

Radicals in Total Synthesis

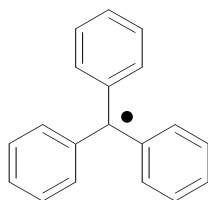
presented by Jon Parrish
September 8th, 2004

Outline

- Background
- Metal-hydride approaches to free radicals
- Organometallic/inorganic reductants
- Organometallic/inorganic oxidants
- Miscellaneous approaches to radicals
- Important radical-based synthetic methods

Background

- The first observed free radical species is attributed to Gomberg (triphenylmethyl radical) in 1900.



- The introduction of tin hydride methods for generating radicals (1970's) increased interest in the synthetic utility of radicals.
- Researchers in free radical chemistry include: Barton, Curran, Giese, Molander (SmI_2), Gansauer (Cp_2TiCl), Snider ($\text{Mn}(\text{OAc})_3$), Newcomb, Zard, Crich, Sibi, Keck, Porter, Hart, Renaud, Murphy, Kende *etc.*

Features of Carbon-Centered Free Radicals

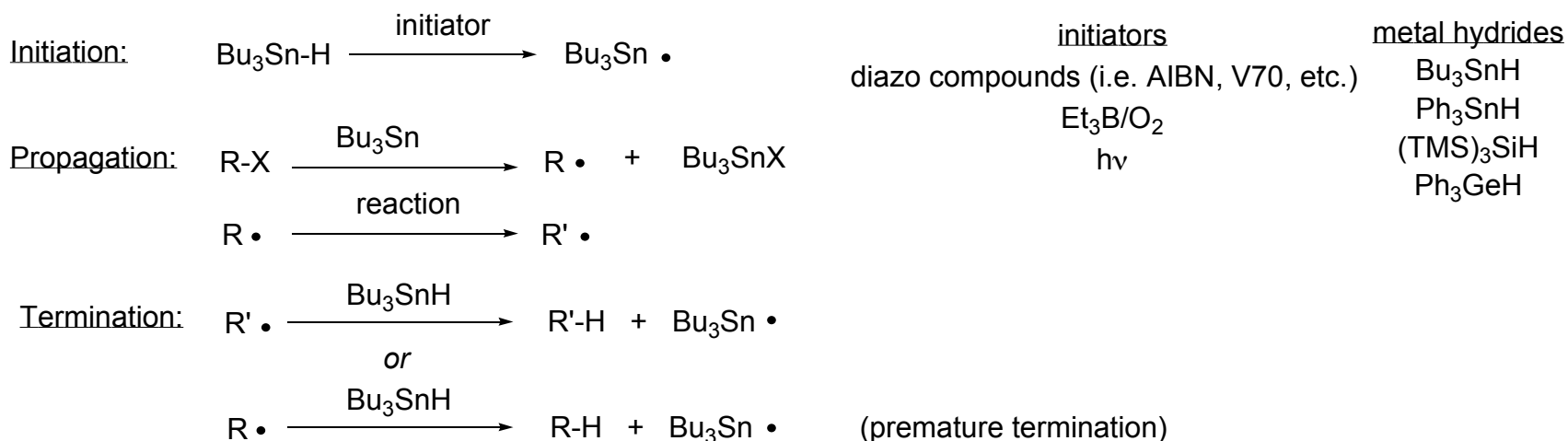
- Radicals are either planar, or slightly pyramidal with a very low barrier to inversion; therefore most free radicals do not retain stereochemical information.
- Radical additions to C=C bonds are typically exothermic and irreversible. Additionally, radicals are not typically associated with metallic counterions or aggregation spheres. As such, they are uniquely capable of forming congested bonds
- In contrast to anions, radicals rarely β -eliminate allowing for radical formation next to oxygen and nitrogen functionalities.
- Radicals are tolerant of a wide variety of functionality including alcohols, amines, esters, etc.
- Most radical reactions involve interaction of the radical SOMO with the olefin LUMO; therefore most radicals are considered nucleophilic

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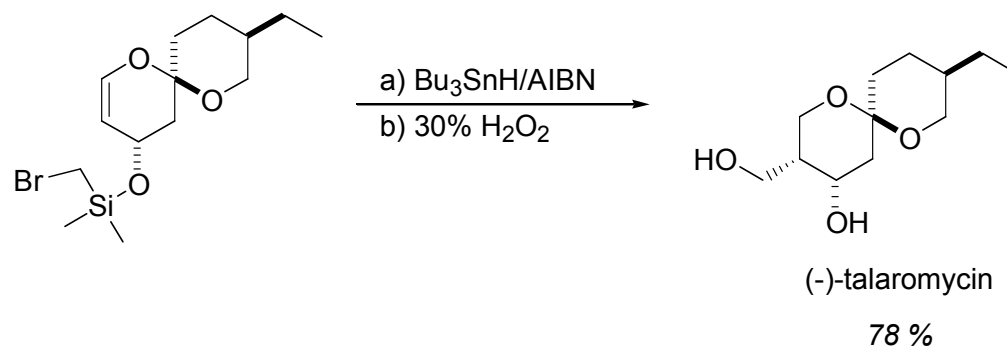
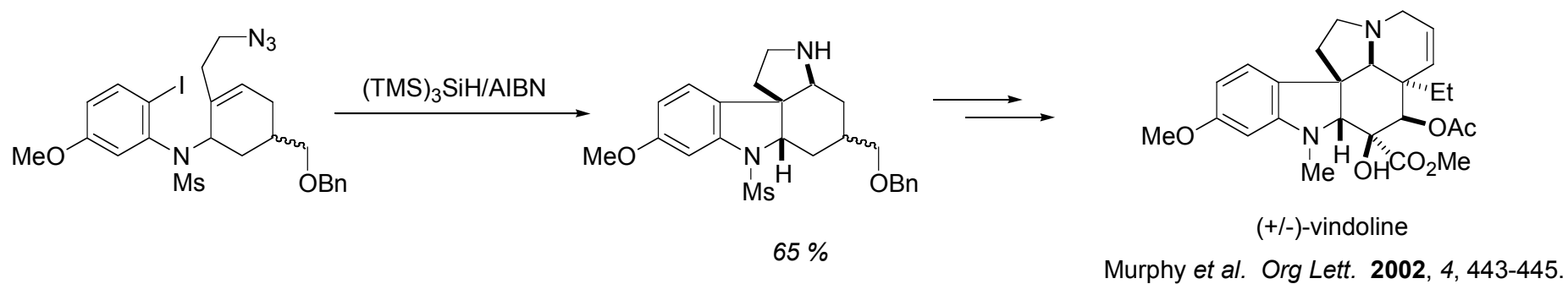
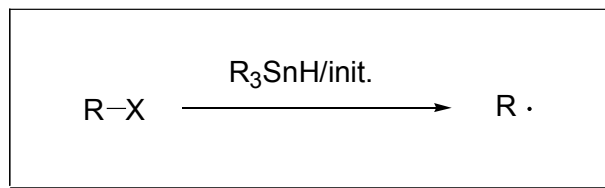
Metal Hydride Reductions

- Typical reaction involves homolysis of a carbon-halogen or carbon-chalcogen bond by a tin or silyl hydride and an initiator.



- The rate of the desired reaction must be faster than unwanted termination by the metal hydride.
- Rate of hydrogen atom donation is $\text{R}_3\text{SnH} > (\text{TMS})_3\text{SiH} > \text{R}_3\text{GeH} > \text{R}_3\text{SiH}$.

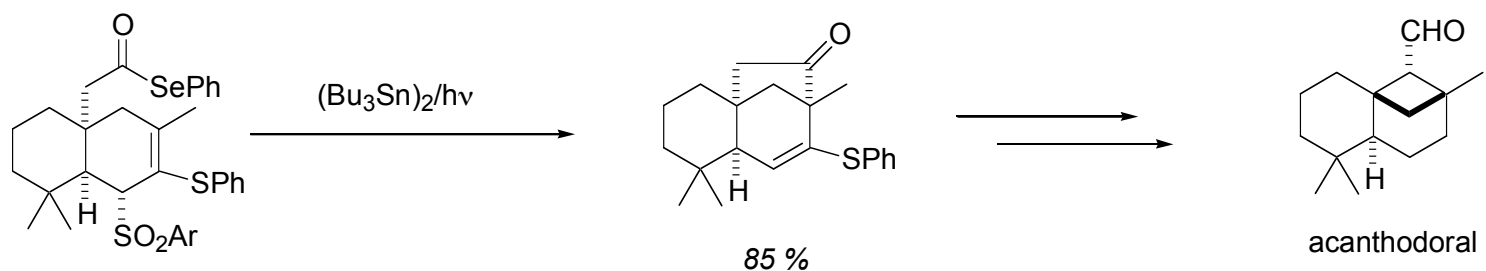
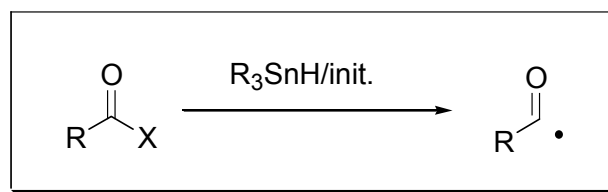
Alkyl/Aryl Radicals from Tin and Silicon Hydrides



