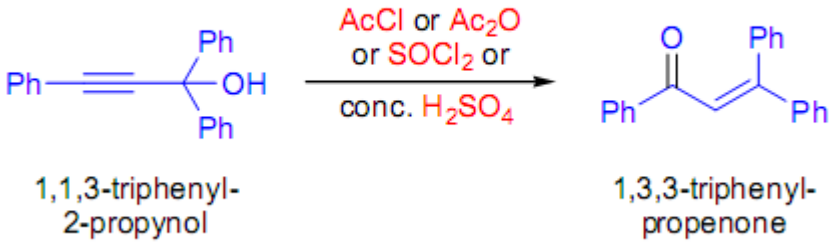
MEYER-SCHUSTER AND RUPE REARRANGEMENT

Meyer and Schuster (1922):

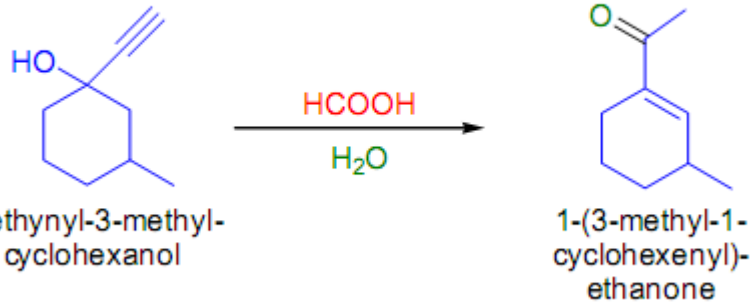


1,1,3-triphenyl-2-propynol

1,3,3-triphenyl-propenone

In 1922, K.H. Meyer and K. Schuster reported that the attempted conversion of 1,1,3-triphenyl-2-propynol to the corresponding ethyl ether with concentrated sulfuric acid and ethanol afforded 1,3,3-triphenyl propenone, an α,β-unsaturated ketone.

Rupe (1924-1928):

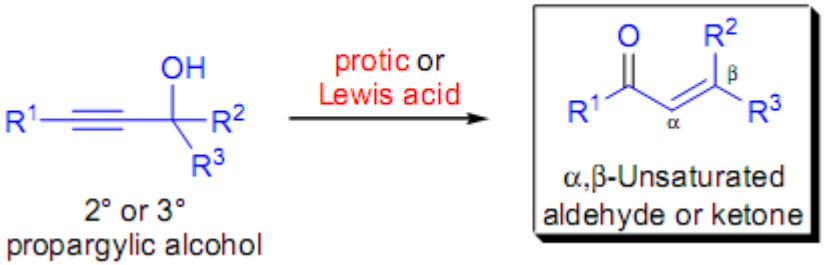


1-ethynyl-3-methyl-cyclohexanol

1-(3-methyl-1-cyclohexenyl)-ethanone

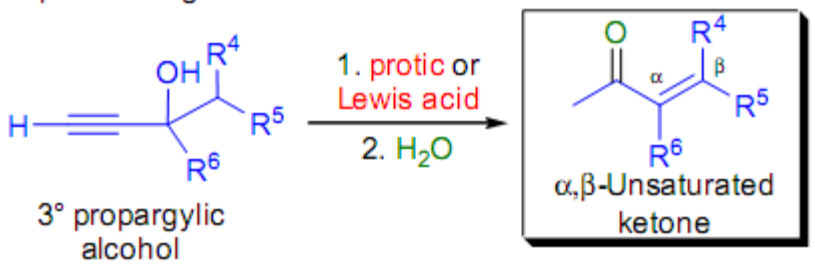
A few years later, H. Rupe and co-workers investigated the acid-catalyzed rearrangement of a large number of α-acetylenic (propargylic) alcohols

Meyer-Schuster rearrangement:



2° or 3°
propargylic alcohol

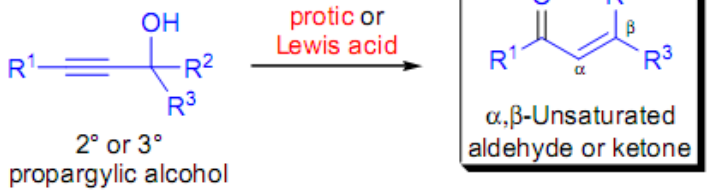
Rupe rearrangement:



3° propargylic
alcohol

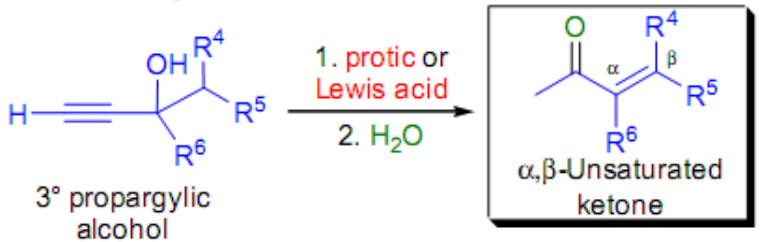
R^1 = H, alkyl, aryl; R^{2-3} = H, aryl or alkyl with no H atoms adjacent to the α-carbon; R^{4-6} = alkyl, aryl; protic acid: H_2SO_4, AcOH, HCO_2H, Dowex-50/HCO_2H, HCl/2-propanol, HCl/Et_2O, *p*-TsOH. etc.; Lewis acid: $HgSO_4$/EtOH, $POCl_3$/pyridine, $HgSO_4/H_2SO_4$

Meyer-Schuster rearrangement:



2° or 3°
propargylic alcohol

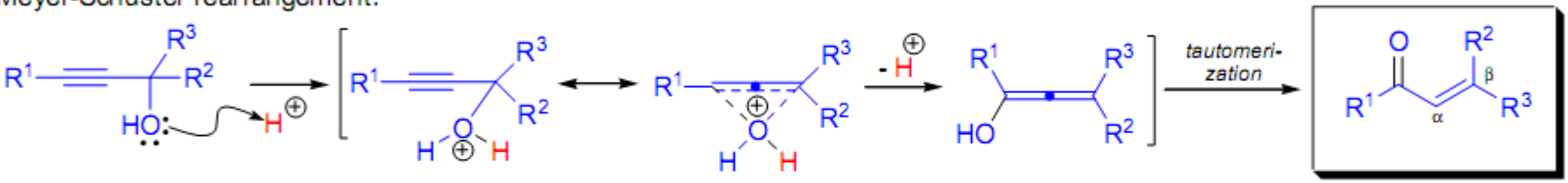
Rupe rearrangement:



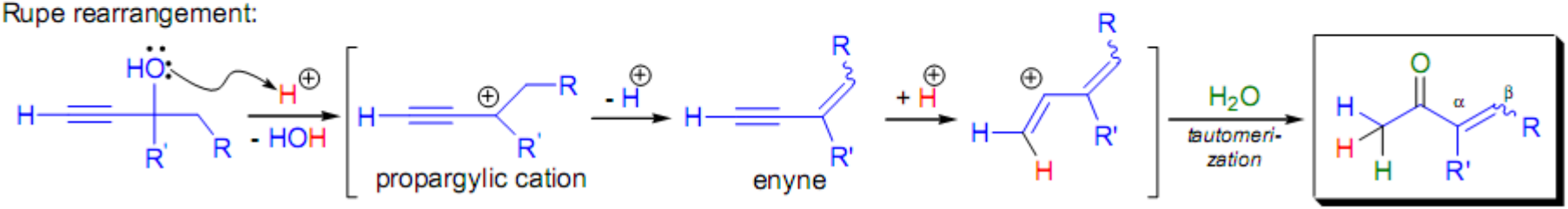
3° propargylic
alcohol

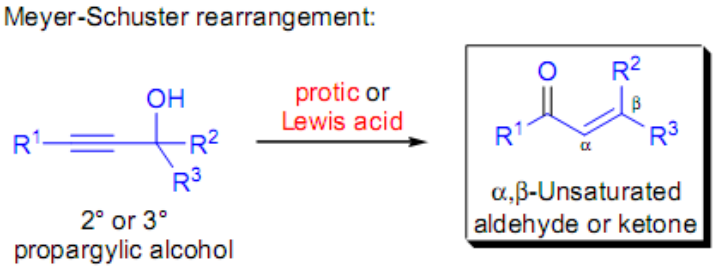
Mechanism: [22,8,23]

