## 1,4-Dioxygenated Compounds

Compounds with a 1,4- relationship between oxygen (or nitrogen) functions are the other major class of difunctional compounds that are almost always made by some form of Umpolung synthesis. Using the same sort of general rationale we used for 1,2-dioxygenated compounds, it is straightforward to come up with at least 3 conceptually possible ways to get access to these systems. They include
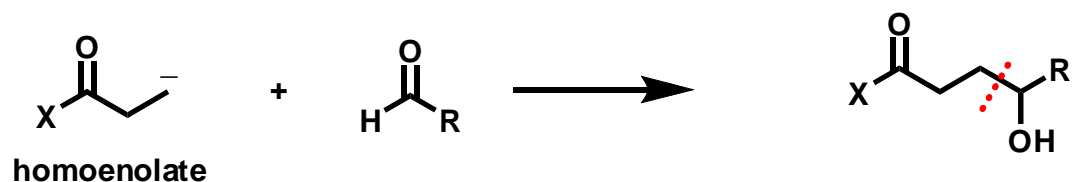
A. Conjugate addition of acyl anion equivalents
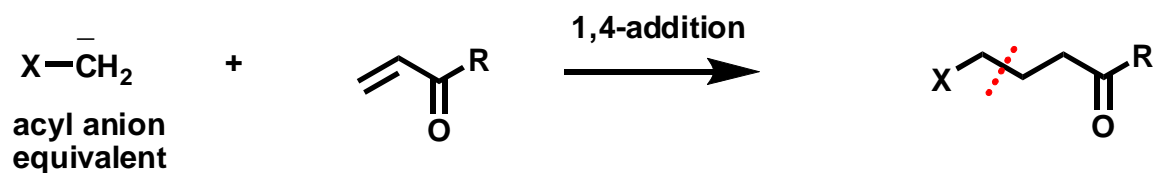
B. Enolate reactions with α- carbonyl cation equivalents
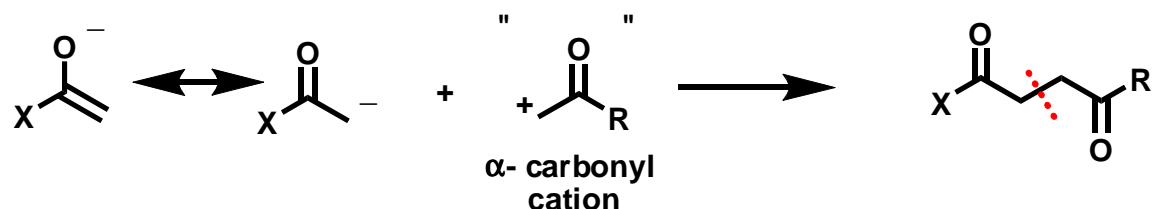

C. Aldol type chemistry of homoenolate equivalents

A. Conjugate Addition of Acyl Anion Equivalents
1. Nitroalkanes revisited

Nitroalkanes are likely the most acidic CH acid sources in organic chemistry. In fact, one nitro function is about as acidifying as *two* carbonyls, so that a nitroalkane is roughly of the same acidity as a β- keto ester.

Extending that analogy to its chemistry, it is not surprising that nitroalkane anions (also called nitronates) react very similarly, preferring 1,4- (conjugate) addition over 1,2- addition when the choice is available.
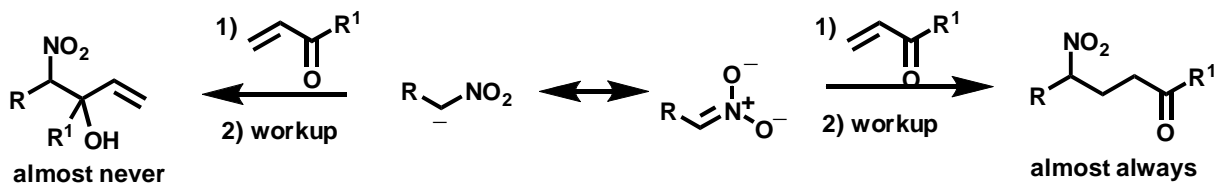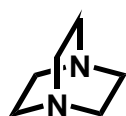
The base for this reaction is usually very weak. Common bases include such things as:
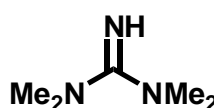
3° amine bases – Et_3N, i-Pr_2NEt, DABCO, tetramethylguanidine

