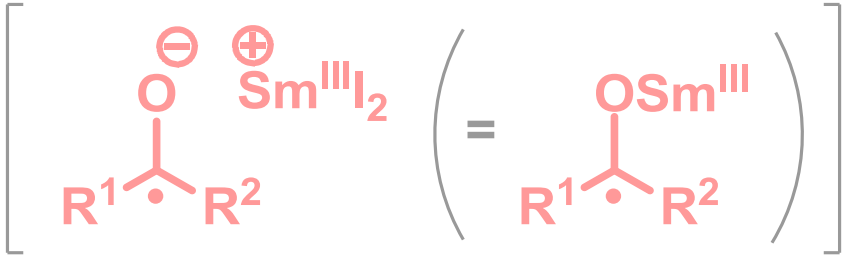
Ketyl Radical Anion in Samarium Iodide (SmI_2) Chemistry

the "Kagan Reagent"



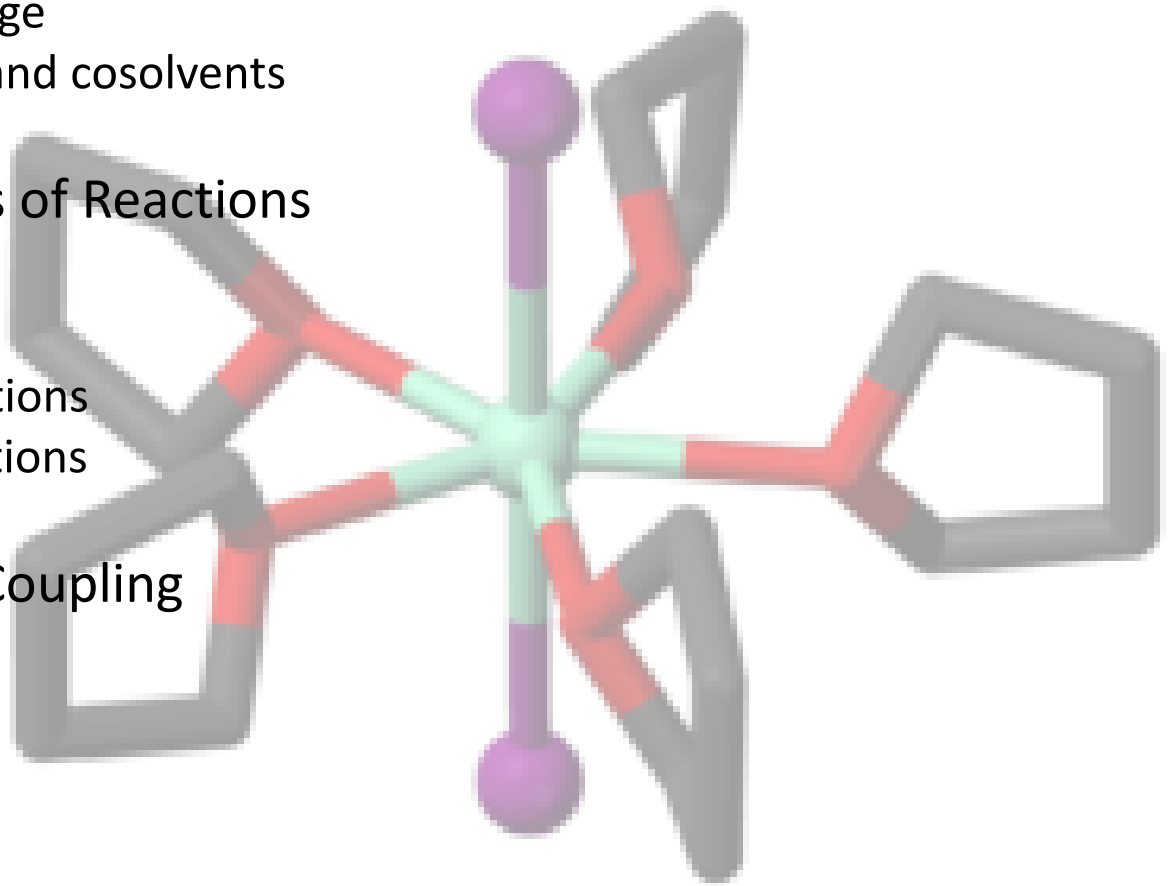
2013. 2. 12.

Hyung Min Chi

Group Meeting Presentation

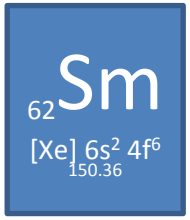
Outline

- The reagent: Samarium Iodide (SmI_2)
  - Characteristic features
  - Preparation and usage
  - Effects of additives and cosolvents
- Representative Types of Reactions
- Pinacol Coupling
  - Intermolecular reactions
  - Intramolecular reactions
- Ketyl-Alkene/Arene Coupling
  - Alkene
  - Arene
- Sequential Reactions



X-ray crystallographic data of $[Sm(THF)_5]I_2$ from: *J. Am. Chem. Soc.* **1995**, *117*, 8999–9002.

Samarium

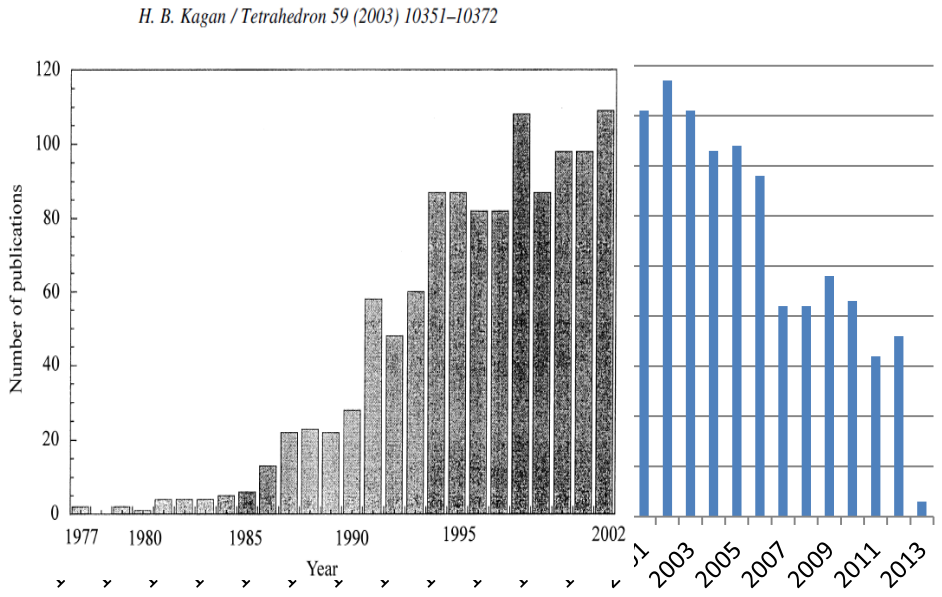


- Sm: atomic number 62
  - Discovered in 1879 by the French chemist Paul Émile Lecoq de Boisbaudran from mineral samarskite
  - Lanthanides: preferentially exists in the +3 oxidation state. Loss of the three outermost electrons ($5d^1$, $6s^2$) to adopt Xe-like electronic configuration.
  - The +2 oxidation state is most relevant for samarium (f, near half-filled)
  - Several compounds of samarium(II) are also known: SmO, monochalcogenides SmS, SmSe and SmTe, and samarium(II) iodide.
  - 4 stable Sm isotopes (^{152}Sm as major) and 3 extremely long-lived radioisotopes

Wikipedia*: Search word" Samarium"*
D. J. Procter, R. A. Flowers II, T. Skrydstrup, *Organic Synthesis using Samarium Diiodide: A Practical Guide*, RSC Publishing, Cambridge, **2009**.

Samarium Iodide

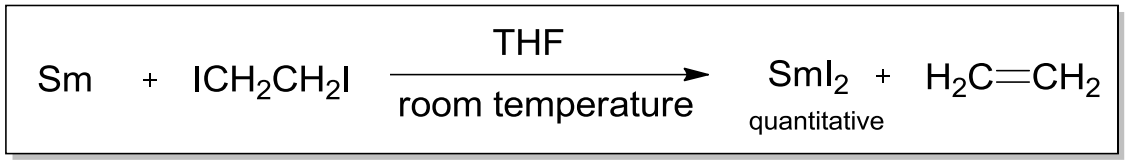
- First publication (Kagan, 1977) followed by a full paper (1980)
  - Molander, Procter, Inanaga, Skrydstrup, Imamoto, Concellon, Ressig, Flowers, Zhang
- Powerful one-electron reducing agent
  - Green solid, dark blue solution in THF
- Various reaction types:
  - Radical cyclizations
  - Ketyl-olefin coupling reactions
  - Pinacolic coupling reactions
  - Barbier-type reactions
  - Aldol-type reactions
  - Reformatsky-type reactions
  - Nucleophilic acyl substitutions



Kagan, Nouv J. Chim. **1977**, *1*, 5.
Kagan, JACS **1980**, *102*, 2693.
Kagan, *Tetrahedron* **2003**, *59*, 10351
Publication Search (Scifinder)

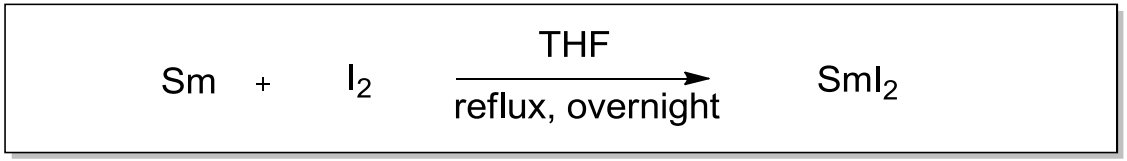
How do one prepare SmI_2?

