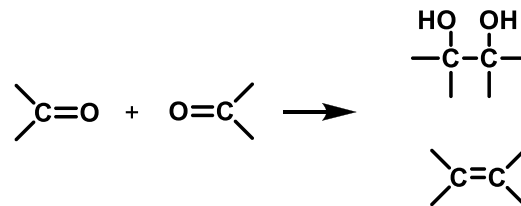
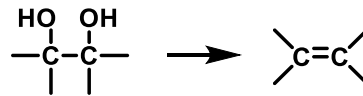
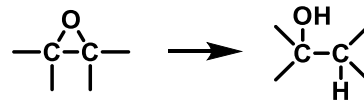
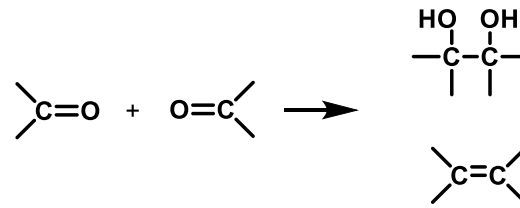
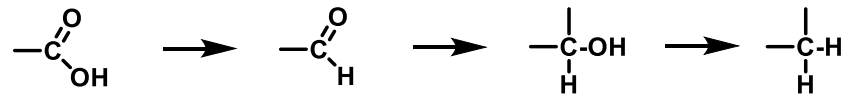
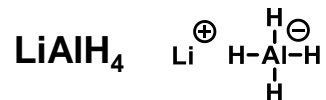
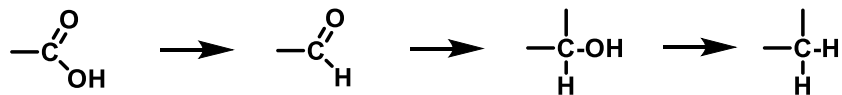


Organic synthesis

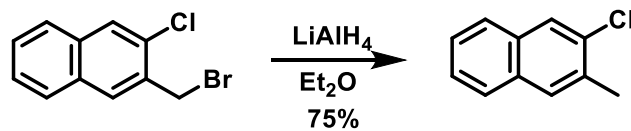
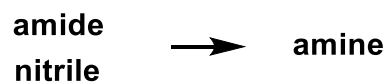
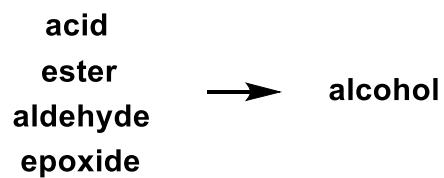
Kamil Paruch

Masaryk University, Brno

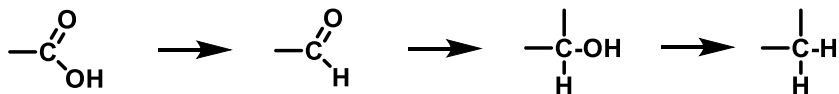




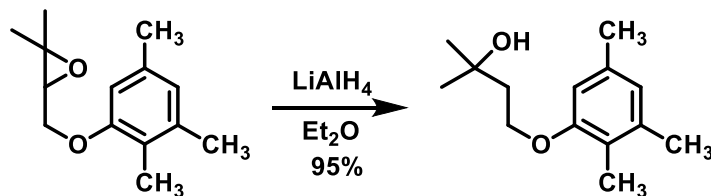
- strong, quite unselective reducing agent



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



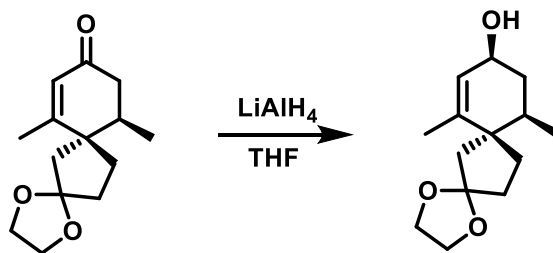
epoxides: typically, attack of H^- on less substituted C



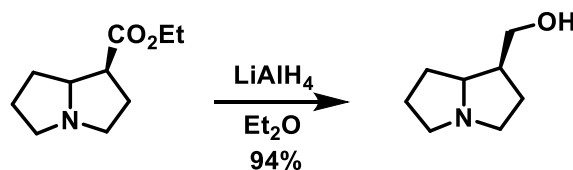
J. Org. Chem. **1989**, *54*, 2620.

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

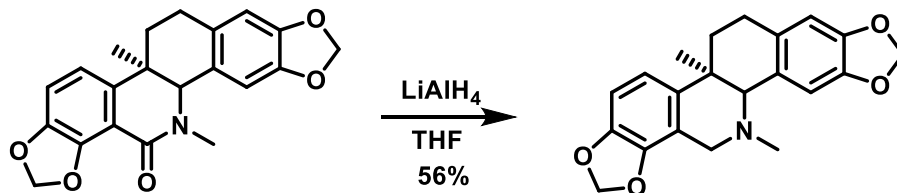
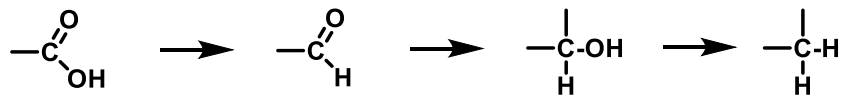
α,β -unsaturated ketones: predominant 1,2-reduction



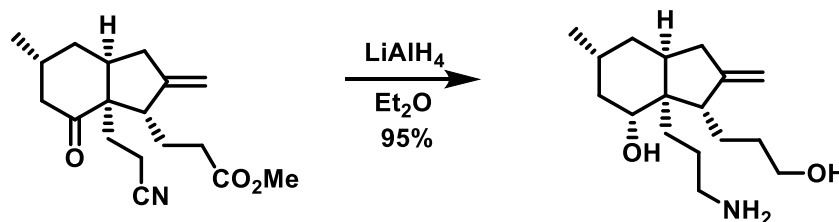
reduction of carbonyl compounds with LAH: typically *no* racemization (epimerization)



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

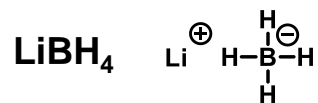
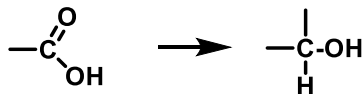
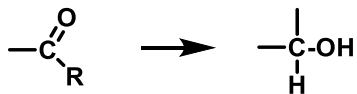


