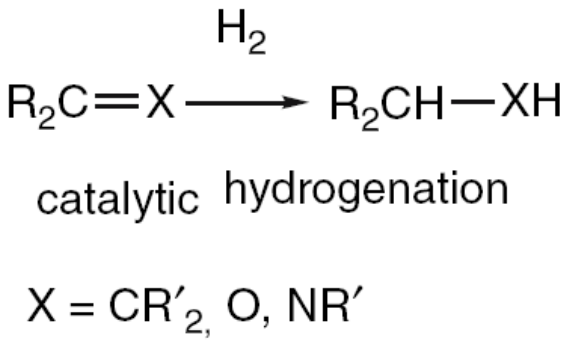
Reduction in Organic Synthesis

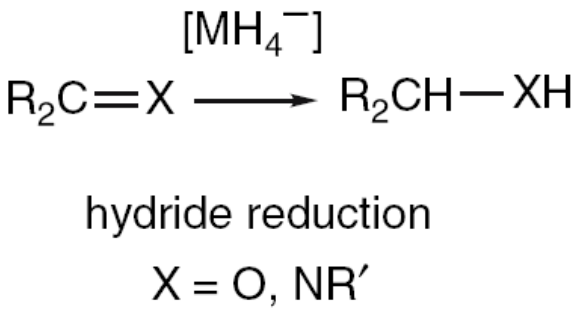
- Reduction (electronation) = complete transfer of electrons to a molecular entity
- Oxidation state (CH_3CHO, CH_3CH_2OH)

- Categories of reduction:

1) **Catalytic hydrogenation** – addition of hydrogen

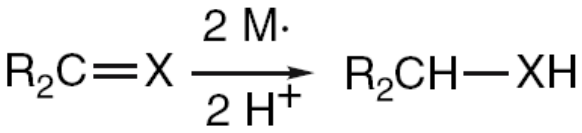


2) **Hydride reduction** – complex hydrides (S_N)



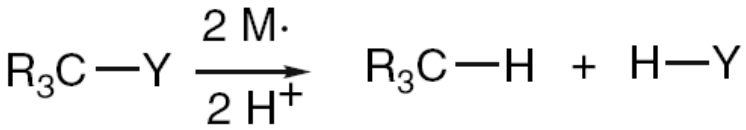
Reduction in Organic Synthesis

3) **Addition of electrons** – metal, solvent



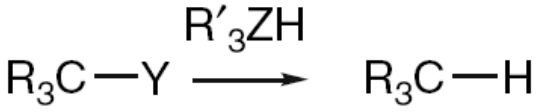
reduction by metals

4) **Reductive removal of functional groups**



dissolving metals

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



hydrogen atom donors

Y = halogen, thio ester

Z = Sn, Si

Reduction in Organic Synthesis

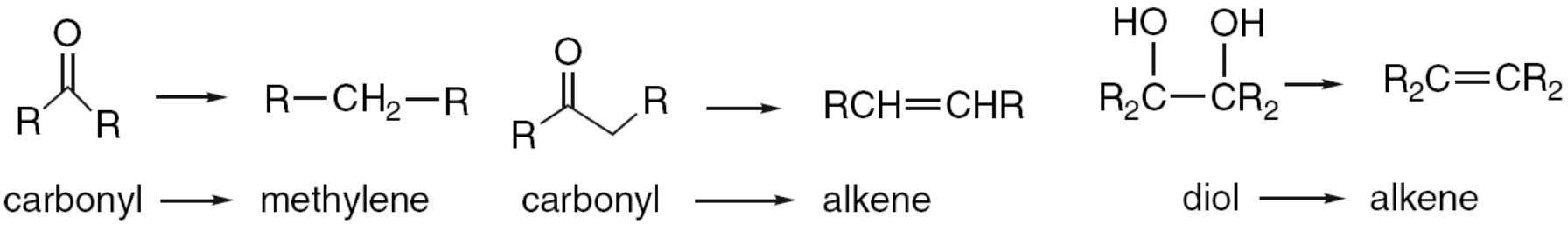
5) **Reductive coupling** – radicals

X=O

M· = Na^0, Ti^{II}, Sm^{II}

reductive coupling

6) **Reductive removal of oxygen**



reductive deoxygenation

Reduction in Organic Synthesis

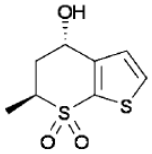
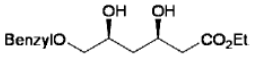
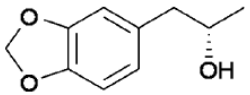
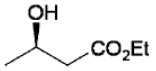
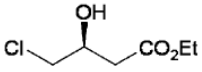
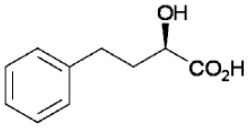
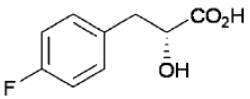
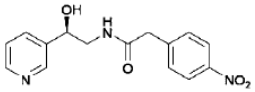
- old reductive methods – transfer of electrons (Na-ROH, Zn-HCl, Li-NH_3)
- Standard reduction potentials at 25 °C
- $HCOOH \rightarrow MH_4^-$ (H…L)

	Reduction Half-Reaction		$E°$ (V)	
Stronger oxidizing agent	$F_2(g) + 2e^-$	$\longrightarrow 2F^-(aq)$	2.87	Weaker reducing agent
	$H_2O_2(aq) + 2H^+(aq) + 2e^-$	$\longrightarrow 2H_2O(l)$	1.78	
	$MnO_4^-(aq) + 8H^+(aq) + 5e^-$	$\longrightarrow Mn^{2+}(aq) + 4H_2O(l)$	1.51	
	$Cl_2(g) + 2e^-$	$\longrightarrow 2Cl^-(aq)$	1.36	
	$Cr_2O_7^{2-}(aq) + 14H^+(aq) + 6e^-$	$\longrightarrow 2Cr^{3+}(aq) + 7H_2O(l)$	1.33	
	$O_2(g) + 4H^+(aq) + 4e^-$	$\longrightarrow 2H_2O(l)$	1.23	
	$Br_2(aq) + 2e^-$	$\longrightarrow 2Br^-(aq)$	1.09	
	$Ag^+(aq) + e^-$	$\longrightarrow Ag(s)$	0.80	
	$Fe^{3+}(aq) + e^-$	$\longrightarrow Fe^{2+}(aq)$	0.77	
	$O_2(g) + 2H^+(aq) + 2e^-$	$\longrightarrow H_2O_2(aq)$	0.70	
	$I_2(s) + 2e^-$	$\longrightarrow 2I^-(aq)$	0.54	
	$O_2(g) + 2H_2O(l) + 4e^-$	$\longrightarrow 4OH^-(aq)$	0.40	
	$Cu^{2+}(aq) + 2e^-$	$\longrightarrow Cu(s)$	0.34	
	$Sn^{4+}(aq) + 2e^-$	$\longrightarrow Sn^{2+}(aq)$	0.15	
	$2H^+(aq) + 2e^-$	$\longrightarrow H_2(g)$	0	
	$Pb^{2+}(aq) + 2e^-$	$\longrightarrow Pb(s)$	- 0.13	
	$Ni^{2+}(aq) + 2e^-$	$\longrightarrow Ni(s)$	- 0.26	
	$Cd^{2+}(aq) + 2e^-$	$\longrightarrow Cd(s)$	- 0.40	
	$Fe^{2+}(aq) + 2e^-$	$\longrightarrow Fe(s)$	- 0.45	
	$Zn^{2+}(aq) + 2e^-$	$\longrightarrow Zn(s)$	- 0.76	
	$2H_2O(l) + 2e^-$	$\longrightarrow H_2(g) + 2OH^-(aq)$	- 0.83	
	$Al^{3+}(aq) + 3e^-$	$\longrightarrow Al(s)$	- 1.66	
	$Mg^{2+}(aq) + 2e^-$	$\longrightarrow Mg(s)$	- 2.37	
Weaker oxidizing agent	$Na^+(aq) + e^-$	$\longrightarrow Na(s)$	- 2.71	Stronger reducing agent
	$Li^+(aq) + e^-$	$\longrightarrow Li(s)$	- 3.04	

Reduction in Organic Synthesis

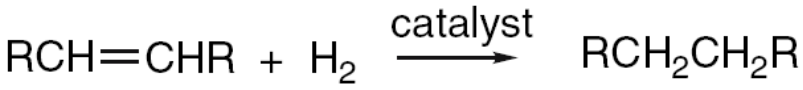
- Enzymatic reduction (reductases) – highly selective, narrow substrate scope

