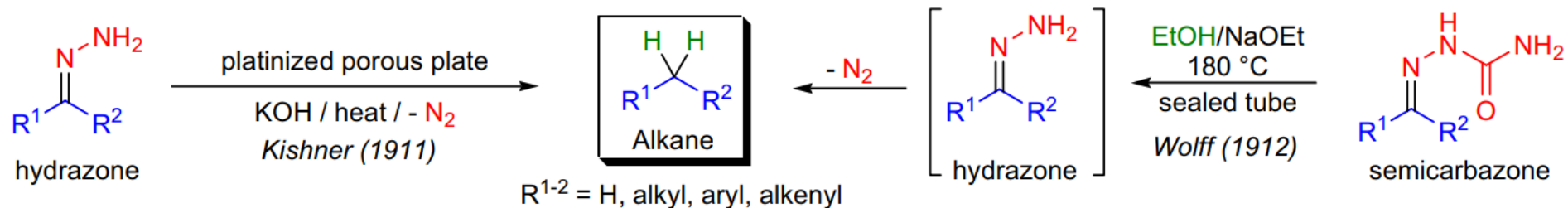


WOLFF-KISHNER-HUANG REDUCTION

黄鸣龙 (1898.8.6~1979.7.1)

- 1918 Graduat from the Zhejiang Provincial College of Medicine.
- 1924 Obtain PhD from the University of Berlin, Germany.
- 1925 professor of Zhejiang Provincial College of Medicine.
- 1934 Work in research in Germany and the UK.
- 1940 senior researcher at Academia Sinica.
- 1945 visiting professor at Harvard University.
- 1952 Chair of Department of Chemistry, Academy of Military Medical Sciences of PLA.
- 1955 academician of Chinese Academy of science
- 1956 senior researcher at the Shanghai Institute of Organic Chemistry





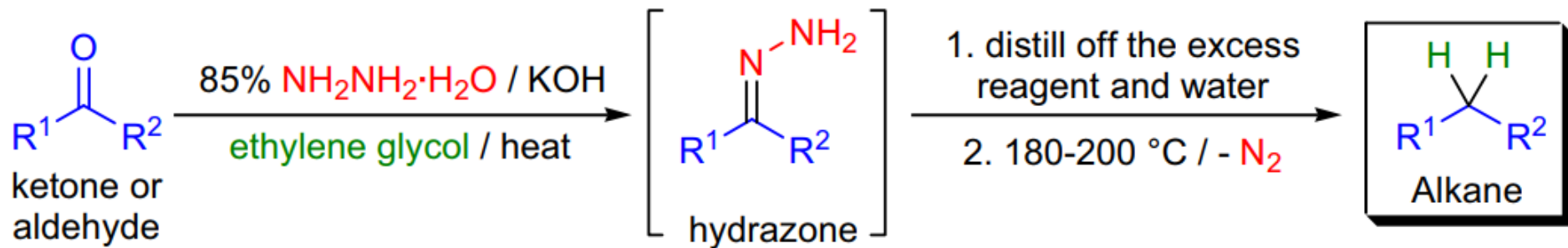
- Long time (couple of days)
- high-boiling solvent and high temperature
- excess base (sodium metal, NaOEt...)

Mary Barns Soffer's modification:

Using high-boiling solvent diethylene glycol instead of EtOH.

J. Am. Chem. Soc., **1945**, 67,1435

Huang Minlon's modification:

