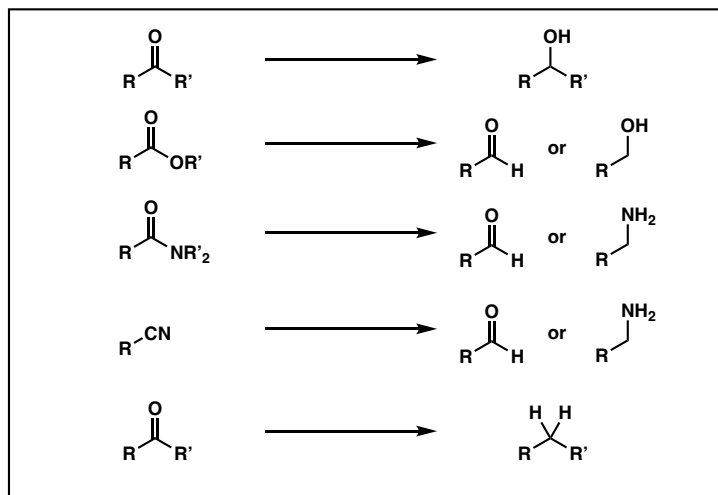


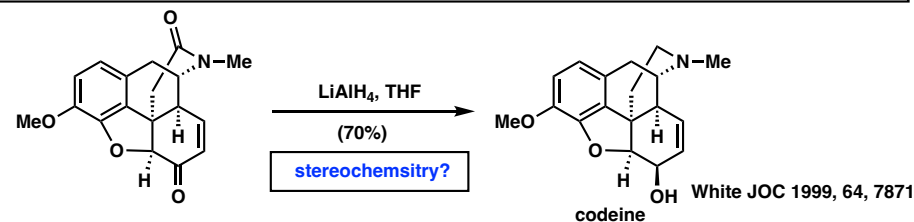
1. Reduction of $\text{R}-\text{C}(=\text{O})-\text{X}$ to $\text{R}-\text{CH}(\text{OH})-\text{X}$ and related reactions

A. Aluminum-based reagent

a. Lithium Aluminium Hydride (LiAlH_4)

- highly reactive, non-selective
- grey solid or ether solution
- work-up tip— 1:1:1:3 rule: for 1 g of LiAlH_4 , quench with 1 mL of H_2O , 1 mL of 20% NaOH , 3 mL of H_2O

preparation of reagent



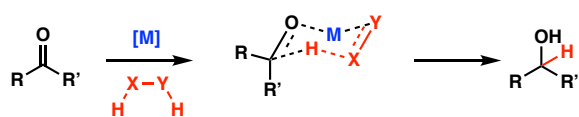
mechanism for amide reduction

General mechanistic considerations

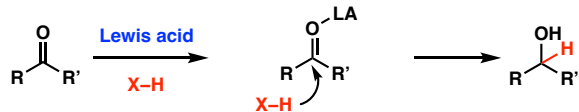
Type I



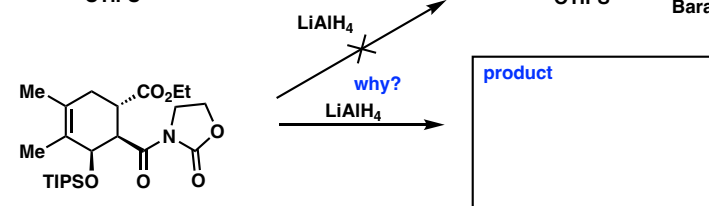
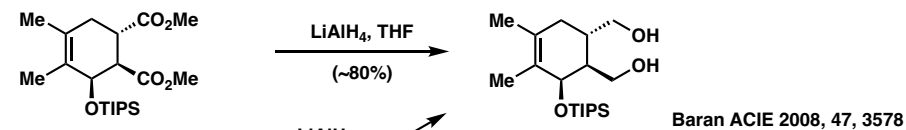
Type II



Type III



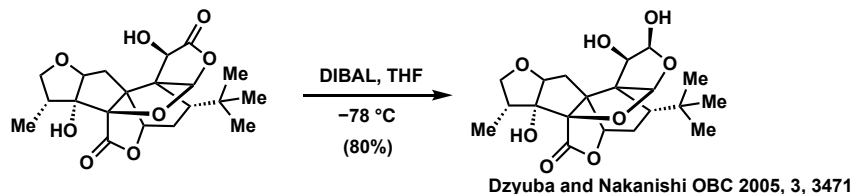
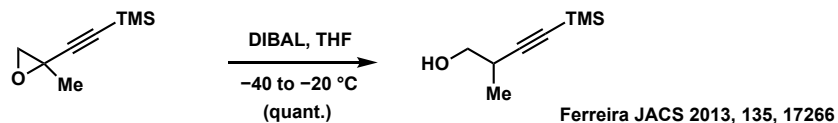
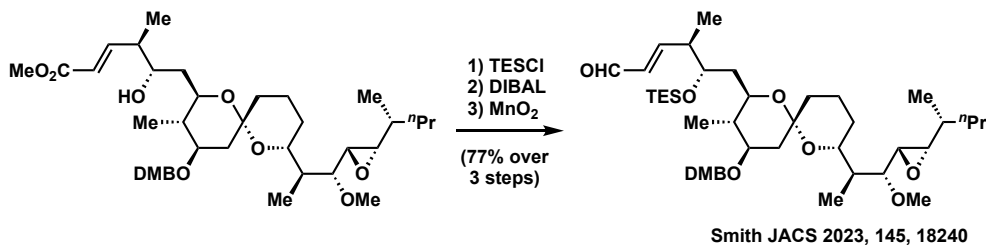
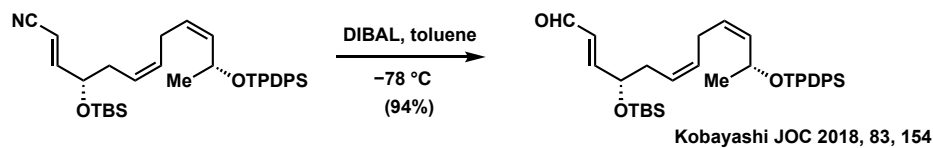
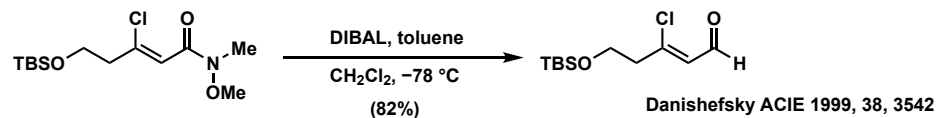
Type III



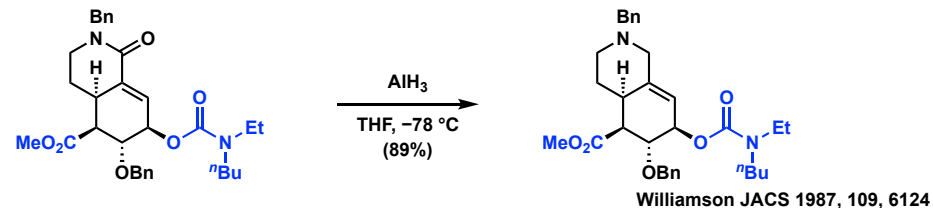
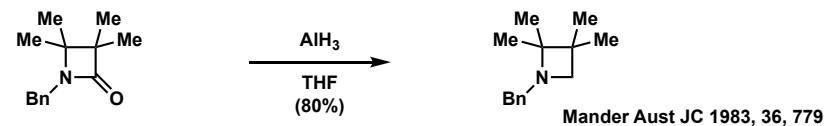
a 2-step solution

b. Diisobutylaluminum hydride (DIBAL-H)

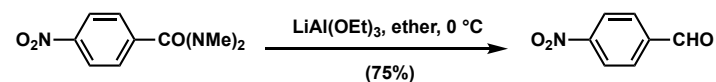
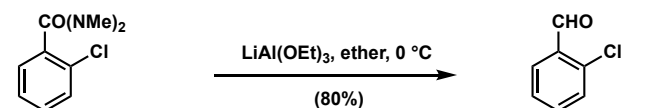
- at low temperature, reduces non-hindered ester to aldehyde, lactone to lactol
- a good reagent to reduce nitrile to aldehyde
- solvent can be toluene, CH_2Cl_2 and hexane. ester and THF diminish reduction capability

c. Aluminum hydride (AlH_3), Alane

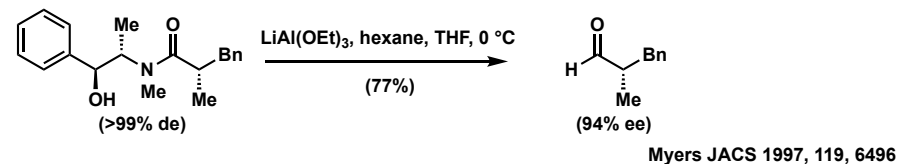
- similar reducing capability as LiAlH_4

d. $\text{LiAl}(\text{OMe})_3$, $\text{LiAl}(\text{OEt})_3$, $\text{LiAl}(\text{Ot-Bu})_3$

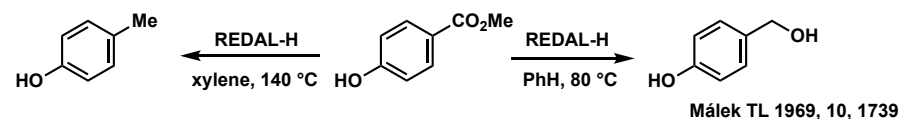
- selective reduction of amides to aldehyde