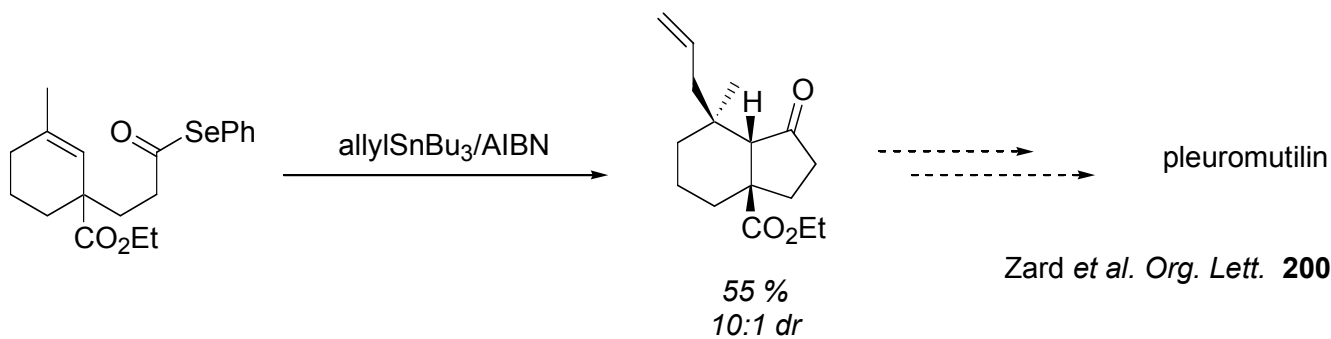
Crimmins, M. T. and O' Mahony, R. *JOC* **1989**, 54, 1157.

Acyl Radicals from Tin Hydrides

- Acyl radicals are considered more nucleophilic than alkyl radicals; prefer to react with electron-poor olefins

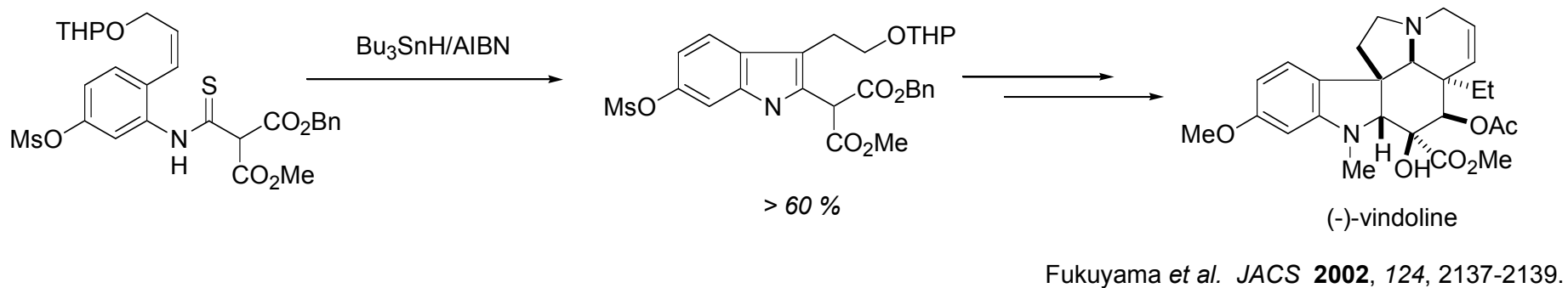
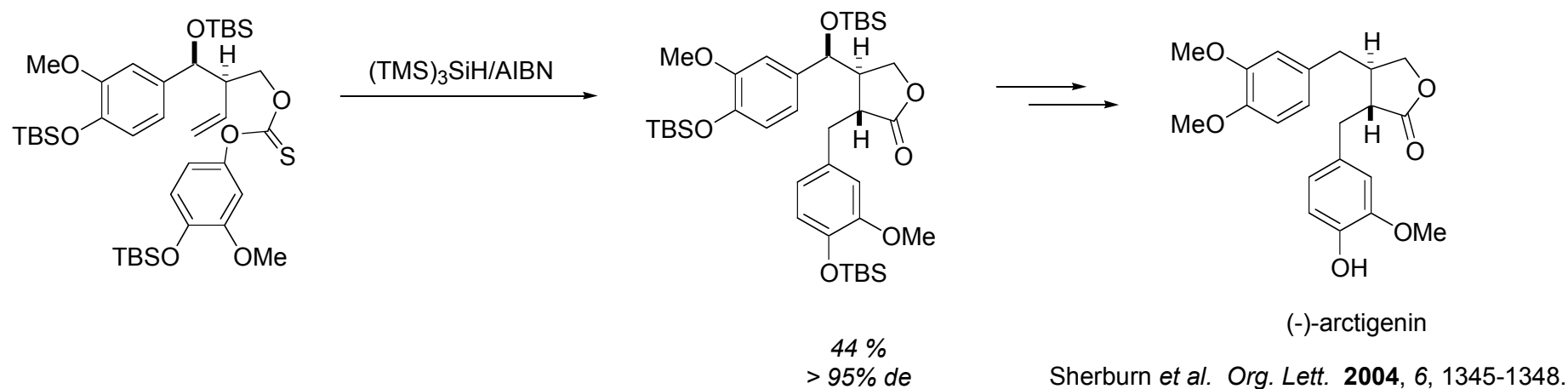


Koreeda *et al. Org. Lett.* **2004**, *6*, 537-540.



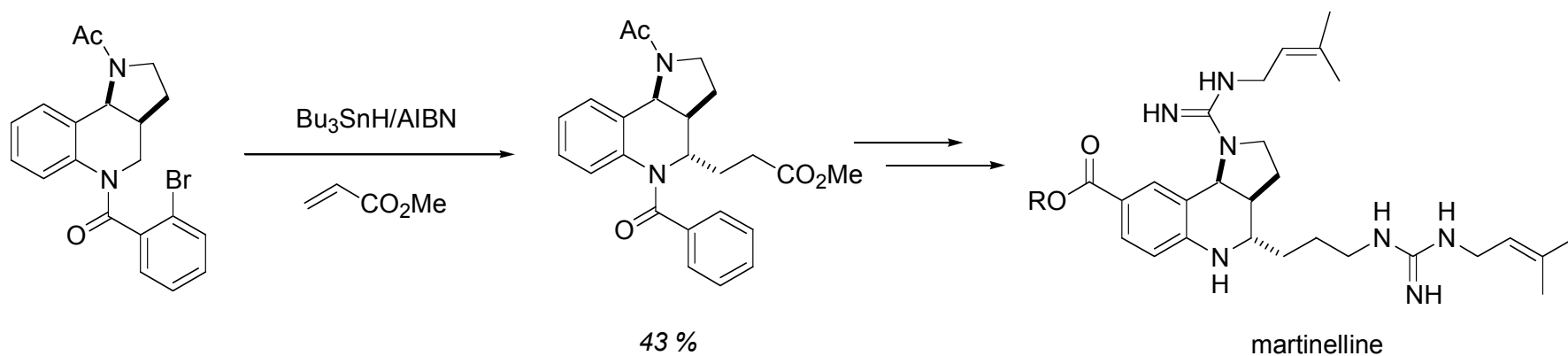
Zard *et al. Org. Lett.* **2003**, *5*, 325-328.

Miscellaneous Radicals from Tin Hydrides

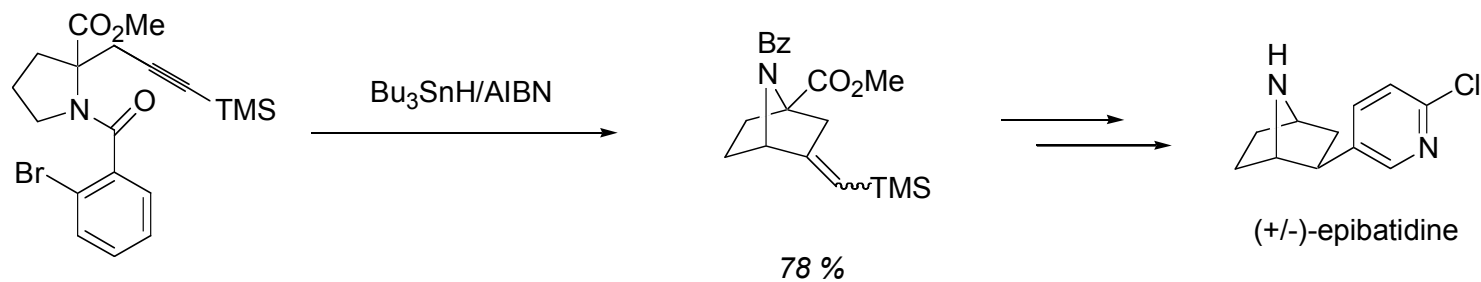


Atom Transfer Reactions

- An initially formed radical can also abstract an appropriately distanced group forming a second radical species that can, in turn, undergo additional chemistry.