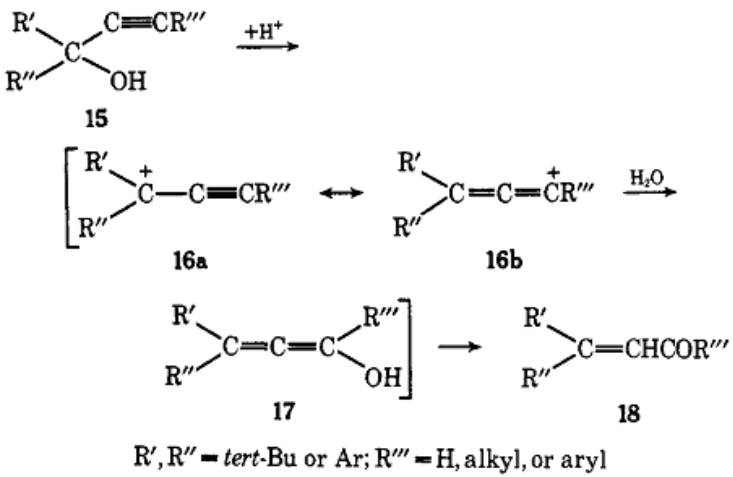
Meyer-Schuster rearrangement:



Rupe rearrangement:







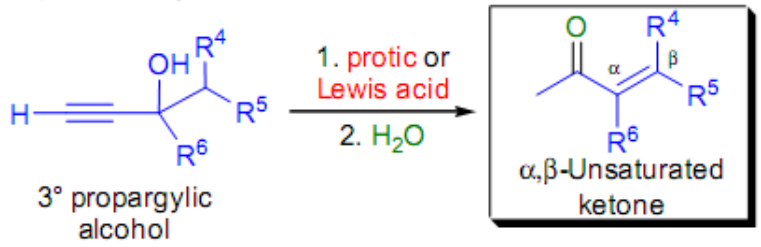
The general features of this transformation are:

1) when the substrate contains a terminal alkyne, the product is an aldehyde, whereas substrates containing disubstituted alkynes yield ketones

2) the substrates, 2° or 3° propargylic alcohols, may not have a proton at their α-position so that the initial propargylic cation can isomerize to an allenyl cation, which provides the product carbonyl compound

3) the rearrangement can be catalyzed by both protic and Lewis acids under anhydrous or aqueous conditions.

Rupe rearrangement:



1) the product is always the α,β-unsaturated ketone regardless of the substitution of the triple bond

2) the substrates are tertiary propargylic alcohols that have hydrogen atoms available at their α-position

3) most often strong protic acids mixed with alcohol solvents are used to bring about the rearrangement, but certain Lewis acid such as mercury(II)-salts and even dehydrating agents (SOCl2, P2O5, etc.) were shown to be effective

The disadvantages of the above two rearrangements are:

1) certain substrates may give rise to a mixture of Rupe and Meyer-Schuster rearrangement products

