

## Module II

## Reduction Reactions

### Lecture 14

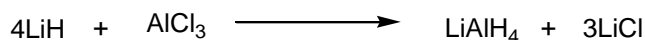
#### 2.1.1 Lithium Aluminum Hydride (LAH)

##### 2.1.1.1 Introduction

Lithium aluminum hydride (LAH) is a strong reducing agent with chemical formula  $\text{LiAlH}_4$ . It can reduce a variety of functional groups such as aldehydes, esters, acids, ketones, nitriles, epoxides and azides. It vigorously reacts with water and all the reactions are performed in polar aprotic solvents.

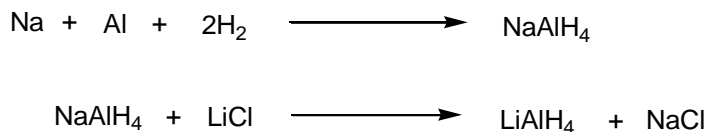
##### 2.1.1.2 Preparation

It was first prepared by treating lithium hydride ( $\text{LiH}$ ) with aluminum chloride ( $\text{AlCl}_3$ ) (Scheme 1).



Scheme 1

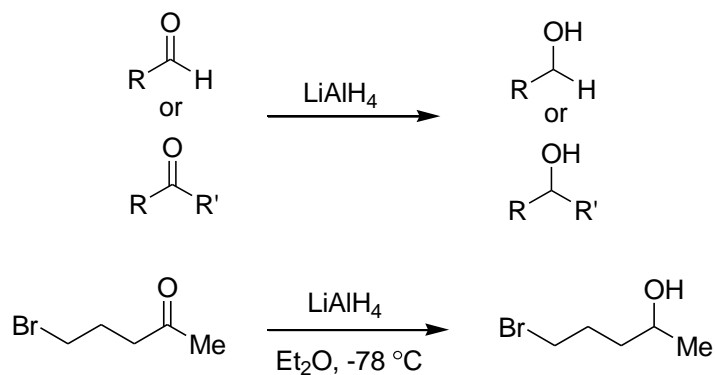
In industrial scale, it is prepared from sodium aluminum hydride which is prepared by reaction of sodium, aluminum and hydrogen at high temperature and pressure (Scheme 2).



Scheme 2

### 2.1.1.3 Reduction of Aldehydes and Ketones

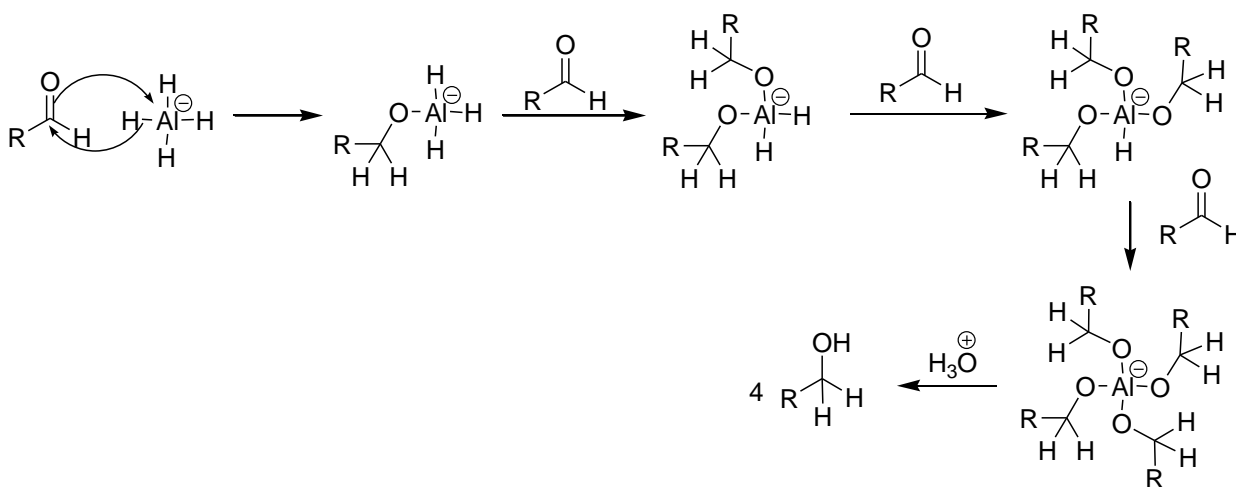
The aldehydes and ketones are reduced to give the corresponding alcohols when treated with LAH (Scheme 3). For the reduction of aldehydes and ketones, the reaction is generally performed in ether solvents at low temperature.



Scheme 3

#### Mechanism

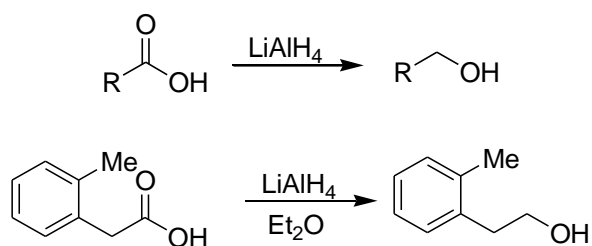
The hydride from LAH is transferred to the carbonyl group to form alkoxy anion which then forms complex with aluminum (Scheme 4). Similarly, four hydride atoms are replaced by four alkoxy groups and the aluminum complex thus formed is then hydrolyzed by dilute acid to give the desired alcohol.



Scheme 4

### 2.1.1.4 Reduction of Acids

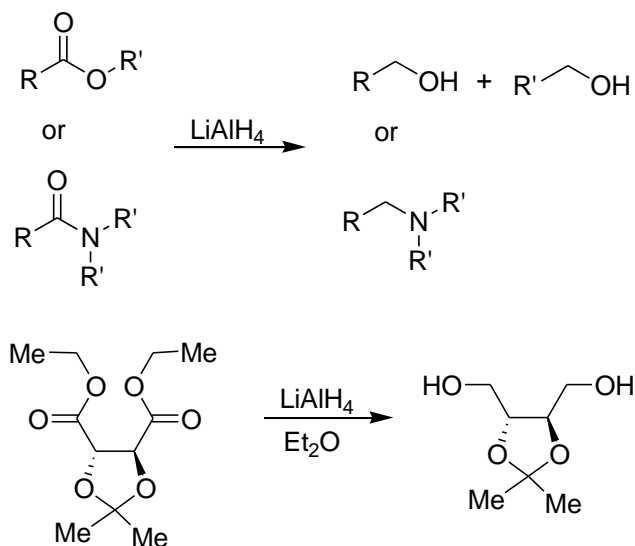
The acids are often reduced with LAH to prepare the corresponding alcohols (Scheme 5). The other comparable method for reduction of acid is using  $\text{BH}_3$  as a reducing agent. The three hydride ions are consumed for reducing one acid group.

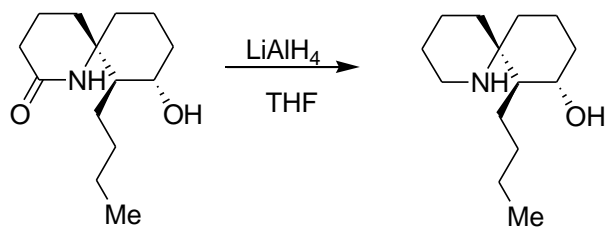


Scheme 5

### 2.1.1.5 Reduction of Esters and Amides

The esters and amides are reduced to the corresponding alcohols and amines, respectively, when treated with LAH (Scheme 6). Each molecule of ester or amides consumes two molecules of hydride ions.

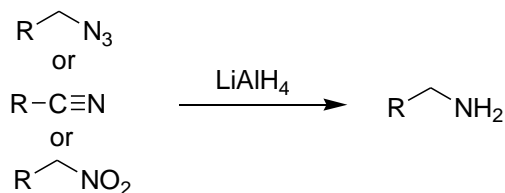




Scheme 6

### 2.1.1.6 Reduction of Azides, Nitriles and Nitro Compounds

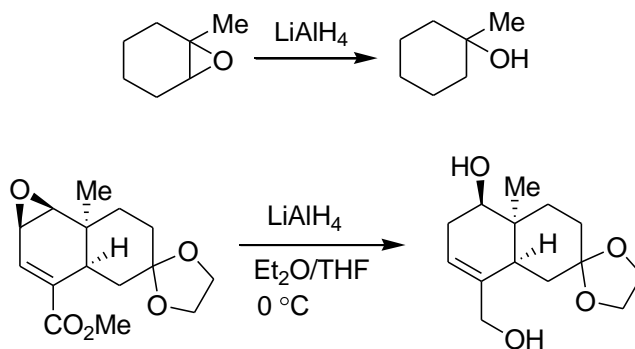
The azides, nitriles and nitro compounds are reduced to the corresponding amines in presence of LAH (Scheme 7). The aromatic nitro compounds do not give the desired amines.



Scheme 7

### 2.1.1.7 Reduction of Epoxides

The epoxides are reduced to the corresponding alcohols (Scheme 8). The hydride ion is transferred to the less hindered side of the epoxides.



Scheme 8

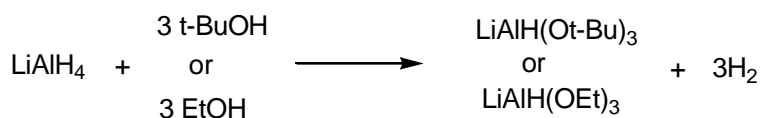
## 2.1.2 Lithium Trialkoxyaluminum Hydride [LiAlH(OR)<sub>3</sub>]

### 2.1.2.1 Introduction

Though LAH is a powerful reducing agent but is less selective. The reactivity and selectivity can be modified by replacing the three hydride ion with alkoxy groups such as *tert*-butoxy or ethoxy group. The resulting reagents are less reactive but more selective than LAH.

### 2.1.2.2 Preparation

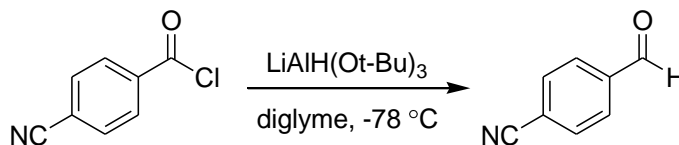
The lithium trialkoxyaluminum hydride can be prepared by treating LAH with the alcohol and better to prepare *in situ* prior to use (Scheme 9).



Scheme 9

#### 2.1.2.2.1 Lithium tri-*t*-Butoxyaluminum Hydride [LiAlH(Ot-Bu)<sub>3</sub>]

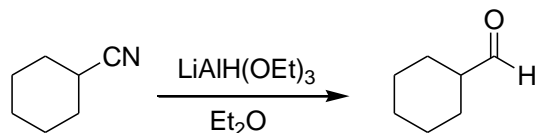
This is less reactive compared to LAH and reduces aldehydes and ketones to alcohols and acid chlorides to aldehydes (Scheme 10). The other functional groups such as acids, amides and nitriles do not react or react very slowly.



Scheme 10

#### 2.1.2.2.2 Lithium tri-Ethoxyaluminum Hydride [LiAlH(OEt)<sub>3</sub>]

Lithium tri-ethoxyaluminum hydride is comparatively stronger reducing agent than lithium tri-*t*-butoxyaluminum hydride (Scheme 11). It can reduce amides and nitriles to the corresponding aldehydes in good yield.

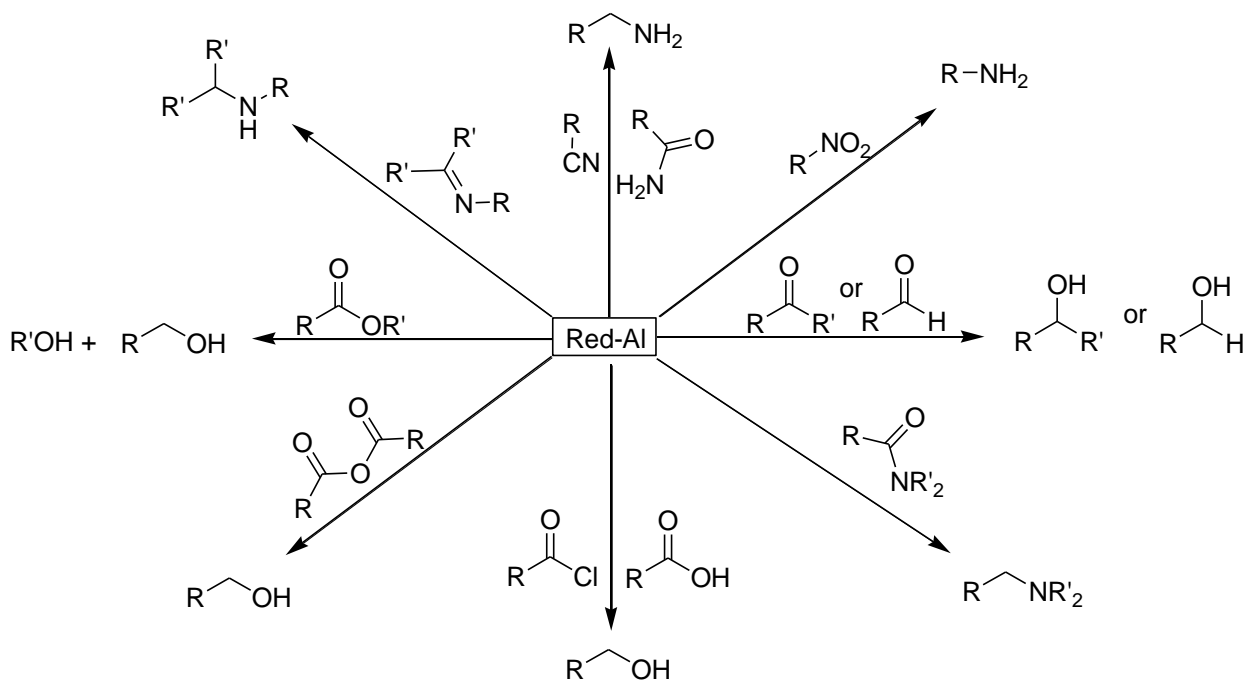


Scheme 11

### 2.1.3 Sodium bis(2-Methoxyethoxy)aluminum Hydride (SMEH) [ $\text{NaAlH}_2(\text{OCH}_2\text{CH}_2\text{OMe})_2$ ]

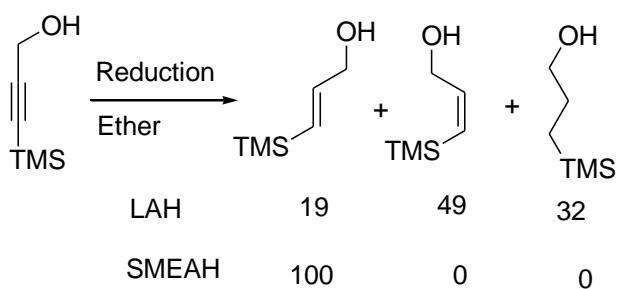
Sodium bis(2-methoxyethoxy)aluminum hydride (SMEAH) is a commercially available reducing agent with trade name Red-Al. It is more selective than LAH and the reduction can be carried out in aromatic hydrocarbons as well as other ethers solvent (Scheme 12).

M. Gugelchuk, *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons., Inc., L. A. Paquette, Ed., New York, 1995, **7**, 4518.