KF on alumina (Al_2O_3)
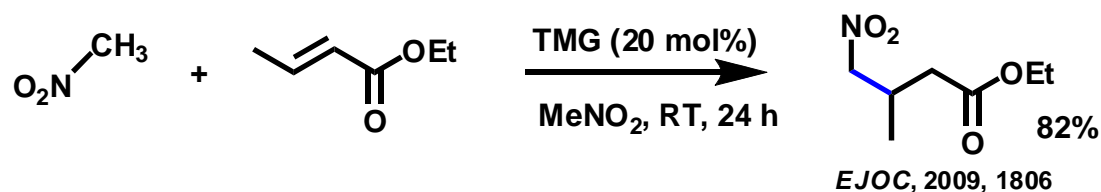
Basic alumina (Al_2O_3)


DABCO   **tetramethylguanidine**

Some examples, just randomly chosen from the literature, include the following. Note how the nitroalkane is always in a substantial excess.

EJOC, **2009**, **1806**

JCS Perkin 1, **1983, 2253**

2. **Nitroalkenes as α- carbonyl cations.** The converse of the reaction, where one uses a nitroalkene as the Michael acceptor, will also work. In this case, the nitroalkene is function as an α- carbonyl cation.
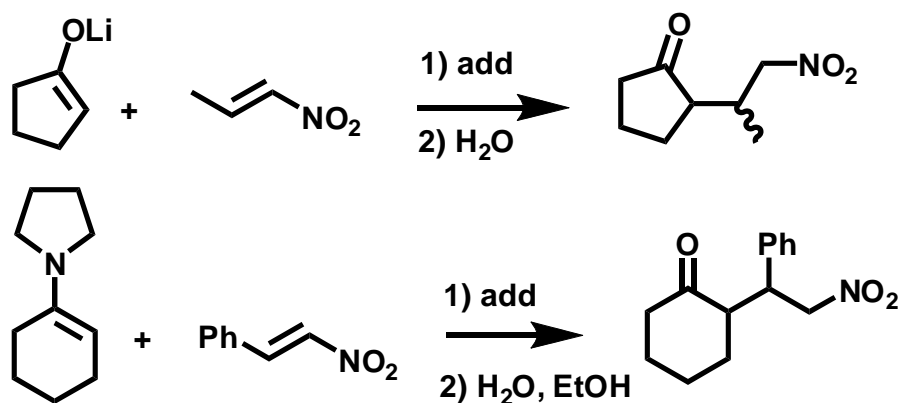
In addition, there are Lewis acid version of both types of the reactions know, but especially using nitroalkene substrates (see: Yoshikosi, A.; Miyashita, M. *Acc. Chem. Res. 1985, 18,* 284*).*
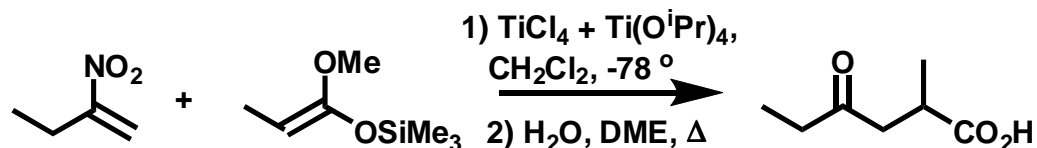
So the question at this point is how is the nitroalkane version of a Michael type reaction a 1,4-dioxygenated compound, and what happened in the above case that got that deoxygenated compound.