Brown T 1979, 35, 567

e. $\text{NaAlH}_2(\text{OCH}_2\text{CH}_2\text{OMe})_2$, REDAL-H

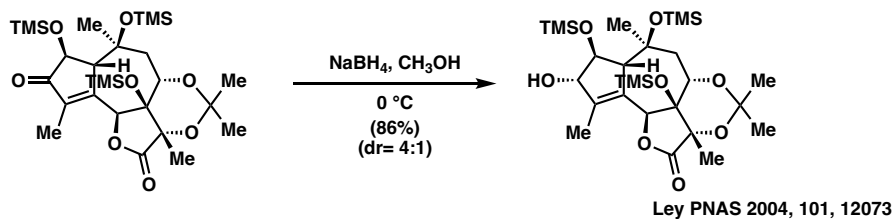
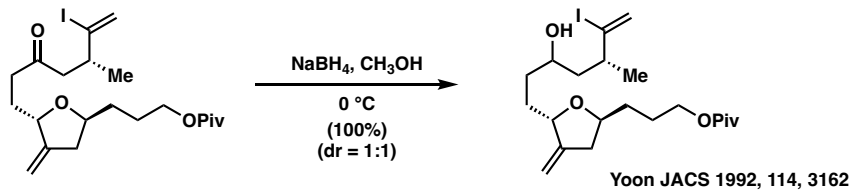
- a more bench-stable LiAlH_4



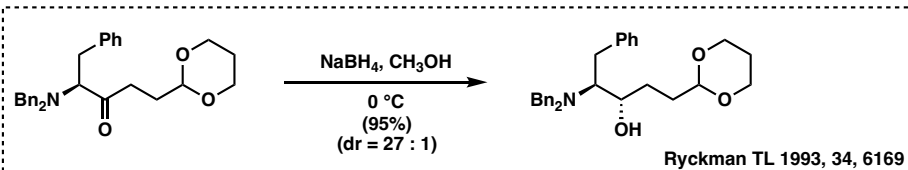
B. Boron-based reagent

a. NaBH₄

- most commonly used reagent to reduce aldehyde and ketone to alcohol
- requires alcoholic solvent/H₂O to develop H-bonding with carbonyl to promote reduction
- reagent will slowly react with solvent: H₂O > MeOH > EtOH > PrOH > BuOH



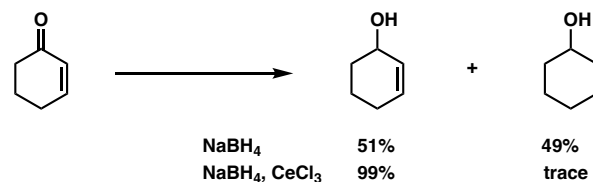
Stereochemistry



Stereochemistry

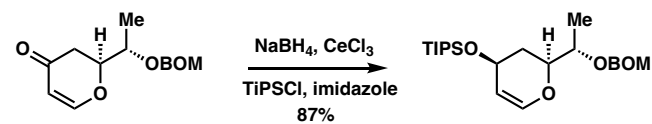
b. NaBH₄, CeCl₃·9H₂O (cat.)

Luche reduction



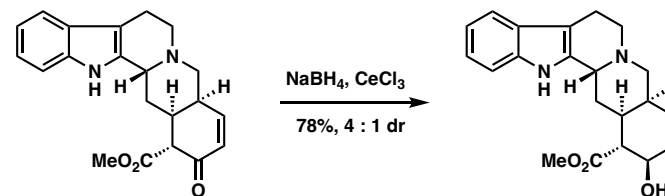
Luche JACS 1978, 100, 2226

Mechanism



Danishefsky JACS 1997, 119, 10073

Stereochemistry

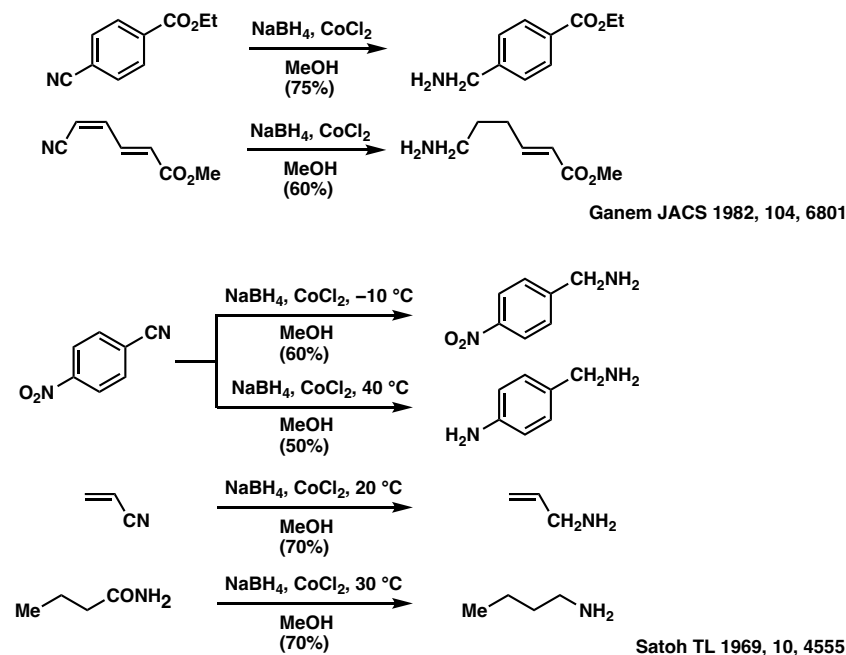


Dauda TL 2000, 41, 5631

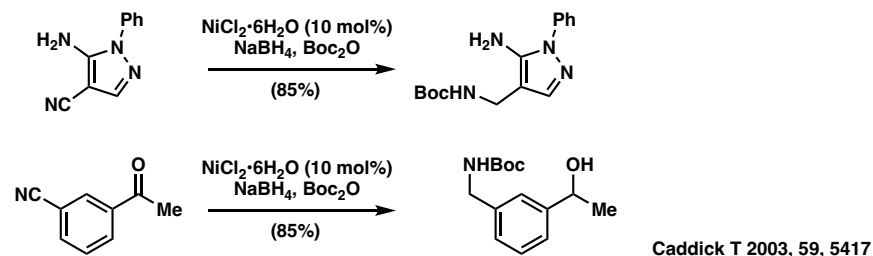
Stereochemistry

c. NaBH_4 , CoCl_2

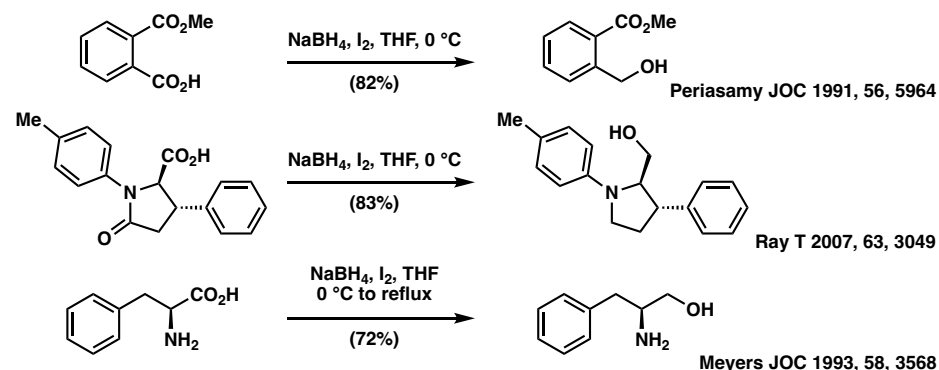
- generate Co_2B as a black granular precipitate, which steadily evolving H_2
- reduce nitrile, amide and nitro to primary amine

d. NaBH_4 , $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$

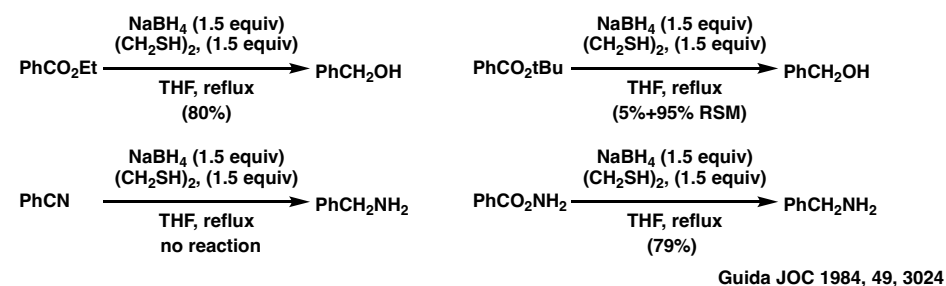
- generate Ni_2B as a colloidal black material, which behaves similar to Raney Ni
- reduce nitrile, nitro to primary amine
- reduce olefin to alkane

e. NaBH_4 , I_2

- very effective way to reduce carboxylate acid to alcohol, often used in preparation of amino alcohols
- can also reduce amides to amines

f. NaBH_4 , $\text{HSCH}_2\text{CH}_2\text{SH}$

- reduce ester with primary and secondary alcohol, but not tertiary alcohol
- reduce amide but not nitrile to amine

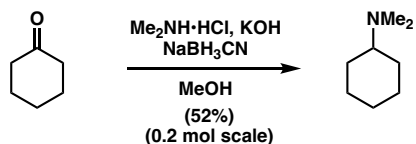
g. Miscellaneous reductions with NaBH_4 + Metal saltsReduction of PhCN with NaBH_4 -Transition Metal System

NiCl_2	75%
$\text{Co}(\text{OBz})_2$	50%
OsCl_4	78%
IrCl_3	75%
PtCl_2	80%

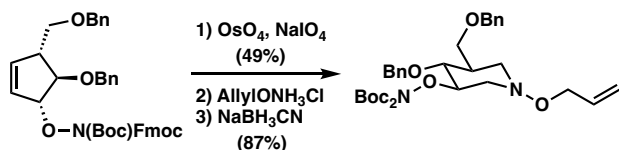
Satoh TL 1969, 10, 4555

h. NaCNBH_3

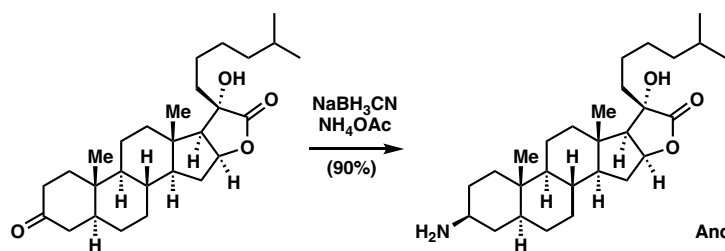
- less reactive than NaBH_4
- stable in aqueous solution
- often used for reductive amination (Borch reaction)



