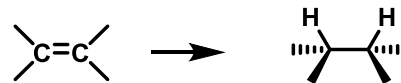
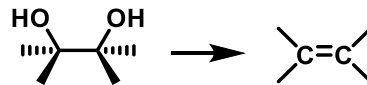
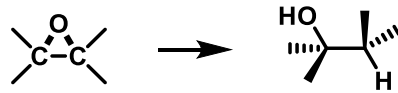
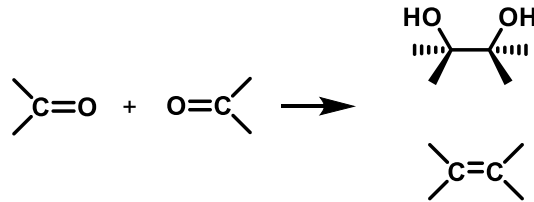
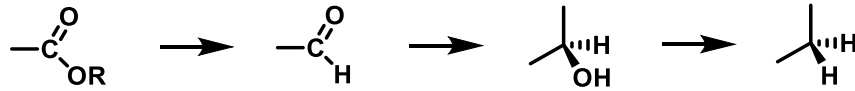
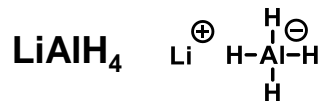
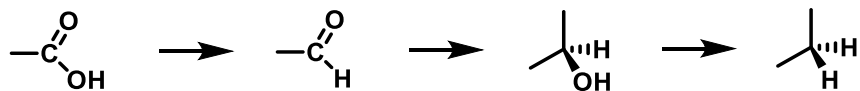


Organic synthesis

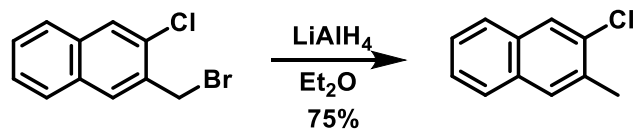
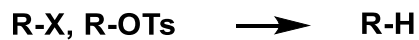
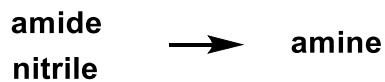
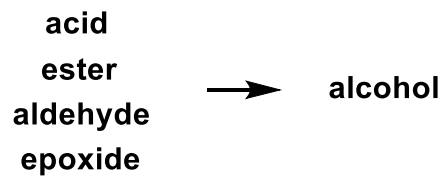
Kamil Paruch

Masaryk University, Brno

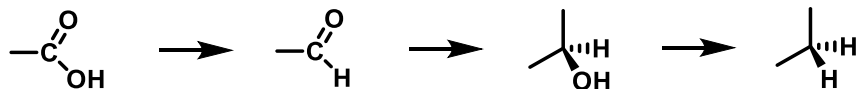




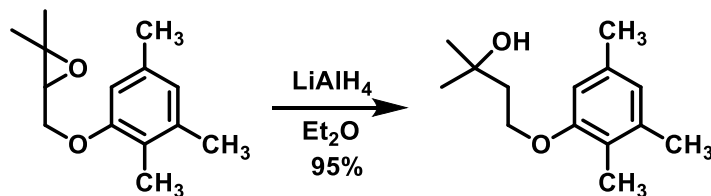
- strong, quite unselective reducing agent



J. Org. Chem. **1958**, 23, 1483.



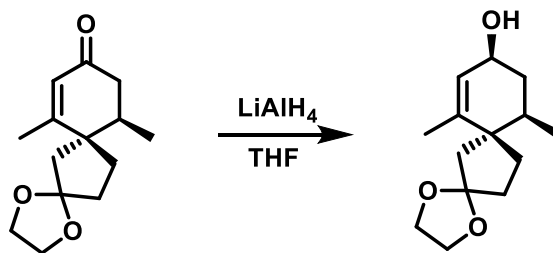
epoxides: typically, attack of H^- on less substituted C



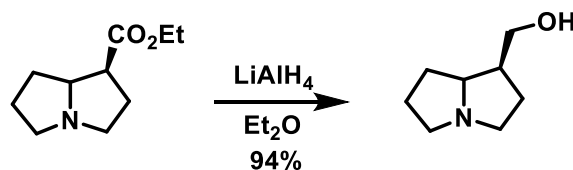
J. Org. Chem. **1989**, *54*, 2620.

reduction of $\text{C}=\text{O}$: attack at less sterically hindered site

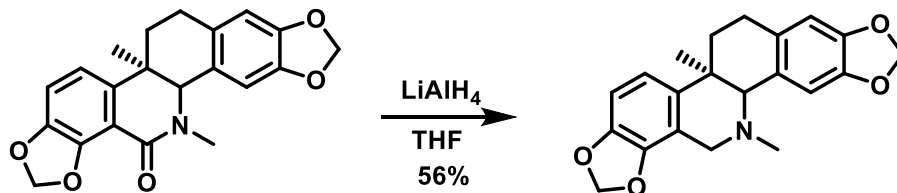
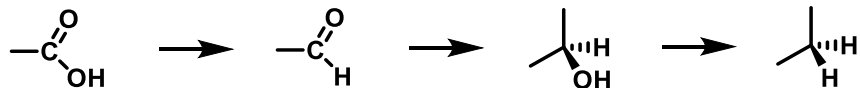
α,β -unsaturated ketones: predominant 1,2-reduction



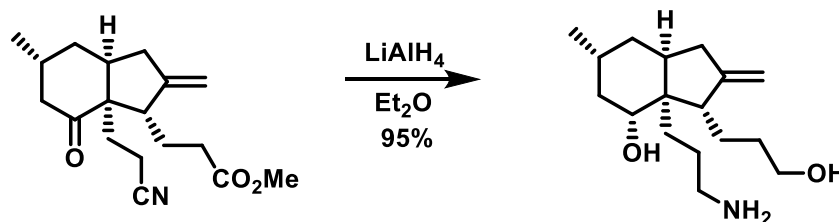
reduction of carbonyl compounds with LAH: typically *no* racemization (epimerization)



J. Chem. Soc., Perkin Trans. 1 **1981**, 909.

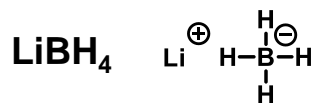
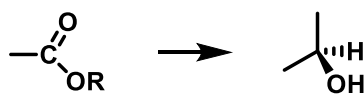
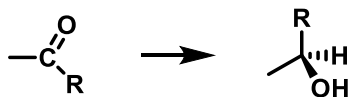


J. Chem. Soc., Perkin Trans. 1 **1980**, 212.

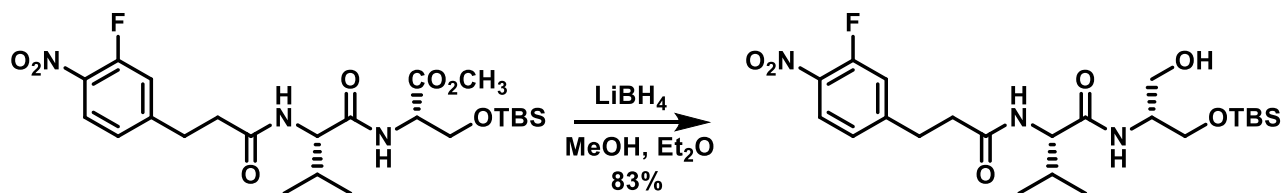


J. Org. Chem. **1989**, 54, 1548.

LiAlH_4 can act as a base:



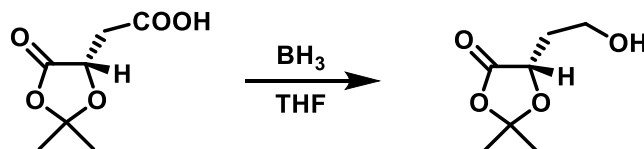
- reduction of esters to alcohols (in the presence of carboxylic acids, amides, nitriles)



Synlett. **2000**, 1363.

BH_3 : sold as $\text{BH}_3 \cdot \text{THF}$ or $\text{BH}_3 \cdot \text{Me}_2\text{S}$

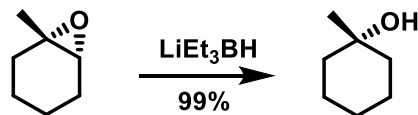
- reduction of *carboxylic acids* in the presence of esters and other functional groups
- hydroboration of alkenes



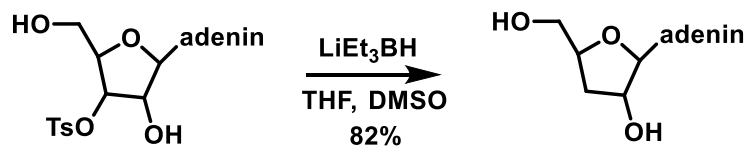
J. Am. Chem. Soc. **1980**, 102, 2117.