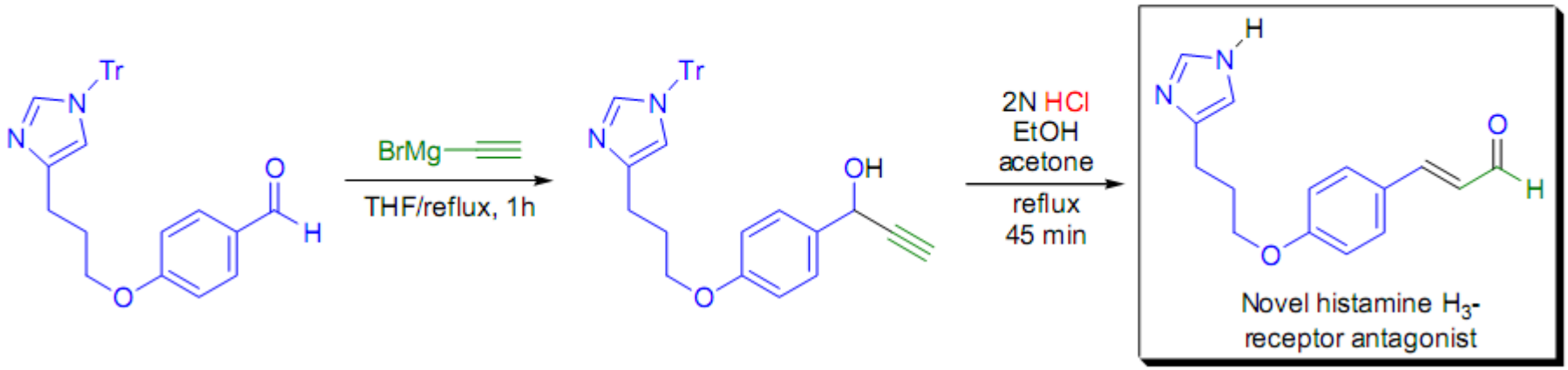
2) low yields are observed when the product (especially aldehydes) undergoes self-condensation, or is readily oxidized under the reaction conditions

3) acid-sensitive functionalities in the substrate may give undesired elimination products

4) the initial propargylic cation occasionally undergoes Wagner-Meerwein or Nametkin rearrangement.

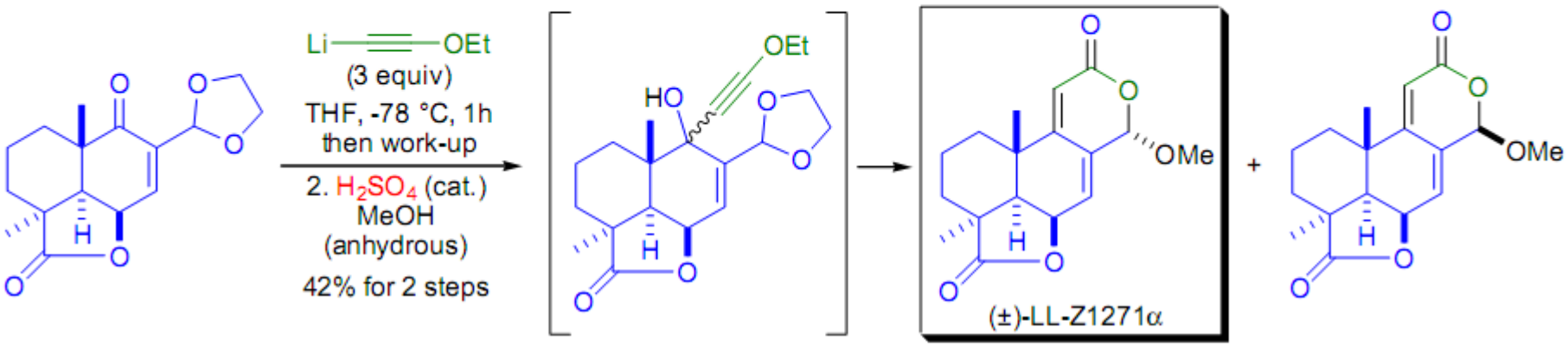
Synthetic Applications

H. Stark and co-workers prepared novel histamine H_3-receptor antagonists with carbonyl-substituted 4-[(3-phenoxy)propyl]-1*H*-imidazole structures.[25] The *Meyer-Schuster rearrangement* was used for the synthesis of one of the compounds. The *p*-hydroxybenzaldehyde derivative was reacted with ethynylmagnesium bromide to afford a secondary propargylic alcohol. Upon hydrolysis with 2N HCl in a refluxing ethanol/acetone mixture, the corresponding *p*-hydroxy cinnamaldehyde was obtained.



