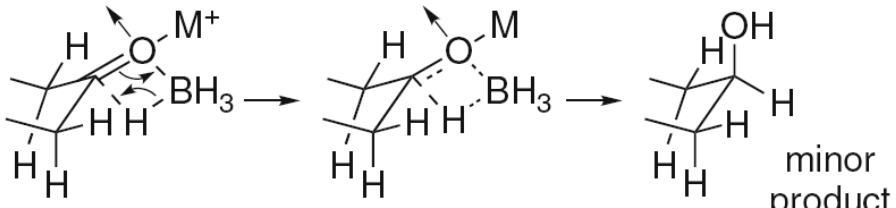
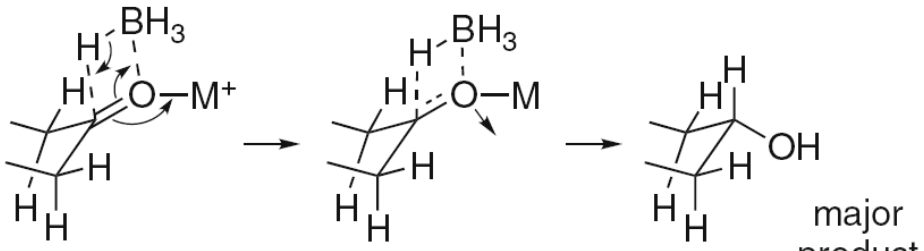
Hydride Reduction – Stereoselectivity

Steric Approach Control

Alkylborohydrides:
- high SAC (LUMO)
- equat. OH preffered



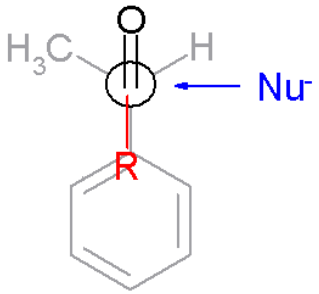
Torsional strain increases as oxygen passes through an eclipsed conformation



Oxygen moves away from equatorial hydrogens; no torsional strain

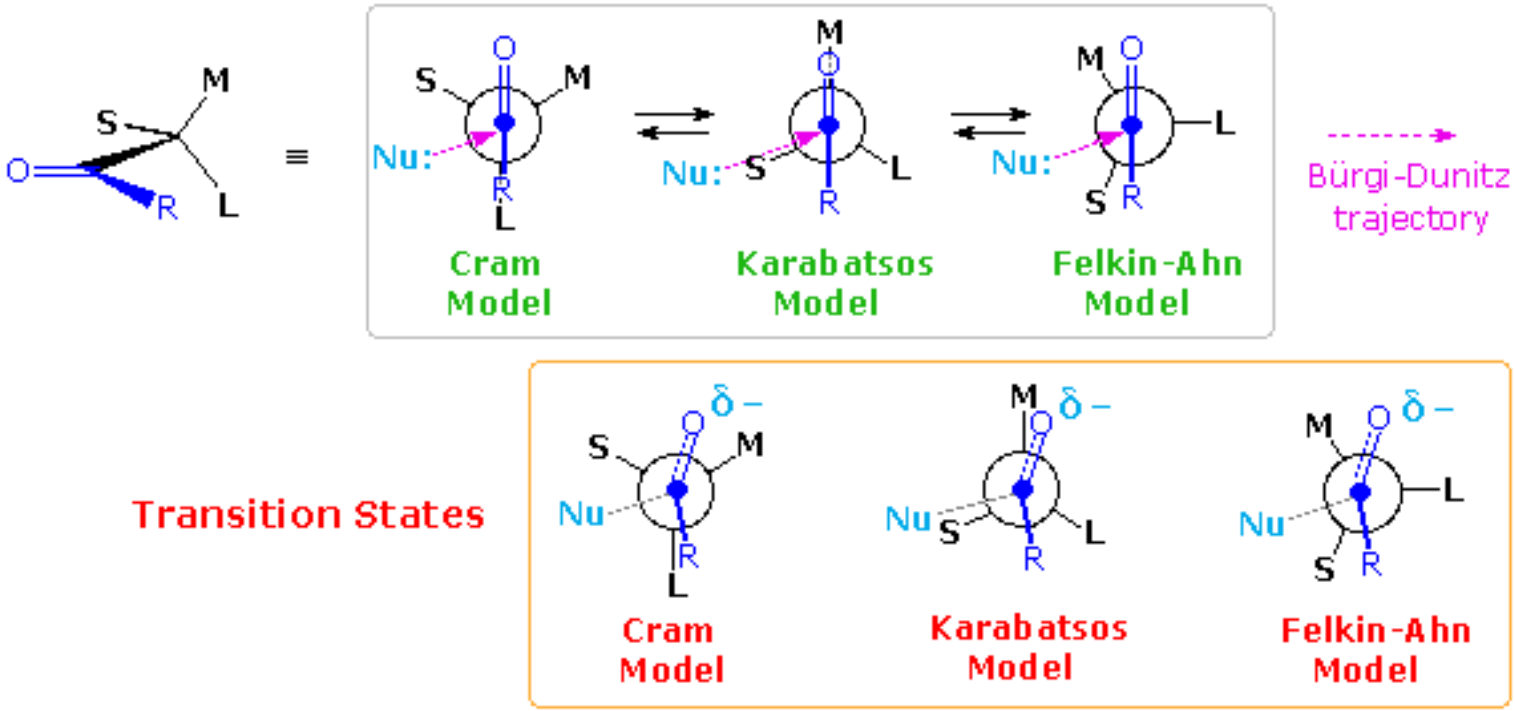
Cram´s Rule

- relative size of substituents: S,M,L



Hydride Reduction – Stereoselectivity

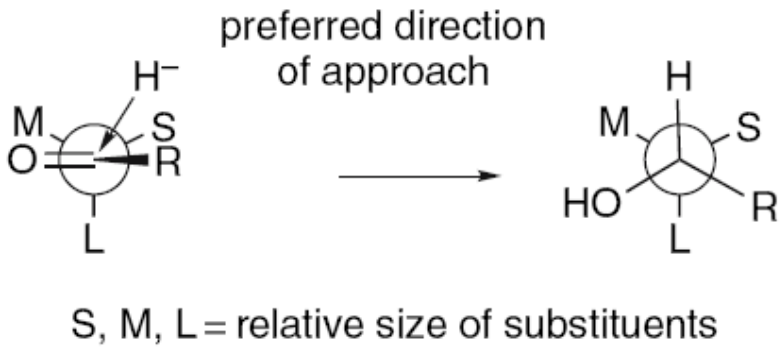
Felkin – Ahn Model



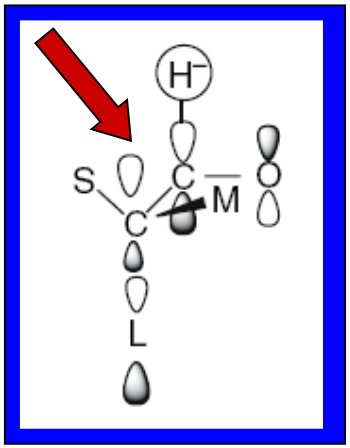
Hydride Reduction – Stereoselectivity

Felkin – Ahn Model

- stereoelectronic effect
- L is perpendicular to the plane of the CO
- interaction between the LUMO and the antibonding orbital of the C−L bond



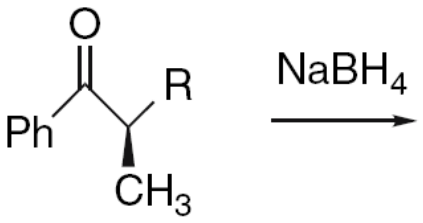
S, M, L = relative size of substituents

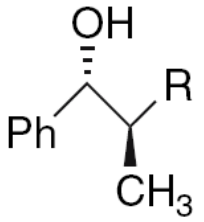


Reduction in Organic Synthesis

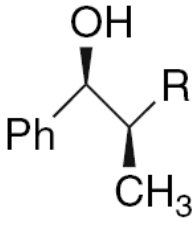
Hydride Reduction – Stereoselectivity

Examples

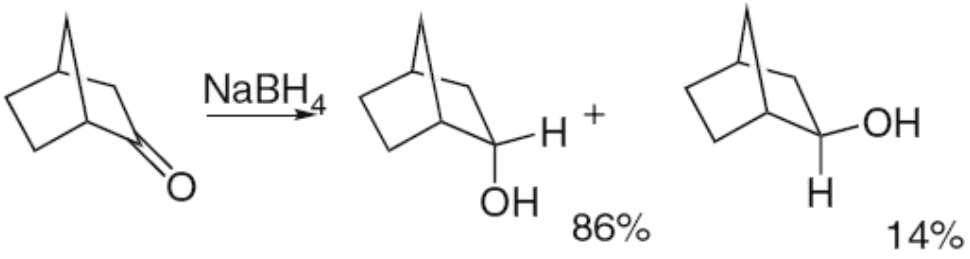


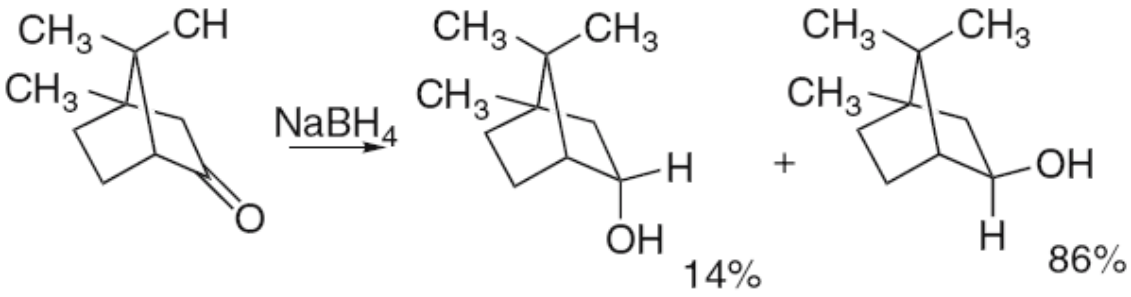


+



R	*anti:syn*
C_2H_5	57:43
$CH_2{=}CH$	70:30
$HC{\equiv}C$	89:11



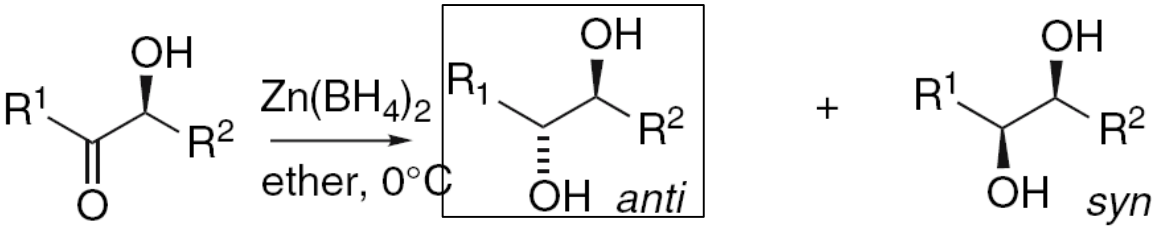


Hydride Reduction – Stereoselectivity

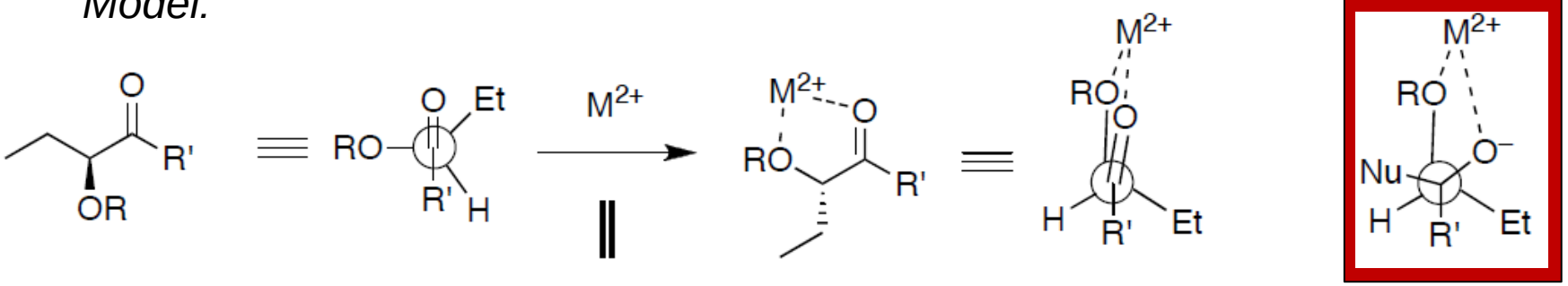
Chelation Control

- donor substituents
- specific complexation (substituent, the carbonyl oxygen, LA)
- preferred conformation

α-hydroxy and α-alkoxyketones, α,β-epoxyketones are reduced to *anti* 1,2-diols: $Zn(BH_4)_2$, (Li^+, $NaBH_4/La^{3+}$, Ca^{2+}, Ce^{3+})



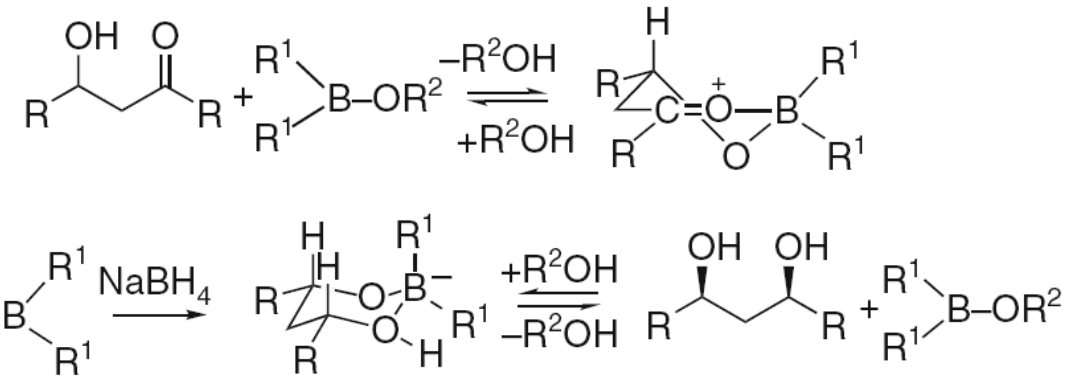
Model:



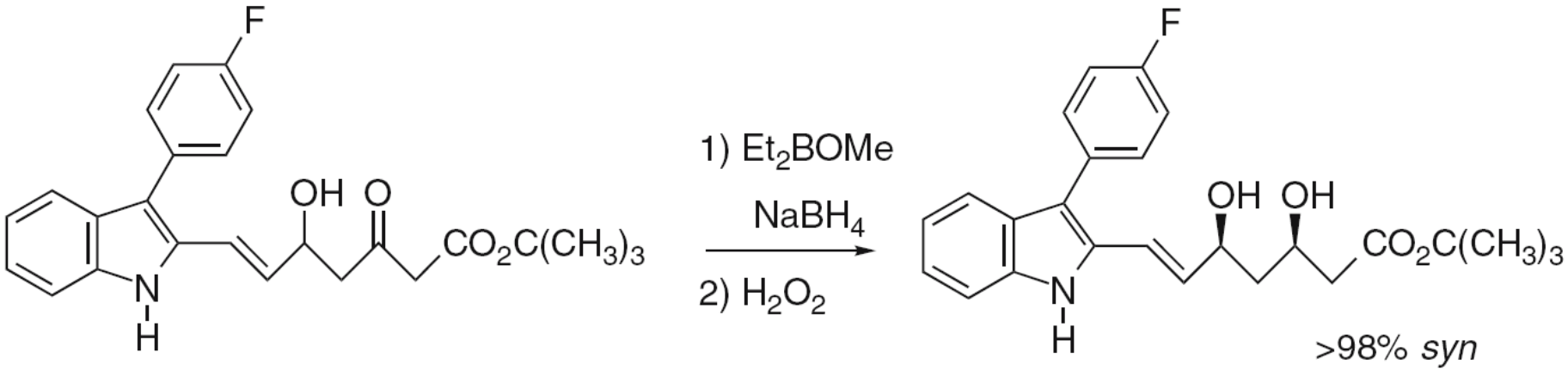
Hydride Reduction – Stereoselectivity

Chelation Control

β-hydroxyketones are reduced to *syn* 1,3-diols



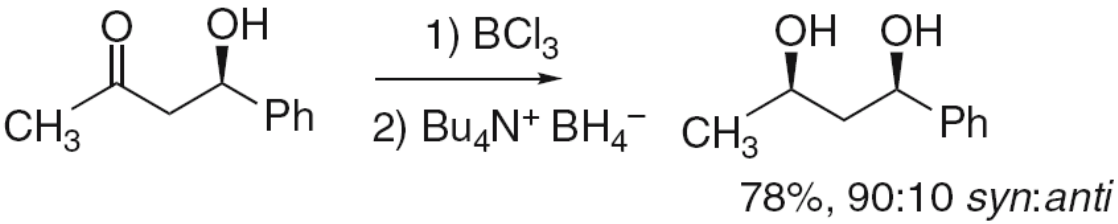
Example



Hydride Reduction – Stereoselectivity

Chelation Control

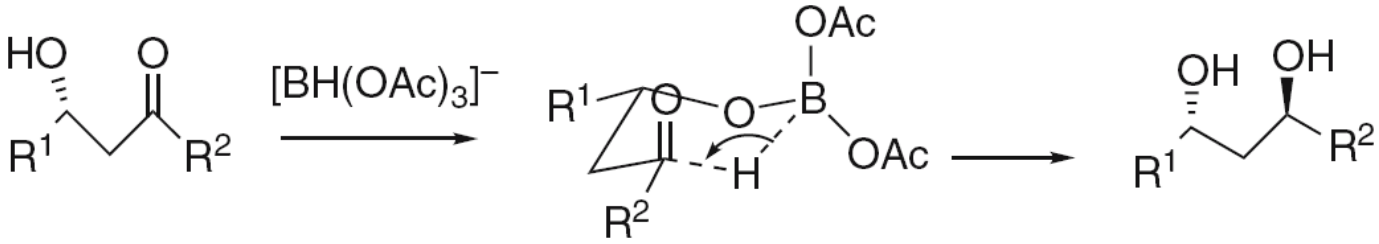
Chelates with BCl_3, $TiCl_4$, etc.



78%, 90:10 *syn*:*anti*

Watch out!

β-hydroxyketones are reduced to *anti* 1,3-diols / $Me_4N^+BH(OAc)_3^-$



Reduction in Organic Synthesis

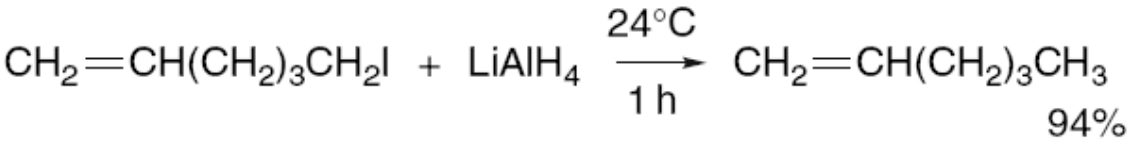
Hydride Reduction – Other Functional Groups

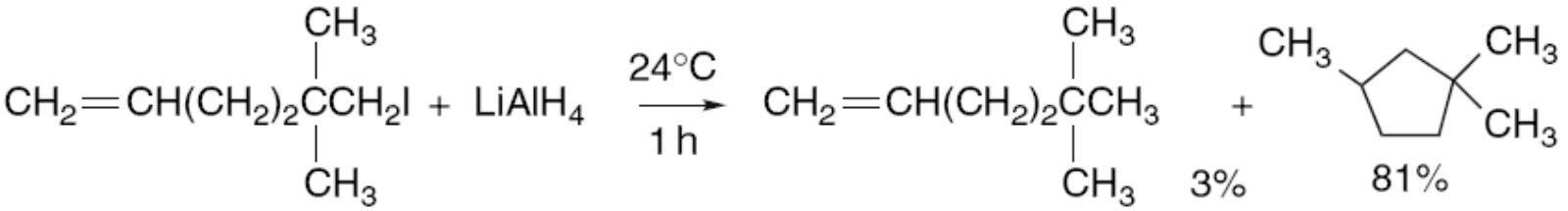
- hydrogenolysis
- RX, RSO_2R', epoxides
- $LiAlH_4$, $NaBH_3$, $LiHBR_3$
- dipolar aprotic solvents

RX

I > Br > Cl

benzyl ~ allyl > primary > secondary > tertiary

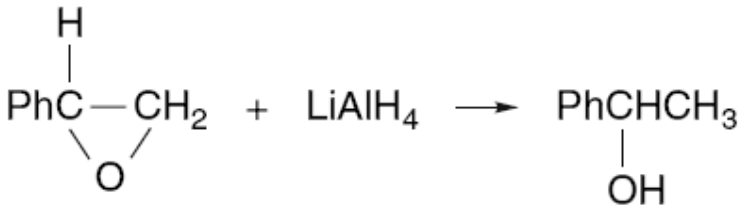




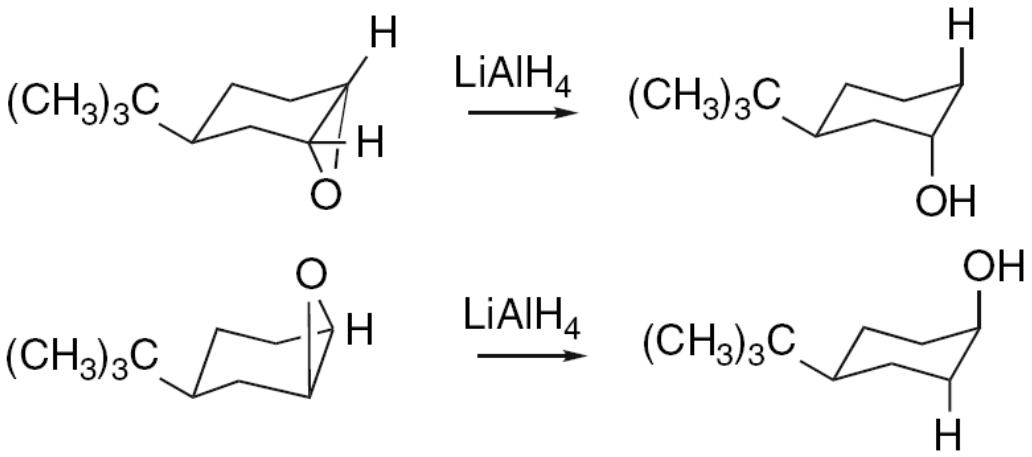
Hydride Reduction – Other Functional Groups

Epoxides

H^- on less hindered carbon



- cyclohexene epoxides (diaxial opening)

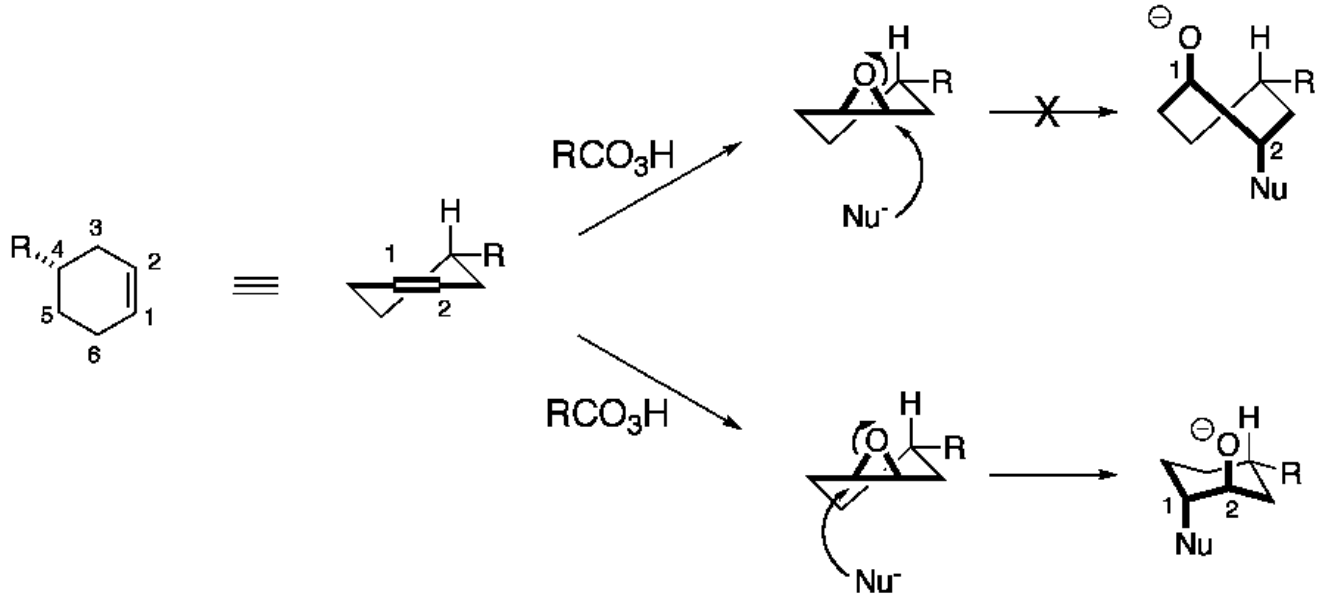


Appendix

Fürst-Plattner Rule

The Fürst-Plattner rule (also known as **the *trans*-diaxial effect**) describes the addition of nucleophiles to cyclohexene derivatives.

Nucleophilic **opening of the epoxide** can occur by attack at either the 1 or 2 position. The major product formed is from attack at the 1 position due to the instability of the twist boat product formed by addition at the 2 position (disfavored by approximately 5 kcal / mol). The Fürst-Plattner rule also applies to nucleophilic additions to imines and halonium ions.