The key feature of nitroalkanes is that have a tautomerism just like keto-enol tautomerism occurring (although here the other tautomer is called an *aci*-nitro or isonitro compound), and that tautomer is imine like. In other words, the C=N double bond of that tautomer can be hydrolyzed under acidic conditions. This is called the **Nef reaction**.
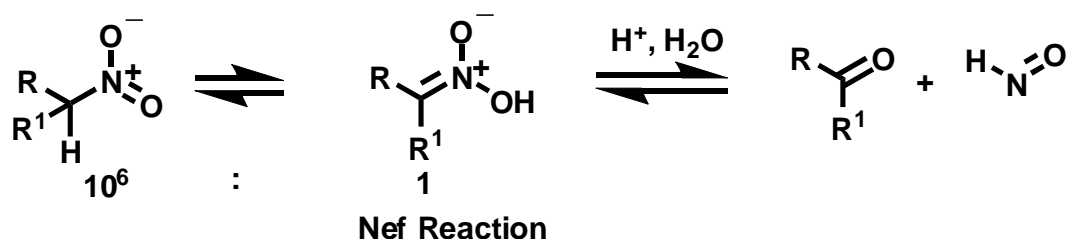

Nef Reaction

Usually the Nef reaction isn't performed simply with aqueous acid, such as the one above, as there are many modifications including one under both oxidizing conditions and under reducing conditions. For a review on these, I suggest ..

Ballini, R.; Petrini, M. *Tetrahedron* **2004**, *60*, 1017; Pinnick, H. W. *Org. React.* **1990**, *38*, 655.

The most common conditions are reducing ones, either TiCl$_3$ in H$_2$O (pH < 1, acidic), or TiCl$_3$ + NaOAc (or NH$_4$OAc) in H$_2$o (pH 5-6, *almosti* neutral). The latter set of near neutral conditions is so that acid sensitive functional groups, such as acetals, survive the process. It's a bit of a guess, a reasonable mechanistic proposal for the Ti^{III} mediated Nef involves reduction of the *aci*-nitro tautomer to an oxime.
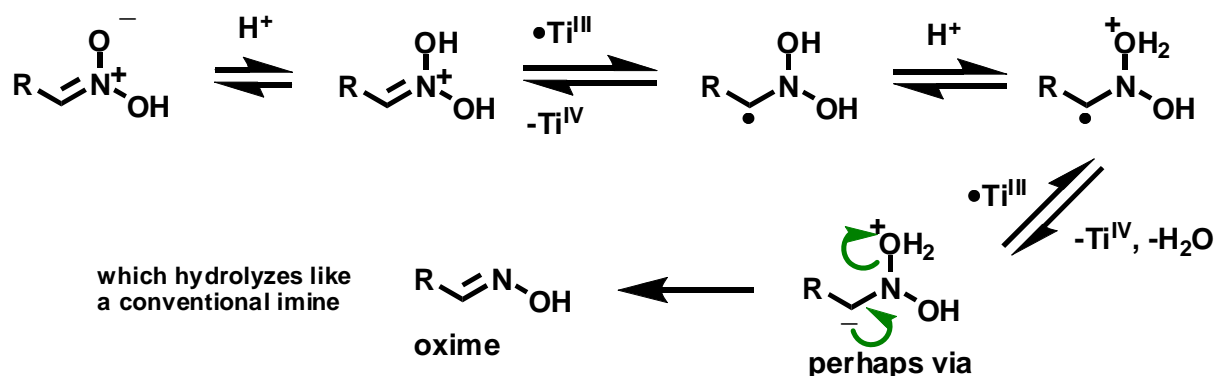
Some of oxidizing reagents, which won't be discussed further, include dimethyldioxirane (DMD) and KMnO$_4$; these are usually employed under basic conditions. The Ballini/Petrini review has an extensive discussion of reagents.

