

General References

Carey, F. A.; Sundberg, R. J. In *Advanced Organic Chemistry Part B*, Plenum Press: New York, **1990**, p. 615-664.

Hudlicky, M. In *Reductions in Organic Chemistry 2nd Ed.*, American Chemical Society Monograph 188: Washington DC, **1996**, p. 19-30.

Brown, H. C.; Ramachandran, P. V. In *Reductions in Organic Synthesis: Recent Advances and Practical Applications*, Abdel-Magid, A. F. Ed.; American Chemical Society: Washington DC, **1996**, p. 1-30.

Seyden-Penne, J. In *Reductions by the Alumino- and Borohydrides in Organic Synthesis, 2nd Ed.*, Wiley-VCH: New York, **1997**, p. 1-36.

Reactivity Trends

- Following are general guidelines concerning the reactivities of various reducing agents.

Substrates, Reduction Products

	<u>Iminium Ion</u>	<u>Acid Halide</u>	<u>Aldehyde</u>	<u>Ester</u>	<u>Amide</u>	<u>Carboxylate Salt</u>
Hydride Donors						
LiAlH ₄	Amine	Alcohol	Alcohol	Alcohol	Amine	Alcohol
DIBAL	–	Alcohol	Alcohol	Alcohol or Aldehyde	Amine or Aldehyde	Alcohol
NaAlH(O-t-Bu) ₃	–	Aldehyde	Alcohol	Alcohol (slow)	Amine (slow)	–
AlH ₃	–	Alcohol	Alcohol	Alcohol	Amine	Alcohol
NaBH ₄	Amine	–	Alcohol	–**	–	–
NaCNBH ₃	Amine	–	Alcohol (slow)	–	–	–
Na(AcO) ₃ BH	Amine	–	Alcohol (slow)	Alcohol (slow)	Amine (slow)	–
B ₂ H ₆	–	–	Alcohol	Alcohol (slow)	Amine (slow)	Alcohol
Li(Et) ₃ BH	–	Alcohol	Alcohol	Alcohol	Alcohol (tertiary amide)	–
H ₂ (catalyst)	Amine	Alcohol	Alcohol	Alcohol	Amine	–

** α -alkoxy esters are reduced to the corresponding alcohols.

– indicates no reaction or no productive reaction (alcohols are deprotonated in many instances, e.g.)

• Catalytic hydrogenation is used for the reduction of many organic functional groups. The reaction can be modified with respect to catalyst, hydrogen pressure, solvent, and temperature in order to execute a desired reduction.

• A brief list of recommended reaction conditions for catalytic hydrogenations of selected functional groups is given below.

Substrate	Product	Catalyst	Catalyst/Compound Ratio (wt%)	Pressure (atm)
Alkene	Alkane	5% Pd/C	5-10%	1-3
Alkyne	Alkene	5% Pd(BaSO ₄)	2% + 2% quinoline	1
Aldehyde (Ketone)	Alcohol	PtO ₂	2-4%	1
Halide	Alkane	5% Pd/C	1-15%, KOH	1
Nitrile	Amine	Raney Ni	3-30%	35-70

Adapted from: Hudlicky, M. In *Reductions in Organic Chemistry 2nd Ed.*, American Chemical Society Monograph 188: Washington DC, **1996**, p. 8.

Summary of Reagents for Reductive Functional Group Interconversions:

Acid \longrightarrow **Alcohol**

Lithium Aluminum Hydride (LAH) Lithium Borohydride Borane Complexes

Ester \longrightarrow **Aldehyde**

Diisobutylaluminum Hydride (DIBAL) Reduction of Acid Chlorides, Amides, and Nitriles

Lithium Triethoxyaluminumhydride (LTEAH)

Aldehyde \longrightarrow **Alcohol**

Reductive Amination Luche Reduction Samarium Iodide

Sodium Borohydride Ionic Hydrogenation

Aldehyde \longrightarrow **Alkane**

Deoxygenation of Tosylhydrazones Desulfurization with Raney Nickel

Wolff-Kishner Reduction Clemmensen Reduction

Alcohol \longrightarrow **Alkane**

Barton Deoxygenation Diazene-Mediated Deoxygenation

Reduction of Alkyl Tosylates Radical Dehalogenation

Acid \longrightarrow **Alkane**

Barton Decarboxylation



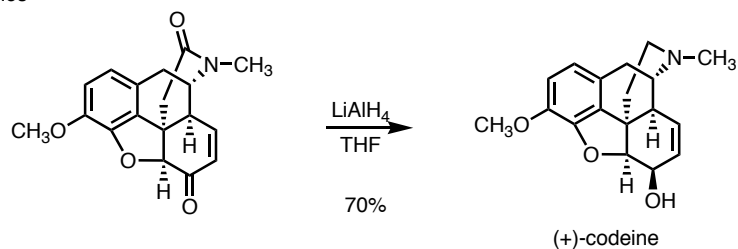
Lithium Aluminum Hydride (LAH): LiAlH_4

- LAH is a powerful and rather nonselective hydride-transfer reagent that readily reduces carboxylic acids, esters, lactones, anhydrides, amides and nitriles to the corresponding alcohols or amines. In addition, aldehydes, ketones, epoxides, alkyl halides, and many other functional groups are reduced readily by LAH.
- LAH is commercially available as a dry, grey solid or as a solution in a variety of organic solvents, e.g., ethyl ether. Both the solid and solution forms of LAH are highly flammable and should be stored protected from moisture.
- Several work-up procedures for LAH reductions are available that avoid the difficulties of separating by-products of the reduction. In the Fieser work-up, following reduction with n grams of LAH, careful successive dropwise addition of n mL of 15% NaOH solution, and 3 n mL of water provides a granular inorganic precipitate that is easy to rinse and filter. For moisture-sensitive substrates, ethyl acetate can be added to consume any excess LAH and the reduction product, ethanol, is unlikely to interfere with product isolation.
- Although, in theory, one equivalent of LAH provides four equivalents of hydride, an excess of the reagent is typically used.

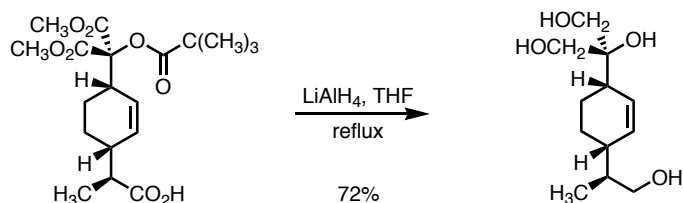
Paquette, L. A. In *Handbook of Reagents for Organic Synthesis: Oxidizing and Reducing Reagents*, Burke, S. D.; Danheiser, R. L., Eds., John Wiley and Sons: New York, **1999**, p. 199-204.

Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis* **1967**, 581-595.

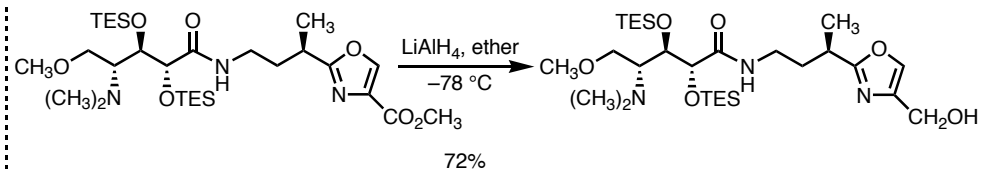
Examples



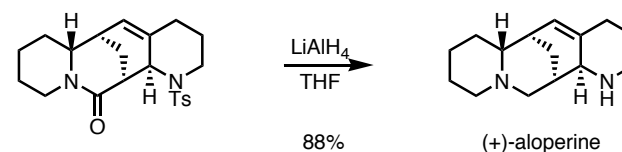
White, J. D.; Hrnčiar, P.; Stappenbeck, F. *J. Org. Chem.* **1999**, *64*, 7871-7884.



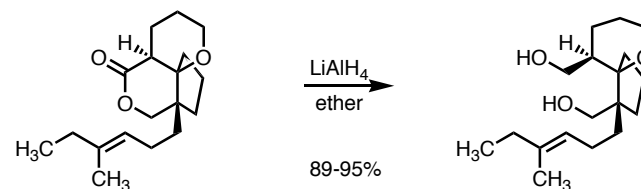
Bergner, E. J.; Helmchen, G. *J. Org. Chem.* **2000**, *65*, 5072-5074.



Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434-9453.

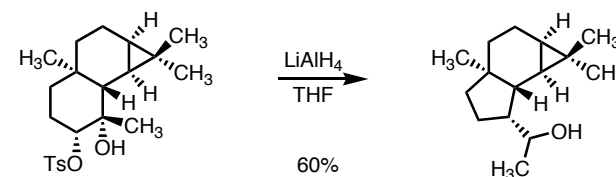


Brosius, A. D.; Overman, L. E.; Schwink, L. *J. Am. Chem. Soc.* **1999**, *121*, 700-709.



Heathcock, C. H.; Ruggeri, R. B.; McClure, K. F. *J. Org. Chem.* **1992**, *57*, 2585-2599.

- In the following example, rearrangement accompanied reduction.



Bates, R. B.; Büchi, G.; Matsuura, T.; Shaffer, R. R. *J. Am. Chem. Soc.* **1960**, *82*, 2327-2337.

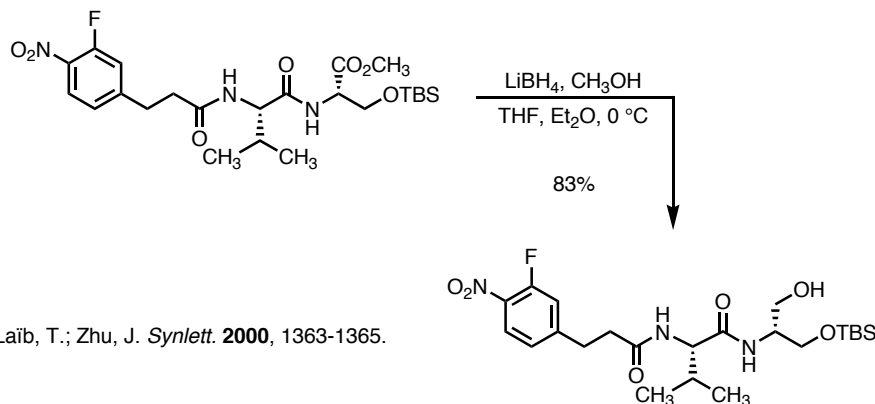
Lithium Borohydride: LiBH₄

- Lithium borohydride is commonly used for the selective reduction of esters and lactones to the corresponding alcohols in the presence of carboxylic acids, tertiary amides, and nitriles. Aldehydes, ketones, epoxides, and several other functional groups can also be reduced by lithium borohydride.
- The reactivity of lithium borohydride is dependent on the reaction medium and follows the order: ether > THF > 2-propanol. This is attributed to the availability of the lithium counterion for coordination to the substrate, promoting reduction.
- Lithium borohydride is commercially available in solid form and as solutions in many organic solvents, e.g., THF. Both are inflammable and should be stored protected from moisture.