- Kagan
  - Samarium metal with 1,2-diiodoethane in THF
  - Solutions could be stored under inert atmosphere in presence of a small amount of metal



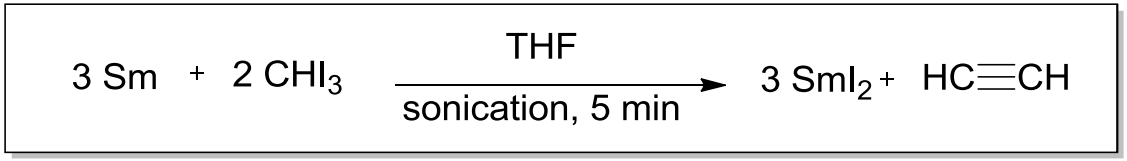
JACS **1980**, *102*, 2693.

- Imamoto
  - Samarium metal with iodine in THF



Chem. Lett. **1987**, 501.

- Concellón
  - Samarium metal with iodoform in THF



Eur. J. Org. Chem. **2003**, 1775.

Effects of Additives and cosolvents

- Reactivity can be altered with:
  - Lewis bases: HMPA, DBU, TMU, DMI, TMG…
    - Dissociate aggregates in THF
    - Increase Sm(II)/Sm(III) reduction potential
    - Higher diastereoselectivity: formation of sterically encumbered species
    - Stabilize reactive intermediate
  - Proton sources: MeOH, tBuOH, phenol, glycols, H_2O
    - Impact regiochemical, stereochemical outcome
    - Generates more powerful reductants upon coordination
  - Inorganic additives: Li salts/bases, NiI_2, $FeCl_3$
    - Coupling of alkyl iodides, ketones, pinacolic couplings
    - Reduction of aryl esters, acids, amides
    - Conjugate addition of alkyl iodides

Inanaga, *Chem. Lett.* **1987**, 1487.
Molander, *J. Org. Chem.* **1992**, *57*, 3132.
Kagan, *Synlett* **1996**, 633-634.

Reduction potential?

- Redox potential of the SmI_2–SmI_2^+ couple has been established through the use of linear sweep and cyclic voltammetry and was found to be approximately –1.41 V, determined for a solution of SmI_2 in THF.

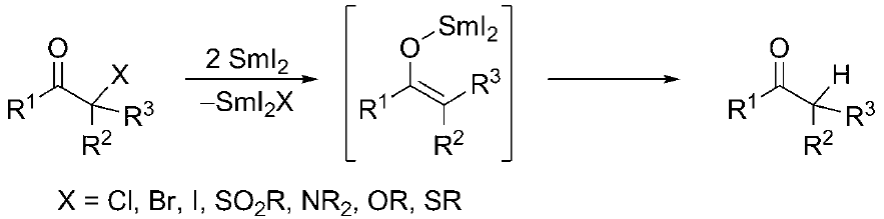
- Upon addition of 4 equiv of HMPA as an additive, the reduction potential is increased to –1.79 V.

- upon the inclusion of 500 equiv of water, the reduction potential can be increased as far as –1.9 V.

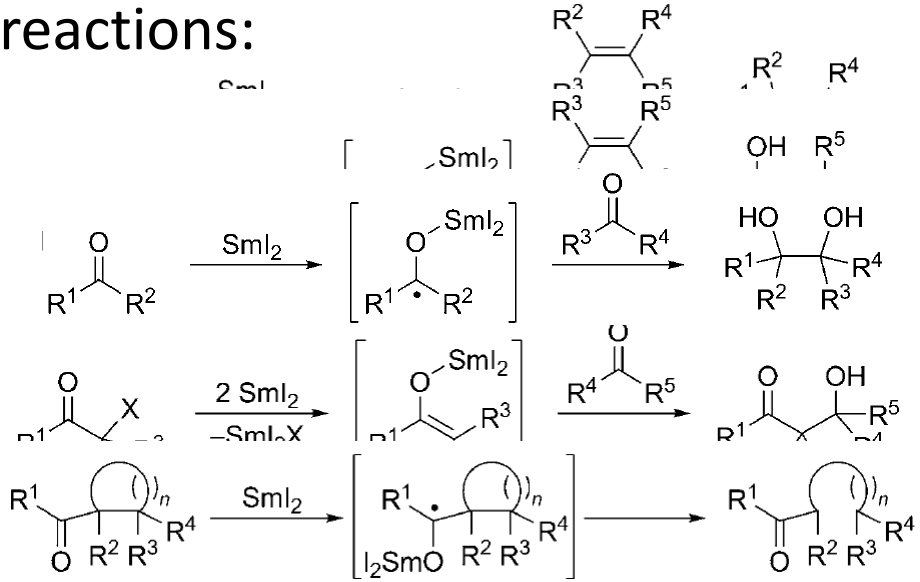
D. J. Procter, R. A. Flowers II, T. Skrydstrup, *Organic Synthesis using Samarium Diiodide: A Practical Guide*, RSC Publishing, Cambridge, **2009**.
Flowers II, *Tetrahedron Lett.*, **1997**, *38*, 1137.
Flowers II, *J. Am. Chem. Soc.*, **2005**, *127*, 18093.

Reaction types

- Reductions
  - Halide reductions / Eliminations
  - Carbonyl reductions



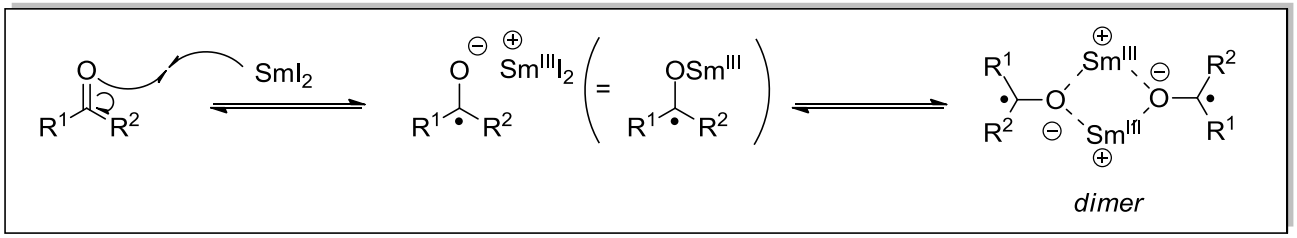
- Carbon-Carbon bond forming reactions:
  - Radical additions/cyclizations
  - Ketyl-olefin coupling
  - Pinacolic coupling
  - Barbier-type reactions
  - Reformatsky-type reactions
  - Fragmentation reactions



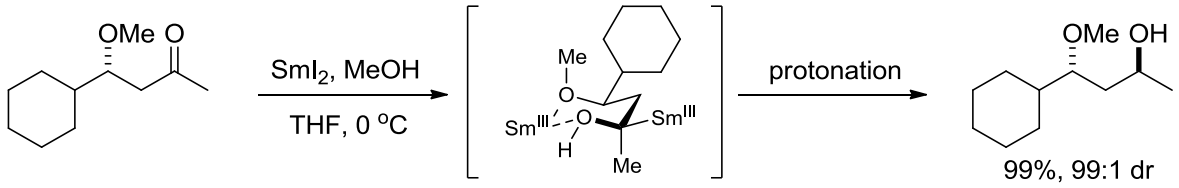
Nicolaou, *Angew. Chem. int. Ed.* **2009**, *48*, 7140.

Ketyl Radical Anion

- Ketyl radical anion
  - Single electron from SmI_2

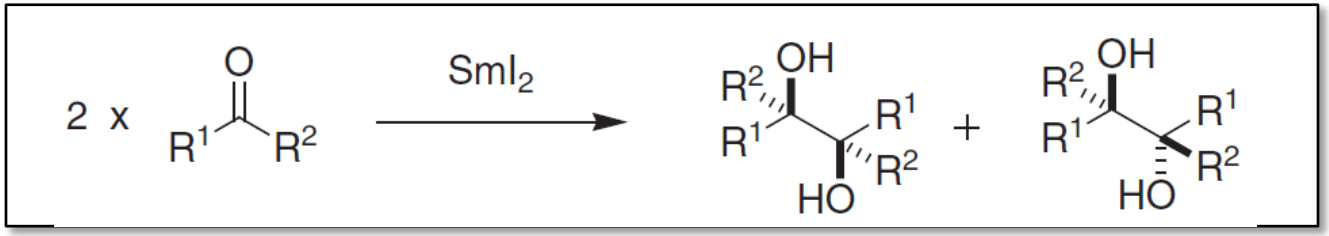


- Carbonyl reduction
  - Directed reduction: β-alkoxy ketones
  - Proximal Lewis basic methoxy groups

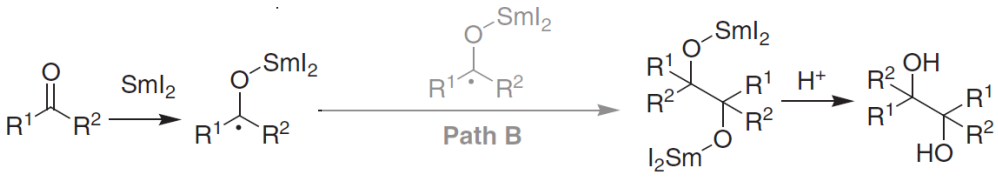


Keck, *Org. Lett.* **2000**, *2*, 2307.