Selected examples of industrial-scale ketone reductions:

	*Neurospora crassa*	>85	>98	Multi ton	Astra Zeneca
	*Acinetobacter calcoaceticus* (cell extract)	92	99	n.d.	Bristol-Myers Squibb
	*Zygosaccharomyces rouxii*	96	>99.9	300 L	Eli Lilly
	*Lactobacillus brevis* (cell extract)	96	99.8	35 ta^{-1}	Wacker Chemie
	*Geotrichium candidum*	95	99	Multi kg	Bristol-Myers Squibb
	*Staphylococcus epidermidis* (isolated DH)	91	99.9	n.d.	Ciba
	*Staphylococcus epidermidis* (isolated DHs)	99	99.0	Multi kg	Pfizer
	*Candida sorbophilia*	82.5	>98	Multi kg	Merck

Reduction in Organic Synthesis

Addition of Hydrogen – catalytic hydrogenation



- Pd, Pt, Rh, Ru, Ni
- heterogeneous hydrogenation – catalyst (preparation × activity)
- homogeneous hydrogenation

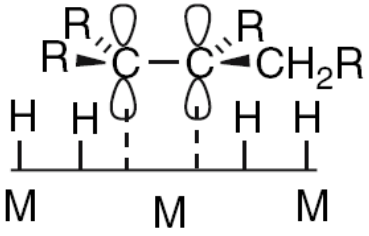
- relative activity towards C=C

Rh > Ir > Ru > Pt > Pd > Ni > Fe > Co > Os

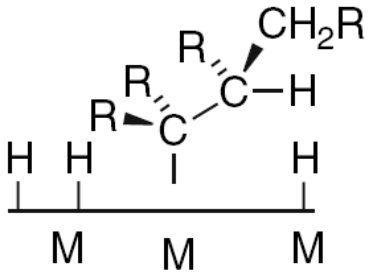
- non-specific × **$CuO.Cr_2O_3$** esters, amides, (not Ar)
- Pt catalysts (not COOH, COOR, $CONH_2$)
- catalytic poisons: sulfides, amines, phosphines, heavy metals a their halogens

Addition of Hydrogen – heterogeneous hydrogenation

- process not fully described
  - adsorption of H_2 on metal
  - adsorption of C=C on metal



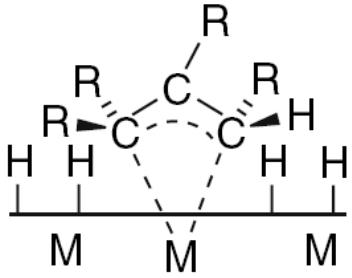
A π-complex



B σ-bond

most important intermediate
reversibility
isomerisation

- other intermediates



C π-allyl complex

Reduction in Organic Synthesis

Addition of Hydrogen – heterogeneous hydrogenation

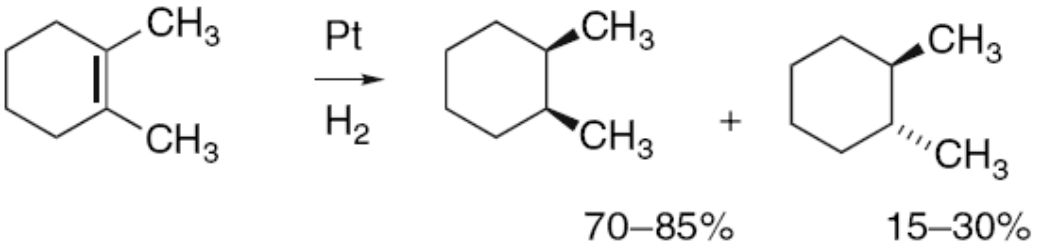
TABLE 1

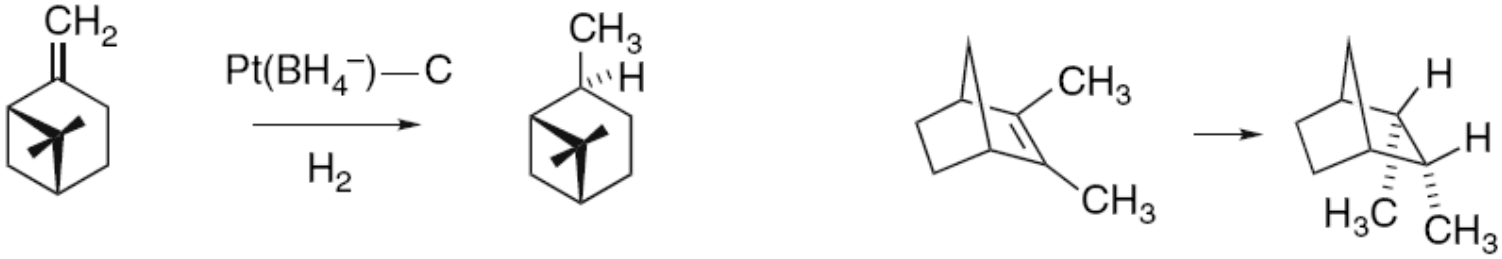
Influence of Reaction Variables

Increased variable	Effect on H_2 availability	Effect on migration	Effect on isomerization
Pressure	+	−	−
Agitation	+	−	−
Solvent	+	−	−
Inhibitors	+	−	−
Catalyst activity	−	+	+
Temperature	−	+	+
Metal concentration	−	+	+
Catalyst concentration	−	+	+

Addition of Hydrogen – heterogeneous hydrogenation

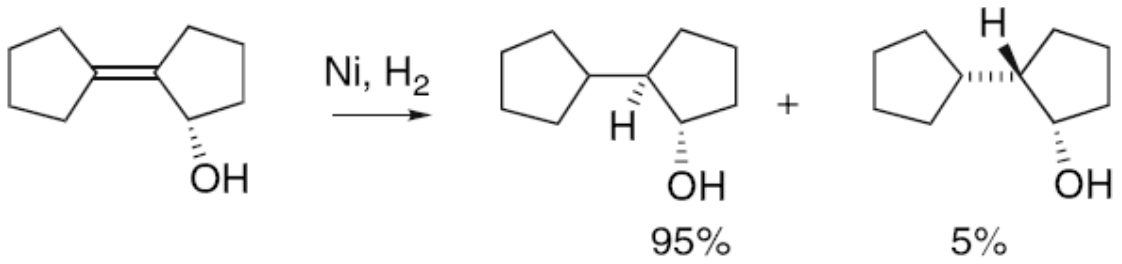
- mostly **syn** addition mechanism
- sterically demanding systems - *trans*-addition

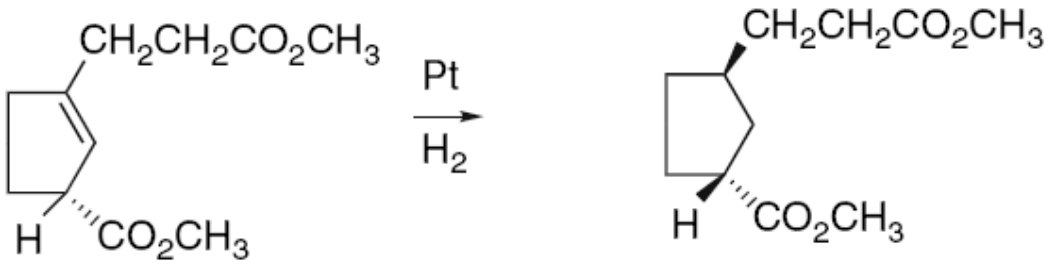




Addition of Hydrogen – heterogeneous hydrogenation

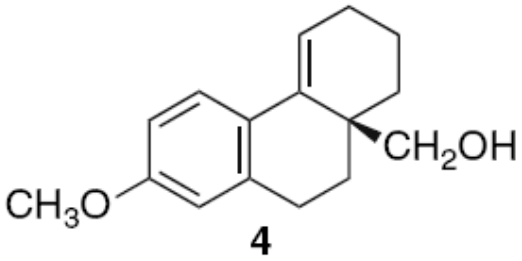
- steric effects x functional groups (polar)
- *cis*-addition