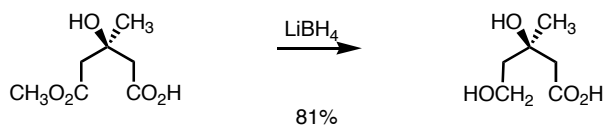
Nystrom, R. F.; Chaikin, S. W.; Brown, W. G. *J. Am. Chem. Soc.* **1949**, *71*, 3245-3246.

Banfi, L.; Narisano, E.; Riva, R. In *Handbook of Reagents for Organic Synthesis: Oxidizing and Reducing Reagents*, Burke, S. D.; Danheiser, R. L., Eds., John Wiley and Sons: New York, **1999**, p. 209-212.

Examples



Laib, T.; Zhu, J. *Synlett.* **2000**, 1363-1365.



Huang, F.-C.; Lee, L. F.; Mittal, R. S. D.; Ravikumar, P. R.; Chan, J. A.; Sih, C. J. *J. Am. Chem. Soc.* **1975**, *97*, 4144-4145.

Borane Complexes: BH₃·L

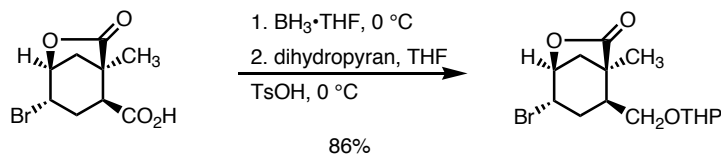
- Borane is commonly used for the reduction of carboxylic acids in the presence of esters, lactones, amides, halides and other functional groups. In addition, borane rapidly reduces aldehydes, ketones, and alkenes.
- Borane is commercially available as a neat complex with tetrahydrofuran (THF) or dimethylsulfide or in solution. In addition, gaseous diborane (B₂H₆) is available.
- The borane-dimethylsulfide complex exhibits improved stability and solubility compared to the borane-THF complex.
- Competing hydroboration of carbon-carbon double bonds can limit the usefulness of borane-THF as a reducing agent.

Yoon, N. M.; Pak, C. S.; Brown, H. C.; Krishnamurthy, S.; Stocky, T. P. *J. Org. Chem.* **1973**, *38*, 2786-2792.

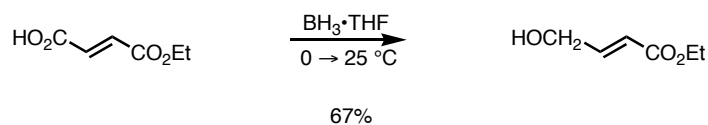
Lane, C. F. *Chem. Rev.* **1976**, *76*, 773-799.

Brown, H. C.; Stocky, T. P. *J. Am. Chem. Soc.* **1977**, *99*, 8218-8226.

Examples

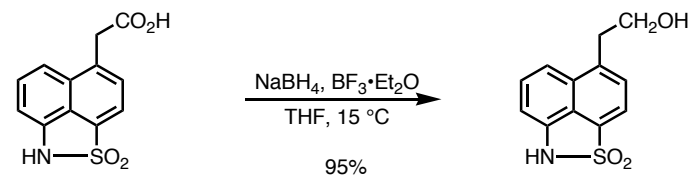


Corey, E. J.; Sachdev, H. S. *J. Org. Chem.* **1975**, *40*, 579-581.

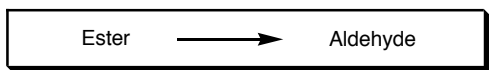


Kende, A. S.; Fludzinski, P. *Org. Synth.* **1986**, *64*, 104-107.

- The combination of boron trifluoride etherate and sodium borohydride has been used to generate diborane in situ.



Miller, R. A.; Humphrey, G. R.; Lieberman, D. R.; Ceglia, S. S.; Kennedy, D. J.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **2000**, *65*, 1399-1406.



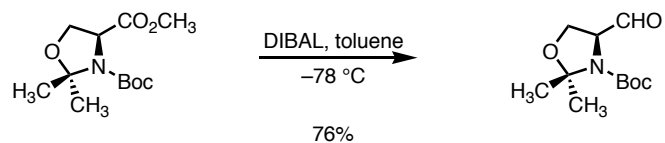
Diisobutylaluminum Hydride (DIBAL): *i*-Bu₂AlH

- At low temperatures, DIBAL reduces esters to the corresponding aldehydes, and lactones to lactols.
- Typically, toluene is used as the reaction solvent, but other solvents have also been employed, including dichloromethane.

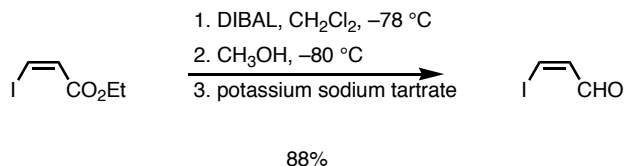
Miller, A. E. G.; Biss, J. W.; Schwartzman, L. H. *J. Org. Chem.* **1959**, *24*, 627-630.

Zakharkin, L. I.; Khorlina, I. M. *Tetrahedron Lett.* **1962**, *3*, 619-620.

• Examples

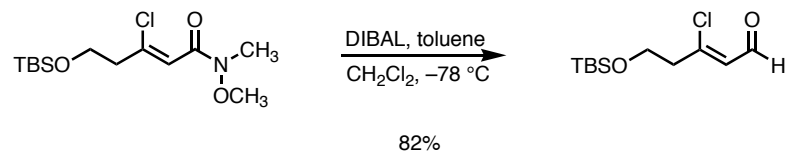


Garner, P.; Park, J. M. *Org. Synth.* **1991**, *70*, 18-28.

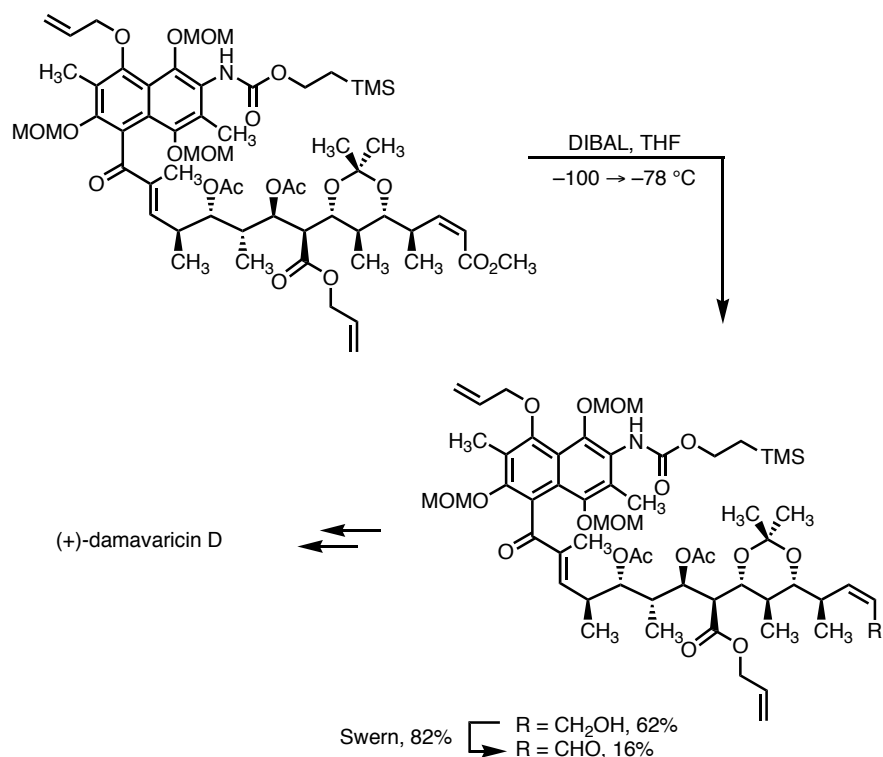


Marek, I.; Meyer, C.; Normant, J.-F. *Org. Synth.* **1996**, *74*, 194-204.

- Reduction of *N*-methoxy-*N*-methyl amides, also known as Weinreb amides, is one of the most frequent means of converting a carboxylic acid to an aldehyde.

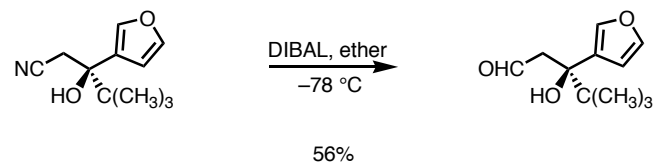


Trauner, D.; Schwarz, J. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3542-3545.



Roush, W. R.; Coffey, D. S.; Madar, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 11331-11332.

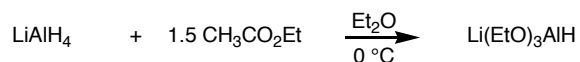
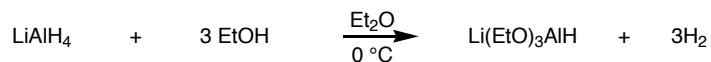
- Nitriles are reduced to imines, which hydrolyze upon work-up to furnish aldehydes.



Crimmins, M. T.; Jung, D. K.; Gray, J. L. *J. Am. Chem. Soc.* **1993**, *115*, 3146-3155.

Lithium Triethoxyaluminumhydride (LTEAH): Li(EtO)₃AlH

- LTEAH selectively reduces aromatic and aliphatic nitriles to the corresponding aldehydes (after aqueous workup) in yields of 70-90%.
- Tertiary amides are efficiently reduced to the corresponding aldehydes with LTEAH.
- LTEAH is formed by the reaction of 1 mole of LAH solution in ethyl ether with 3 moles of ethyl alcohol or 1.5 moles of ethyl acetate.

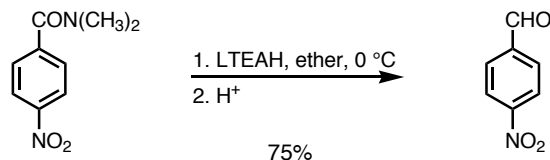
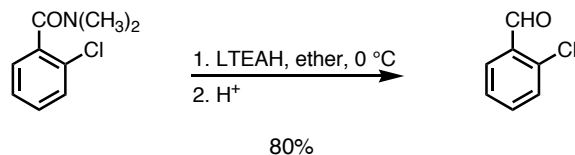


Brown, H. C.; Shoaf, C. J. *J. Am. Chem. Soc.* **1964**, *86*, 1079-1085.

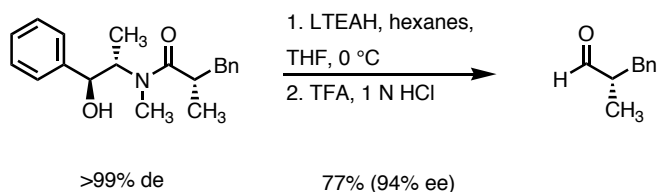
Brown, H. C.; Garg, C. P. *J. Am. Chem. Soc.* **1964**, *86*, 1085-1089.