Borch JACS 1971, 93, 2897
OrgSyn 1972, 52, 124



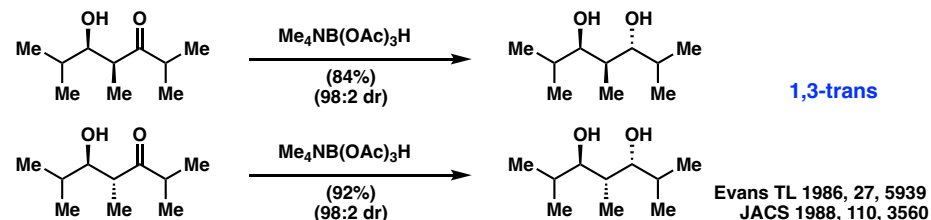
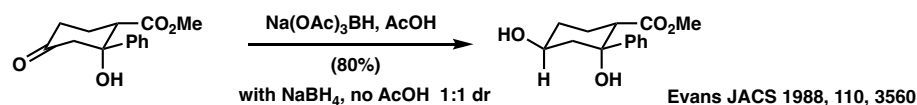
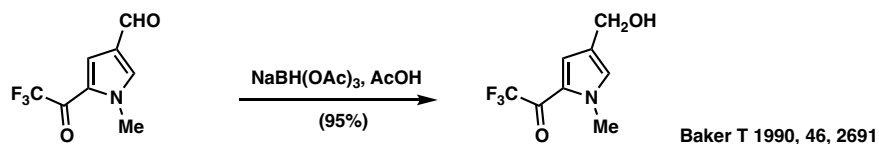
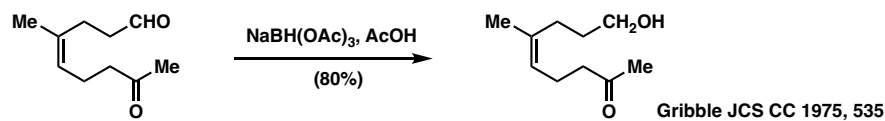
Crich JACS 2014, 136, 14852



Anderson OL 2013, 15, 3918

i. $\text{NaBH}(\text{OAc})_3, \text{Me}_4\text{NBH}(\text{OAc})_3$

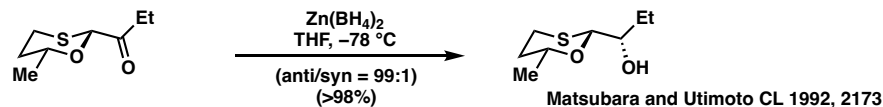
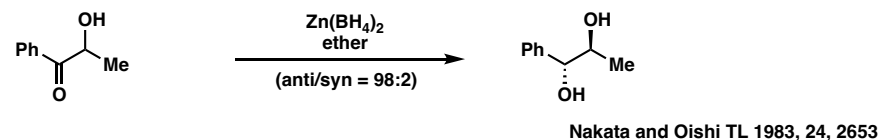
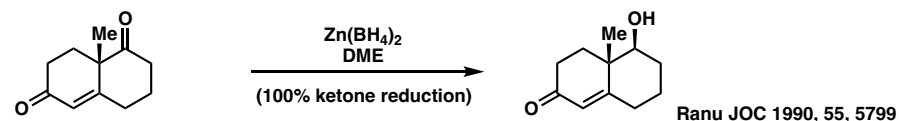
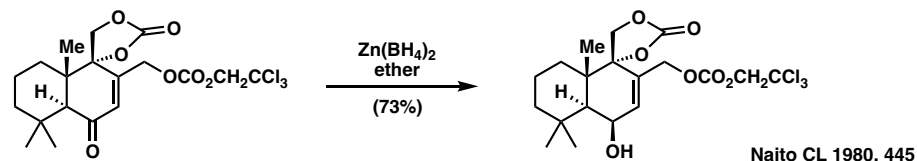
- reduce aldehyde but not ketone
- often used from reductive amination
- diastereoselectively reduce β -hydroxyketone via directed reduction



Transition State

j. $\text{Zn}(\text{BH}_4)_2$

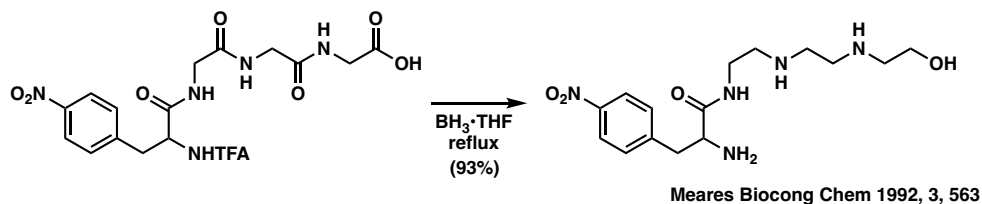
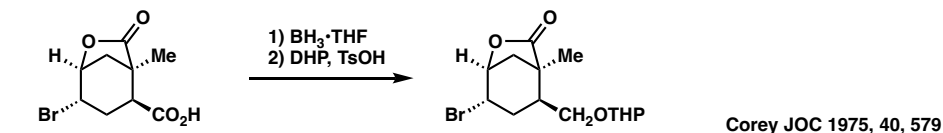
- carbonyl oxygen can coordinate with Zinc, to promote 1,2-reduction
- Coordination enabled 1,2-anti reduction



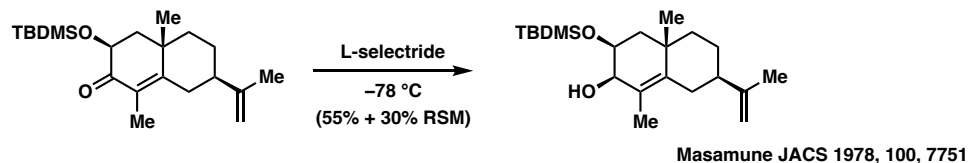
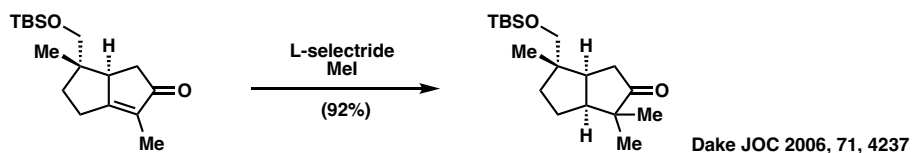
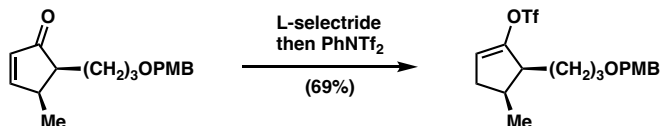
Transition States of all these reactions

k. BH_3

- commercially available in $\text{BH}_3 \cdot \text{Me}_2\text{S}$ (pure or as a 1M solution in THF), $\text{BH}_3 \cdot \text{THF}$ (1N in THF) and other forms
- can be in situ generated via $\text{NaBH}_4 + \text{BF}_3 \cdot \text{OEt}_2$, may have higher reactivity compared with commercial bottles
- selective reduction of acid in the presence of ester, amide, halides

l. $\text{LiH}(\text{sec-Bu})_3$ L-selectride

- very bulky
- undergoes 1,4-reduction of enone to give enolate

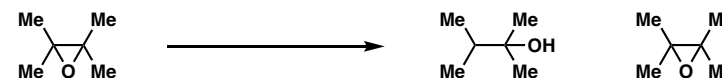
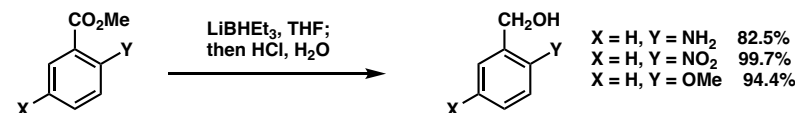
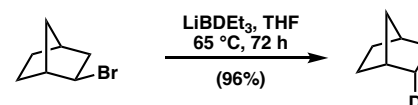
m. LiBHET_3 super hydride

- super nucleophilic hydride
- can reduce alkyl halide, tosylate and epoxide effectively

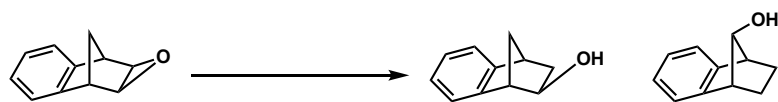
Table 1 Reactivity of Et_3BH^- in comparison to other nucleophiles

Reagent	Relative Nucleophilicity
Et_3BH^-	9 400 000
$n\text{-BuS}^-$	680 000
PhS^-	470 000
AlH_4^-	230 000
I^-	3 700
EtO^-	1 000
BH_4^-	940
Br^-	500
PhO^-	400
NO_3^-	1

The above table is taken from the following paper: Brown JOC 1983, 48, 3085



LiAlH_4 , THF, 25 °C, 48 h (100%) (0%)
 LiBH_4 , THF, 25 °C, 48 h (0%) (100%)
 LiBHET_3 , THF, 65 °C, 24 h (100%) (0%)

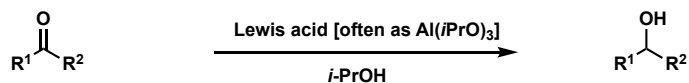


LiAlH ₄ , Et ₂ O, reflux, 24 h	(15%)	(85%)
BH ₃ ·THF, reflux, 4h	(54%)	(23%)
LiBHET ₃ , THF, 65 °C, 24 h	(93%)	(<0.1%)