Addition of Hydrogen – heterogeneous hydrogenation

- *cis*-addition favored in non-polar solvents



4

Solvent	% *cis*	% *trans*
Hexane	61	39
DME	20	80
EtOH	6	94

- directing effect

aminomethyl > hydroxymethyl > CH=O > ester

- Lewis basicity

Reduction in Organic Synthesis

Addition of Hydrogen – heterogeneous hydrogenation

Metal Catalysts

Pt

$$3\ Pt + 4\ HNO_3 + 18\ HCl \rightarrow 3\ H_2[PtCl_6] + 4\ NO + 8\ H_2O$$

$$H_2PtCl_6 + NaNO_2 \rightarrow PtO_2 + 2H_2 \rightarrow Pt\ (black) + 2H_2O$$

$$PtO_2 + NaBH_4 \rightarrow Pt\ (black)$$

- Adams catalyst

Pd

$$PdCl_2 + NaBH_4 \rightarrow Pd$$

- Lindlar catalyst + chinolin, sulfur, $Pb(OAc)_2$

Reduction in Organic Synthesis

Addition of Hydrogen – heterogeneous hydrogenation

Metal Catalysts

Rh

$$RhCl_3 + NaBH_4 \rightarrow Rh$$ *also* Rh_2O_3

- mixed catalysts (Rh+Pt)

Ni

$$Ni/Al + NaOH \rightarrow RaNi + Na_3AlO_3$$
$$Ni(OAc)_2 + NaBH_4 \rightarrow Ni\text{-}P1,\ Ni\text{-}P2$$

- Raney nickel (RaNi) – high porosity, pyrophoric

- Ni_xB_y (Ni_2B)

- NiW, NiW_6

Addition of Hydrogen – heterogeneous hydrogenation

Other catalysts

$Cu_2Cr_2O_5$ (Adkins, Cu/Cr)

- **$CuO.Cr_2O_3$**
- high temperature, high pressure
- low cost, industrial application, various activity
- analogously Zn/Cr, etc.

MoS_x WS_x, CoMoS, NiMoS

- hydrocracking
- industrial application, various activity

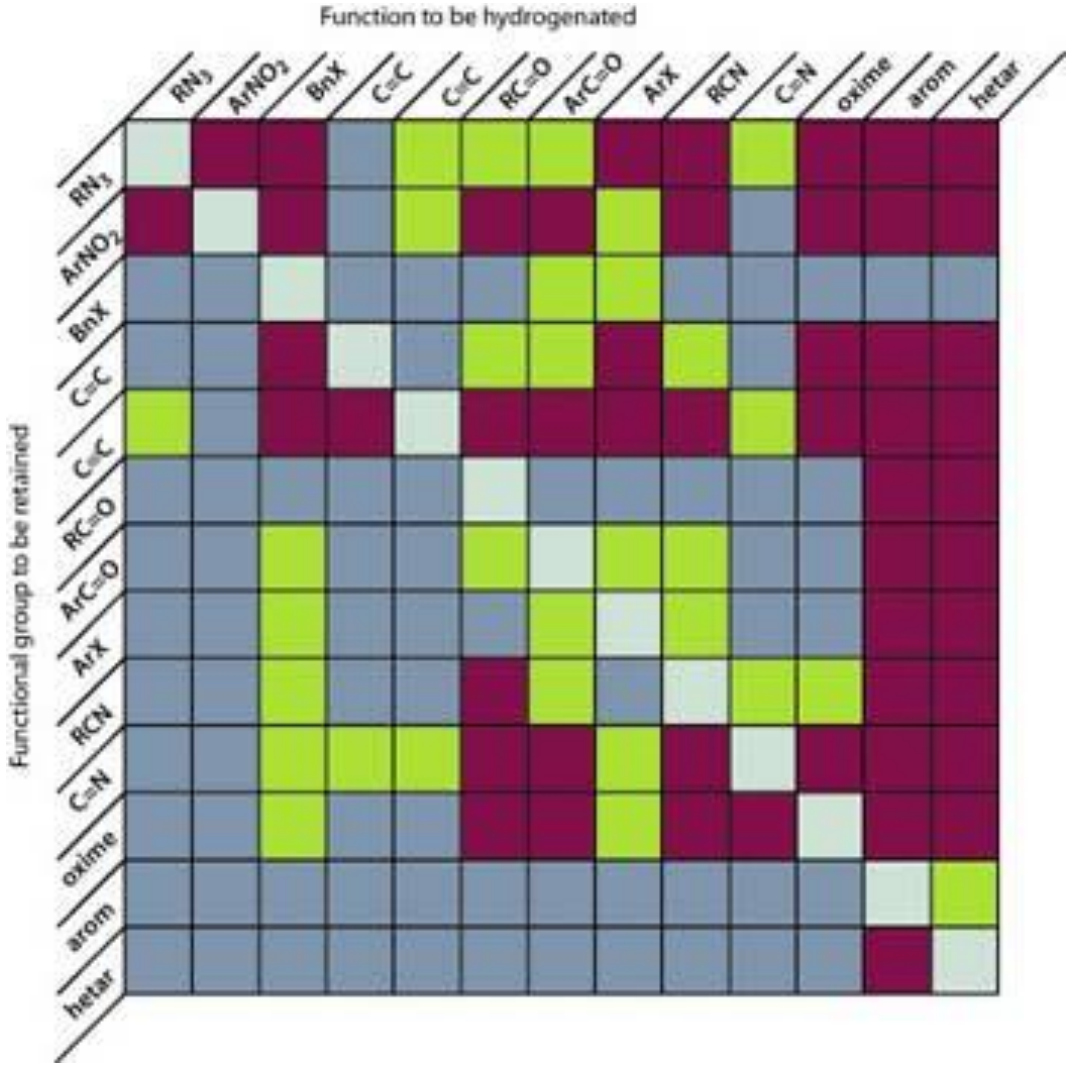
Reduction in Organic Synthesis

Addition of Hydrogen – heterogeneous hydrogenation

Substrate	Reaction	Metal	Solvent
azides	RN_3 -> RNH_2	Pd, Pt, Ni	polar
aromatic nitro groups	$ArNO_2$ -> $ArNH_2$	Ni, Pd, Pt	various
benzyl derivatives (debenzylation)	$ArCH_2X$ -> $ArCH_3$ + HX X = OR, NR_2	Pd	protic, acidic or basic
alkenes	$R_2C=CR_2$ -> $R_2HC-CHR_2$	Pd, Pt, Rh, Ni	various
alkynes	RC≡CR -> RHC=CHR	Pd/Pb	low polarity
aliphatic C=O groups	R_2CO -> R_2CHOH	Ni, Ru, Pt, Rh	polar
aromatic C=O groups	ArCOR -> ArCH(OH)R	Pd, Pt, Cu	polar
aryl halides	ArX -> ArH X = Cl, Br, I	Pd	basic
nitriles	RCN -> RCH_2NH_2	Ni, Ph / Pd, Pt	basic / acidic
imines	$R_2C=NR$ -> R_2CHNHR	Pd, Pt	various
oximes	$R_2C=NOR$ R_2CHNH_2	Ni / Pt, Pd	basic / acidic
(hetero)aromatic rings		Rh, Ru, Pt	various

Reduction in Organic Synthesis

Addition of Hydrogen – heterogeneous hydrogenation



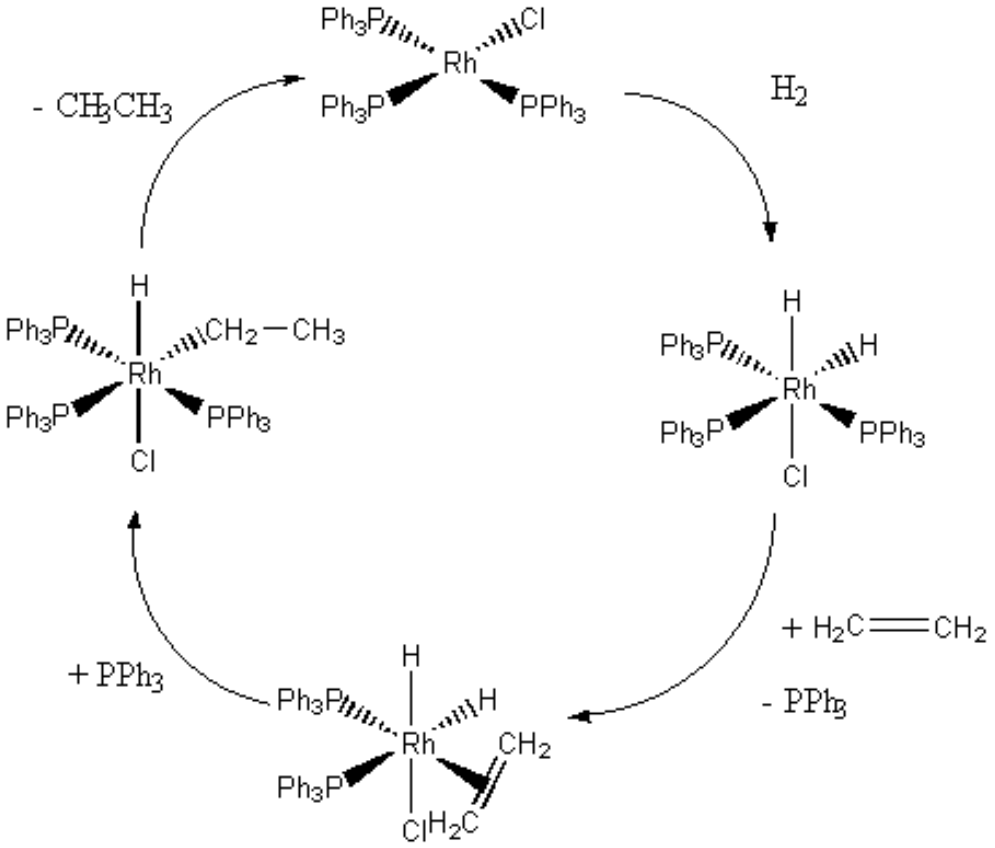
Addition of Hydrogen – homogeneous hydrogenation