J. Chem. Soc., Perkin Trans. 1 **1980**, 212.

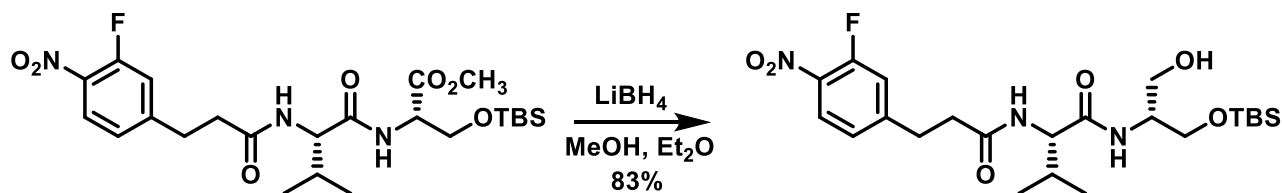


J. Org. Chem. **1989**, 54, 1548.

note: LiAlH_4 can also act as a base



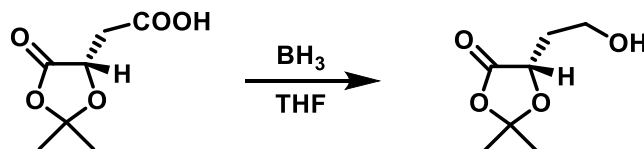
- reduction of esters to alcohols (in the presence of carboxylic acids, amides, nitriles)



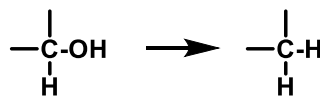
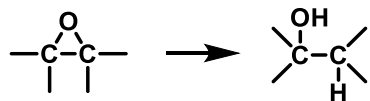
Synlett. 2000, 1363.

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

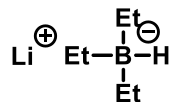
- reduction of *carboxylic acids* in the presence of esters and other functional groups
- hydroboration of alkenes



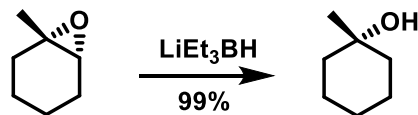
J. Am. Chem. Soc. 1980, 102, 2117.



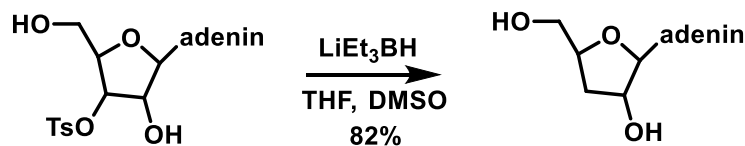
LiEt₃BH (Super Hydride)



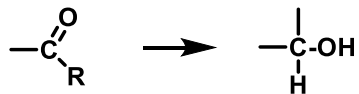
- donor of strongly nucleophilic hydride
- reduction of halides, sulfonates, opening of epoxides (attack on less sterically hindered C)



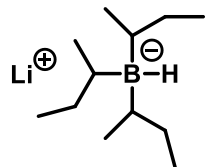
J. Am. Chem. Soc. **1973**, 95, 8486.



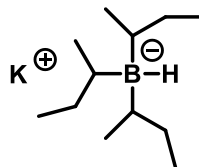
J. Am. Chem. Soc. **1983**, 105, 6736.



Selectrides

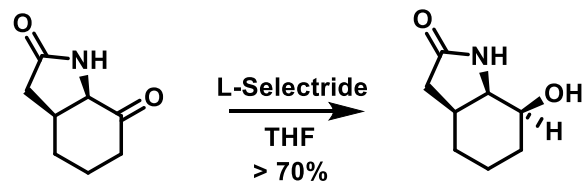


L-Selectride

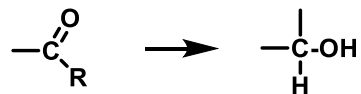


K-Selectride

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



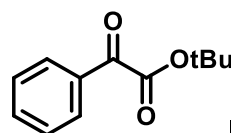
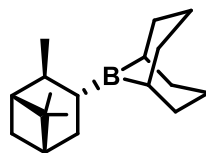
J. Org. Chem. **1988**, *53*, 4006.



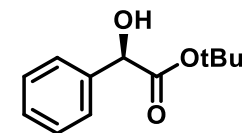
enantioselective reduction

chiral boranes

Alpine-borane



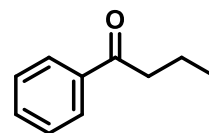
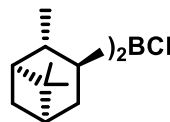
Alpine-borane



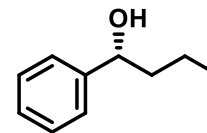
92% ee

Ipc₂BCl

• more reactive



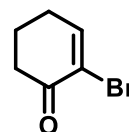
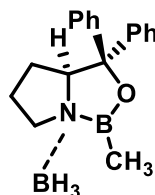
Ipc₂BCl



98% ee

chiral oxazaborolidines + BH₃

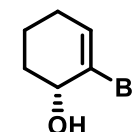
- catalytic amount
- activation of BH₃ by complexation



oxazaborolidine 5%

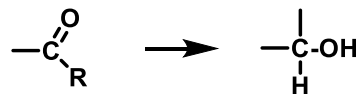
BH₃·Me₂S, THF

99%



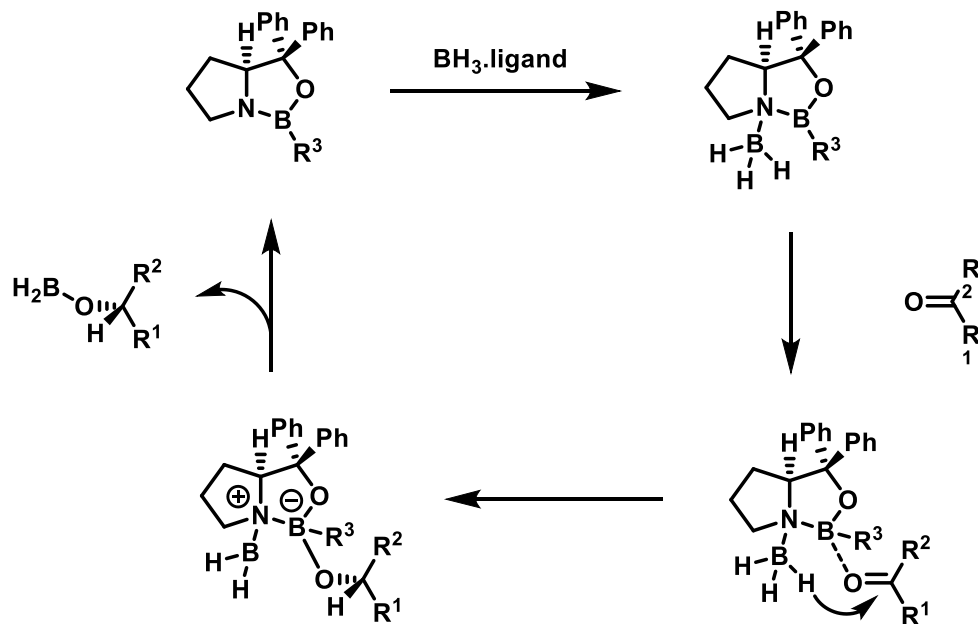
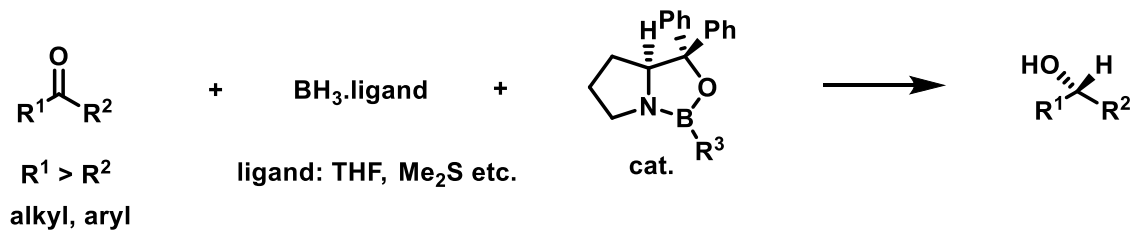
96% ee