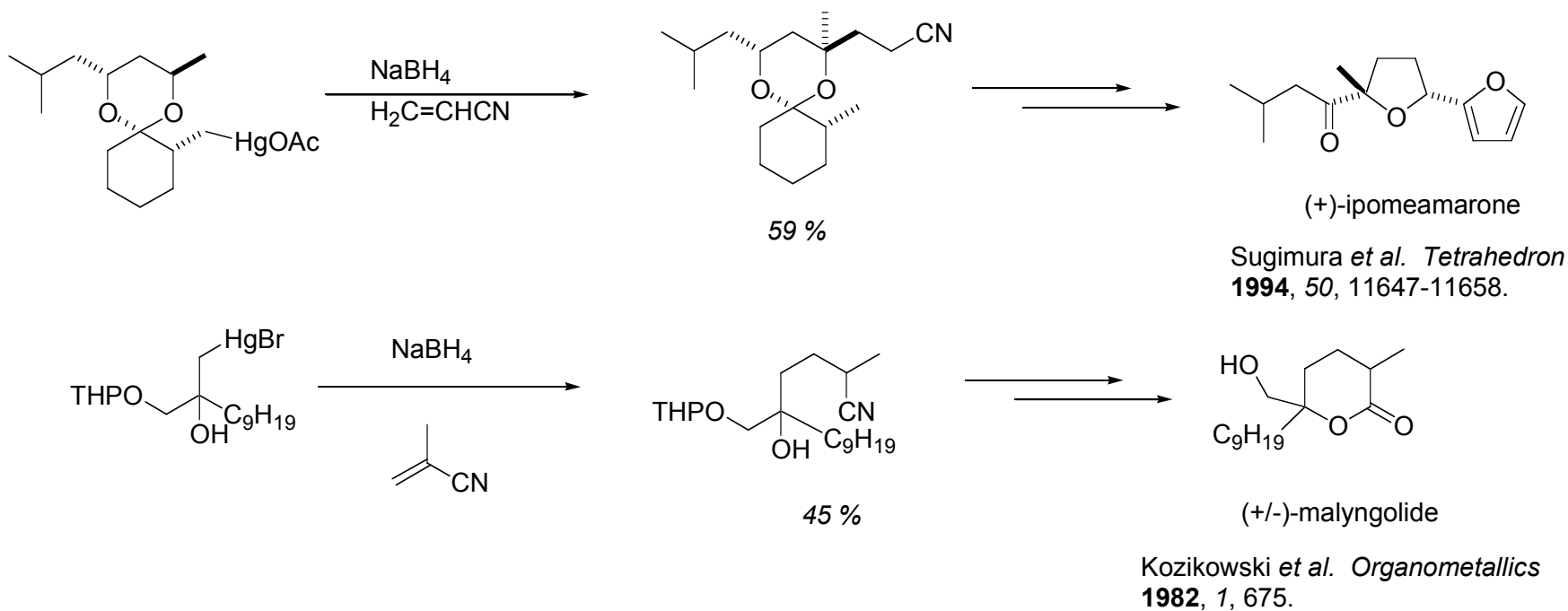
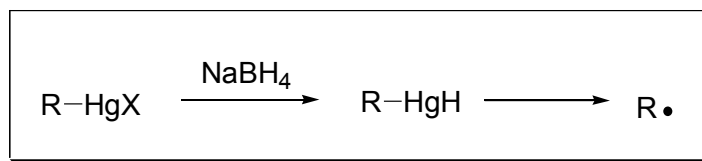
Naito *et al.* *Tet. Lett.* **2004**, 45, 3481-3484.



Ikeda *et al.* *JCS, Perkin I*, **1997**, 3339-3344.

Organomercury Reduction

- This older method of radical formation involves reduction of an organomercurial to an alkyl radical.
- The mercurial hydride species is an excellent hydrogen atom donor frequently leading to premature reduction of radical intermediates.

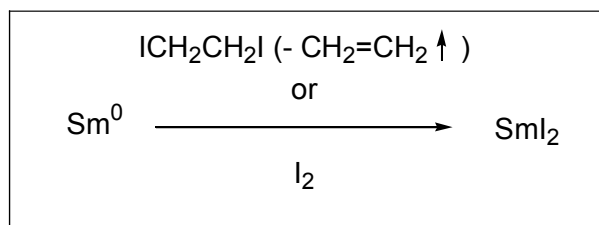


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Samarium (II) Iodide

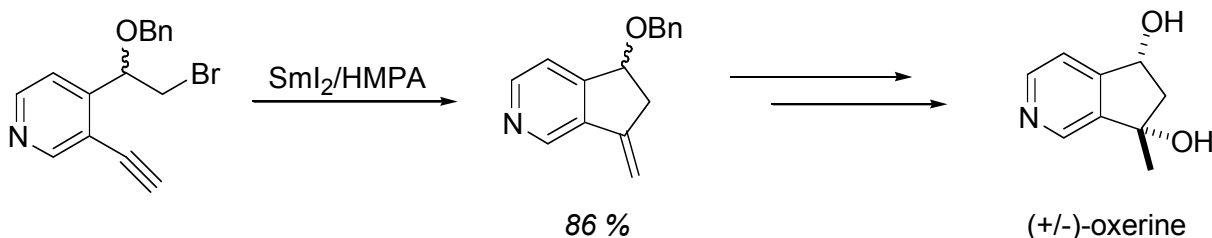
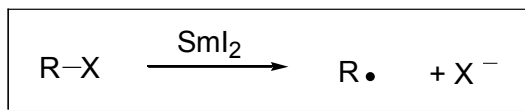
- Typically formed by the oxidation of samarium (0) with either 1,2-diiodoethane or iodine.



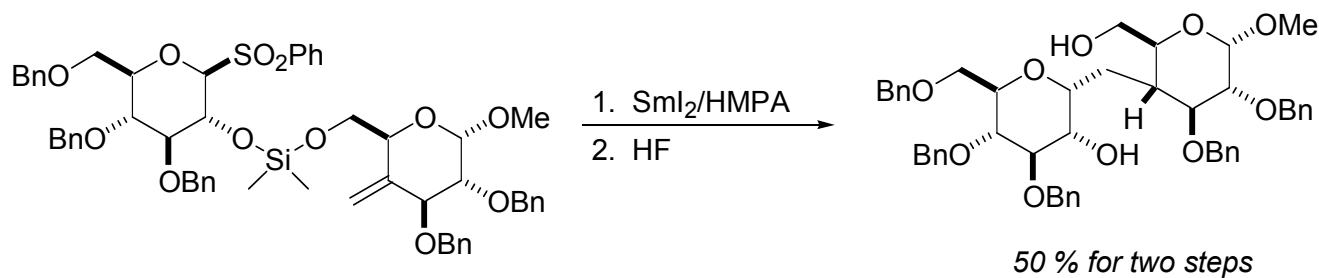
- Samarium (II) forms dark blue/purple solutions and is most often used in tetrahydrofuran.
- Reactivity can be enhanced by adding Lewis basic additives like NMP, DMPU or HMPA (E^0 for $\text{SmI}_2 = -0.98$ V, $\text{SmI}_2/\text{HMPA} = -1.75$ V).
- see a) Procter *et al.* *Chem. Rev.* **2004**, 104, 3371-3403.
b) Molander *et al.* *Chem. Rev.* **1996**, 96, 307-338.

Alkyl/Aryl Radicals from SmI_2

- Single electron reduction of labile bonds with SmI_2 can lead to a variety of alkyl/aryl/vinyl radical species.
- Alkyl radicals (in particular) are susceptible to further reduction to form anionic organosamarium species limiting radical reactivity.