Brown, H. C.; Tsukamoto, A. *J. Am. Chem. Soc.* **1964**, *86*, 1089-1095.

- Examples



Brown, H. C.; Krishnamurthy, S. *Tetrahedron* **1979**, *35*, 567-607.



Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496-6511.

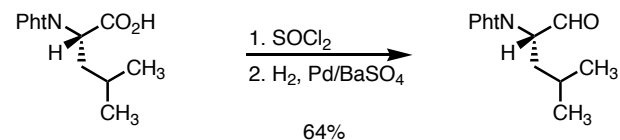
Reduction of Acid Chlorides

- The Rosemund reduction is a classic method for the preparation of aldehydes from carboxylic acids by the selective hydrogenation of the corresponding acid chloride.
- Over-reduction and decarbonylation of the aldehyde product can limit the usefulness of the Rosemund protocol.
- The reduction is carried out by bubbling hydrogen through a hot solution of the acid chloride in which the catalyst, usually palladium on barium sulfate, is suspended.

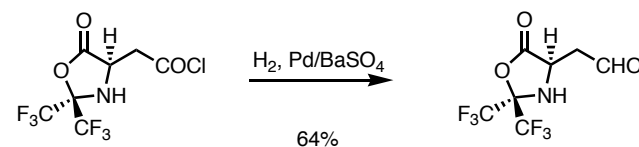
Rosemund, K. W.; Zetzsche, F. *Chem. Ber.* **1921**, *54*, 425-437.

Mosetting, E.; Mozingo, R. *Org. React.* **1948**, *4*, 362-377.

- Examples

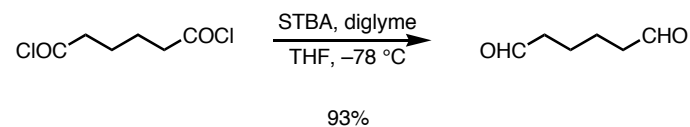
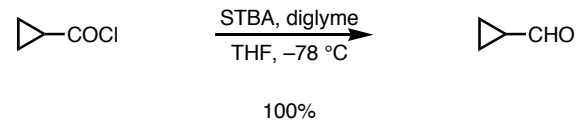


Johnson, R. L. *J. Med. Chem.* **1982**, *25*, 605-610.



Winkler, D.; Burger, K. *Synthesis* **1996**, 1419-1421.

- Sodium tri-*tert*-butoxyaluminumhydride (STBA), generated by the reaction of sodium aluminum hydride with 3 equivalents of *tert*-butyl alcohol, reduces aliphatic and aromatic acid chlorides to the corresponding aldehydes in high yields.



diglyme = (CH₃OCH₂CH₂)₂O

Cha, J. S.; Brown, H. C. *J. Org. Chem.* **1993**, *58*, 4732-4734.

Aldehyde or Ketone \longrightarrow Alkane

Deoxygenation of Tosylhydrazones

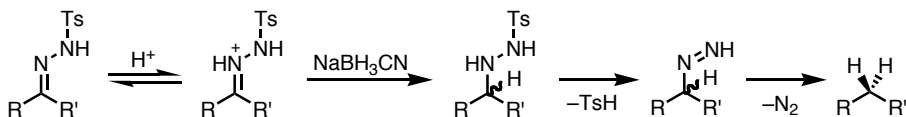
- Reduction of tosylhydrazones to hydrocarbons with hydride donors, such as sodium cyanoborohydride, sodium triacetoxyborohydride, or catecholborane, is a mild and selective method for carbonyl deoxygenation.
- Esters, amides, nitriles, nitro groups, and alkyl halides are compatible with the reaction conditions.
- Most hindered carbonyl groups are readily reduced to the corresponding hydrocarbon.
- However, electron-poor aryl carbonyls prove to be resistant to reduction.

Hutchins, R. O.; Milewski, C. A.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1973**, *95*, 3662-3668.

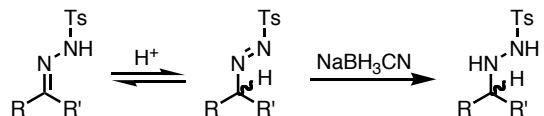
Kabalka, G. W.; Baker, J. D., Jr. *J. Org. Chem.* **1975**, *40*, 1834-1835.

Kabalka, G. W.; Chandler, J. H. *Synth. Commun.* **1979**, *9*, 275-279.

- Two possible mechanisms for reduction of tosylhydrazones by sodium cyanoborohydride have been suggested. Direct hydride attack by sodium cyanoborohydride on an iminium ion is proposed in most cases.

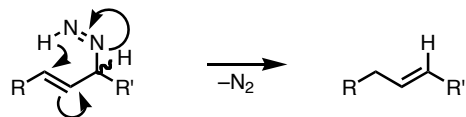


- However, reduction of an azohydrazone is proposed when inductive effects and/or conformational constraints favor tautomerization of the hydrazone to an azohydrazone.



Miller, V. P.; Yang, D.-y.; Weigel, T. M.; Han, O.; Liu, H.-w. *J. Org. Chem.* **1989**, *54*, 4175-4188.

- α,β -Unsaturated carbonyl compounds are reduced with concomitant migration of the conjugated alkene.
- The mechanism for this "alkene walk" reaction apparently proceeds through a diazene intermediate which transfers hydride by 1,5-sigmatropic rearrangement.

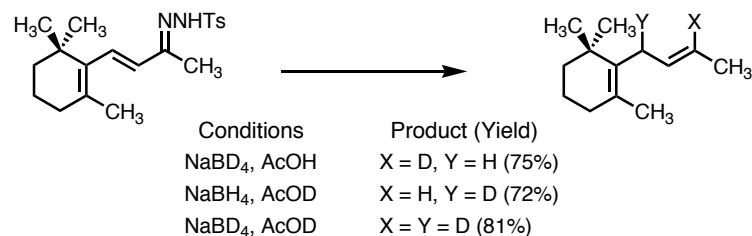


Hutchins, R. O.; Kacher, M.; Rua, L. *J. Org. Chem.* **1975**, *40*, 923-926.

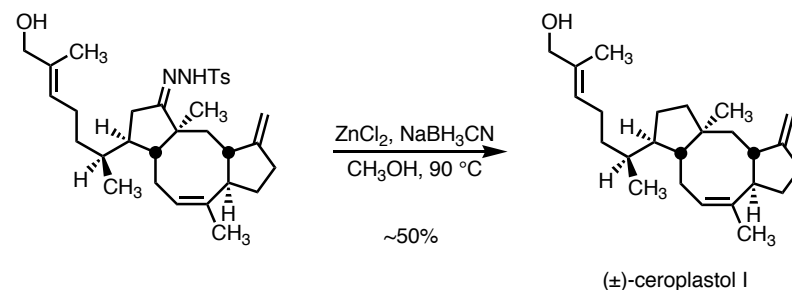
Kabalka, G. W.; Yang, D. T. C.; Baker, J. D., Jr. *J. Org. Chem.* **1976**, *41*, 574-575.

Examples

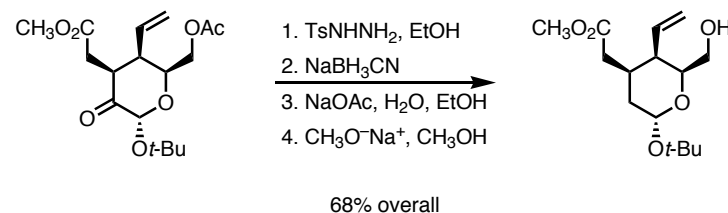
- In the following example, exchange of the tosylhydrazone N-H proton is evidently faster than reduction and hydride transfer.



Hutchins, R. O.; Natale, N. R. *J. Org. Chem.* **1978**, *43*, 2299-2301.



Boeckman, R. K., Jr.; Arvanitis, A.; Voss, M. E. *J. Am. Chem. Soc.* **1989**, *111*, 2737-2739.



Hanessian, S.; Faucher, A.-M. *J. Org. Chem.* **1991**, *56*, 2947-2949.

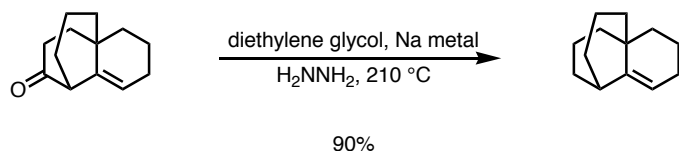
Wolff–Kishner Reduction

- The Wolff–Kishner reduction is a classic method for the conversion of the carbonyl group in aldehydes or ketones to a methylene group. It is conducted by heating the corresponding hydrazone (or semicarbazone) derivative in the presence of an alkaline catalyst.
- Numerous modified procedures to the classic Wolff–Kishner reduction have been reported. In general, the improvements have focused on driving hydrazone formation to completion by removal of water, and by the use of high concentrations of hydrazine.
- The two principal side reactions associated with the Wolff–Kishner reduction are azine formation and alcohol formation.

Todd, D. *Org. React.* **1948**, *4*, 378-423.

Hutchins, R. O.; Hutchins, M. K. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, Vol. 8, p. 327-362.

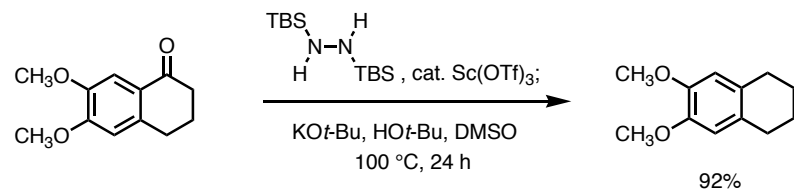
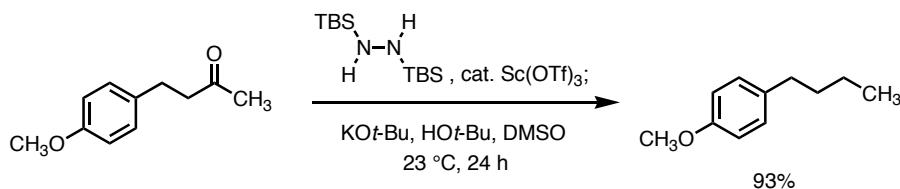
- Examples



Piers, E.; Zbozny, M. *Can. J. Chem.* **1979**, *57*, 1064-1074.

Reduced-Temperature Wolff-Kisher-Type Reduction

- *N-tert*-butyldimethylsilylhydrazine (TBSH) derivatives serve as superior alternatives to hydrazones.
- TBSH derivatives of aliphatic carbonyl compounds undergo Wolff-Kishner-type reduction at 23 °C; derivatives of aromatic carbonyl undergo reduction at 100 °C.