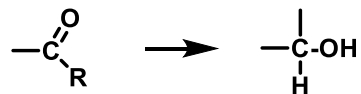
J. Am. Chem. Soc. **1993**, *115*, 4419.



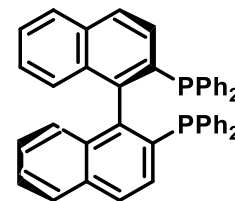
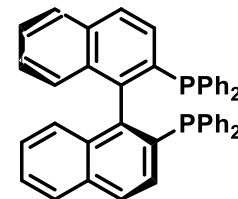
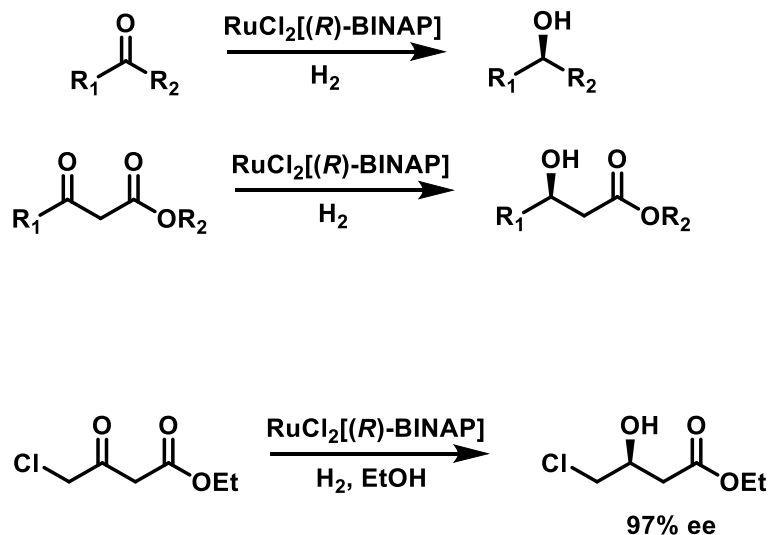
enantioselective reduction

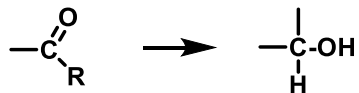
Corey-Bakshi-Shibata reduction (CBS reduction)





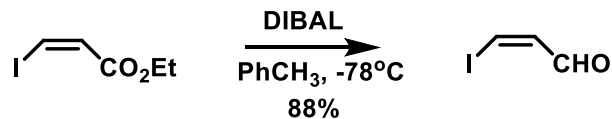
enantioselective reduction

catalytic hydrogenation (of β -ketoesters)*(R)*-BINAP*(S)*-BINAP*J. Am. Chem. Soc.* **1988**, 110, 629.



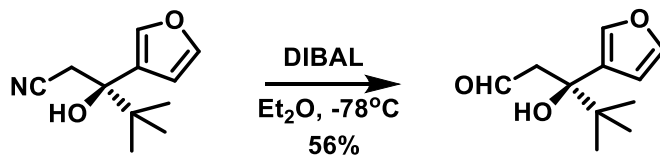
DIBAL : *i*-Bu₂AlH

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

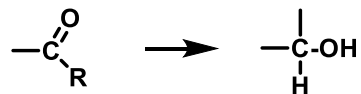


Org. Synth. **1996**, 74, 194.

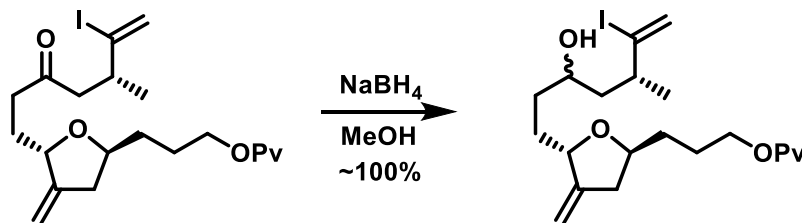
- reduction of nitriles to imines (which are hydrolyzed to aldehydes during work-up)



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

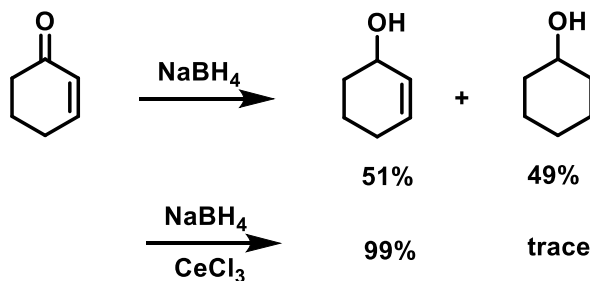


- selective reductant: reduction of aldehydes, ketones and acid chlorides in the presence of other reducible groups
(CO₂R, CN, NO₂, epoxides)
- compatible with alcoholic solvents

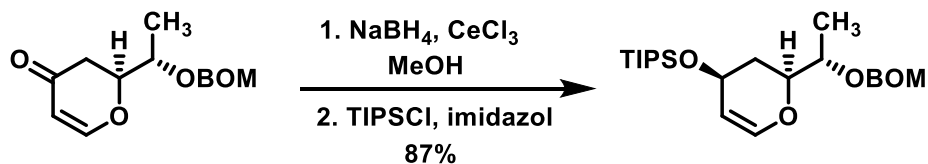


J. Am. Chem. Soc. **1992**, 114, 3162.

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



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

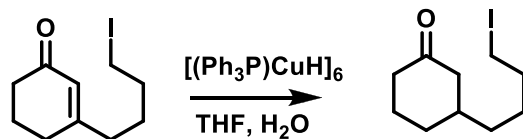
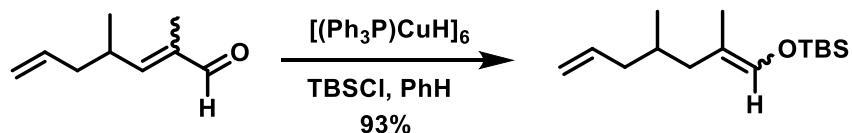


