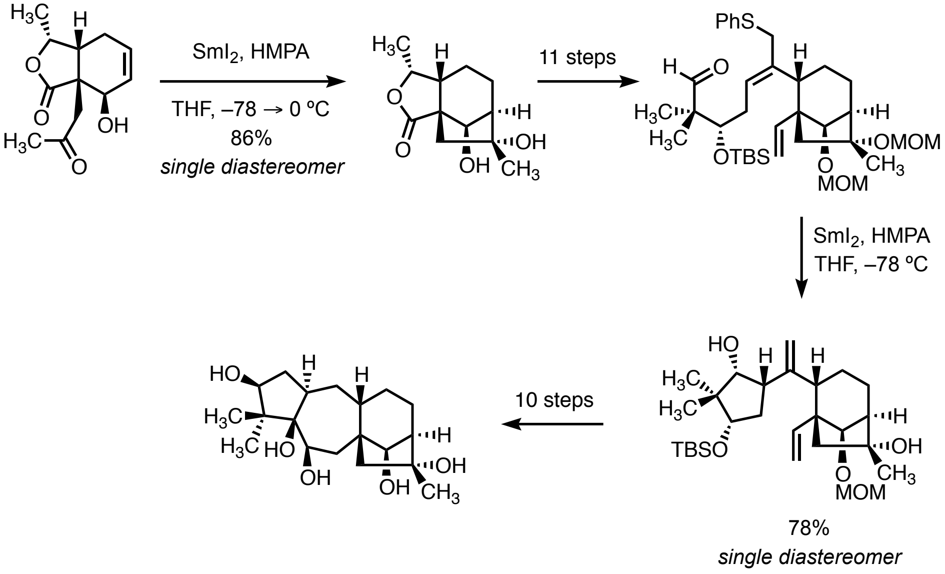
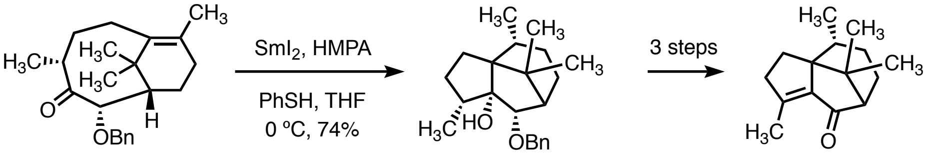
- Multiple SmI_2-mediated cyclizations were used in the synthesis of (–)-grayanotoxin III:



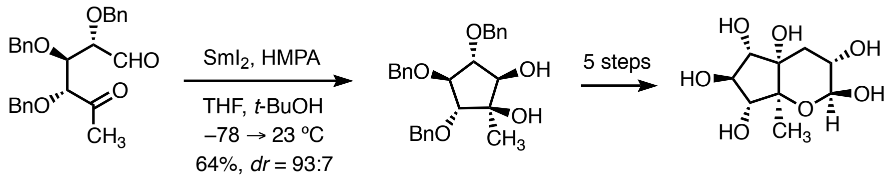
Kan, T.; Hosokawa, S.; Nara, S.; Oikawa, M.; Ito, S.; Matsuda, F.; Shirahama, H. *J. Org. Chem.* **1994**, 5532–5534.

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



(–)-patchoulenone

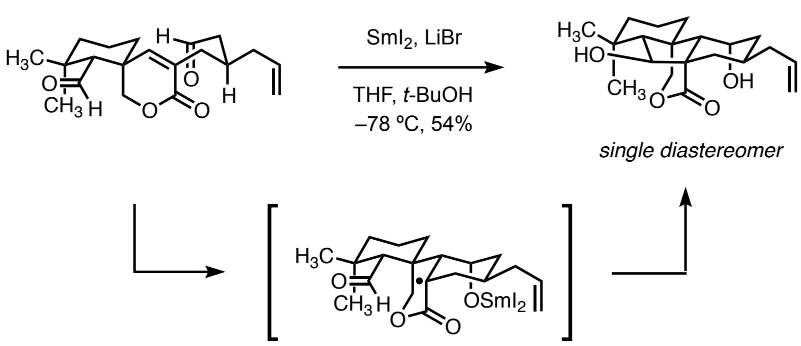
Banwell, M. G.; Hockless, D. C. R.; McLeod, M. D. *New. J. Chem.* **2003**, *27*, 50–59.



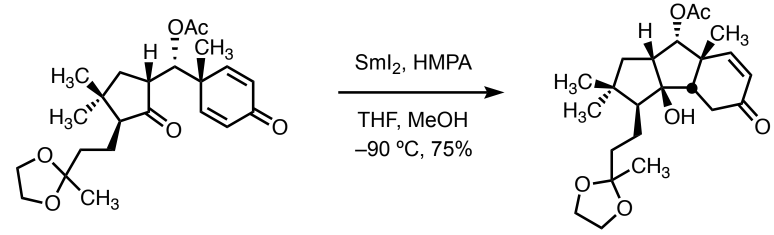
caryose

Adinolfi, M.; Barone, G.; Iadonisi, A.; Mangoni, L.; Manna, R. *Tetrahedron* **1997**, *53*, 11767–11780.

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

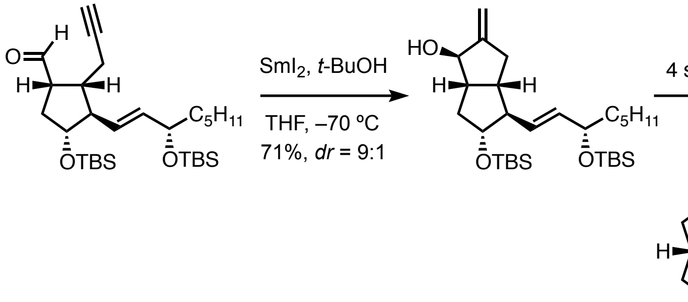


Cha, J. Y.; Yeoman, J. T. S.; Reisman, S. E. *J. Am. Chem. Soc.* **2011**, *133*, 14964–14967.



Arseniyadis, S.; Yashunsky, D. V.; Dorado, M. M.; Alves, R. B.; Toromanoff, E.; Toupet, L.; Potier, P. *Tetrahedron Lett.* **1993**, *34*, 4927–4930.

- Synthesis of isocarbacyclin:



Bannai, K.; Tanaka, T.; Okamura, N.; Hazato, A.; Sugiura, S.; Manabe, K.; Tomimori, K.; Kato, Y.; Kurozumi, S.; Noyori, R. *Tetrahedron* **1990**, *46*, 6689–6704.

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