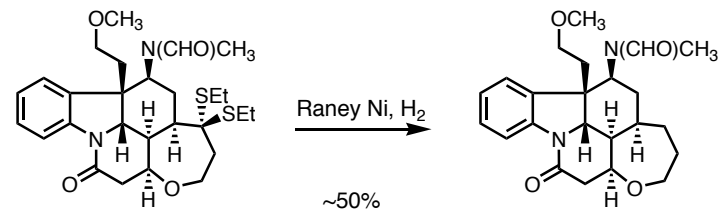
Furrow, M. E.; Myers, A. G. *J. Am. Chem. Soc.* **2004**, *126*, 5436.

Desulfurization With Raney Nickel

- Thioacetal (or thioketal) reduction with Raney nickel and hydrogen is a classic method to prepare a methylene group from a carbonyl compound.
- The most common limitation of the desulfurization method is the competitive hydrogenation of alkenes.

Pettit, G. R.; Tamelen, E. E. *Org. React.* **1962**, *12*, 356-521.

- Example



Woodward, R. B.; Brehm, W. J. *J. Am. Chem. Soc.* **1948**, *70*, 2107-2115.

Clemmensen Reduction

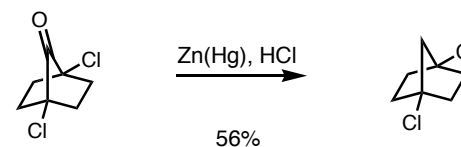
- The Clemmensen reduction of ketones and aldehydes using zinc and hydrochloric acid is a classic method for converting a carbonyl group into a methylene group.
- Typically, the classic Clemmensen reduction involves refluxing a carbonyl substrate with 40% aqueous hydrochloric acid, amalgamated zinc, and an organic solvent such as toluene. This reduction is rarely performed on polyfunctional molecules due to the harsh conditions employed.
- Anhydrous hydrogen chloride and zinc dust in organic solvents has been used as a milder alternative to the classic Clemmensen reduction conditions.

Vedejs, E. *Org. React.* **1975**, *22*, 401-415.

Yamamura, S.; Ueda, S.; Hirata, Y. *J. Chem. Soc., Chem. Commun.* **1967**, 1049-1050.

Toda, M.; Hayashi, M.; Hirata, Y.; Yamamura, S. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 264-266.

- Example



Marchand, A. P.; Weimer, W. R., Jr. *J. Org. Chem.* **1969**, *34*, 1109-1112.

Aldehyde or Ketone \longrightarrow Alcohol

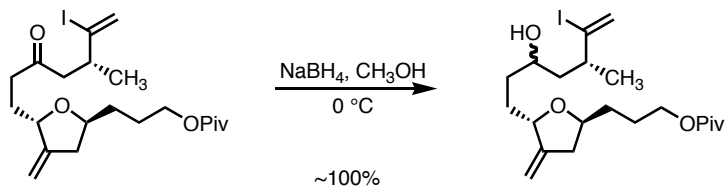
Sodium Borohydride: NaBH₄

- Sodium borohydride reduces aldehydes and ketones to the corresponding alcohols at or near 25 °C. Under these conditions, esters, epoxides, lactones, carboxylic acids, nitro groups, and nitriles are not reduced.
- Sodium borohydride is commercially available as a solid, in powder or pellets, or as a solution in various solvents.
- Typically, sodium borohydride reductions are performed in ethanol or methanol, often with an excess of reagent (to counter the consumption of the reagent by its reaction with the solvent).

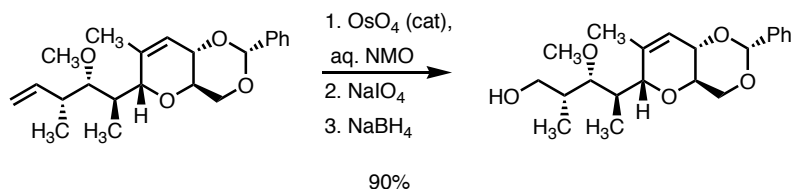
Chaikin, S. W.; Brown, W. G. *J. Am. Chem. Soc.* **1949**, *71*, 122-125.

Brown, H. C.; Krishnamurthy, S. *Tetrahedron* **1979**, *35*, 567-607.

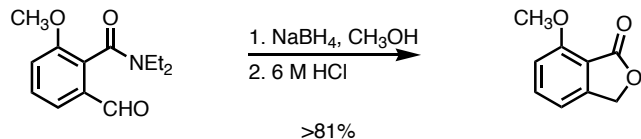
- Examples



Aicher, T. D.; Buszek, K. R.; Fang, F. G.; Forsyth, C. J.; Jung, S. H.; Kishi, Y.; Matelich, M. C.; Scola, P. M.; Spero, D. M.; Yoon, S. K. *J. Am. Chem. Soc.* **1992**, *114*, 3162-3164.



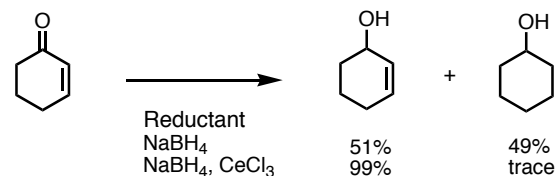
Ireland, R. E.; Armstrong, J. D., III; Lebreton, J.; Meissner, R. S.; Rizzacasa, M. A. *J. Am. Chem. Soc.* **1993**, *115*, 7152-7165.



Wang, X.; de Silva, S. O.; Reed, J. N.; Billadeau, R.; Griffen, E. J.; Chan, A.; Snieckus, V. *Org. Synth.* **1993**, *72*, 163-172.

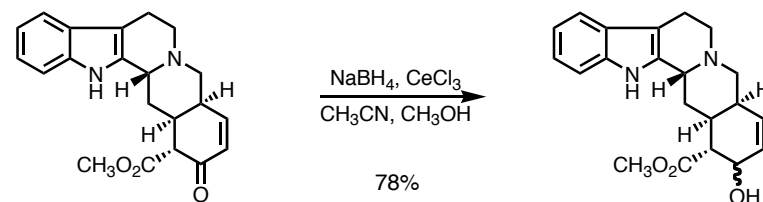
Luche Reduction

- Sodium borohydride in combination with cerium (III) chloride (CeCl₃) selectively reduces α,β -unsaturated carbonyl compounds to the corresponding allylic alcohols.
- Typically, a stoichiometric quantity of cerium (III) chloride and sodium borohydride is added to an α,β -unsaturated carbonyl substrate in methanol at 0 °C.
- Control experiments reveal the dramatic influence of the lanthanide on the regiochemistry of the reduction.

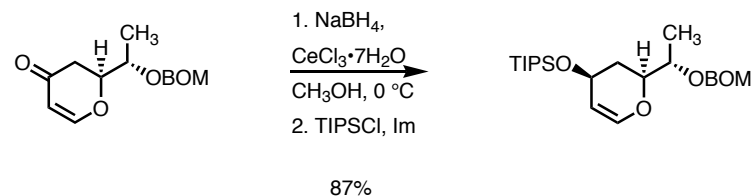


Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226-2227.

- Examples



Binns, F.; Brown, R. T.; Dauda, B. E. N. *Tetrahedron Lett.* **2000**, *41*, 5631-5635.



Meng, D.; Bertinato, P.; Balog, A.; Su, D.-S.; Kamenecka, T.; Sorensen, E. K.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 10073-10092.

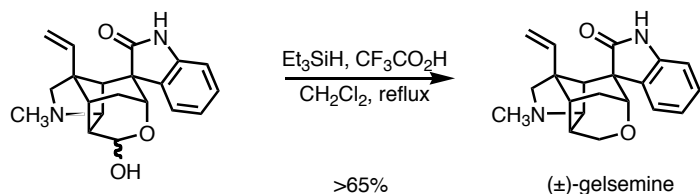
Ionic Hydrogenation

- Ionic hydrogenation refers to the general class of reactions involving the reduction of a carbonium ion intermediate, often generated by protonation of a ketone, alkene, or a lactol, with a hydride donor.
- Generally, ionic hydrogenations are conducted with a proton donor in combination with a hydride donor. These components must react with the substrate faster than with each other.
- Organosilanes and trifluoroacetic acid have proven to be one of the most useful reagent combinations for the ionic hydrogenation reaction.
- Carboxylic acids, esters, amides, and nitriles do not react with organosilanes and trifluoroacetic acid. Alcohols, ethers, alkyl halides, and olefins are sometimes reduced.

Kursanov, D. N.; Parnes, Z. N.; Loim, N. M. *Synthesis* **1974**, 633-651.

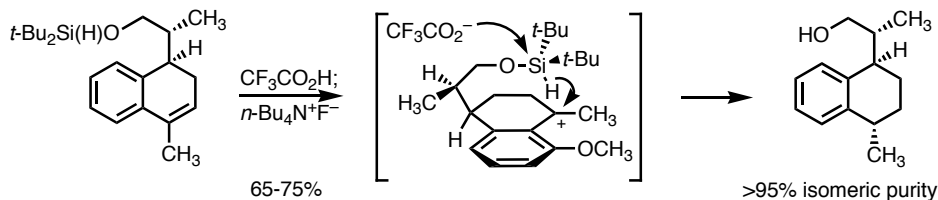
Examples

- The ionic hydrogenation has been used to prepare ethers from the corresponding lactols.



Madin, A.; O'Donnell, C. J.; Oh, T.; Old, D. W.; Overman, L. E.; Sharp, M. J. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2934-2936.

- Intramolecular ionic hydrogenation reactions have been used in stereoselective reductions.



McCombie, S. W.; Cox, B.; Lin, S.-I.; Ganguly, A. K.; McPhail, A. T. *Tetrahedron Lett.* **1991**, *32*, 2083-2086.

Samarium Iodide: SmI_2

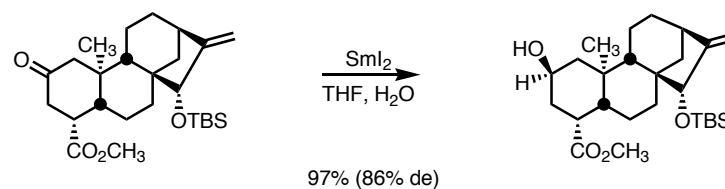
- Samarium iodide effectively reduces aldehydes, ketones, and alkyl halides in the presence of carboxylic acids and esters.
- Aldehydes are often reduced much more rapidly than ketones.

Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693-2698.

Molander, G. A. *Chem. Rev.* **1992**, *92*, 29-68.

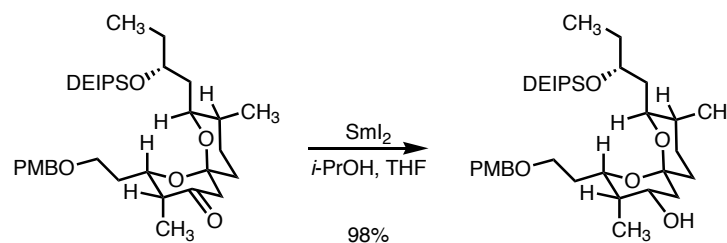
Soderquist, J. A. *Aldrichimica Acta.* **1991**, *24*, 15-23.