Reduction in Organic Synthesis

1) $R_2C{=}X \xrightarrow{H_2} R_2CH{-}XH$

catalytic hydrogenation

X = CR'_2, O, NR′

2) $R_2C{=}X \xrightarrow{[MH_4^-]} R_2CH{-}XH$

hydride reduction

X = O, NR′

3) $R_2C{=}X \xrightarrow[2\ H^+]{2\ M\cdot} R_2CH{-}XH$

reduction by metals

4) $R_3C{-}Y \xrightarrow[2\ H^+]{2\ M\cdot} R_3C{-}H + H{-}Y$

dissolving metals

Y = halogen, oxygen substituents, α–to carbonyl groups

$R_3C{-}Y \xrightarrow{R'_3ZH} R_3C{-}H$

hydrogen atom donors

Y = halogen, thio ester

Z = Sn, Si

5) $R_2C{=}X + M\cdot \longrightarrow R_2\overset{\overset{X}{|}}{C}{}^{\cdot} \longrightarrow R_2\overset{\overset{-X}{|}}{C}-\overset{\overset{X^-}{|}}{C}R_2$ or $R_2C{=}CR_2$

X=O

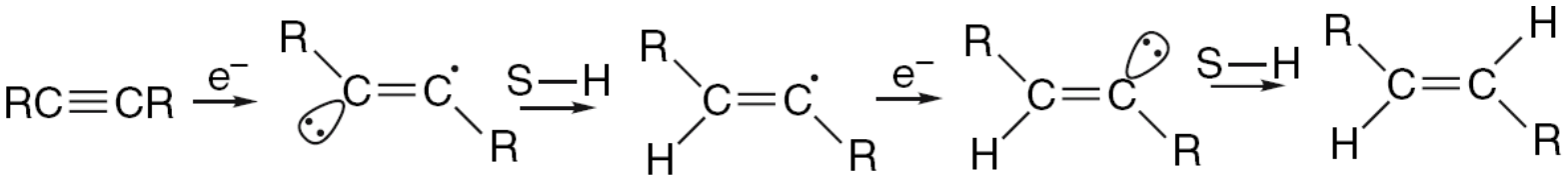
M· = Na^0, Ti^{II}, Sm^{II}

reductive coupling

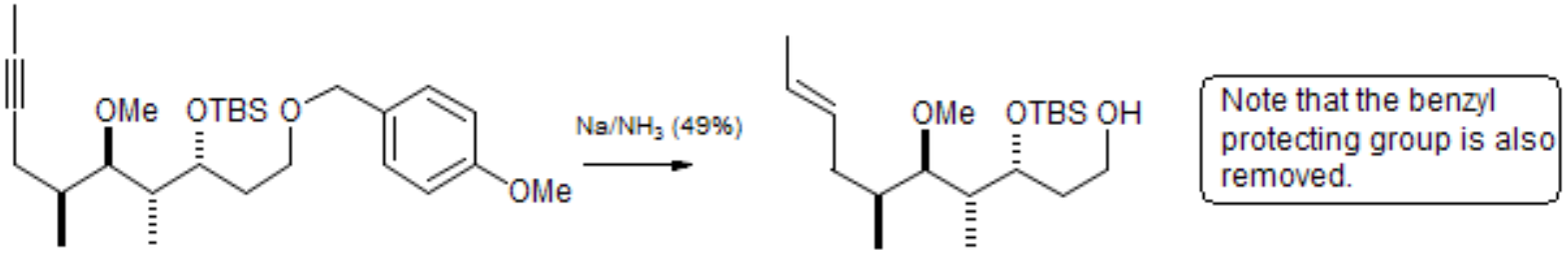
Addition of Electrones and Hydrogen (3)

Reduction of alkynes

- Na or Li/NH_3
- Na/HMPA/*t*-BuOH



Example

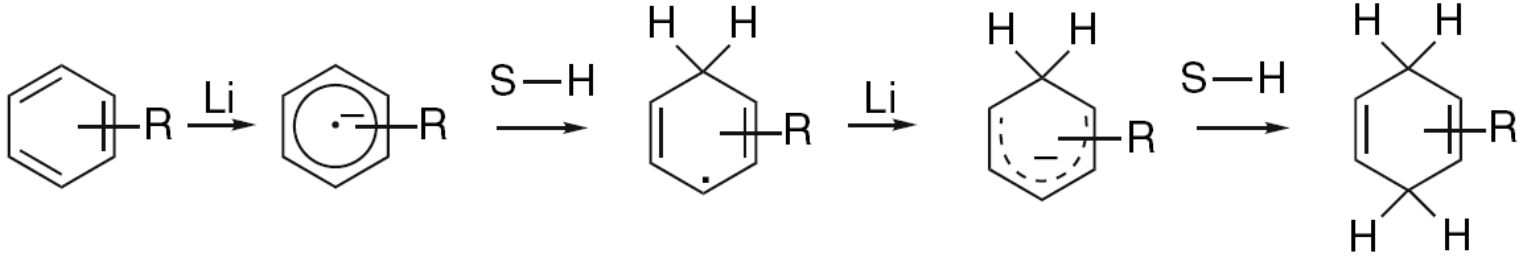


Addition of Electrones and Hydrogen (3)

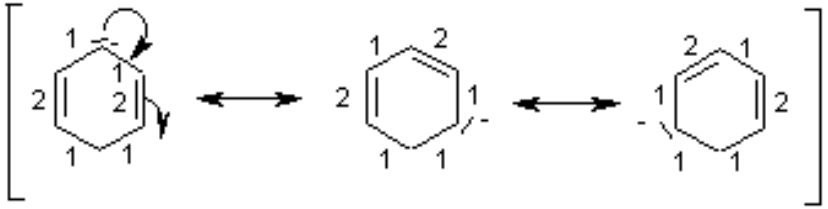
Reduction of aromates

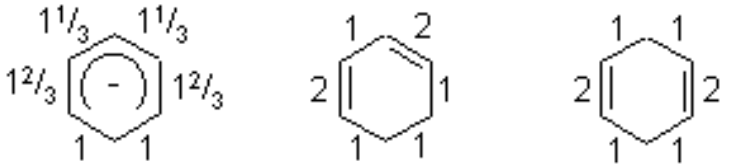
Birch reduction

- partial reduction of aromates (Li or Na/NH_3)
- ROH (H source)
- isolated C=C much less reactive
- Benkeser reduction (Li/HNR^1R^2)



Why not 1,3-diene?



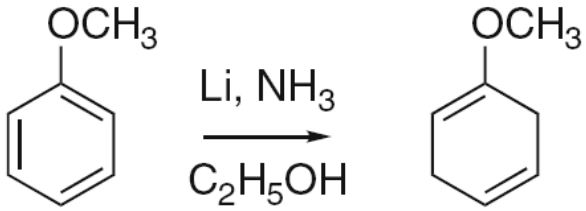


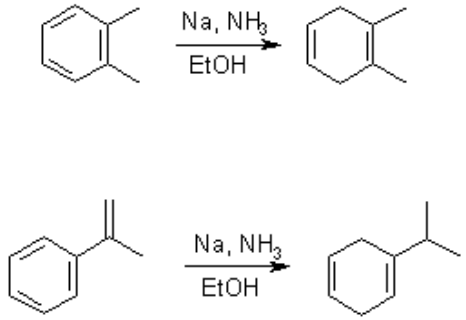
Addition of Electrones and Hydrogen (3)

Reduction of aromates

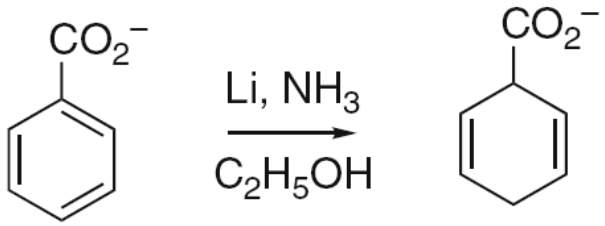
Birch reduction

ERS protonation in *ortho* position





EWG protonation in *para* position



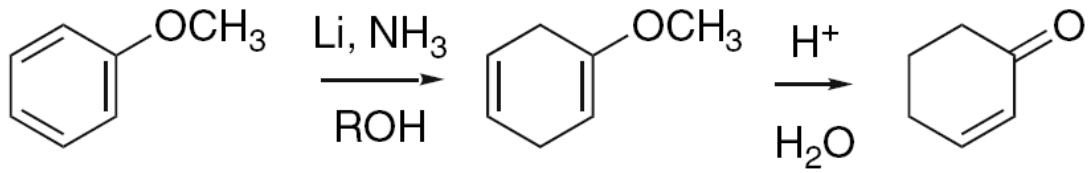
Addition of Electrones and Hydrogen (3)

Reduction of aromates

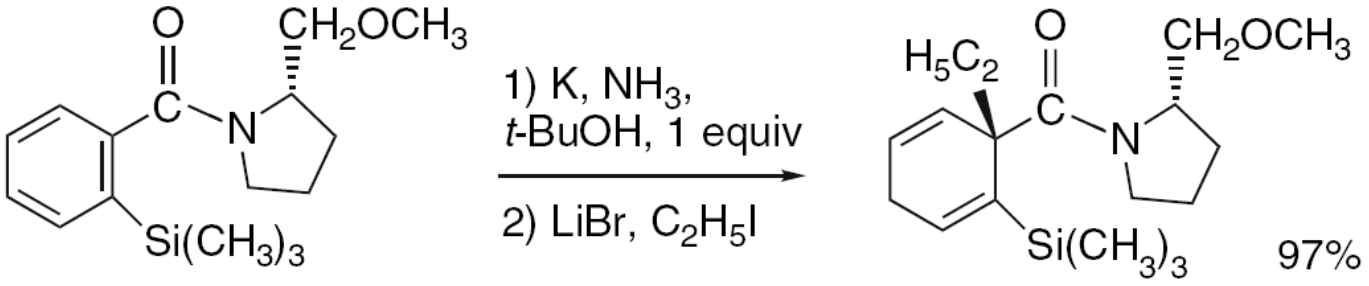
Birch reduction

Methoxybenzenes

- *via* hydrolysis of enol ethers



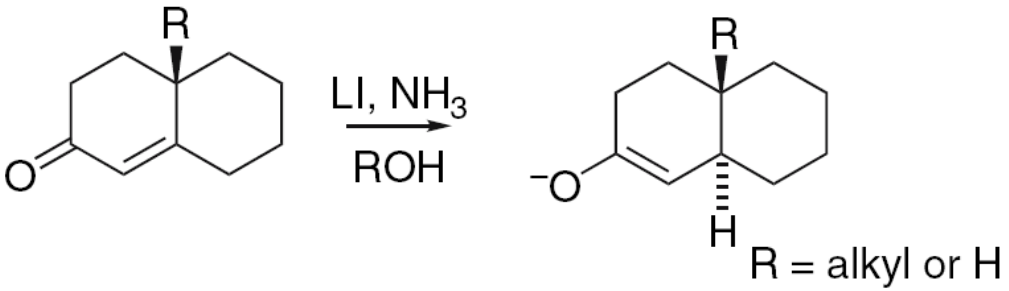
Tandem reactions



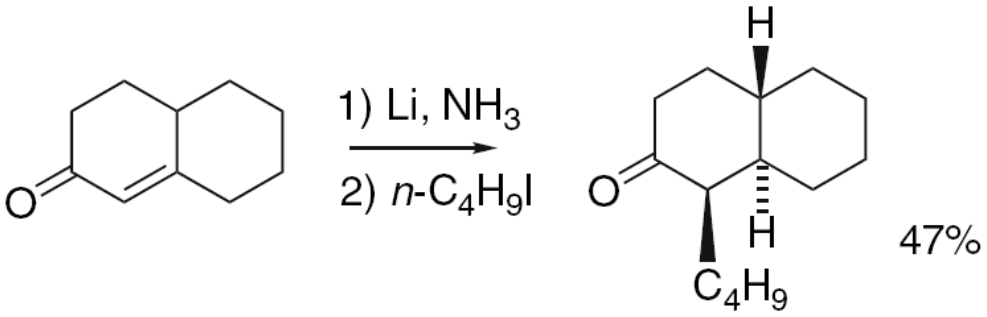
Addition of Electrones and Hydrogen (3)

Reduction of α,β-unsaturated ketones

- Li/NH_3,
- ROH (H source, excess)



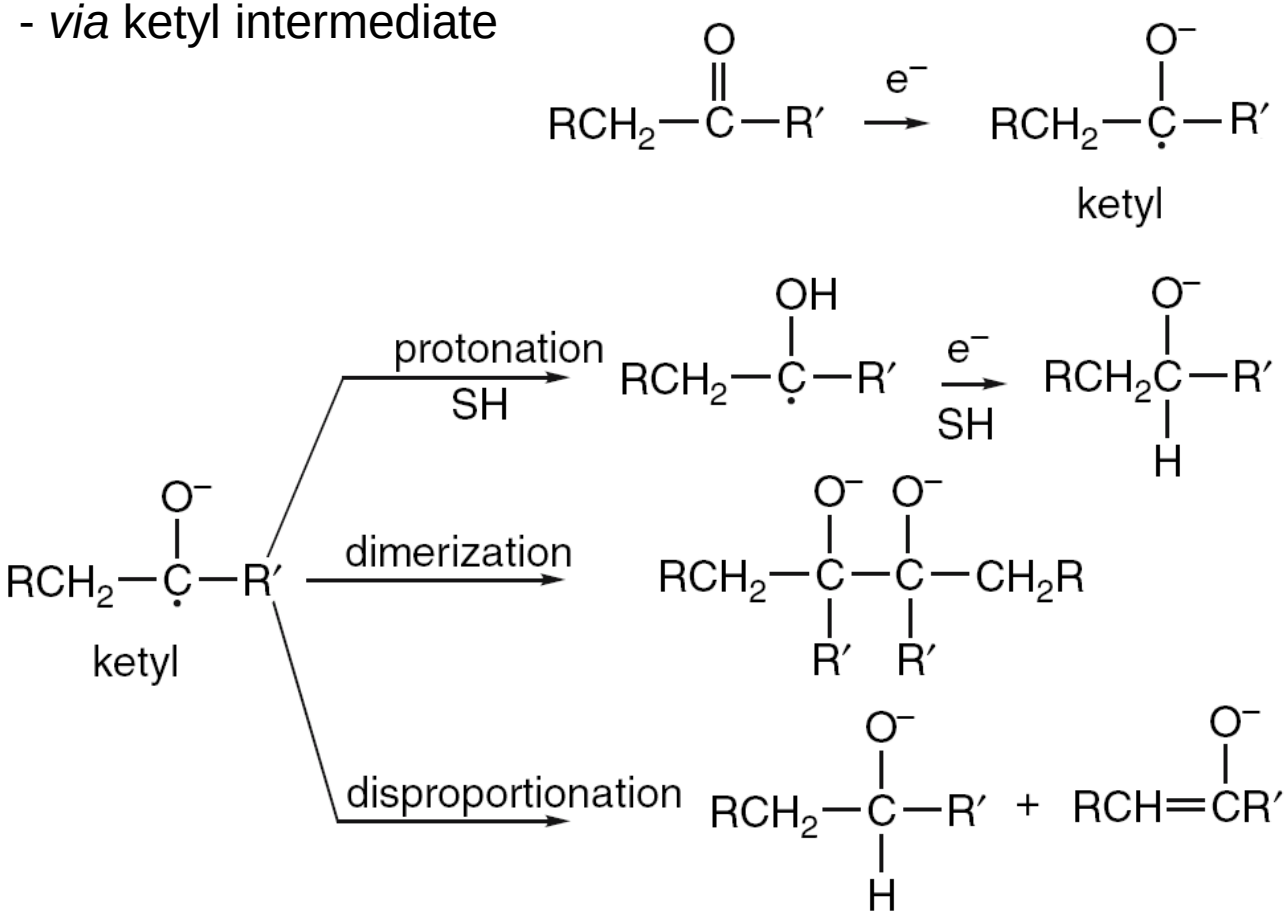
Watch out!



