Reduction

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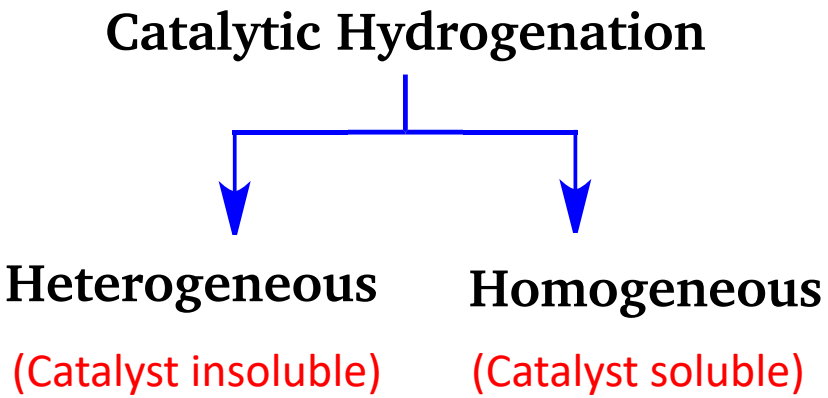
CH (401) slides should not be used for commercial purposes

Reduction

- Hydrogenation
- Boron Reagents
- Aluminium Reagents
- Tin Hydrides
- Silanes
- Dissolving Metal Reductions
- Diimide Reductions

Hydrogenation



Heterogeneous Hydrogenation

Heterogeneous Catalysis

Catalyst is insoluble in the reaction medium

Reactions take place on the surface of the catalyst

Active sites on the catalytic surface is responsible for selectivity & reactivity

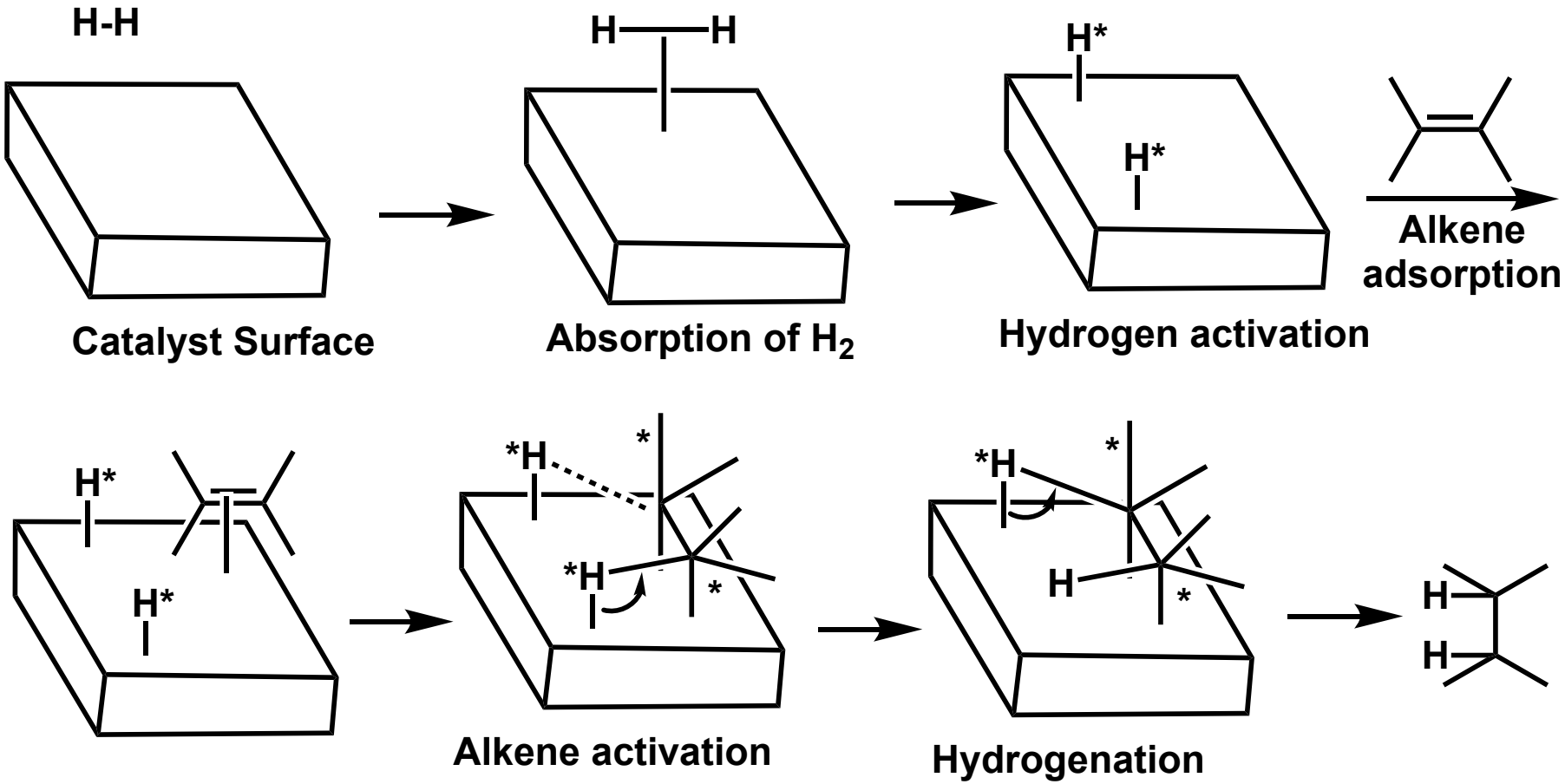
Active sites: Part of the catalytic surface where substrate and H_2 adsorb on

Poisoning: Reactivity of the substrate is reduced by blocking the active sites

Poisoning the catalyst may increase the selectivity

Heterogenous reduction is a surface phenomenon and not fully understood

Heterogeneous Catalysis



Heterogeneous Catalytic Hydrogenation

Transition metals get adsorbed onto a solid support

Metal- Pd, Pt, Rh, Ni

Support- Charcoal, Alumina, Silica

Solvents- MeOH, EtOH, EtOAc, AcOH, Et_2O, Hexanes

Increasing order of activity

H_2, Ra-Ni

H_2, Pd-C

H_2, Pt-C

H_2, Rh/Al_2O_3

Order of reactivity

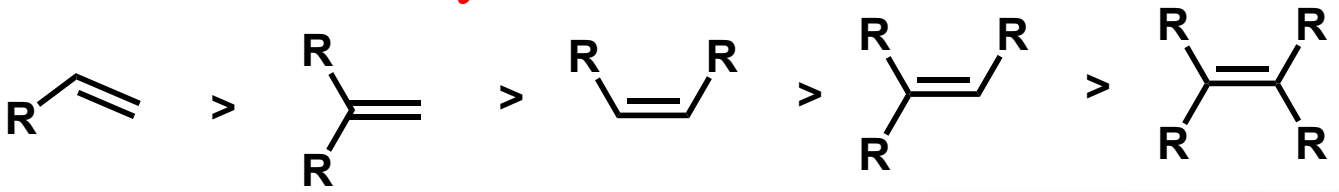
Pt = C=O > C=C > [H] > Ar

Ru = C=O > C=C > Ar > [H]

Pd = C=C > [H] > C=O > Ar

[H] -Hydrogenolysis

Order of alkene reactivity

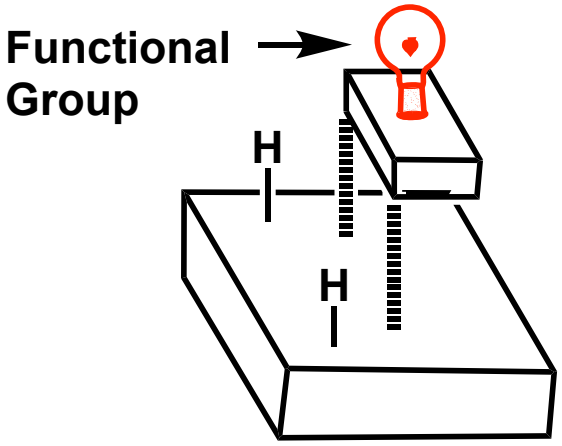


Stereoselectivity

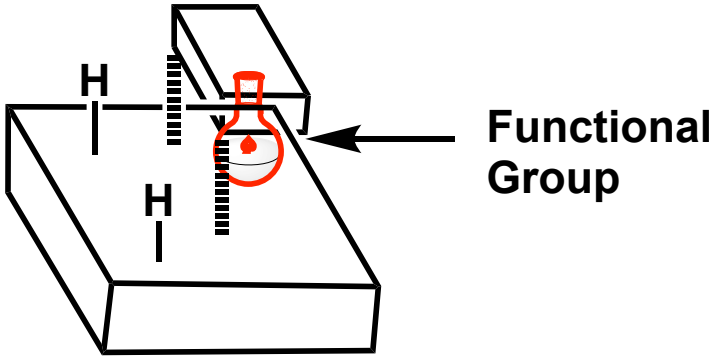
There are two types of functional groups.

Type I- which do not get anchored to the catalyst surface

Type II- gets anchored to the catalyst surface



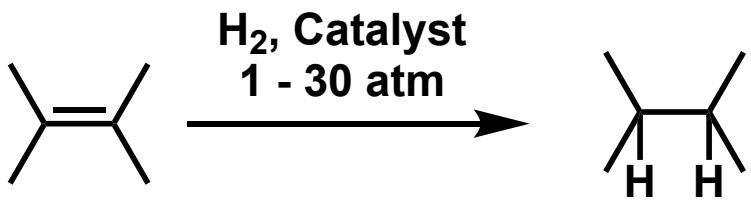
Hydrogen adds from the least hindered side of the double bond



Hydrogen adds from the same side of the functional group

Haptophilicity of a functional group plays an important role in stereoselectivity

Heterogeneous Catalytic Hydrogenation



Properties:

Reduces olefins & acetylenes to saturated hydrocarbons

Sensitive to steric effects & choice of solvents

Polar functional groups, like hydroxyl groups can sometimes direct the delivery of H_2

cis-addition of H_2

Catalysts can be poisoned

Order of solvent reactivity is-

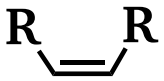
Hexane < EtOAc < EtOH < HOAc < HOAc/HCl

Decreasing Order of Reactivity

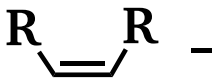
FACILE

$ROCl \rightarrow RCHO$

$RNO_2 \rightarrow RNH_2$

$RC{\equiv}CR \rightarrow$ 

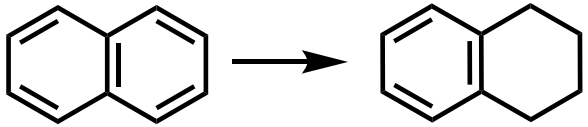
$RCHO \rightarrow RCH_2OH$

 $\rightarrow RCH_2CH_2R$

$RCOR \rightarrow RCH(OH)R$

DIFFICULT

$RCN \rightarrow RCH_2NH_2$

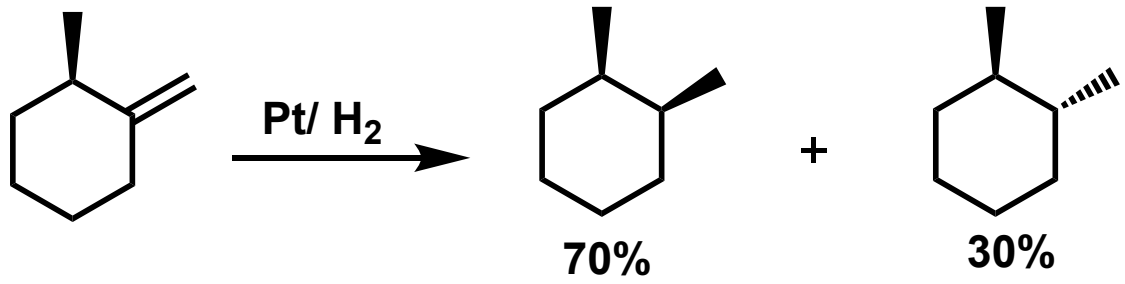


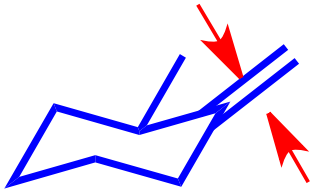
$RCOOR \rightarrow RCH_2OH + ROH$

$RCONHR \rightarrow RCH_2NHR$

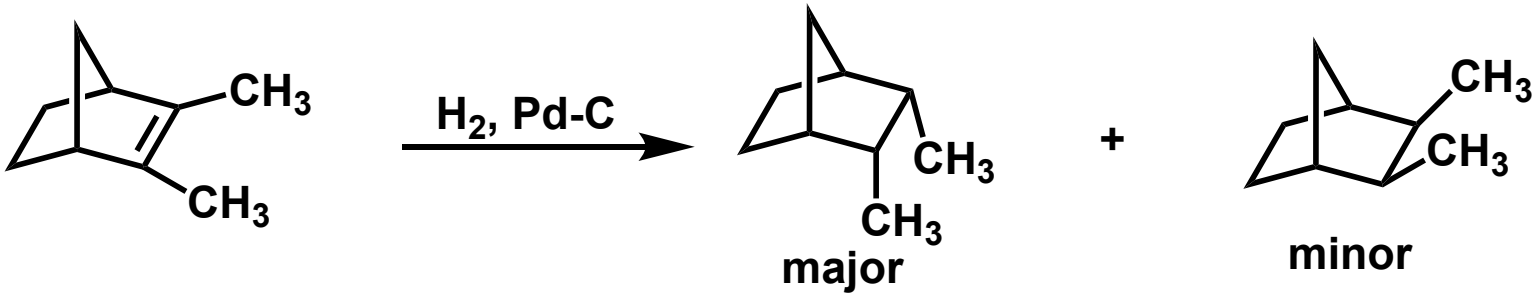
$RCOO^- \rightarrow$ INERT

Heterogeneous Catalytic Hydrogenation



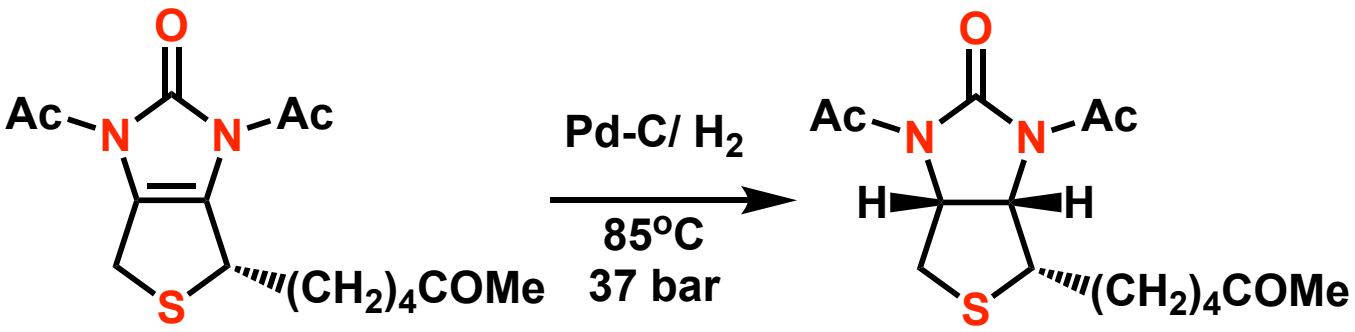


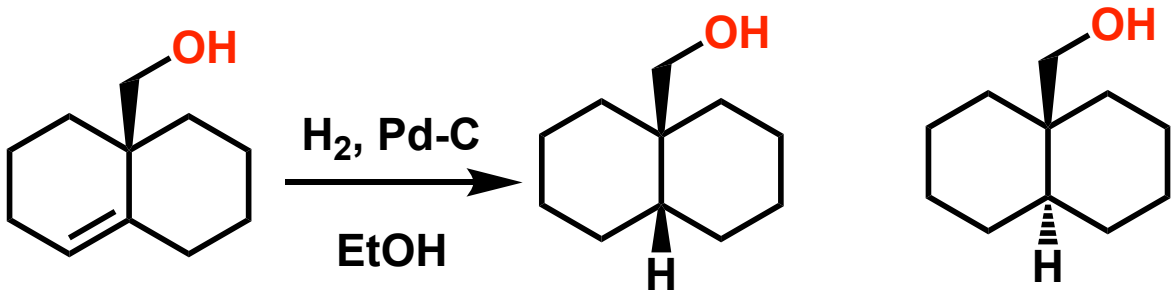
Equatorial attack is predominant



Hydrogen will approach from *exo* side

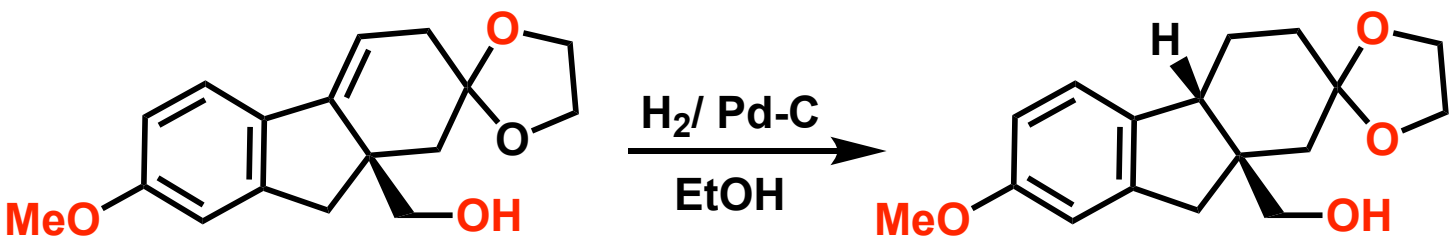
Directed Heterogeneous Hydrogenation

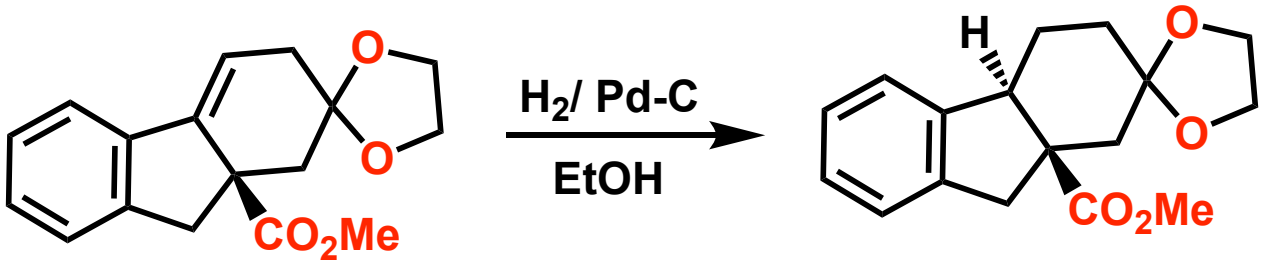


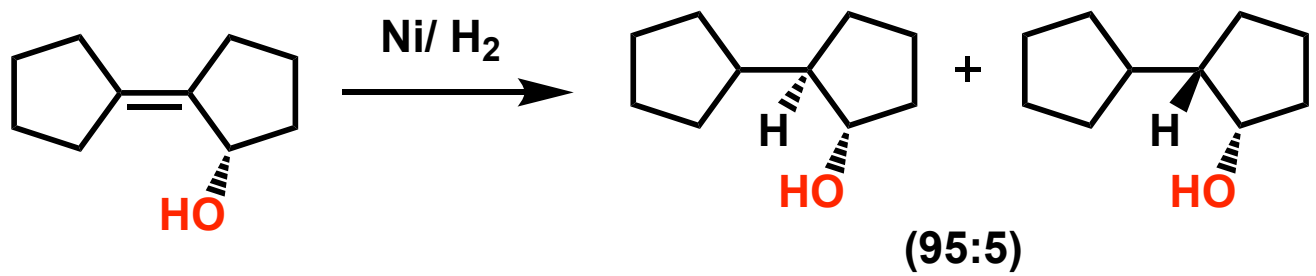


Hydroxy group delivers hydrogen from the same side

Directed Heterogeneous Hydrogenation

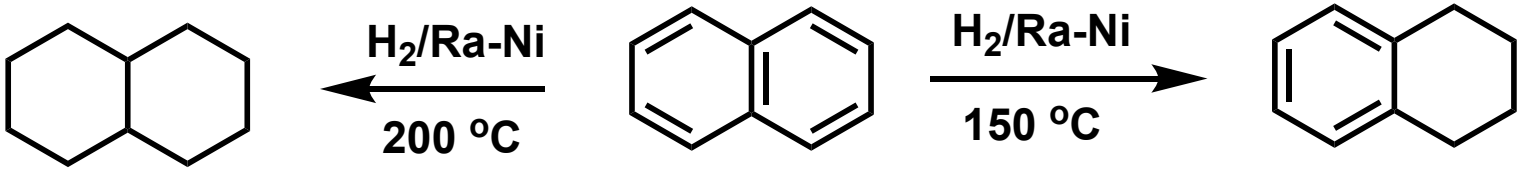


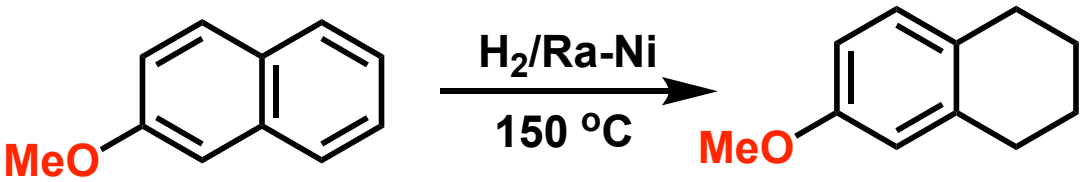




Heterogeneous Hydrogenation

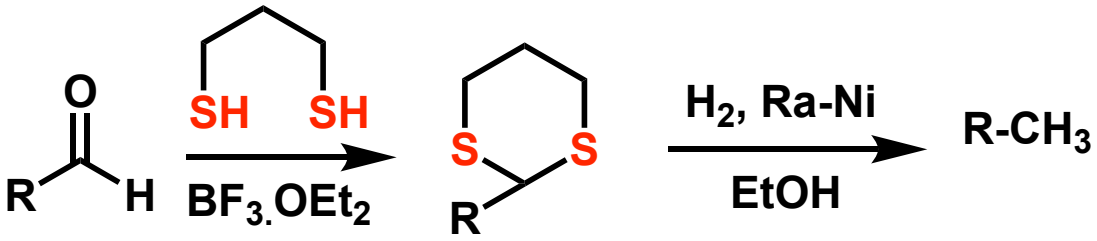
Reduction of aryl groups:





Major product

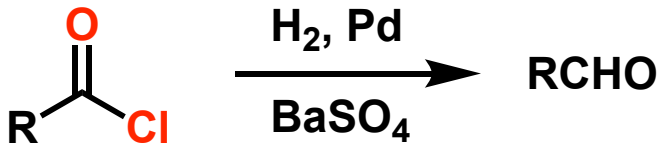
Desulfurization



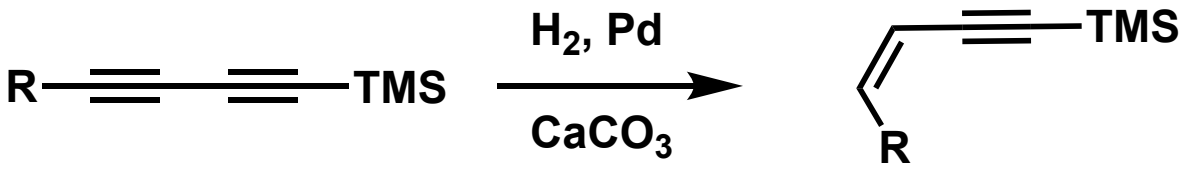
Heterogeneous Hydrogenation

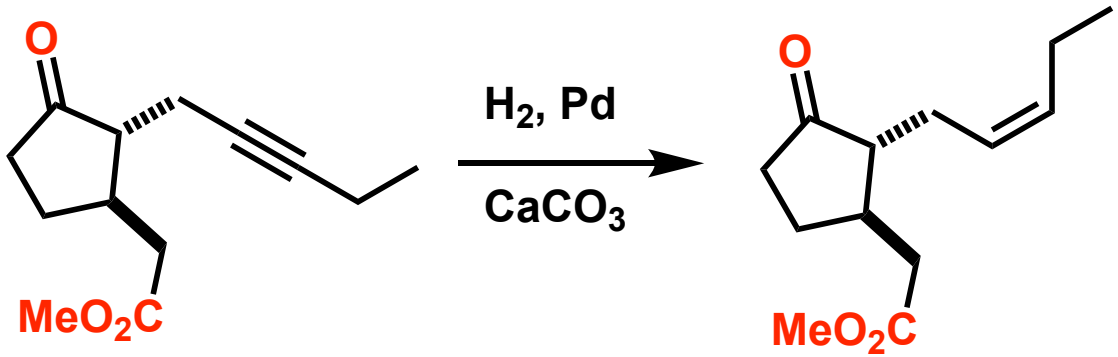
Rosenmund Reduction:

Quinoline is used to poison the catalyst to reduce its activity



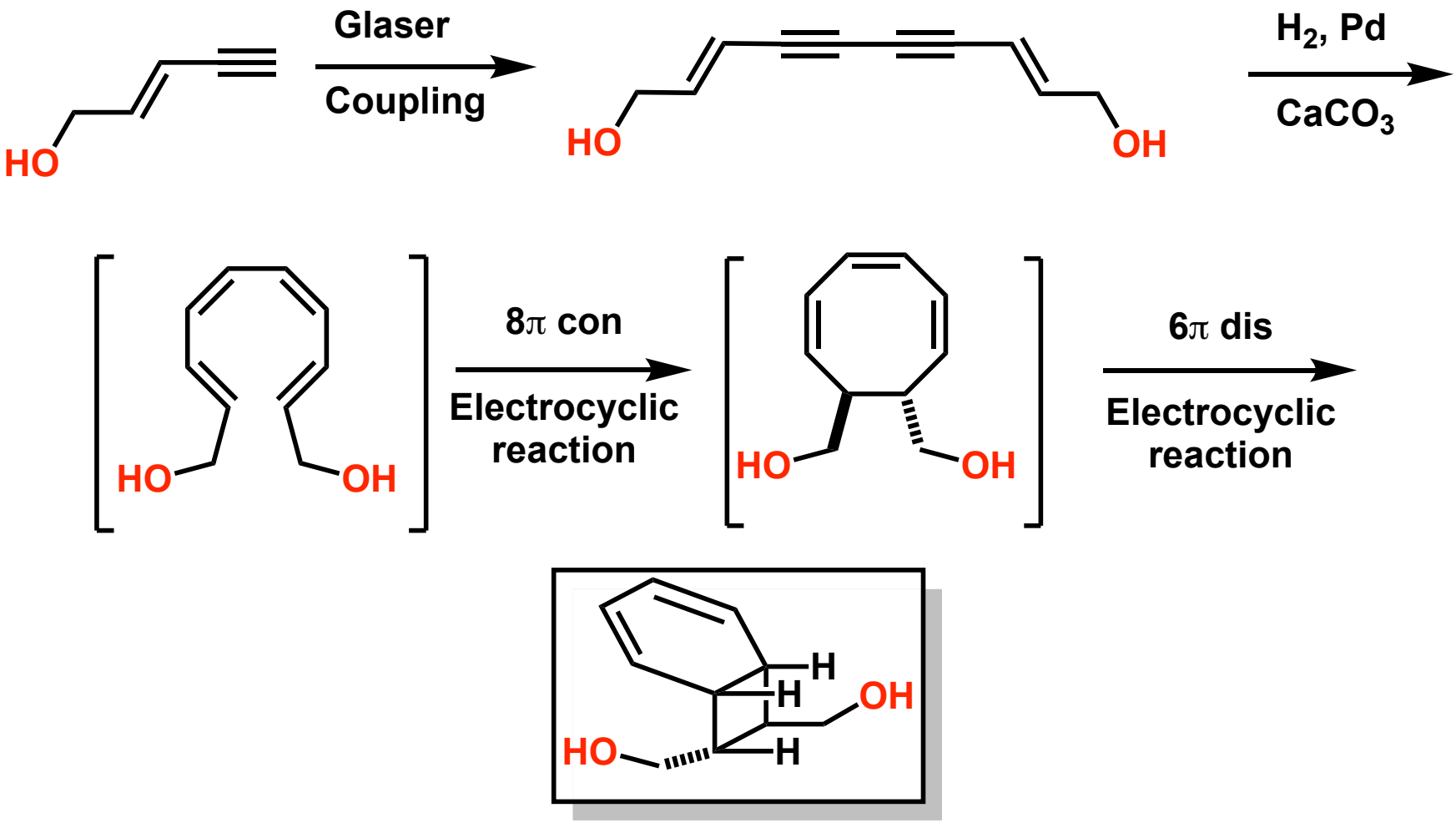
Lindlar Catalyst ($Pd/CaCO_3$)





Heterogeneous Hydrogenation

Lindlar Catalyst ($Pd/CaCO_3$)