Pinacolic Coupling



- Important method for vicinally functionalized C-C bonds

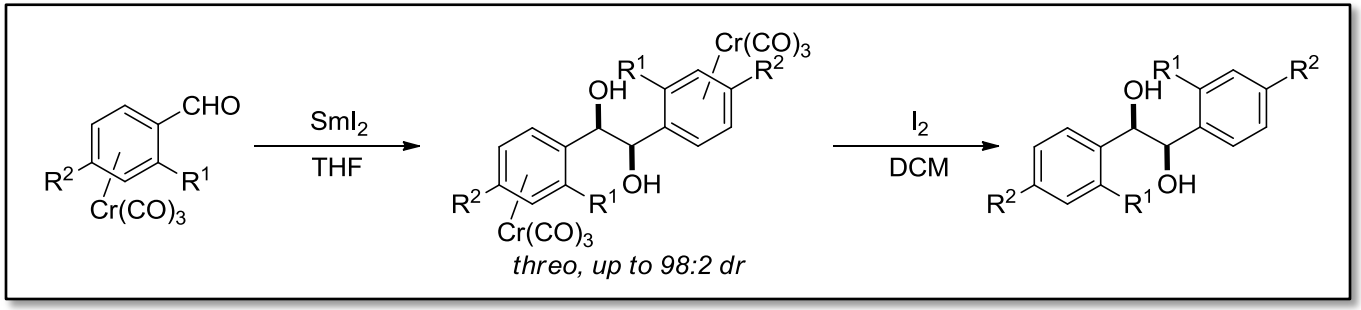


D. J. Procter, R. A. Flowers II, T. Skrydstrup, *Organic Synthesis using Samarium Diiodide: A Practical Guide*, RSC Publishing, Cambridge, **2009**.

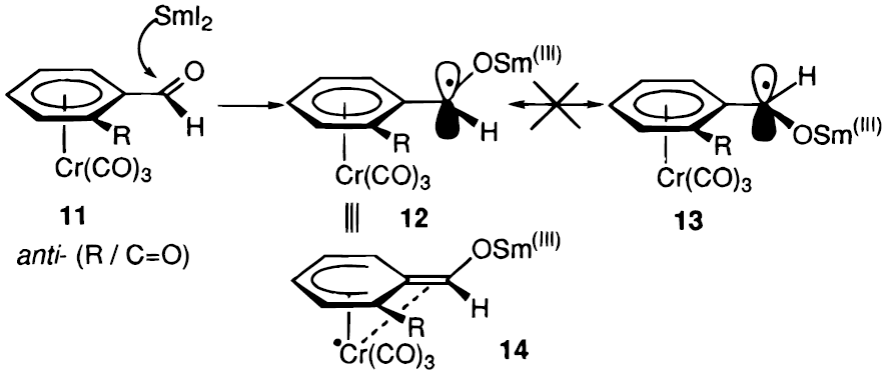
- Aryl aldehydes/ketones>> alkyl aldehydes > alkyl ketones
- Acceleration with additives (ex. HMPA)

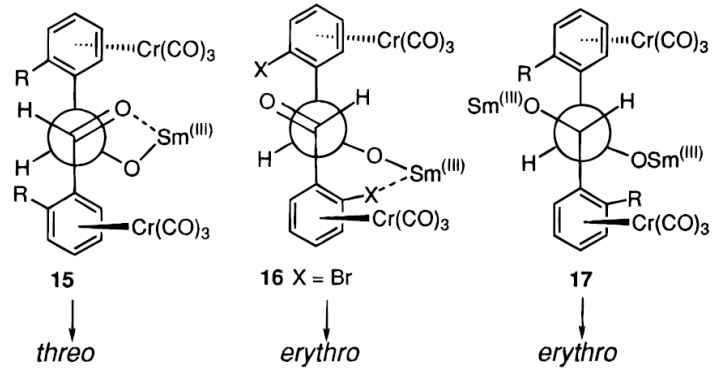
ARKIVOC **2012**, *part i,* 134-151.

Pinacolic Coupling



- Access to optically active ‘threo’ diols
  - Utilizing chromium stabilized benzylic radicals
  - Addition of HMPA results in reversed *erythro* predominance (8:92)

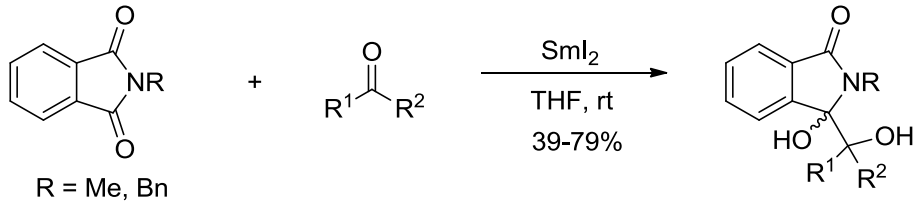




Uemura, *J. Org. Chem.* **1996,** *61,* 6088.

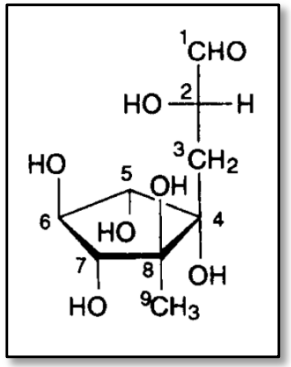
Pinacolic Coupling

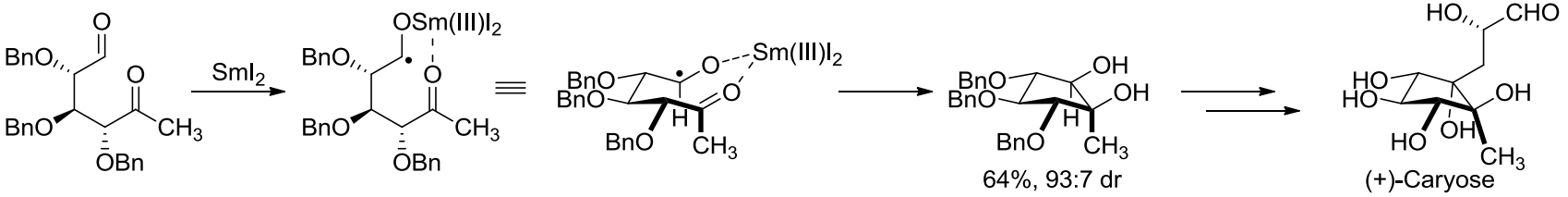
- Cross coupling between phthalimide with aldehydes/ketones
  - No reaction when R = H (trapping of ketyl radical anions)



Yoda, *Tetrahedron Letters* **2000**, *41*, 1775.

- Carbocyclic monosaccharide (+)-Caryose
  - Intramolecular coupling of aldehyde and ketone

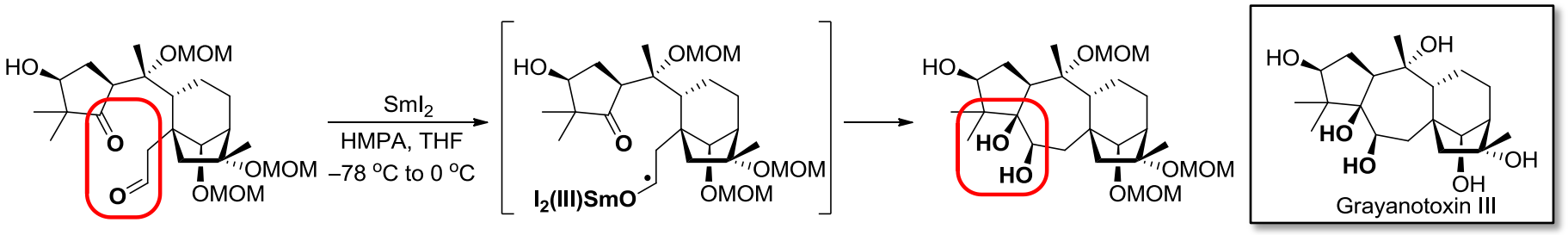




Iadonisi, *Tetrahedron 1997, 53, 11767.*

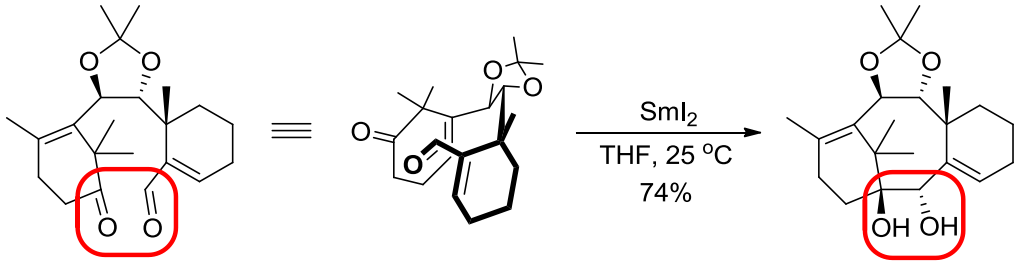
Pinacolic Coupling – in Natural Product Synthesis

- Grayanotoxin III (Matsuda, 1994)
  - highly stereoselective cyclization reactions
  - Aldehyde-ketone / 7-membered ring



Matsuda, *J. Org. Chem.* **1994**, *59*, 5532.