Addition of Electrones and Hydrogen (3)

Reduction of ketones

- *via* ketyl intermediate

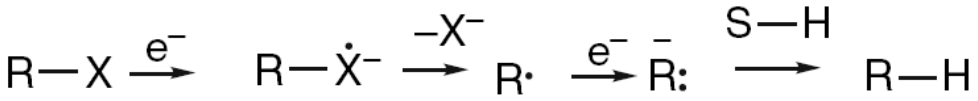


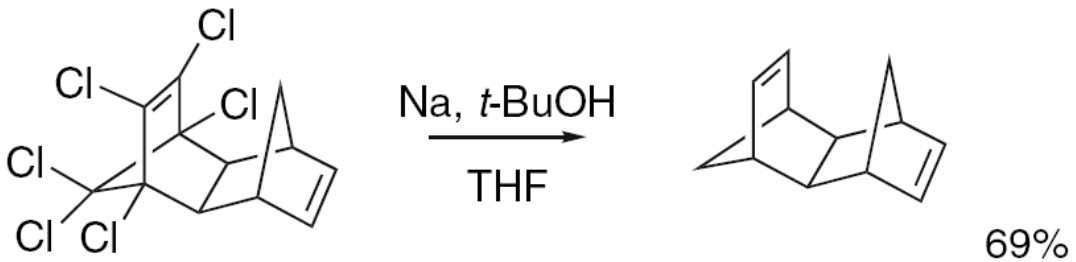
dominat process

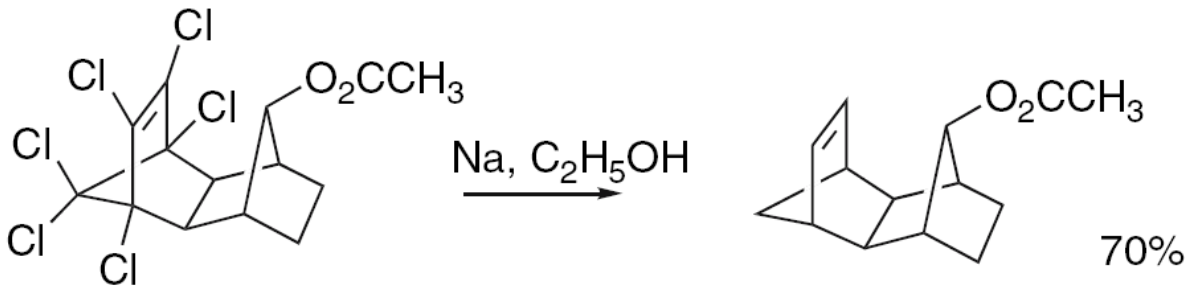
Reductive Removal of Function Groups (4)

Dehalogenation

Li or Na/THF/*t*-BuOH



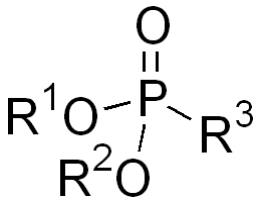


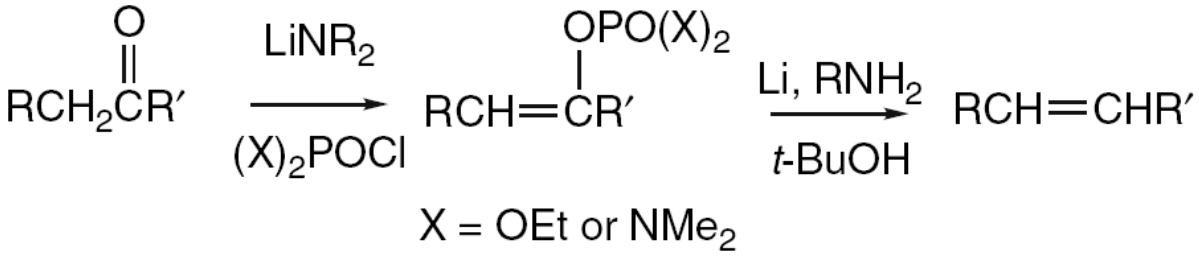


Reductive Removal of Function Groups (4)

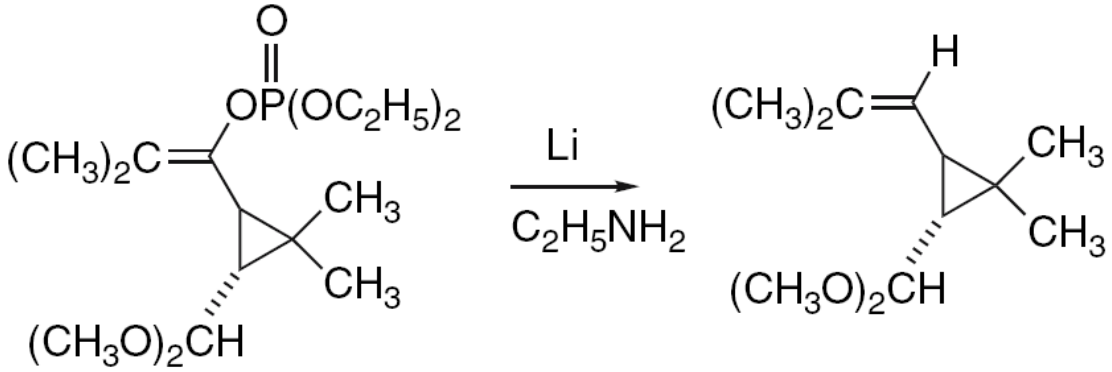
Dephosphonation

- vinyl phosphonates
- ketone → vinyl phosphonate → alkene





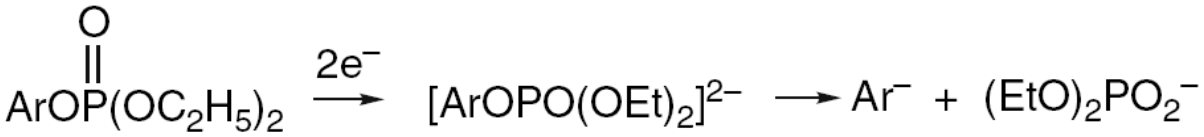
Example



Reductive Removal of Function Groups (4)

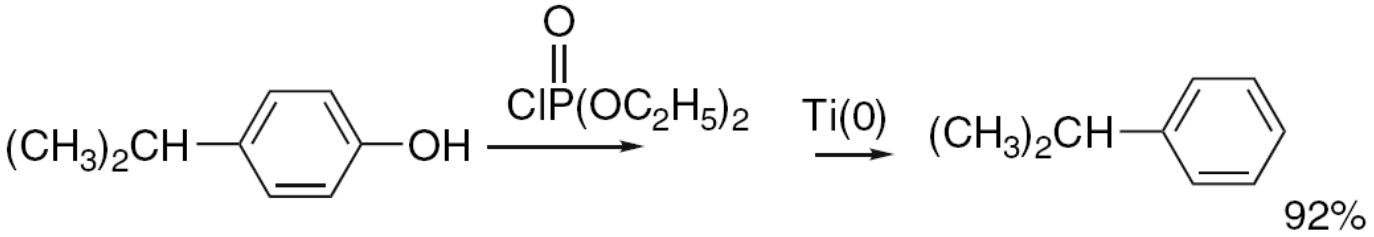
Dephosphonation

- aryl phosphonates
- ArOH → aryl phosphonate → arene



Example

Ti (0) *in situ* ($TiCl_3$/K/THF)

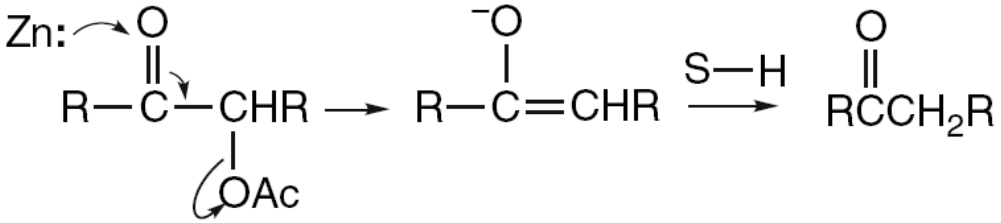


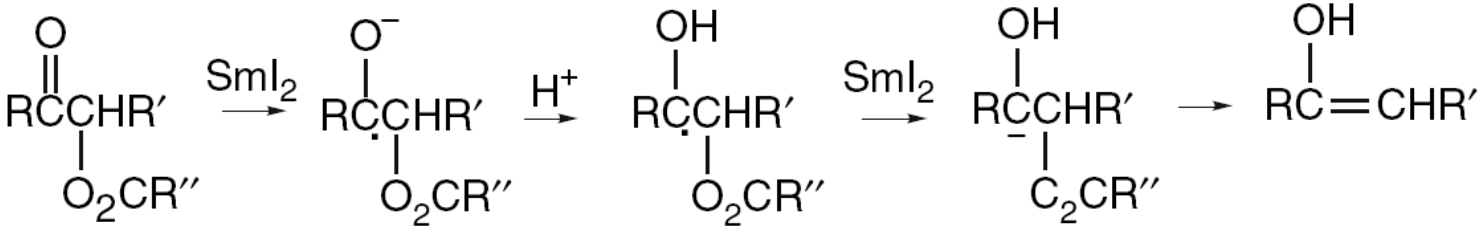
Reductive Removal of Function Groups (4)

Milder Reducing Agents

- Zn, Ca
- Al-Hg
- SmI_2

Reactions: α- deacetoxylation or α- dehydroxylation of ketones

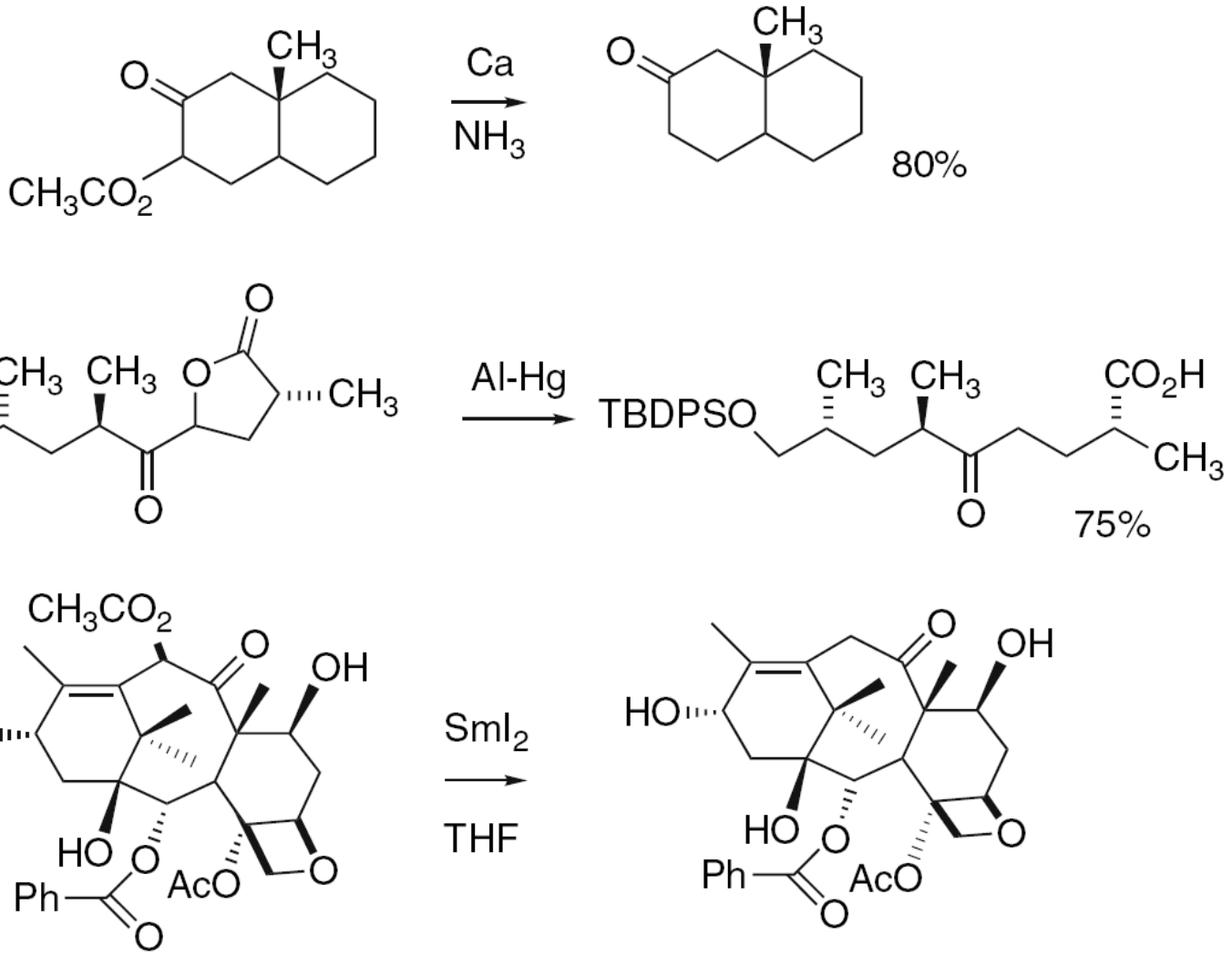




Reduction in Organic Synthesis

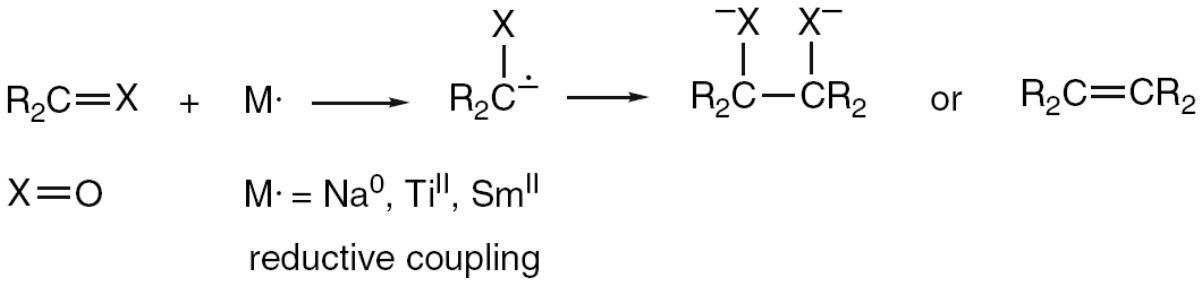
Reductive Removal of Function Groups (4)