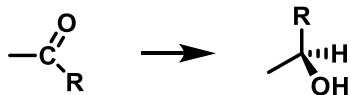
- donor of strongly nucleophilic hydride
- reduction of halides, sulfonates, opening of epoxides (attack on less sterically hindered C)



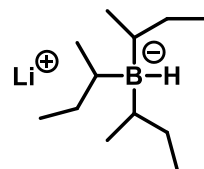
J. Am. Chem. Soc. **1973**, 95, 8486.



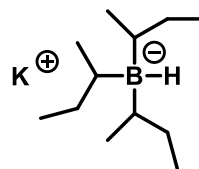
J. Am. Chem. Soc. **1983**, 105, 6736.



Selectrides

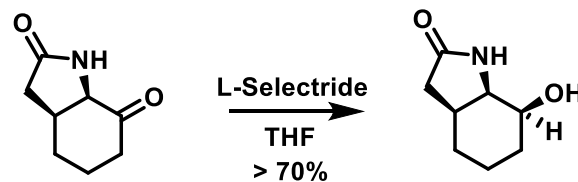


L-Selectride

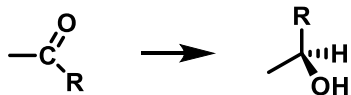


K-Selectride

- bulky donors of hydride
- frequently used for **diastereoselective reductions** (substrate control)



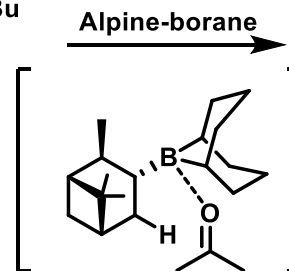
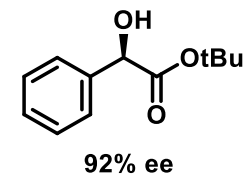
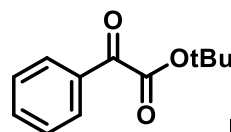
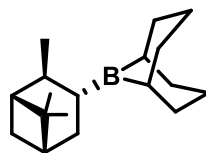
J. Org. Chem. **1988**, 53, 4006.



enantioselective reduction

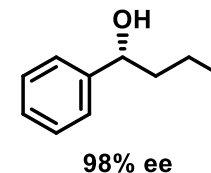
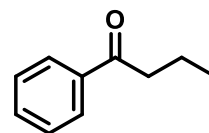
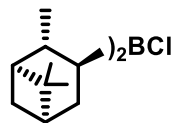
chiral boranes

Alpine-borane



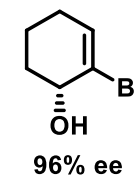
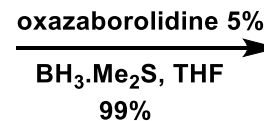
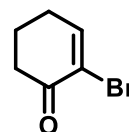
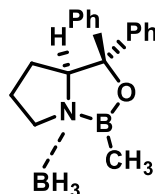
Ipc_2BCl

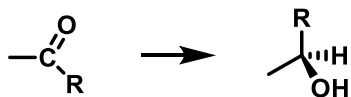
• more reactive



chiral oxazaborolidines + BH_3

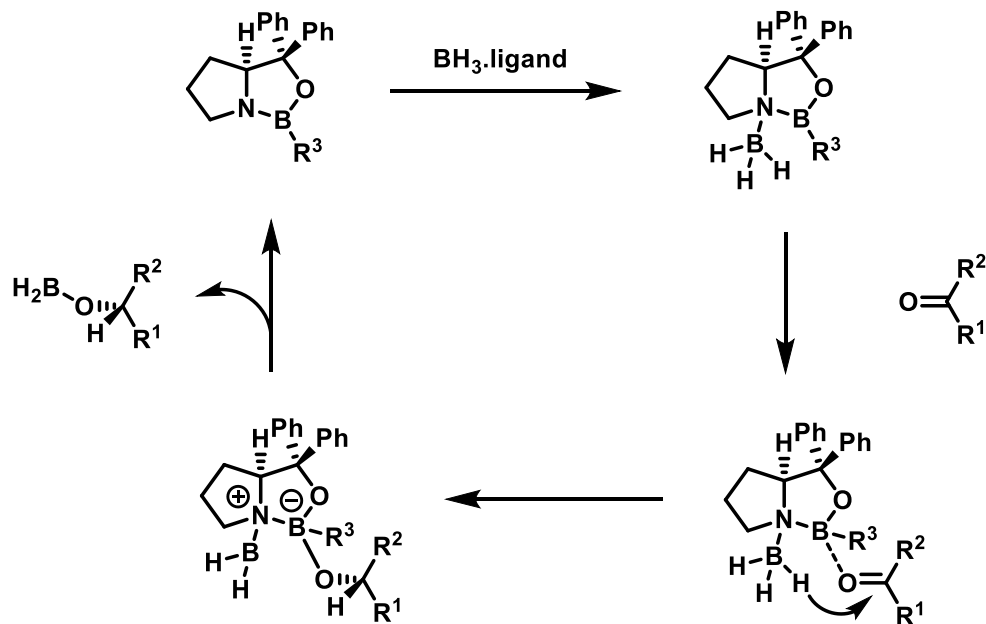
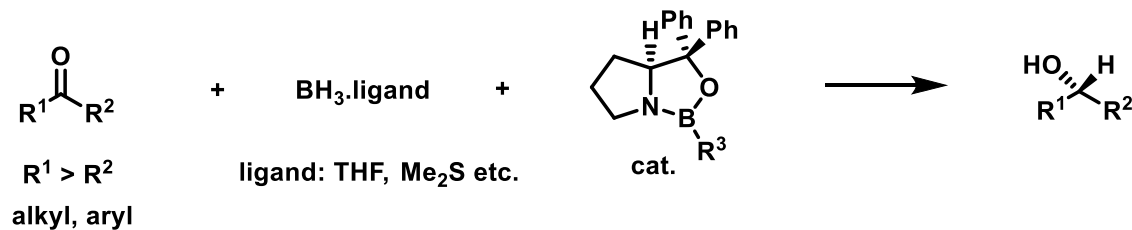
- catalytic amount
- activation of BH_3 by complexation

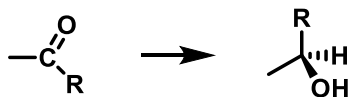




enantioselective reduction

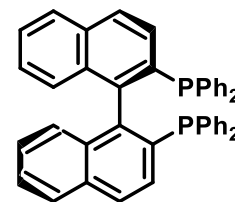
Corey-Bakshi-Shibata reduction (CBS reduction)



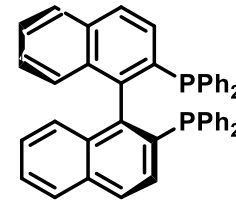


enantioselective reduction

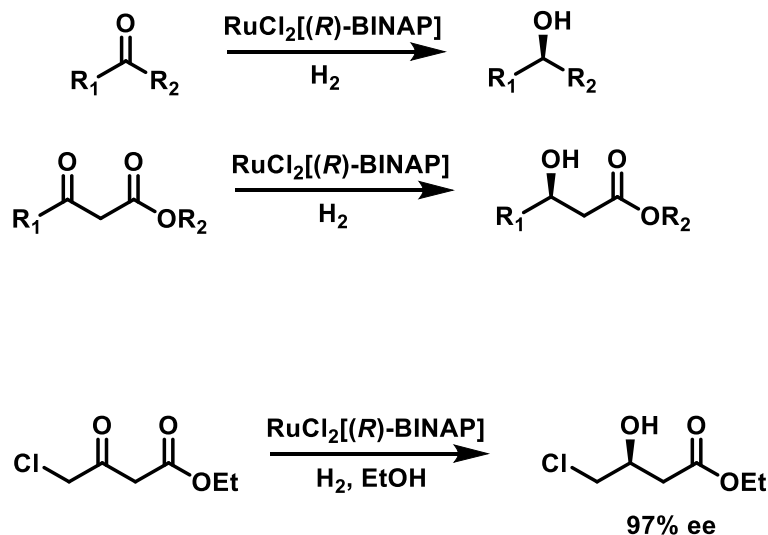
catalytic hydrogenation (of β -ketoesters)