Homogeneous Hydrogenation

Homogeneous Catalysis

Catalyst is soluble in the reaction medium

Mild conditions

Less catalyst required

Improved selectivity

Directed hydrogenations

Asymmetric hydrogenations

Mechanism is much better understood

Homogeneous Catalysts

Two types of homogeneous catalysts
(a) dihydride and
(b) monohydride catalysts

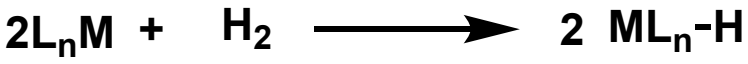
Dihydride Catalysts

Examples

Wilkinson's catalyst: $ClRh(PPh_3)_3$

Crabtree's catalyst: $[Ir(COD)(PCy_3)(Py)]^+PF_6^-$

Monohydride Catalysts

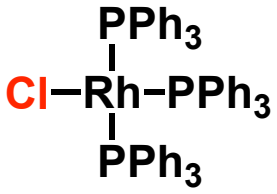


Examples

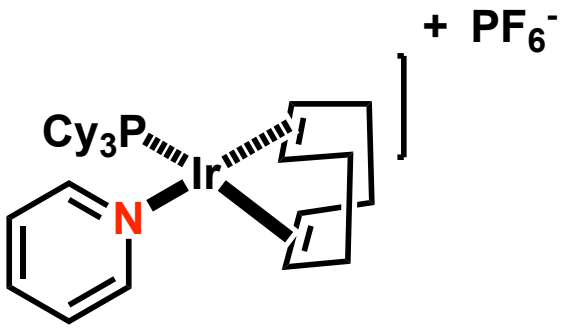
$HClRu(PPh_3)_3$

Cp_2TiH

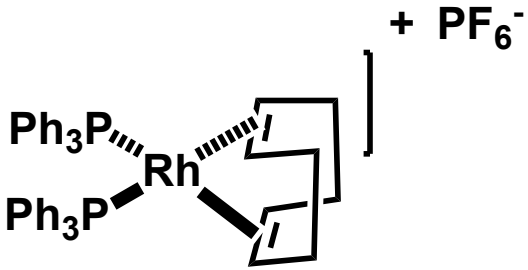
Common Homogeneous Catalysts

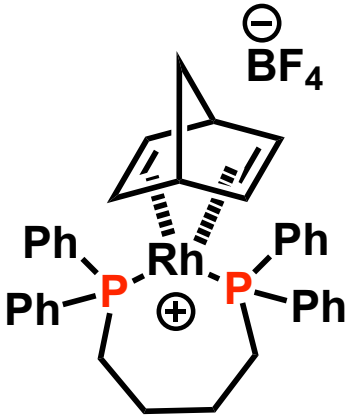


Wilkinson's catalyst

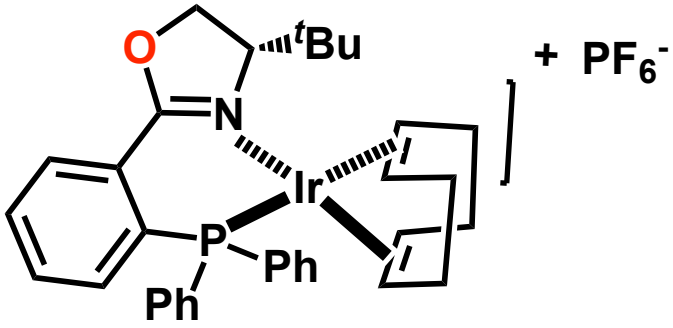


Crabtree's catalyst

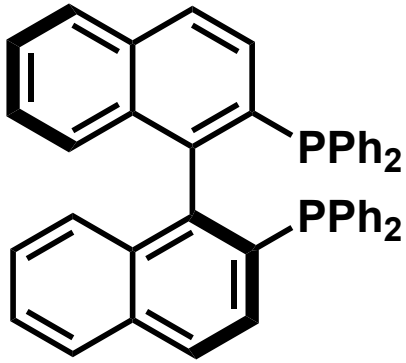




Brown's catalyst



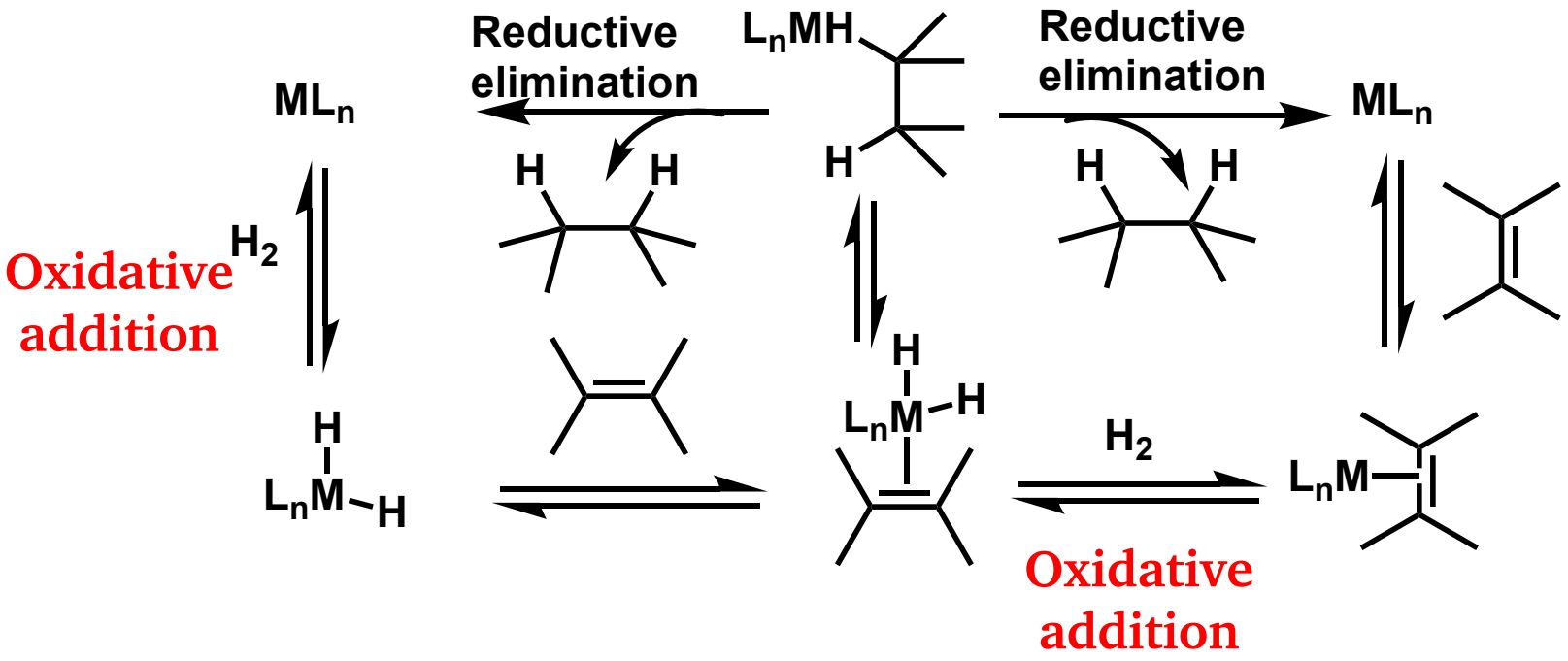
Pfaltz's catalyst



BINAP

Mechanism

Wilkinson's catalyst Crabtree's catalyst

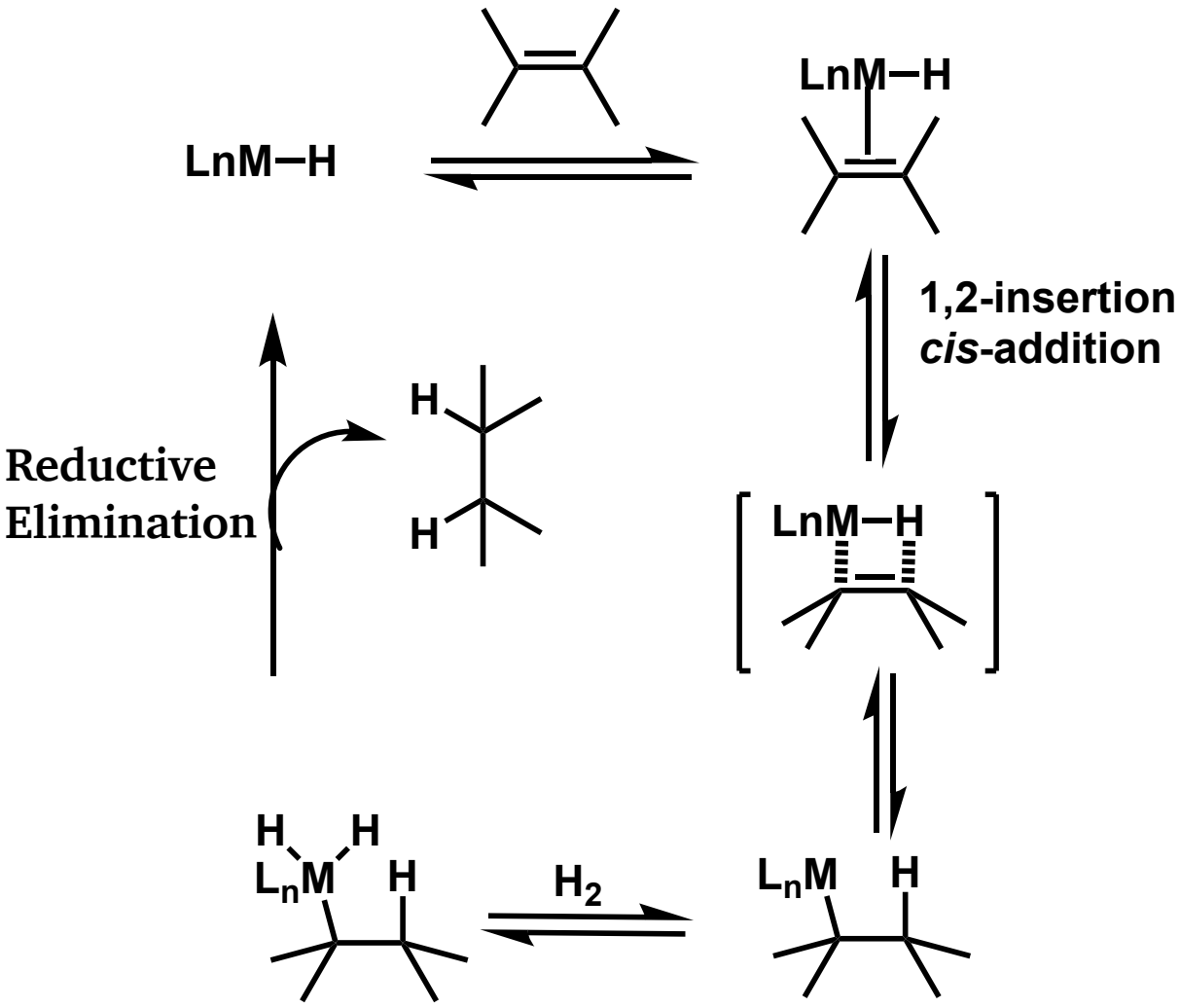


In case of Wilkinson's catalyst, hydrogen adds prior to the substrate

In case of Crabtree's catalyst, substrate adds prior to the hydrogen

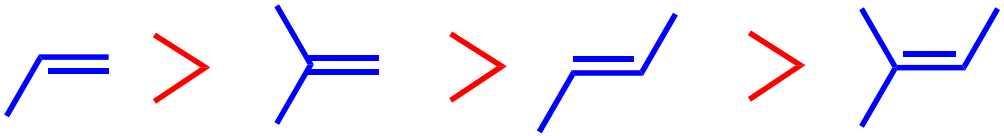
Mechanism

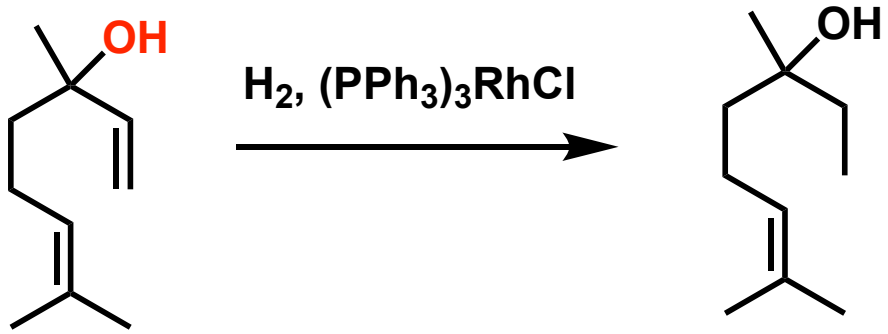
Monohydride catalyst

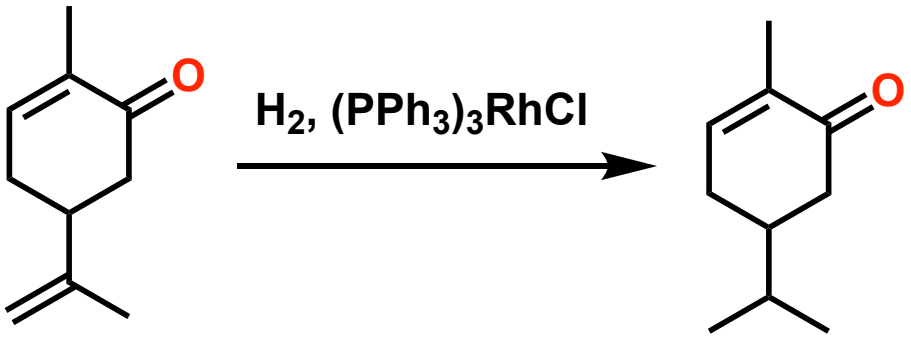


Wilkinson's Catalyst

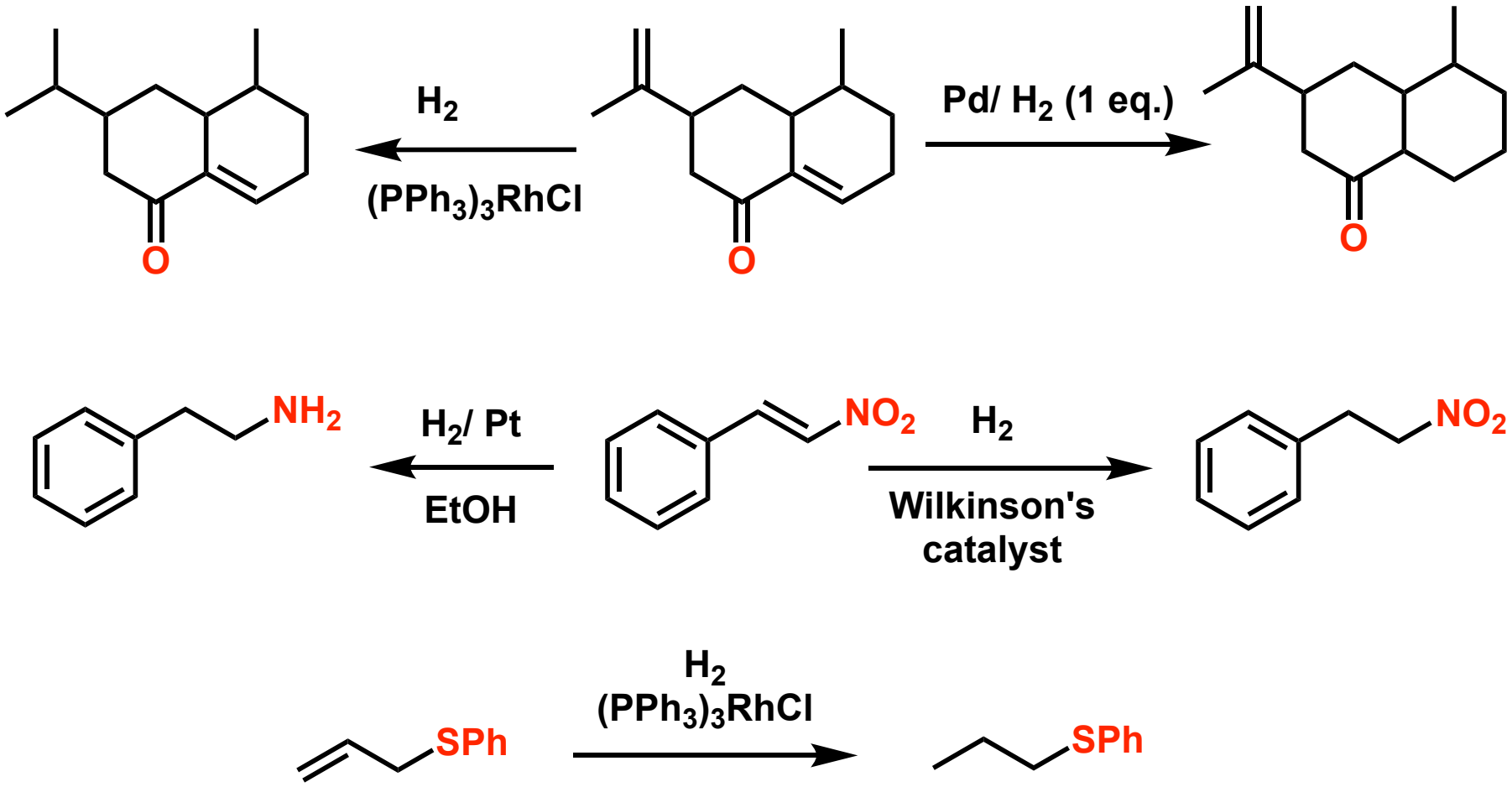
Reactivity



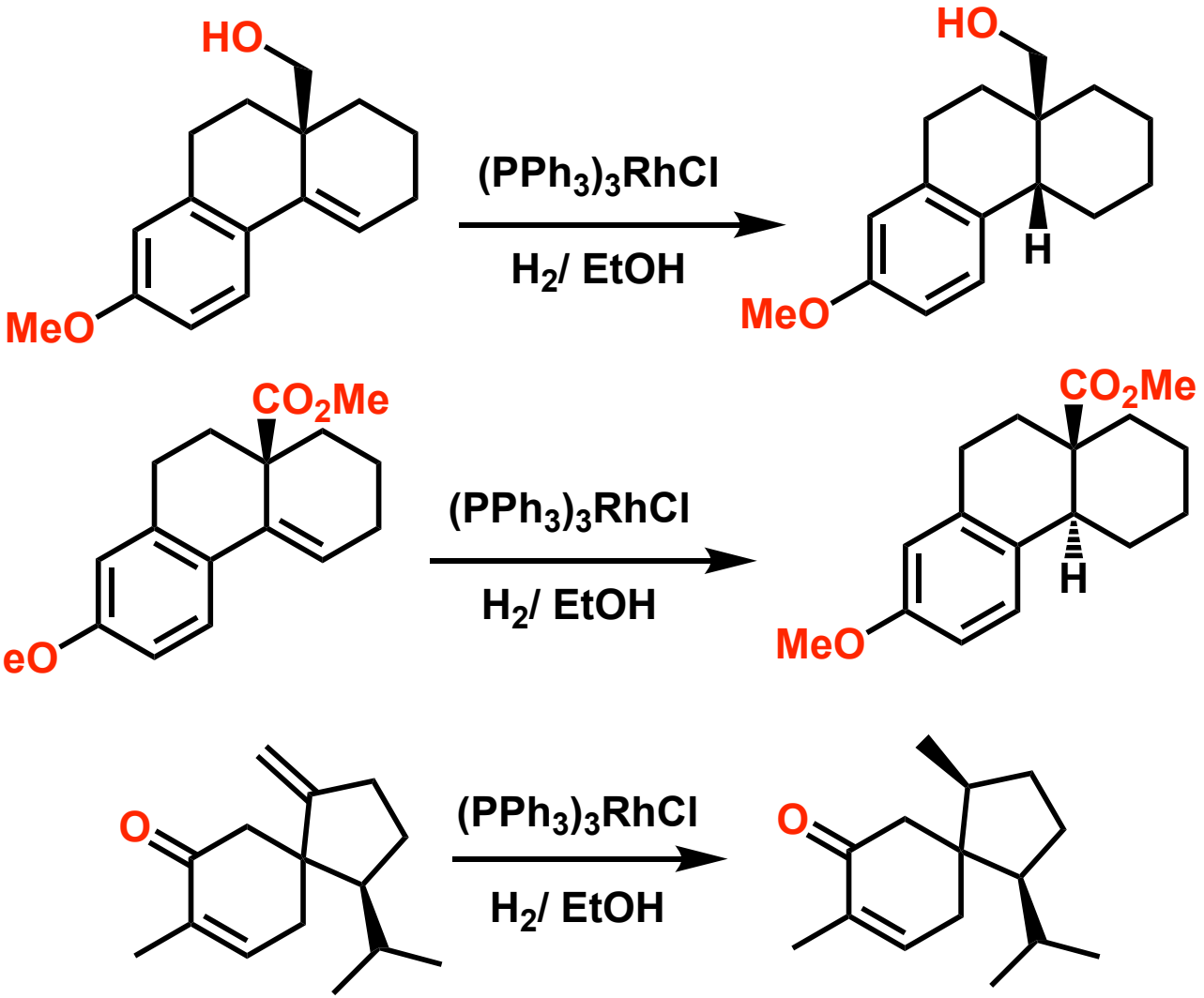




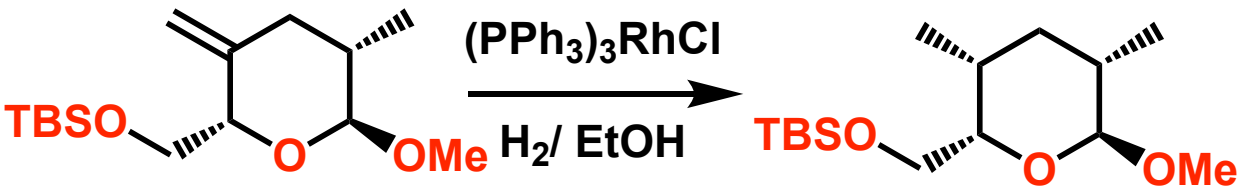
Wilkinson's Catalyst



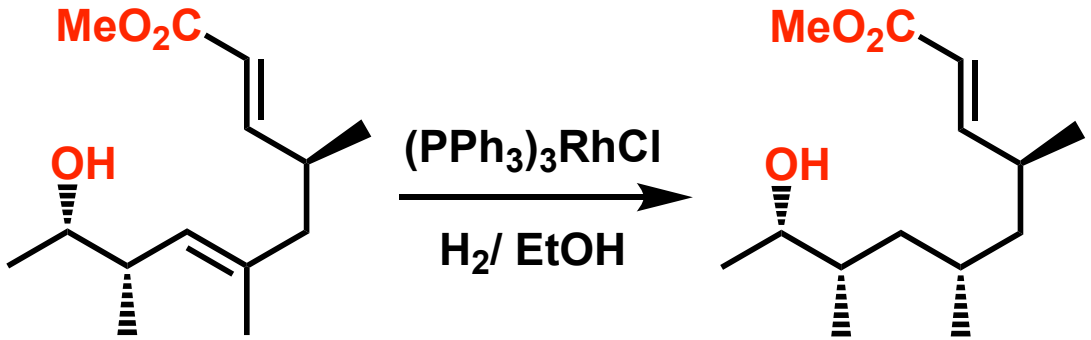
Wilkinson's Catalyst



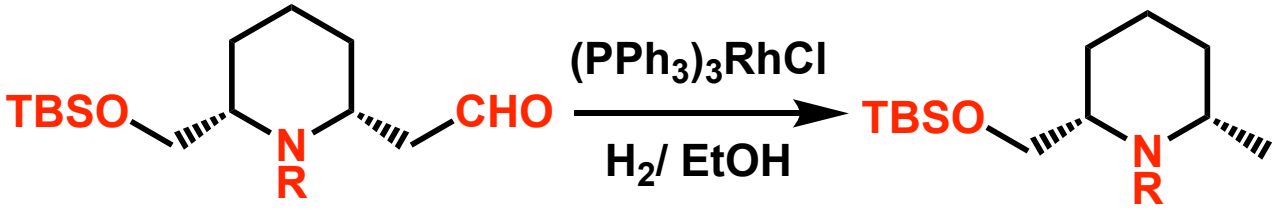
Wilkinson's Catalyst



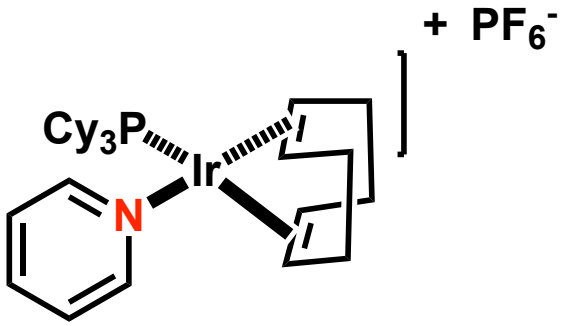
Allylic and homoallylic alcohols are hydrogenated faster than isolated double bonds



Wide range of functional group tolerance, however, aldehydes undergo decarbonylation



Crabtree's catalyst



Crabtree's catalyst is much more reactive than Wilkinson's and hence it is good for hindered alkenes

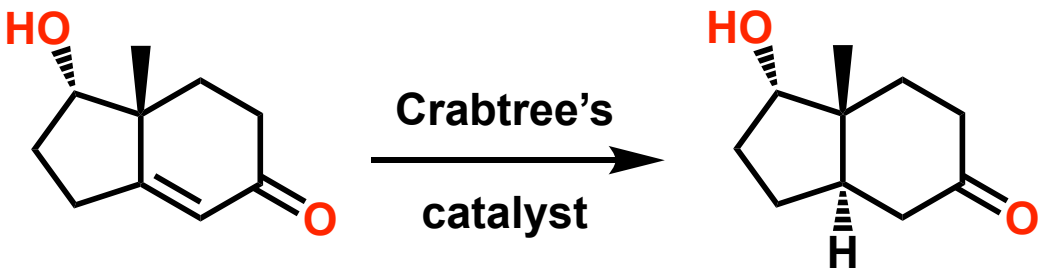
Crabtree's catalyst gives superior directing effect than Wilkinson's for cyclic substrates

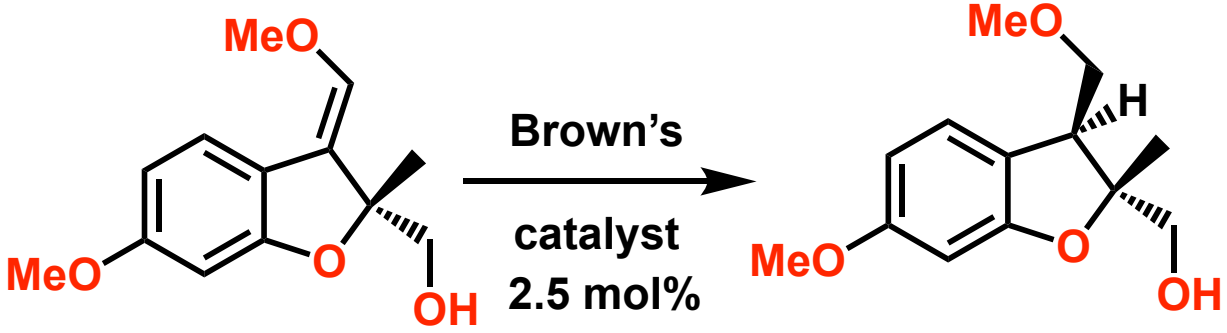
Selectivity is higher in lower concentration of the catalyst

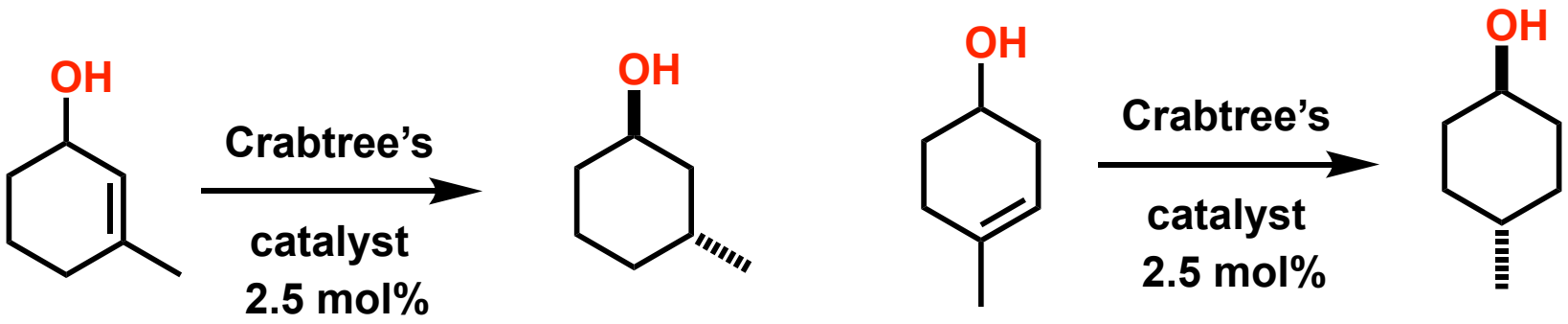
Hydrogenation done at higher pressure suppresses olefin isomerization

Lewis basic groups also can direct the hydrogenation

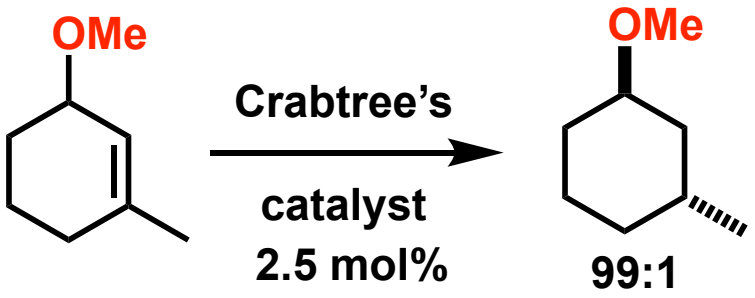
Directed Hydrogenation

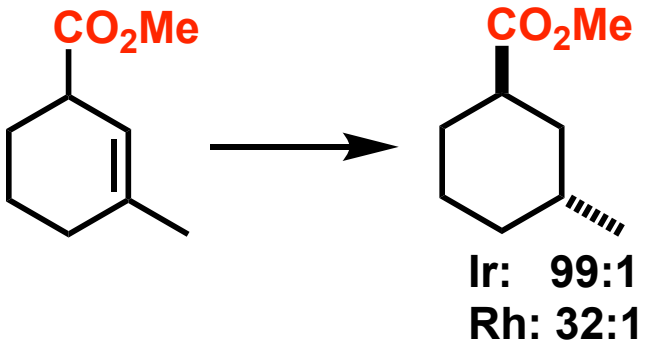


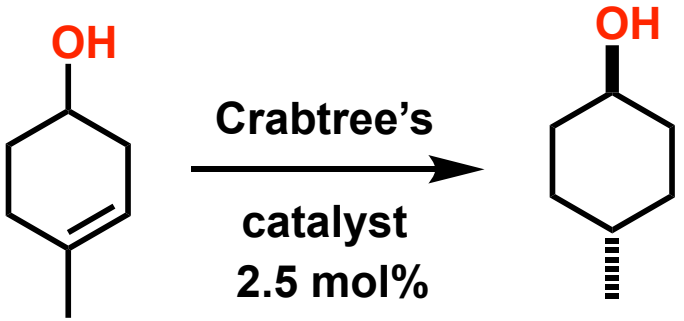


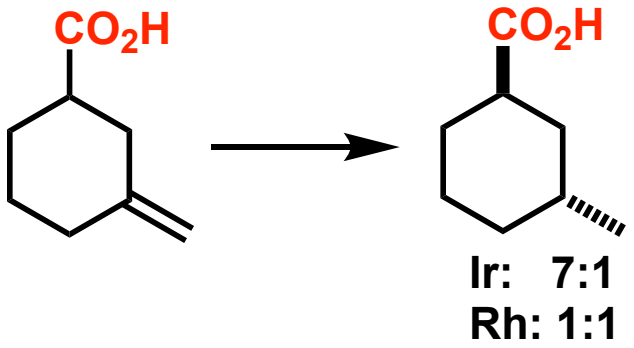


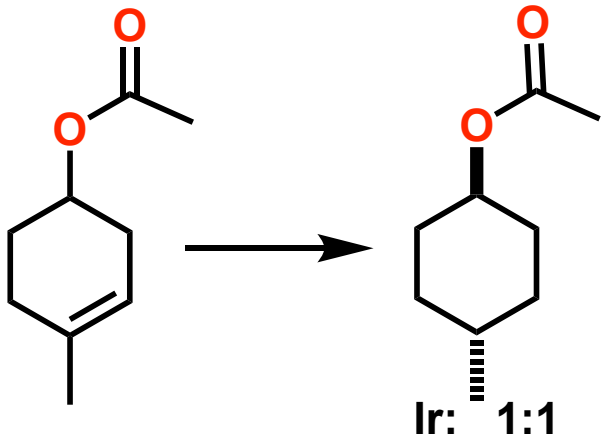
Directed Hydrogenation

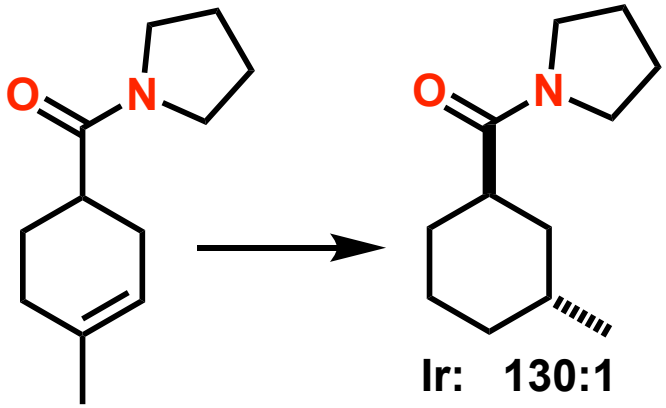






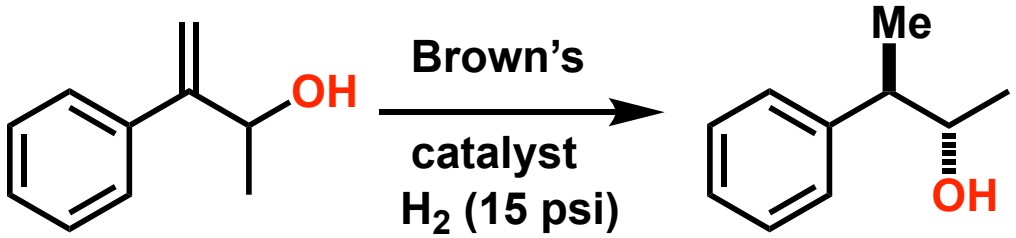


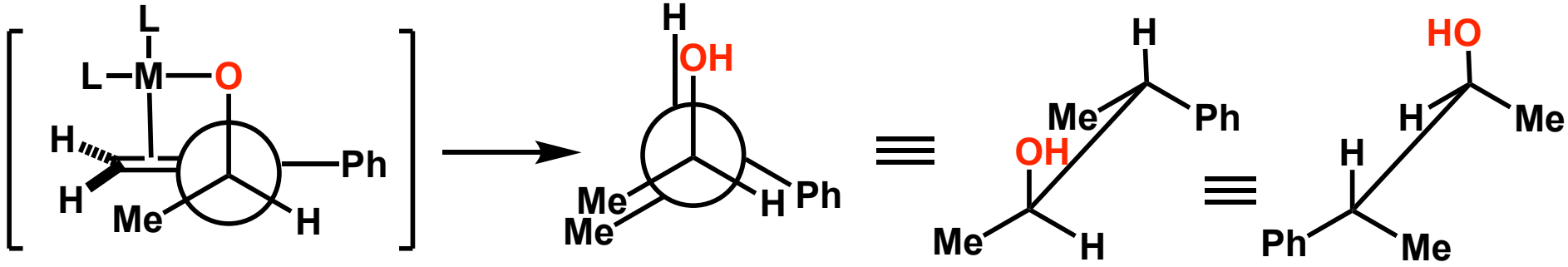


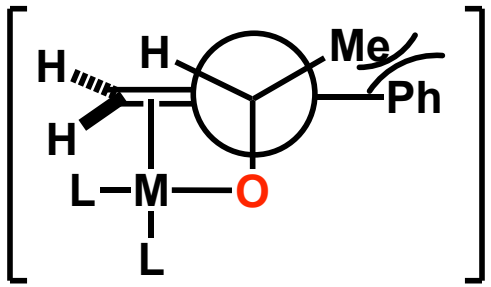


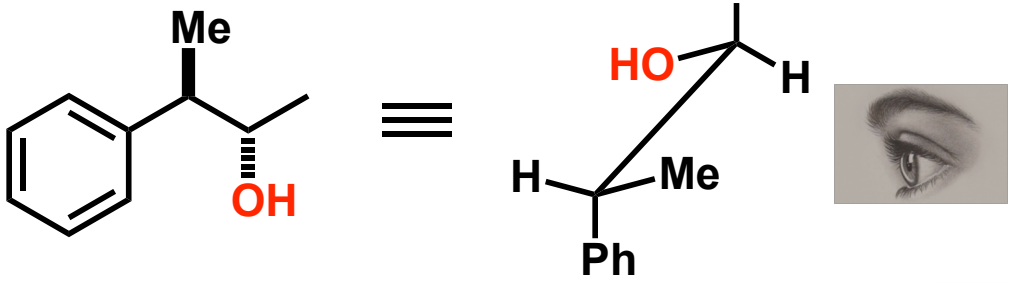
Acyclic Systems

Rhodium catalyst is more selective for acyclic systems



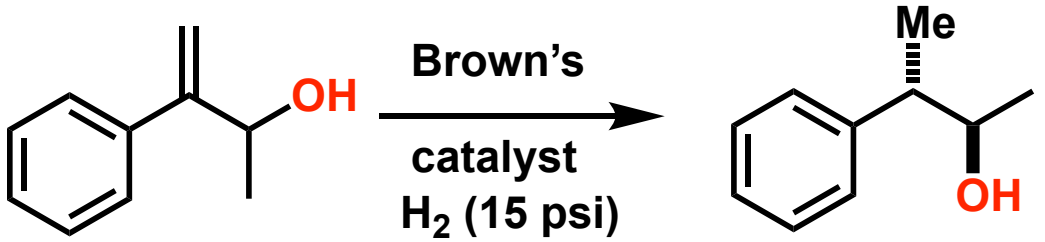


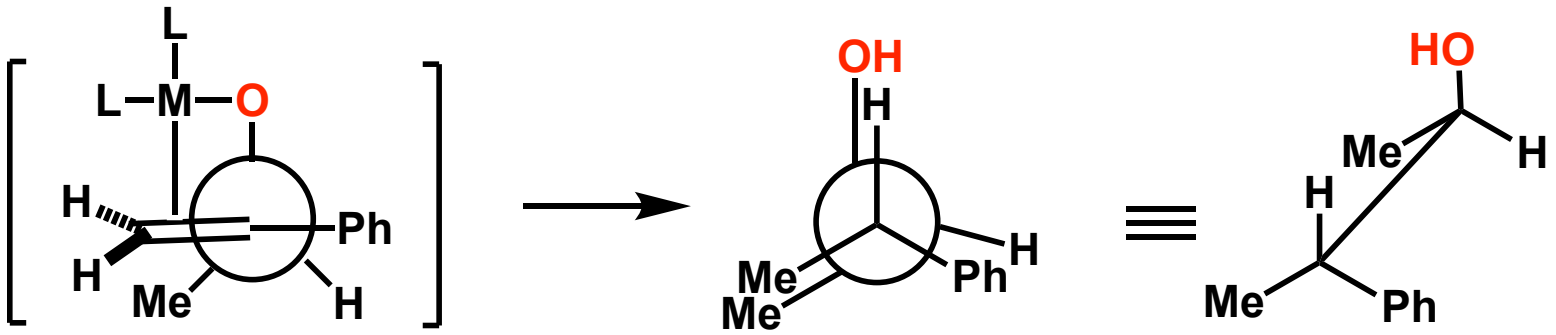


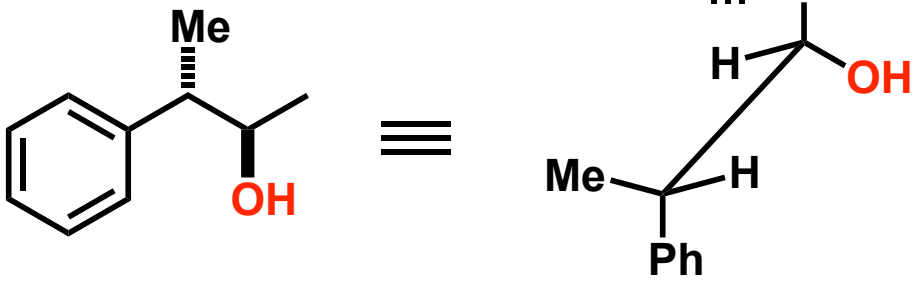


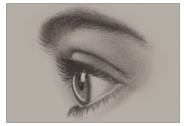
Acyclic Systems

Rhodium catalyst is more selective for acyclic systems



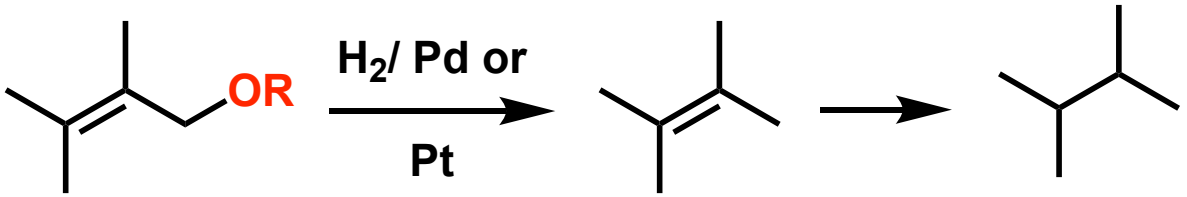


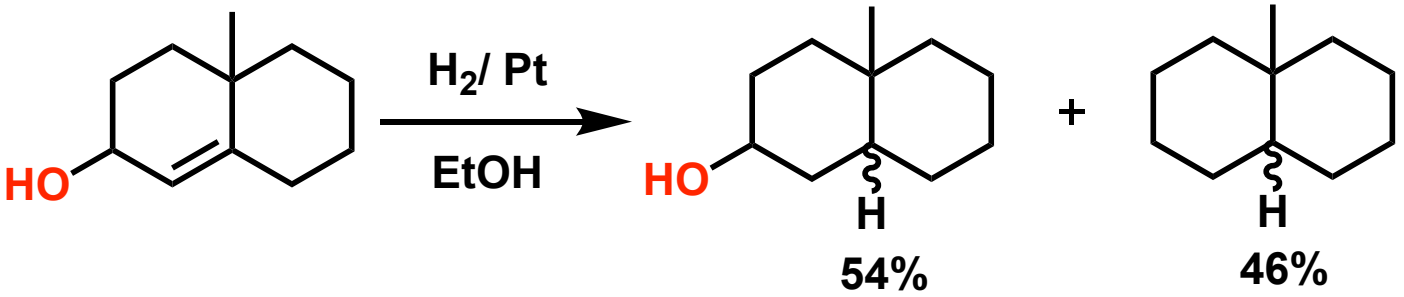




Hydrogenolysis

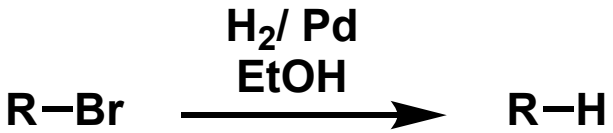
Hydrogenolysis can be done on allylic and benzylic ethers