JOC **1973, 26, 4367**
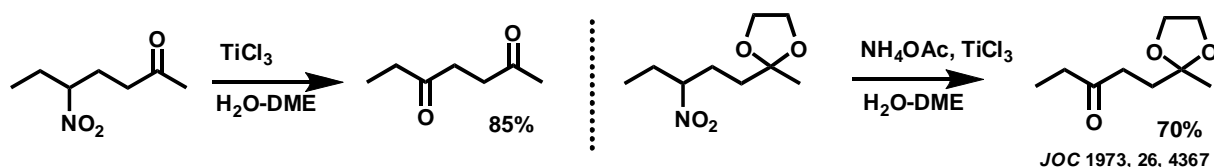
Nitroalkenes are certainly the most common α- carbonyl cation equivalents used for the purpose of 1,4-dioxygenated compound synthesis. There are others, such as ketene dithioacetals, especially as their monoxides. Compounds such as these undergo attack on the alkene by ester or ketone enolates, enamines, lithio- imines, and the anions derived from β-dicarbonyls. An example follows:
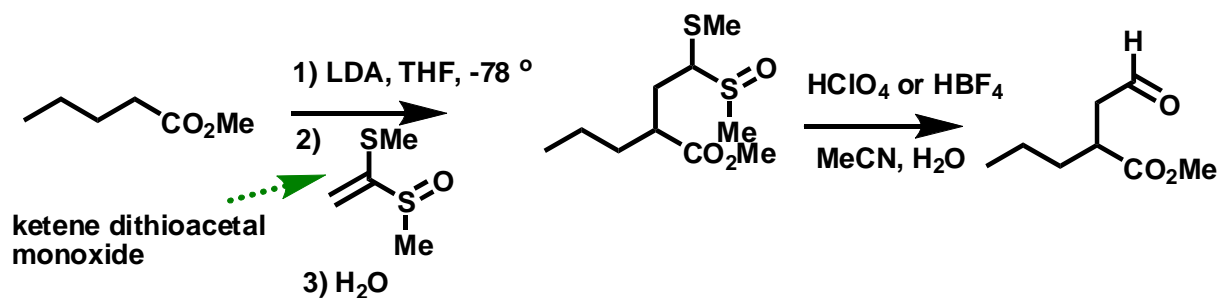

A drawback to these α- carbonyl cation equivalents is the rather involved preparation of the ketene dithioacetal monoxide.

3. Homoenolates (β-Enolates)

In homoenolate chemistry (we'll deal exclusively with the formally anionic site β- to the carbonyl, so β-enolate will be an interchangeable term), there are two significant problems. They are:
  i)   There is no reason for the β- site to be acidified significantly
  ii)   If one actually manages to make one of these, they probably won't survive because...
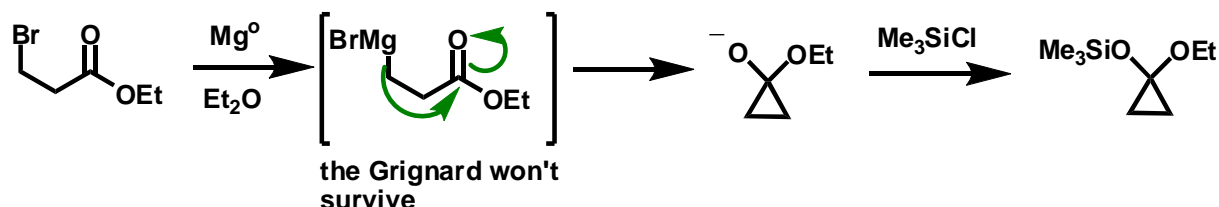