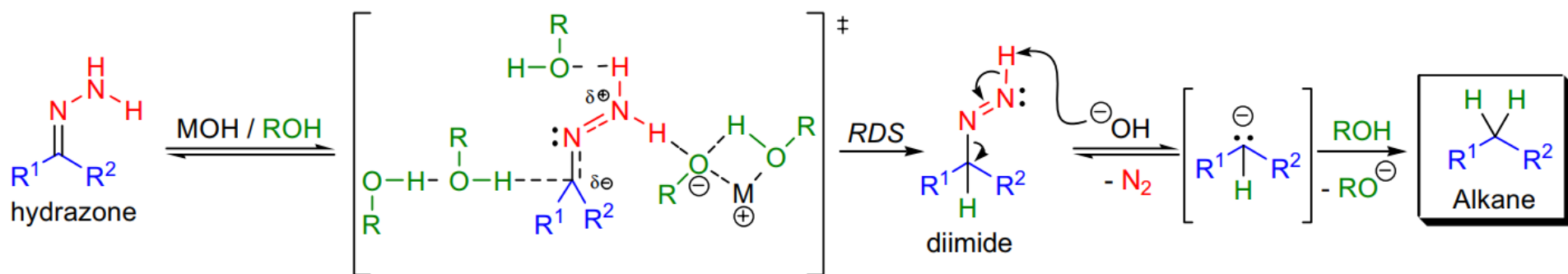


Observed by an coincidence

features

- Because of the distillation of the water and the excess hydrazine, it's easy to reach a high temperature (~200°C). Shortening the reaction time (3-6h), increasing the yields allowing the use of the cheaper hydrazine and sealed tube was never needed.
- Esters, lactones, amides, and lactams are hydrolyzed under the reaction conditions.
- For α,β -unsaturated carbonyl compounds, the use of preformed semicarbazones is advised (hydrazine tends to give pyrazolines with these substrates), which undergo reduction under the original or most of the modified reaction conditions.

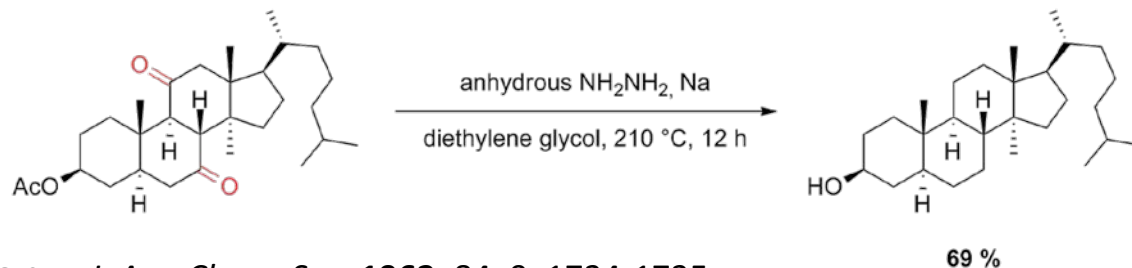
Mechanism:



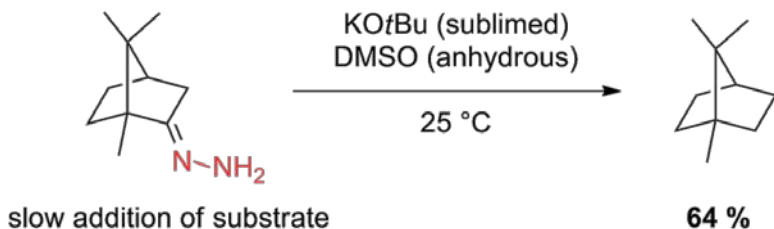
The rate determine step is hydrozone rearrangement by intermolecular proton transfer. Once the diimide formed, it will generate alkane fast by loosing of N₂.

J. Am. Chem. Soc. , **1964**, 86, 2909

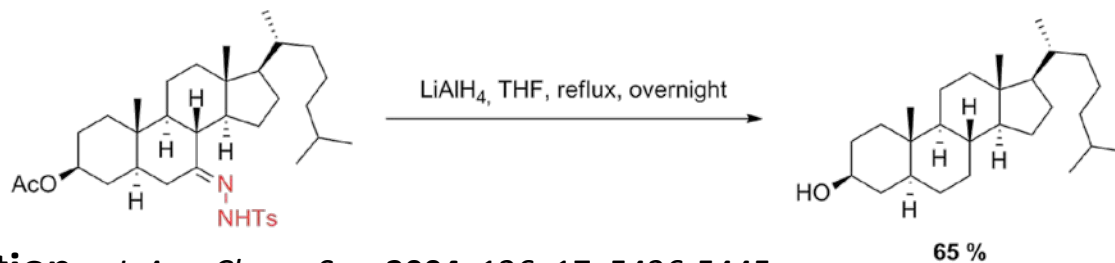
Barton modification *J. Chem. Soc.*, **1955**, 2038-2056