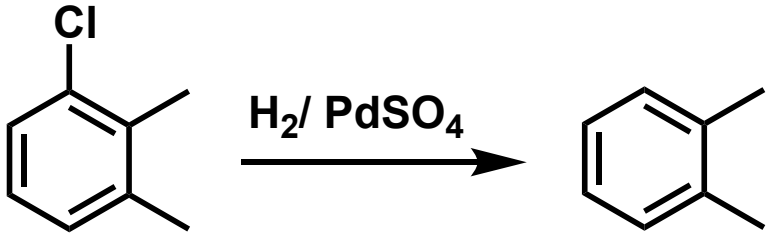


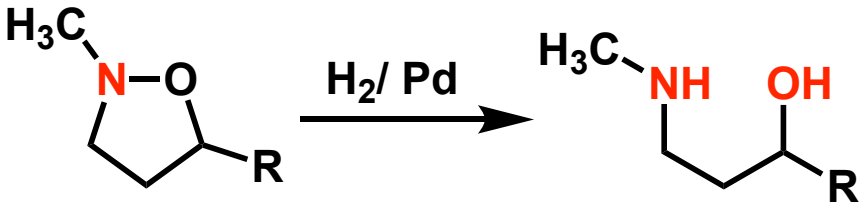


Hydrogenolysis

Hydrogenolysis on alkyl/aryl halides and isoxazolidines







Boron Based Reagents

- $NaBH_4$
- $NaBH_4/CeCl_3$
- $NaCNBH_3$
- $Zn(BH_4)_2$
- $LiBH_4$
- $NaBH_4/NiCl_2$
- $Na(OAc)_3BH$
- $Me_4N(OAc)_3BH$
- K-Selectride
- L-Selectride
- Superhydride

Sodium borohydride

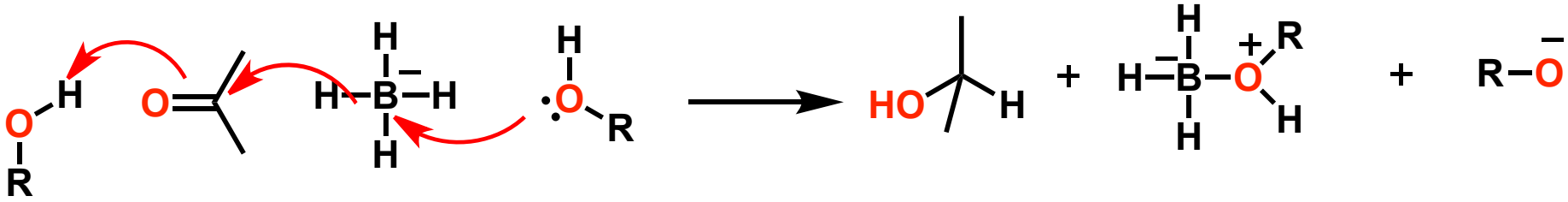
$NaBH_4$

Temperature: 0-25 °C

Substrate: RCHO, RCOR, RCOCl, $R_2C{=}NR$

Solvents: EtOH, MeOH, Dimethoxy ethane (DME)

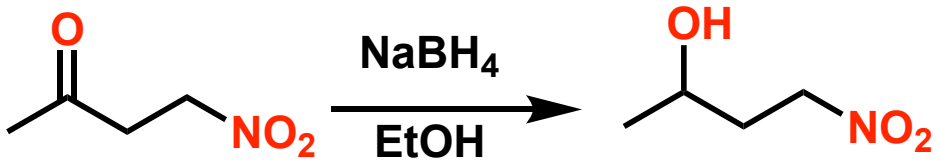
Mechanism:

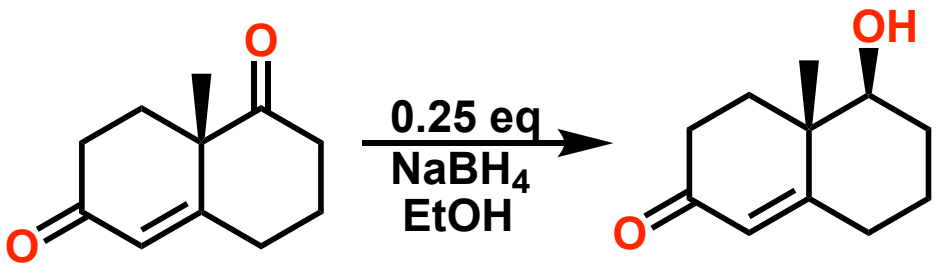


0.25 equivalents of $NaBH_4$ is required

Sodium borohydride

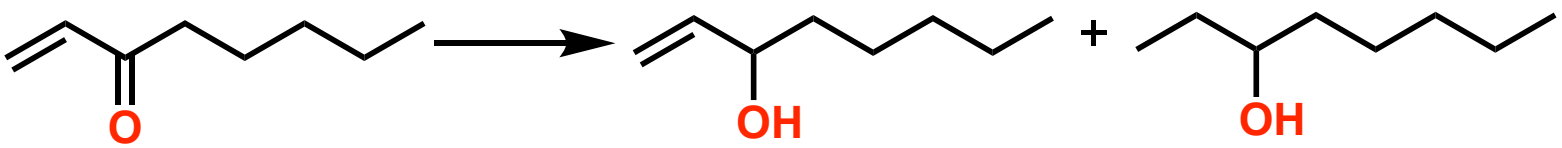
Selectivity





Luche Reduction

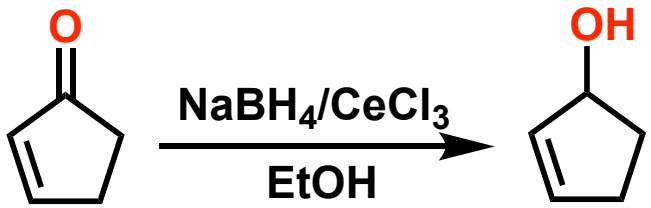
$CeCl_3$ is a good Lewis acid & highly oxophilic

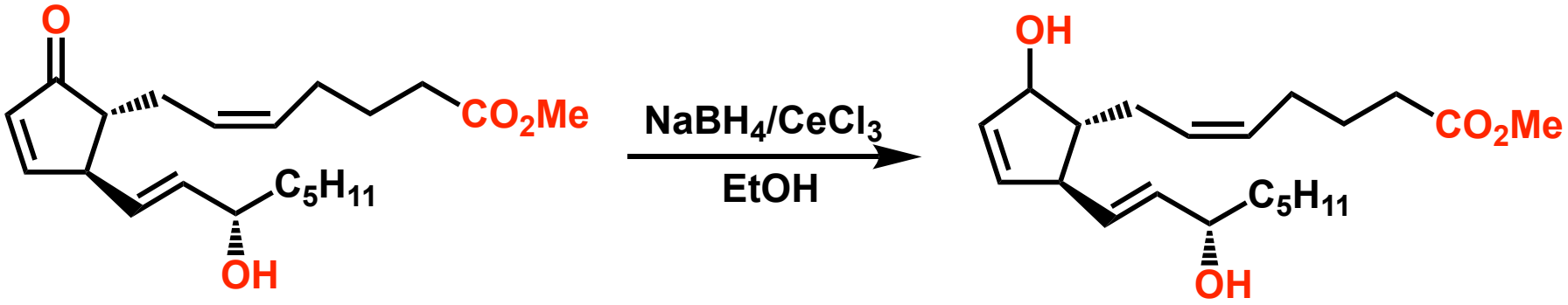


$NaBH_4$	80-90%	10-20%
$NaBH_4$ / $CeCl_3$(1:1)/MeOH	100%	0%

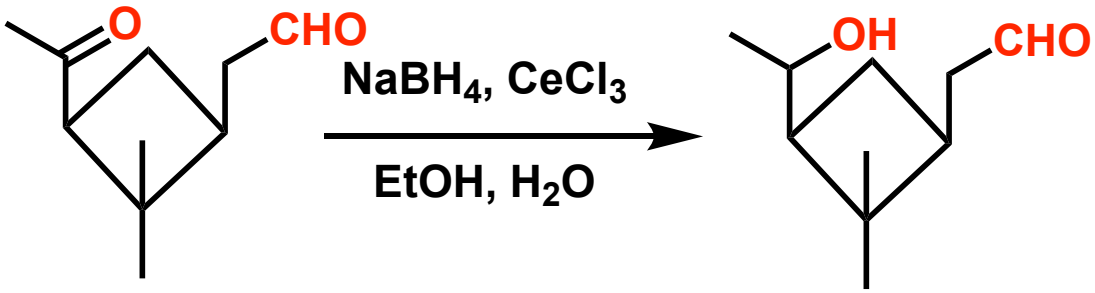
Sodium borohydride

Luche Reduction



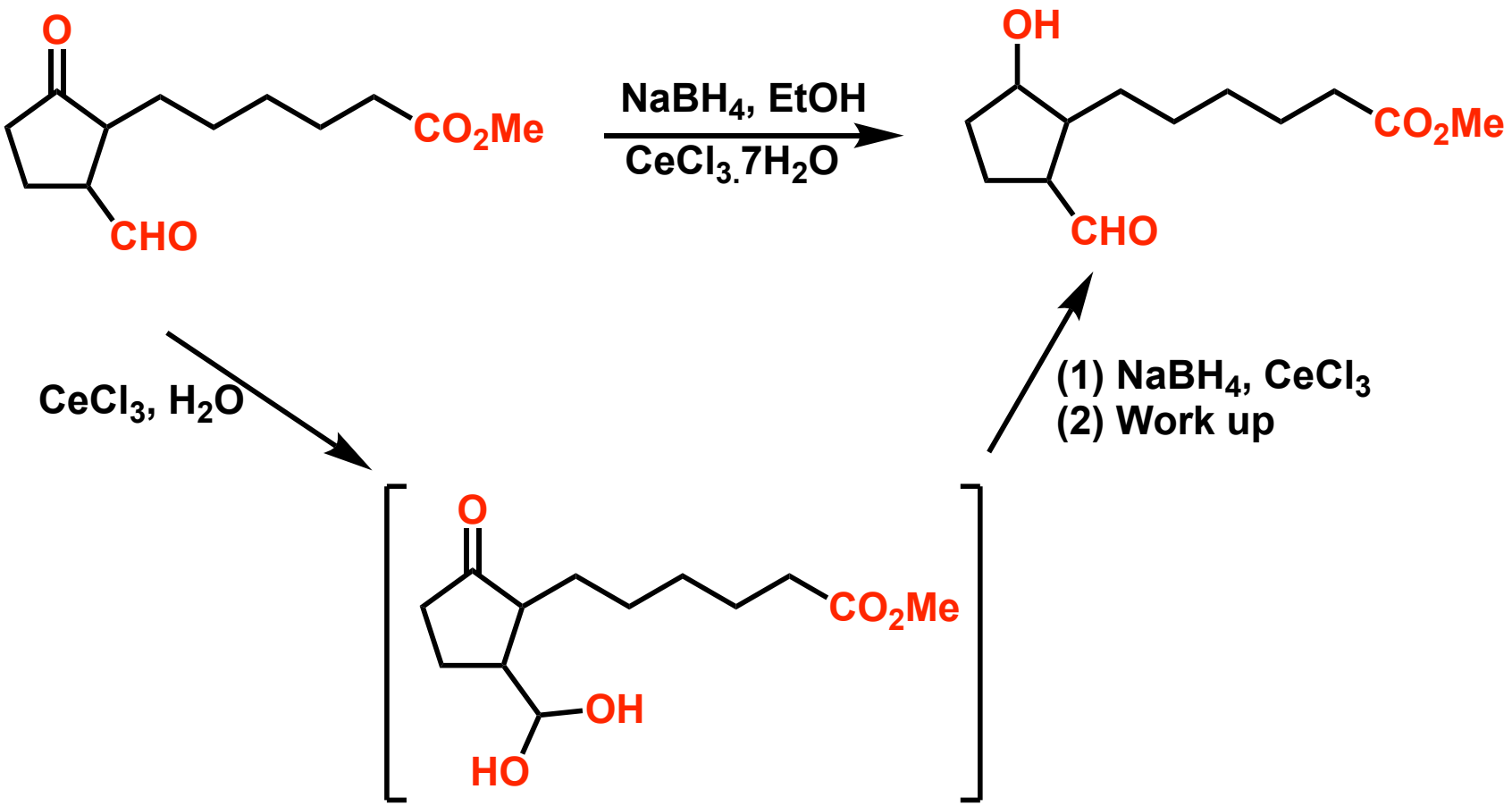


Selective reduction of ketones in presence of aldehydes:



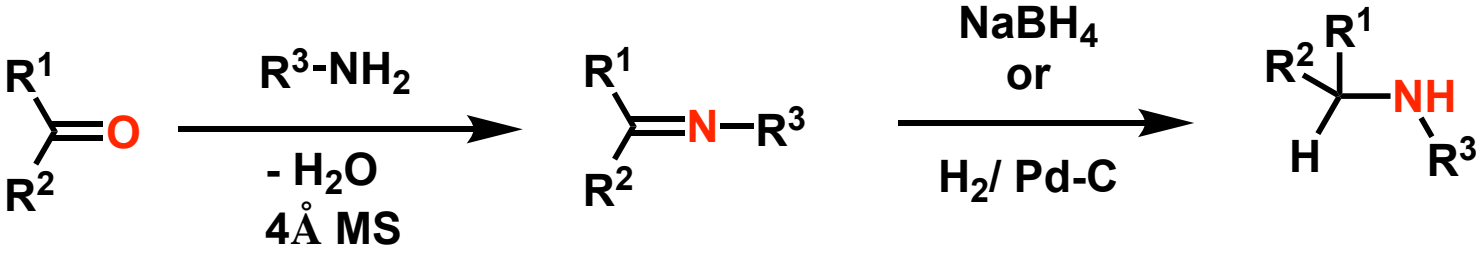
Sodium borohydride

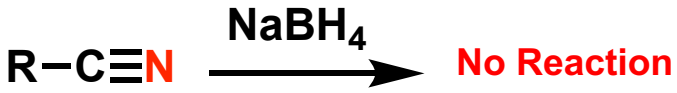
Selective reduction of ketones in presence of aldehydes and esters:



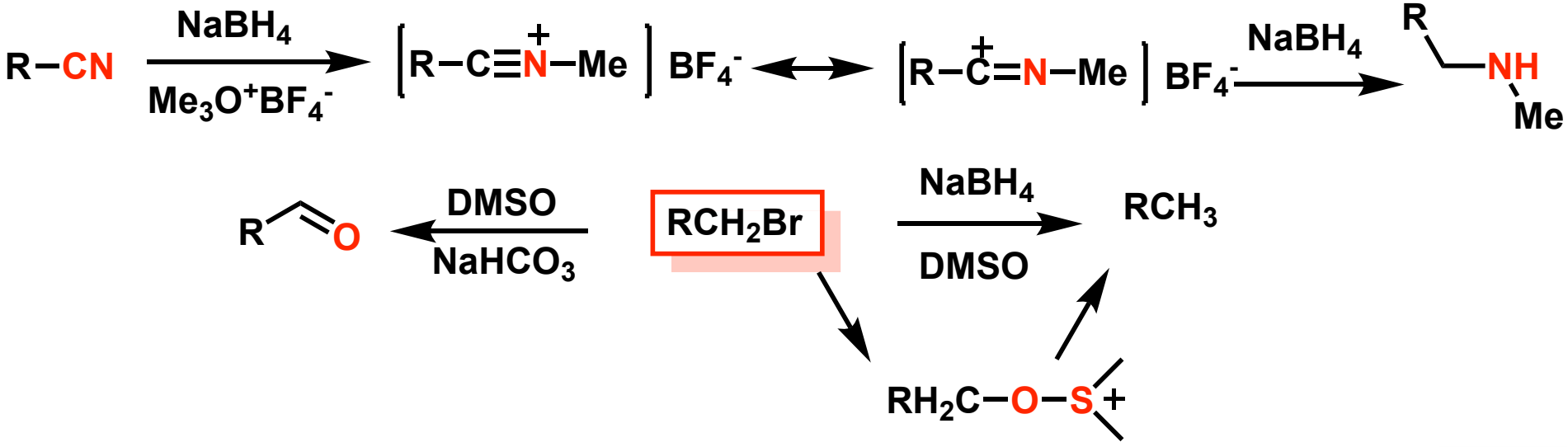
Sodium borohydride

Reduction of imines:

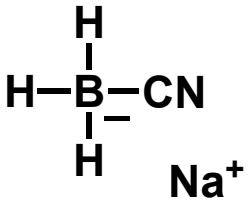




$NaBH_4$ can't reduce RCN unless Meerwein's salt ($Me_3O^+BF_4^-$) is used



Sodium Cyanoborohydride

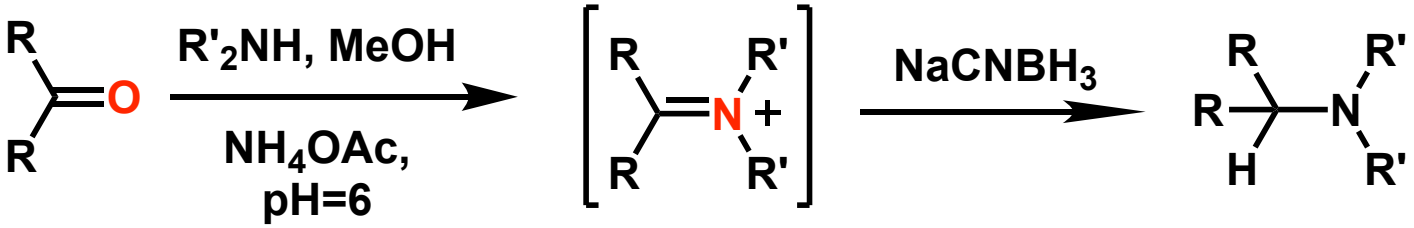


At pH 3-4, It reduces aldehydes & ketones
At pH 6-8, It reduces iminium ions

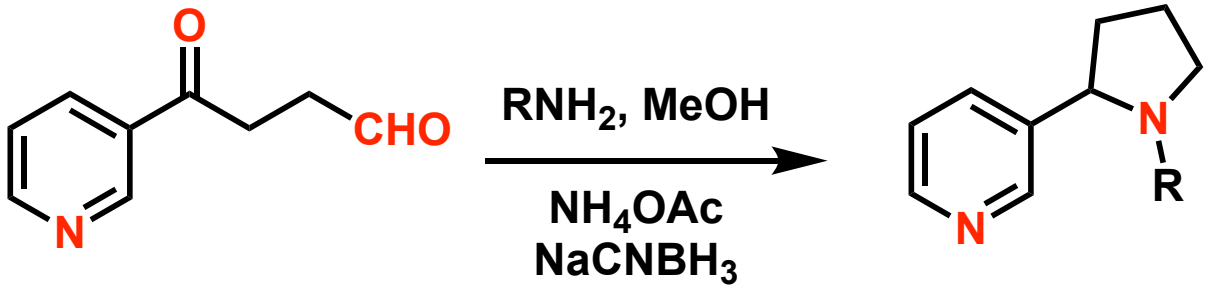
Less reactive than $NaBH_4$. Used predominantly in reductive aminations (Borsch Reduction)

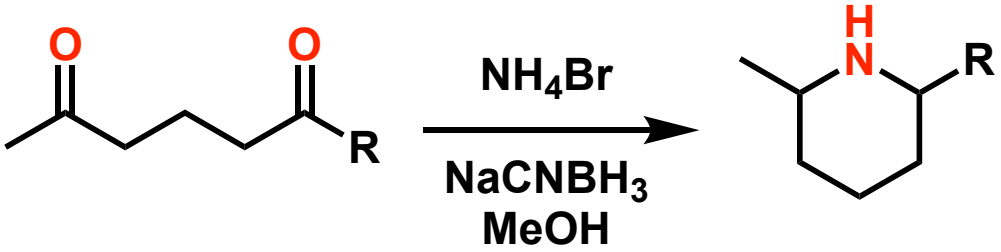
Electron withdrawing cyano group decreases the ease of hydrogen transfer

$NaBH_3CN$ reduces iminium ions much more quickly than ketone or aldehyde

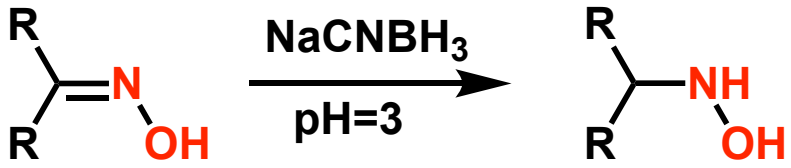


Sodium Cyanoborohydride

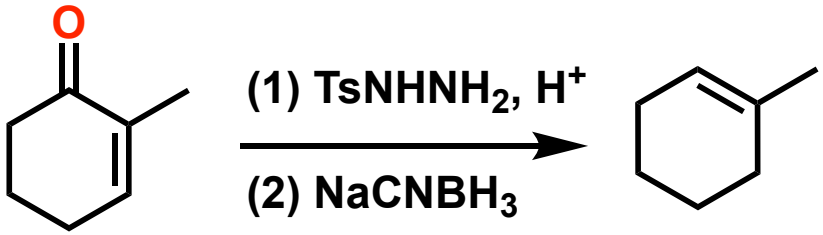




Reduction of oximes:

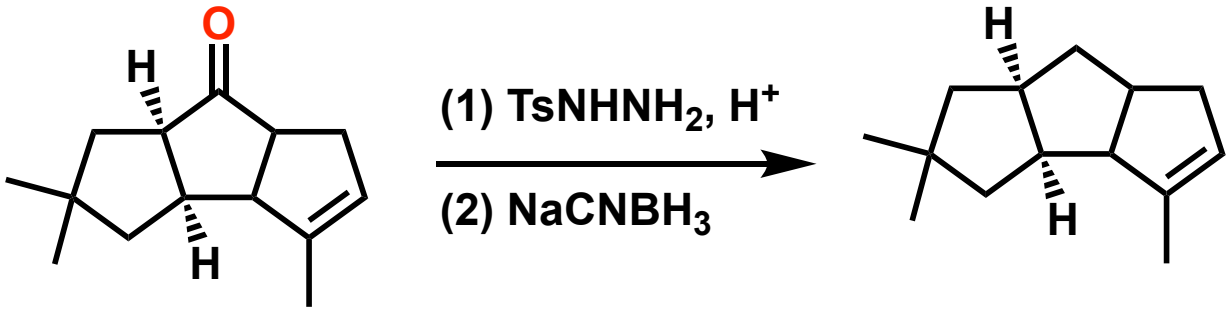


α,β- Unsaturated ketones:

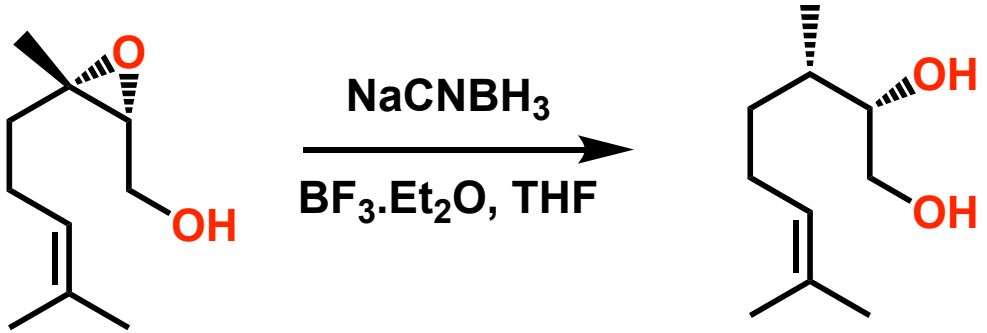


Sodium Cyanoborohydride

Reduction of tosylhydrazones:



Epoxide openings:



Drawback:

Sometimes strong acids can release HCN from $NaCNBH_3$

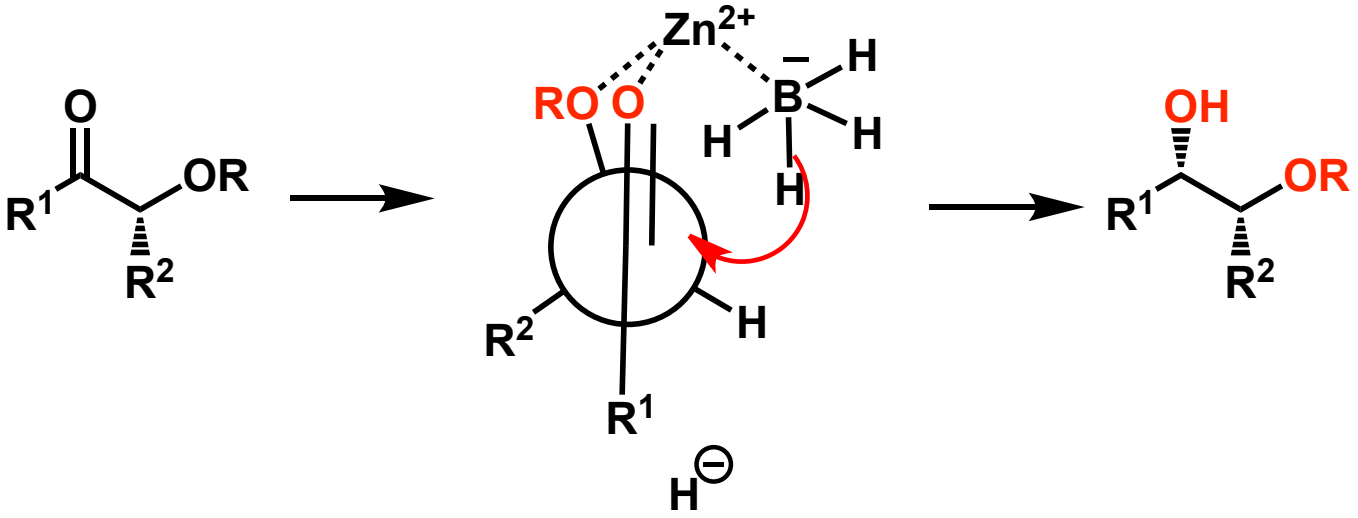
Zinc Borohydride

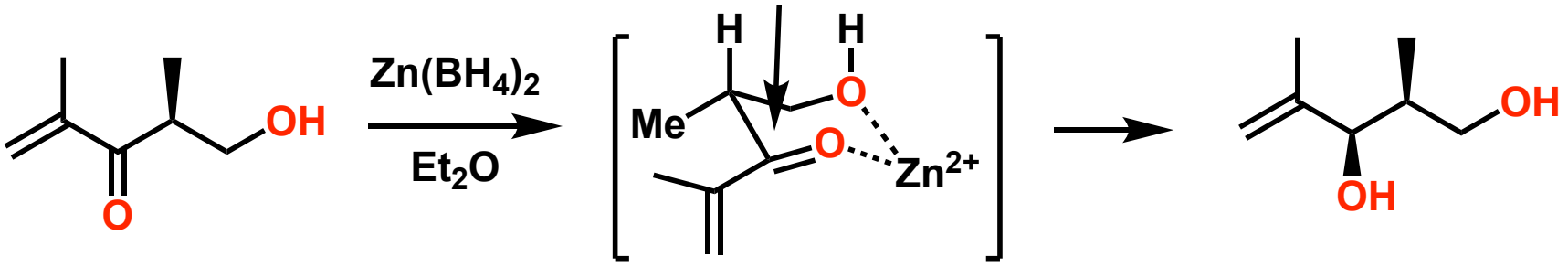
Preparation

$ZnCl_2$ (Ether) + $NaBH_4$ ⟶ $Zn(BH_4)_2$

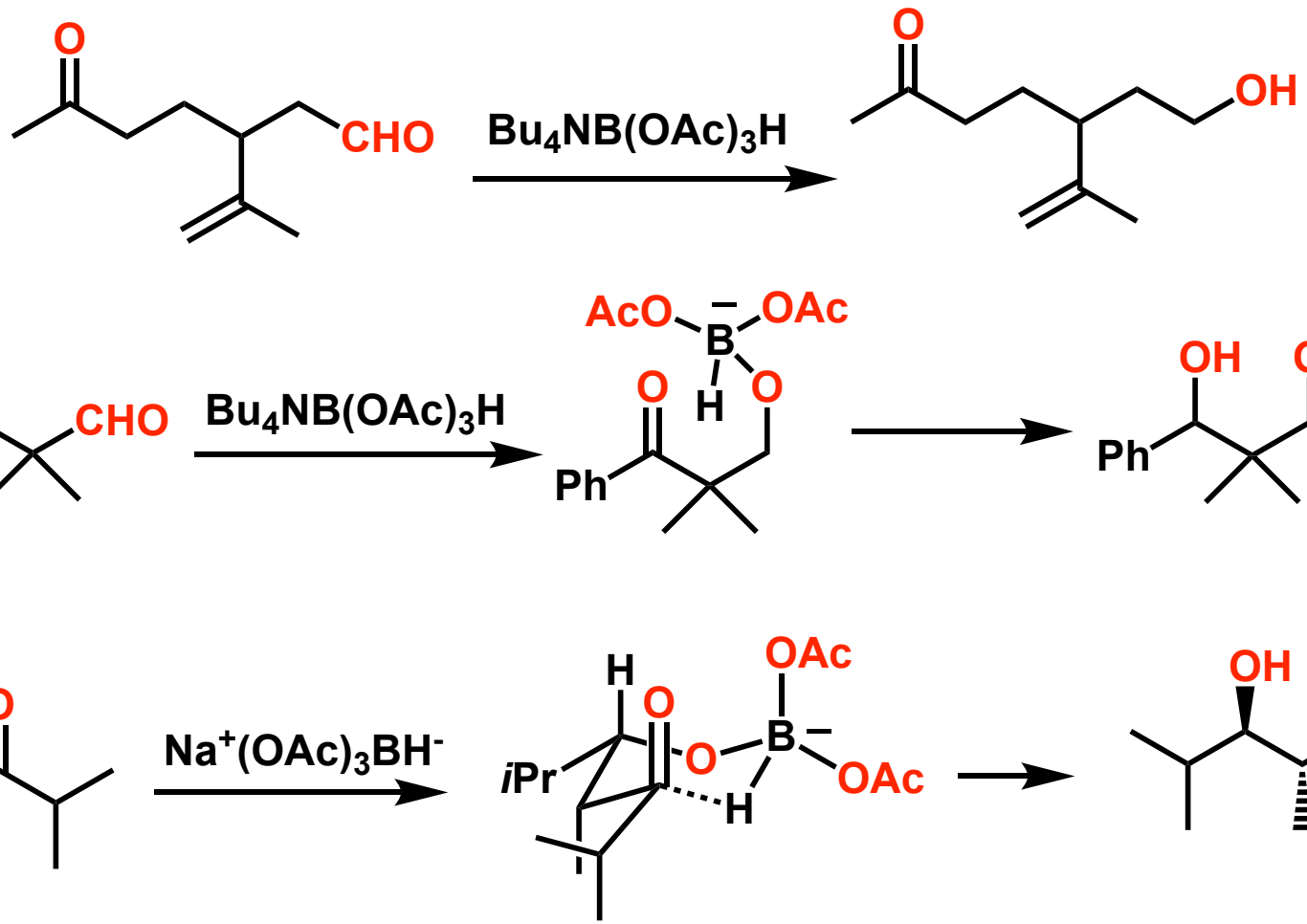
Good for base sensitive groups

Chelation control model



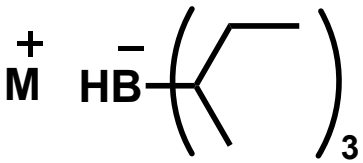


$NaB(OAc)_3H$ & $Me_4NB(OAc)_3H$



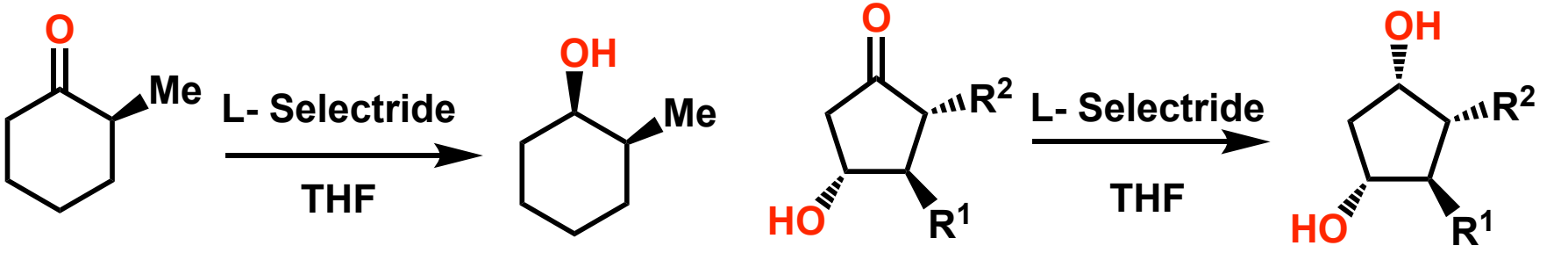
Alkylborohydrides

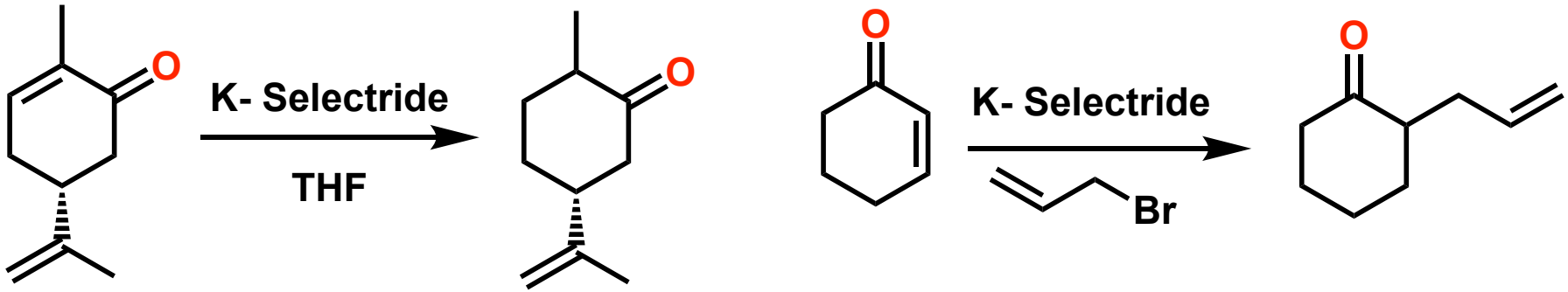
Selectrides:



M^+ = Li (L-Selectride)

= K (K-Selectride)



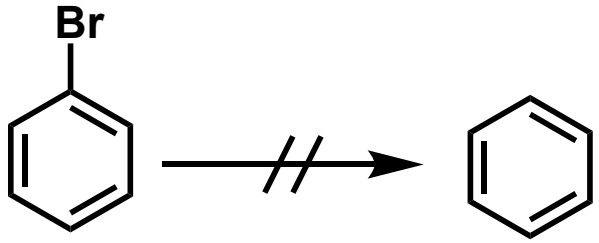


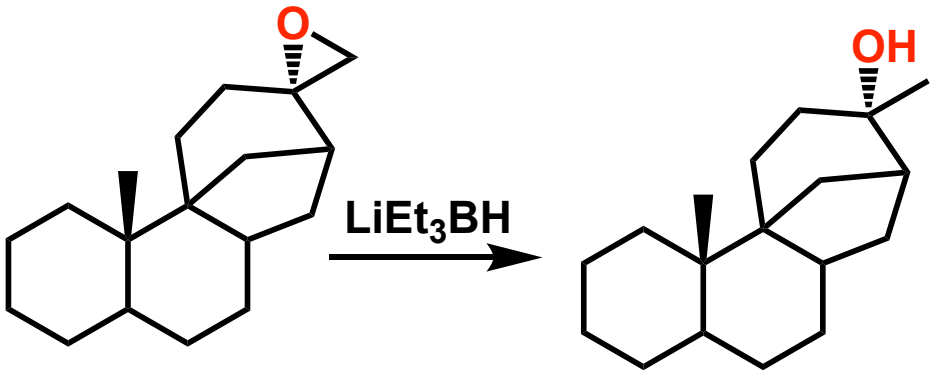
Alkylborohydrides

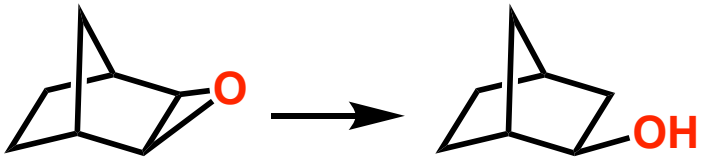
Superhydride: $LiBHEt_3$

Very reactive hydride source

Reduce ketones, aldehydes, esters, epoxides and C-X bonds



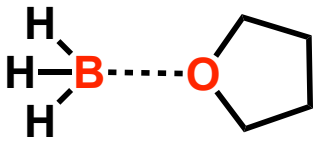




LAH 73%

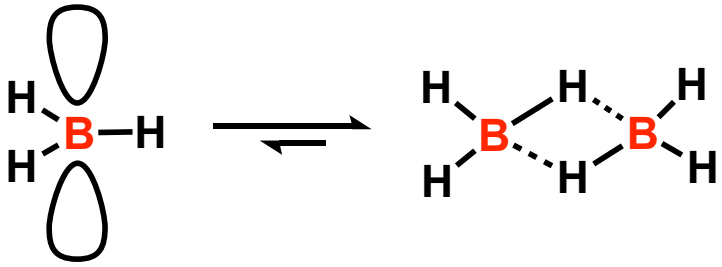
$LiEt_3BH$ 100%

Boranes



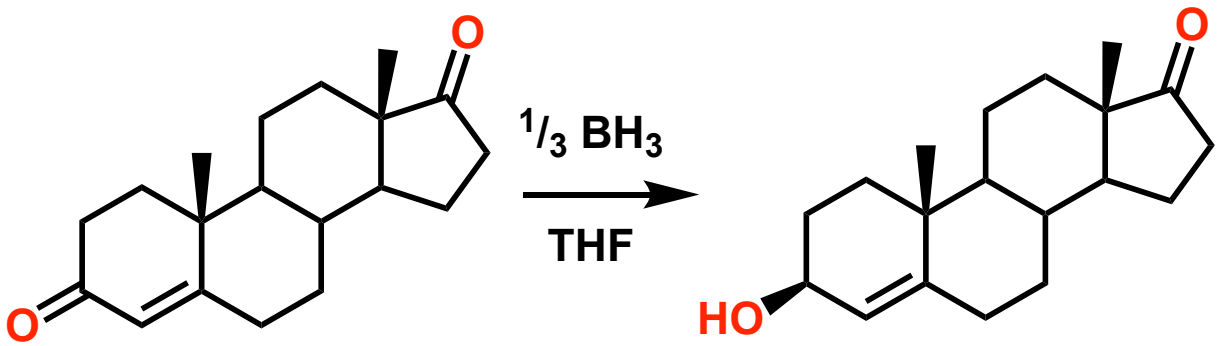
BH_3.THF

$BH_3.SMe_2$



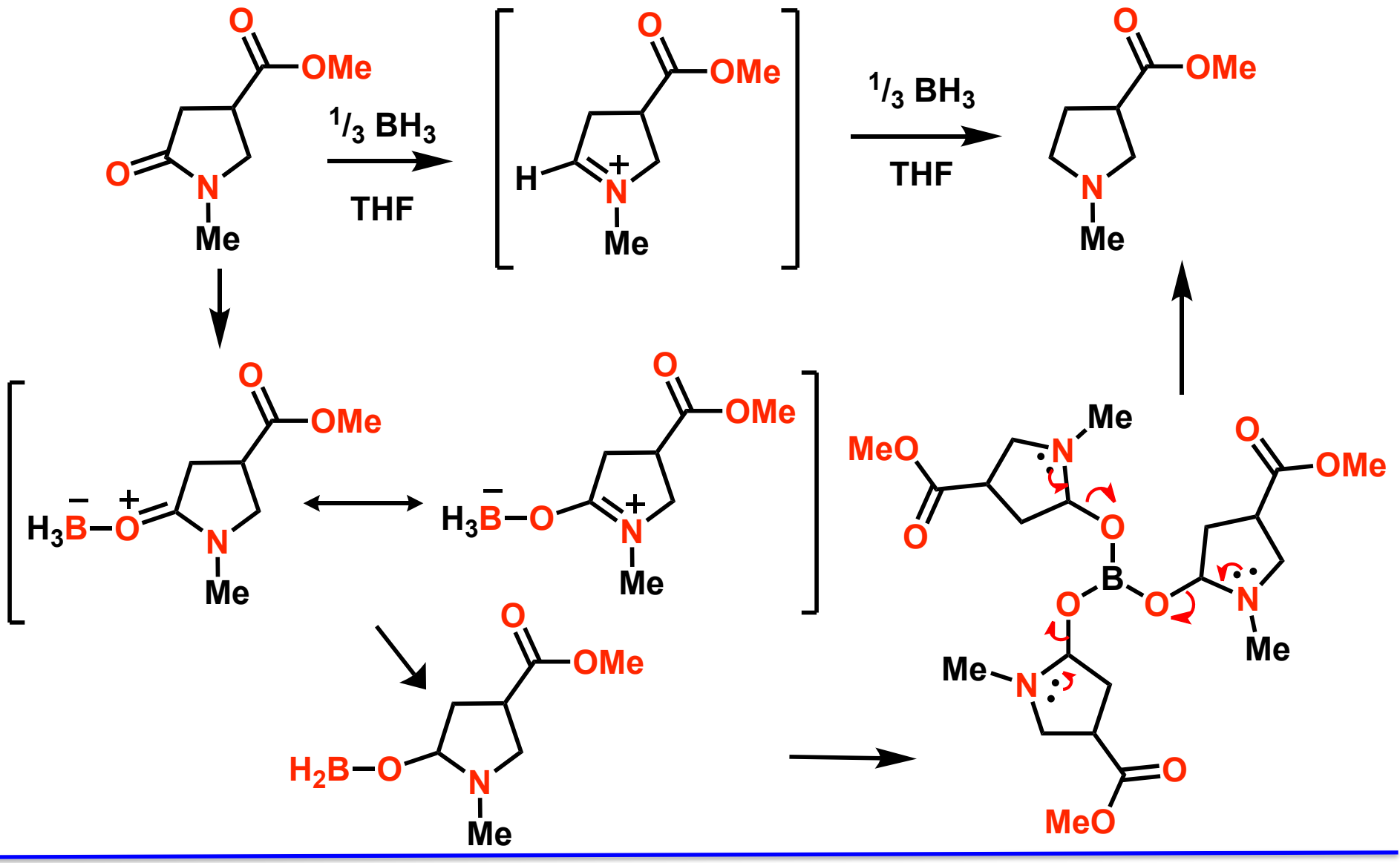
Diborane exists as a dimer

Borane is highly electrophilic. So, they attack the most electron rich center



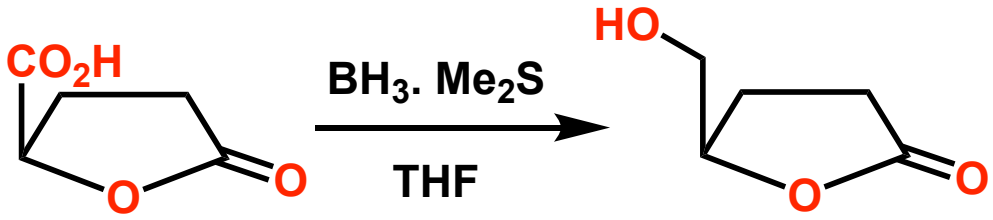
Similarly between an amide and ester, amide gets reduced first

Boranes

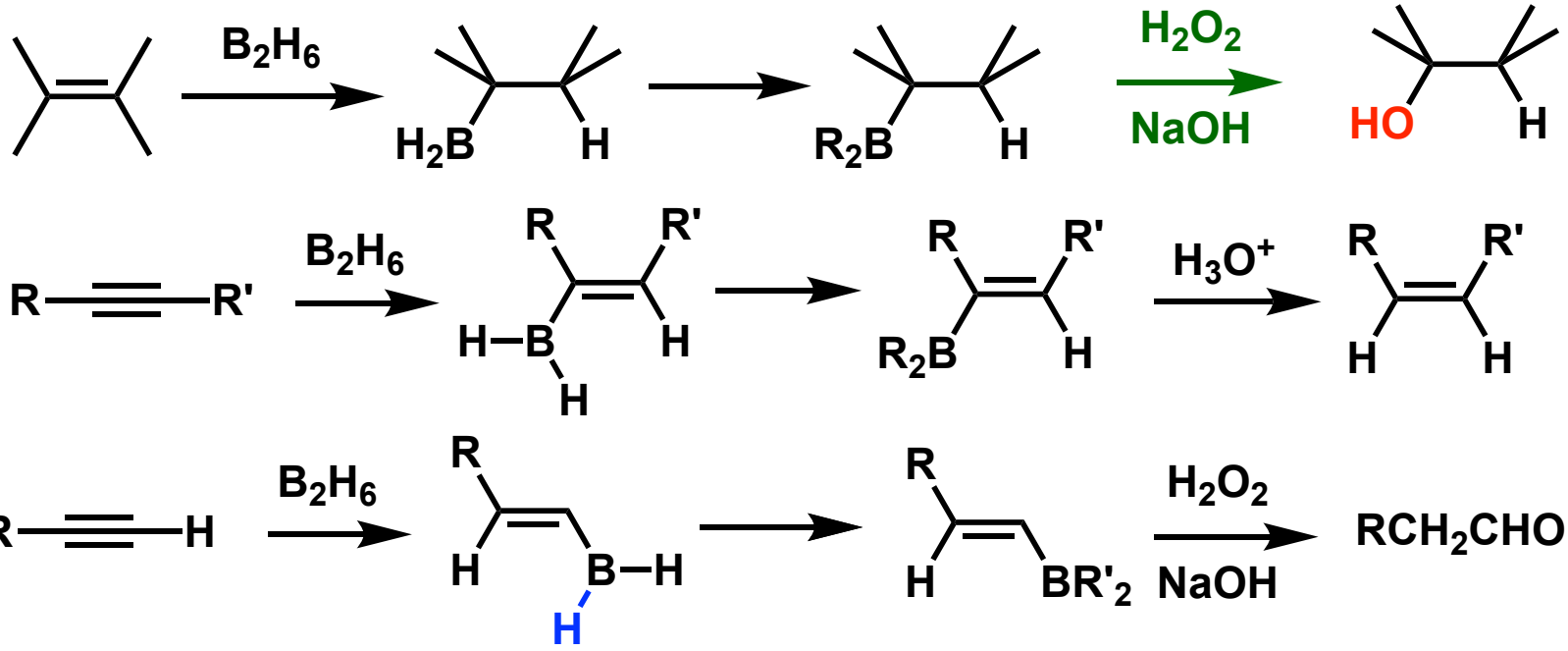


Boranes

BH_3 reduces carboxylic acids to primary alcohols in the presence of esters, nitro and cyano groups

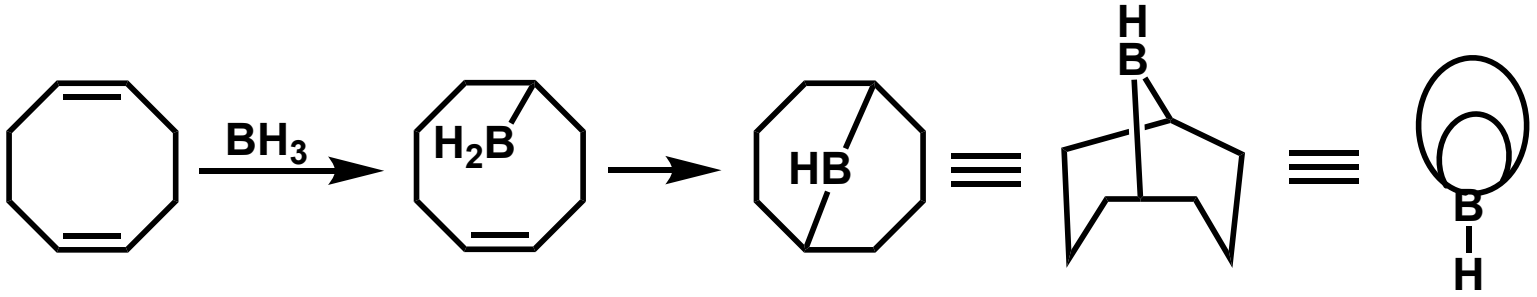


Hydroboration:

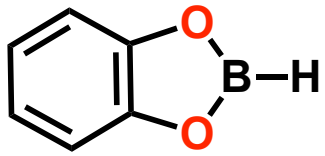


Boranes

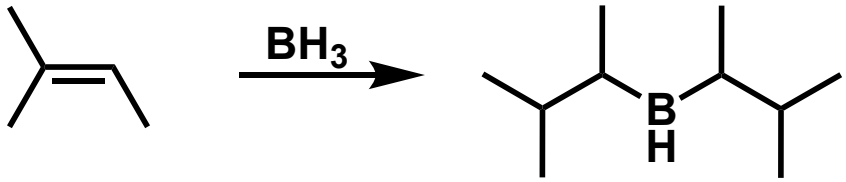
9-BBN



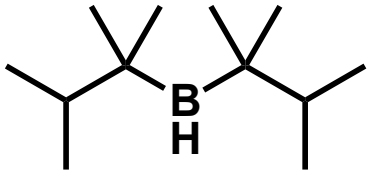
Catechol borane



Disiamyl borane(Sia_2BH)

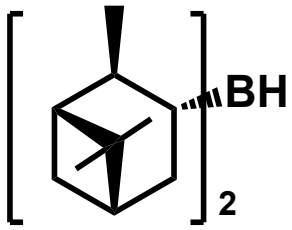


Thexyl borane

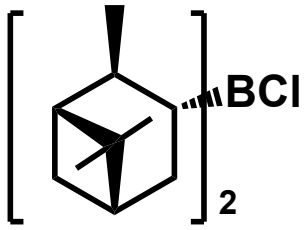


Chiral Boranes

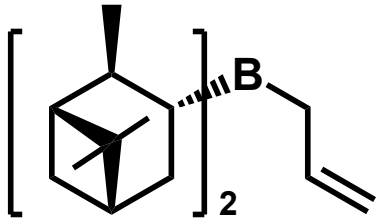
Pinylborane



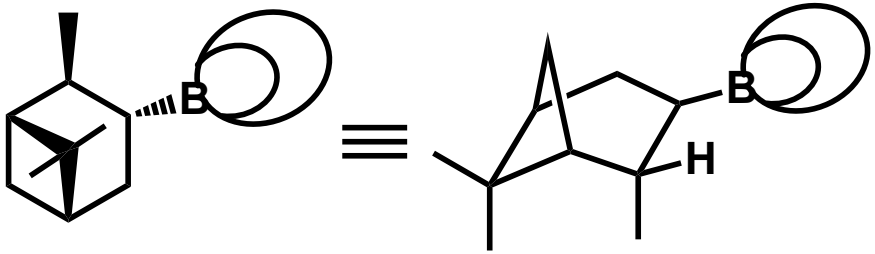
$(Ipc)_2BCl$



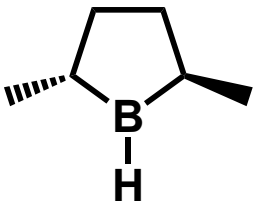
Brown's chiral allylborane



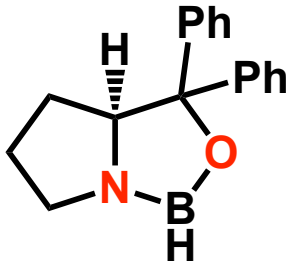
Alpine borane



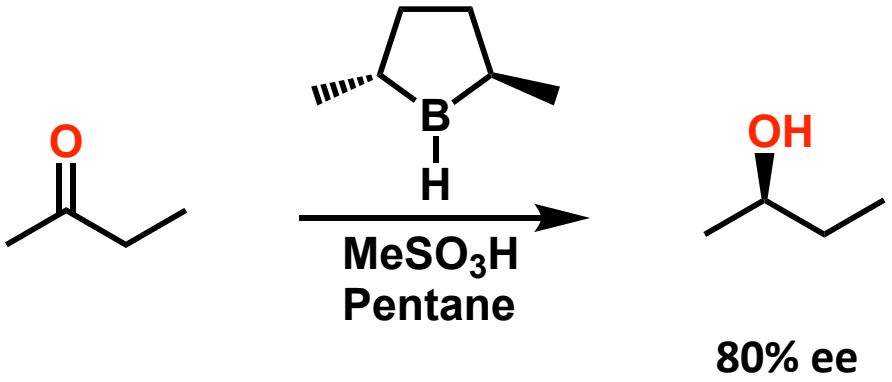
Masamune's oxoborolane



CBS (Corey-Bakshi-Shibata)

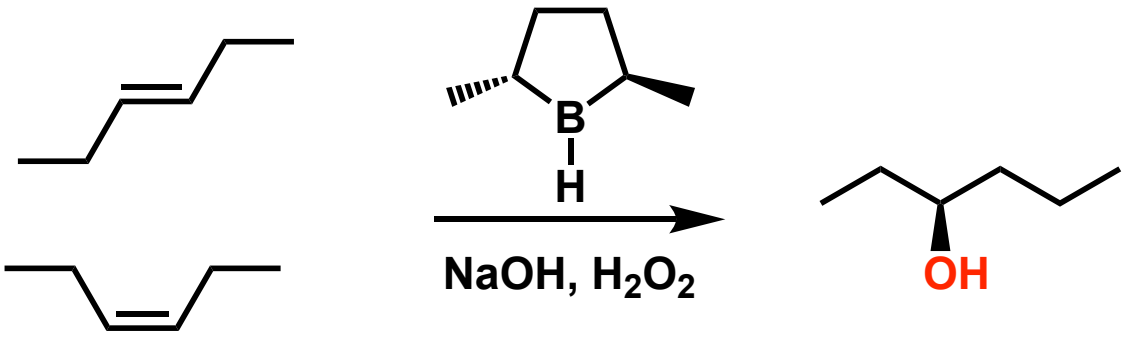


Asymmetric Reduction/Hydroboration



80% ee

Asymmetric hydroboration

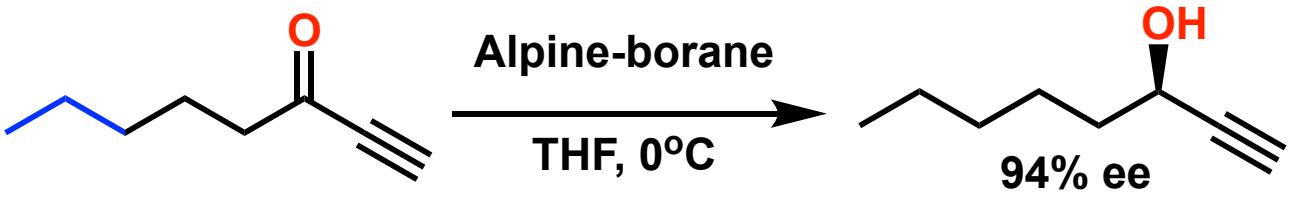


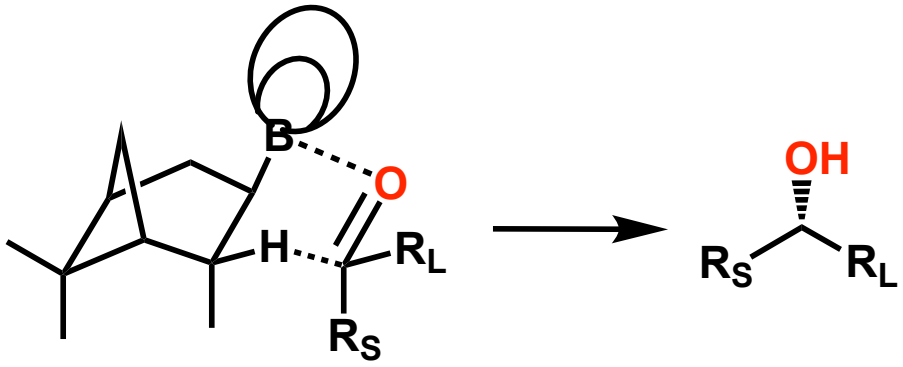
99% ee

Asymmetric Reduction/Hydroboration

Alpine Borane

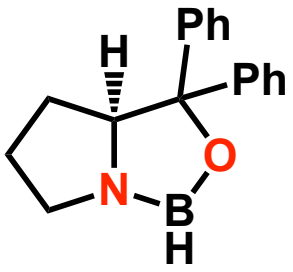
Works best for aryl & acetylenic ketones. Because of steric hindrance it is fairly unreactive



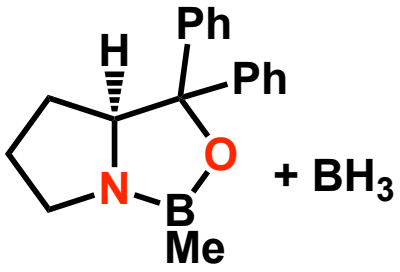


Asymmetric Reduction/Hydroboration

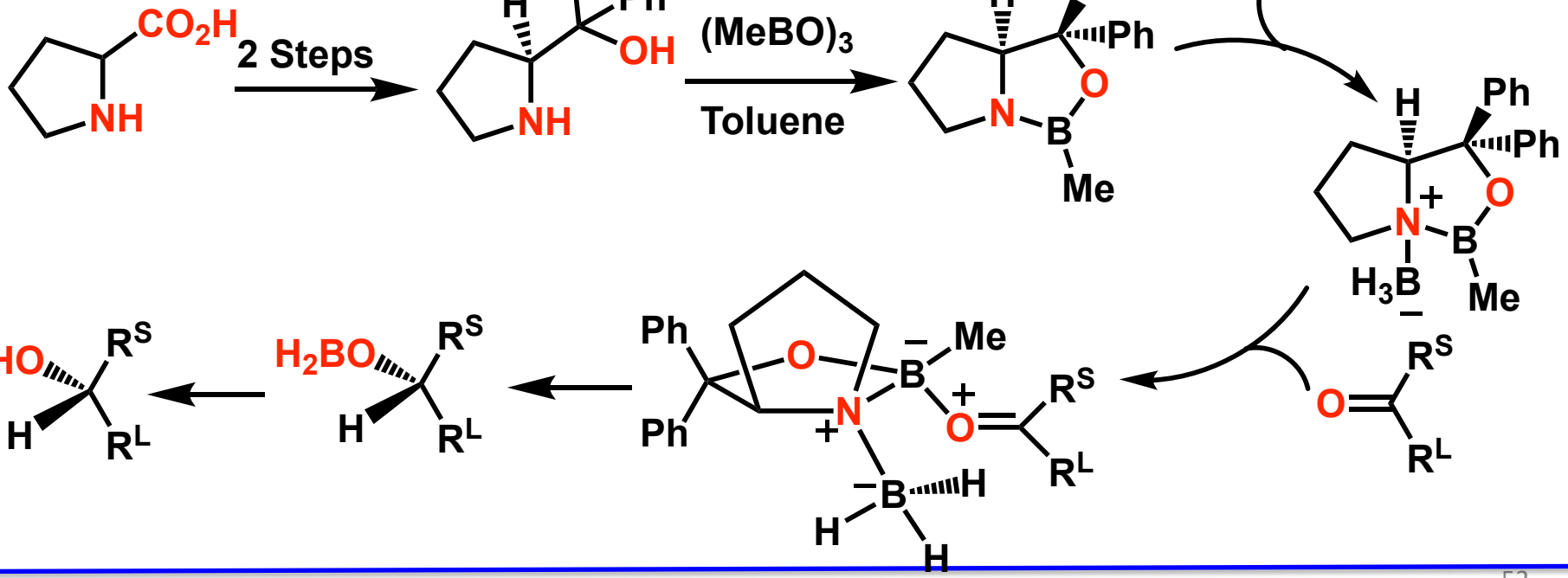
Oxazoborolidine



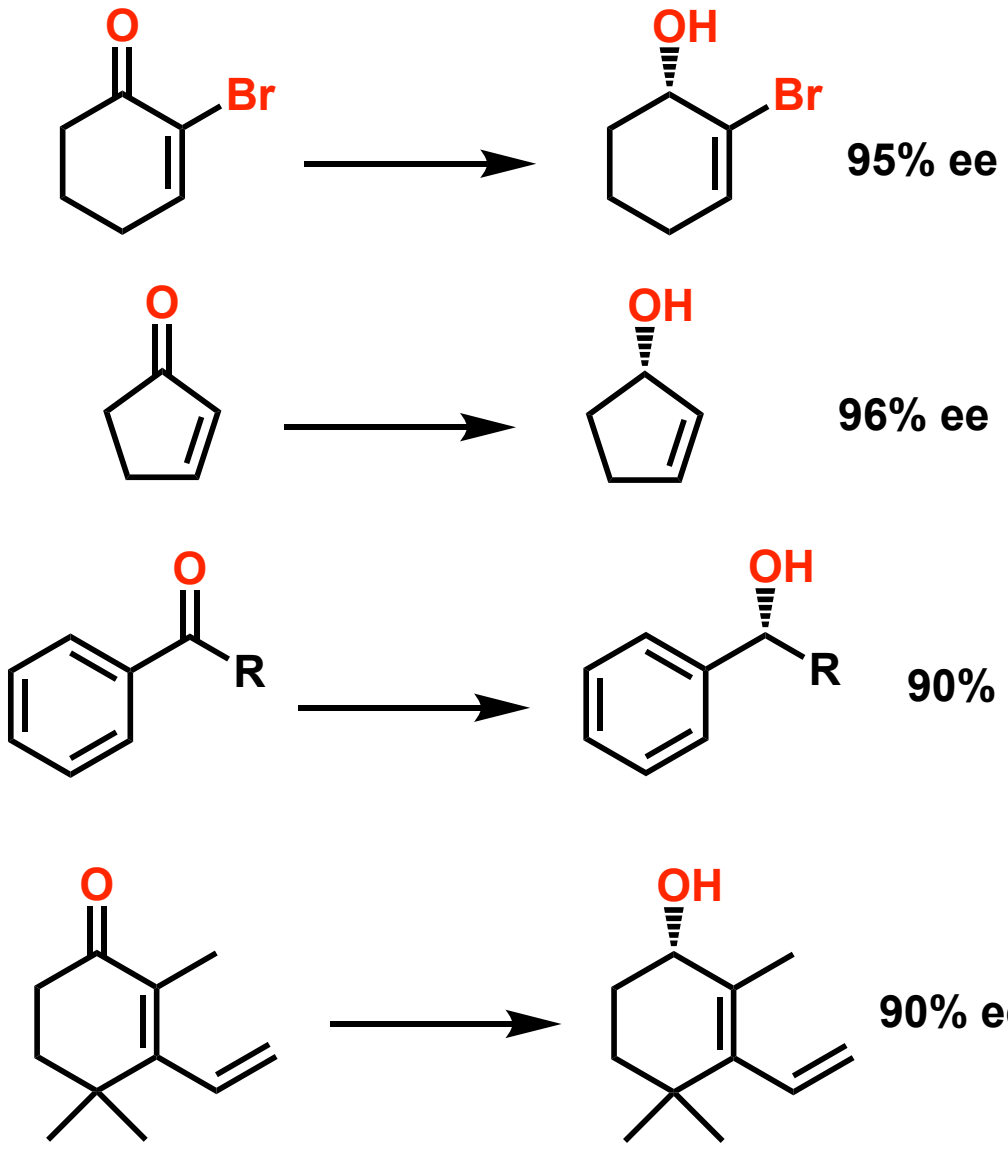
Stoichiometric



Catalytic

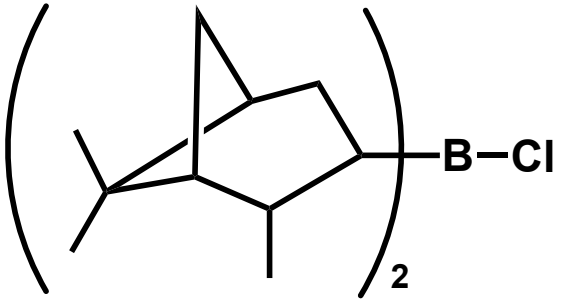


Oxazoborolidine



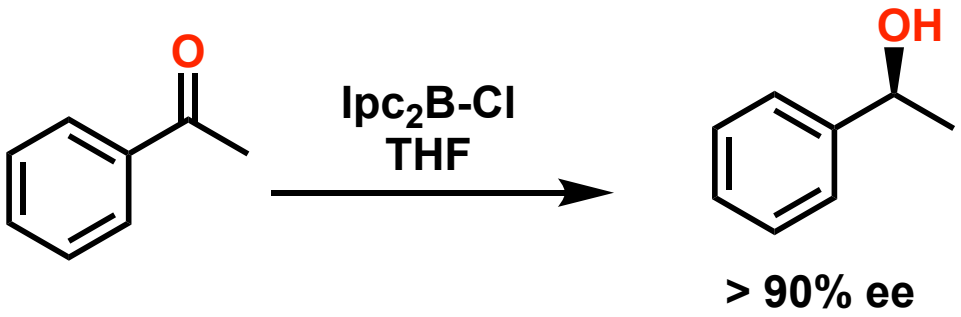
DIP-Cl

Chlorodiisopinylcamphenyl borane (DIP-Cl)