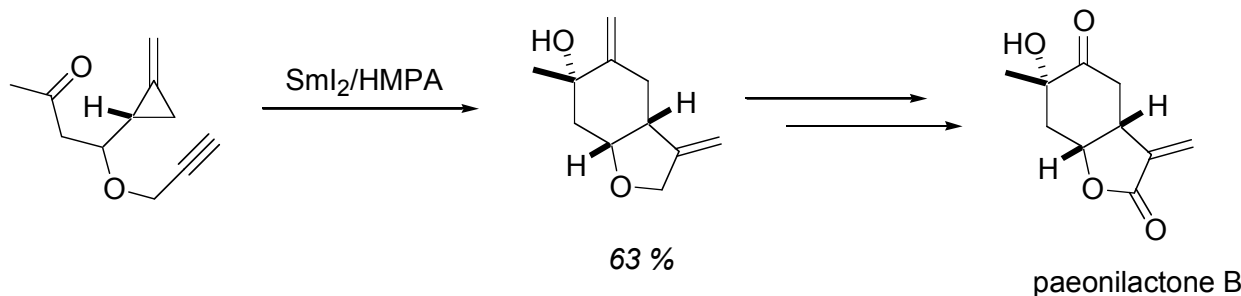
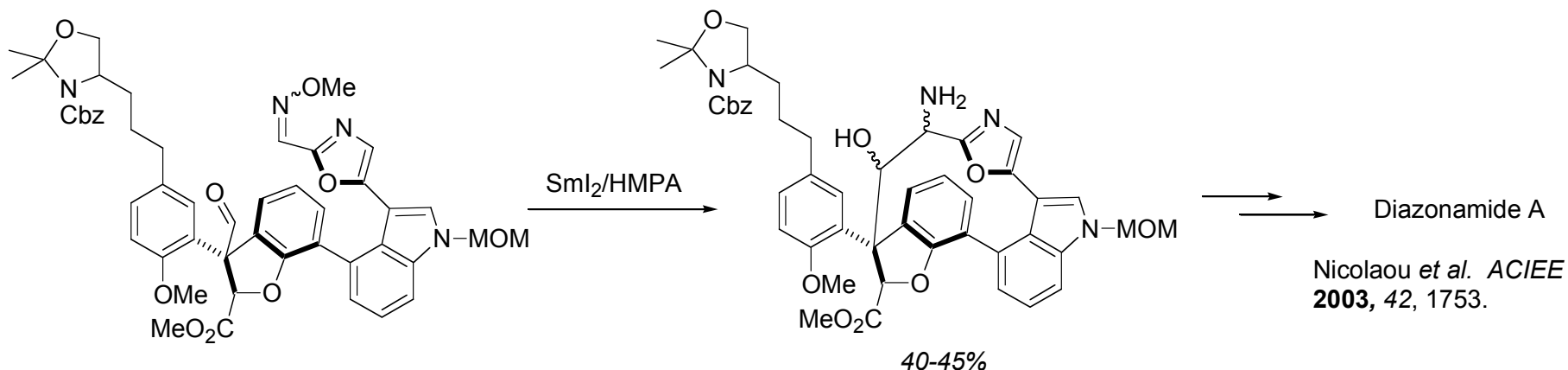
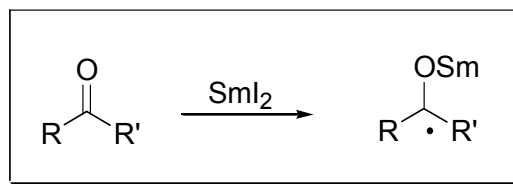
Ohta *et al.* *Tetrahedron* **1994**, 50, 13575.



Sinay *et al.* *Synlett.* **1994**, 420.

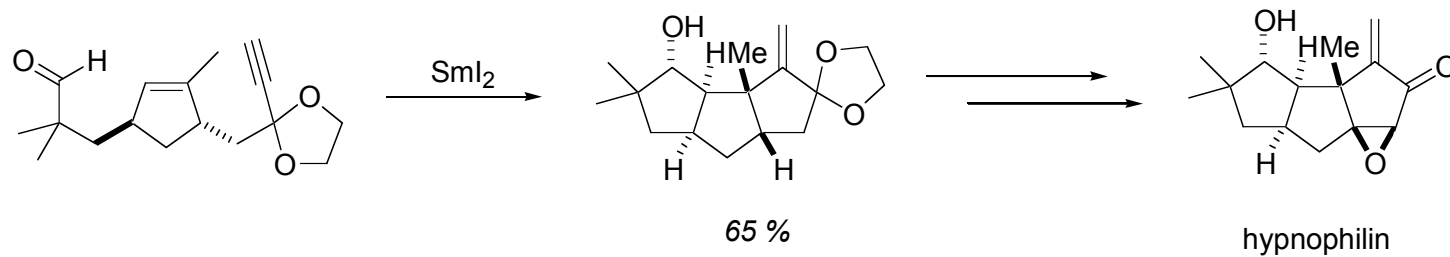
Ketyl Radicals from SmI₂

- Most aldehydes and ketones can be reduced with samarium(II) iodide to yield ketyl radical species; reduction of esters, amides or nitriles are rare

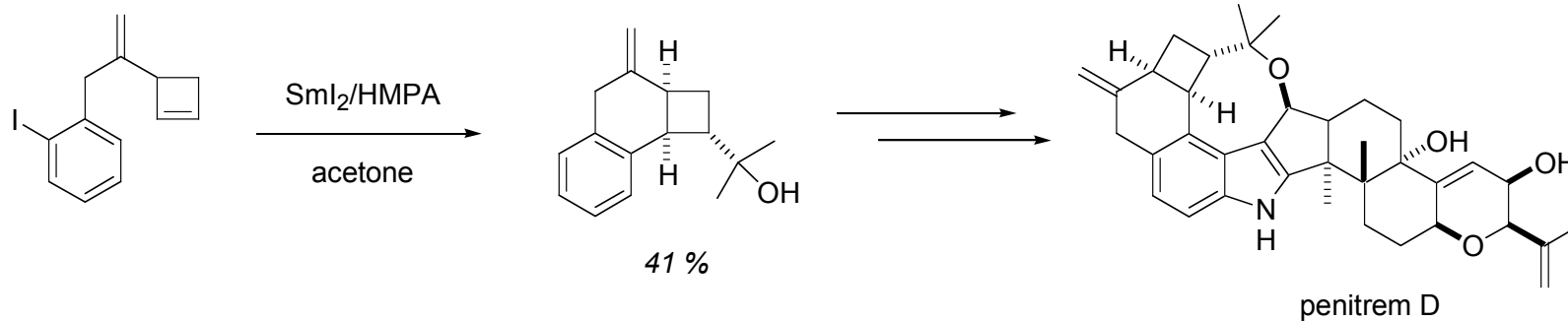


Kilburn *et al.* *Chem. Commun.* **1998**, 1875.

Cascade Reactions with SmI_2



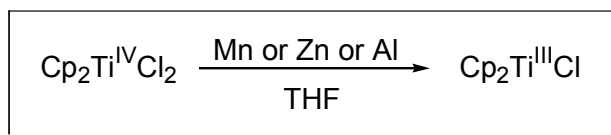
Curran et al. *Tetrahedron* **1985**, 41, 3943-3958.



Curran et al. *Org. Lett.* **2003**, 5, 419.

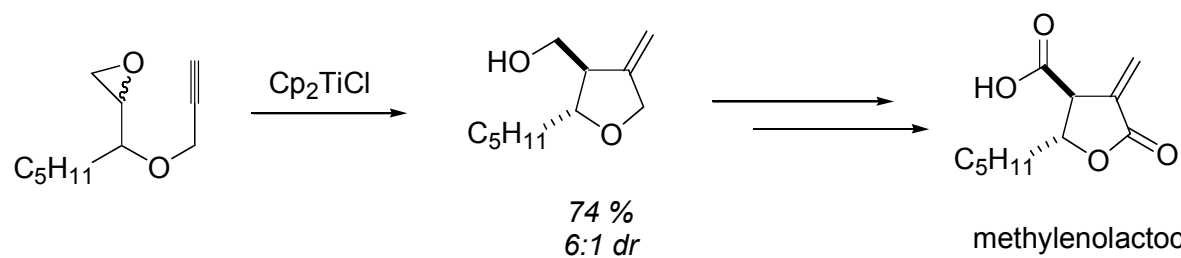
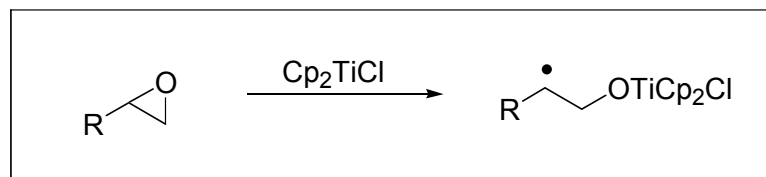
Titanocene (III) Chloride

- Homogenous dark-green colored reagent formed by the reduction of titanocene dichloride (commercially available) with either zinc, aluminum or manganese. Must be used in THF!

