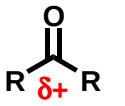
Umpolung Synthesis

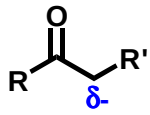
-see Furhop, J.-H.; Li, G. *Organic Synthesis-Concepts and Methods*, Wiley-VCH, 2003.

Organic molecules have innate reactivity patterns imposed upon them by virtue of the functional groups within their structures. This was taken advantage of extensively in the 331 course; for example:

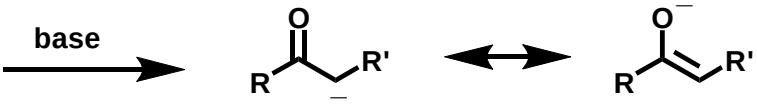


due to the electronegativity difference between O and C

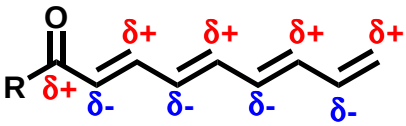
and



due to

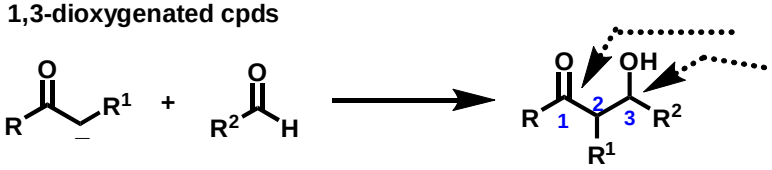


In fact, this pattern of alternating reactivity can continue infinitely as long as the conjugated multiple bonds continue, as in



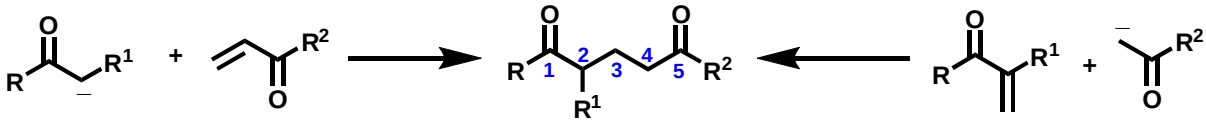
As a result, certain functional group patterns are easy to make, such as 1,3-dioxygenated compounds, or 1,5-dioxygenated compounds. The same could be said for nitrogen containing compounds, but we will focus on the former.

1,3-dioxygenated cpds



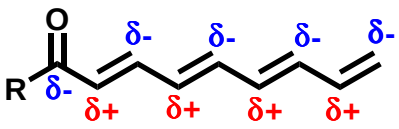
can manipulate oxidation states by oxidation/reduction reactions

1,5-dixogenated cpds



So, the question then becomes, how does one go about making 1,2-dioxygenated and 1,4-dioxygenated compounds?

What is required is some way of inverting reactivity of carbonyl or carbonyl-like compounds. This 'inverted' reactivity is called Umpolung reactivity (or Umpolung synthesis).



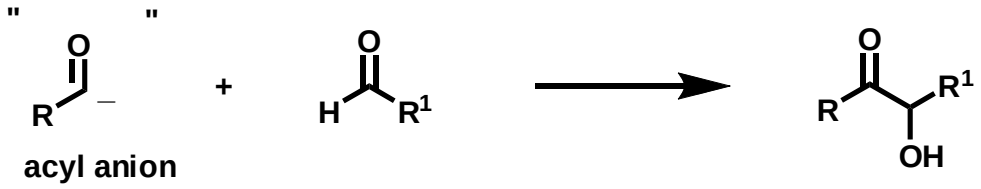
Umpolung reactivity

-For a text, see *Umpoled Synthons*, Hase, T. A., Ed.; Wiley Interscience, 1987.

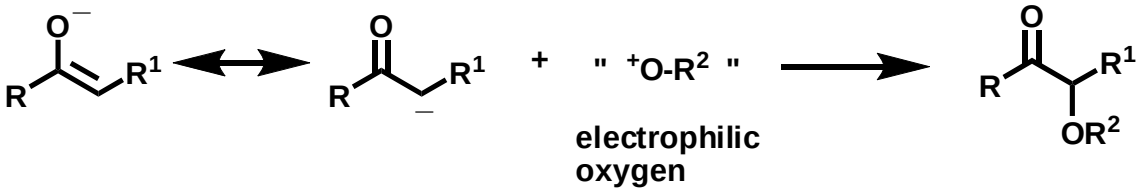
Let's start with 1,2-dioxygenated compounds

1,2-Dioxygenated compounds

Reasoning from first principles, making these compounds with require one of two approaches, either:

