

2302774 – Advance Organic Synthesis

Lecture 3

Oxidation and Reduction

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Recommended Textbook:

Chapter 24, 34 and 45 in *Organic Chemistry*, 1st Edition, J. Clayden, N. Greeves, S. Warren, **2001**, Oxford University Press

Reduction of carbonyl groups

Reduction of aldehydes and ketones to alcohols

Sodium hydride, NaH, is so small and has such a high charge density that it only ever reacts as a base (1s orbital is **too small** to interact with LUMO (π^*) of the C=O)

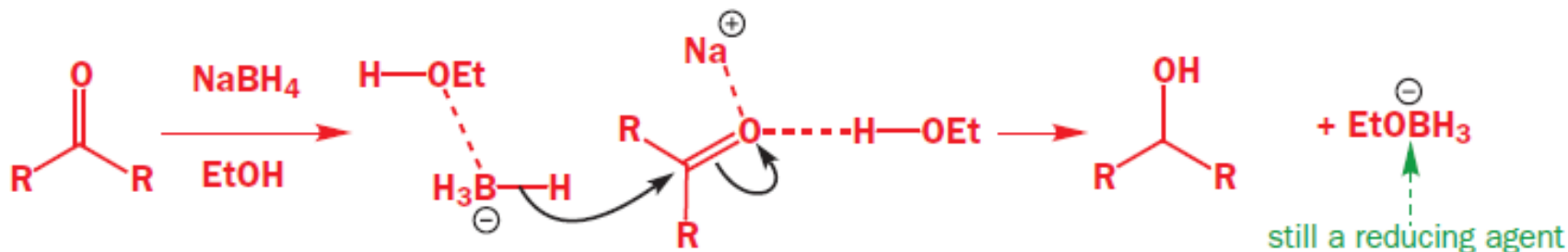
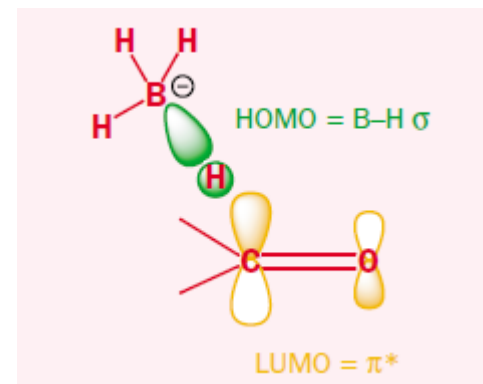


nucleophilic attack by H^-
never happens



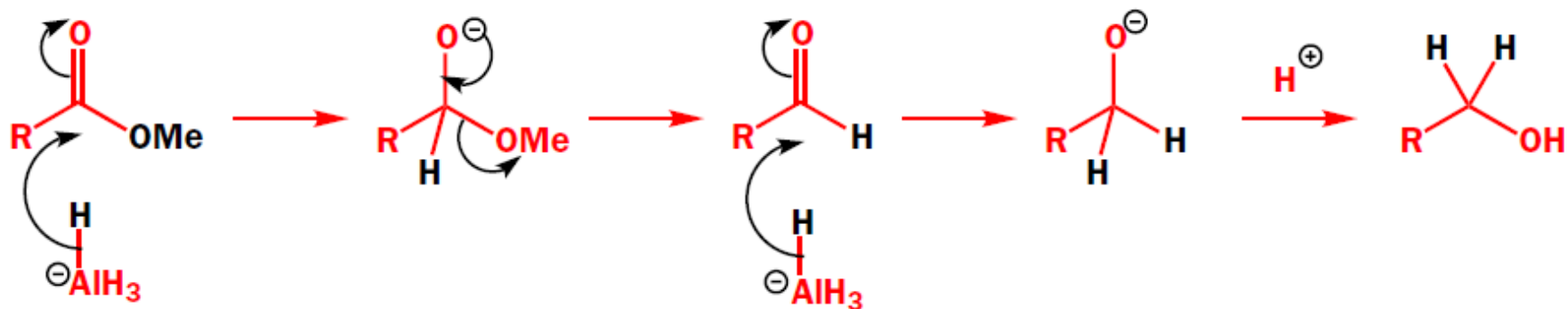
H^- *always* reacts as a base

NaBH_4 has a better orbital match (B–H σ orbital as the HOMO); It will reduce only in **protic solvents** (usually ethanol, methanol, or water) or in the presence of electrophilic **metal cations** such as Li^+ or Mg^{2+}



Reduction of carbonyl groups

Reduction of esters to alcohols: LiAlH_4 is often the best reagent

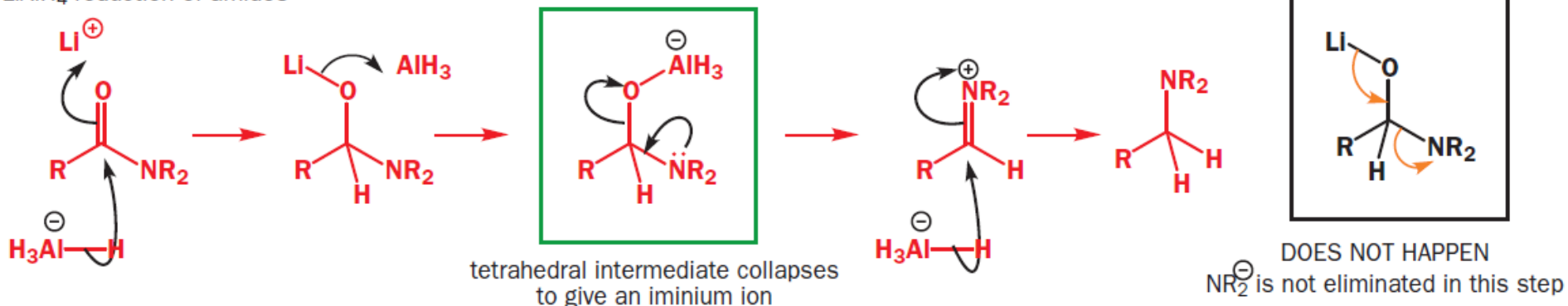


LiBH_4 is a milder alternative; it will reduce esters but not acids or amides



Reduction of amides to amines: use LiAlH_4 ; there is a key difference in mechanism comparing to the reduction of ester

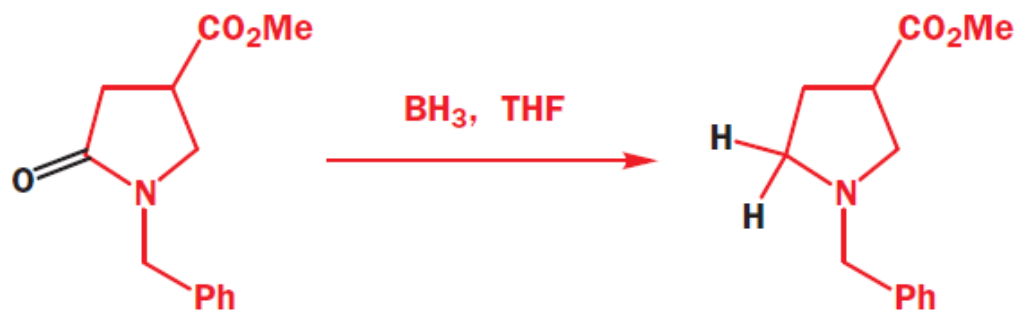
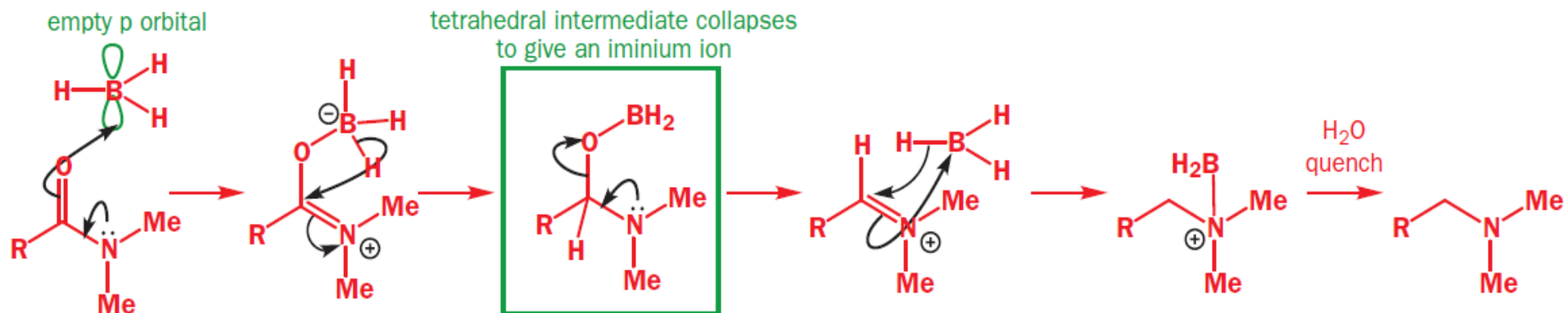
LiAlH_4 reduction of amides



Reduction of carbonyl groups

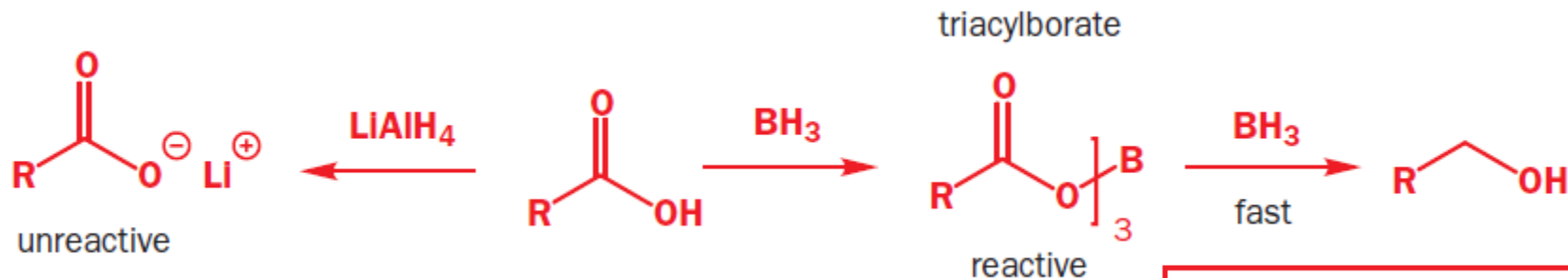
Borane (BH₃): Borane is a gas with the structure B₂H₆, but it can be 'tamed' as a liquid by complexing it with ether (Et₂O), THF, or dimethyl sulfide (Me₂S)

Borane's reactivity is dominated by its desire to **accept an electron pair** into its empty p orbital; reduces **electron-rich carbonyl groups** fastest

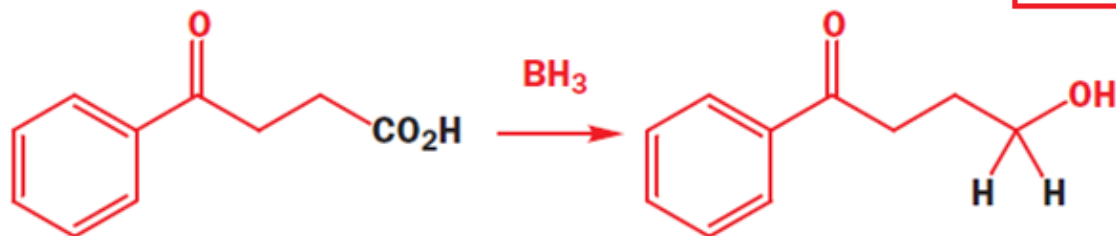
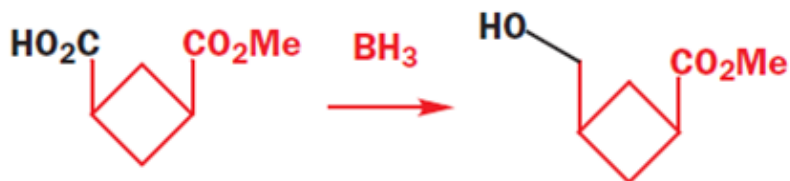


Reduction of carbonyl groups

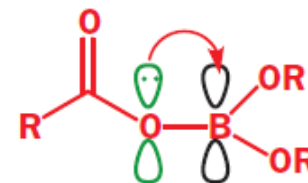
Borane is an excellent reagent for reducing **carboxylic acids**



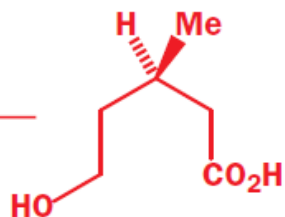
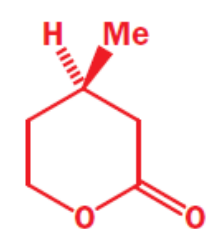
Examples:



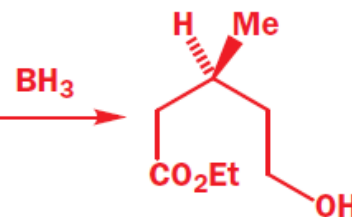
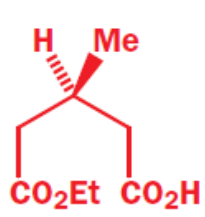
oxygen donates lone pair electrons into boron's empty p orbital



enantiomer of other lactone

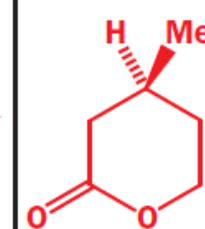


single enantiomer made using enzyme



H^+

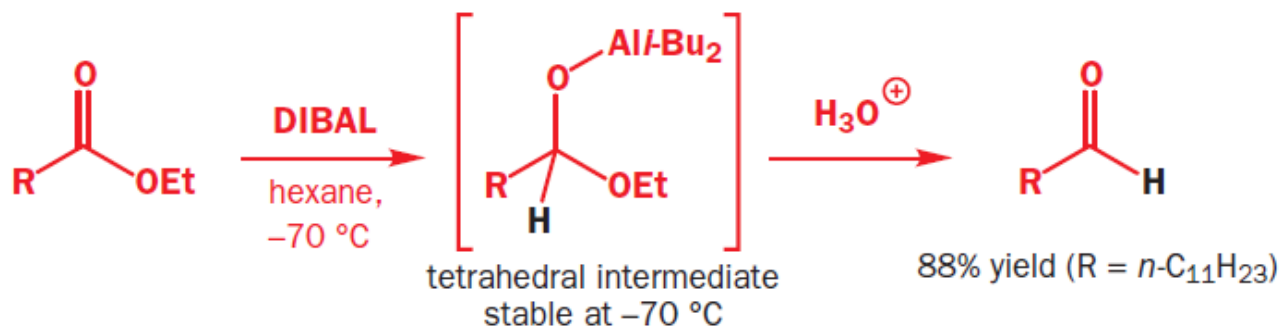
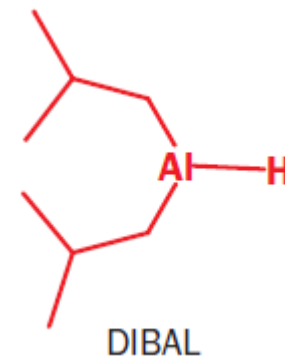
enantiomer of other lactone



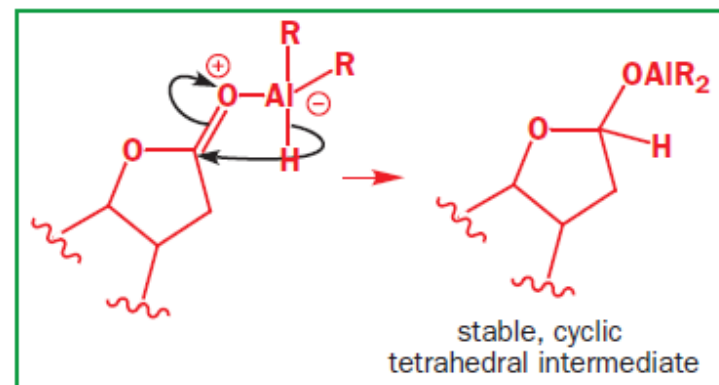
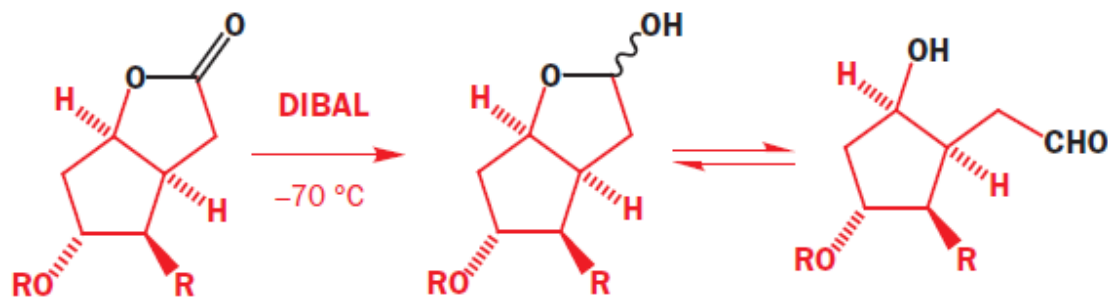
Reduction of carbonyl groups

Reduction of esters to aldehydes: The **aldehyde is more readily reduced** than the ester, so the reduction carries on to the alcohol oxidation level

Use **DIBAL** (similar to BH_3); it becomes a reducing agent only after it has formed a **Lewis acid–base complex**, so it too reduces **electron-rich carbonyl groups** most rapidly

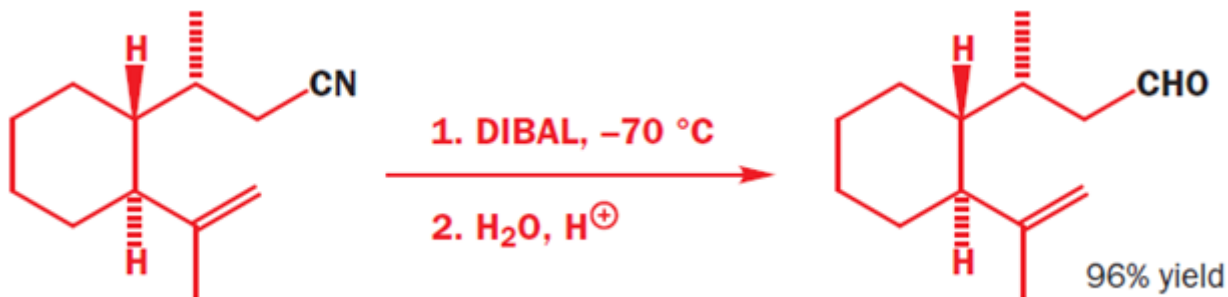


The tetrahedral intermediate is **stable** at $-70\text{ }^\circ\text{C}$. Only in the aqueous work-up does it collapse to the aldehyde, so that **no further reduction** is possible.

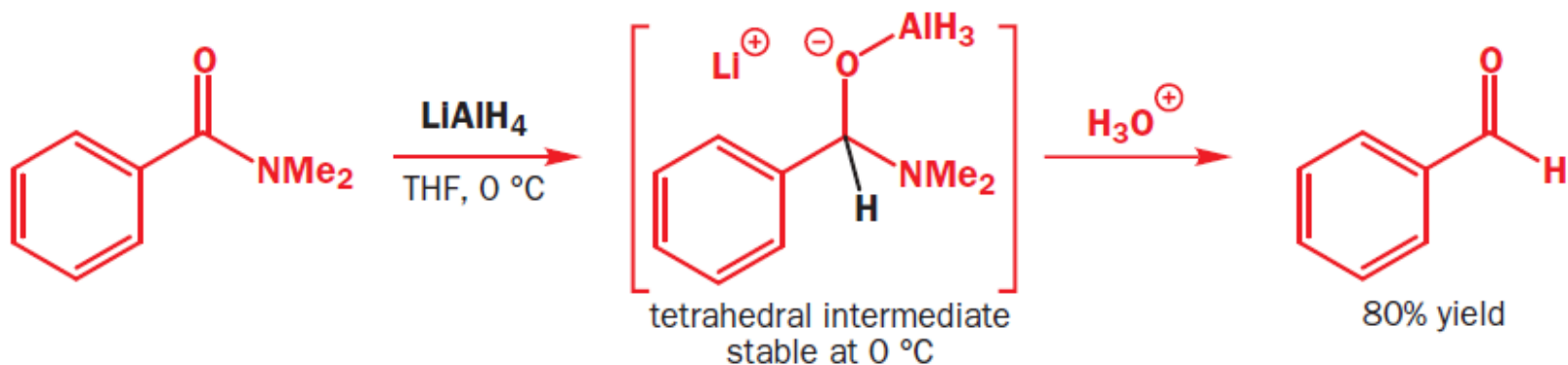


Reduction of carbonyl groups

Reduction of nitriles to aldehydes: use **DIBAL**



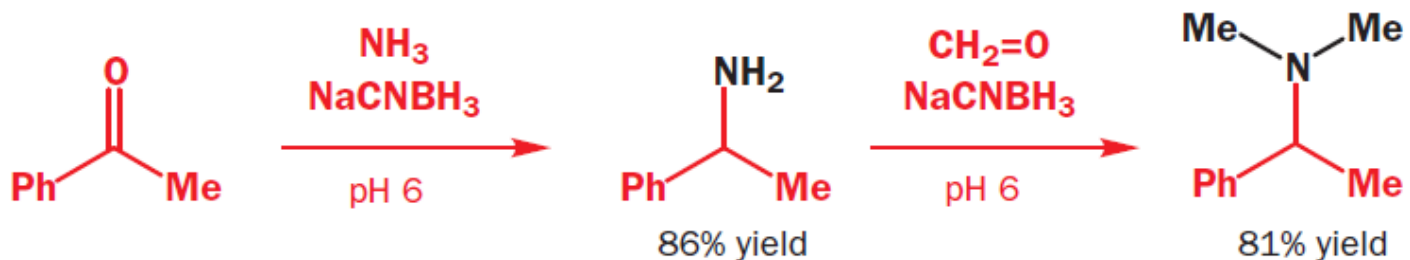
Reduction of amides to aldehydes: use **LiAlH₄** at low temperature; the **tetrahedral intermediates** are rather **more stable** than those from ester reduction



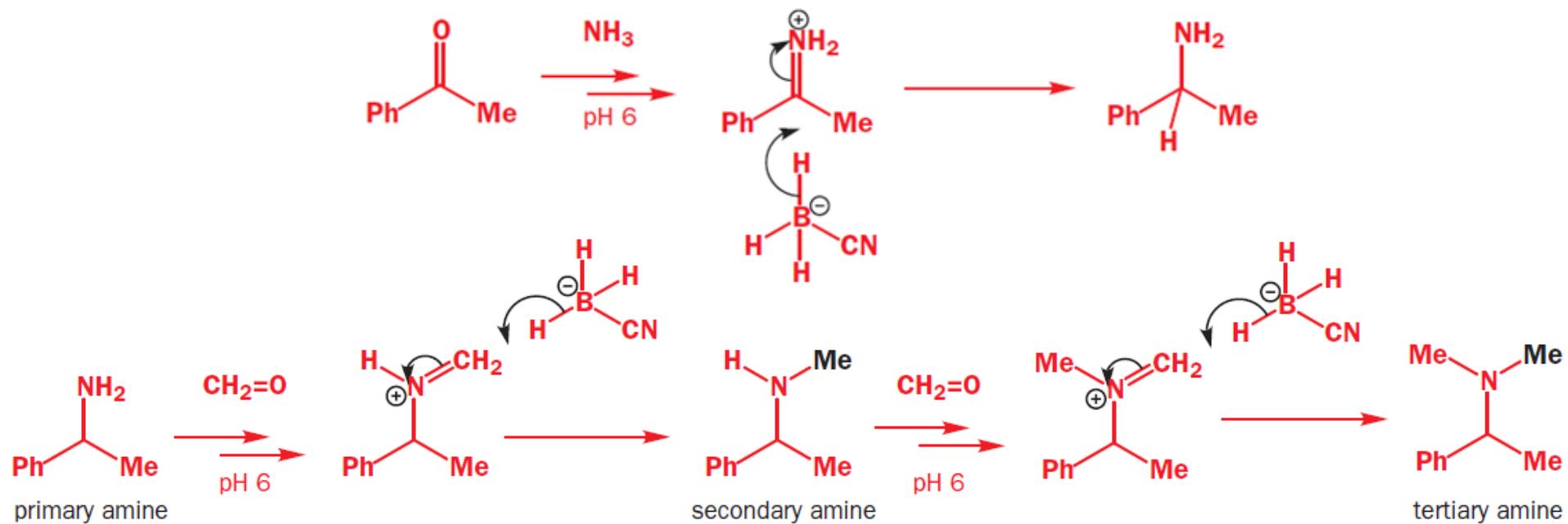
Reduction of carbonyl groups

Reduction of iminium ions to amines: Reductive Ammination

NaBH_3CN or $\text{NaBH}(\text{OAc})_3$ are milder reducing agents; when added to a typical imine-formation reaction

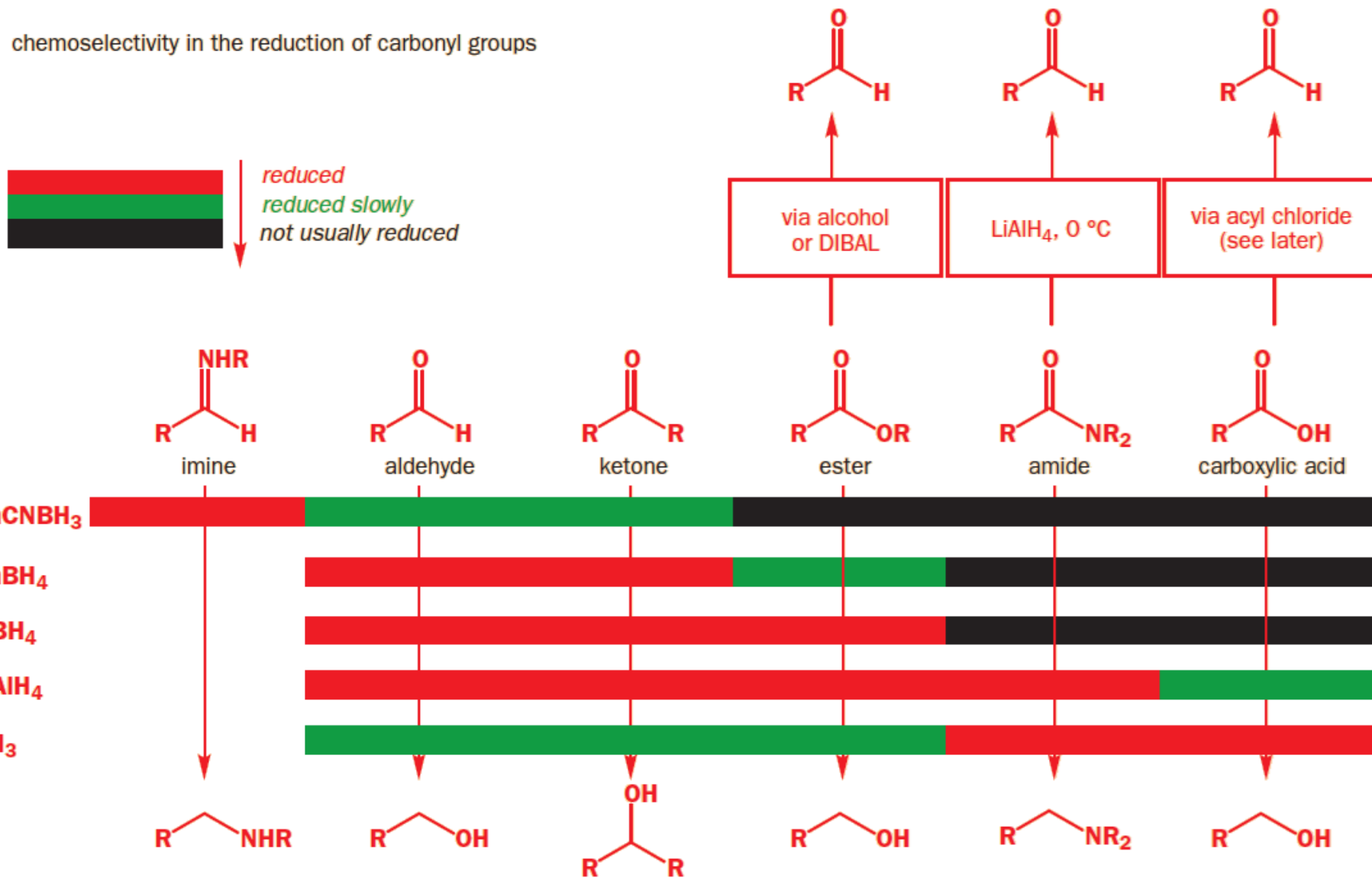


They **reacts with the iminium ion** but not with the starting carbonyl compound



Reduction of carbonyl groups - Chemoselectivity

chemoselectivity in the reduction of carbonyl groups



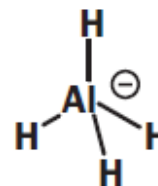
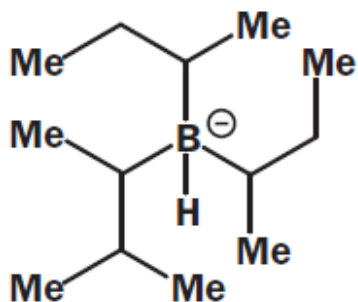
Reduction of carbonyl groups

Diastereoselectivity in cyclic system: 6-membered ring



large nucleophile: 96% equatorial attack

small nucleophile: 90% axial attack



1,3-Diaxial interaction

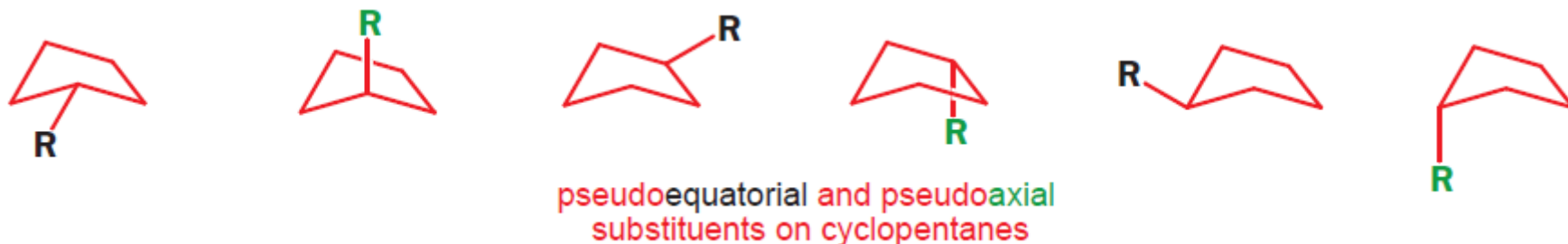


Torsional strain effect

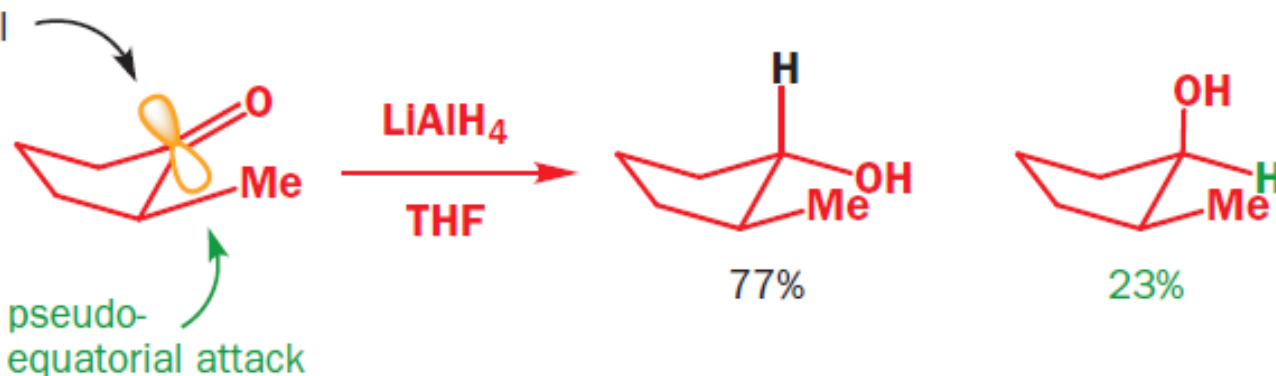


Reduction of carbonyl groups

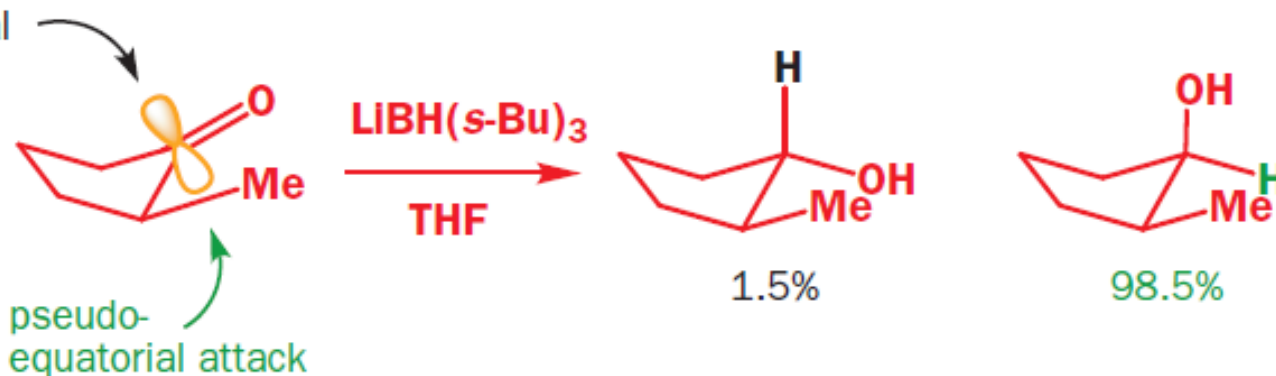
Diastereoselectivity in cyclic system: 5-membered ring



pseudoaxial attack

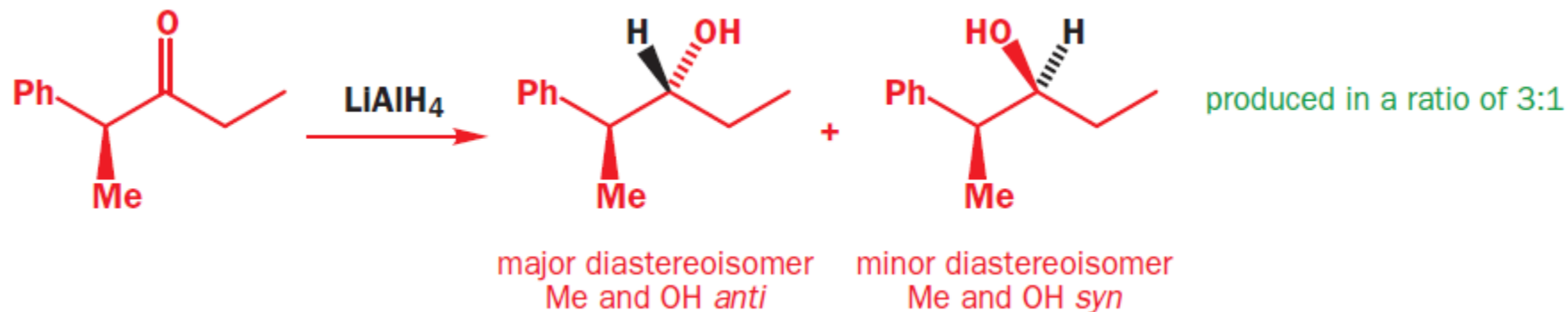


pseudoaxial attack

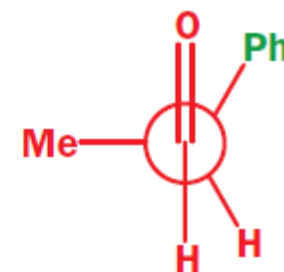
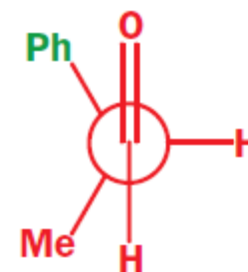
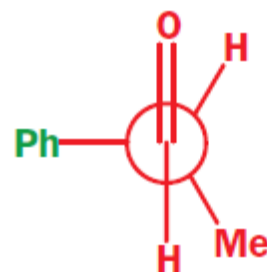
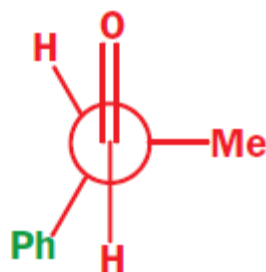
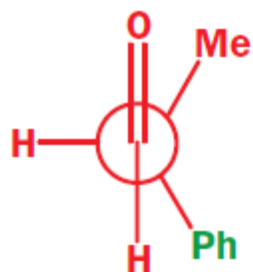
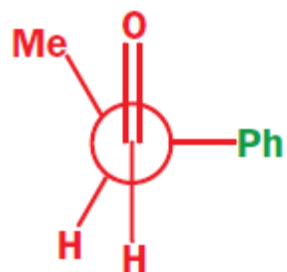
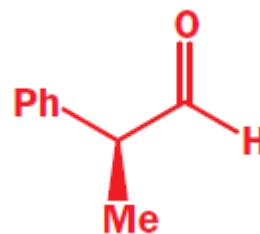


Reduction of carbonyl groups

Diastereoselectivity in acyclic system:

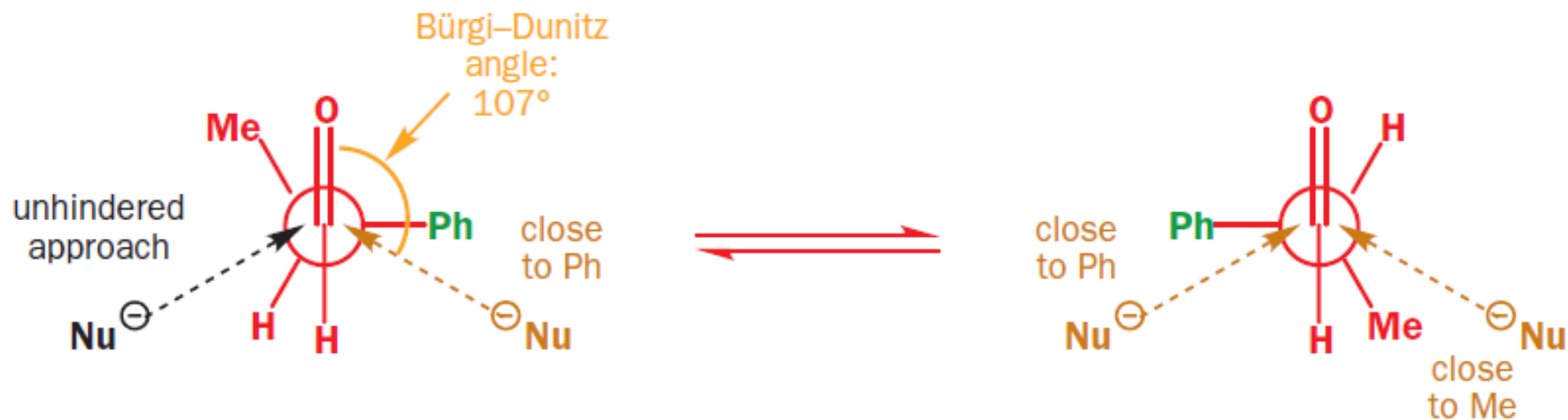


The conformation of a chiral aldehyde:



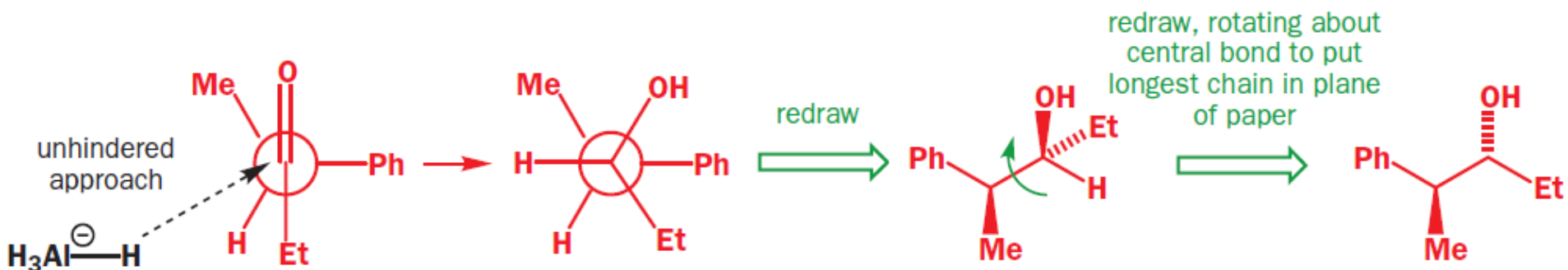
Reduction of carbonyl groups

Diastereoselectivity in acyclic system: Felkin-Ahn model



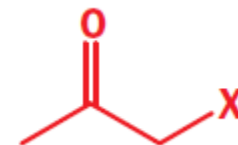
the black flight path is the best

the three brown flight paths are hindered by Ph or Me



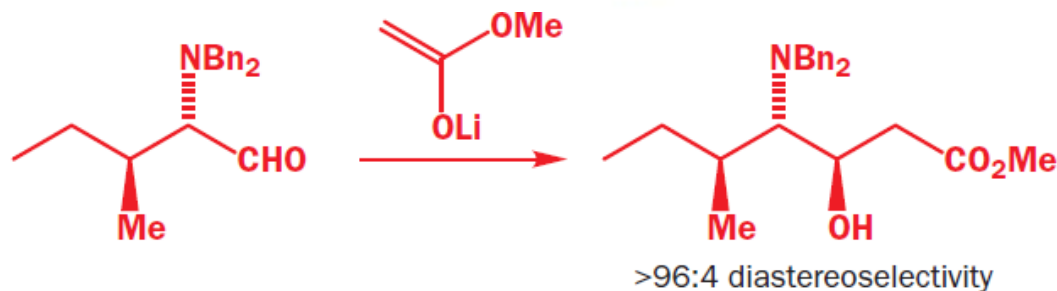
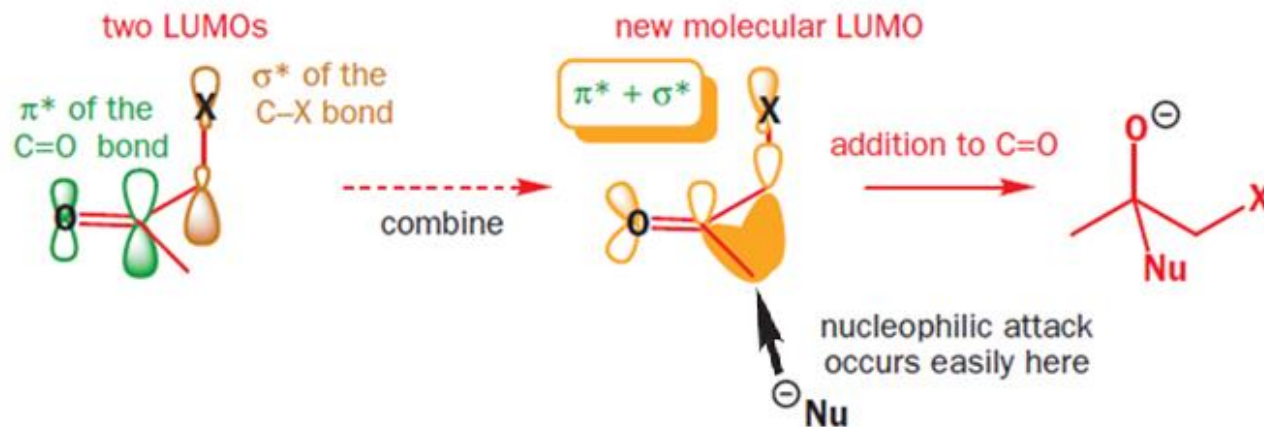
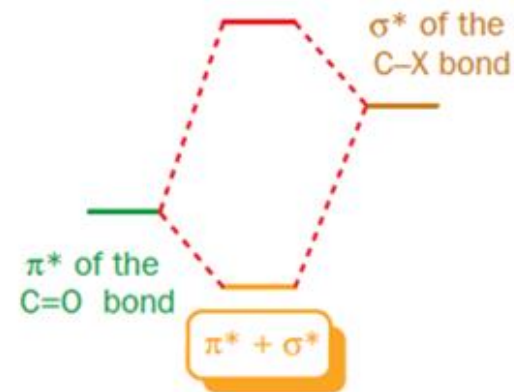
Reduction of carbonyl groups

Electronegative elements (N, O, S, etc) will lie **perpendicular** to the carbonyl group in the most reactive conformation

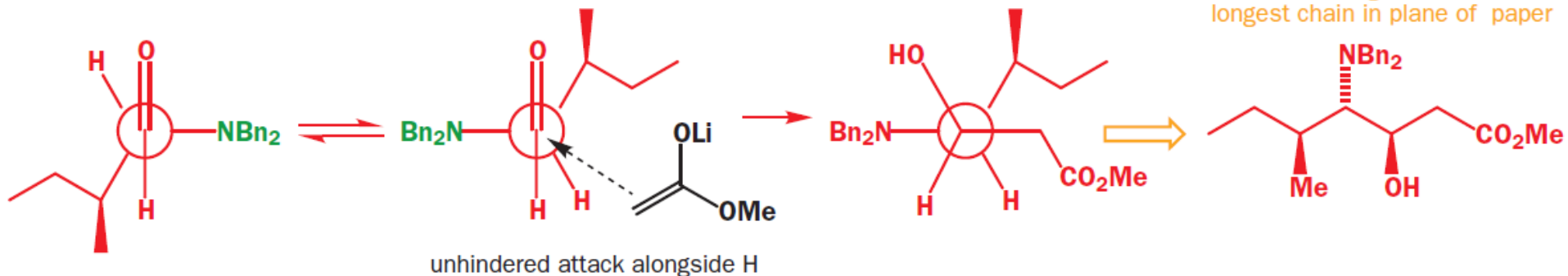


X is an electronegative group but not a leaving group (OR, NR₂, SR, etc.)

in energy terms:

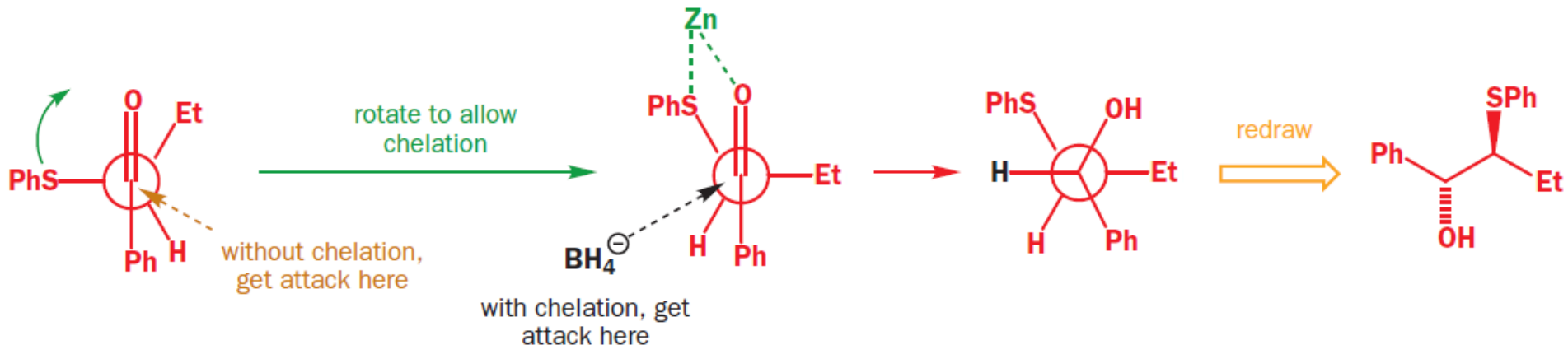
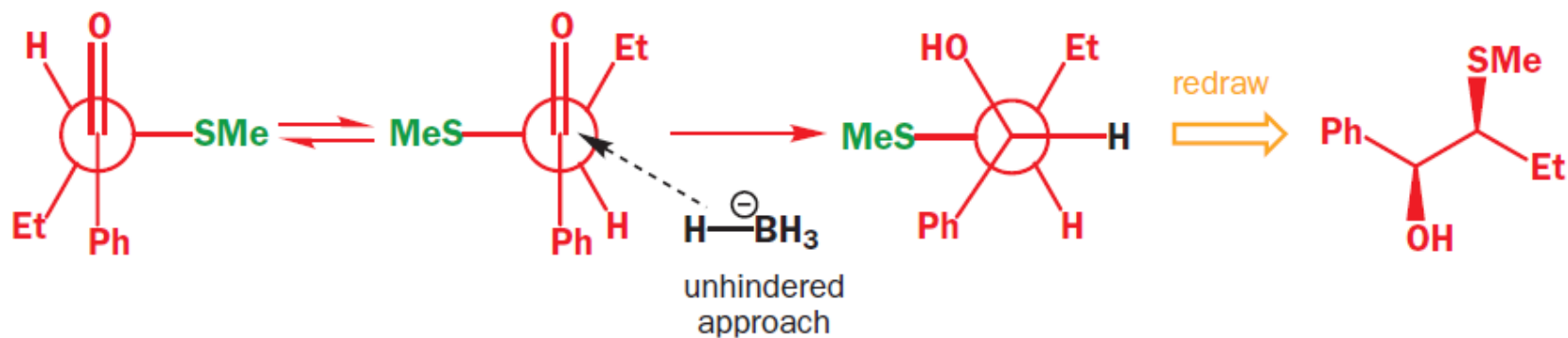
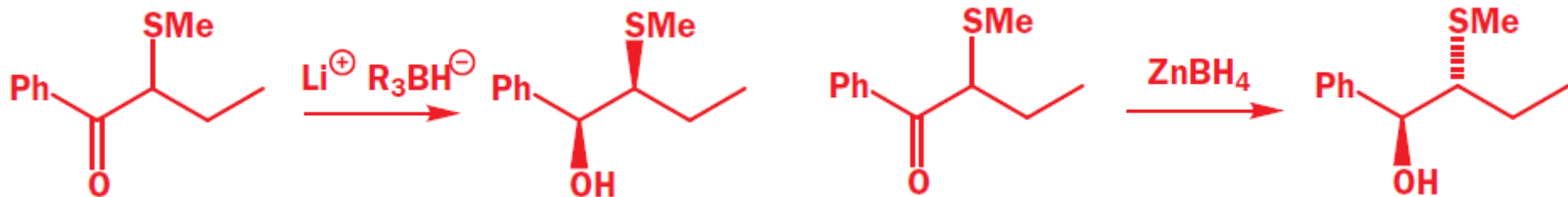


redraw, rotating bond to put longest chain in plane of paper



Reduction of carbonyl groups

Diastereoselectivity in acyclic system: Chelation can reverse stereoselectivity

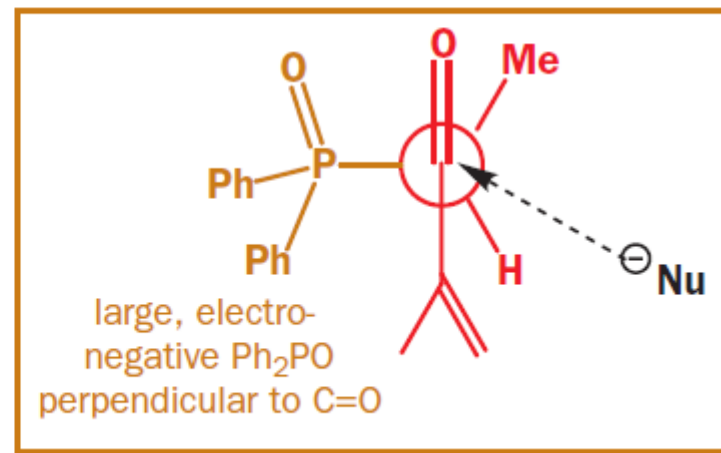
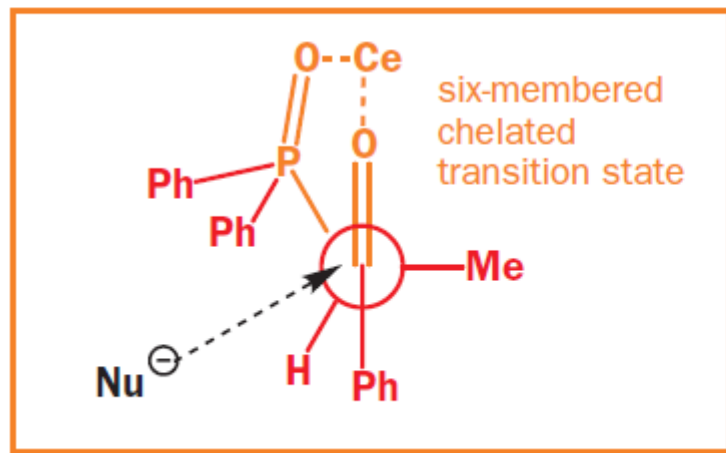
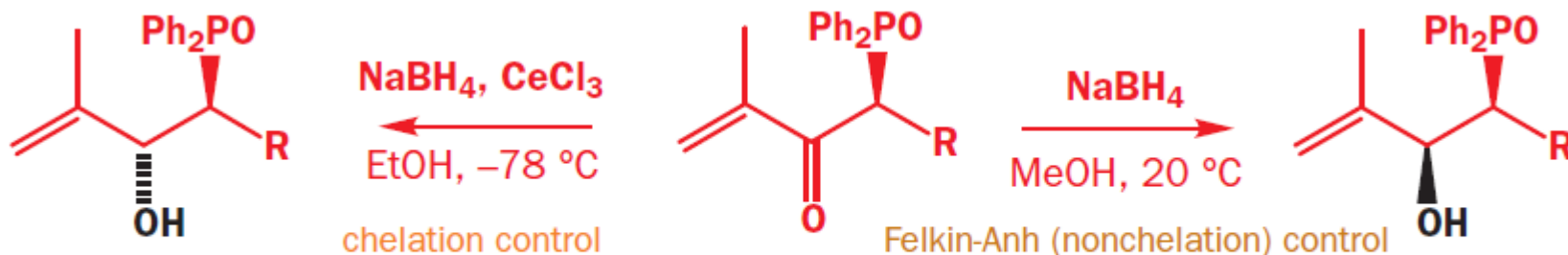


Reduction of carbonyl groups

Diastereoselectivity in acyclic system: **Chelation can reverse stereoselectivity**

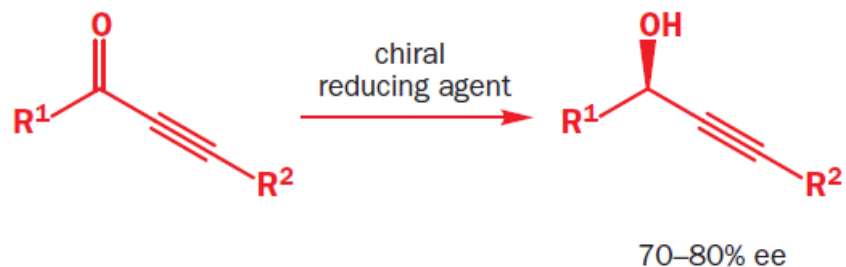
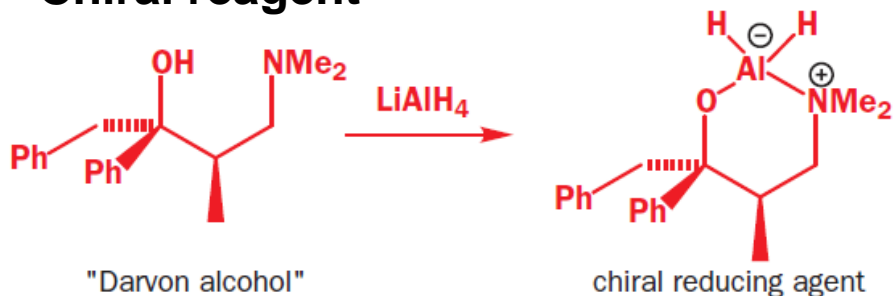
Metals not usually involved in chelation: **Li⁺** (often), **Na⁺**, **K⁺**

Metals commonly involved in chelation: **Li⁺** (sometimes), **Mg²⁺**, **Zn²⁺**, **Cu²⁺**, **Ti⁴⁺**, **Ce³⁺**

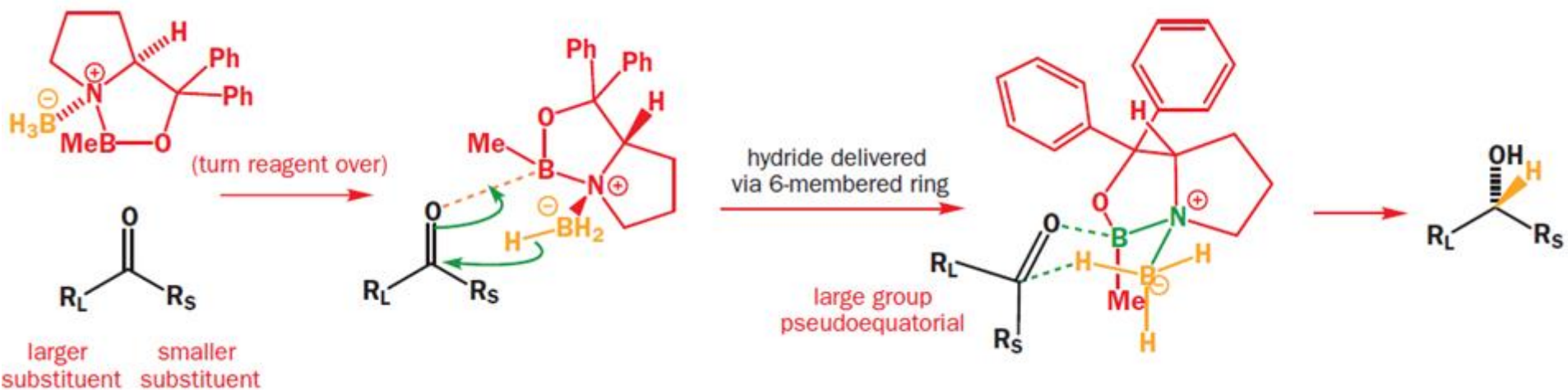
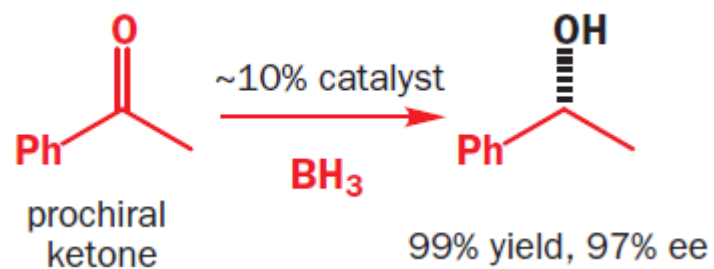
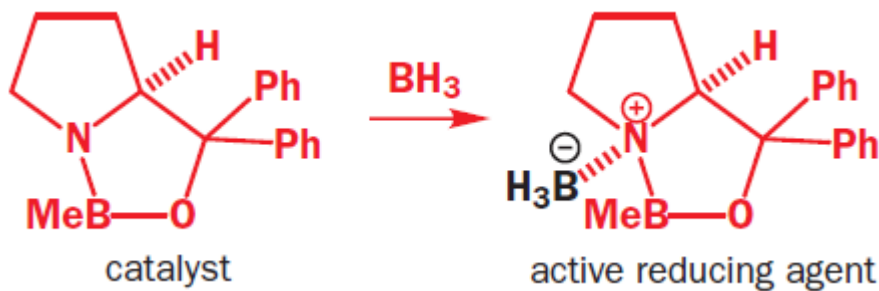


Reduction of carbonyl groups - Enantioselectivity

Chiral reagent

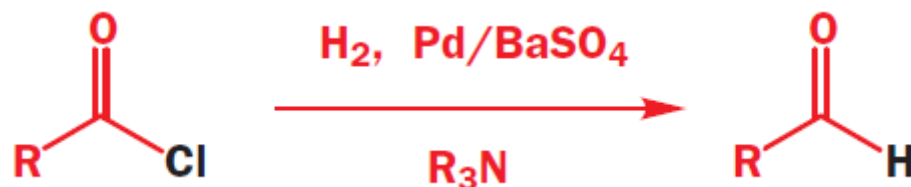


Chiral catalyst – CBS reagent:

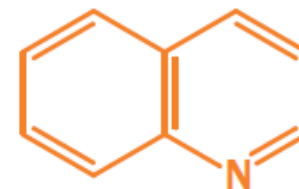


Catalytic hydrogenation

Rosenmund reaction: hydrogenolysis of a **C–Cl bond of acid chlorides** (reducing compounds at the carboxylic acid oxidation level to **aldehydes**)



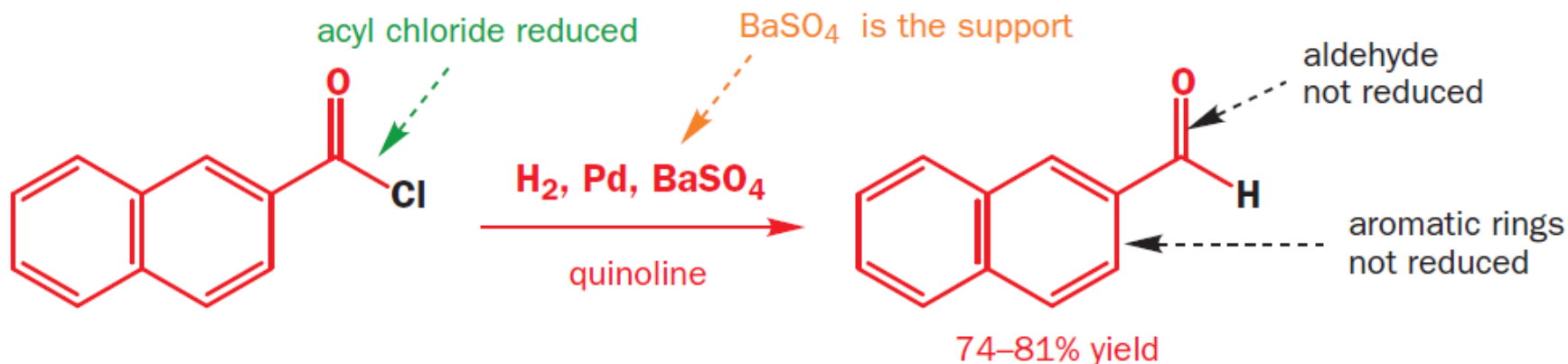
the tertiary amine



quinoline

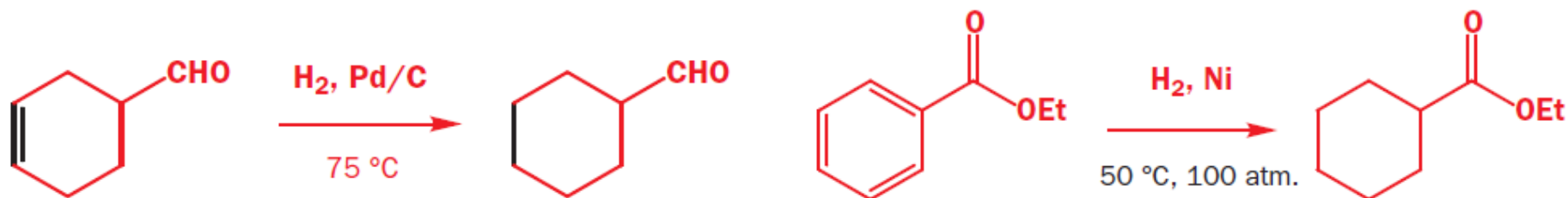
The **tertiary amine** is needed both to **neutralize** the HCl produced in the reaction and to moderate the activity of the catalyst (and **prevent overreduction**)

BaSO₄ (and **CaCO₃**) are commonly used as **supports with more easily reduced substrates** because they allow the products to escape from the catalyst more rapidly and **prevent overreduction**



Catalytic hydrogenation

Catalytic hydrogenations have a totally different chemoselectivity from the reduction using nucleophilic reducing agents (hydrides); they have chemoselectivity for **C=C double bonds** and **benzylic C-X bonds** over C=O groups

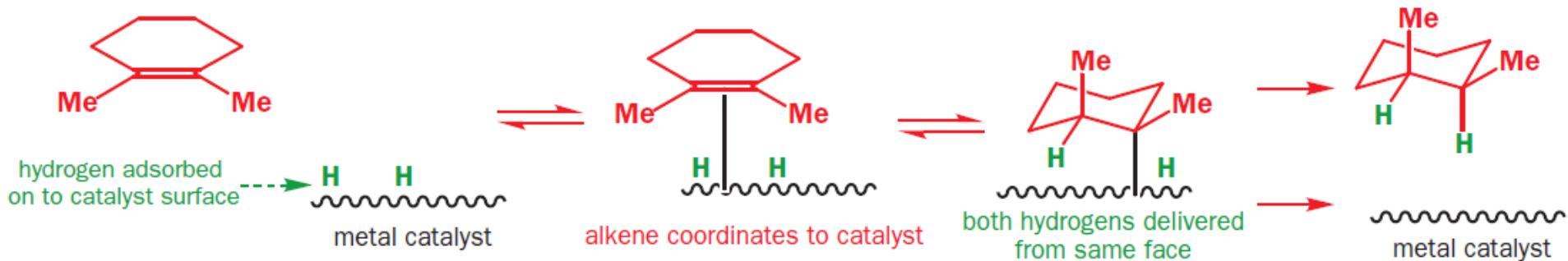


The choice of catalyst depends on the compound to be reduced. **Palladium** and **platinum** are the most commonly used

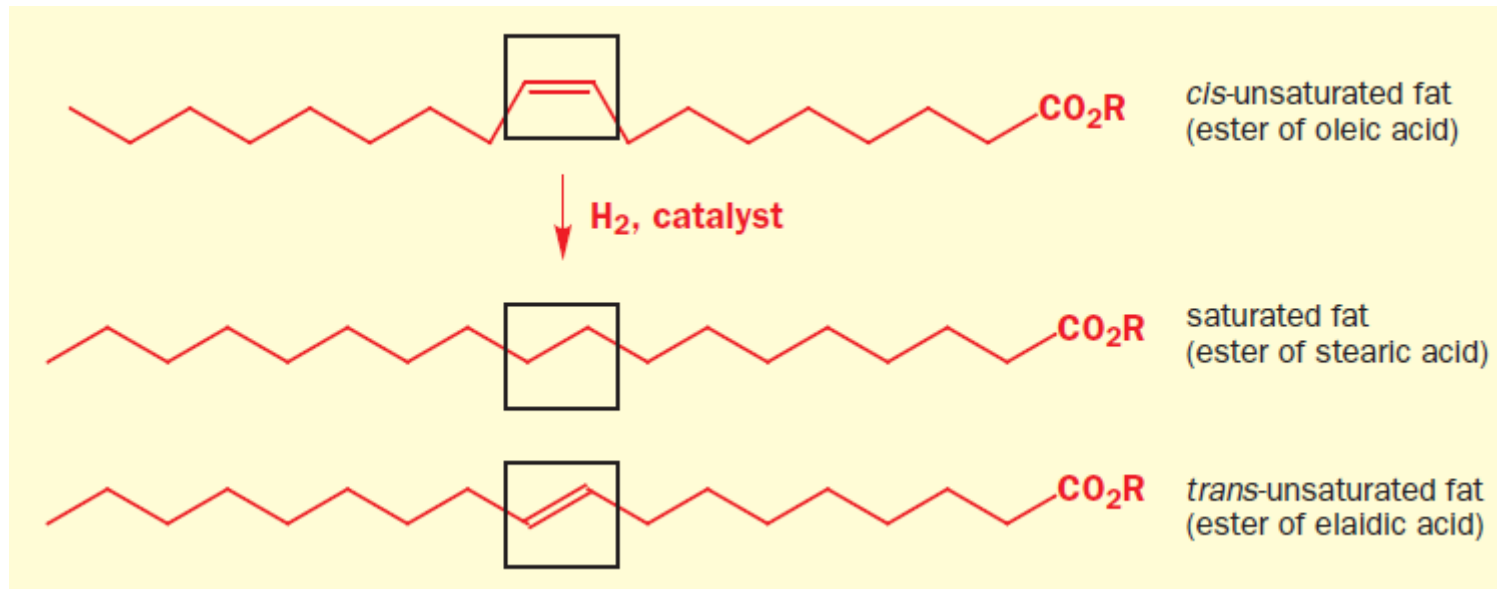
Substrate	Usual choice of metal
benzyl amine or ether	Pd
alkene	Pd, Pt, or Ni
aromatic ring	Pt or Rh, or Ni under high pressure

Catalytic hydrogenation

Reduction of alkenes: mechanism starts with **coordination of the double bond** to the catalyst surface; **two hydrogen atoms are transferred** to the alkene, and they are often both **added to the same face** of the alkene (***syn*-selective**)



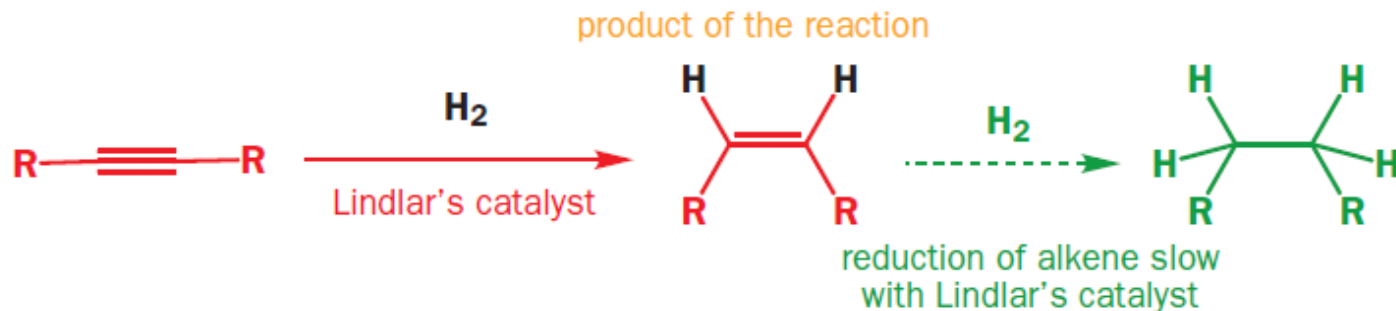
trans-Fat



Catalytic hydrogenation

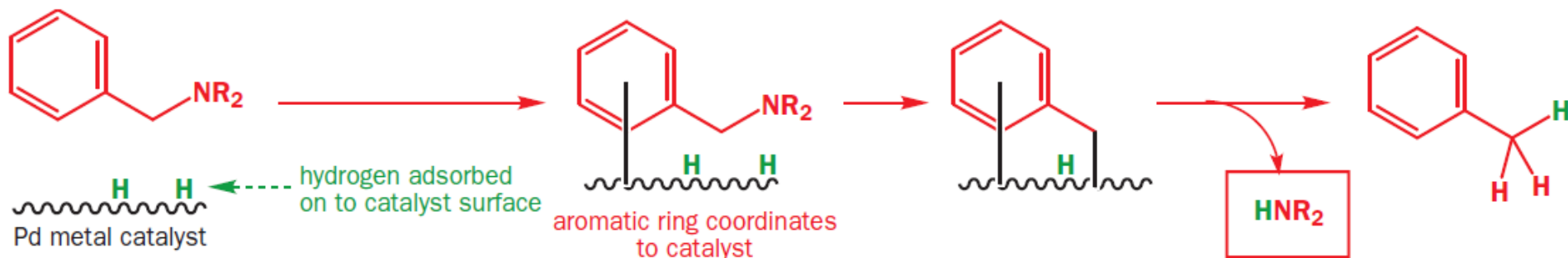
Reduction of alkynes: most palladium catalysts would reduce alkynes all the way to **alkanes**; use **Lindlar's catalyst** (Pd/CaCO₃ deliberately **poisoned with lead**). Best selectivities are obtained if **quinoline** is added to the reaction

Lindlar's catalyst =
Pd, CaCO₃, Pb(OAc)₂



Reduction of benzylic/allylic C–X bond (X = N, O):

benzyl amine **coordinates** to the metal catalyst via the **electron-rich aromatic ring**

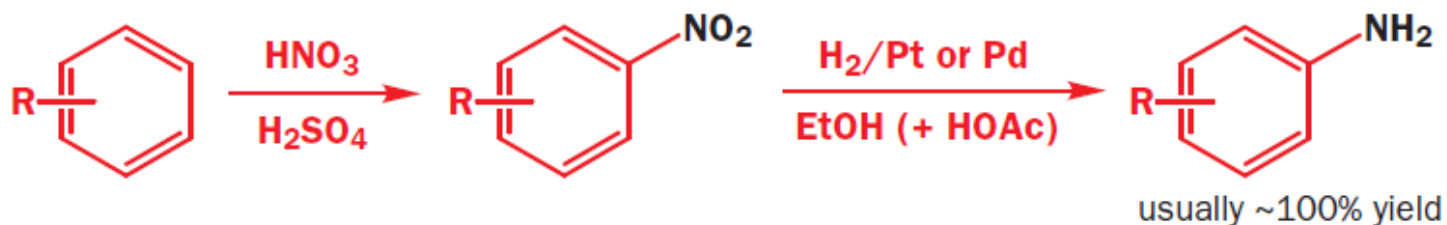


Benzyl groups, and their hydrogenolysis, as a means for **temporary protection of amines and alcohols**

Catalytic hydrogenation

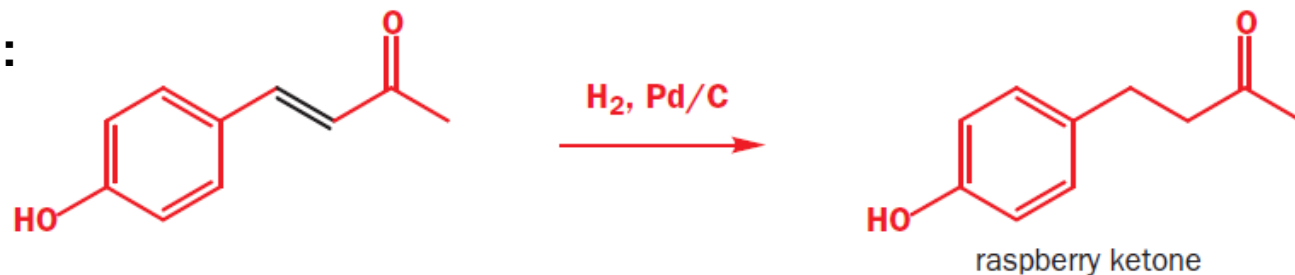
21

Reduction of nitro group: The reduction can be carried out by Sn/HCl but catalytic hydrogenation is much simpler

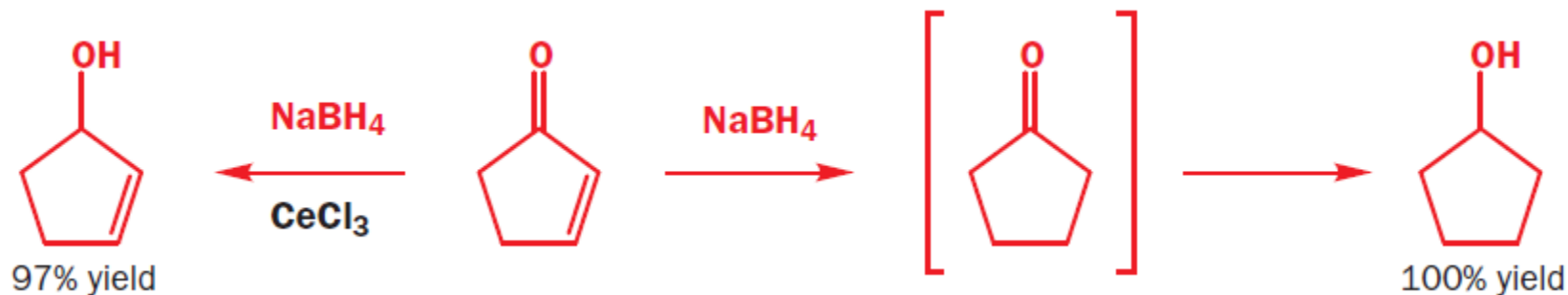


Reduction of unsaturated carbonyl compounds:

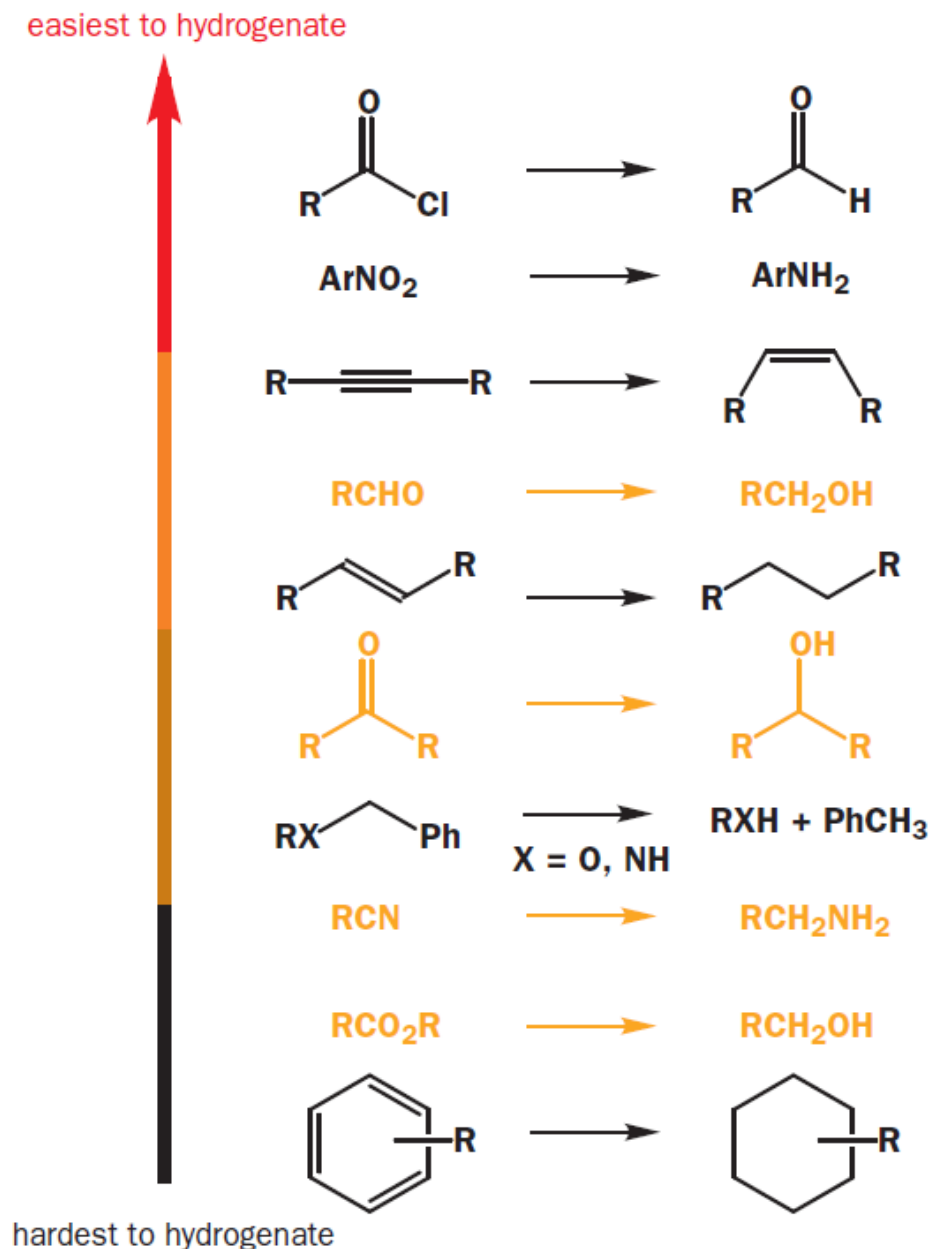
- **C=C bond reduction:**



- **C=O bond reduction:** The way to get regioselective addition directly to the carbonyl group is to add a **hard, Lewis-acidic** metal salt, such as CeCl₃

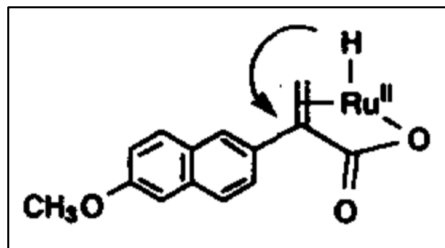


Sequence of Reactivity towards Hydrogenation

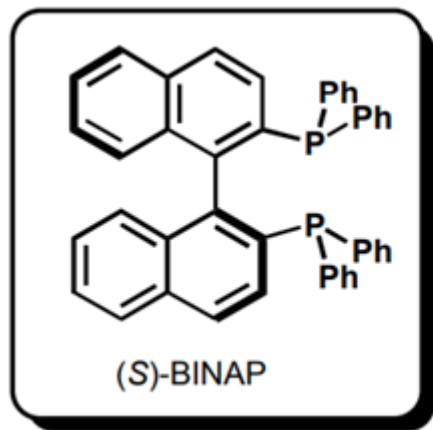
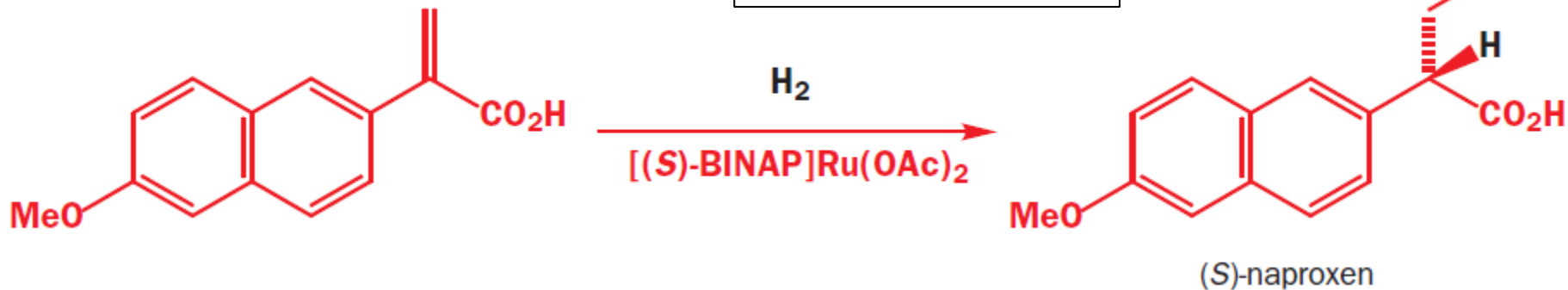


Catalytic hydrogenation

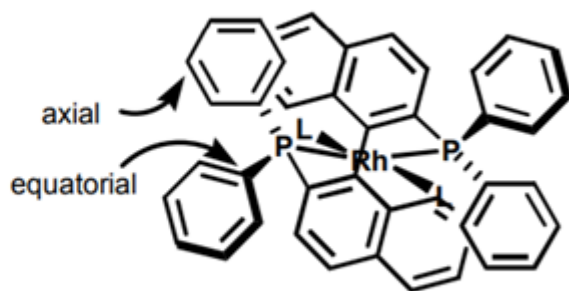
Asymmetric Hydrogenation:



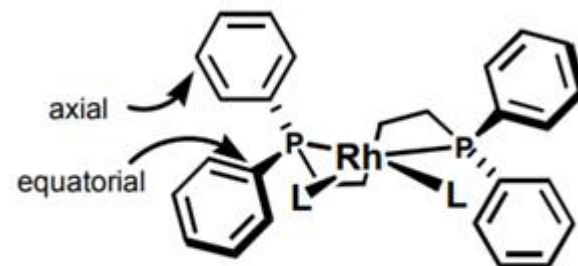
A.S.C. Chan et al. / Inorganica Chimica Acta 234 (1995) 95-100



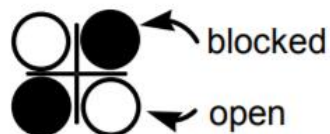
Axial chirality



Simplified by removing backbone:



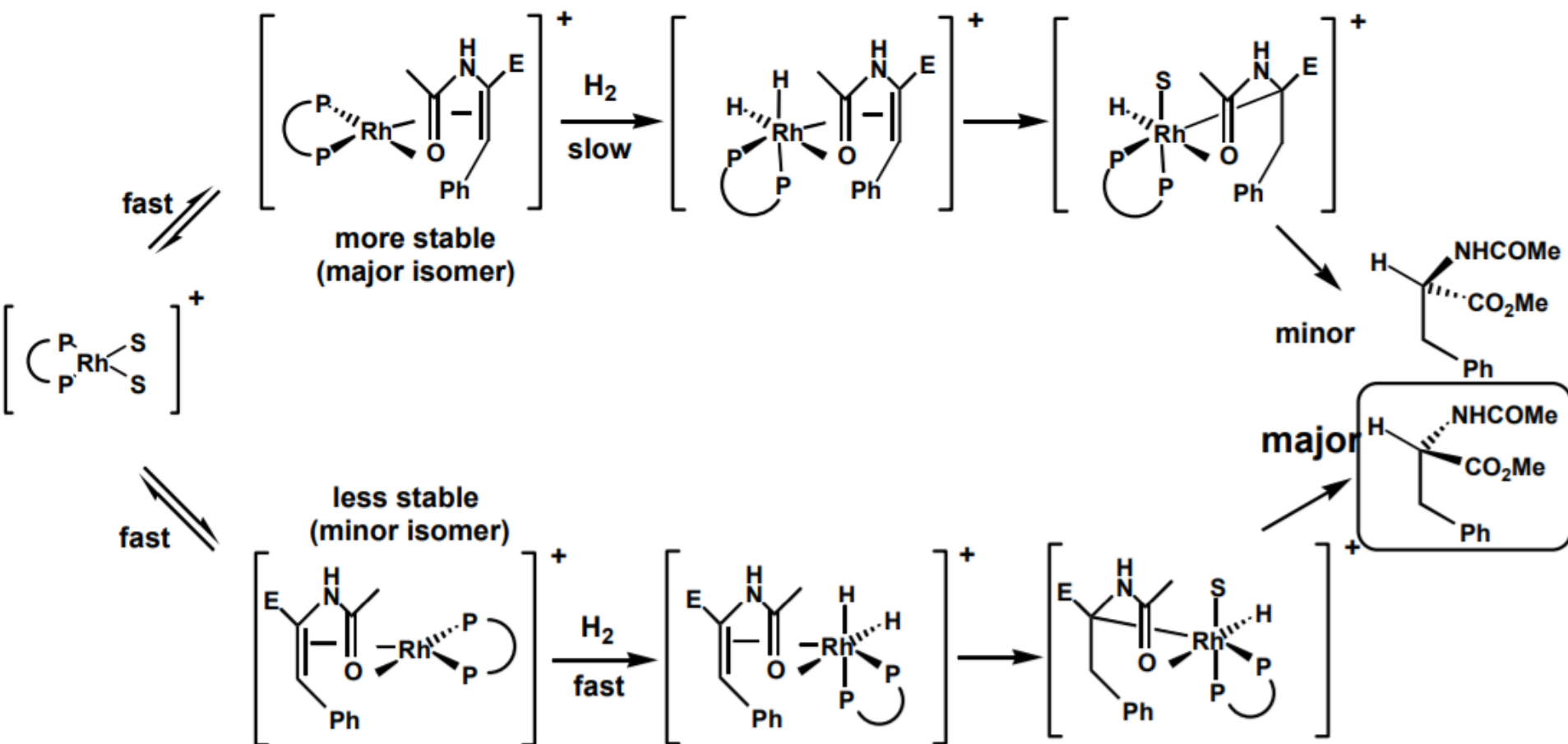
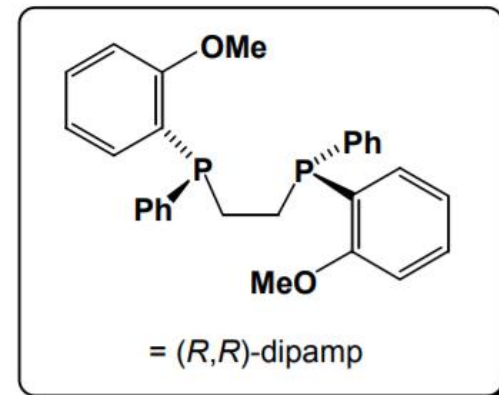
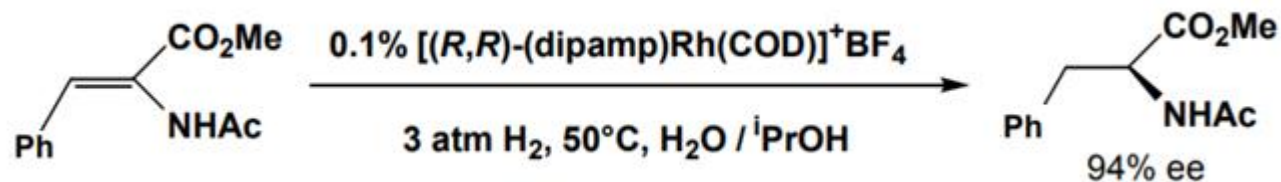
Chiral environment has 4 quadrants, two "blocked" and two "open":



equatorially disposed phenyl groups block coordination in that 'quadrant'

Catalytic hydrogenation

Asymmetric Hydrogenation:

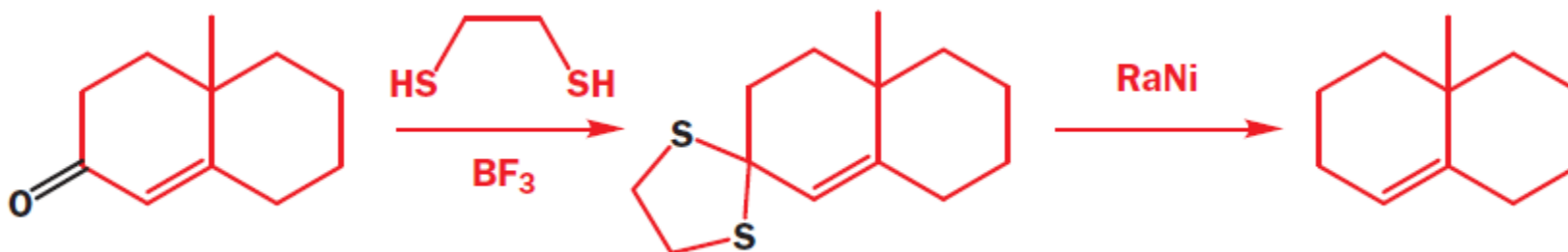


Functional Groups Removal using Reduction

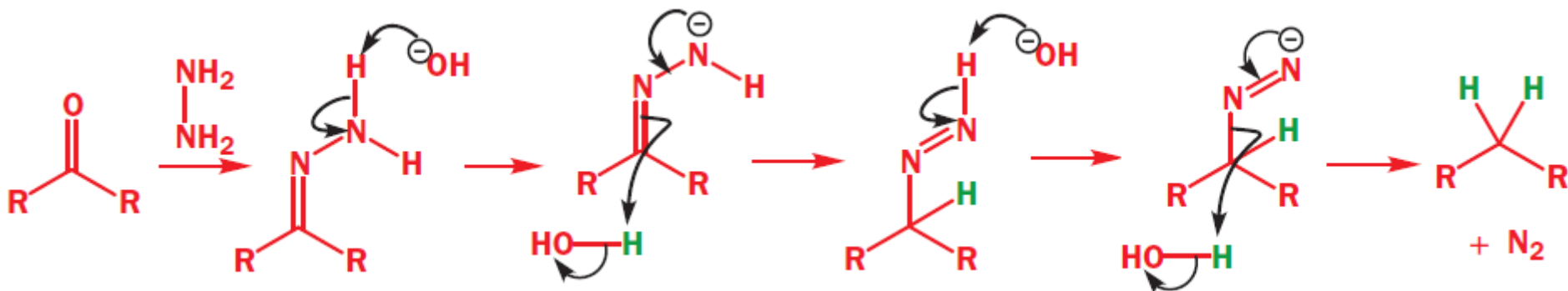
- 1) From Alkenes: Hydrogenation
- 2) From Alcohols: Elimination then hydrogenation
- 3) From Alcohols: Tosylation then H^- reagent



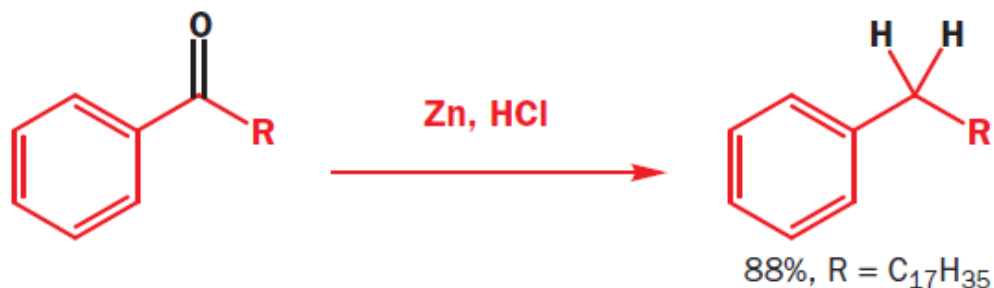
- 4) From Carbonyl: *via* Thioacetals (weak C-S bond) then **RaNi** (Raney nickel is a finely divided form of nickel which adsorbed some H_2)



- 5) From Carbonyl: Wolf-Kishner reduction



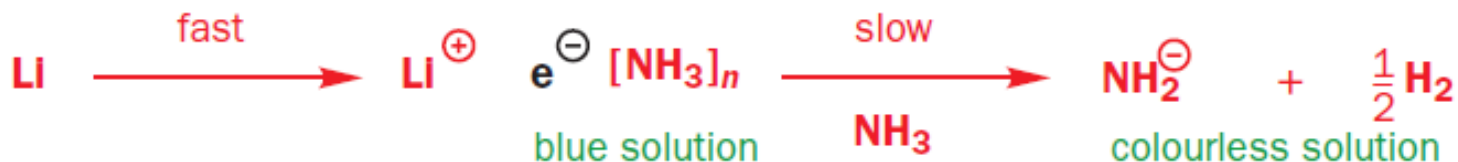
6) From Carbonyl: Clemmensen reduction



As the **zinc** metal dissolves in **HCl**, it **gives up two electrons**; in the presence of a carbonyl compound, the electrons go to **reduce the C=O bond** (normally it will reduce the H⁺ to H₂)

Dissolving Metal Reductions

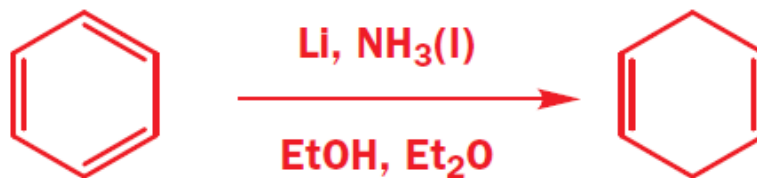
Group 1 metals, such as sodium or lithium, readily **give up their single outer-shell electron** as they dissolve in solvents such as liquid ammonia or ethanol; it will reduce any functional group with a low-energy π^* orbital



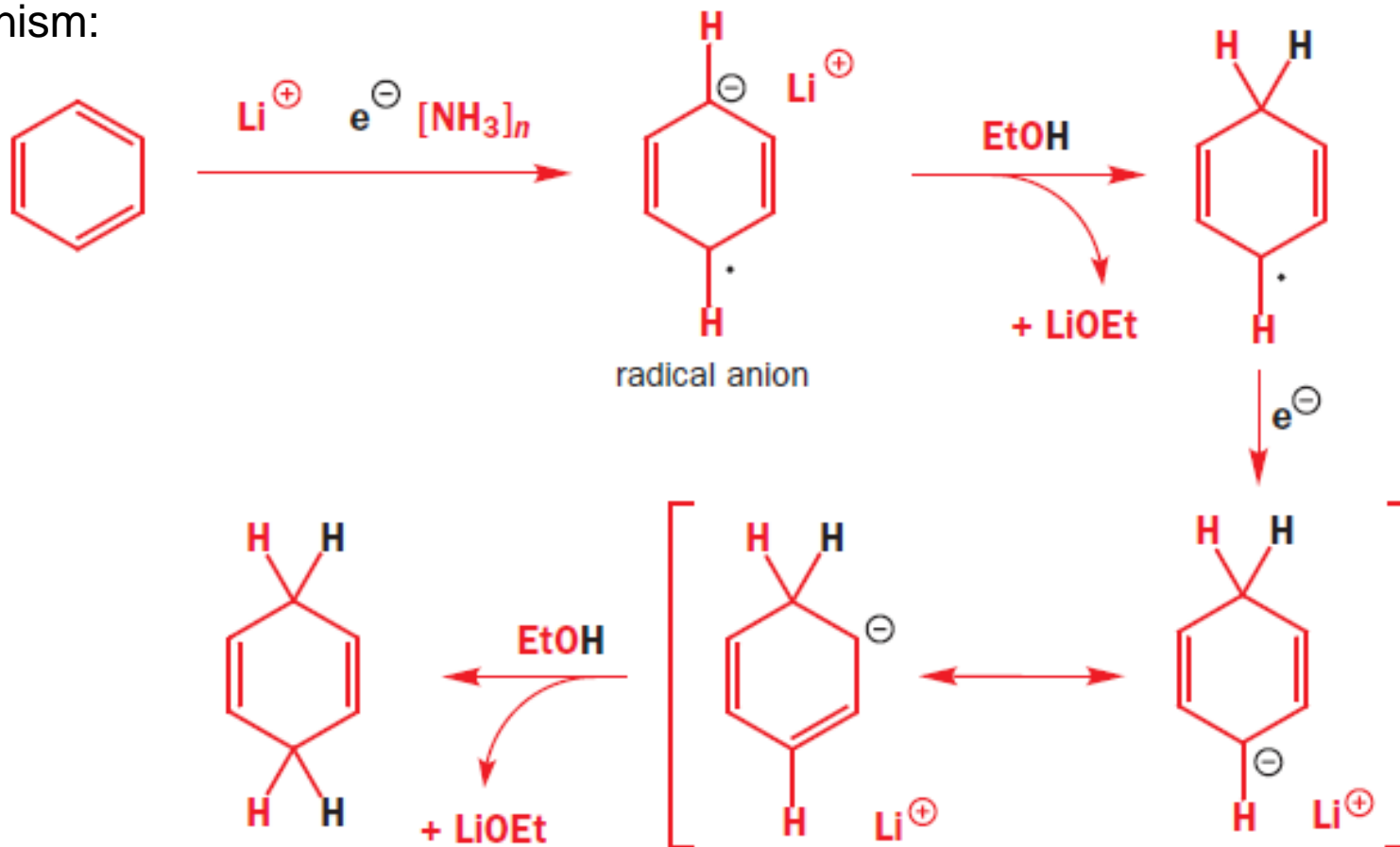
When lithium or sodium dissolve in ammonia they give an **intense blue solution** of solvated electrons

Dissolving Metal Reductions

Birch Reduction: dissolving metal reduction of aromatic rings, giving an unconjugated diene

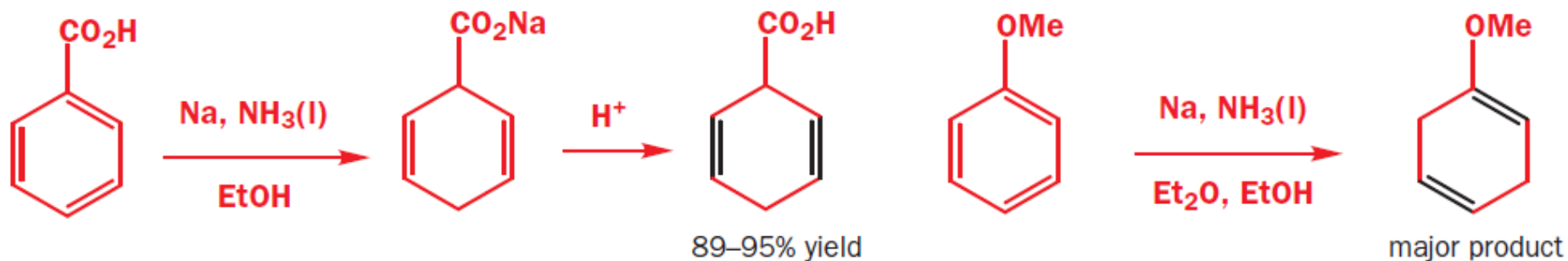


Mechanism:

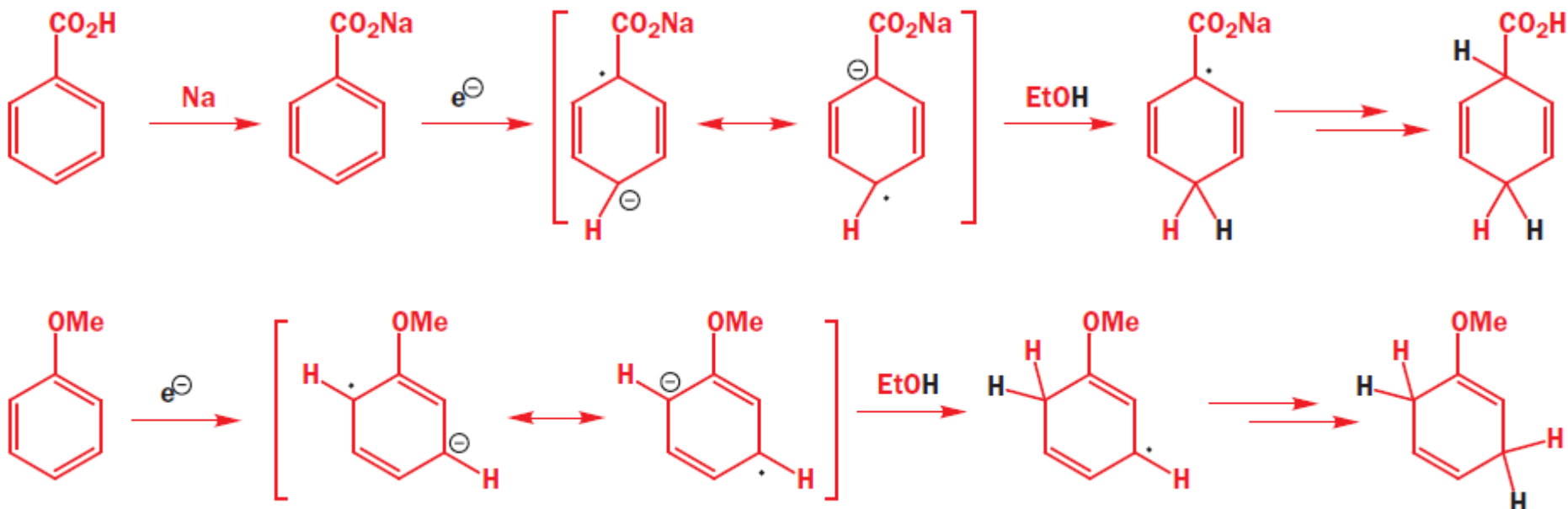


Dissolving Metal Reductions

Birch Reduction:



- **Electron-withdrawing groups** promote *ipso*, *para* reduction
- **Electron-donating groups** promote *ortho*, *meta* reduction

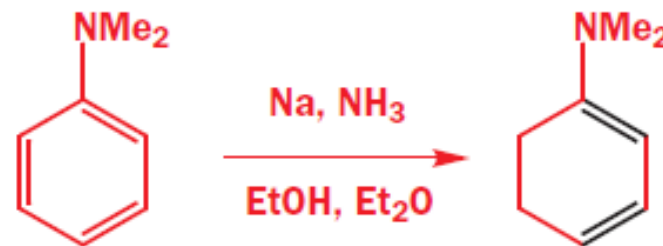
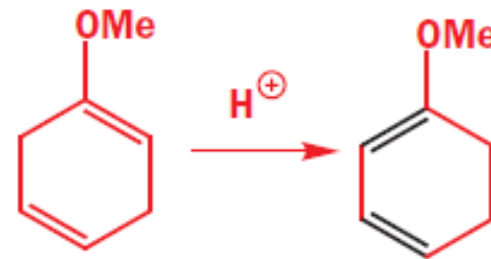


Dissolving Metal Reductions

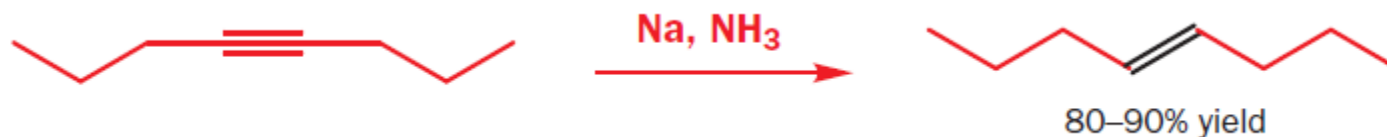
29

Birch Reduction: the unconjugated alkene products can be **isomerised into conjugated dienes** using an **acid catalyst**

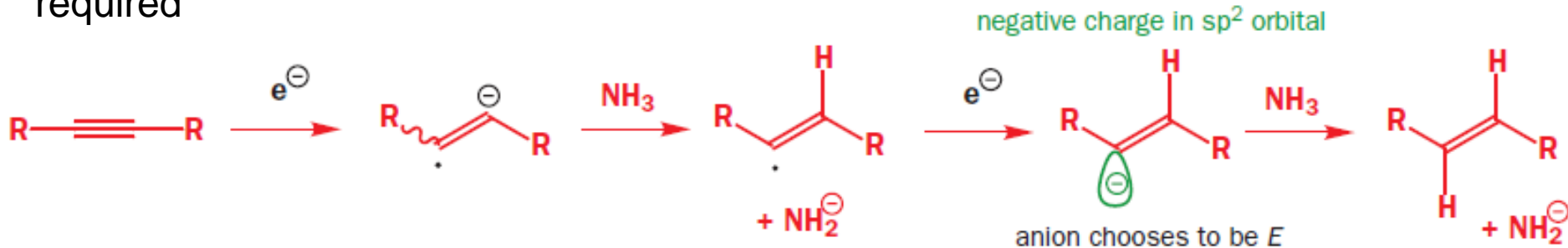
With anilines, it is impossible to stop the isomerization, and Birch reduction always gives **conjugated enamines**



Reduction of Alkynes: giving **trans alkenes**



vinyl anion is basic enough to deprotonate ammonia, so no added proton source is required



Chemoselective for C=C double bonds

peracids, RCO_3H (Chapter 20)

osmium tetroxide, OsO_4 (Chapter 35)

ozone, O_3 (Chapter 35)

^anot dealt with in this chapter.

Chemoselective for alcohols or carbonyl compounds

Cr(VI) compounds

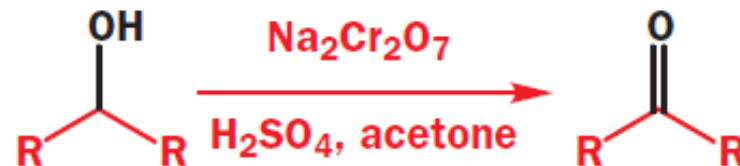
Mn(VII) compounds

some high oxidation state Hal, N, or S compounds

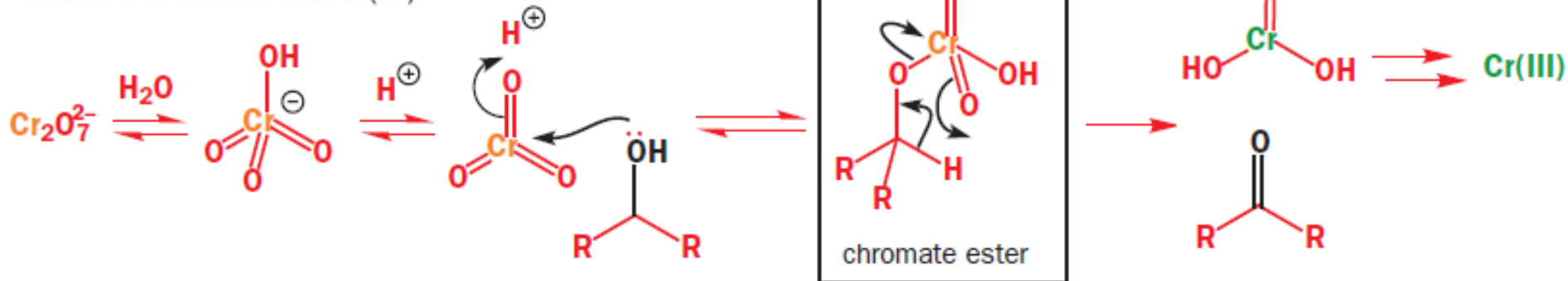
Oxidation of secondary alcohols to ketones: (overoxidation is difficult)

Use **Jones oxidation**:

sodium dichromate in dilute sulfuric acid (not suitable for acid-sensitive alcohols)



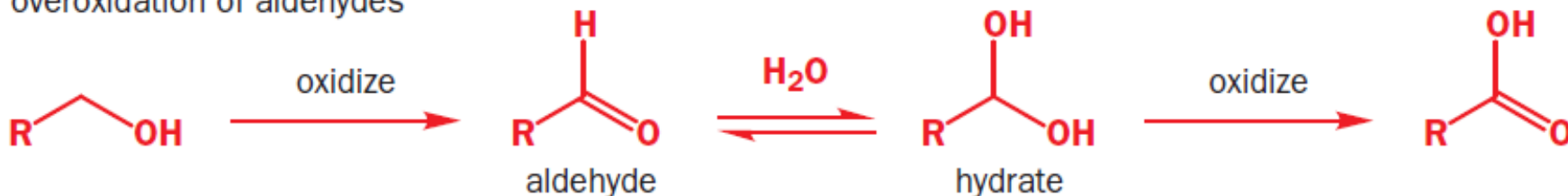
oxidation of alcohols with Cr(VI)



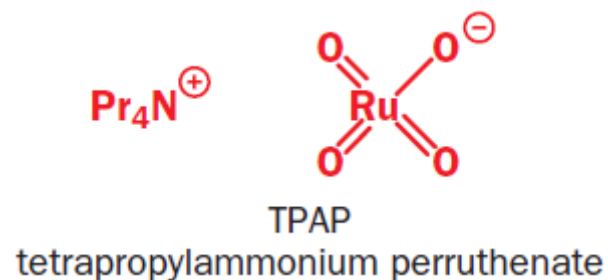
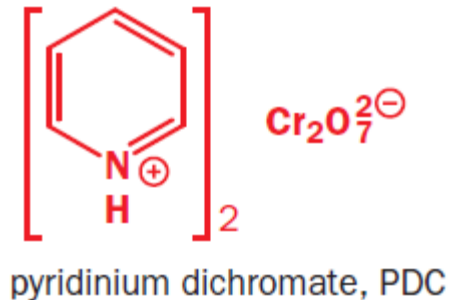
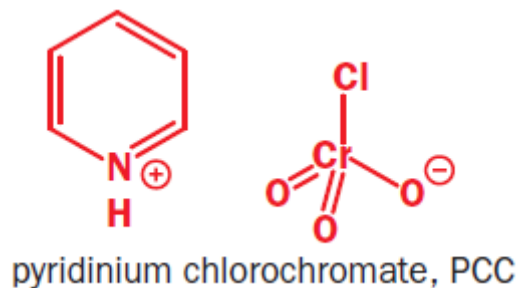
Oxidizing agents

Oxidation of primary alcohols to aldehydes: (overoxidation is easy *via* the hydrate)

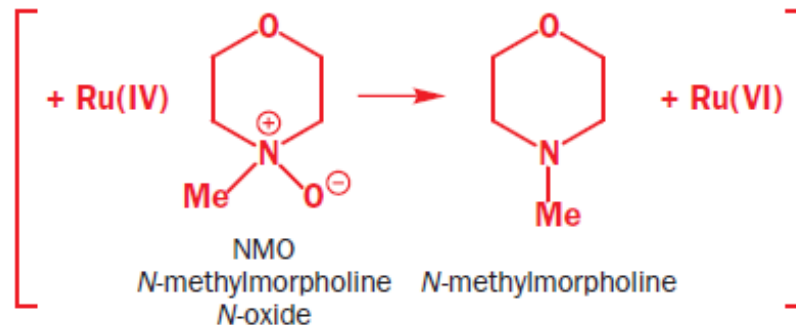
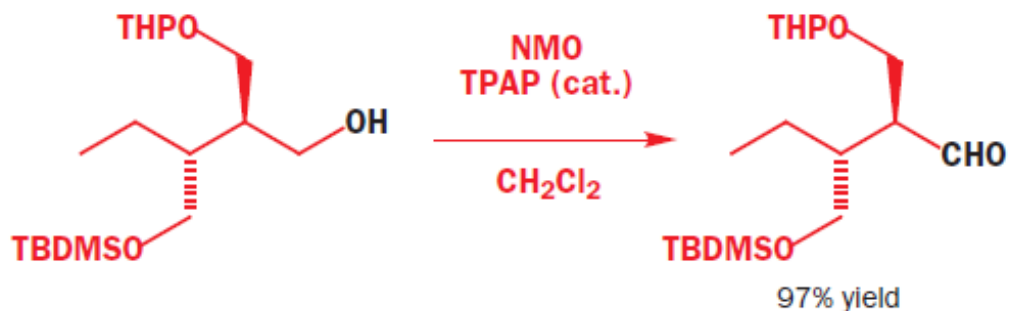
overoxidation of aldehydes



The key thing is to **avoid water**; so use **PCC**, **PDC** or **TPAP** (soluble in DCM)



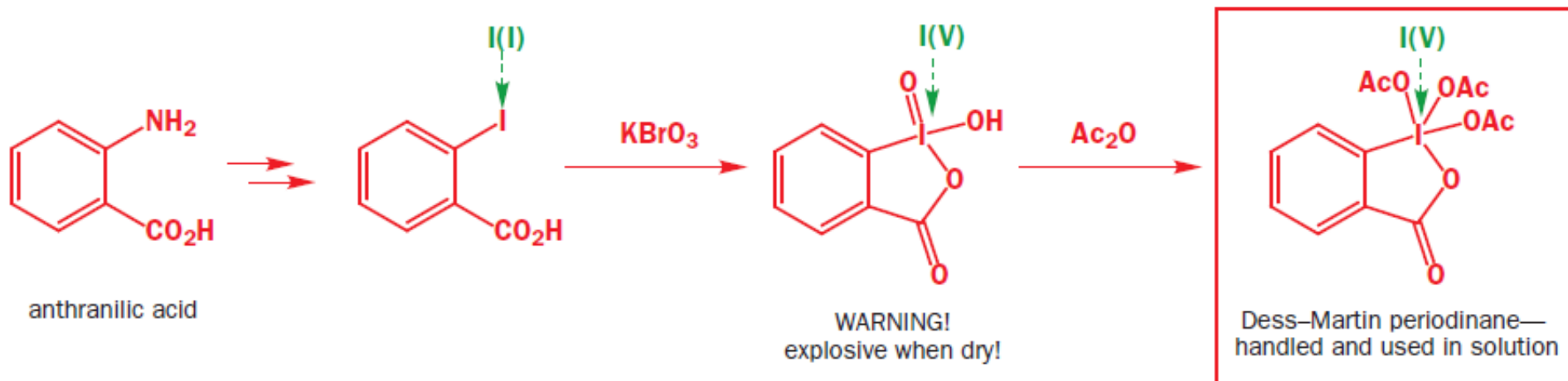
TPAP can be used **catalytically**. The stoichiometric oxidant is '**NMO**'



Oxidizing agents

Oxidation of primary alcohols to aldehydes:

Use **Dess–Martin periodinane** (Iodine(V) reagent made from 2-iodobenzoic acid)



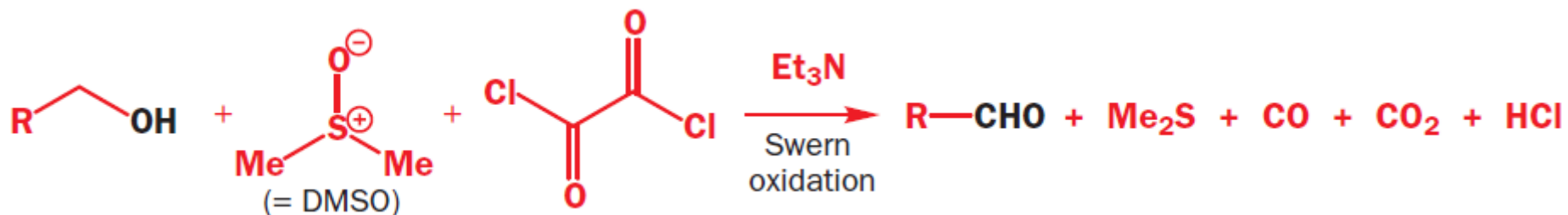
It will oxidize even **very sensitive alcohols** to carbonyl compounds; it oxidise *cis*-allylic alcohol without isomerizing it to trans



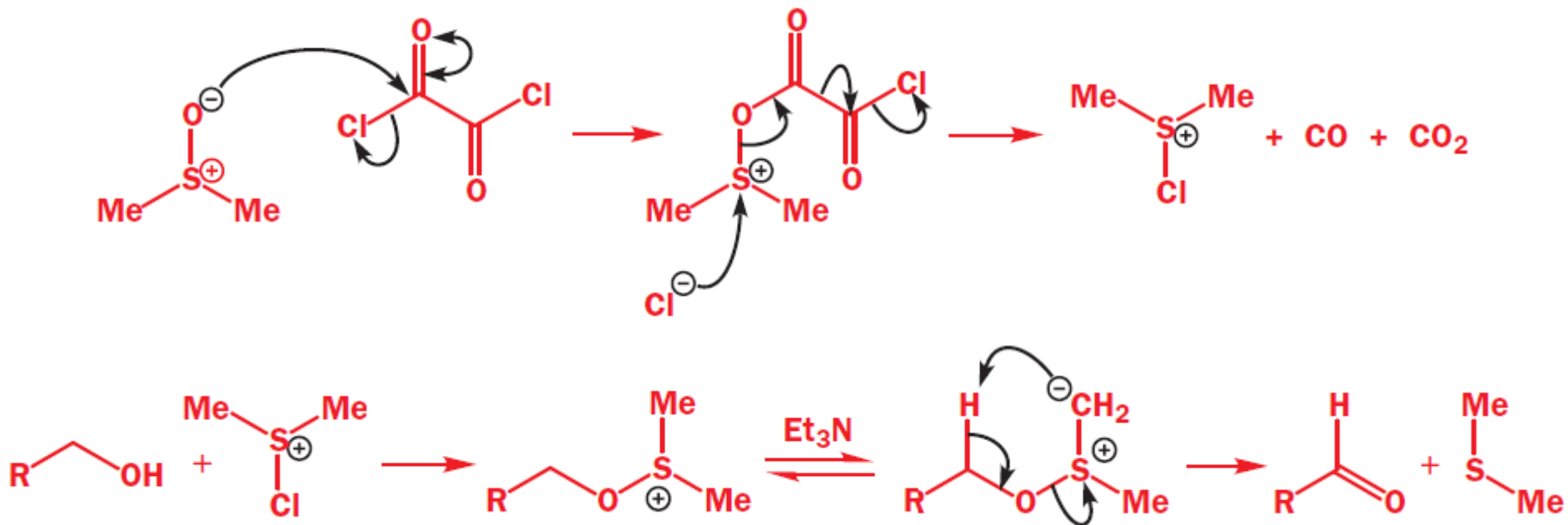
Oxidizing agents

Oxidation of primary alcohols to aldehydes:

Use **Swern oxidation** (uses a sulfoxide [S(IV)] as the oxidizing agent)

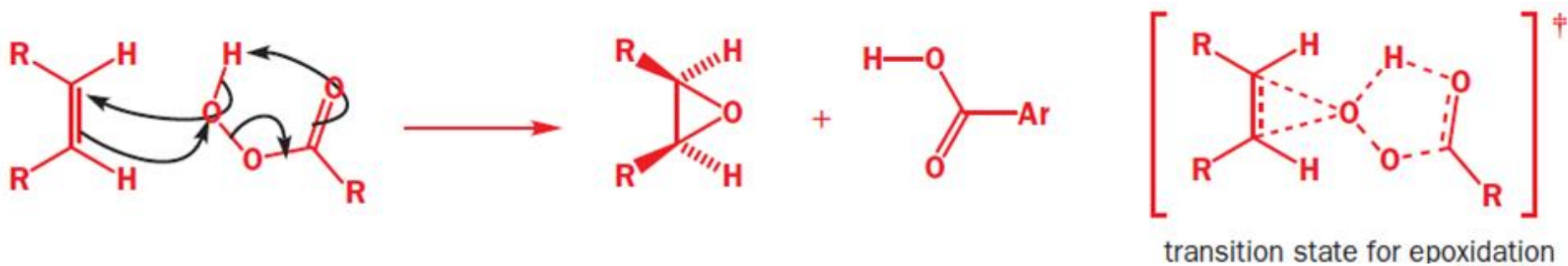
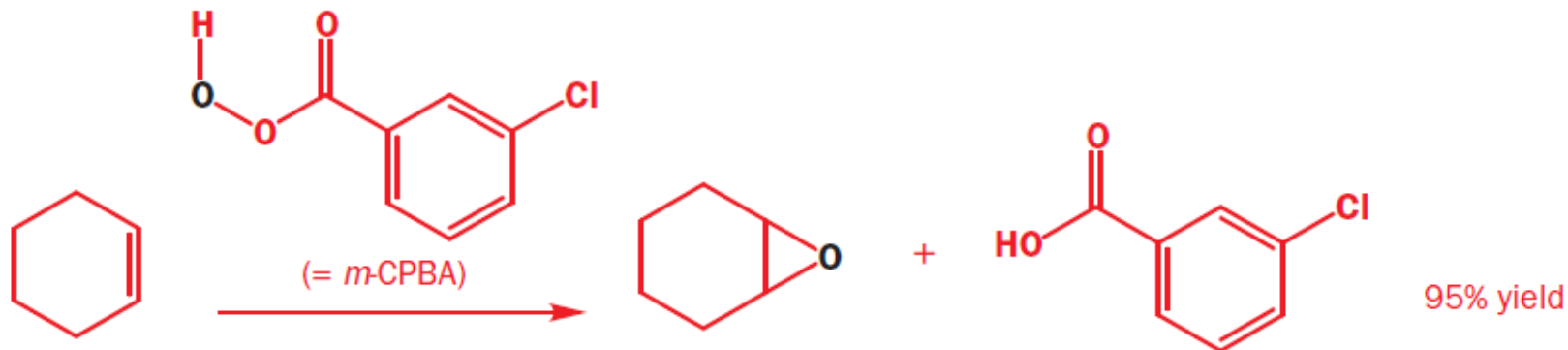


Mechanism

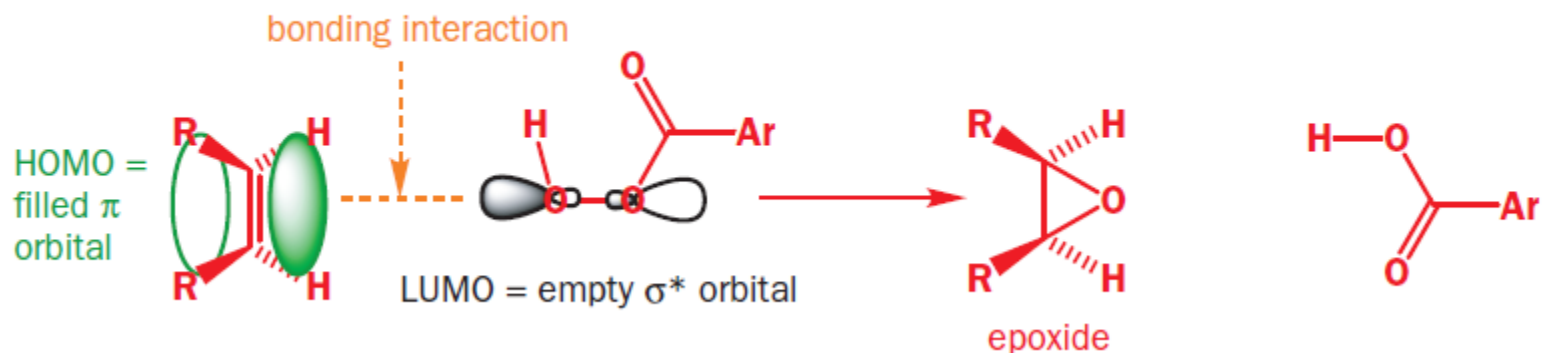


Oxidizing agents

Oxidation of alkenes to epoxides: the most commonly used epoxidizing agents are **peroxy-carboxylic acids** such as *m*-CPBA

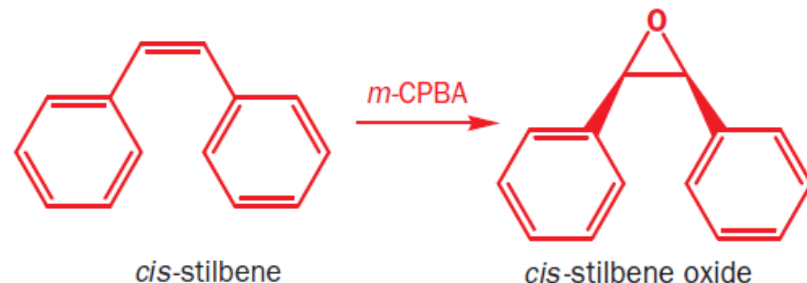
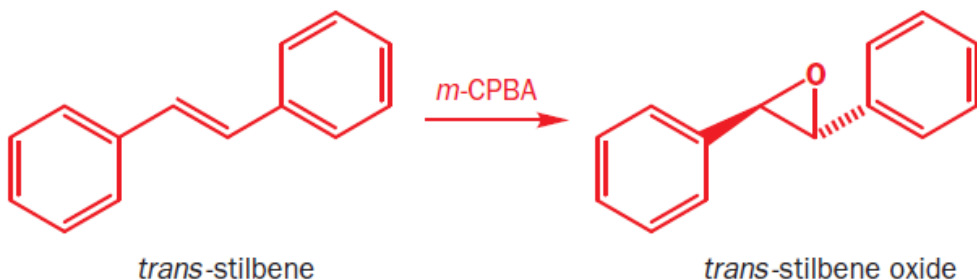


electrophilic attack by a peroxy-acid on an alkene

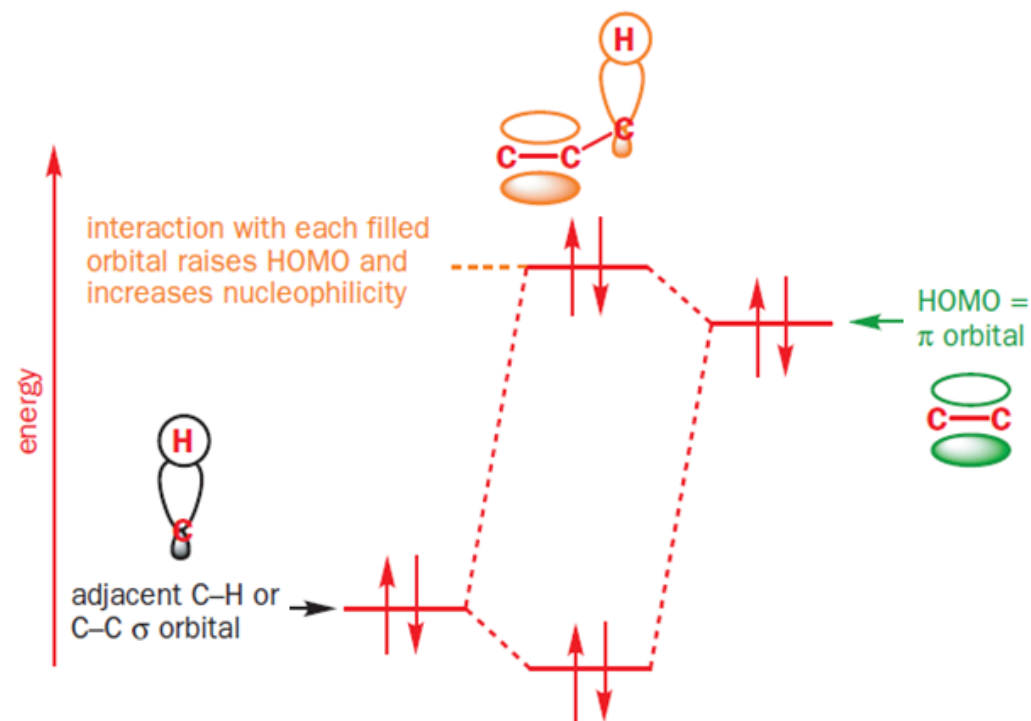


Oxidizing agents

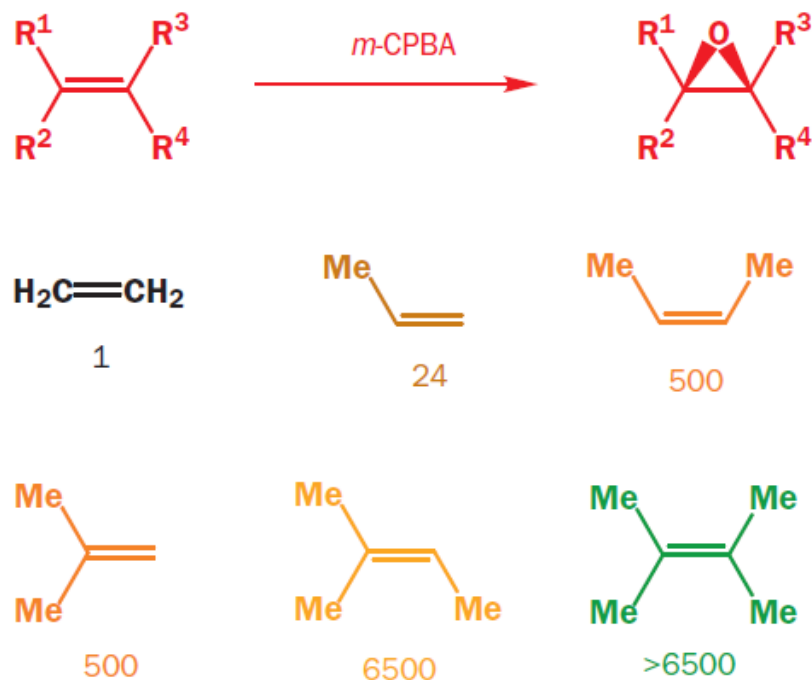
Oxidation of alkenes to epoxides: Epoxidation is **stereospecific**



More substituted alkenes epoxidize **faster**

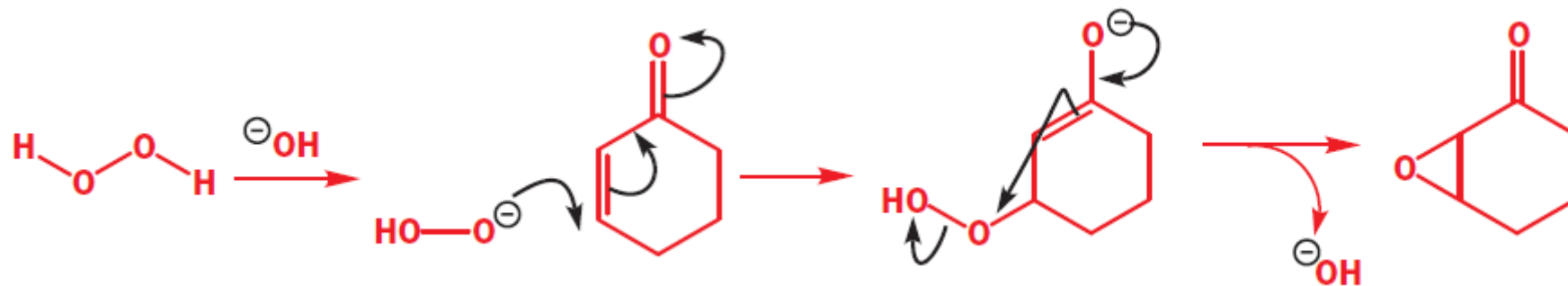


relative rates of reaction of alkenes with *m*-CPBA

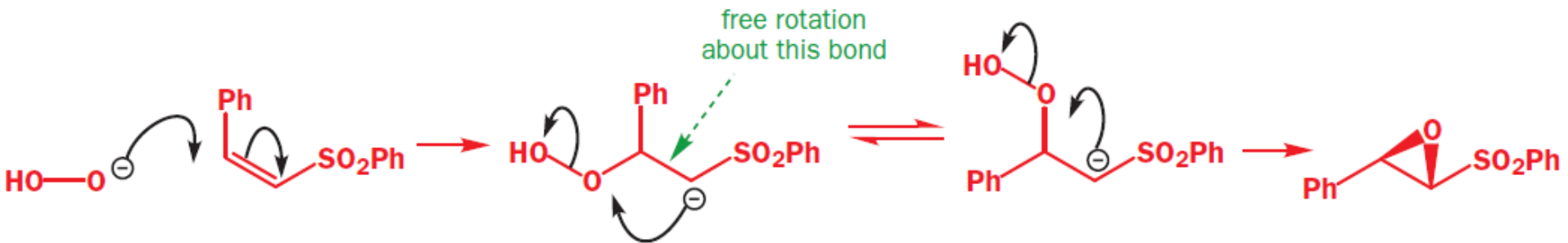
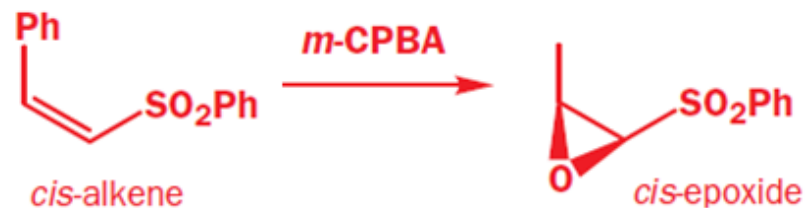
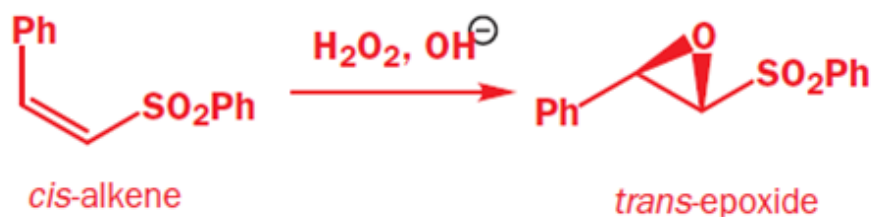


Oxidizing agents

Nucleophilic epoxidation: Use H_2O_2 (good nucleophile due to **alpha effect**) in **base**

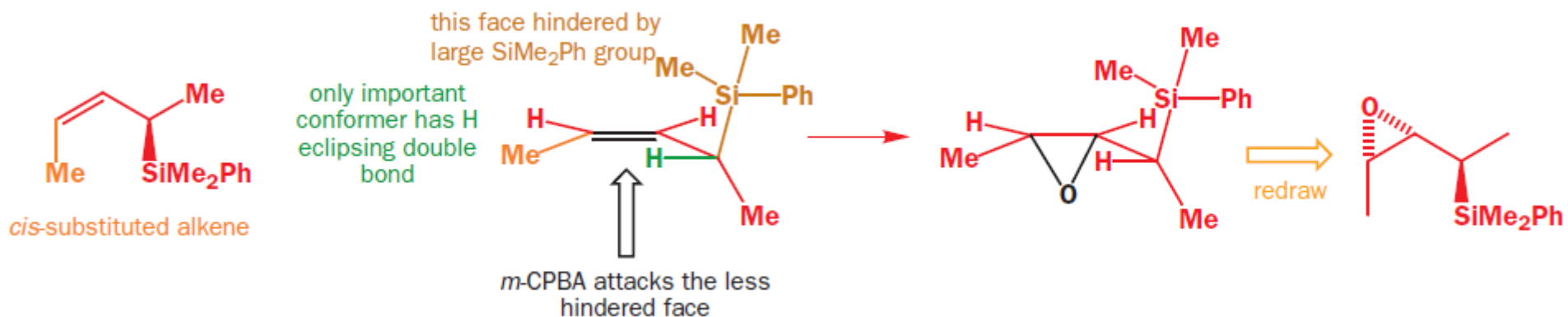


Nucleophilic epoxidation is a **two-step** reaction: there is **free rotation** about the bond marked in the anionic intermediate, and the **more stable, *trans*-epoxide** results

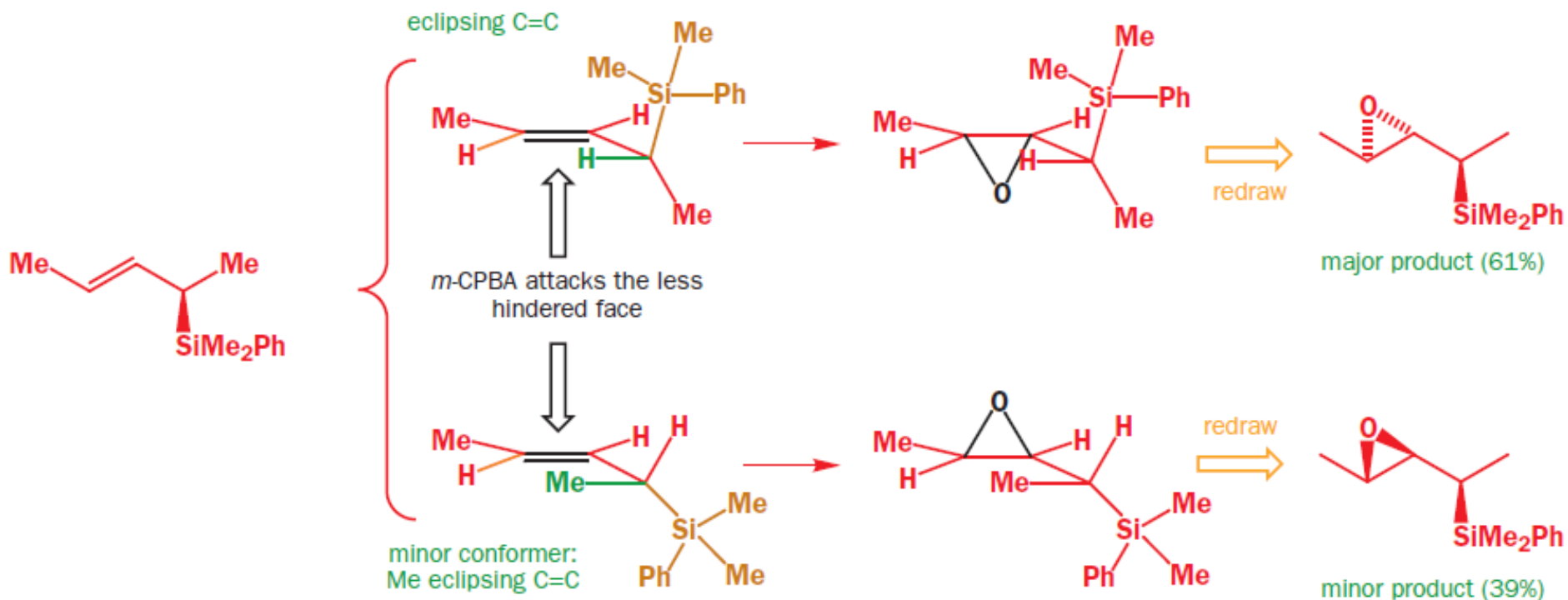


Oxidizing agents

Diastereoselective epoxidation of alkenes:

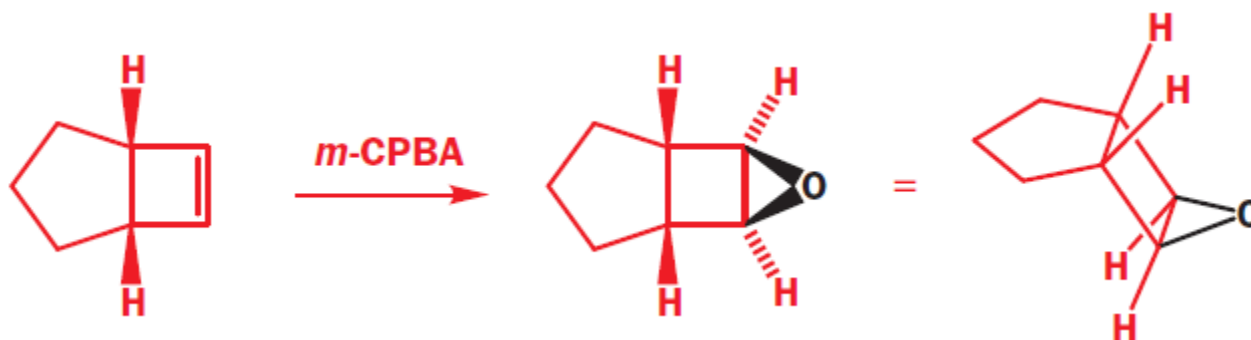
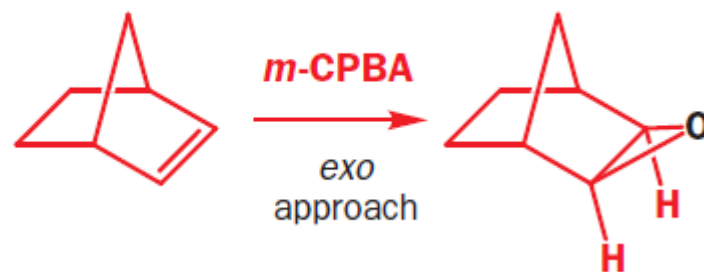
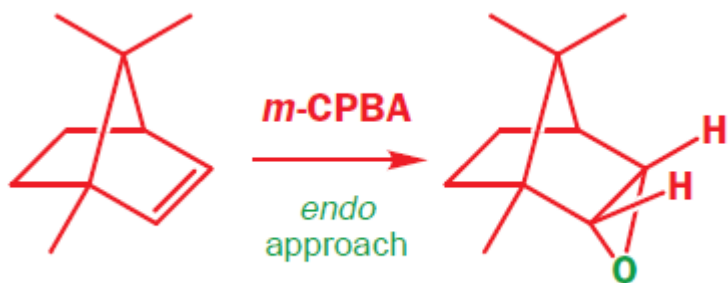
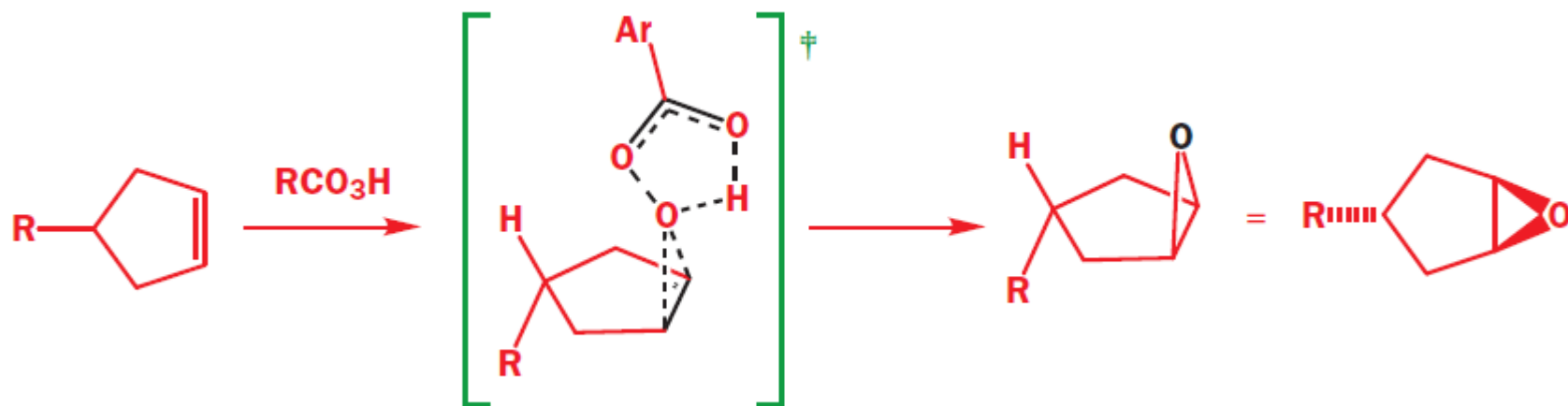


Without the *cis* substituent, selectivity is much lower



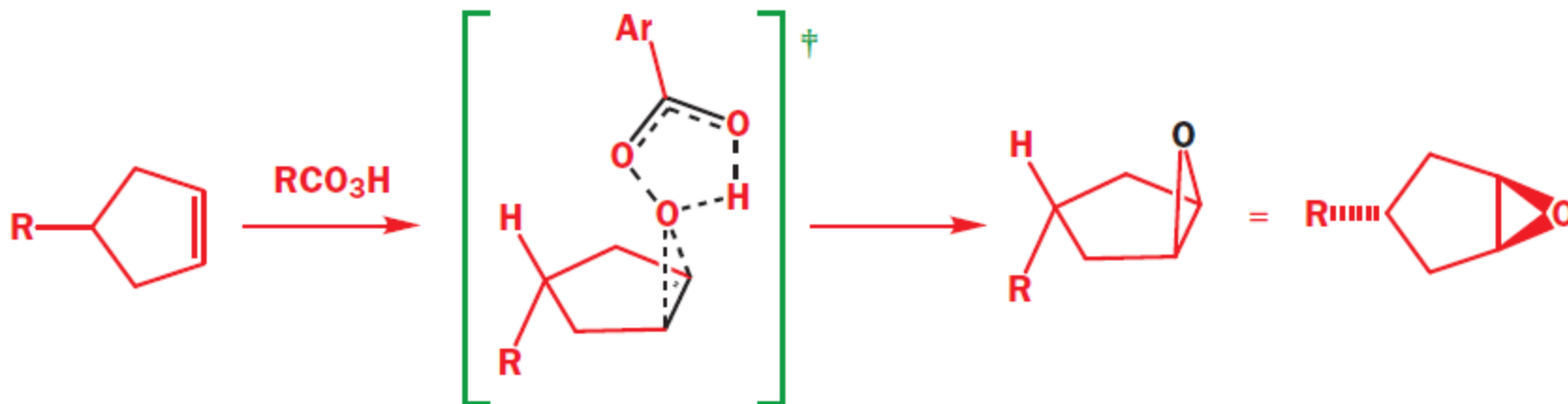
Oxidizing agents

Oxidation of alkenes to epoxides: stereoselectivity in a ring system

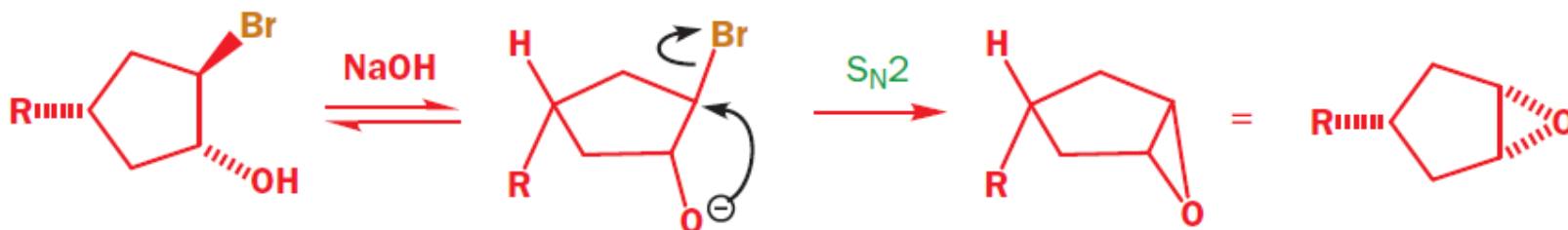
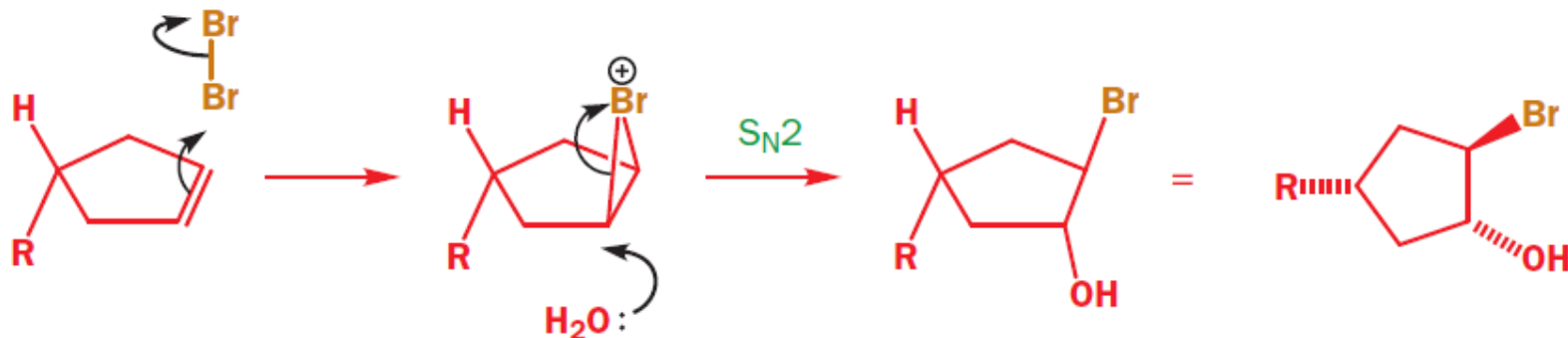


Oxidizing agents

Oxidation of alkenes to epoxides: stereoselectivity in a ring system

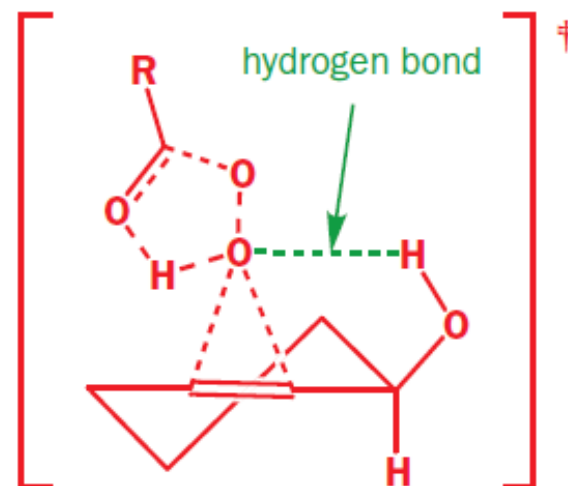
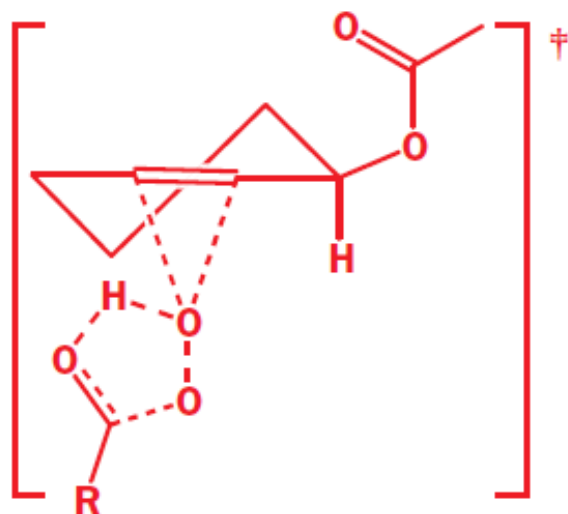
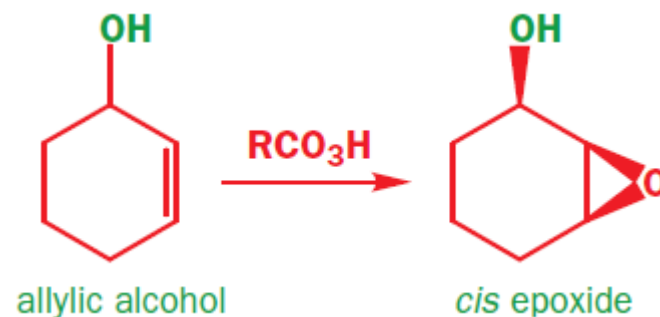
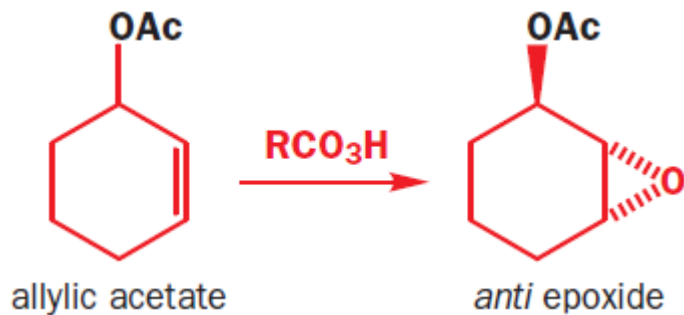


Bromination in water: giving opposite stereoselectivity



Oxidizing agents

Oxidation of alkenes to epoxides: stereoselectivity in a ring system

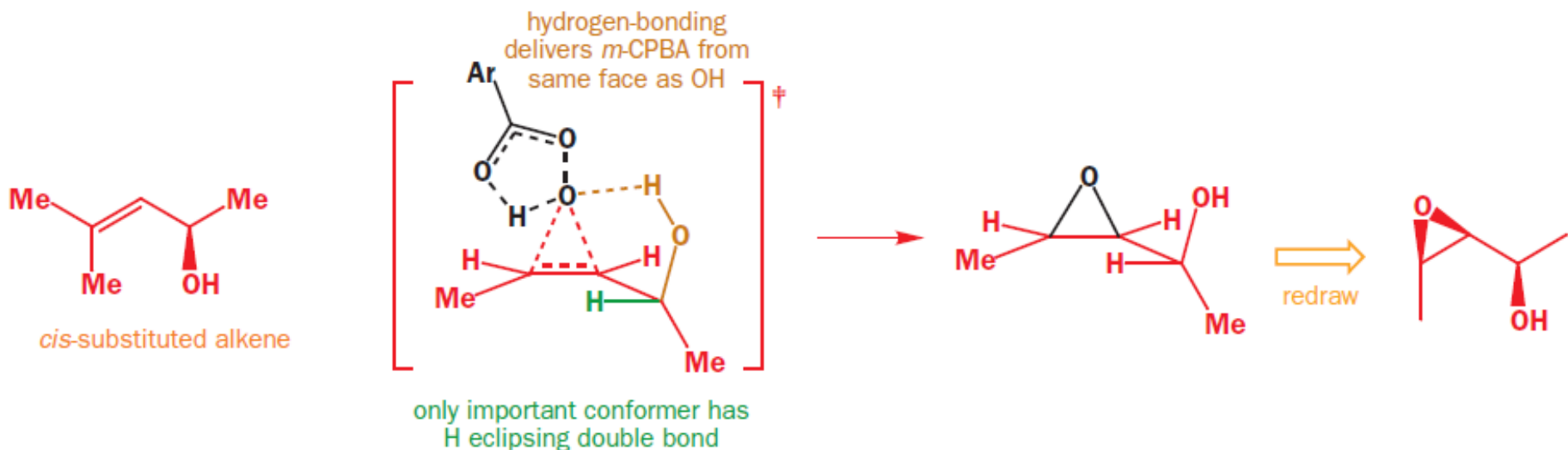
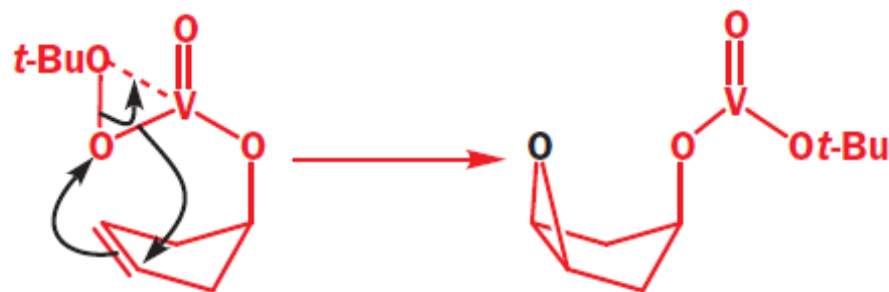
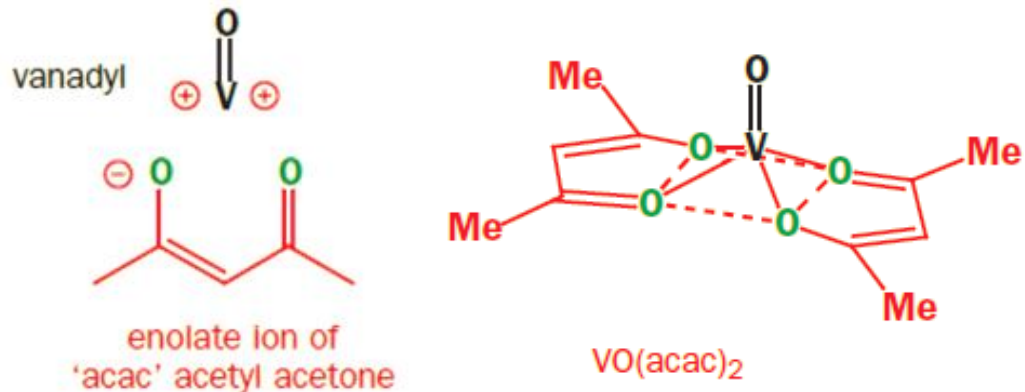
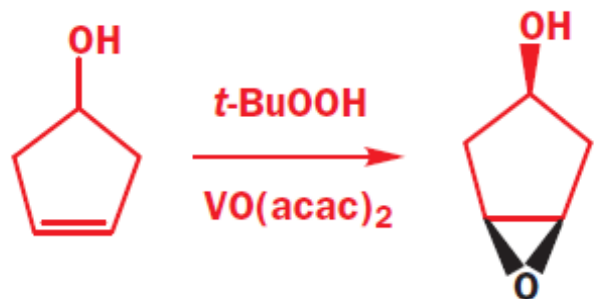


green hydrogen bond favours attack on same face as OH

Oxidizing agents

Oxidation of alkenes to epoxides:

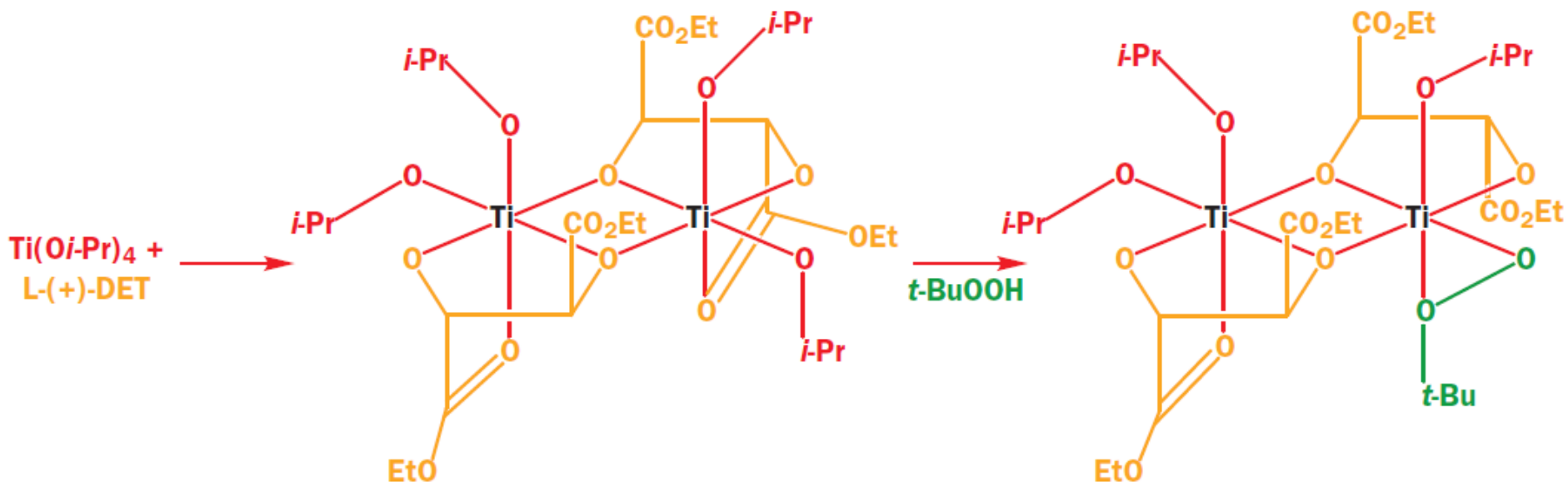
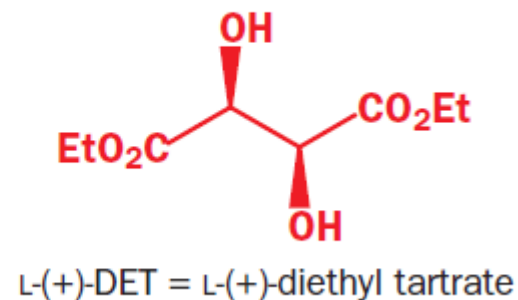
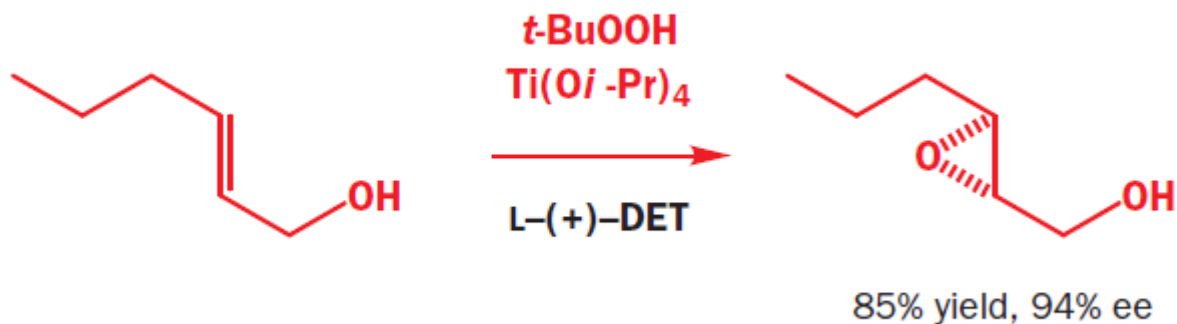
using vanadium complex $\text{VO}(\text{acac})_2$ combined with $t\text{-BuOOH}$, giving *syn* epoxide

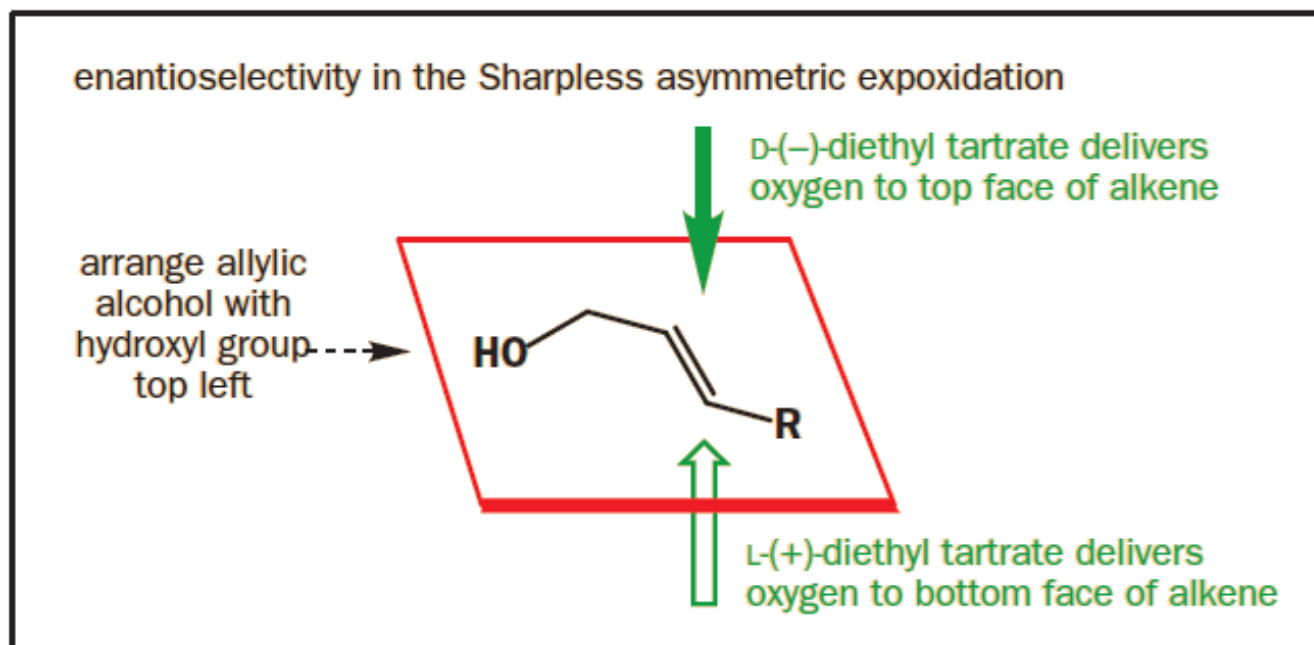
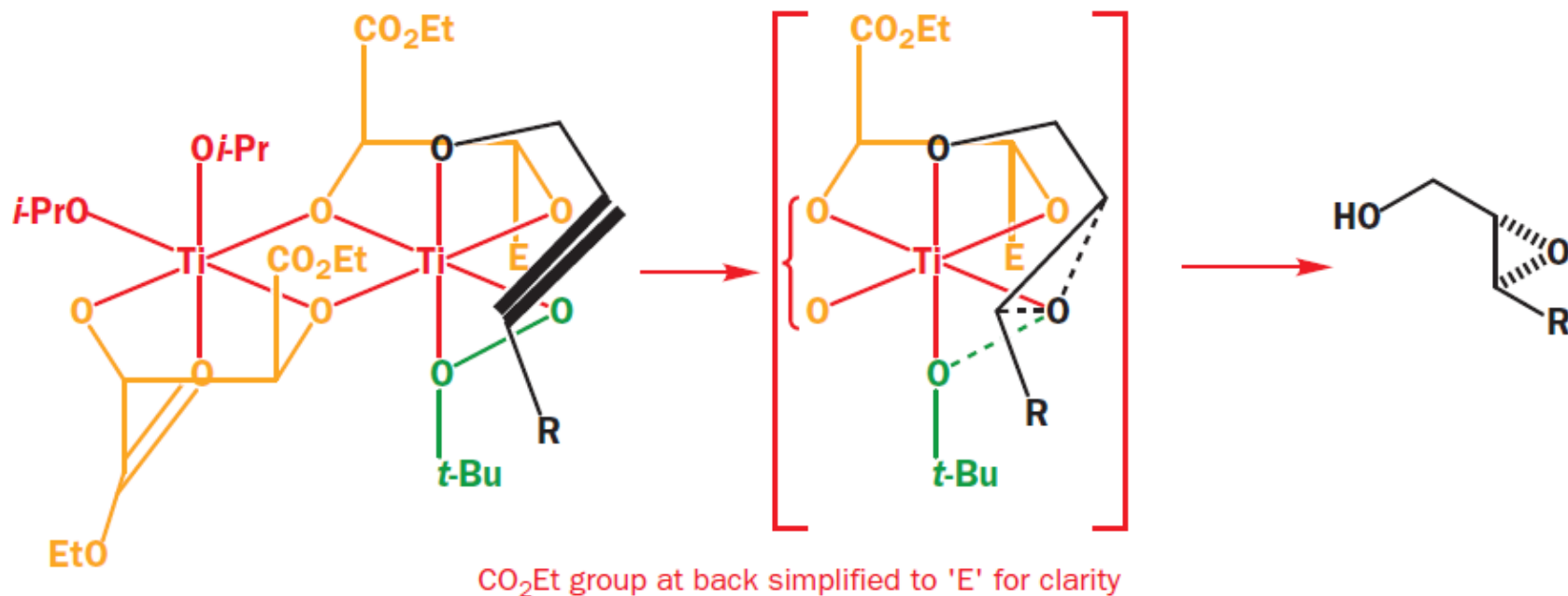


Oxidizing agents

Asymmetric epoxidation of allylic alcohol

by adding a **chiral ligand** to the titanium catalyst, it might lead to asymmetric reaction. The ligand that works best is **diethyl tartrate**

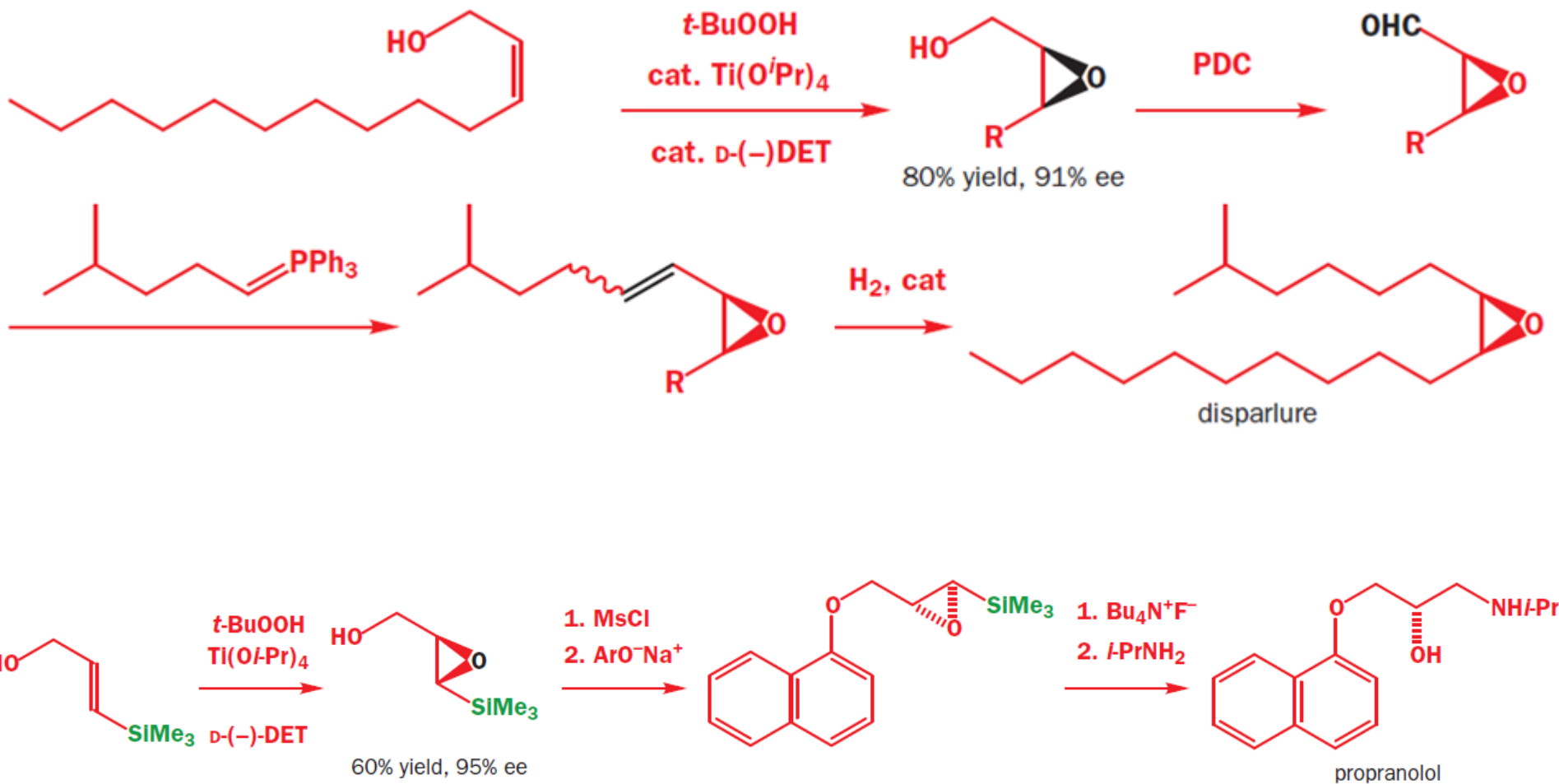




Oxidizing agents

Asymmetric epoxidation of allylic alcohol

Examples:

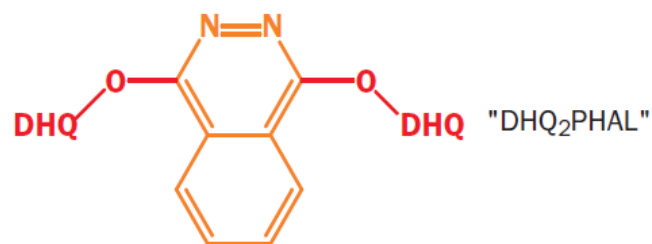
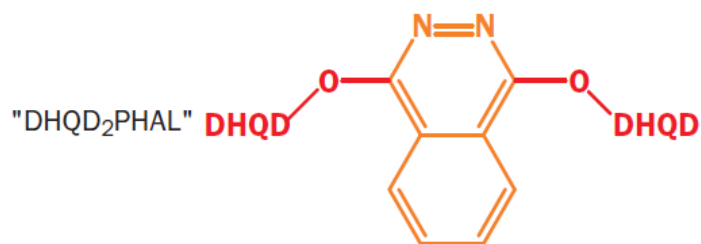
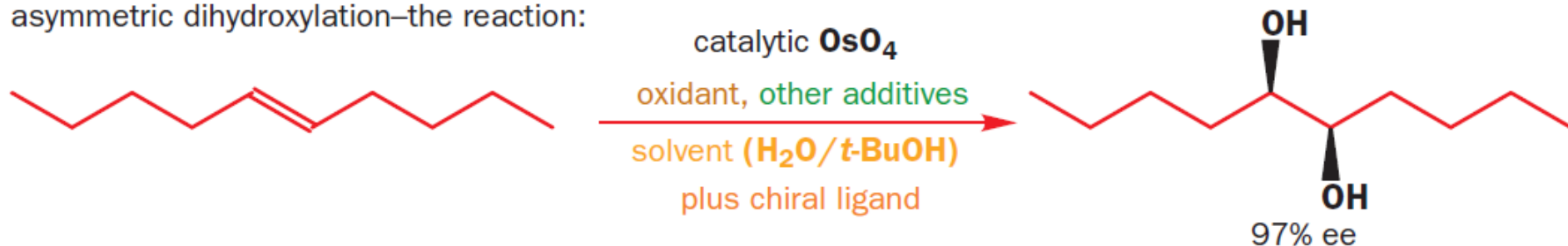


Oxidizing agents

Asymmetric dihydroxylation

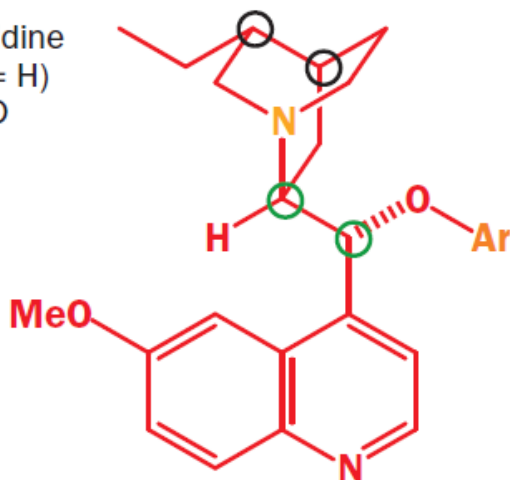
chiral version of the **syn dihydroxylation** of alkenes by **osmium tetroxide**

asymmetric dihydroxylation—the reaction:

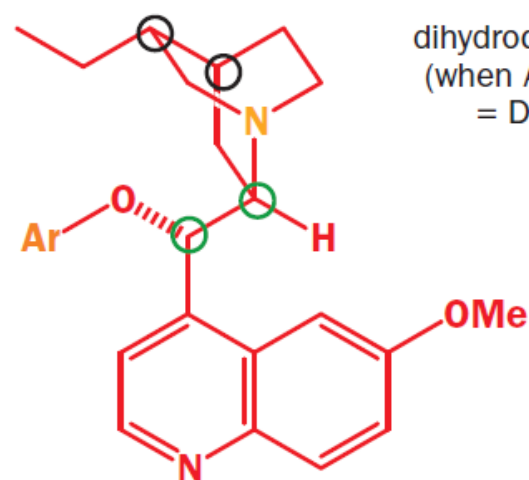


phthalazine-based ligands

dihydroquinidine
(when Ar = H)
= DHQD



dihydroquinine
(when Ar = H)
= DHQ



Oxidizing agents

Asymmetric dihydroxylation

