

Carey & Sundberg Chapter 5 problems: 1a,b,c,d,f,h,j; 2; 3a-g, n,o; 4b,j,k,l; 9; 11;
 Smith: Chapter 4 March: Chapter 19

Reductions

1. Hydrogenation
2. Boron Reagents
3. Aluminium Reagents
4. Tin Hydrides
5. Silanes
6. Dissolving Metal Reductions

Hydrogenations

Heterogeneous Catalytic Hydrogenation

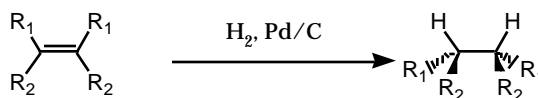
Transition metals absorbed onto a solid support

metal: Pd, Pt, Ni, Rh

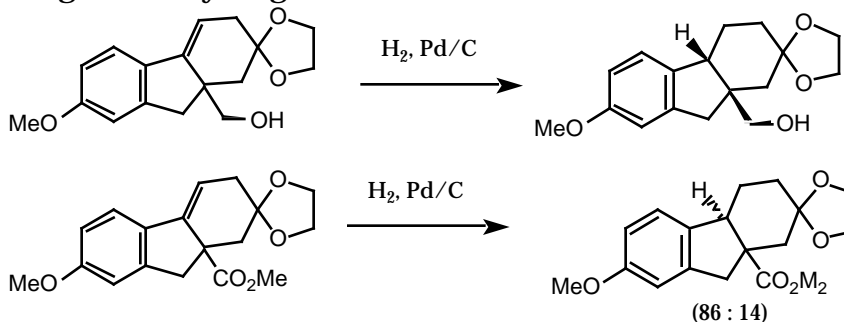
support: Carbon, alumina, silica

solvent: EtOH, EtOAc, Et₂O, hexanes, etc.

- Reduction of olefins & acetylenes to saturated hydrocarbons.
- Sensitive to steric effects and choice of solvent
- Polar functional groups, i.e. hydroxyls, can sometimes direct the delivery of H₂.
- Cis addition of H₂.

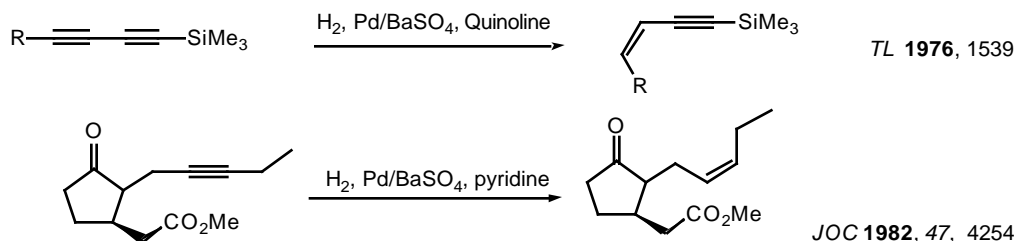


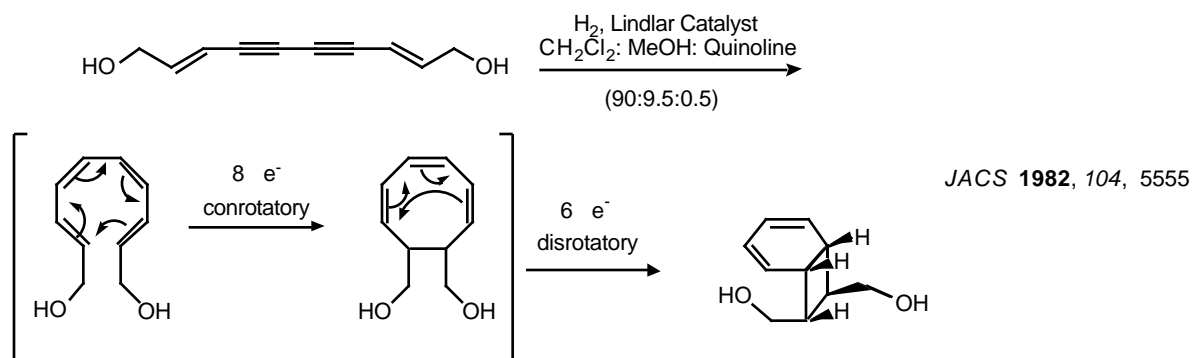
- Catalyst can be "poisoned"
- Directed heterogeneous hydrogenation



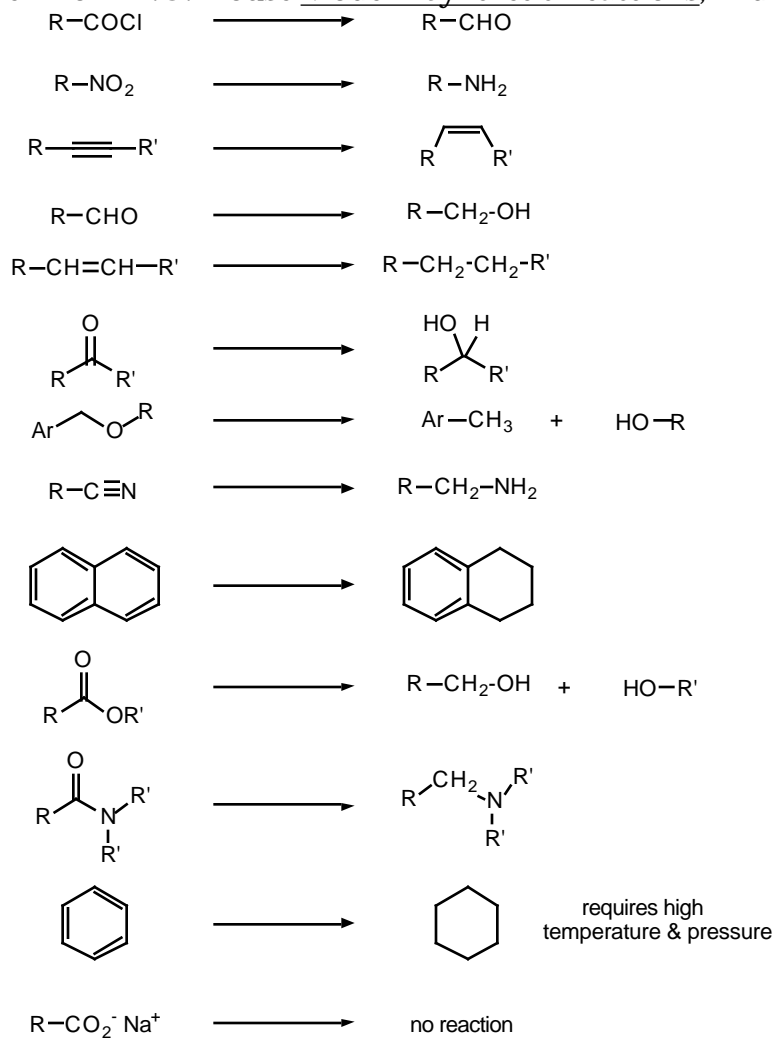
Lindlar Catalyst (Pd/ BaSO₄/ quinoline)- partially poisoned to reduce activity; will only reduce the most reactive functional groups.

acetylenes + H₂, Pd/BaSO₄/ quinoline cis olefins (Lindlar Reduction)
 Acid Chlorides + H₂, Pd/BaSO₄ Aldehydes (Rosemund Reduction)
Org. Rxn. **1948**, 4, 362



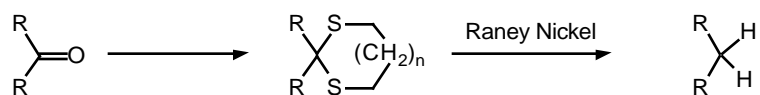


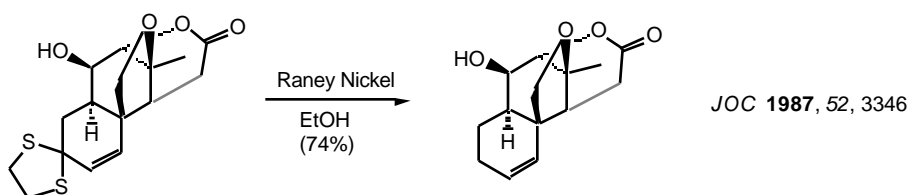
Ease of Reduction: (taken from H.O. House Modern Synthetic Reactions, 2nd edition)



Raney Nickel Desulfurization,

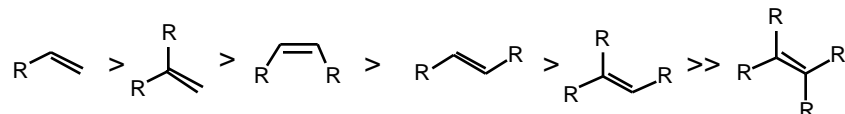
Reviews: *Org. Rxn.* **1962**, 12, 356; *Chem. Rev.* **1962**, 62, 347.



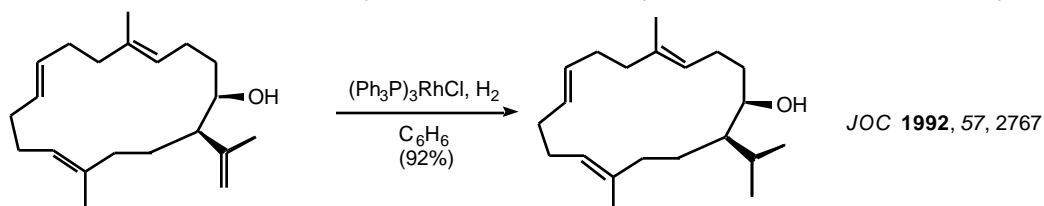


Homogeneous Catalytic Hydrogenation

- catalyst is soluble in the reaction medium
- catalyst not "poisoned" by sulfur
- very sensitive to steric effects
- terminal olefins faster than internal; cis olefins faster than trans



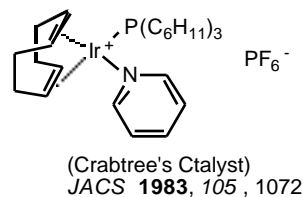
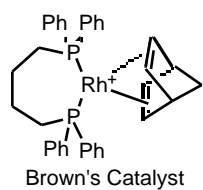
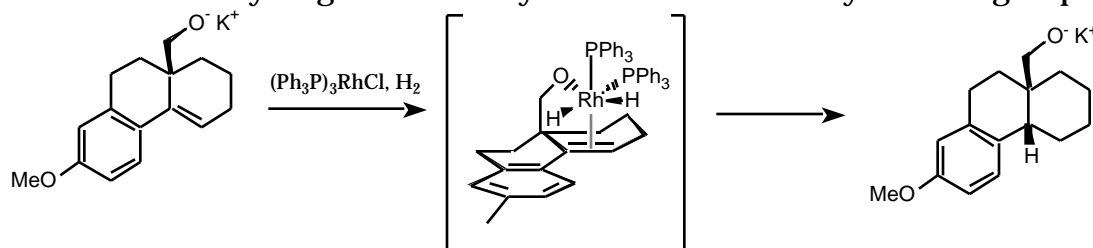
- $(Ph_3P)_3RhCl$ (Wilkinson's Catalyst); $[R_3P Ir(COD)py]^+ PF_6^-$ (Crabtree's Catalyst)



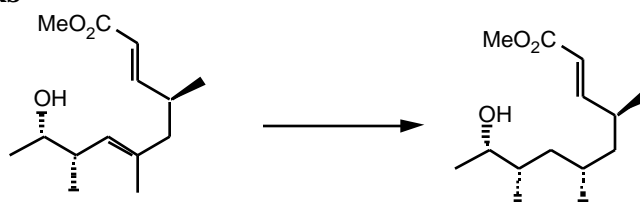
Directed Hydrogenation

Review: *Angew. Chem. Int. Ed. Engl.* **1987**, 26, 190

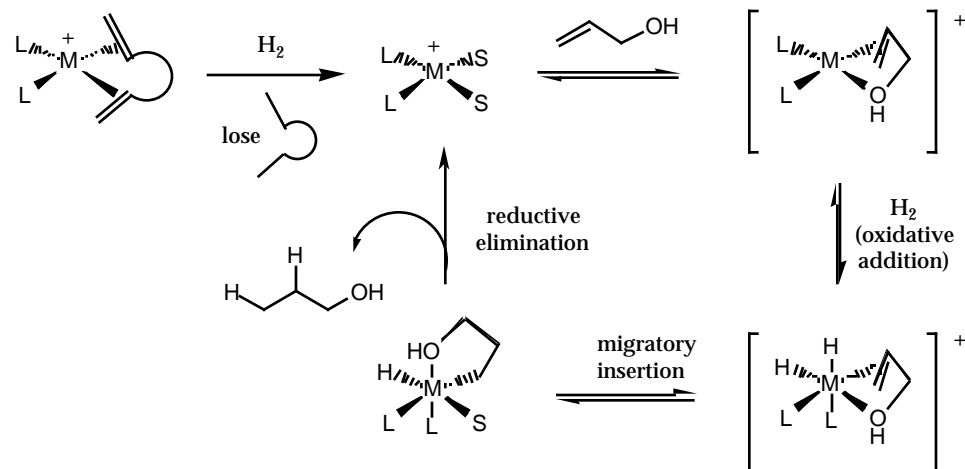
- Diastereocontrolled hydrogenation of allylic alcohols directed by the -OH group



Regioselective Hydrogenation- allylic and homoallylic alcohols are hydrogenated faster than isolated double bonds



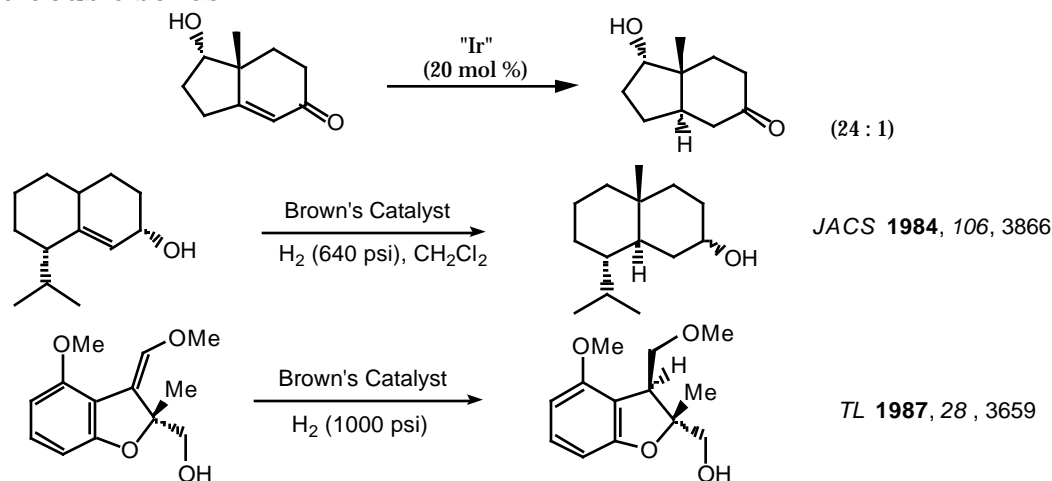
mechanism:



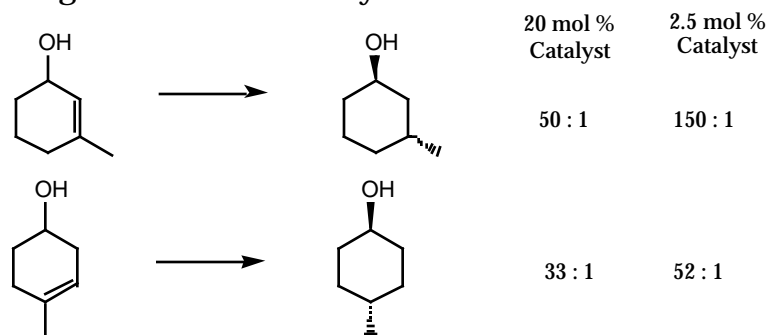
Diastereoselective Hydrogenation: since -OH directs the H_2 , there is a possibility for control of stereochemistry

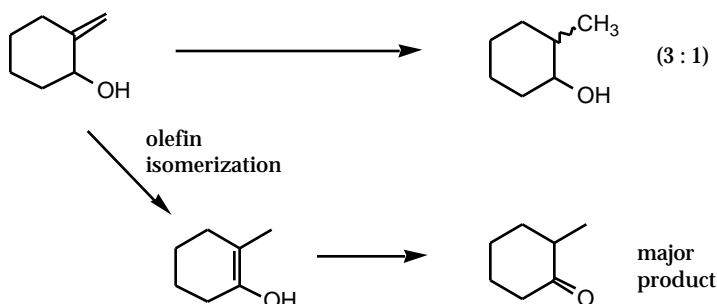
- sensitive to: H_2 pressure
- catalyst conc.
- substrate conc.
- solvent.