J. Am. Chem. Soc. **1997**, 119, 10073.

note

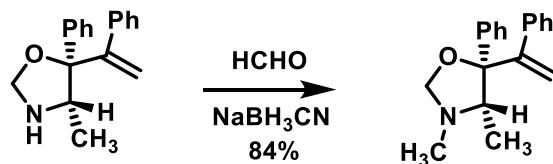
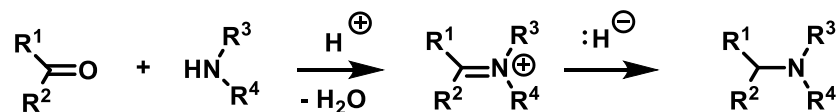
Stryker reduction: 1,4-reduction

- 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

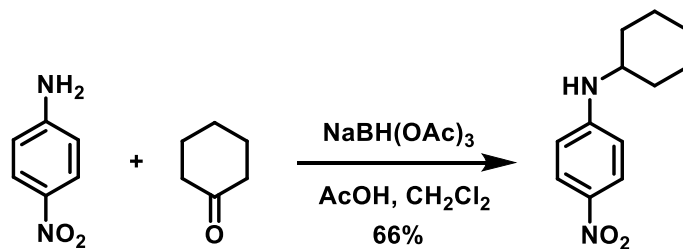
*Tetrahedron Lett.* **1990**, 31, 3237.

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

- selective reduction of imines and iminium salts; stable under mildly acidic conditions



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



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

alkylative amination

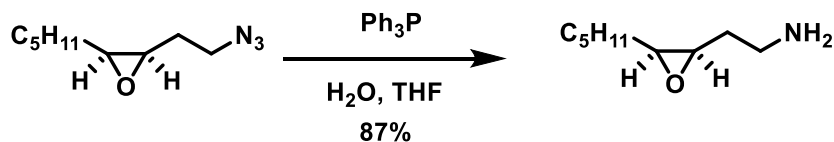
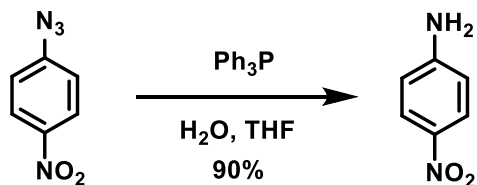
- formally analogous to reductive amination -> complex tertiary amines (frequent motifs in medchem)
- but historically difficult to carry out

Roopender Kumar, Nils J. Flodén, William G. Whitehurst & Matthew J. Gaunt

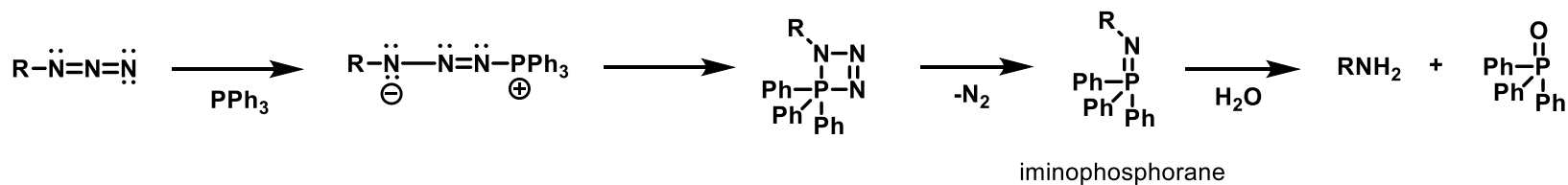
Nature **2020**, <https://doi.org/10.1038/s41586-020-2213-0>

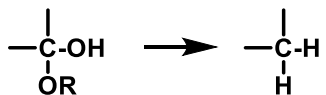


Staudinger reaction



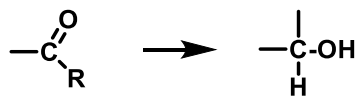
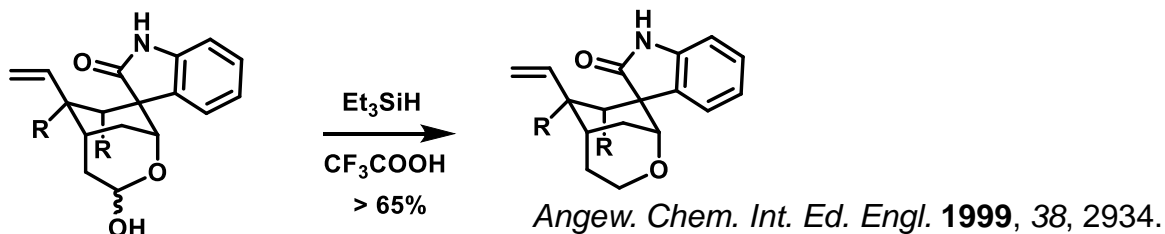
Tetrahedron Lett. **1983**, 24, 763.





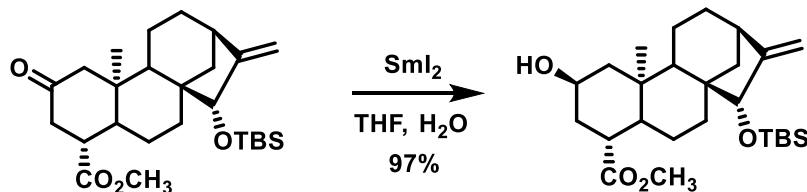
„ionic hydrogenation“

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

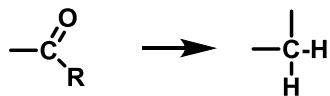


SmI_2

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

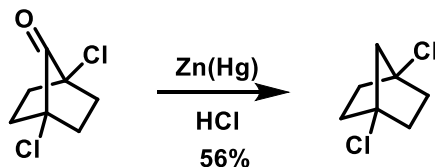


J. Am. Chem. Soc. **1990**, 112, 7001.



Clemmensen reduction

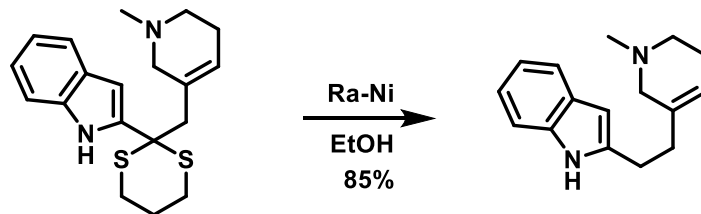
- strongly acidic conditions; limited use



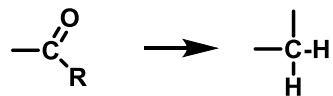
J. Org. Chem. **1969**, 34, 1109.