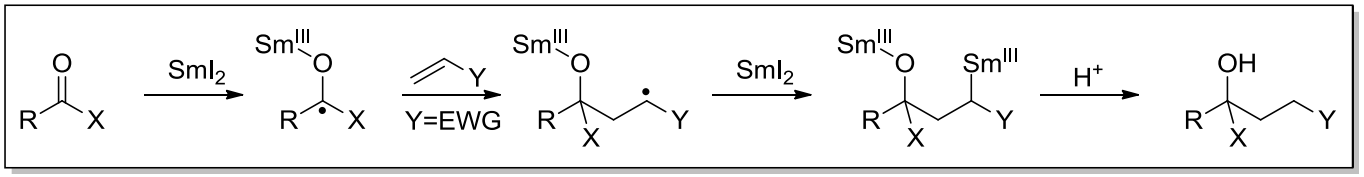
- Taxol (Swindell, 1997)
  - B-ring of taxane skeleton / 8-membered ring
  - endo boat-chair transition structure



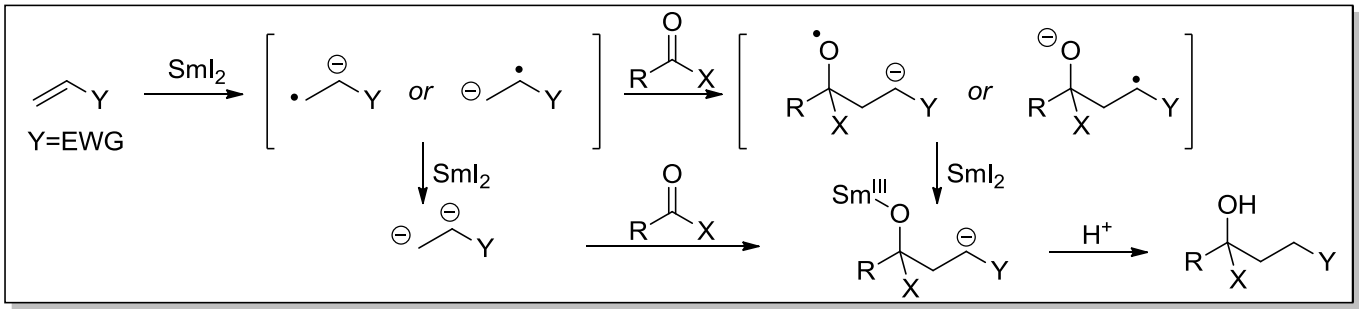
Swindell, *Tetrahedron Lett.* **1996**, *37*, 2321.

Ketyl-Alkene Coupling

- Extensive studies for its usefulness in C-C bond formation
  - Alkenes, alkynes and aromatic systems
  - Additives to boost up reactivity (proton sources or HMPA)
  - Traditional mechanism: ‘carbonyl first’



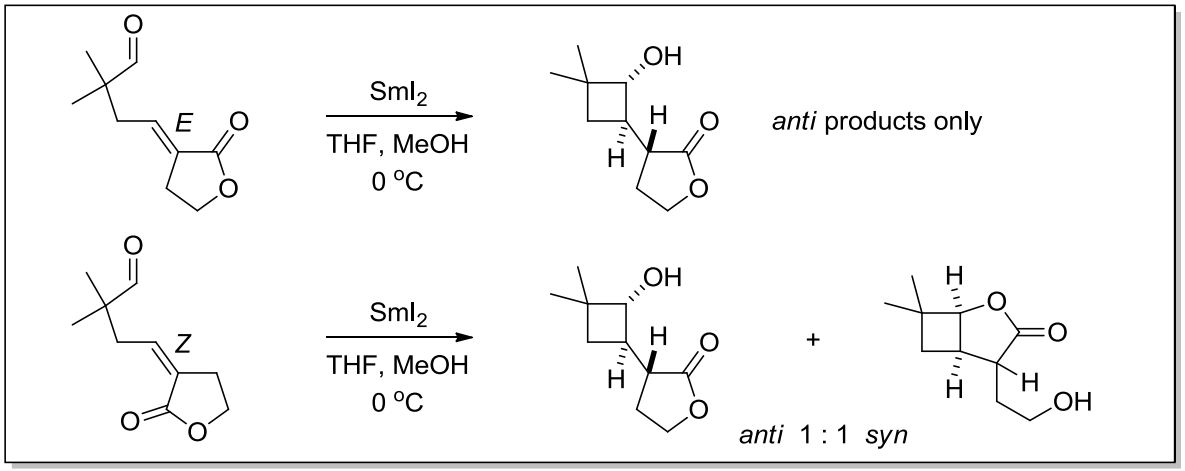
  - Alternative mechanism: ‘alkene first’



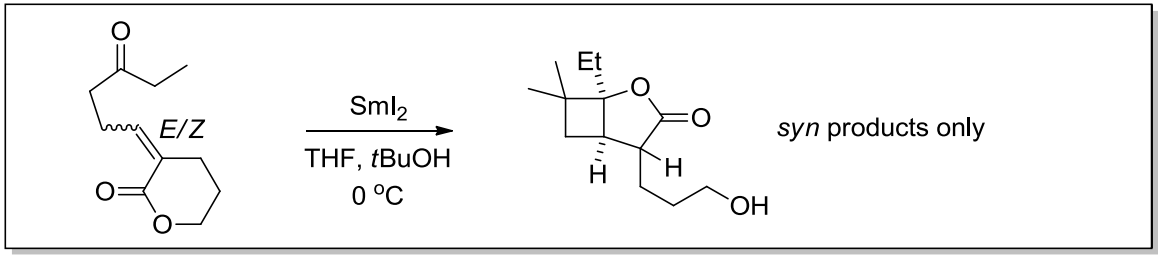
D. J. Procter, R. A. Flowers II, T. Skrydstrup, *Organic Synthesis using Samarium Diiodide: A Practical Guide*, RSC Publishing, Cambridge, **2009**.

Ketyl-Alkene Coupling

- Dependence of reaction outcome on the stereochemistry of the alkene may give information
  - Traditional mechanism: double-bond dependant



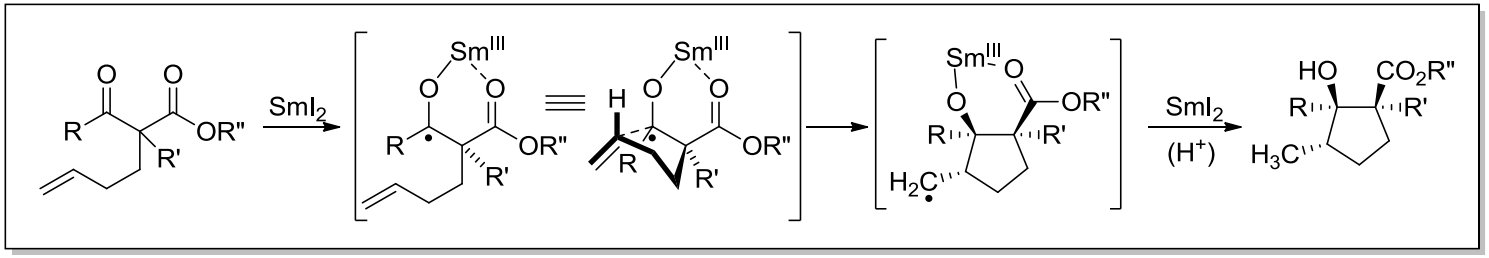
  - Alternative mechanism: no effect of alkene stereochemistry



D. J. Procter, R. A. Flowers II, T. Skrydstrup, *Organic Synthesis using Samarium Diiodide: A Practical Guide*, RSC Publishing, Cambridge, **2009**.