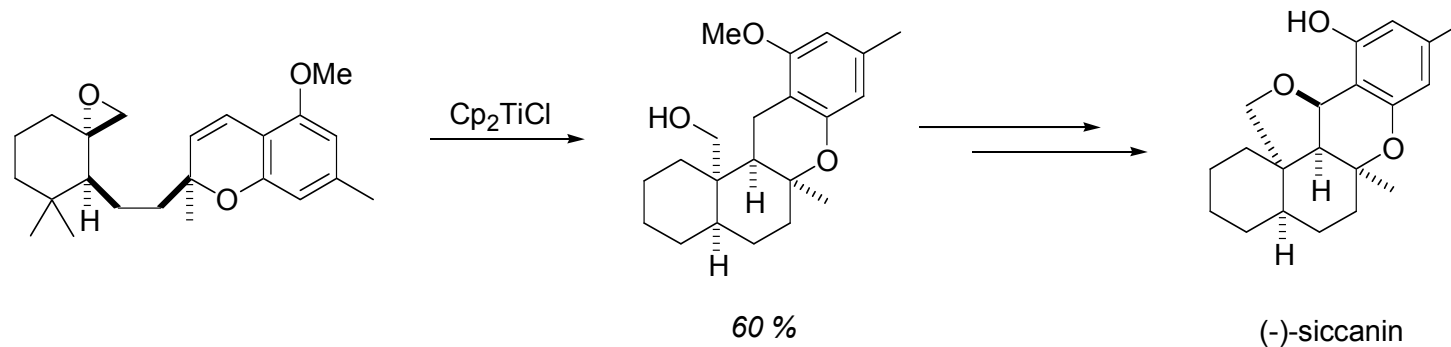


- Cp_2TiCl is a mild reductant ($E^0 = -0.75$) selective for the formation of α -alkoxy radicals from epoxides; it does not react with simple organohalides or ketones. In addition, Cp_2TiCl does not appreciably reduce radicals to organometallic anionic species.
- The radical formed from reductive opening of epoxides will reliably form at the site producing the more stable radical (typically, the more substituted site)
- see Gansauer *et al.* *Chem. Rev.* **2000**, *100*, 2771-2788.

Titanocene(III)-mediated Cyclizations



methylenolactocin
Roy *et al.* *JOC*, **1998**, 63, 2829-2834.



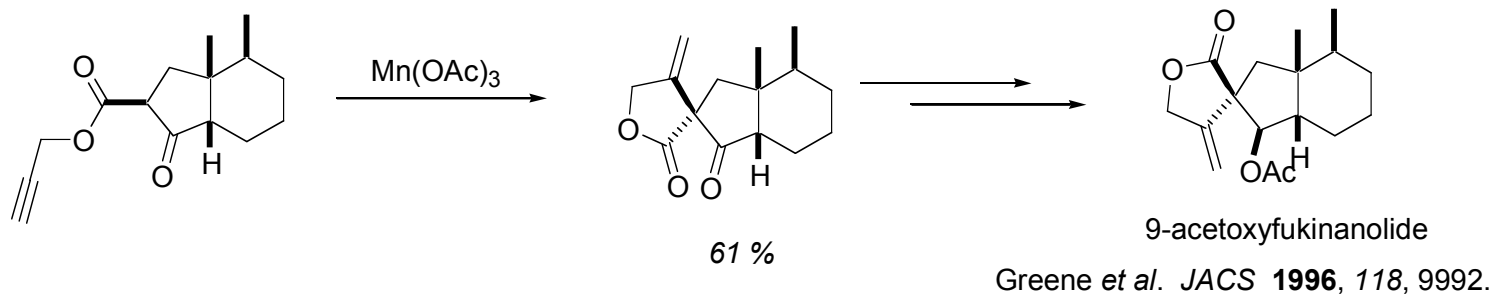
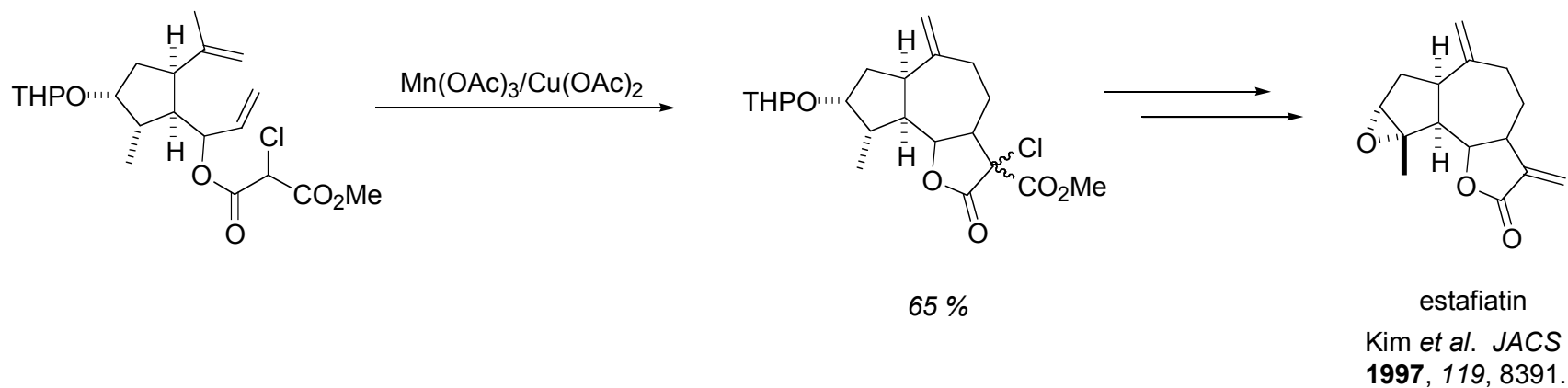
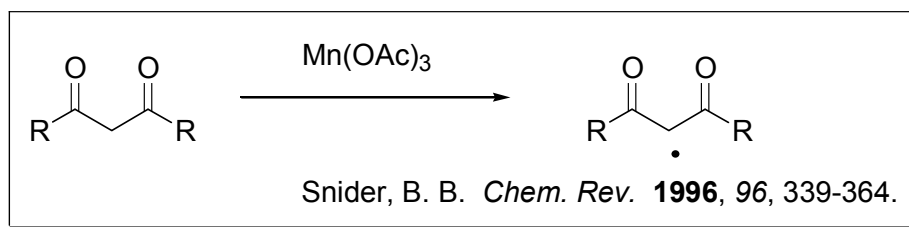
(-)-siccanin
Trost *et al.* *JACS*, ASAP.

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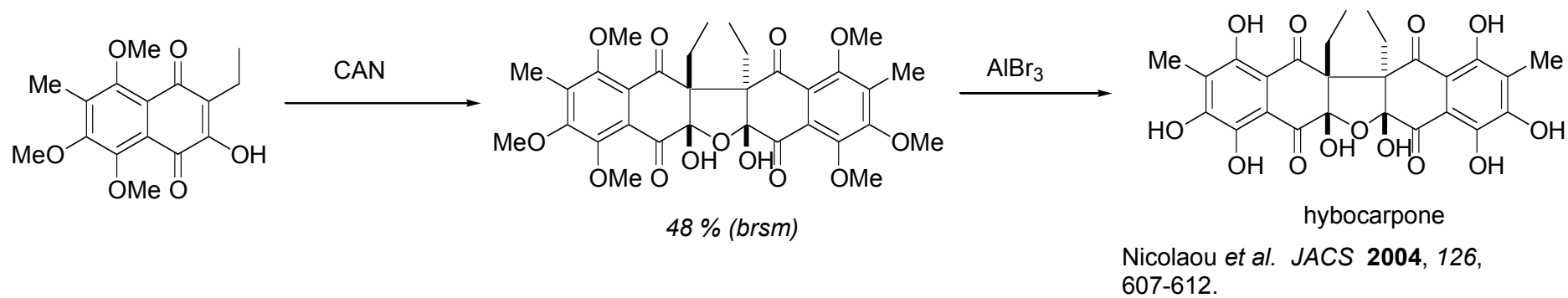
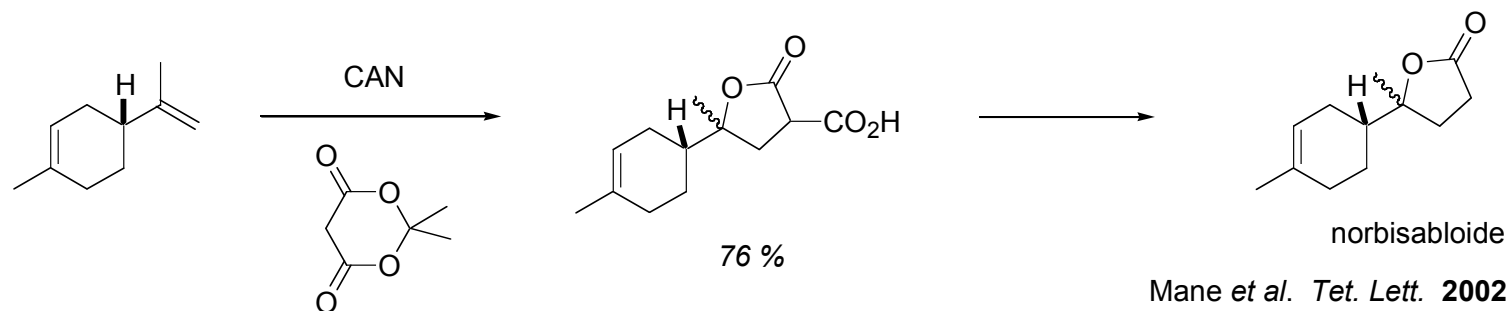
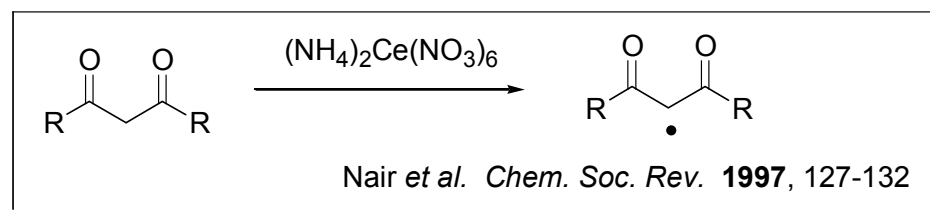
Manganese (III) Acetate