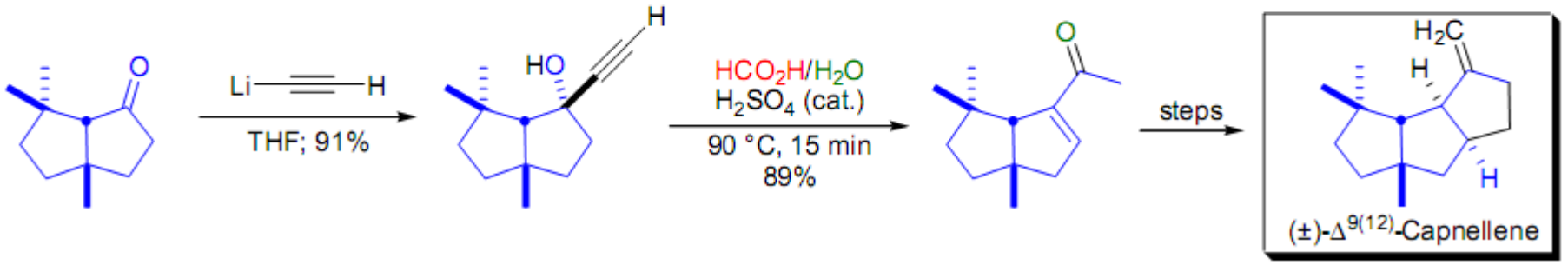
Synthetic Applications

In the laboratory of S.C. Welch, the *Meyer-Schuster rearrangement* was the key step in the stereoselective total synthesis of the antifungal mold metabolite (±)-LL-Z1271α.[26] A tricyclic enone acetal was treated with lithium ethoxyacetylide, and the crude product was exposed to H_2SO_4 in anhydrous methanol, which brought about the rearrangement and afforded the desired product in 30% yield along with 12% of an epimer.