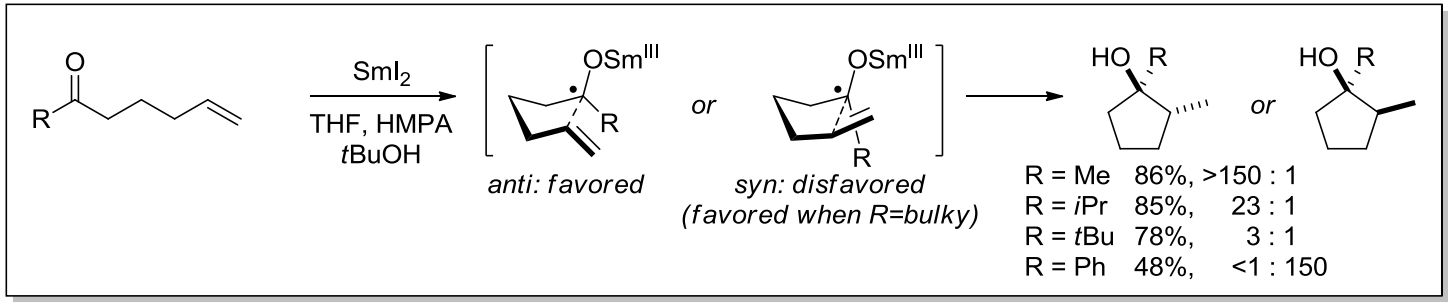
Ketyl-Alkene Coupling (Intramolecular)

- First reported in 1987 by Molander
  - 5-exo-radical cyclization, chelation of Sm(III)
  - Single diastereomer



Molander, *Tetrahedron Lett.* **1987**, *28,* 4367.

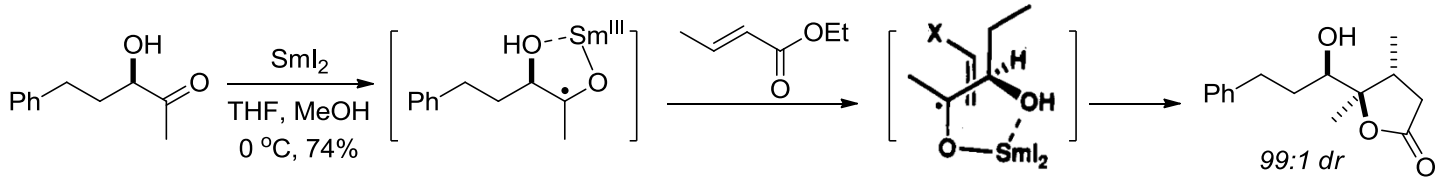
  - Intramolecular: commonly used to from 4 to 8-membered rings
  - Chair-like transition structures
  - Diastereoselectivity control



Molander, *J. org. Chem.* **1995**, *60,* 872.

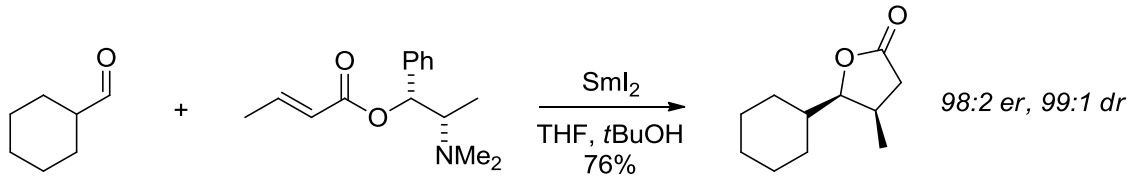
Ketyl-Alkene Coupling (Intermolecular)

- High levels of asymmetric induction with chelating substituent
  - A-hydroxyketone with enoates
  - HMPA reduces the diastereoselectivity



Matsuda, *J. Org. Chem.* **1994**, *59*, 6600.

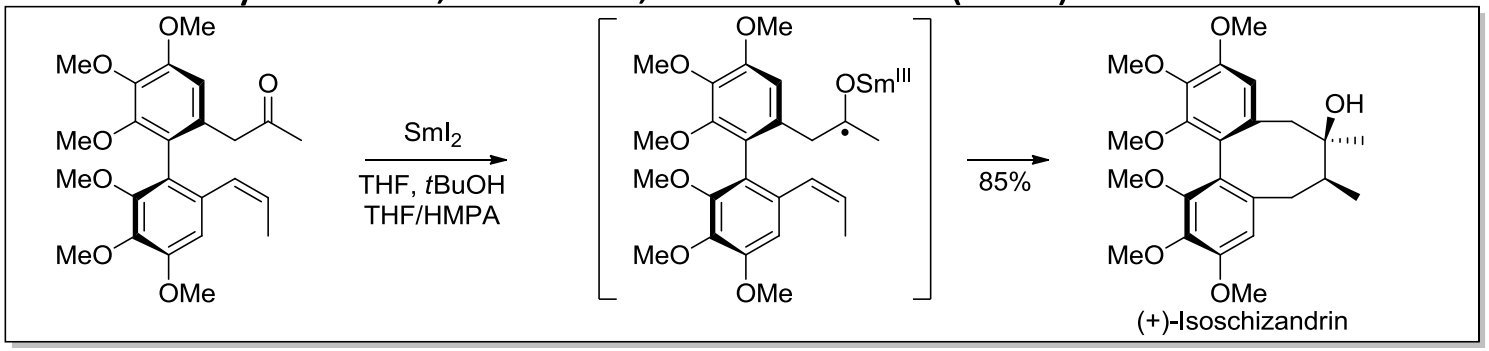
- Enantioselective synthesis of chiral butylrolactones
  - N-methylephedrinyl crotonate
  - Automatic liberation of the auxiliary



Fukuzawa, *J. Am. Chem Soc.* **1997**, *119*, 1482.

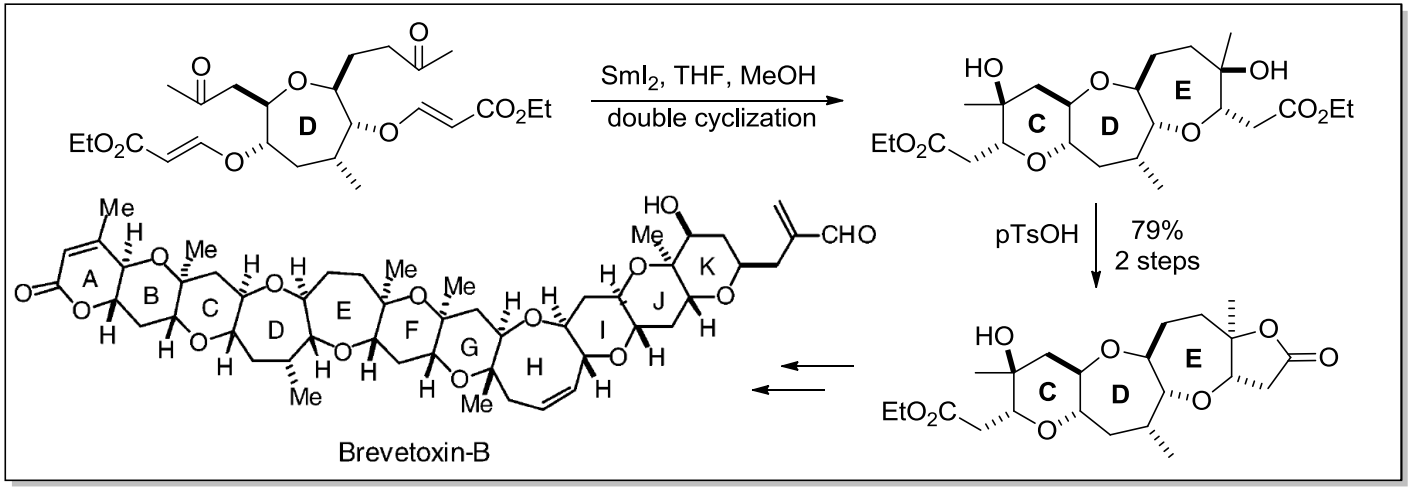
Ketyl-Alkene Coupling (Natural products)

- Total synthesis of (+)-isoschizandrin
  - 8-endo cyclization, >18:1 dr, no loss of ee (98%)



Molander, *J. Org. Chem.* **2003**, *68*, 9533.