Regioselective Hydrogenation- allylic and homoallylic alcohols are hydrogenated faster than isolated double bonds



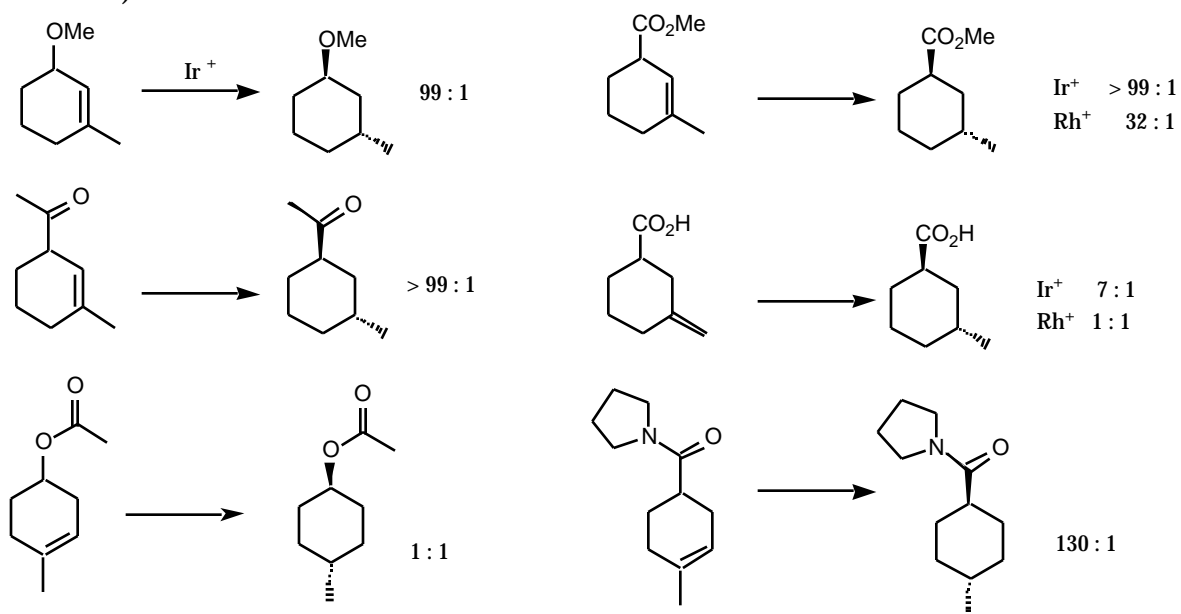
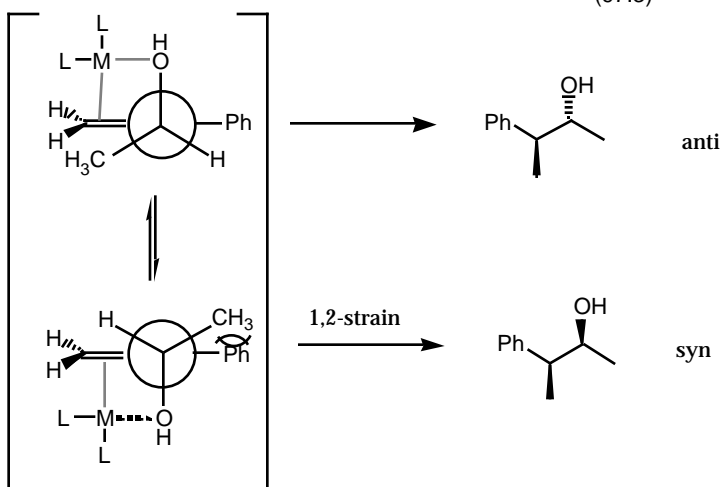
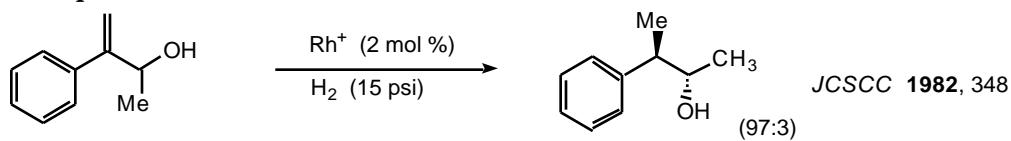
Selectivity is often higher with lower catalyst concentration:

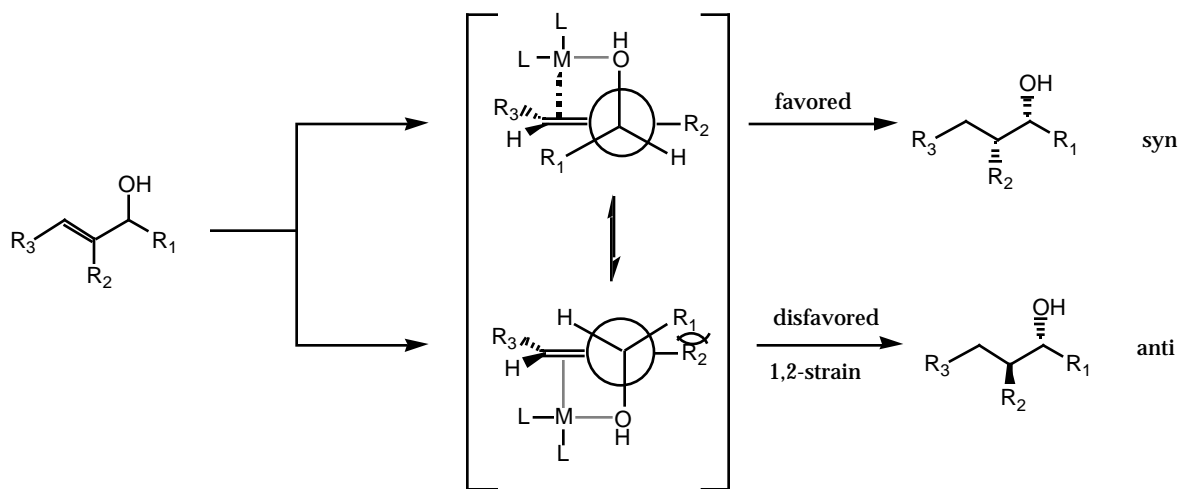


Olefin Isomerization:


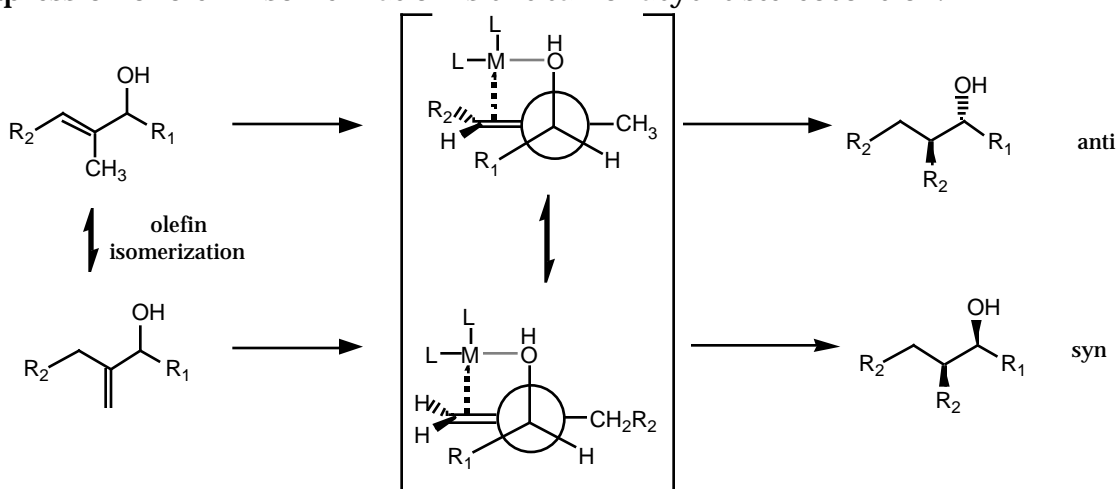
- Conducting the hydrogenation at high H₂ pressures suppresses olefin isomerization and often gives higher diastereoselectivity.

Other Lewis basic groups can direct the hydrogenation. (Ir seems to be superior to Rh for these cases)


Acyclic Examples


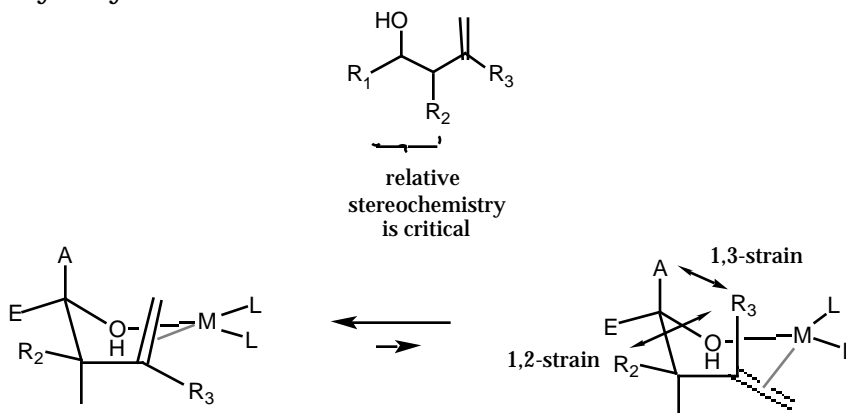


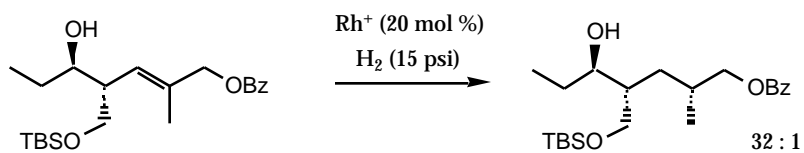
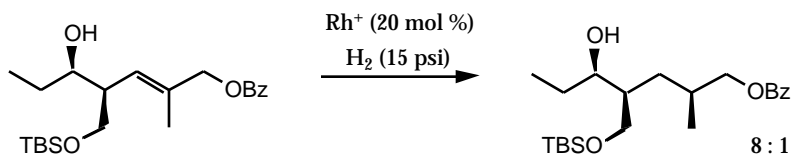
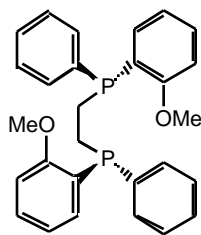
- Suppression of olefin isomerization is critical for acyclic stereocontrol !



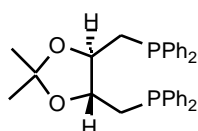
- Rh⁺ catalyst is more selective than Ir⁺ for acyclic stereoselection.