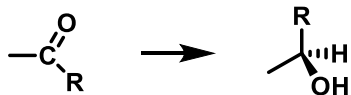
(R)-BINAP



(S)-BINAP

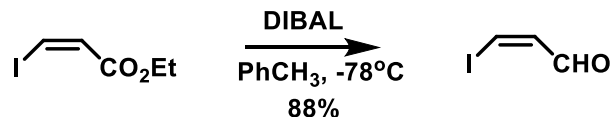


J. Am. Chem. Soc. **1988**, 110, 629.



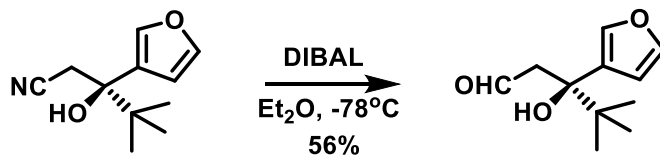
DIBAL : $i\text{-Bu}_2\text{AlH}$

- formation of stable tetrahedral adduct after first reduction \rightarrow another reduction does not proceed
- reduction of esters to aldehydes (low temperature)

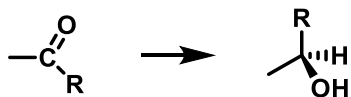


Org. Synth. **1996**, 74, 194.

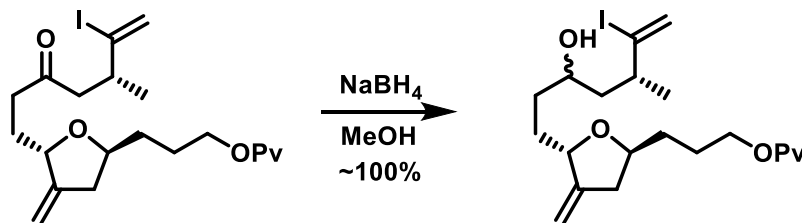
- reduction of nitriles to imines (which are hydrolyzed to aldehydes during work-up)



J. Am. Chem. Soc. **1993**, 115, 3146.

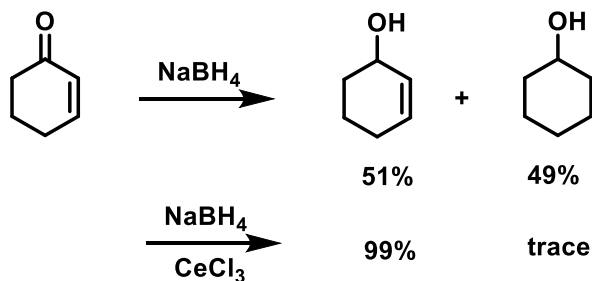


- selective reductant: reduction of aldehydes, ketones and acid chlorides in the presence of other reducible groups
(CO₂R, CN, NO₂, epoxides)
- compatible with alcoholic solvents

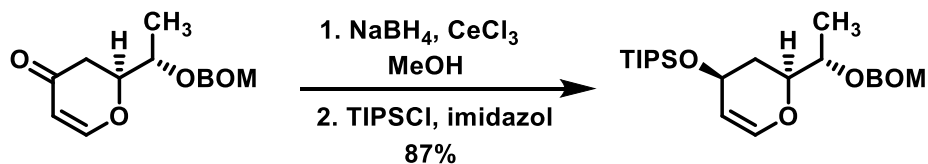


J. Am. Chem. Soc. **1992**, 114, 3162.

α,β -unsaturated ketones: 1,2-reduction (in combination with lanthanide salts - **Luche reduction**)



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

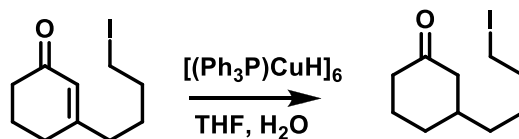
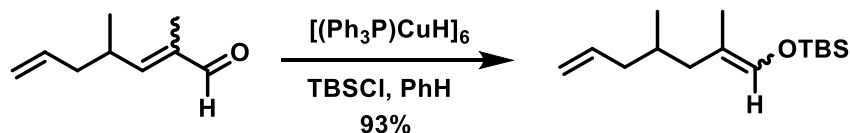


J. Am. Chem. Soc. **1997**, 119, 10073.

note

Stryker reduction: 1,4-reduction

- complementary to 1,2-reduction of α,β -unsaturated ketones, aldehydes, nitriles, sulfones
- highly chemoselective: isolated C=C, C=O and many protecting groups typically not affected
- $[(\text{Ph}_3\text{P})\text{CuH}]_6$ commercially available



Tetrahedron Lett. **1990**, 31, 3237.

chemoselective reduction of aldehydes vs. ketones
with $\text{NaBH}(\text{O}-\text{CH}(\text{CF}_3)_2)_3$

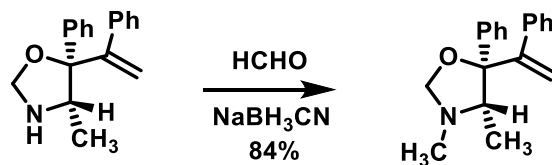
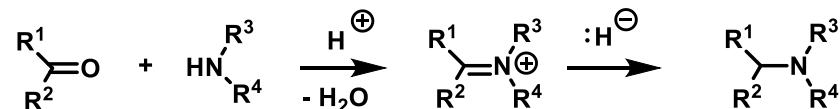
Synlett **2008**, 16, 2523.

reductive amination: NaBH_4 , $\text{NaBH}(\text{OAc})_3$, NaBH_3CN

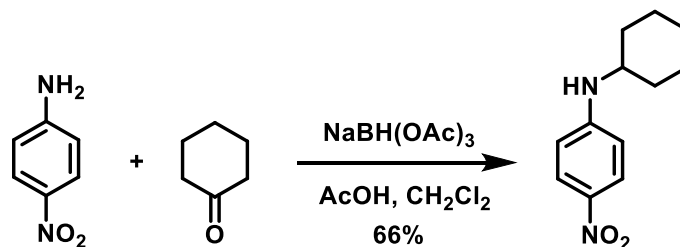
note: „Cs effect“ mono-alkylation *J. Org. Chem.* **2002**, *67*, 674.

irreproducible in our hands: phenethyl amine + BnBr

- selective reduction of imines and iminium salts; stable under mildly acidic conditions
- optimal pH: typically 4-5 (equilibrium of protonated/non-protonated carbonyl & imine & amine)