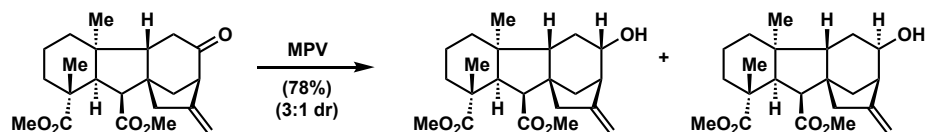
Yamamoto, EROS, 2007
doi.org/10.1002/047084289X.rt219.pub3

mechanism

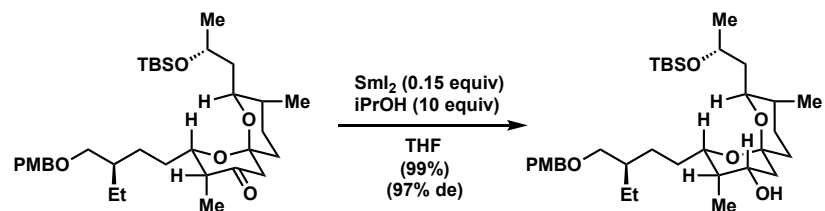
C. Meerwein-Ponndorf-Verley (MPV) reduction



mechanism

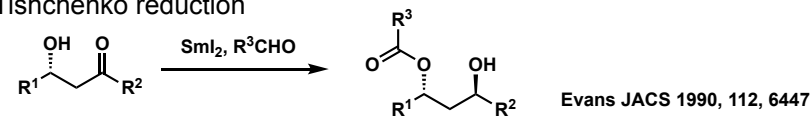


Ihara JACS 2000, 122, 9036



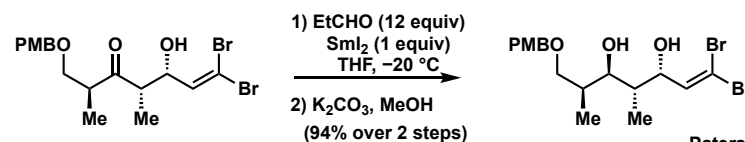
Evans JOC 1990, 55, 6260

D. Evans-Tishchenko reduction

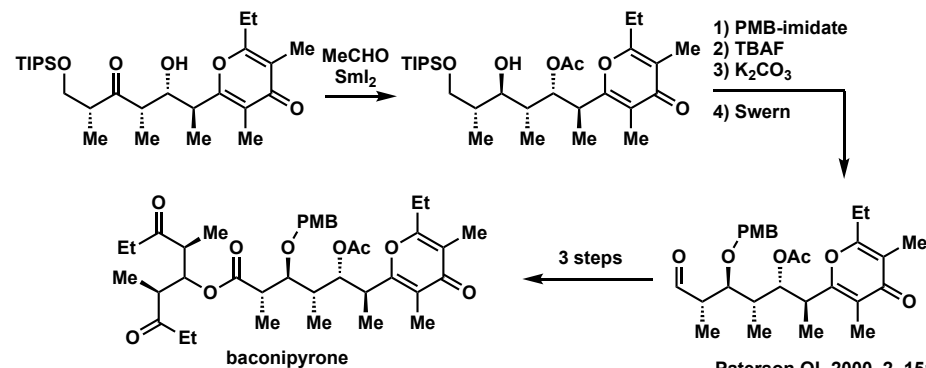


Evans JACS 1990, 112, 6447

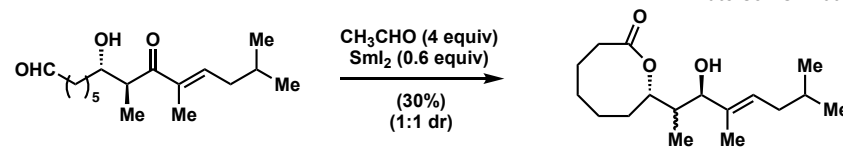
mechanism



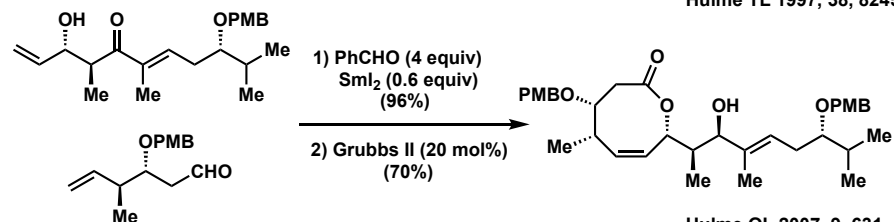
Paterson OL 2011, 13, 4398



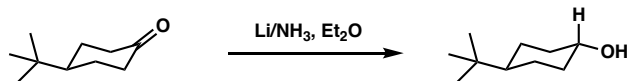
Paterson OL 2000, 2, 1513



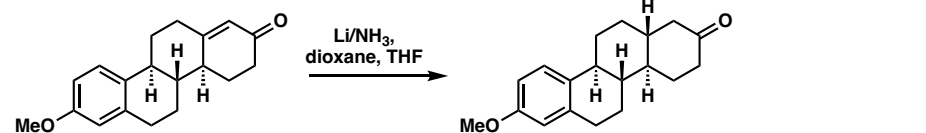
Hulme TL 1997, 38, 8245



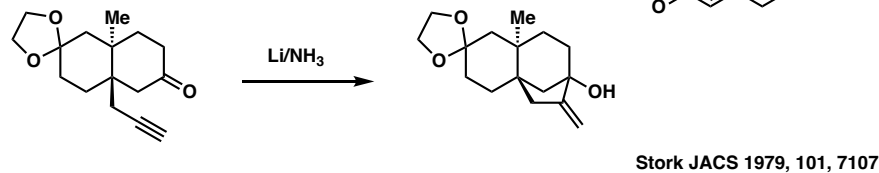
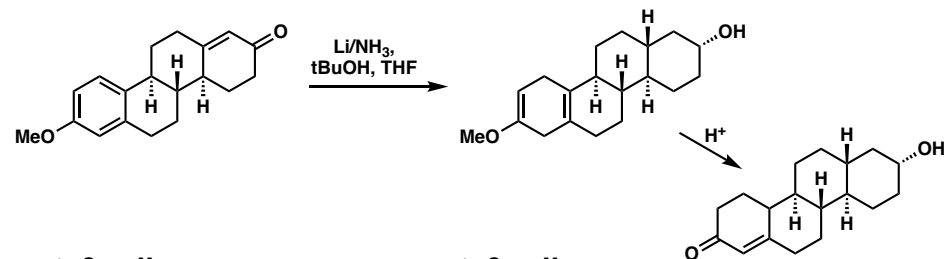
Hulme OL 2007, 9, 631

E. Li/NH₃ reduction

mechanism



Johnson JOC 1963, 28, 1856

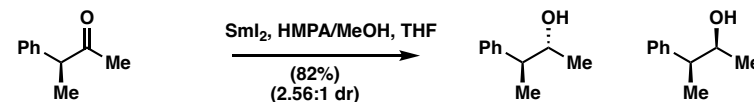


Stork JACS 1979, 101, 7107

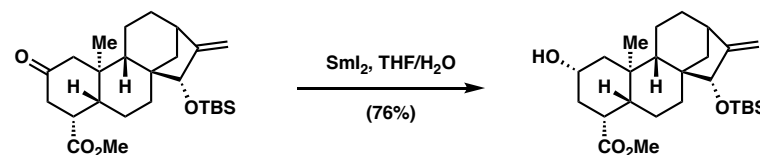
mechanism

F. SmI₂reactions of SmI₂ will be covered in a later chapter

- readily generate ketyl radical from ketone/aldehyde
- very sensitive to oxygen
- tunable reductive capability by additive (HMPA/H₂O...)