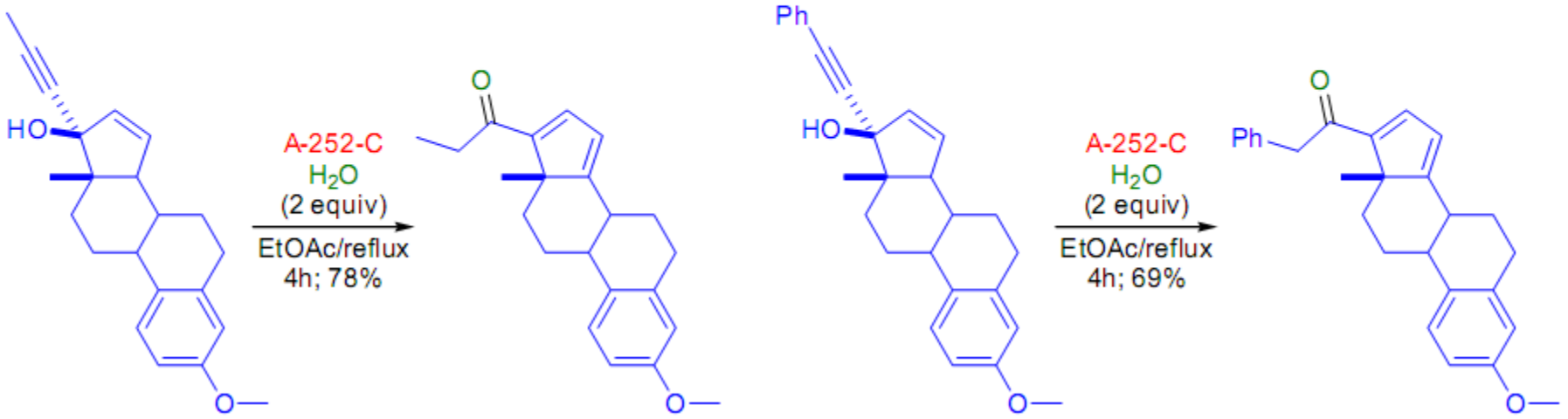
Synthetic Applications

The first fully stereoselective total synthesis of the linear triquinane sesquiterpene (±)-capnellene was achieved by L.A. Paquette et al.[24] The C-ring is a fused cyclopentenone moiety, and the authors tried to assemble it using the *Nazarov cyclization*. However, the dienone precursor failed to undergo the cyclization under a variety of conditions, so an alternative strategy was sought that was based on the *Rupe rearrangement*. The treatment of the bicyclic tertiary propargylic alcohol substrate with formic acid and trace amounts of sulfuric acid afforded high yield of the α,β-unsaturated methyl ketone product. Interestingly, the double bond of the enone did not end up in the most substituted position as it is expected in most cases.

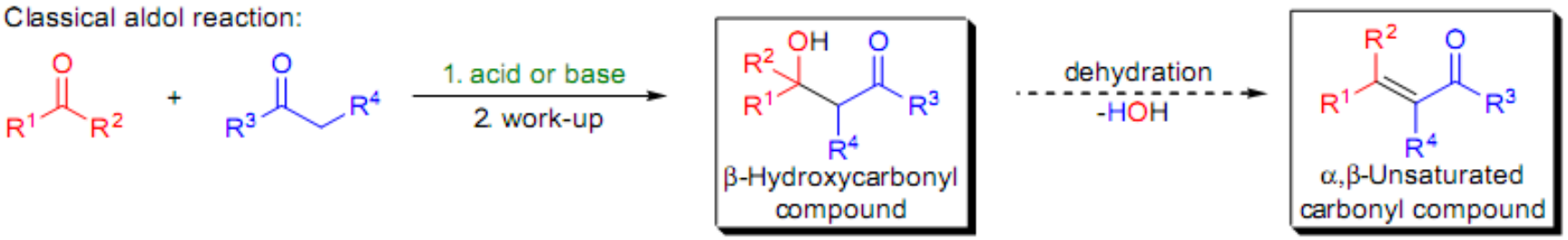


Synthetic Applications

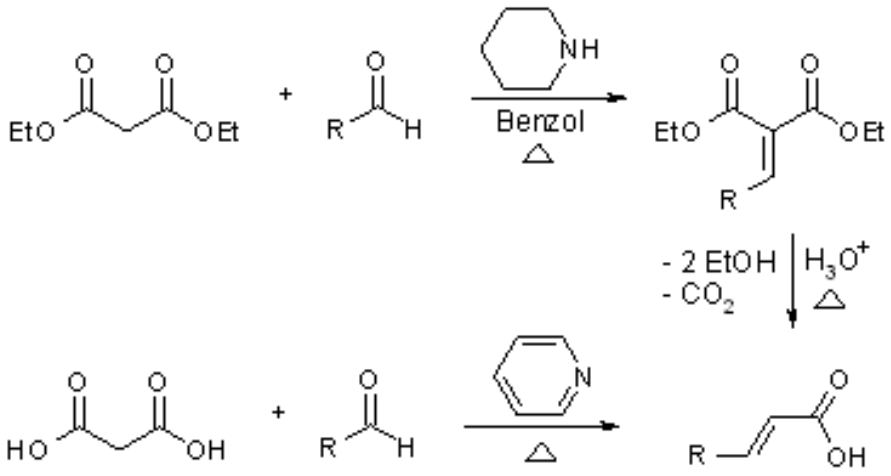
One of the disadvantages of the *Rupe rearrangement* is the harsh reaction conditions needed, making it very difficult to adapt the reaction to large-scale synthesis of unsaturated ketones. The research team of H. Weinmann investigated the rearrangement of a steroidal tertiary propargylic alcohol using a variety of acid catalysts.[15] They found that the macroporous Amberlyst-type resin A-252C in refluxing ethyl acetate containing 2 equivalents of water were ideal for the rearrangement in a pilot plant on a 64 kg scale.