Examples



Reductive Coupling of Carbonyl Compounds (5)

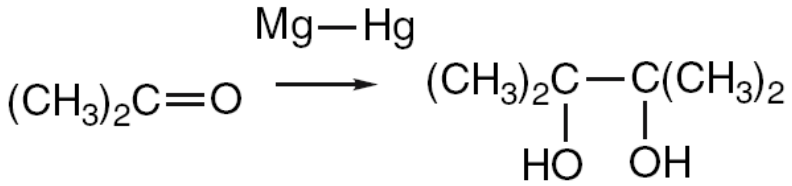
- one-electron process (radicals)



Formation of Diols

Pinacols

- Mg-Hg, $MgCl_2$



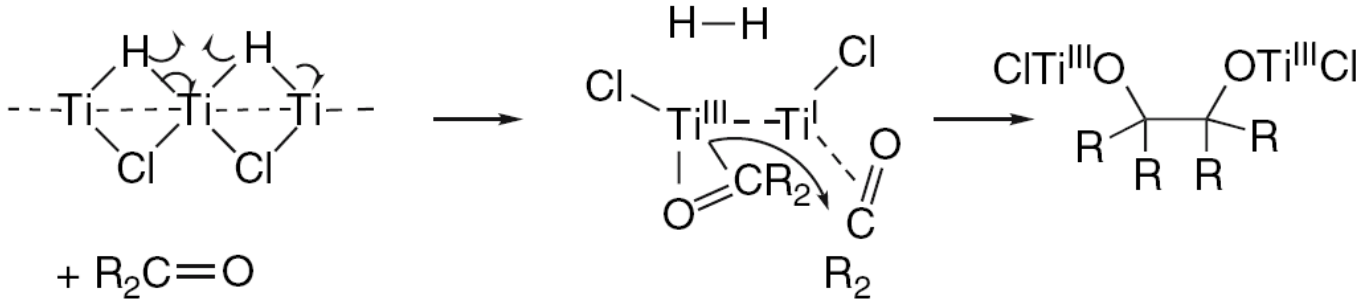
Reductive Coupling of Carbonyl Compounds (5)

Formation of Diols

- low-valent titanium: Ti(II) resp. $(HTiCl)_n$ or $TiCl_2$

  $TiCl_3/LiAlH_4$
  Mg-Hg or $Zn/TiCl_4$
  $TiCl_3$-Mg/catechol
  $TiCl_3$/Zn-Cu

  solvent: THF
  especially ArCOR and ArCHO

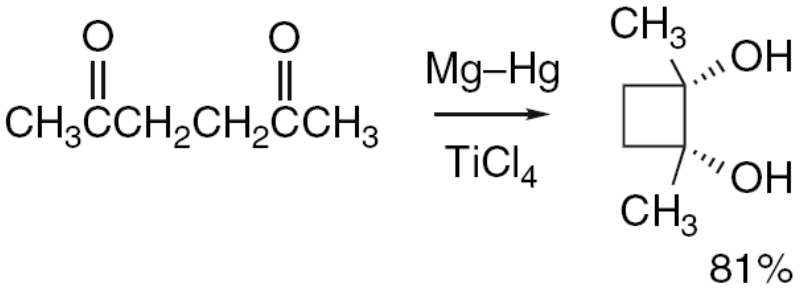


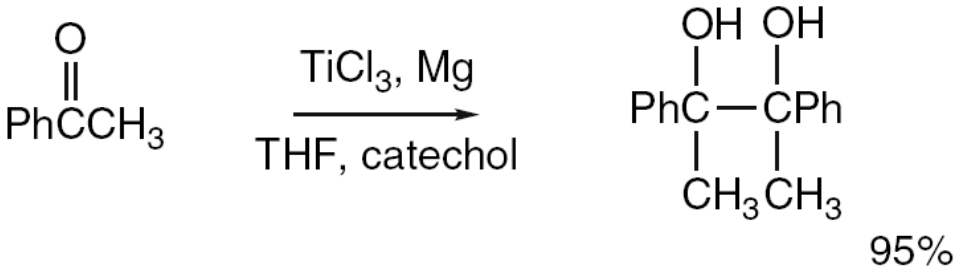
Reductive Coupling of Carbonyl Compounds (5)

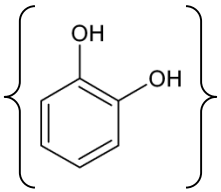
Formation of Diols

low-valent titanium

Examples



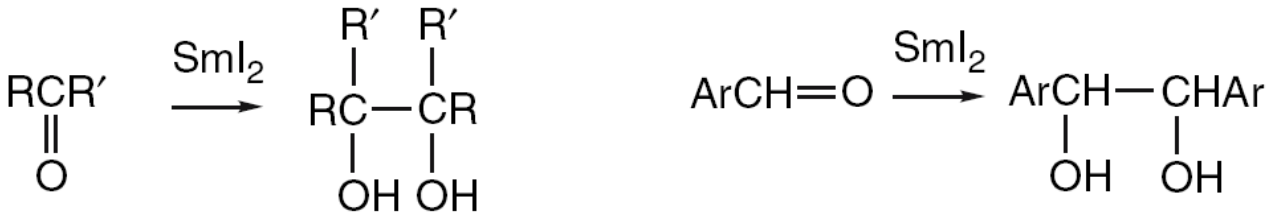




Reductive Coupling of Carbonyl Compounds (5)

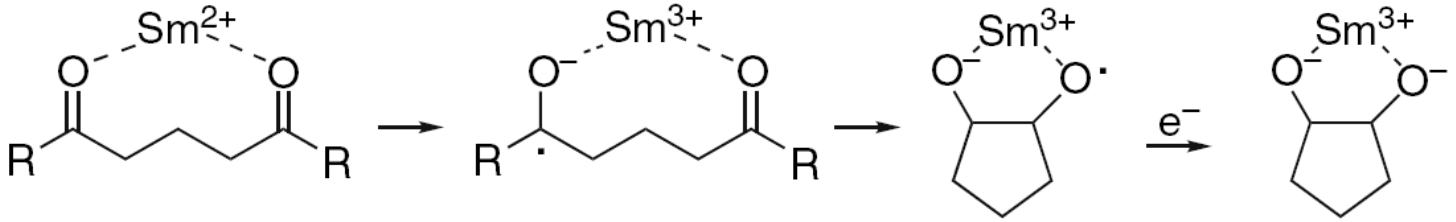
Formation of Diols

SmI_2 or $SmBr_2$



1,4-diketones and 4-ketoaldehydes

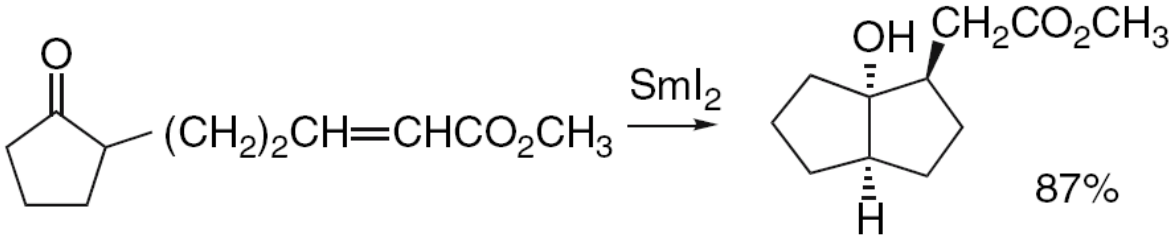
- cyclizations



Reductive Coupling of Carbonyl Compounds (5)

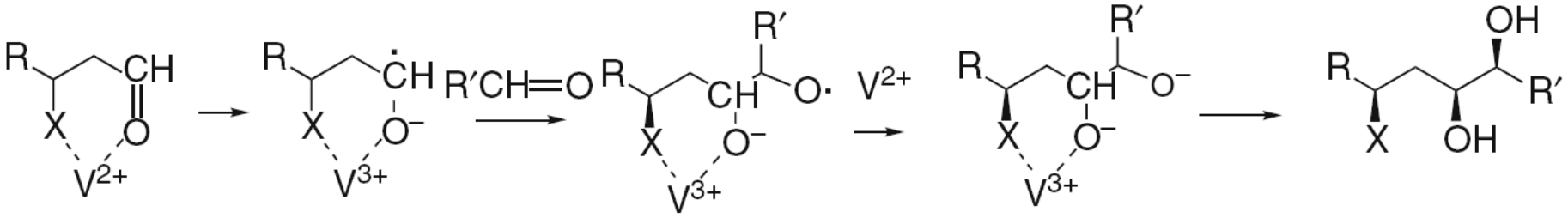
SmI_2 or $SmBr_2$

Cyclization of enones



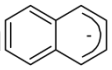
VCl_3/Zn

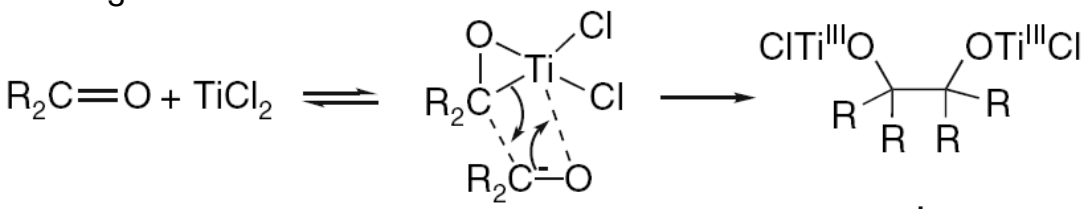
- preparation of diols (formylamides, amidoaldehydes, phosphinoylaldehydes)
- chelated intermediates

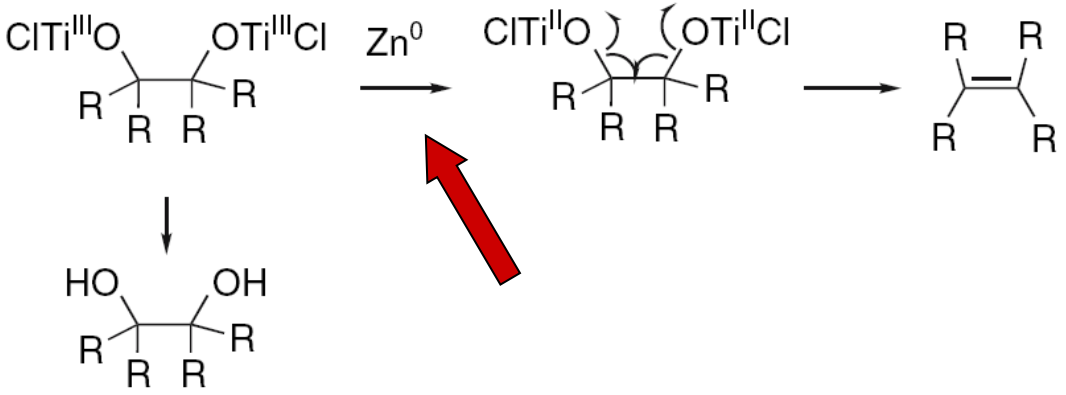


Reductive Coupling of Carbonyl Compounds (5)

McMurry Reaction

- formation of alkenes
- low-valent titanium:
  $TiCl_3$/Zn-Cu or Zn
  $TiCl_3/C_8K$, $TiCl_3$/  Na^+

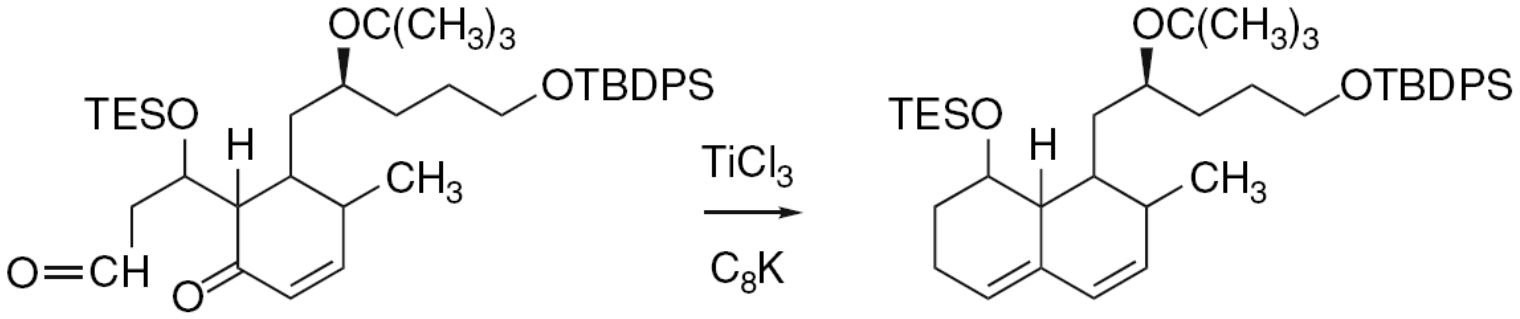


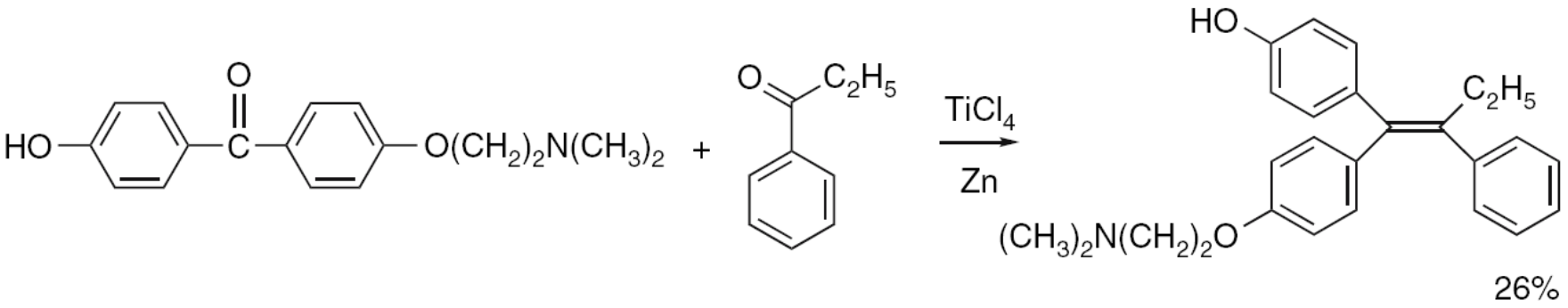


Reductive Coupling of Carbonyl Compounds (5)