Acyclic homoallylic systems:

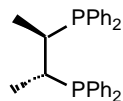


Tetrahedron Lett. **1985**, 26, 6005*Asymmetric Homogeneous Hydrogenation***- Chiral ligands for homogeneous hydrogenation of olefins and ketones**

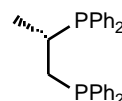
DIPAMP



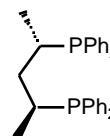
DIOP



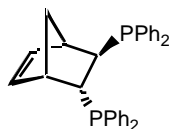
CHIRAPHOS



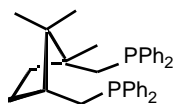
R = -CH₃ PROPPOS
 = -Ph PHENPHOS
 = -C₆H₁₁ CYCPHOS



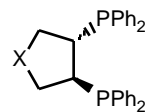
DBPP



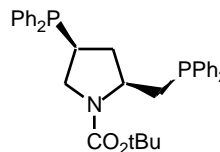
NORPHOS



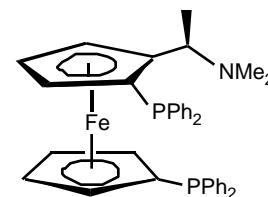
CAMPHOS



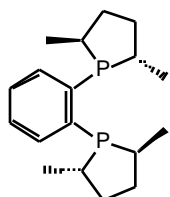
X = CH₂ DPCP
 X = N-R PYRPHOS



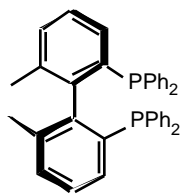
BPPM



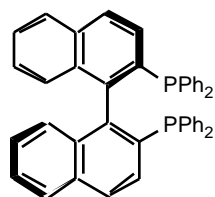
PPPFA



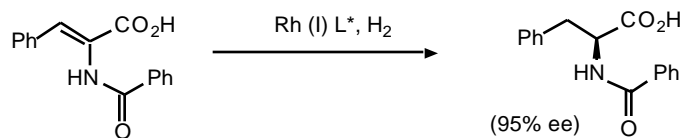
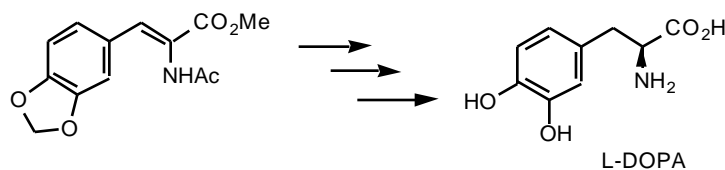
DUPHOS



DIPHEMP

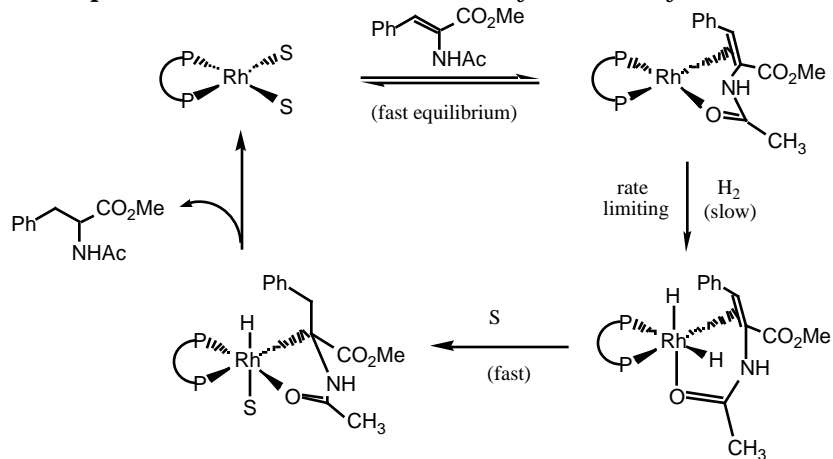


BINAP

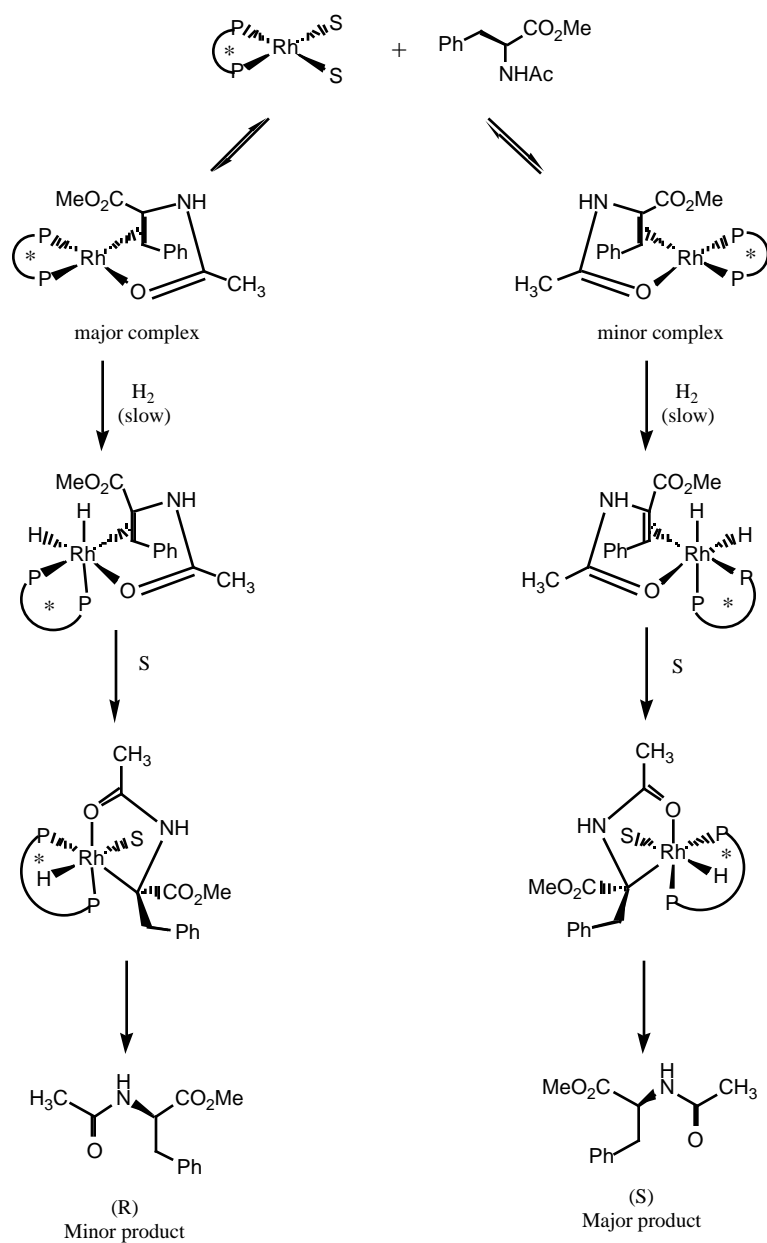
ACR **1983**, 16, 106.

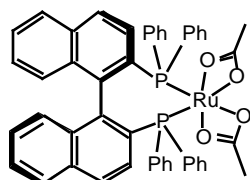
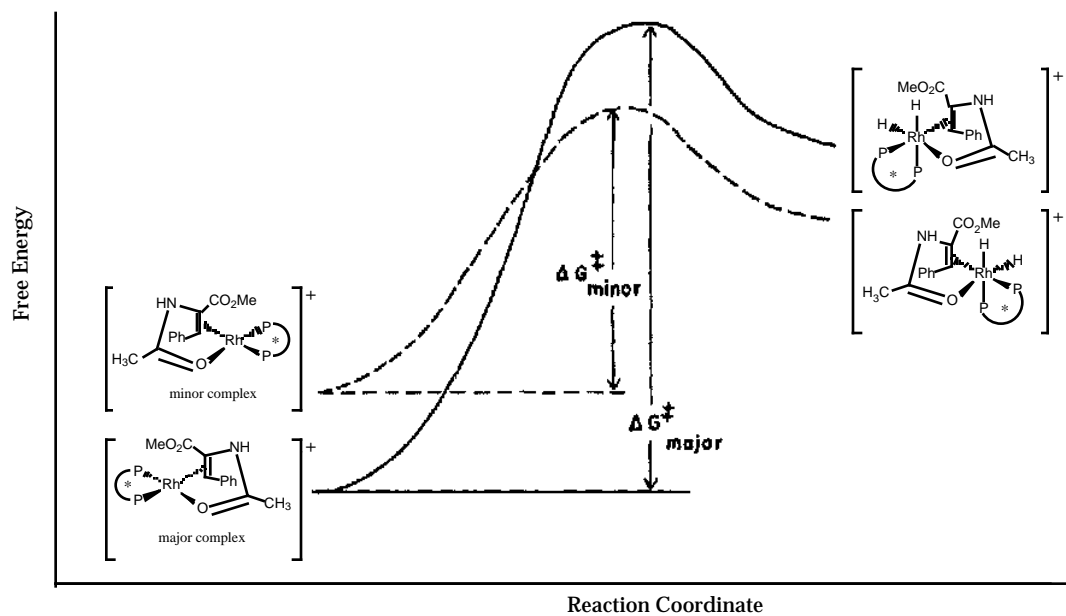
DIOP	85% ee
DIPAMP	96% ee
PPPFA	93% ee
BINAP	100% ee
NORPHOS	95% ee
BPPM	91% ee

General Mechanism: J. Halpern *Science* **1982**, 217, 401 *Asymmetric Synthesis* **1985**, vol 5, 41.

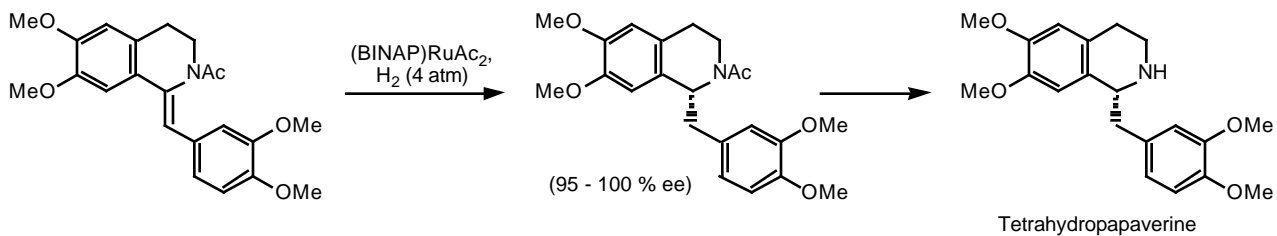
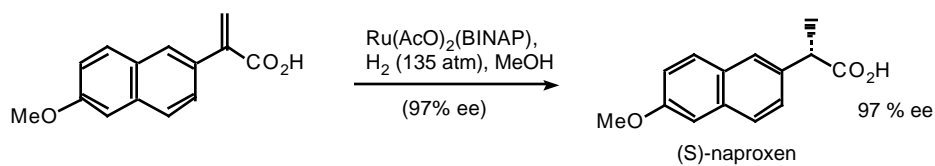
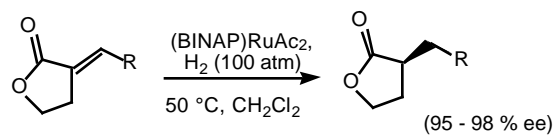
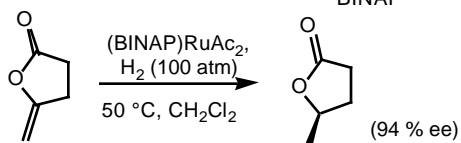


Detailed Mechanism:

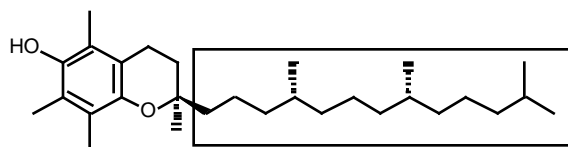
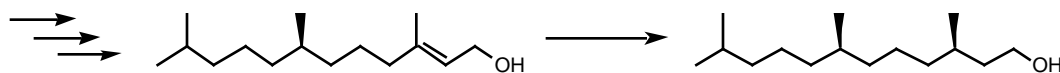
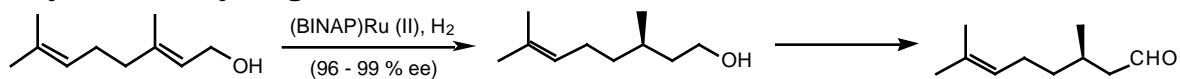




ACR 1990, 23, 345.

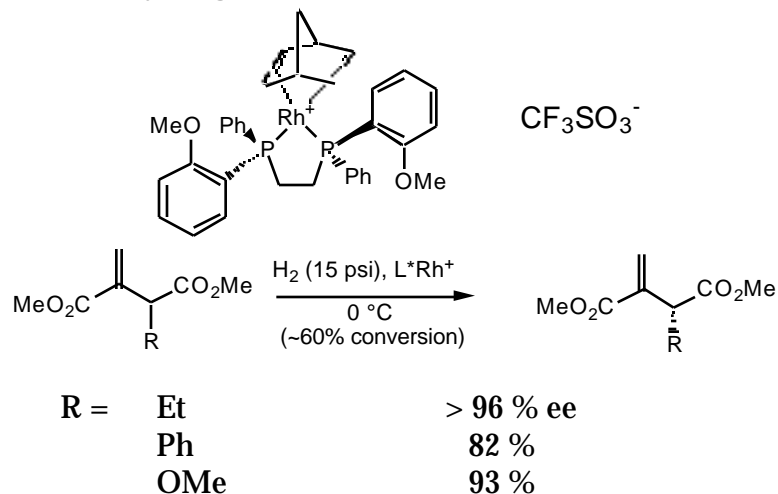
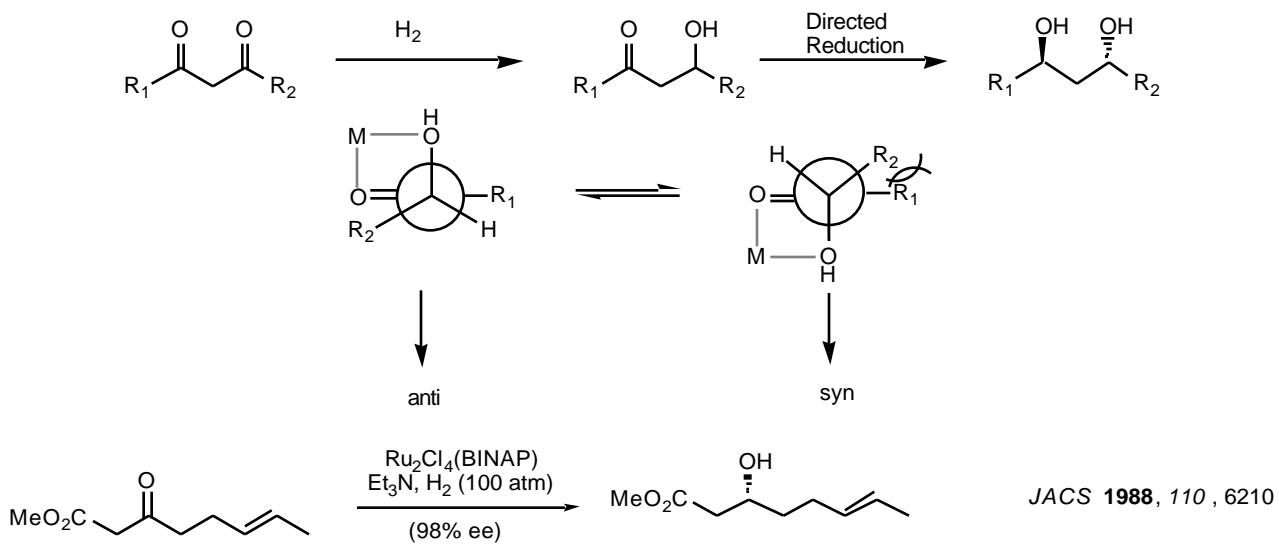
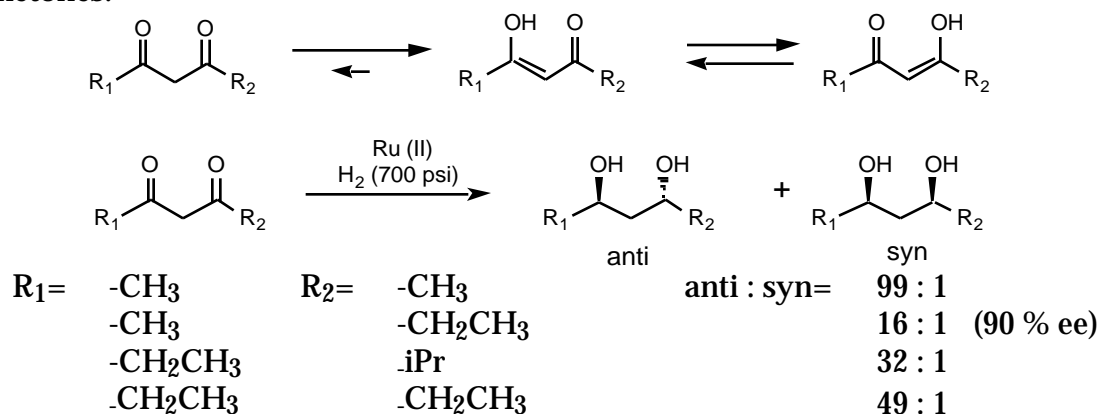