Wilkinson´s catalyst

- **$(Ph_3P)_3RhCl$**

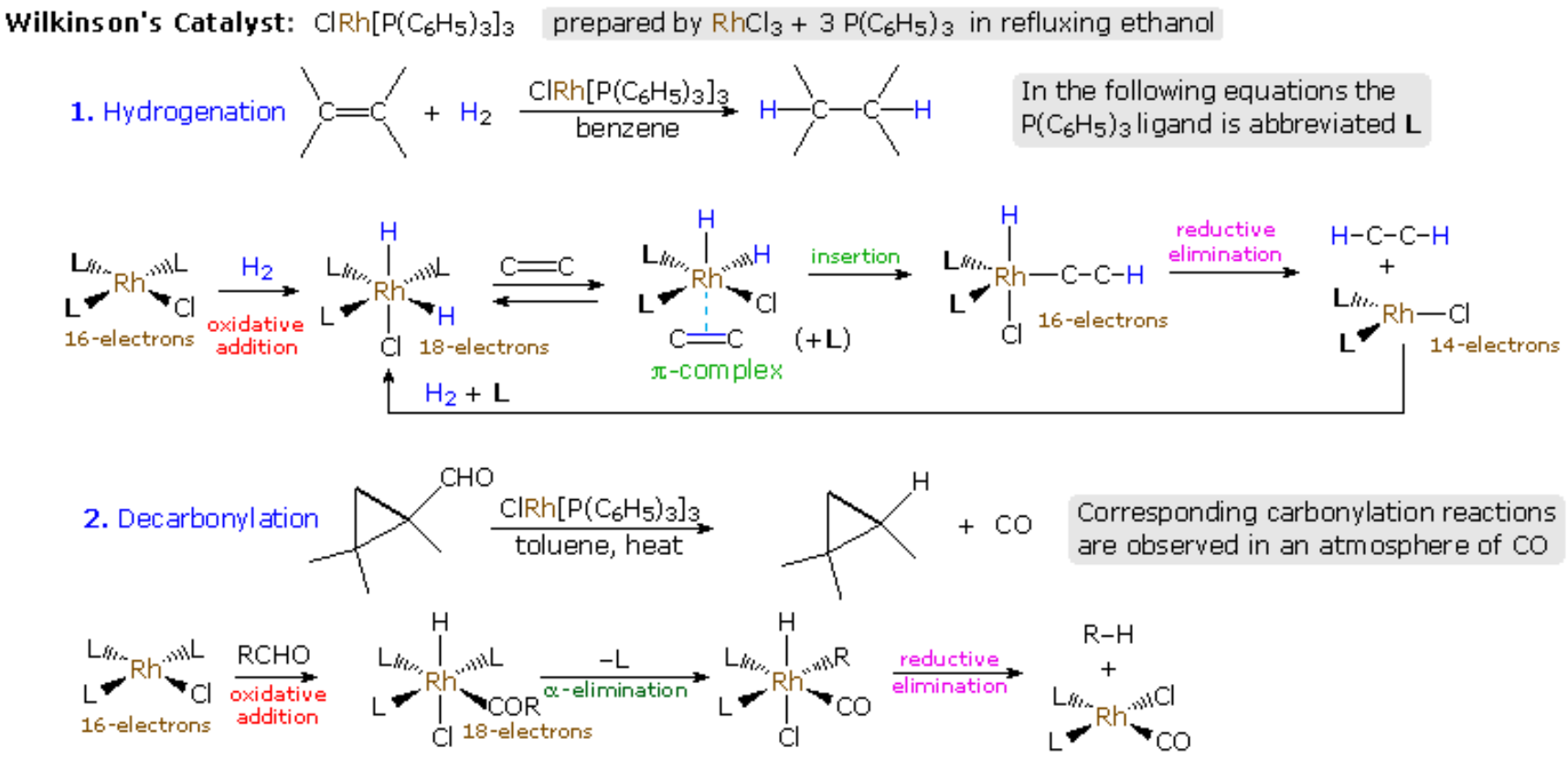
$$RhCl_3.3H_2O + Ph_3P \rightarrow \mathbf{(Ph_3P)_3RhCl} \quad \text{(EtOH, reflux)}$$

- oxidative addition
- double bond coordination
- insertion
- reductive elimination



Reduction in Organic Synthesis

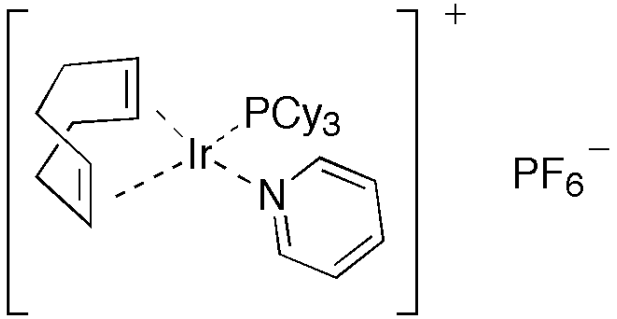
Addition of Hydrogen – homogeneous hydrogenation



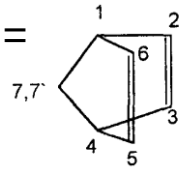
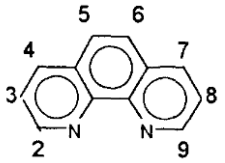
Addition of Hydrogen – homogeneous hydrogenation

Vaska's catalyst - **$(Ph_3P)_2(CO)IrCl$**

Crabtree's catalyst
- **$[Cy_3P(COD)pyIr]^+PF_6^-$**



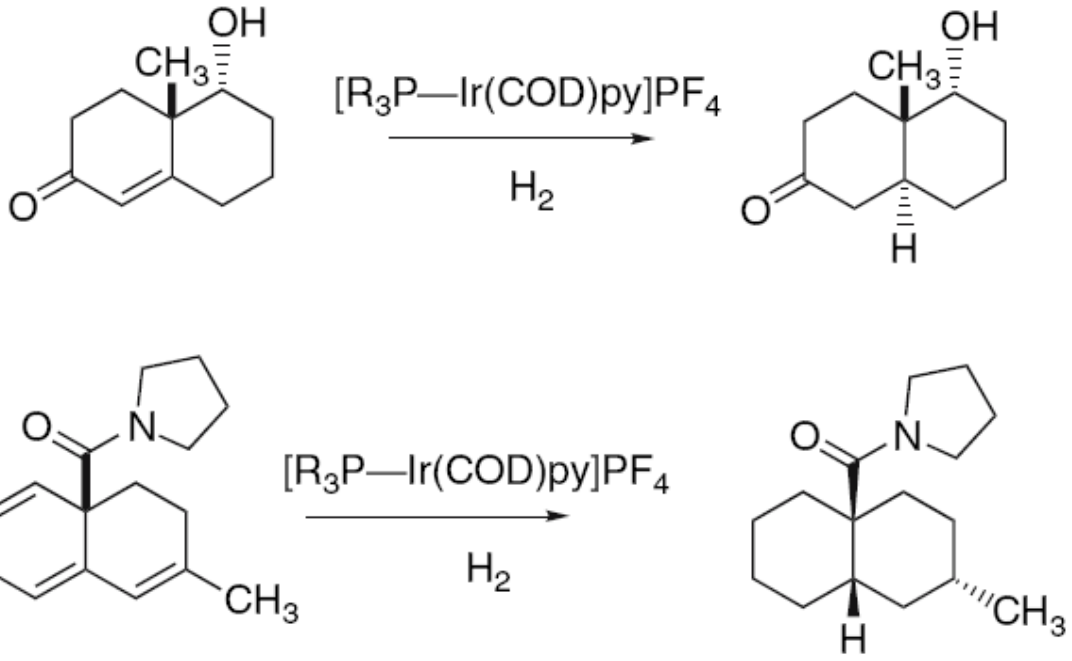
Other catalysts:
-**$(Ph_3P)_3RuHCl$, $(Ph_3P)_3RuCl_2$, $Rh(nbd)(dppb)BF_4$**