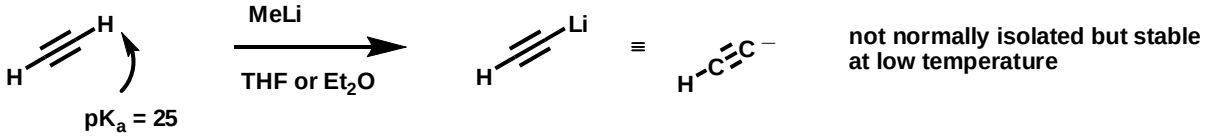


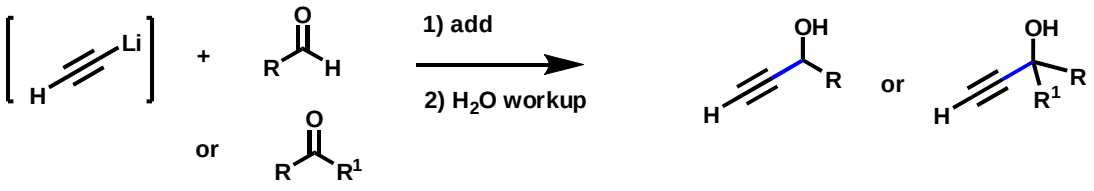
or



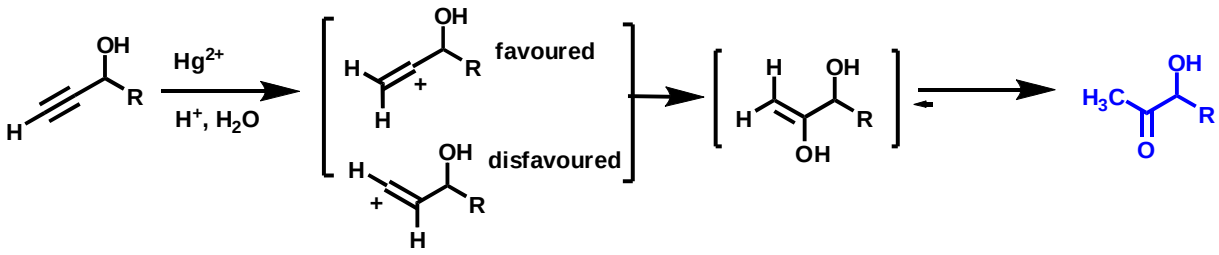
A. We'll start with the 1st approach. What can we possibly do for an acyl anion equivalent?
(see Wyatt, Warren, Ch. 14; Furhop, Ch. 1.7)

1) **Acetylide anions.** Recall that terminal alkynes are relatively acidic, especially for hydrocarbons. This can be used; so…

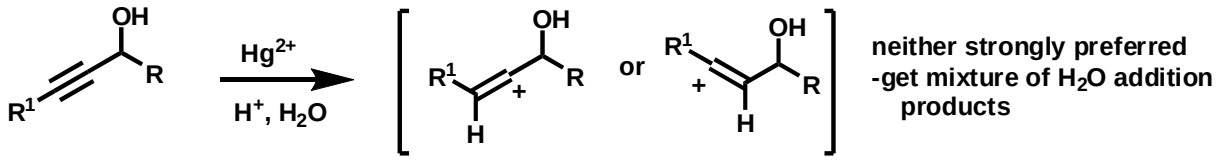




This can be convertable into a 1,2-dioxygenated compound, by an electrophilic addition of water across the triple bond. Recall that this requires an Hg^{2+} salt to make this happen.



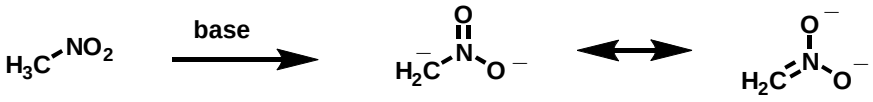
This is somewhat limited, because it is only applicable to the anion of acetylene (ethyne) itself. If there are more substituents on the alkyne, there is a problem with the regiochemistry of H_2o addition to the propargyl alcohol. On the other hand, since acetylene/acetylide is small, this transformation often works with sterically hindered carbonyl partners.