McMurry Reaction

Examples

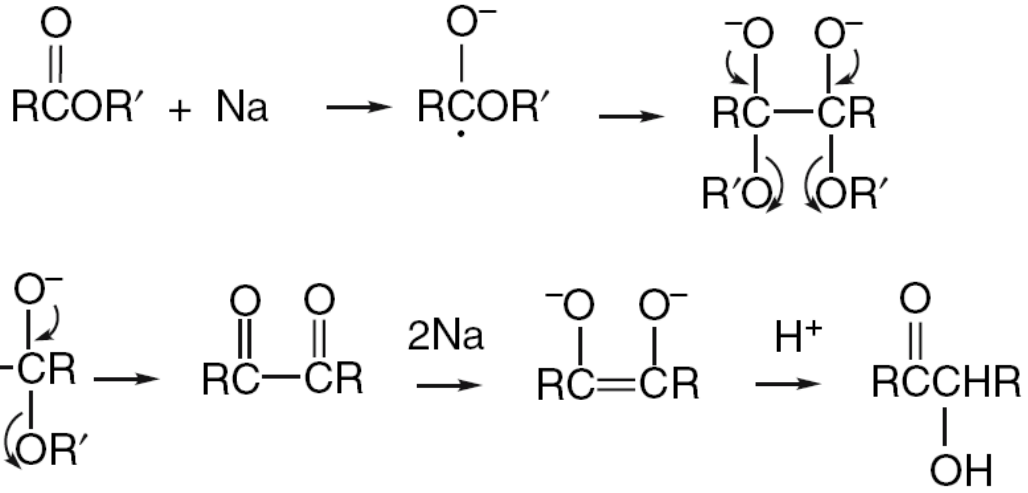




Reductive Coupling of Carbonyl Compounds (5)

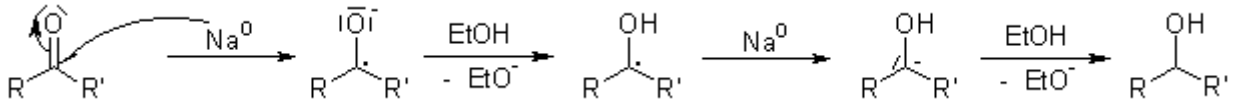
Acyloin condensation *(formation of α-hydroxyketones from esters)*

- *Na/inert solvent*
- H_2O or H_3O^+ work up



Watch out!

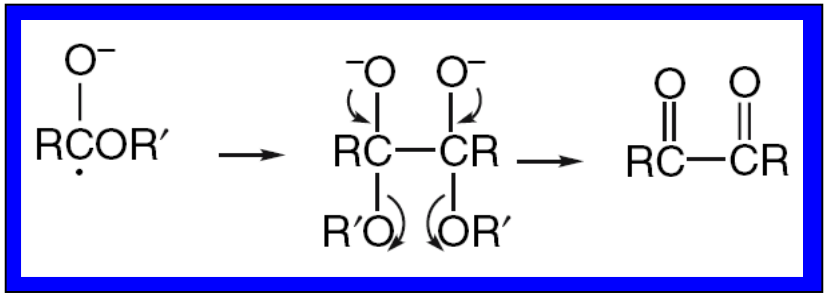
*Na/ROH (*Bouveault-Blanc Reduction)

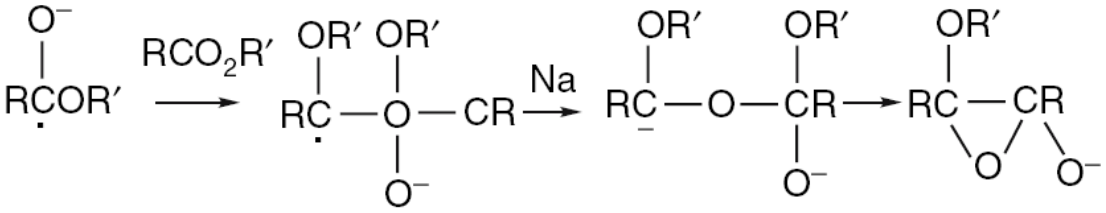


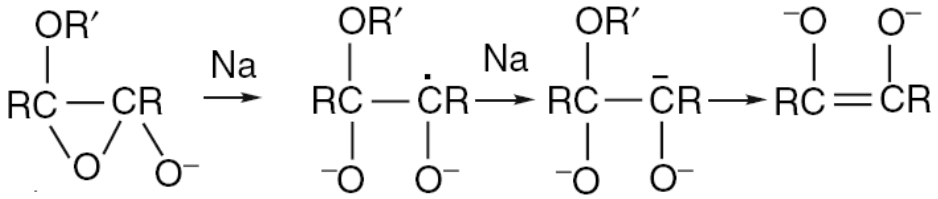
Reductive Coupling of Carbonyl Compounds (5)

Acyloin condensation *(formation of α-hydroxyketones from esters)*

Look insight!



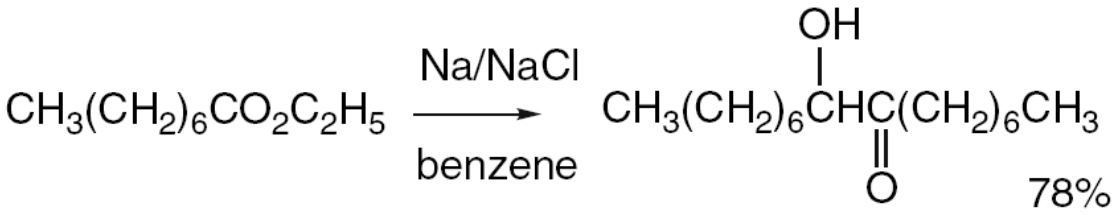


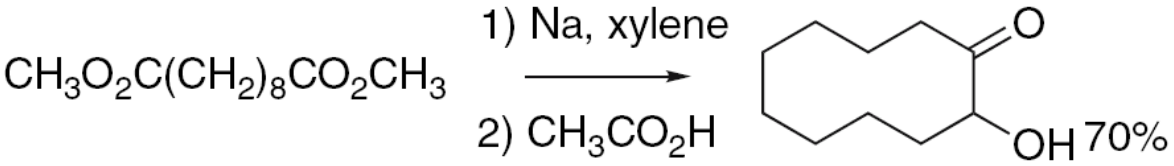


Reductive Coupling of Carbonyl Compounds (5)

Acyloin condensation

Examples





Reduction in Organic Synthesis

1) $R_2C{=}X \xrightarrow{H_2} R_2CH{-}XH$

catalytic hydrogenation

X = CR'_2, O, NR′

2) $R_2C{=}X \xrightarrow{[MH_4^-]} R_2CH{-}XH$

hydride reduction

X = O, NR′

3) $R_2C{=}X \xrightarrow[2\ H^+]{2\ M\cdot} R_2CH{-}XH$

reduction by metals

4) $R_3C{-}Y \xrightarrow[2\ H^+]{2\ M\cdot} R_3C{-}H + H{-}Y$

dissolving metals

Y = halogen, oxygen substituents, α–to carbonyl groups

$R_3C{-}Y \xrightarrow{R'_3ZH} R_3C{-}H$

hydrogen atom donors

Y = halogen, thio ester

Z = Sn, Si

5) $R_2C{=}X + M\cdot \longrightarrow R_2C^{\cdot -}(X) \longrightarrow R_2C(^{-}X)-CR_2(X^{-})$ or $R_2C{=}CR_2$

X=O

$M\cdot = Na^0, Ti^{II}, Sm^{II}$

reductive coupling

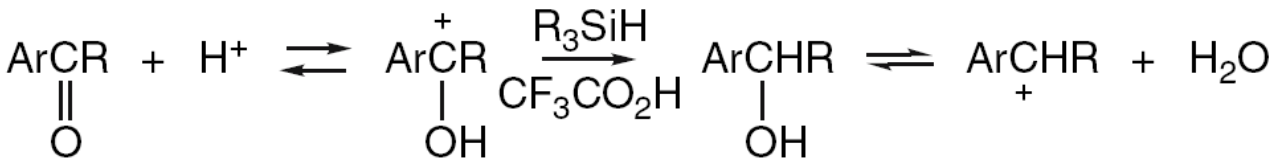
Hydrogen Atom Donors – Group IV Hydride Donors (6)

Silicon Hydrides (R_3SiH)

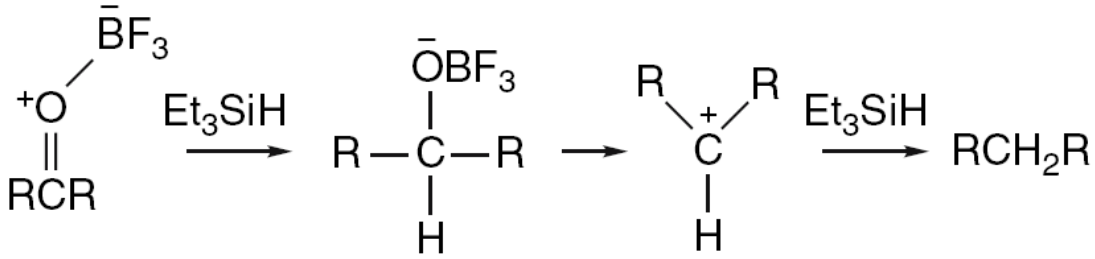
- weak hydride donors (stable to mild acids and oxidizing agents)
- carbonyl, imine reduction in presence of LA, BA or nucleophilic catalyst

Aromatic and aliphatic aldehydes and ketones

-reduction to alkylarenes (R_3SiH/H-acid)



- reduction to alkanes (R_3SiH/BF_3)



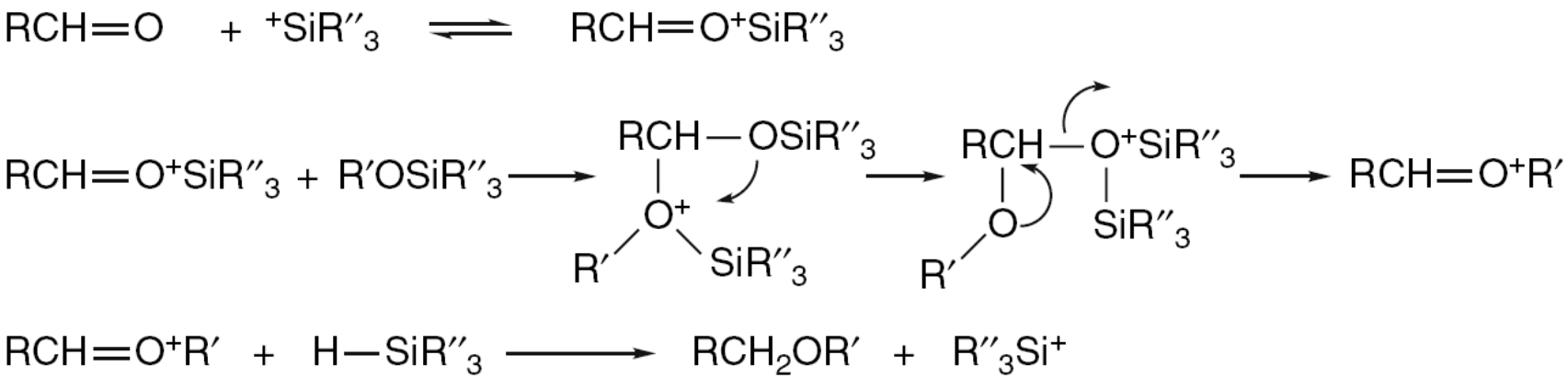
Hydrogen Atom Donors – Group IV Hydride Donors (6)

Silicon Hydrides (R_3SiH)

Reductive Condensation

- R_3SiH/TMSI or TMSOTf, $Cu(OTf)_2$, etc. (cat.)