Directed Asymmetric Hydrogenation



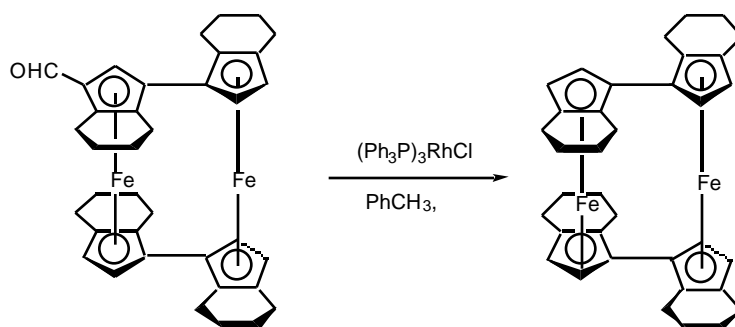
J. Am. Chem. Soc. 1987, 109, 1596

Kinetic Resolution by Directed Hydrogenation

Hydrogenation of Carbonyls
1,3-diketones:

Decarbonylations

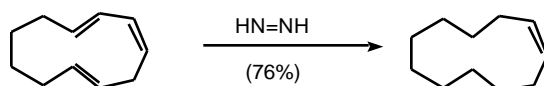
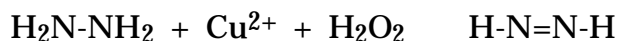
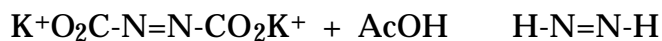




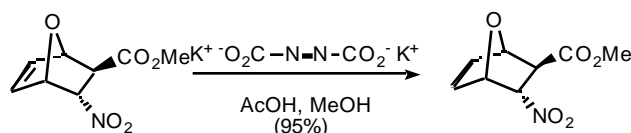
JOC 1990, 55, 3688

Diimide $\text{HN}=\text{NH}$ Review: *Organic Reactions* **1991**, 40J. *Chem. Ed.* **1965**, 254

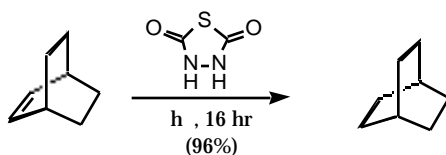
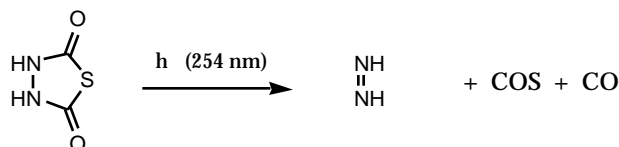
- Only reduces double bonds
- Syn addition of H_2
- will selectively reduce the more strained double bond
- Unstable reagent which is generated *in situ*



ACIEE 1965, 271



JACS 1986, 108, 5908



TL 1993, 34, 4137

Metal HydridesReview on Metal Hydride Selectivity: *Chem Soc Rev.* **1976**, 5, 23*Comprehensive Organic Synthesis* **1991**, vol 8, 1.**Boron Hydrides** Review: *Chem. Rev.* **1986**, 86, 763.

- NaBH_4 reduces ketones and aldehydes
- LiBH_4 reduces ketones, aldehydes, esters and epoxides. THF soluble
- $\text{LiBH}_4/\text{TMSCl}$ stronger reducing agent. *ACIEE* **1989**, 28, 218.
- $\text{Zn}(\text{BH}_4)_2$ reduces ketones and aldehydes
- $\text{R}_4\text{N} \text{BH}_4$ organic soluble (CH_2Cl_2) borohydrides. *Synth Commun.* **1990**, 20, 907
- LiEt_3BH reduces ketones, aldehydes, esters, epoxides and R-X
- $\text{Li s-Bu}_3\text{BH}$ reduces ketones, aldehydes, esters and epoxides (hindered borohydride)
- $\text{Na}(\text{CN})\text{NH}_3$ reduces iminium ions, ketones and aldehydes
- $\text{Na}(\text{AcO})_3\text{BH}$ reduces ketones and aldehydes (less reactive)
- NaBH_2S_3 reduces ketones and aldehydes

Sodium Borohydride NaBH₄

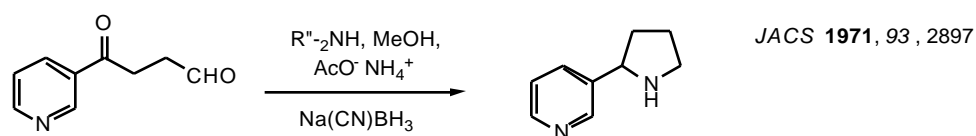
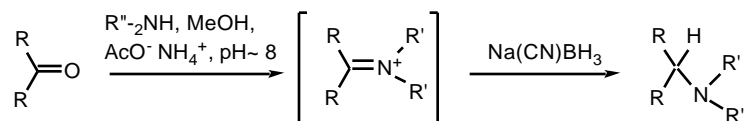
- reduces aldehydes and ketones to alcohols
- does not react with acids, esters, lactones, epoxides or nitriles.
- Additives can increase reactivity.

Sodium Cyanoborohydride Na(CN)BH₃

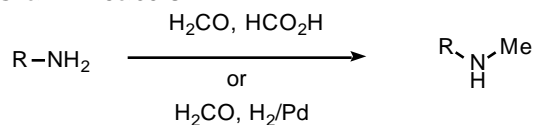
Reviews: *Synthesis* **1975**, 136; *OPPI* **1979**, 11, 201

- less reactive than NaBH₄
- used in reductive aminations (Borch Reduction)

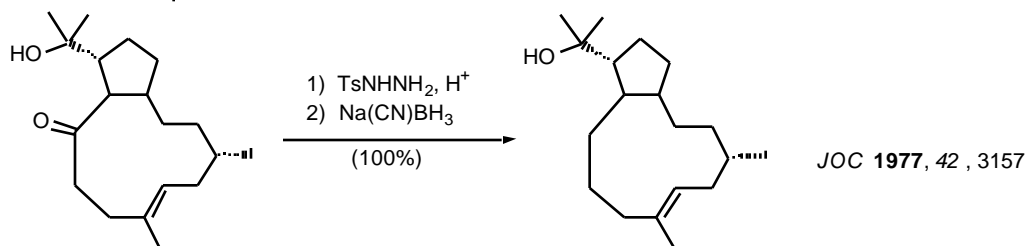
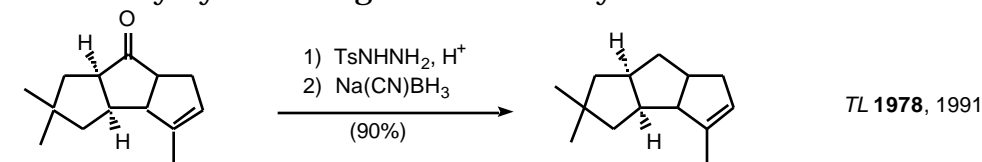
Na(CN)BH₃ reduces iminium ions much more quickly than ketones or aldehydes



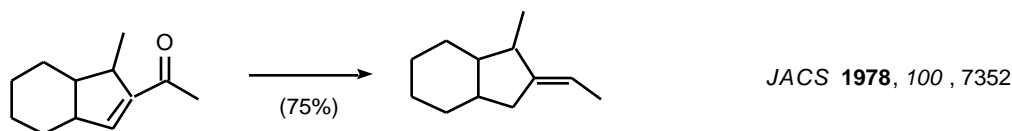
- Related to Eschweiler-Clark Reaction



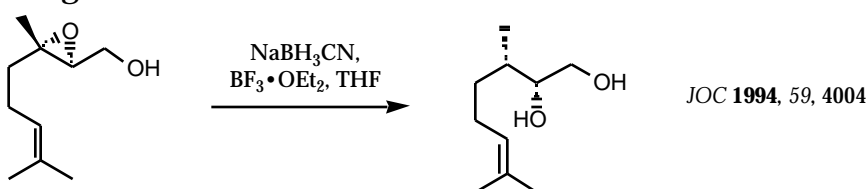
- Reduction of tosylhydrazones gives saturated hydrocarbon



- migration of the olefin occurs w/ α , β -unsaturated ketones



- Epoxide opening



NaBH_2S_3 Lalancette Reduction

Synthesis **1972**, 526 *Can. J. Chem.* **1970**, 48, 735.

$\text{NaBH}_4/\text{NiCl}_2$ *Chem. Pharm. Bull.* **1981**, 29, 1159; *Chem. Ber.* **1984**, 117, 856.

Ar-NO₂ Ar-NH₂

Ar-NO Ar-NH₂

R₂C=N-OH R₂CH-NH₂

$\text{NaBH}_4/\text{TiCl}_4$

Synthesis **1980**, 695.

R-COOH R-CH₂-OH

R-COOR' R-CH₂-OH

R-CN R-CH₂-NH₂

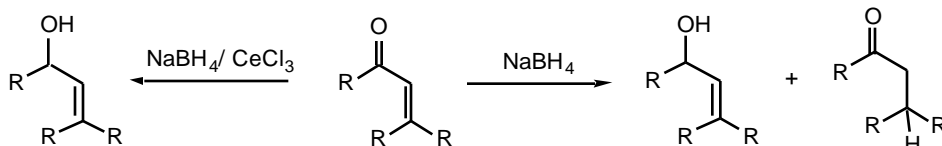
R-CONH₂ R-CH₂-NH₂

R₂C=N-OH R₂CH-NH₂

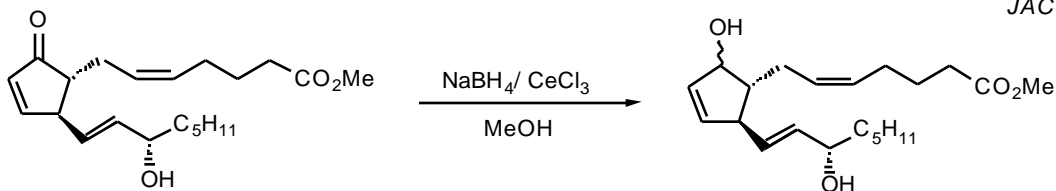
R-SO₂-R' R-S-R'

$\text{NaBH}_4/\text{CeCl}_3$ Luche Reduction

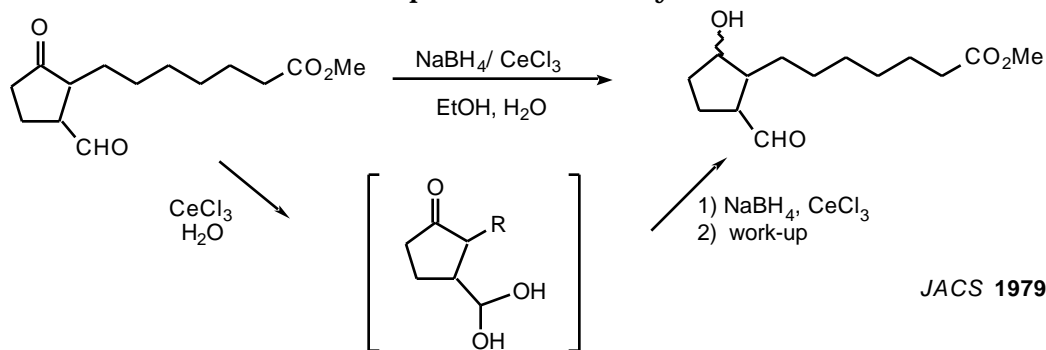
reduced, -unsaturated ketones in a 1,2-fashion



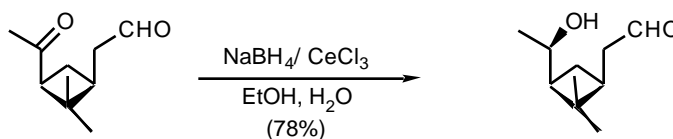
JCS **1978**, 601
JACS **1978**, 100, 2226



- selective reduction of ketones in the presence of aldehydes.



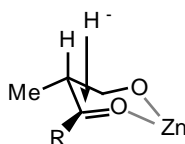
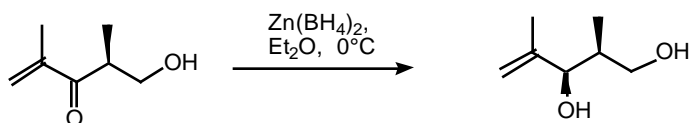
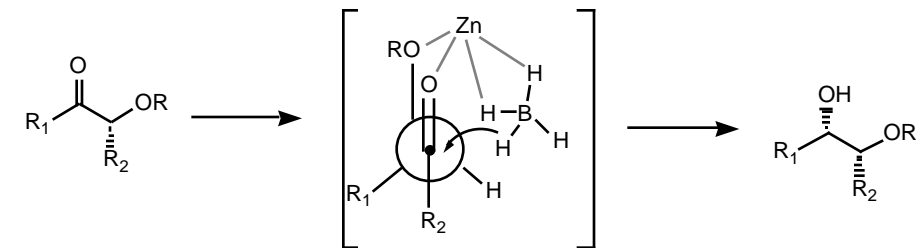
JACS **1979**, 101, 5848



Zinc Borohydride $Zn(BH_4)_2$ *Synlett* **1993**, 885.