Other Sources of X-$^{-}CH_2$

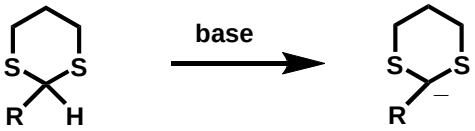
Cyanide ion ^{-}CN commercially available as NaCN, KCN, from H-C≡N $pK_a = 9.2$

Nitroalkanes



pK_a = 10 (H_2O)
17.2 (DMSO - Bordwell pK_a)

Dithianes

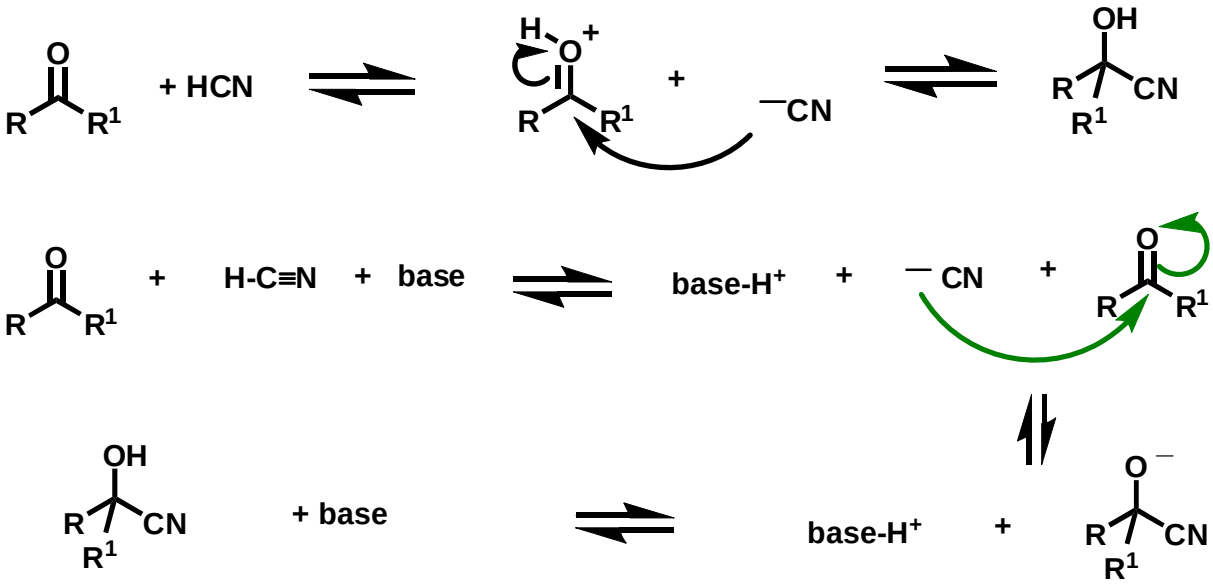


anion stabilized by
-polarizability of weaker C-S bond
-overlap with σ* of C-S (negative hyperconjugation)

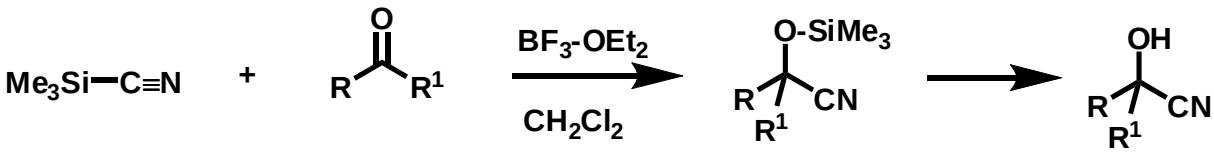
pK_a = 36.5 - 39
pK_a LDA = 41-44 (DMSO), 35.7 (H_2O)

2. Cyanide Ion

Cyanide ion will add to most aldehydes and ketones reversibly to give a cyanohydrin. It is more often base catalyzed, but acid and Lewis acid catalyzed versions are known as well.

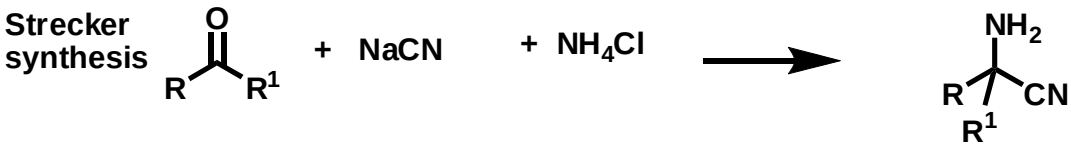


This sometimes has problems with forcing the reaction to the product side, and a competing *benzoin condensation*, so the reaction is usually performed by trimethylsilyl cyanide and a Lewis acid.



Hydrolysis of the nitrile function can now give the α-hydroxy acid. Acidic conditions are usually used because of the competing cyanohydrin reversal under basic conditions.

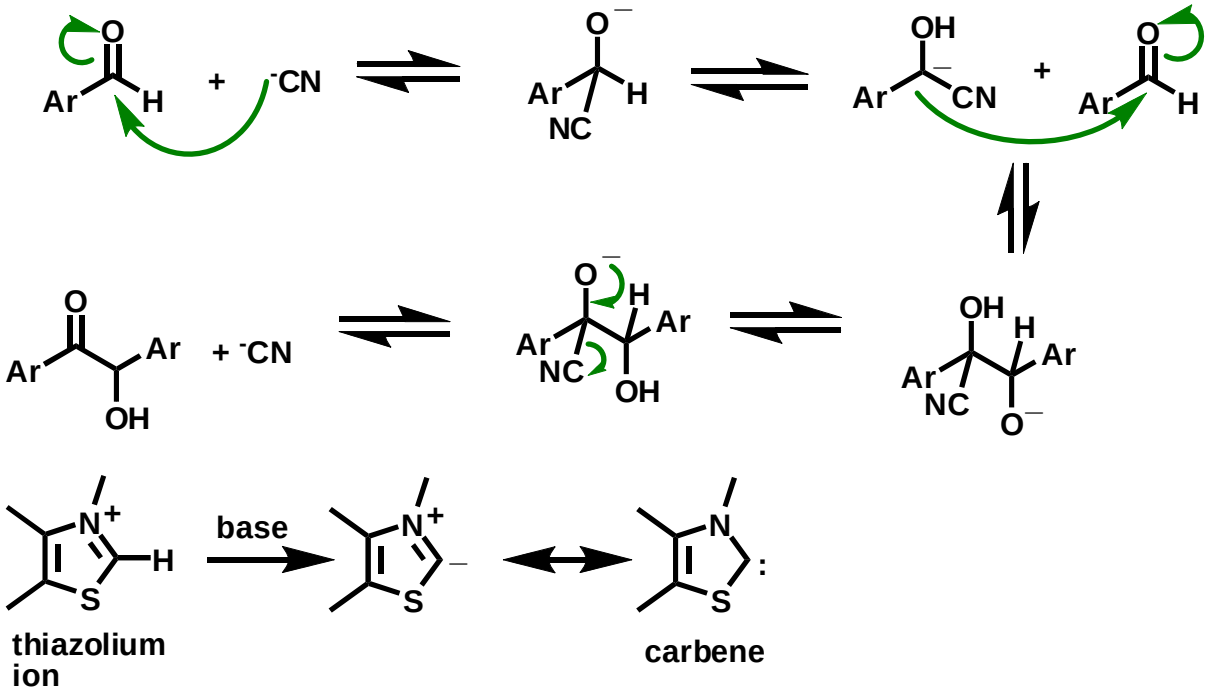
For some related chemistry, see the Strecker amino acid synthesis, and the benzoin condensation.



Note: The benzoin condensation is becoming increasingly important

The benzoin condensation is becoming increasingly important, so it is worth some elaboration. The original version is cyanide ion catalyzed, and involves yet another acyl anion equivalent in the process. The reaction is most often accomplished on aldehydes without acidic α- protons, to avoid aldol type

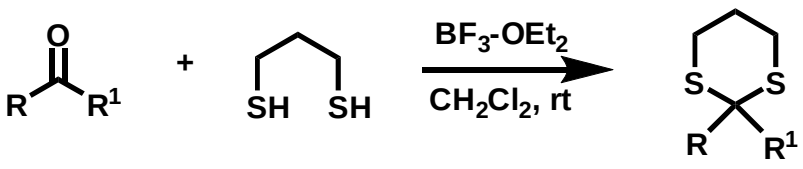
reactions competing; there are exceptions. In addition, it is normally a dimerization of two identical aromatic aldehydes or an intramolecular reaction, so that 'crossed' Benzoin regiochemistry issues are avoided. Finally, practically, cyanide sources largely have been replaced by things like thiazolium ions. Note that the deprotonated thiazolium may be considered as an N-heterocyclic carbene (NHC); it is the NHC that would serve in an analogous manner to cyanide ion.



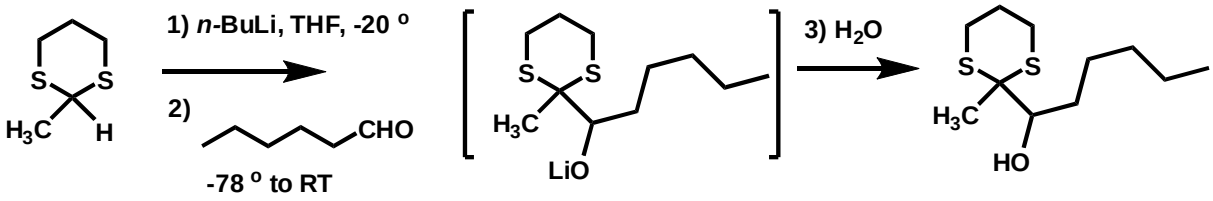
3. Dithianes

See Clayden p 1254 (1st ed), p. 660 (2nd ed)