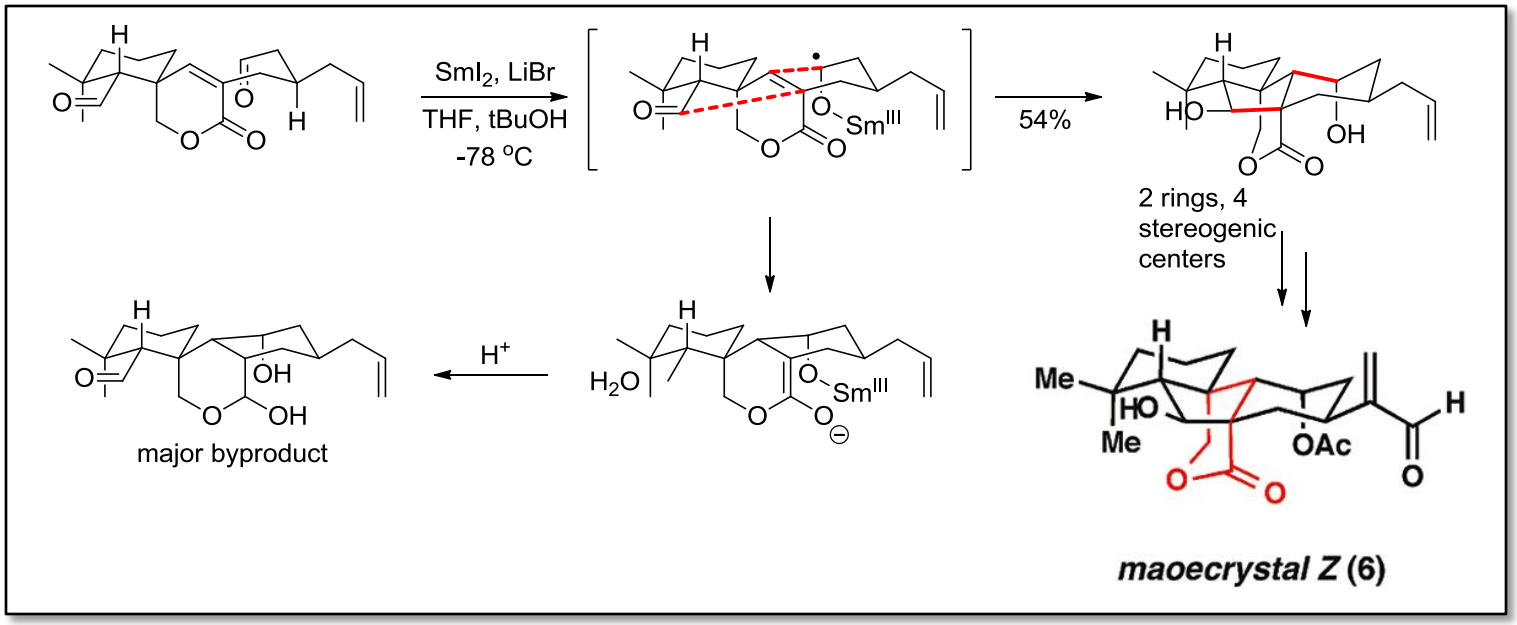
- Total synthesis of brevetoxin B



Nakata, J. Am. Chem. Soc. **2004**, *126*, 14374.

Ketyl-Alkene Coupling

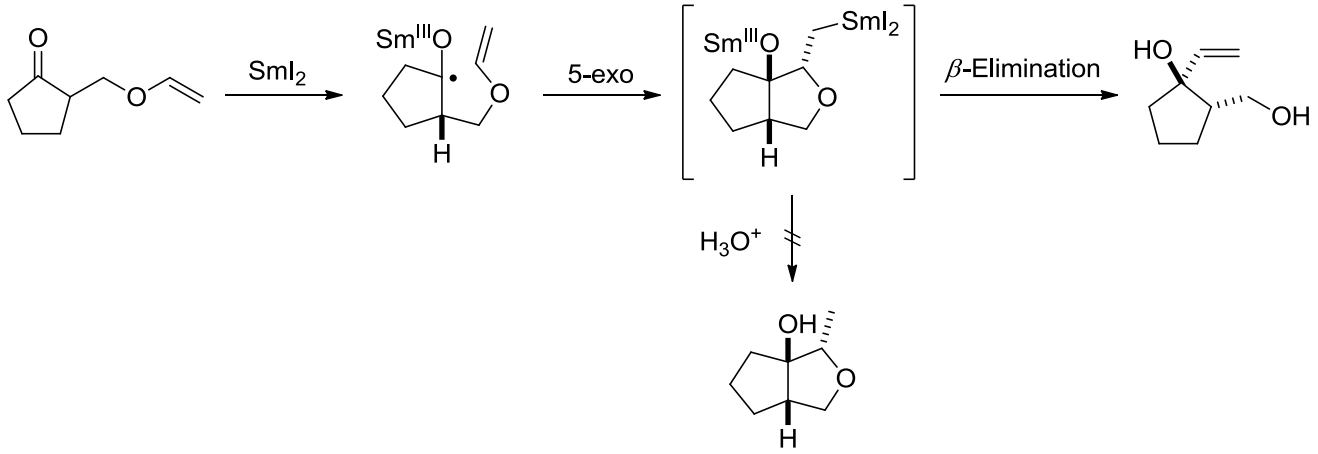
- Maoecrystal Z
  - Construction of two rings, reductive cascade cyclization
  - Use the right powder: LiBr as additive for higher yield (LiCl low yield)
  - Monocyclized byproduct

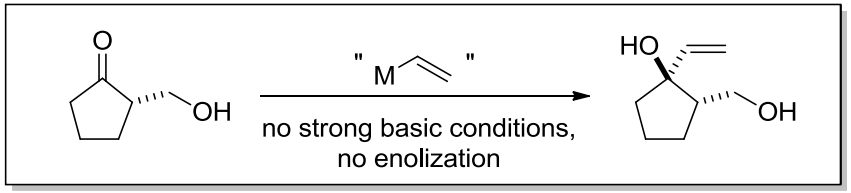


Reisman, J. Am. Chem. Soc. **2011**, *133*, 14964.

Ketyl-Alkene Coupling (alkenylation)

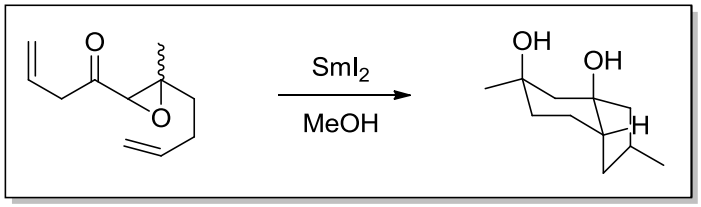
- Sequential Ketyl-Olefin Coupling/*â*-Elimination Reactions
  - Net delivery of alkenyl to a carbonyl group



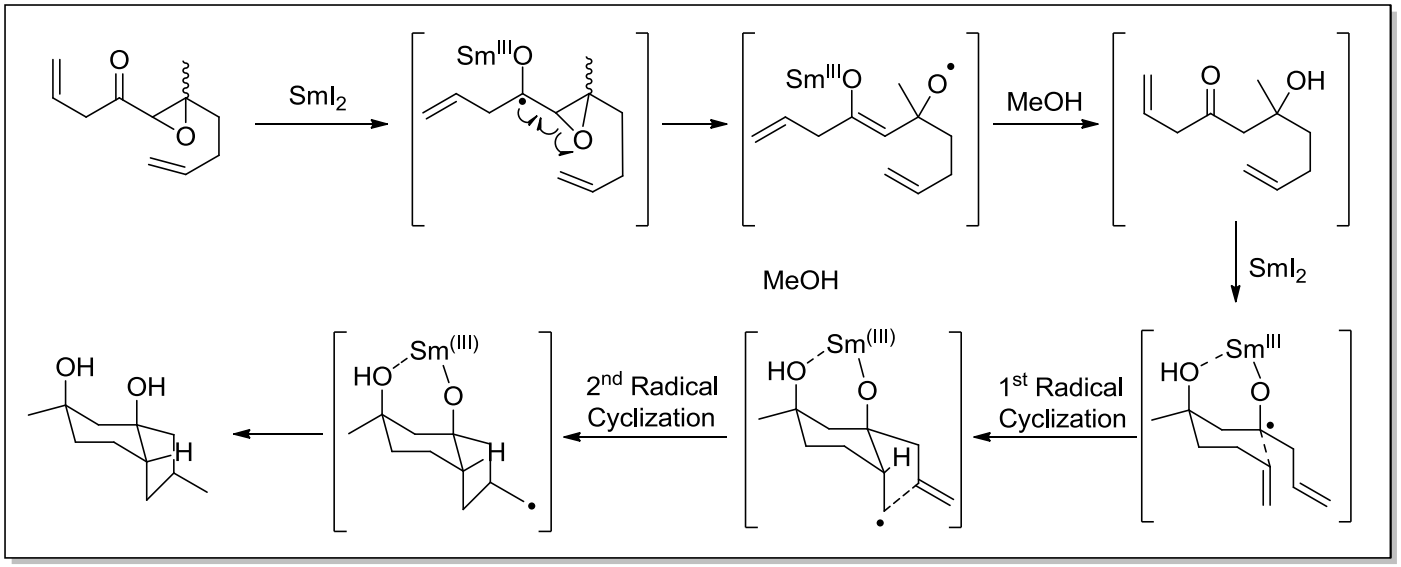


Molander, J. Am. Chem. Soc. **1998**, *63*, 812.

Ketyl-Alkene Coupling (fragmentation)



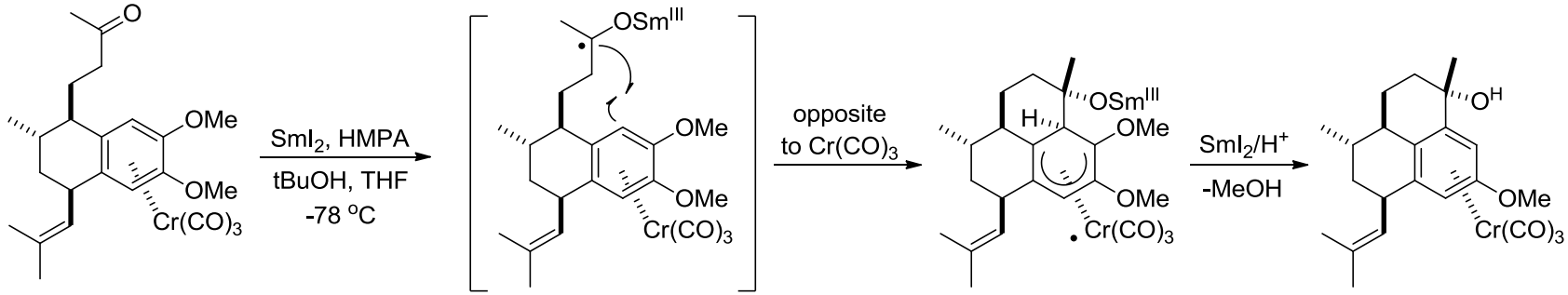
- Fragmentation/Sequential cyclization
  - Ketyl formation / epoxide fragmentation / tandem cyclization
  - chelation of the ketyl oxygen and the hydroxyl group



Molander, *Tetrahedron*. **1998**, *54*, 5819.