Examples



Singh, A. K.; Bakshi, R. K.; Corey, E. J. *J. Am. Chem. Soc.* **1987**, *109*, 6187-6189.

- In the following example, a samarium-catalyzed Meerwein–Ponndorf–Verley reduction successfully reduced the ketone to the alcohol where many other reductants failed.



Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001-7031.

Reductive Amination

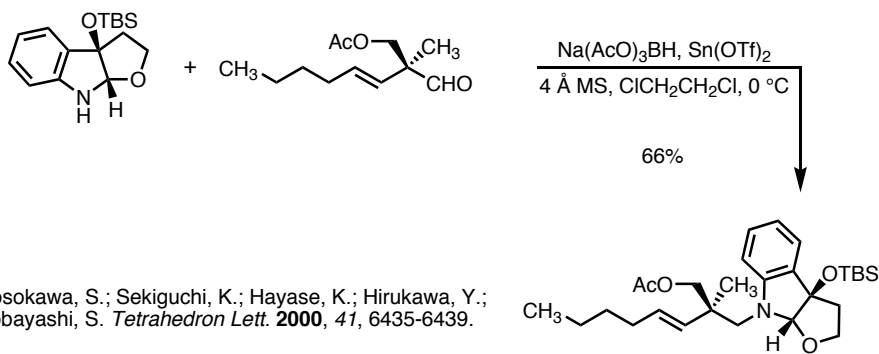
- The reductive amination of aldehydes and ketones is an important method for the synthesis of primary, secondary, and tertiary amines.
- Iminium ions can be reduced selectively in the presence of their carbonyl precursors. Reductive aminations are often conducted by in situ generation of the imine (iminium ion) intermediate in the presence of a mild acid.
- Reagents such as sodium cyanoborohydride and sodium triacetoxyborohydride react selectively with iminium ions and are frequently used for reductive aminations.

Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897-2904.

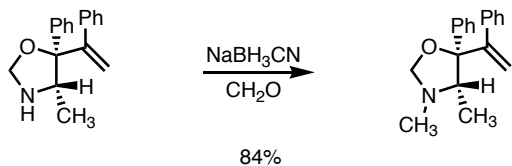
Abdel-Magid, A. F.; Maryanoff, C. A.; Carson, K. G. *Tetrahedron* **1990**, *31*, 5595-5598.

Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849-3862.

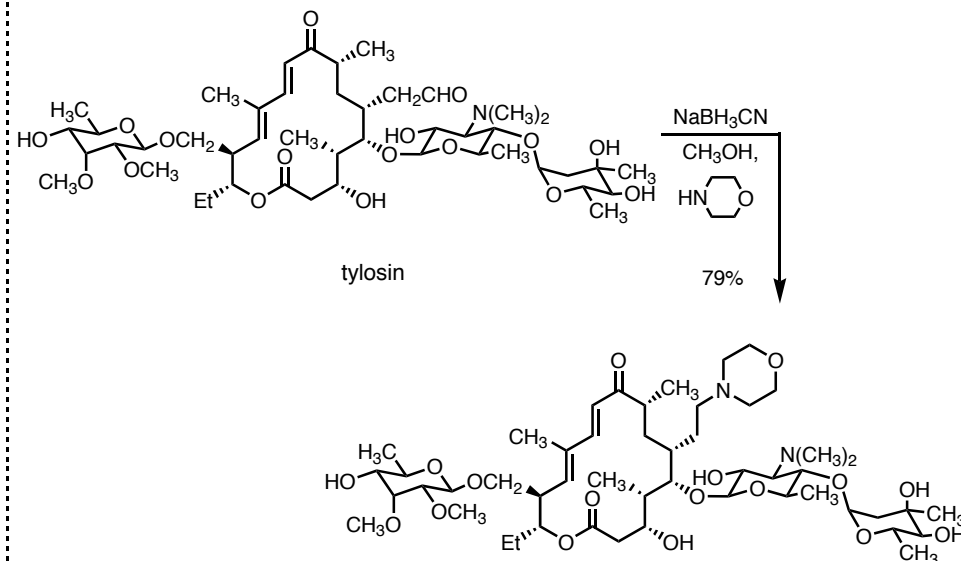
- Examples



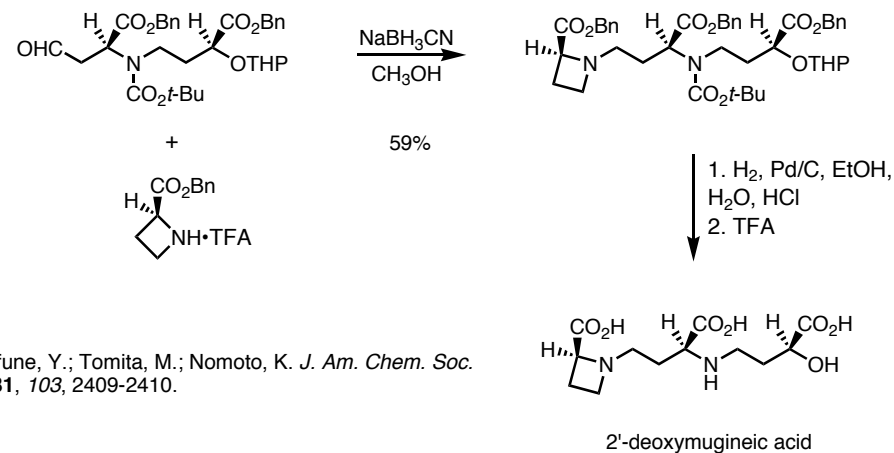
Hosokawa, S.; Sekiguchi, K.; Hayase, K.; Hirukawa, Y.; Kobayashi, S. *Tetrahedron Lett.* **2000**, *41*, 6435-6439.



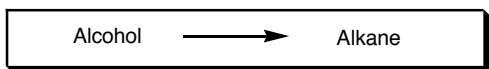
Jacobsen, E. J.; Levin, J.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 4329-4336.



Matsubara, H.; Inokoshi, J.; Nakagawa, A.; Tanaka, H.; Omura, S. *J. Antibiotics* **1983**, *36*, 1713-1721.

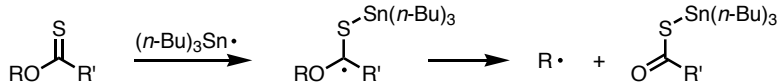


Ohfuné, Y.; Tomita, M.; Nomoto, K. *J. Am. Chem. Soc.* **1981**, *103*, 2409-2410.



Barton Deoxygenation

- Radical-induced deoxygenation of *O*-thiocarbonate derivatives of alcohols in the presence of hydrogen-atom donors is a versatile and widely-used method for the preparation of an alkane from the corresponding alcohol.
- The Barton deoxygenation is a two-step process. In the initial step, the alcohol is acylated to generate an *O*-thiocarbonate derivative, which is then typically reduced by heating in an aprotic solvent in the presence of a hydrogen-atom donor.
- The method has been adapted for the deoxygenation of primary, secondary, and tertiary alcohols. In addition, monodeoxygenation of 1,2- and 1,3-diols has been achieved.
- The accepted mechanism of reduction proceeds by attack of a tin radical on the thiocarbonyl sulfur atom. Subsequent fragmentation of this intermediate generates an alkyl radical which propagates the chain.



Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. I* **1975**, 1574-1585.

Barton, D. H. R.; Motherwell, W. B.; Stange, A. *Synthesis* **1981**, 743-745.

Barton, D. H. R.; Hartwig, W.; Hay-Motherwell, R. S.; Motherwell, W. B.; Stange, A. *Tetrahedron Lett.* **1982**, 23, 2019-2022.

Barton, D. H. R.; Zard, S. Z. *Pure Appl. Chem.* **1986**, 58, 675-684.

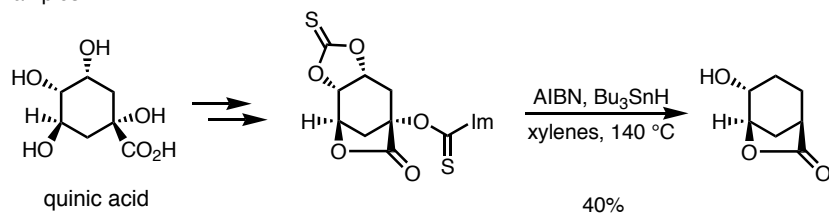
Barton, D. H. R.; Jaszberenyi, J. C. *Tetrahedron Lett.* **1989**, 30, 2619-2622.

Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *Tetrahedron Lett.* **1990**, 31, 3991-3994.

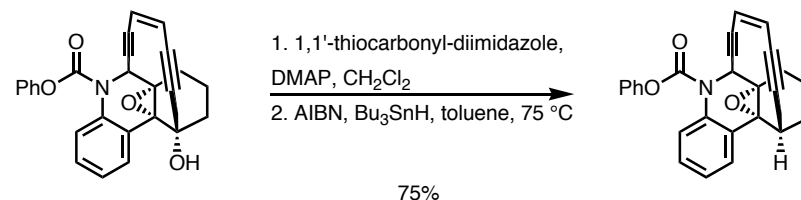
Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *Tetrahedron Lett.* **1990**, 31, 4681-4684.

Barton, D. H. R.; Blundell, P.; Dorchak, J.; Jang, D. O.; Jaszberenyi, J. C. *Tetrahedron* **1991**, 47, 8969-8984.

Examples

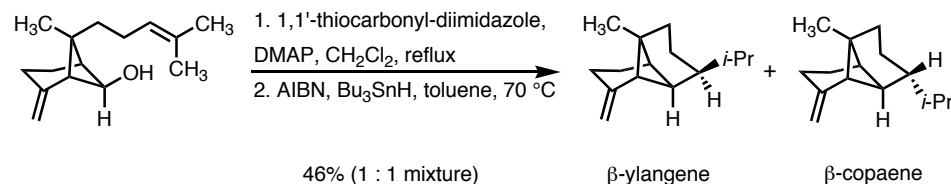


Mills, S.; Desmond, R.; Reamer, R. A.; Volante, R. P.; Shinkai, I. *Tetrahedron Lett.* **1988**, 29, 281-284.



Nicolaou, K. C.; Hwang, C.-K.; Smith, A. L.; Wendeborn, S. V. *J. Am. Chem. Soc.* **1990**, 112, 7416-7418.

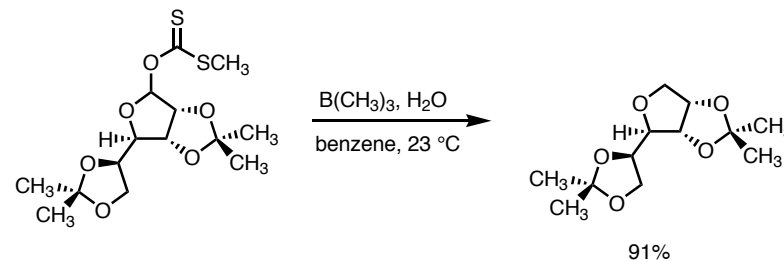
- In the following example, the radical generated during the deoxygenation reaction undergoes 6-exo-trig radical cyclization.



