Organic Chemistry-4

Semester-4, CBCS

Course: CEMA CC-4-8-TH

Course taught by: Kaushik Basu, Department of Chemistry, SPCMC, Kolkata

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Recommended texts:

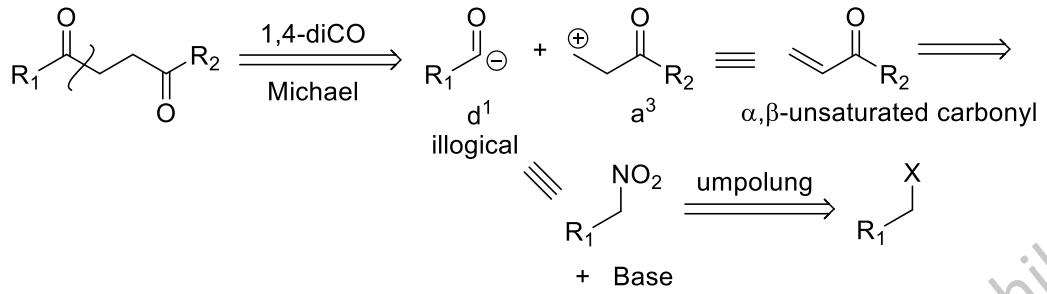
1. Study Guide to Organic Chemistry, Volume 2, by Saha, Chakraborty, Saha & Basu, Techno World, ISBN 9788192669588,
2. Organic Chemistry, Second Ed. by Clayden, Greeves & Warren, OUP, ISBN 9780198728719

The Logic of Organic Synthesis: Analysis of bifunctional target molecules:

C] 1,4-bifunctional compounds:

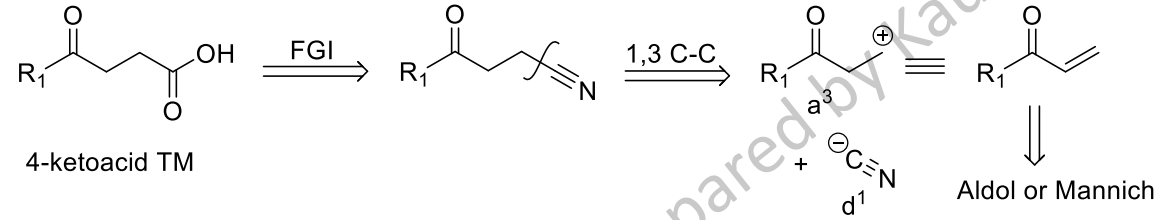
The following is a summary of the retrosynthetic strategies one can commonly adopt when the target molecule contains two heteroatom-based functional groups placed at an 1,4-relation. These target molecules are dissonant systems, so umpolung strategy will be necessary.

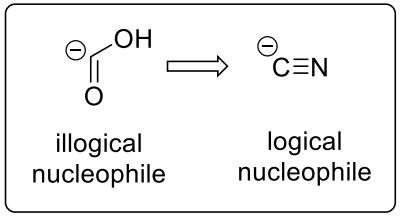
1.



1. Nitroalkane anions are excellent Michael donors
2. Demasking nitro to carbonyl by McMurry reaction, $TiCl_3$, $H_3O^{\oplus}$

2.





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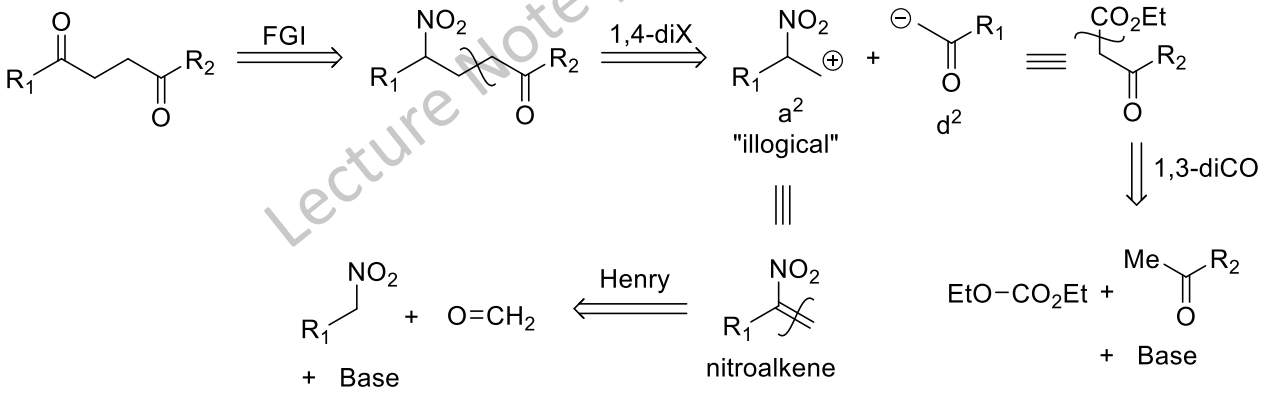

Demasking nitro to carbonyl by McMurry reaction, $TiCl_3$, H_3O

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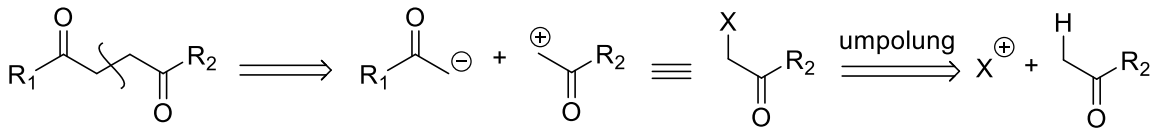
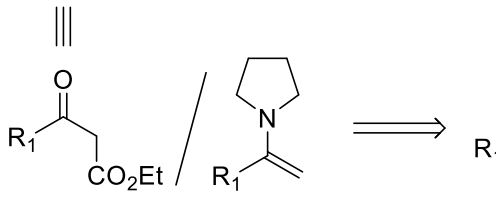