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

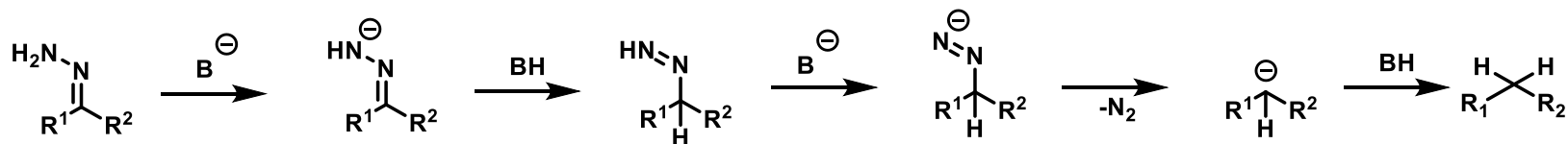
- Ra-Ni (+ H₂)



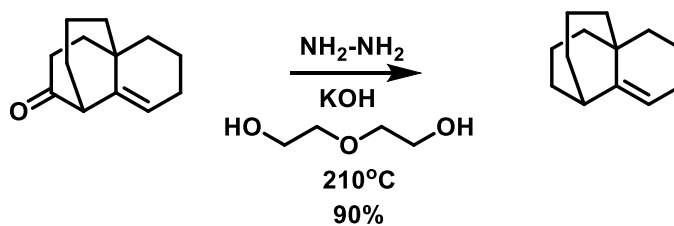
Heterocycles **1991**, 32, 663.



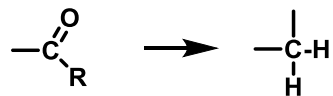
Kizhner-Wolff reduction



traditional protocol:

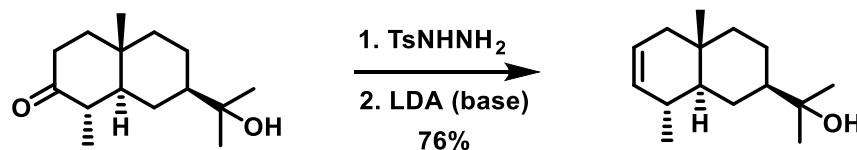
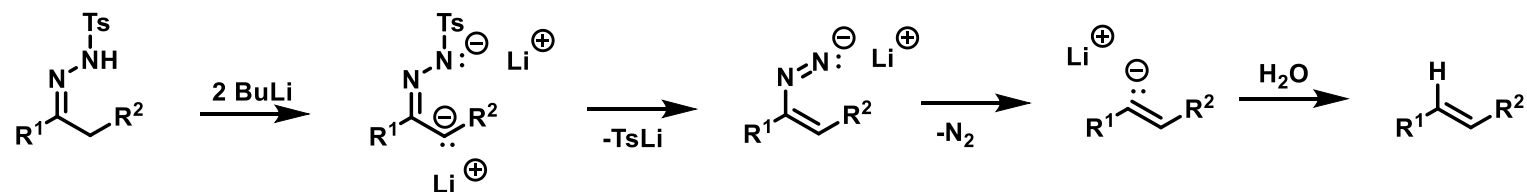
*Can. J. Chem.* **1979**, *57*, 1064.

low temperature variant: t-BuOK, DMSO



Shapiro reaction

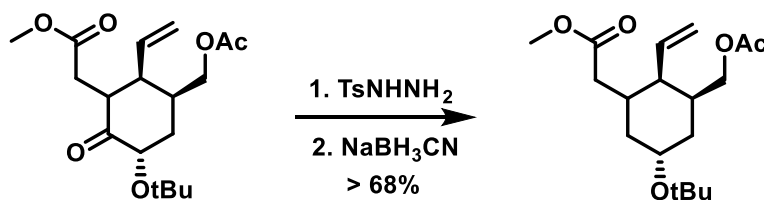
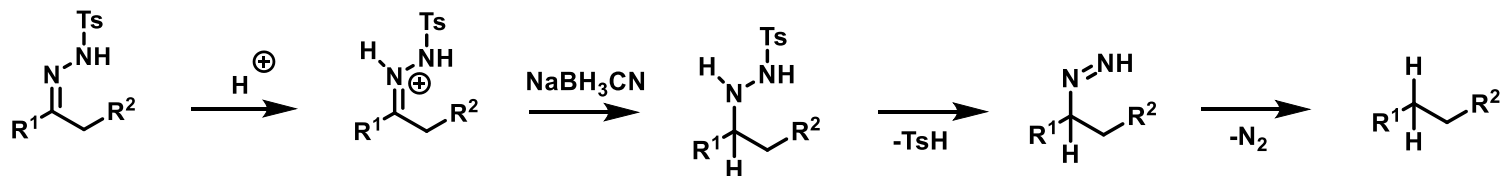
- ketones (aldehydes) \rightarrow tosylhydrazones \rightarrow alkenes



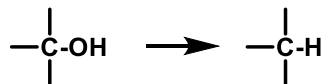
Can. J. Chem. **1983**, *61*, 1111.

reduction of tosylhydrazones by hydrides

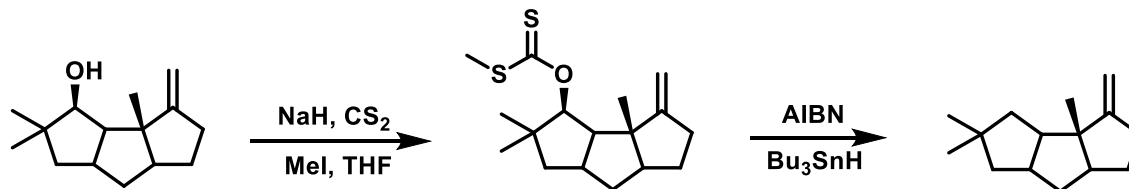
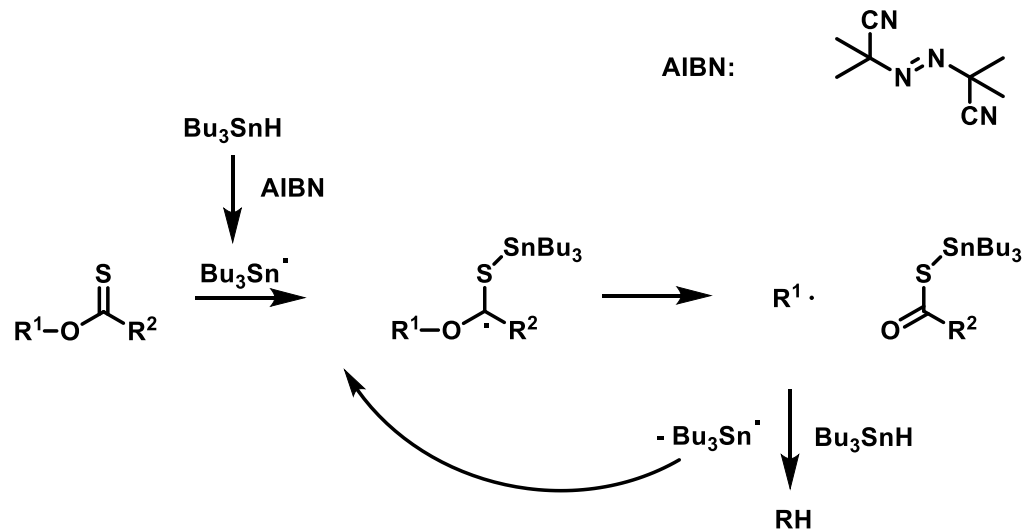
- mild & chemoselective (esters, amides, nitro, nitriles... tolerated) removal of O from carbonyl