Note: Abbreviations: {***dppb*** = $Ph_2P(CH_2)_4PPh_2$, ***nbd*** =  , ***phen*** =  }

Addition of Hydrogen – homogeneous hydrogenation

Stereochemistry of homogeneous hydrogenation

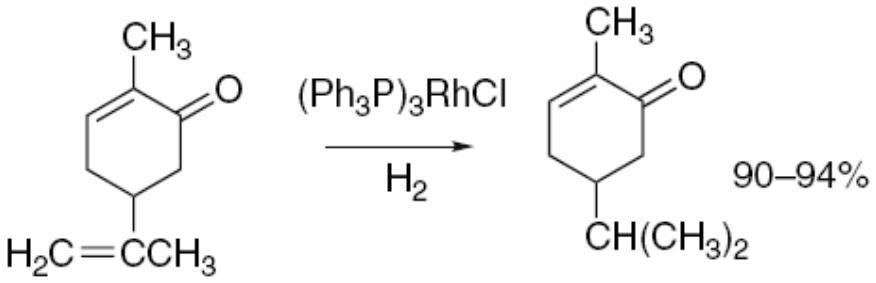
- influence of directing function groups
- especially for catalysts with 2 el. ligands
- similar to heterogeneous hydrogenation - (OH, $CONR^1R^2$, $COOR^1R^2$, OR^1)



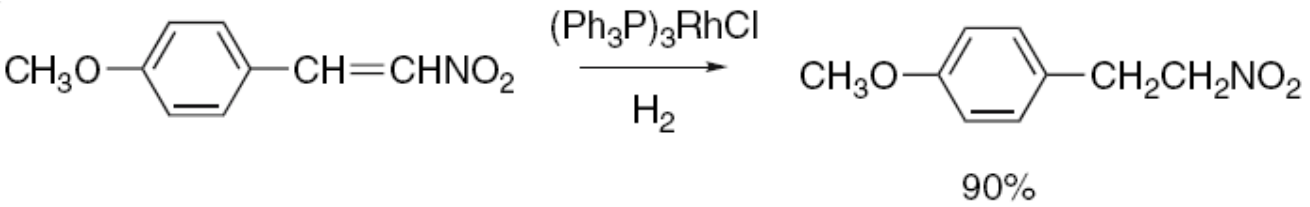
Addition of Hydrogen – homogeneous hydrogenation

Selectivity of homogeneous hydrogenation

- higher selectivity in comparison to heterogeneous catalysis
  - isolated and conjugated double bond



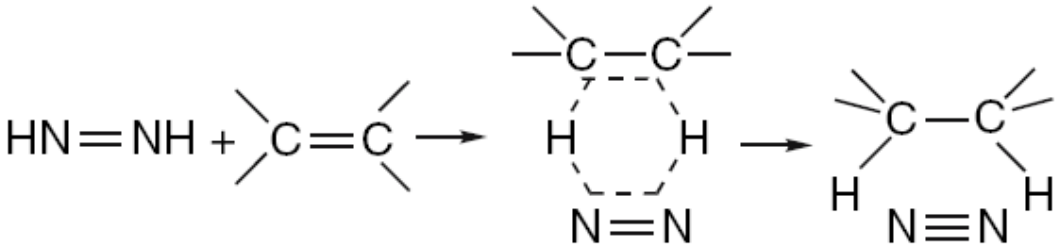
  - C=C vs. NO_2



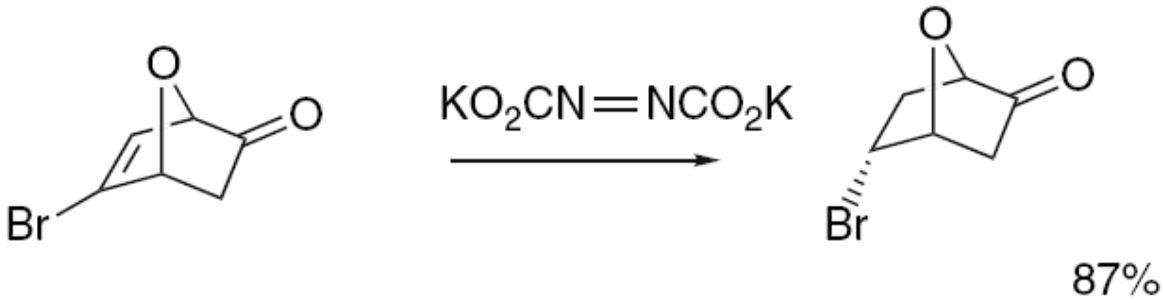
Addition of Hydrogen – transfer hydrogenation

HN=NH

- unstable, generated *in situ*
- alkenes, (not *nitro*, *cyano, carbonyl, carboxy* group)
- higher stress strain cycle → higher reactivity, terminal > internal
- *syn* addition



Př.



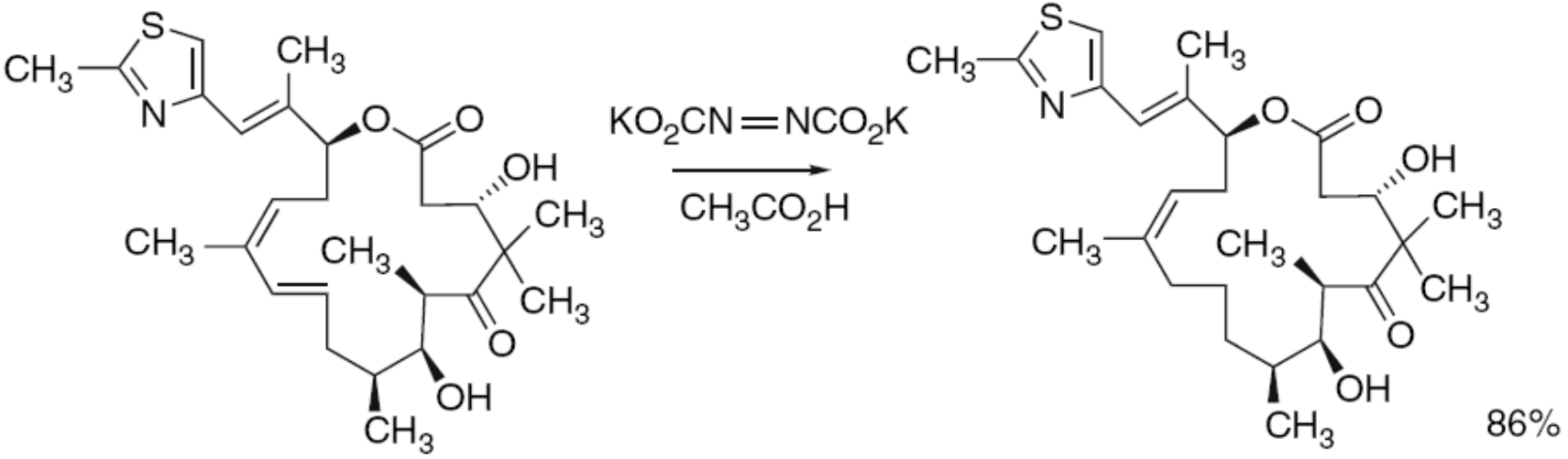
87%

Reduction in Organic Synthesis

Addition of Hydrogen – transfer hydrogenation

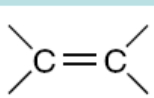
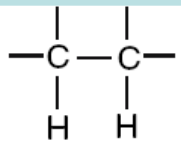
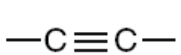
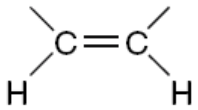
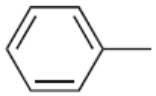
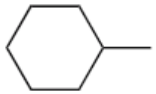
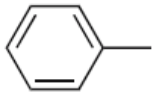
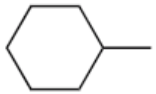
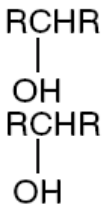
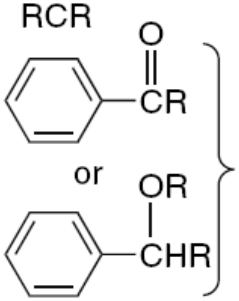
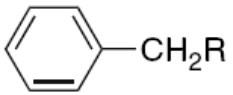
HN=NH

$$(CH_2{=}CHCH_2S)_2 \xrightarrow[\text{heat}]{C_7H_7SO_2NHNH_2} (CH_3CH_2CH_2S)_2 \qquad 93\text{–}100\%$$