ALDOL REACTION

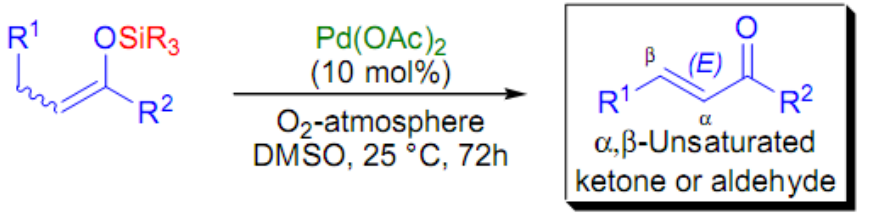


KNOEVENAGEL CONDENSATION

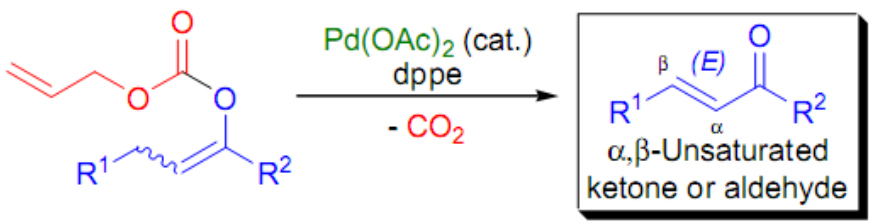


SAEGUSA OXIDATION

Catalytic process (*Larock modification*,1995):

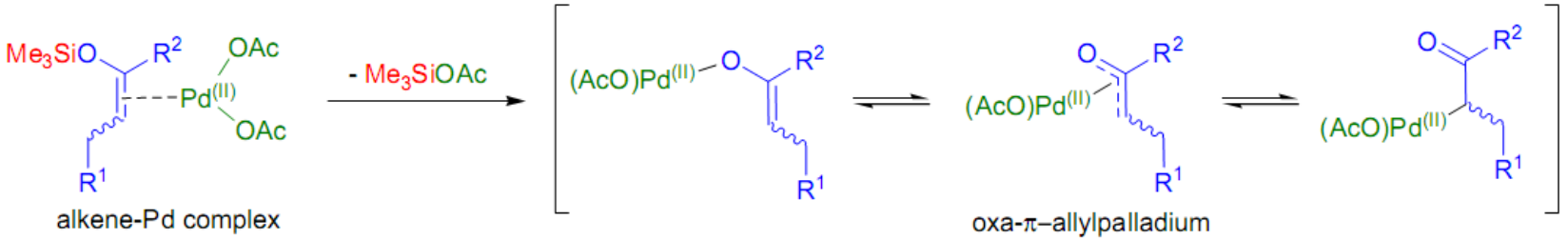


Allyl enol carbonate modification:

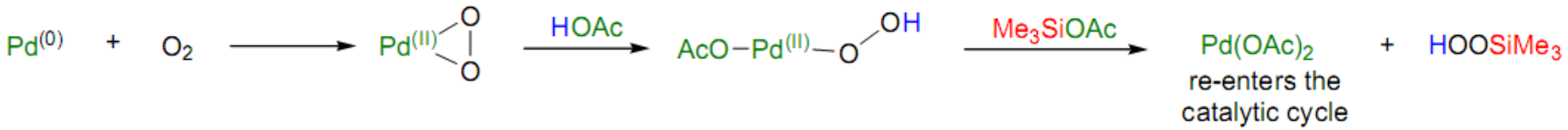


R^{1-2} = H, alkyl, aryl; SiR_3 = TMS, TBDMS; n = 1-7

When substoichiometric/stoichiometric amounts of $Pd(OAc)_2$ is used:



When the oxidation takes place under an oxygen atmosphere with catalytic amounts of $Pd(OAc)_2$:



PERKIN REACTION