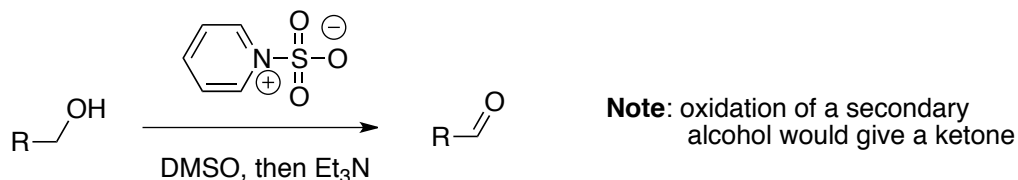


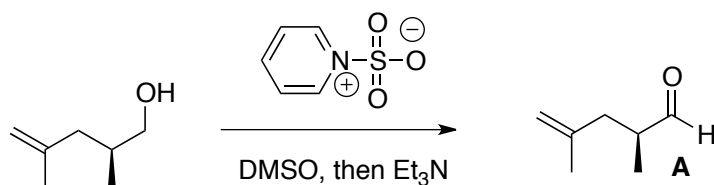
CHEM 330

Topics Discussed on Nov. 20

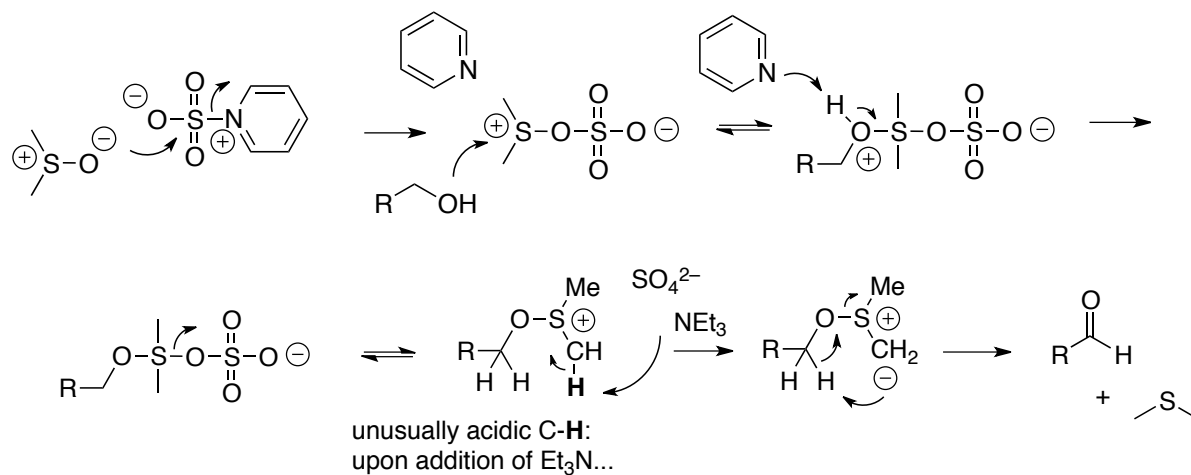
The Perekh-Doering oxidation: oxidation of primary alcohols to aldehydes and of secondary alcohols to ketones by reaction with DMSO and pyridine-SO₃ complex, followed by Et₃N



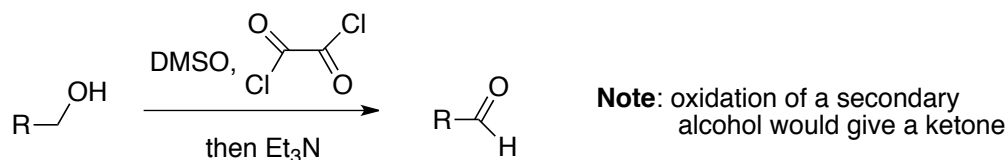
Successful Perekh-Doering oxidation of the alcohol to the aldehyde without erosion of stereochemical integrity:



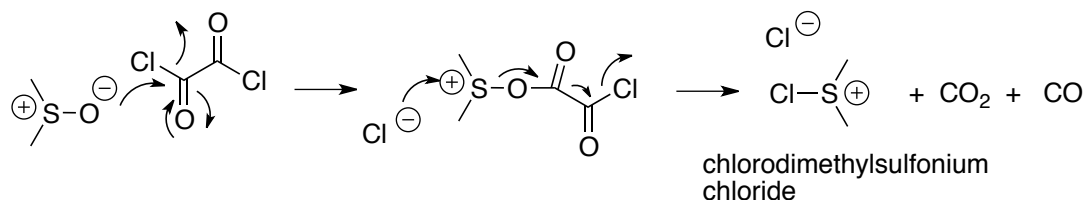
Presumed mechanism of the activation of DMSO with the pyridine-sulfur trioxide complex during the Perekh-Doering reaction:



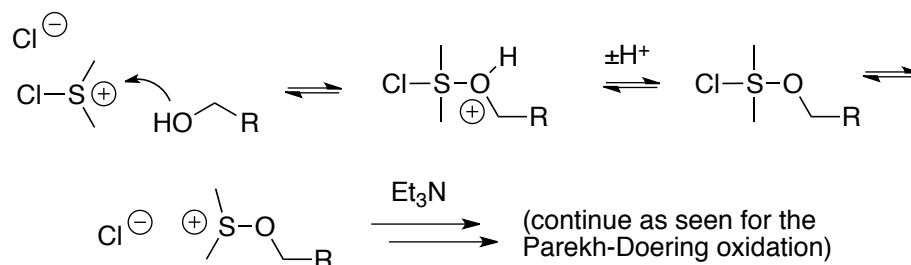
The Swern oxidation: a more recent, widely used oxidation method that involves the activation of DMSO with oxalyl chloride (Cl-CO-CO-Cl):



Presumed mechanism of the Swern oxidation:



Then:

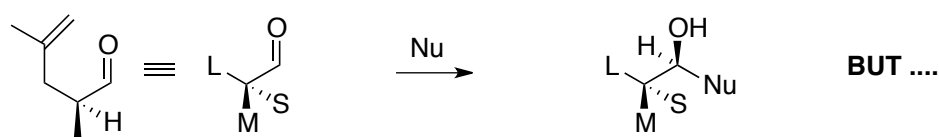


Stereochemical aspects of the aldol step in the synthesis of the Prelog-Djerassi lactone: in the reaction of a chiral substrate with a chiral reagent ("double distereoselection"), the stereochemical preferences of one may reinforce ("match") or oppose ("mismatch") those of the other.

- matched substrate-reagent pairs tend to react with high stereoselectivity;
- mismatched substrate-reagent pairs tend to react with poor stereoselectivity

Mismatch in the above aldol reaction

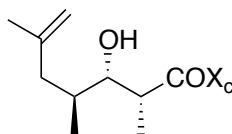
the Cram-Felkin model predicts *Si*-face reactivity for aldehyde **A**. However, the aldol reaction must proceed through *Re*-face addition.



the chirality of the α -center induces *Si* face reactivity

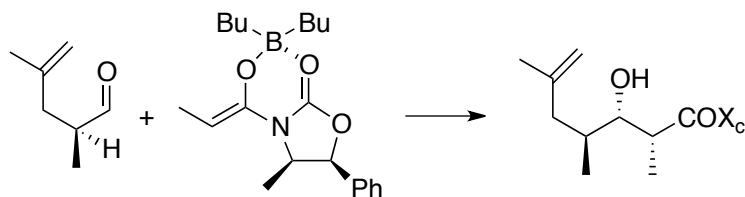
The configuration of the OH-bearing carbon in the major product of a nucleophilic C=O addition would result from *Si*-face attack

... **BUT:**



is the product of *Re* face attack. The Evans enolate causes the aldehyde to react "unnaturally" i.e. from the *less reactive* face. In other words, the aldehyde wants to react from the *Si* face, but the enolate forces it to react from the *Re* face → **mismatch**

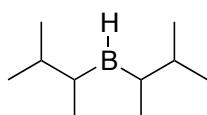
Hopefully, a norephedrin-derived Evans boron enolate such as the one shown below will be able to circumvent the innate stereochemical preferences of the aldehyde:



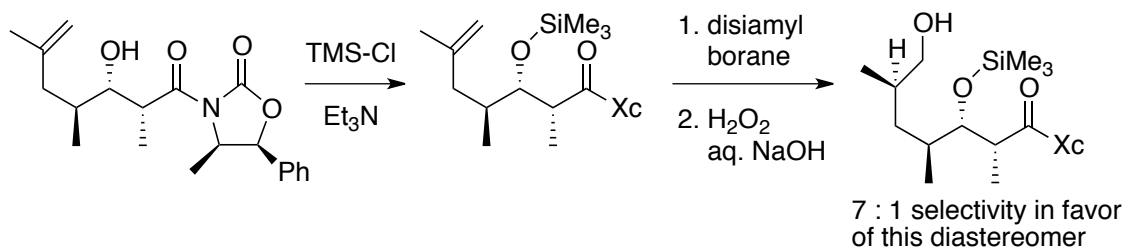
Extremely high level of diastereoselectivity in the reaction above (400 parts of desired product to 1 part of a mixture of 3 other stereoisomers!)

Ability of Evans enolates to circumvent innate stereochemical properties of aldehydes possessing an α -stereogenic carbon as one of the reasons for their success

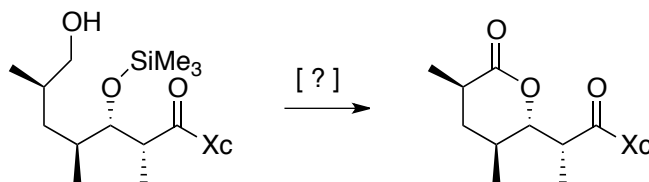
Disiamyl borane (structure below): a hindered hydroboration agent that effects highly diastereoselective hydroboration reactions.



Stereoselective hydroboration of the above aldol product after protection of the OH group as a TMS ether:



Synthesis of the Prelog-Djerassi lactone: the final oxidation



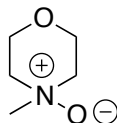
Greater nucleophilicity of primary alcohols (less sterically hindered) relative to secondary alcohols

Principle: the greater nucleophilicity of primary vs. secondary alcohols permits the selective oxidation of primary alcohols in the presence of secondary alcohols by the use of appropriate reagents

Perruthenate ion, RuO_4^- : the Ru(VII) analog of permanganate ion (MnO_4^-)

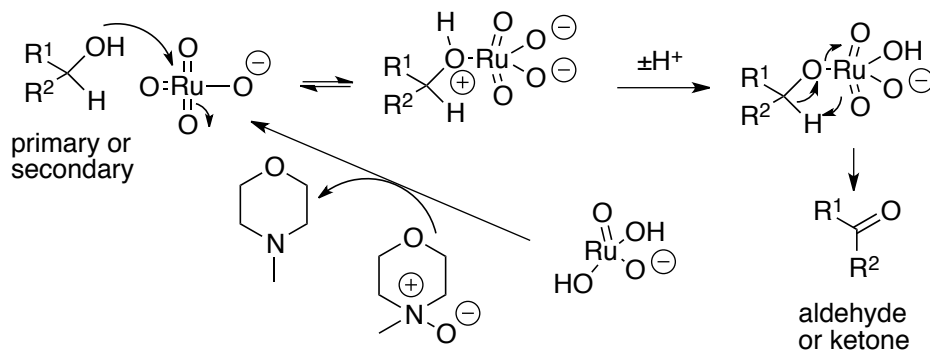
Formation of perruthenate ion by the action of appropriate oxidants upon compounds containing Ru in lower oxidation states; e.g. $(\text{Ph}_3\text{P})_2\text{RuCl}_2$

N-methylmorpholine-N-oxide (NMO, structure below) as a common oxidant:



The Sharpless perruthenate oxidation: reaction of primary and secondary alcohols with $(\text{Ph}_3\text{P})_2\text{RuCl}_2$ / NMO

Presumed mechanism of perruthenate oxidation of primary and secondary alcohols to the corresponding carbonyl compounds:



Principle: RuO_4^- oxidizes primary alcohols to aldehydes faster than it oxidizes secondary alcohols to ketones.

Completion of the synthesis of the PDL