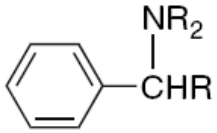
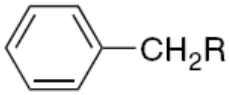
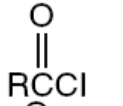
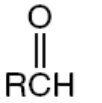
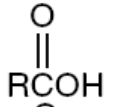
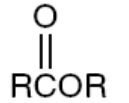
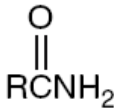
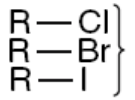
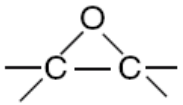
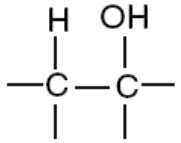
Reduction in Organic Synthesis

Hetero- and Homogeneous Hydrogenation

Reactant	Product	Catalyst	Conditions
		Pd, Pt, Ni, Ru, Rh	Rapid at room temperature (R.T.) and 1 atm except for highly substituted or hindered cases
		Lindlar	R. T. and low pressure, quinoline or lead added to deactivate catalyst
		Rh, Pt	Moderate pressure (5–10 atm), 50–100°C
		Ni, Pd	High pressure (100–200 atm), 100–200°C
		Pt, Ru	Moderate rate at R. T. and 1–4 atm. acid-catalyzed
		Cu–Cr, Ni	High pressure, 50–100°C
		Pd	R. T., 1–4 atm. acid-catalyzed

Reduction in Organic Synthesis

Hetero- and Homogeneous Hydrogenation

Reactant	Product	Catalyst	Conditions
		Pd, Ni	50–100°C, 1–4 atm
		Pd	R. T., 1 atm. quinoline or other catalyst moderator used
	RCH_2OH	Pd, Ni, Ru	Very strenuous conditions required
	RCH_2OH	Cu–Cr, Ni	200°C, high pressure
$RC{\equiv}N$	RCH_2NH_2	Ni, Rh	50–100°C, usually high pressure, NH_3 added to increase yield of primary amine
	RCH_2NH_2	Cu–Cr	Very strenuous conditions required
RNO_2	RNH_2	Pd, Ni, Pt	R. T., 1–4 atm
	R_2CHNHR	Pd, Pt	R. T., 4–100 atm
	R—H	Pd	Order of reactivity: I > Br > Cl > F, bases promote reactions for R = alkyl
		Pt, Pd	Proceeds slowly at R. T., 1–4 atm, acid-catalyzed

Reduction with Complex Metal Hydrides

Group III Hydride-Donors

- transfer of H^-
- various central atom, regio- and stereoselectivity
- **$LiAlH_4$** a **$NaBH_4$**
- $NaBH_3CN$, $LiBHR_3$, $LiAlH(OR)_3$, $NaAlH_2(OCH_2CH_2OCH_3)_2$, $LiAH_xCl_{4-x}$, aj.

$$\mathbf{4\ LiH\ +\ AlCl_3\ \rightarrow\ LiAlH_4\ +\ 3\ LiCl}$$

$$\mathbf{4\ NaH\ +\ B(OMe)_3\ \rightarrow\ NaBH_4\ +\ 3\ MeONa}$$

- **$LiAlH_4$** more reactive then **$NaBH_4$**
- „non-polarized C=C is not reduced“

Reduction with Complex Metal Hydrides

$NaBH_4$

- reduction of RCHO, R_1COR_2, RCOCl
- solvents: MeOH, EtOH, H_2O, THF

$LiAlH_4$

- reduction of polar unsaturated systems
- solvents: Et_2O, THF, dioxan

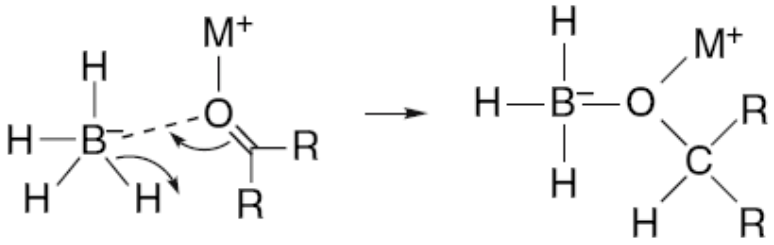
!!!

$$LiAlH_4 + 4\,H_2O \rightarrow LiOH + Al(OH)_3 + 4H_2$$

Reduction in Organic Synthesis

Reduction with Complex Metal Hydrides

$NaBH_4$



- formation of alkoxyboranes

$$BH_4^- + R_2CO \longrightarrow R_2CHO\bar{B}H_3$$

$$R_2CHO\bar{B}H_3 + R_2CO \longrightarrow [R_2CHO]_2\bar{B}H_2$$

$$[R_2CHO]_2\bar{B}H_2 + R_2CO \longrightarrow [R_2CHO]_3\bar{B}H$$

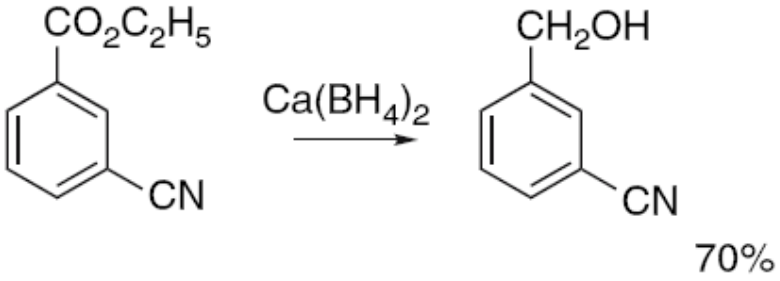
$$[R_2CHO]_3\bar{B}H + R_2CO \longrightarrow [R_2CHO]_4\bar{B}$$

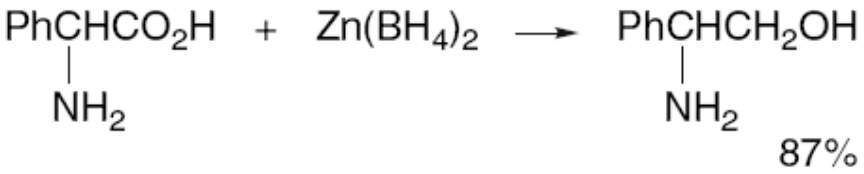
$$[R_2CHO]_4\bar{B} + 4\ SOH \longrightarrow 4\ R_2CHOH + \bar{B}(OS)_4$$

Reduction with Complex Metal Hydrides

Modified $NaBH_4$

- increased reactivity (LA) – change of Na^+ to Li^+, resp. Ca^{2+} , Zn^{2+}
- $LiBH_4$, $Ca(BH_4)_2$: $RCOOR^1 \rightarrow RCH_2OH$