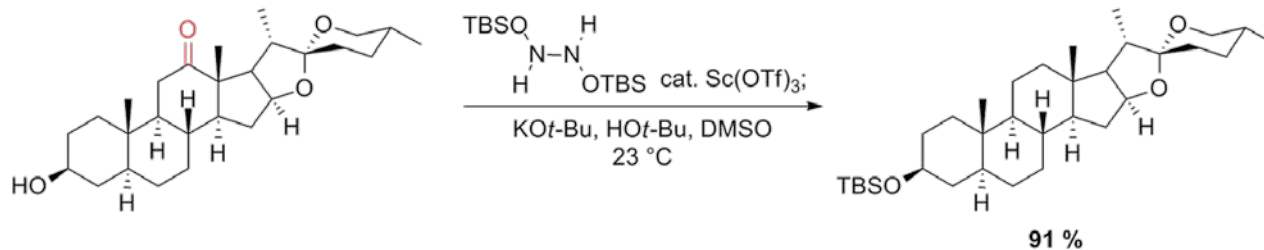
Cram modification *J. Am. Chem. Soc.* **1962**, 84, 9, 1734-1735



Caglioti reaction *Tetrahedron*, **1963**, 7, 1127-1131

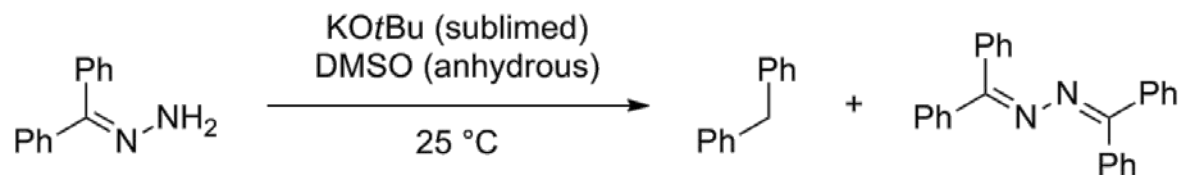


Myers modification *J. Am. Chem. Soc.* **2004**, 126, 17, 5436-5445



Side reactions

Azine formation



slow addition over 8 h

89 %

11 %

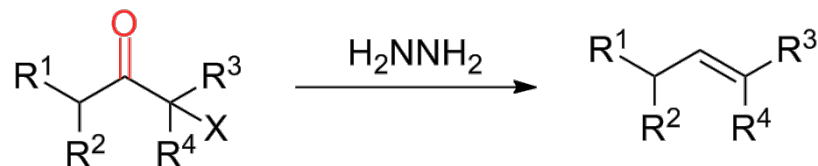
slow addition over 0.5 h

72 %

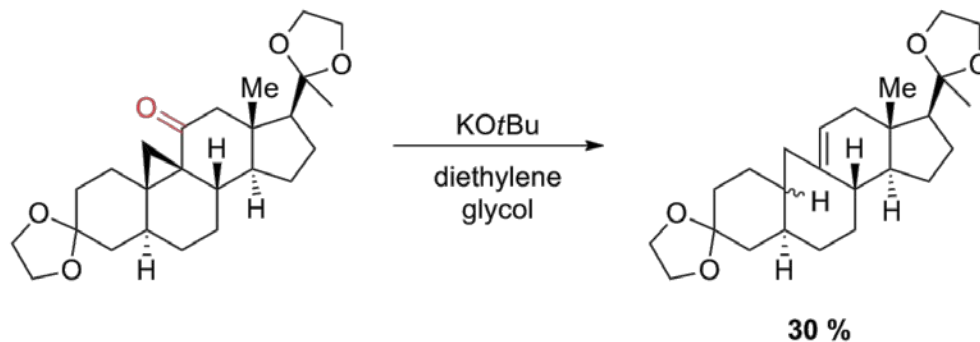
22 %

Reduction of ketones to alcohols

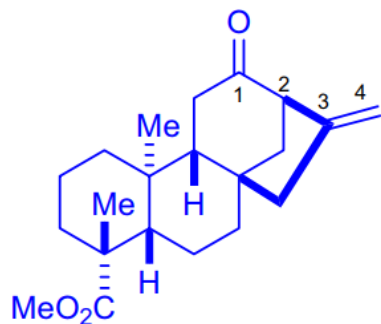
Kishner–Leonard elimination



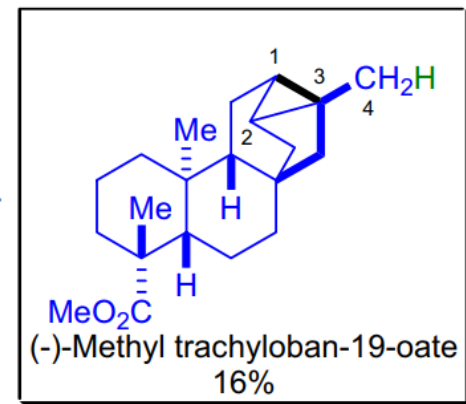