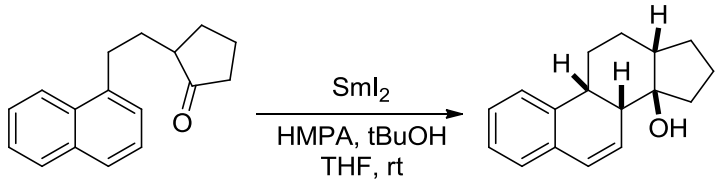
Ketyl-Arene Coupling

- Arenes used as radical acceptors
  - Tetralin-$Cr(CO)_3$ complex: stereochemistry control, arene activation



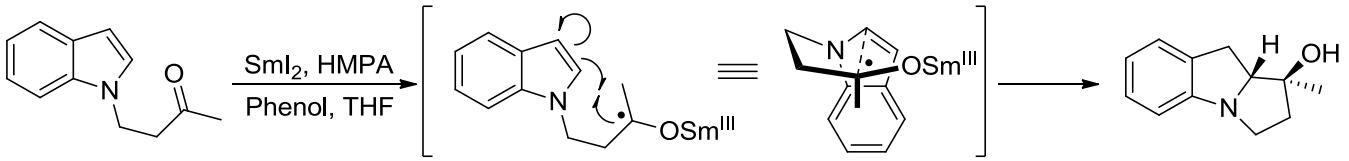
Schmalz, *Angew. Chem. int. Ed.* **1995**, *34*, 2383.

  - Naphthyl ketones: steroid-like scaffold



Reissig, *Chem. Eur. J.* **2007**, *13*, 6047.

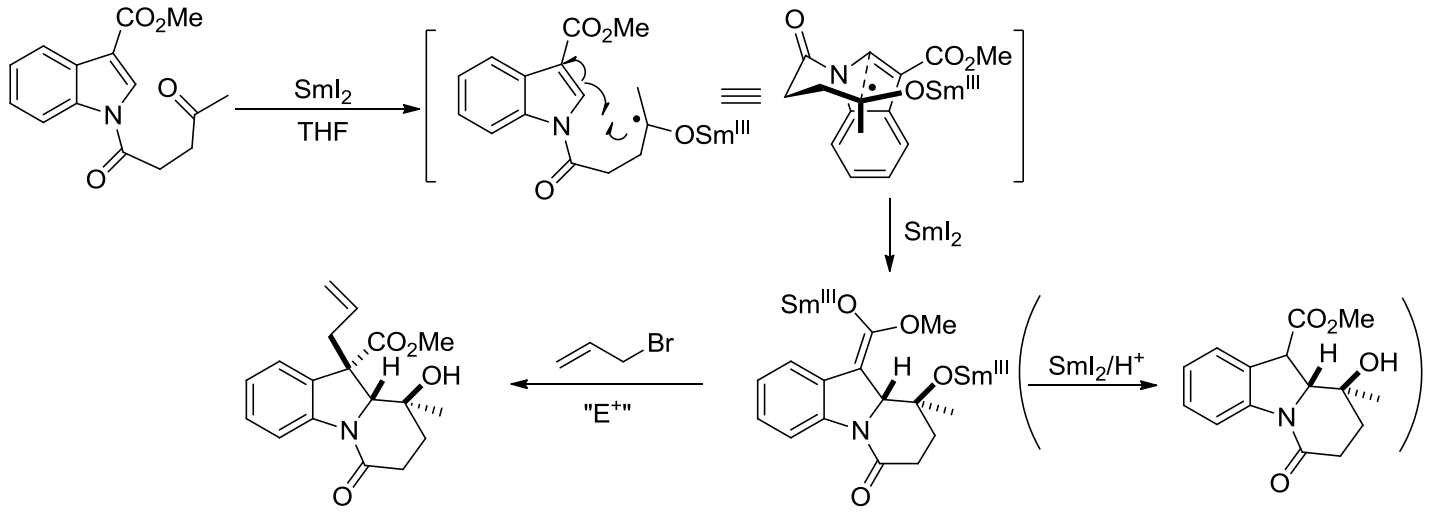
  - Indolyl ketones



Reissig, *Org. Lett.* **2003**, *5*, 4305.

Ketyl-Arene Coupling

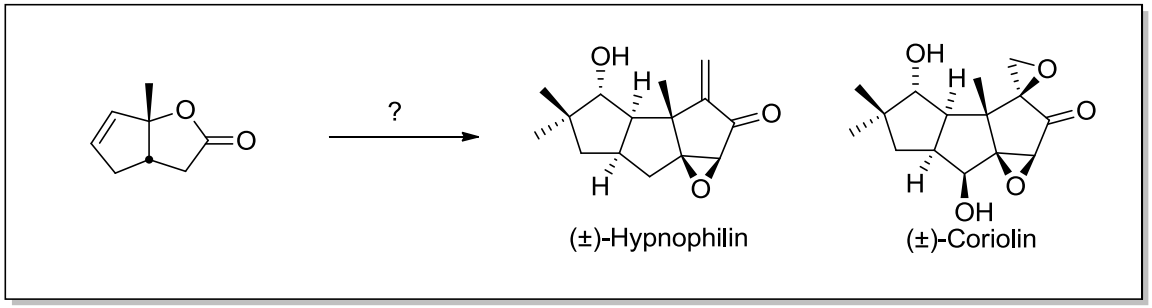
- Quenching with electrophiles
  - Three contiguous stereogenic center with a quat-carbon
  - High degree of diastereoselectivity from ordered transition state

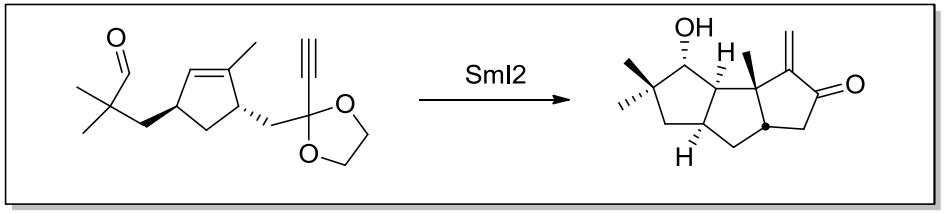


Reissig, *Org. Lett.* **2003**, *5*, 4305.

Sequential Reactions

- Entire sequence of reaction promoted in cascade fashion
  - Multiple bonds formed in a one pot process - no need of intermediate isolation
  - Create significant molecular complexity: rings/stereogenic centers
  - Although conceptually attractive, design of sequential reactions can be overwhelming

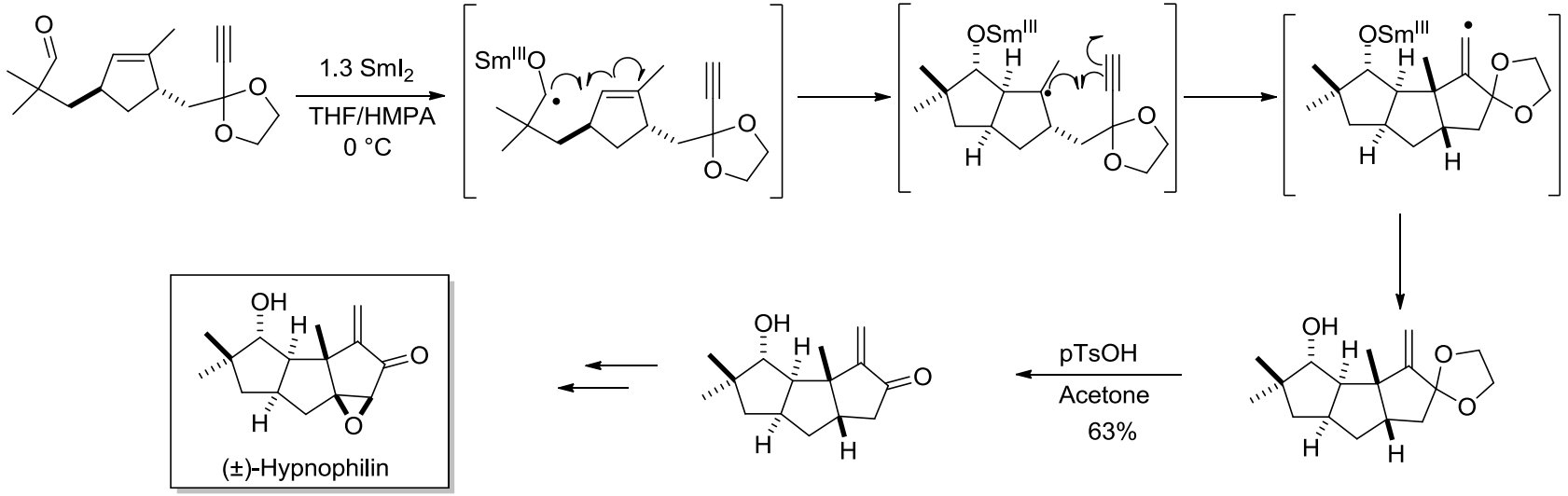




Curran, *J. Am. Chem. Soc.* **1988**, *110*, 5064.