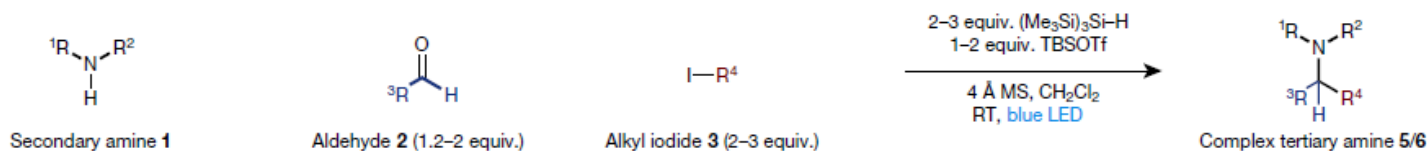
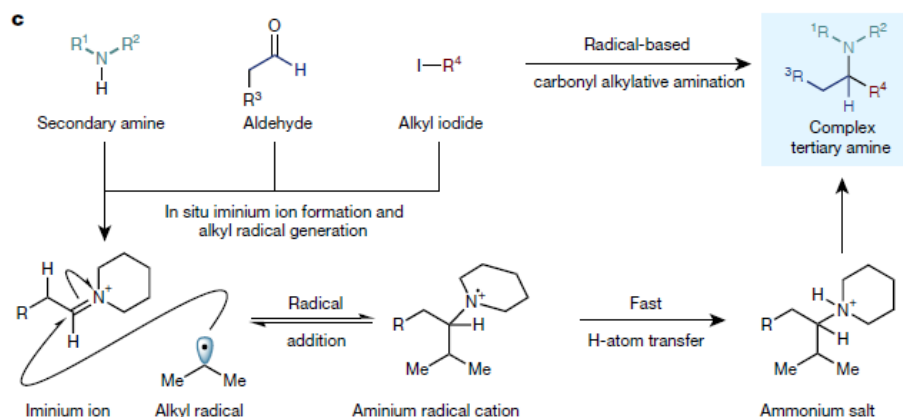
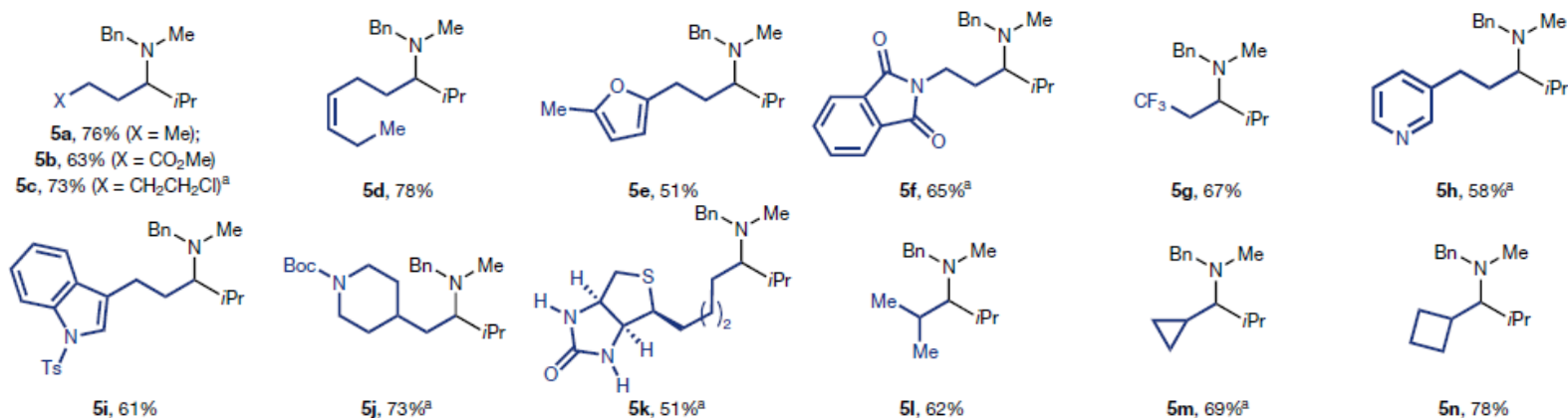
J. Am. Chem. Soc. **1988**, *110*, 4329.



Tetrahedron Lett. **1984**, *25*, 5449.

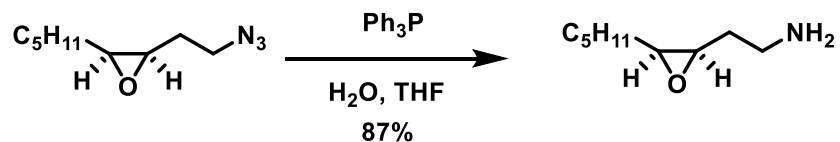
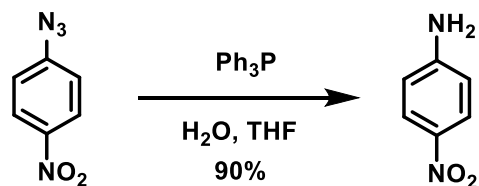
alkylative amination

- formally analogous to reductive amination -> complex tertiary amines (frequent motifs in medchem)
- but historically difficult to carry out

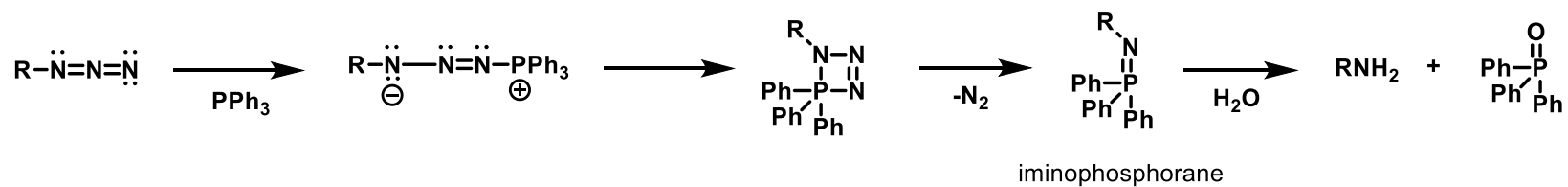
Nature **2020**, 581, 415.**a** Scope of aldehyde component

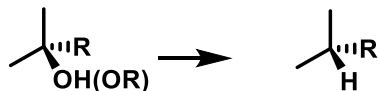


Staudinger reaction



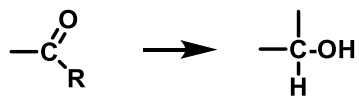
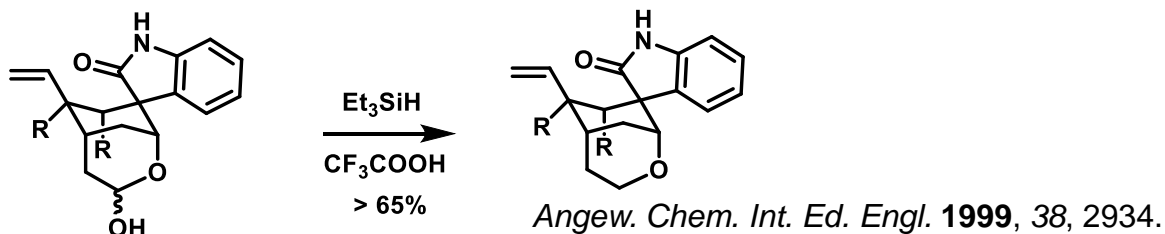
Tetrahedron Lett. **1983**, 24, 763.





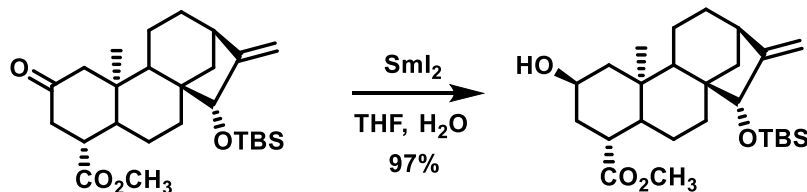
„ionic hydrogenation“

- combination of proton donor (CF_3COOH) and hydride donor (Et_3SiH)
- typically selective with ketones, alkenes and lactones

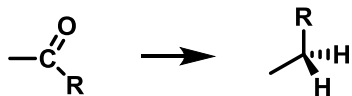


SmI_2

- reduction of aldehydes and ketones in the presence of carb. acids and esters

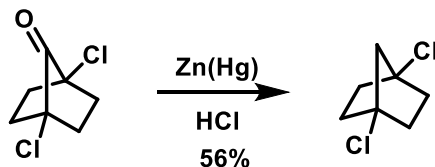


J. Am. Chem. Soc. **1990**, 112, 7001.



Clemmensen reduction

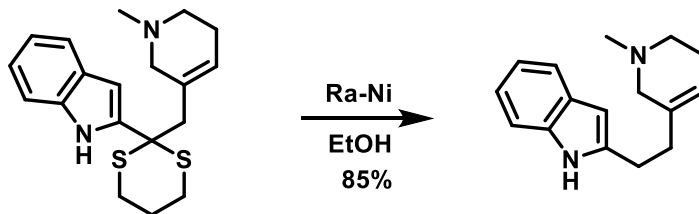
- strongly acidic conditions; limited use



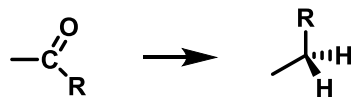
J. Org. Chem. **1969**, 34, 1109.

reduction of thioacetals (thioketals), also thiols, thioethers, sulfoxides and sulfones

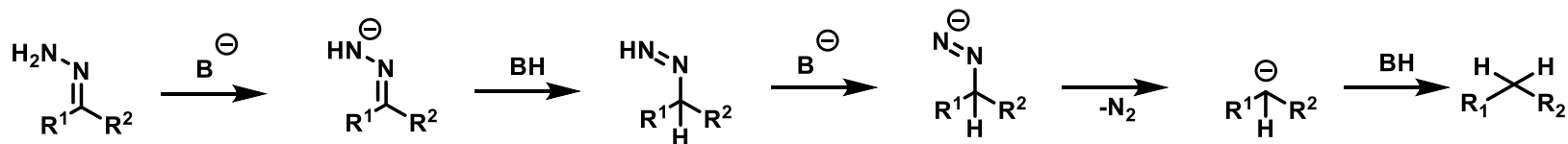
- Ra-Ni (+ H₂)



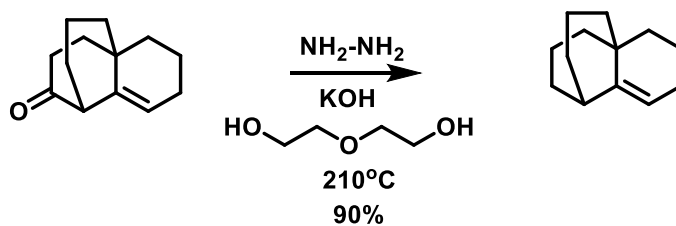
Heterocycles **1991**, 32, 663.