$ZnCl_2$ (ether) + $NaBH_4$ $Zn(BH_4)_2$

- Ether solution of $Zn(BH_4)_2$ is neutral- good for base sensitive compounds
- Chelation control model

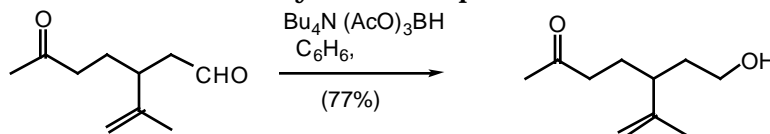


TL **1983**, 24, 2653, 2657, 2661

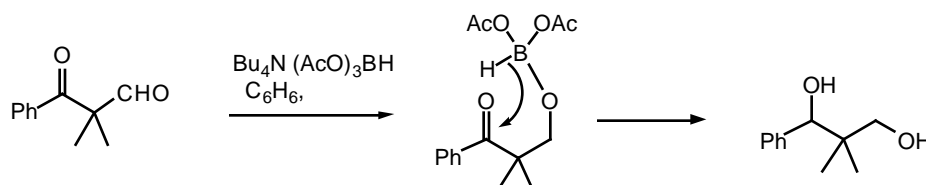
$Na^+ (AcO)_3BH$, $Me_4N^+ (AcO)_3BH$

Review: *OPPI* **1985**, 17, 317

- used in Borch reductive amination *TL* **1990**, 31, 5595; *Synlett* **1990**, 537
- selective reduction of aldehydes in the presence of ketones

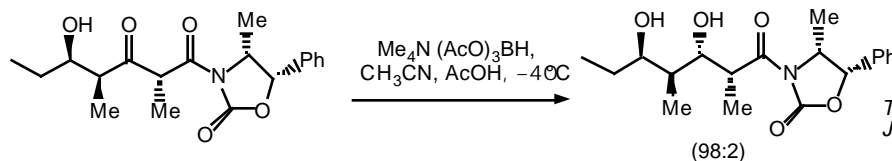


TL **1983**, 24, 4287

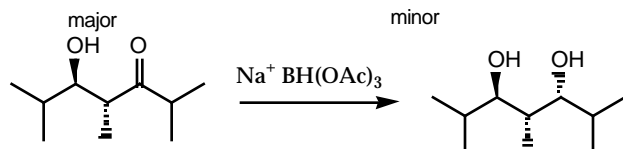
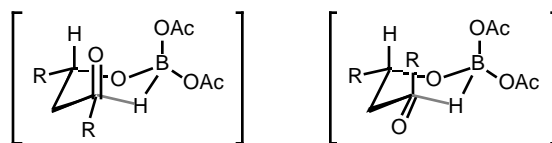


-hydroxyl-directed reduction of ketones

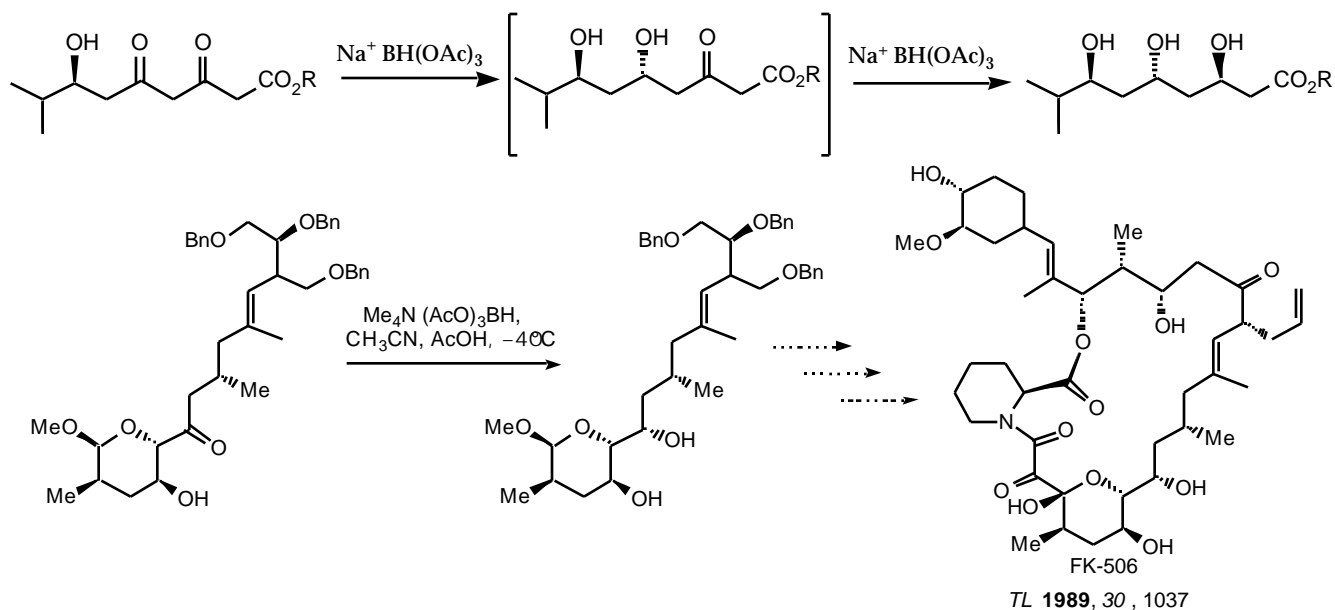
TL **1983**, 24, 273; *TL* **1984**, 25, 5449



TL **1986**, 27, 5939
JACS **1988**, 110, 3560



50 : 1



$(\text{Ph}_3\text{P})_2\text{Cu BH}_4$

reduction of acid chlorides to aldehydes
 reduction of alkyl and aryl azides to amines

JOC **1989**, 45, 3449

J. Chem. Res. (S) **1981**, 17

$\text{R}_4\text{N BH}_4$ organic soluble borohydride (CH_2Cl_2)

$\text{R}_4\text{N} = \text{BnEt}_3\text{N}$ or Bu_4N Heterocycles **1980**, 14, 1437, 1441
 reduction of amides to amines
 reduction of nitriles to amines

$\text{BnEt}_3\text{N BH}_4 / \text{Me}_3\text{SiCl}$

reduction of carboxylic acids to alcohols

Synth. Commun. **1990**, 20, 907

$\text{LiBH}_4 / \text{Me}_3\text{SiCl}$

ACIEE **1989**, 28, 218.

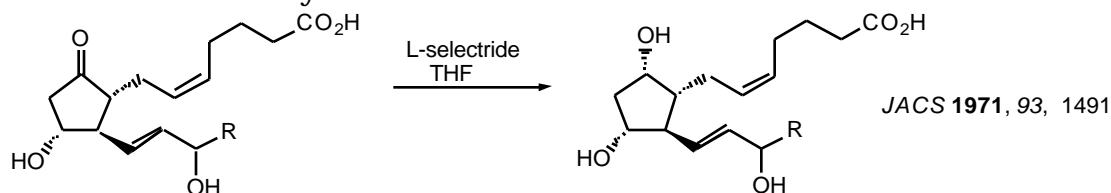
Alkyl Borohydrides

Selectrides

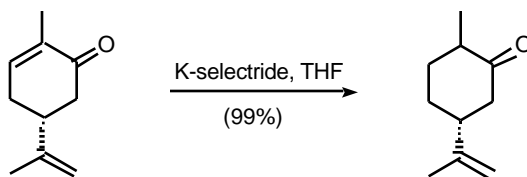


- hindered reducing agent

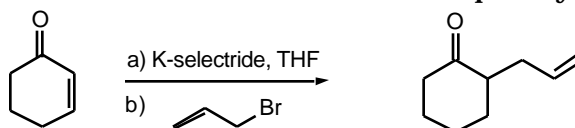
increased selectivity based on steric considerations



- selective 1,4-reductions of α,β -unsaturated carbonyl compounds.
JOC 1975, 40, 146; JOC 1976, 41, 2194



- 1,4-reduction generates an enolate which can be subsequently alkylated.



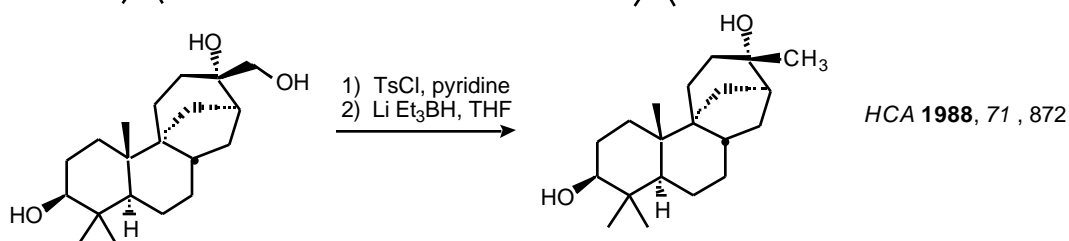
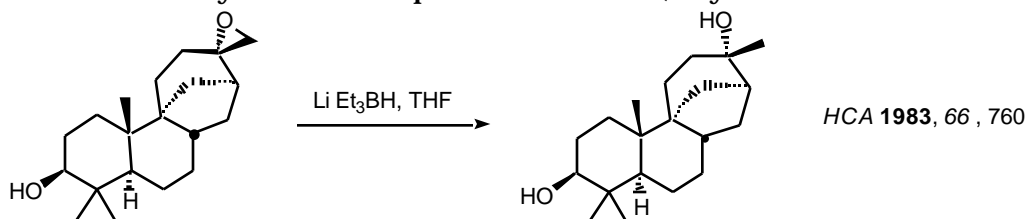
$\text{K}^+ \text{HBPh}_3$

Syn. Comm. 1988, 18, 89.

- even greater 1,4-selectivity

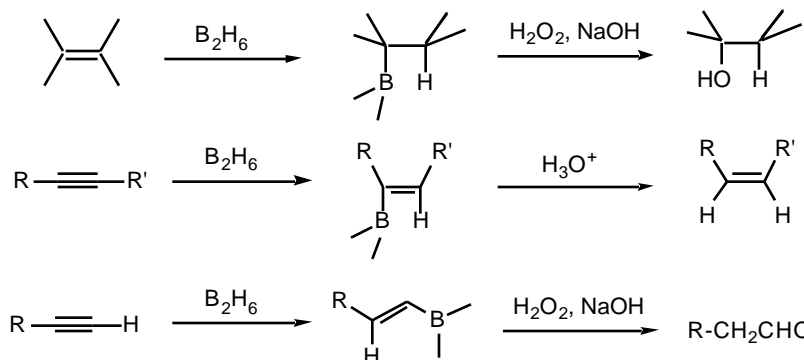
$\text{Li}^+ \text{HBET}_3$ (Super Hydride)

- very reactive hydride source
- reduces ketones, aldehydes, esters, epoxides and C-X (alkyl halides and sulfonates)

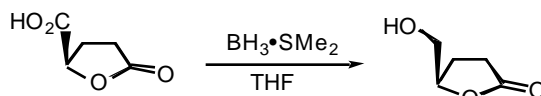


Boranes

Hydroboration

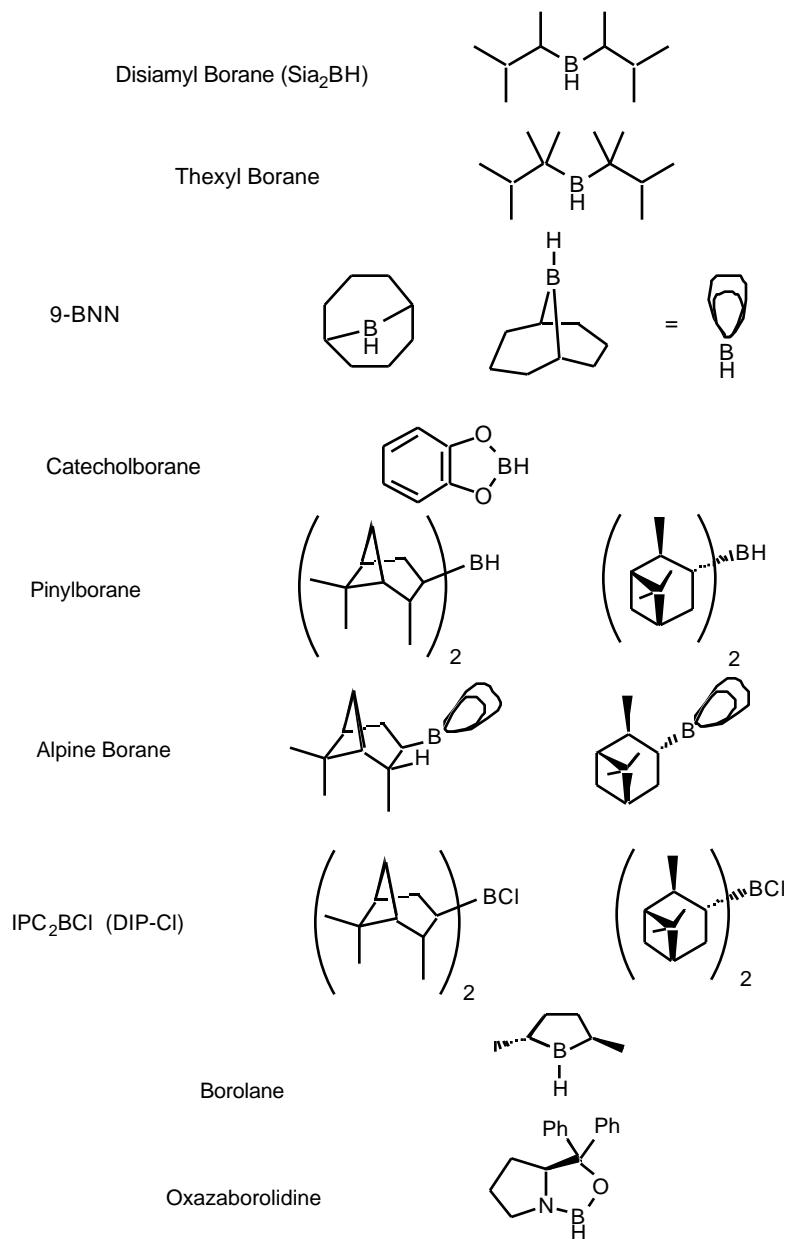


- BH_3 reduces carboxylic acids to 1° alcohols in the presence of esters, nitro and cyano groups.
- BH_3 reduces amides to amines



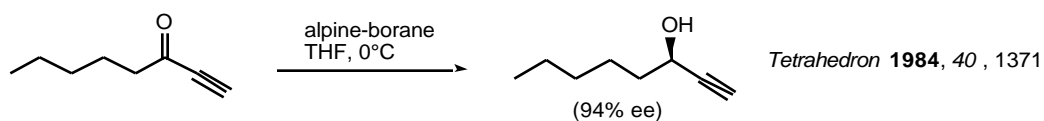
- Boranes also reduce ketones and aldehydes to the corresponding alcohols.

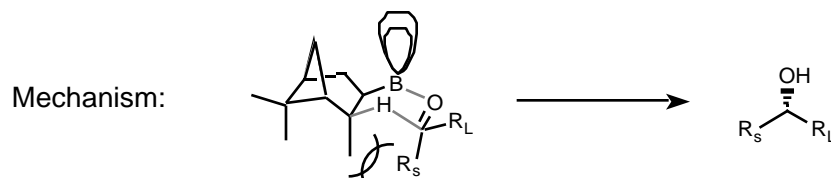
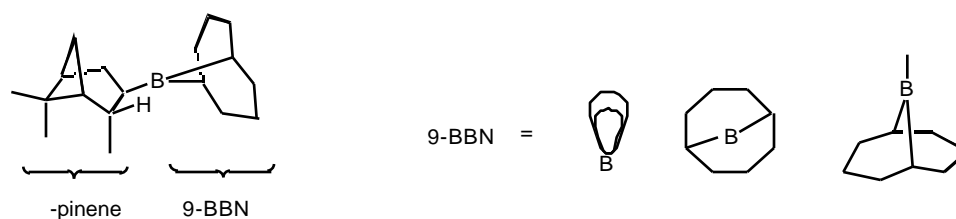
Hindered Boranes

Asymmetric Reduction of Unsymmetrical Ketones Using Chiral Boron ReagentsReview: *Synthesis* **1992**, 605.