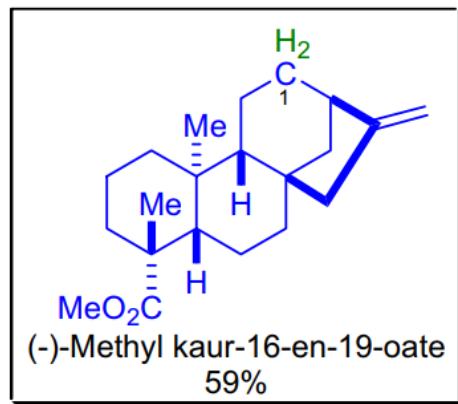
Cleavage or rearrangement



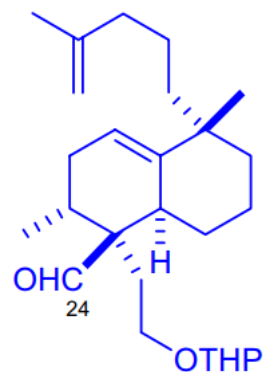
Applications



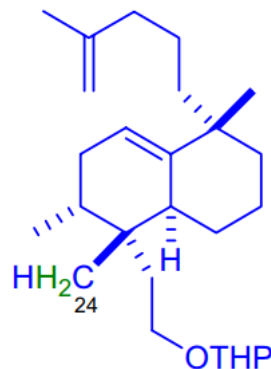
1. $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ (72 equiv)
135 °C, 2h
di(ethylene glycol)
 2. cool to room temperature
 3. KOH (9.1 equiv), 200 °C, 10h
 4. CH_2N_2 (xs), Et_2O
- 75% for four steps



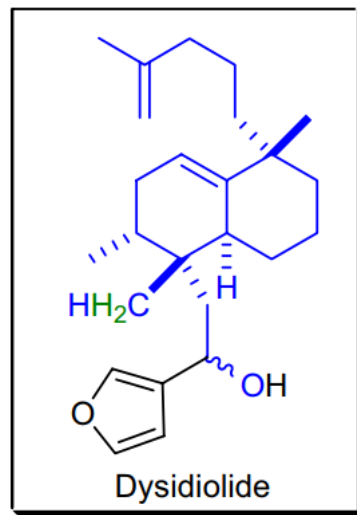
J. Org. Chem. **2000**, 65, 4565-4570



- $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ (12 equiv)
 - KOH (9 equiv)
- 200 °C, 2h, di(ethylene glycol)
95%

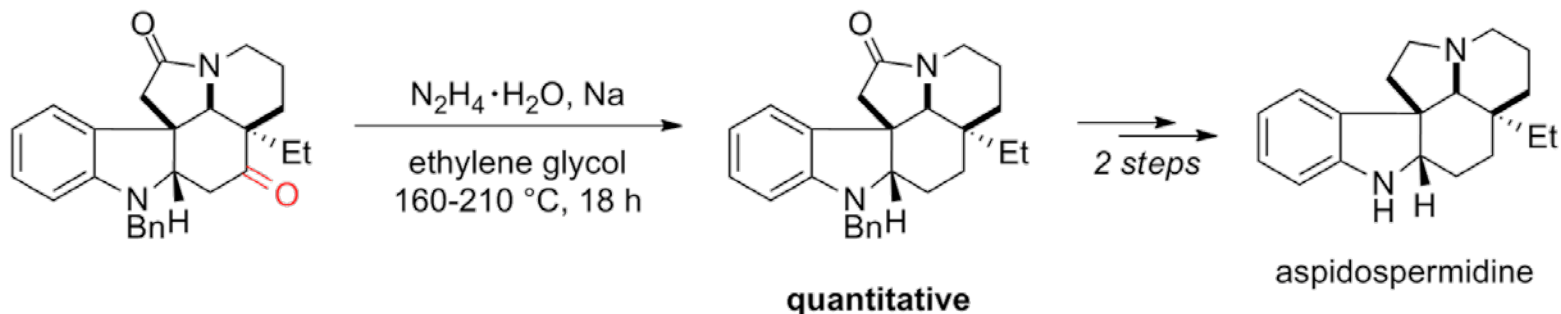


steps

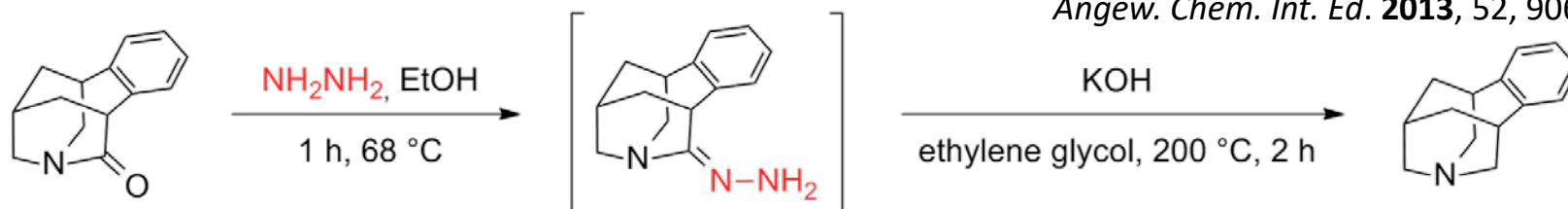


J. Org. Chem. **2001**, 66, 1429-1435

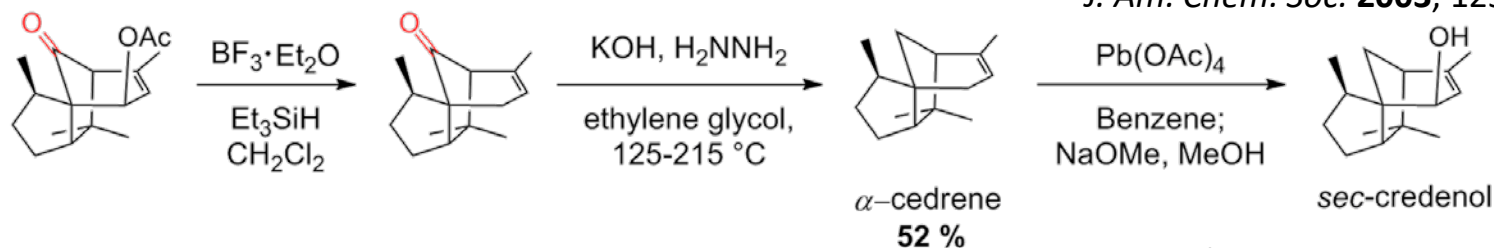
Applications



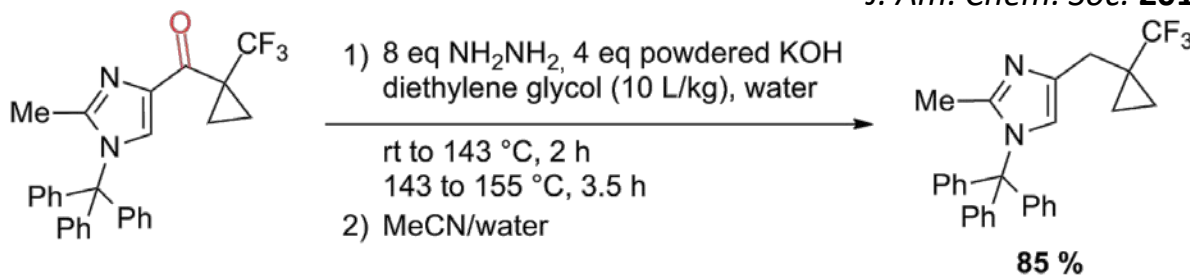
Angew. Chem. Int. Ed. **2013**, 52, 906–910



J. Am. Chem. Soc. **2003**, 125, 11, 3268-3272



J. Am. Chem. Soc. **2011**, 133, 5, 1603-1608



Org. Process Res. Dev. **2009**, 13, 3, 576-580