The siloxycyclopropane is drawn at the end because that actually turns out to be useful; in reality it's made using Na° metal rather than Mg°. For the moment however, let's address the initial problem about what can be done to stop this. Reasonable tactics include:
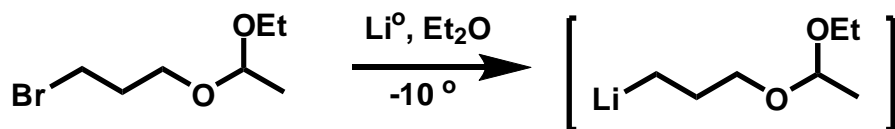
  i)   Protect the carbonyl, if it's easily done. The corresponding aldehyde is well known for this.
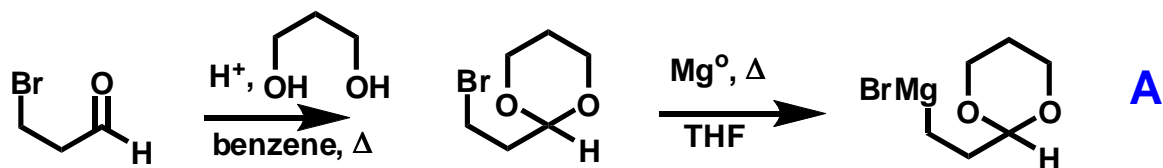
Grignard reagent **A** is surprisingly not very nucleophilic, but reacts well with acid chlorides in the presence of Cu^{+1} salts.
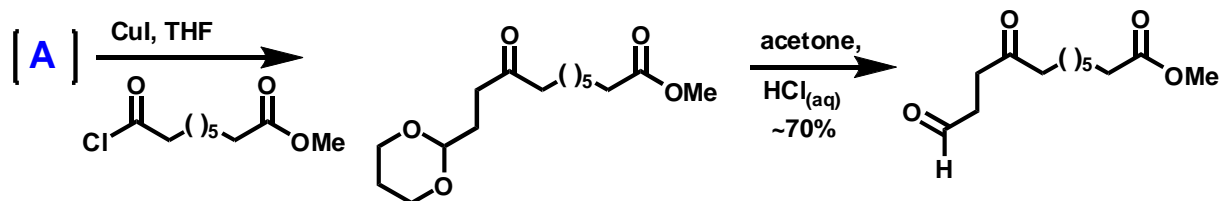

For aldehyde and ketone electrophiles, the ethoxyethyl protected alcohol derivative seems to work better (see Stowell, J. C.*Chem Rev*. **1984**, *84*, 409*.)*


ii)   **Siloxycyclopropanes as masked homoenolates**

(see Kuwajima, I. Nakamura, E. *Comprehensive Organic Synthesis*, Vol. 2, Ch. 1.14.)

The siloxycyclopropanes are stable in the absence of water and can be stored, and in the presence of Lewis acids (especially Ti^{IV} and Zn^{II} ones) are actually in equilibrium with their homoenolate counterparts, i.e.,
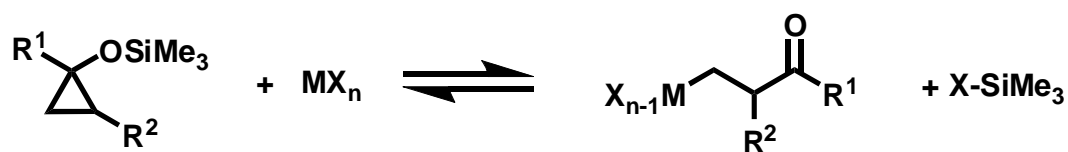

The most common example is with siloxycyclopropanes derived from esters, and $TiCl_4$, which is stabilized by coordination of the carbonyl oxygen to titanium...
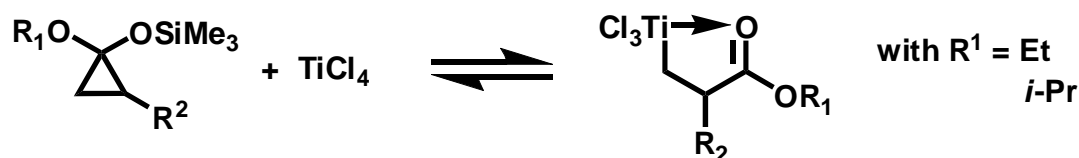

These are not highly, highly nucleophilic species, so that you couldn't alkylate an alkyl halide with these, but due to the strongly Lewis acidity of Ti^{IV} and at least moderate nucleophilicity, these will attack

aldehydes at 0 °C. While a clear rationale is lacking, the attacking ketones can be done, but usually only if ½ an equivalent of Ti(OPr-i)$_4$ is added.