Alpine Borane

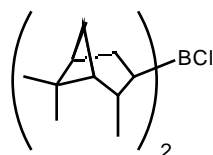
Midland Reduction

JACS **1979**, 111, 2352; *JACS* **1980**, 112, 867review: *Chem. Rev.* **1989**, 89, 1553.

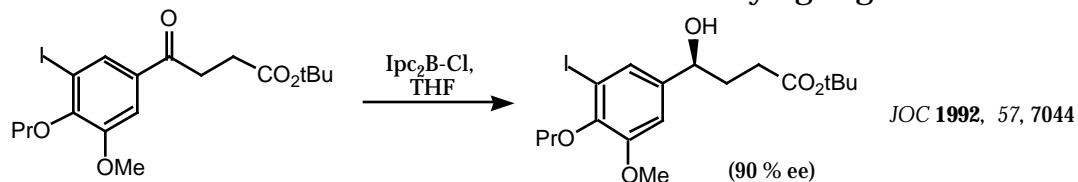


- works best for aryl- and acetylenic ketones
- because of steric hindrance, alpine-borane is fairly unreactive

Chloro Diisopinylcamphenylborane (DIP-Cl, Ipc_2BCl) H.C. Brown
 Review: ACR **1992**, 25, 16. Aldrichimica Acta **1994**, 27 (2), 43

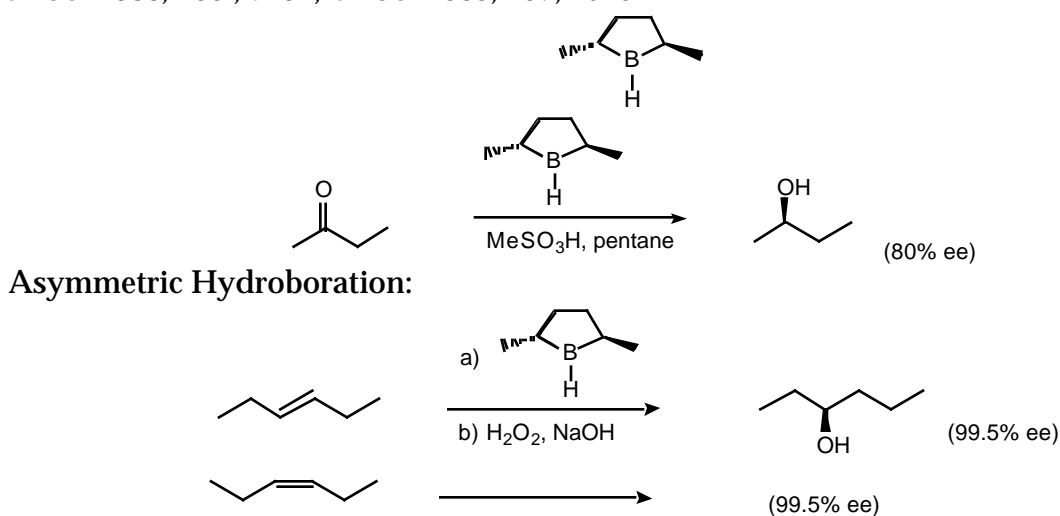


- Cl increases the Lewis acidity of boron making it a more reactive reagent
- saturated ketones are reduced to chiral alcohols with varying degrees of ee.

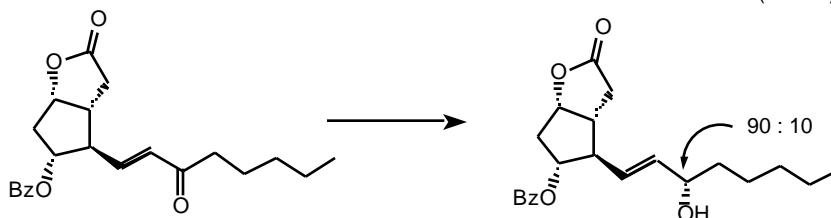
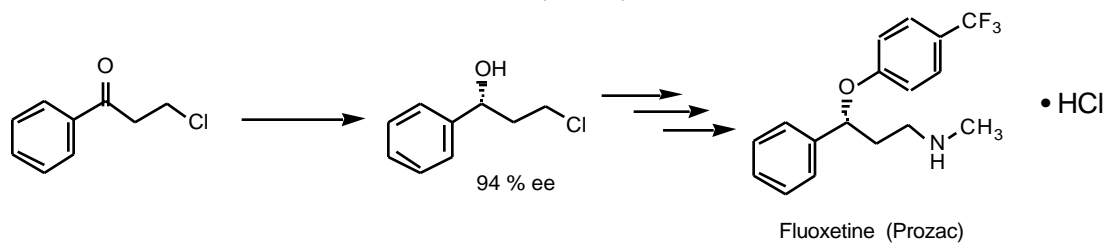
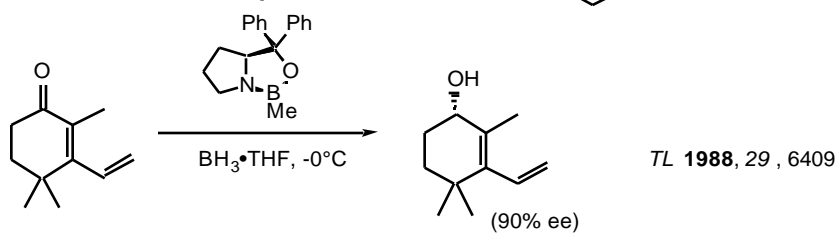
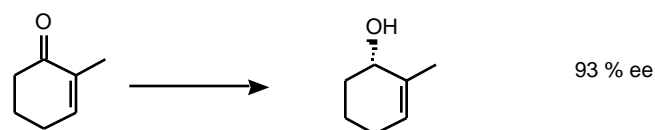
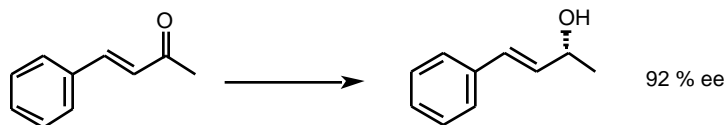
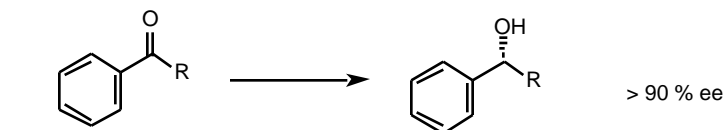
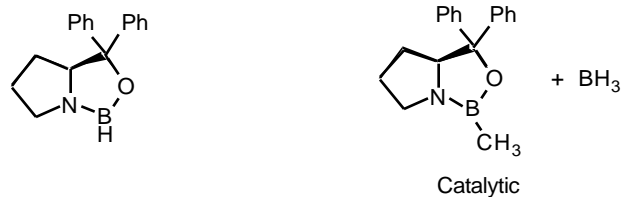


Borolane (Masamune's Reagent)

JACS **1986**, 108, 7404; JACS **1985**, 107, 4549



Oxazaborolidine (Corey)

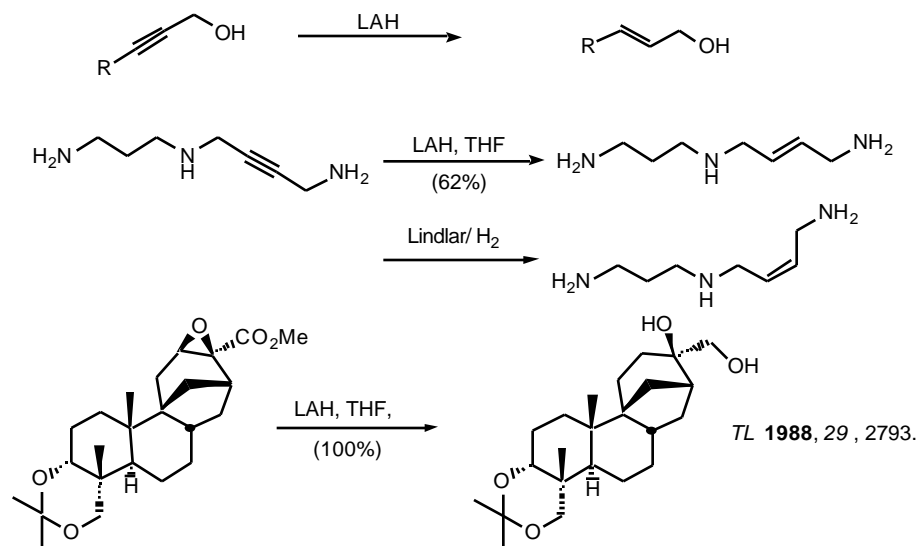
JACS **1987**, 109, 7925; TL **1990**, 31, 6111; TL **1992**, 33, 4141

Aluminium Hydrides

1. LiAlH_4
2. AlH_3
3. $\text{Li}(\text{tBuO})_3\text{AlH}$
4. $(\text{iBu})_2\text{AlH}$ DIBAL-H
5. $\text{Na}(\text{MeOCH}_2\text{CH}_2\text{O})_2\text{AlH}_2$ REDAL

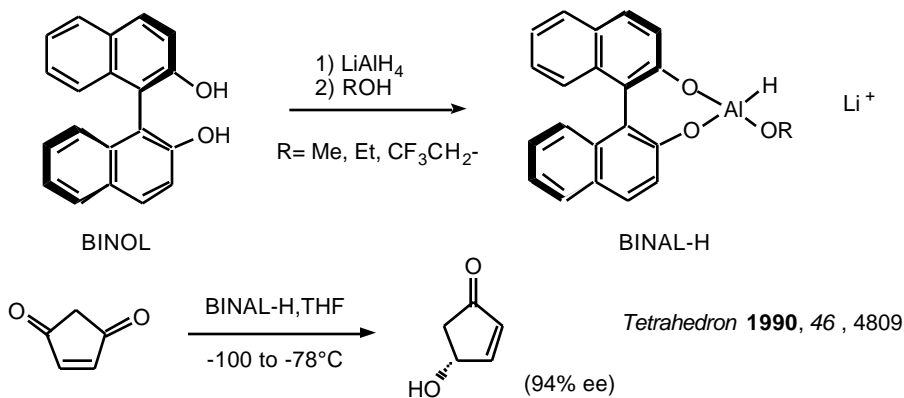
Lithium Aluminium Hydride LiAlH_4 (LAH) *Chem. Rev.* **1986**, 86, 763 *Org. Rxn.* **1951**, 6, 469.

- very powerful reducing agent
- used as a suspension in ether or THF
- Reduces carbonyl, carboxylic acids and esters to alcohols
- Reduces nitrile, amides and aryl nitro groups to amines
- opens epoxides
- reduces C-X bonds to C-H
- reduces acetylenic alcohols to trans-allylic alcohols

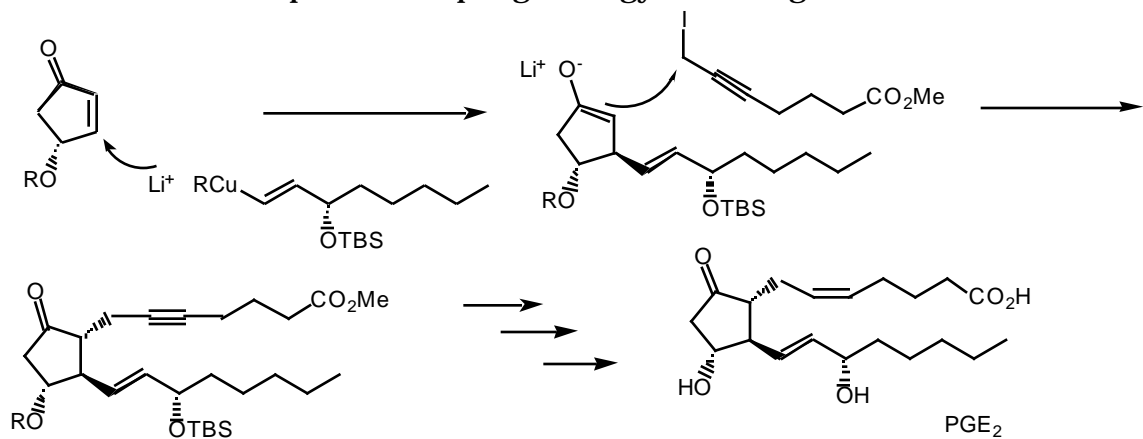


BINAL-H (Noyori)

- Chiral aluminium hydride for the asymmetric reduction of prochiral ketones



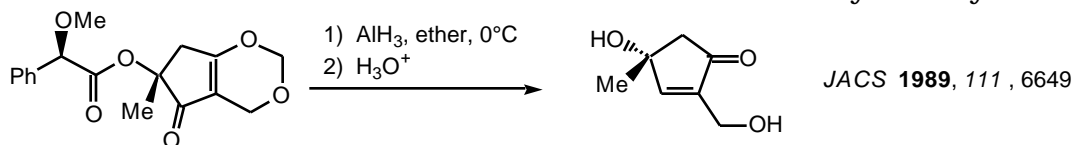
Intermediate for 3-Component Coupling Strategy to Prostaglandins



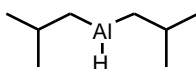
Alane AlH_3

$\text{LiAlH}_4 + \text{AlCl}_3$ AlH_3

- superior to LAH for the 1,2-reduction of α,β -unsaturated carbonyls to allylic alcohols