$$R^1COR^2 + ROSiMe_3 \rightarrow R_1R_2CHOR$$

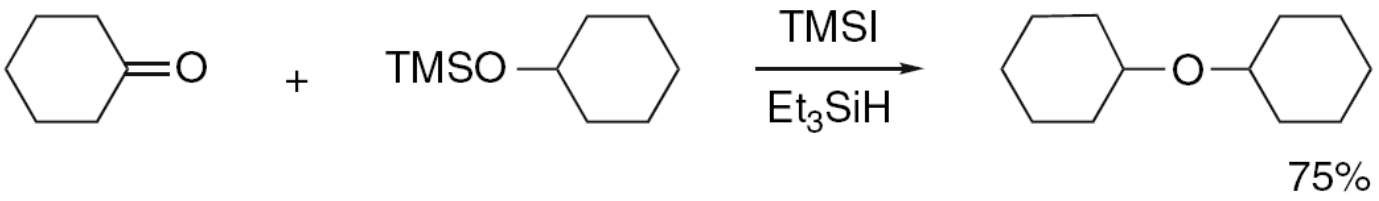


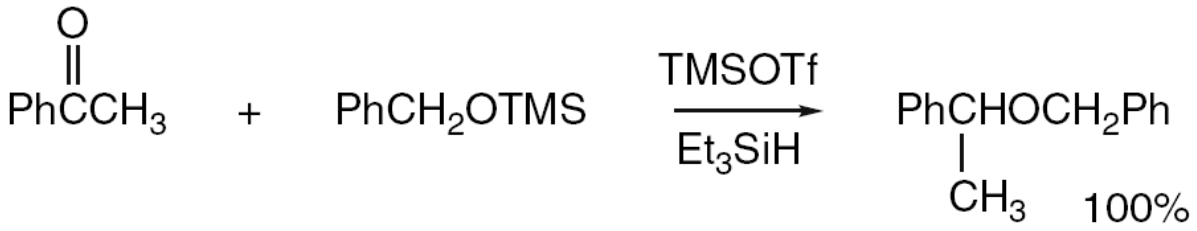
Hydrogen Atom Donors – Group IV Hydride Donors (6)

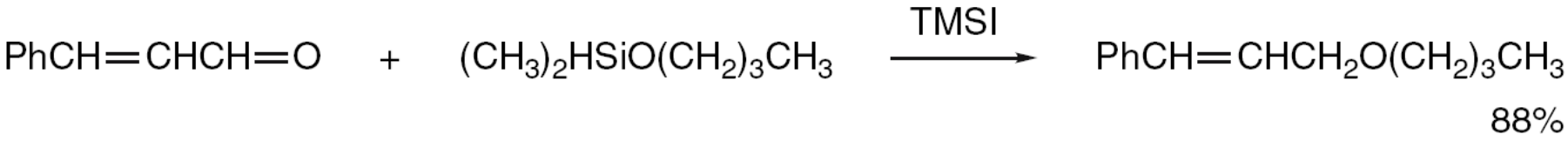
Silicon Hydrides (R_3SiH)

Reductive Condensation

Examples



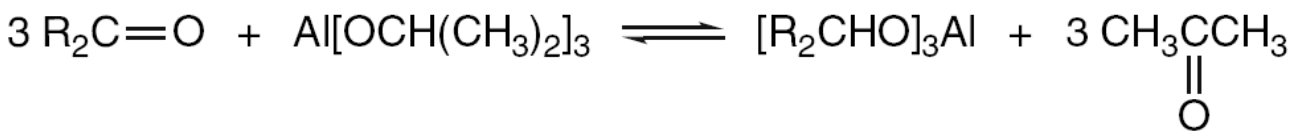




Other Reduction Reactions

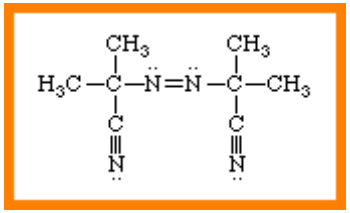
Meerwein-Pondorff-Verley

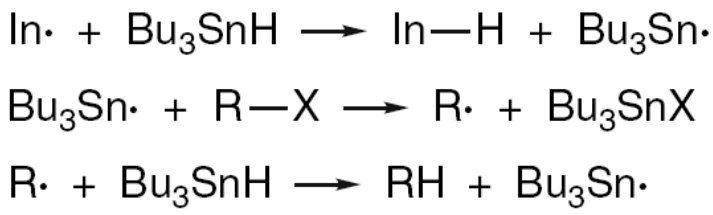
- aluminium alkoxides



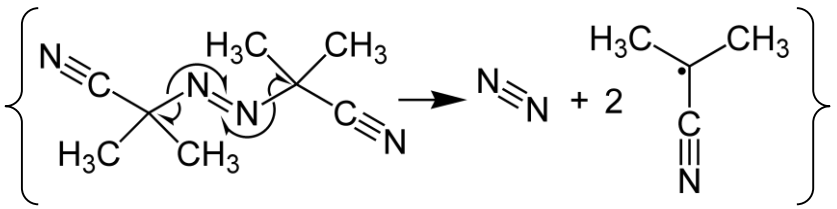
Bu_3SnH

- hydrogenolysis of RX
- RI > RBr > RCl > RF
- initiator (AIBN)



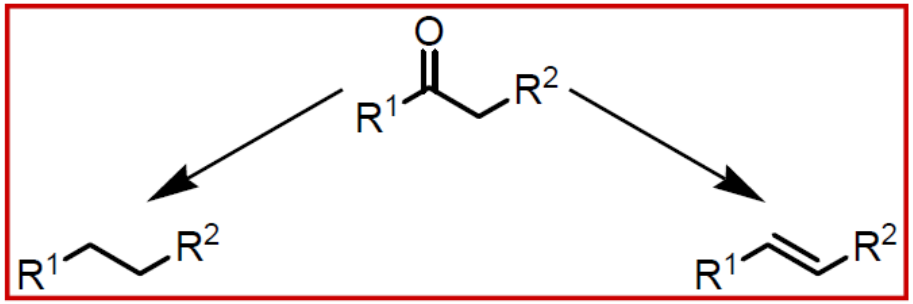


(In· = initiator)



Reductive Deoxygenation

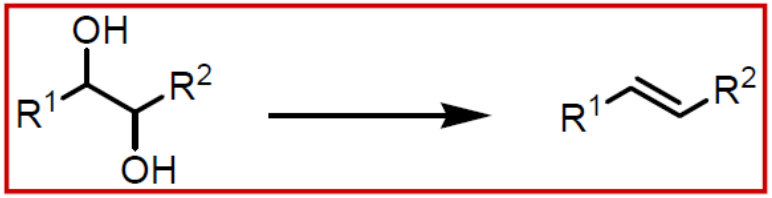
A) Reductive Deoxygenation of Carbonyl Group



- to alkanes

to alkenes

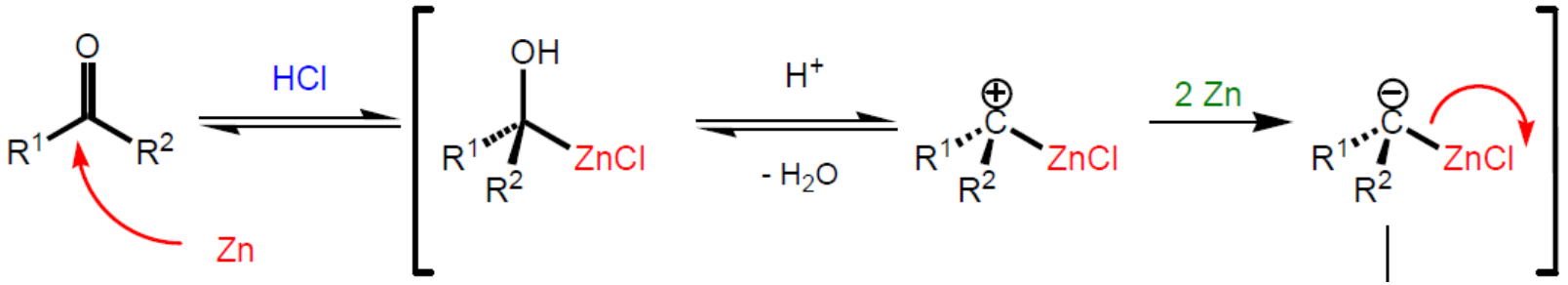
B) Reductive transformation of diols to alkenes

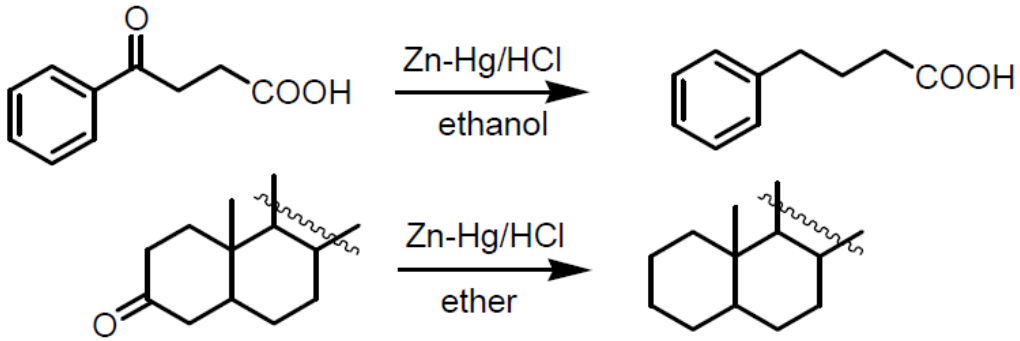


Reductive Deoxygenation of Carbonyls

1) Clemmensen Reduction

- Zn/HCl, Zn(Cu)/HCl in EtOH, Et_2O
- substrates: arylketones (good) > aliphatic ketones > unsaturated ketones (C=C also reduced), mechanism: unknown
- variations: hot EtOH/HCl(conc.), Zn in Et_2O + HCl (g), etc.

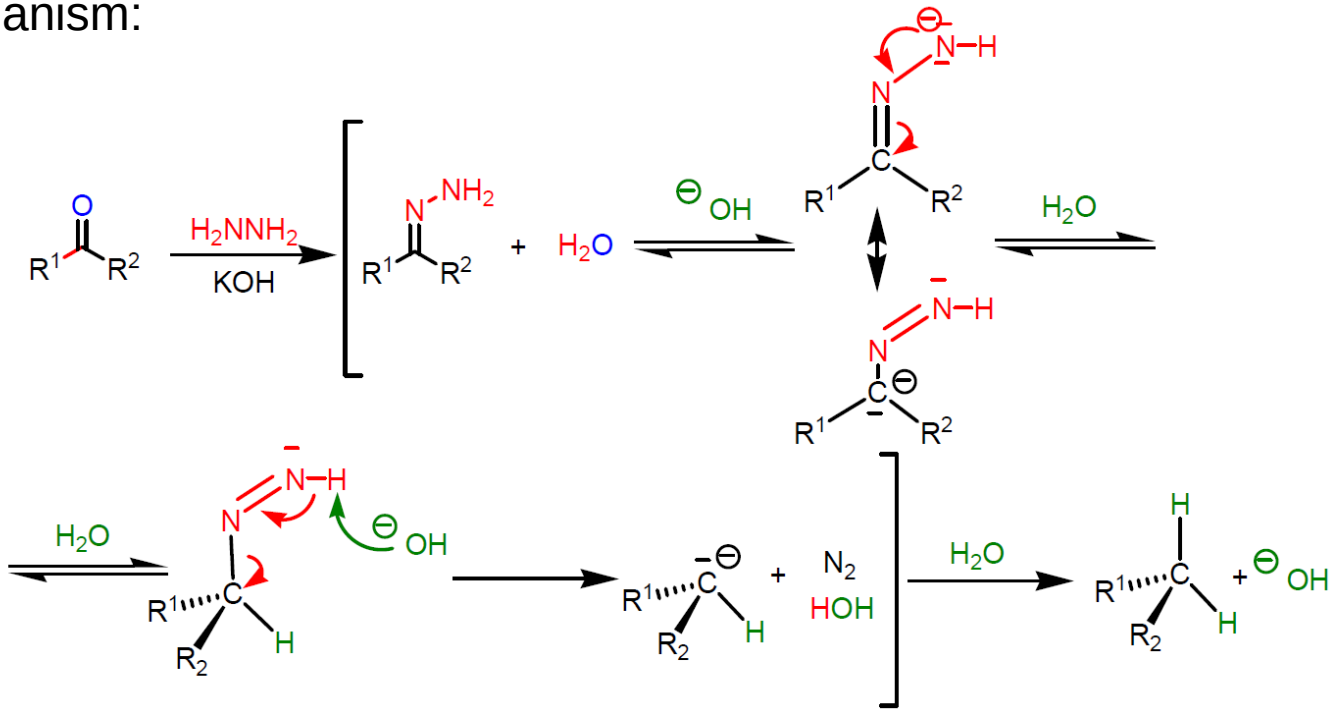




Reductive Deoxygenation of Carbonyls

2) Wolf-Kižněr Reduction

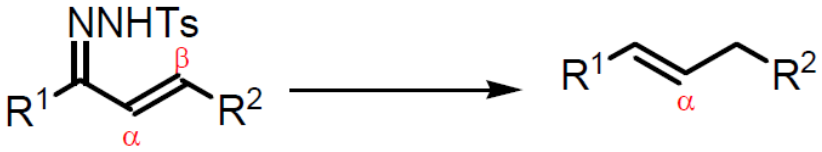
- 1. step: formation of hydrazide
- 2. step: thermal cleavage + deprotonation of hydrazide with base
- substrates: arylketones, alkylketones (good)
- base: KOH, *t*BuOK
- solvents: DMSO, DME (b.p. 85°C), $[MeO(CH_2)_2]_2O$ (b.p. 162°C)
- mechanism:



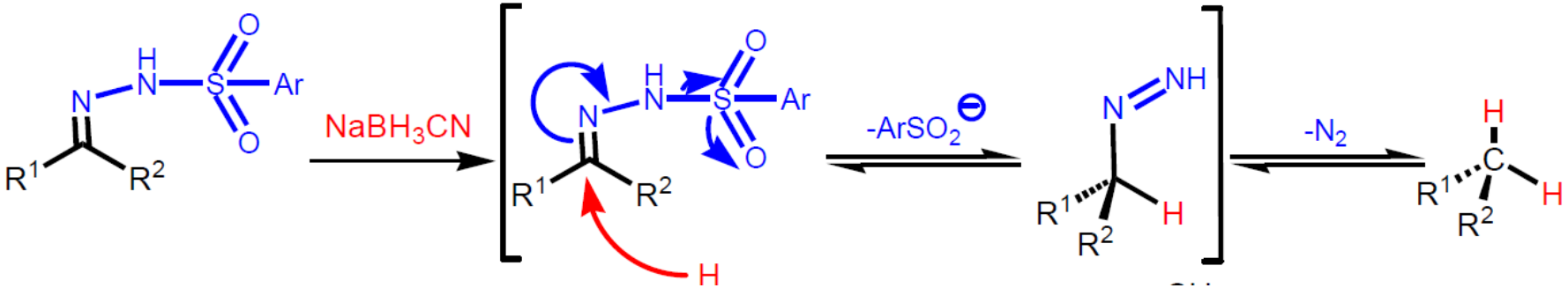
Reductive Deoxygenation of Carbonyls

2) Wolf-Kižněr Reduction - variation

- reduction of tosylhydrazides
- 1. step: formation of tosylhydrazide
- 2. step: reduction
- reagent: $NaBH_4$, $NaBH_3CN$, $LiAlH_4$, etc.
- α,β-unsaturated tosylhadrazides are reduced to alkenes