67% for
R^2 = H, R^1 = i-Pr
(85:15 syn:$anti$)

1/2 equiv
Ti(OPr-i)$_4$

+ 1/2 Ti(OPr-i)$_2$Cl$_2$
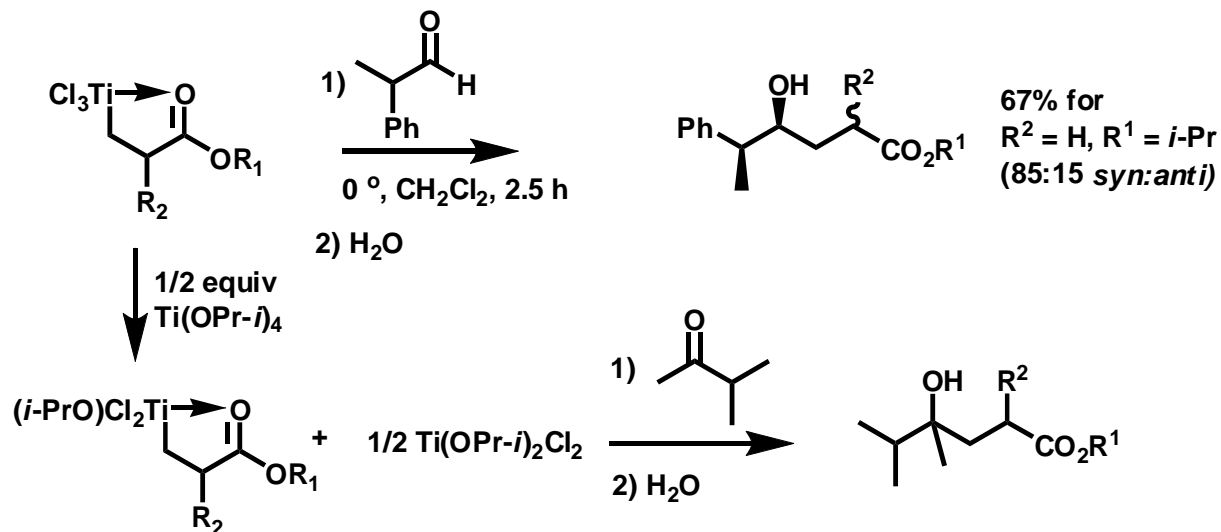
That's about it for the range of nucleophiles with Ti. Many other metals/Lewis acids can be used to make the analogous homoenolates, but the other really useful one is with Zn^{II}, as mentioned before.

+ 1/2 ZnCl$_2$ ⇌
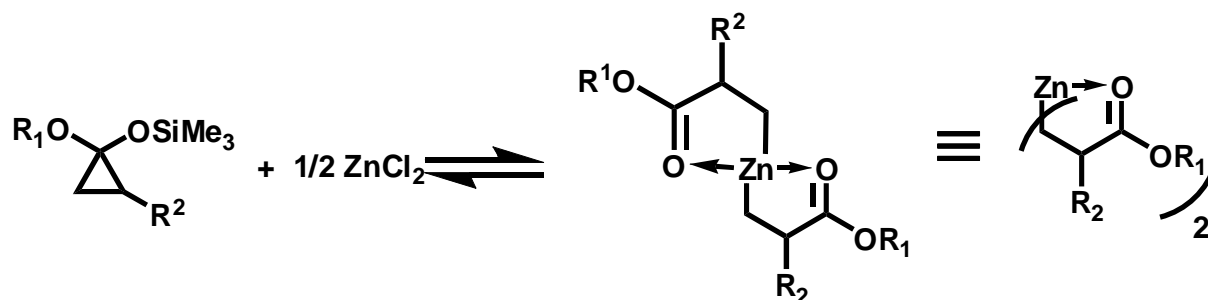
These reagents are a bit more flexibile than their titanium counterparts, and can be used for a few different types of reactions, including:

i)   Conjugate (1,4-)(Michael type) addition reactions with an added Cu^{I} source such as CuBr•SMe$_2$
ii)   React with acid chlorides, in an acylation reaction, in the presence of a catalyst such as PdCl$_2$
iii) Undergo a cross coupling reaction (see later, this is called a Negishi cross coupling) with aryl or vinyl halide or triflates in the presence of a palladium catalyst