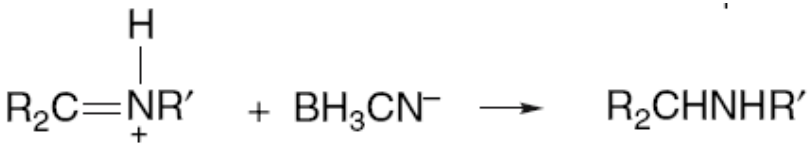


- high selectivity: Ce^{3+} *(Luche)* $\rightarrow$ 1,2-addition

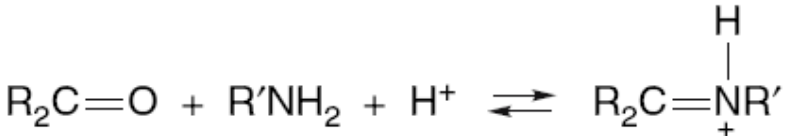
Reduction with Complex Metal Hydrides

Modified $NaBH_4$

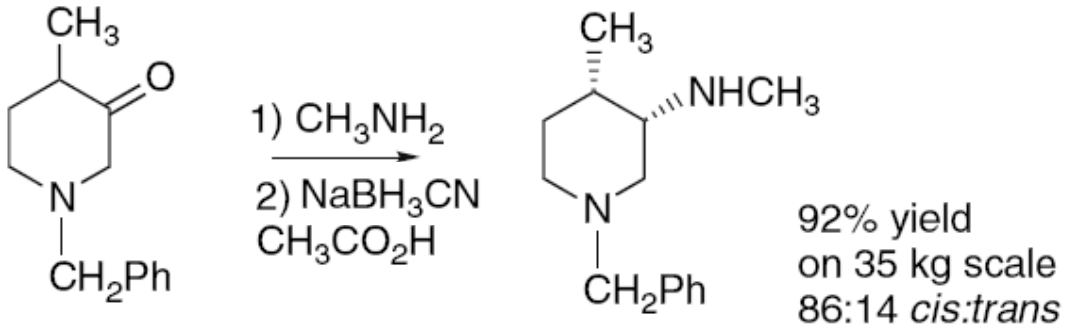
$NaBH_3CN$



- pH 4 and lower
- reductive amination



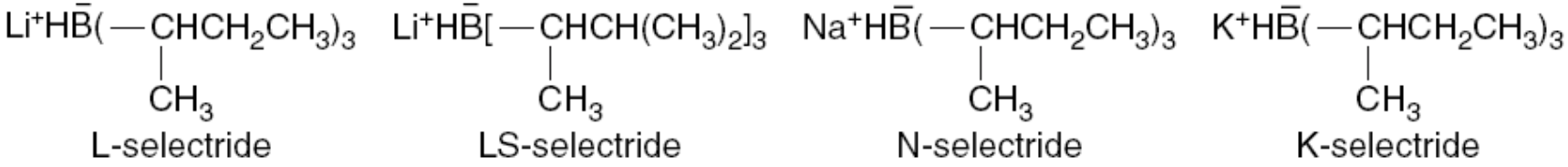
Ex.



Reduction with Complex Metal Hydrides

Modified $NaBH_4$

Selectrides



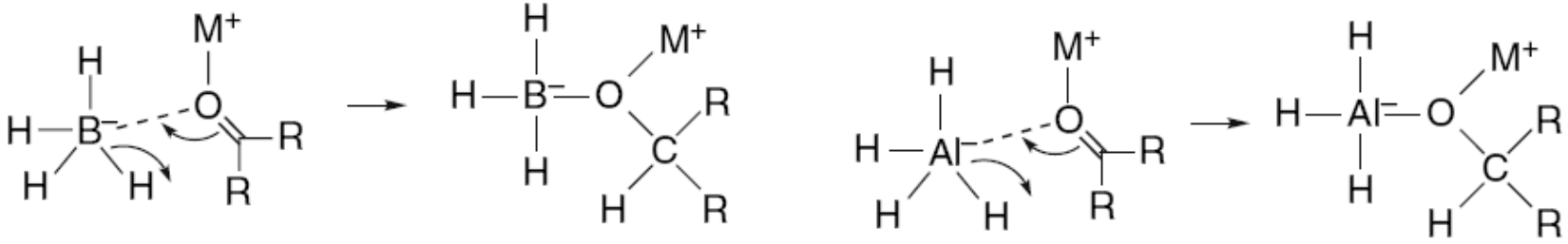
Superhydride (LiTEBH)

$LiBHEt_3$

- hydrogenolysis RX, lactones, epoxides

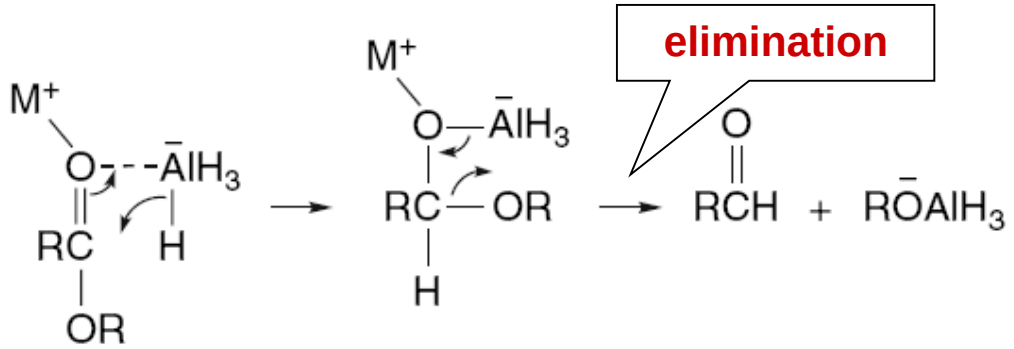
Reduction with Complex Metal Hydrides

$LiAlH_4$



59. D. C. Wigfield and R. W. Gowland, *J. Org. Chem.*, **42**, 1108 (1977).

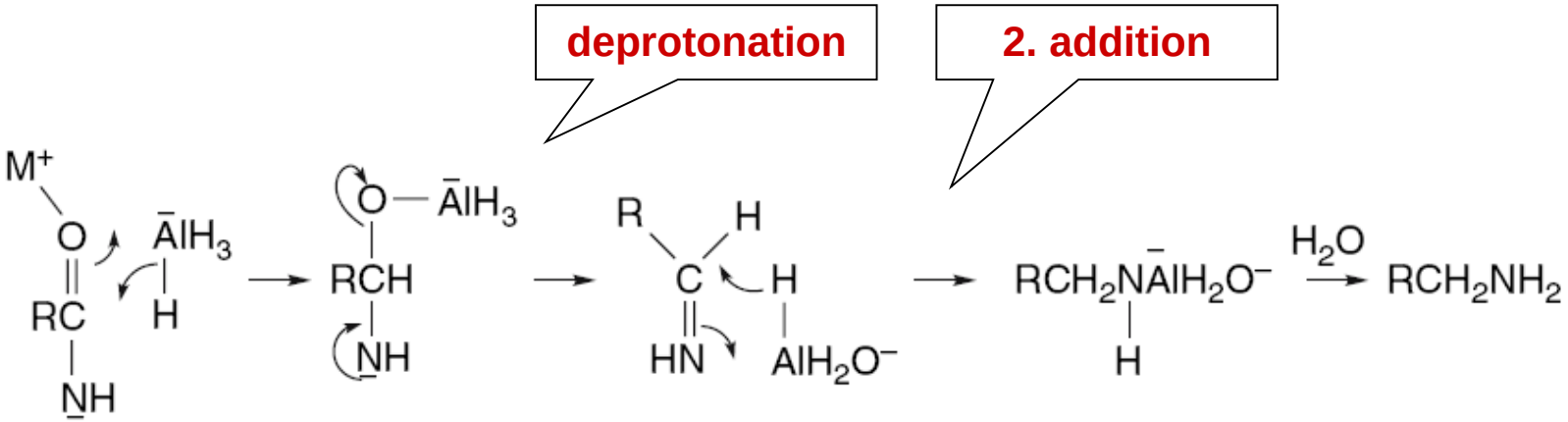
- reduction of esters



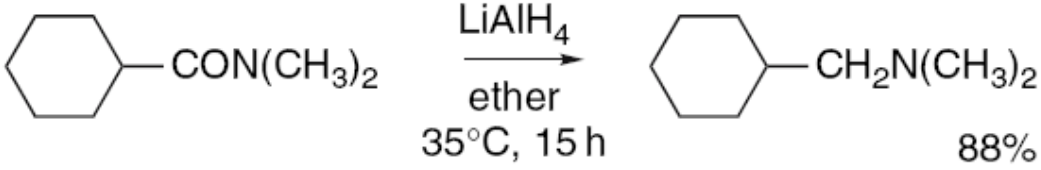
Reduction with Complex Metal Hydrides

$LiAlH_4$

- reduction of amides
- *slower to esters ($LiAlH_4$, reflux or $LiAlH_4/AlCl_3$)*



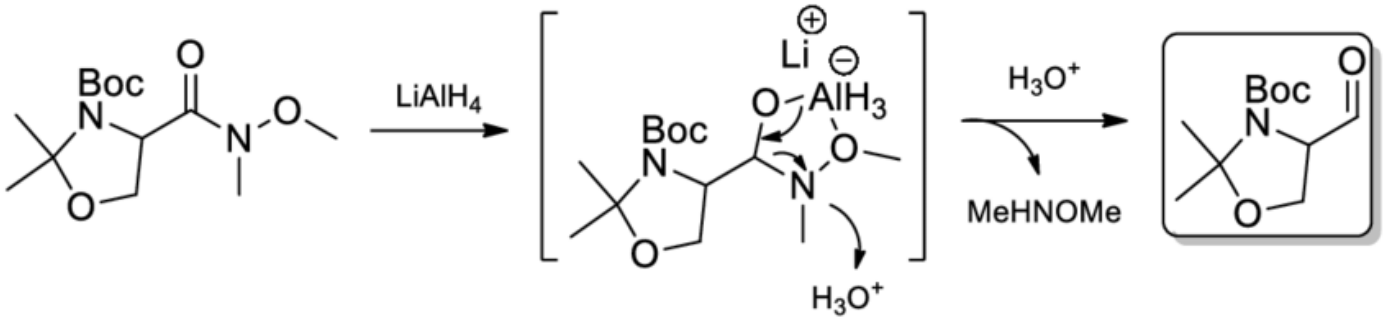
Např.



