The Art of Heterogeneous Catalytic Hydrogenation Part 2

Applications

by Bill Boulanger
Adjunct Professor, Department of Chemistry
University of Illinois at Urbana-Champaign
wboulang@illinois.edu

Topics to be covered

- Applications of Heterogeneous Catalytic Reductions
  - Simple Reductions
  - Differential reductions
  - hydrogenolysis
- Equipment
- Tour of the High Pressure Lab

Recommended Books:

- *Heterogeneous Catalysis for the Synthetic Chemist*
  - Robert L Augustine (1996)
  - Good for theory, kinetics, applications & Equipment
- Practical Catalytic Hydrogenation, Techniques and Applications
  - Morris Freifelder 1971
  - Alchemic secrets of success

Recommended References

- Catalytic Hydrogenation over Platinum Metals
  - P. N. Rylander 1967

Factors That Impact Reduction Choices

- Functional group reduced
- Local structure
- Presence of other reducible groups
- Products that act as inhibitors/poisons
- Desirability of hydrogenolysis as one of the actions
- Equipment limitations

Olefins

Under mild conditions, ease of reduction *can be* correlated inversely with degree of substitution (except when conjugated)

RHC=CH2 , RHC=CHR > R_2C=CHR > R_2C=CR_2

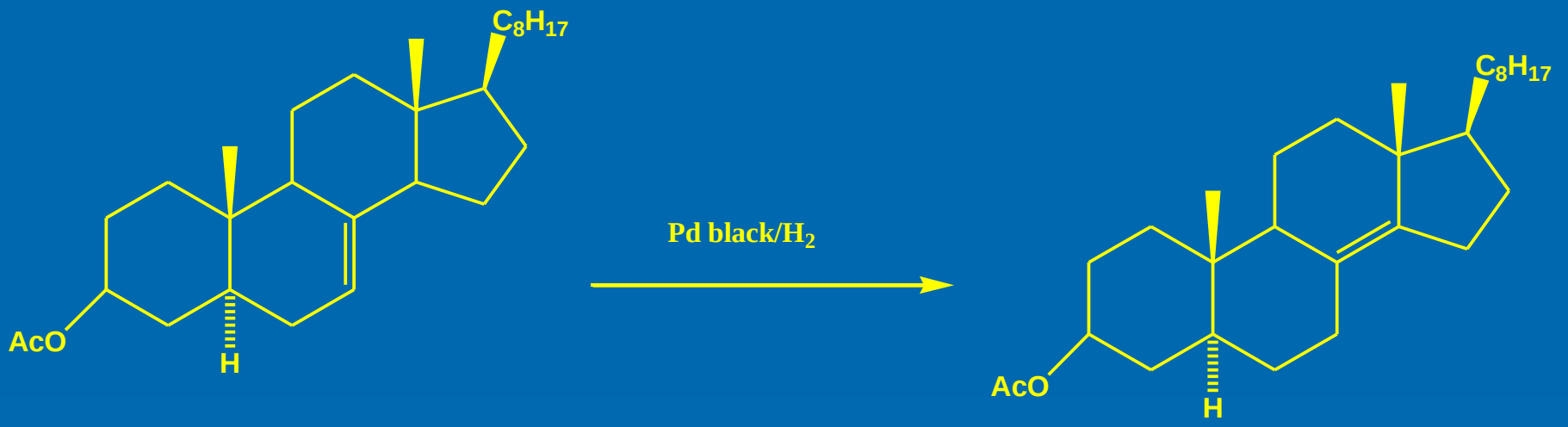
Many different catalysts reduce double bonds.

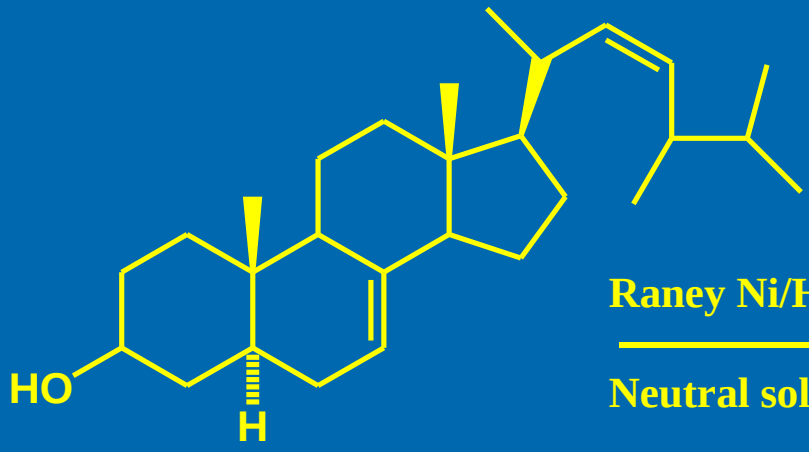
The key to differentiating reduction of double bonds is monitoring equivalents hydrogen consumed.

Olefins continued

- Bond migrations prior to reduction are common and may result in scrambling of nearby stereochemistry (Requires H_2!)
- Certain groups act as directors

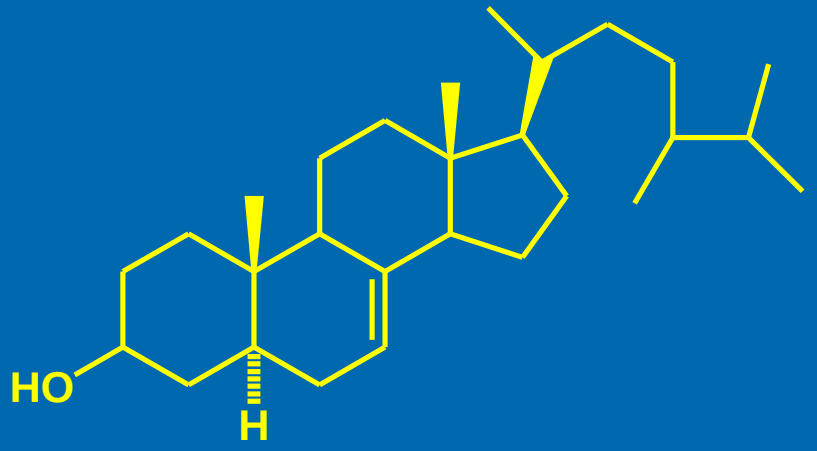
Bond Migration: More with Ni, Pd, less with Pt

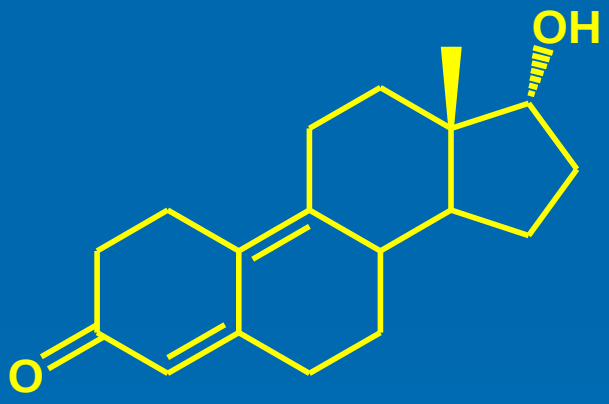




Raney Ni/H_2

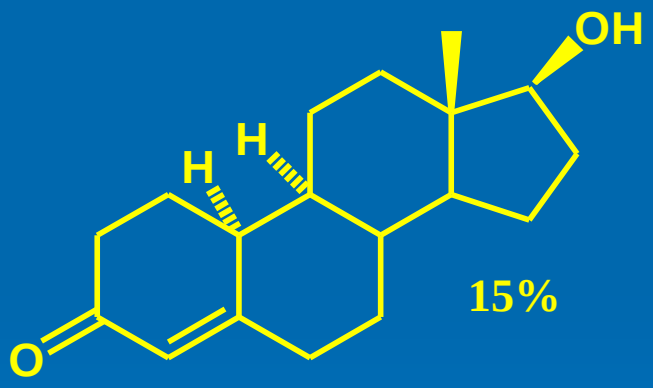
Neutral solvent



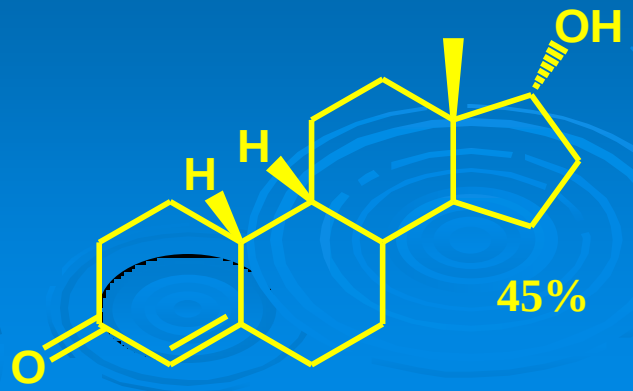


Pd/$SrCO_3$/H_2

RT 3 Atm. EtOH

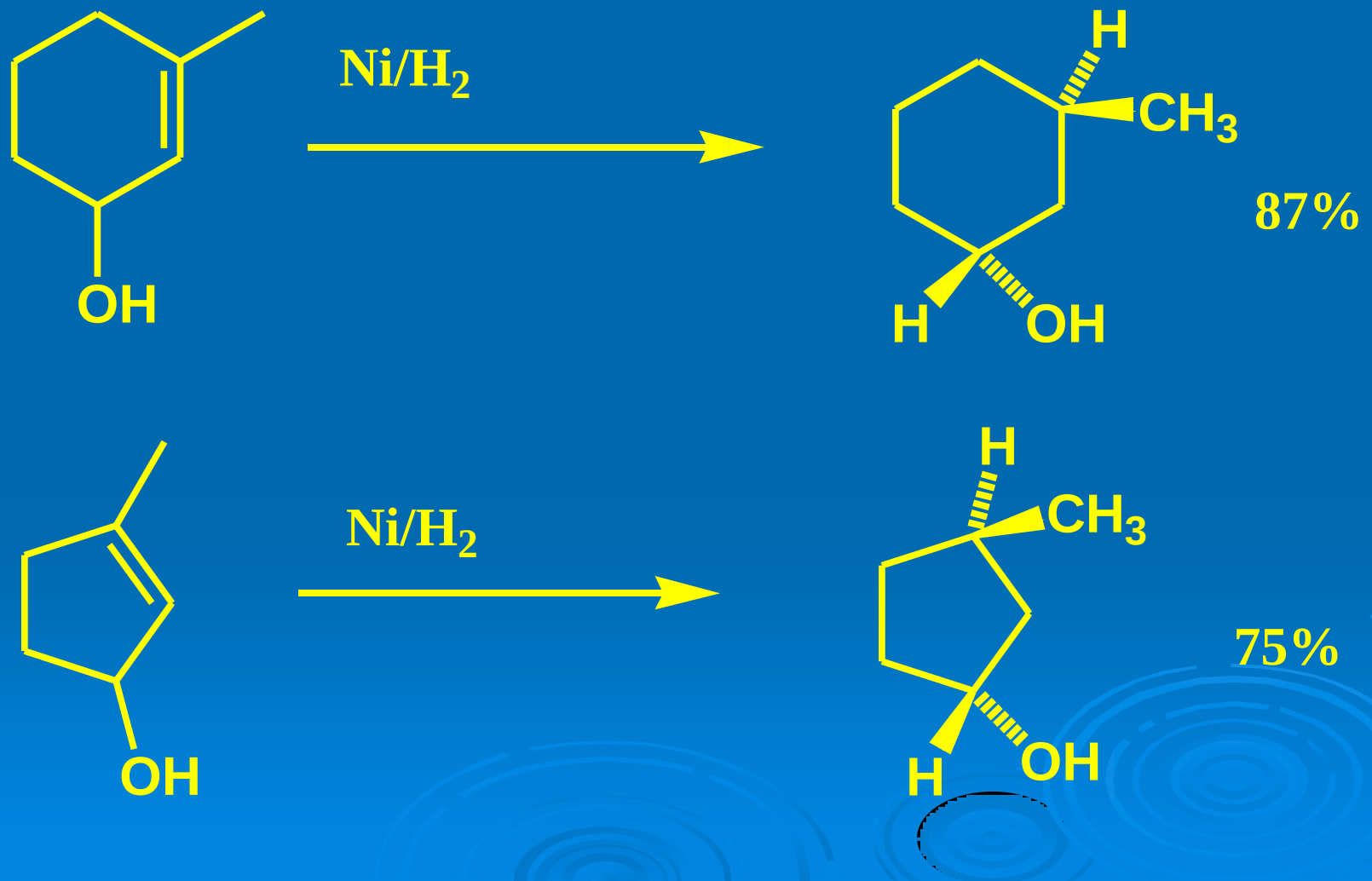


15%

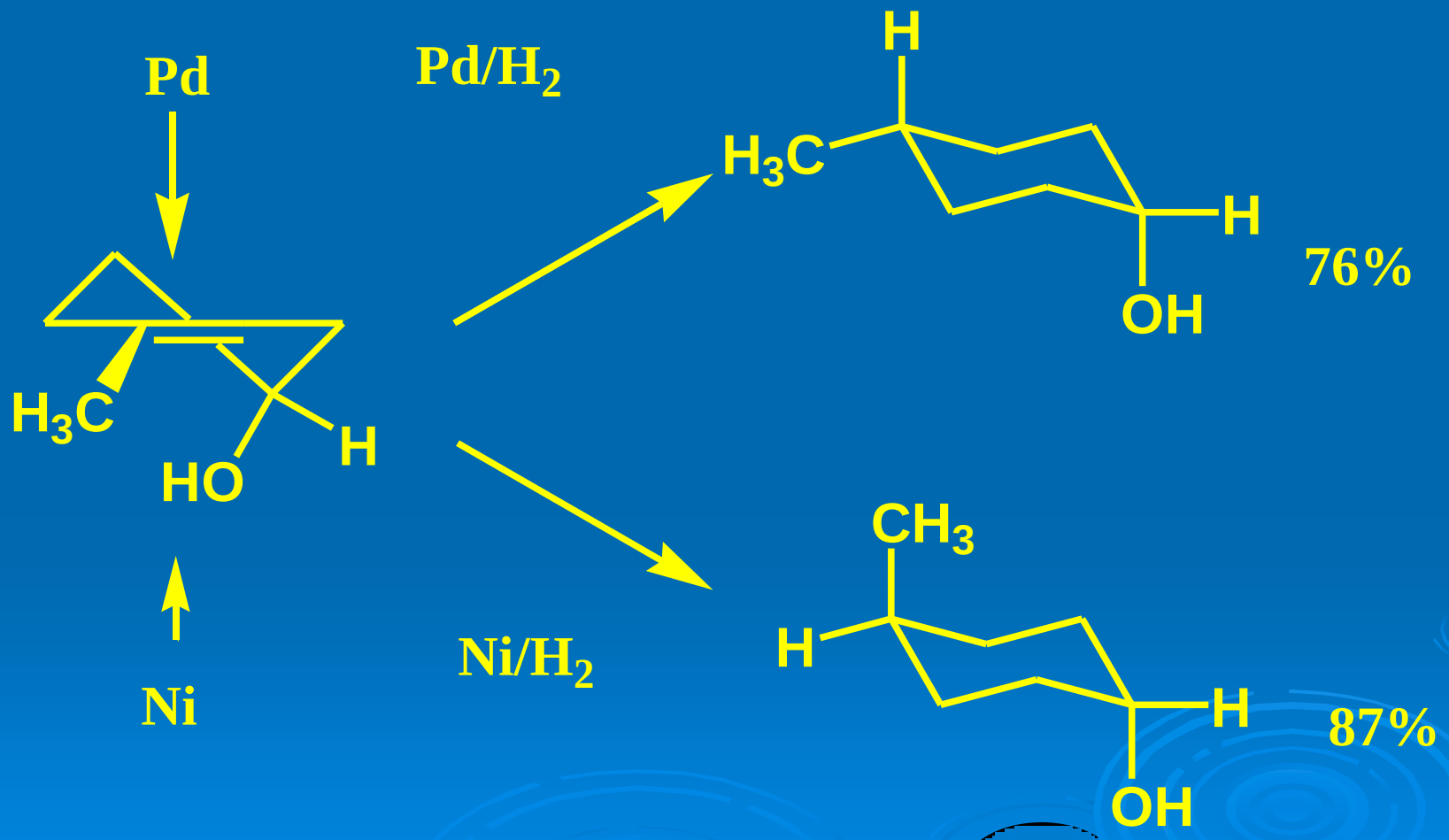


45%

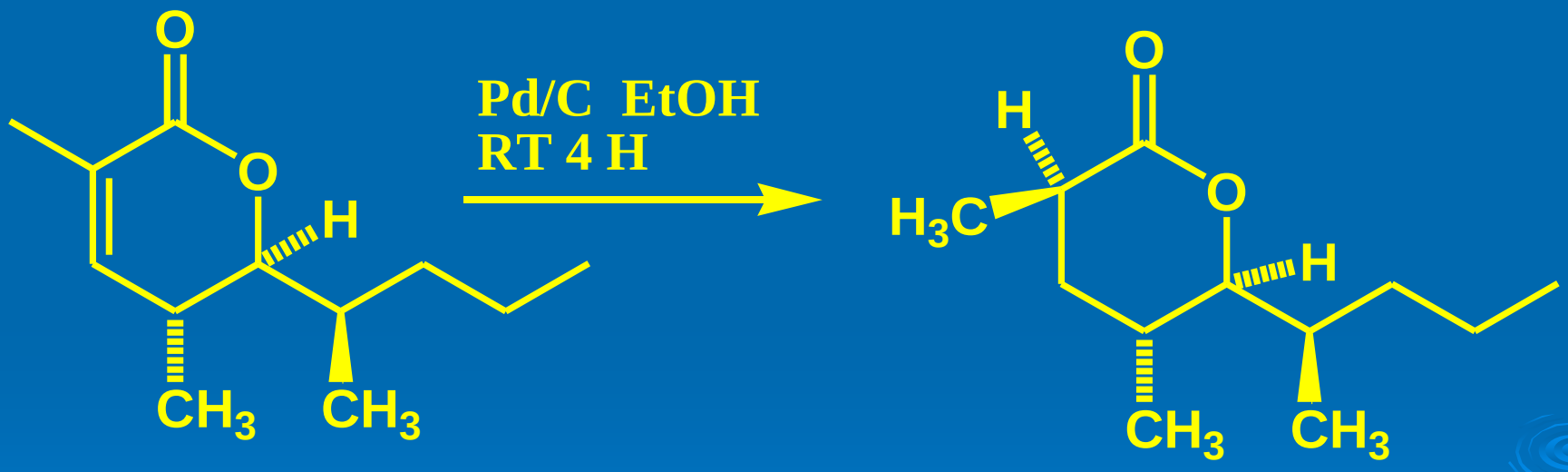
Access to catalyst surface influences stereochemistry



Catalyst approach: OH blocks Pd but favors Ni

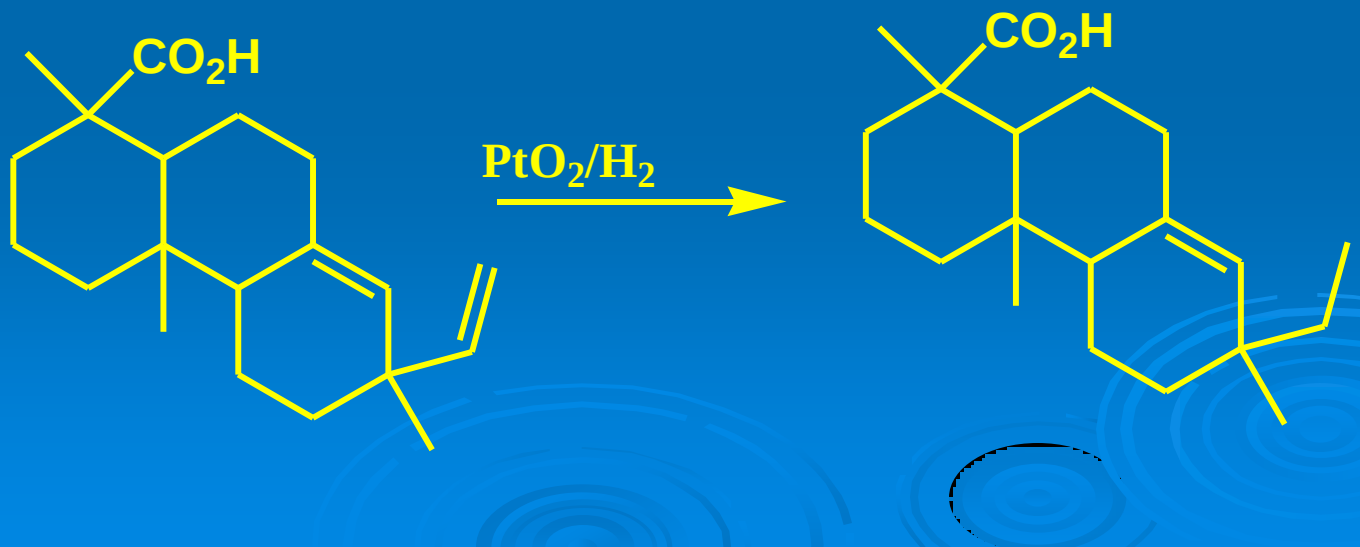


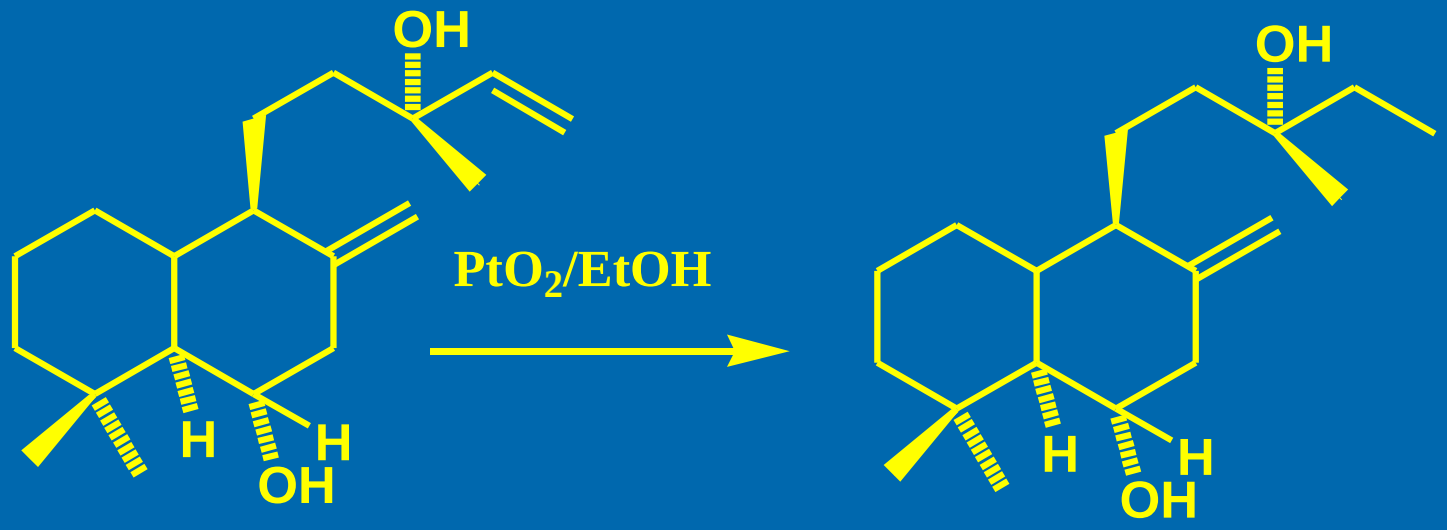
Hydrogen Addition is from the Least Hindered Side

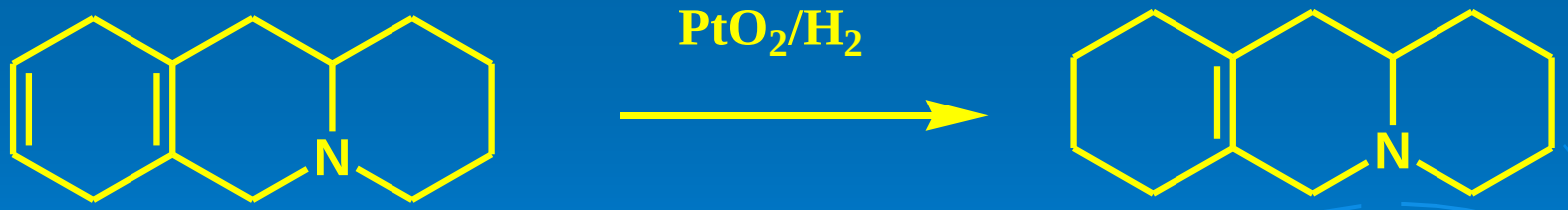


Selective Reduction of Polyenes

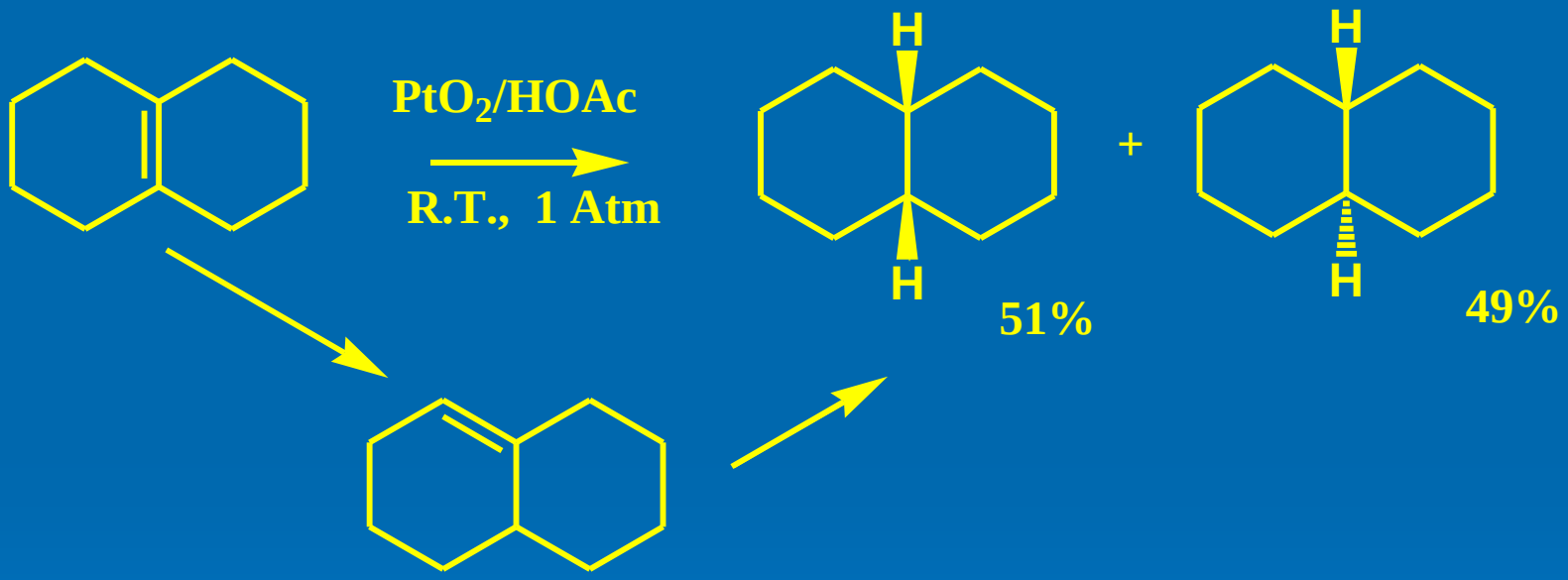
- Pd and Ni often cause bond migration
- Greatly influenced by local structure
- Conjugated di- and polyenes give mixtures except in special cases



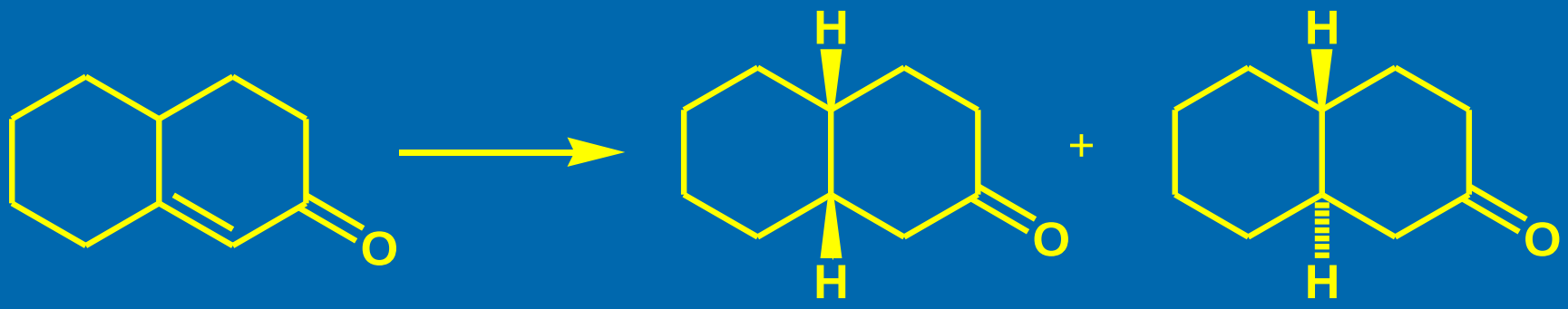

OH
H
H
OH
PtO2/EtOH
OH
H
H
OH


N
PtO2/H2
N

Catalyst Addition is in Equilibrium



Effect of Solvent and Pressure on Stereochemistry

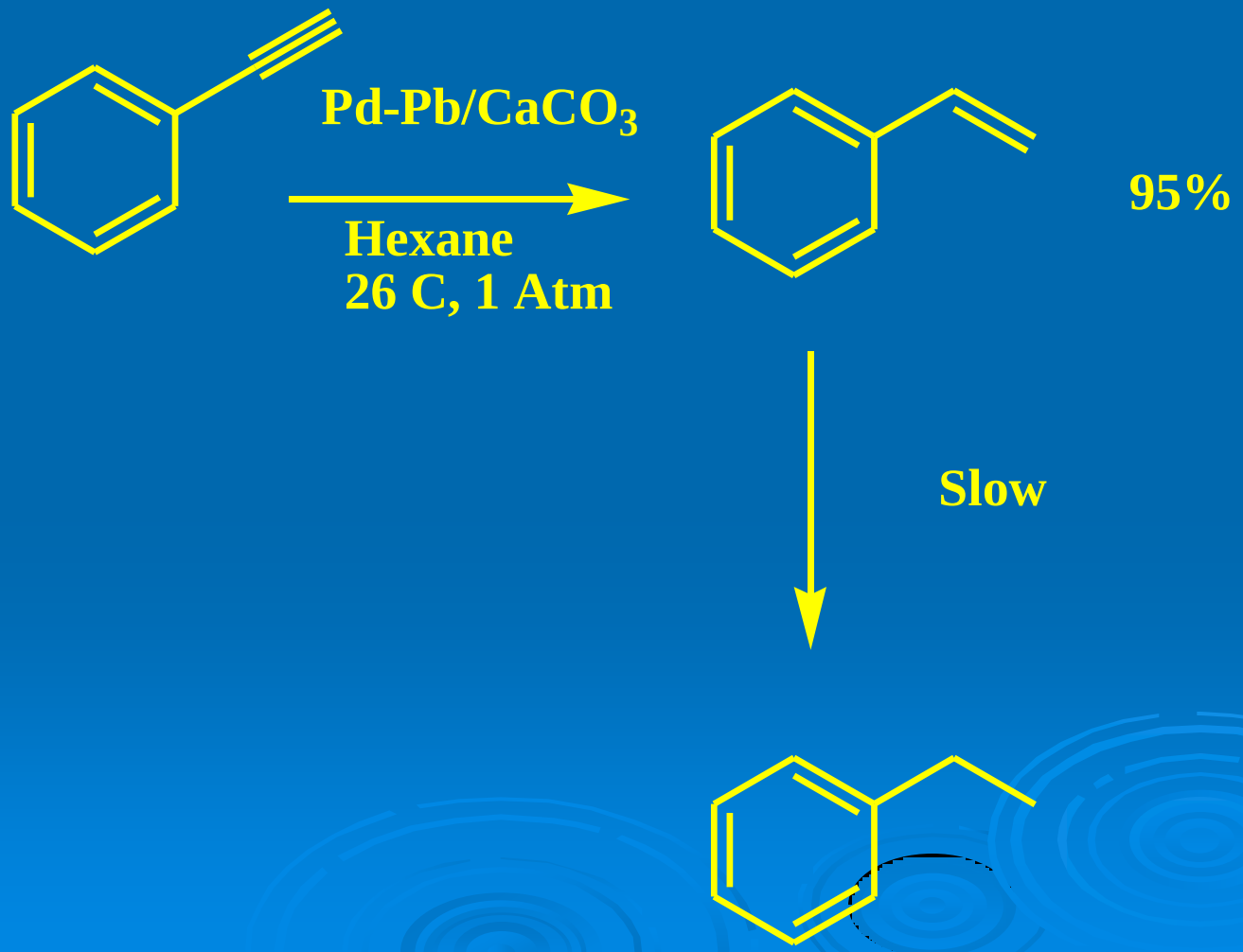


Solvent	Percent *cis* Product	
	Low H2 Press	High H2 Press
n-Hexane	77	48
DMF	86	75
tert-Butyl Alcohol	91	48
Ethanol	78	48
0.3 N HCl/Ethanol	91	80
0.3 N NaOH	50	50

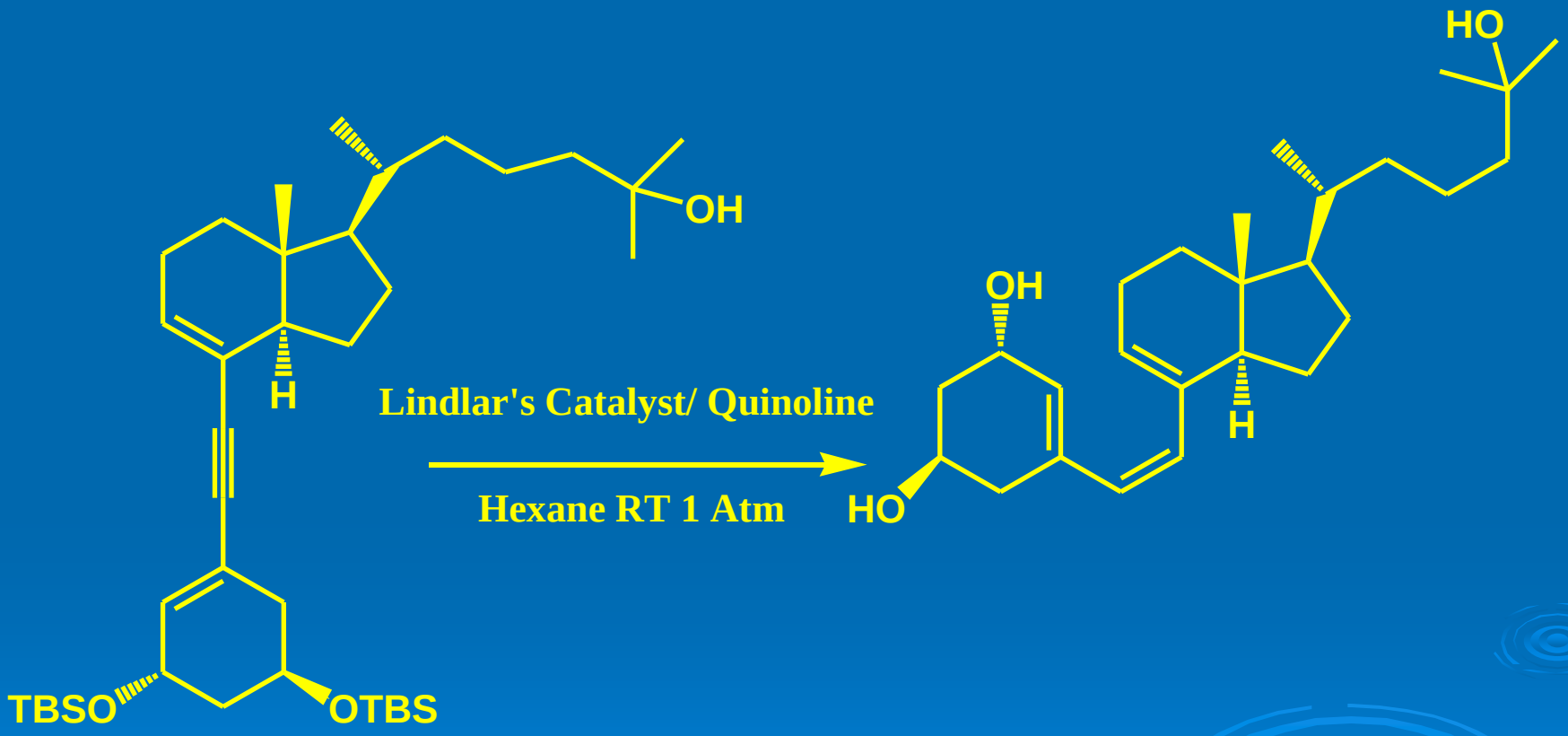
Alkyne Reduction

- Usual catalysts: Lindlar's ($Pd/CaCO_3$) Pd/BaSO4, Nickel boride, Cu and Co.
- Selectivity for cis reduction: Pd >Rh >Pt > Ru> Ir
- Quinoline commonly used as a modifier.

Reduction of Alkynes: a Game of Relative Rate



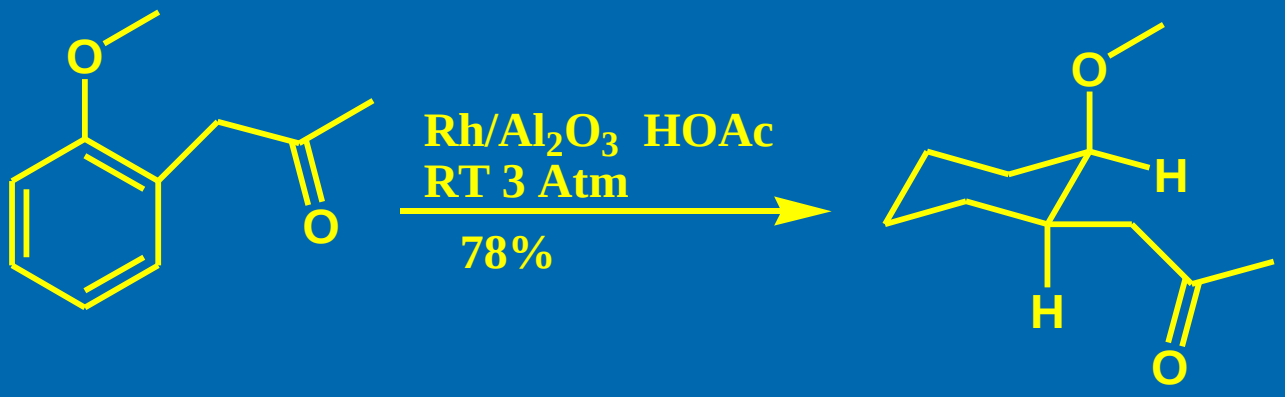
Alkyne Reduction

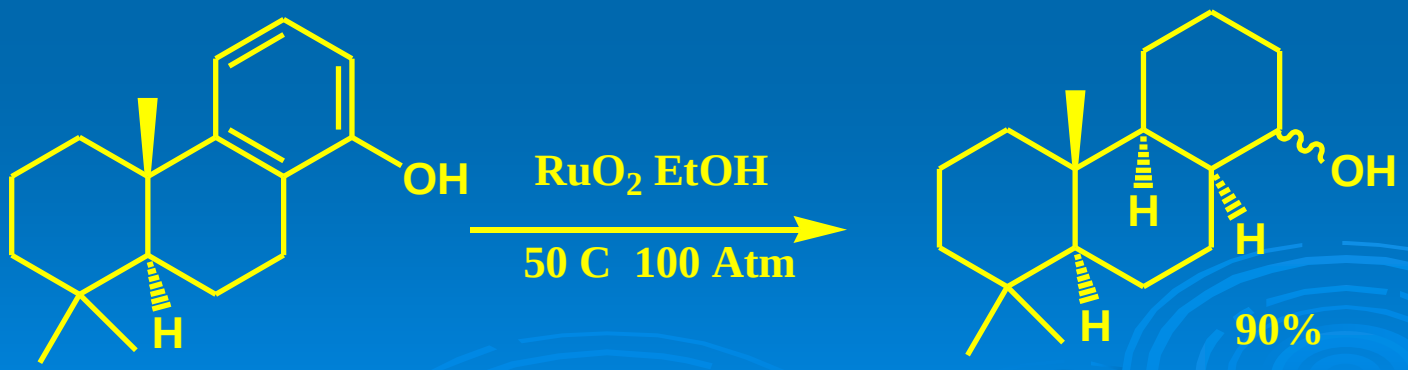


Aromatic Reduction

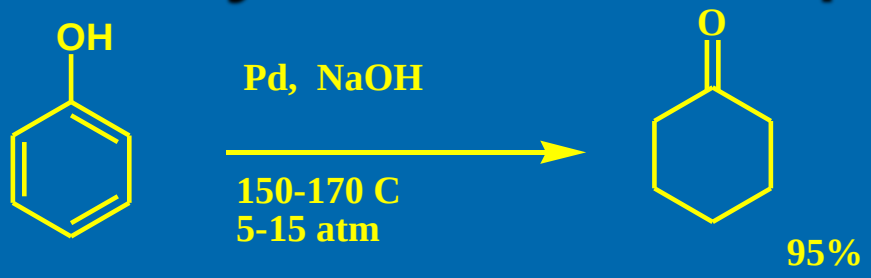
- Catalyst Activity: Rh > Ru > Pt > Ni > Pd > Co
- Ru minimizes C-O and C-N hydrogenolysis.
- C-Halide bonds do not survive aromatic reductions
- Correct choice of conditions allows other functionalities to survive

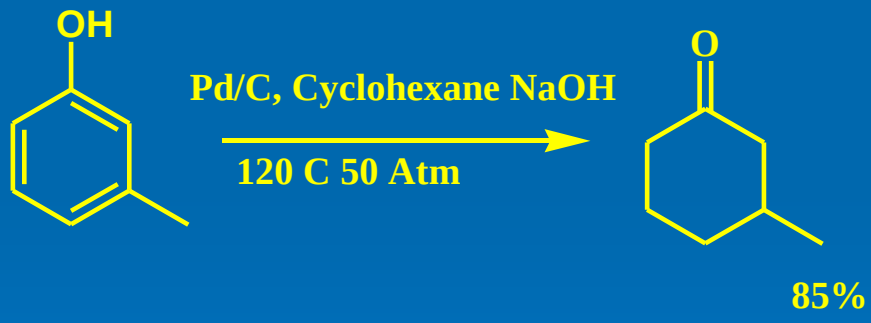
Aromatic Reduction

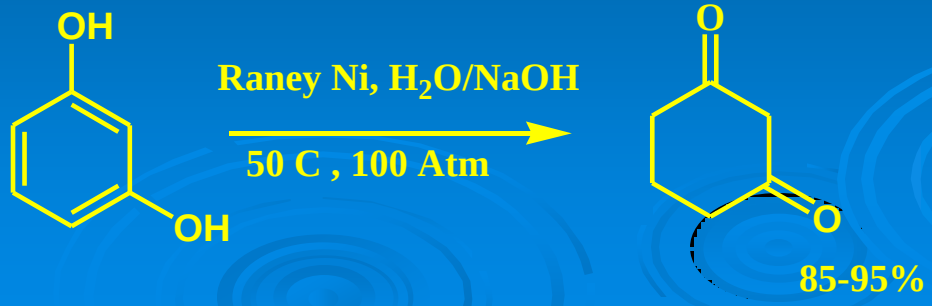




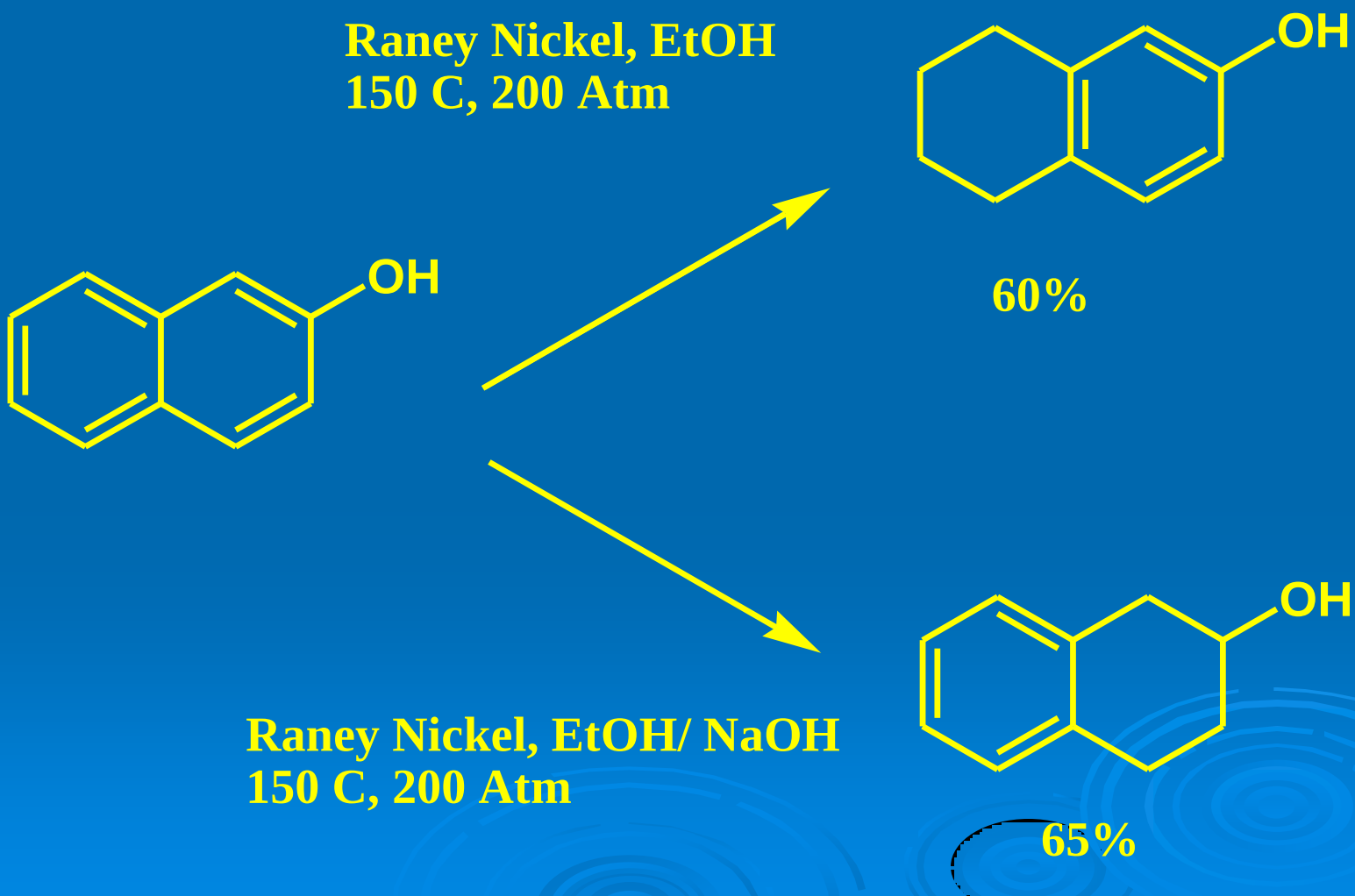
Phenols to Cyclohexanones: thin film on catalyst modifies products



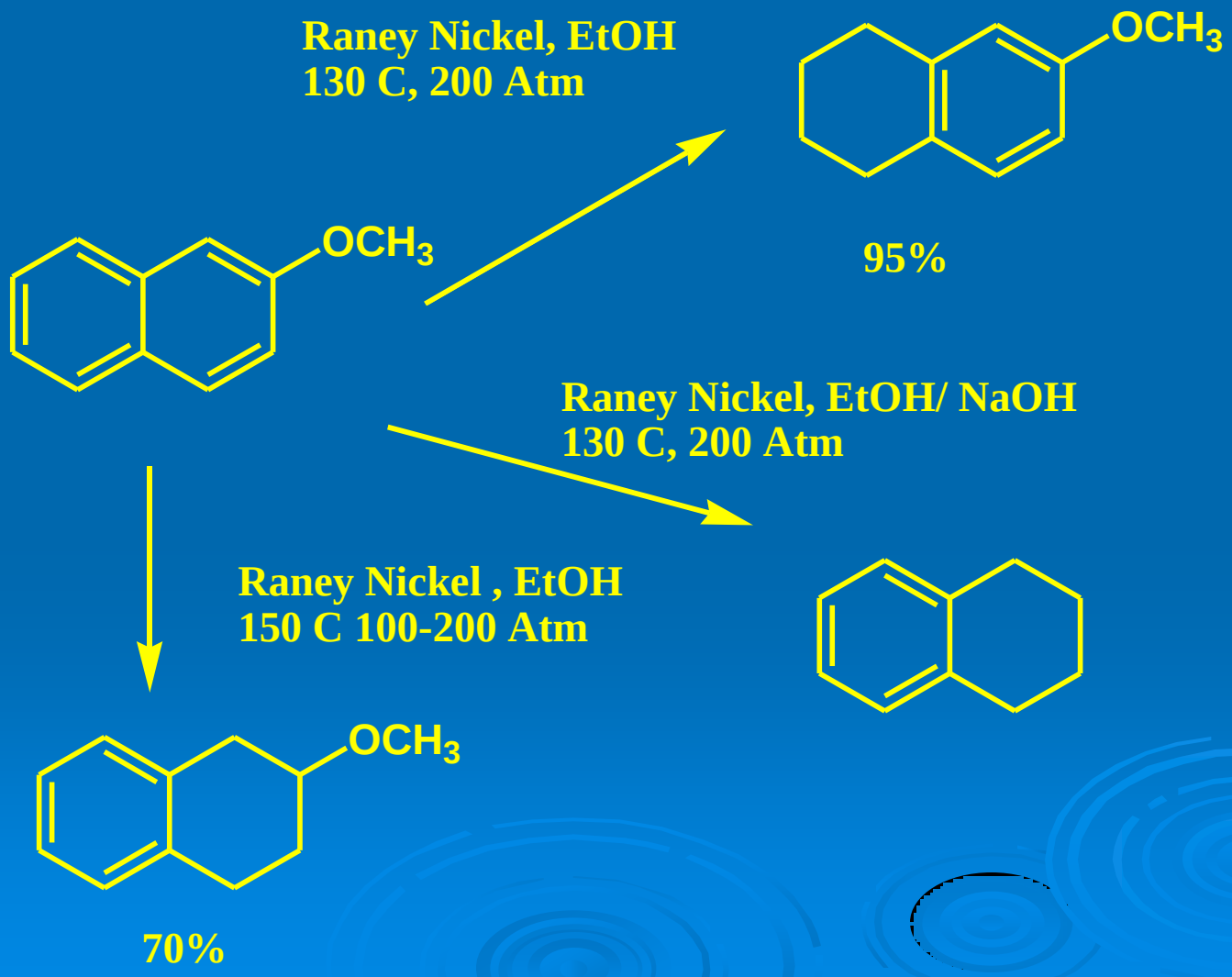




Ring Differentiation in Aromatic Reduction



Ring Differentiation in Aromatic Reduction

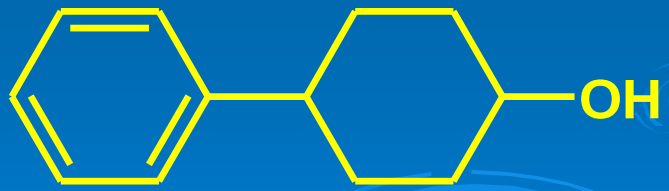


Ring Differentiation in Aromatic Reduction

Pd/C H_2O/HOAc
125 C 65 atm

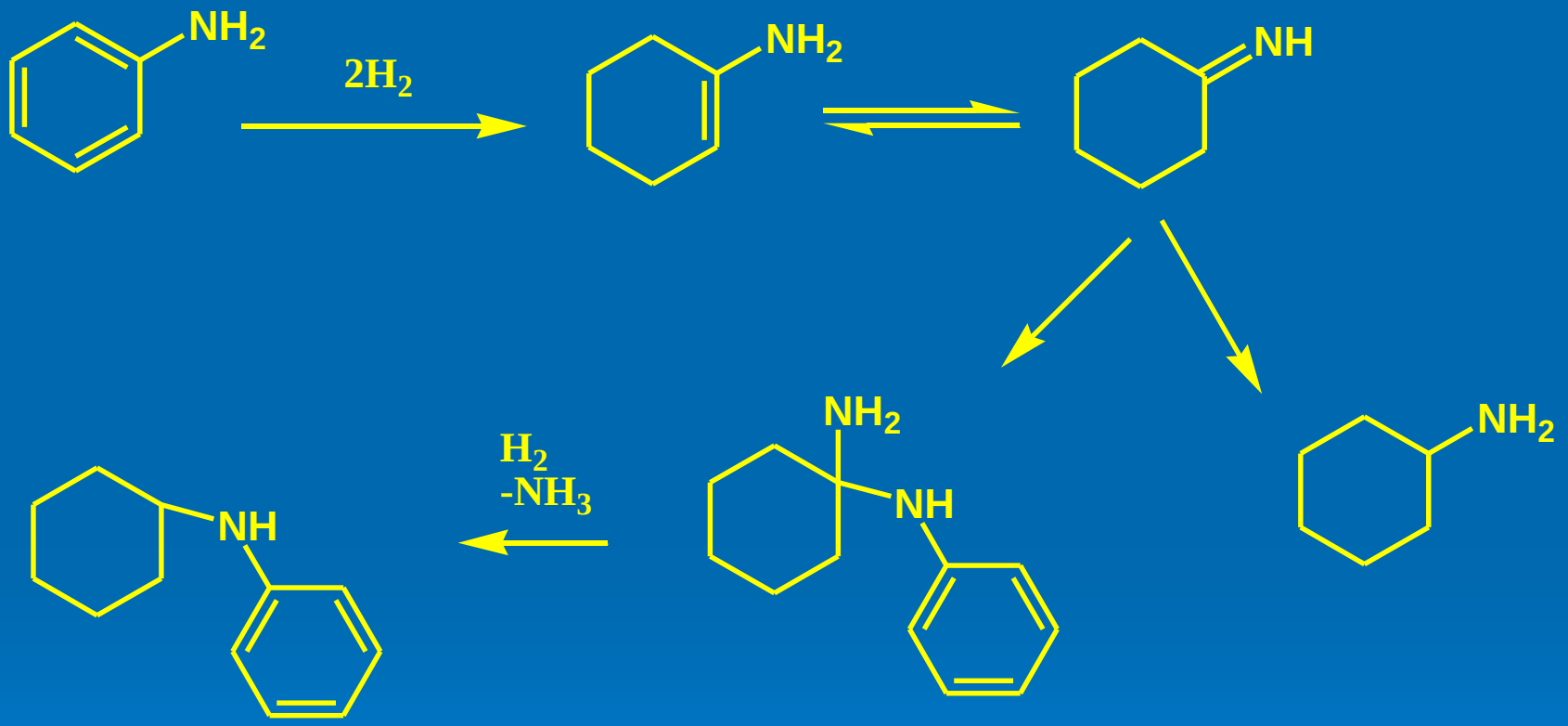
> 90%

Pd/C Cyclohexane
113 C 65 atm



53%

Other Aromatic Reductions



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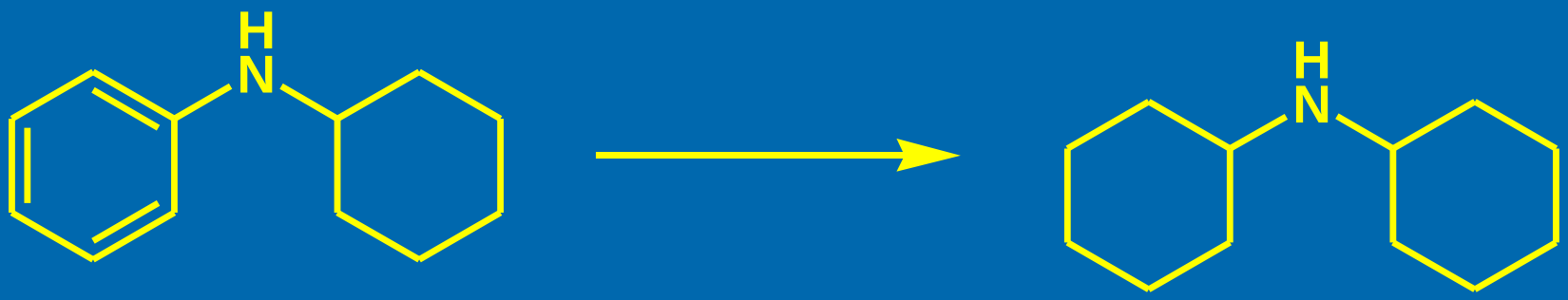
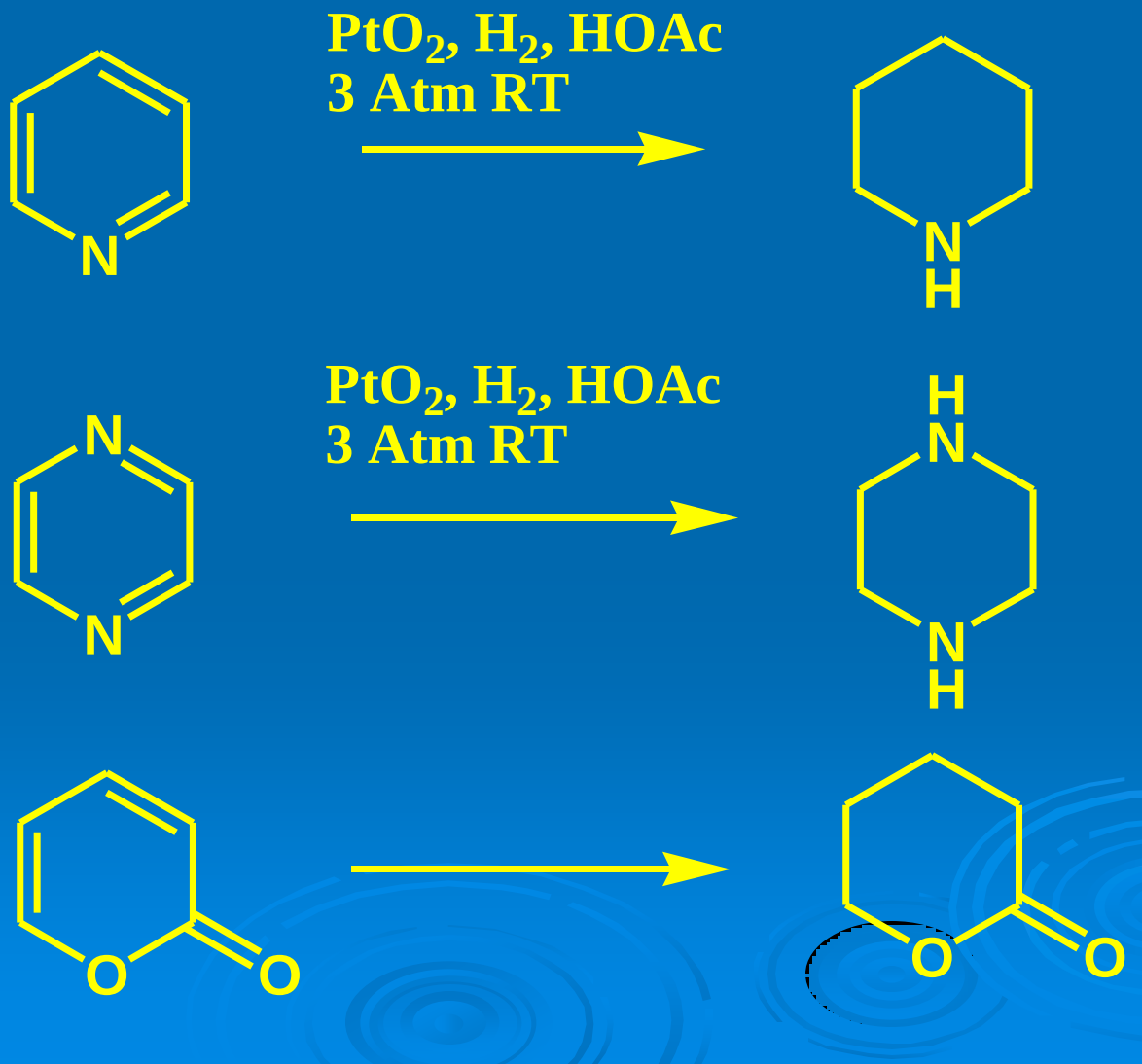
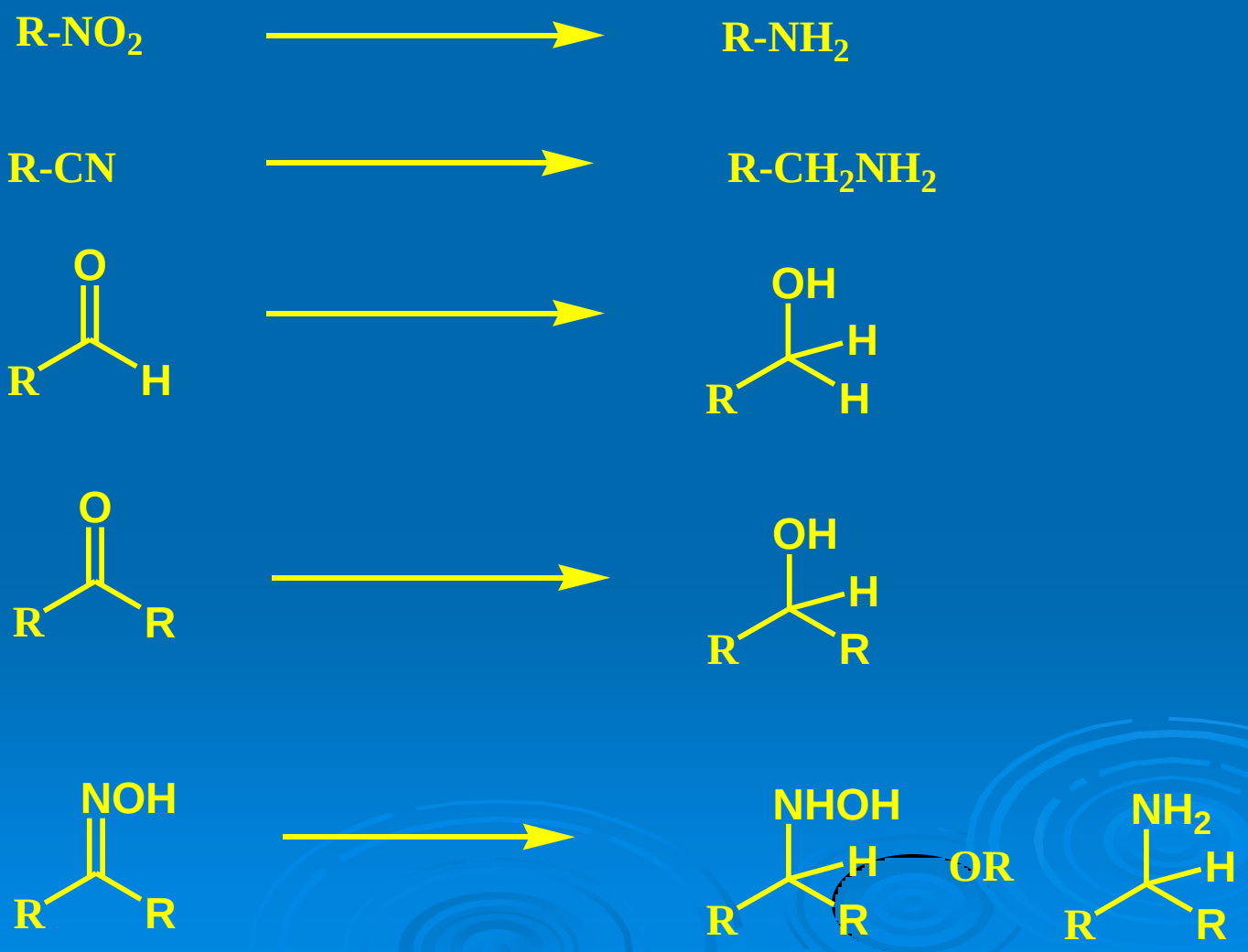


Dicyclohexylamine

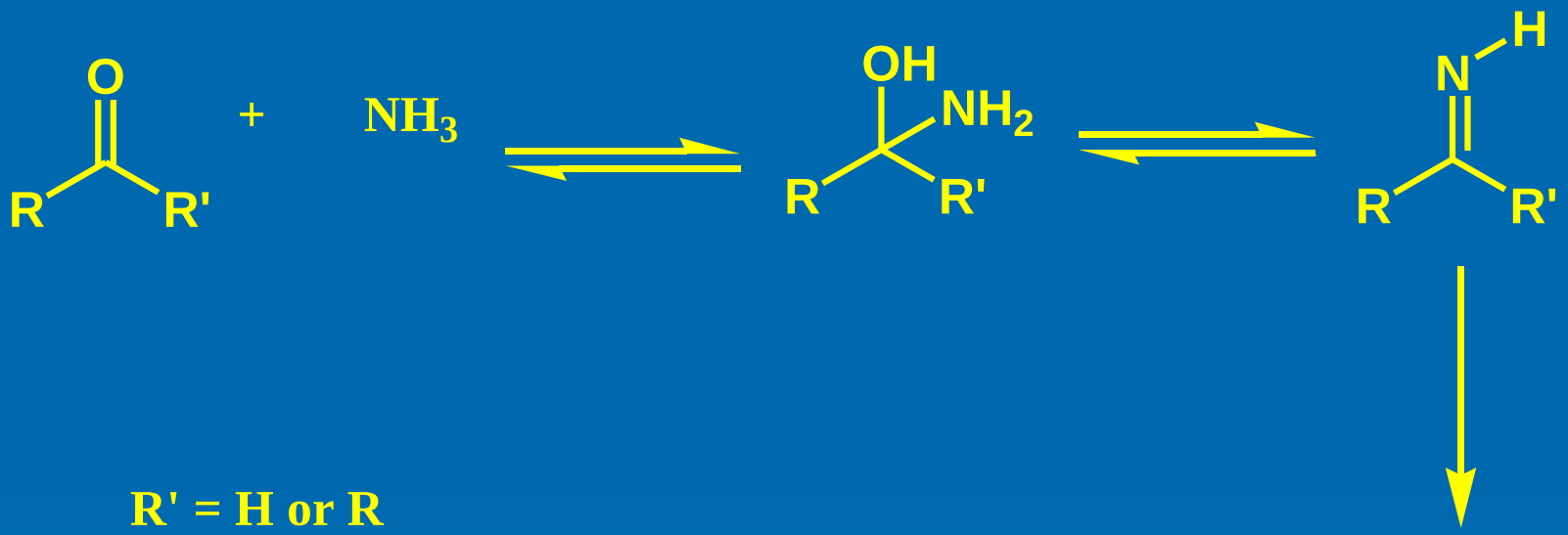
Heterocyclic Reductions



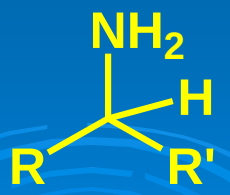
Some Functional Group Reductions: faster than Aromatic



Reductive Amination



R' = H or R



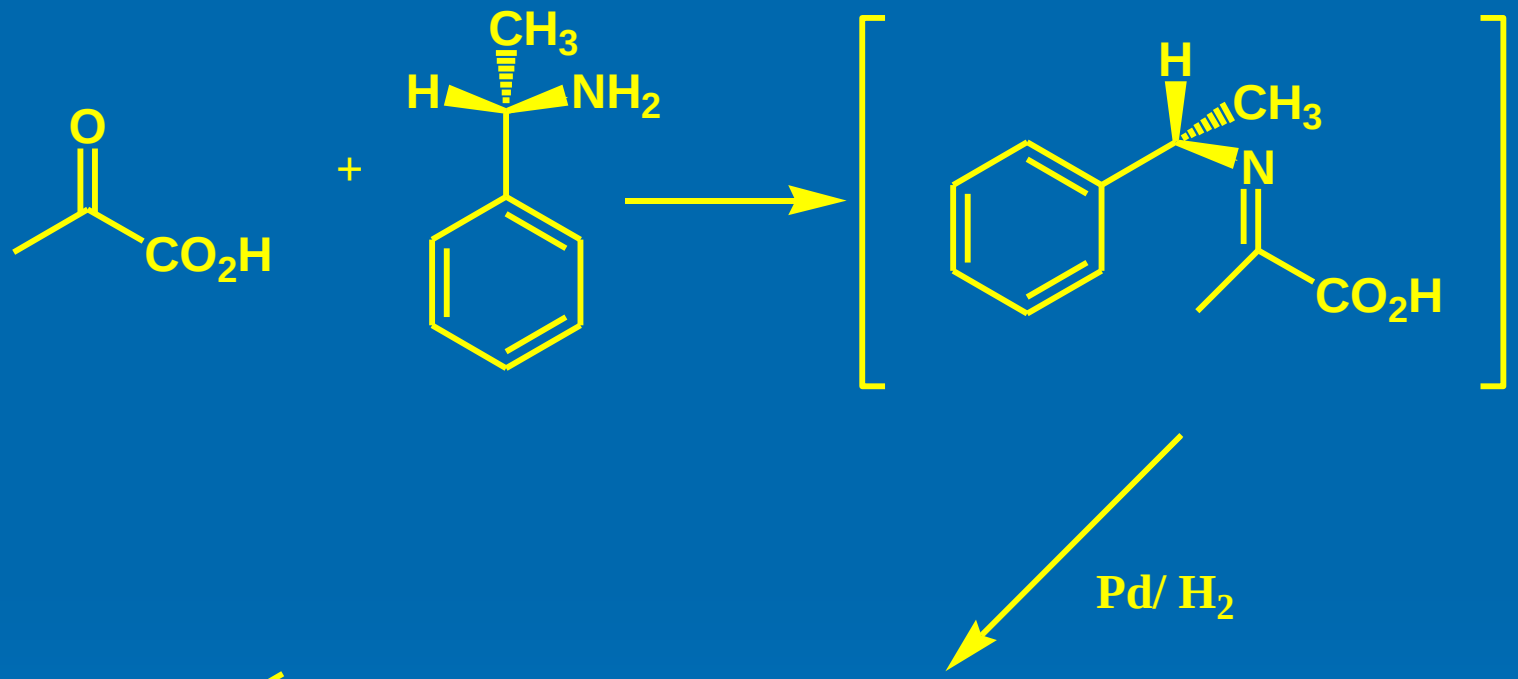
Reductive Amination

- Takes advantage of relative ease of imine reduction.
- Takes advantage of equilibrium between imine and ketone in presence of an amine.
- Some aldehydes produce significant byproducts of diamine and polymers.
- Use of one eq. acid improves yield of primary amine

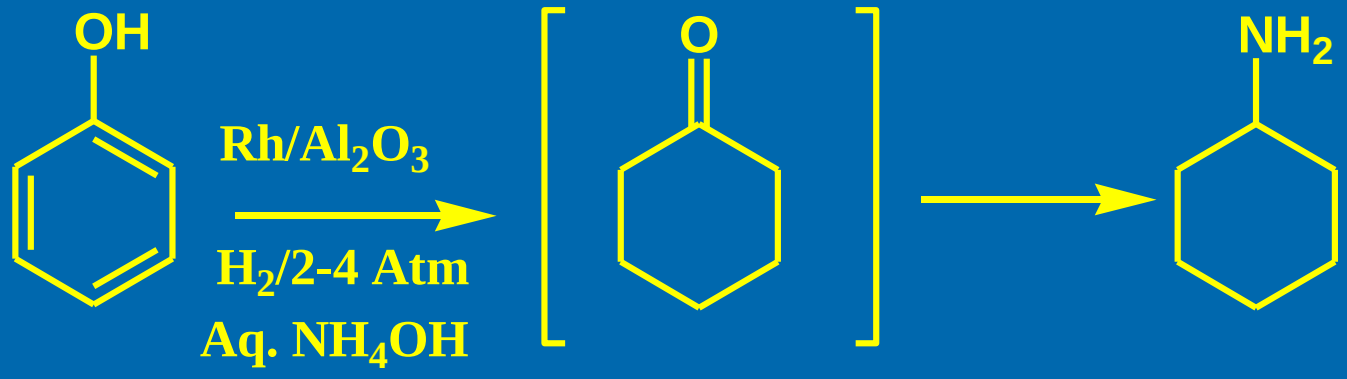
Reductive Amination

- Raney Nickel is the catalyst of choice
- Palladium, Rhodium and Platinum do not perform as well as RaNi
- Ruthenium on carbon has been used successfully
- Use of 1 eq. ammonium acetate or HOAc significantly improves results
- Aromatic Halides have been reported to survive conditions (using Rhodium)
- Can be done on sensitive aromatics, like furan.

Reductive Amination



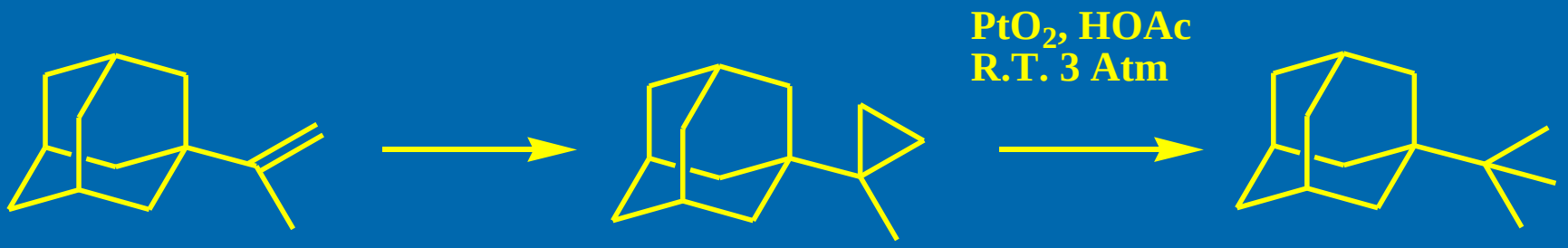
Reductive Amination

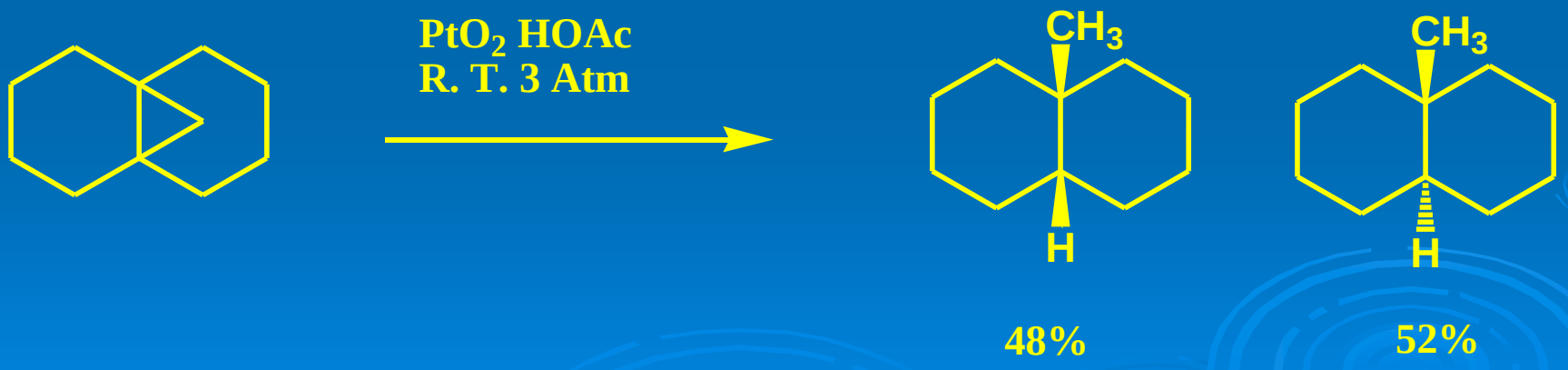


Hydrogenolysis

- Reductive cleavage of sigma bonds:
- C-C, C-N, C-O, C-S and others
- Choice of catalyst, structure of substrate, and solvent greatly influence whether double bond reduction continues on to hydrogenolysis.

Carbon-Carbon Hydrogenolysis

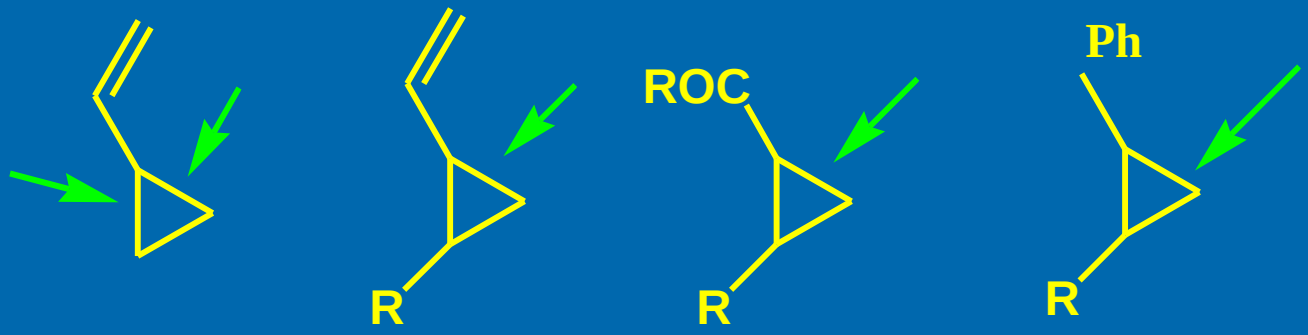


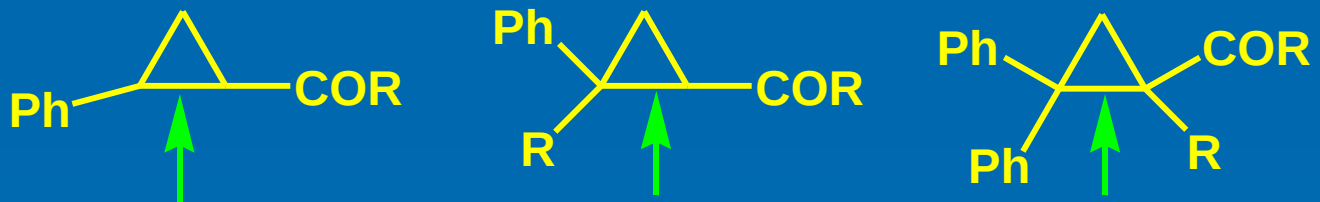


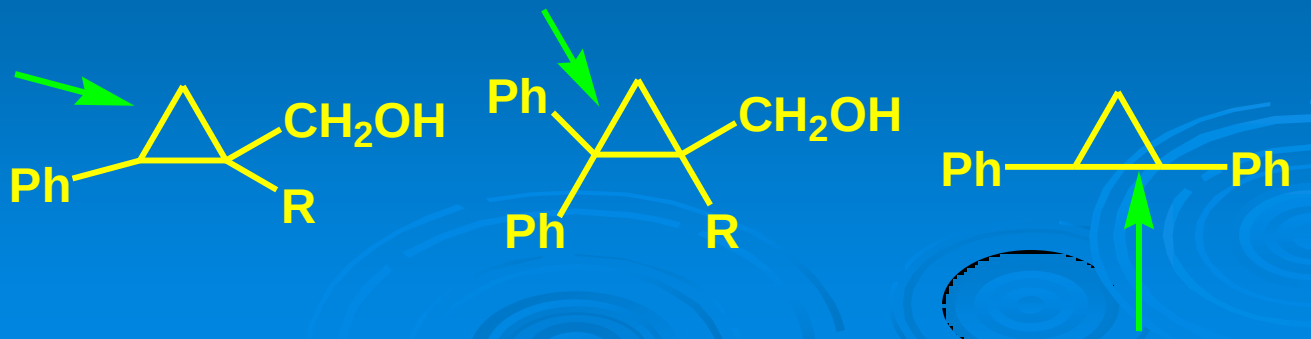
48%

52%

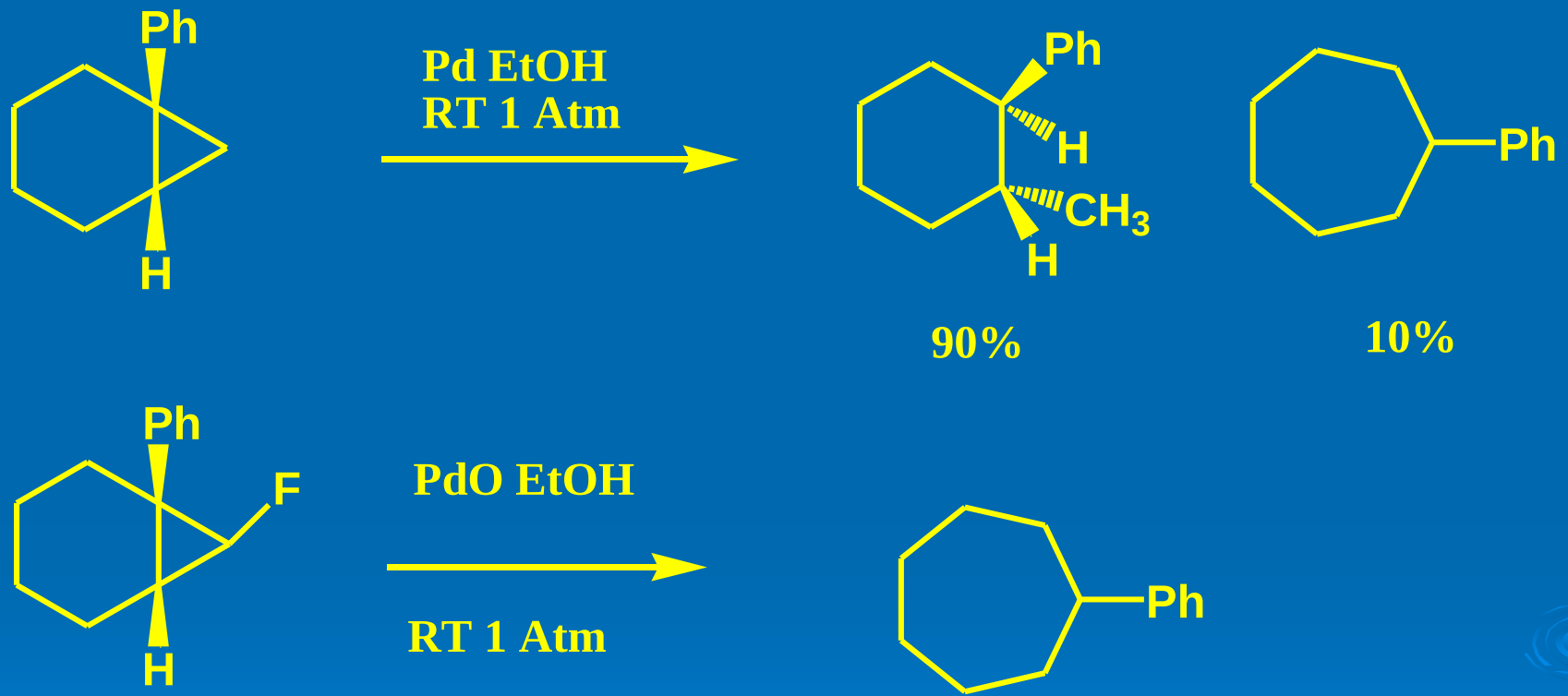
Carbon-Carbon Hydrogenolysis







Halogen Weakens Opposite bond



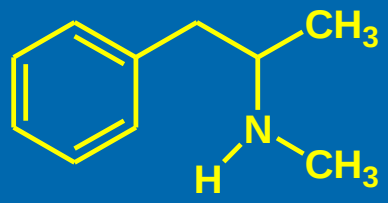
C-O Hydrogenolysis

- Generally benzyl alcohols, ethers and esters
- Often facilitated by acid
- Frequently occurs in competition with aromatic ring reduction
- Palladium favors hydrogenolysis while platinum favors ring reduction.

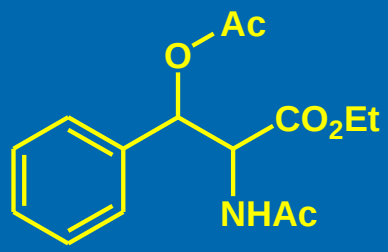
C-O Hydrogenolysis

Pd H_2O/H_2SO_4

60 C 3.5 Atm

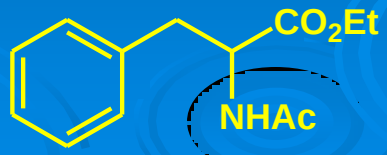


Difficult to reduce

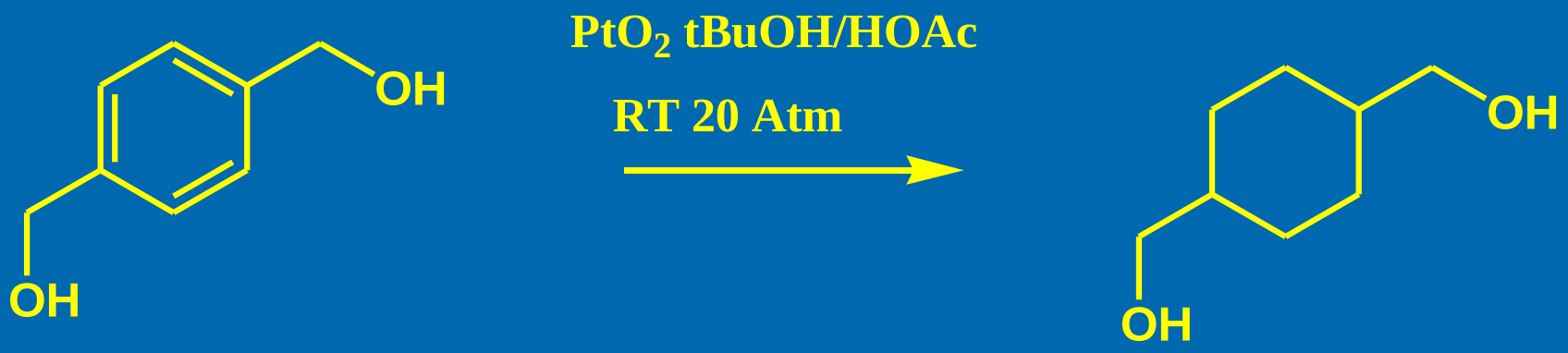


Pd/$BaSO_4$ EtOH/ Et_3N

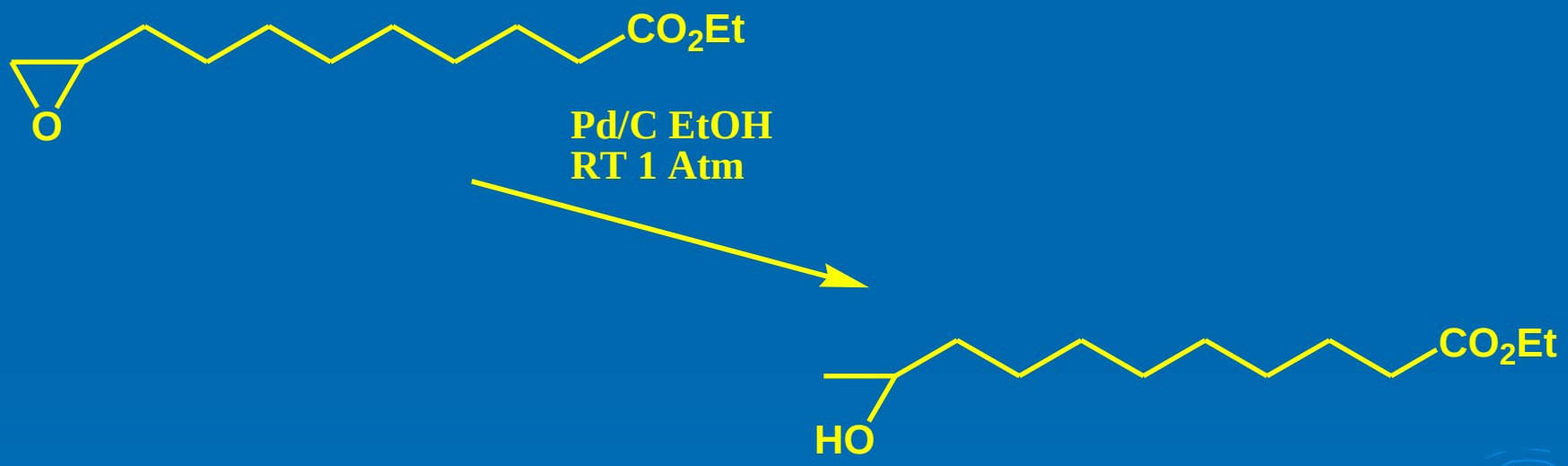
70 C 3.5 Atm



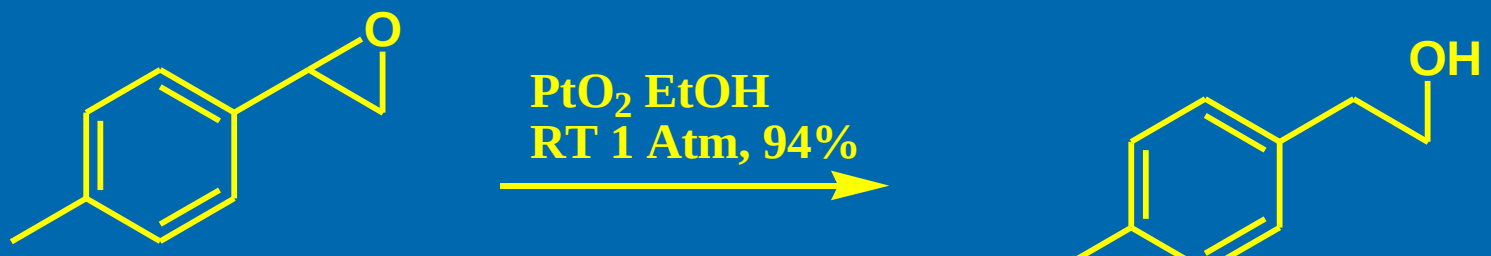
Contrasting Pt with Pd



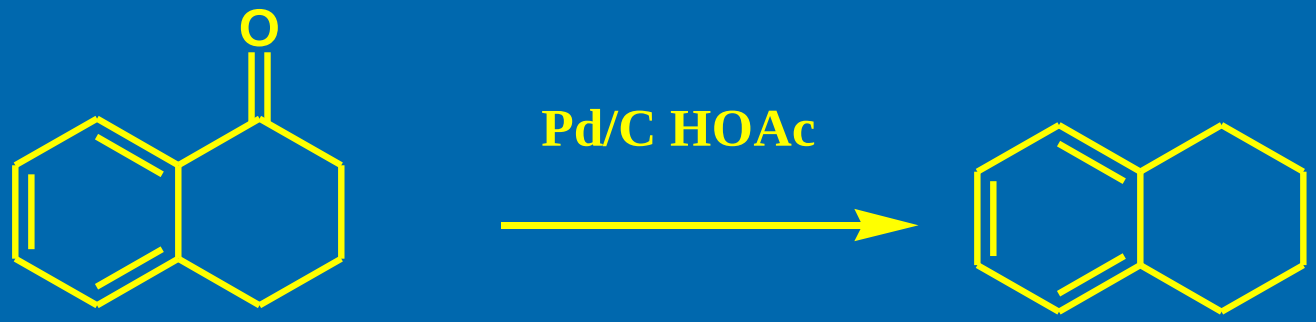
C-O Hydrogenolysis

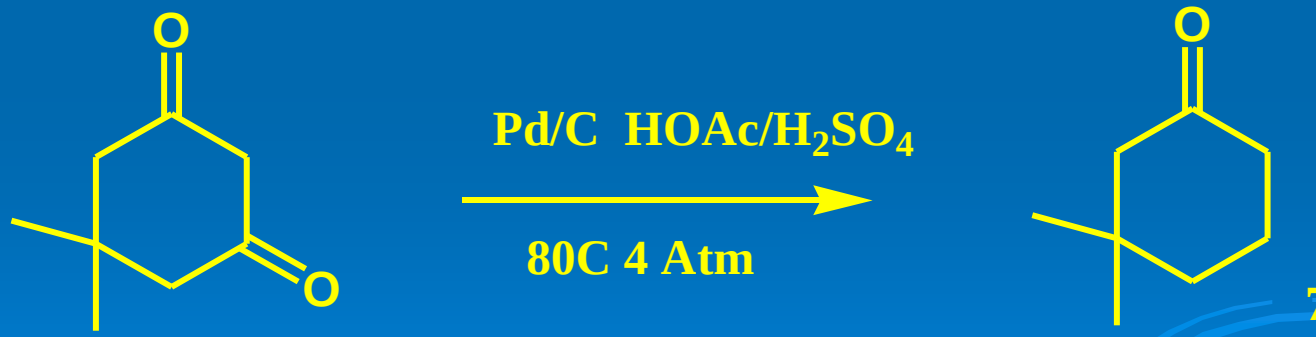


C-O Hydrogenolysis

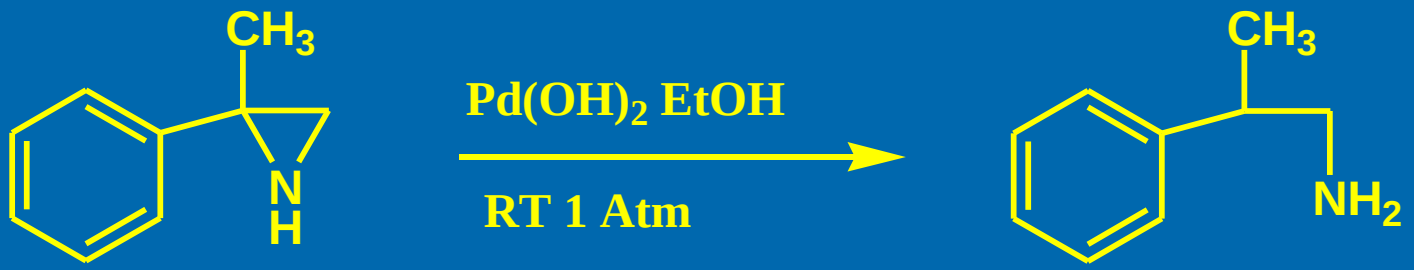


Carbonyl Hydrogenolysis

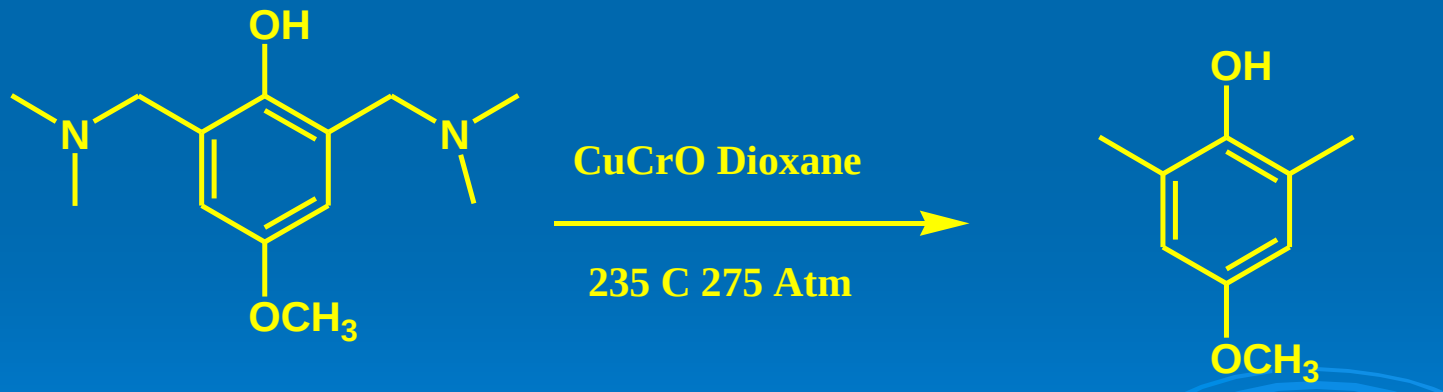




C-N Hydrogenolysis

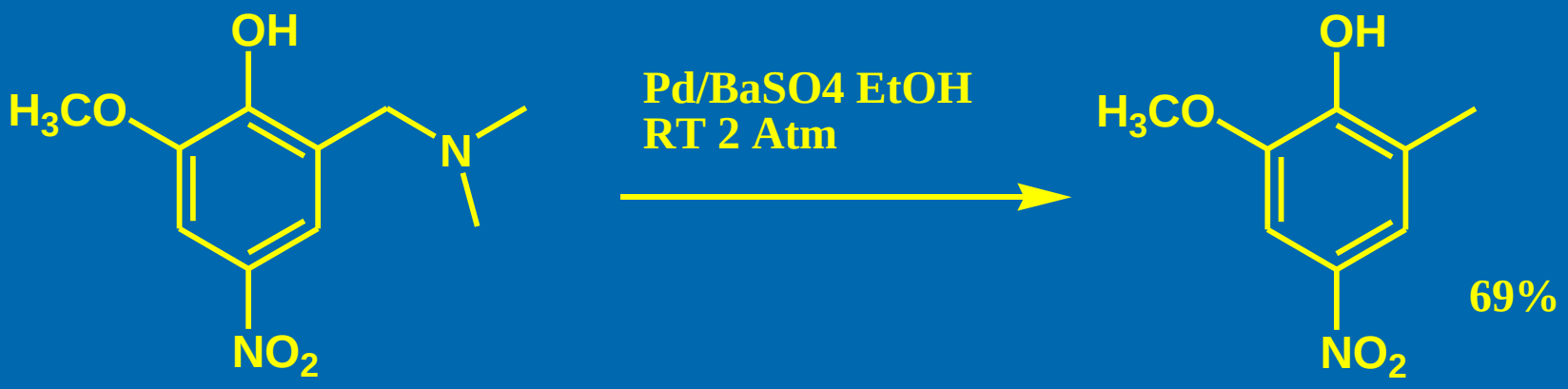


100%



90%

C-N Hydrogenolysis



Parr Shaker Demo and HP Lab Tour

Hydrogenolysis: Carbon-Carbon