(Ph$_3$P)$_2$PdCl$_{2(cat)}$

Et$_2$O
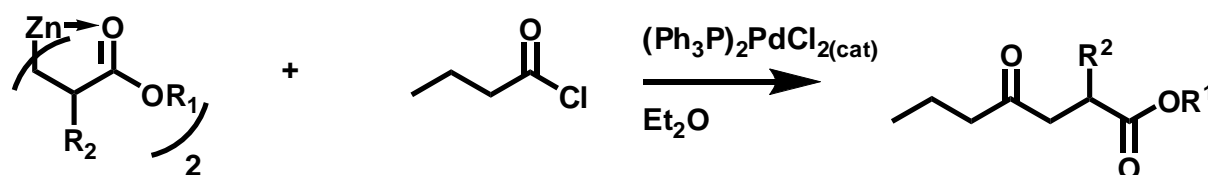
4. Buy Them

Finally, it is worth keeping in mind that several 1,4-dioxygenated compounds, or disguised versions, a readily available commercially. Some examples are:

ethyl levulinate   **butyne-1,4-diol**   **butene-1,4-diol (mostly Z-)**   **furan**
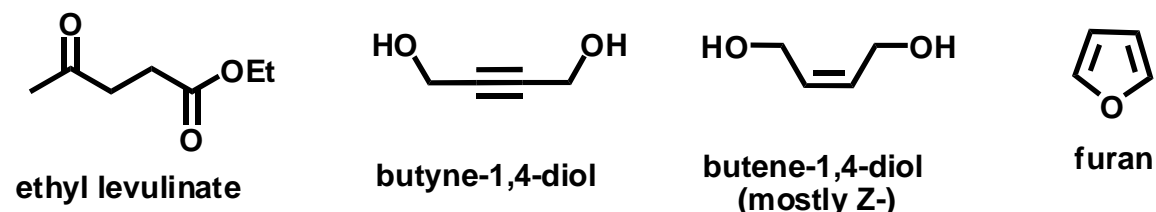
Furan is the curious one, but the important point is that furans hydrolyze in with acid to a 1,4-dicarbonyl.

**furan**   **via a small amount of**
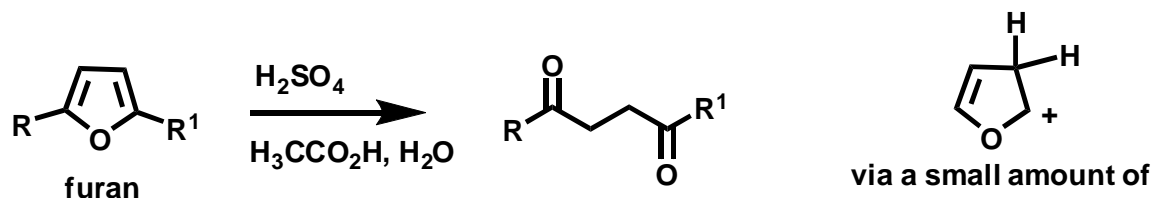
These difunctionalized furans are pretty easy to get access to because almost all the reactivity of furan is at the C2 and C5 positions (next to the oxygen atom)


but often complicated by polymerization

directed lithiation we'll see soon
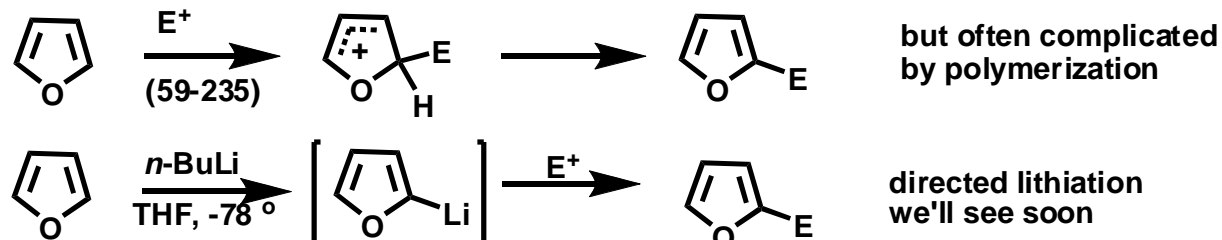
Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979,** *26,* **1.**