- Mild reductant used to form radicals from β -carbonyls

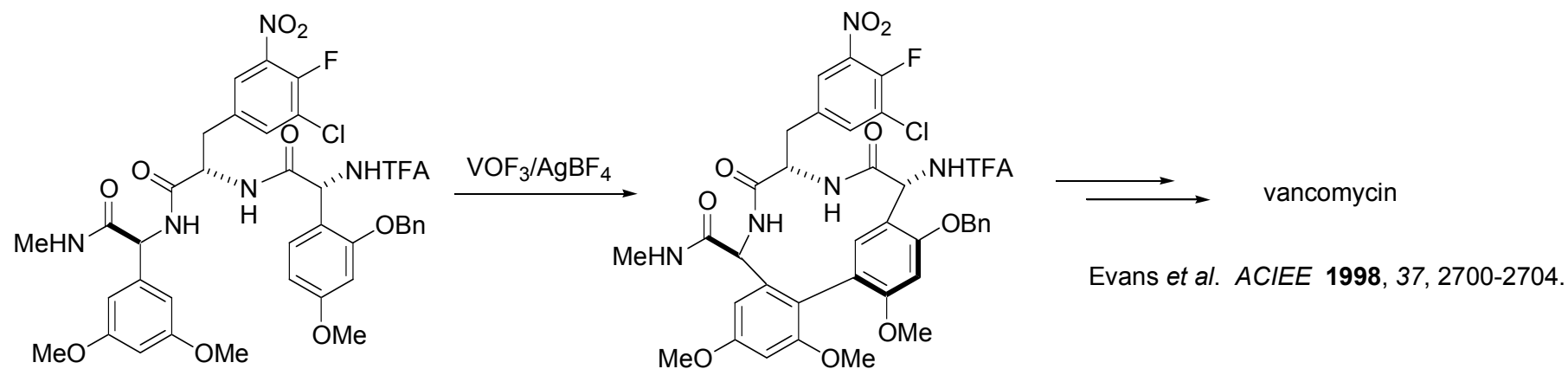


Ceric Ammonium Nitrate

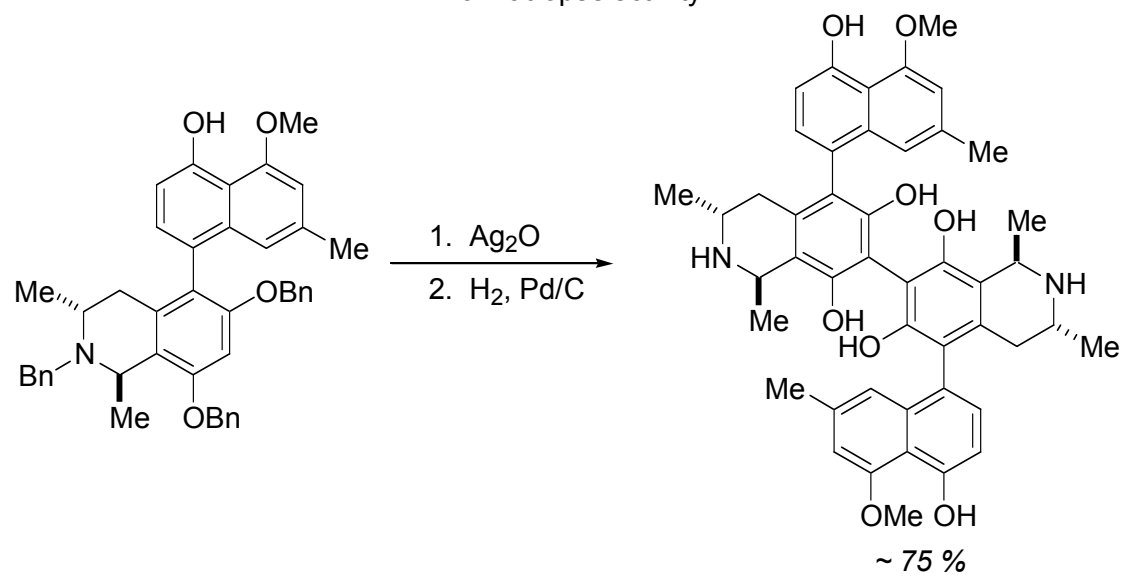
- Lanthanide alternative to manganese acetate; can be used at lower temperatures and in more solvents.



Aromatic Oxidation



Evans *et al.* *ACIEE* **1998**, 37, 2700-2704.



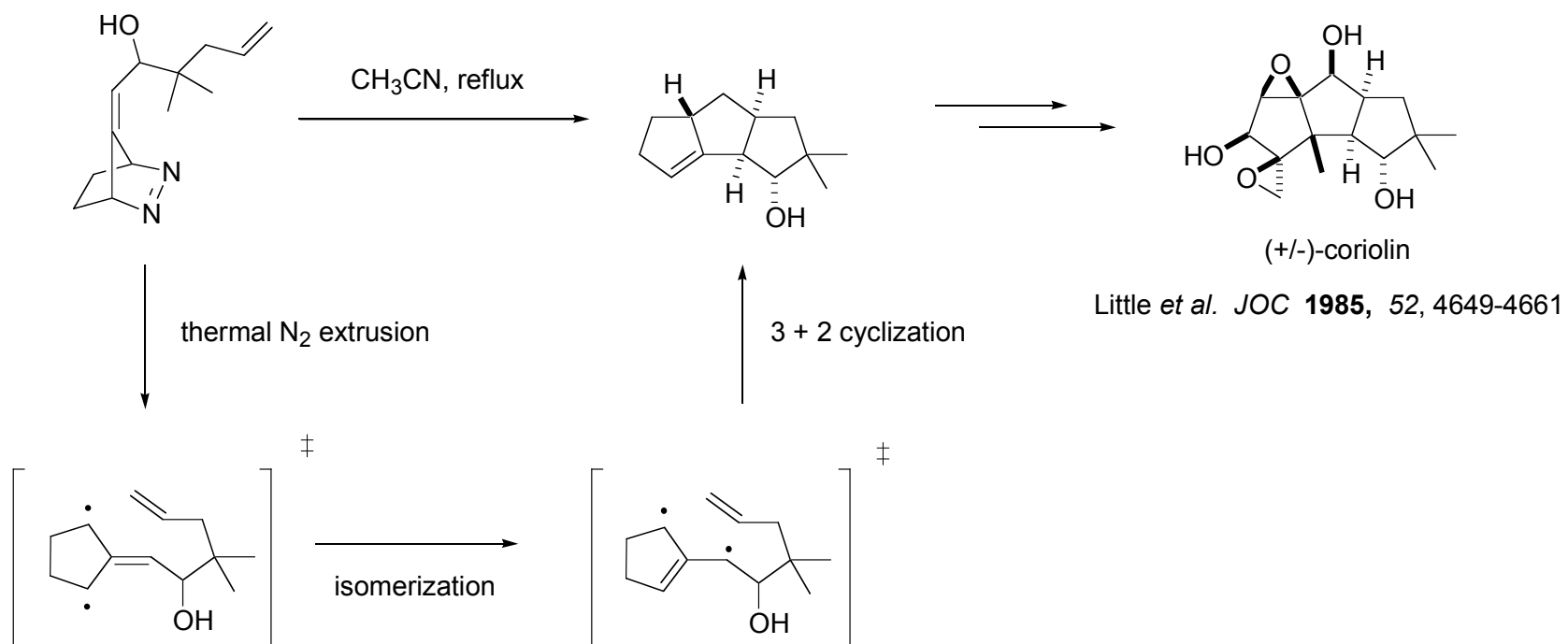
(+/-)-michellamines

Hoye *et al.* *JOC* **1999**, 64, 7184-7201.

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Diradicals

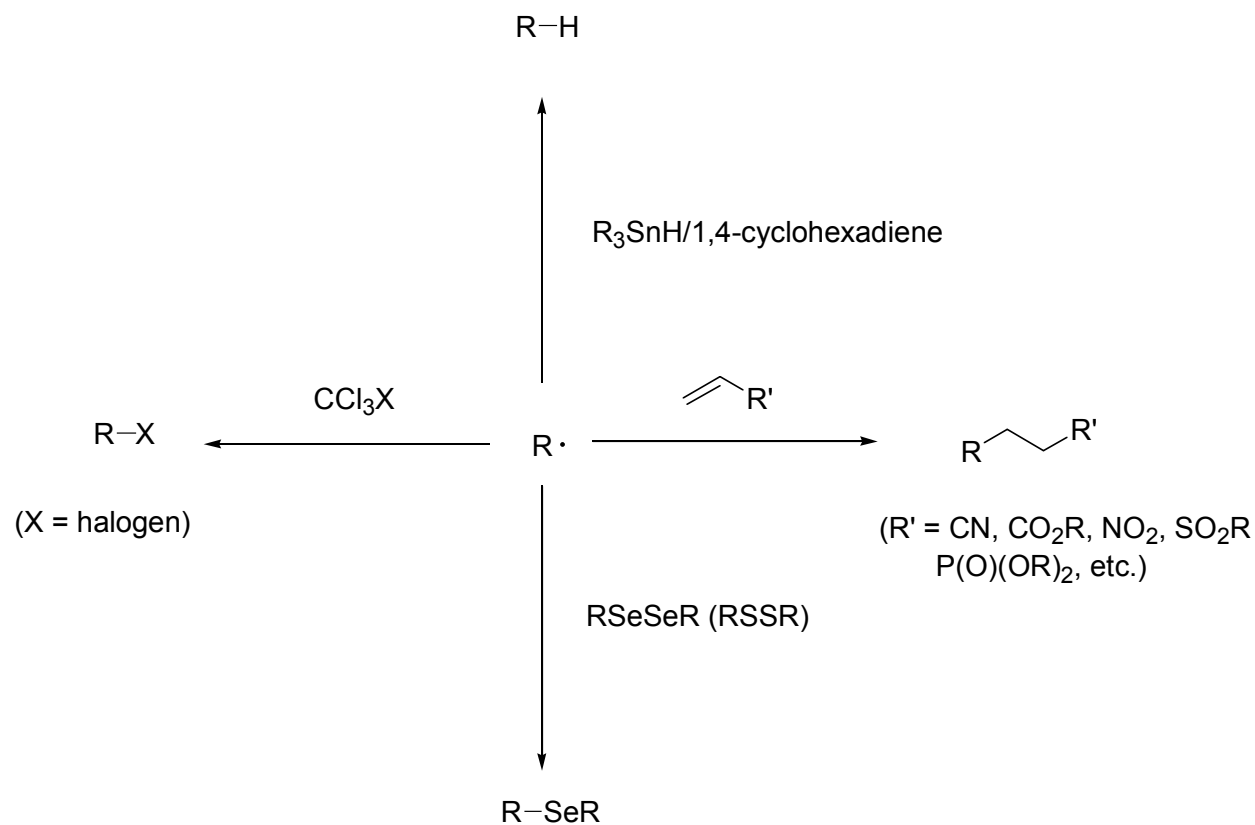


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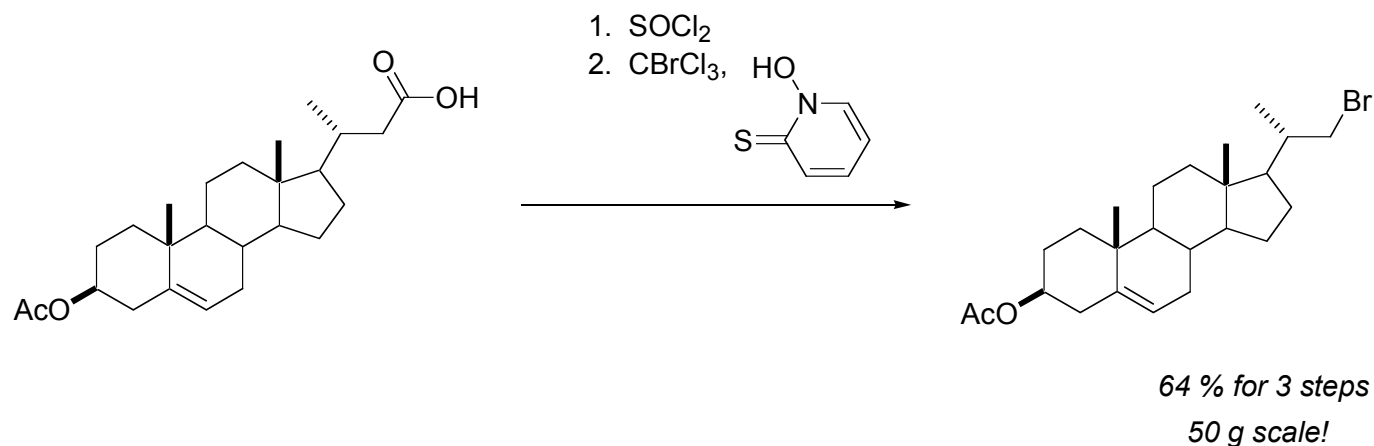
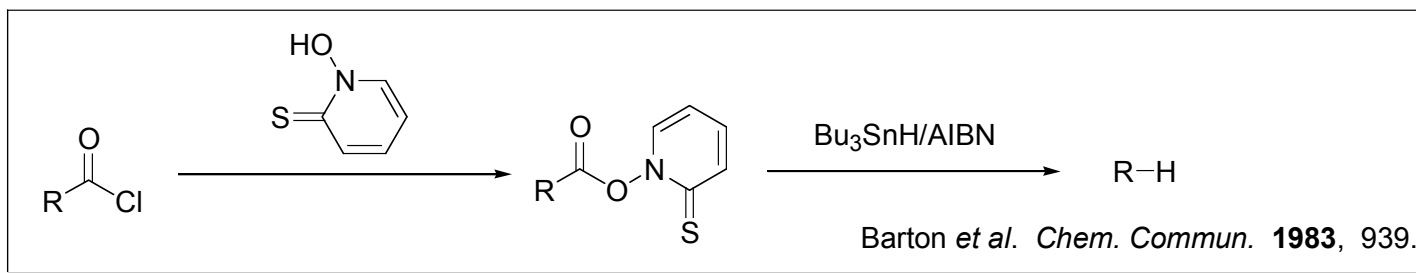
Intermolecular Radical Traps

- Radicals can be trapped with a variety of intermolecular reagents to add functionality.



Barton Decarboxylation

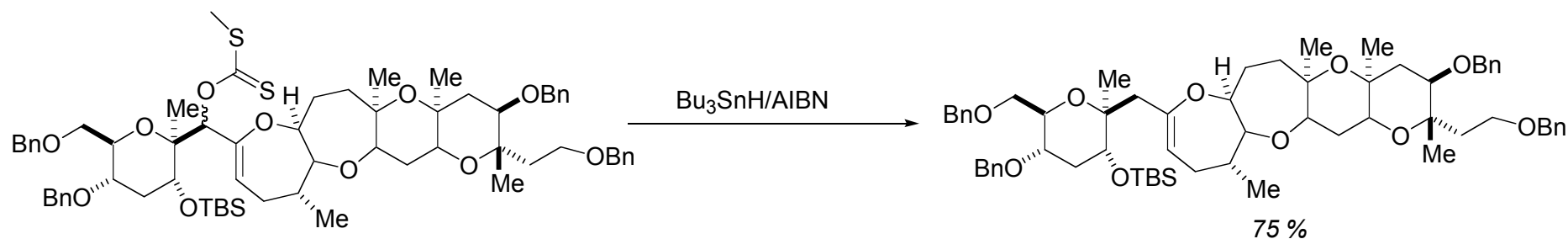
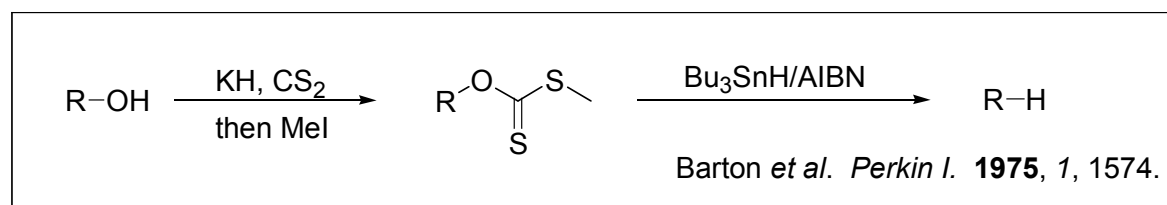
- Method for reductive removal of carboxylic acid moiety; intermediate radical species can also be trapped before reduction.



Kutner *et al.* *Org. Process Res. Dev.* **1998**, 2, 290-293.