Chlorine increases the Lewis acidity of boron making it more reactive

Saturated ketones are reduced to chiral alcohols with varying degrees of ee



Boron based reagents

Comparison Between Borohydride and Boranes

Borohydrides	Boranes
Negatively charged	Neutral
Nucleophilic	Electrophilic
Valence shell of boron is completed octet	Boron contains six electrons and a vacant p-orbital
Hydride transfer occurs intermolecularly	Hydride transfer occurs via a Lewis acid-base complex

Aluminium based reagents

- $LiAlH_4$
- AlH_3
- DIBAL-H
- Red-Al
- $Li(O^tBu)_3AlH$
- MPV reduction
- BINAL-H

Lithium Aluminium Hydride

Very powerful reducing reagent

Available as either powder or pellet

Used as a suspension in ether or THF

Reacts violently with water, alcohol

Reduces carbonyl, carboxylic acid & ester

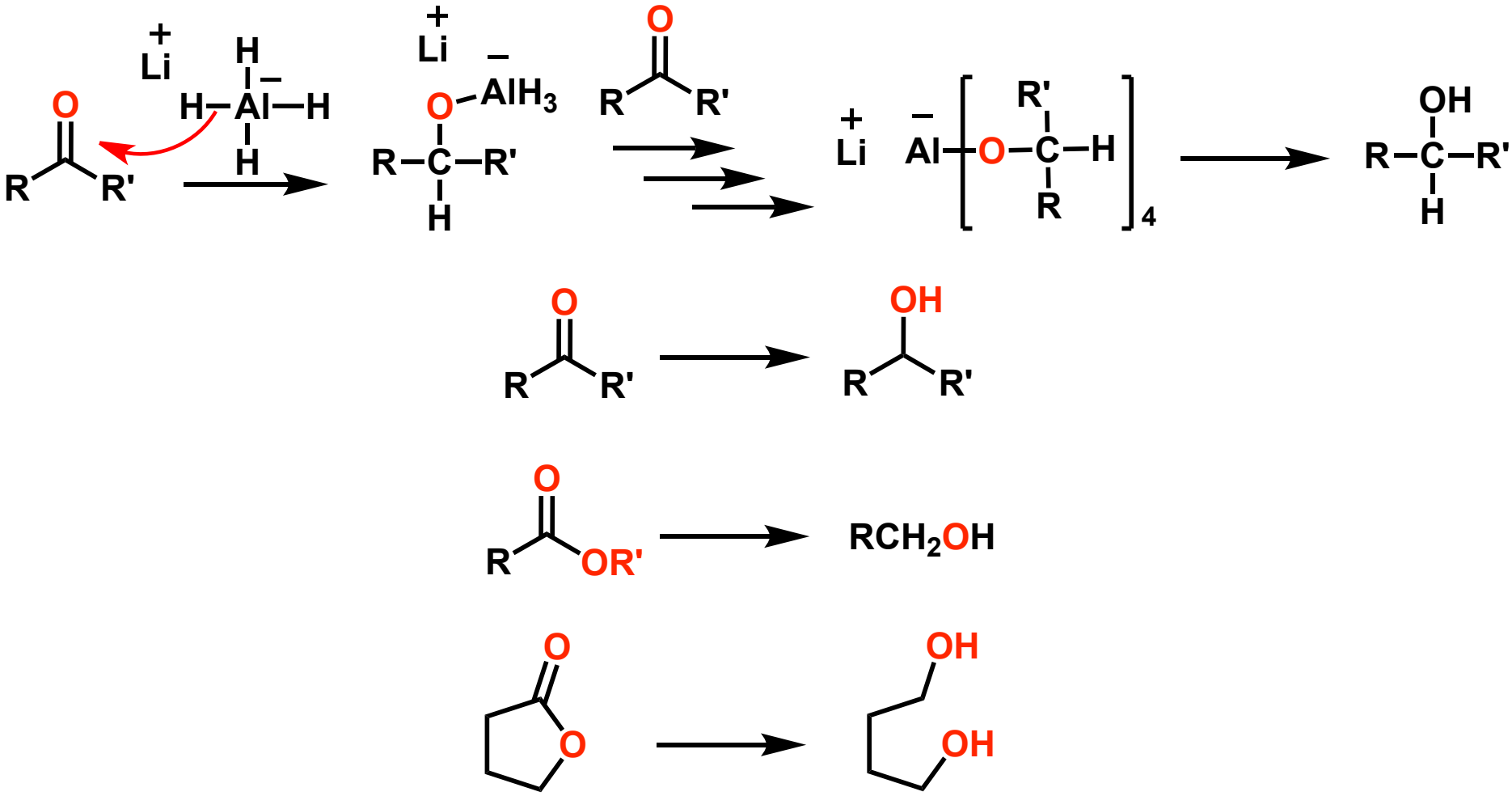
Reduces acetylene to olefin

Reduces C-X bond, opens epoxide

Reduces nitrile, amide & aryl nitro group to amine

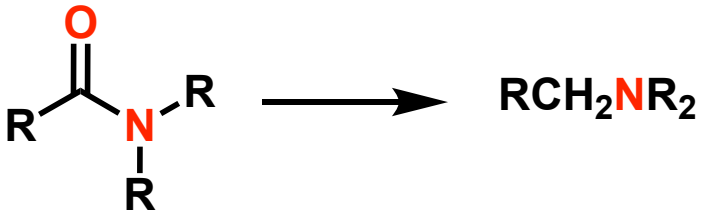
Lithium Aluminium Hydride

Mechanism

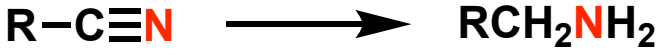


Lithium Aluminium Hydride

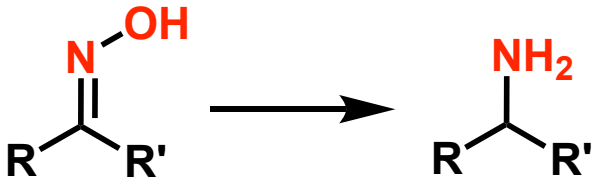
Amides



Nitriles

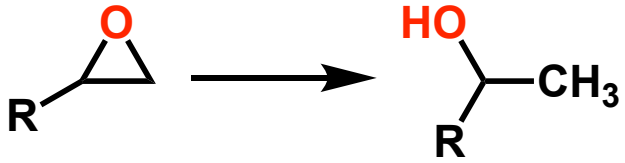


Oximes

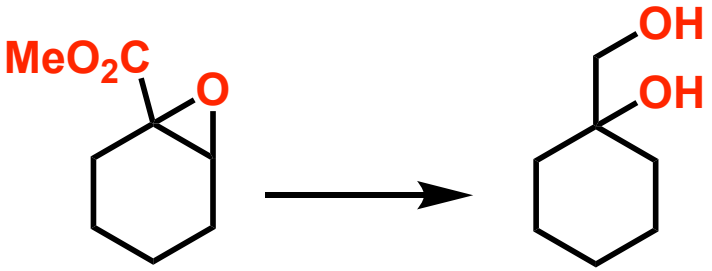


Nitro

Epoxides

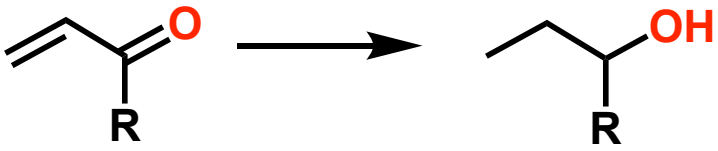


Epoxyesters

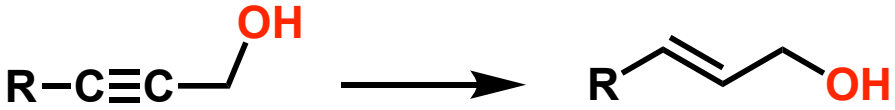


Lithium Aluminium Hydride

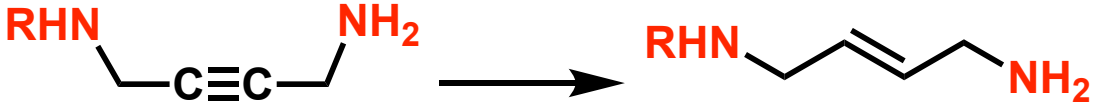
Unsaturated Ketones



Propargylic Alcohols

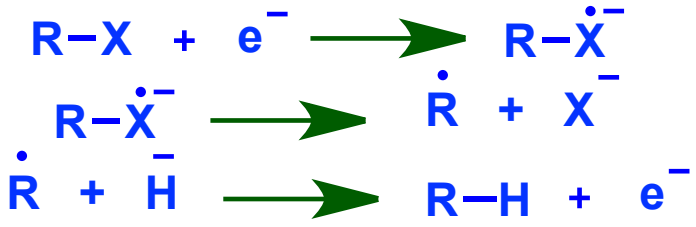


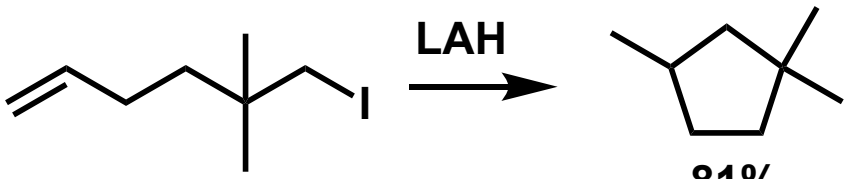
Propargylic Amines



Alkyl Halides

Reduction of alkyl halides go via radical mechanism

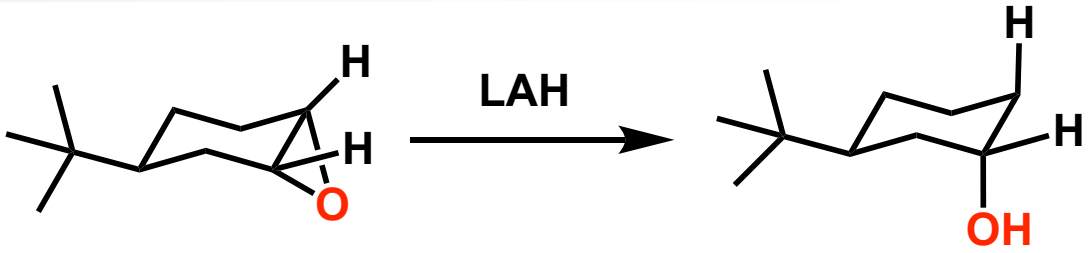




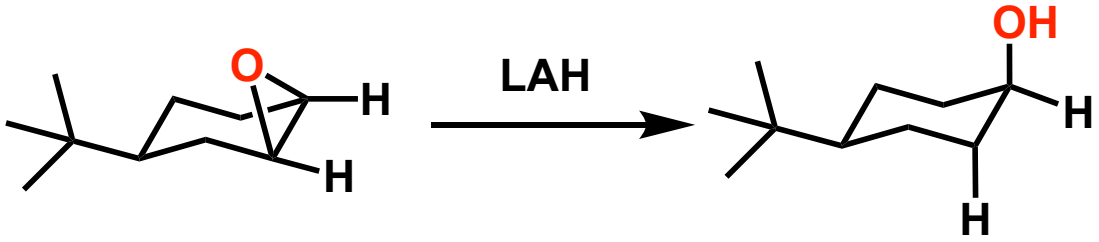
81%

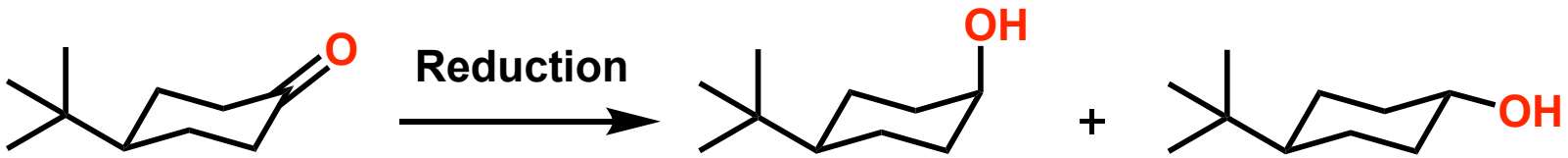
Lithium Aluminium Hydride

Epoxide Opening



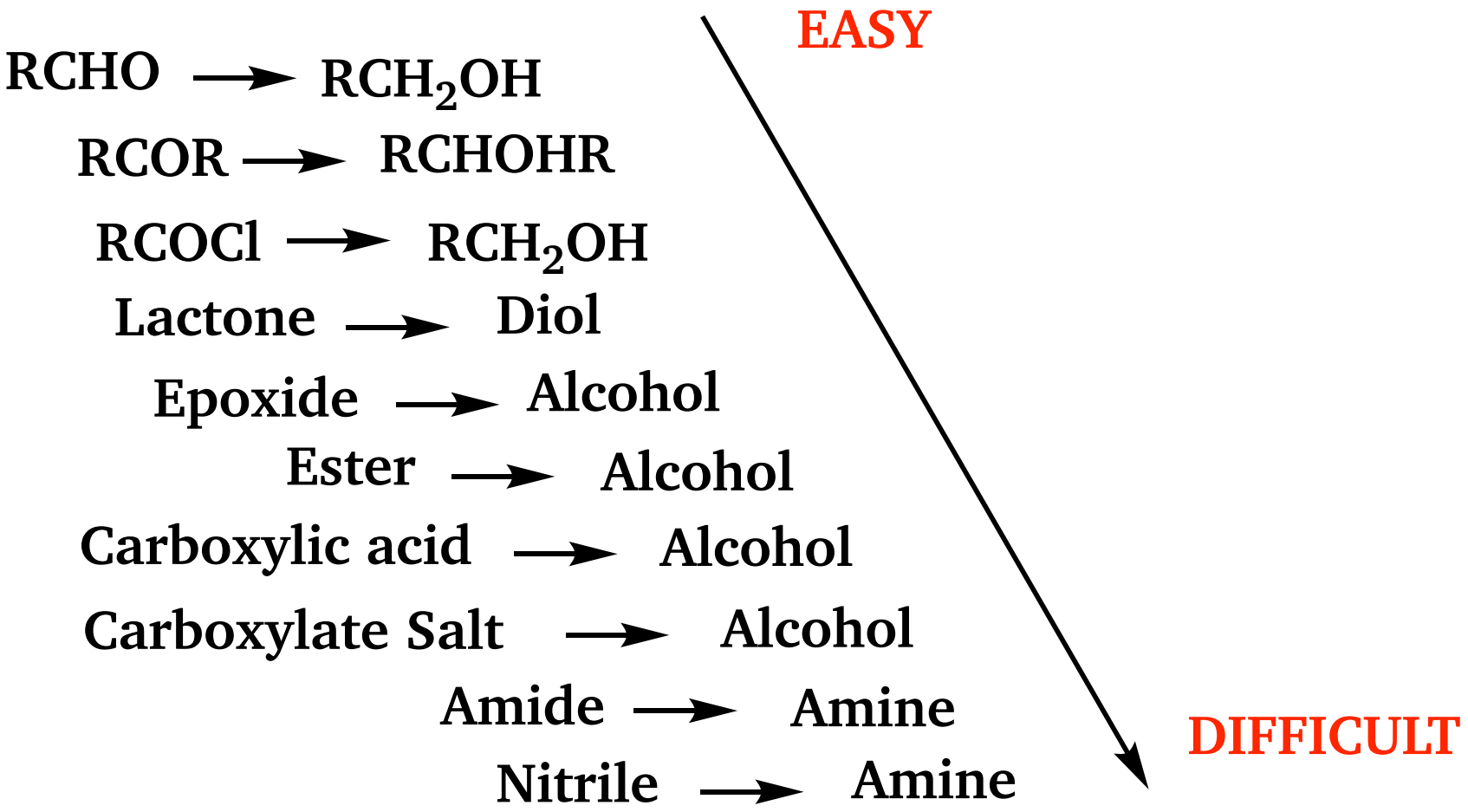
Axial attack





LAH	10	90
L-Selectride	93	7

Lithium Aluminium Hydride



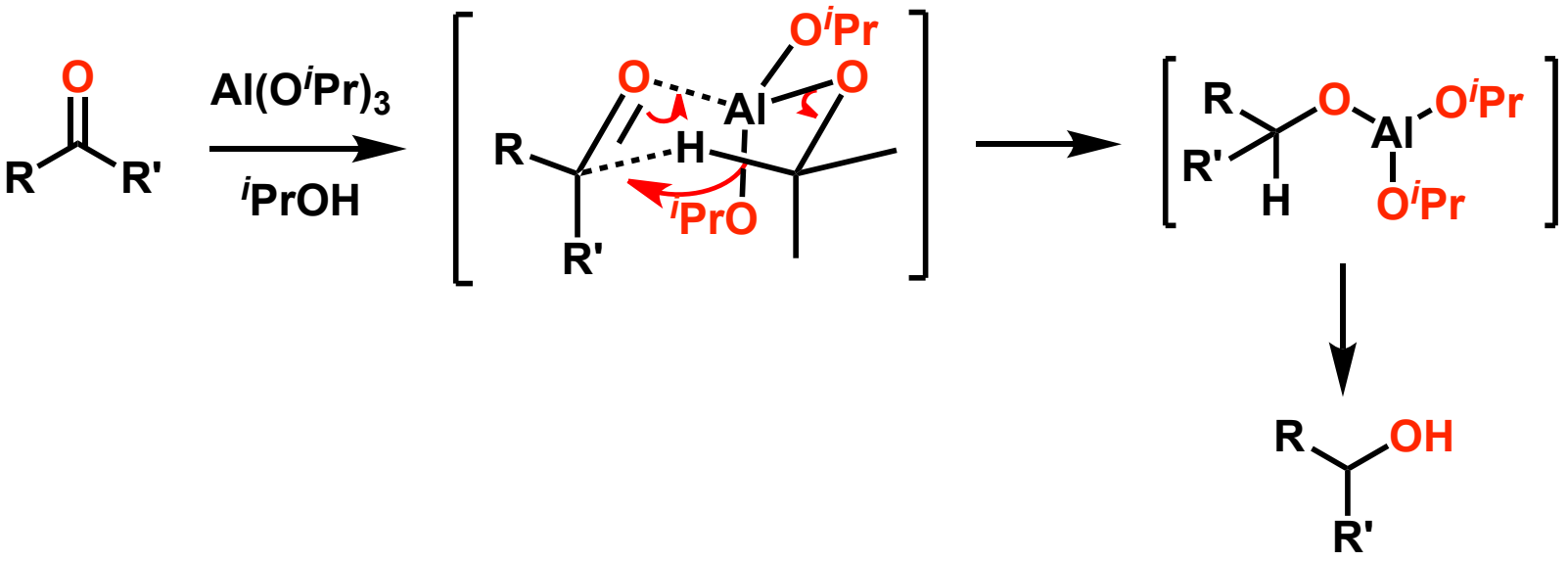
MPV Reduction

$Al(O^iPr)_3$ is the reagent

Isopropanol is the hydride donor

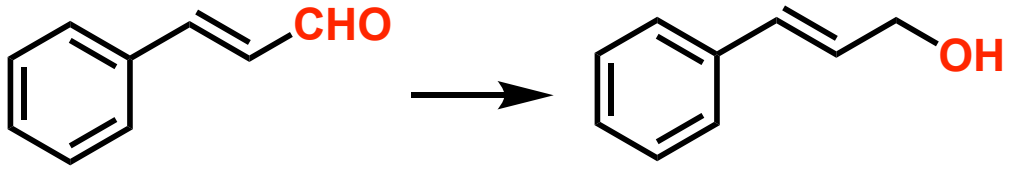
By-product is acetone

Reverse process is known as Oppenauer oxidation

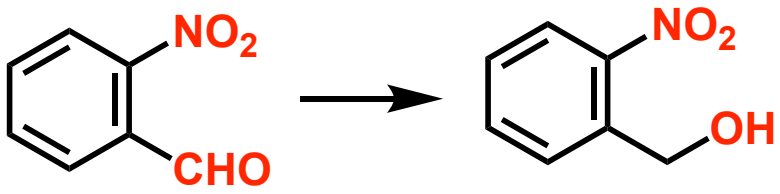


MPV Reduction

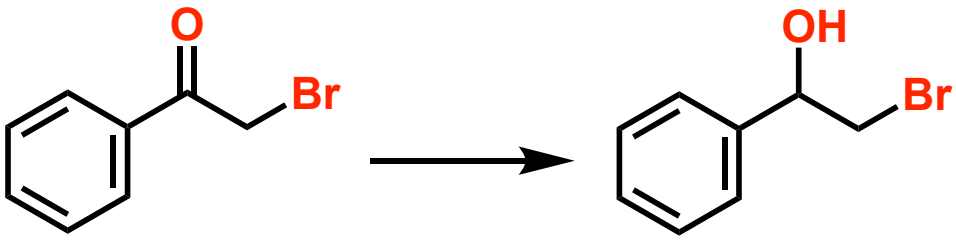
Selective reduction of aldehydes



Selective reduction of aldehydes



Selective reduction of ketones

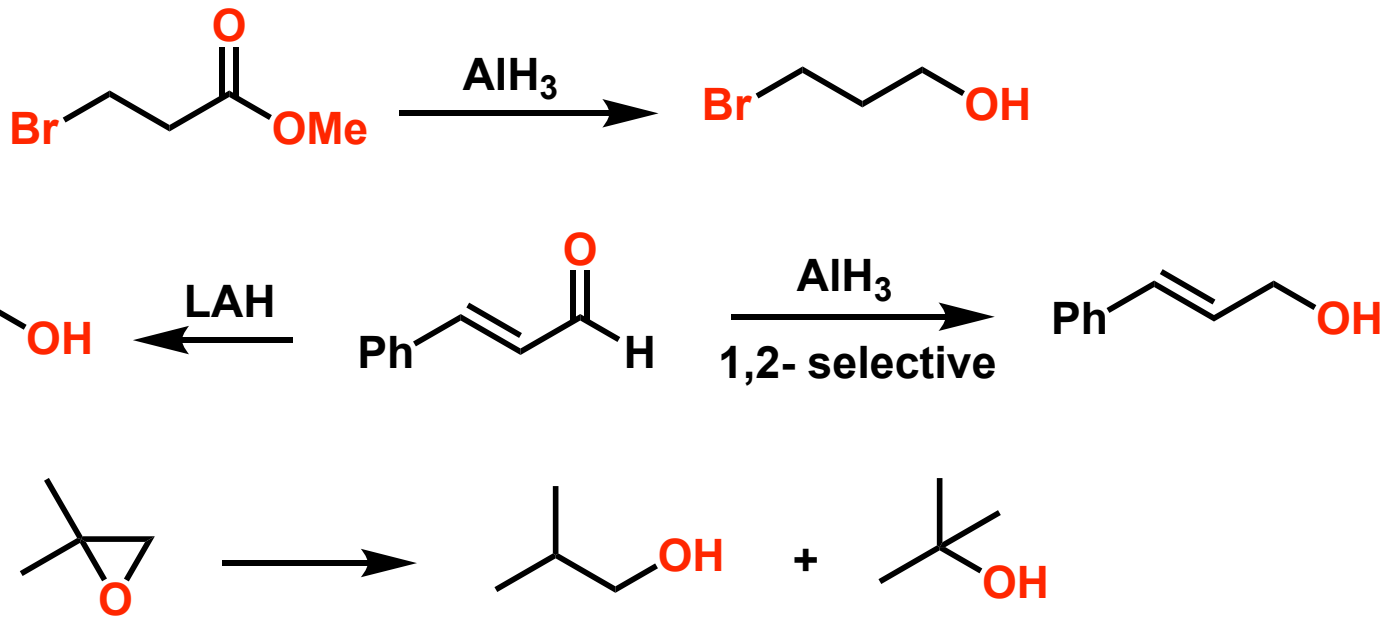


Alane (AlH_3)

Preparation:

$$AlCl_3 + LAH \longrightarrow AlH_3 + 3LiCl$$

It is inert to olefin & nitro group



LAH: 2:98

AlH_3: 95:5

$LiAl(O^tBu)_3H$

Preparation:

Less reactive than LAH

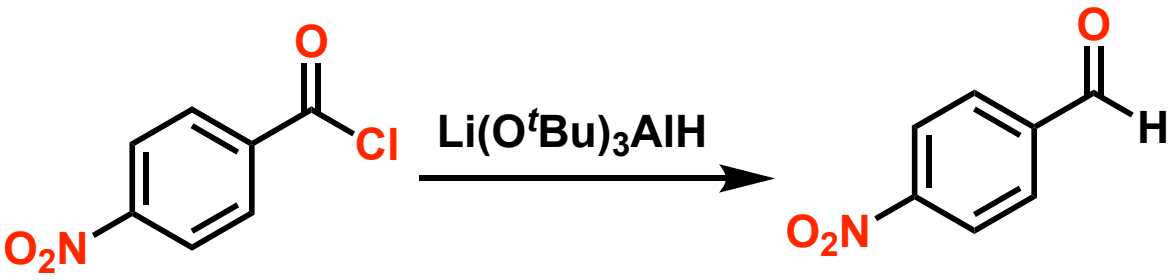
Partial reduction is possible

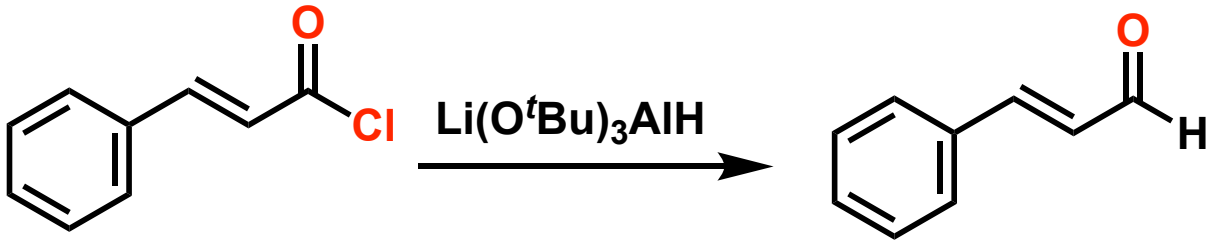
Highly hindered reducing agent

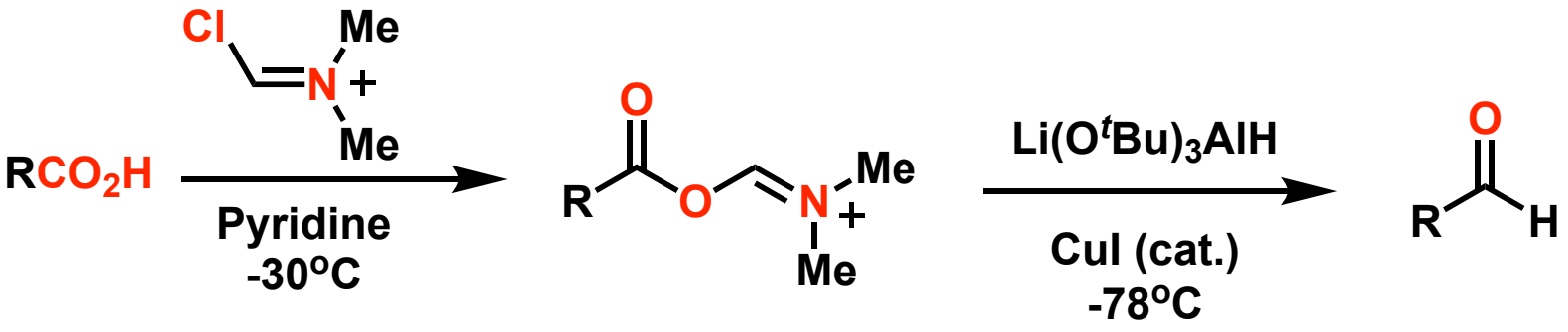
Reduces the most reactive functional group

$LiAl(O^tBu)_3H$

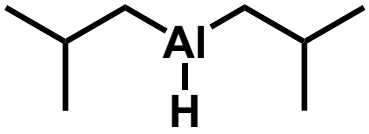
Alternative to Rosenmund reduction







Diisobutyl Aluminium Hydride (DIBAL-H)

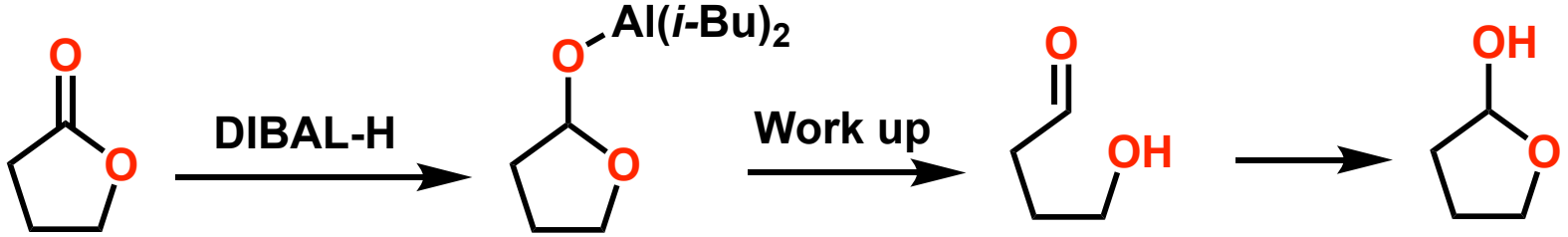


It is highly pyrophoric

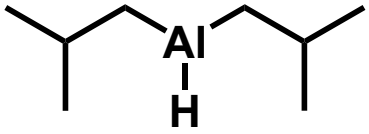
Available as 1M soln in THF, CH_2Cl_2, toluene etc.,

This also comes in cylinder in 1 Kg, 8 Kg etc., for industrial use

Reduces lactones to lactol at lower temperature

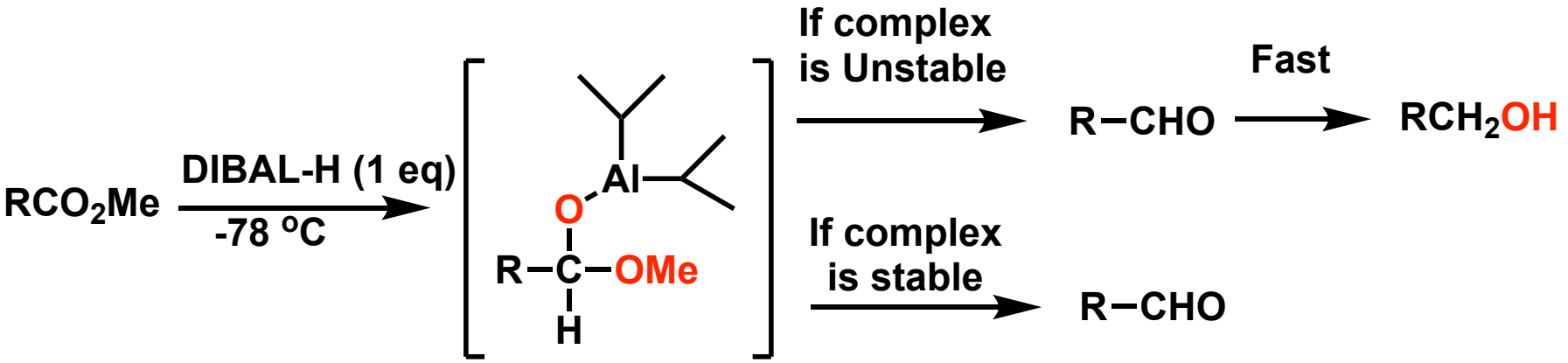


Diisobutyl Aluminium Hydride (DIBAL-H)



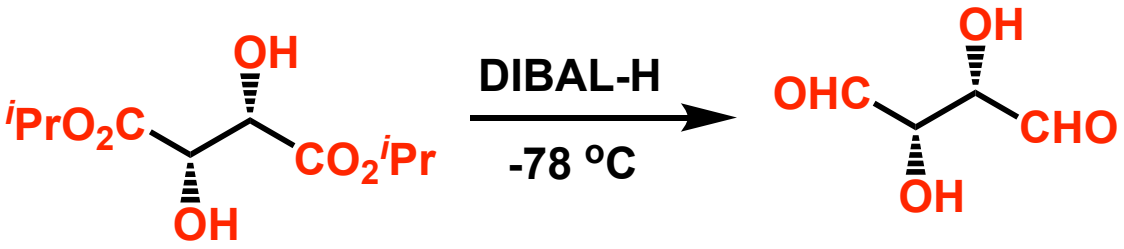
Reduces ketones, esters and aldehydes to alcohols