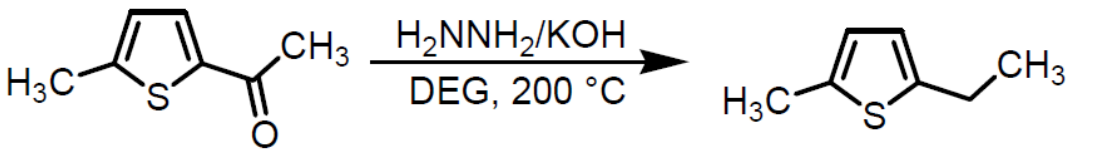
- mechanism:

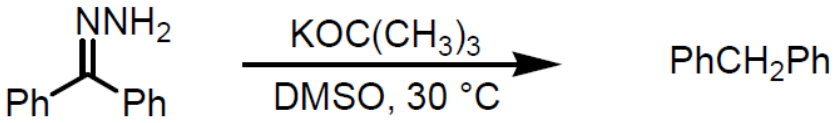


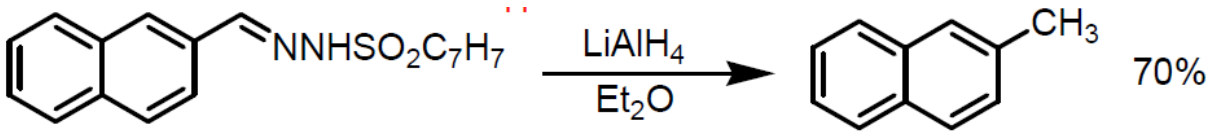
Reduction in Organic Synthesis

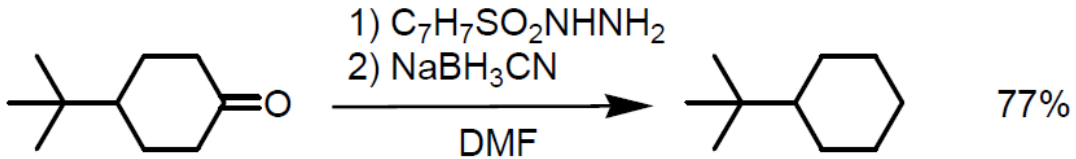
Reductive Deoxygenation of Carbonyls

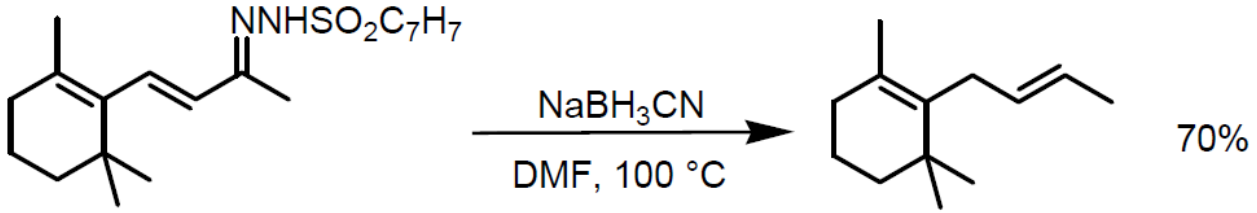
Examples







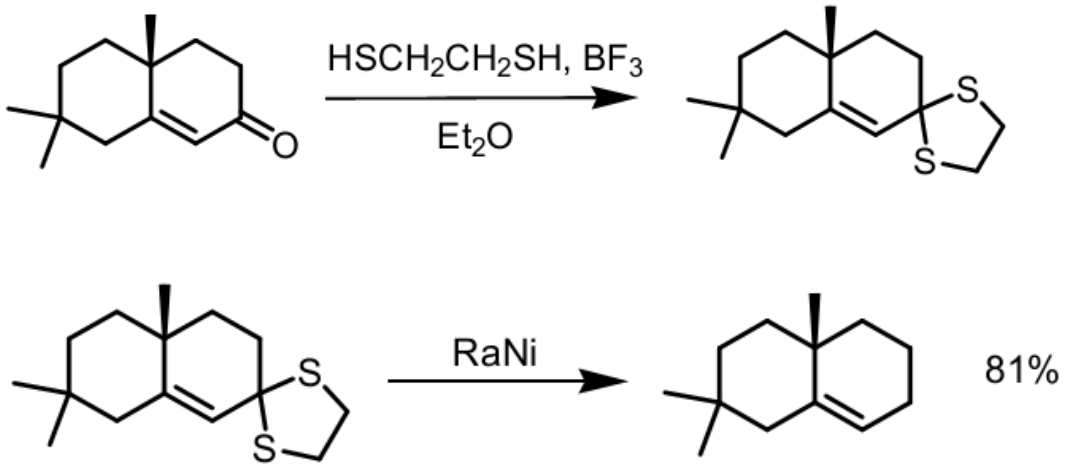




Reductive Deoxygenation of Carbonyls

3) Mozingo Desulfonylation

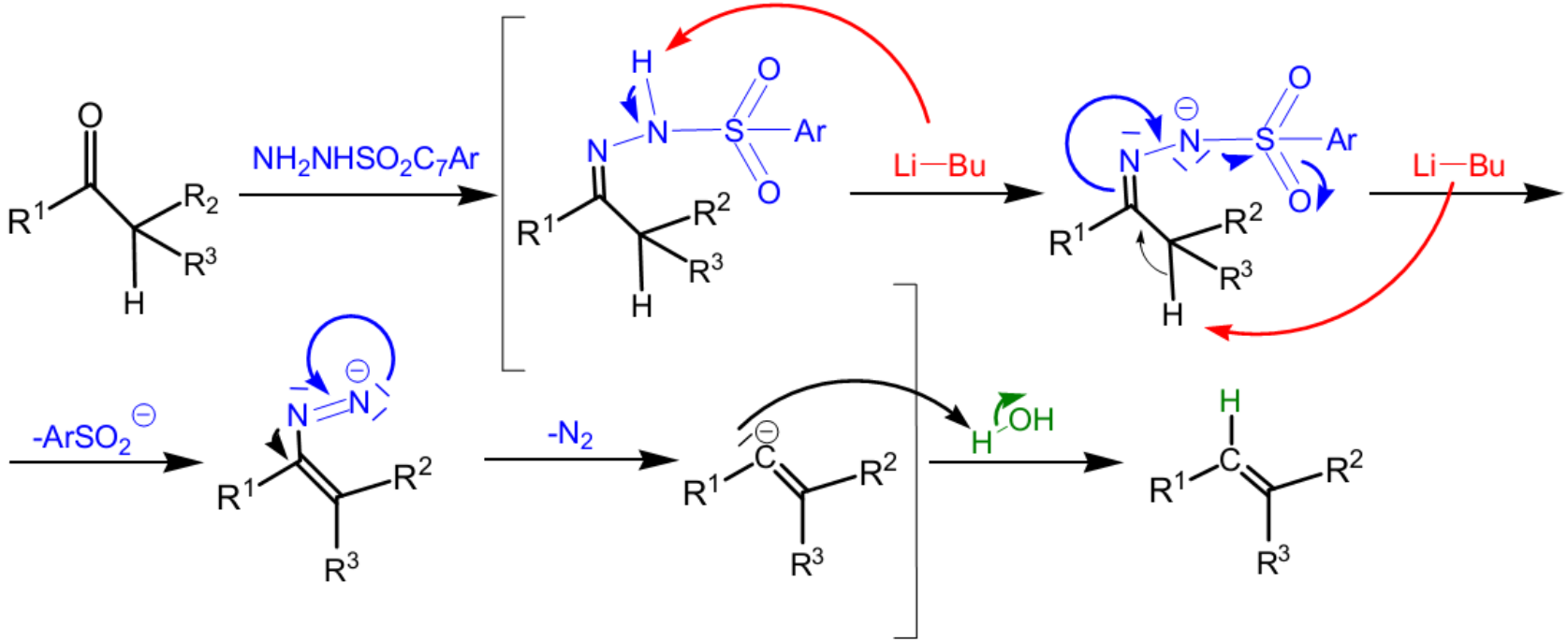
- 1. step: dithioacetal formation
- 2. step: desulfonylation
- reducing agent (excess): RaNi, Ni_2B, etc.
- substrates: ketones, α,β-unsaturated ketones



Reductive Deoxygenation of Carbonyls

4) Shapiro Reaction

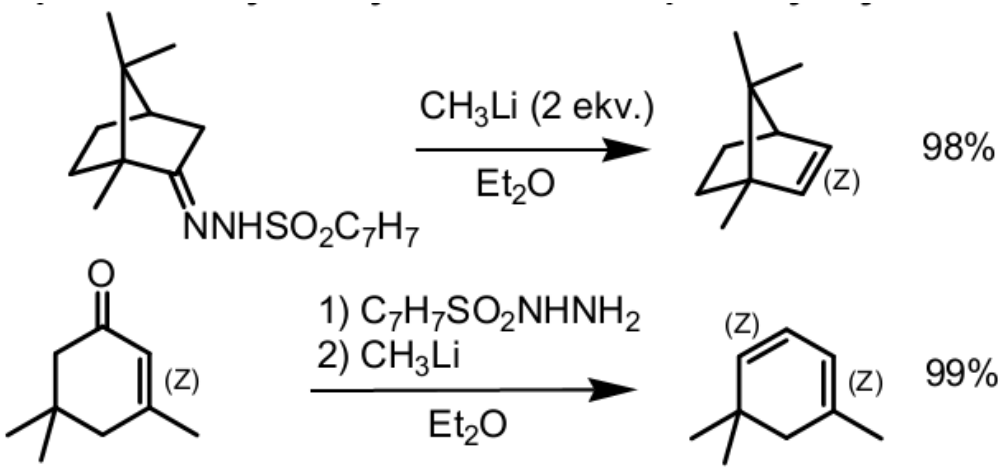
- aldehydes and ketones → alkenes /vinyl lithium
- base: BuLi, LDA, etc.
- substrates: cyclic or aliphatic ketones and aldehydes
- tosylhydrazones of α,β-unsaturated ketones → dienes
- mechanism

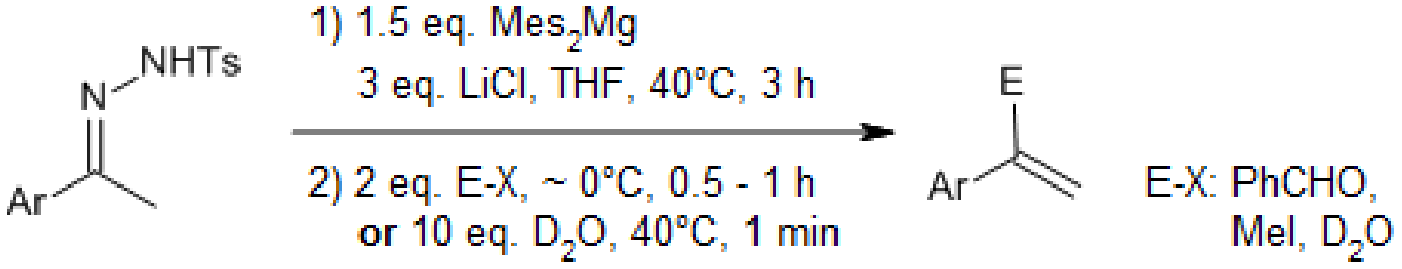


Reductive Deoxygenation of Carbonyls

4) Shapiro Reaction

Examples





W. J. Kerr, A. J. Morrison, M. Pazicky, T. Weber, *Org. Lett.*, **2012**, *14*, 2250-2253.

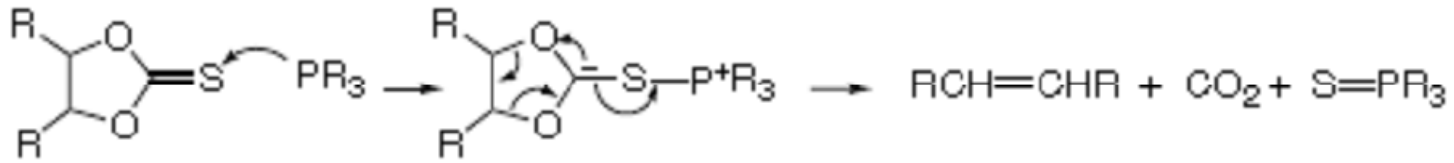
Reduction in Organic Synthesis

Reductive Deoxygenation

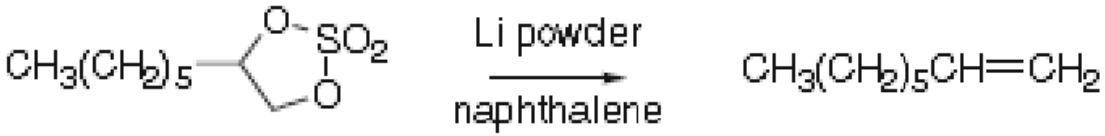
B) Reductive Removal of OH groups

not direct (functionalization – deoxygenation)

PEt_3 (1,3-dioxolan-2-thione)



Li/Napht (sulfon-esters)



I_2/KI/PPh_3