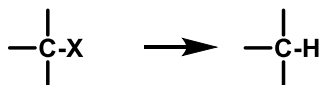
J. Org. Chem. **1991**, *56*, 2947.



Barton-McCombie deoxygenation

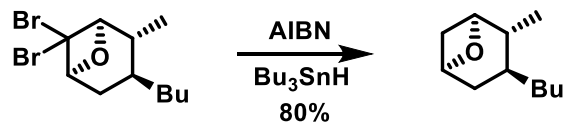


J. Am. Chem. Soc. **1986**, *108*, 3443.

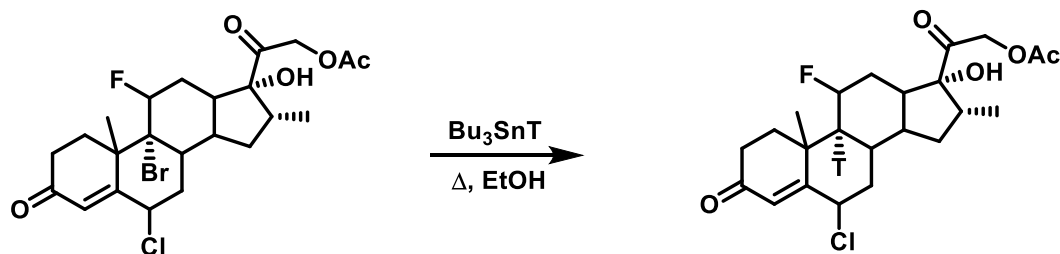


radical dehalogenation

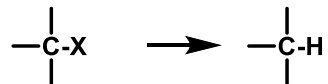
- radical source: Bu_3SnH
- Br and I more reactive than Cl and F
- also useful for removal of NO_2



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

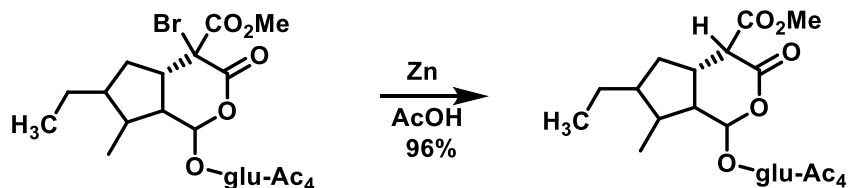


J. Org. Chem. **1979**, 44, 151.

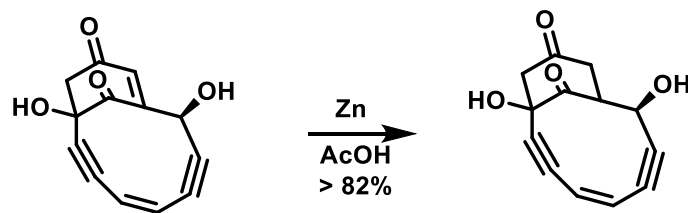


dehalogenation with Zn/AcOH

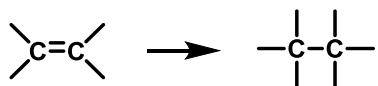
- chemoselective reduction of α -haloketones, α,β -unsaturated ketones



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



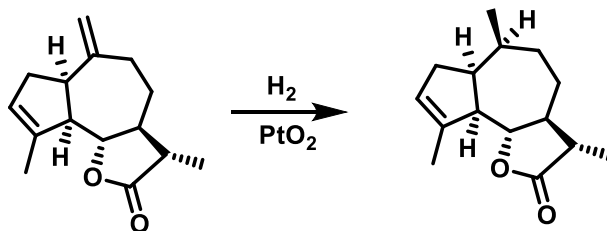
J. Org. Chem. **1989**, 54, 2781.



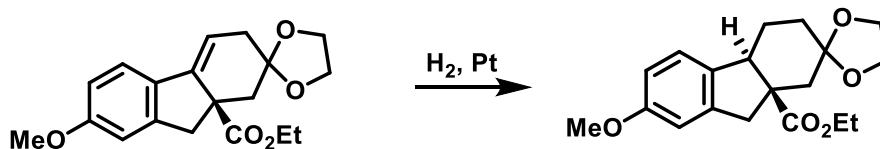
catalytic hydrogenation (of alkenes)

- 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.

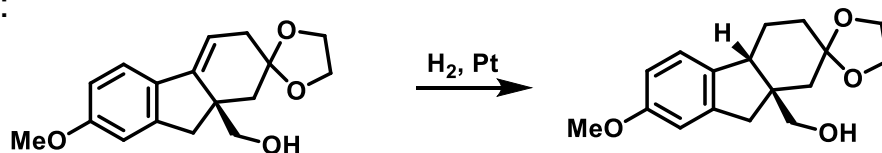


Tetrahedron **1972**, 28, 3583.