Under careful reactions conditions, at lower temperature and the use of one equivalent of DIBAL-H reduces esters to aldehyde

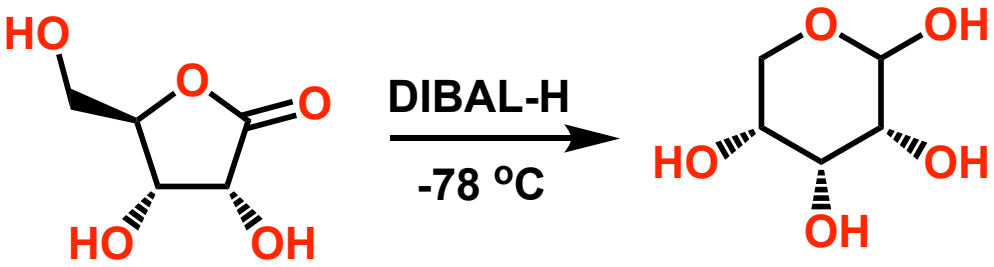


Diisobutyl Aluminium Hydride (DIBAL-H)

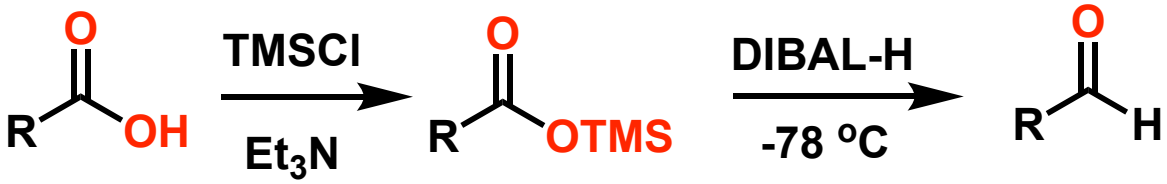
Esters to aldehydes



Lactones to lactols

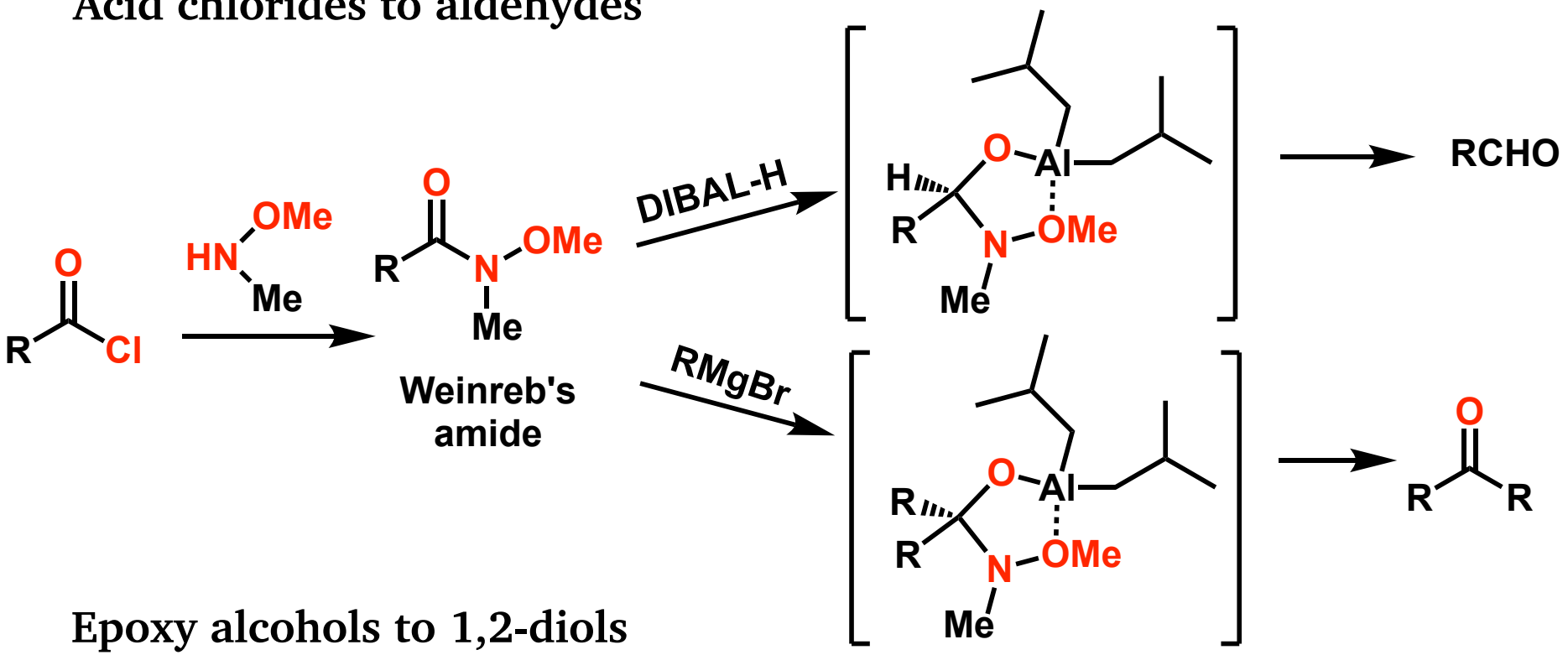


Acids to aldehydes

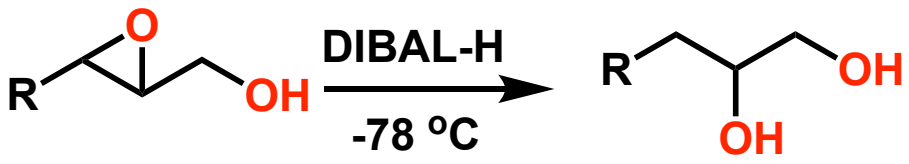


Diisobutyl Aluminium Hydride (DIBAL-H)

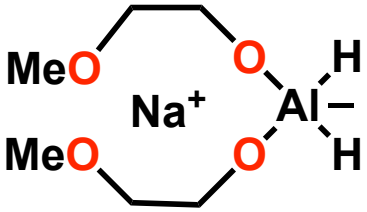
Acid chlorides to aldehydes



Epoxy alcohols to 1,2-diols

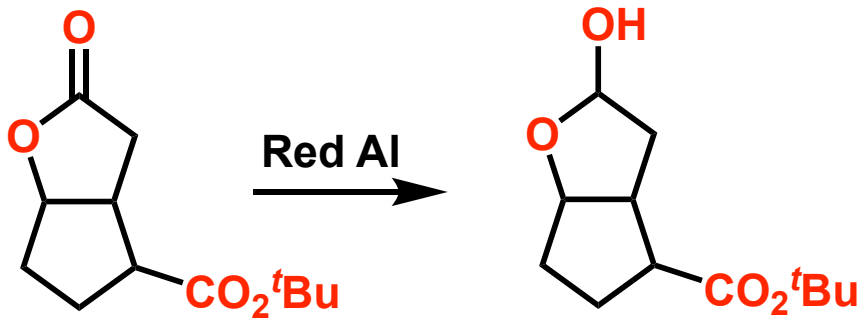


Red-Al

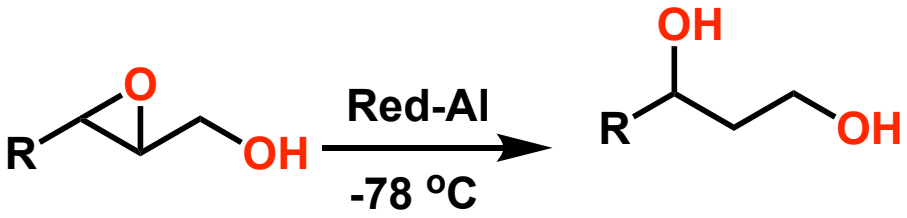


Sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al)

Reduces lactones in the presence of bulky ester

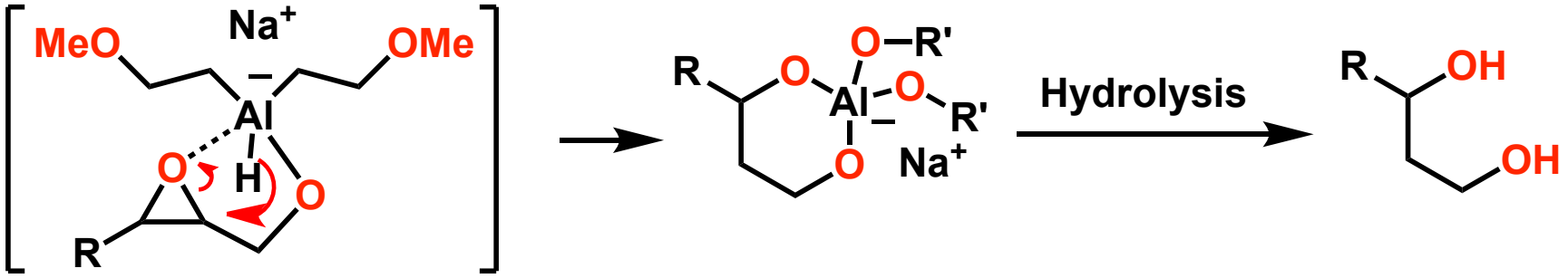


Epoxy alcohols to 1,3-diols

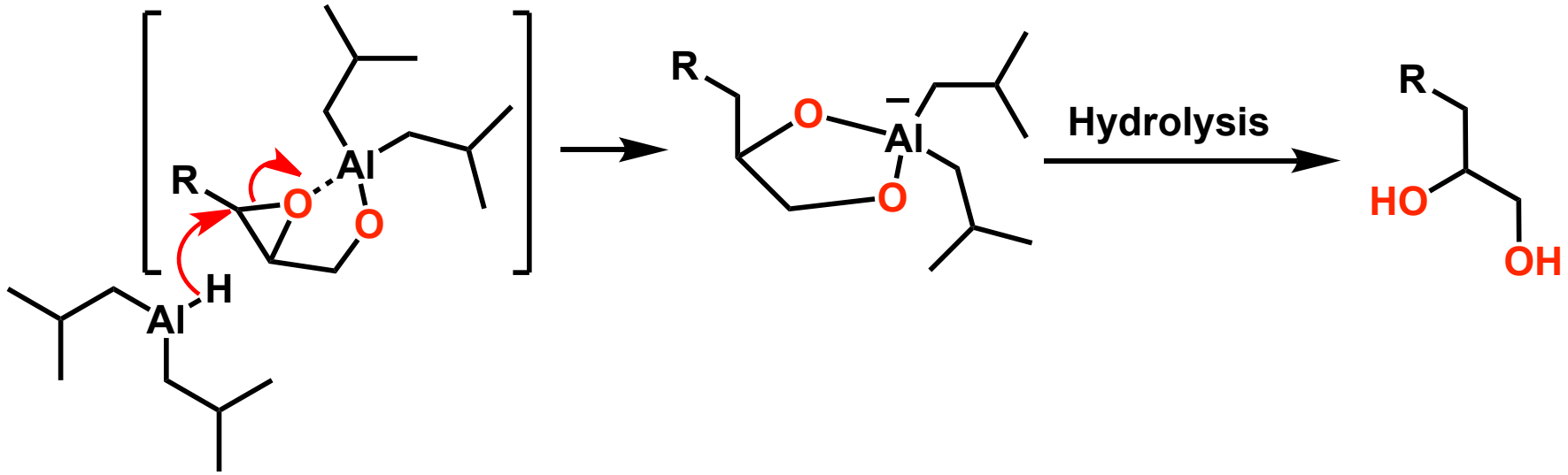


Regioselective opening of epoxyalcohols

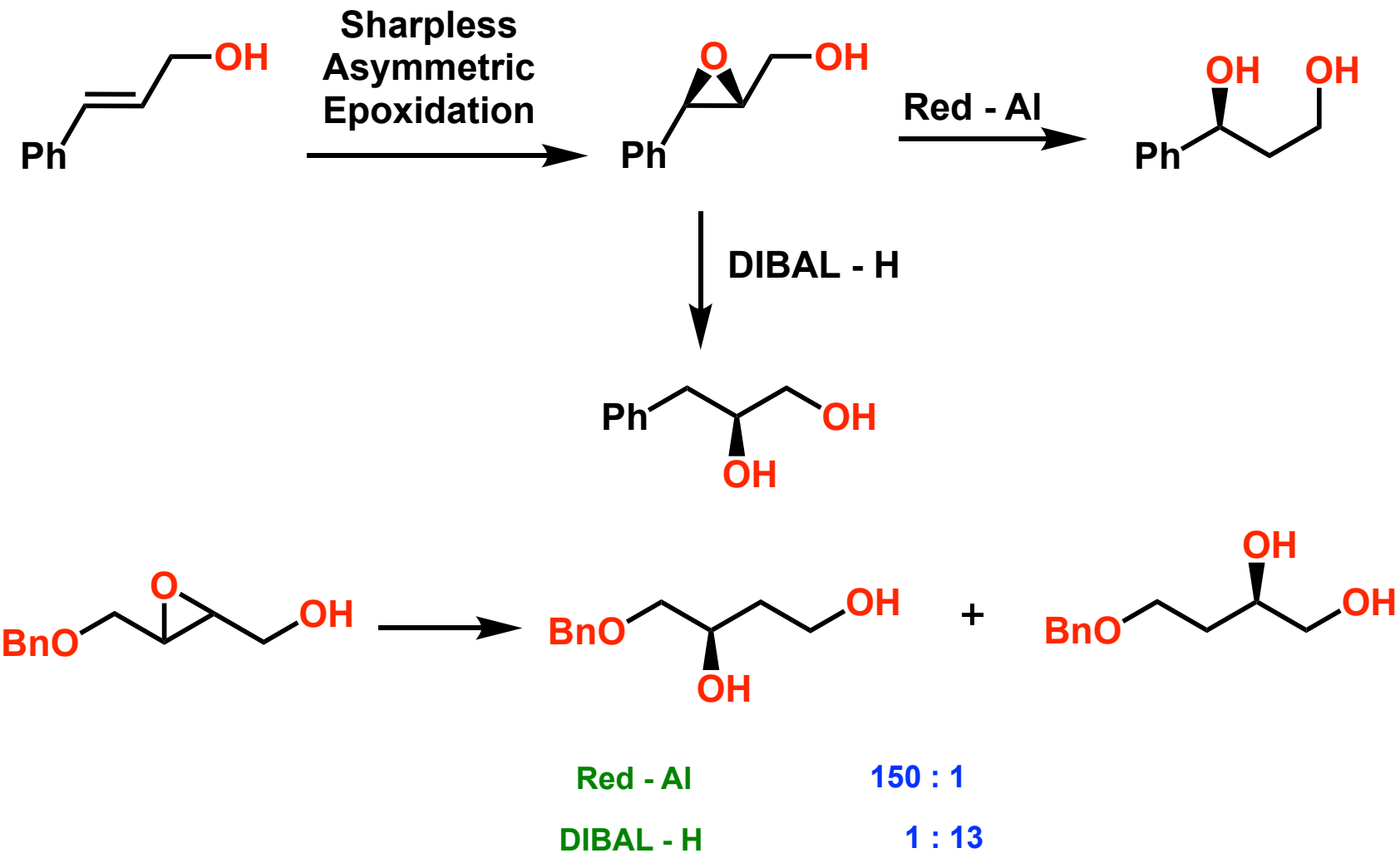
Opening of epoxide by Red-Al



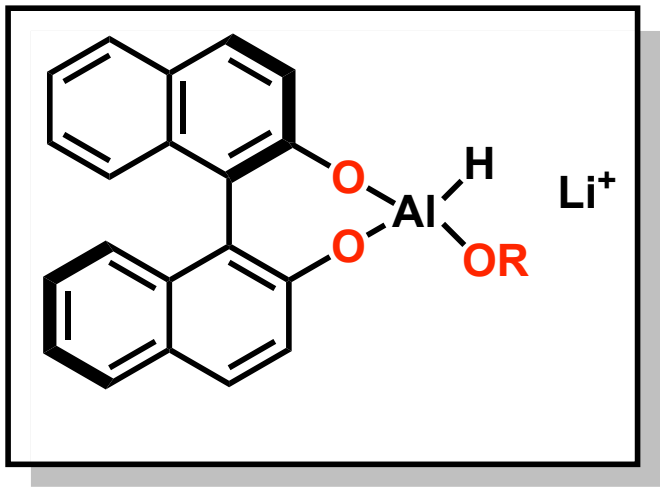
Opening epoxide by DIBAL-H:



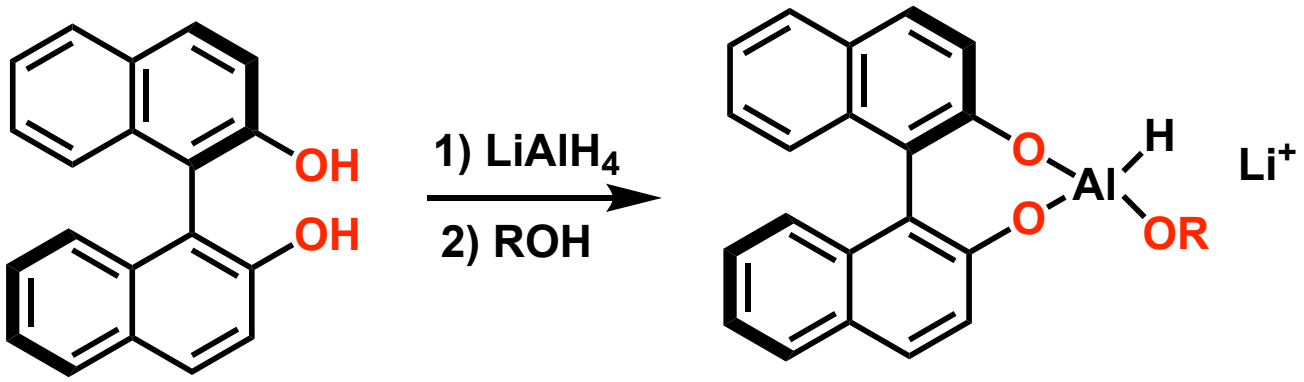
Regioselective opening of epoxyalcohols



BINAL-H

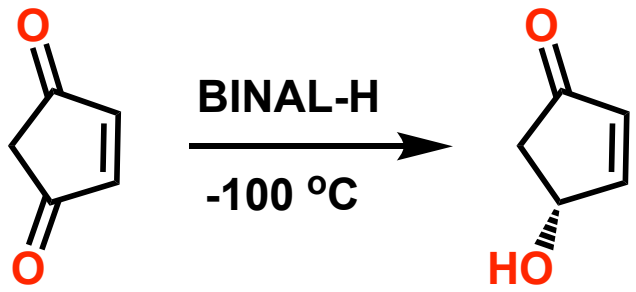


Preparation:

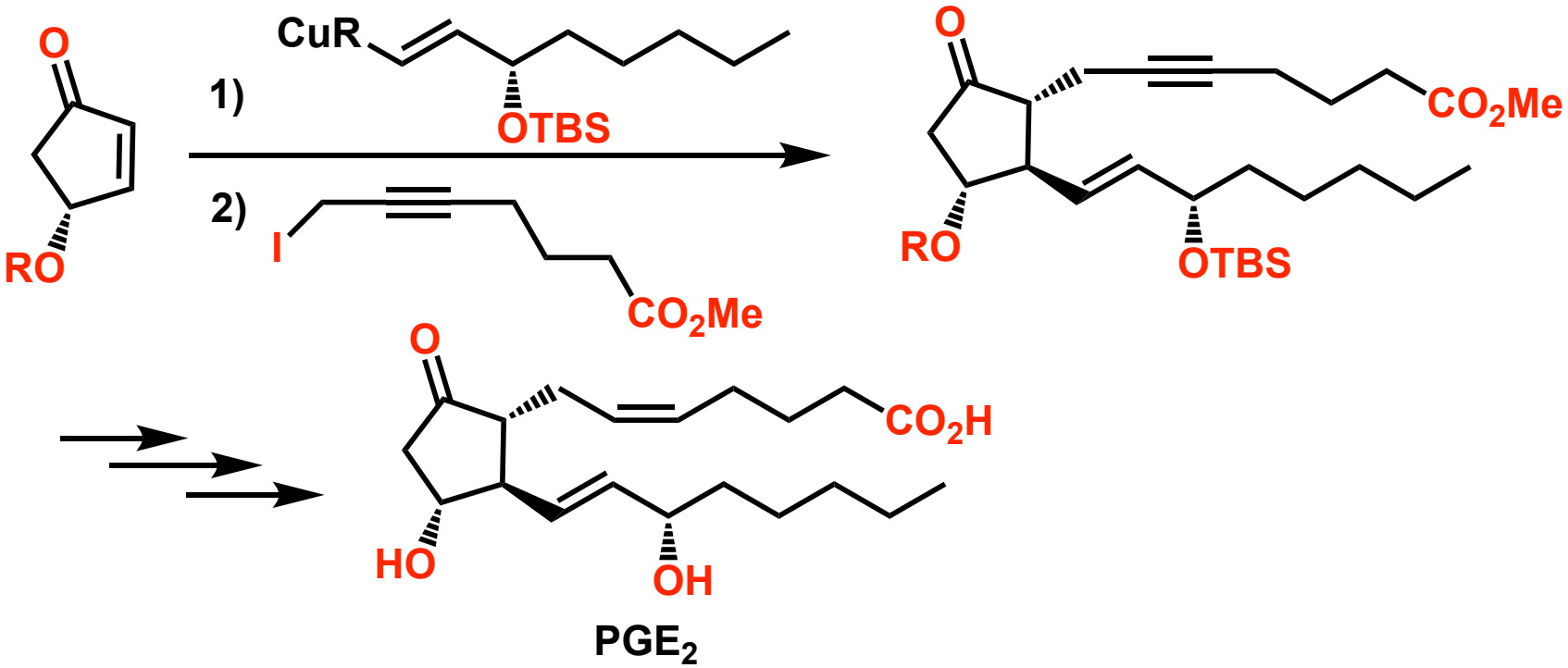


R = Me, Et, CF_3CH_2-

BINAL-H



Synthesis of Prostaglandins

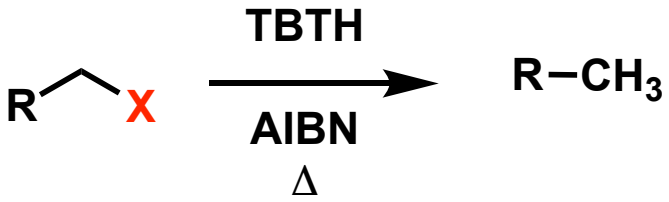


PGE_2

Tri-*n*-butyltinhydride (TBTH)

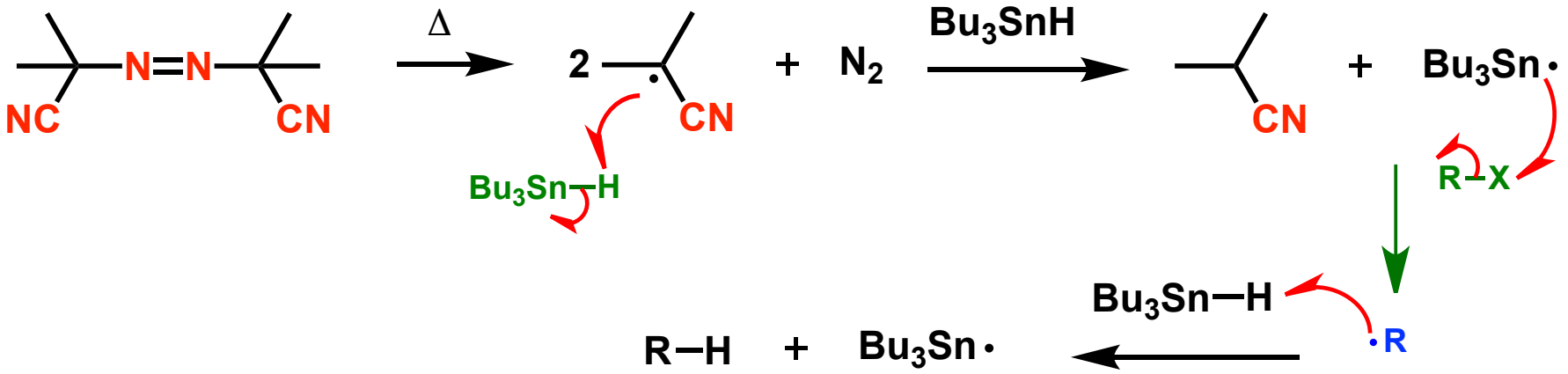
Used to reduce alkyl halides

Usual hydrogen donor is tributyltin hydride



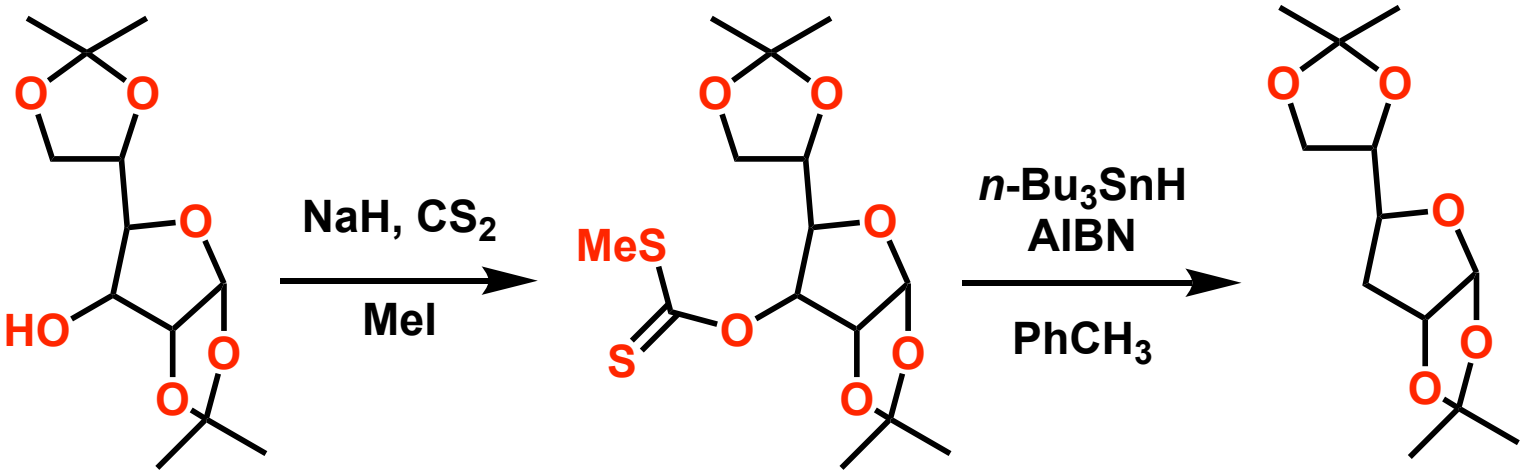
AIBN - Azobisisobutyronitrile

Mechanism:

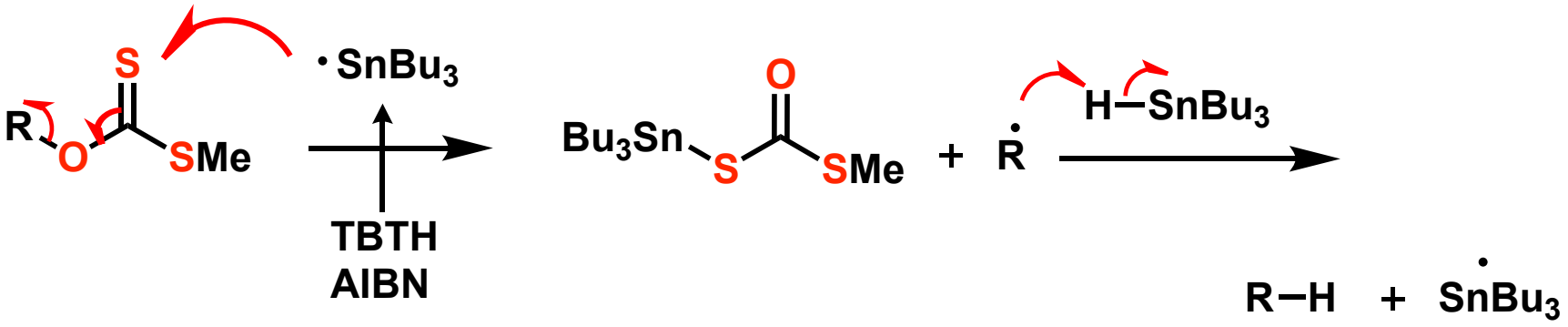


Tri-*n*-butyltinhydride (TBTH)

Barton- McCombie Reaction: Deoxygenation

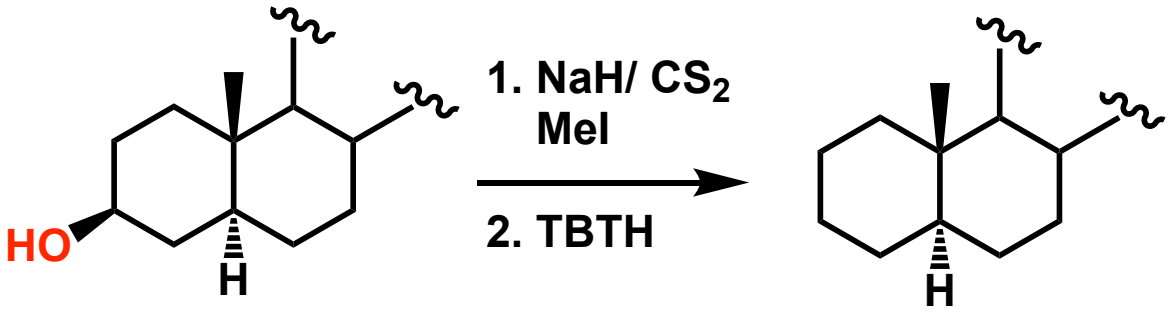


Mechanism:

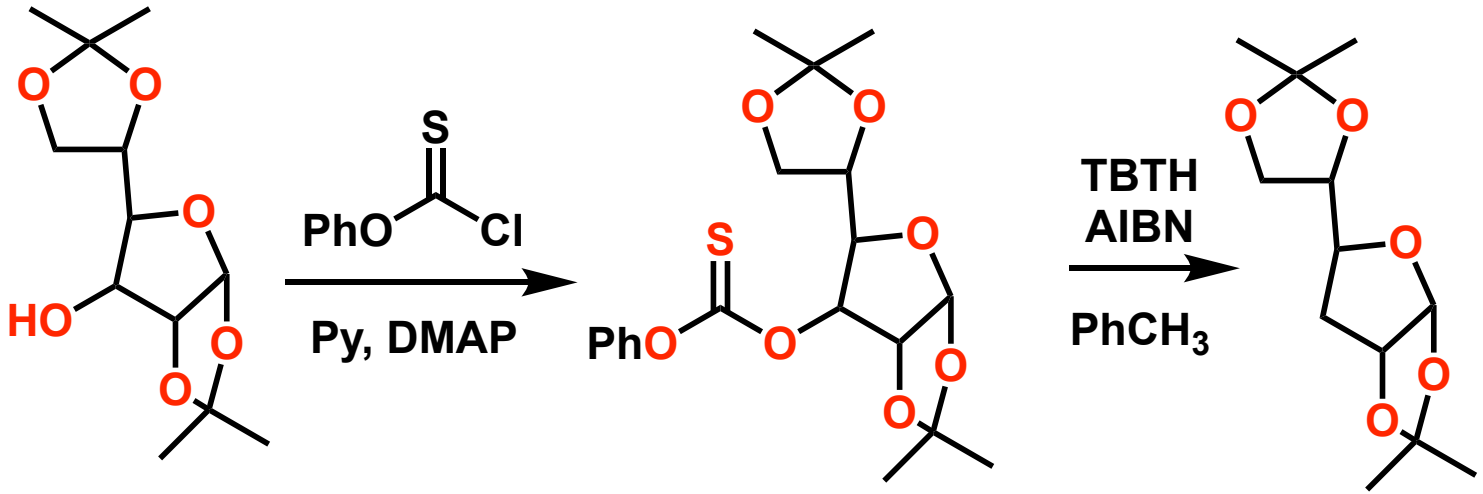


Tri-*n*-butyltinhydride (TBTH)

Barton- McCombie Reaction:

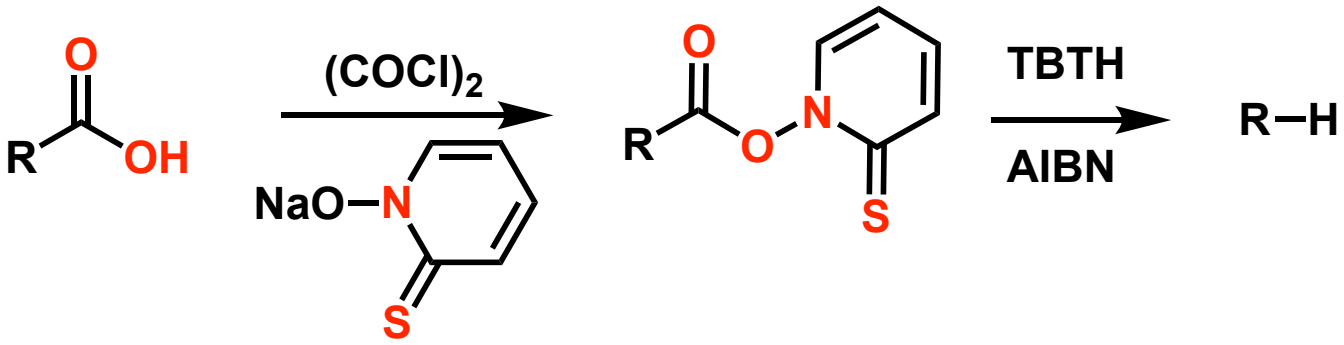


Thiocarbonate Modification:

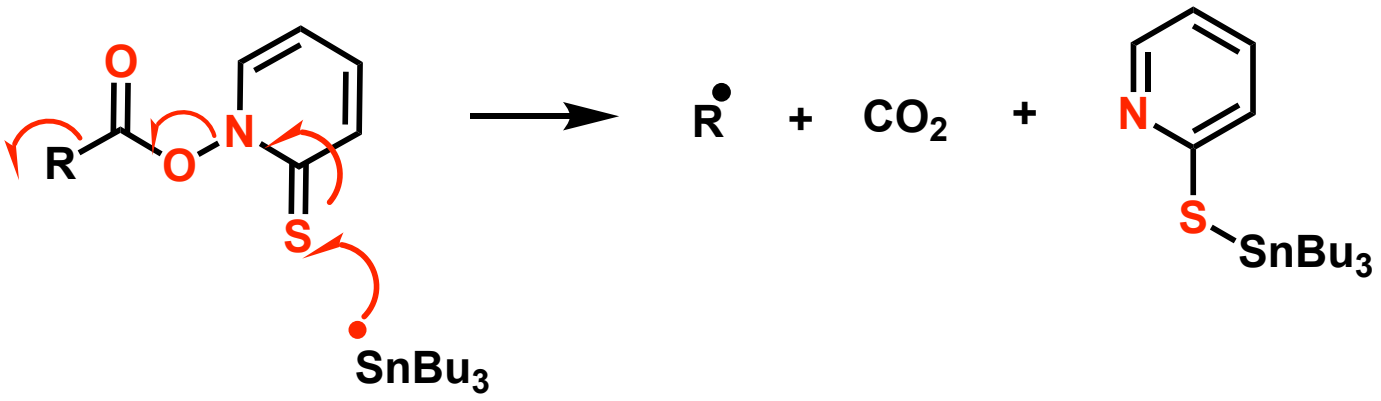


Tri-*n*-butyltinhydride (TBTH)

Barton's Decarboxylation

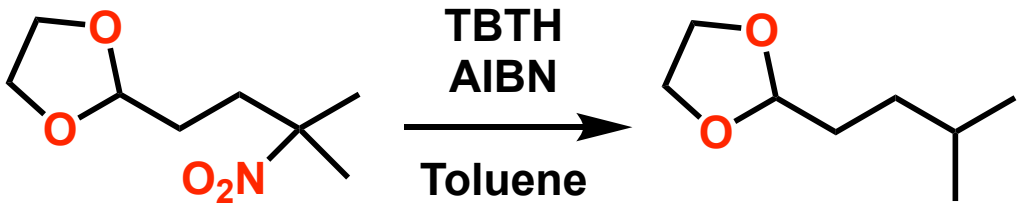


Mechanism:

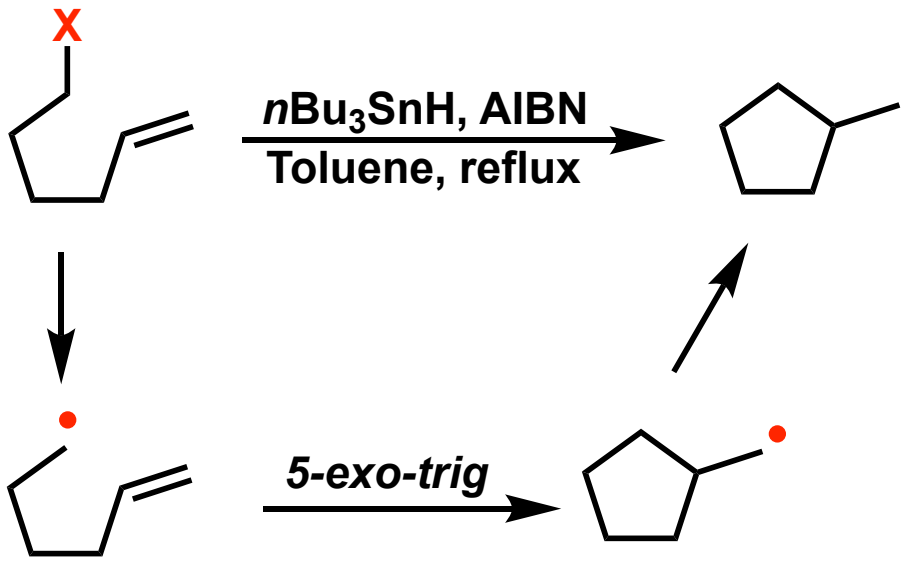


Tri-*n*-butyltinhydride (TBTH)

Removal of Nitro groups



Radical Cyclization Reaction



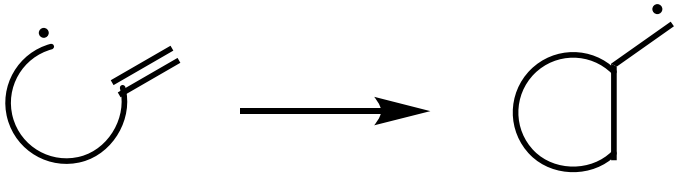
Baldwin's Rules

Exo, Endo

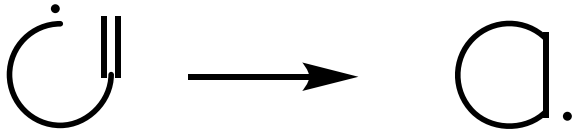
Dig, Trig, Tet

Diagonal **Trigonal** **Tetrahedral**

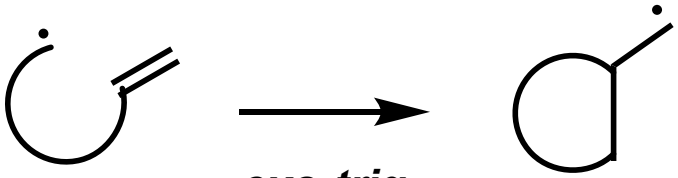
n-exo-trig ***n-endo-trig*** **n = ring size**



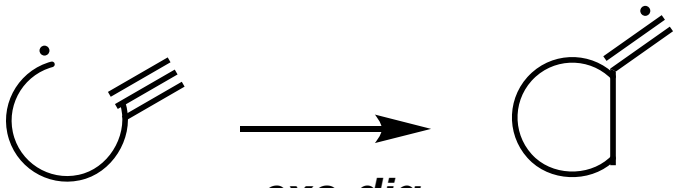
π e⁻ outside - *exo*



π e⁻ inside - *endo*



exo-trig



exo-dig

Baldwin's Rules

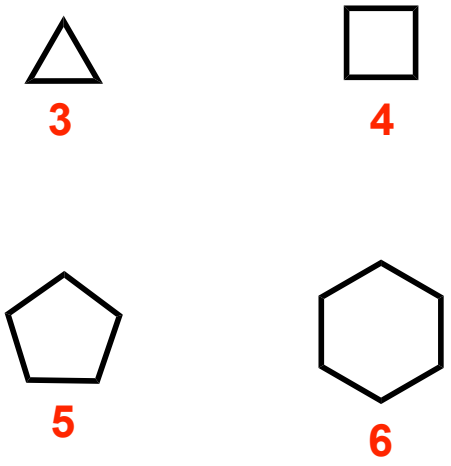
Used for the nomenclature of ring closure reactions

Rule1

n- indicate the ring size being formed

3 membered ring = 3

4 membered ring = 4, etc.,



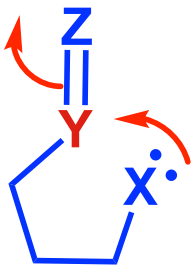
Baldwin's Rules

Rule 2

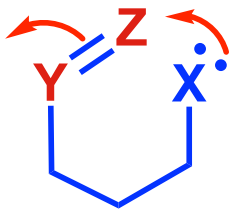
Indicate where displaced electrons end up

If the displaced electron pair ends up outside the ring being formed; then it is called "*exo*"

If the displaced electron pair ends up within the ring being formed; then it is called "*endo*"



5-Exo



6-Endo

Baldwin's Rules

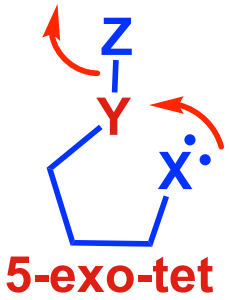
Rule 3

Indicate geometry of electrophilic atom (attached atom)

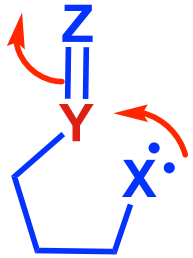
If hybridization is sp3, then Tet (tetrahedral)

If hybridization is sp2, then Trig (trigonal)

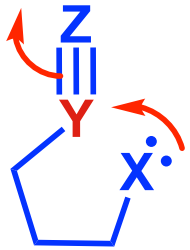
If hybridization is sp, then Dig (digonal)



5-exo-tet



5-exo-trig



5-exo-dig

Baldwin's Rules

All *Exo Tet* reactions are favored

5-*Endo Tet* 6-*Endo-Tet* reactions are disfavored

All *Exo Trig* reactions are favored

3-*Endo Trig, 4-Endo-Trig* and *5-Endo-Trig* reactions are disfavored

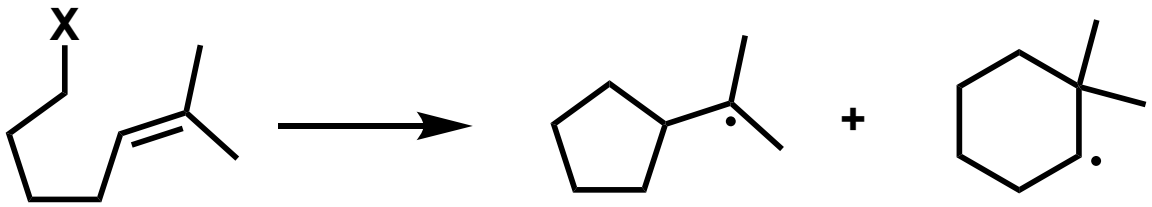
6-*Endo Trig onwards reactions* are favored

All *Endo Dig* reactions are favored

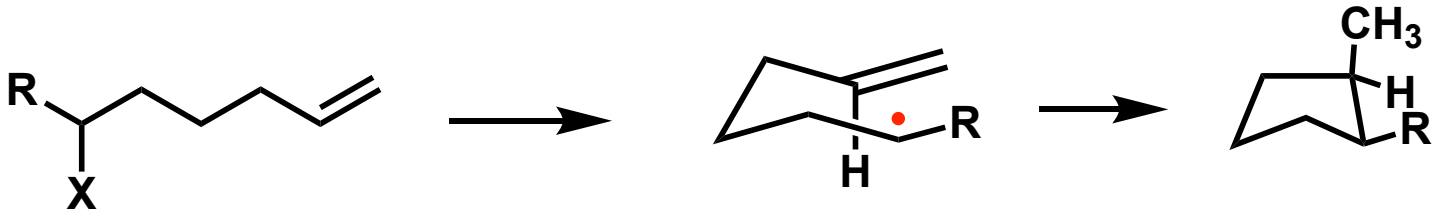
3-*Exo Dig* and *4-Exo-Dig* reactions are disfavored

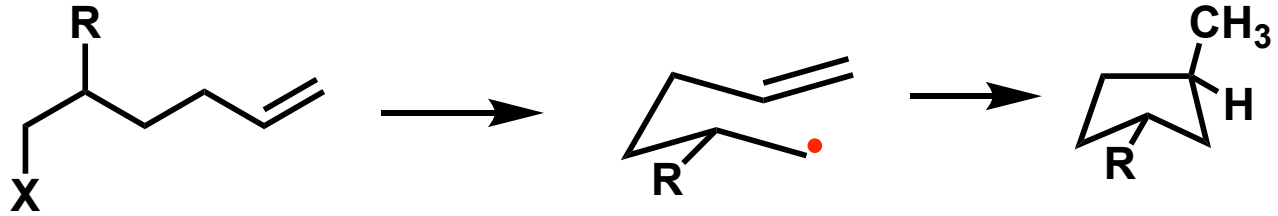
5-*Exo Dig onwards reactions* are favored

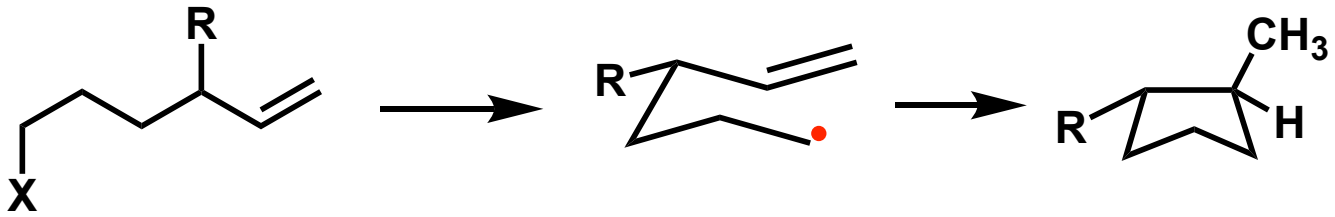
Radical Cyclization



Major

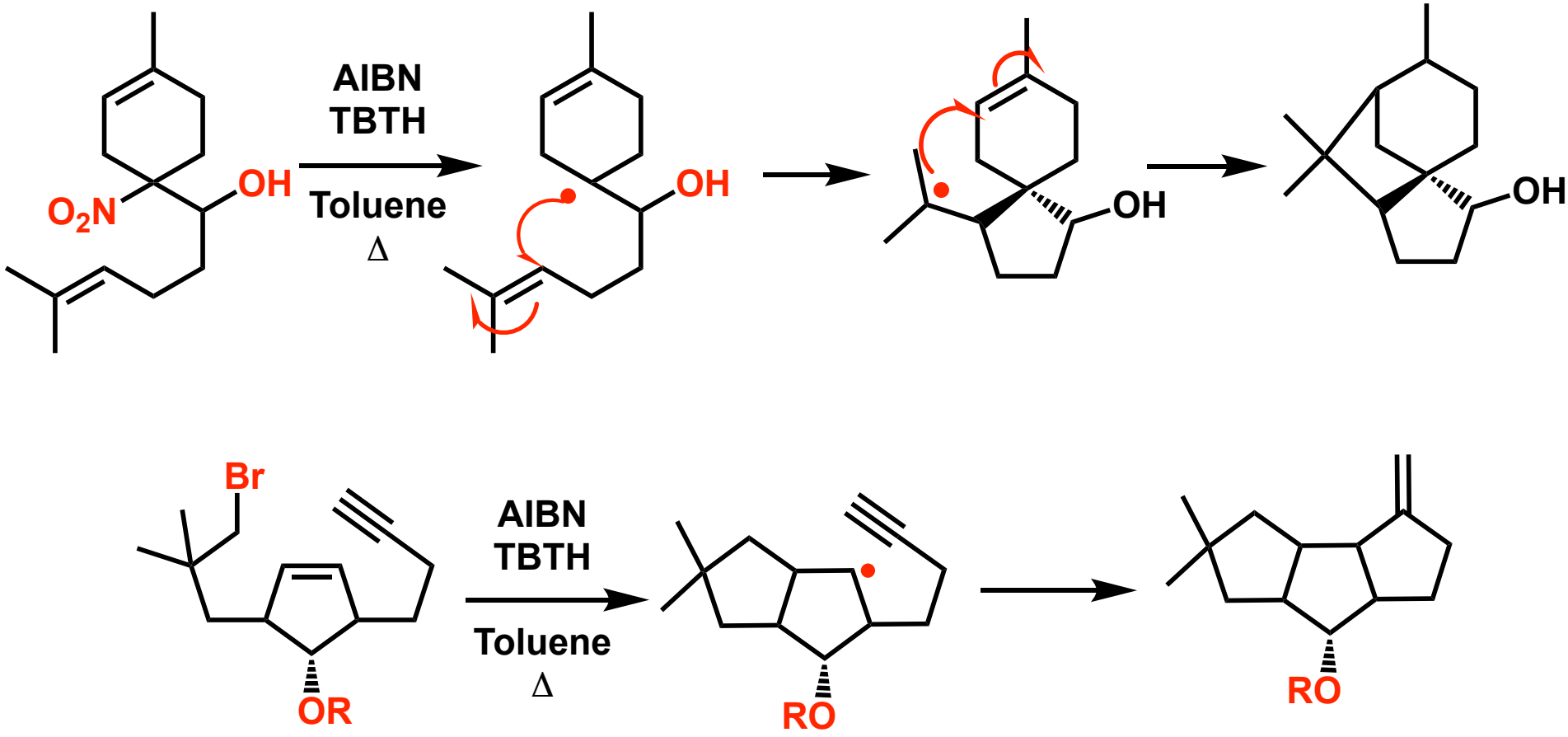




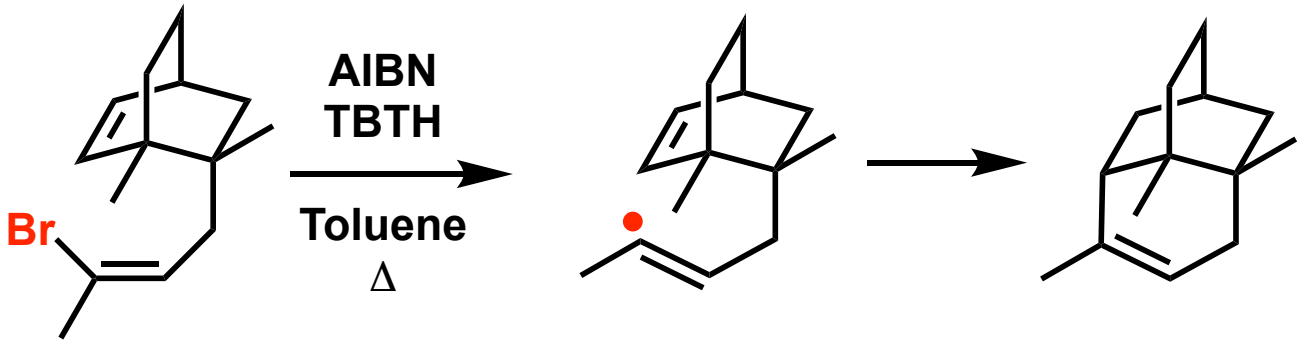


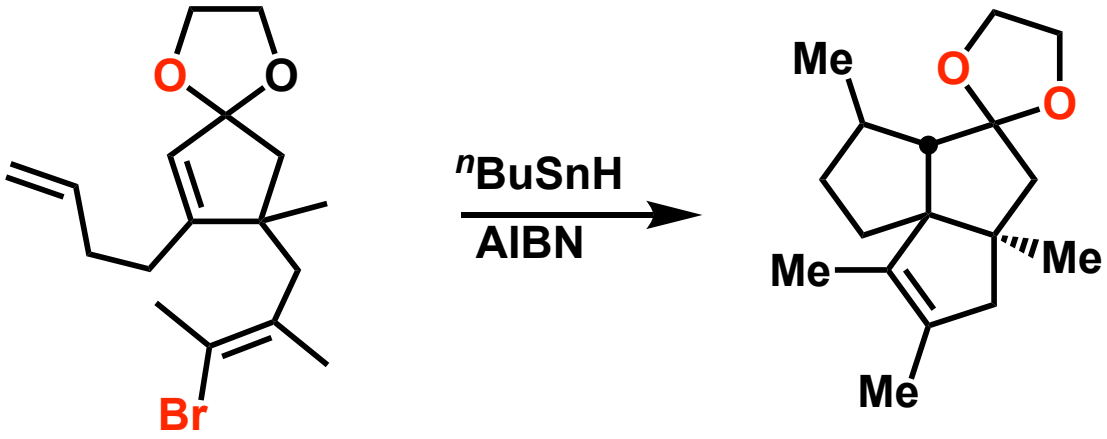
Radical Cyclization

Tandem Reactions



Radical Cyclization Reaction

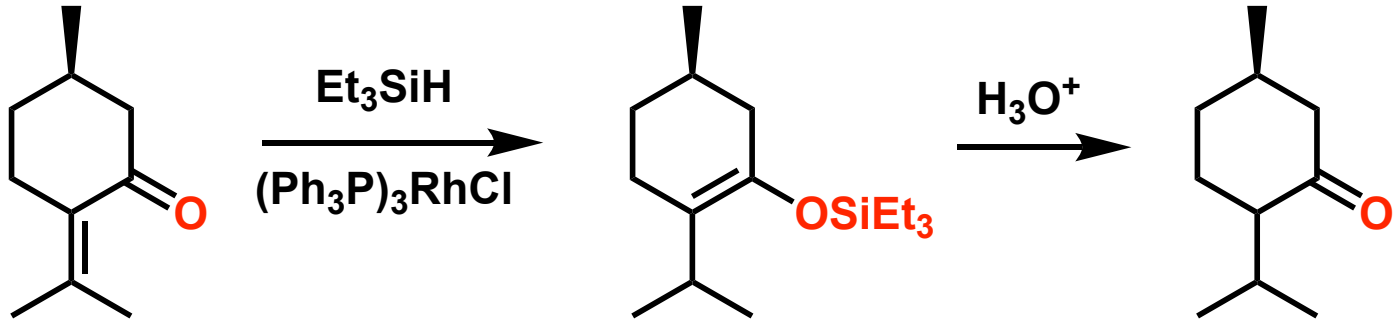




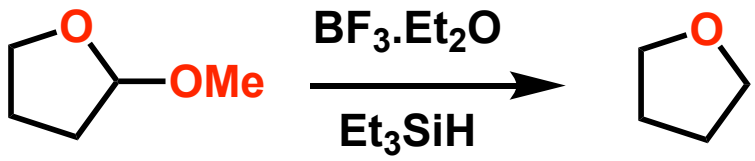
Silanes

Most commonly used silane reagents are Et_3SiH, *i*-Pr_3SiH

Hydrosilylation:



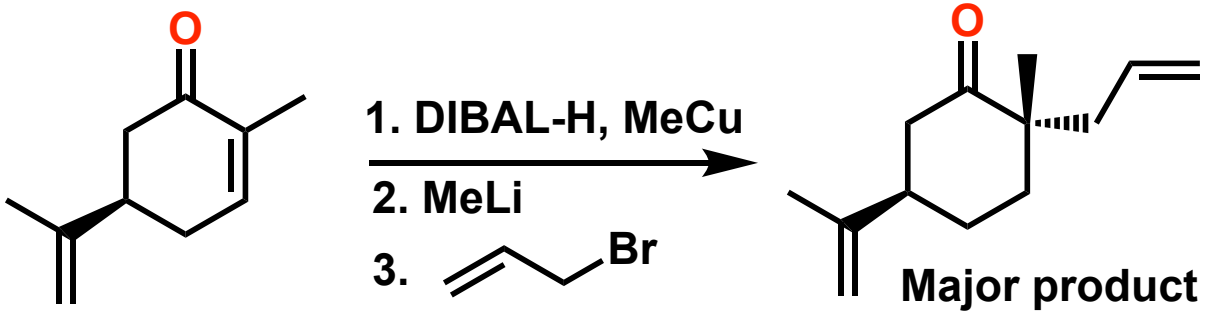
Reduction Of Lactol Ethers:

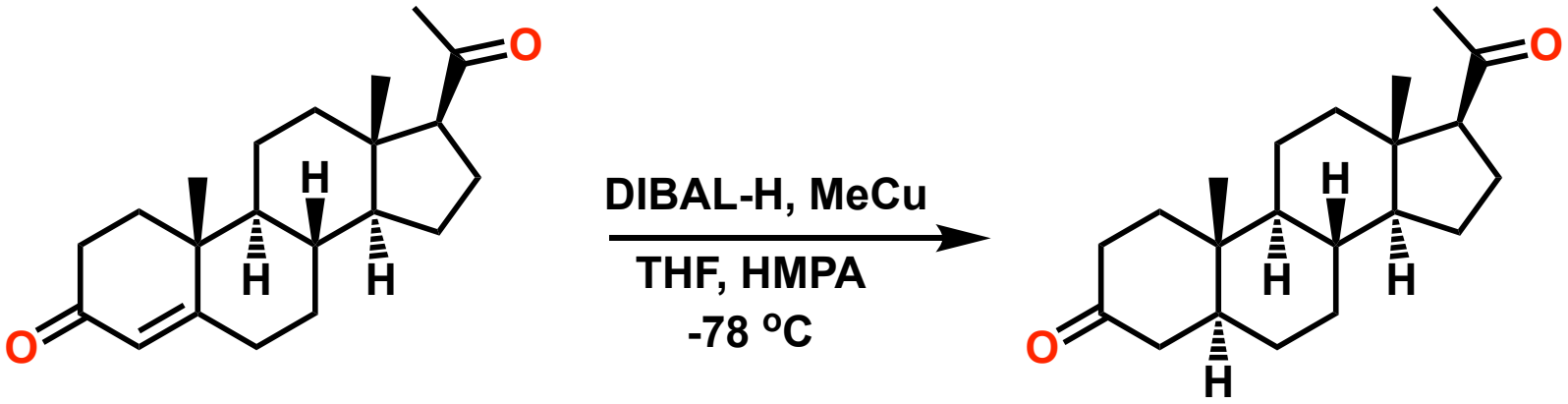


Copper Hydride

CuH:

Selective 1,4-Reduction

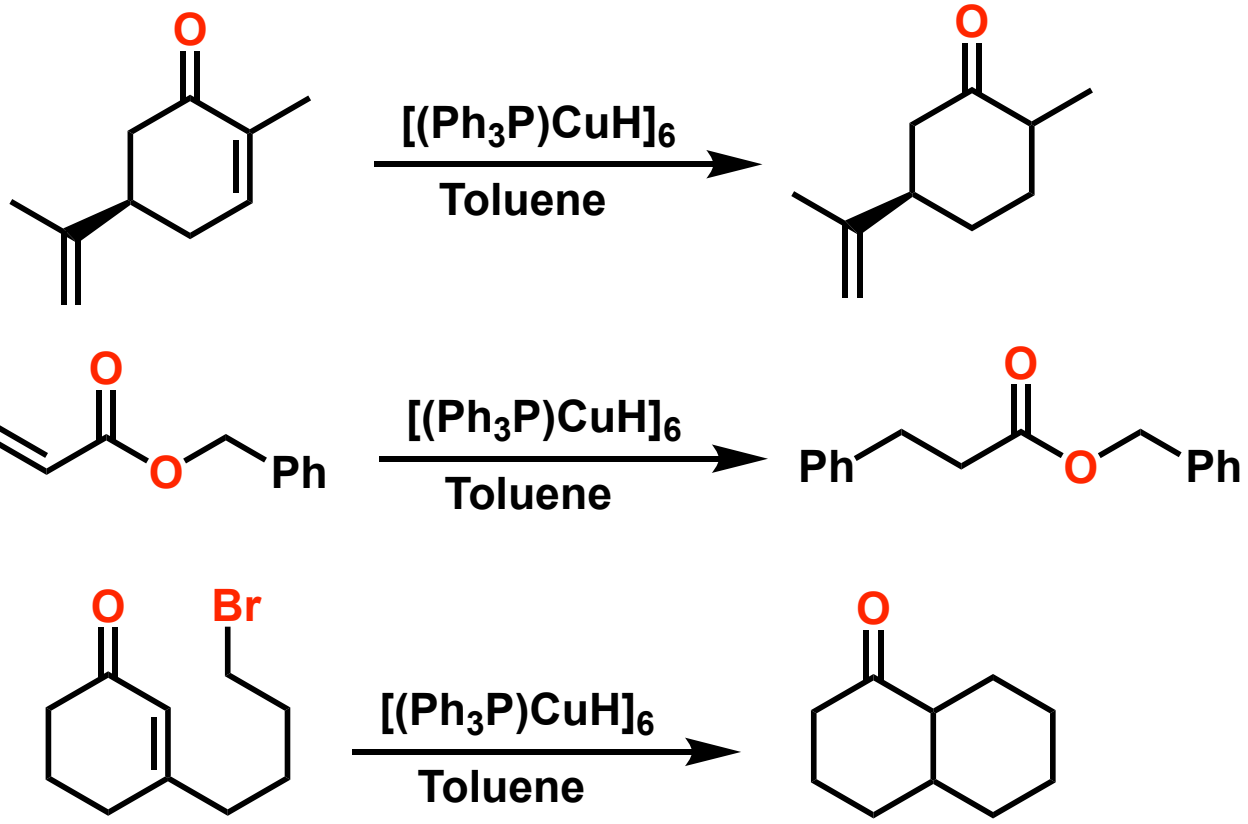




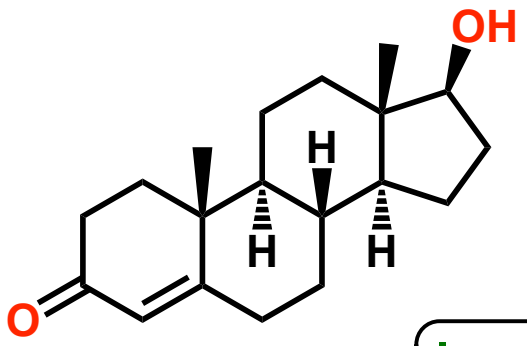
Stryker Reagent

$[(Ph_3P)CuH]_6$ cluster

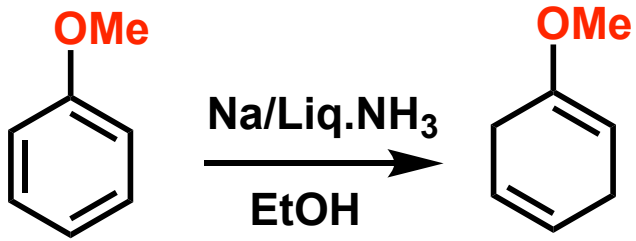
Selective 1,4-Reduction

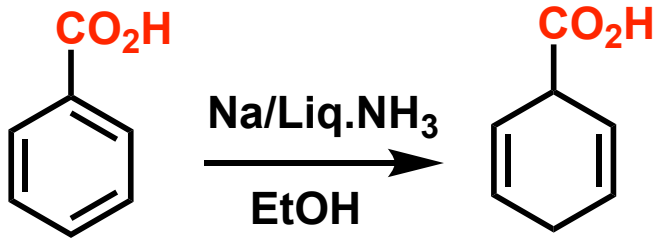


Birch Reduction



Impact of World War II in the discovery of Birch reduction



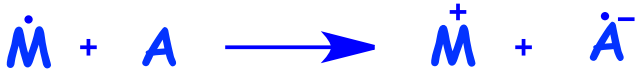


J. Chem. Soc. **1944**, 430

Birch Reduction

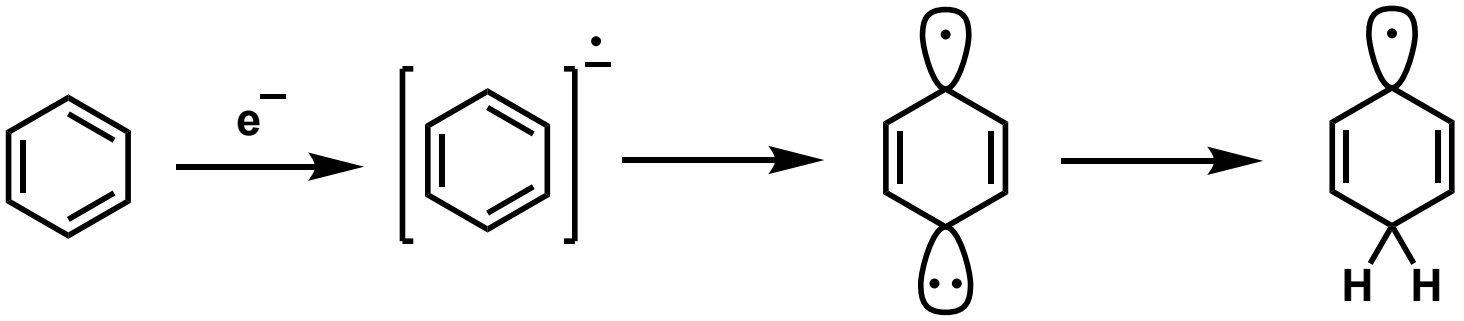
Dissolving Metal Reduction

Birch Reduction



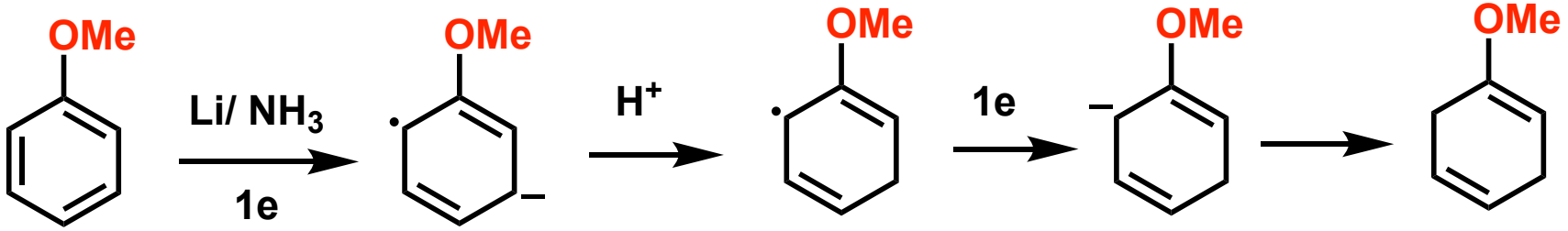
Li, Na, K, Ca, in Liquid ammonia, Et_2NH, $EtNH_2$, ROH, H_2O

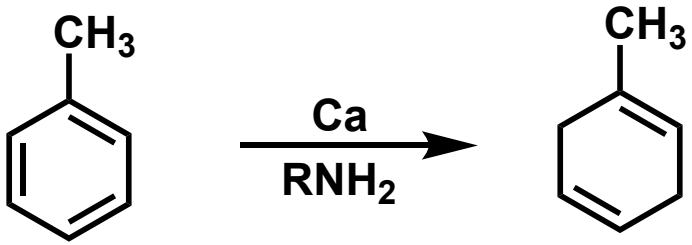
Partial Reduction Of Aromatic Rings:



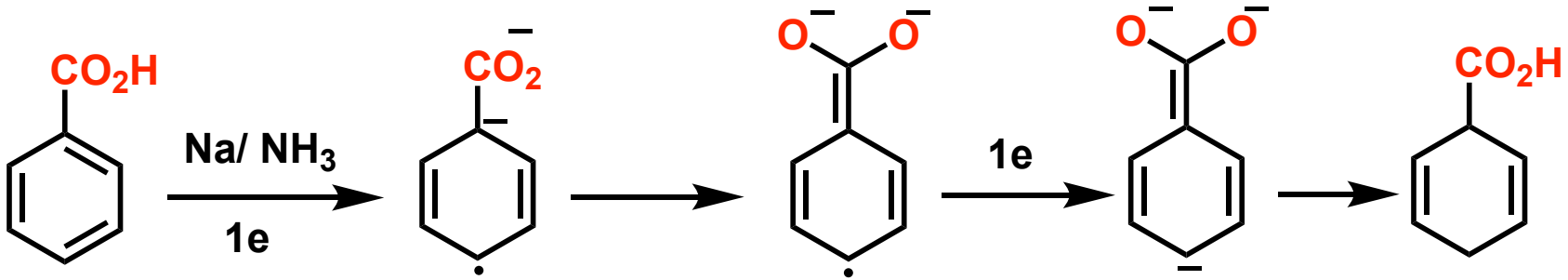
Birch Reduction

Electron Donating Substituents



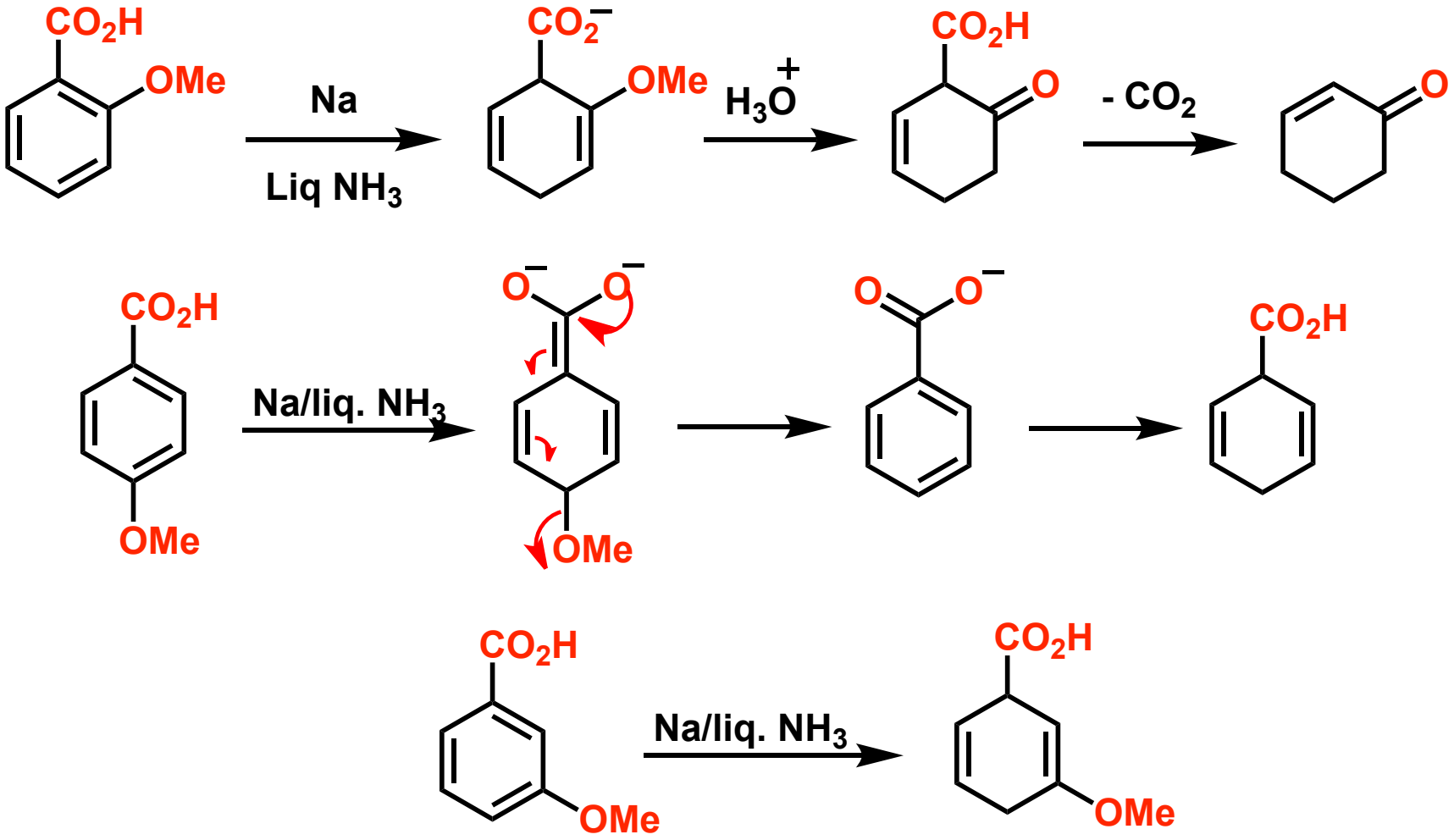


Electron Withdrawing Substituents



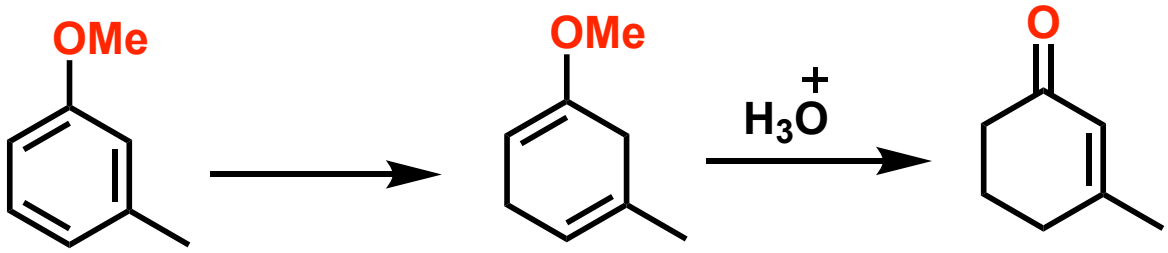
Birch Reduction

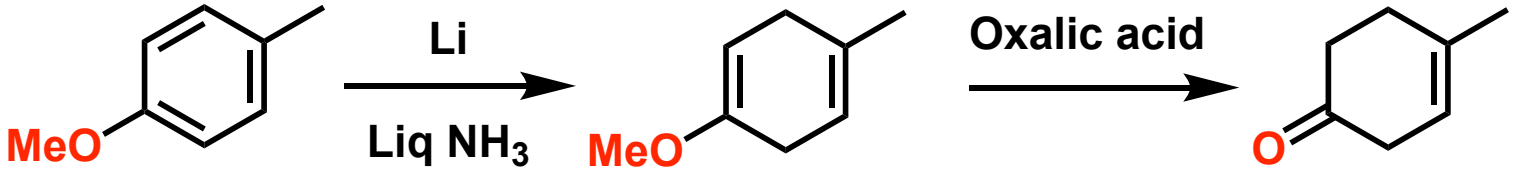
Electron Donating and Withdrawing Substituents

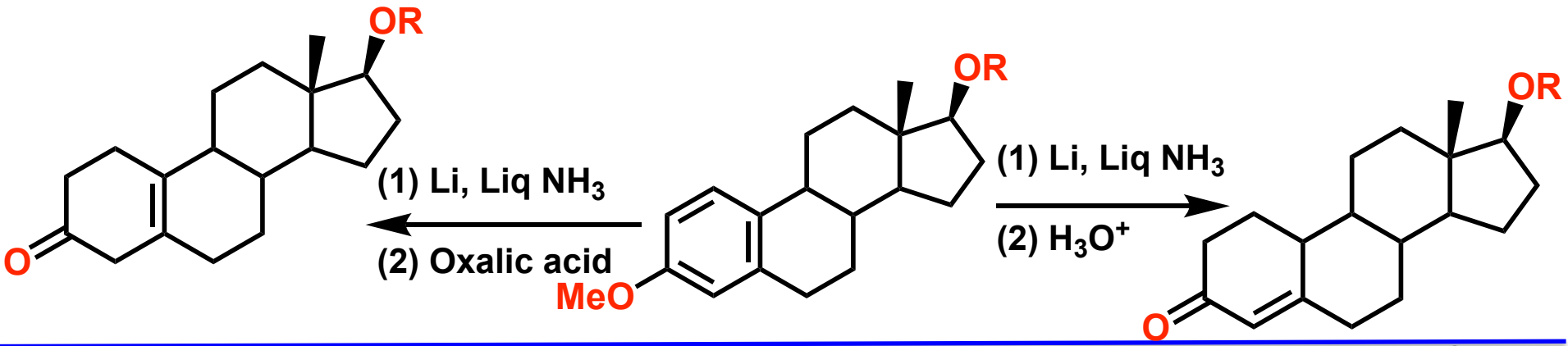


Birch Reduction

Ketones and nitro groups get reduced keeping esters and nitriles untouched

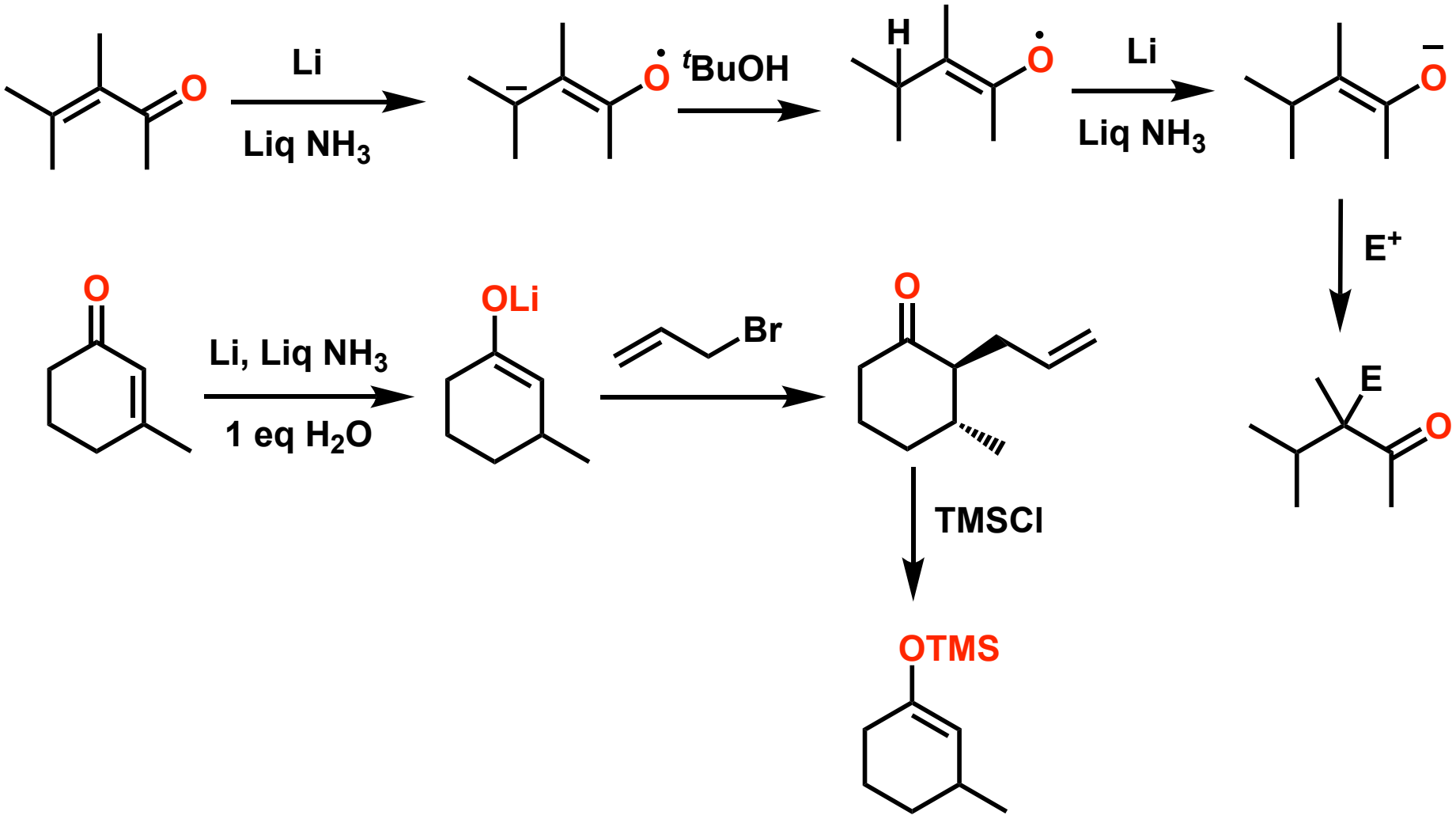






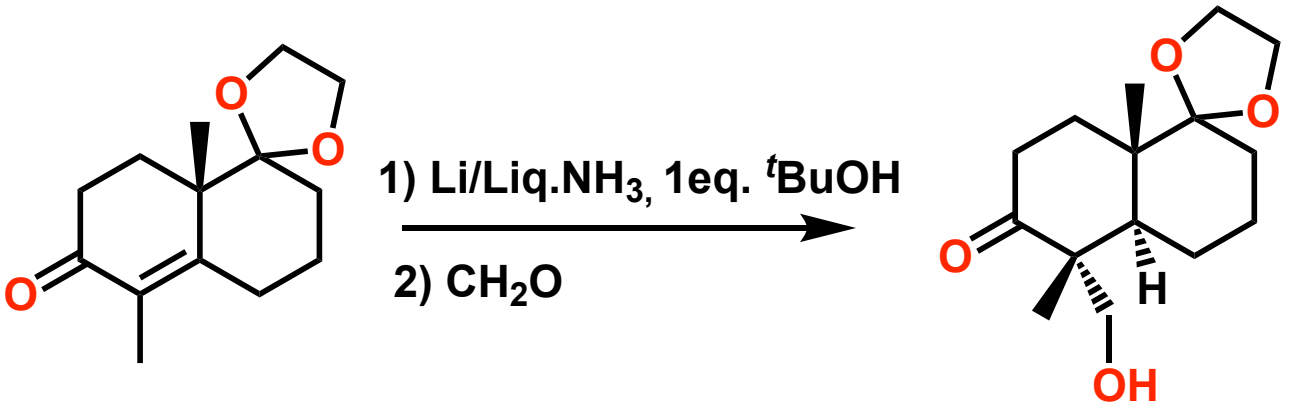
Birch Reduction

α,β- unsaturated compounds are reduced in 1,4-fashion

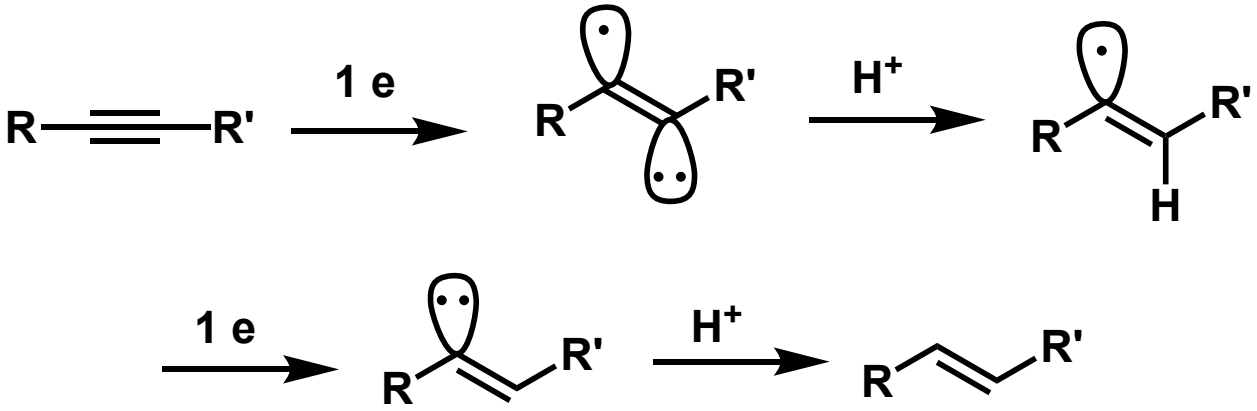


Birch Reduction

α,β- unsaturated compounds are reduced in 1,4-fashion

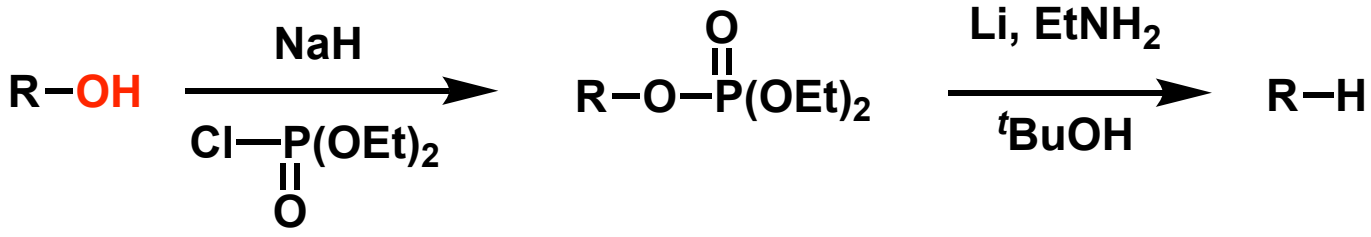


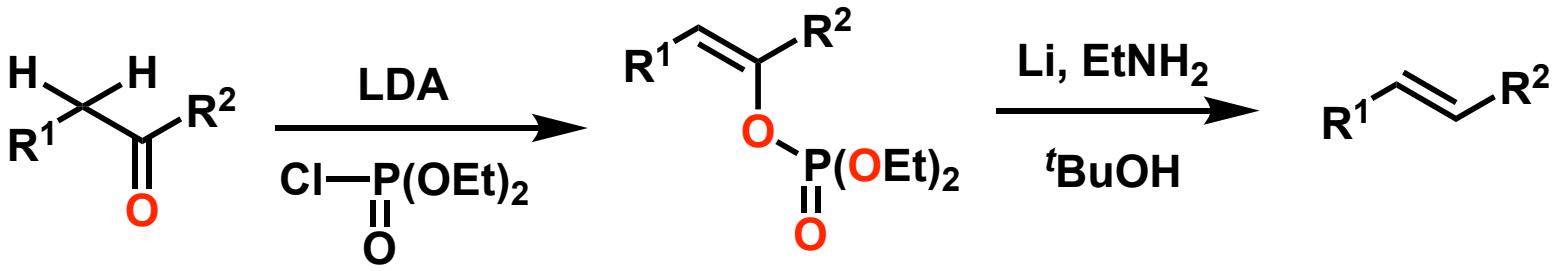
Reduction of Alkynes:



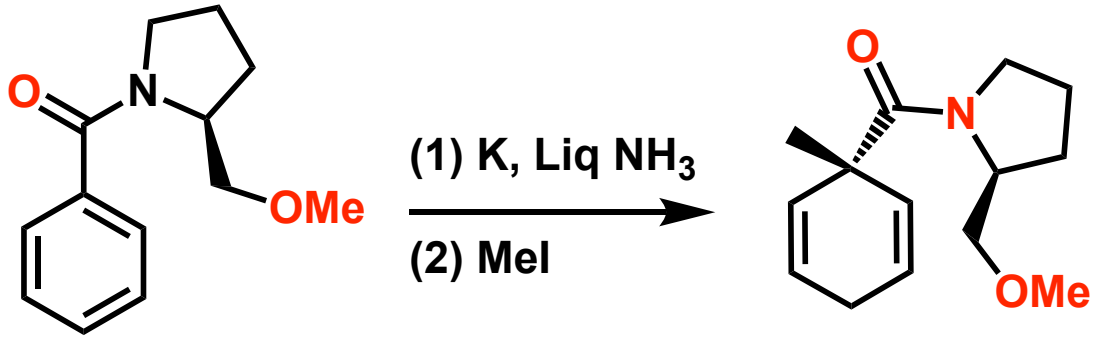
Birch Reduction

Reduction of Phosphates:



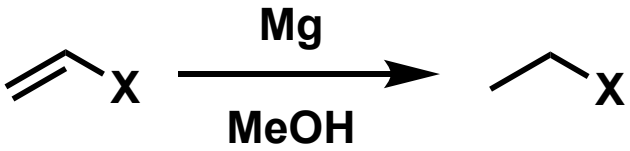


Asymmetric Birch Reduction:

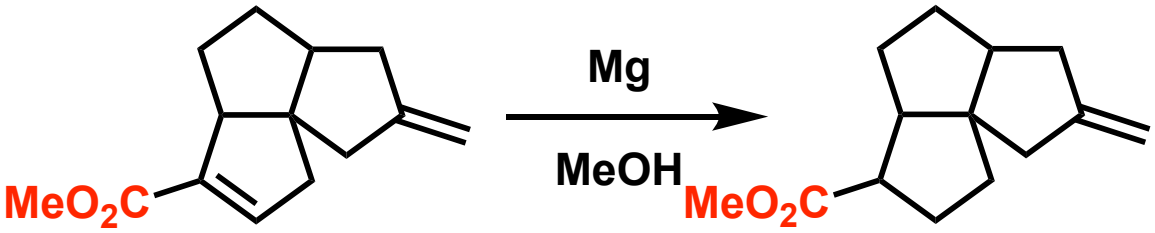


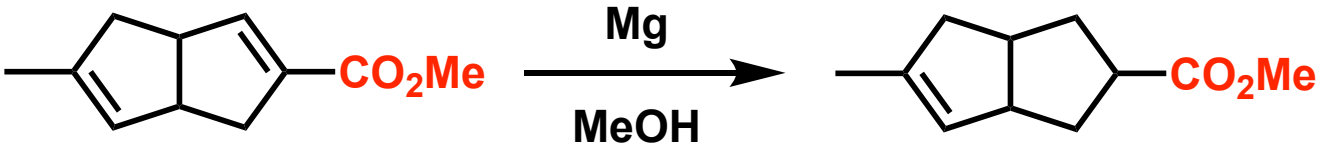
Mg in ROH

Mg in MeOH:

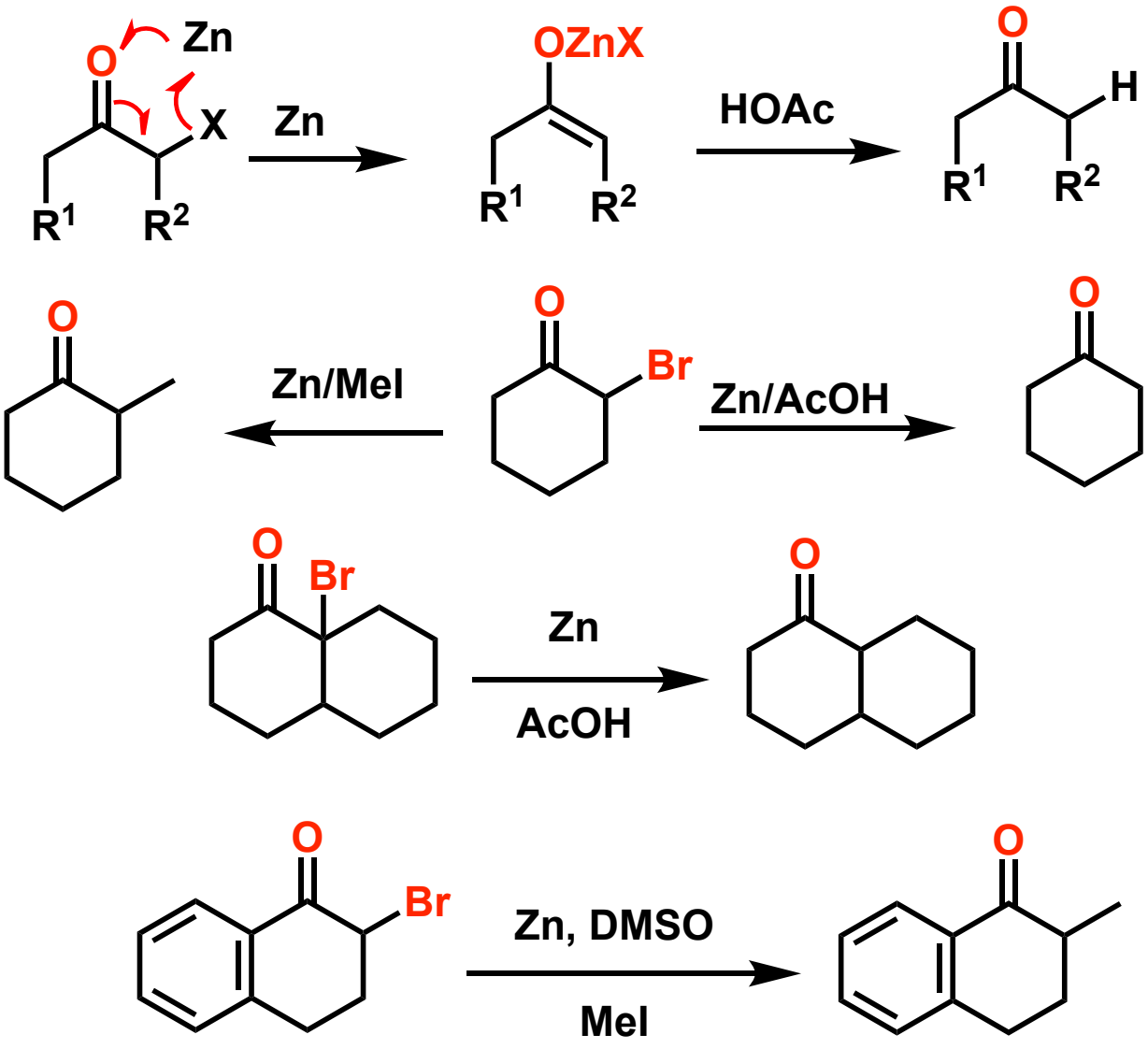


$X = CN, COOR, CONR_2$

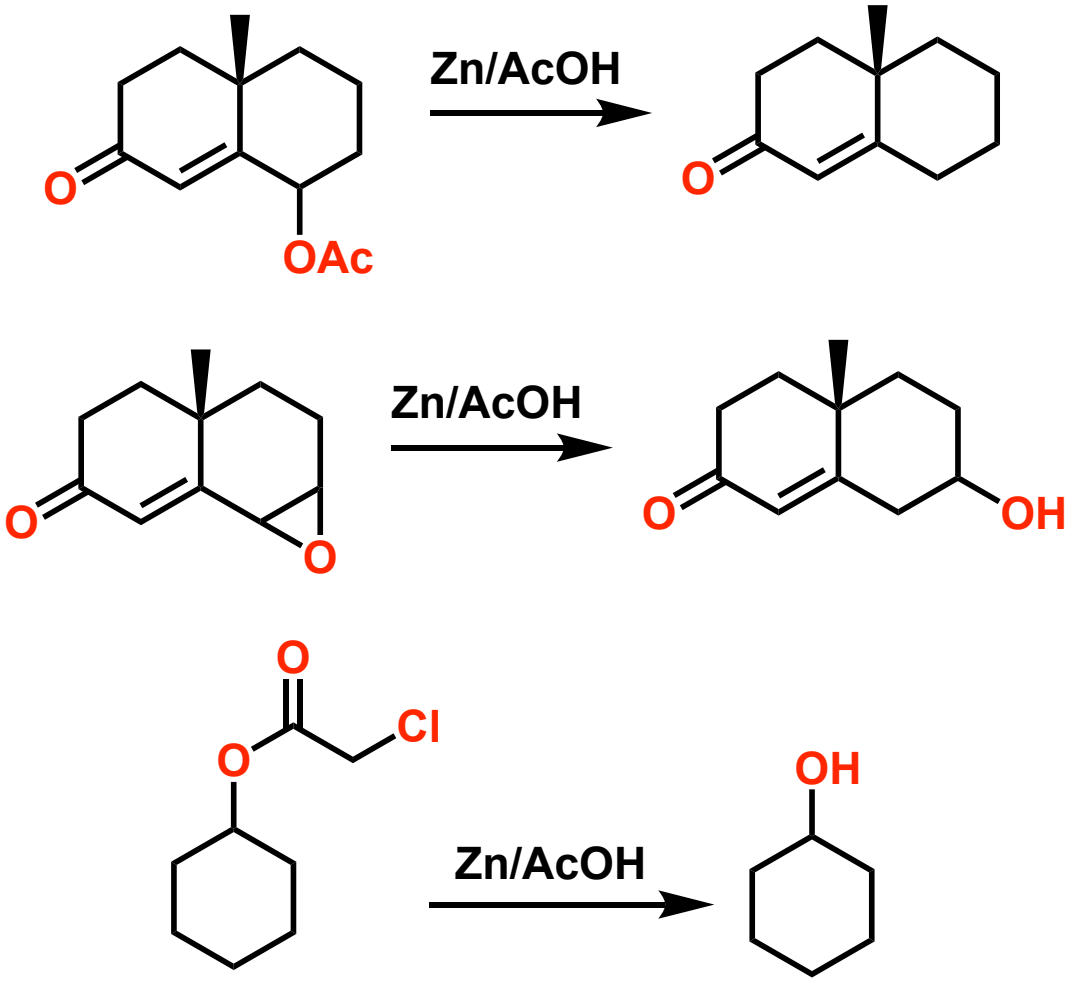




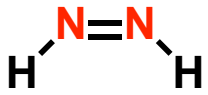
Zn in AcOH



Zn in AcOH



Diimide

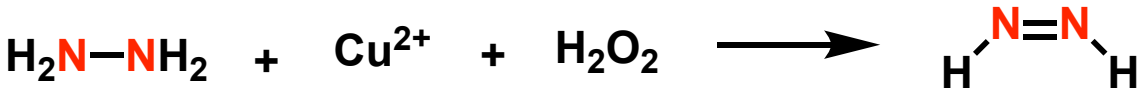


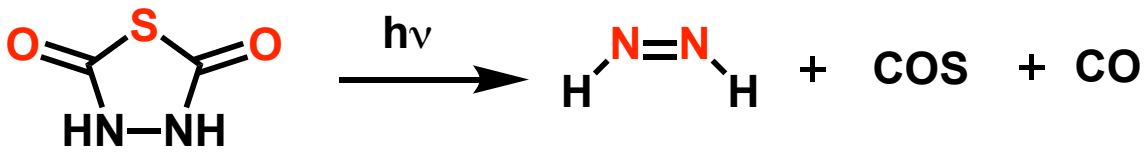
Reduces only double bonds

Selectively reduces the more strained double bonds

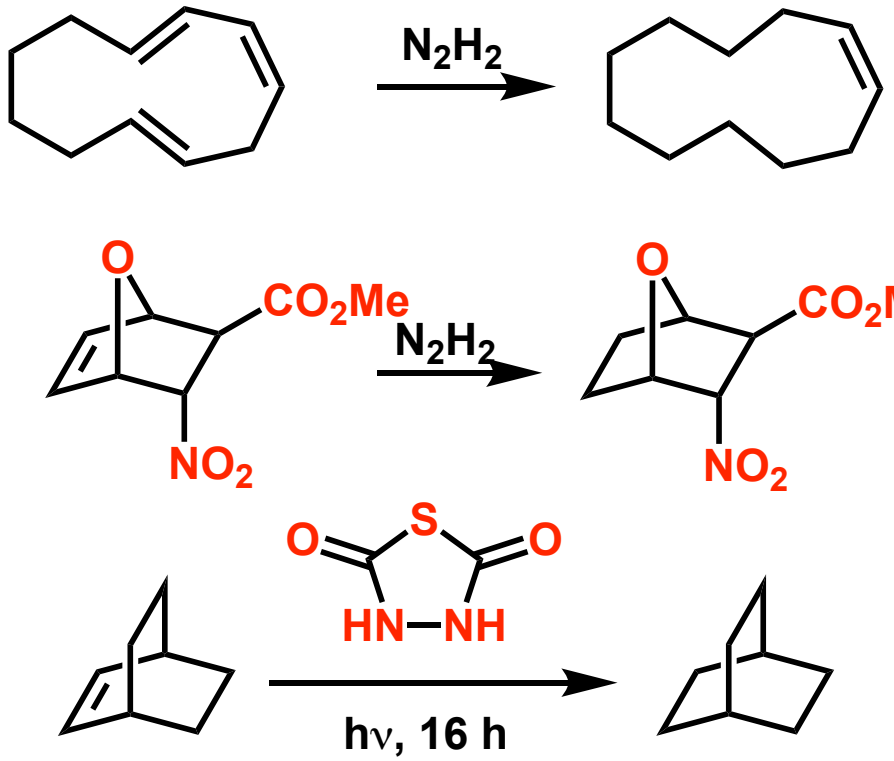
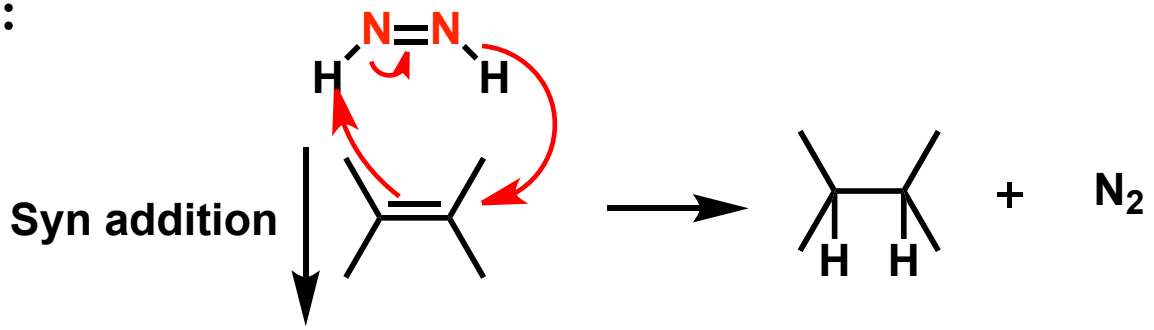
Syn addition of Hydrogen

Unstable reagent: Always prepared *in situ*





Diimide



Mechanism: