

Rouen Cathedral
Claude Monet, 1892-94

7. Reductions

The synthesis of an organic compound must pay attention to ...

Carbon backbone
(Chapters 2–4)



Functional groups

Functional Group Interconversion (FGI)

I. Nucleophilic Substitutions

Electrophilic Additions to C=C

Addition-Eliminations on Carboxylic Acids and Derivatives

II. Reductions

III. Oxidations

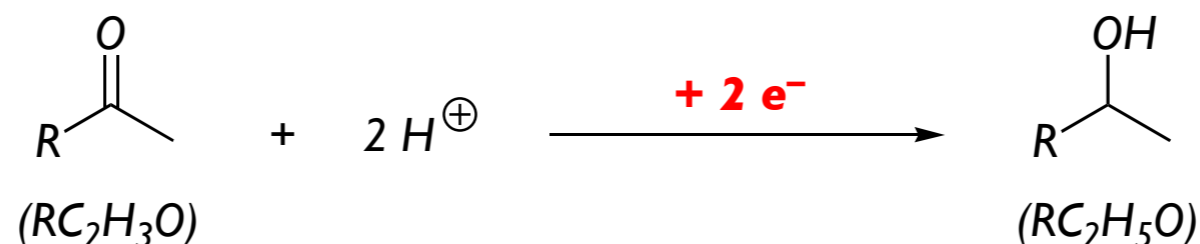
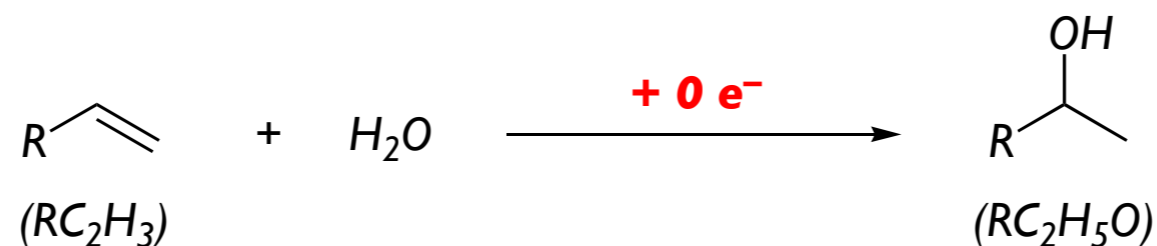
III. Oxidations

Mechanism!!!

■ **Redox: electronic, e^- , interchange**

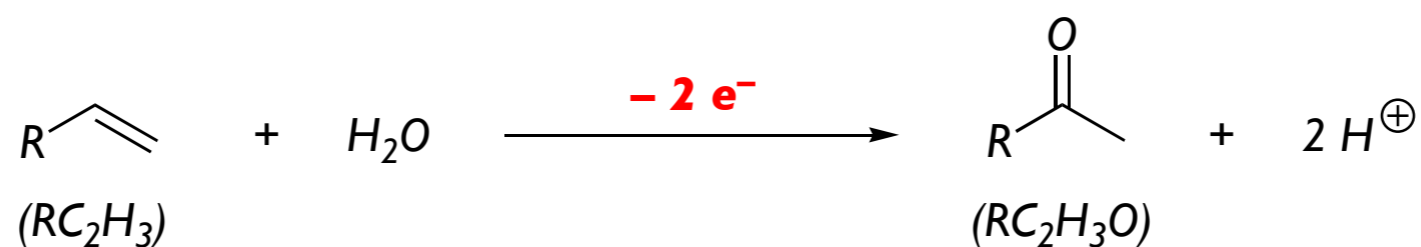
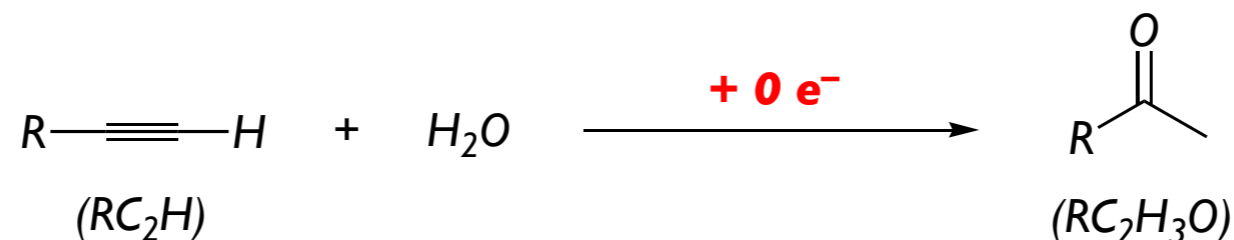
Reduction: gain Oxidation: loss

Hydration



Reduction

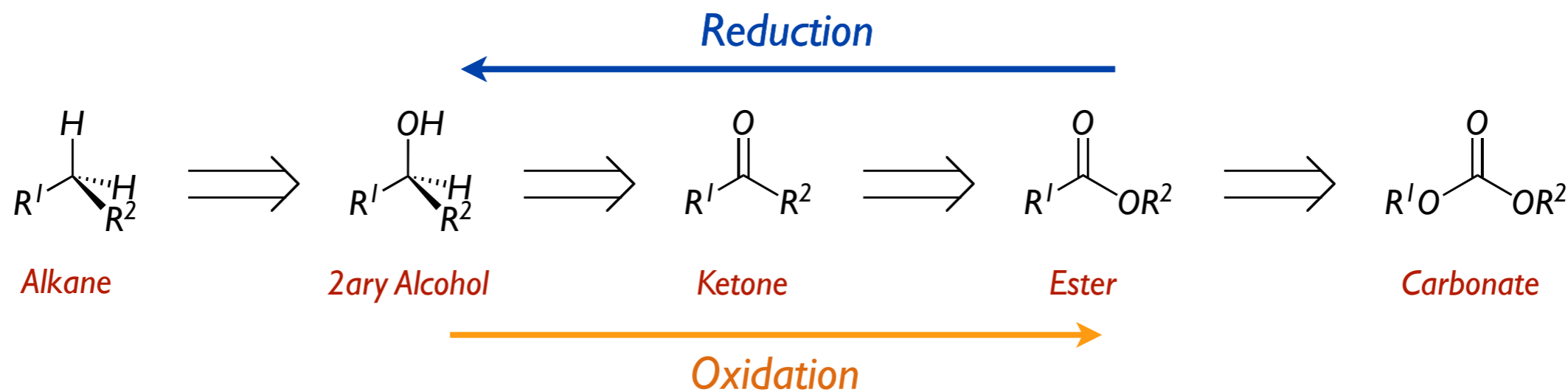
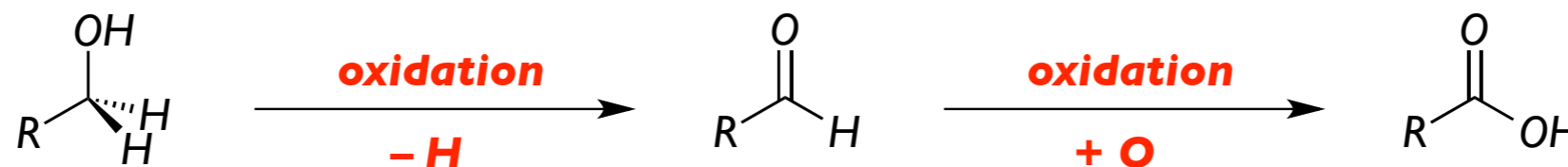
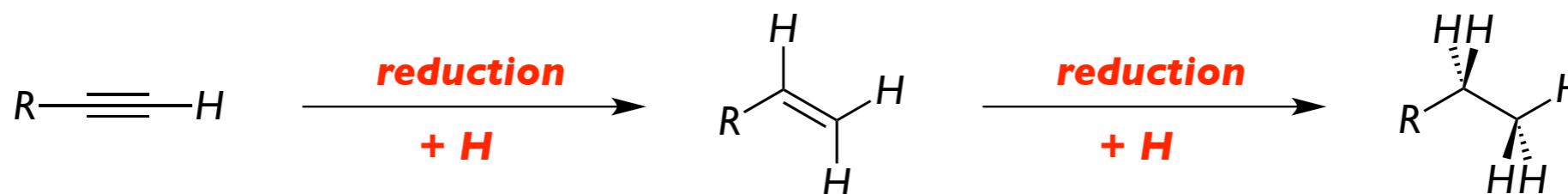
Hydration



Oxidation

■ **Redox: interchange of H or O**

Reduction: gain of H/loss of O Oxidation: gain of O/loss of H

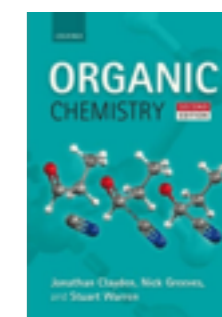


■ *Reductive processes:*

- a) *Dissolving metal reductions*
- b) *Radical reductions*
- c) *Reductions with hydrides*
- d) *Catalytic hydrogenations*
- e) *Carbonyl deoxygenation reactions*

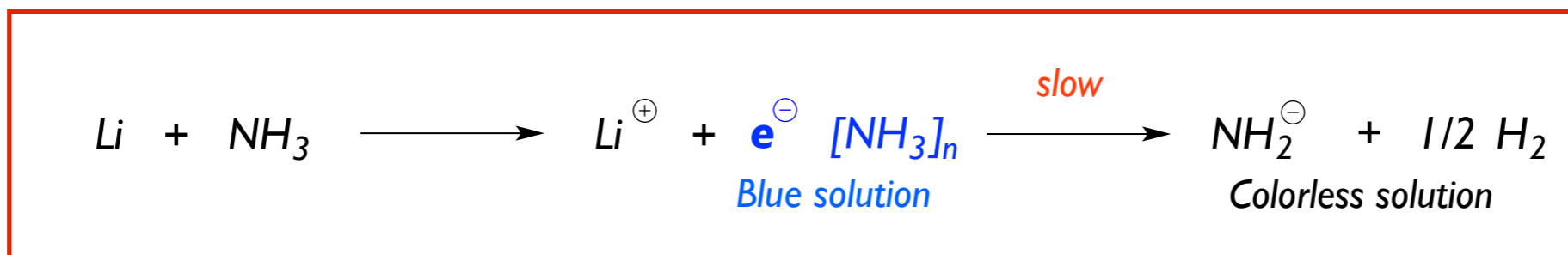


Different Chaps.



*Chap. 23
mainly*

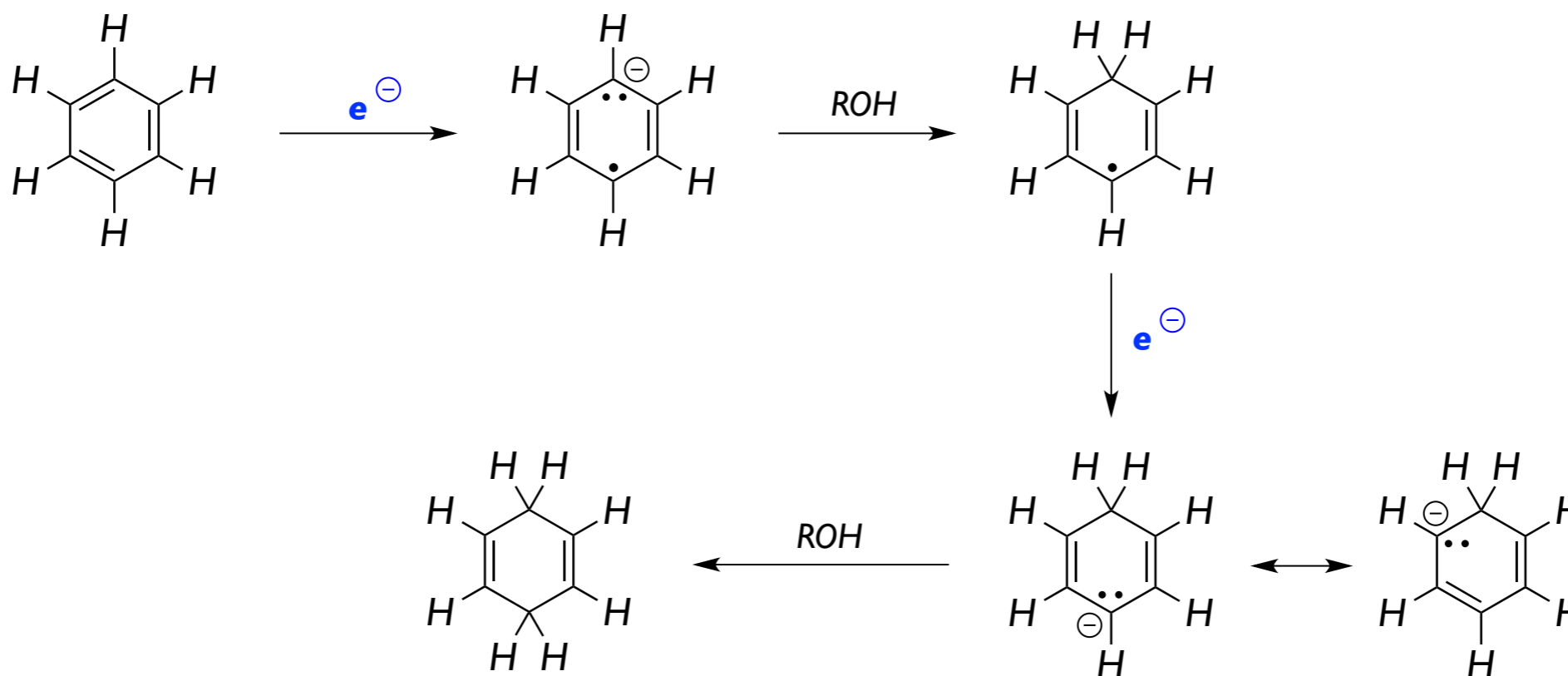
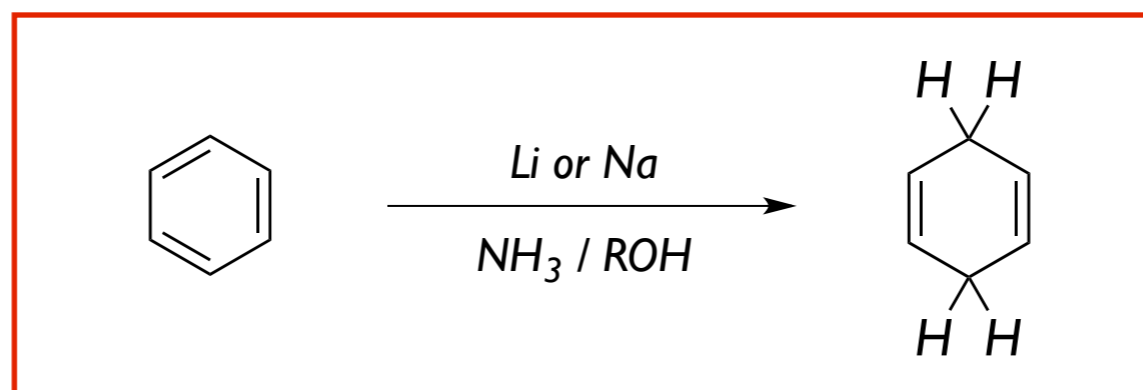
- *Lithium or sodium metals give very easily the electron from the valence shell*



Electrons are the simplest reducing agents and they reduce any functional group with a low-energy π^ orbital :*

BIRCH REDUCTION
ALKYNE REDUCTION
CARBONYL REDUCTION

■ Birch reduction converts phenyl groups in 1,4-cyclohexadienes

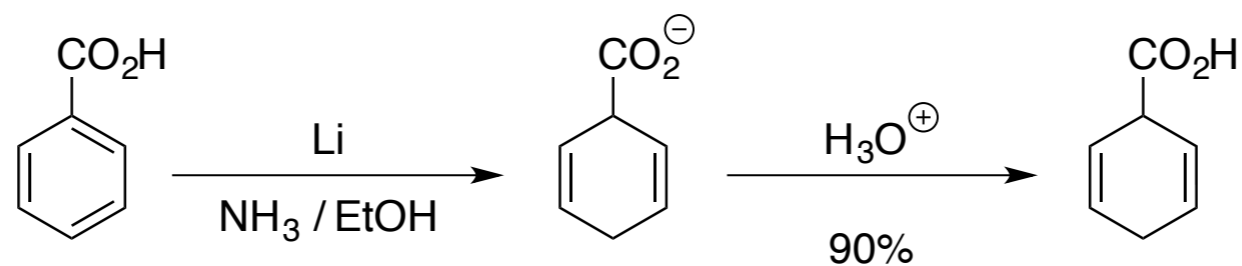
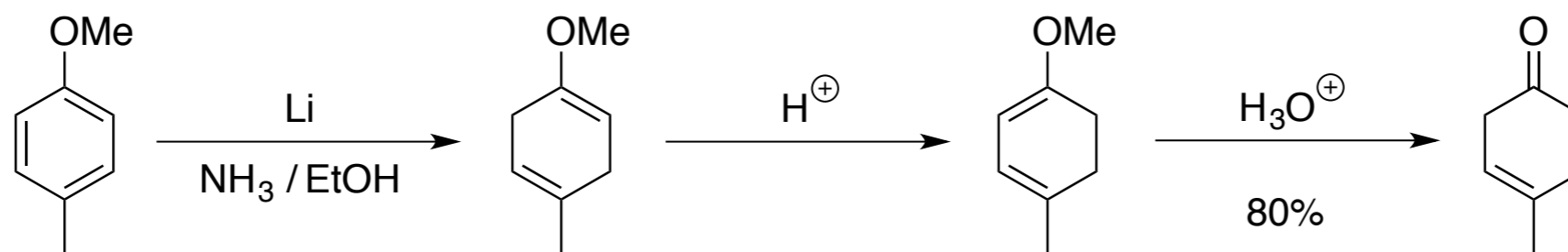


The reduction proceeds with a remarkable regioselectivity ...

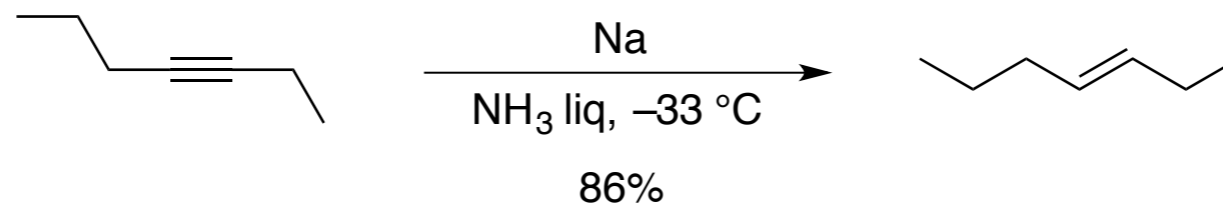
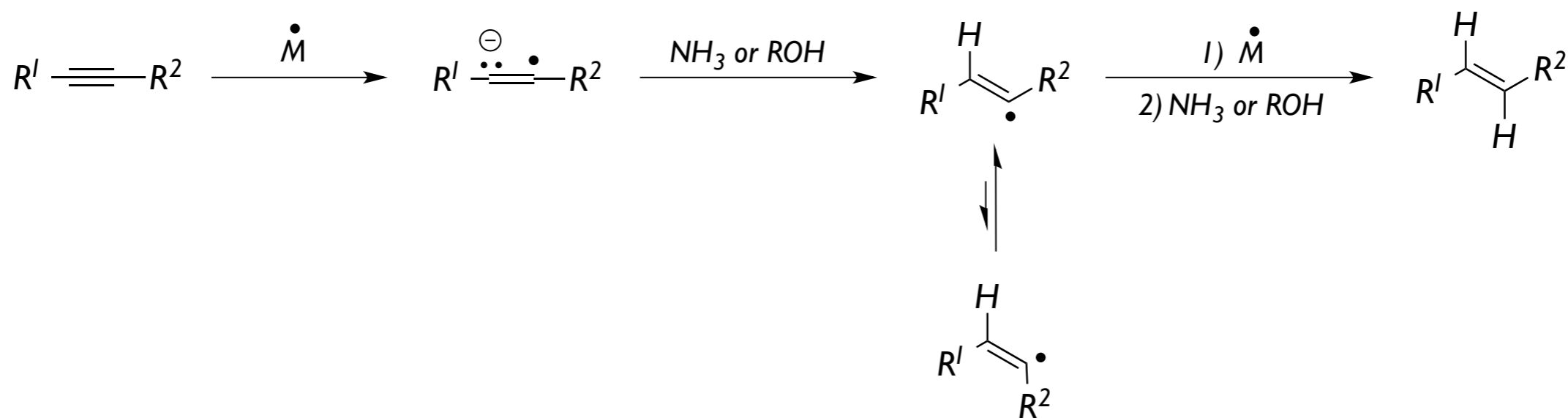
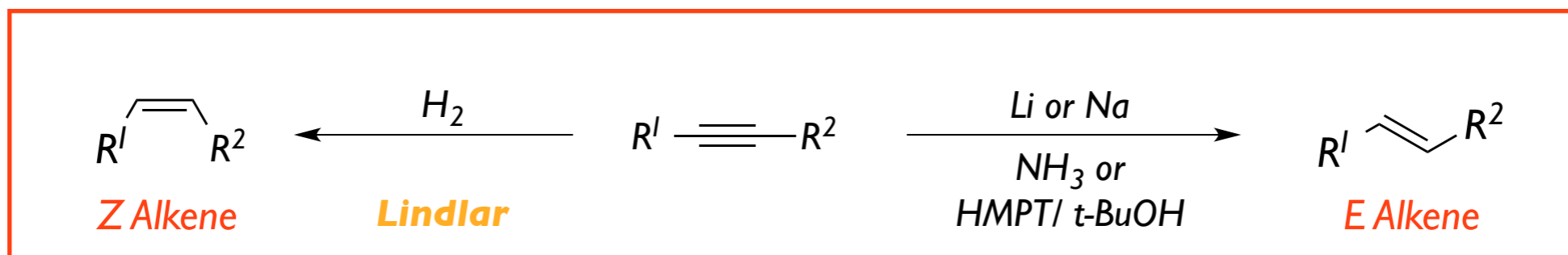


EWG: CO₂R, CN, NO₂

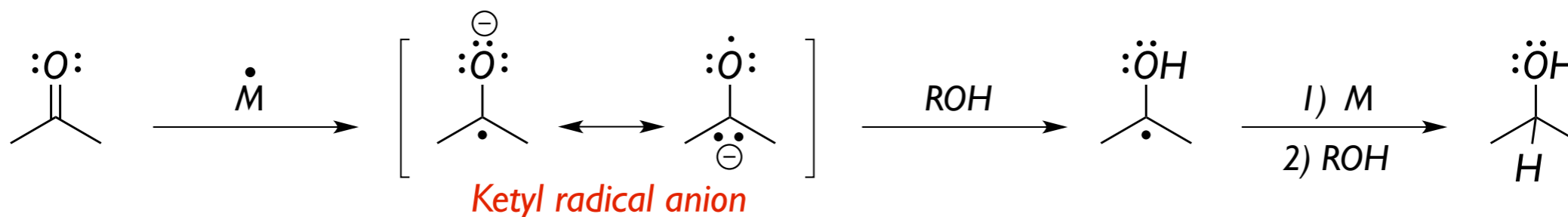
EDG: OMe, NR₂, Alkyl



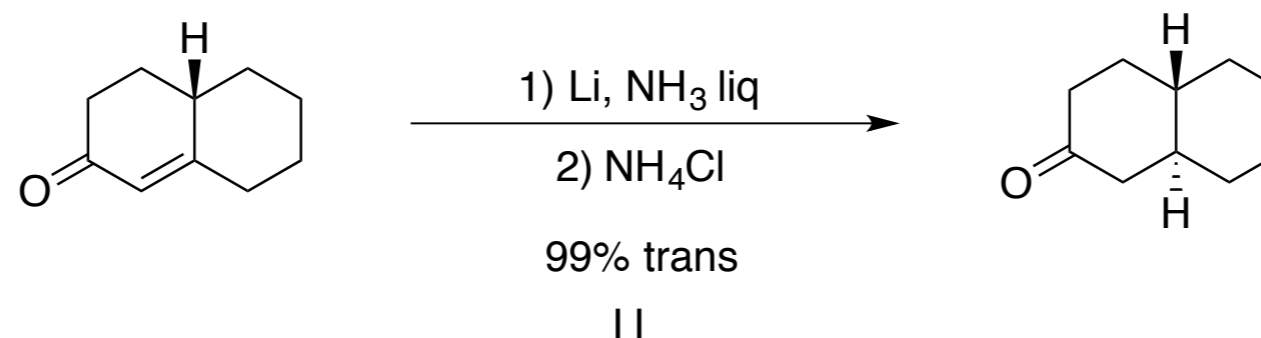
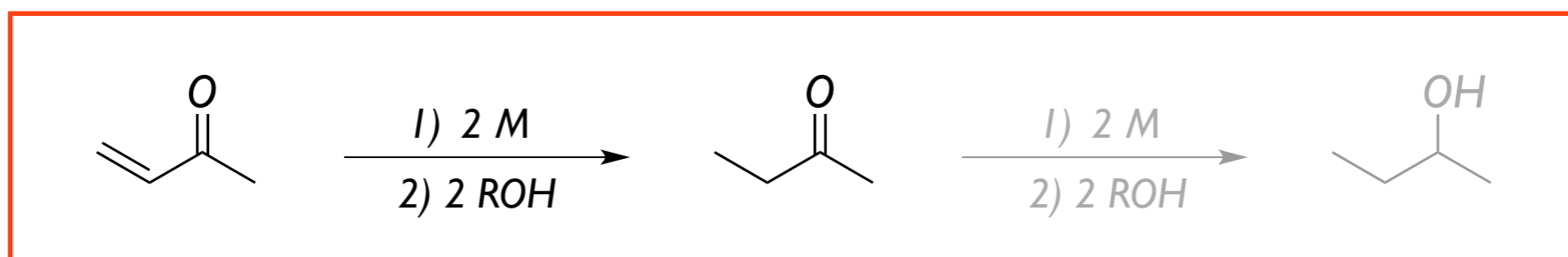
■ Alkynes are converted into *E*-alkenes stereoselectively



■ Carbonyl groups can be reduced to alcohols

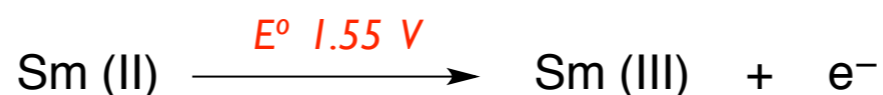
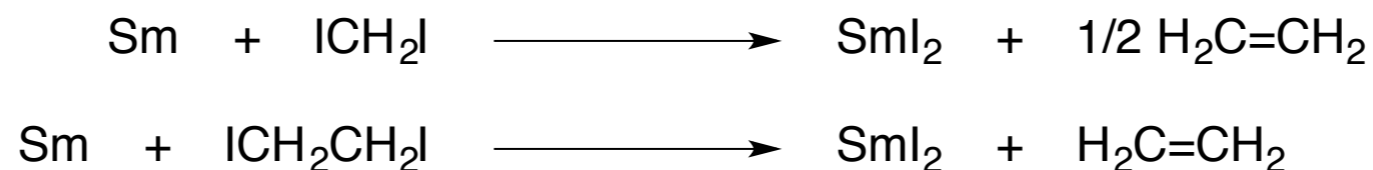


For a synthetic point of view this procedure is not very important.
It is more useful the reduction of unsaturated carbonyl groups



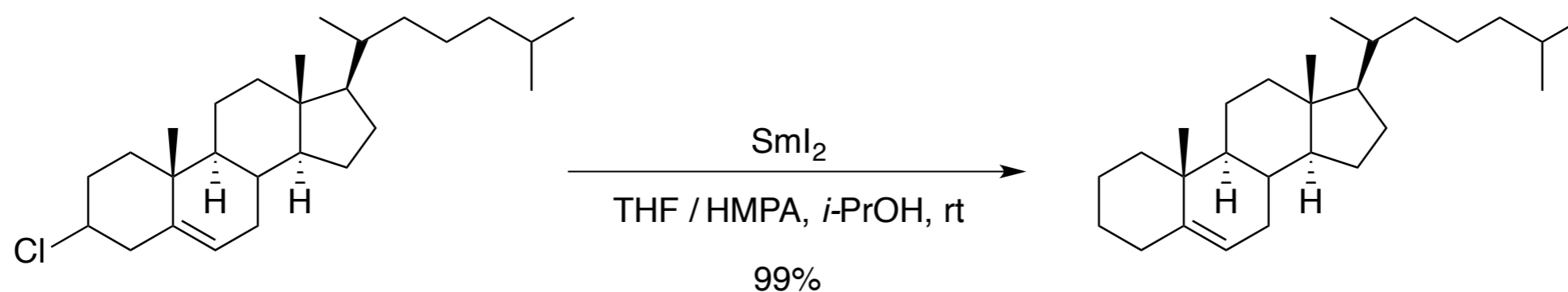
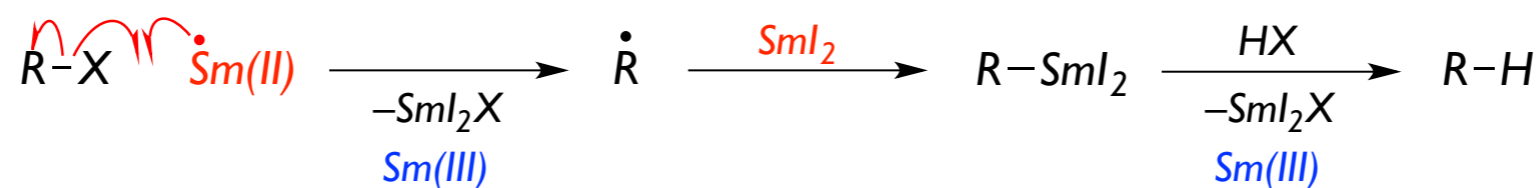
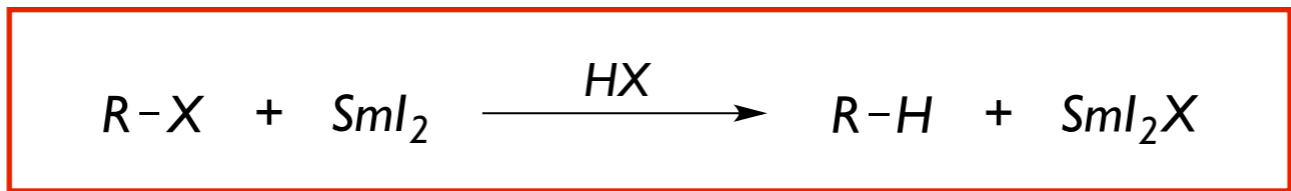
Samarium diiodide (SmI₂) is a single-electron reducing agent particularly useful in C-C bond formations and transformations of several functional groups

Nicolaou, K. C. *ACIE* 2009, 48, 7140; Procter, D. J. *ACIE* 2012, 51, 9238

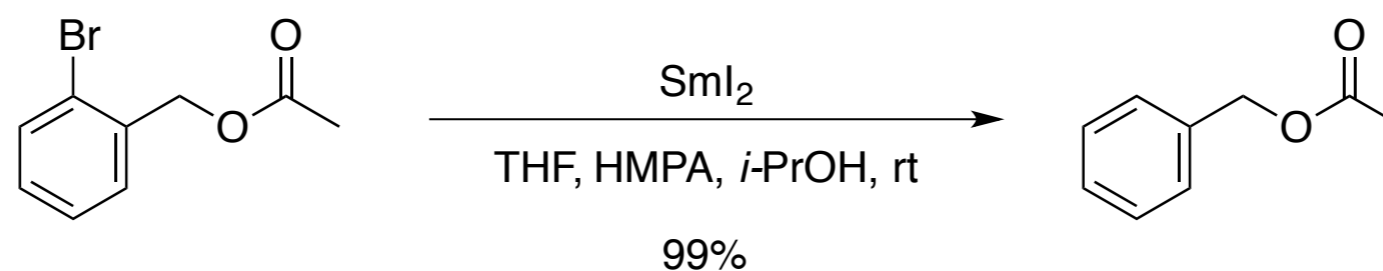


The reactivity of SmI₂ is significantly affected by the choice of solvent. It reduces organic halides, aldehydes, ketones and α-functionalized carbonyls

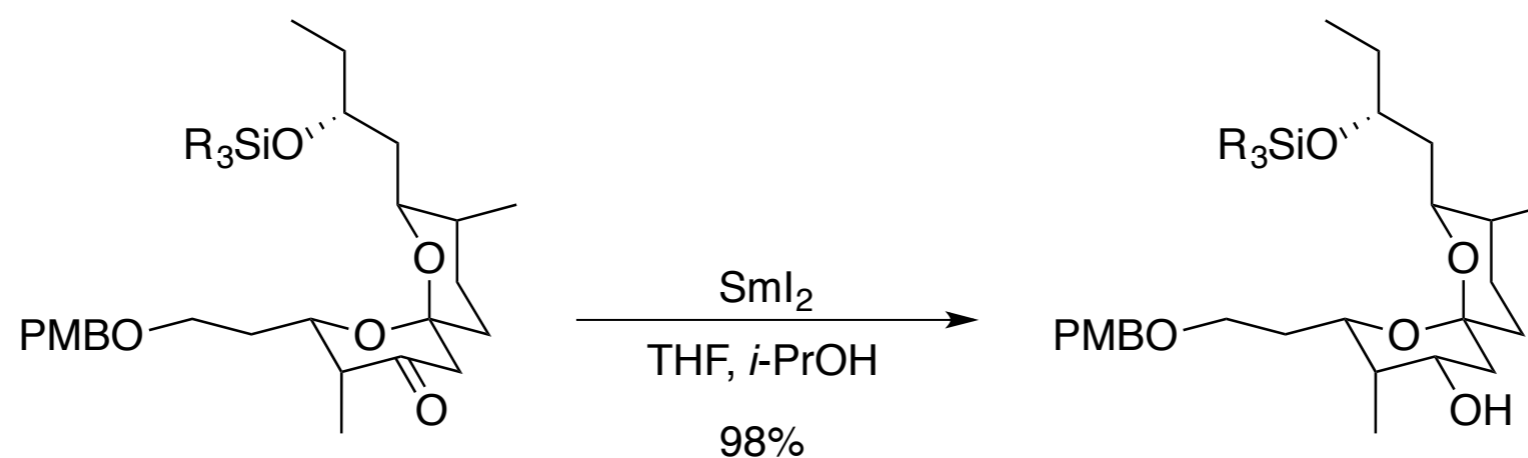
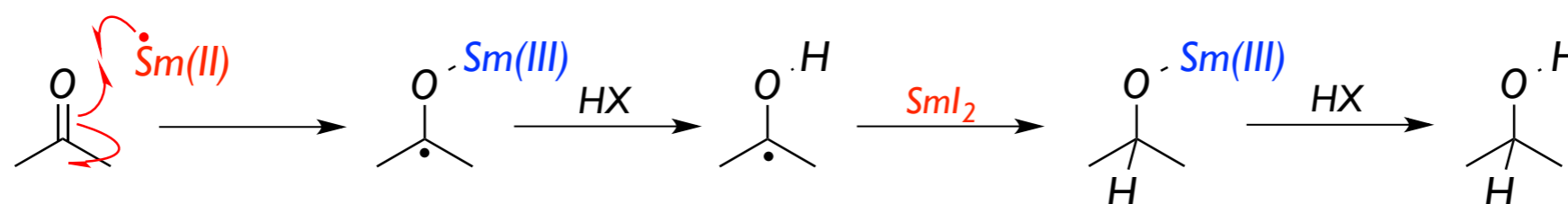
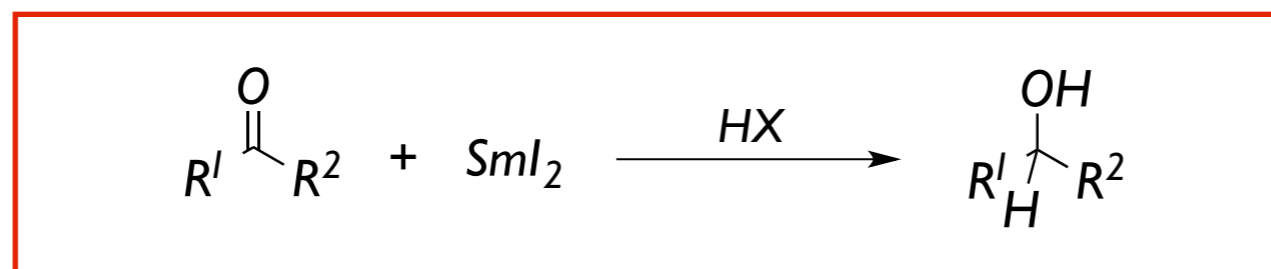
■ Organic halides can be reduced to hydrocarbons



Corey, E.J. *JACS* 1987, 109, 6187

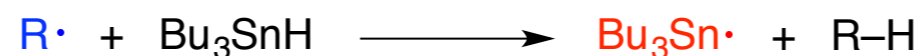
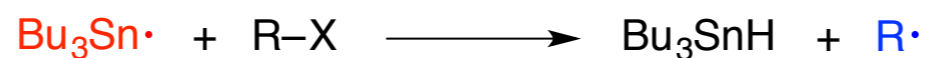
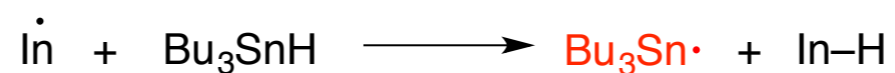


■ Aldehydes and ketones can be reduced to alcohols

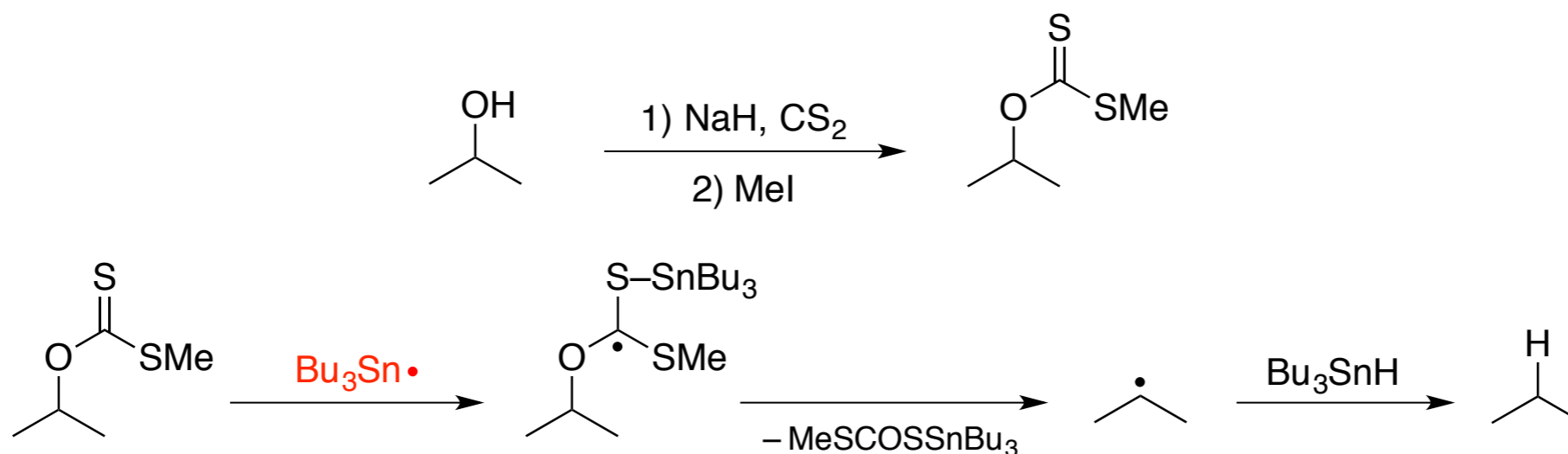


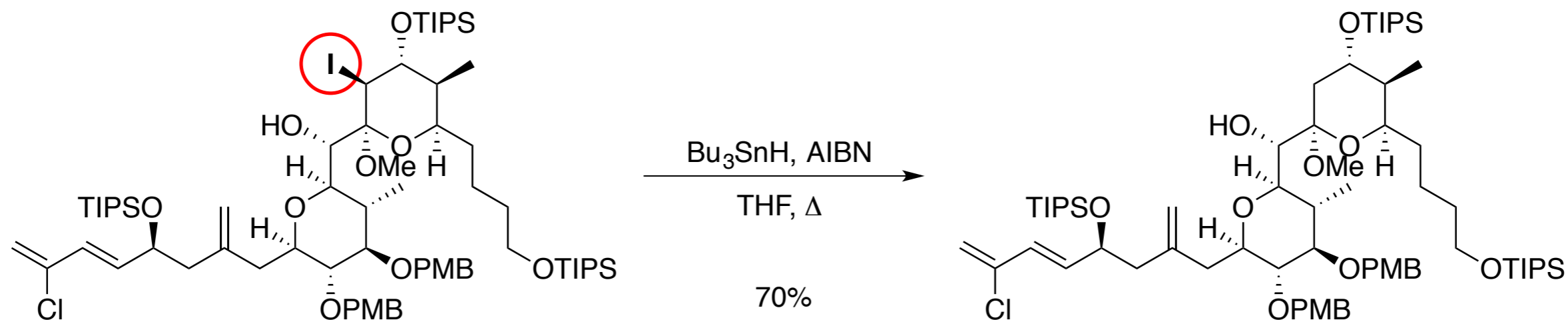
Evans, D.A. *JACS* 1990, 112, 7001

Alkyl bromides and iodides are easily reduced to the corresponding alkanes through a free-radical process with $n\text{-Bu}_3\text{SnH}$.



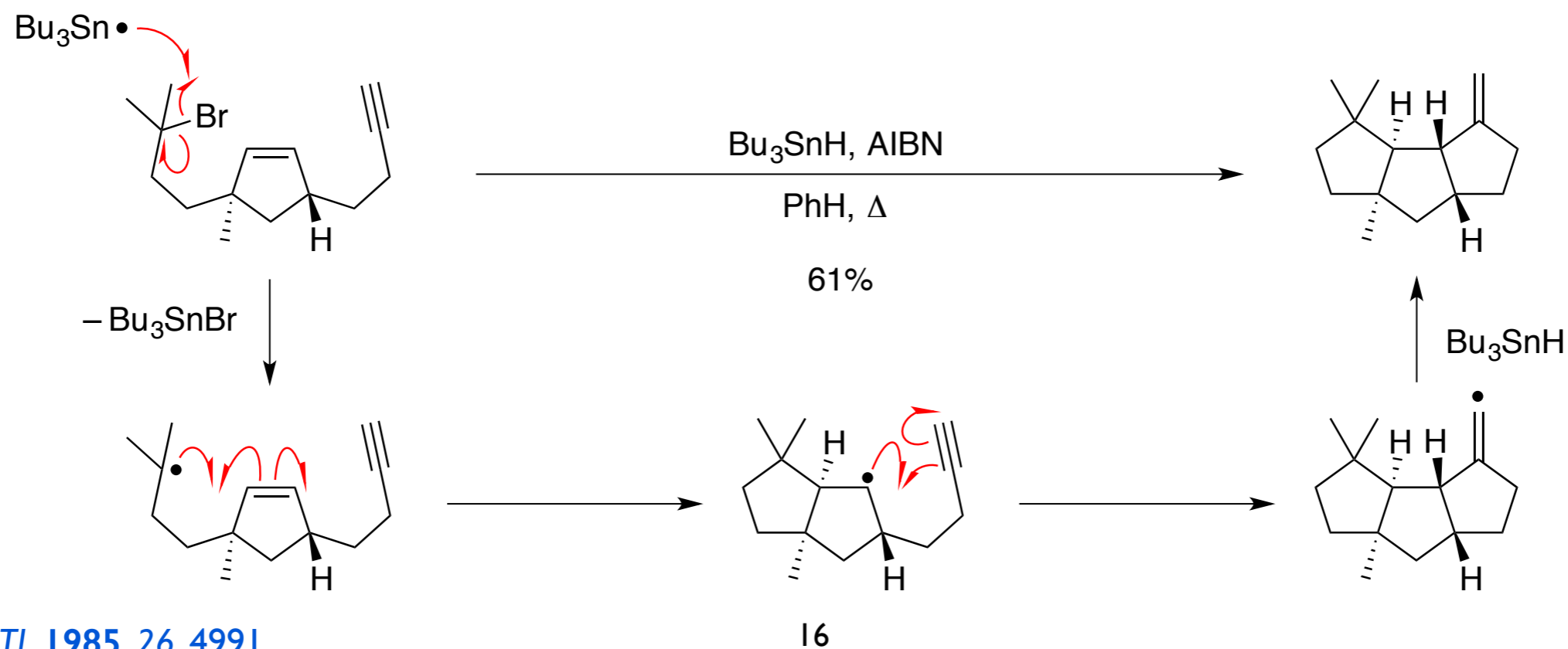
A parallel transformation involves a radical-promoted deoxygenation of *O*-thiocarbonate derivatives of alcohols in a two-step process named **Barton-McCombie reaction**





Kishi, Y. *ACIE* 1998, 37, 137

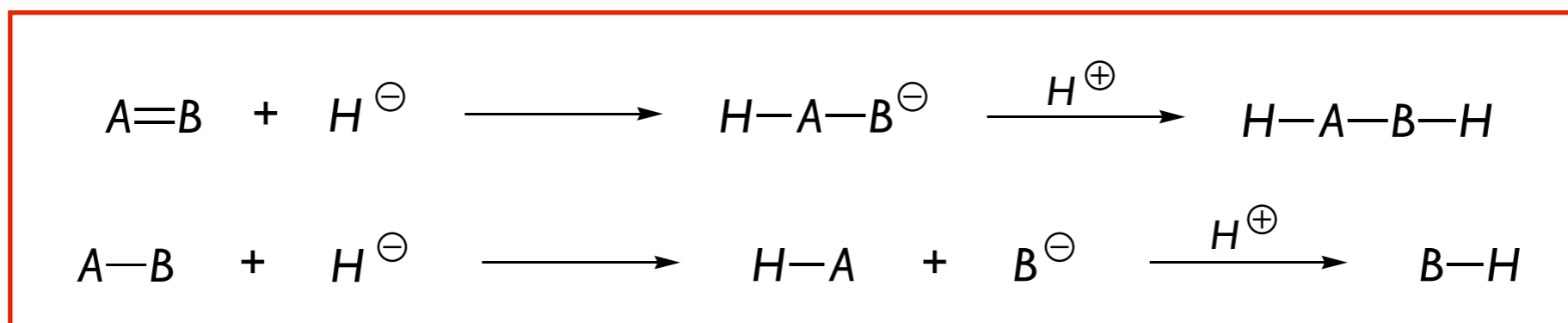
The radical generated during the dehalogenation reaction can undergo a tandem radical cyclization



Curran, D. *TL* 1985, 26, 4991

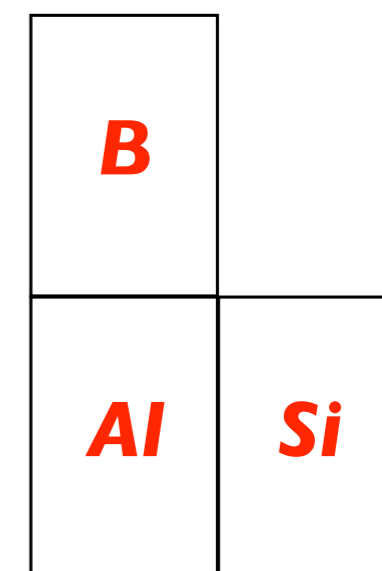
Pere Romea, 2014

■ *Formal addition of H^- to a double or a simple bond*

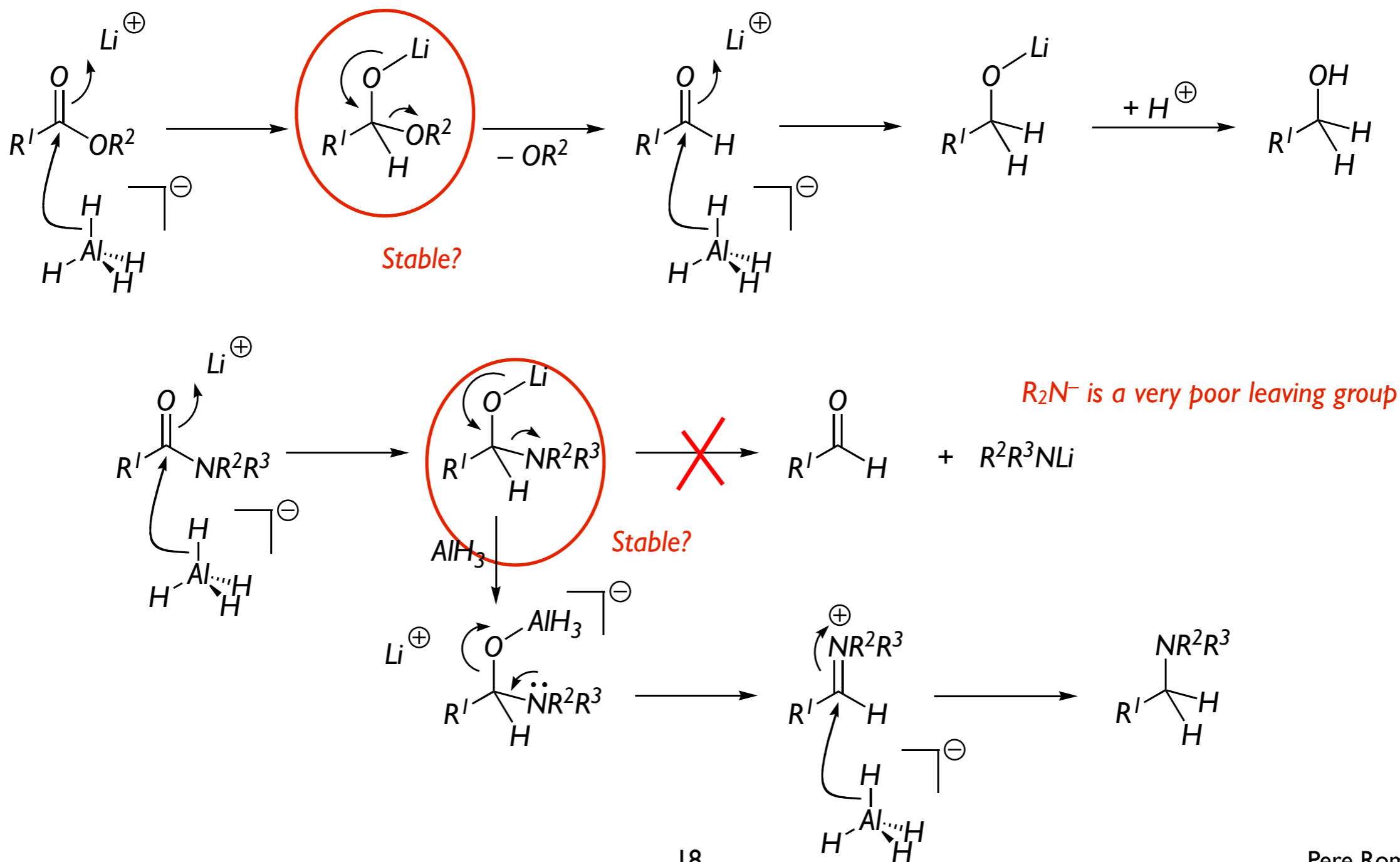


*Hydrides, $M-H$,
 used for the reduction of organic compounds
 are from three elements close in the periodic table:
 boron, aluminum, and silicon*

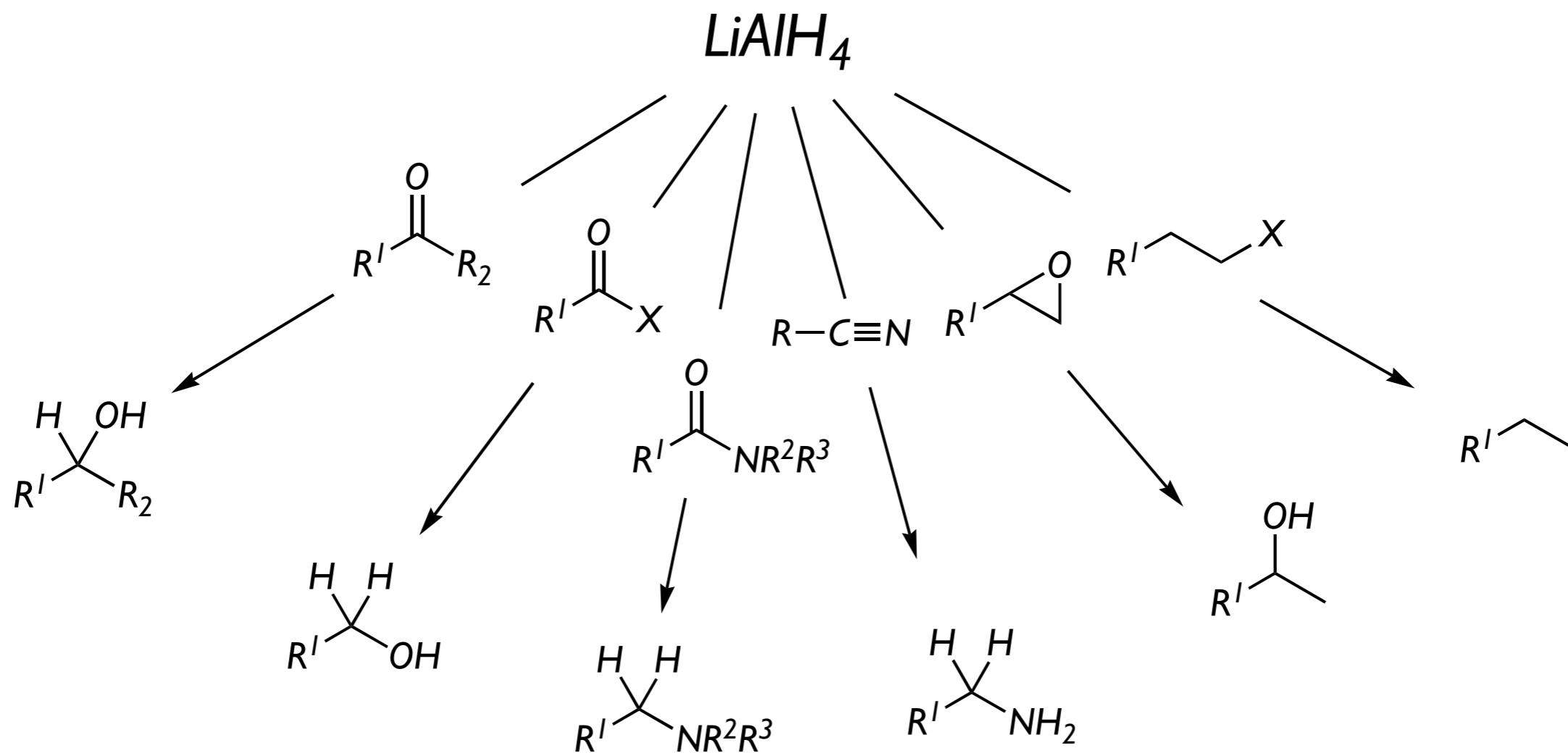
*Their reactivity fairly depends on the element:
 aluminium hydrides are more active than the boron counterparts,
 and these more than the silicon ones*

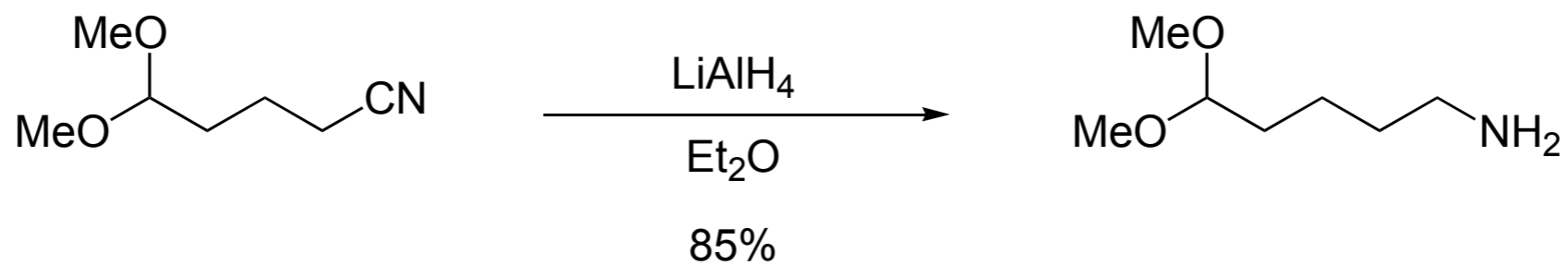
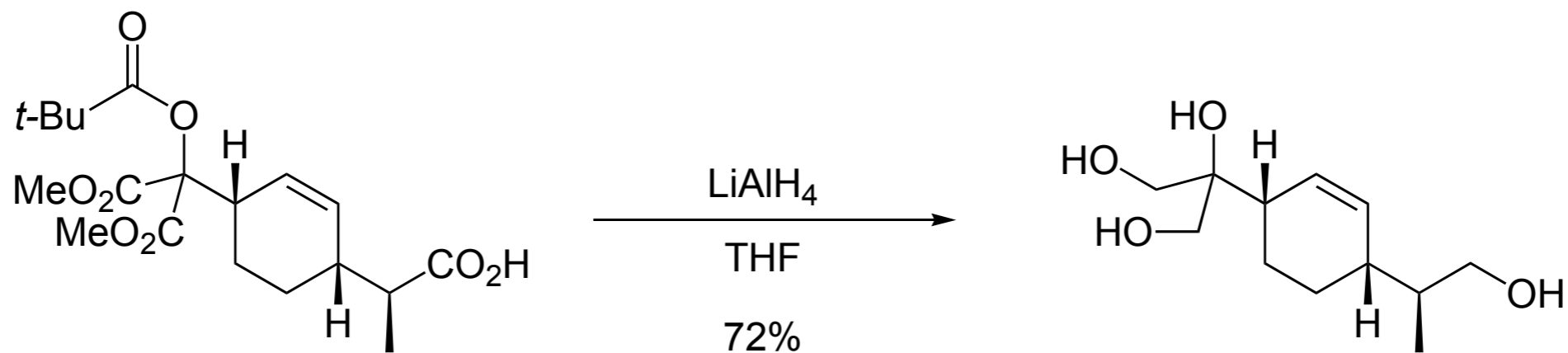
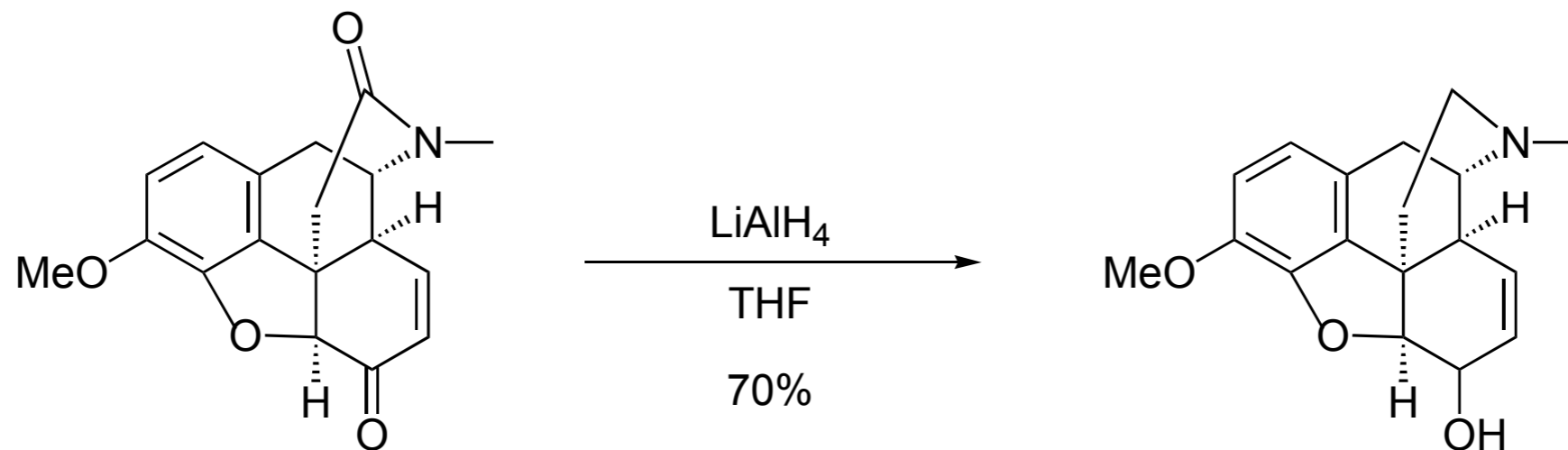


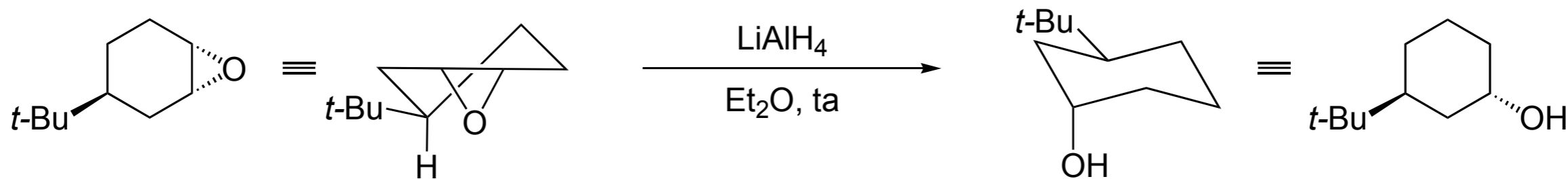
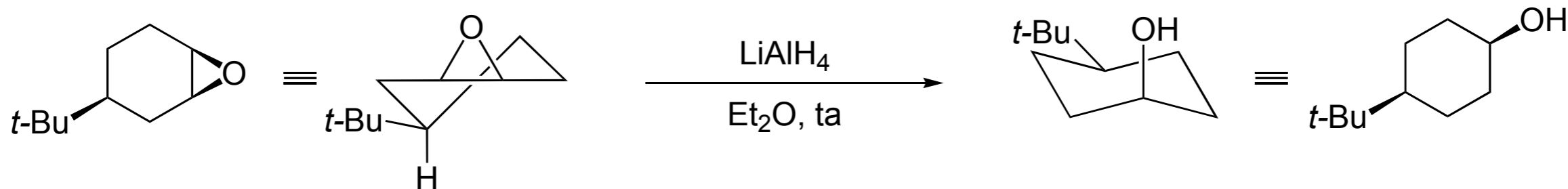
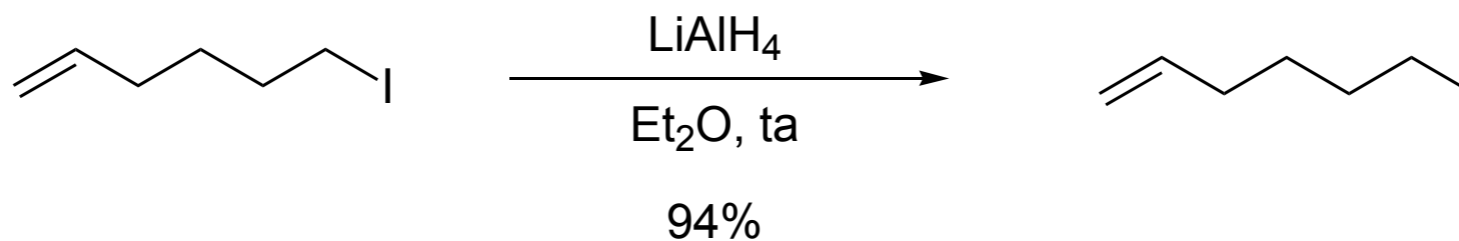
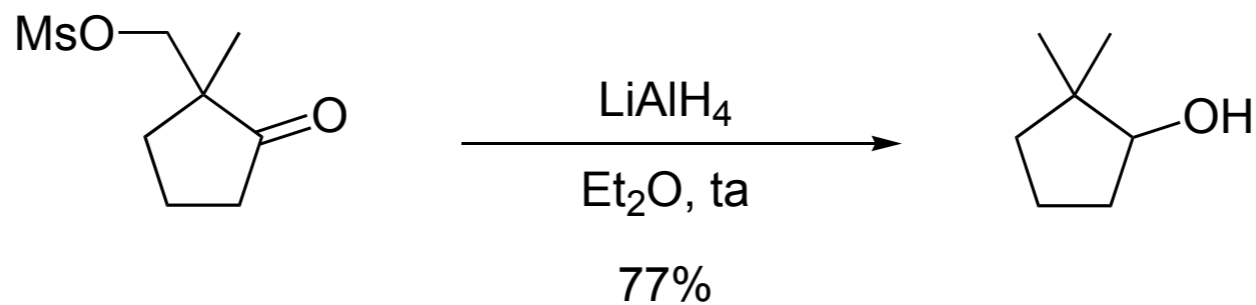
■ *Lithium aluminum hydride, LiAlH₄, the strongest reducing agent?*



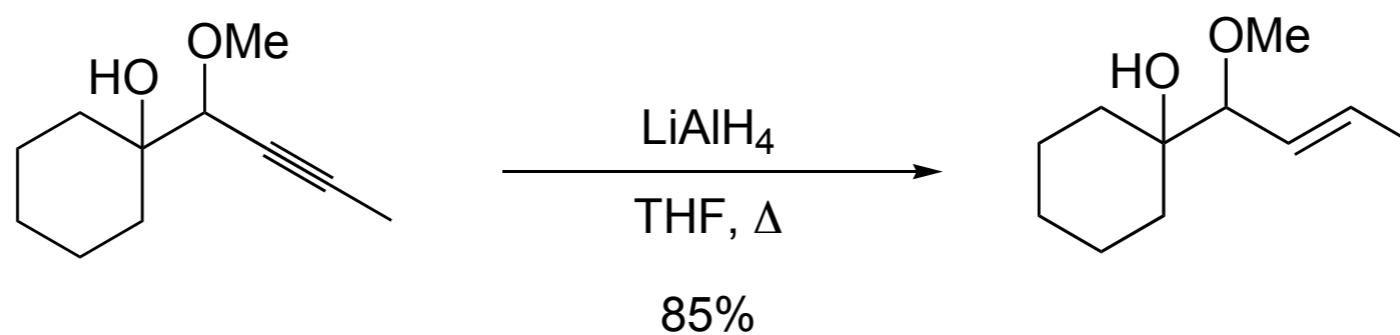
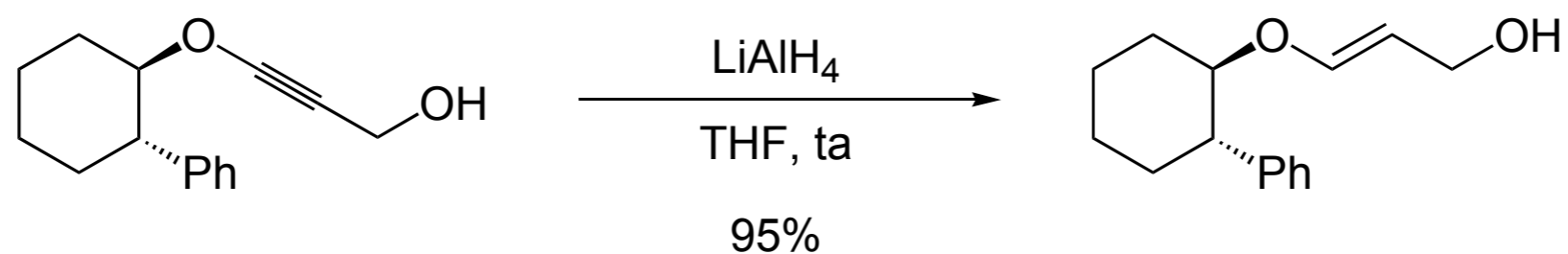
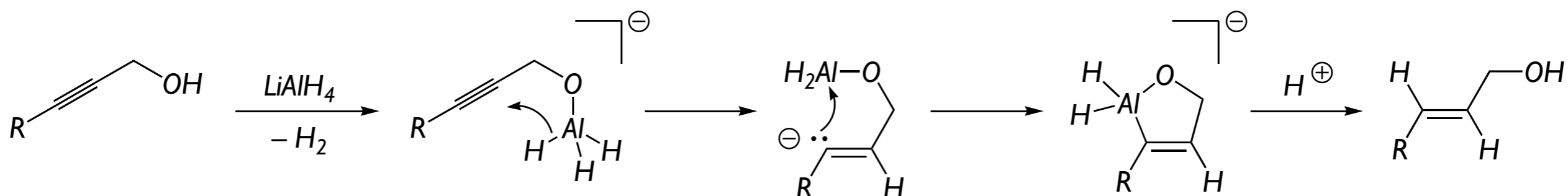
- LiAlH₄ is commercially available, very sensitive to water.
- Dry ethereal solvents are required.
- LiAlH₄ is a very strong & non chemoselective reductor.





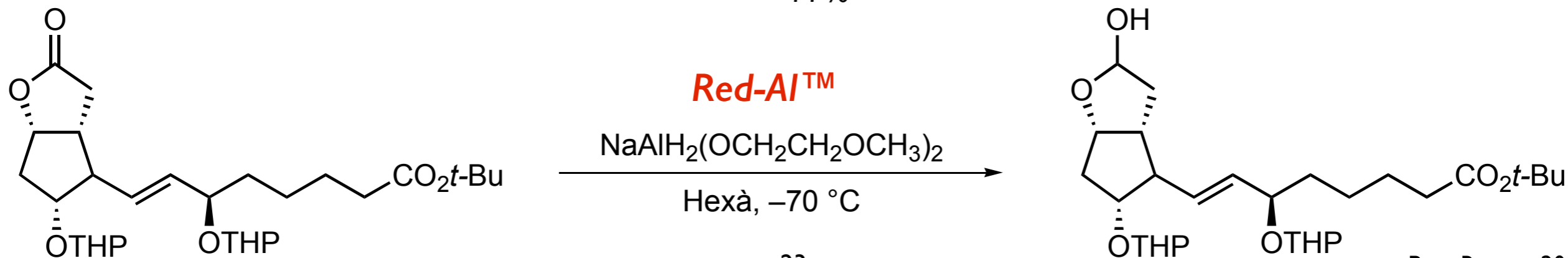
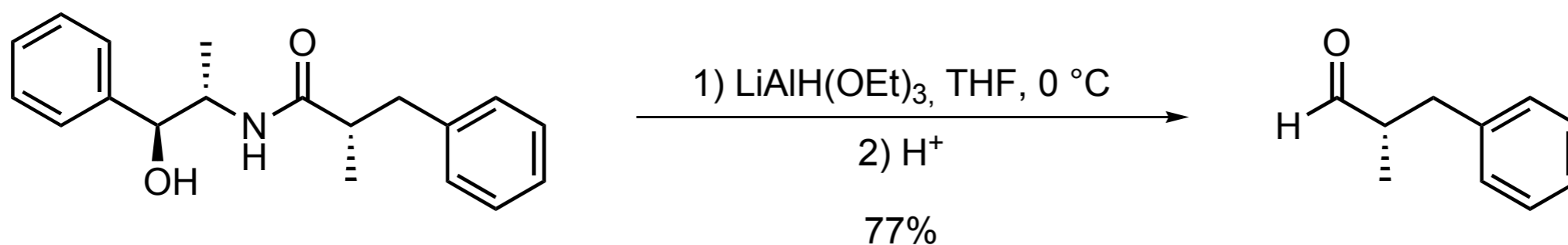
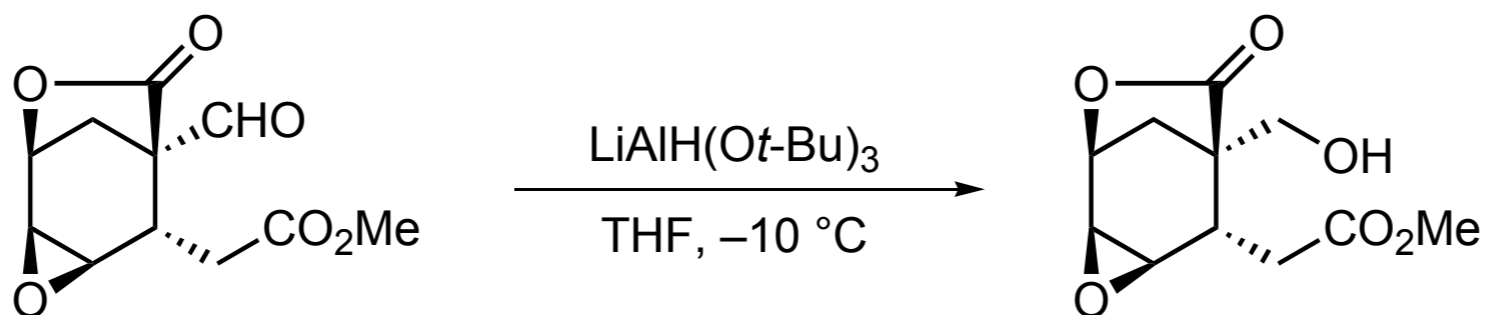


LiAlH₄ can even be active on propargylic and homopropargylic alcohols ...

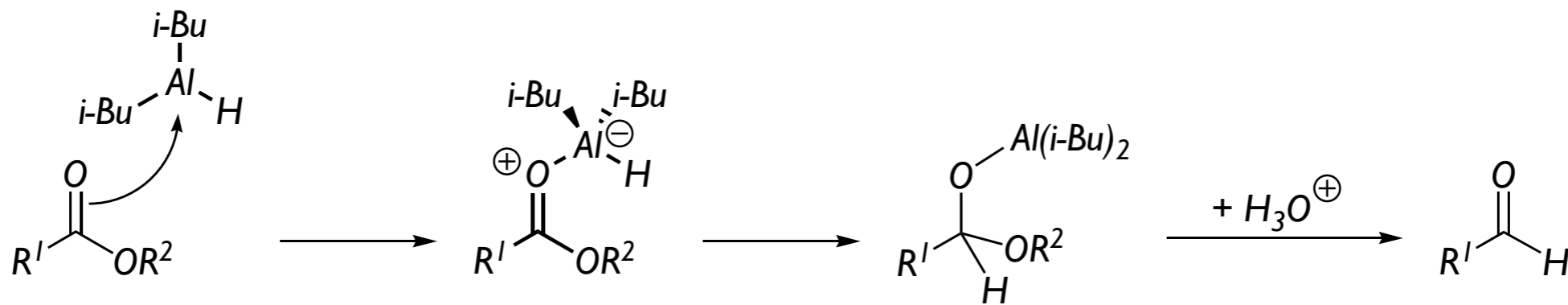




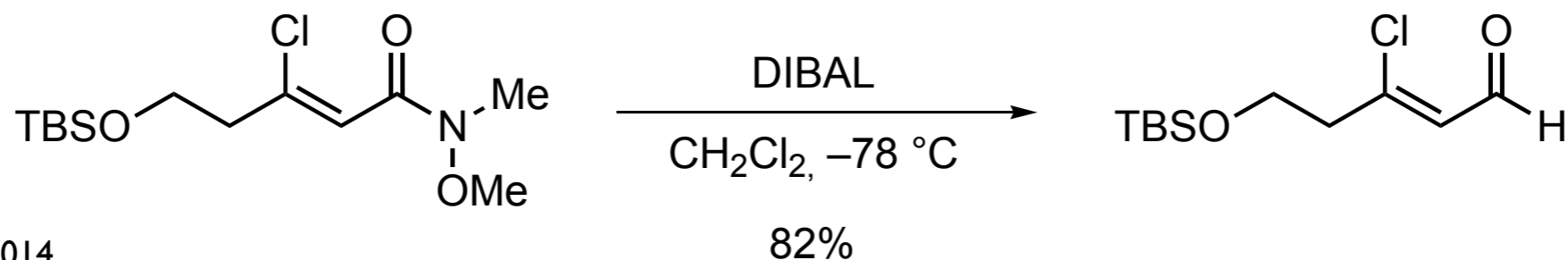
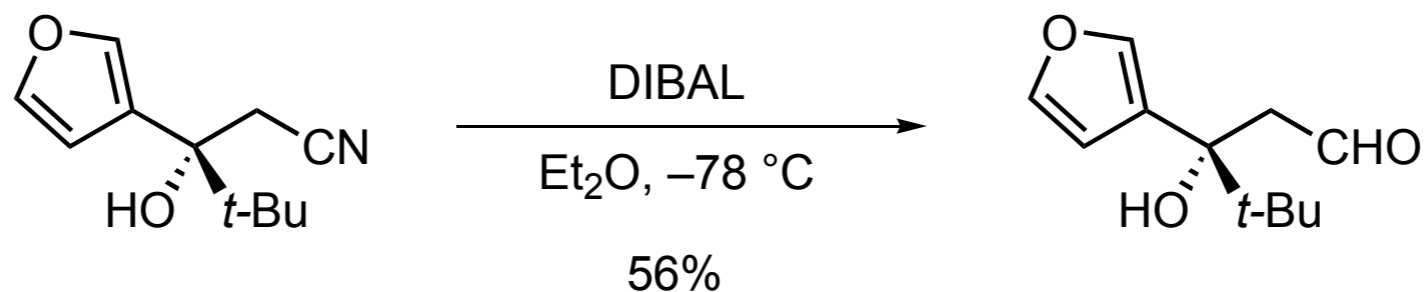
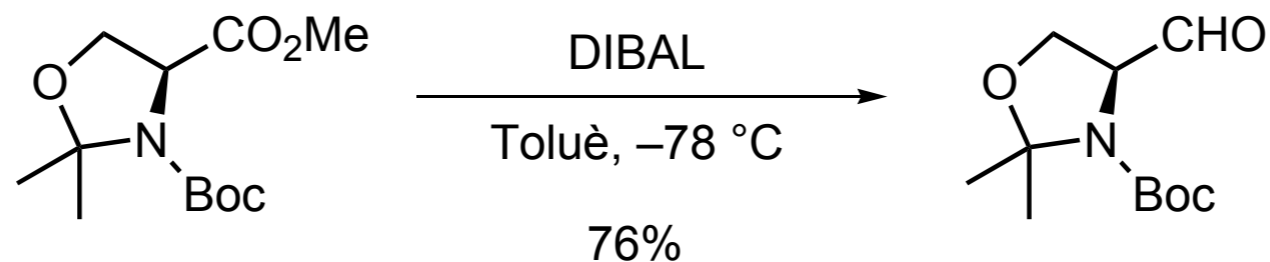
- Alkoxyde ligands, OR, reduce the reactivity of aluminum hydride: they become more chemoselective
- The presence of one or two H⁻ permet to tune the reactivity



■ A highly selective reducing agent to aldehydes: *i*-Bu₂AlH (DIBAL or DIBALH)

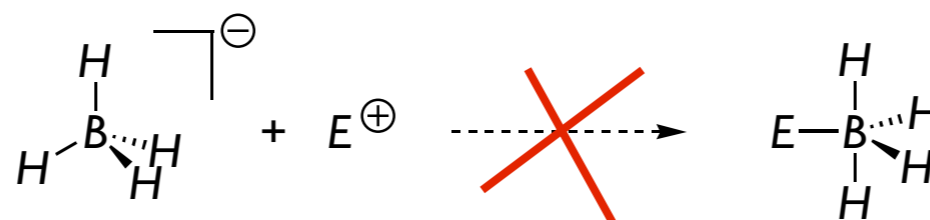


Somehow stable at low T

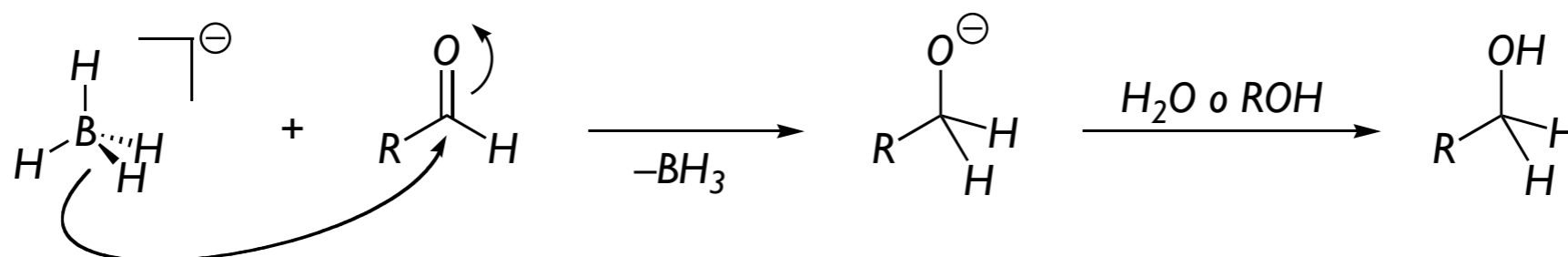


■ Sodium borohydride, NaBH₄, the mildest agent?

The boron atom has no electron pairs available



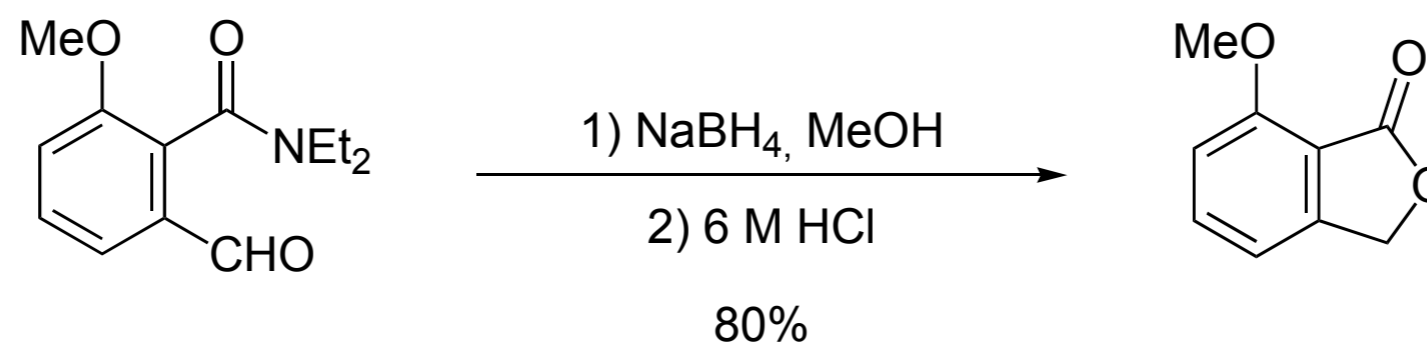
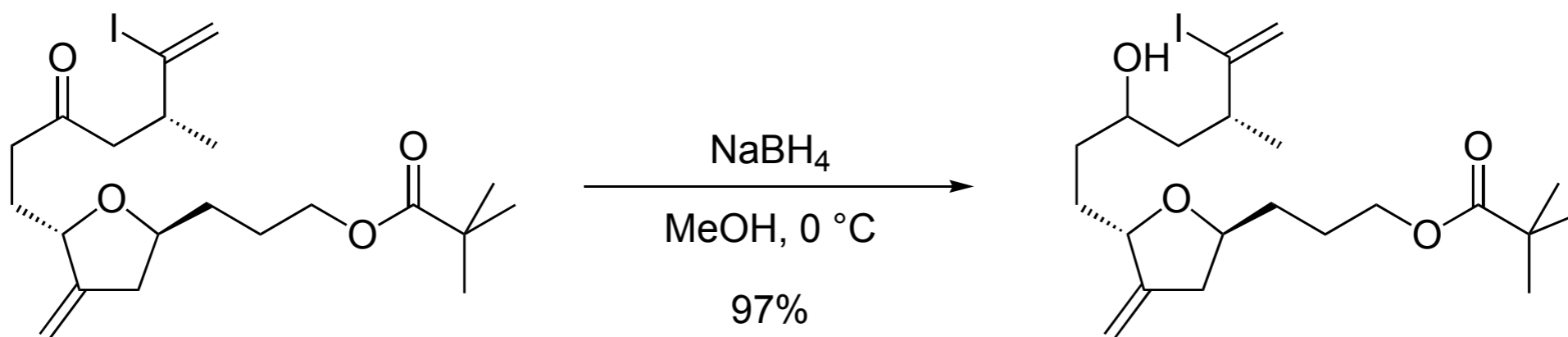
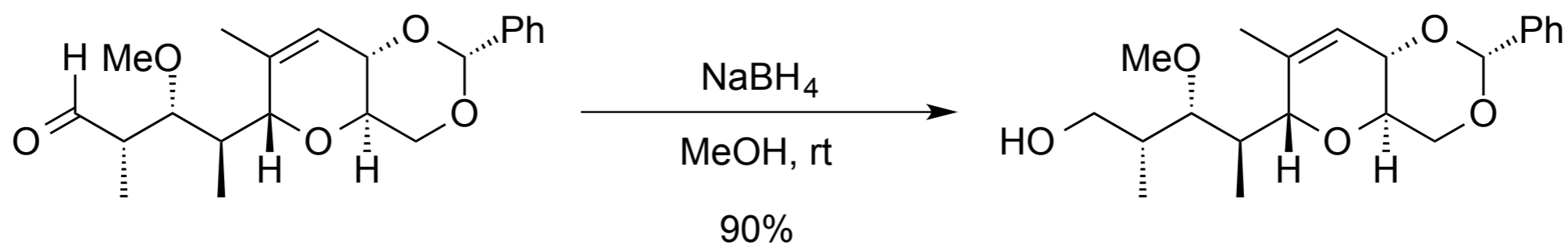
The boron atom cannot accept 10e (octet rule)



- Sodium borohydride is a solid very easy to handle and commercially available
- The reductions with NaBH₄ are carried out in methanol, ethanol, or even water at 0 °C or room temp
- NaBH₄ reduces aldehydes and ketones to the corresponding alcohols.

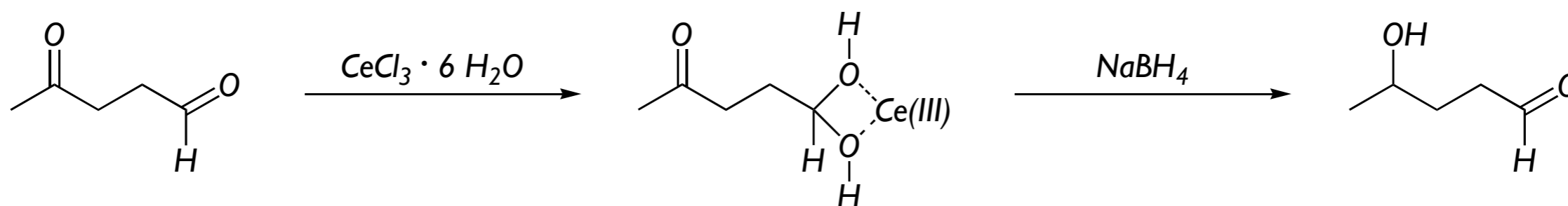
Carboxylic acids, esters, nitriles, epoxides, or nitro compounds are not affected.

NaBH₄ is a very chemoselective reductor

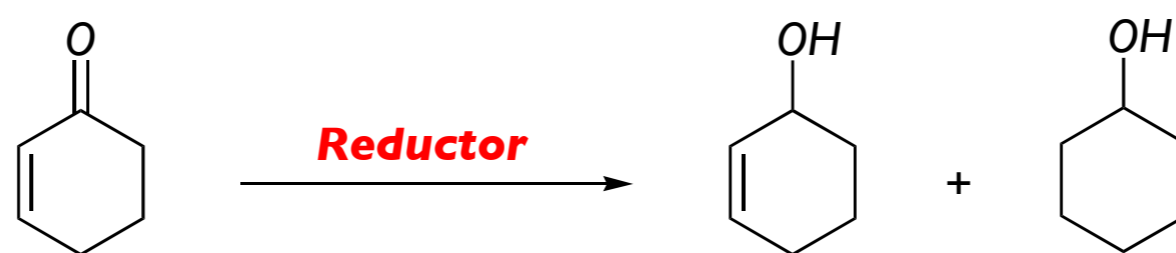


■ *Even more selective with CeCl₃ (Luche reduction)*

Aldehydes vs Ketones



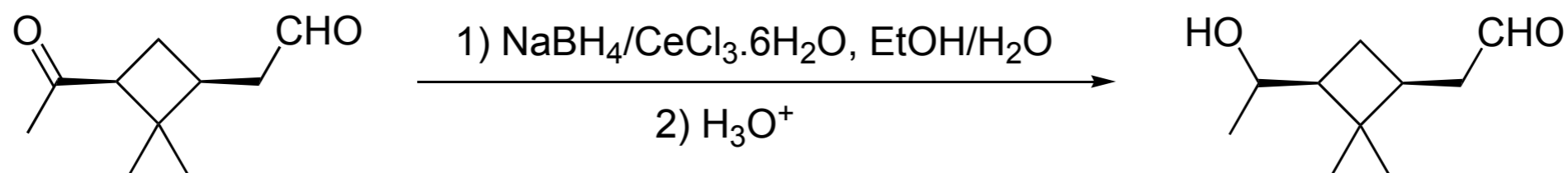
Unsaturated Ketones



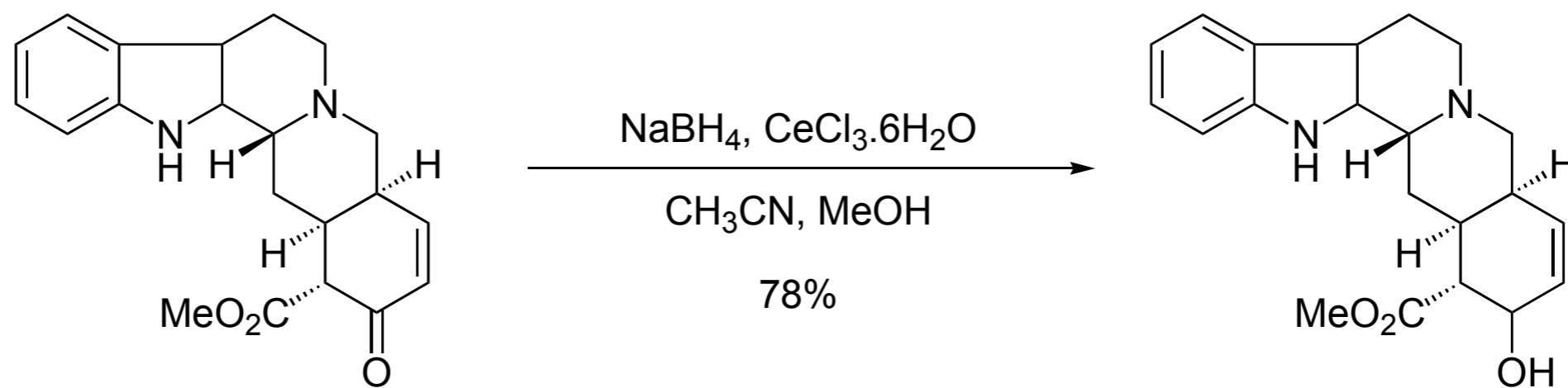
NaBH ₄	59%	41%
NaBH ₄ / CeCl ₃ ·6H ₂ O	99%	traces

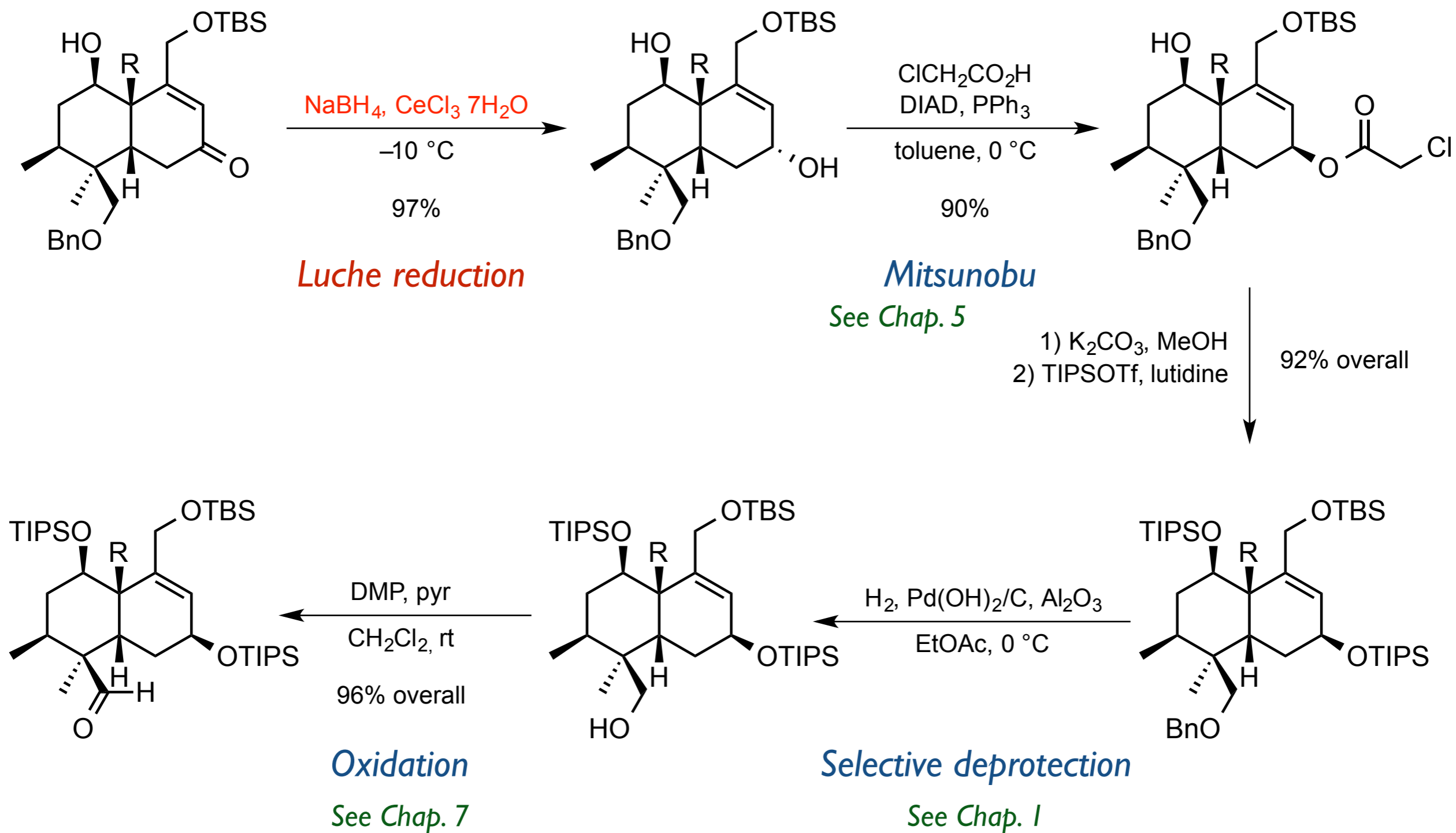
■ *Even more selective with CeCl₃ (Luche reduction)*

Aldehydes vs Ketones



Unsaturated Ketones





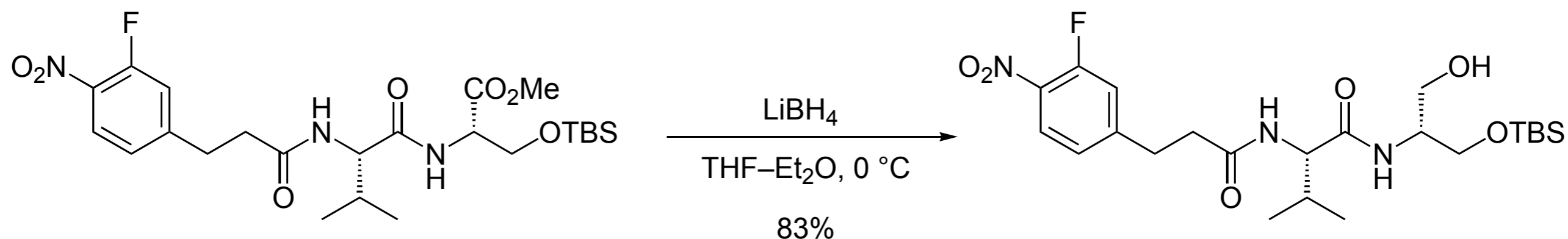
Nakada, M. *OL* 2014, 16, 4734

■ ... and less selective but more powerful with a different cation: LiBH₄

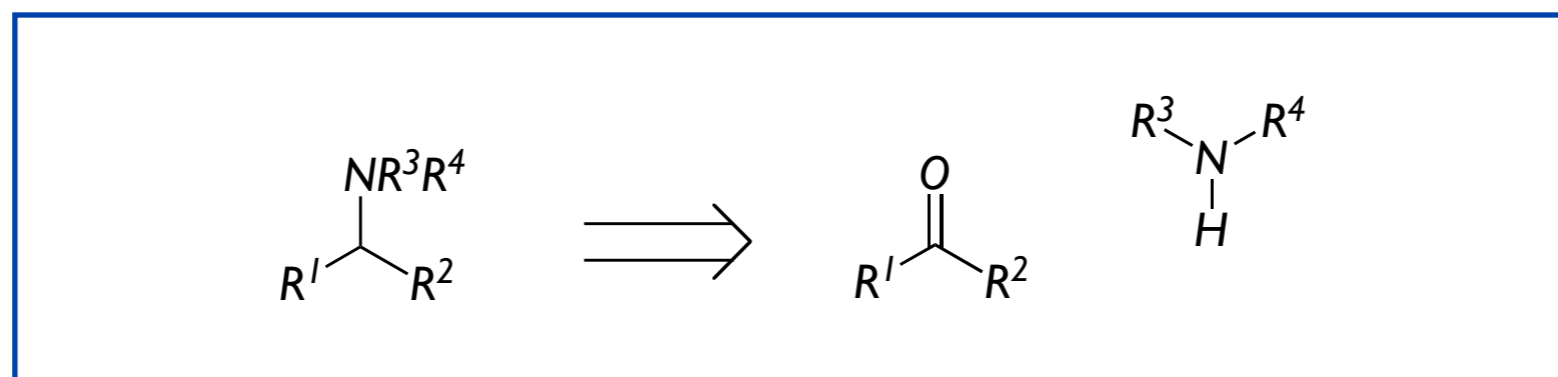
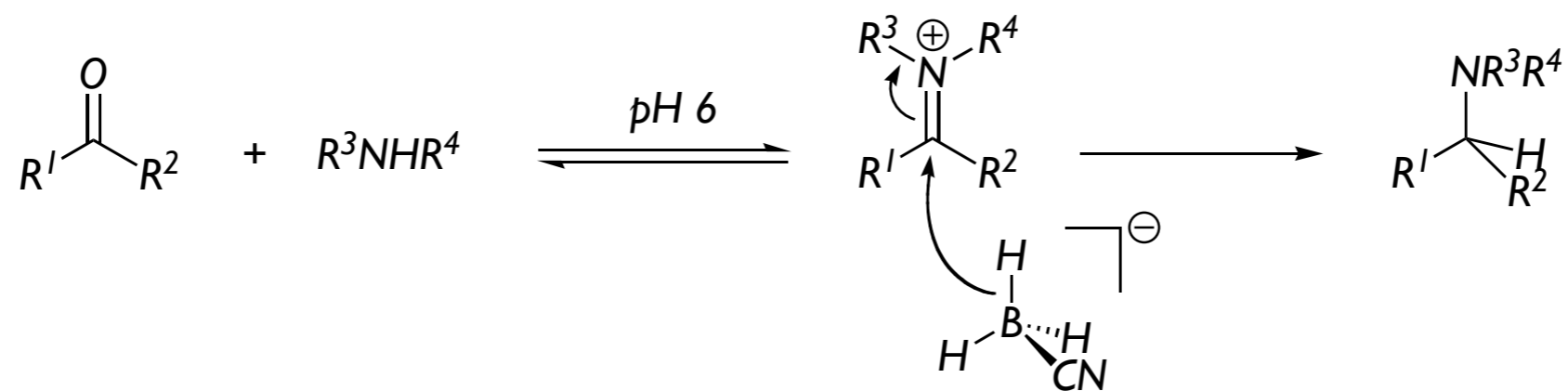
- The substitution of the cation, Li⁺ instead of Na⁺, enhances its solubility in organic solvents
- Li⁺ cation can bind the oxygen of aldehydes, ketones, esters, and epoxides, which increases their electrophilicity:

LiBH₄ reduces aldehydes and ketones as well as esters and epoxides.

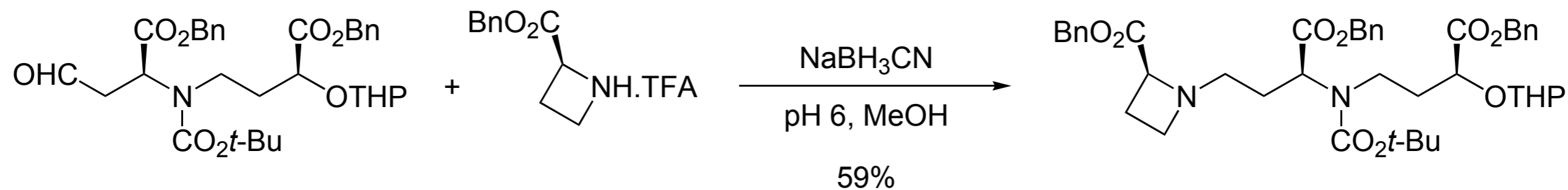
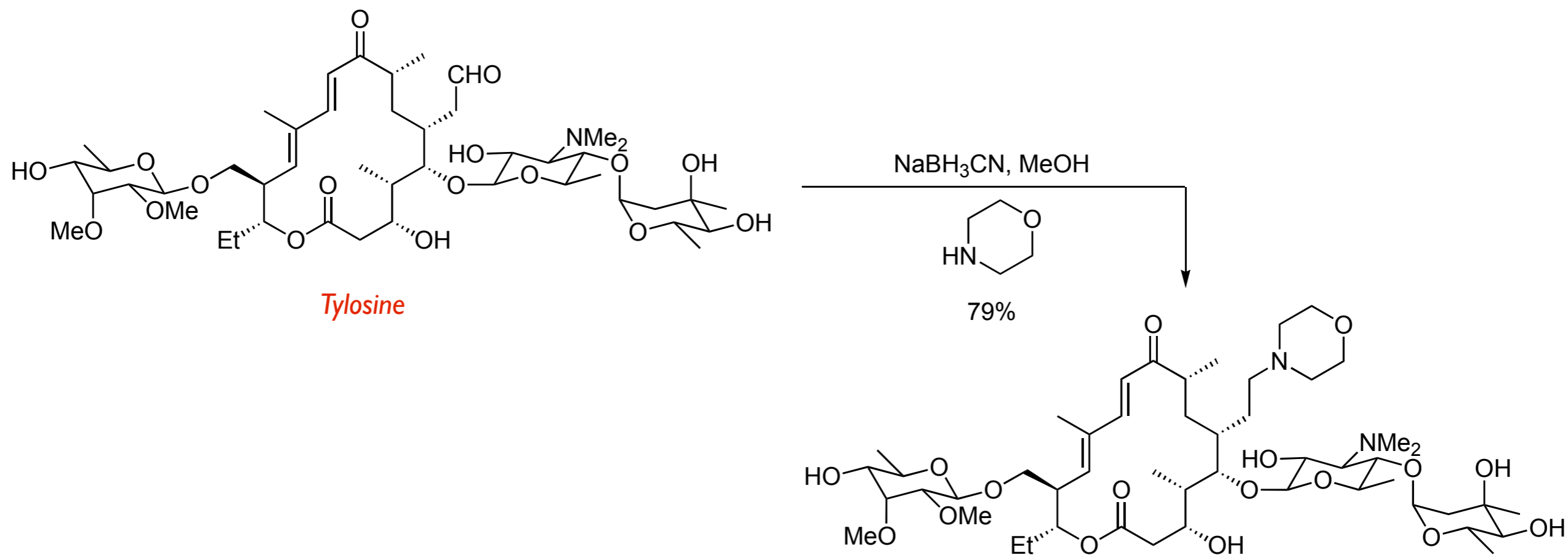
- Carboxylic acids, amides, or nitriles are not affected
- Solvents: Et₂O, THF > i-PrOH



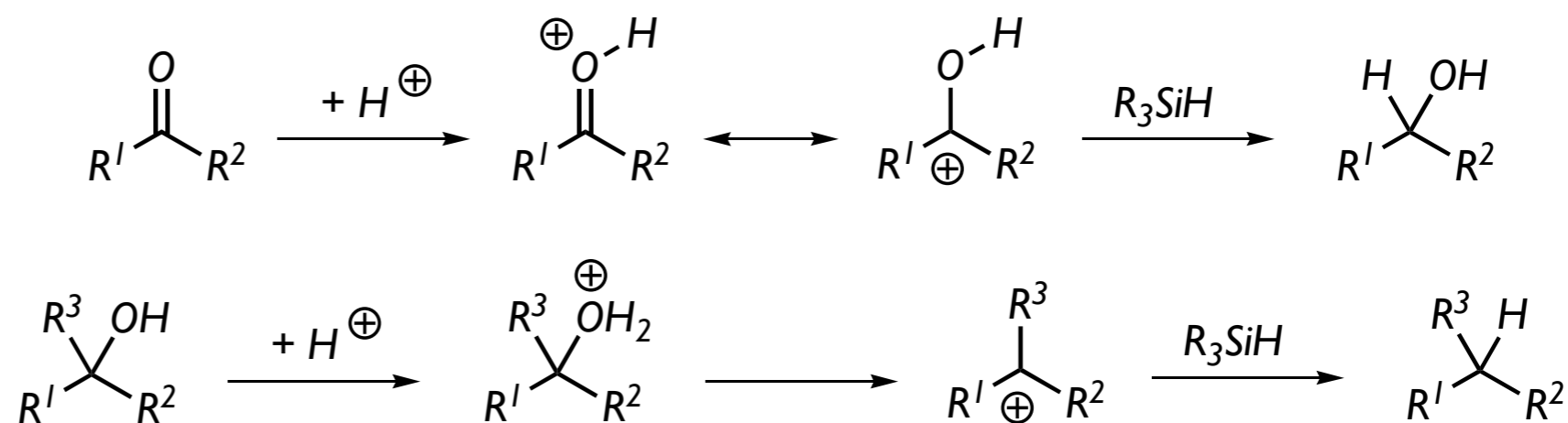
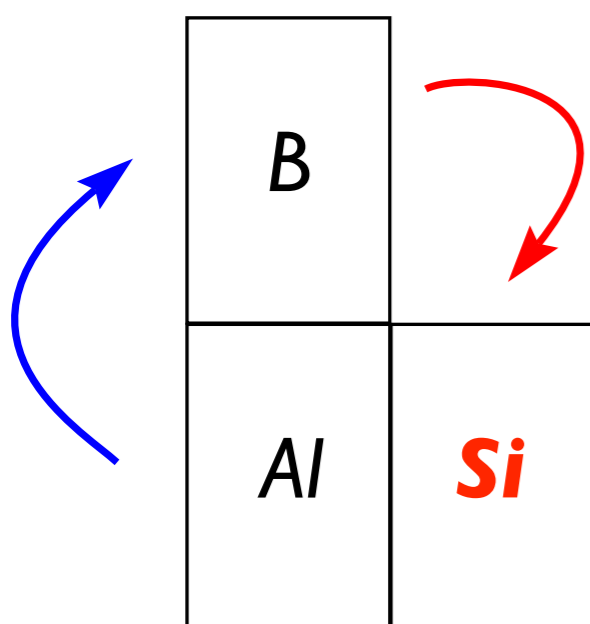
■ *The mildest agent: sodium cyanoborohydride, NaBH₃CN*



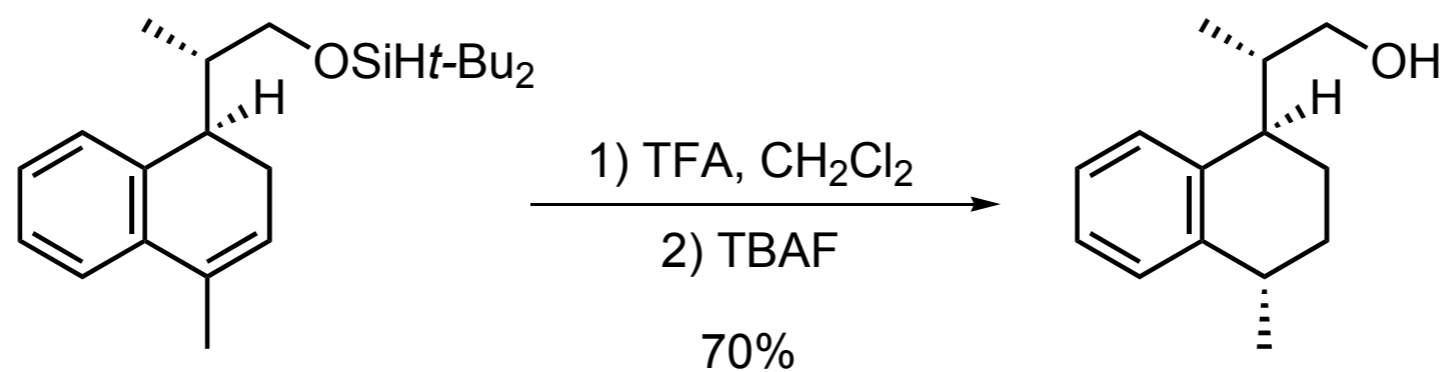
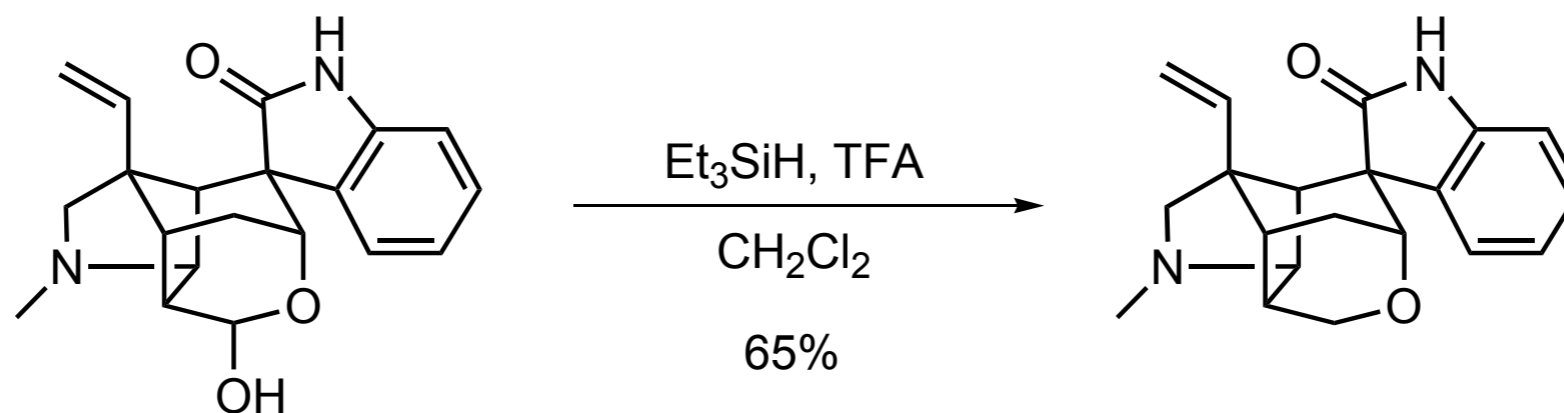
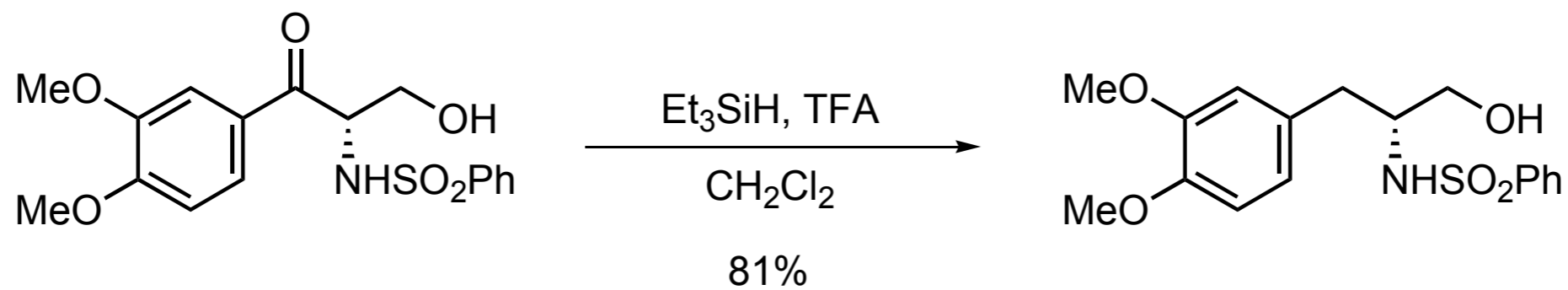
- *The reductive amination of aldehydes and ketones is an important method to synthesize 1ary, 2ary, and 3ary amines*
- *Iminium cations are prepared in situ in a slightly acid medium and can be selectively reduced in the presence of the parent carbonyls*



- Protonation of alkenes, alcohols, carbonyls, ... produce carbocations that can be reduced with silicon-based hydrides as Et₃SiH



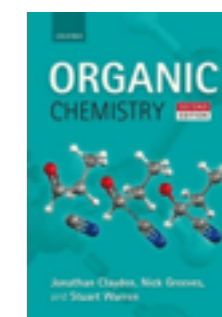
- These ionic hydrogenations are used to proceed in the presence of a strong acid (TFA) and an organosilicon donor
- Such a combination affects alcohols, ethers, alkenes, and carbonyls.
- Carboxylic acids and their derivatives are not affected



- *Reductive processes:*
 - a) *Dissolving metal reductions*
 - b) *Radical reductions*
 - c) *Reductions with hydrides*
 - d) *Catalytic hydrogenations*
 - e) *Carbonyl deoxygenation reactions*

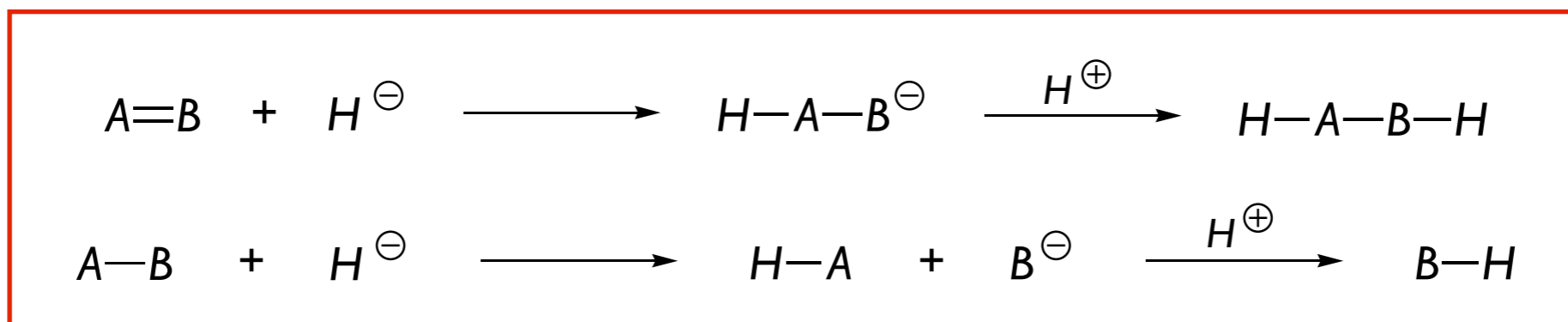


Different Chaps.

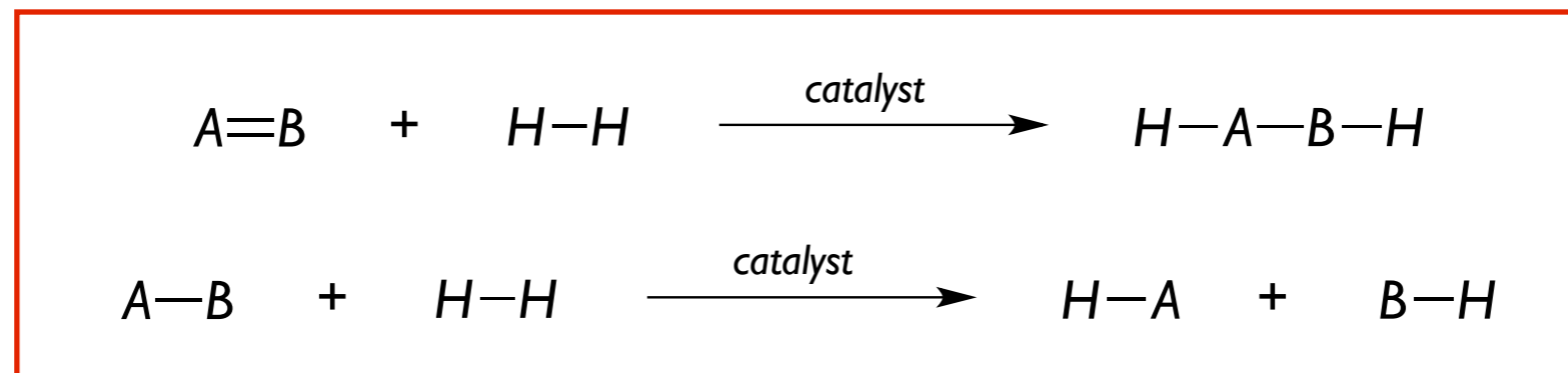


*Chap. 23
mainly*

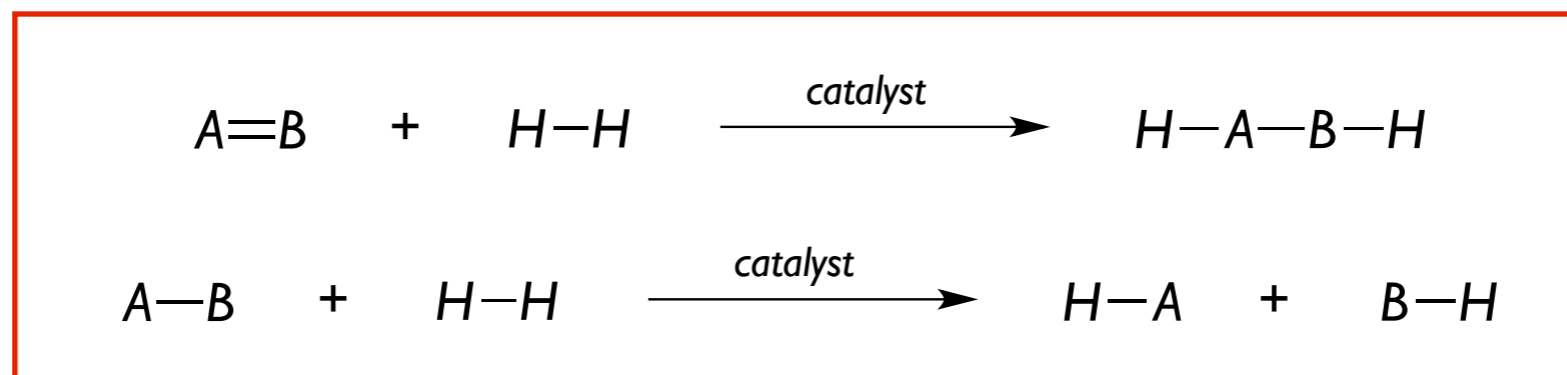
■ *Formal addition of H^- to a double or a simple bond*



■ *Hydrogenation: addition of $H-H$ catalyzed by a metal*



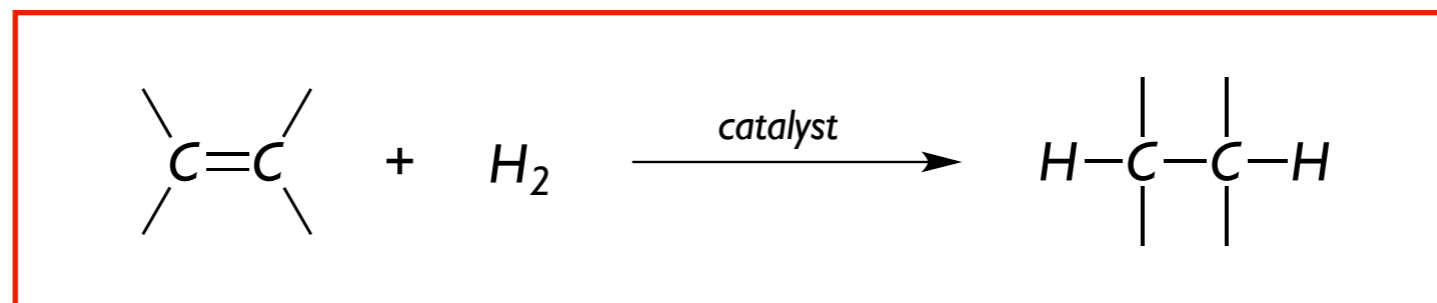
■ Catalytic hydrogenations



Depending on the catalyst, hydrogenations can be ...

- **heterogeneous**, when the catalyst is a finely dispersed metal on a solid and inert support (C, Al₂O₃, ...);
then, the hydrogenation occurs on the surface of the catalyst,
- **homogeneous**, when the catalyst is a metal complex soluble in the solvent that contains the unsaturated substrate.

■ Alkenes into alkanes



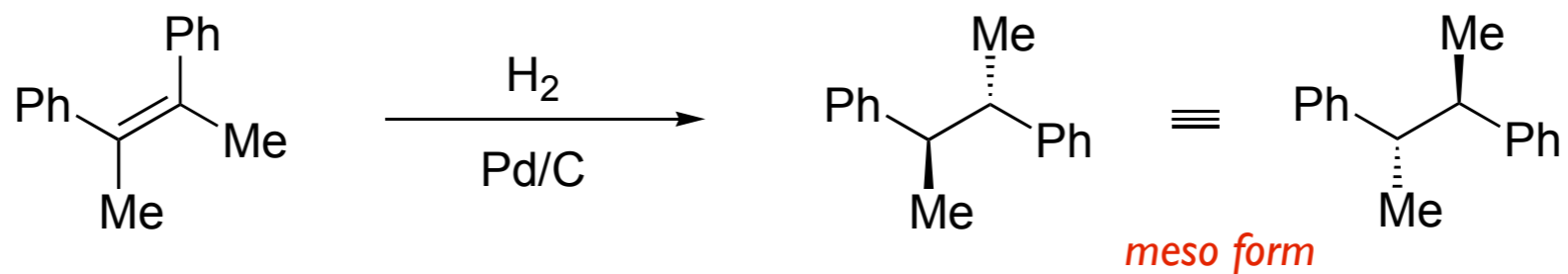
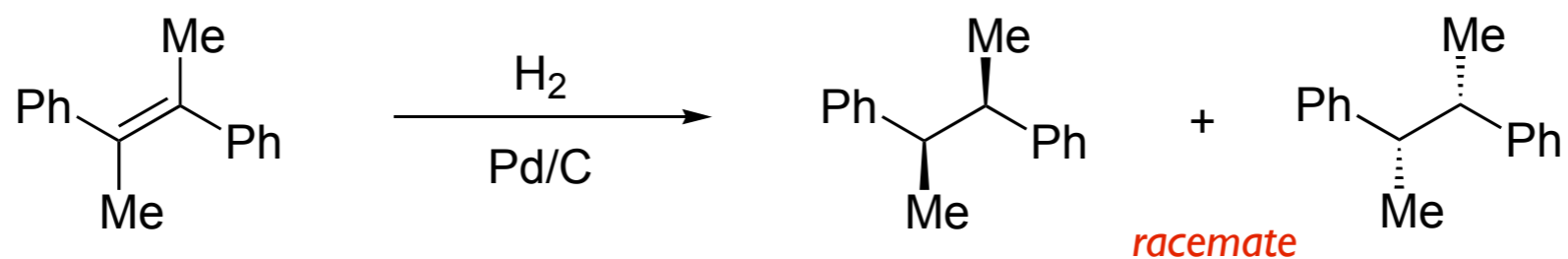
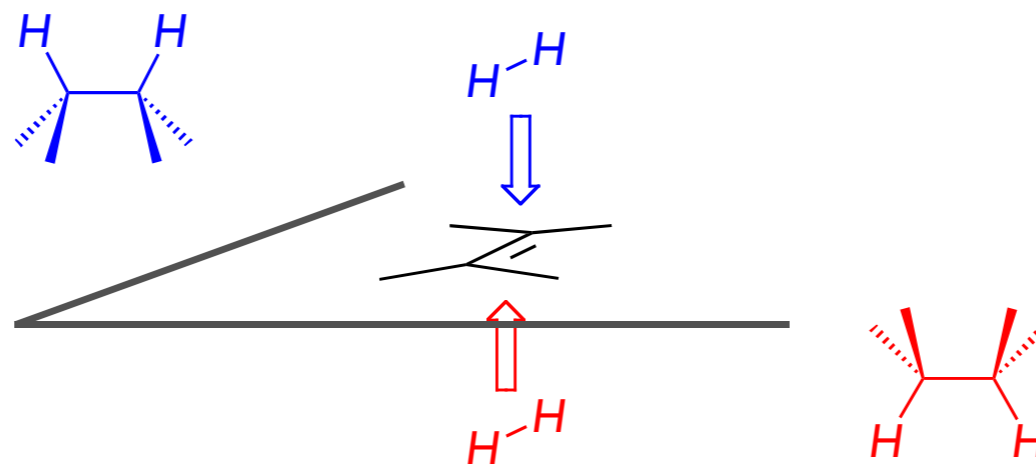
Catalyst: **Pd/C** (10%), PtO₂, Rh/C, Rh/Al₂O₃ (5%), Ru/C (5%), Ni-Raney

Hydrogenations with heterogeneous catalysts are very simple reactions. They are usually carried out by shaking the reaction mixture under a hydrogen atmosphere at low (1–5 atm) or high pressure (5–300 atm), at room temperature or heating.

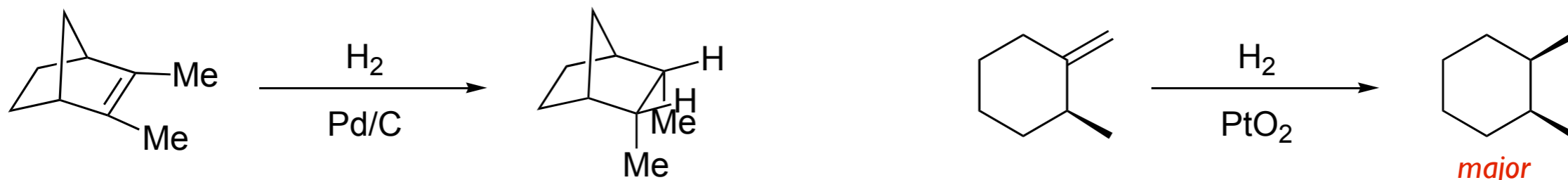
The catalyst is finally removed by filtration

These hydrogenations are highly stereoselective: **syn addition**

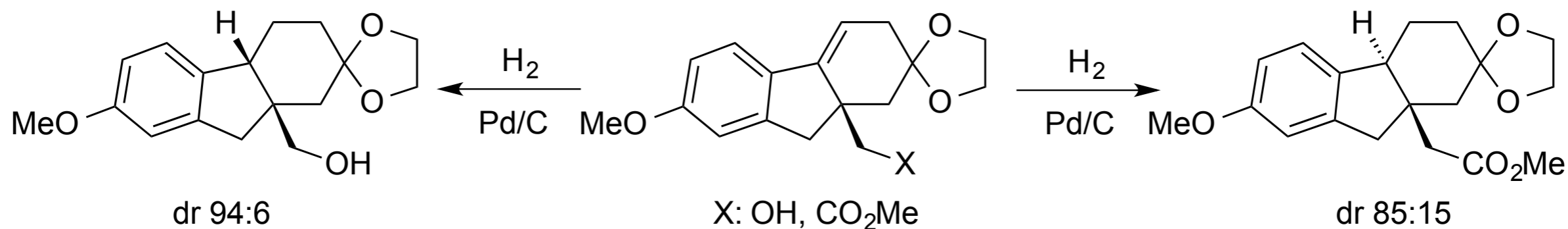
Both hydrogen atoms add to the same face of the π system



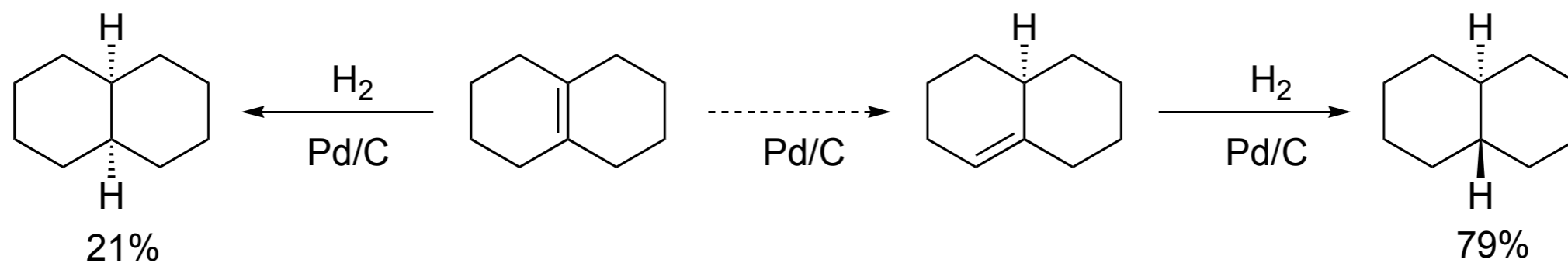
Steric effects usually rule the hydrogenation of the diastereotopic faces of olefines



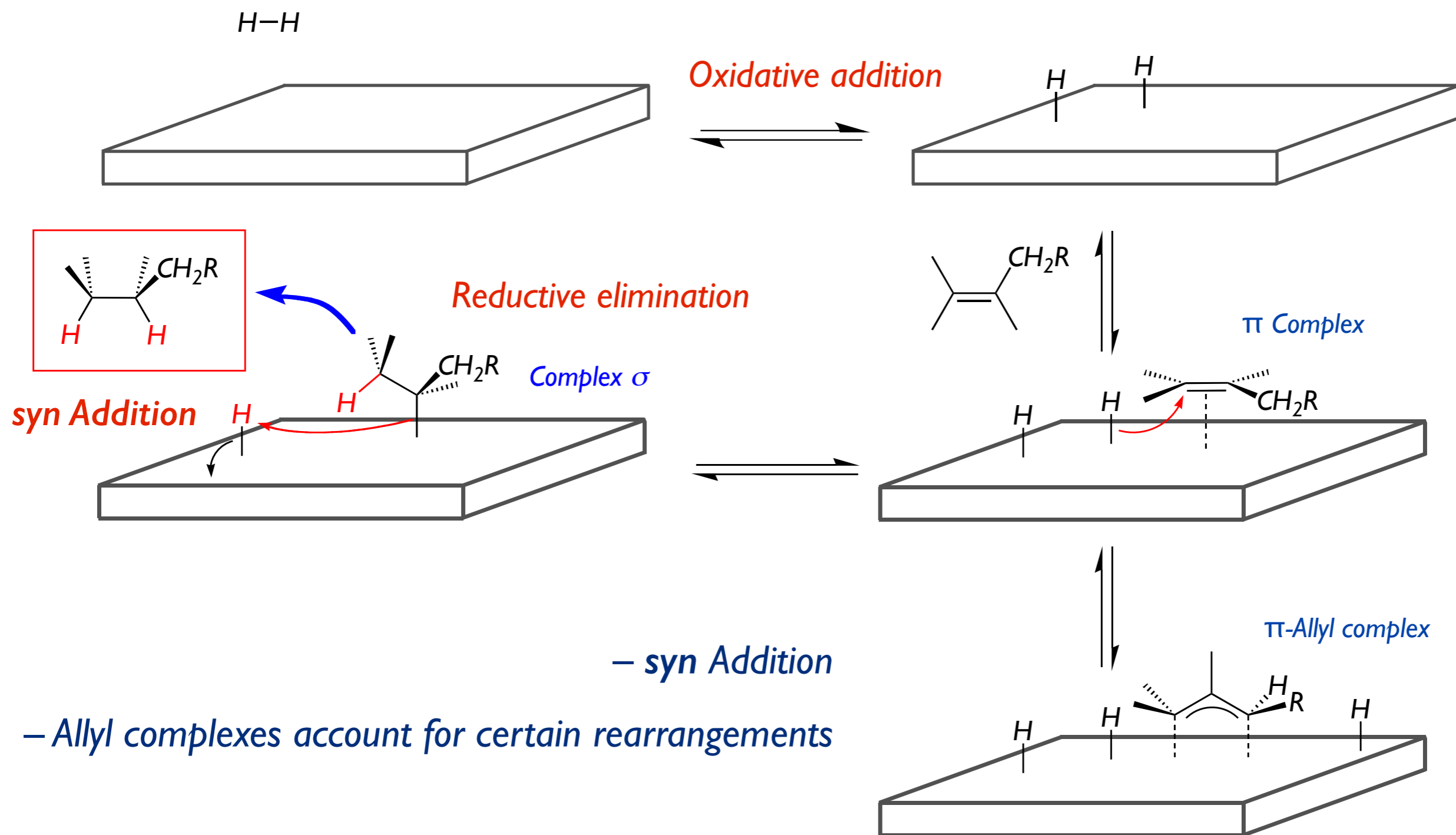
The stereochemical outcome can be affected by the presence of functional groups as OH or NH_2



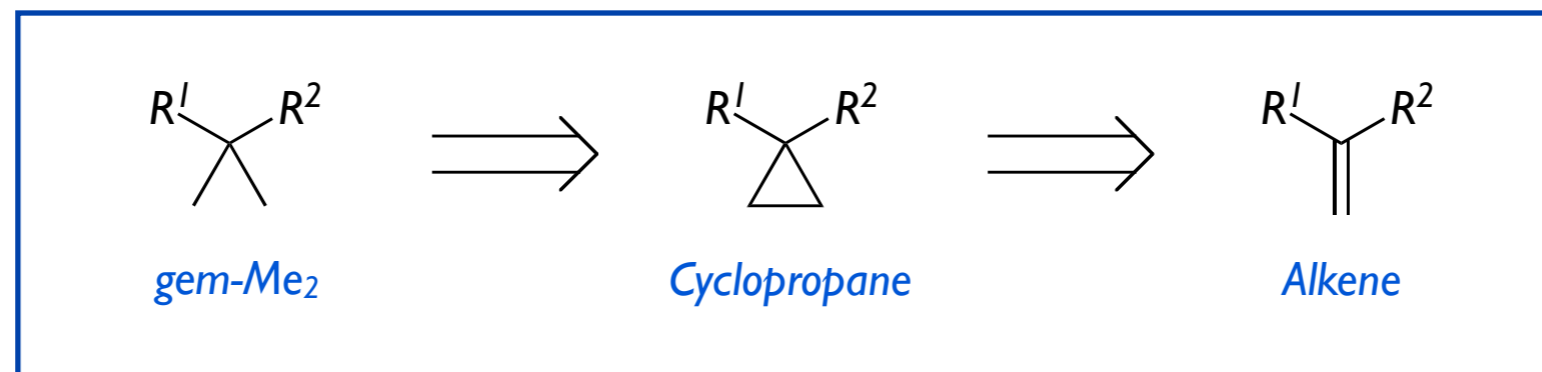
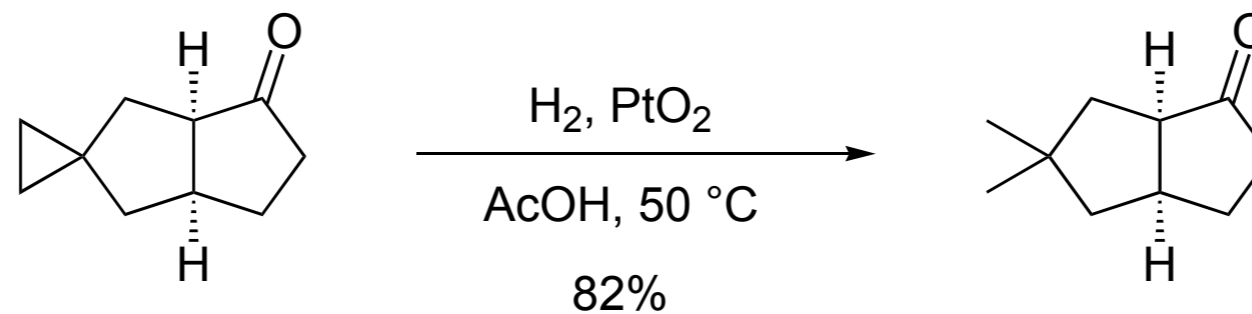
Occasionally, unexpected rearrangements can modify the stereochemical outcome of these reactions



The mechanism of a heterogeneous hydrogenation is rather complex



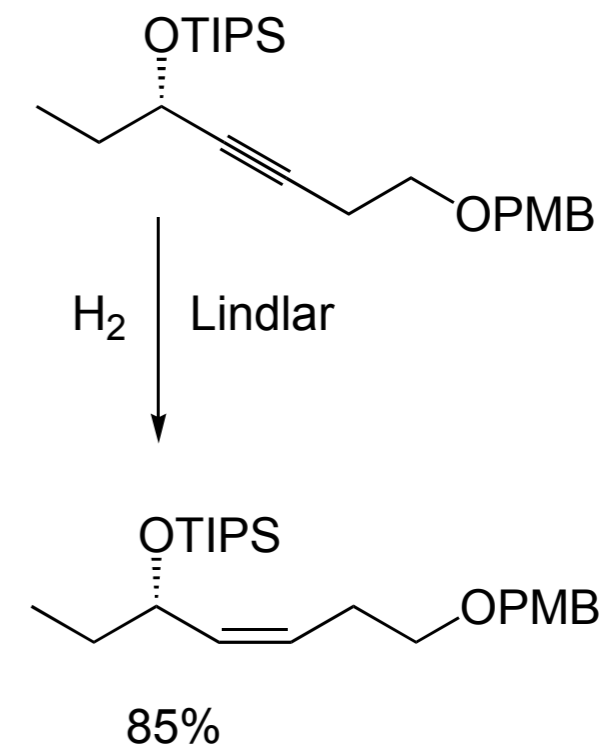
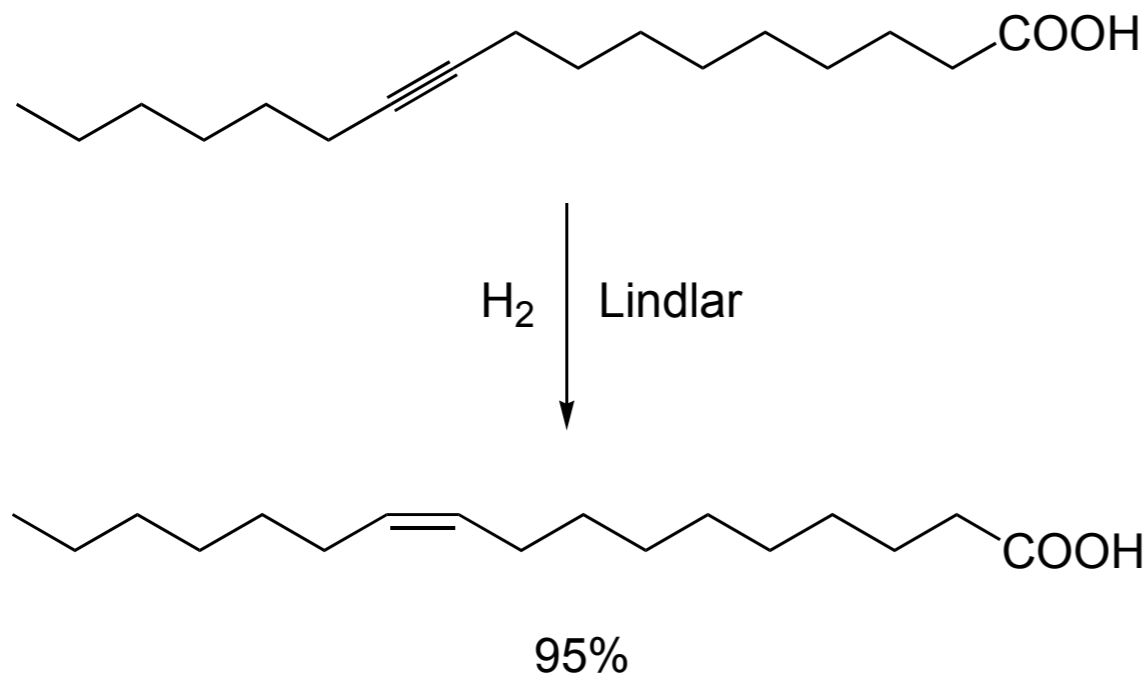
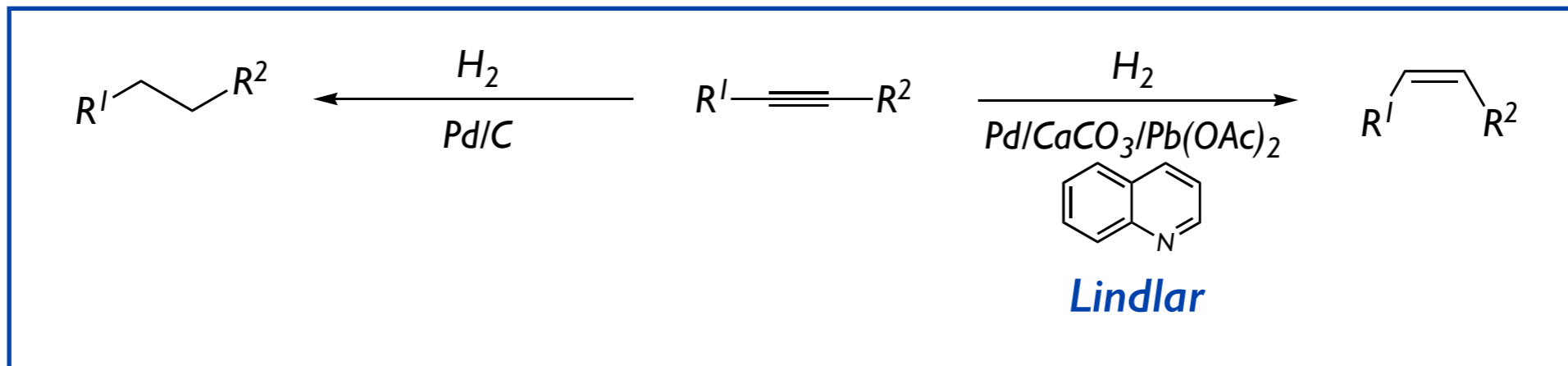
■ Cyclopropanes



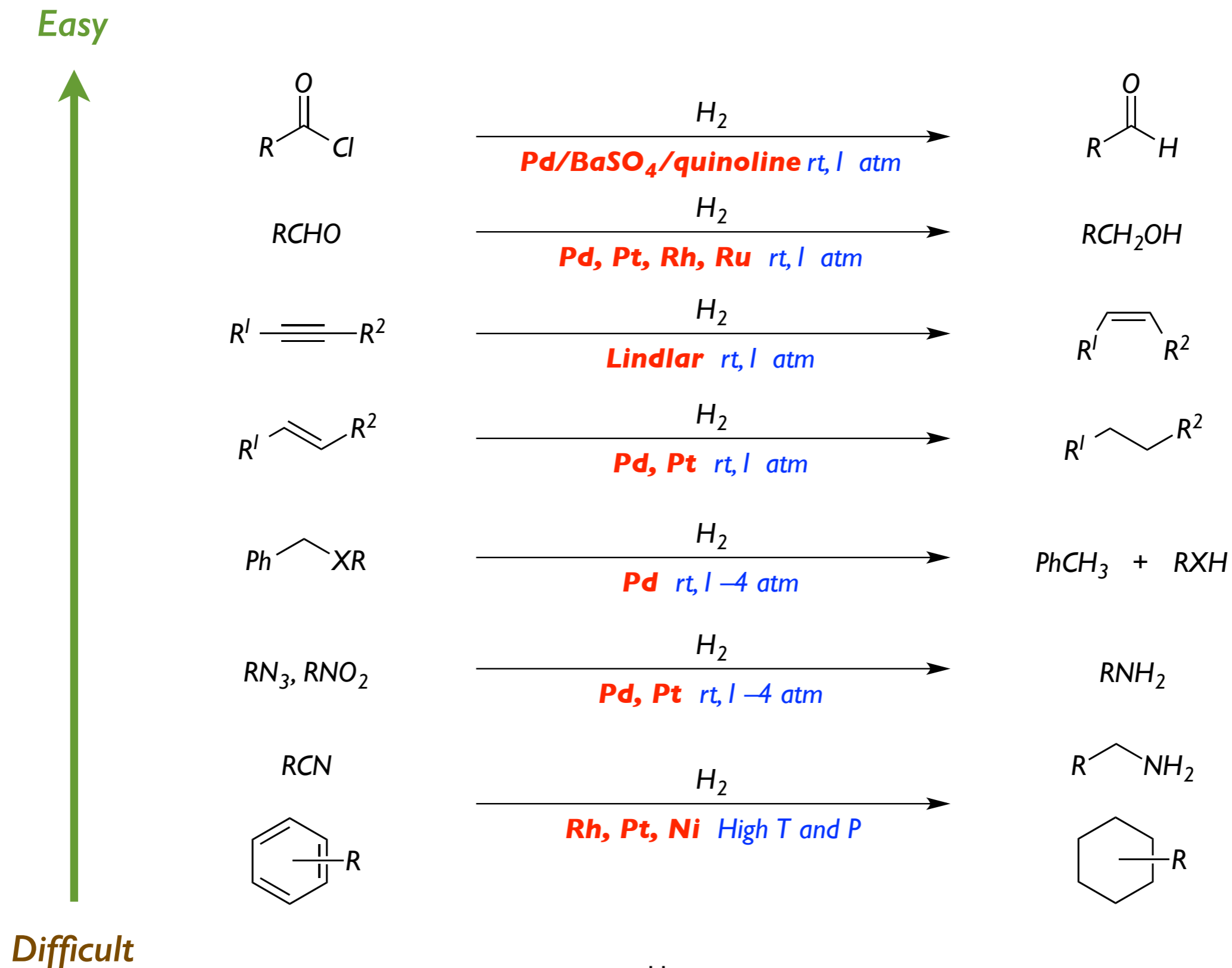
Remember the interesting reactivity of the three-membered rings



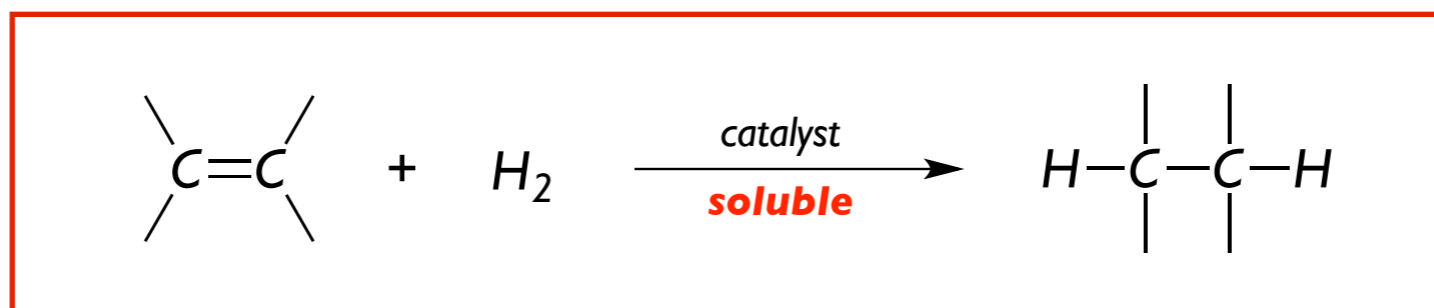
Alkynes into alkenes and alkanes



Chemoselectivity of Catalytic Heterogeneous Hydrogenations



■ *Conversion of alkenes into alkanes*



Catalysts: **Rh (I)**: $[(\text{Ph}_3\text{P})_3\text{RhCl}]$ is known as *Wilkinson catalyst*

Ir(I): $[(\text{cod})\text{Ir}(\text{PCy}_3)\text{pyr}] \text{PF}_6$

Homogenous catalysts are organometallic compounds, derived from transition metals, soluble in common organic solvents as hydrocarbons, ethers, or haloderivatives.

Then, hydrogenations are used to be carried out by stirring the reaction mixture at room temperature under a 1 atm hydrogen atmosphere.

*Hydrogenations with homogeneous catalysts are highly stereoselective: **syn addition***

Importantly, the development of chiral ligands provides enantioselective hydrogenations

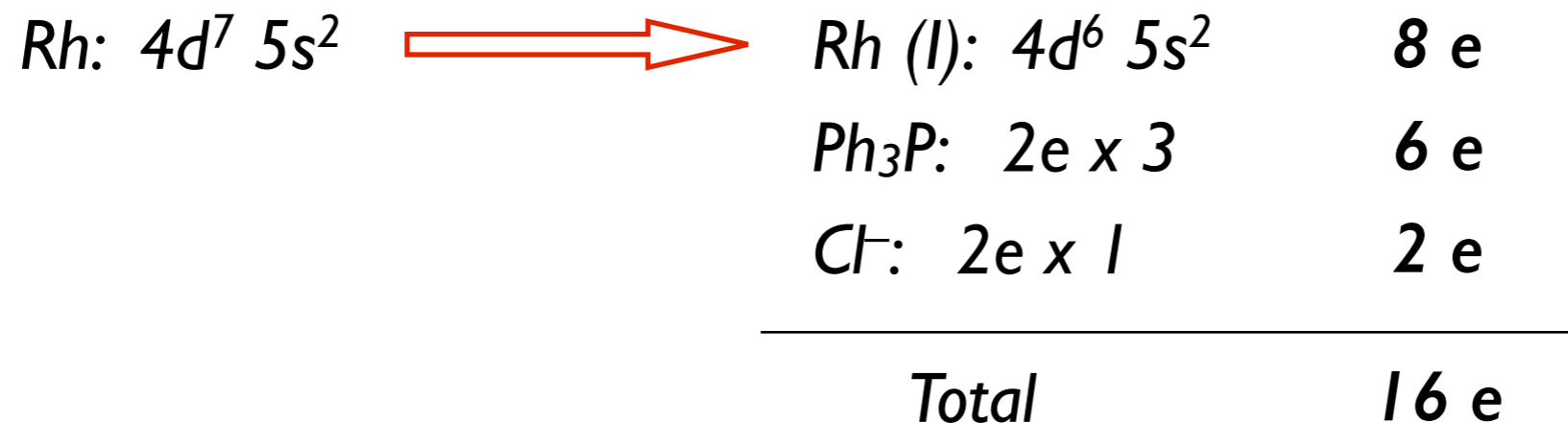
■ The golden rule: 18 electrons

A complex is particularly stable if the metal reaches the noble gas electronic configuration

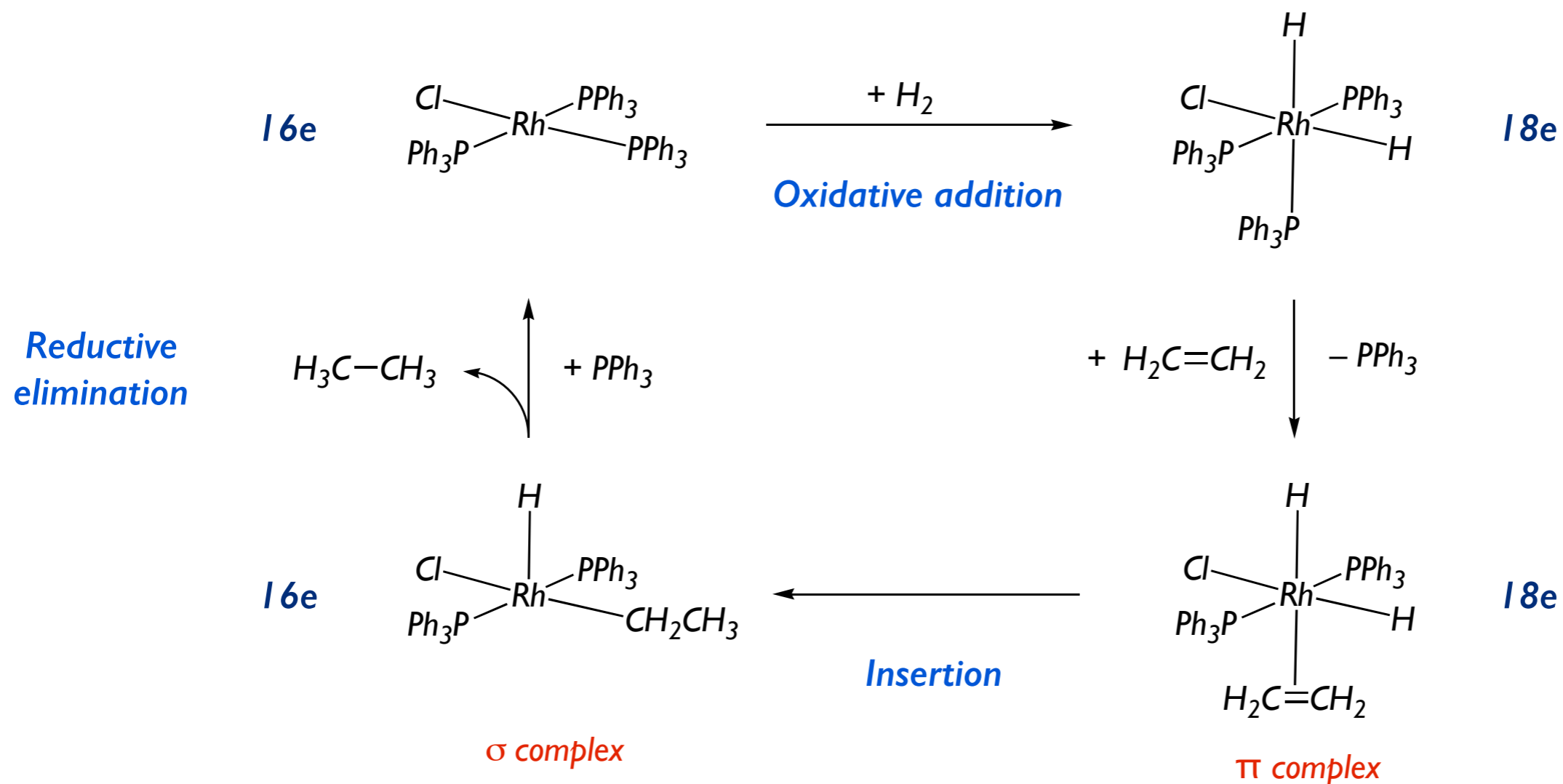
$$1 \text{ orbital } s + 3 \text{ orbitals } p + 5 \text{ orbitals } d = 18 \text{ electrons}$$

A complex becomes particularly reactive if the metal has less than 18 electrons

Wilkinson catalyst: $[(\text{Ph}_3\text{P})_3\text{RhCl}]$?



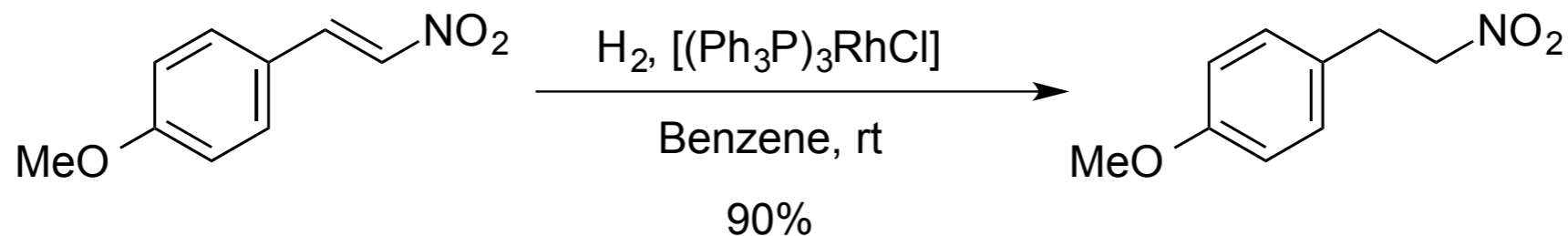
■ Mechanism of the homogeneous hydrogenation with the Wilkinson catalyst



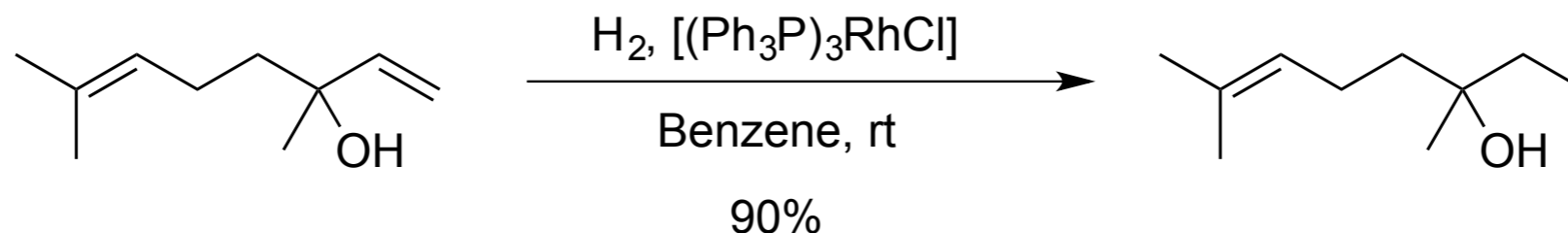
The addition is syn

■ A highly chemo- and regioselective hydrogenation of alkenes

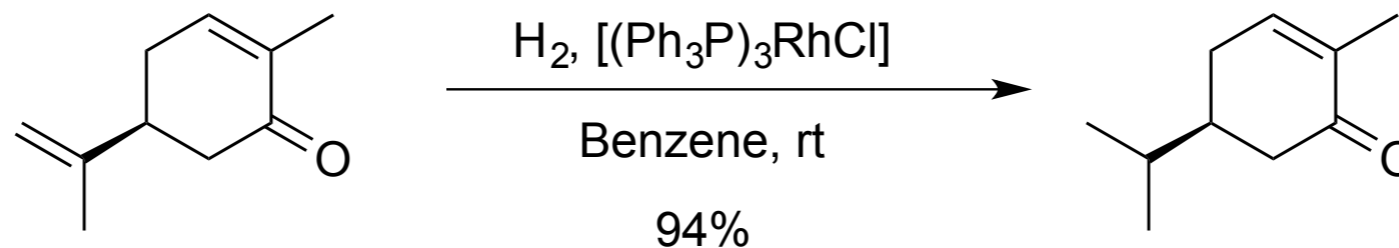
– Carbonyls, nitroderivatives or benzylic groups are not reduced



– The less substituted the more easily reduced



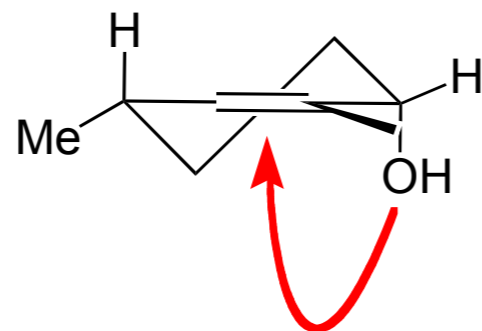
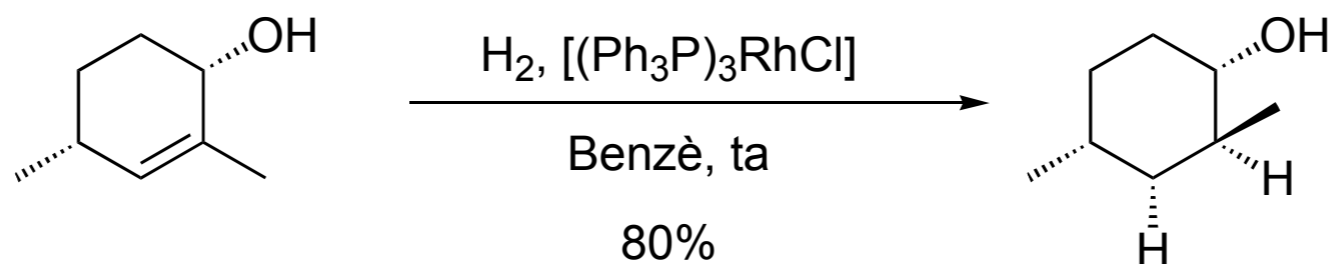
– Conjugated olefines react slowly



■ A major transformation: Homogeneous hydrogenation of alkenes

– Double and triple bonds are reduced without rearrangements

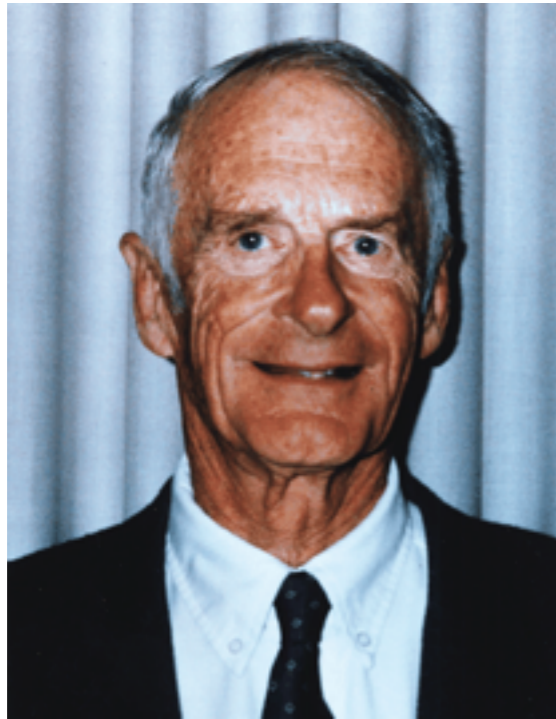
– π -Facial selectivity of the hydrogenation can be affected by polar groups



The hydroxyl group directs the hydrogenation to the lower π -face of the olefin

– Chiral ligands can be attached to the metal, producing enantioselective hydrogenations

Knowles, Noyori & Sharpless: Nobel Prize in Chemistry 2001



William S. Knowles



Ryoji Noyori



Barry S. Sharpless

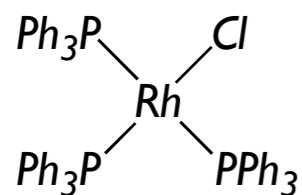
This year's Nobel Laureates in Chemistry have developed molecules that can catalyse important reactions

so that only one of the two mirror image forms is produced.

The catalyst molecule, which itself is chiral, speeds up the reaction without being consumed.

Just one of these molecules can produce millions of molecules of the desired mirror image form

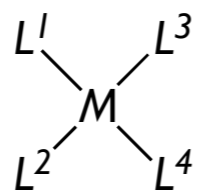
■ From Rh(I) to Ru(II), from Ph₃P to BINAP



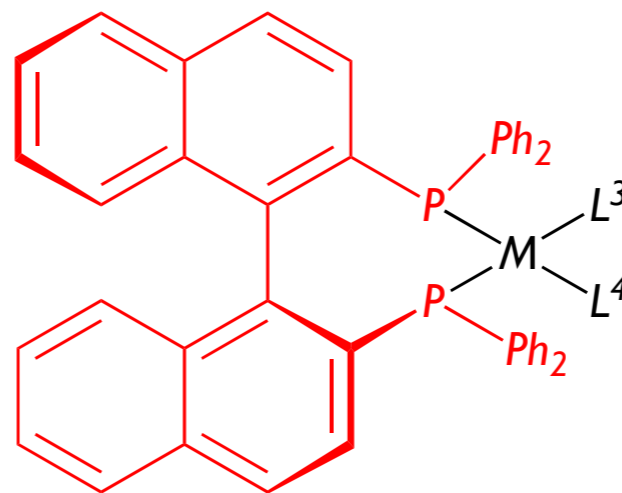
Wilkinson

Rh(I): 5s² 4d⁶

Ph₃P



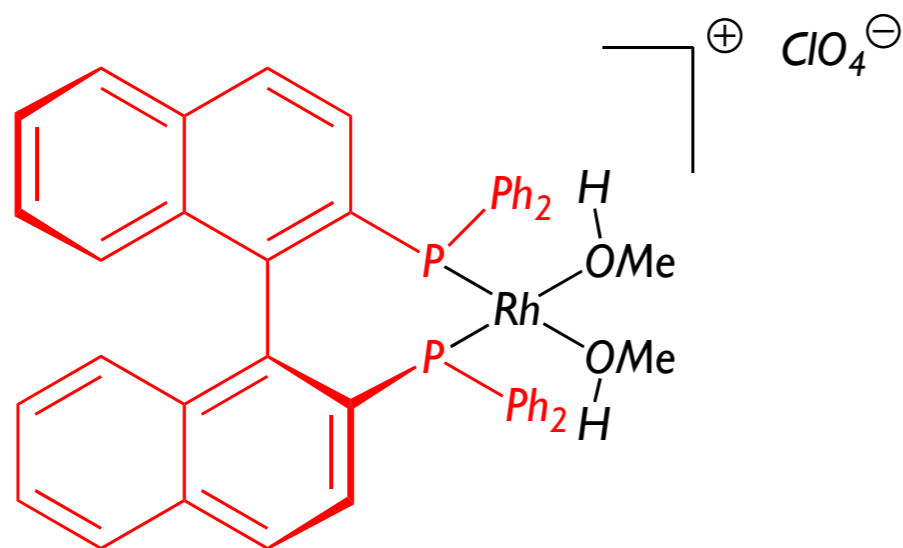
16 e



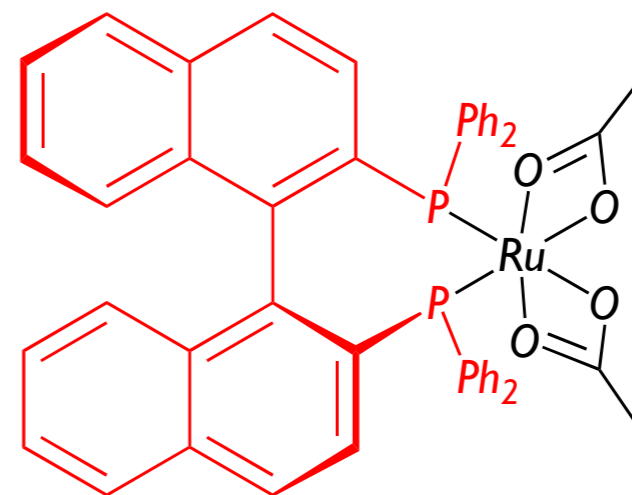
Noyori BINAP

Rh (I): 5s² 4d⁶

Ru(II): 5s² 4d⁴



JACS 1980, 102, 7932



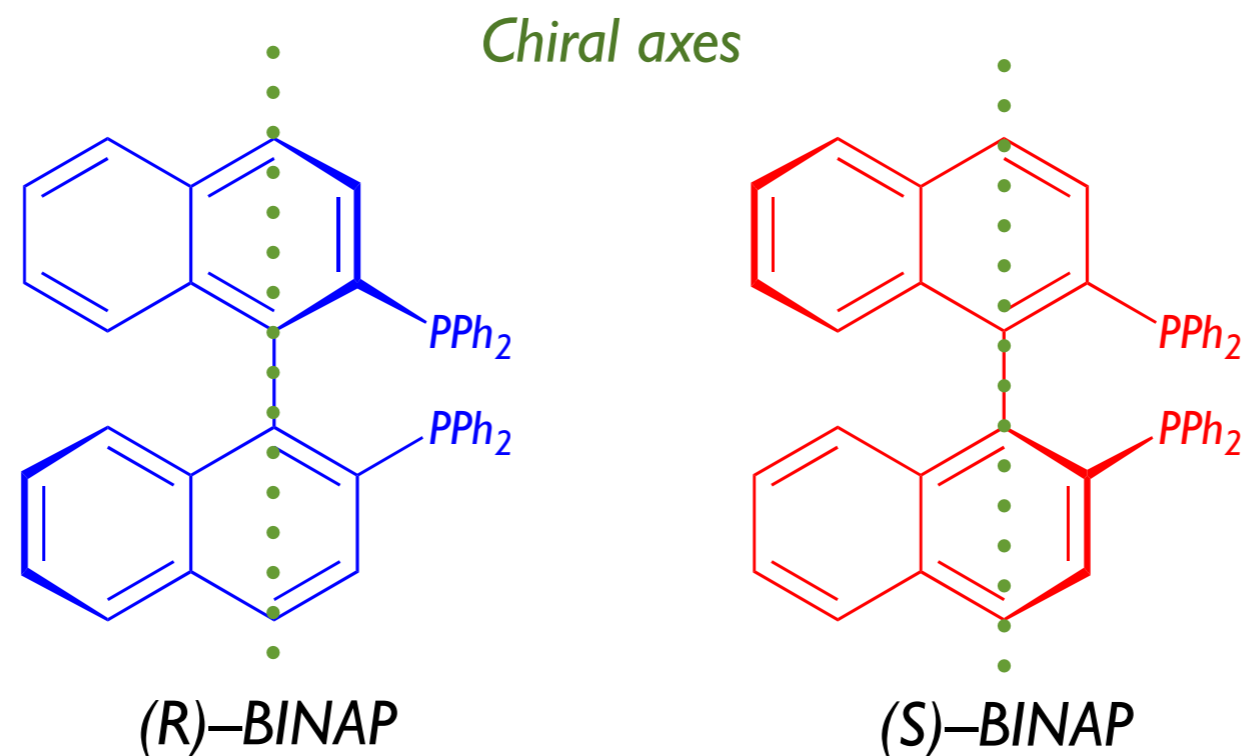
JACS 1986, 108, 7117

■ BINAP: *1,1'*-BINAPhtylPhosphines

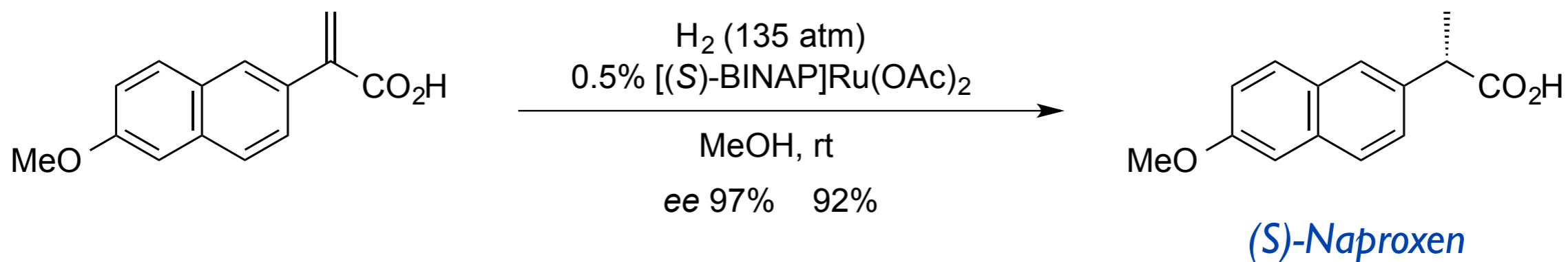
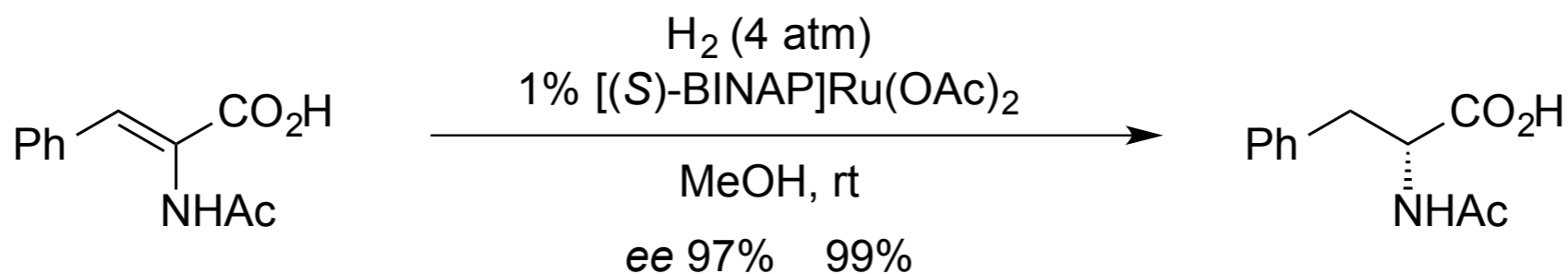
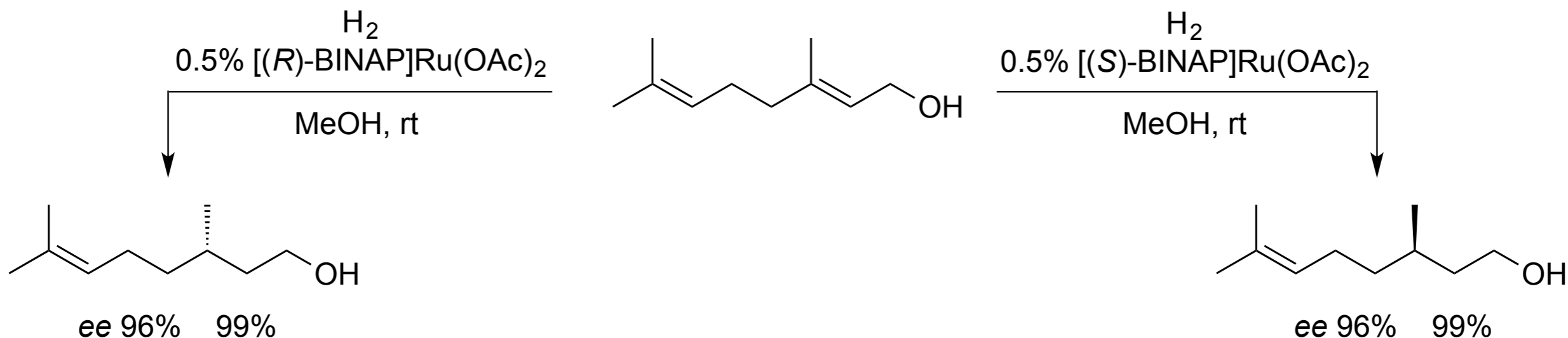
BINAP is a chiral biphosphine without any chiral center.

The lack of free rotation about the ArC–CAr bond and the resultant chiral axis are in the origin of the chirality of this biphosphine.

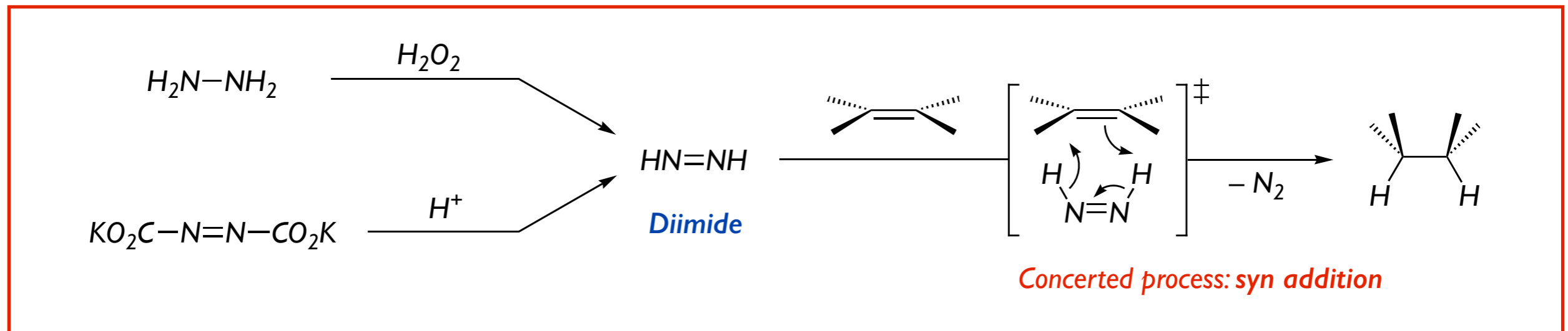
This is a very common ligand in asymmetric synthesis



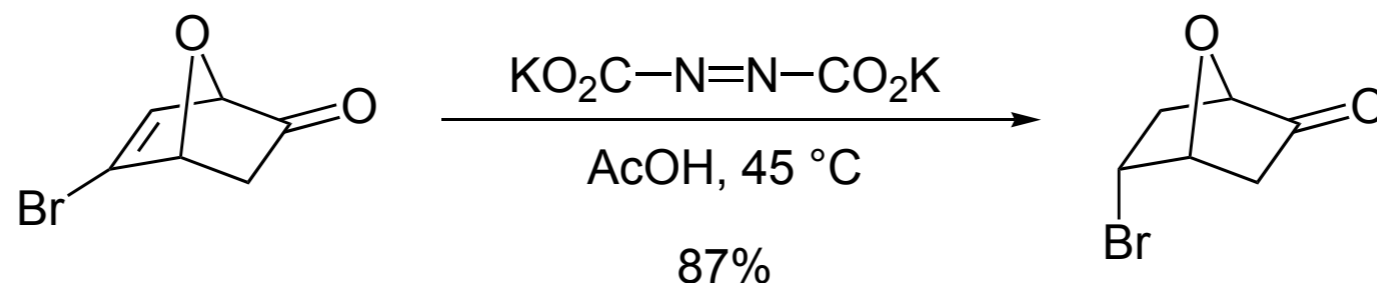
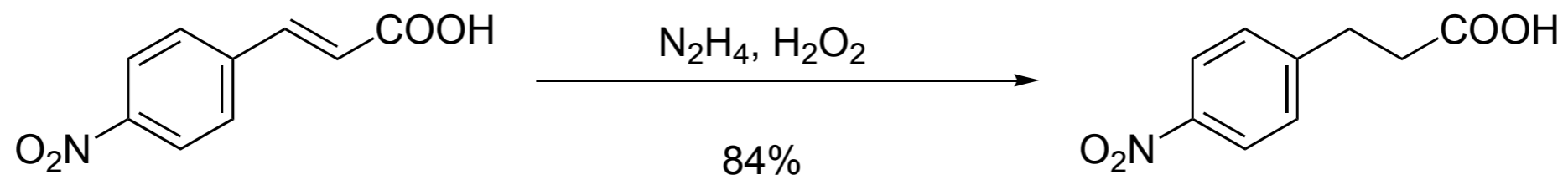
Stereoselectivity of Homogeneous Hydrogenation of Alkenes



■ *Diimide: another hydrogen-transfer agent*



– *This is a very chemoselective process: it only reduces alkenes and alkynes*

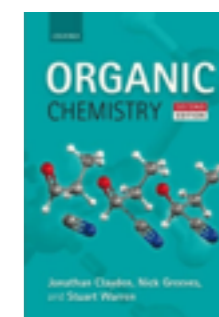


■ Reductive processes:

- a) Dissolving metal reductions
- b) Radical reductions
- c) Reductions with hydrides
- d) Catalytic hydrogenations
- e) Carbonyl deoxygenation reactions



Different Chaps.



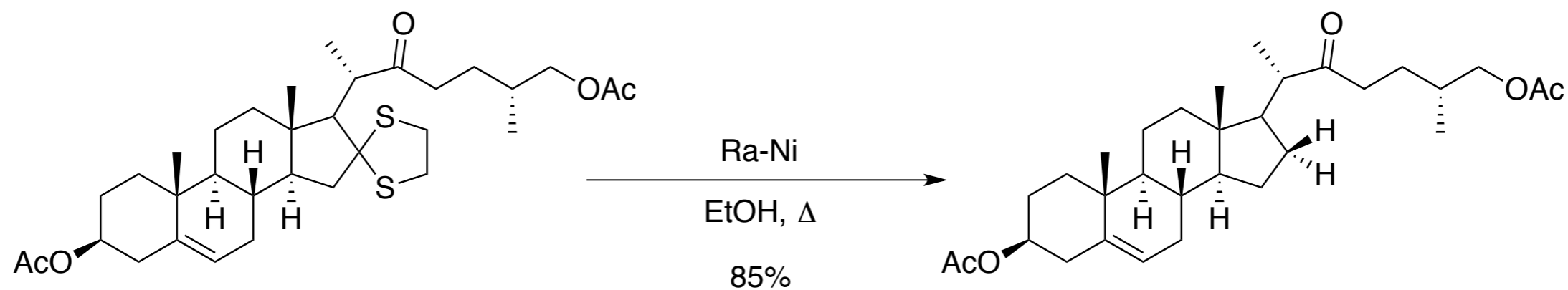
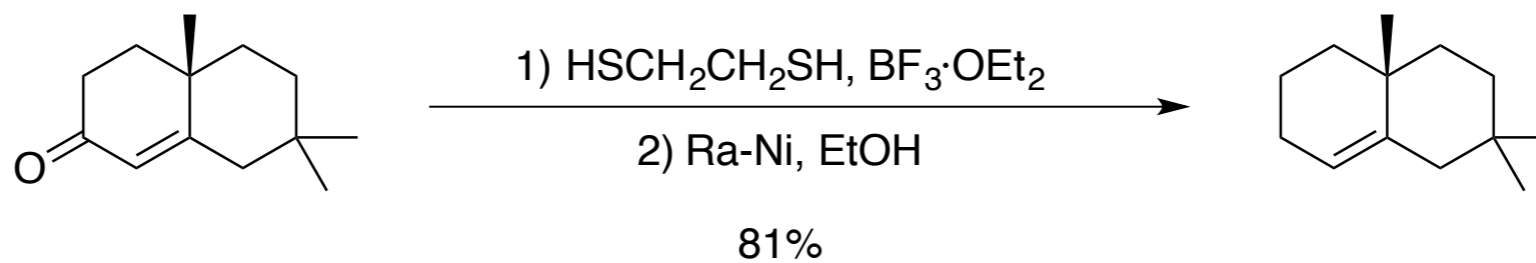
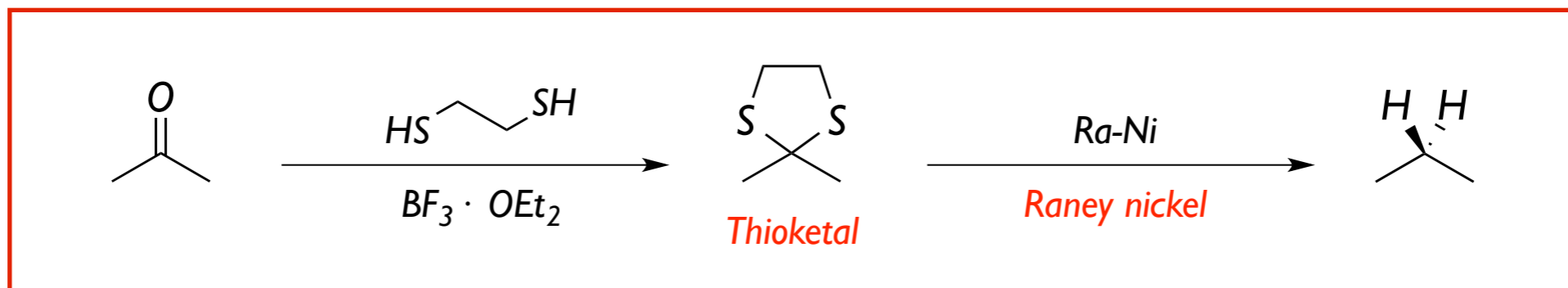
*Chap. 23
mainly*

Carbonyls can be transformed into the corresponding alkanes or alkenes using different two-step processes

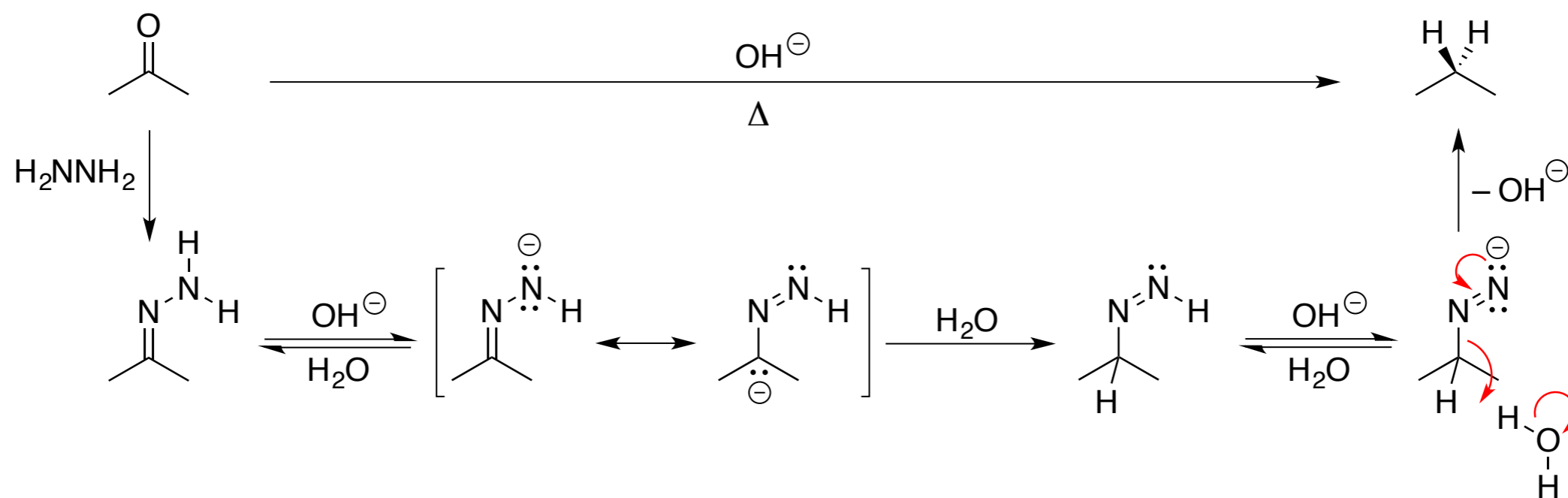
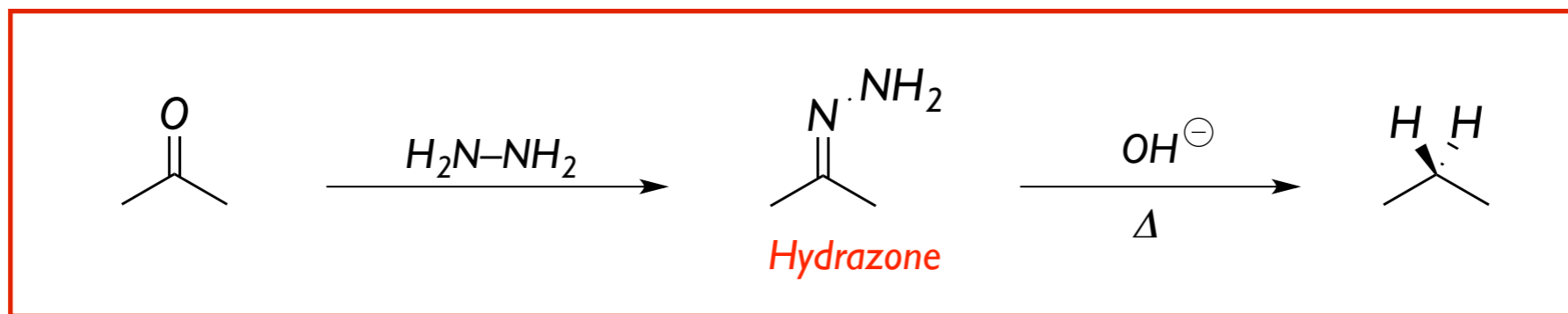
- *From thioketals*

- *From imine derivatives*
 - *Wolff- Kishner reaction*
 - *Reduction of tosylhydrazones*
 - *Shapiro reaction*

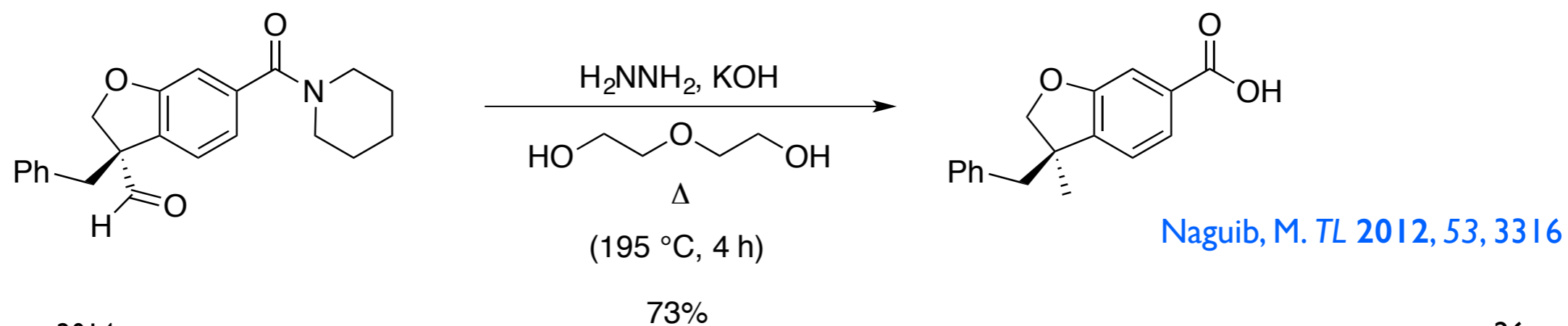
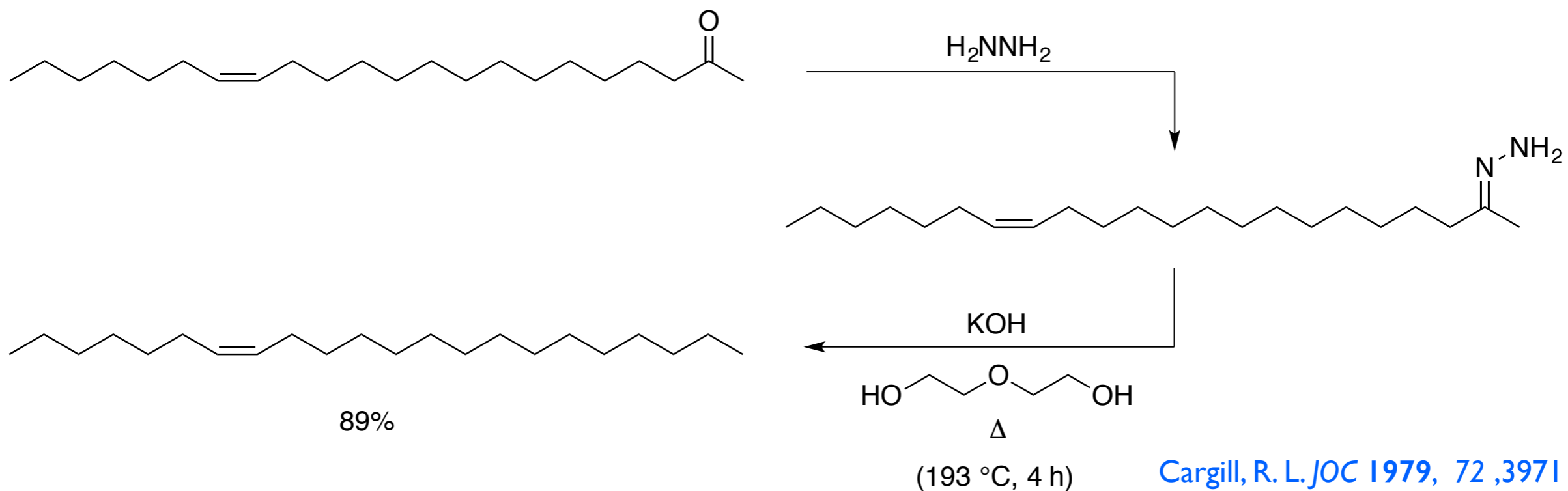
From thioketals



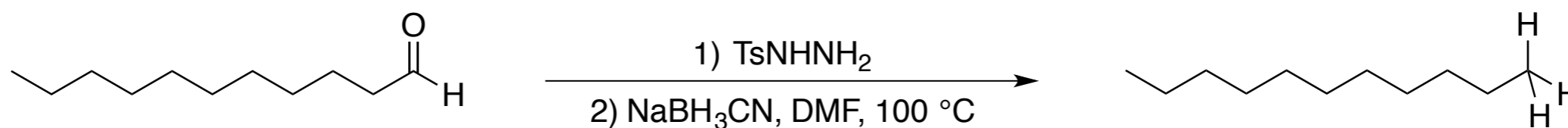
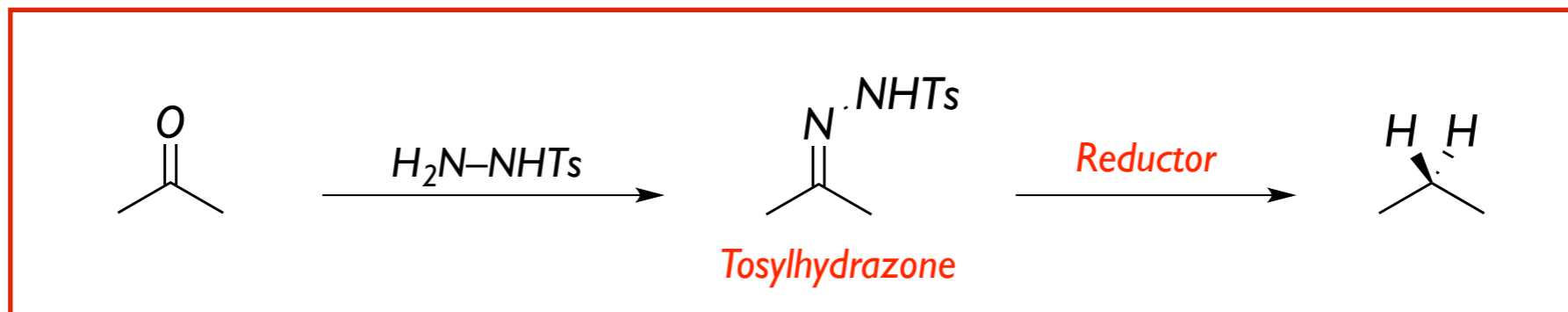
Wolff-Kishner reaction



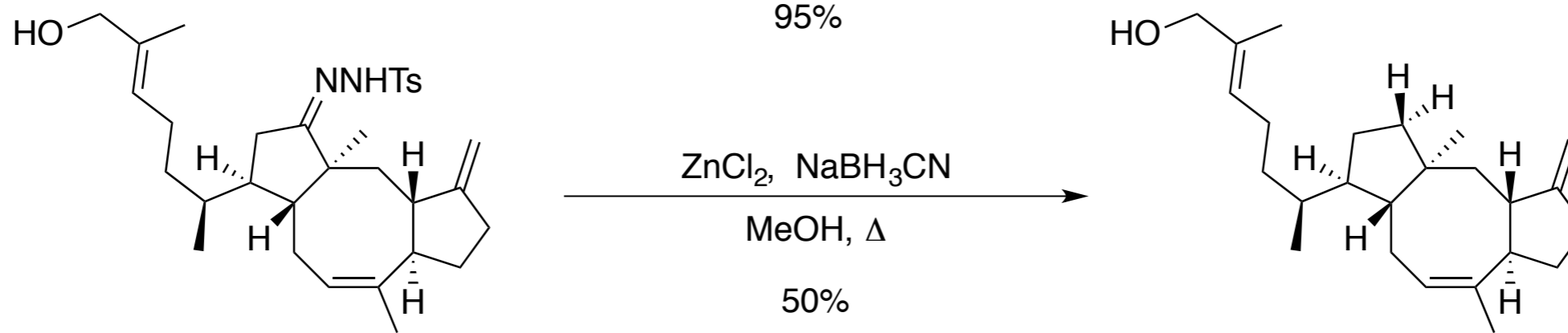
Unfortunately, this reaction requires harsh experimental conditions



■ Reduction of tosylhydrazones

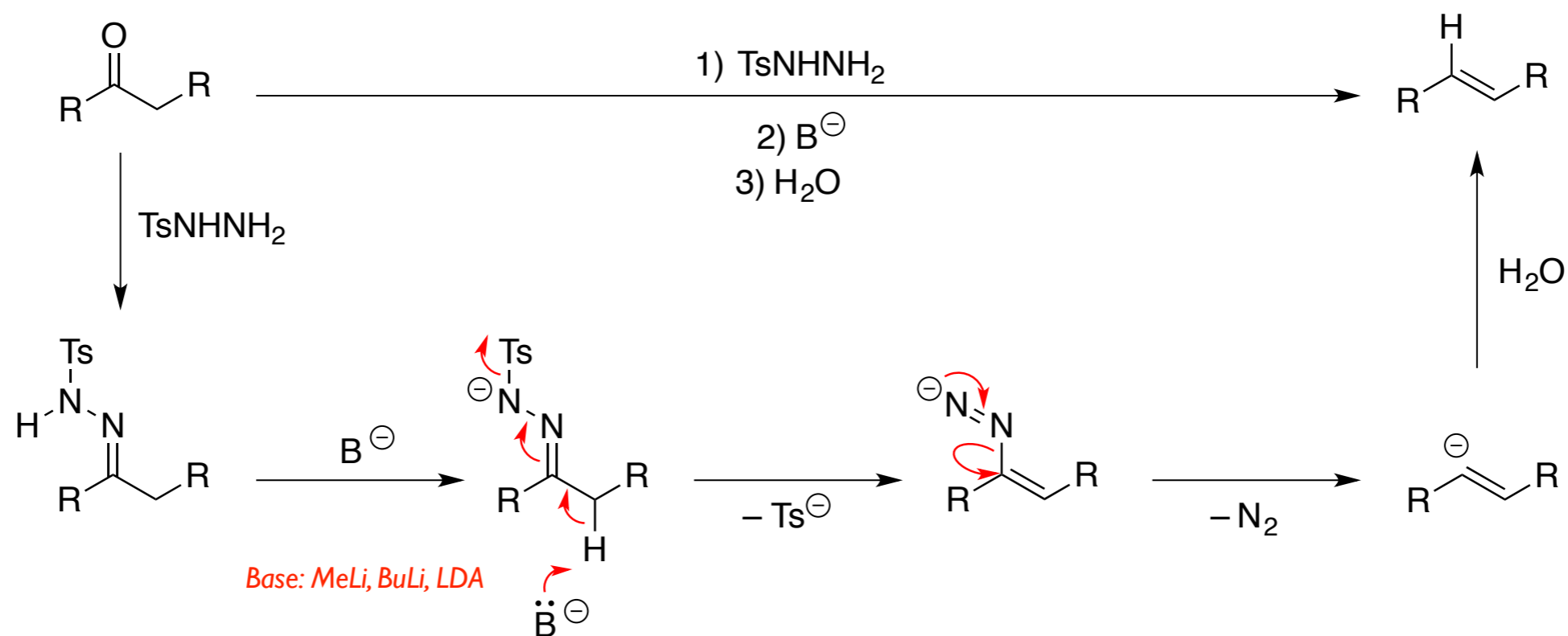
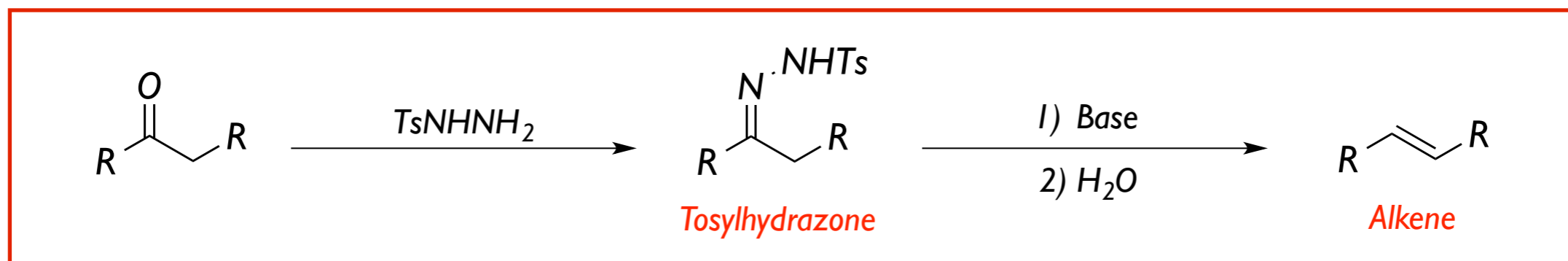


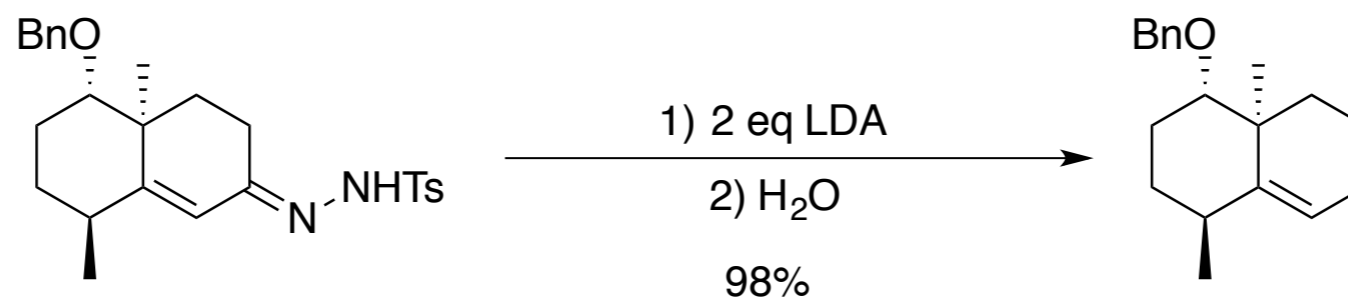
95%



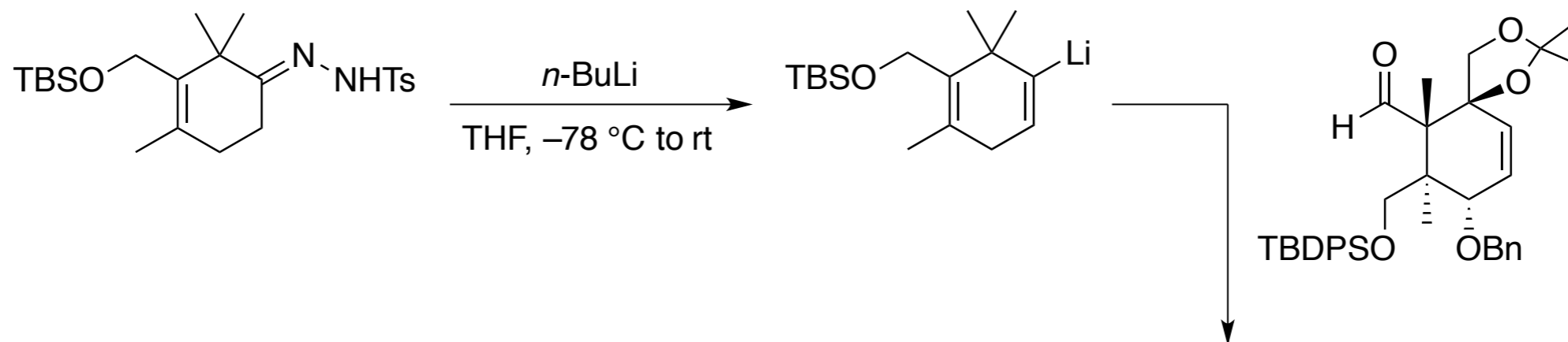
50%

Shapiro reaction

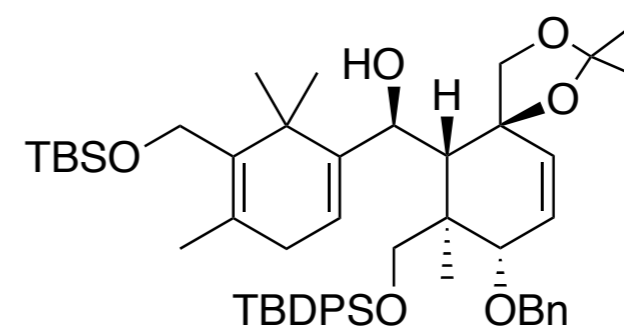
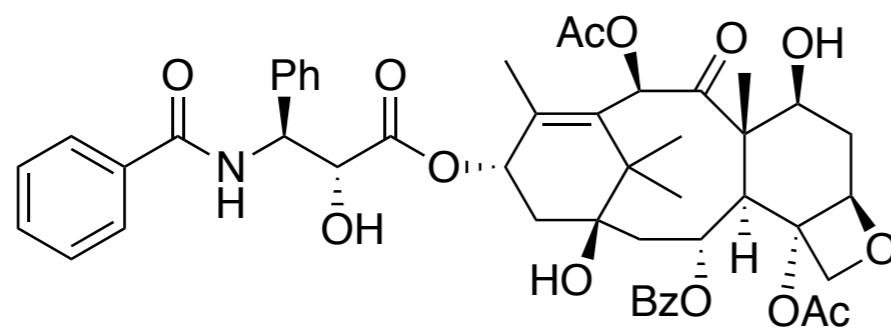




The final anion can be trapped with other electrophiles ...



Taxol



82%