Kulkarni, Y. S.; Niwa, M.; Ron, E.; Snider, B. B. *J. Org. Chem.* **1987**, 52, 1568-1576.

Tin-Free Barton-Type Reduction Employing Water as a Hydrogen Atom Source:

- Trialkylborane acts as both the radical initiator and an activator of water prior to hydrogen atom abstraction.
- Simple concentration of the reaction mixture provides products in high purity.



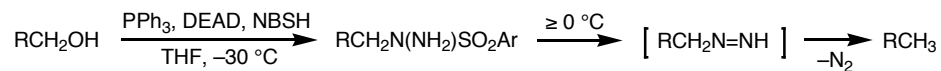
Spiegel, D. A.; Wiberg, K. B.; Schacherer, L. N.; Medeiros, M. R.; Wood, J. L. *J. Am. Chem. Soc.* **2005**, ASAP.

Diazene-Mediated Deoxygenation

• Deoxygenation proceeds by Mitsunobu displacement of the alcohol with *o*-nitrobenzenesulfonylhydrazine (NBSH) followed by in situ elimination of *o*-nitrobenzene sulfonic acid. The resulting monoalkyl diazene is proposed to decompose by a free-radical mechanism to form deoxygenated products.

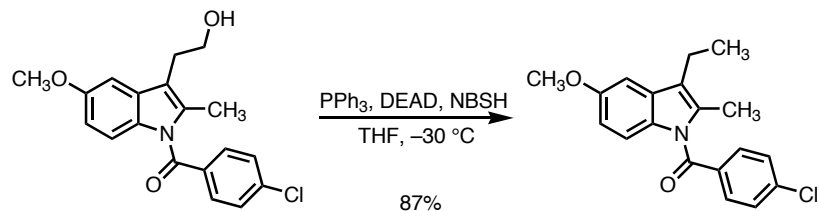
• The deoxygenation is carried out in a single step without using metal hydride reagents.

• The method is found to work well for unhindered alcohols, but sterically encumbered and β -oxygenated alcohols fail to undergo the Mitsunobu displacement and are recovered unchanged from the reaction mixture.

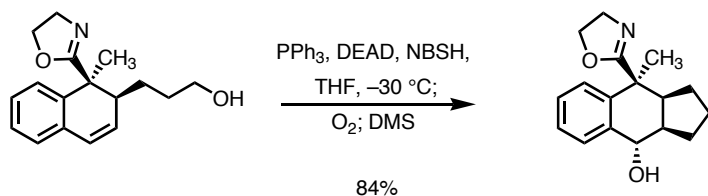


Ar = 2-O₂NC₆H₄

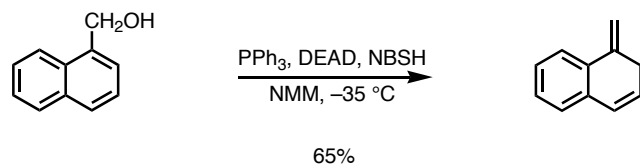
• Examples



• In the following example, the radical generated from decomposition of the diazene intermediate underwent a rapid 5-exo-trig radical cyclization. This generated a second radical that was trapped with oxygen to provide the cyclic carbinol shown after work-up with methyl sulfide.

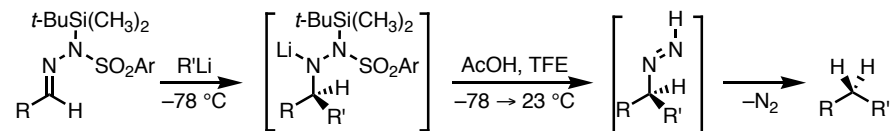


• Monoalkyl diazenes will undergo concerted sigmatropic elimination of dinitrogen in preference to radical decomposition where this is possible.



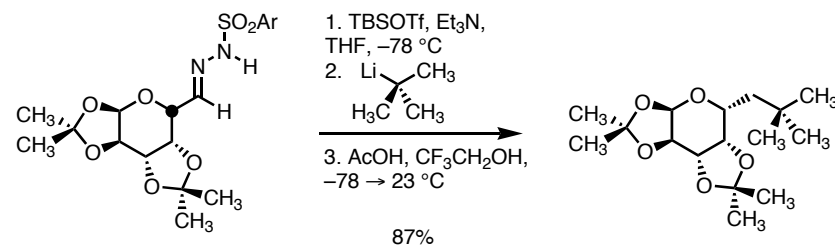
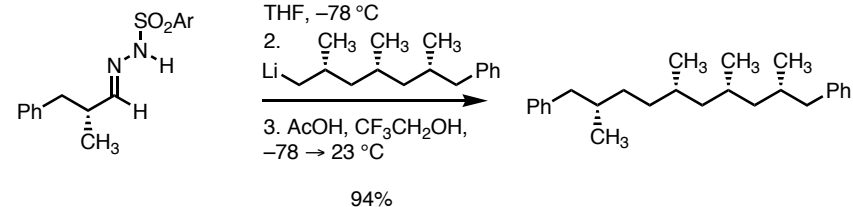
Myers, A. G.; Movassaghi, M.; Zheng, B. *J. Am. Chem. Soc.* **1997**, *119*, 8572-8573.

• In related studies, it was shown that alkyllithium reagents add to *N-tert*-butyldimethylsilyl aldehyde tosylhydrazones at -78 °C and that the resulting adducts can be made to extrude dinitrogen in a free-radical process.

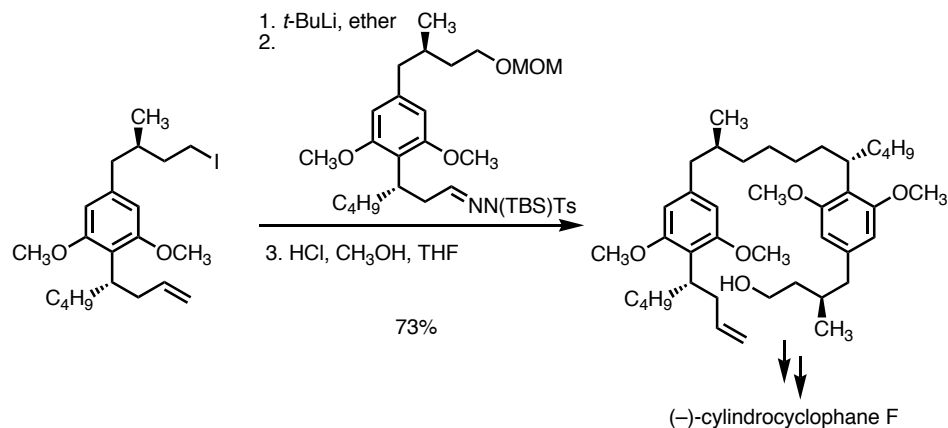


Ar = 2,4,6-triisopropylbenzene

• Examples



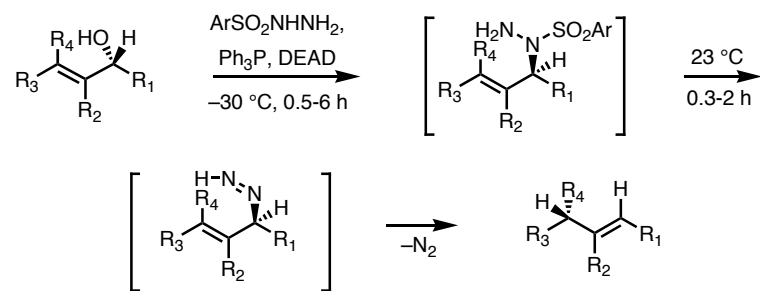
Myers, A. G.; Movassaghi, M. *J. Am. Chem. Soc.* **1998**, *120*, 8891-8892.



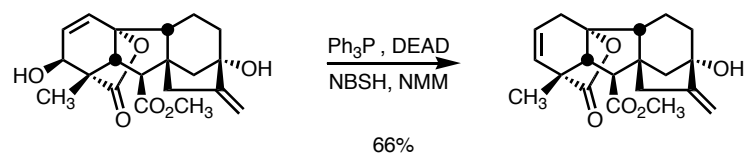
Smith, A. B., III; Kozmin, S. A.; Paone, D. V. *J. Am. Chem. Soc.* **1999**, *121*, 7423-7424.

Mark G. Charest

- Reductive 1,3-transposition of allylic alcohols proceeds with excellent regio- and stereochemical control.

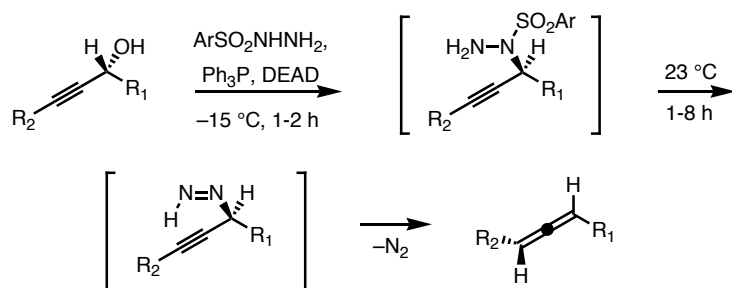


- Example

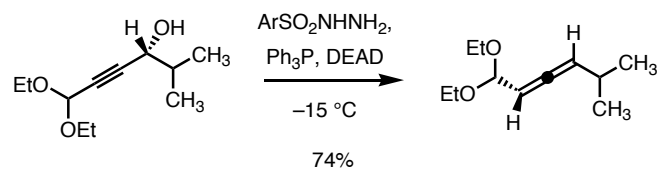


Myers, A. G.; Zheng, B. *Tetrahedron Lett.* **1996**, *37*, 4841-4844.

- In addition, allenes can be prepared stereospecifically from propargylic alcohols.



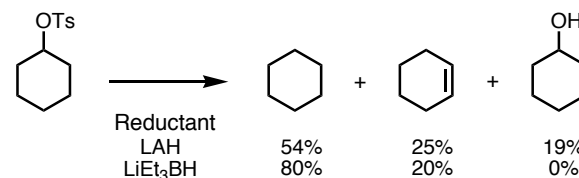
- Example



Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492-4493.

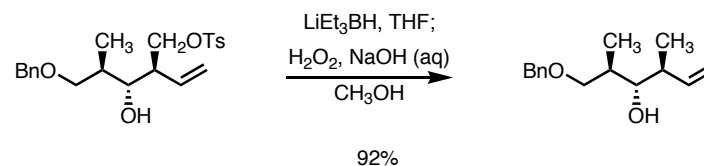
Reduction of Alkyl Tosylates

- p*-Toluenesulfonate ester derivatives of alcohols are reduced to the corresponding alkanes with certain powerful metal hydrides.
- Among hydride sources, lithium triethylborohydride (Super Hydride, LiEt₃BH) has been shown to rapidly reduce alkyl tosylates efficiently, even those derived from hindered alcohols.