Propargyl alcohols are similarly useful, and really give more flexible versions of butyne-1,4-diol; many of them are commercially available.
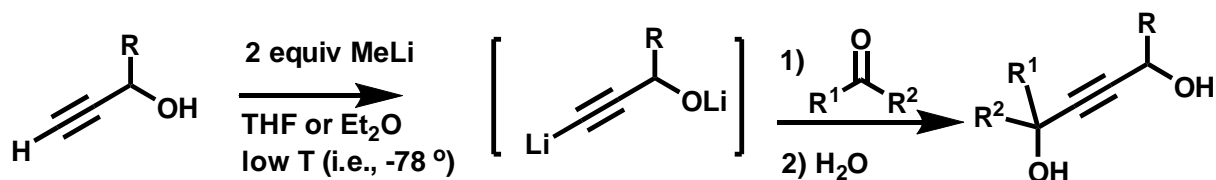

For a simple (and ancient) use of furan chemistry in synthesis, here's an example from Buchi, G.; Wuest, J. *J. Org. Chem.* **1966,** *31,* 977.

cis-jasmone
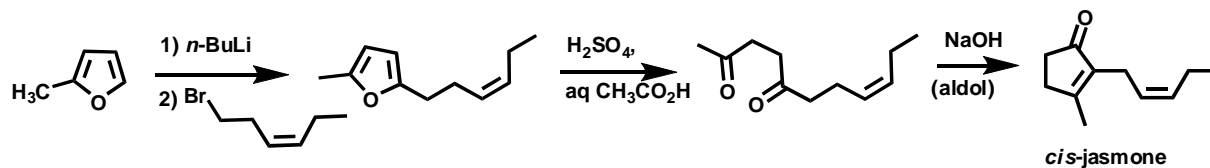
Further comments.

We have been so obsessed with 1,2- and 1,4- deoxygenated systems, that it is easy to forget than these acyl anion equivalents can often be alkylated, to give more sophisticated acyl anion equivalents. Some examples follow.

Hase, p. 50

Hase, p. 23, 27, 29

Hase, p. 51
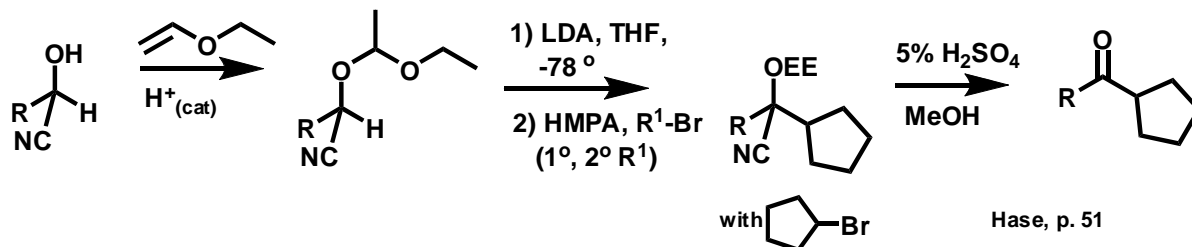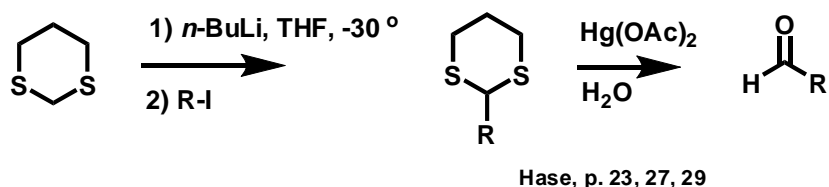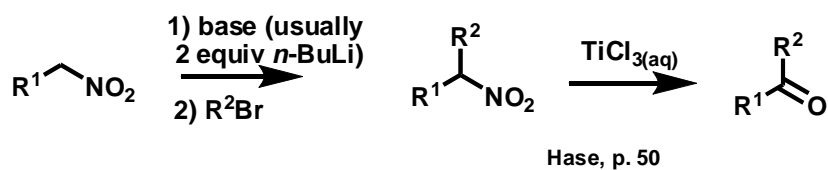
1,6-Dioxygenated Compounds

In principle, these are simply homologated extensions of 1,4-dioxygenated compounds, so we won't cover them explicitly. For an example, though, see Green, J. R. *Synlett* **2012**, *23*, 1271. (warning, *Shameless self-promotion*).