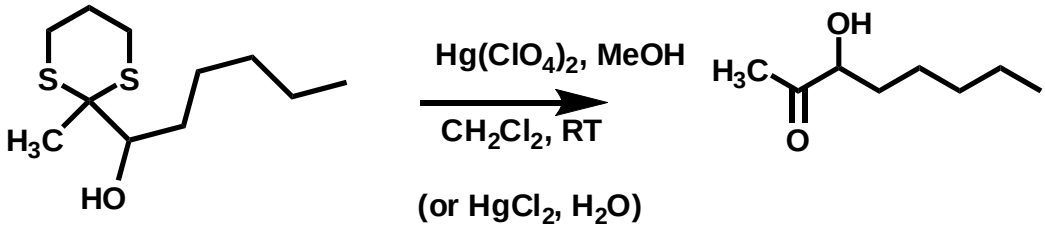
Dithianes are for most purposes simply the sulphur version of acetals. They are made quite similarly, usually using a ketone or aldehyde, a Lewis acid (instead of a protic one), 1,3-propanedithiol, and an appropriate solvent.



These will function as protecting group in for many of the same transformations as conventional acetals, *but* if one of R or R^1 is an H, a strong base (such a *n*-BuLi) will abstract that proton. The resultant anion is highly nucleophilic, and will attack aldehydes and many ketones.



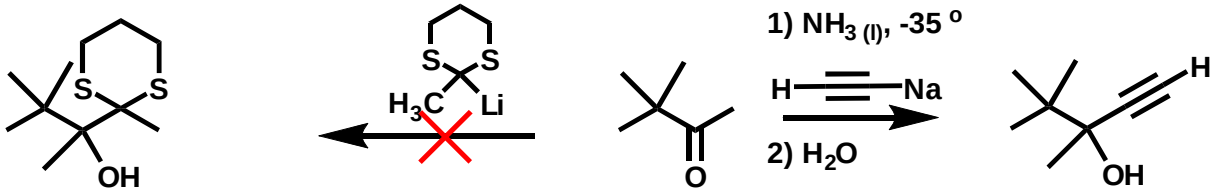
There are several methods of 'hydrolysis ' of dithianes; since S is a 'soft' base, a proton has much less affinity for S thanfor O. As a result, Hg^{2+}, a soft Lewis acid, is excellent where S is concerned.



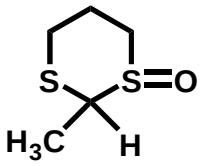
See Comprehensive Organic Synthesis, VI, p. 677; Yus, M. *Tetrahedron* **2003**, *59*, 6147.

For other deprotection conditions, see Wuts, P. G. M. *Protective Groups in Organic Synthesis* (2nd, 4th Ed –my office; 3rd Ed-Dr. Eichhorn)

There is an issue sometimes, that the dithiane anions are more susceptible to steric hindrance than acetylide ions.



Note: There are other version of dithianes which are partially oxidized ones, i.e.,



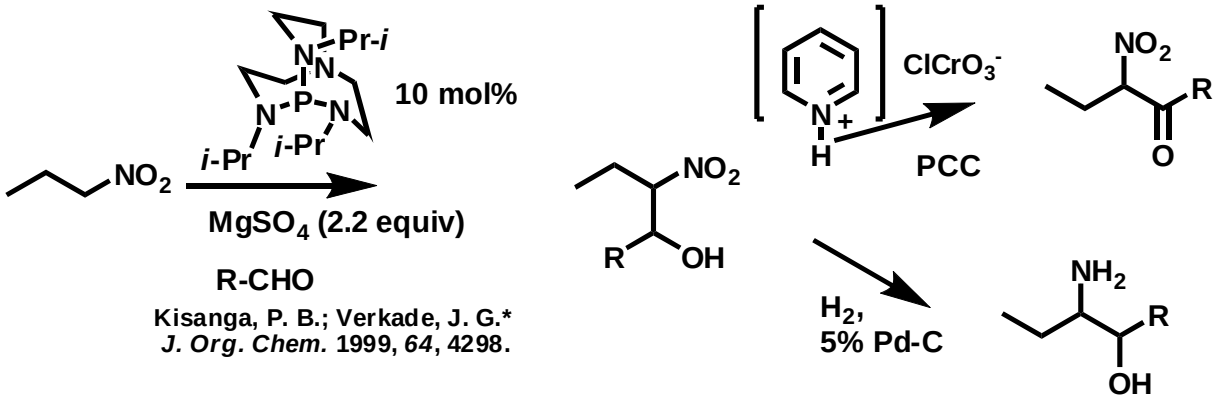
4. And what about **nitro compounds**?