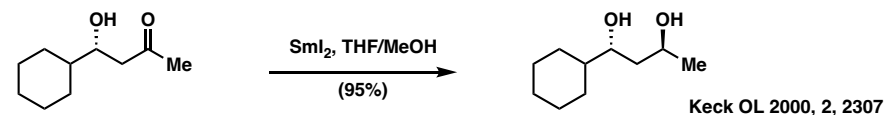
Yamamoto JACS 1988, 110, 4475



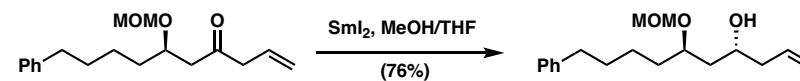
Corey JACS 1987, 109, 6187

mechanism

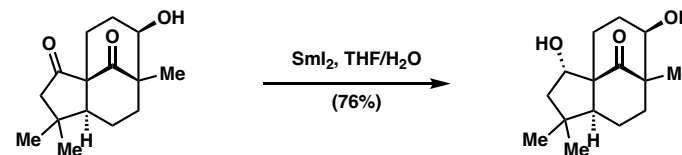
mechanism



Keck OL 2000, 2, 2307



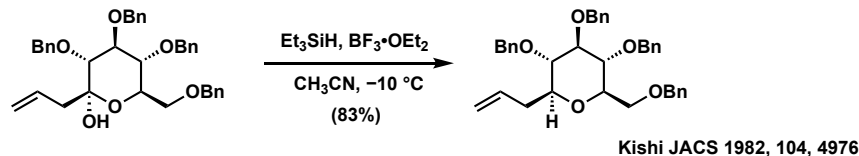
Venkateswarlu HCA 2014, 97, 112



Fu and Liu OL 2021, 23, 290

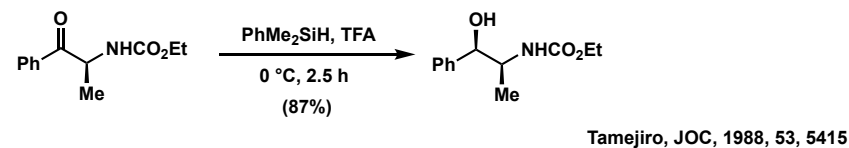
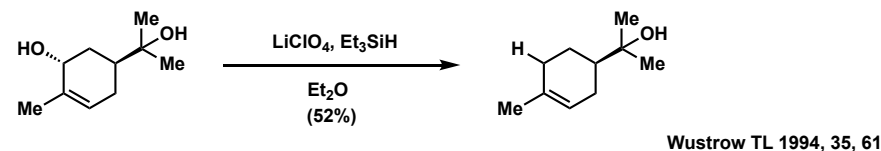
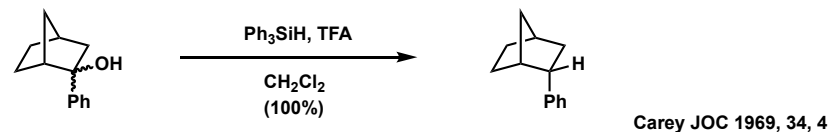
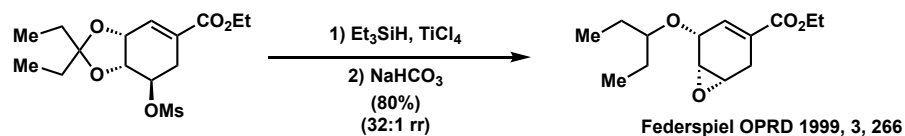
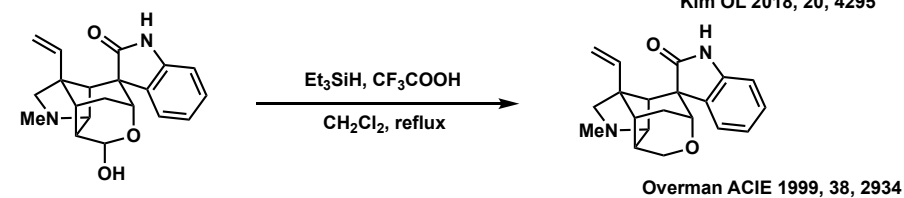
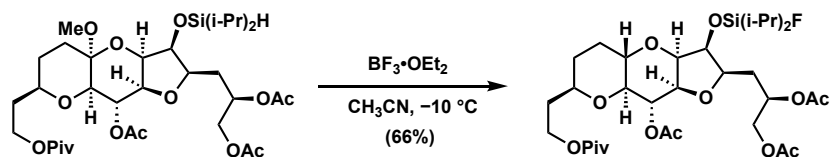
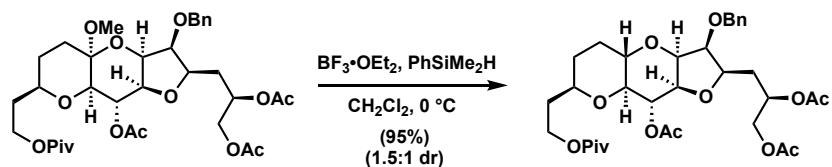
G. Ionic Reduction. Kishi reduction

- typical conditions involve use of Lewis acid to generate carbocation and silane as hydride donor
- can reduce carbonyl to alcohol, alcohol to alkane, alkene to alkane

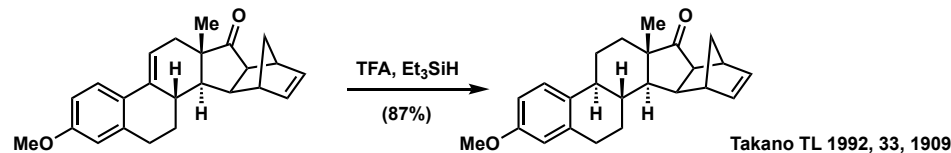


mechanism

mechanism



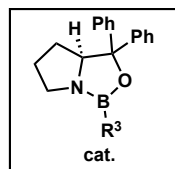
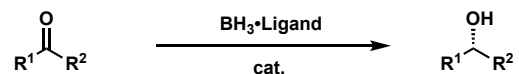
stereochemistry



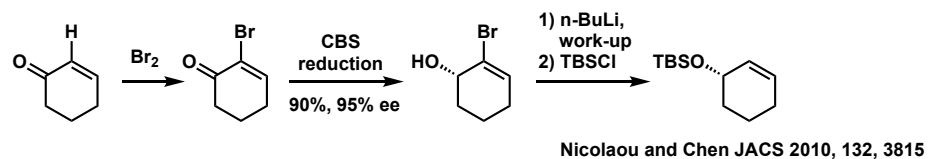
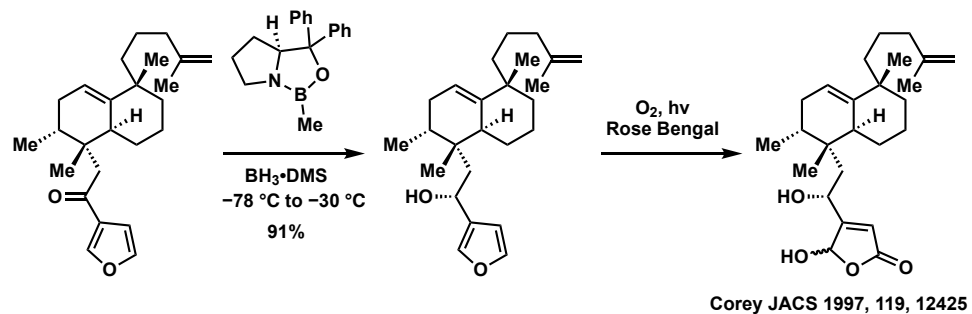
stereochemistry

H. Examples of asymmetric ketone reductions

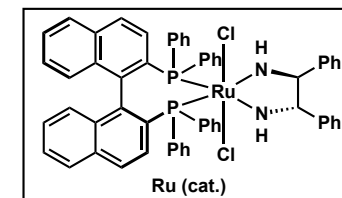
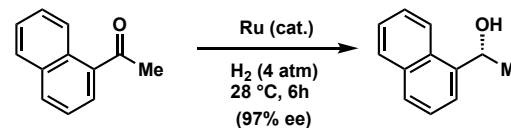
a. Corey-Bakshi-Shibata (CBS) Reduction



mechanism



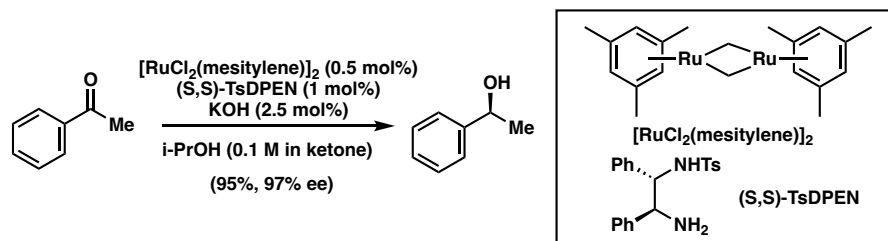
b. Noyori asymmetric hydrogenation of non-directed ketones



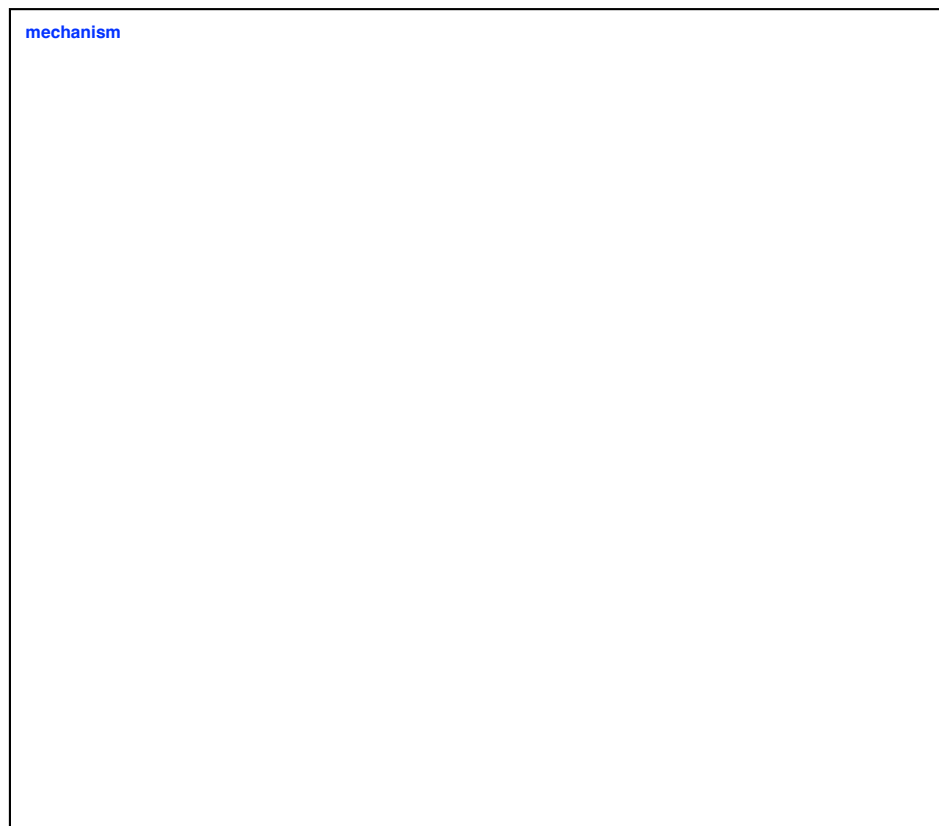
mechanism

Noyori JACS 1995, 117, 2675
JACS 1998, 120, 13529
Morris JACS 2001, 123, 7473

c. Noyori asymmetric transfer hydrogenation of non-directed ketones

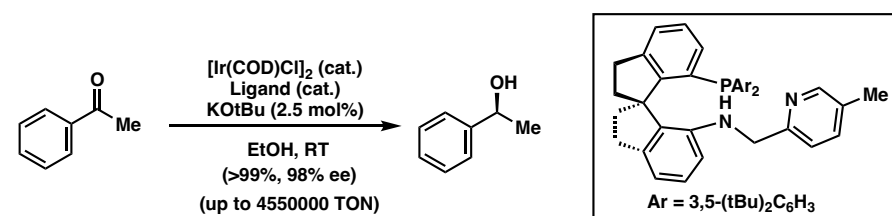


mechanism

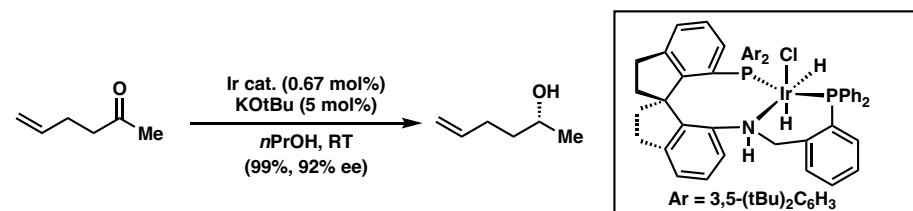
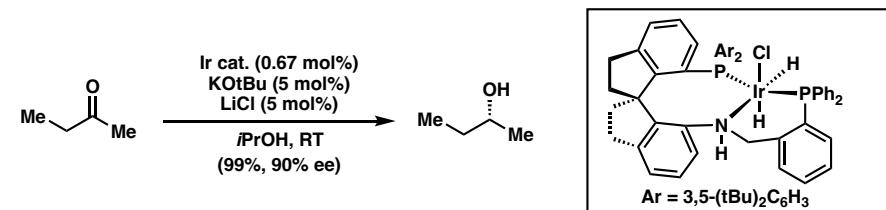