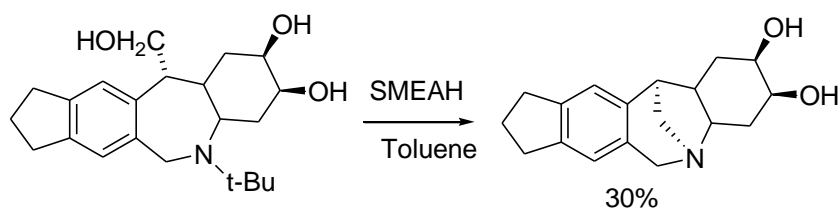


Scheme 12

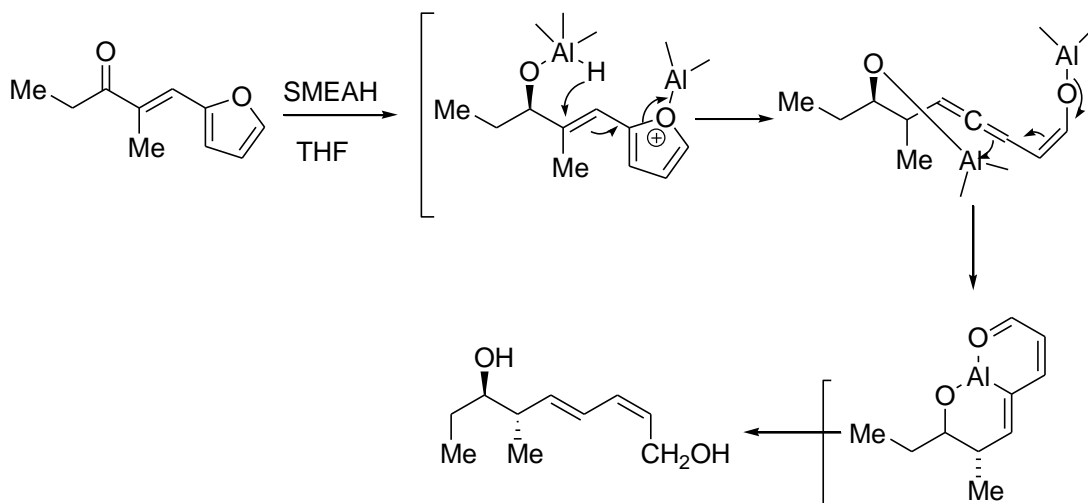
**Examples:**



S. E. Denmark, T. K. Jones, *J. Org. Chem.* **1982**, 47, 4595.



M. Ishizaki, O. Hoshino, Y. Iitaka, *J. Org. Chem.* **1992**, 57, 7285.



R. B. Gammill, L. T. Bell, S. A. Mizsak, *Tetrahedron Lett.* **1990**, 31, 5301.

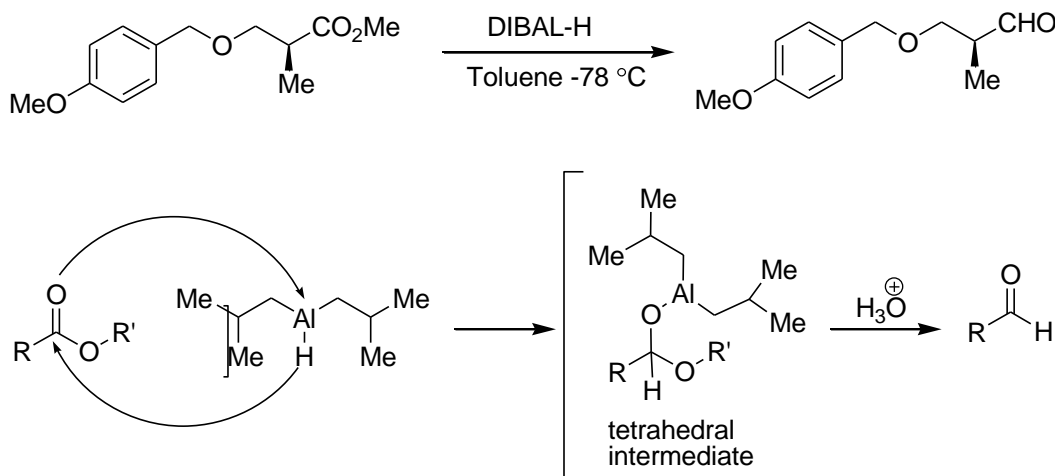
### 2.1.4 Diisobutylaluminum Hydride (DIBAL-H)

The diisobutylaluminum hydride (DIBAL-H) is a commercially available selective reducing agent. It can selectively reduce esters and nitriles to the corresponding aldehydes. The reaction is carried out in inert and moisture free atmosphere.

P. Galatsis, *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, Inc., L. A. Paquette, Ed., New York, 1995, **3**, 1908.

#### 2.1.4.1 Reduction of Esters to Aldehydes

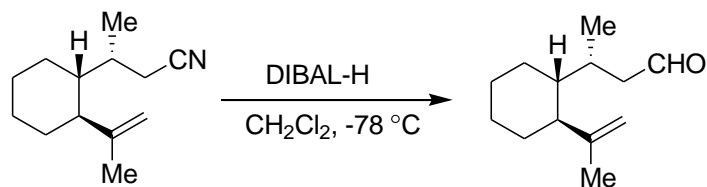
The esters are selectively reduced to the corresponding aldehydes at low temperature. The DIBAL-H transfer one hydride to the ester group and forms a tetrahedral intermediate which is stable at low temperature. The hydrolytic work up of the intermediate gives the desired aldehydes (Scheme 13). The presence of alkoxy or amino group to the close proximity can stabilize the tetrahedral intermediate and hence give better result.



#### 2.1.4.2 Reduction of Nitriles

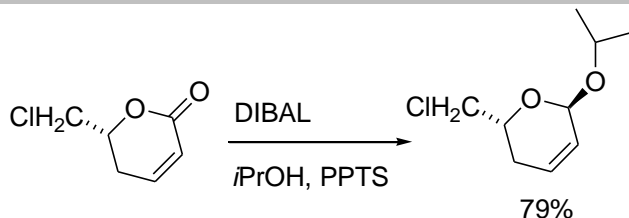
The nitriles are selectively reduced to the corresponding aldehydes with one equivalent of DIBAL-H at low temperature. The use of two equivalent of DIBAL-H gives the corresponding primary amine.



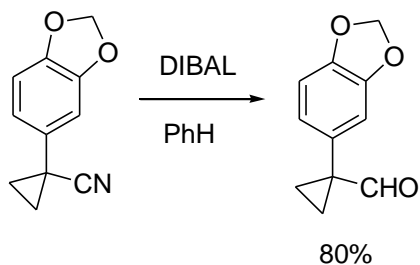


Scheme 14

**Examples:**



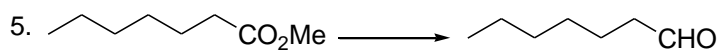
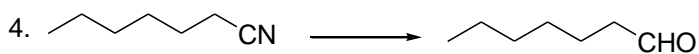
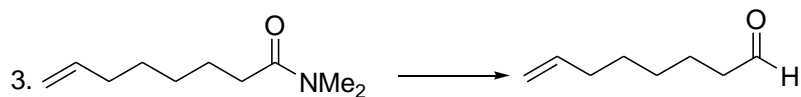
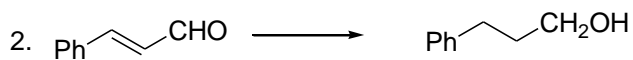
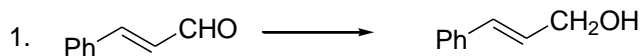
J. L. Vicario, A. Job, M. Wolberg, M. Muller, D. Enders, *Org. Lett.* **2002**, 4, 1023.



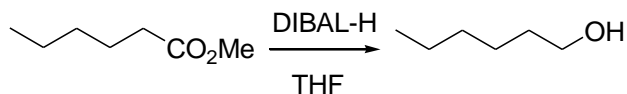
R. V. Stevens, L. E. Dupree, P. L. Lowenstein, *J. Org. Chem.* **1972**, 37, 977.

**Problems**

A. How will you carry out the following reduction reactions using aluminum hydride based reagents?



B. Provide mechanism for the following reaction.



### Text Book

M. B. Smith, *Organic Synthesis*, 2<sup>nd</sup> Ed., McGraw Hill, New York, 2004.

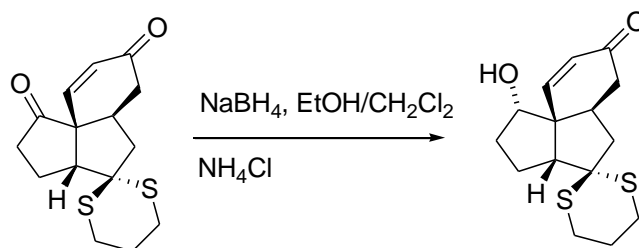
## Lecture 15

### 2.1.5 Borohydrides

Different borohydrides are available depending on the metal cations and ligands such as sodium borohydride, lithium borohydride, zinc borohydride, lithium or potassium trialkylborohydride and sodium cyanoborohydride. All the borohydrides reduce aldehydes and ketones to the corresponding alcohols but due to its counter cations and ligands it shows some special selectivity towards some functional groups.

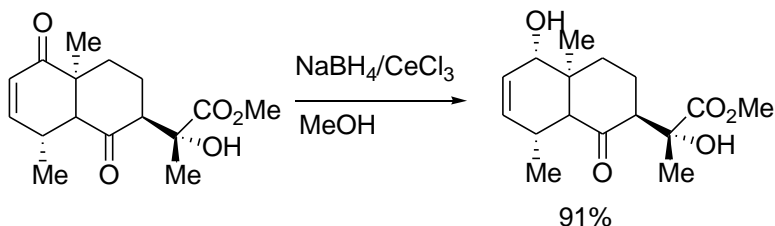
#### 2.1.5.1 Sodium Borohydride (NaBH<sub>4</sub>)

The sodium borohydride is an ideal reducing agent for the reduction of aldehydes and ketones to give the corresponding alcohols (Scheme 1). Unconjugated ketones and aldehydes are rapidly reduced, usually in preference to a conjugated carbonyl group that may be present elsewhere in the molecules. The reactions are performed in polar solvents such as THF, DME, diglyme, hydroxyl solvent and water but the ethanol is the solvent of choice.



Scheme 1

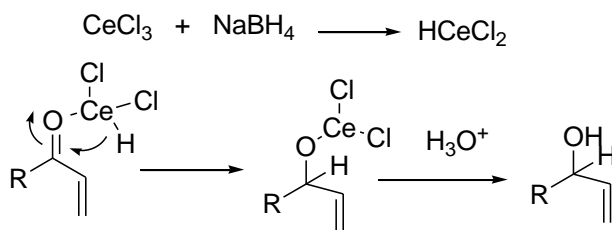
In contrast, in the presence of  $\text{CeCl}_3$ , conjugated ketone is reduced much faster compared to the normal ketone (Scheme 2). The combination of  $\text{NaBH}_4$  and  $\text{CeCl}_3$  is called **Luche reagent** and the reaction is known as **Luche reduction**.



Scheme 2

### Proposed Mechanism

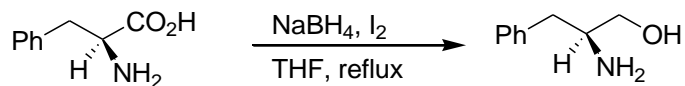
The cerium reagent coordinates to the carbonyl, making only a 1,2-addition possible (Scheme 3).



Scheme 3

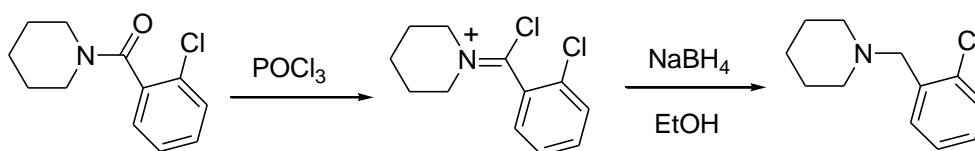
The esters react slowly and the carboxylic acids in normal condition do not react but are reduced to alcohol in presence of catalytic amount of iodine in reflux condition in THF (Scheme 4). This method provides effective route for the

conversions of amino acids to amino alcohols, which serve as ligands for asymmetric catalysis.



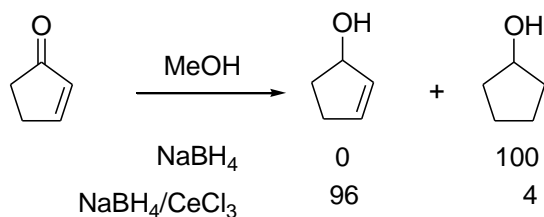
Scheme 4

Amides are not reduced directly by NaBH<sub>4</sub>, but if they are first converted to an iminium salts that readily proceed the reduction to give an amine (Scheme 5).

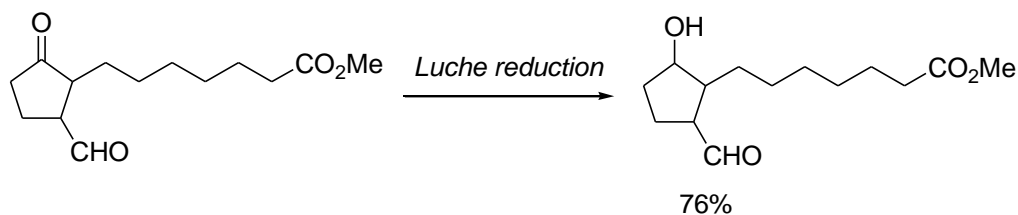


Scheme 5

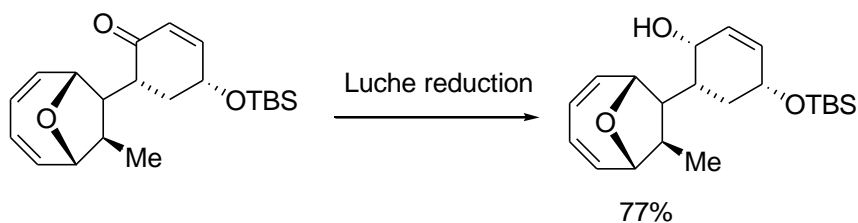
### Examples:



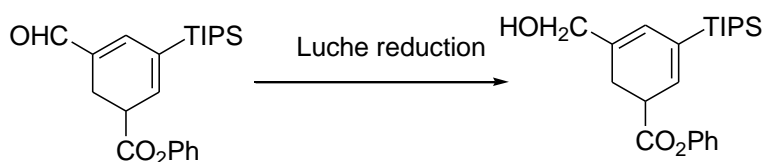
J. L. Luche, *J. Am. Chem. Soc.* **1978**, *100*, 2226.



A. L. Gemal, J. L. Luche, *J. Org. Chem.* **1979**, *44*, 4187.



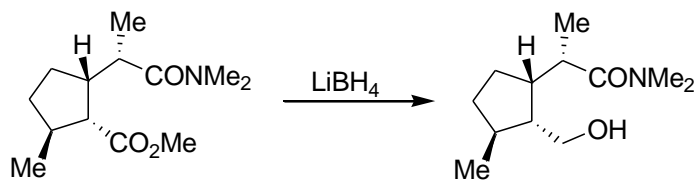
K. Takao, G. Watanabe, H. Yasuki, K. Tadno, *Org. Lett.* **2002**, 4, 2941.



D. L. Comins, A. L. William, *Org. Lett.* **2001**, 3, 3217.

### 2.1.5.2 Lithium Borohydride (LiBH<sub>4</sub>)

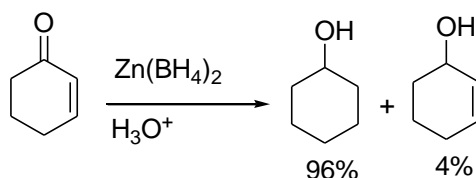
Lithium borohydride is prepared by reaction of NaBH<sub>4</sub> with lithium bromide. It is more powerful reducing agent than NaBH<sub>4</sub>, reducing not only aldehydes, ketones, but also epoxides, esters and lactones (Scheme 6). This is due to the fact that the Li<sup>+</sup> cation is stronger Lewis acid than Na<sup>+</sup> cation. Therefore, Li<sup>+</sup> ion can co-ordinate with carbonyl compound which increases the electrophilicity of carbonyl carbon and facilitates the hydride transfer.



Scheme 6

### 2.1.5.3 Zinc Borohydride [Zn(BH<sub>4</sub>)<sub>2</sub>]

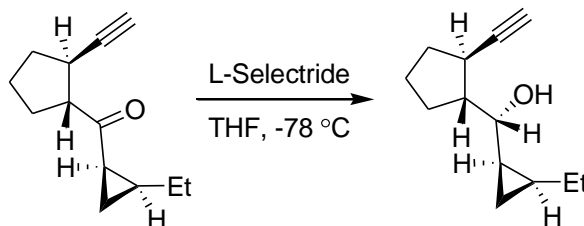
The zinc borohydride is prepared from zinc chloride and  $\text{NaBH}_4$  in ether. It is most useful for the reduction of  $\alpha,\beta$ -unsaturated aldehydes and ketones to give saturated alcohols (Scheme 7).



Scheme 7

#### 2.1.5.4 Lithium or Potassium Trialkylborohydride

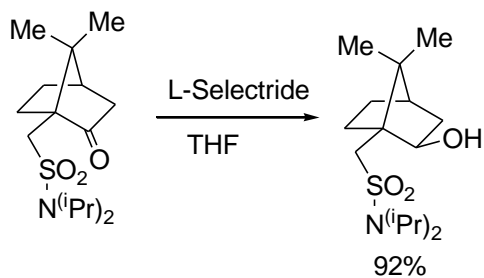
The presence of three alkyl groups in boron atom makes the hydride strongly nucleophile and hence it is a strong reducing agent compared to other borohydrides, and it can reduce the aldehydes and ketones even at  $-78\text{ }^\circ\text{C}$  temperature. The commonly used trialkylborohydrides are lithium triethylborohydride,  $\text{Li}(\text{Et}_3\text{BH})$ , and lithium and potassium tri-*sec*-butylborohydride (L- and K-Selectrides). The bulky L- and K-selectrides can reduce carbonyl compound from less hindered side resulting selective products (Scheme 8).



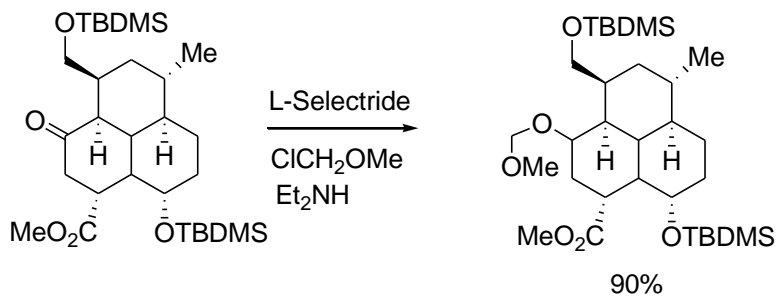
Scheme 8

J. L. Hubbard, *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, Inc., L. A. Pauette, Ed., New York, 1995, **5**, 3172.

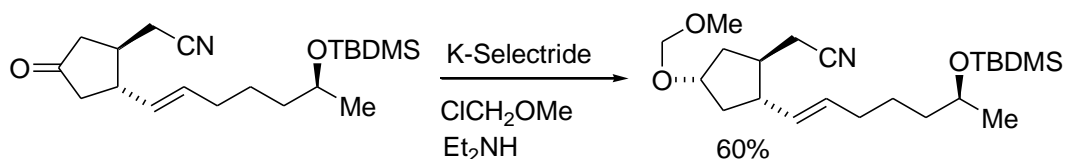
**Examples:**



W. Oppolzer, C. Chapuis, G. Bernardinelli, *Tetrahedron Lett.* **1984**, 25, 5885.

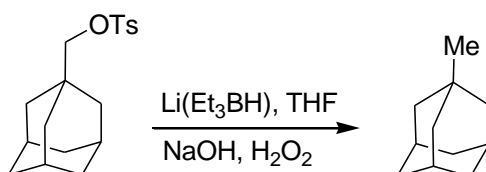


E. Piers, M. A. Romero, *Tetrahedron* **1993**, 49, 5791.



J. Nokami, M. Ohkura, Y. Dan-Oh, Y. Sakamoto, *Tetrahedron Lett.* **1991**, 32, 2400.

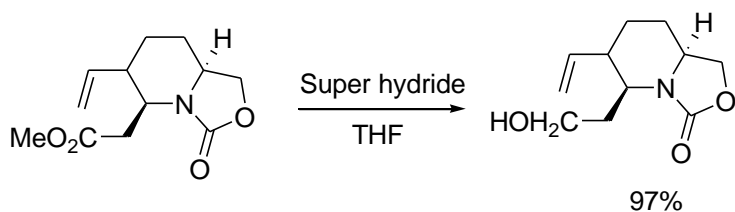
Other than the carbonyl groups, lithium triethylborohydride can reduce primary bromides and tosylates to the corresponding hydrocarbons (Scheme 9). The epoxides are also cleaved to give the alcohols and the hydride is transferred to the less hindered side if epoxides. Lithium triethylborohydride is called super hydride and an extremely powerful source of hydride.



Scheme 9

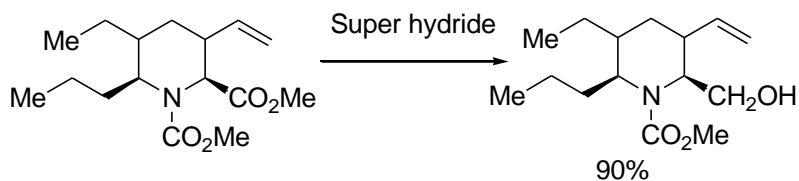
M. Zaidlewicz, H. C. Brown, *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, Inc., L. A. Pauette, Ed., New York, 1995, **5**, 3180.

### Examples:

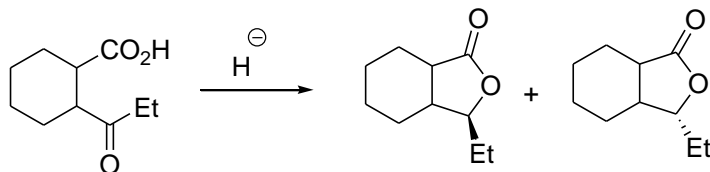


N. Toyooka, M. Okumura, H. Nemoto, *J. Org. Chem.* **2002**, 67, 6078.





N. Toyooka, A. Fukutome, H. Nemoto, J. W. Daly, T. F. Spande, H. M. Garraffo, T. Kaneko, *Org. Lett.* **2002**, *4*, 1715.

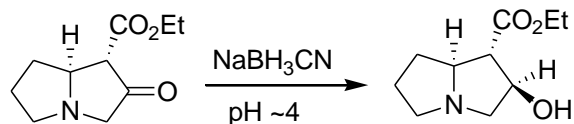


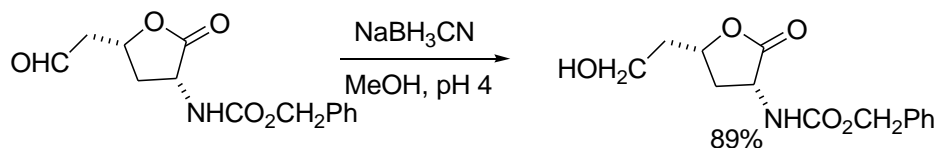
Source	Yield (%)	Ratio	
DIBAL	64	25	75
Super hydride	83	85	15
L-Selectride	65	75	25

N. Pourahmady, E. J. Eisenbraun, *J. Org. Chem.* **1983**, *48*, 3067.

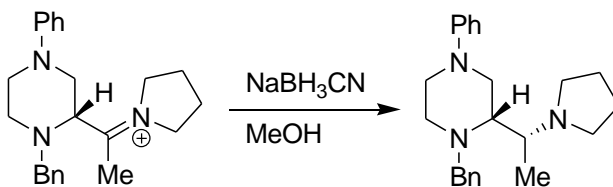
### 2.1.5.5 Sodium Cyanoborohydride (NaBH<sub>3</sub>CN)

NaBH<sub>3</sub>CN is less reactive reducing agent than sodium borohydride due to the presence of electron withdrawing cyano group. Reaction of NaBH<sub>4</sub> with HCN gives NaBH<sub>3</sub>CN, which is soluble in THF, MeOH, H<sub>2</sub>O, HMPA and DMF. NaBH<sub>3</sub>CN cannot reduce the aldehydes or ketones in neutral condition but it reduces the protonated aldehydes and ketones at around pH 3 (Scheme 10). The iminium ion could be reduced to the corresponding amine with almost quantitative yield (Scheme 11).



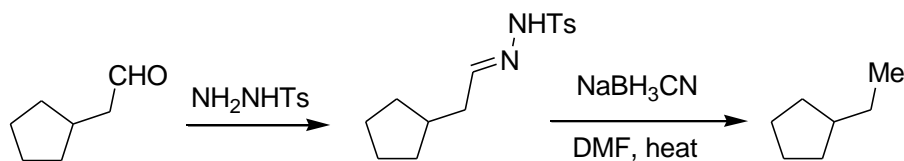


Scheme 10



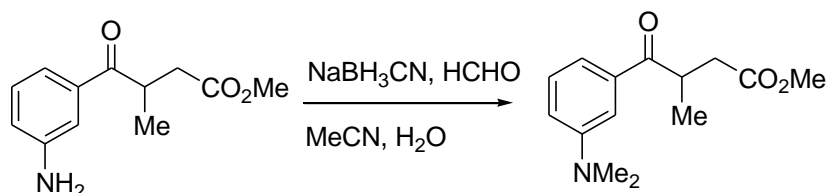
Scheme 11

The other important reaction is the deoxygenation of carbonyl compound via tosyl hydrazone formation (Scheme 12). It can reduce tosyl hydrazone to the corresponding hydrocarbon.



Scheme 12

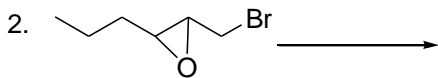
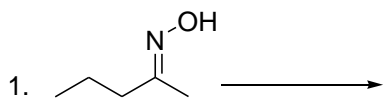
It is also useful for the reductive alkylation of amines. For example, dimethylamino derivative can be prepared from the amine by treatment with HCHO and NaBH<sub>3</sub>CN, even in the presence of functional groups such as the conjugated ketones and the ester. Furthermore, the selectivity for the example shown in Scheme 13 is the major advantage in using NaBH<sub>3</sub>CN rather than other reducing agents.



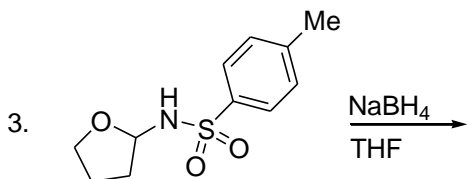
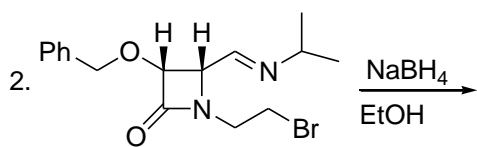
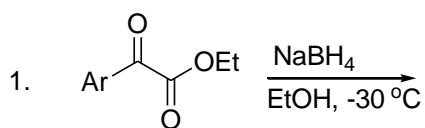
Scheme 31

**Problems:**

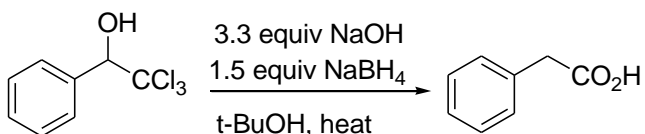
A. Complete the following reactions.



B. What major products would you expect in the following reactions.



C. Provide mechanistic rationale for the following reaction.



**Text Book**

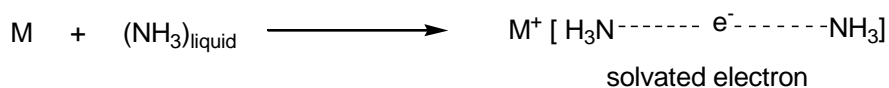
M. B. Smith, *Organic Synthesis*, 2<sup>nd</sup> Ed., McGraw Hill, New York, 2004.

## Lecture 16

### 2.2 Dissolving Metal Reductions (Na-Liq. NH<sub>3</sub>, Li-Liq. NH<sub>3</sub>, etc.)

#### 2.2.1 Introduction

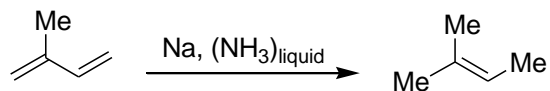
The solution of alkali metal in ammonia (at -33 °C) can generate solvated electrons and metal cations.



These solvated electrons can reduce conjugated double bonds, triple bonds and aromatic compounds. Most of the organic compounds are not soluble in liquid ammonia and, therefore, the compounds are dissolved in THF or Et<sub>2</sub>O and are added to the dissolved metal solution.

#### 2.2.2 Reduction of Conjugated Dienes

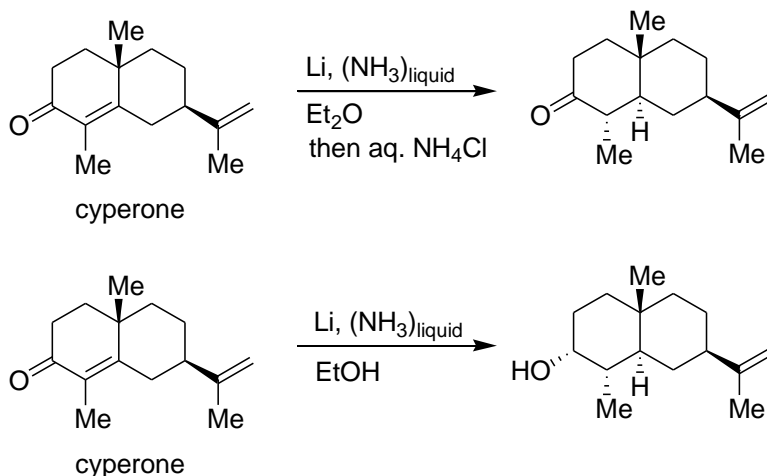
The conjugated dienes are readily reduced to the corresponding 1,4-dihydro compounds with dissolved metal ammonia reagents (Scheme 1).



Scheme 1

#### 2.2.3 Reduction of $\alpha,\beta$ -Unsaturated Ketones

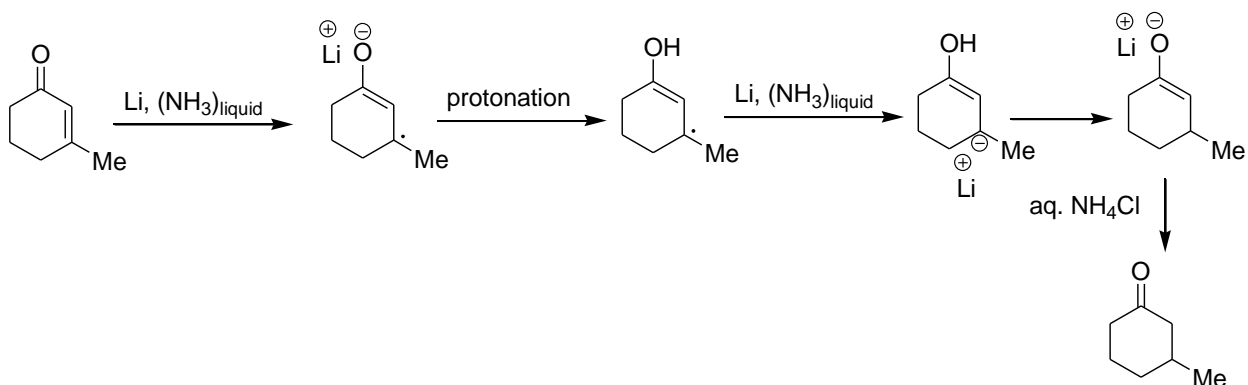
The  $\alpha,\beta$ -unsaturated ketones could be reduced to the corresponding saturated carbonyl compounds or alcohols depending on the reaction conditions with dissolved metal in ammonia (Scheme 2). For examples, the  $\alpha,\beta$ -unsaturated ketone, cyperone, when treated with lithium in ammonia, it gives the corresponding saturated ketone but when treated with lithium in ammonia and ethanol, a good proton source, it gives the corresponding alcohol.



Scheme 2

## Mechanism

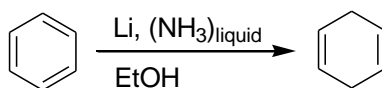
The solvated electron is transferred to the conjugated system to give the radical anion which is protonated by added alcohol or ammonia and then the second electron transfer generates the enolate anion which on protonation during work up gives the desired carbonyl compound (Scheme 3).



## Scheme 3

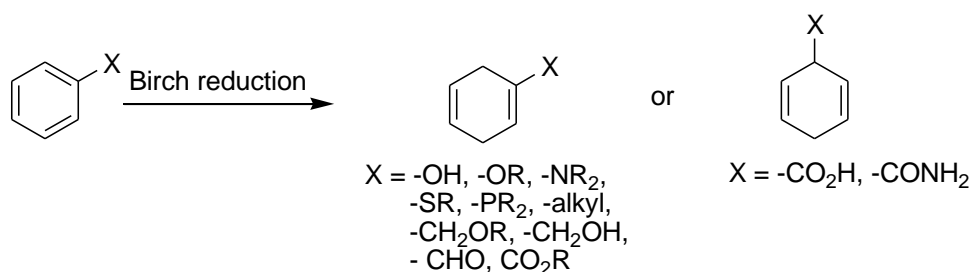
**2.2.4 Reduction of Aromatic Compounds (Birch Reduction)**

The reduction of aromatic compounds to 1,4-cyclohexadiene compounds in presence of alkali metal liquid ammonia and an alcohol is called Birch reduction. A variety of aromatic compounds containing electron donating or electron withdrawing groups could be readily converted to the corresponding 1,4-cyclohexadiene derivatives (Scheme 4).



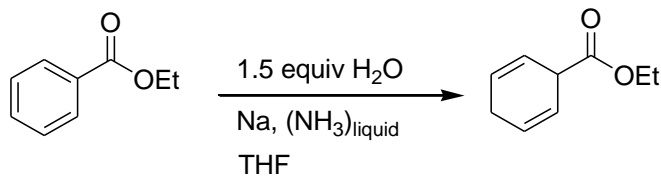
Scheme 4

The regioselectivity towards the products in Birch reduction of substituted aromatic compound depends on the nature of the substituent. For example, the electron donating substituent such as alkyl or alkoxy group remains on the unreduced carbon whereas the electron withdrawing groups such as carboxylic acid or primary amide remains on reduced carbon almost exclusively (Scheme 5).



Scheme 5

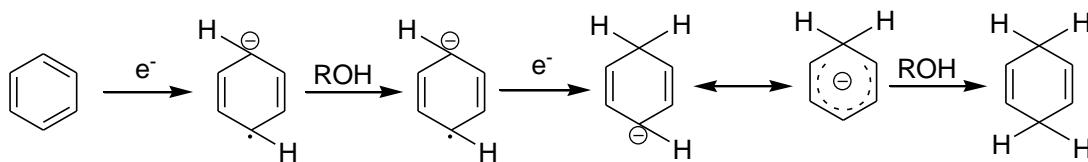
The aldehydes and esters groups are in the electron donation side because these are reduced to the corresponding alcohols in Birch condition before the reduction of aromatic ring (Scheme 6). The addition of one or two equivalent of water or t-BuOH to the  $\text{NH}_3$  before the addition of metal can preserve the ester group in Birch reduction.



Scheme 6

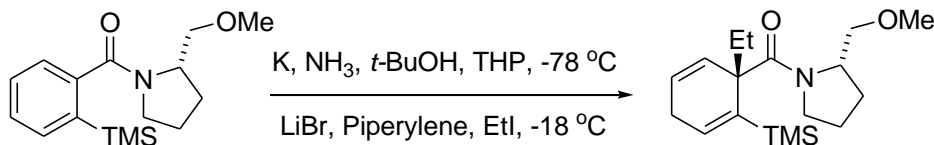
### Mechanism

The solvated electron accepts an electron and generates the radical anion which then takes a proton from the alcohol and forms a radical intermediate (Scheme 7). The radical intermediate then takes another electron and converts to the carbanion which on protonation gives the desired 1,4-cyclohexadiene derivatives. The role of alcohol is to supply the proton because the  $\text{NH}_3$  is not sufficient acidic to supply the proton to all the intermediate anion.

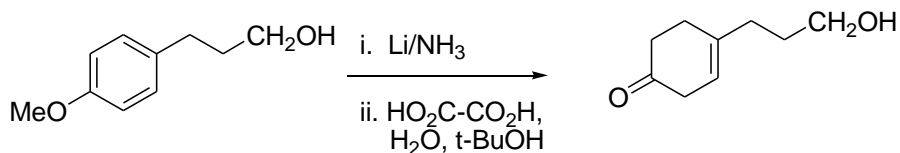


Scheme 7

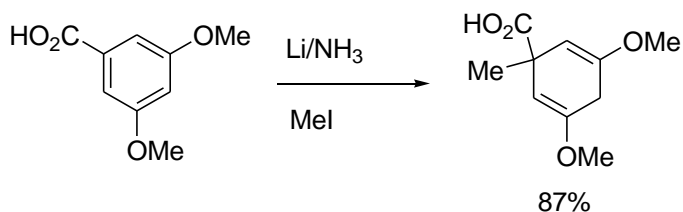
### Examples:



A. G. Schultz, L. Pettus, *J. Org. Chem.* **1997**, 62, 6855.



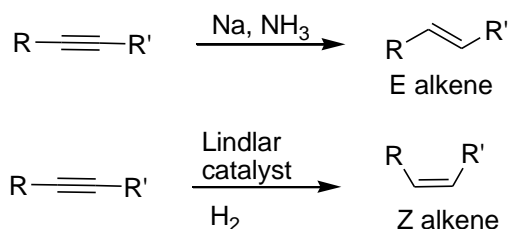
E. J. Corey, N. W. Boaz, *Tetrahedron Lett.* **1985**, 26, 6015.



A. Gopalan, P. Mangus, *J. Am. Chem. Soc.* **1980**, *102*, 1756.

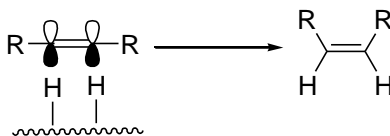
### 2.2.5 Reduction of Alkynes

The reduction of alkynes to *trans* alkenes selectively is carried out by the dissolved metal in ammonia. This reaction specifically gives the *trans* alkenes (E alkenes) whereas the reduction with Lindlar catalyst gives the *cis* alkenes (Z alkenes) (Scheme 8).



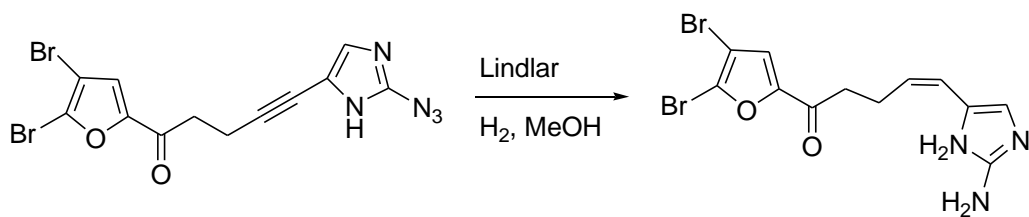
Scheme 8

#### Proposed Mechanism for Lindlar Reduction

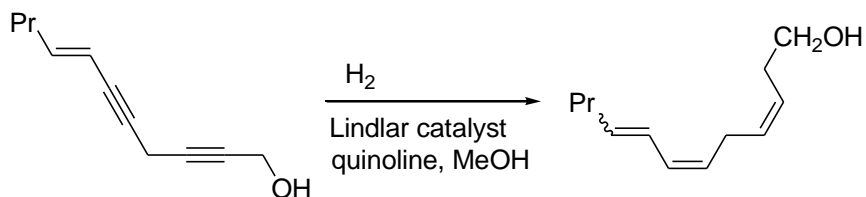


**Examples:**

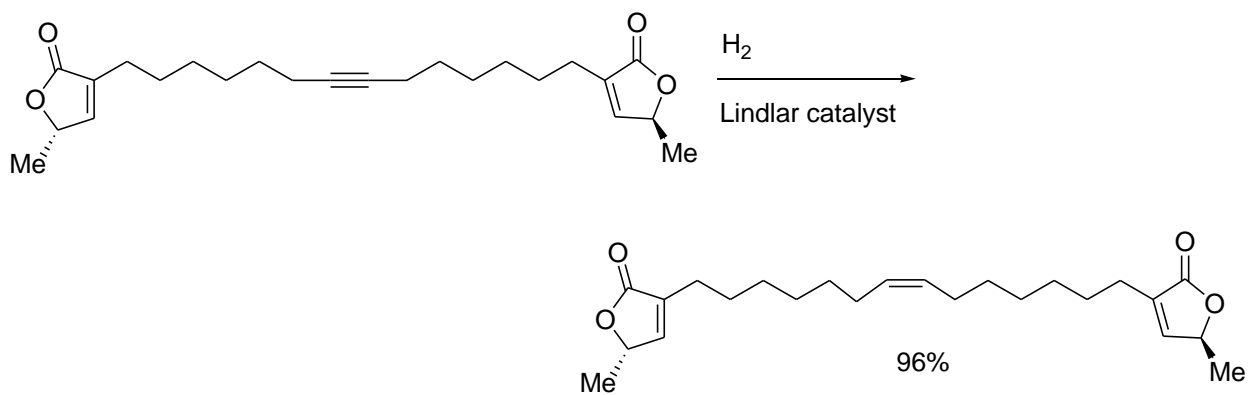




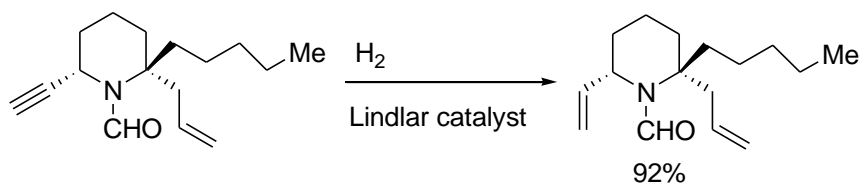
T. Lindel, M. Hochgurtel, *J. Org. Chem.* **2000**, 65, 2806.



A. Tai, F. Matsumura, H. C. Coppel, *J. Org. Chem.* **1969**, 34, 2180.



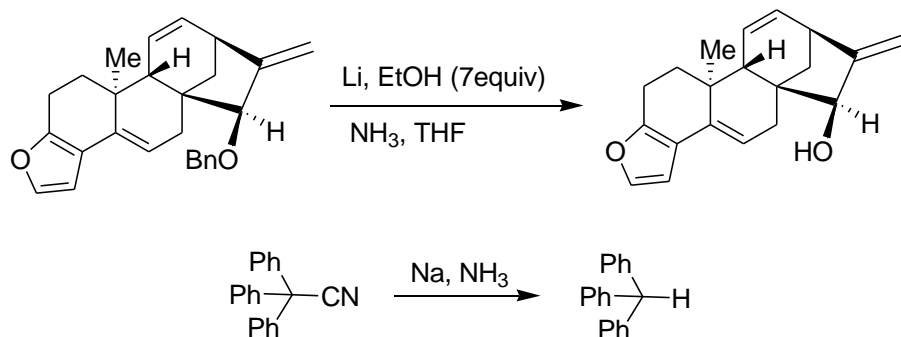
Furstner, T. Dierkes, *Org. Lett.* **2000**, 2, 2463.



T. Itoh, N. Yamazaki, C. Kibayashi, *Org. Lett.* **2002**, 4, 2469.

## 2.2.6 Reductive Deprotection of Benzyl Group

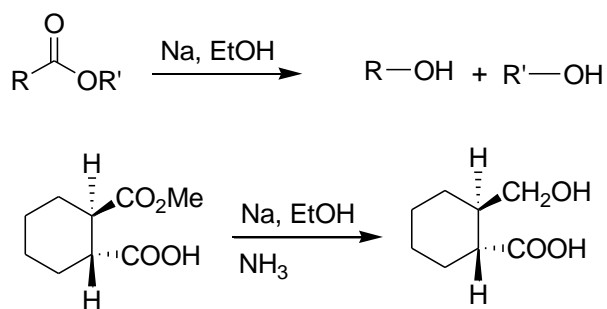
The benzyl group and cyano group (alkyl nitrile) could be deprotected by dissolved metal in ammonia (Scheme 9).



Scheme 9

### 2.2.7 Bouveault-Blanc reduction

The reduction of carboxylic acid esters to the corresponding alcohols in presence of sodium in ethanol is known as Bouveault-Blanc reduction (Scheme 10). This was one of the important methods for the reduction of carboxylic esters before the discovery of lithium aluminum hydride.

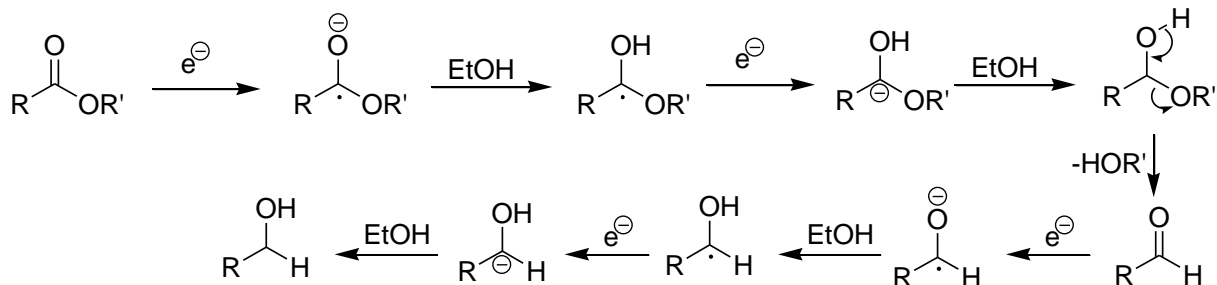


Scheme 10

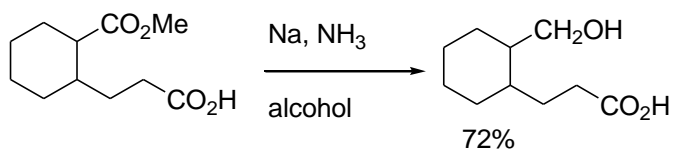
### Proposed Mechanism

The carbonyl group of ester takes an electron and converts to the radical anion which takes a proton from the alcohol and forms the radical intermediate. The

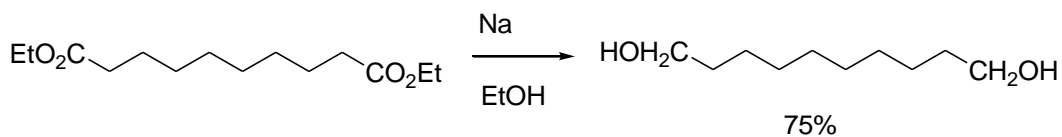
latter takes the second electron and a proton and undergoes elimination of an alcohol to give aldehydes that further proceeds further reduction to give the desired alcohol.



### Examples:



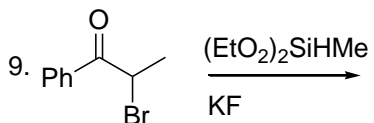
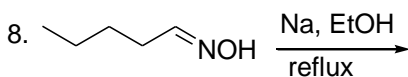
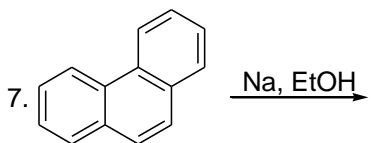
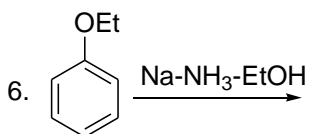
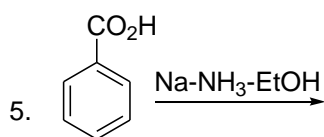
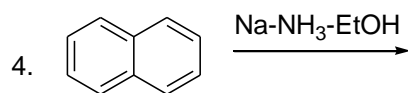
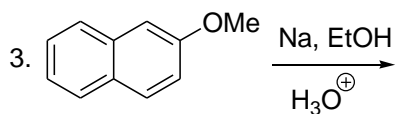
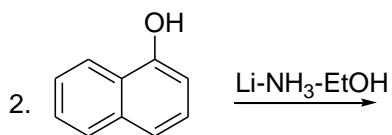
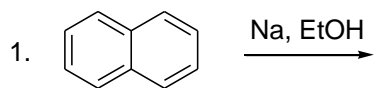
L. A. Paquette, N. A. Nelson, *J. Org. Chem.* 1962, 27, 2272.



R. H. Manske, *Org. Synth.* CV2, 154.

## ***Problems***

Complete the following reactions.



**Text Book**

M. B. Smith, *Organic Synthesis*, 2<sup>nd</sup> Ed., McGraw Hill, New York, 2004.

## Lecture 17

### 2.3 Molecular Hydrogen

#### **2.3.1 Introduction**

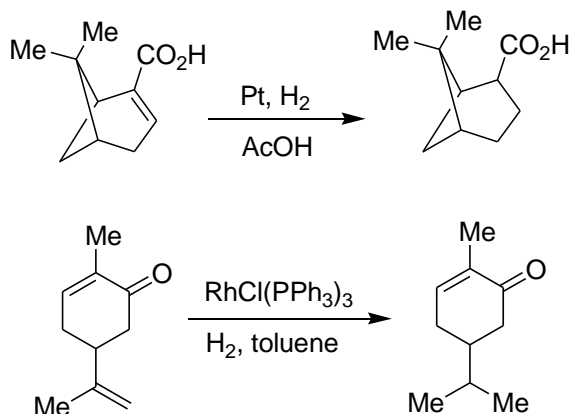
Hydrogen is the most abundant chemical element in the universe with atomic number 1 and symbol H. It has three isotopes hydrogen  $^1\text{H}$ , deuterium  $^2\text{D}$  and tritium  $^3\text{T}$  and the  $^1\text{H}$  is the most abundant (99.98%). The hydrogen  $^1\text{H}$  and deuterium  $^2\text{D}$  are stable isotopes whereas the tritium  $^3\text{T}$  is a radioactive. In organic chemistry, hydrogen is used to reduce a variety of functional groups but the hydrogen gas itself can not reduce any functional groups without a catalyst.

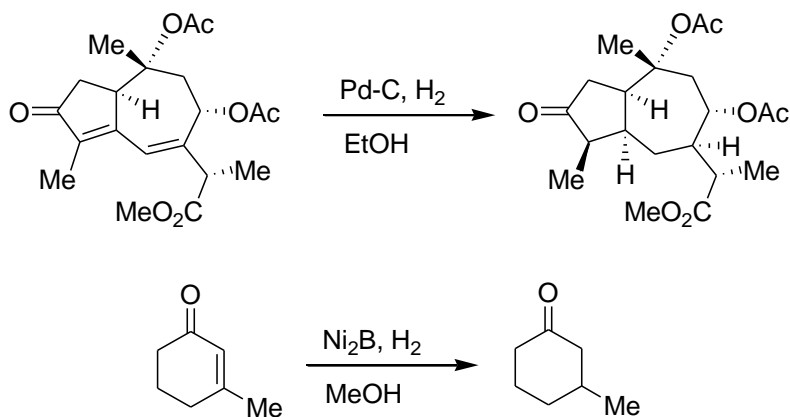
#### **2.3.2 Reduction of Carbon-Carbon Double Bonds**

The reduction of carbon-carbon double bond is academically as well as industrially important transformation (Scheme 1). The order of hydrogenation of substituted double bond is 1,1-di > 1,2-di > 1,2-tri > 1,2-tetra substituted. Different metal catalysts have been used for the purpose. Among them, platinum (Pt), iridium (Ir), ruthenium (Ru), rhodium (Rh), palladium (Pd) and nickel (Ni) catalysts are commonly used.

Ni Catalysts: C. R. Sarko, M. DiMare, *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, Inc., L. A. Paquette, Ed., New York, 1995, 6, 3701; Pd Catalysts: A. O. King, I. Shinka, *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, Inc., L. A. Paquette, Ed., New York, 1995, 6, 3867; E. M. Leahy, *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, Inc., L. A. Paquette, Ed., New York, 1995, 6, 3887; Pt Catalysts: A. O. King, I. Shinka, *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, Inc., L. A. Paquette, Ed., New York, 1995, 6, 4159; 4160; Rh Catalysts: S. Siegel, *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, Inc., L. A. Paquette, Ed., New York, 1995, 6, 4405; Ru Catalysts: S. Siegel, *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, Inc., L. A. Paquette, Ed., New York, 1995, 6, 4410.

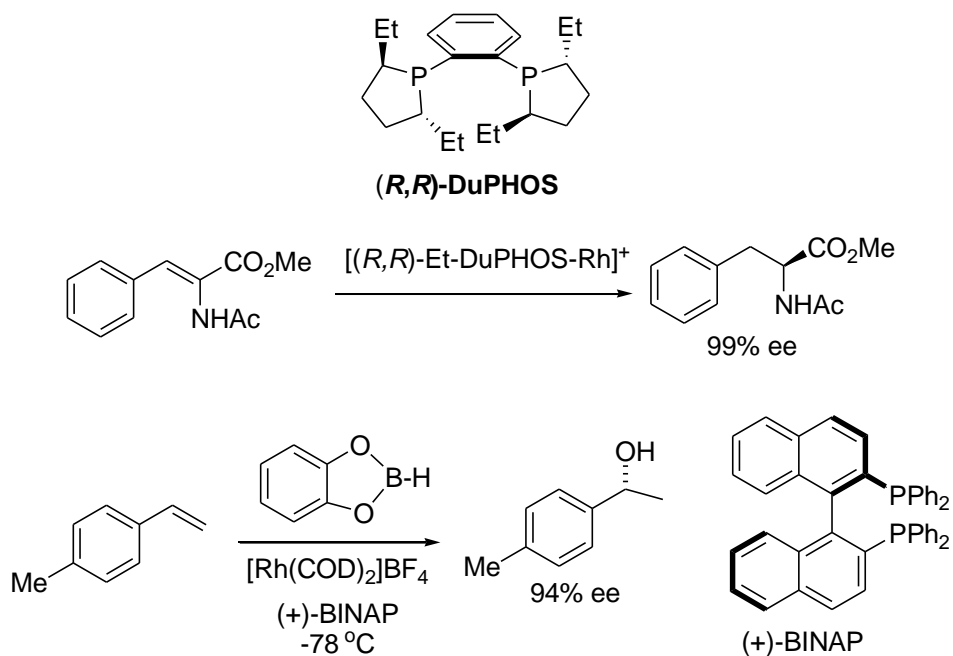
Platinum oxide (PtO<sub>2</sub>) also known as Adam's catalyst is generally used for the platinum catalyzed hydrogenation reaction. Other catalysts such as Pd on charcoal, Wilkinson's catalyst RhCl(PPh<sub>3</sub>)<sub>3</sub>, Crabtree's catalyst [Ir(cod)(PChx<sub>3</sub>)(py)]PF<sub>6</sub>, Ru(OAc)<sub>2</sub>(BINAP), Raney nickel and Nickel boride (Ni<sub>2</sub>B) are used. These reactions are performed in ethyl acetate, alcohols and acetic acid as solvents.





**For mechanism of hydrogenation, see: lecture 33, Principles of Organic Synthesis**

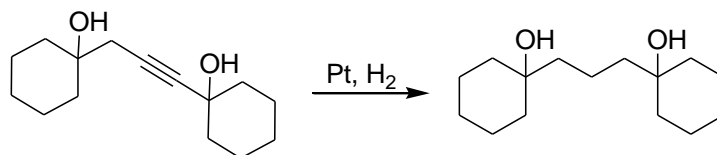
Vast number of chiral catalysts has been developed for asymmetric hydrogenation reactions. Among them, Rh(I) and Ru(II) diphosphine complexes revealed to be the most efficient for hydrogenation of functionalized alkenes (Scheme S).





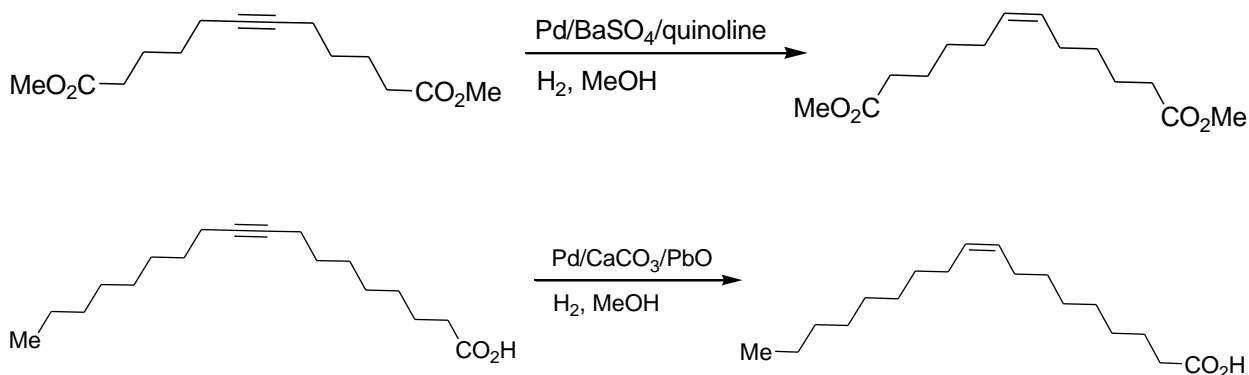
### 2.3.3 Reduction of Carbon-Carbon Triple Bonds

The carbon-carbon triple bonds are reduced to the corresponding carbon-carbon single bonds when treated with Pt, Pd, Raney Ni catalysts and molecular hydrogen (Scheme 3).



Scheme 3

The carbon-carbon triple bonds are selectively reduced to carbon-carbon double bonds in the presence of Lindlar catalyst (Pd/CaCO<sub>3</sub>/PbO) or Rosenmund catalyst (Pd/BaSO<sub>4</sub>/quinoline) and molecular hydrogen (Scheme 4). The hydrogenation of carbon-carbon triple bonds to carbon-carbon double bonds always takes place from same side of the carbon-carbon triple bond providing stereo specifically *cis* alkenes (Z alkenes).

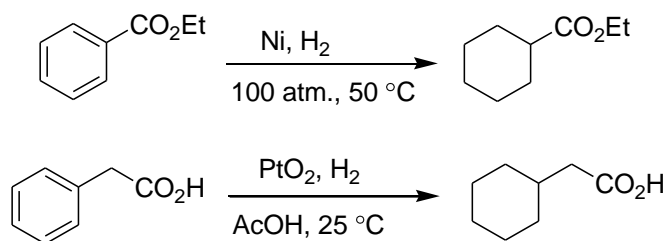


Scheme 4

**For Lindlar Catalyst, see: Lecture 16**

### 2.3.4 Reduction of Aromatic Compounds

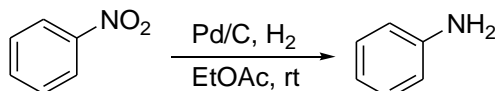
Reduction of aromatic compounds could be performed with molecular hydrogen in the presence of metal catalysts such as Pt, Pd, Rh, Ru and Raney nickel (Scheme 5). The choice of metal catalyst depends on the nature of substrates. For example, the aromatic ring could be selectively reduced in the presence of an ester or acid group using molecular hydrogen with nickel or platinum catalyst.



Scheme 5

### 2.3.5 Reduction of Aromatic Nitro Compounds

The aromatic nitro compounds can be reduced to give the corresponding amines when treated with molecular hydrogen in the presence of Pt, Pd or Ni catalyst (Scheme 6). The reaction is generally performed in methanol, ethanol or ethyl acetate at ambient temperature.

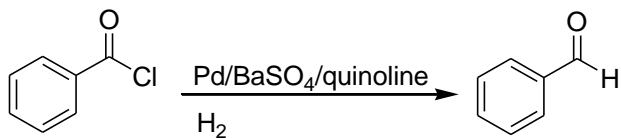


Scheme 6

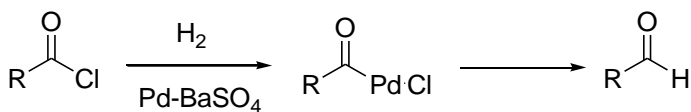
### 2.3.6 Reduction of Acid Chlorides

Acids chlorides undergo reduction to give the corresponding aldehydes in the presence of molecular hydrogen and palladium catalyst (Scheme 7). When Pd/BaSO<sub>4</sub>/quinoline is used as a catalyst along with molecular hydrogen the reaction is called *Rosenmund* reaction.

S. Siegel, *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, Inc., L. A. Paquette, Ed., New York, 1995, **6**, 3861.

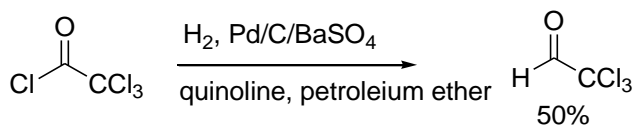


### Proposed Mechanism

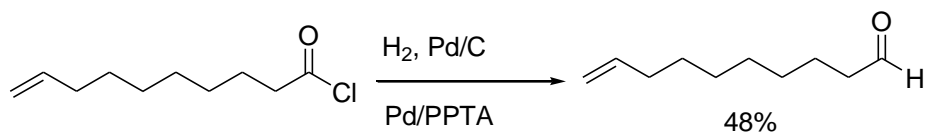


Scheme 7

### Examples:

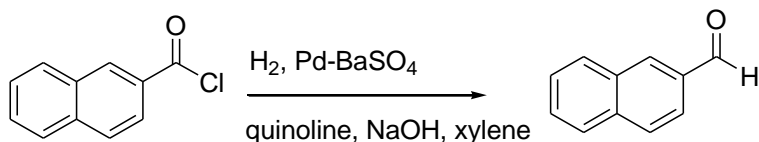


J. W. Sellers, W. E. Bissinger, *J. Am. Soc.* **1954**, *76*, 4486.

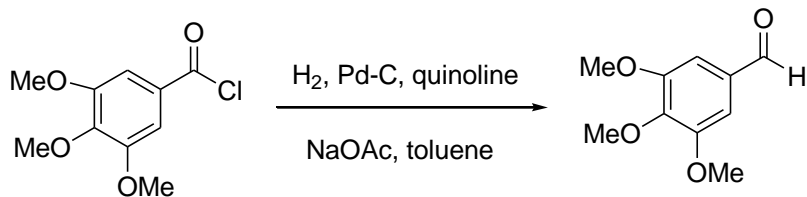


Pd/PPTA = PdCl<sub>2</sub> deposited on poly(p-phenylene terephthalamide)

V. G. Yadav, S. B. Chandalia, *Organic Process Research and Development* **1997**, *1*, 226.



E. B. Hershberg, J. Cason, *Org. Synth.* CV3, 626.

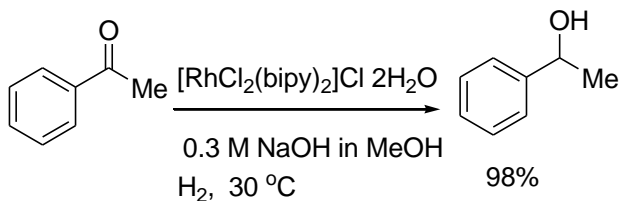


A. I. Rachlin, H. Gurien, D. P. Wagner, *Org. Synth.* **1971**, *51*, 8.

B.

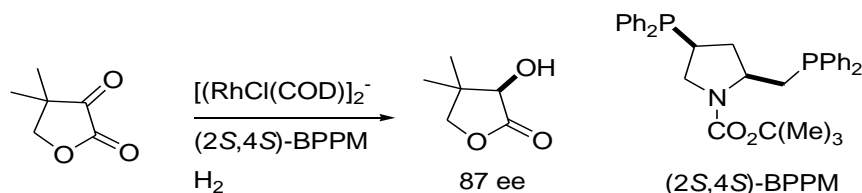
### 2.3.7 Reduction of Aldehydes, Ketones and Esters

Hydrogenation of carbonyls of aldehydes, ketones and esters have been well developed with chiral metal complexes in the presence of molecular hydrogen. For example, rhodium complexes with molecular hydrogen have shown good catalytic activity towards to the reduction of ketonic substrates possessing no functionality adjacent to the carbonyl group (Scheme 8).



Scheme 8

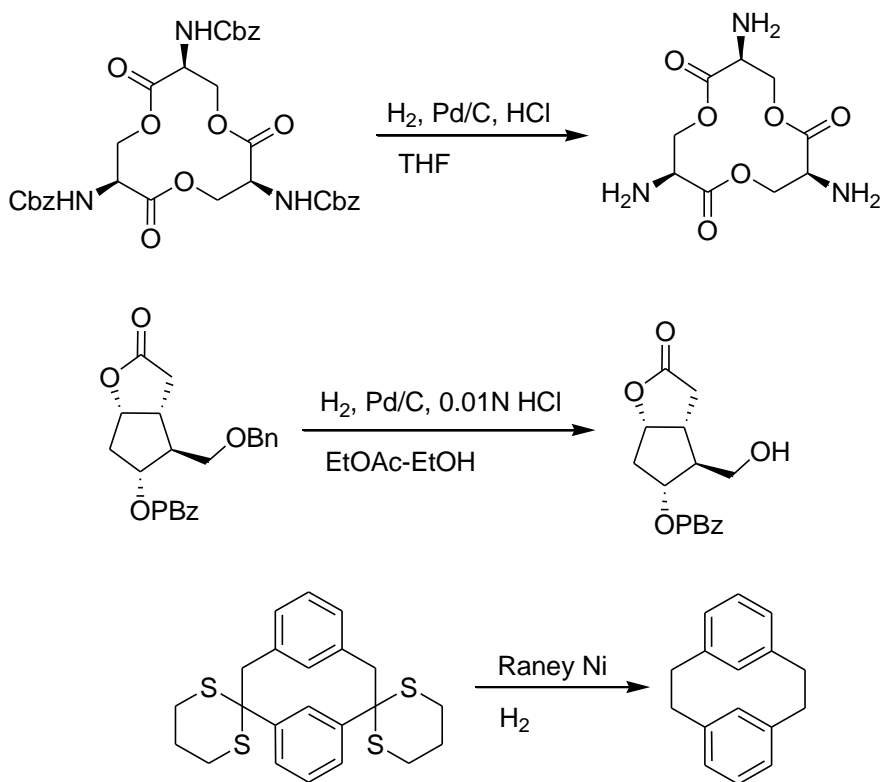
Chiral rhodium phosphine complexes with molecular hydrogen are effective catalysts for the hydrogenation of ketopantolactone with good enantioselectivity (Scheme 9).



Scheme 9

### 2.3.8 Deprotection of Functional Groups

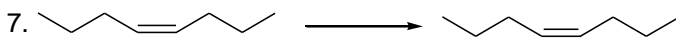
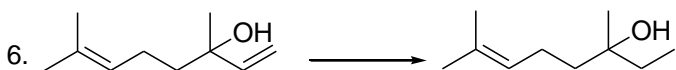
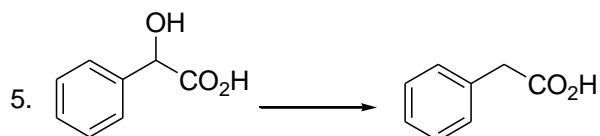
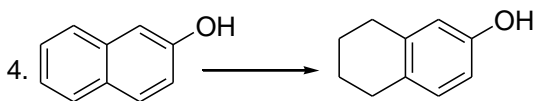
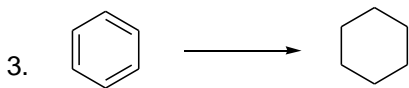
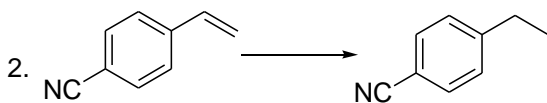
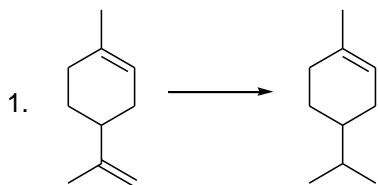
The benzyl ethers, N-Cbz (Cbz = carboxy benzyl), and thioketal groups could be removed by reaction with molecular hydrogen and Pd or nickel catalyst (Scheme 10). The benzyl ethers and N-Cbz are deprotected by Pd-catalyst and molecular hydrogen whereas the thioketal groups are reduced to the corresponding alkanes when treated with Raney nickel and molecular hydrogen.



Scheme 10

## Problems

Provide suitable reagents/catalysts for the following transformations.



## Text Book

M. B. Smith, *Organic Synthesis*, 2<sup>nd</sup> Ed., McGraw Hill, New York, 2004.

## Lecture 18

### 2.4 Miscellaneous Reducing Agents

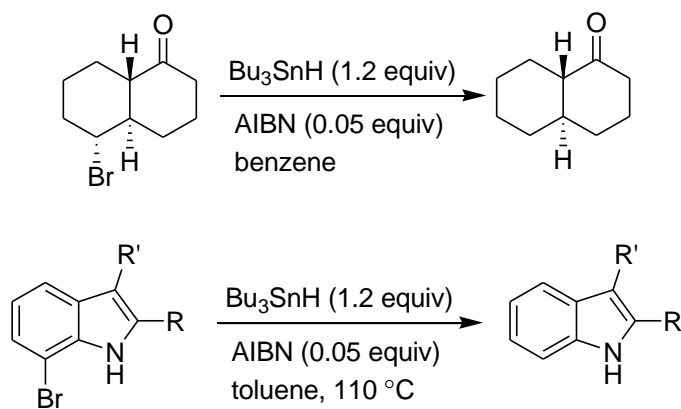
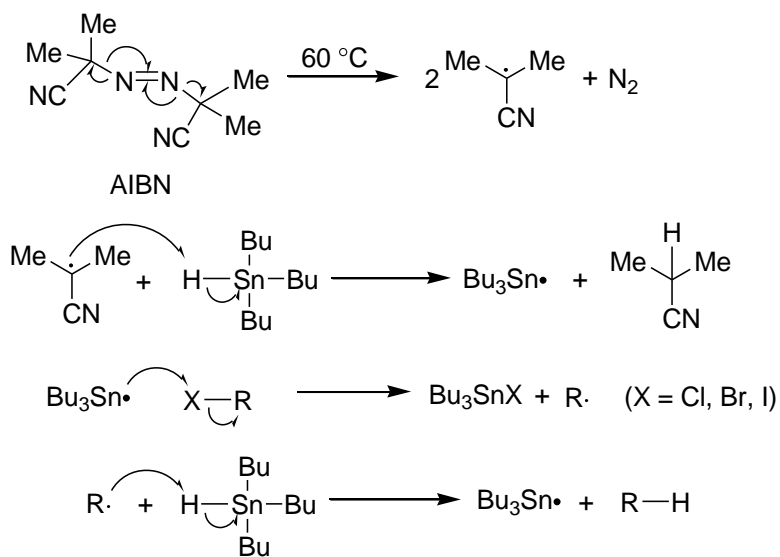
#### 2.4.1 Tributyltin Hydride ( $Bu_3SnH$ )

Tributyltin hydride (TBTH) is an organotin compound can acts as a reducing agent when treated with a radical initiator such as azobisisobutyronitrile (AIBN) or by photo irradiation. It is a colourless liquid and is generally purified by distillation.

T. V. Rajanbabu, *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, Inc., L. A. Paquette, Ed., New York, 1995, 7, 5016.

##### 2.4.1.1 Reductive Dehalogenation

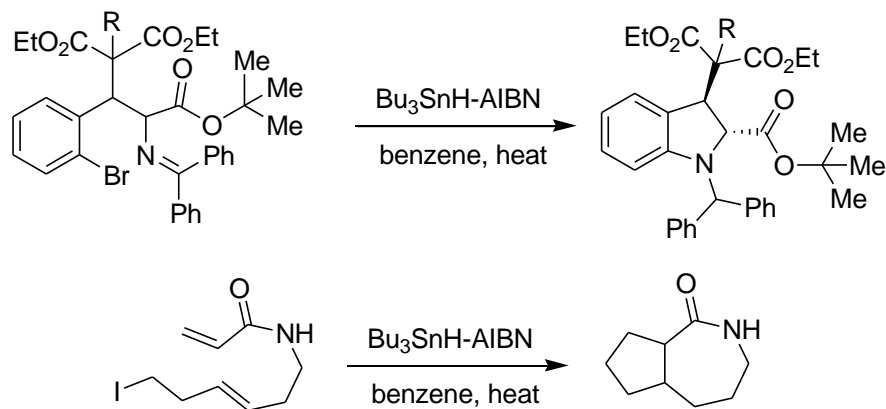
The halogens are removed by TBTH in presence of AIBN in aromatic hydrocarbon solvent such as benzene, toluene. The AIBN acts as a radical initiator and needed in catalytic amount (2-5 mol %). The reactivity order of the halogens is  $I > Br > Cl$  and F does not work under these conditions (Scheme 1-2).



### 2.4.1.2 Radical Cyclization

The radical cyclization of the suitably substituted halides could be performed in presence of TBTH to give the desired cyclized products (Scheme 3). The reaction undergoes via radical pathway.

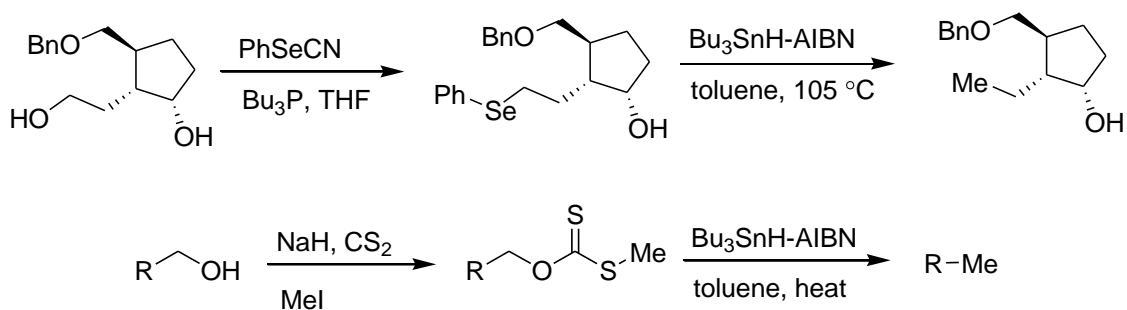




Scheme 3

### 2.4.1.3 Reductive Dehydroxylation via Thiocarbonyl and Selenides Derivatives

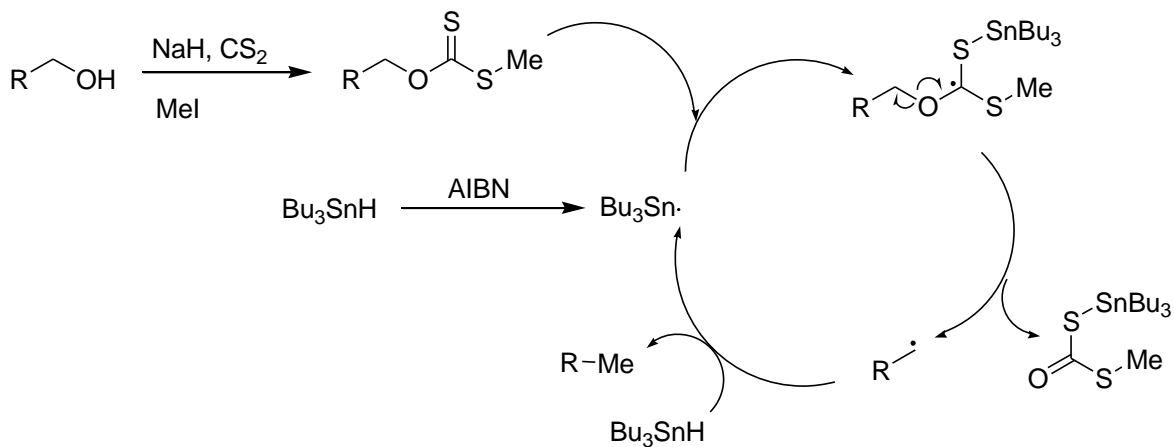
Reductive dehydroxylation *via* thiocarbonyl and selenide derivatives in presence of TBTH is an important method in synthetic organic chemistry. The thioacylation or selenation of alcohols gives thioesters or selenides which is then treated with  $\text{Bu}_3\text{SnH-AIBN}$  reagent to give the desired dehydroxylated product (Scheme 4). The advantage of this method is that it works in such cases where other methods fail.



Scheme 4

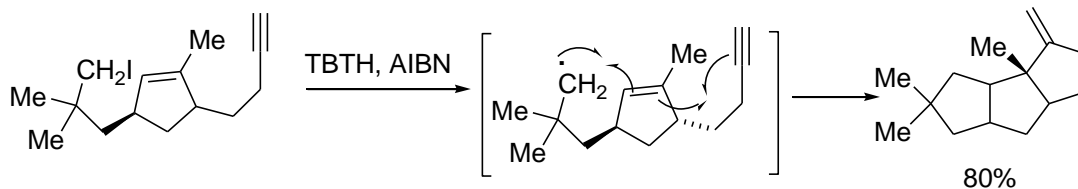
#### Mechanism

The tributyltin radical reacts with the sulfur atom to give a radical intermediate which then cleaves to give the desired radical and reacts with TBTH to regenerate the tributyltin radical and the product (Scheme 5).

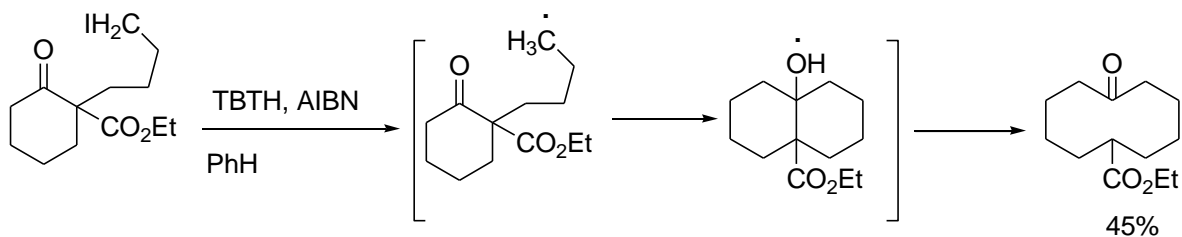


Scheme 5

**Examples:**



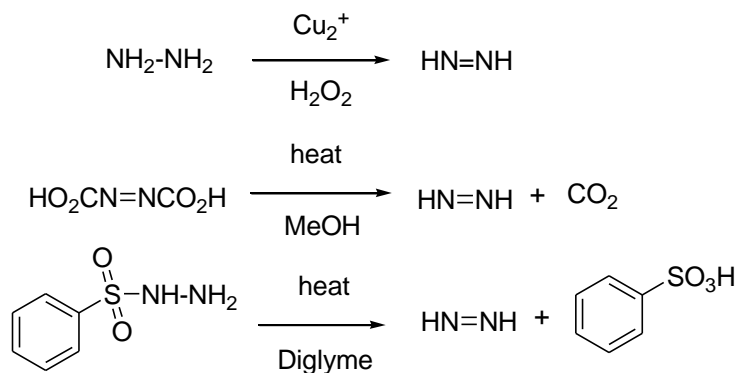
D. P. Curran, D. M. Rakiewicz, *Tetrahedron* **1985**, *41*, 3943.



P. Dowd, S. C. Choi, *J. Am. Chem. Soc.* **1987**, *109*, 6548.

## 2.4.2 Diimide (HN=NH)

Diimide can be prepared *in situ*, by the copper-catalyzed oxidation of hydrazine in the presence of hydrogen peroxide or oxygen as terminal oxidant or the decomposition of azodicarboxylic acid or sulfonylhydrazines (Scheme 6).

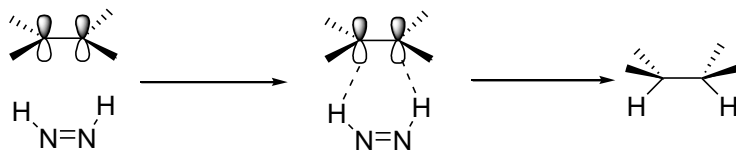


Scheme 6

D. J. Pasto, *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, Inc., L. A. Paquette, Ed., New York, 1995, **3**, 1892.

The reduction using diimide finds unique applications because:

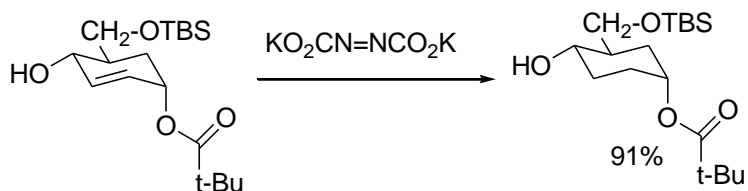
- The reagent is extremely tolerant of other functional groups
- The reduction is highly stereoselective and takes place *cis*-addition, from the less-hindered face.



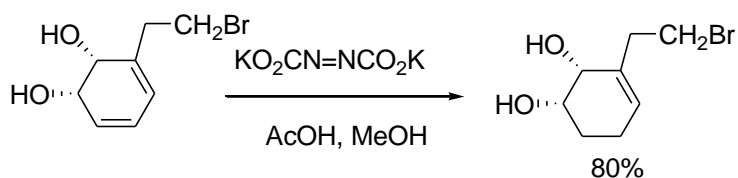
- Reactivity decreases with increasing substitution about the alkene bond.
- Alkynes show greater reactivity compared to alkenes.
- Alkenes with electron withdrawing groups show greater reactivity compared to those with electron donating groups.

- Use of deuterium or tritium-labeled diimide gives a method of *cis*-reduction without scrambling of label.

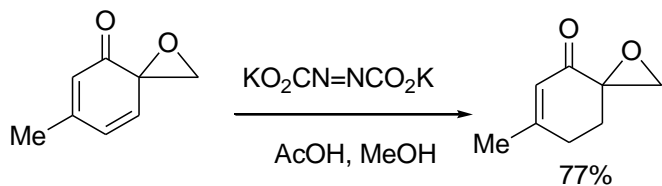
**Examples:**



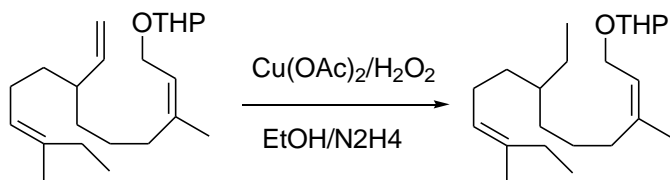
M. H. Haukaas, G. A. O'Doherty, *Org. Lett.* **2002**, 4, 1771.



D. A. Frey, C. Daun, T. Hudlicky, *Org. Lett.* **1999**, 1, 2085.



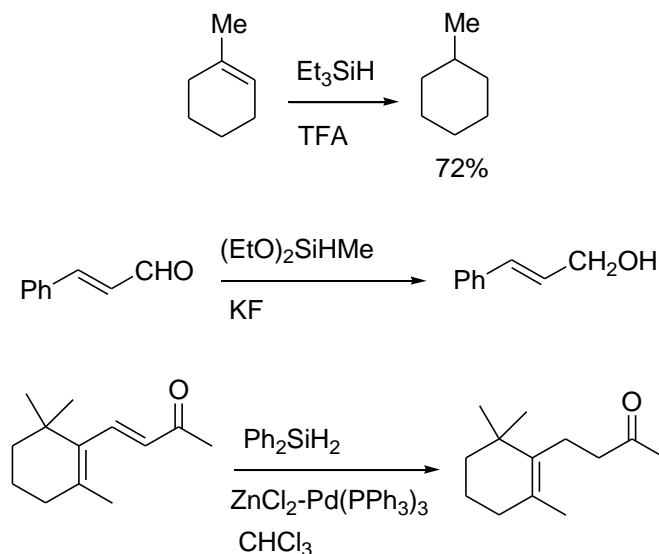
E. J. Corey, J. P. Dittame, *J. Am. Chem. Soc.* **1985**, 107, 256.



E. J. Corey, H. Yamamoto, *J. Am. Chem. Soc.* **1970**, 90, 6636.

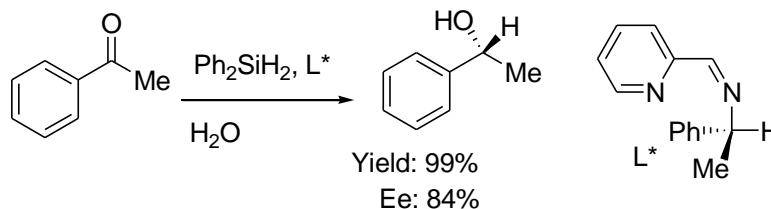
### 2.4.3 Silanes

Silane hydrides can be used for the reduction of carbonyls and alkenes. Addition of transition metal salts such as  $\text{ZnCl}_2$  or copper salts to the silane facilitates the reduction (Scheme 7).



Scheme 7

Asymmetric reduction involving silanes is possible when a chiral additive is used. For an example, acetophenone can be reduced to (*R*)-phenyl ethanol with good enantioselectivity in the presence of chiral ligand (Scheme 8).

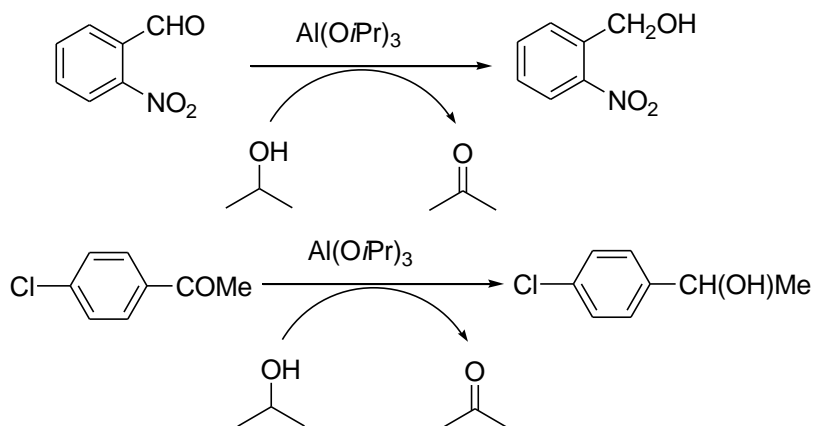


Scheme 8

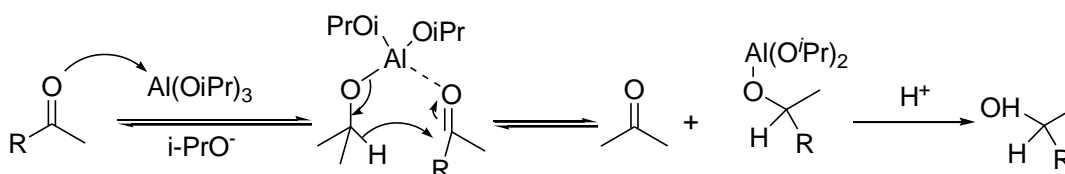
### 2.4.4. Meerwein-Ponndorf-Verley Reduction

The reduction of aldehydes and ketones to the corresponding alcohols with aluminum isopropoxide  $[\text{Al}(\text{O}^i\text{Pr})_3]$  in the presence of 2-propanol (reverse of the

Oppenauer Oxidation) is called Meerwein-Ponndorf-Verley reduction (Scheme 9).

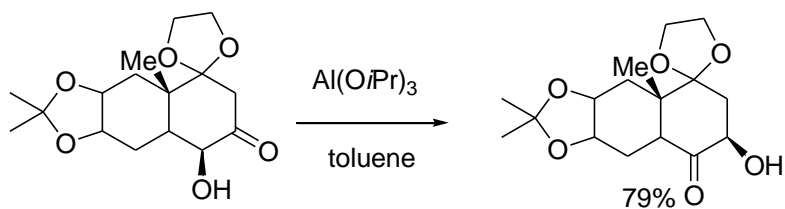


### Mechanism

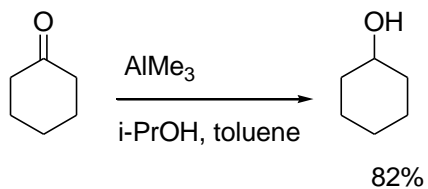


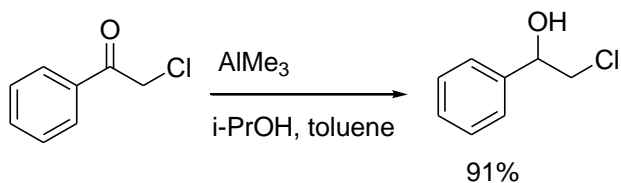
Scheme 9

### Examples:



T. K. Shing, C. M. Lee, H. Y. Lo, *Tetrahedron Lett.* **2001**, 42, 8361.

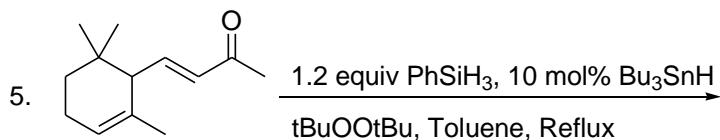
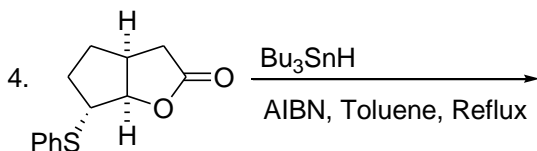
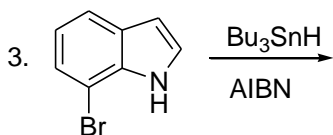
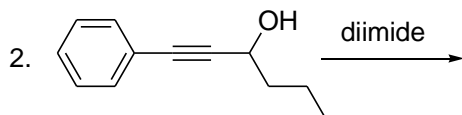
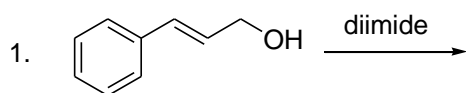




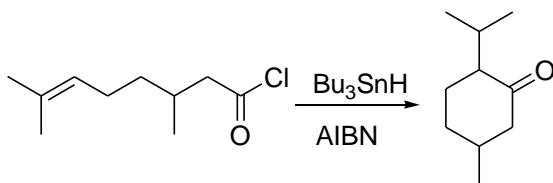
E. J. Campbell, H. Zhou, S. T. Nguyen, *Org. Lett.* **2001**, 3, 2391.

## Problems

A. Predict the major products for the following reactions.



B. Provide mechanistic rationale for the following reaction.



## **Text Book**

M. B. Smith, *Organic Synthesis*, 2<sup>nd</sup> Ed., McGraw Hill, New York, 2004.

## **Lecture 19**

### **2.5 Photoreductions and Bio-reductions**

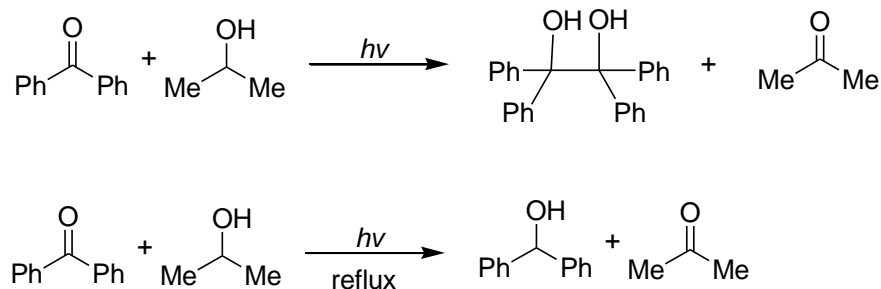
#### **2.5.1 Photoreduction**

The electron transfer to a certain functional groups can be induced by irradiation with light source. Reductions are possible when a proton source along with a sensitizer and a source of irradiation are employed. The reduction proceeds *via* photo-induced electron transfer (PET).

##### **2.5.1.1 Reduction of Carbonyl Compound**

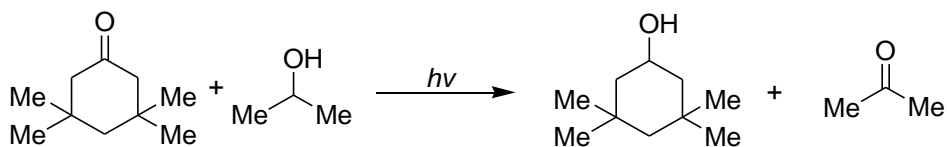
The aliphatic and aromatic carbonyl compounds are reduced to a variety of products depending on the reduction conditions. For examples, the aromatic ketones, benzophenone or acetophenone, in isopropanol or methanol undergo photoreduction to give dimeric pinacol in good yield (Scheme 1). In contrast, benzophenone in isopropanol under reflux condition undergoes photoreduction to give the secondary alcohol  $\text{Ph}_2\text{CHOH}$ .