It is possible to get aldol type reactions with nitro compounds and aldehydes or ketones; it is well known as the **Henry** reaction.

-in fact, the nitro group is so electron withdrawing that a dianion nitroalkanes can be made

The problem with the Henry reaction approach, though, is that the 'hydrolysis' of the nitro function to a carbonyl is not successful for these types of compounds. Elimination reactions and 'retro'-Henry

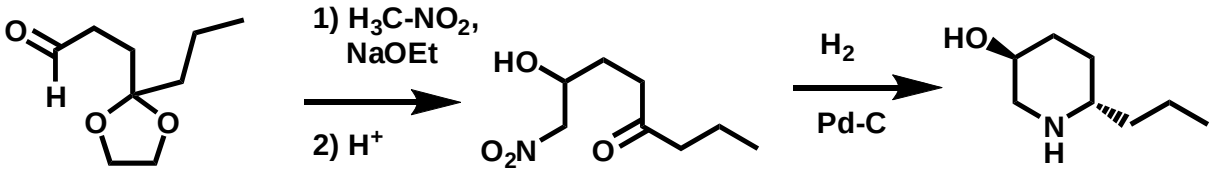
reactions compete. On the other hand, there are other transformations of a nitro compound that do work to give other types of 1,2-difunctionalized compounds.



Kisanga, P. B.; Verkade, J. G.*
J. Org. Chem. 1999, *64*, 4298.

For reviews on the Henry reaction, see; Rosini, G. *Comprehensive Organic Synthesis*, II, Ch. 1.10 (p. 321)
Rosini, G.; Ballini, R. *Synthesis*, **1988**, 833.
Luzzio, F. A. *Tetrahedron*, **2001**, *57*, 915.

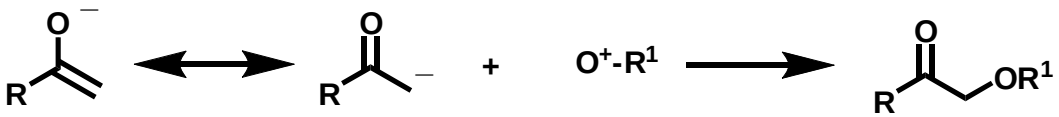
An example of its use in synthesis….



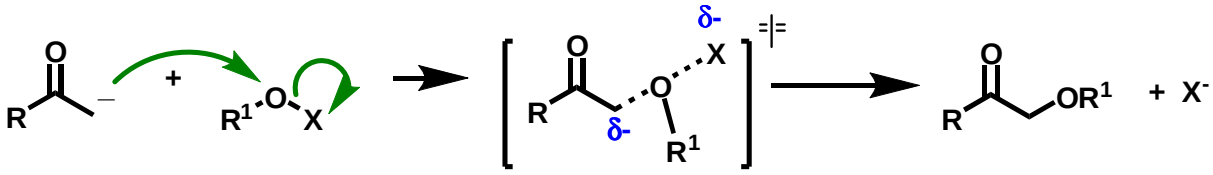
Brown, E. *Tetrahedron* 1973, *29*, 455.

B. Oxygen Electrophiles for Enolates

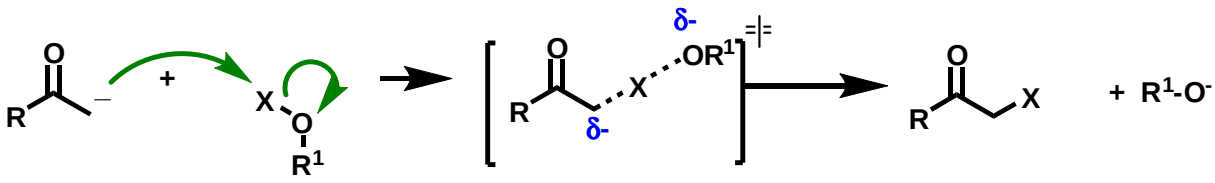
The alternative approach to doing an aldol- type reaction on an acyl anion equivalent, is to react a fairly conventional enolate with some O^+ equivalent. This is obviously very difficult due to the electronegative nature of oxygen, and the representation below is the six valent electron, O^+ species that you've been told is not accessible.



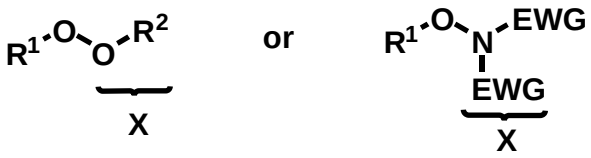
In truth, it's really not *quite* as bad as that, since many reactions of enolates are S_N2, and so we don't really need a truly cationic oxygen. What we really need is for …….



to be better than….