Noyori JACS 1995, 117, 7562
 JACS 2000, 122, 1466
 ACR 1997, 30, 97

d. Selected recent advances on catalytic asymmetric hydrogenation of ketone

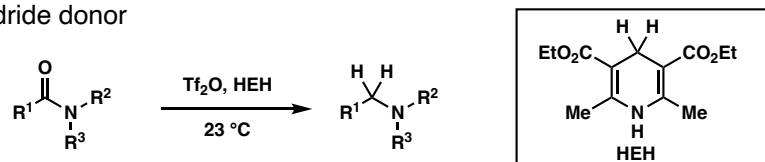


Zhou ACIE 2011, 50, 7329

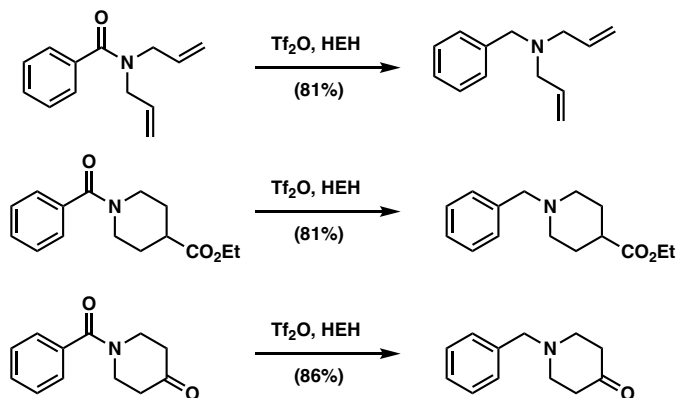


Zhou NatCatal 2020, 3, 621

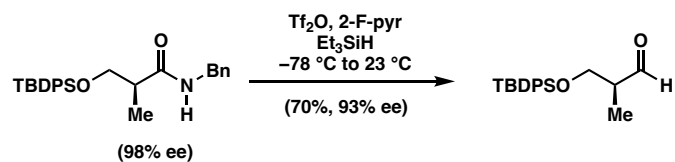
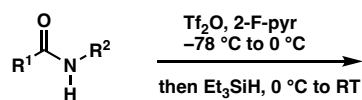
I. Selective amide reduction

a. Tf_2O + Hydride donor

mechanism

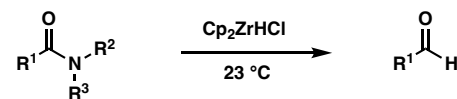
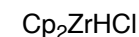


Charette JACS 2008, 130, 18

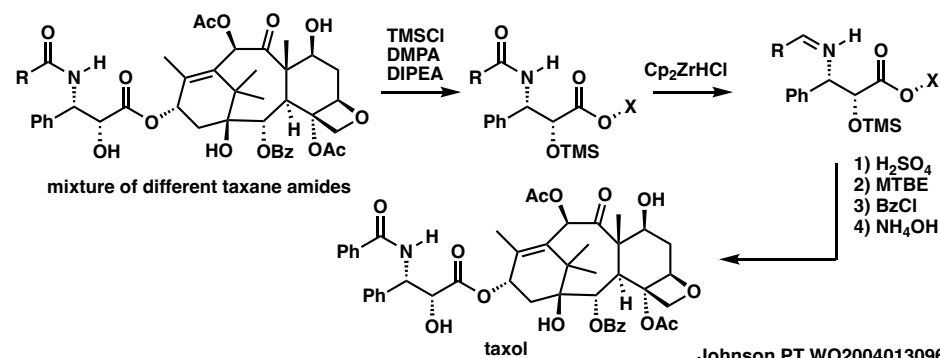
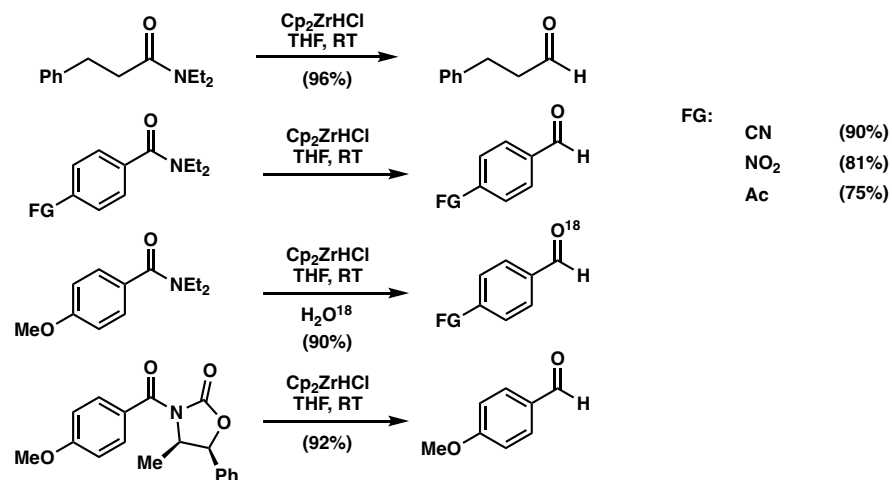


Charette JACS 2010, 132, 12817

b. Schwartz reagent

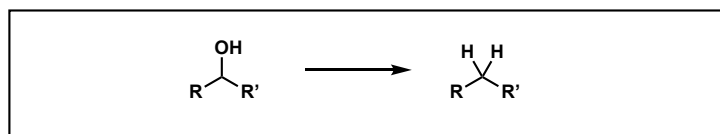


mechanism

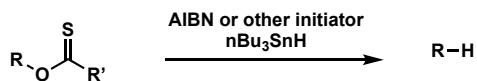


Johnson PT WO2004013096A2

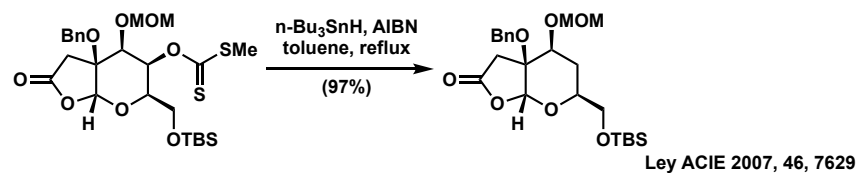
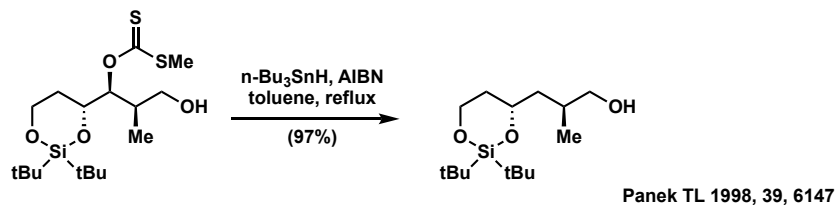
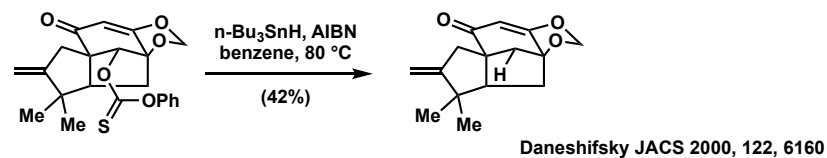
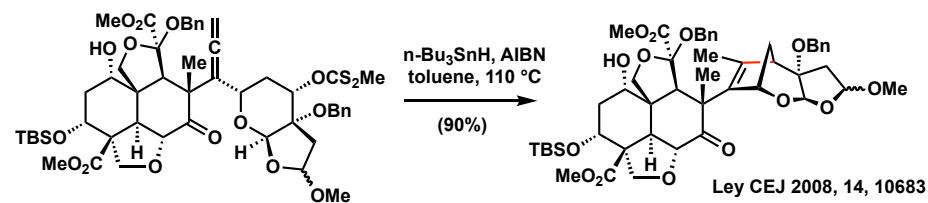
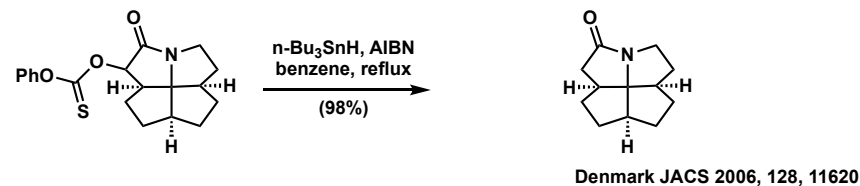
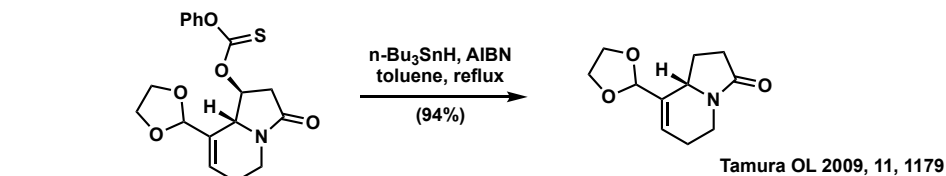
2. Reduction of alcohol to alkane



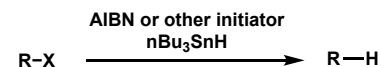
A. Barton-McCombie deoxygenation



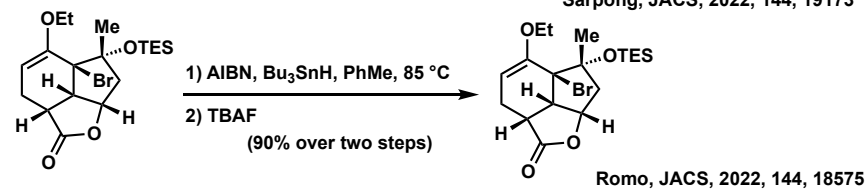
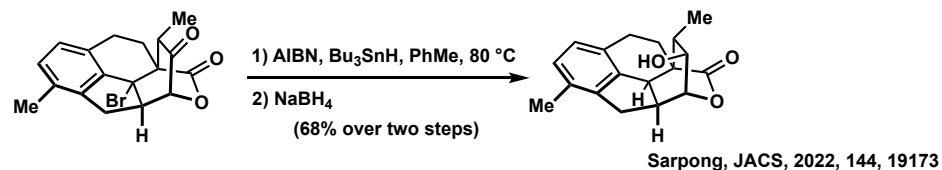
mechanism



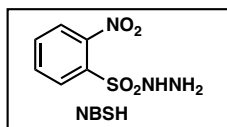
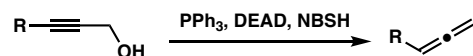
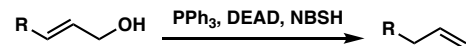
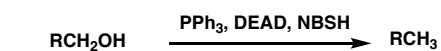
B. Halogenation—Radical dehalogenation



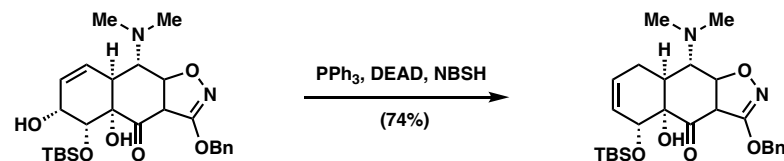
mechanism



C. Diazene-mediated deoxygenation



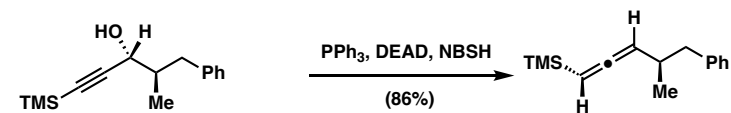
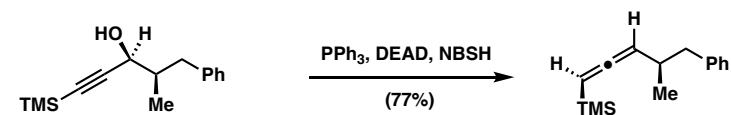
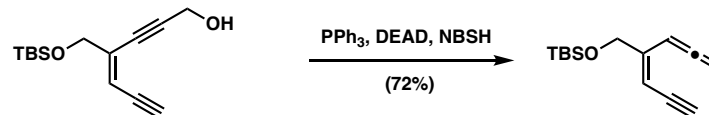
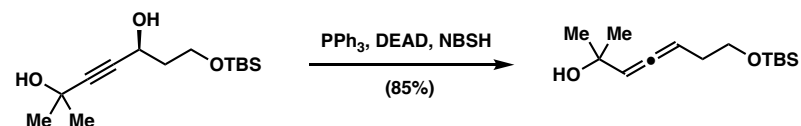
mechanism



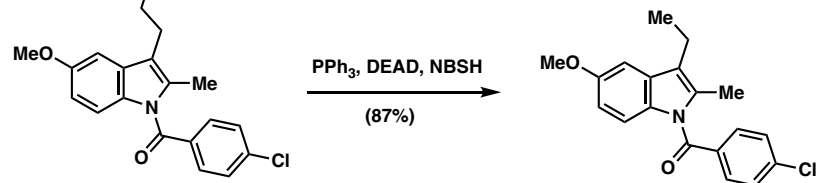
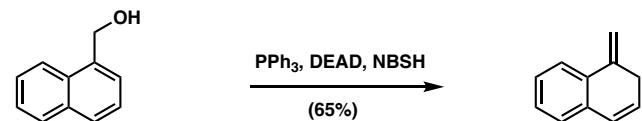
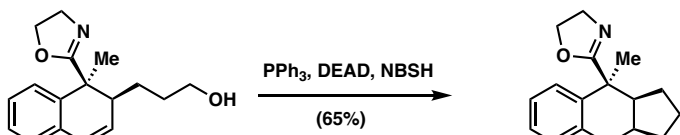
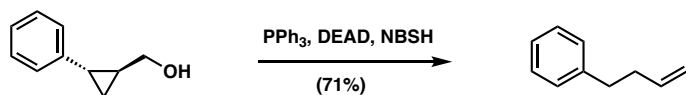
Myers Science 2005, 308, 395



Magnus BMCL 2013, 23, 4870

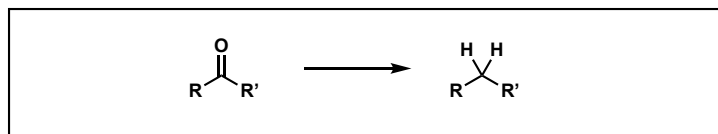


Myers JACS 1996, 118, 4492

Myers JACS 1997, 119, 8572
JACS 1996, 118, 4492

Myers JACS 1997, 119, 8572

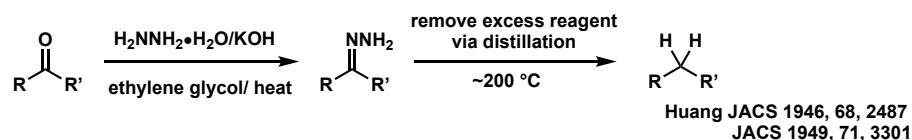
3. Reduction of ketone and aldehyde to alkanes



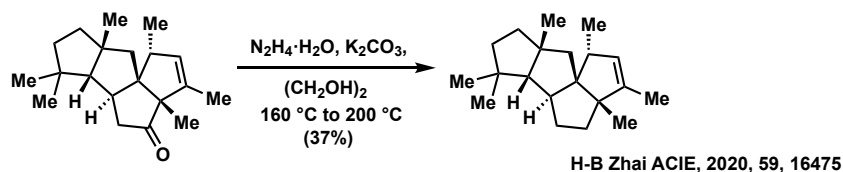
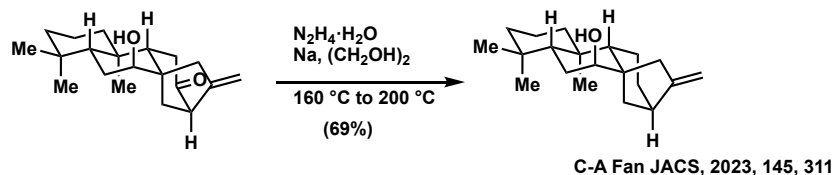
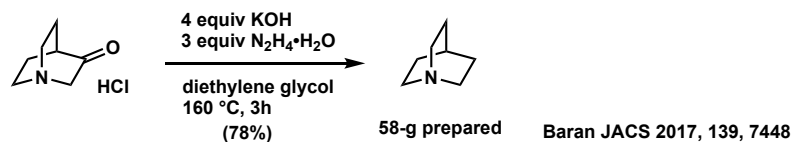
A. Wolff-Kishner Reduction

a. Huang-Minlong modification

- strongly basic conditions, high temperature

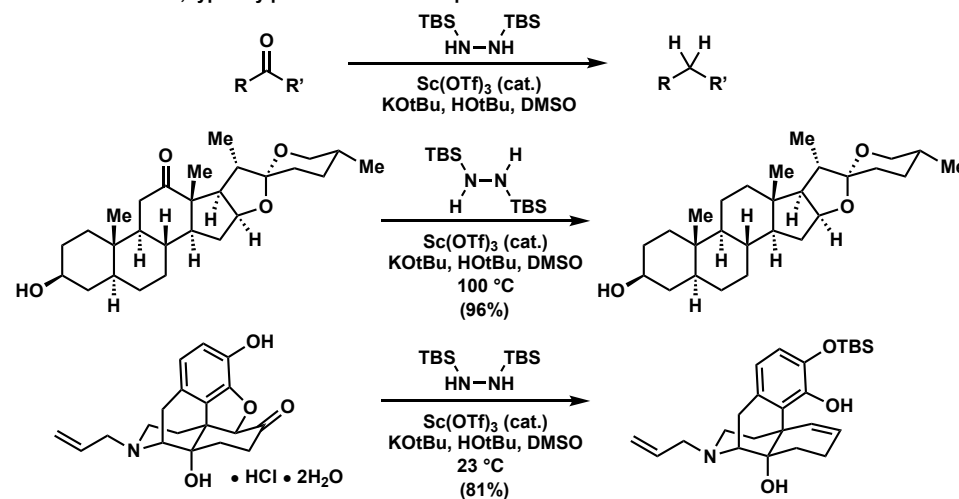


mechanism



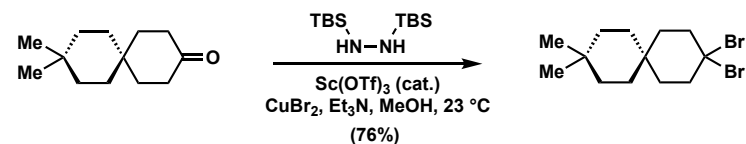
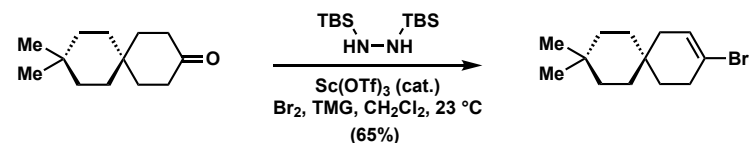
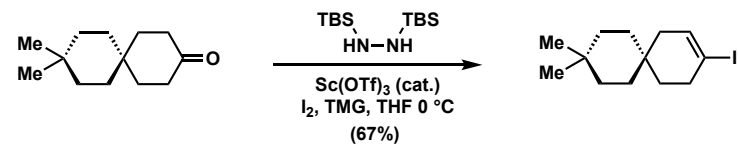
b. Myers modification