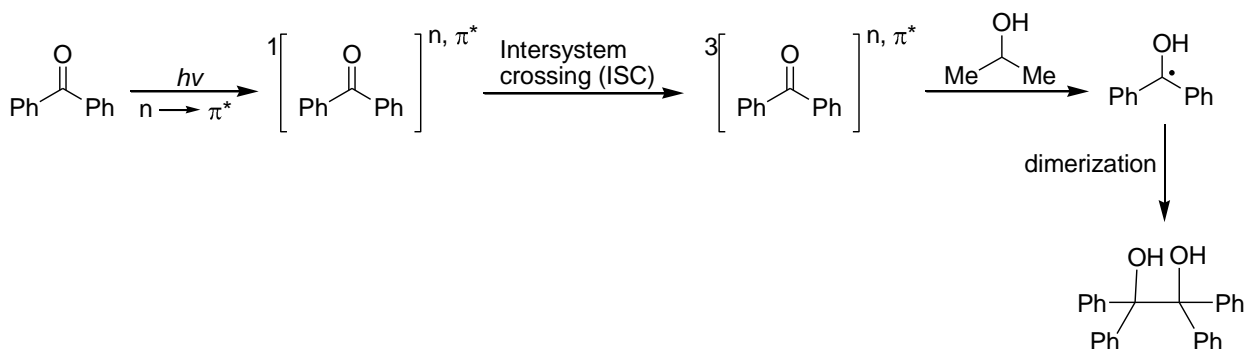


Scheme 1

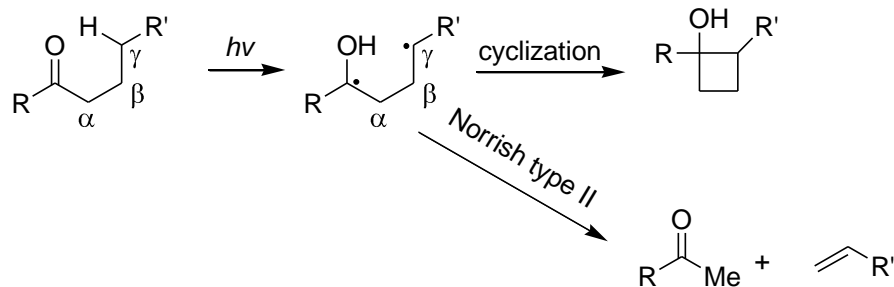
Aliphatic compounds undergo reduction of carbonyl compound to give the corresponding alcohols (Scheme 2). The reaction proceeds *via* excitation of benzophenone from ground state to excited  $[n,\pi^*]$  singlet state (Scheme 3). The excited  $[n,\pi^*]$  singlet state then undergoes intersystem-crossing to give  $[n,\pi^*]$  triplet state which abstracts proton from the alcohol to generate diphenylhydroxymethyl radical which then dimerises to give the benzopinacol.



Scheme 2

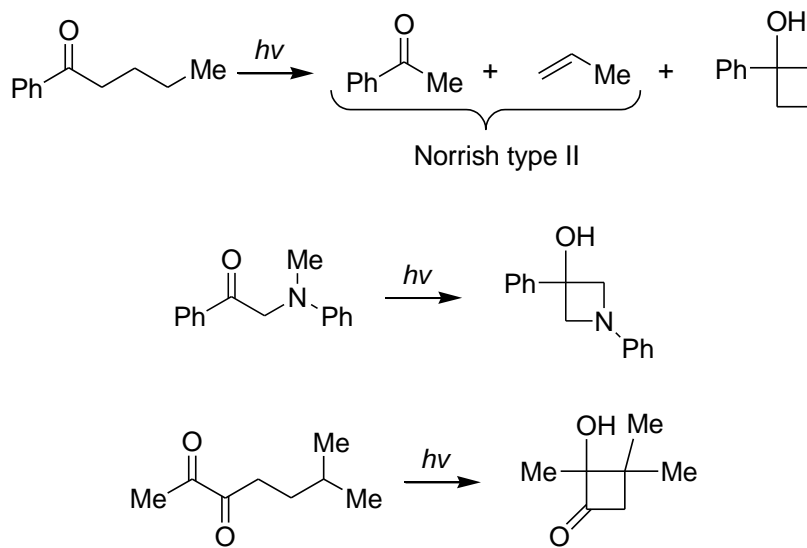


Scheme 3

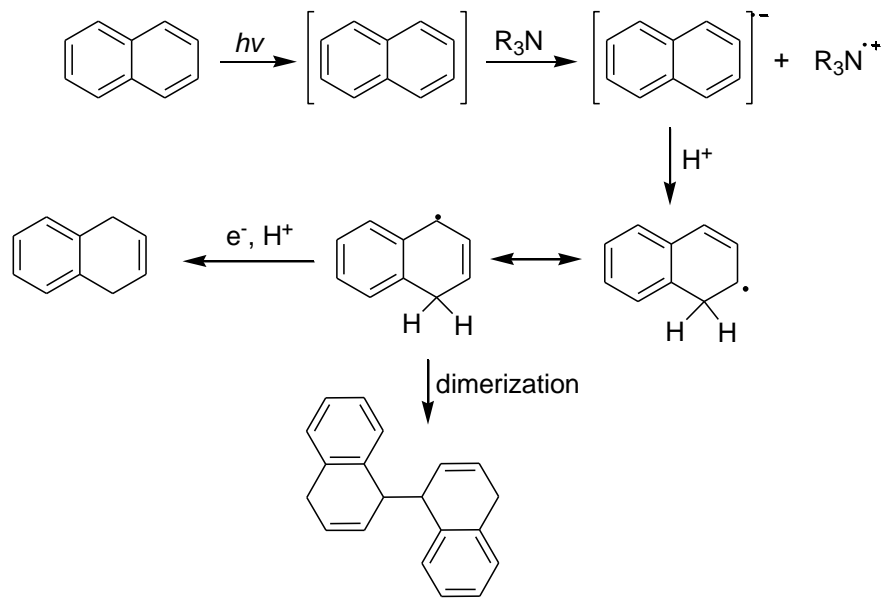


Scheme 4

The intramolecular cyclization of carbonyl compounds *via*  $\gamma$ -hydrogen abstraction is also possible to give four membered cyclic alcohols (Scheme 4). This reaction is facilitated by the presence of a heteroatom at the  $\beta$ -position of the alkyl chain. The side reaction which can give degradation products is known as Norrish type II reaction (Scheme 5).



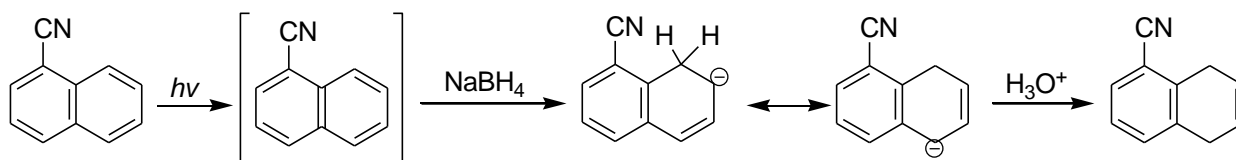
Scheme 5



### 2.5.1.2 Reduction of Aromatic Compounds

The aromatic hydrocarbons such as benzene, biphenyl, naphthalene and anthracene in their excited states react with amine to give reduced or aminated products. The reaction involves the transfer of lone pair electron of amine to the excited state singly occupied molecular orbital of aromatic compound (Scheme 6).

The excited aromatic compounds could also be reduced by hydride source such as sodium borohydride, lithium aluminum hydride or metal hydride (Scheme 7). The reaction may undergo *via* the following sequences.

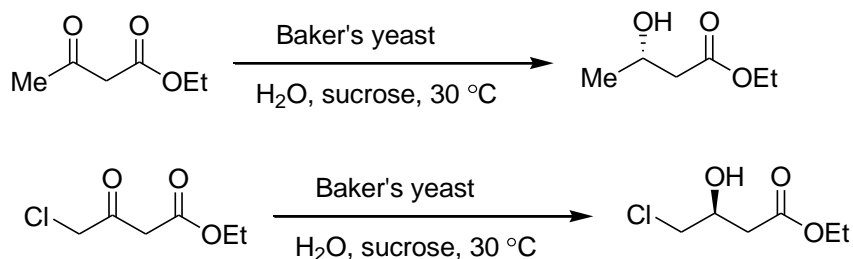


## 2.5.2 Bio-reduction

The bio-reduction is one of the important procedures in biological system. There are mainly two different pathways through which most of the biological reductions takes place, enzymatic and non-enzymatic reduction. The advantages of these protocols are, it is very much substrate specific, that they work under ambient condition in aqueous medium.

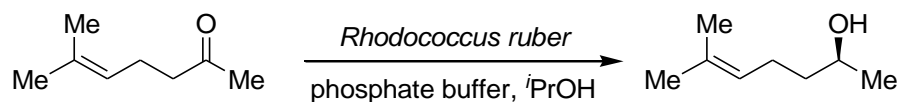
### 2.5.2.1 Reduction of Carbonyl Group

The reductions of carbonyl groups have been studied most by using different bio-reductants such as Baker's yeast or with reductase enzyme. For example, the reductions of  $\beta$ -ketoesters have been studied extensively (Scheme 8). The ethyl acetoacetate could be reduced to give the corresponding 3-hydroxybutyrate. On the other hand, 4-chloroacetoacetate when reduced with Baker's yeast, gives the corresponding (S)-alcohol with opposite selectivity. Therefore, the stereochemistry of the reduced product depends on the shape and size of the prochiral starting substrates. It also says that the *Baker's yeast* has at least two different active reducing sites.



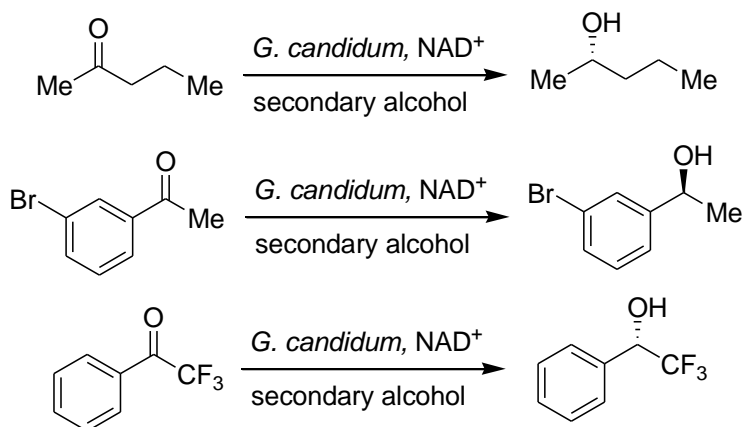
Scheme 8

The reduction with Baker's yeast is very much substrate dependant and it works well with  $\beta$ -keto substrates but it is less selective with other keto-functional substrates. Therefore, it promoted further study on this subject for better results. For example, a better result has been achieved with lyophilized whole cells of *Rhodococcus ruber* DSM 44541, for asymmetric reduction of aryl ketones and other unfunctional ketones with good enantiomeric excess (Scheme 9).



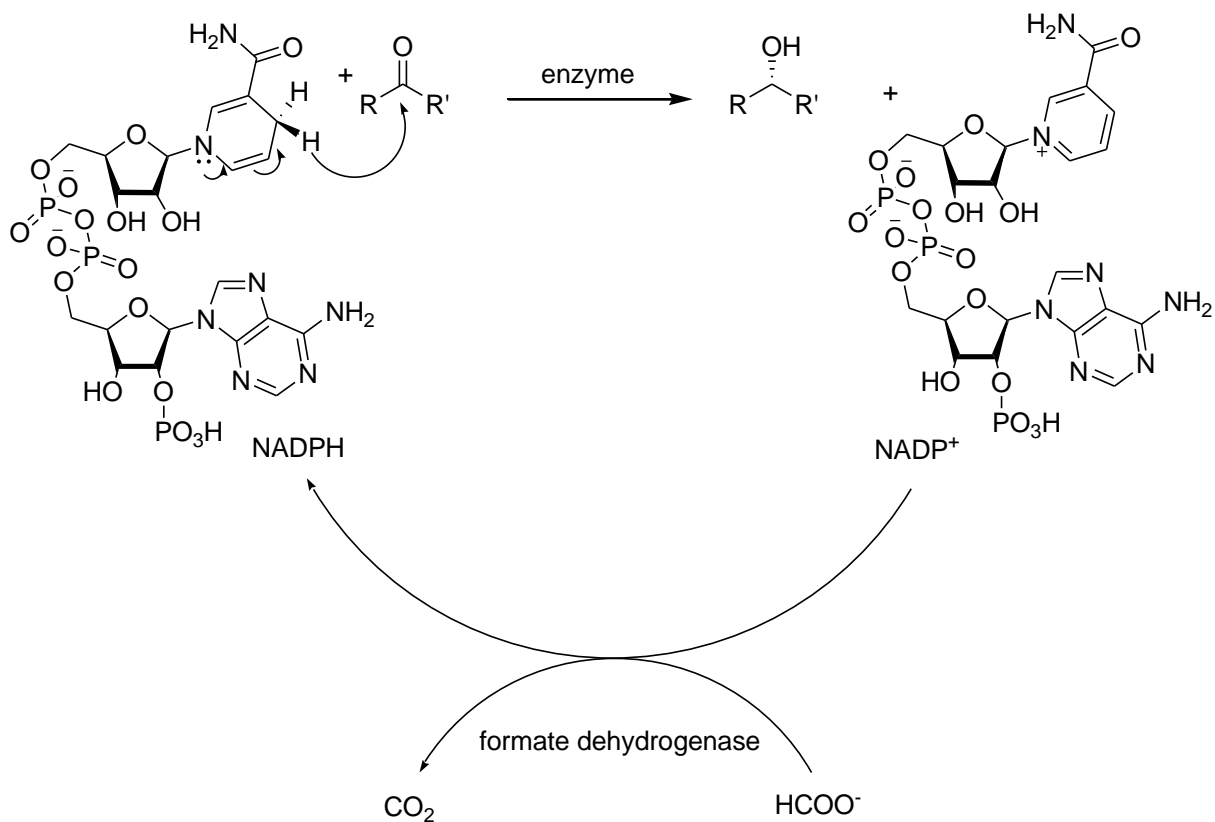
Scheme 9

Another important microorganism is *Geotrichum candidum* which can perform the asymmetric reduction of aliphatic, aromatic and trifluoromethane substituted ketones with very high enantioselectivity (Scheme 10).



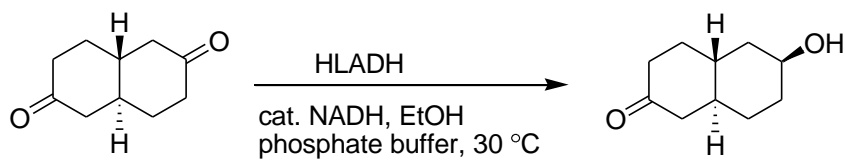
Scheme 10

The reduction with isolated enzymes have also been studied and the advantage of this protocol is that it reduces the effect of other interfering enzymes which are present in a cell but the weak point is that the stability of isolated enzymes and use of expensive specific co-factor such as NADP (Nicotinamide adenine dinucleotide phosphate) (Scheme 11).



Scheme 11

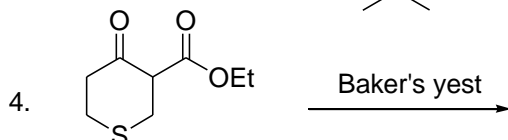
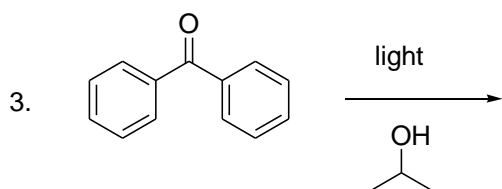
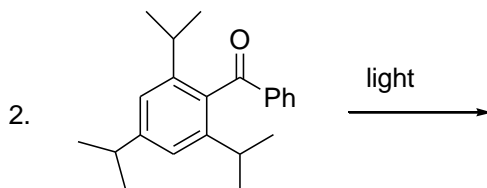
For an example, the following symmetrical diketone could be reduced by enzyme horse liver alcohol dehydrogenase (HLADH) to give the corresponding chiral alcohol with high enantioselectivity (Scheme 12).



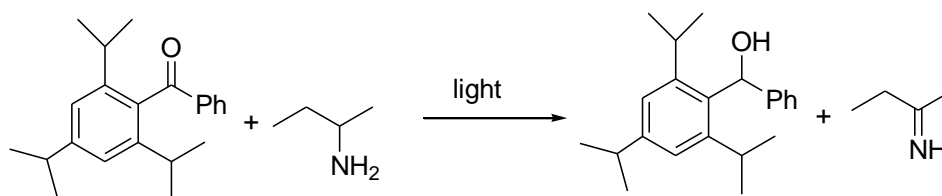
Scheme 12

**Problems:**

A What products would you expect from the following reactions?



B. Rationalize the following photoreduction process.



**Text Book**

M. B. Smith, *Organic Synthesis*, 2<sup>nd</sup> Ed., McGraw Hill, New York, 2004.