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

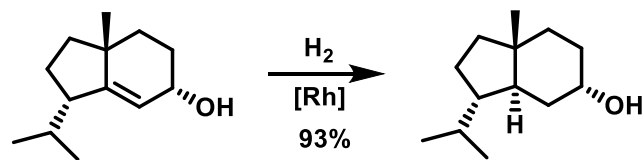
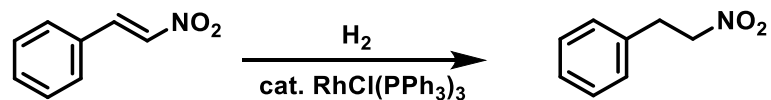
but:



homogenous

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

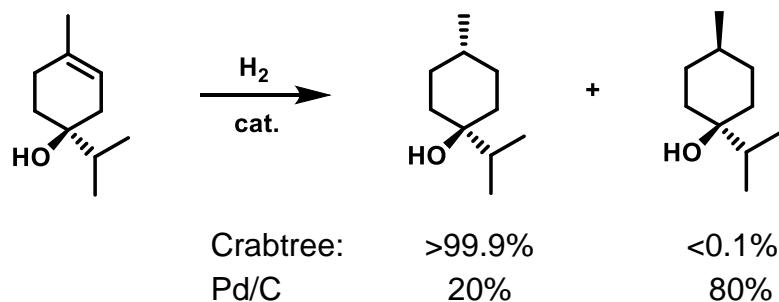
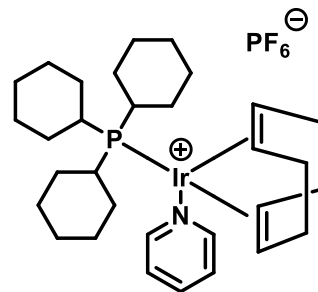
- compatible with CO, COOR, CN, NO₂
- stereoselective *cis*-hydrogenation



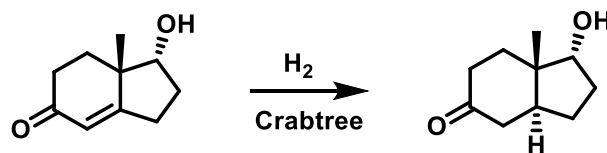
J. Am. Chem. Soc. **1985**, *107*, 4339.

Crabtree's catalyst:

- frequently used for directed hydrogenations

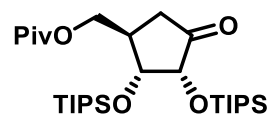


Organometallics **1987**, 2, 681.

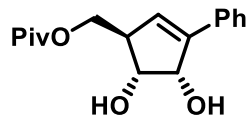


J. Am. Chem. Soc. **1983**, 105, 1072.

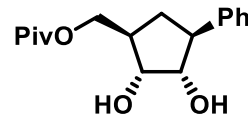
(Pd/C: cis-isomer)



3 steps



H₂
Crabtree



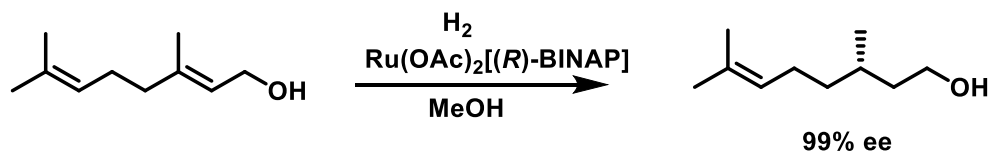
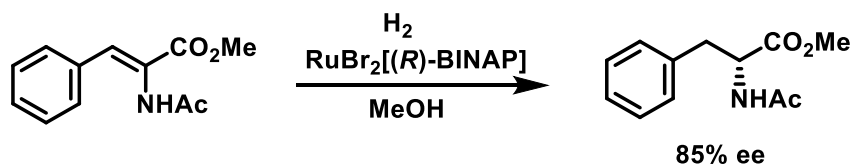
J. Org. Chem. **2017**, 82, 3382.

(only the desired diastereomer)

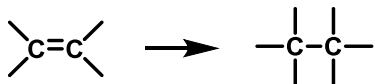


asymmetric catalytic hydrogenation (of olefins)

- complexes of metals with chiral phosphines

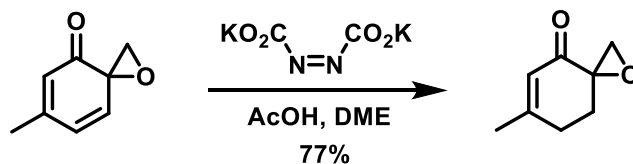
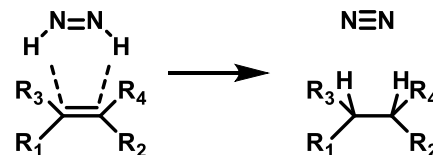


J. Am. Chem. Soc. **1987**, *109*, 1596.

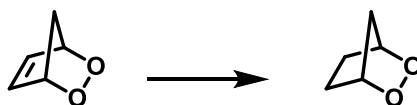


reduction with diimide

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

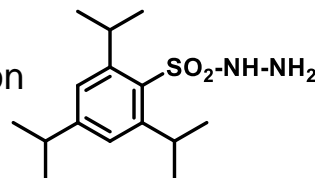


J. Am. Chem. Soc. **1985**, 107, 256.



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

alternative generation of diimide: thermal decomposition

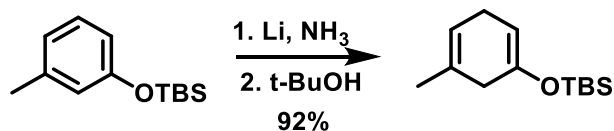
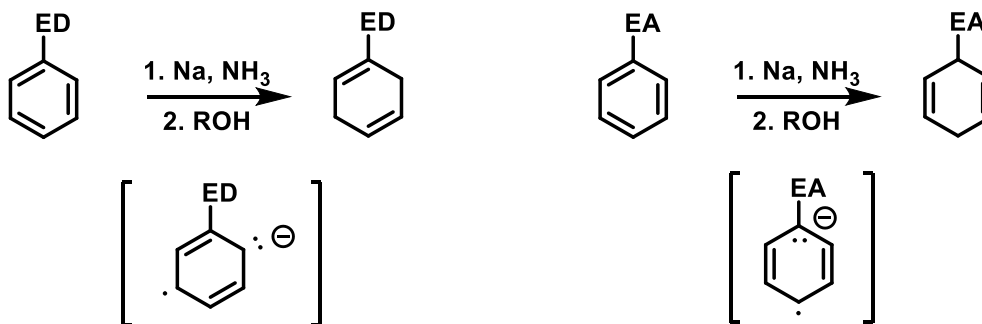


Tetrahedron **1976**, 32, 2157.

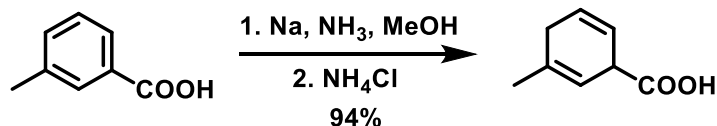


Birch reduction

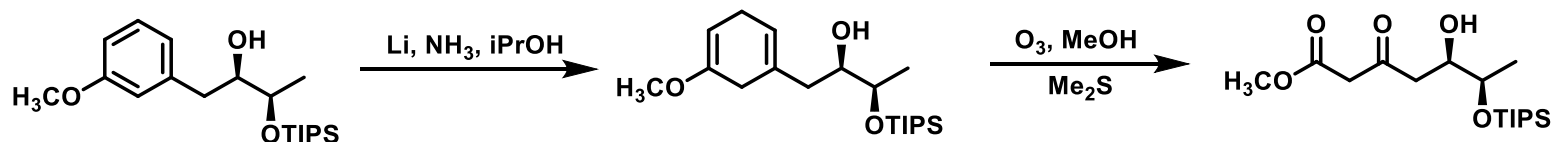
- Na, K, Li in liquid NH₃ -> reduction of aromatic rings
- product is generated from the corresponding radical-anion (regioselectivity is given by its stabilization -> depends on substituents)



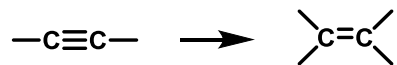
J. Org. Chem. **1977**, *42*, 2032.



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

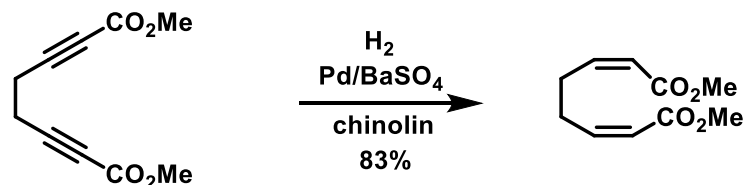


J. Org. Chem. **1991**, *56*, 741.



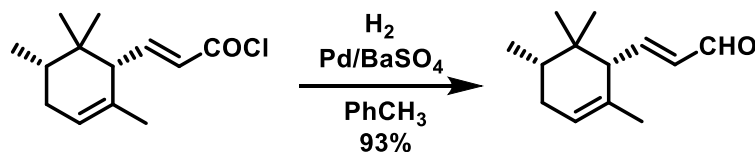
reduction of alkynes

cis: H_2 + Lindlar catalyst (Pd/BaSO_4)

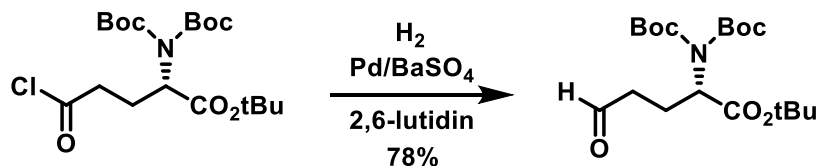


J. Org. Chem. **1972**, 37, 4317.

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

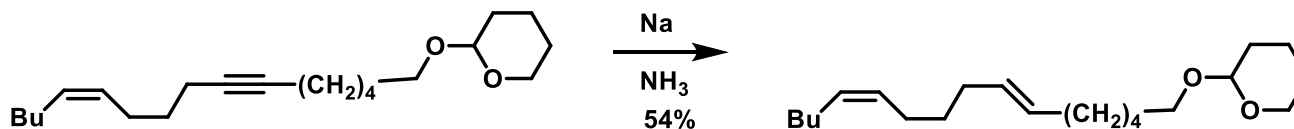
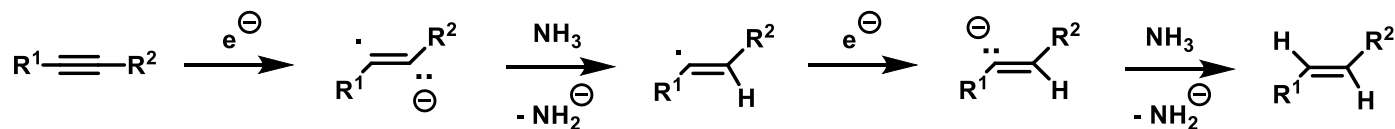


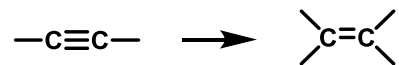
Helv. Chim. Acta **1989**, 72, 1400.



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

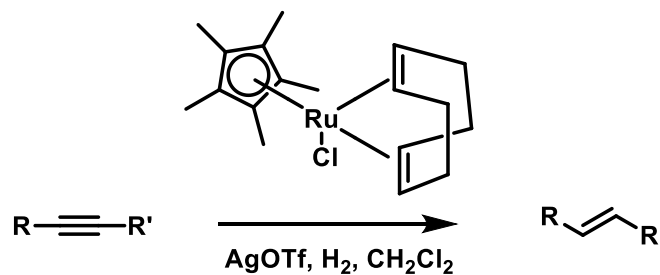
trans: Na in liquid NH_3





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

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



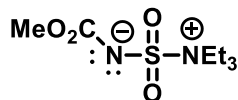
Angew. Chem. Int. Ed. **2013**, 52, 355.

- cyclic & acyclic alkynes
- tolerated: OH, OTs, NO₂, SMe, COOH etc.

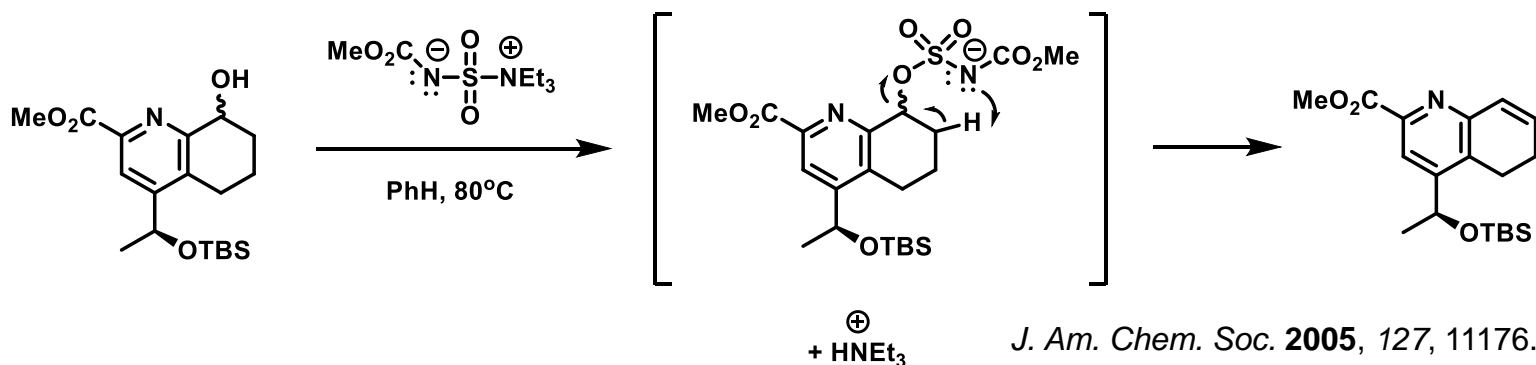
elimination of H₂O

Burgess reagent

- for sec. & tert. OH



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



Martin sulfurane

- for sec. & tert. OH