Kizhner-Wolff reduction

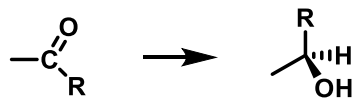


traditional protocol:



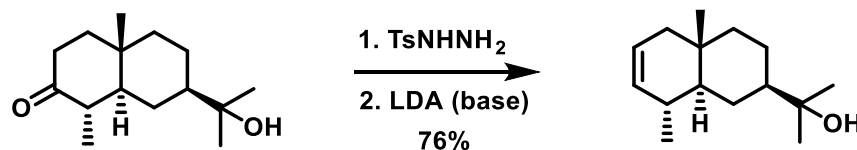
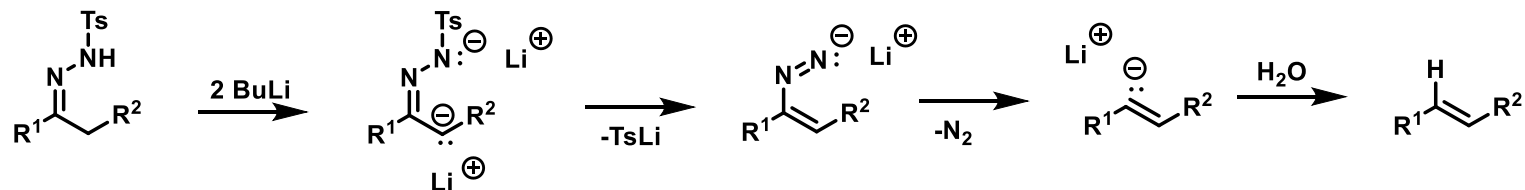
Can. J. Chem. **1979**, 57, 1064.

low temperature variant: $t\text{-BuOK}$, DMSO



Shapiro reaction

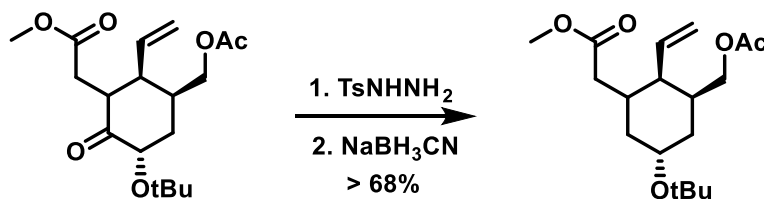
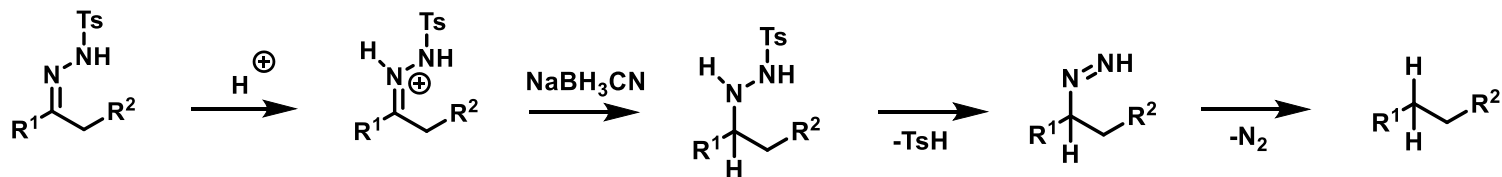
- ketones (aldehydes) \rightarrow tosylhydrazones \rightarrow alkenes



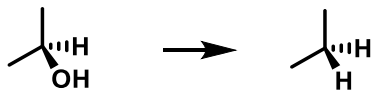
Can. J. Chem. **1983**, *61*, 1111.

reduction of tosylhydrazones by hydrides

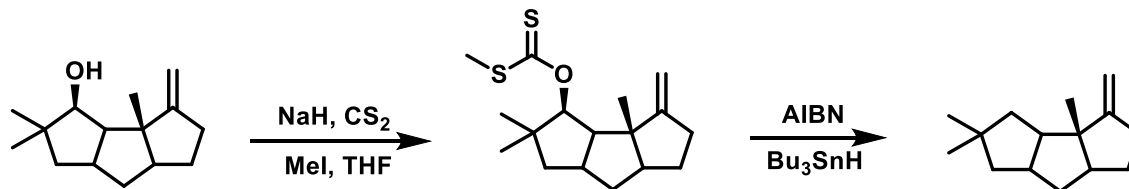
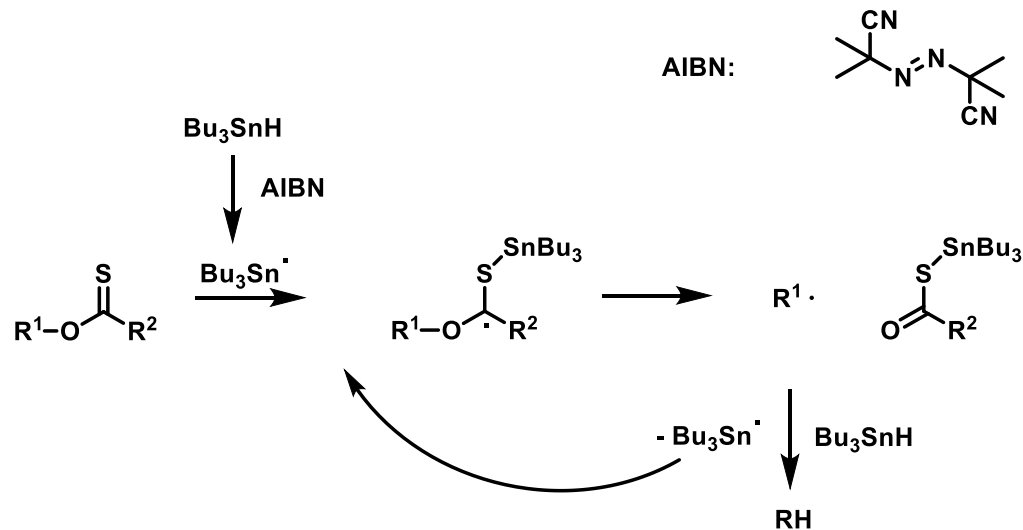
- mild & chemoselective (esters, amides, nitro, nitriles... tolerated) removal of O from carbonyl



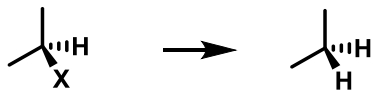
J. Org. Chem. **1991**, *56*, 2947.



Barton-McCombie deoxygenation

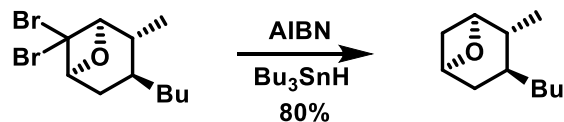


J. Am. Chem. Soc. **1986**, *108*, 3443.

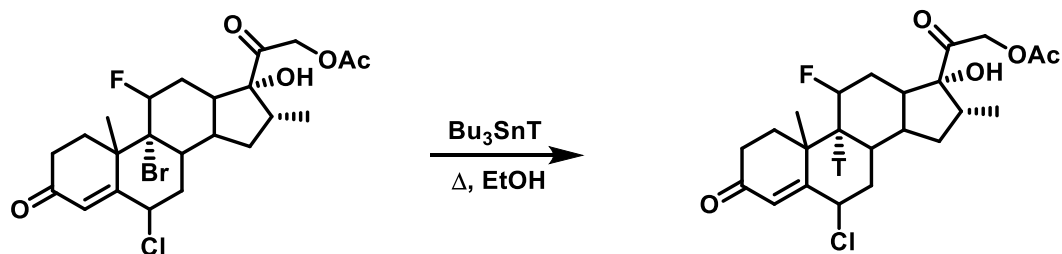


radical dehalogenation

- radical source: Bu_3SnH
- Br and I more reactive than Cl and F
- also useful for removal of NO_2

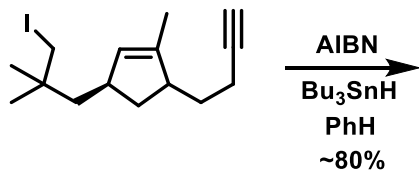


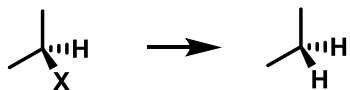
J. Am. Chem. Soc. **1991**, 113, 8980.