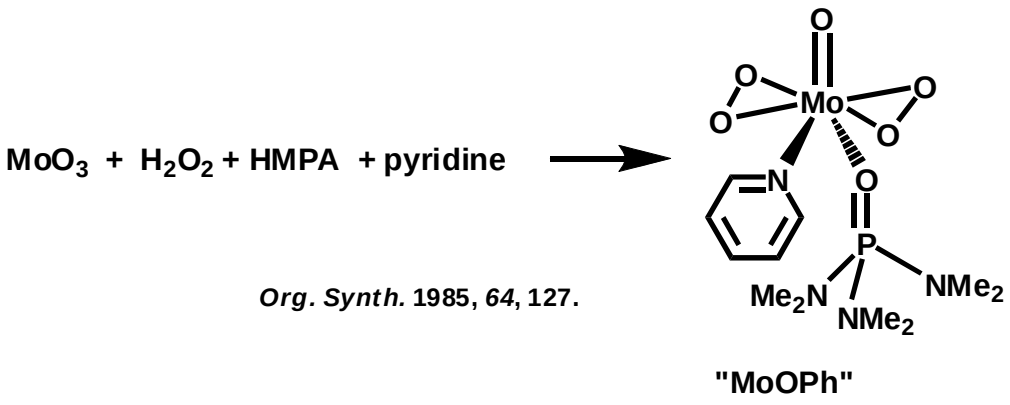
As a result, there is a reasonable chance at being successful with reagents such as..



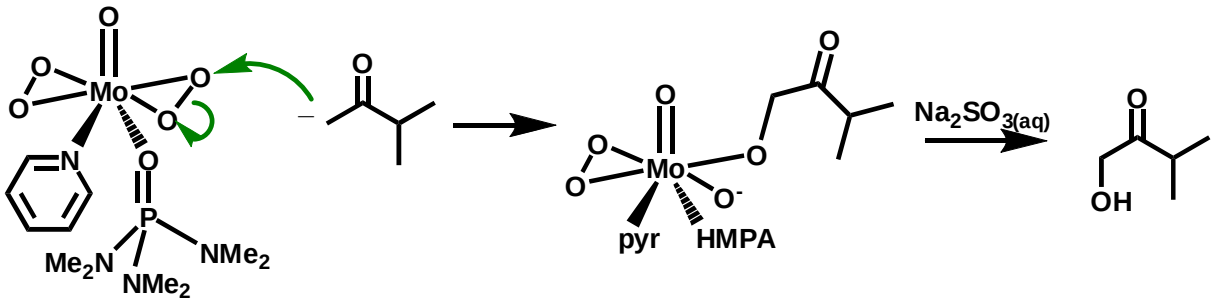
especially using the relief of ring strain to help the reaction.

There are two particularly well known manifestations of this.

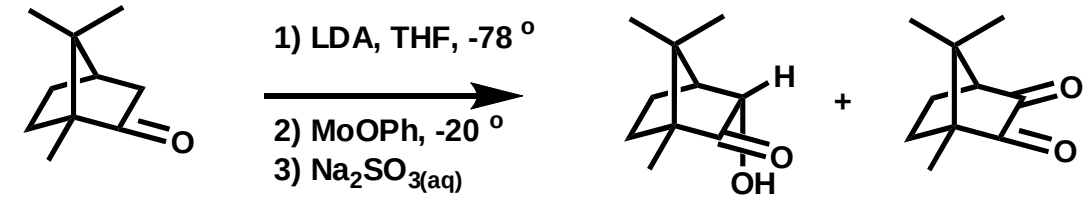
1) **The Vedejs reagent**, known of MoOPh, which is MoO_5-pyr-HMPA.
   It's prepared by oxidation of MoO_3…



It reacts with enolates by attack on one of the oxygen atoms, with opening of the 3 membered ring.



An actual example..



D-(+)-camphor

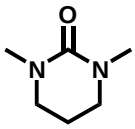
77%

Advantages - This works well with enolates derived from.. Ketones, esters (or lactones), amides, nitriles.