Reduction with Complex Metal Hydrides

$LiAlH_4$

- tercial amides (Weinreb amide) → *aldehydes*



- carboxylic acids (higher temperature, THF) → *alcohols (not common)*
- anhydrides → *diols*
- α,β -unsaturated esters → *allylic alcohols (better DIBAL-H)*
- nitriles → *amines*
- aliphatic, aromatic nitro compounds → *amines*
- hydrazones → *alkanes („deoxygenation“)*
- propargylic alcohols → *allylic alcohols*

Reduction with Complex Metal Hydrides

$LiAlH_4$

$$LiAlH_4 + 2\ ROH \longrightarrow LiAlH_2(OR)_2 + 2\ H_2$$

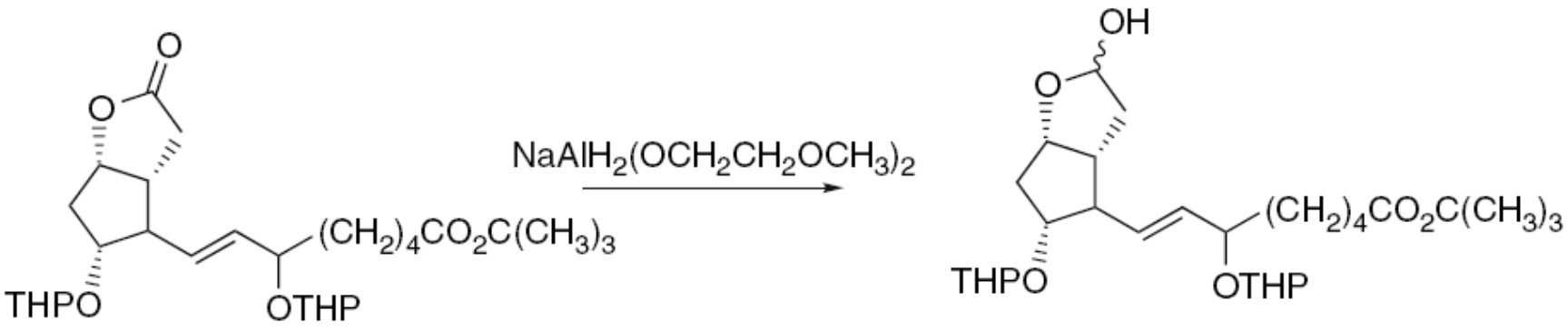
$$LiAlH_4 + 3\ ROH \longrightarrow LiAlH(OR)_3 + 3\ H_2$$

R = $MeOCH_2CH_2$ Red-Al (Synhydrid, Vitride)

R = Me, Et, t-Bu

- better solubility in organic solvents
- higher selectivity: RCN, $RCONR_2 \rightarrow$RCHO

Ex.

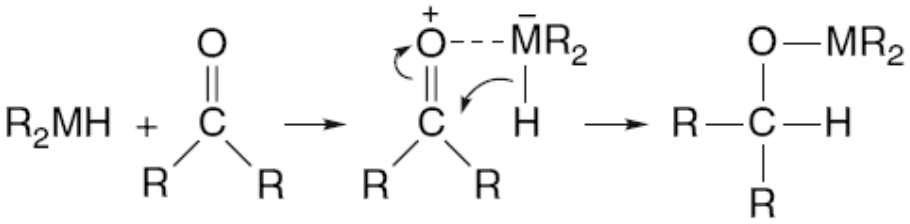


Reduction in Organic Synthesis

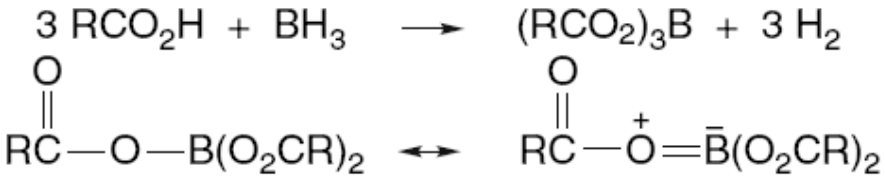
Other hydrides: Borane, Alane

BH_3, AlH_3

- LA, electophilic addition
- borane: BH_3.THF (more reactive, 1M), BH_3.Me_2S (more stable, 10M solution)
- alane: $LiAlH_4$ + $AlCl_3$
- FG not reduced: NO_2, RX, (RCOCl, RCOOR-reflux)



RCOOH

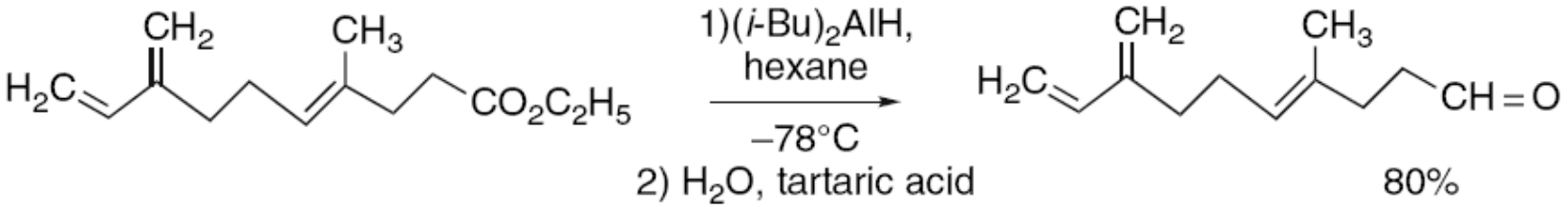


Reduction in Organic Synthesis

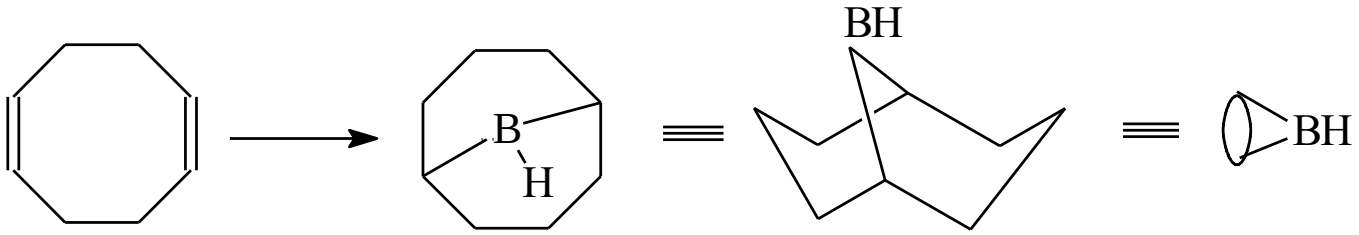
Other hydrides

DIBAL-H

- pyrophoric
- lactones → lactoles
- RCN, $RCOOR^1$ → RCHO
- α,β -unsaturated esters → allylic alcohols



Pozn.



9- borabicyklo [3,3,1] nonan = 9 - BBN

Reduction in Organic Synthesis

Reduction with Metal Hydrides - Summary

	Reactant					
	Iminium ion	Acyl chloride	Aldehyde or ketone	Ester	Amide	Carboxylate salt
	Most reactive →					Least reactive
Hydride donor			Product[a]			
$LiAlH_4$[b]	Amine	Alcohol	Alcohol	Alcohol	Amine	Alcohol
Red-Al[c]		Alcohol	Alcohol	Alcohol	Amine	Alcohol
$LiAlH(OtBu)_3$[d]		Aldehyde[e]	Alcohol	Alcohol	Aldehyde[f]	
$NaBH_4$[b]	Amine		Alcohol	Alcohol[f]		
$NaBH_3CN$[g]	Amine					
B_2H_6[h]			Alcohol		Amine	Alcohol[i]
AlH_3[j]		Alcohol	Alcohol	Alcohol	Amine	Alcohol
Disiamylborane[k]			Alcohol		Aldehyde[e]	
DIBAlH			Alcohol	Aldehyde[e]	Aldehyde[e]	Alcohol