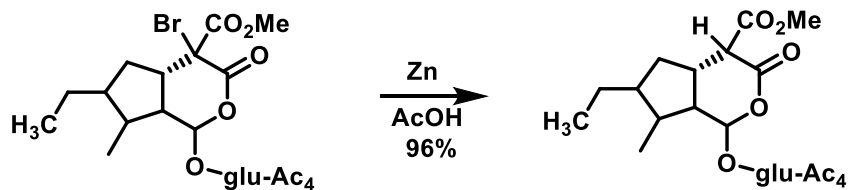
J. Org. Chem. **1979**, 44, 151.

radical reactions: possibility of alternative pathways (-> side reactions)

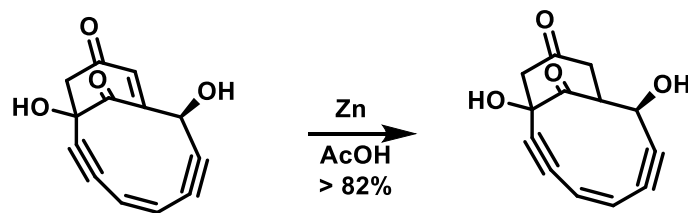


**dehalogenation with Zn/AcOH**

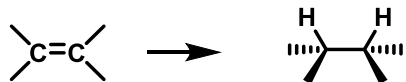
- chemoselective reduction of α -haloketones, α,β -unsaturated ketones



J. Org. Chem. **1988**, 53, 1100.



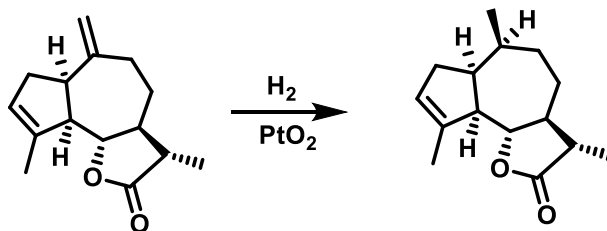
J. Org. Chem. **1989**, 54, 2781.



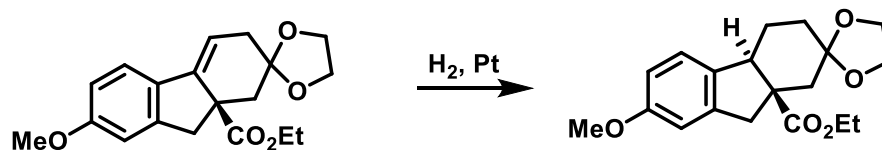
catalytic hydrogenation (of alkenes)

- substituted alkenes are typically less reactive
 - syn- addition from sterically less hindered site
- but:* addition of H₂ can be directed using proper polar substituents

heterogenous: typically with Pd/C, Pd(OH)₂, Pt, PtO₂ etc.

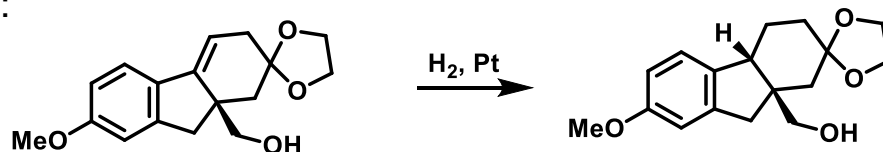


Tetrahedron **1972**, 28, 3583.



J. Chem. Soc. **1957**, 3107.

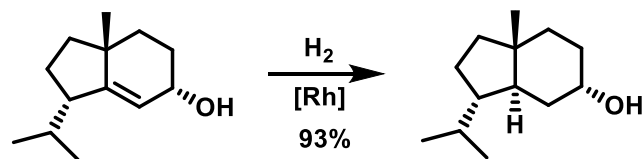
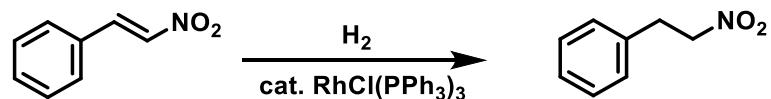
but:



homogenous

Wilkinson catalyst: $\text{RhCl}(\text{PPh}_3)_3$

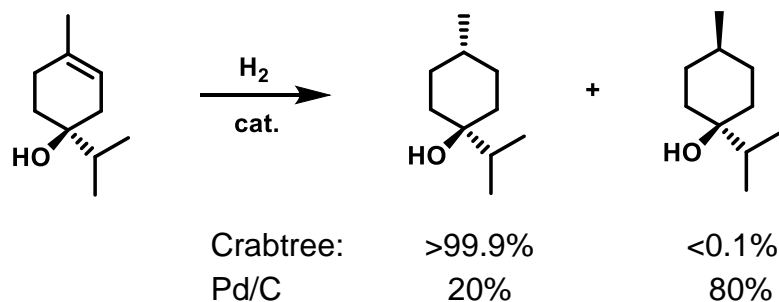
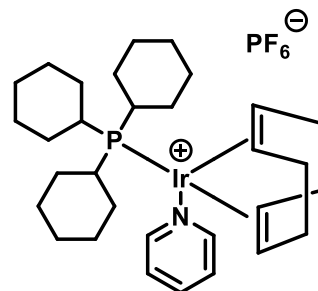
- compatible with CO, COOR, CN, NO₂
- stereoselective *cis*-hydrogenation



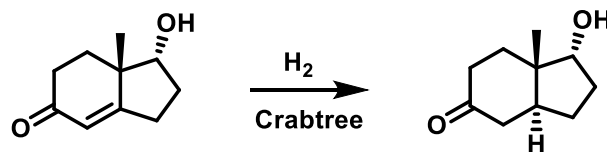
J. Am. Chem. Soc. **1985**, *107*, 4339.

Crabtree's catalyst:

- frequently used for directed hydrogenations

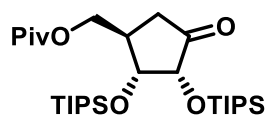


Organometallics **1987**, 2, 681.

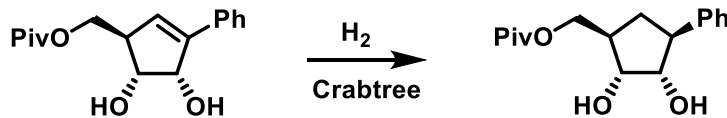


J. Am. Chem. Soc. **1983**, 105, 1072.

(Pd/C: cis-isomer)

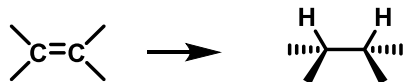


3 steps



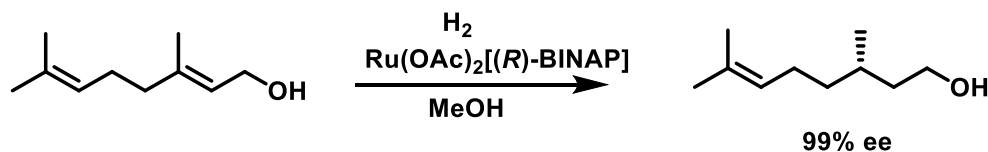
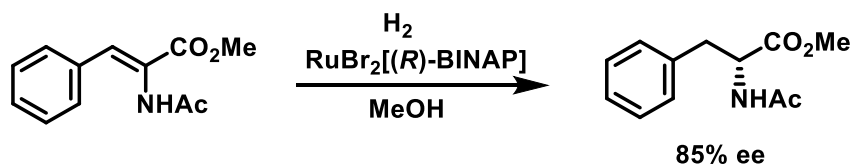
J. Org. Chem. **2017**, 82, 3382.