Disadvantages – i) One can get some α-diketone as side- product

ii) It works poorly with unhindered (i.e., methyl derived) enolates

iii) HMPA is a carcinogen – on the other hand, the DMPU adduct (known as MoOPD) is known, and it seems to work reasonably well (Anderson, J. D.; Smith, S. C. *Synlett* **1990**, 107)

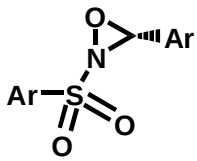


1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
= DMPU

2) **The Davis Oxaziridines**

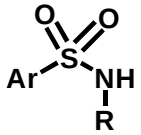
If you substitute a 3 membered ring with an oxygen and a nitrogen (oxaziridine) with a strong electron withdrawing group on N, the N^- is actually the better leaving group…

oxaziridine

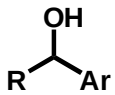


strong electron withdrawing group

pK$_a$'s



pK$_a$ 17 (DMSO)
?? (H$_2$O)

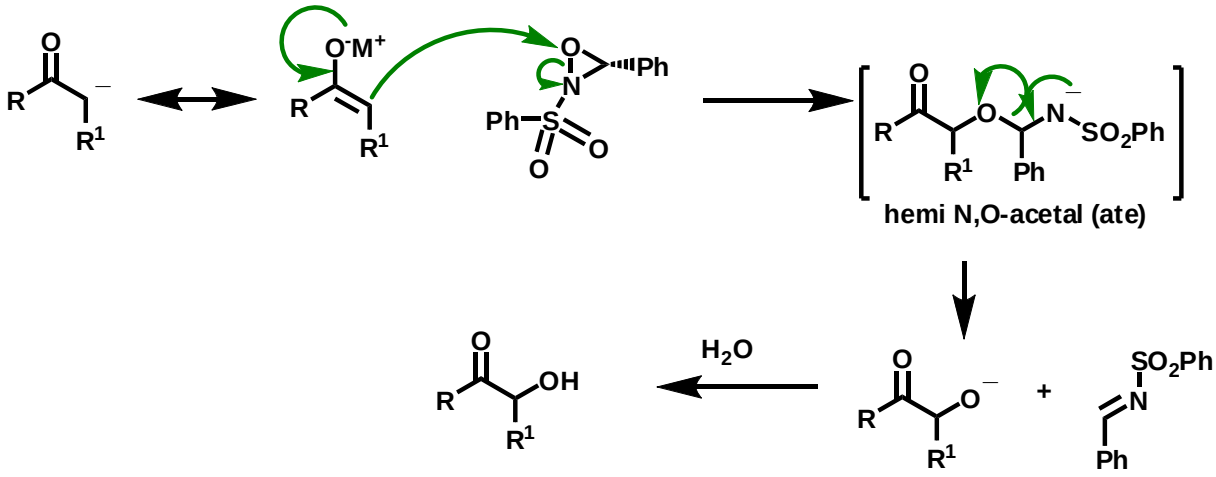


pK$_a$ 29-30 (DMSO)
17 (H$_2$O)

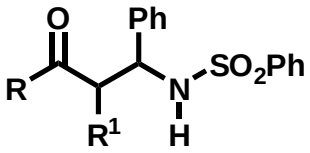
See Davis, F. A.; Shepperd, A. C. *Tetrahedron* **1989**, *45*, 5703 (general)

Davis, F. A.; Chen, B.-C. *Chem. Rev.* **1992**, *92*, 919. (asymmetric)

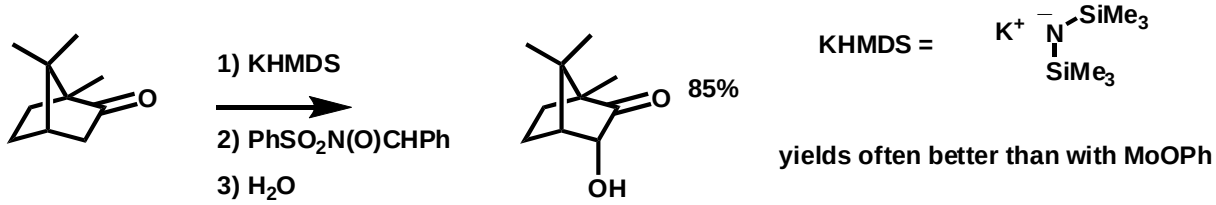
So if an enolate is reacted with an N-sulfonyl oxaziridine…



There is one drawback - if the breakdown of the N,O-acetal ate intermediate is too fast relative to the attack of the enolate on the oxaziridine, you'll get a competing amount of …



This is the major side product for oxygenation of ketone and ester enolates. It is substantial with **lithium** enolates, but much *less* significant with **sodium** or (especially) **potassium** enolates. For amide enolates, which tend to be more reactive, the lithium enolates are normally fine. So….



Aside: There is also an excellent method for α- hydroxyl incorporation using silyl enol ethers, involving an epoxidation. It is sometimes called the Rubottom oxidation. (COS VII, p. 163)