- mild conditions, typically proceed at room temperature



mechanism

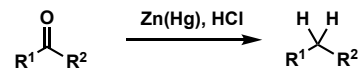
Additional transformations



Myers JACS 2004, 126, 5436

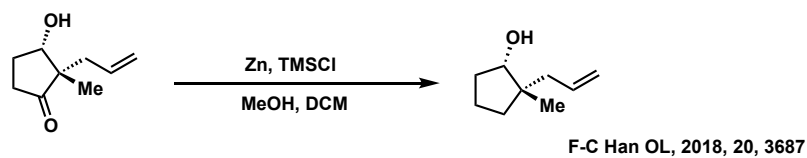
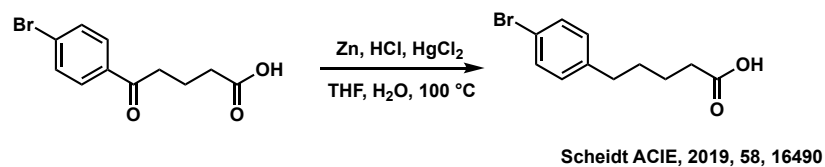
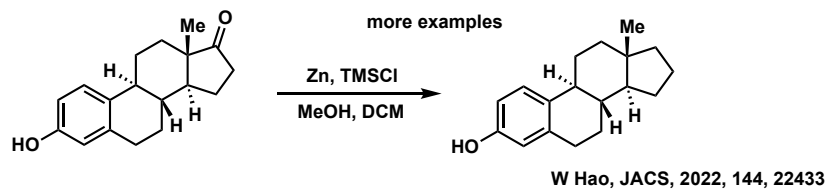
B. Clemmensen reduction. Zn(Hg), HCl

- strongly acidic conditions

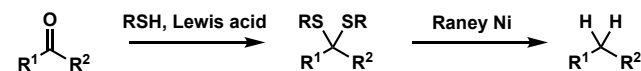


proposed mechanism 1

proposed mechanism 2

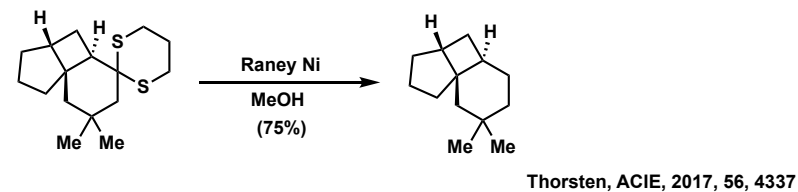
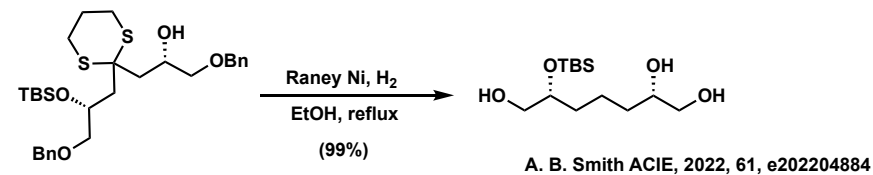
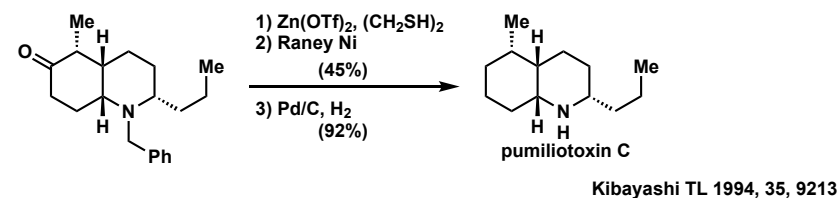


C. De-sulfurization of Thioacetal(ketal) with Raney Ni



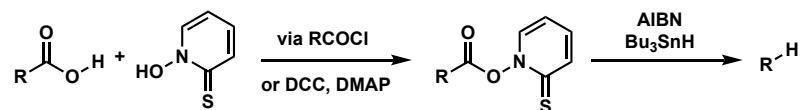
mechanism step 1

mechanism step 2

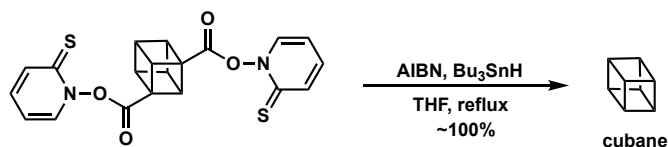


4. Decarboxylation of acid to alkane

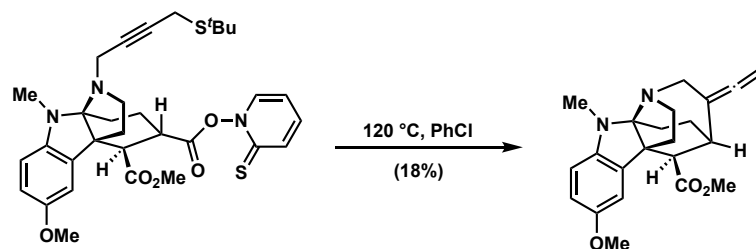
A. Barton radical decarboxylation deoxygenation



mechanism:

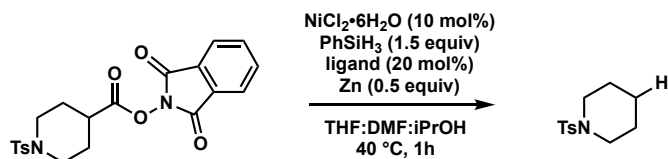


Eaton ACIEE 1992, 31, 1421



MacMillan JACS, 2013, 135, 6442

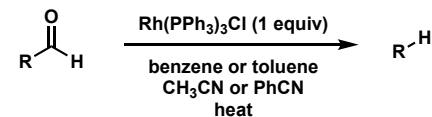
A modern version



Baran ACIE 2017, 56, 260

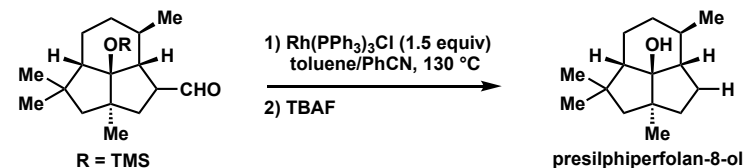
5. Decarbonylation of aldehyde

A. decarboxylation of aldehyde to alkane

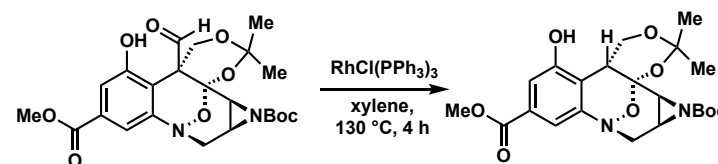


Tsuji JACS 1968, 90, 99

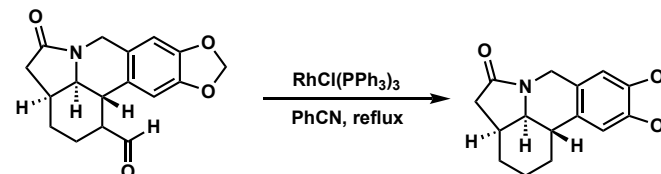
mechanism:



Snyder JACS 2017, 139, 5007

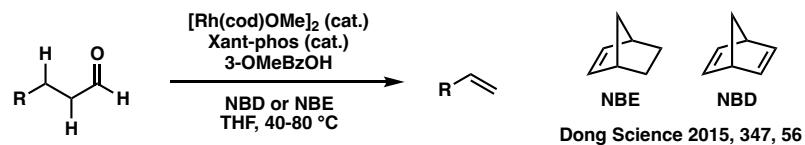


Belema JOC, 1997, 62, 1083

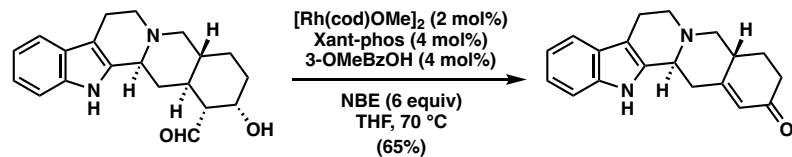
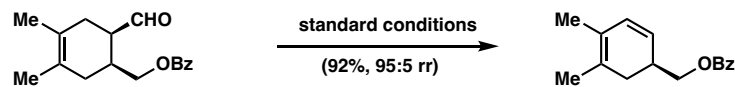
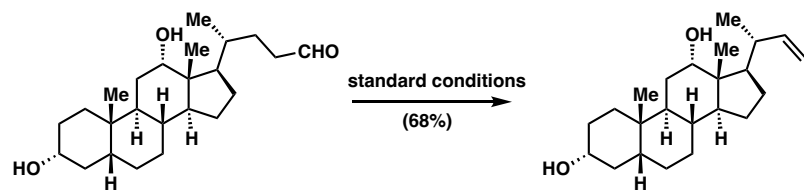


Xu OBC, 2012, 10, 8211

B. decarboxylation of aldehyde to alkene



mechanism:



Dong Science 2015, 347, 56