(only the desired diastereomer)

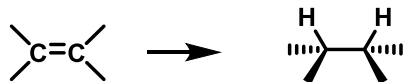


asymmetric catalytic hydrogenation (of olefins)

- complexes of metals with chiral phosphines

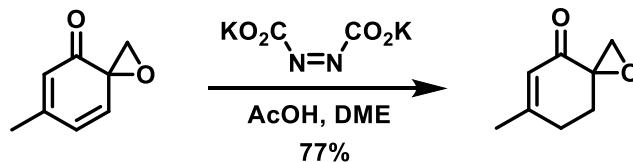
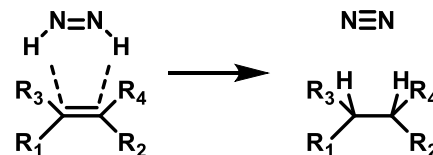


J. Am. Chem. Soc. **1987**, *109*, 1596.

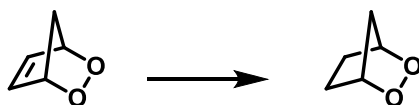


reduction with diimide

- *in situ* generation
- selective cis- reduction of C=C
- tolerated: C=O, C=N, NO₂, OBn etc.

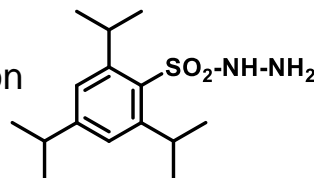


J. Am. Chem. Soc. **1985**, 107, 256.

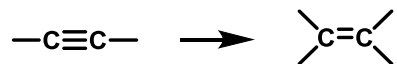


J. Org. Chem. **1977**, 42, 3987.

alternative generation of diimide: thermal decomposition

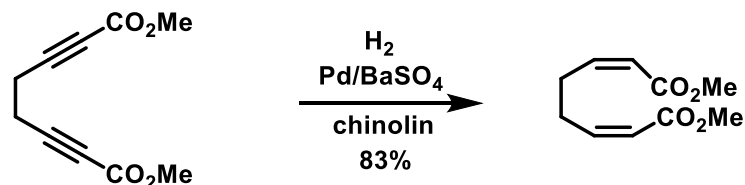


Tetrahedron **1976**, 32, 2157.



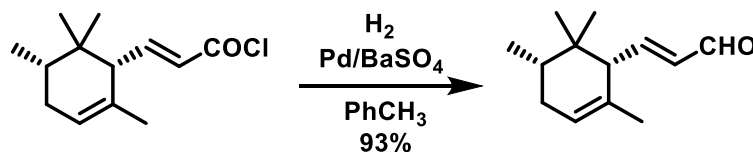
reduction of alkynes

cis: H₂ + Lindlar catalyst (Pd/BaSO₄)

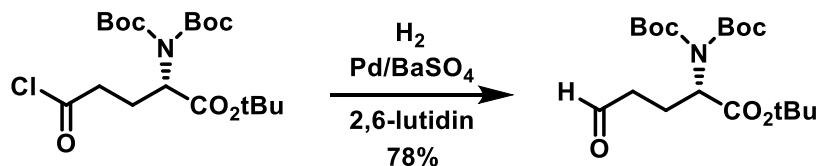


J. Org. Chem. **1972**, 37, 4317.

note. used also for chemoselective reduction of COCl to CHO (Rosenmund reduction)



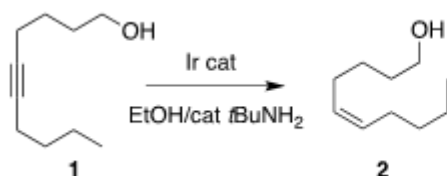
Helv. Chim. Acta **1989**, 72, 1400.



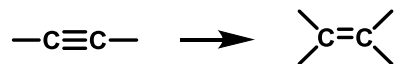
Helv. Chim. Acta **1990**, 73, 405.

newer protocols:

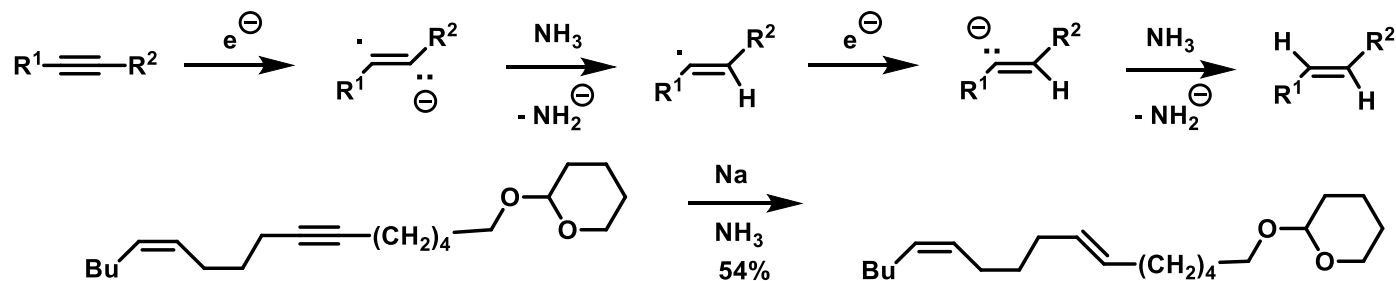
e.g. Ir catalyst in EtOH (serving as a reducing medium): conversion of **1** to **2**



J. Am. Chem. Soc. **2021**, 143, 4824.

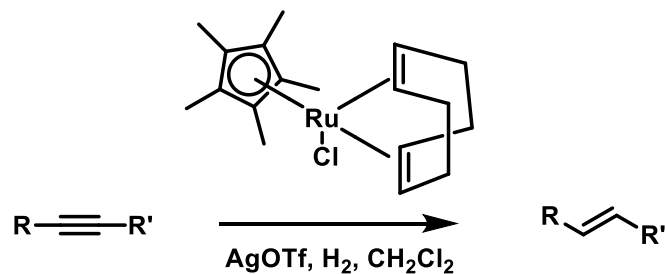


trans: Na in liquid NH_3



trans: modern methods: Pd- or Ru-catalyzed semi-hydrogenation

Angew. Chem. Int. Ed. **2013**, 52, 806.

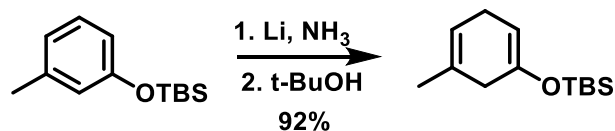
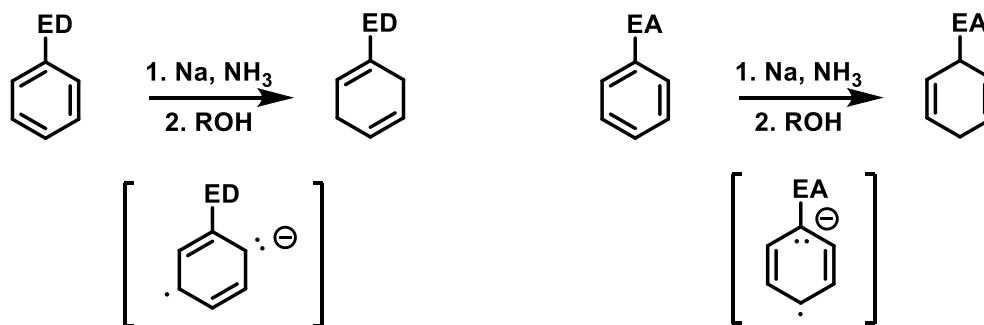


Angew. Chem. Int. Ed. **2013**, 52, 355.

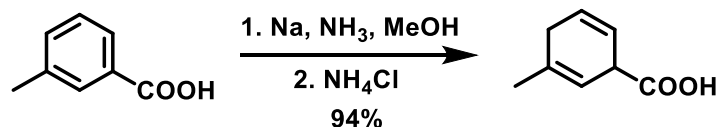
- cyclic & acyclic alkynes
- tolerated: OH, OTs, NO_2 , SMe, COOH etc.