Barton-McCombie Deoxygenation

- Mild method for deoxygenation of alcohol moiety (*cf.* sulfonate reduction with LAH); again the transient radical can also be trapped.

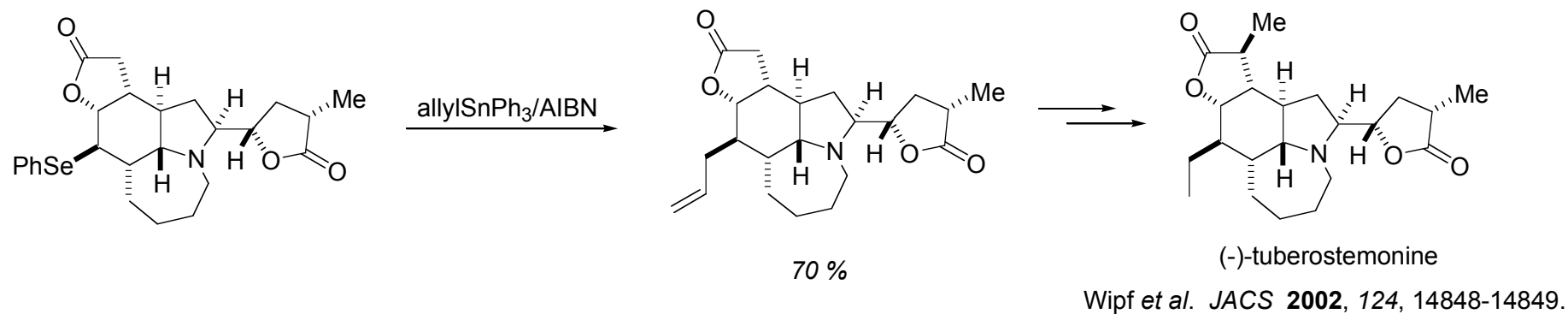
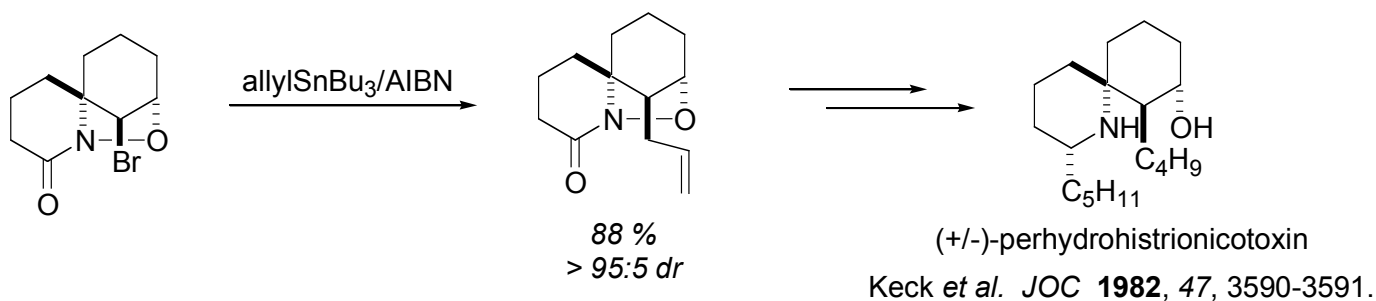
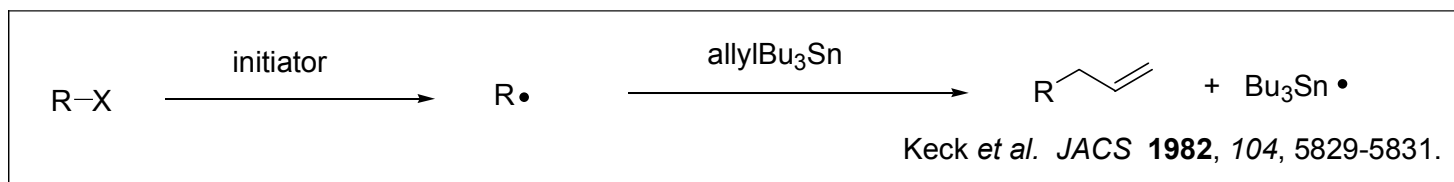


towards brevetoxin B

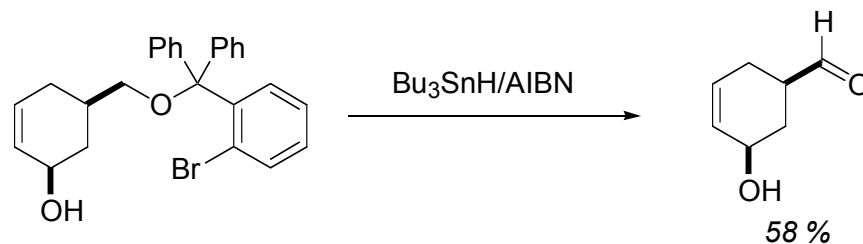
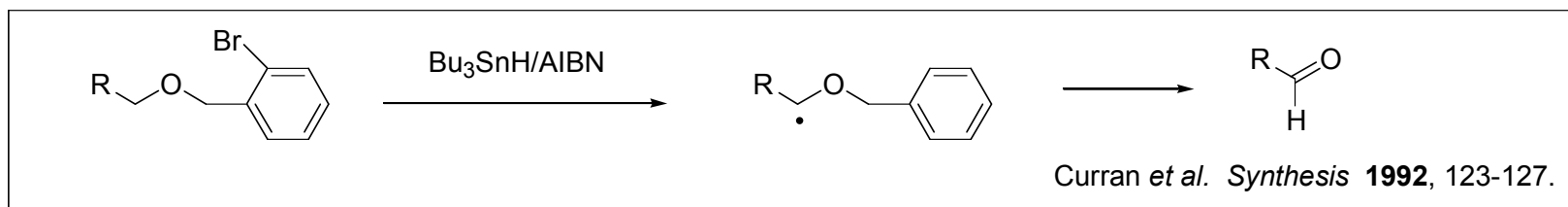
Nicolaou *et al.* *JACS* **1997**, 119, 10239-10251.

Keck Allylation

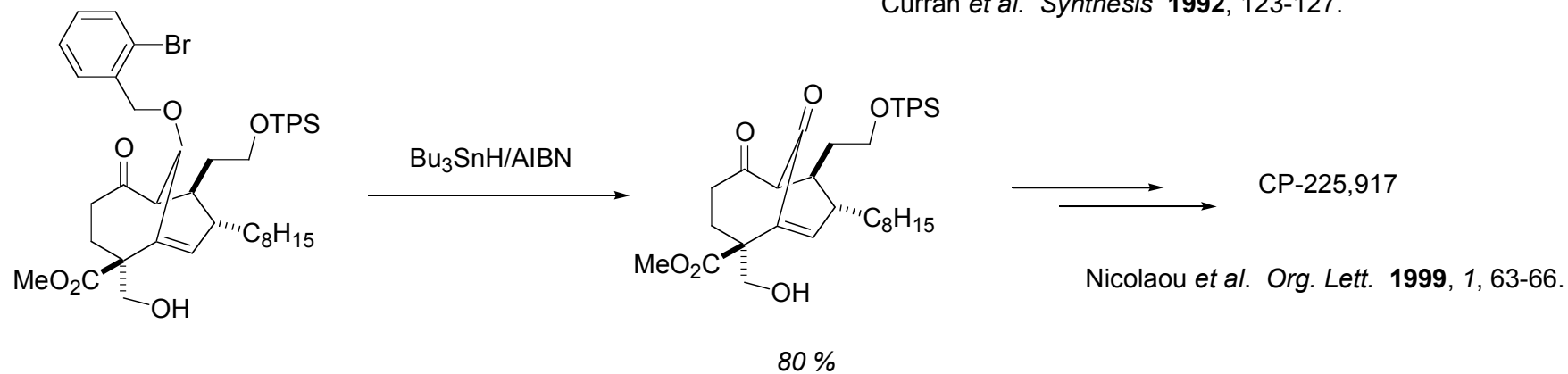
- Mild method for functionalization of carbon-halogen bonds; works best with secondary halides.



Self-Oxidizing Protecting Group



Curran *et al.* *Synthesis* **1992**, 123-127.



Conclusions

- Radical chemistry can be a powerful, selective method for carbon-carbon bond forming reactions (particularly cyclizations).
- The mild, neutral reaction conditions and functional group compatibility of carbon-centered radicals lend itself well toward use in complex systems associated with natural product synthesis.
- Future work is needed to expand the number of reliable radical-based synthetic methods, particularly those of an intermolecular fashion.

Important References

- Sibi, M. P.; Renaud, R., *Eds. Radicals in Organic Synthesis*; Wiley-VCH: New York, 2001.
- Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon Press: Oxford, 1986.
- Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; Wiley-VCH: New York, 1996.
- Curran *et al.* "Radical Reactions in Natural Product Synthesis," *Chem. Rev.* 1991, 91, 1237-1286.
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