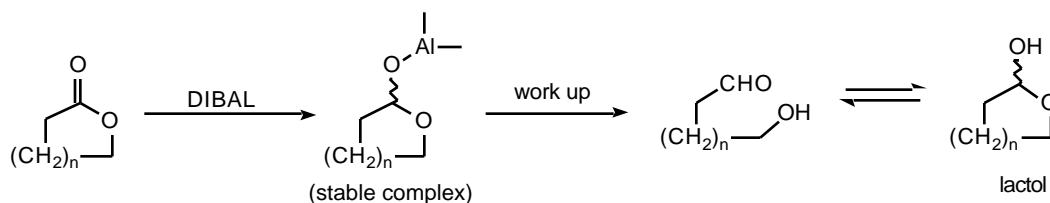


Diisobutyl Aluminium Hydride DIBAL or DIBAL-H



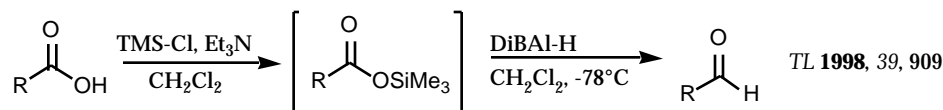
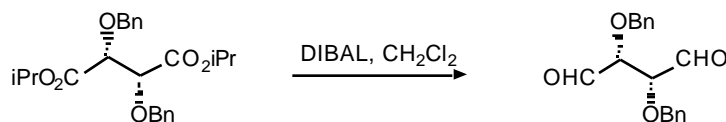
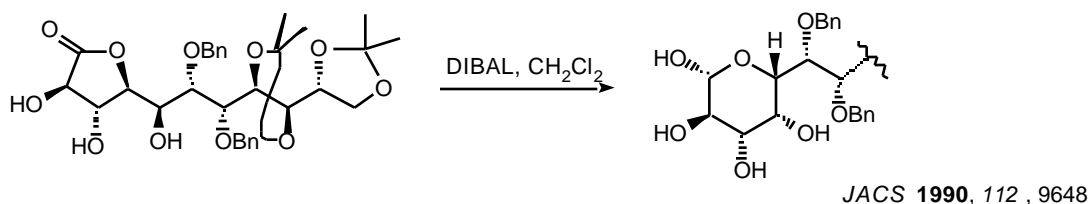
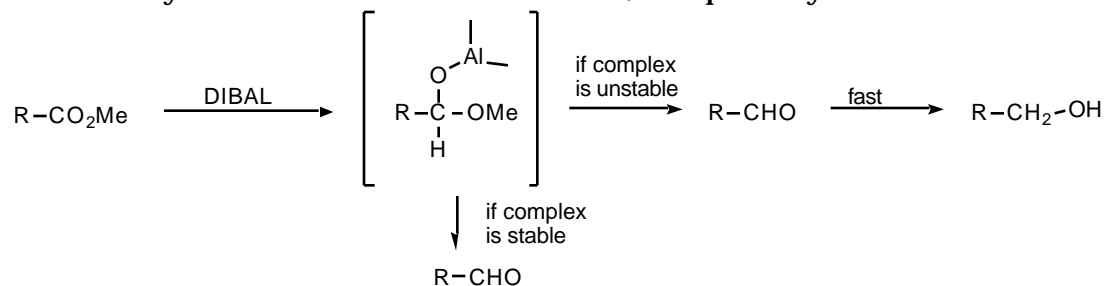
- Reduces ketones and aldehydes to alcohols

- reduces lactones to hemi-acetals



- reduces esters to alcohols

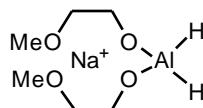
- under carefully controlled reactions conditions, will partially reduce an ester to an aldehyde



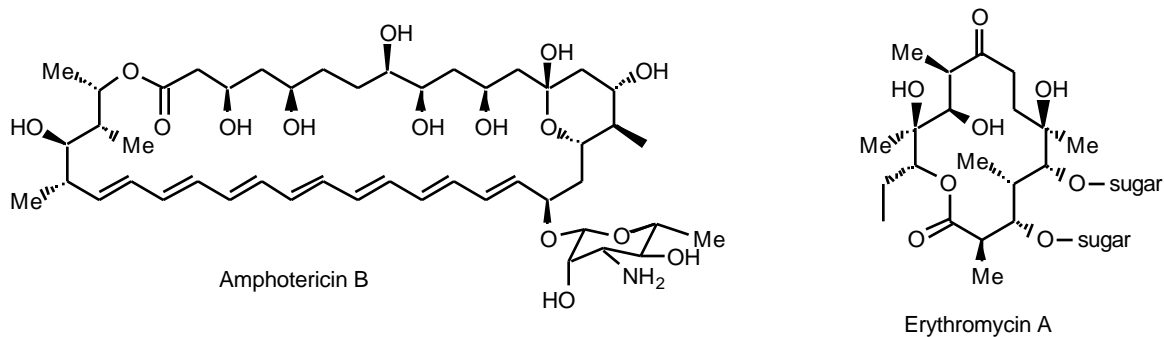
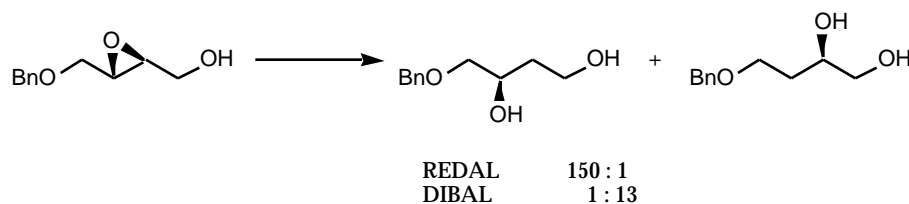
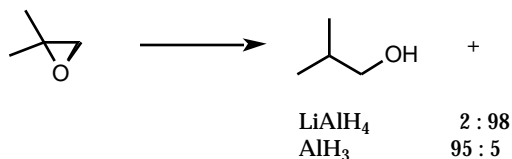
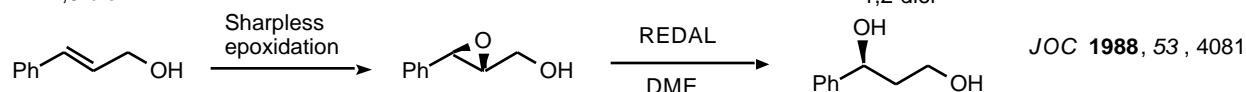
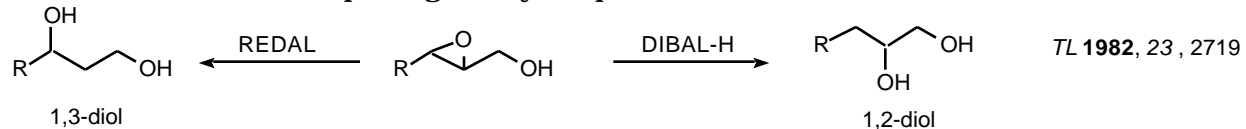
Reduction of O-Methyl hydroxamic acids



Sodium Bis(2-Methoxyethoxy)Aluminium Hydride **REDAL**
Organic Reactions **1988**, 36, 249 *Organic Reactions* **1985**, 36, 1.



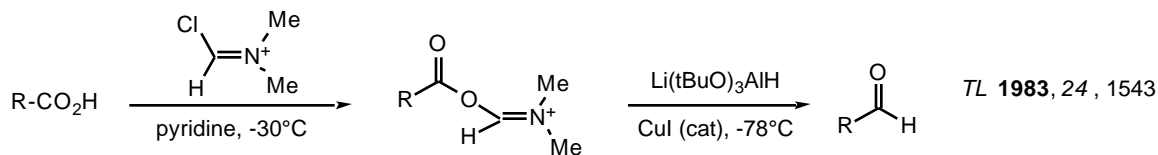
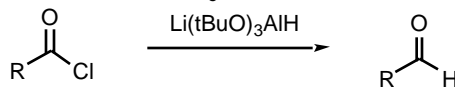
- "Chelation" directed opening fo allylic epoxides



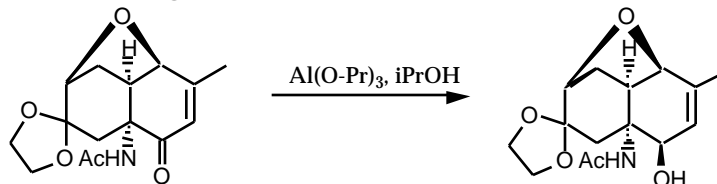
Lithium Tri(*t*-Butoxy)aluminium Hydride

$\text{Li}^+ (\text{tBuO})_3\text{AlH}$

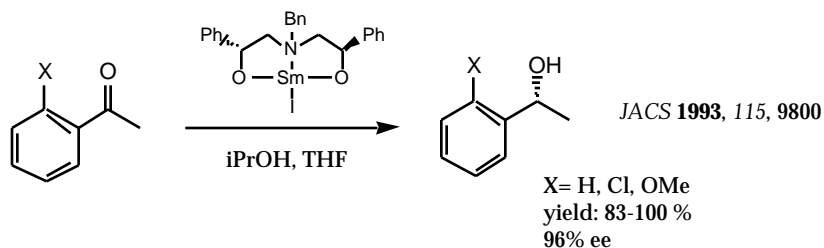
- hindered aluminium hydride, will only react with the most reactive FG's



Meerwein-Ponndorf-Verley Reduction: **opposite of Oppenauer oxidation**
Synthesis **1994**, 1007 *Organic Reactions* **1944**, 2, 178



Asymmetric M-P-V Reduction

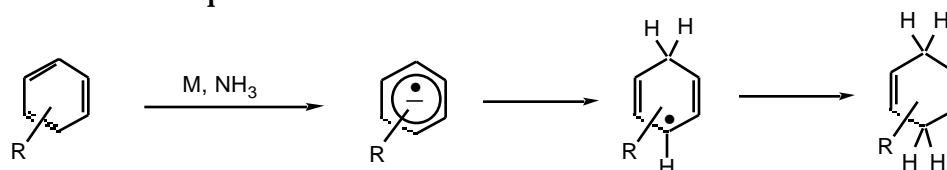


Dissolving Metal Reductions

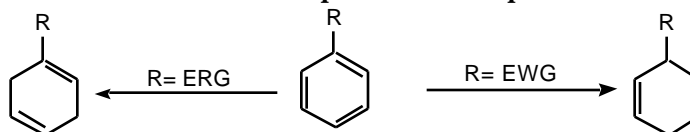
 Birch Reductions reduction of aromatic rings *Organic Reactions* **1976**, 23, 1.

Tetrahedron **1986**, 42, 6354. *Comprehensive Organic Synthesis* **1991**, vol. 8, 107.

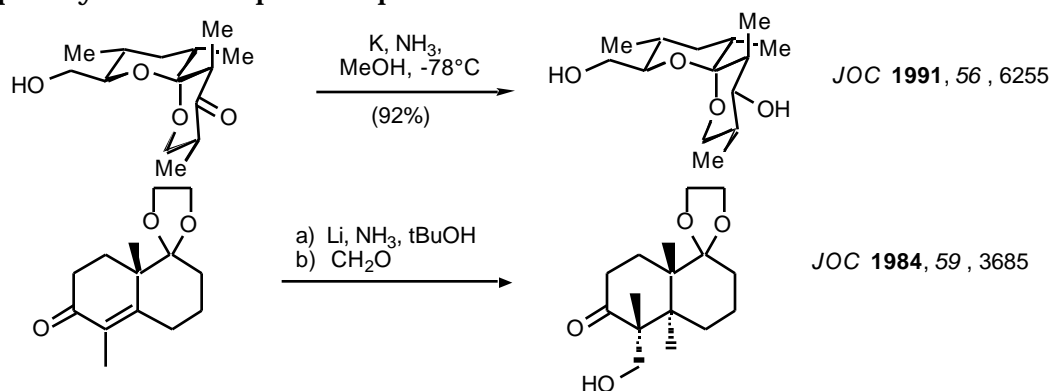
- Li, Na or K metal in liquid ammonia



- position of the double bond in the final product is dependent of the nature of the substituent

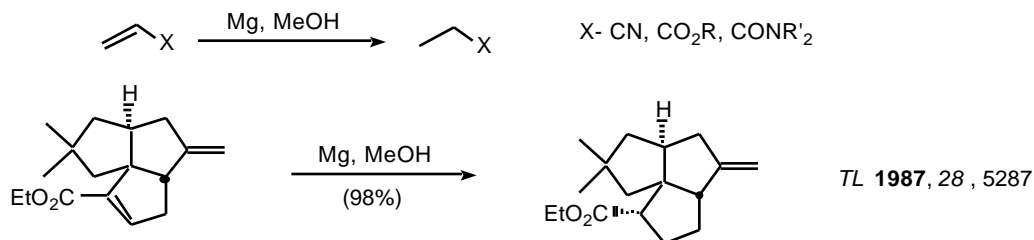
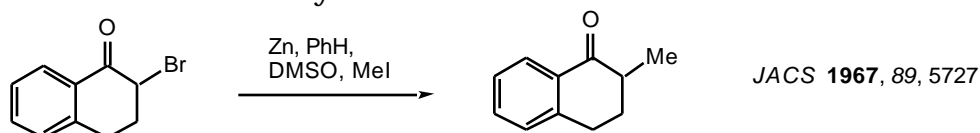


- ketones and nitro groups are also reduced but esters and nitrile are not.

 - α,β -unsaturated carbonyl cmpds are reduced in a 1,4-fashion to give an enolate which can be subsequently used to trap electrophiles


Other Metals

- Mg

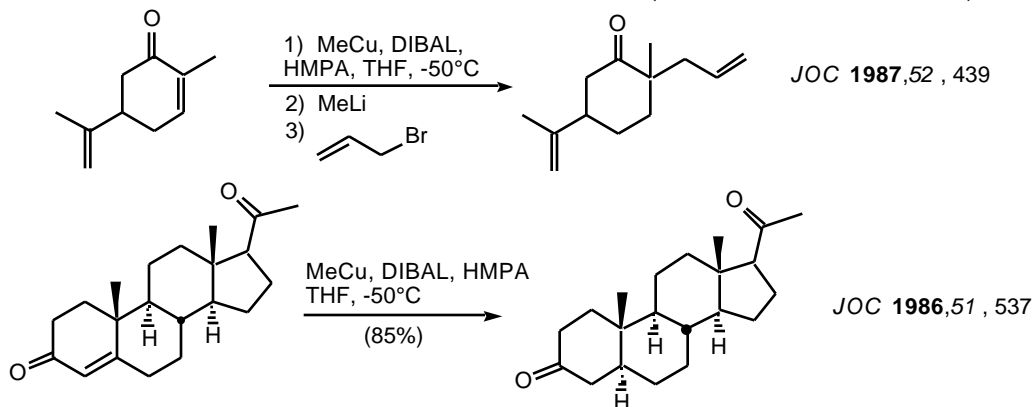

 - Zn reduction of α -halocarbonyls




"Copper Hydrides"

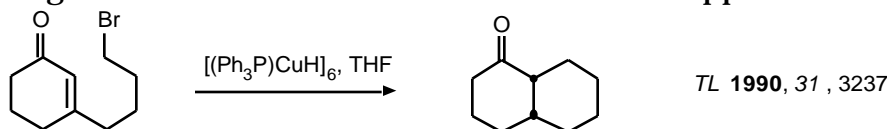
LAH or DIBAL-H + MeCu "CuH"

- selective 1,4-reduction of α,β -unsaturated ketones (even hindered enones)



$[(\text{Ph}_3\text{P})\text{CuH}]_6$ Stryker Reagent
 JACS 1988, 110, 291; TL 1988, 29, 3749

- 1,4-reduction of α,β -unsaturated ketones and esters; saturated ketones are not reduced
- halides and sulfonates are not reduced
- 1,4-reduction gives an intermediate enolate which can be trapped with electrophiles.