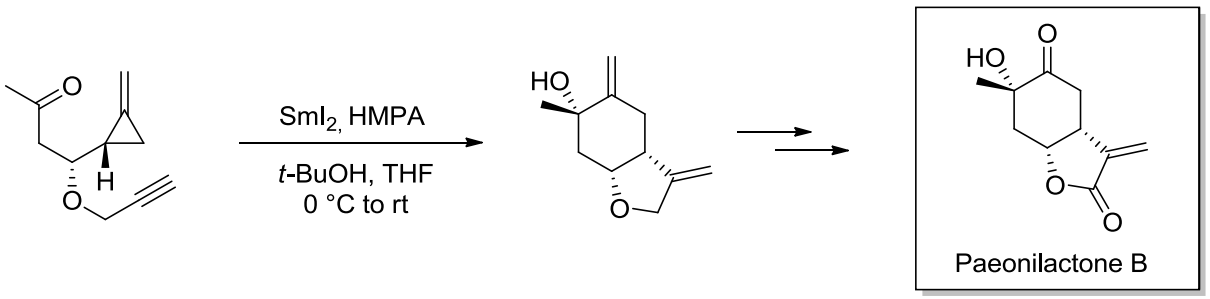
Sequential Reactions

- Total synthesis of (±)-hipnophilin
  - Tandem radical cyclization: formation of cis-anti-cis ring fusion
  - Low yields in absence of HMPA
  - Lower diastereoselectivity with DMPU



Curran, *J. Am. Chem. Soc.* **1988**, *110*, 5064.

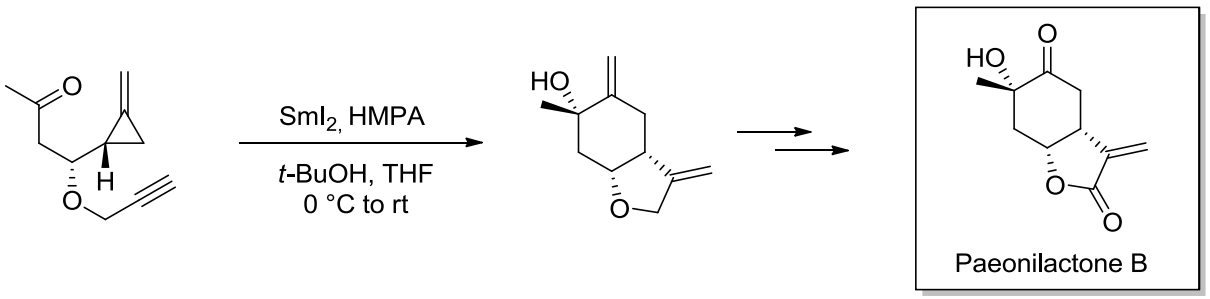
Sequential Reactions (with fragmentation)



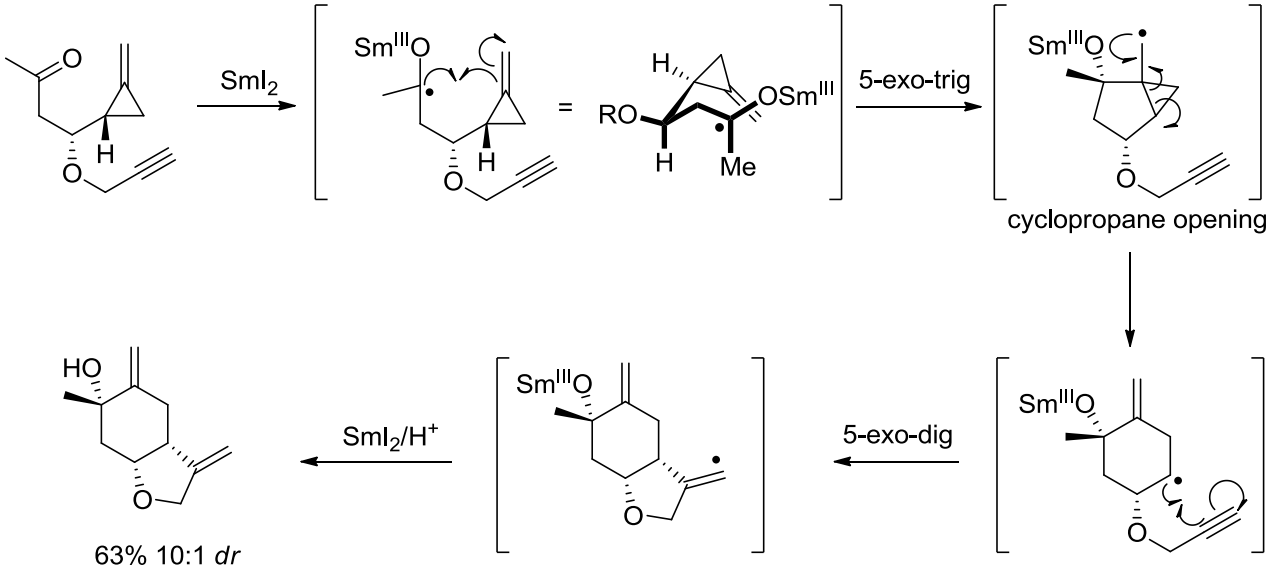
- Provide a mechanism
  - Rationalize the stereochemistry of the outcome

Kilburn, *Chemical Communications (Cambridge)* **1998**, 1875-1876.

Sequential Reactions (with fragmentation)



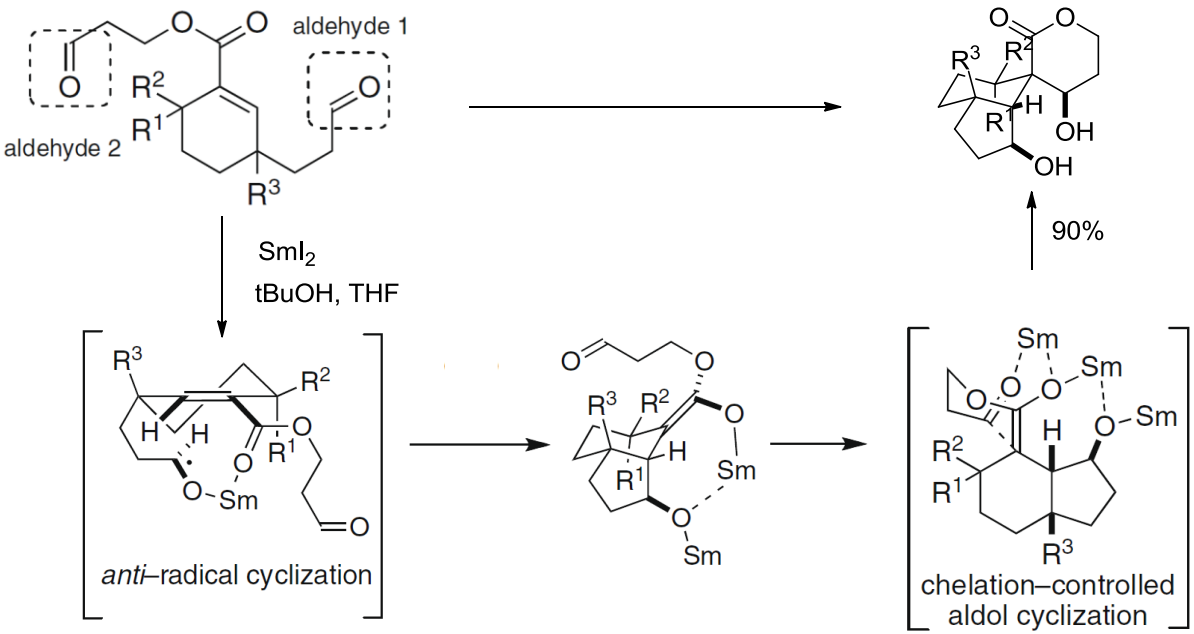
- Sequential radical cyclization reaction
  - Formation of ketyl radical anion / cyclize / fragmentation / cyclize
  - Stereochemistry set in initial cyclization which proceeds through a chair-like transition state



Kilburn, *Chemical Communications (Cambridge)* **1998**, 1875-1876.

Sequential Reactions

- Programmed sequence?
  - Two aldehydes in one substrate
  - Reduction of carbonyl groups with SmI_2 may be reversible
  - Chelation controlled cyclization



Procter, *Tetrahedron Lett.* **2009**, *50*, 3224-3226.

Conclusions

- Synthetic utility of samarium diiodide (SmI_2) has grown significantly last three decades
- SmI_2 provides mild conditions, tolerant to many functional groups
- Fine tuning of reactivity is available: solvents, cosolvents, additives
- Virtually limitless potential to increase molecular complexity: sequential/cascade reactions
- Generally exhibits high diastereoselectivity resulting from highly organized transition states

Useful References

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