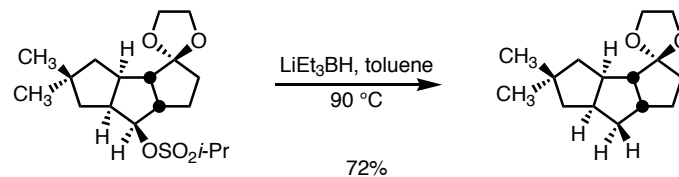
Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1976**, *41*, 3064-3066.

- Examples



Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, *112*, 5290-5313.

- In the following example, selective C-O bond cleavage by LiEt₃BH could only be achieved with a 2-propanesulfonate ester. The corresponding mesylate and tosylate underwent S-O bond cleavage when treated with LiEt₃BH.



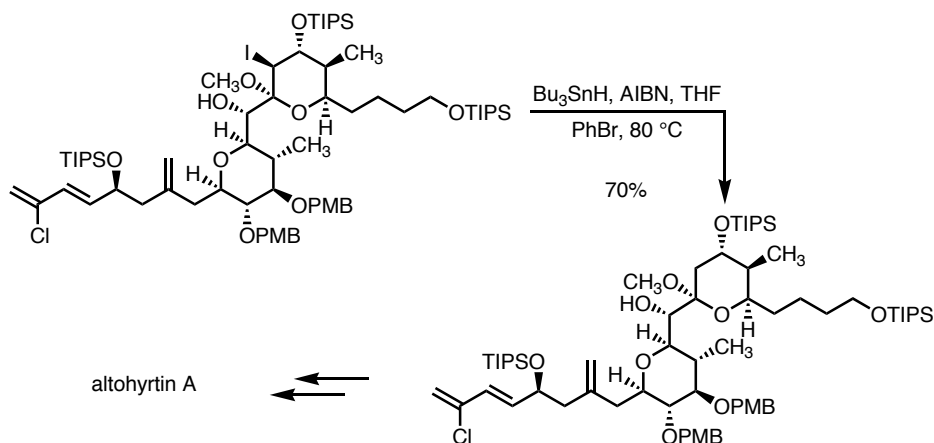
Hua, D. H.; Venkataraman, S.; Ostrander, R. A.; Sinai, G.-Z.; McCann, P. J.; Coulter, M. J.; Xu, M. *J. Org. Chem.* **1988**, *53*, 507-515.

Radical Dehalogenation

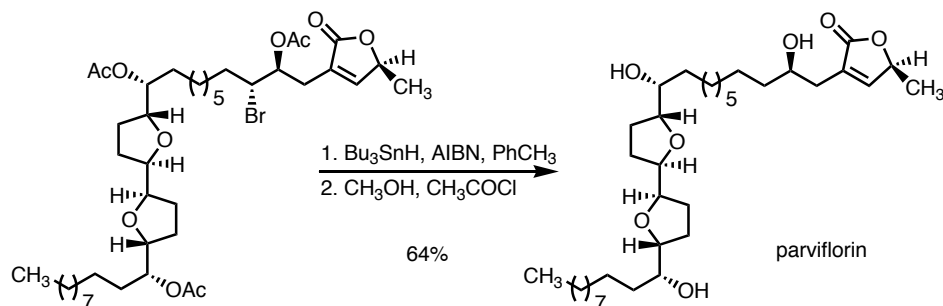
- Alkyl bromides and iodides are reduced efficiently to the corresponding alkanes in a free-radical chain mechanism with tri-*n*-butyltin hydride.
- The reduction of chlorides usually requires more forcing reaction conditions and alkyl fluorides are practically unreactive.
- The reactivity of alkyl halides parallels the thermodynamic stability of the radical produced and follows the order: tertiary > secondary > primary.
- Triethylboron-oxygen is a highly effective free-radical initiator. Reduction of bromides and iodides can occur at $-78\text{ }^{\circ}\text{C}$ with this initiator.

Neumann, W. P. *Synthesis* **1987**, 665-683.

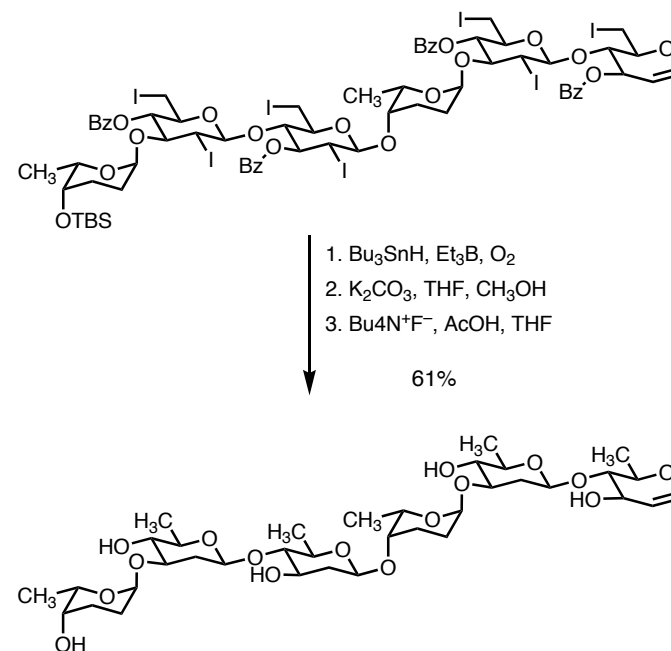
Miura, K.; Ichinose, Y.; Nozaki, K.; Fugami, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 143-147.



Guo, J.; Duffy, K. J.; Stevens, K. L.; Dalko, P. I.; Roth, R. M.; Hayward, M. M.; Kishi, Y. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 187-196.

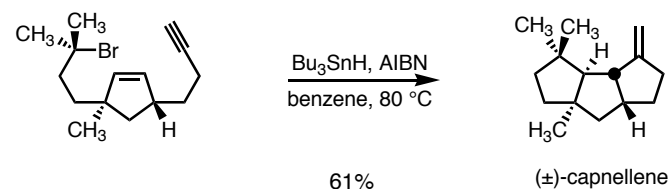


Trost, B. M.; Calkins, T. L.; Bochet, C. G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2632-2635.

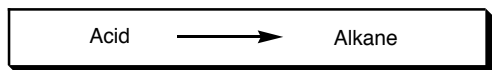


Roush, W. R.; Bennett, C. E. *J. Am. Chem. Soc.* **2000**, *122*, 6124-6125.

- In the following example, the radical generated during the dehalogenation reaction undergoes a tandem radical cyclization.

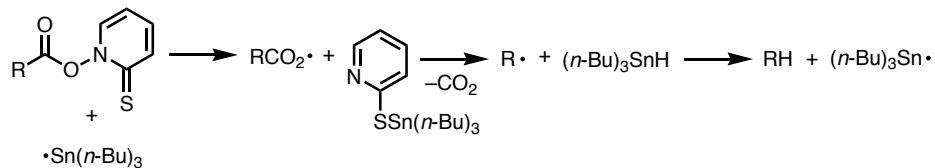


Curran, D. E.; Chen, M.-H. *Tetrahedron Lett.* **1985**, *26*, 4991-4994.



Barton Decarboxylation

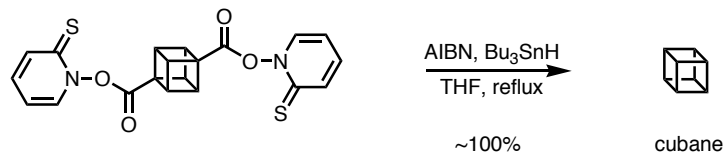
- *O*-Esters of thiohydroxamic acids are reduced in a radical chain reaction by tin hydride reagents.
- These are typically prepared by the reaction of commercial *N*-hydroxypyridine-2-thione with activated carboxylic esters.



Barton, D. H. R.; Circh, D.; Motherwell, W. B. *J. Chem. Soc., Chem. Commun.* **1983**, 939-941.

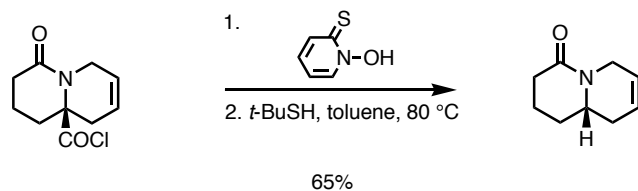
Barton, D. H. R.; Bridon, D.; Fernandez-Picot, I.; Zard, S. Z. *Tetrahedron* **1987**, 43, 2733-2740.

- Examples

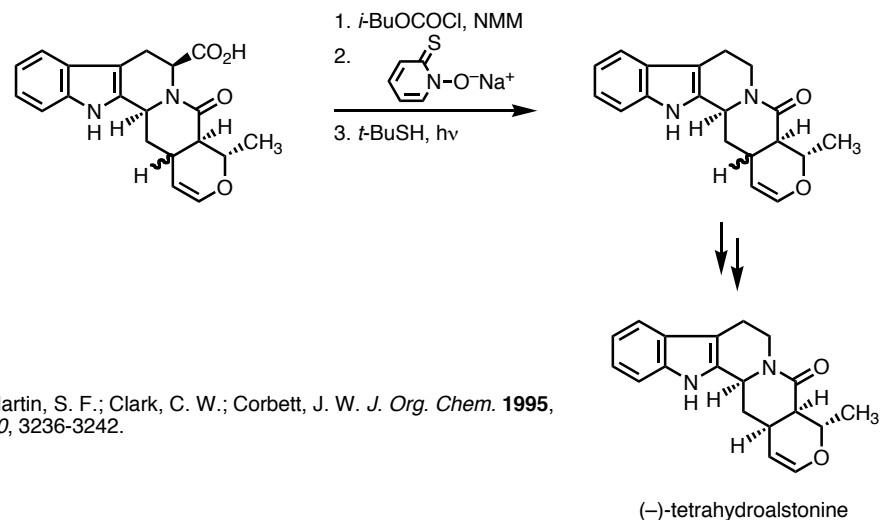


Eaton, P. E. *Angew. Chem., Int. Ed. Engl.* **1992**, 31, 1421-1436.

- The Barton decarboxylation is known to be stereoselective in rigid bicycles.

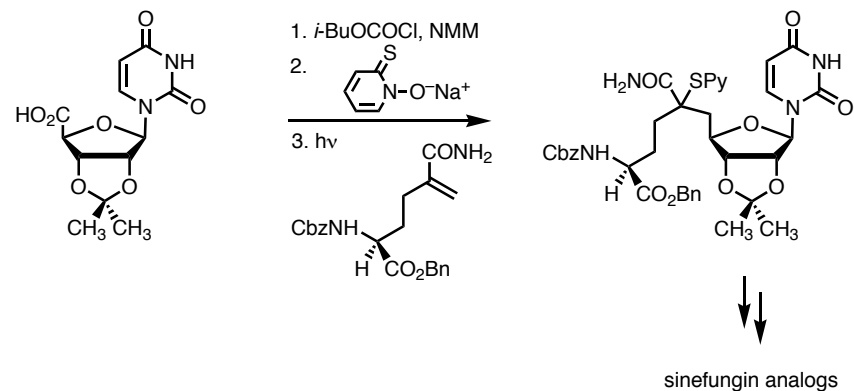


Diedrichs, N.; Westermann, B. *Synlett.* **1999**, 1127-1129.