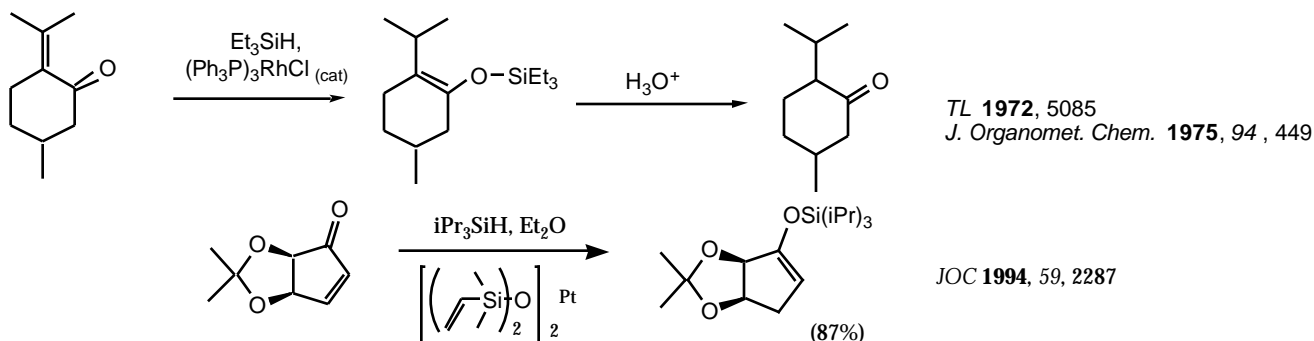


Silyl Hydrides

- Hydrosilylation

$\text{Et}_3\text{SiH} + (\text{Ph}_3\text{P})_3\text{RhCl}$ (cat)

- selective 1,4-reduction of enones, 1,2-reduction of saturated ketones to alcohols.



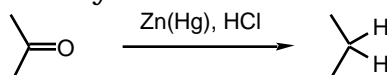
- Buchwald Reduction

JACS 1991, 113, 5093

- catalytic reagent prepared from $\text{Cp}_2\text{TiCl}_2 + n\text{BuLi}$ and stoichiometric $(\text{Et})_3\text{SiH}$ in THF will reduce ester, ketones and aldehydes to alcohols under very mild conditions.
- α,β -unsaturated esters are reduced to allylic alcohols
- free hydroxyl groups, aliphatic halides and epoxides are not reduced

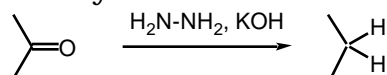
Clemmensen Reduction *Organic Reactions* **1975**, 22, 401
Comprehensive Organic Synthesis **1991**, vol 8, 307.

- reduction of ketones to saturated hydrocarbons



Wolff-Kishner Reduction *Organic Reactions* **1948**, 4, 378
Comprehensive Organic Synthesis **1991**, vol. 8, 327.

- reduction of ketones to saturated hydrocarbons



Radical Deoxygenation

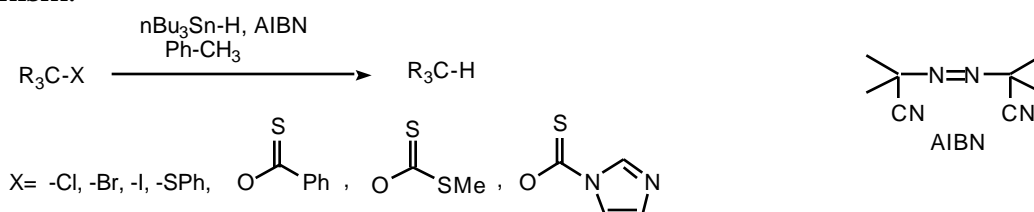
Review: *Tetrahedron* **1983**, 39, 2609 *Chem. Rev.* **1989**, 89, 1413.

Comprehensive Organic Synthesis **1991**, vol. 8, 811

Tetrahedron **1992**, 48, 2529

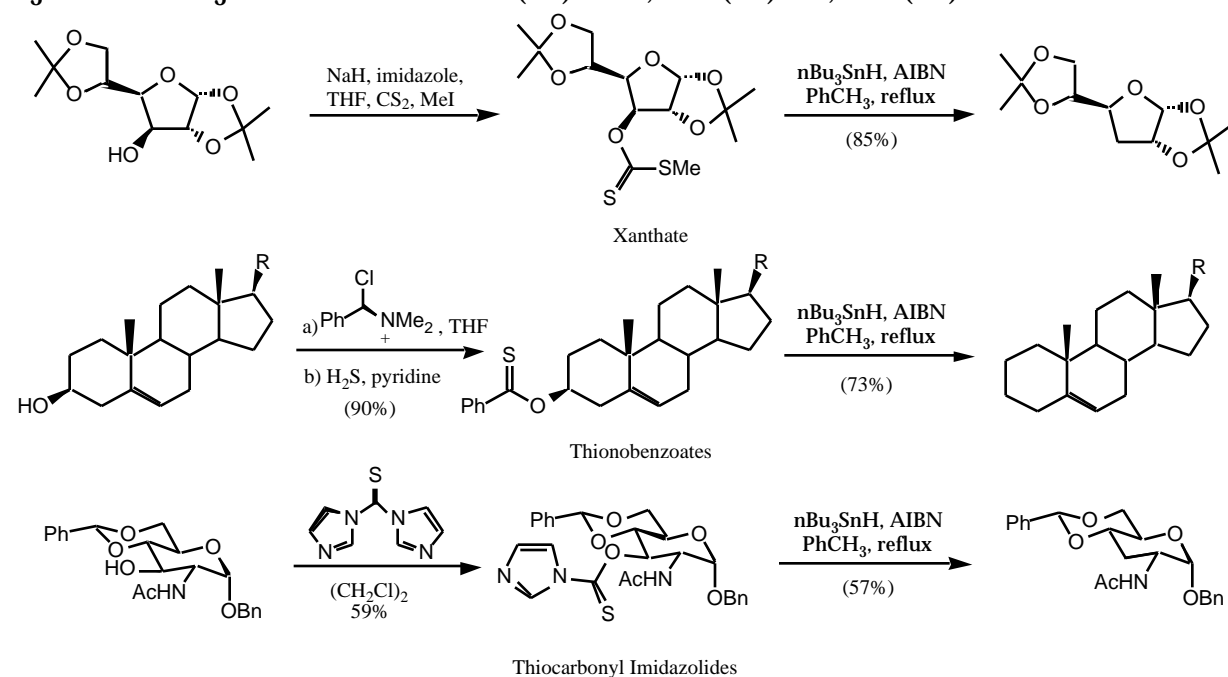
W. B. Motherwell, D. Crich *Free Radical Chain Reactions in Organic Synthesis*
 (Academic Press: 1992)

- free radical reduction of halide, thio ethers, xanthates, thionocarbonates by a radical chain mechanism.

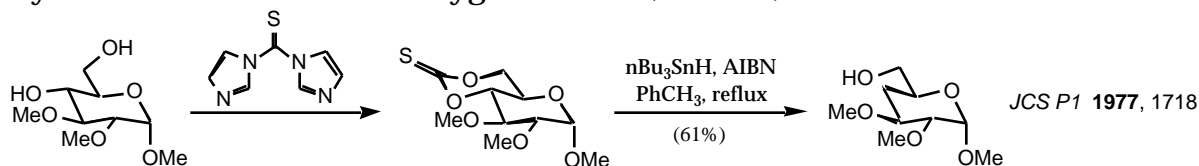


Barton-McCombie Reduction
JCS P1 **1975**, 1574

R_3C-X R_3C-H X = -OC(=S)-SMe, -OC(=S)-Im, -OC(=S)Ph

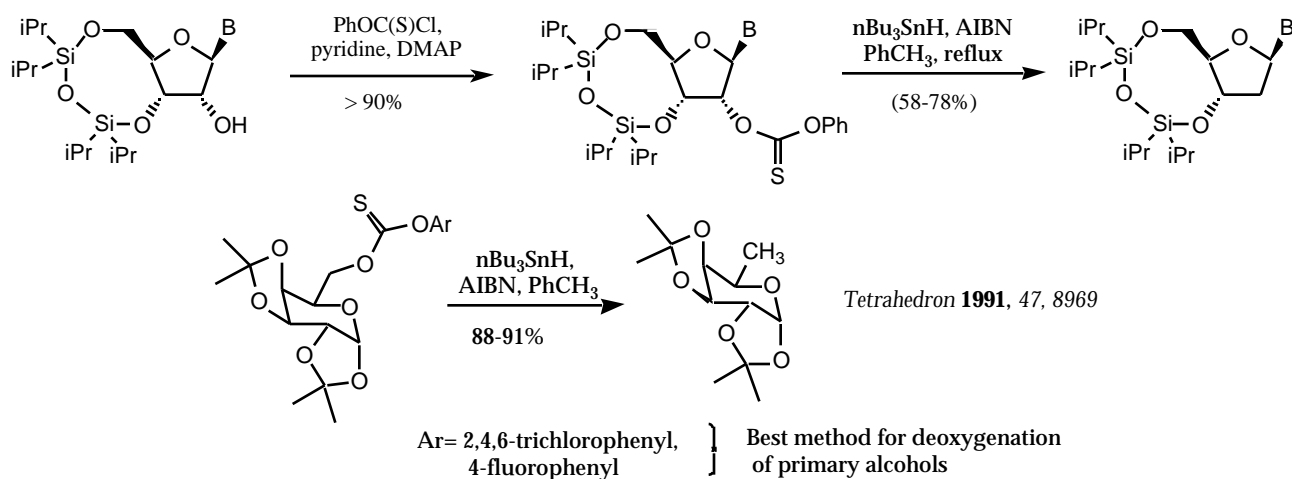
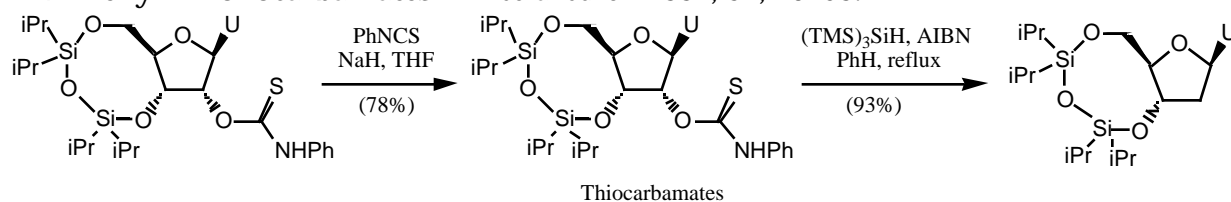


- Cyclic Thionocarbonates: deoxygenation of 1,2- and 1,3-diols to alcohols

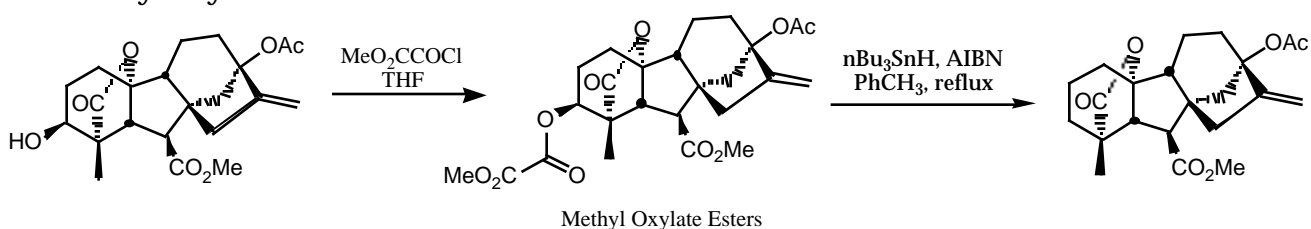


- Thionocarbonate Modification (Robbins)

JACS **1981**, 103, 932; *JACS* **1983**, 105, 4059.

- N-Phenyl Thionocarbonates *Tetrahedron* **1994**, 34, 10193.

- Methyl oxylates



- Water Soluble Tin Hydride: $[\text{MeO}(\text{CH}_2)_2\text{O}(\text{CH}_2)_3]_3\text{SnH}$ / 4,4'-Azo(bis-4-cyanovaleric acid)
TL **1990**, 31, 2957

- Silyl Hydride Radical Reducing Agents

- replacement for $n\text{Bu}_3\text{SnH}$

$(\text{Me}_3\text{Si})_3\text{SiH}$ *Chem Rev.* **1995**, 95, 1229.

JOC **1991**, 56, 678; *JOC* **1988**, 53, 3641; *JACS* **1987**, 109, 5267

Ph_2SiH_2 / Et_3B / Air

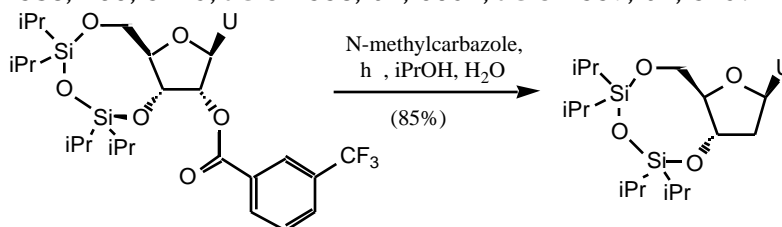
TL **1990**, 31, 4681; *TL* **1991**, 32, 2569

- hypophosphorous acid as radical chain carrier

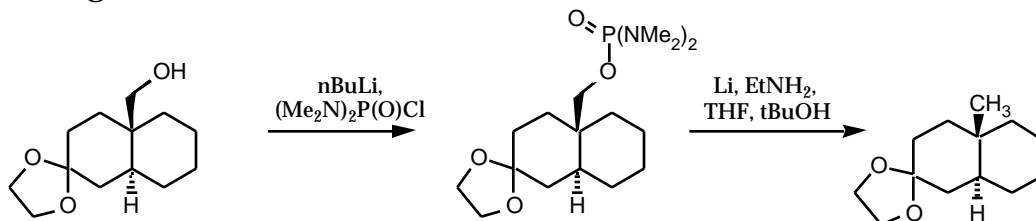
JOC **1993**, 58, 6838

- Photosensitized electron transfer deoxygenation of m-trifluoromethylbenzoates

JACS **1986**, *108*, 3115, *JOC* **1996**, *61*, 6092, *JOC* **1997**, *62*, 8257

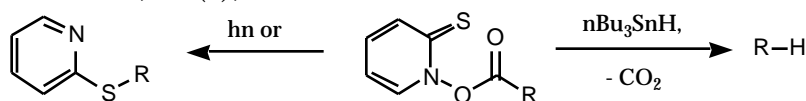


Dissolving Metal: *JACS* **1972**, *94*, 5098



Radical Decarboxylation: Barton esters

Aldrichimica Acta **1987**, *20* (2), 35



Radical Deamination

Comprehensive Organic Synthesis **1991**, vol. 8, 811

Reduction of Nitroalkanes *JOC* **1998**, *63*, 5296