Birch reduction

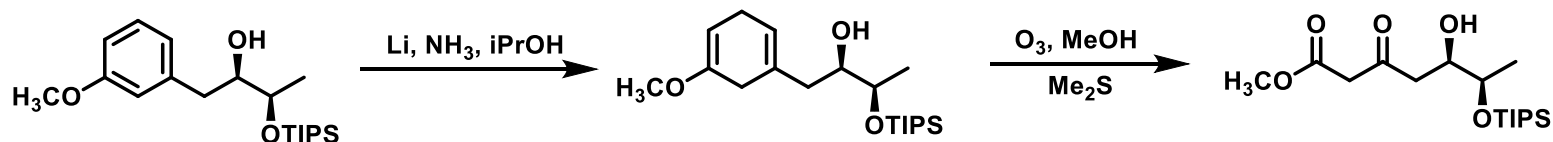
- Na, K, Li in liquid NH_3 \rightarrow reduction of aromatic rings
- product is generated from the corresponding radical-anion
(regioselectivity is given by its stabilization \rightarrow depends on substituents)



J. Org. Chem. **1977**, *42*, 2032.

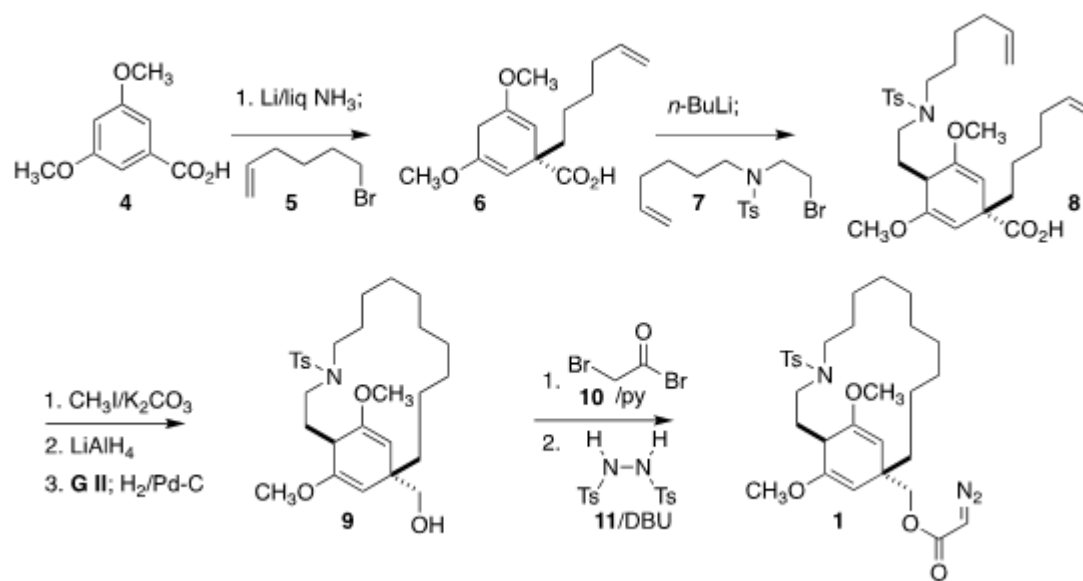


J. Am. Chem. Soc. **1963**, *85*, 41.



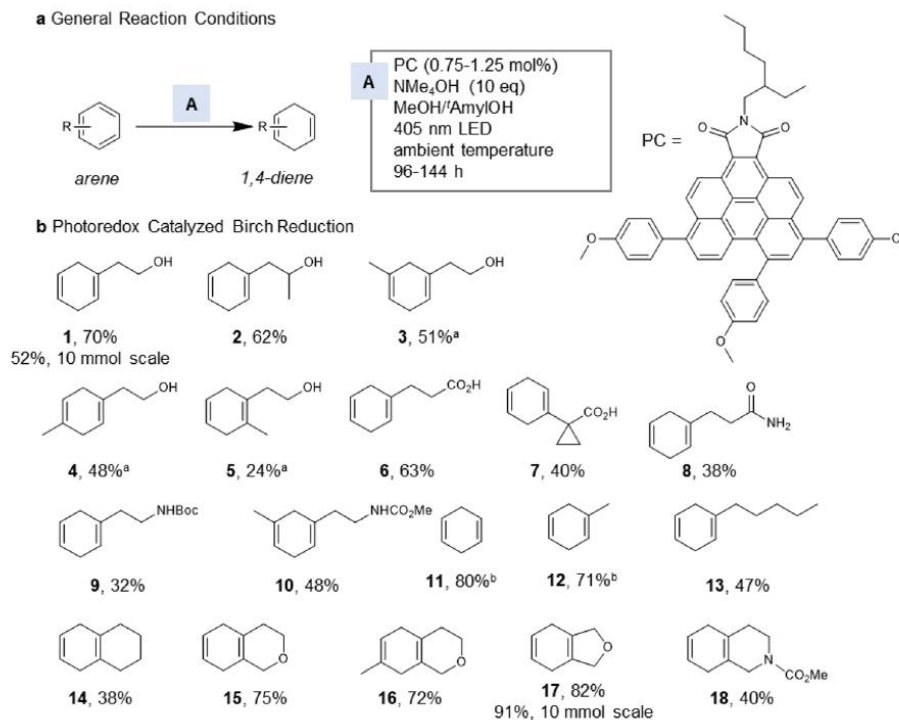
J. Org. Chem. **1991**, *56*, 741.

alkylation of the in situ formed radical-anion:



Angew. Chem. Int. Ed. **2021**, *60*, 9666.

visible light-driven Birch reduction

J. Am. Chem. Soc. **2020**, *142*, 13573.

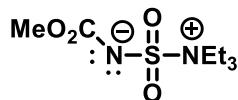
modern (more user-friendly) variant of Birch reduction

Science **2021**, *374*, 741.Li (wire) + NH₂CH₂CH₂NH₂ in THF, ice bath

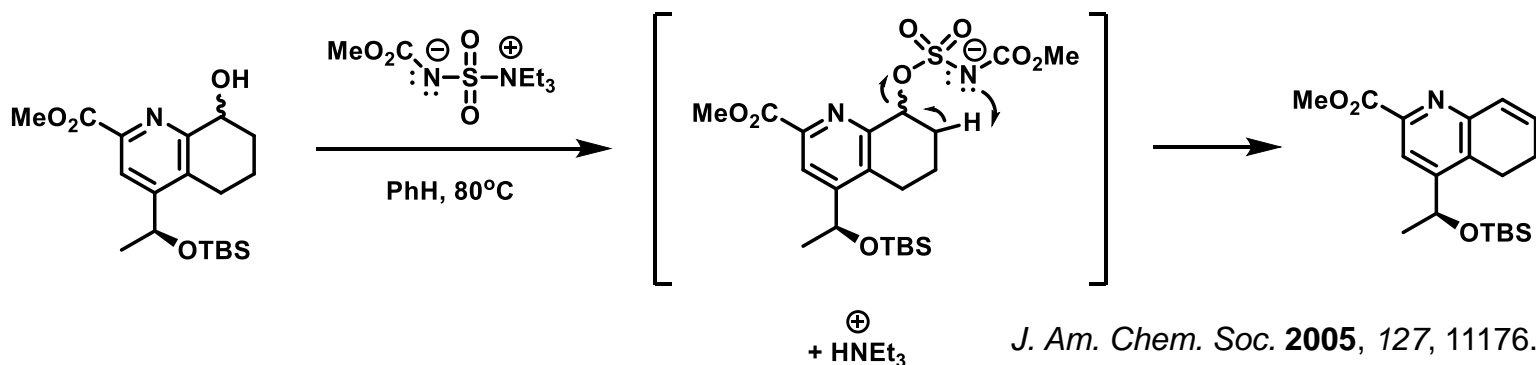
elimination of H₂O

Burgess reagent

- for sec. & tert. OH

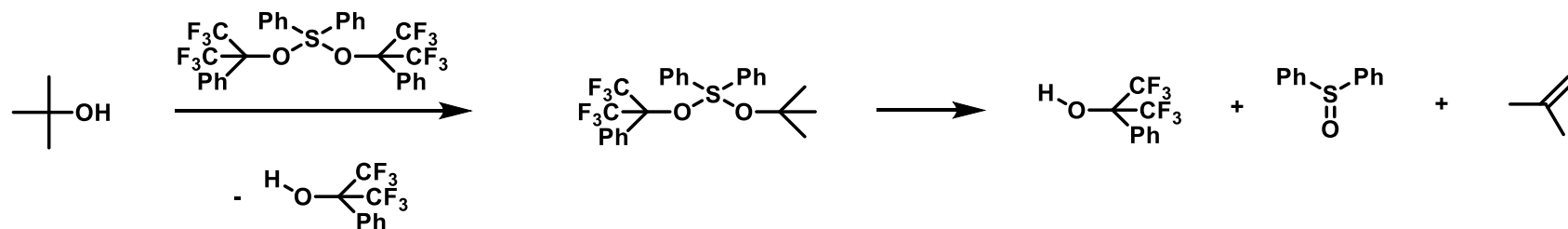
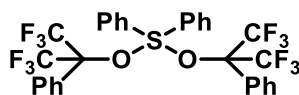


J. Org. Chem. **1973**, 38, 26.



Martin sulfurane

- for sec. & tert. OH



J. Am. Chem. Soc. **1971**, 93, 4327.