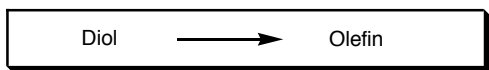


Martin, S. F.; Clark, C. W.; Corbett, J. W. *J. Org. Chem.* **1995**, 60, 3236-3242.

- In the following example, the alkyl radical generated from the decarboxylation reaction was trapped with an electron-deficient olefin. This produced a second radical intermediate that continued the chain to give the stereoisomeric mixture of products shown.



Barton, D. H. R.; Géro, S. D.; Lawrence, F.; Robert-Gero, M.; Quiclet-Sire, B.; Samadi, M. *J. Med. Chem.* **1992**, 35, 63-67.



General Reference:

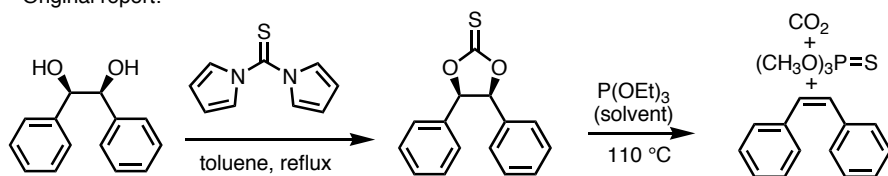
Block, E. *Org. React.* **1984**, 30, 457.

Corey-Winter Olefination:

This is a two-step procedure. The diol is converted to a thioncarbonate by addition of thiocarbonyldiimidazole in refluxing toluene. The intermediate thioncarbonate is then desulfurized (with concomitant loss of carbon dioxide) upon heating in the presence of a trialkylphosphite.

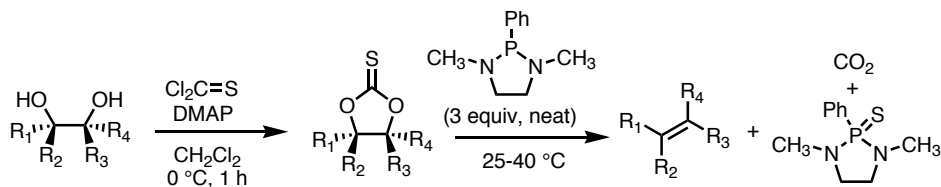
The elimination is stereospecific.

Original report:

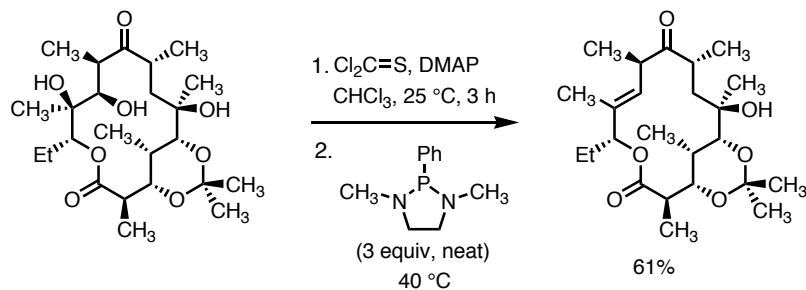


Corey, E. J.; Winter, R. A. E. *J. Am. Chem. Soc.* **1963**, 85, 2677.

Milder conditions have been reported for both the formation of the thioncarbonate intermediate and the subsequent decomposition to the desired olefin.

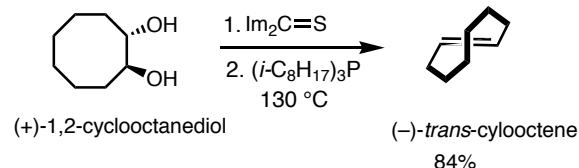


These milder conditions have been used effectively for the olefination of highly functionalized diols:



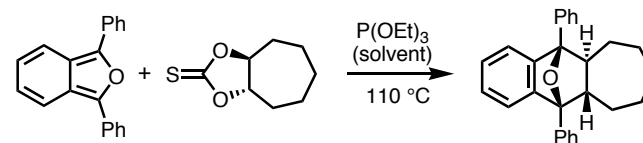
Corey, E. J.; Hopkins, P. B. *Tetrahedron Lett.* **1982**, 23, 1979.

This method has been useful in the preparation of highly strained *trans*-cycloalkenes:



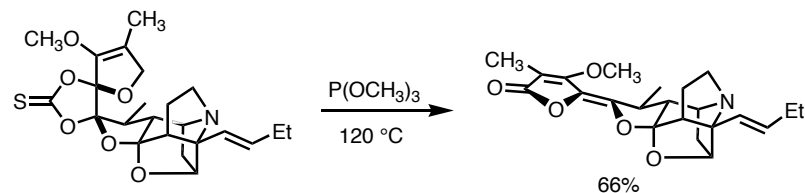
Corey, E. J.; Shulman, J. I. *Tetrahedron Lett.* **1968**, 8, 3655.

In an initial attempt to prepare *trans*-cycloheptene, the only product observed was the *cis*-isomer. Performing the olefination reaction in the presence of 2,5-diphenyl-3,4-isobenzofuran traps the highly strained olefin before isomerization to the *cis*-isomer can occur.



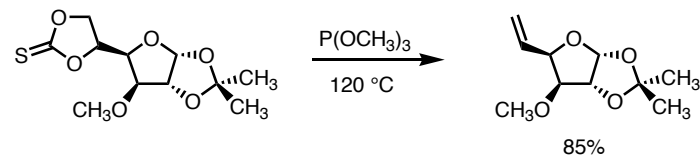
Corey, E. J.; Winter, R. A. E. *J. Am. Chem. Soc.* **1965**, 87, 934.

Synthesis examples:



Bruggemann, M.; McDonald, A. I.; Overman, L. E.; Rosen, M. D.; Schwink, L.; Scott, J. P. *J. Am. Chem. Soc.* **2003**, 125, 15284.

Preparation of Unsaturated Sugars:

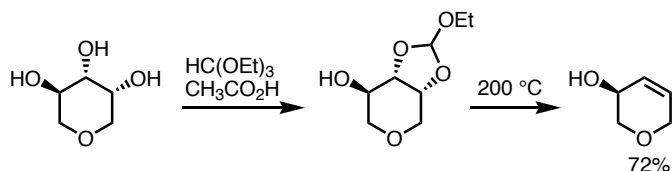


Barton, D. H. R.; Stick, R. V. *J. Chem. Soc., Perkin Trans. 1*, **1975**, 1773.

Eastwood Deoxygenation:

Crank, G.; Eastwood, F. W. *Aust. J. Chem.* **1964**, *17*, 1385.

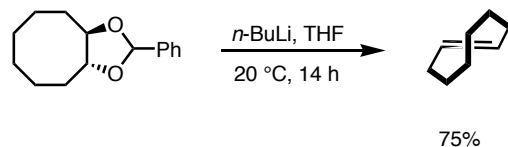
- A vicinal diol is treated with ethyl orthoformate at high temperature (140-180 °C), followed by pyrolysis of the resulting cyclic orthoformate (160-220 °C) in the presence of a carboxylic acid (typically acetic acid).
- The elimination is stereospecific.
- Not suitable for functionalized substrates.



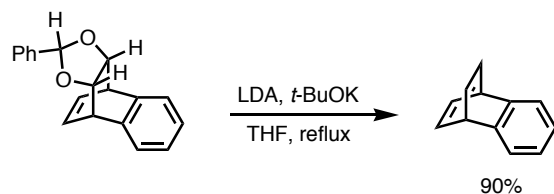
Fleet, G. W. J.; Gough, M. J. *Tetrahedron Lett.* **1982**, *23*, 4509.

Base Induced Decomposition of Benzylidene Acetals:

- The elimination is stereospecific.
- Long reaction times and high temperatures under extremely basic conditions make this an unsuitable method for functionalized substrates.



Hines, J. N.; Peagram, M. J.; Whitham, G. H.; Wright, M. *J. Chem. Soc., Chem. Commun.* **1968**, 1593.



Pu, L.; Grubbs, R. H.; *J. Org. Chem.* **1994**, *59*, 1351.

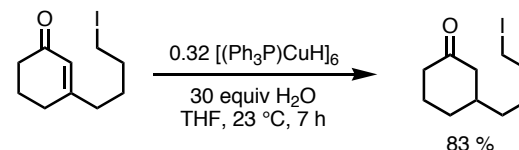
α,β -Unsaturated Carbonyl \longrightarrow Carbonyl

Catalytic Hydrogenation:

- The carbon-carbon double bond of α,β -unsaturated carbonyl compounds can be reduced selectively by catalytic hydrogenation, affording the corresponding carbonyl compounds.
- This method is not compatible with olefins, alkynes, and halides.

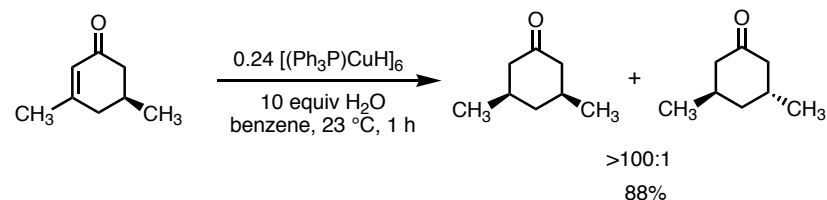
Stryker Reduction:

- α,β -Unsaturated carbonyl compounds undergo selective 1,4-reduction with $[(\text{Ph}_3\text{P})\text{CuH}]_6$.
- $[(\text{Ph}_3\text{P})\text{CuH}]_6$ is stable indefinitely, provided that the reagent is stored under an inert atmosphere. The reagent can be weighed quickly in the air, but the reaction solutions must be deoxygenated. The reaction is unaffected by the presence of water (in fact, deoxygenated water is often added as a proton source).
- α,β -Unsaturated ketones, esters, aldehydes, nitriles, sulfones, and sulfonates are all suitable substrates.
- This method is compatible with isolated olefins, halides, and carbonyl groups (in contrast to reduction by catalytic hydrogenation).
- Each of the six hydrides of the copper cluster can be transferred.
- TBS-Cl is often added during the reduction of α,β -unsaturated aldehydes to suppress side reactions arising from aldol condensation of the copper enolate intermediates.



Koenig, T. M.; Daeuble, J. F.; Brestensky, D. M.; Stryker, J. M. *Tetrahedron Lett.* **1990**, *31*, 3237.

- The reduction is highly stereoselective, with addition occurring to the less hindered face of the olefin:



Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291.