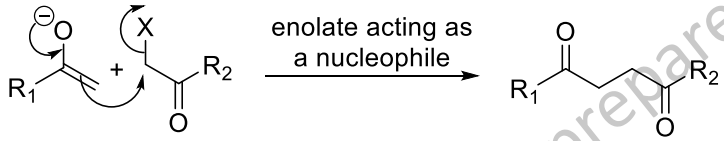
1,4-dicarbonyl d^2 (logical) a^2 (illogical) α-halocarbonyl

halogenation at the α-position may include regioselectivity issue

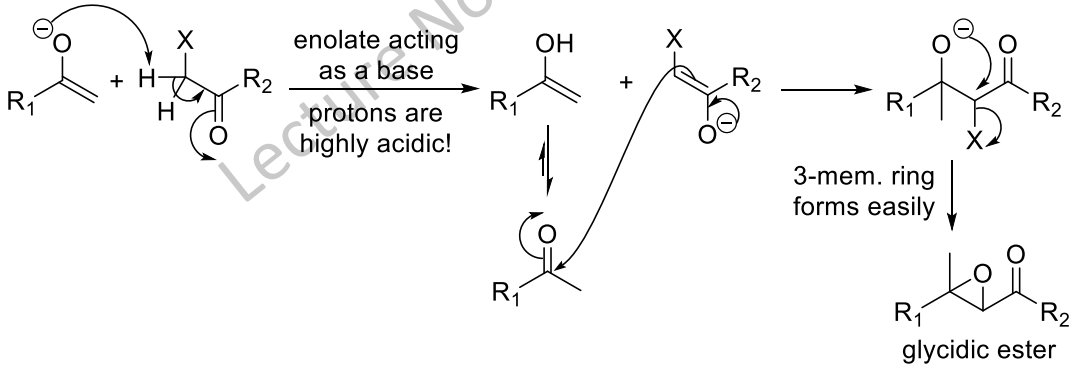


specific enol equivalent is needed for the d^2 synthon otherwise Darzen's reaction would take over...

desired outcome:



possible side reaction:



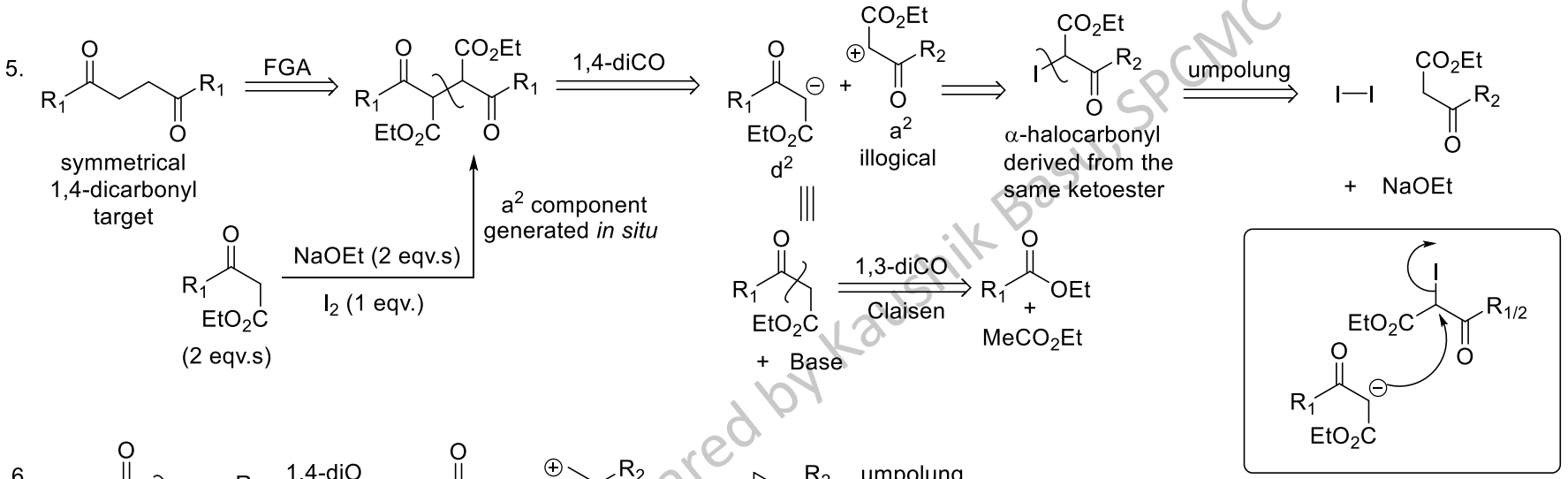
glycidic ester

to minimise this, we must reduce the basicity of the enolate; we need specific enol equivalents

The Logic of Organic Synthesis: Analysis of bifunctional target molecules:

C] 1,4-bifunctional compounds (contd.):

The following is a summary of the retrosynthetic strategies one can commonly adopt when the target molecule contains two heteroatom-based functional groups placed at an 1,4-relation. These target molecules are dissonant systems, so umpolung strategy will be necessary.



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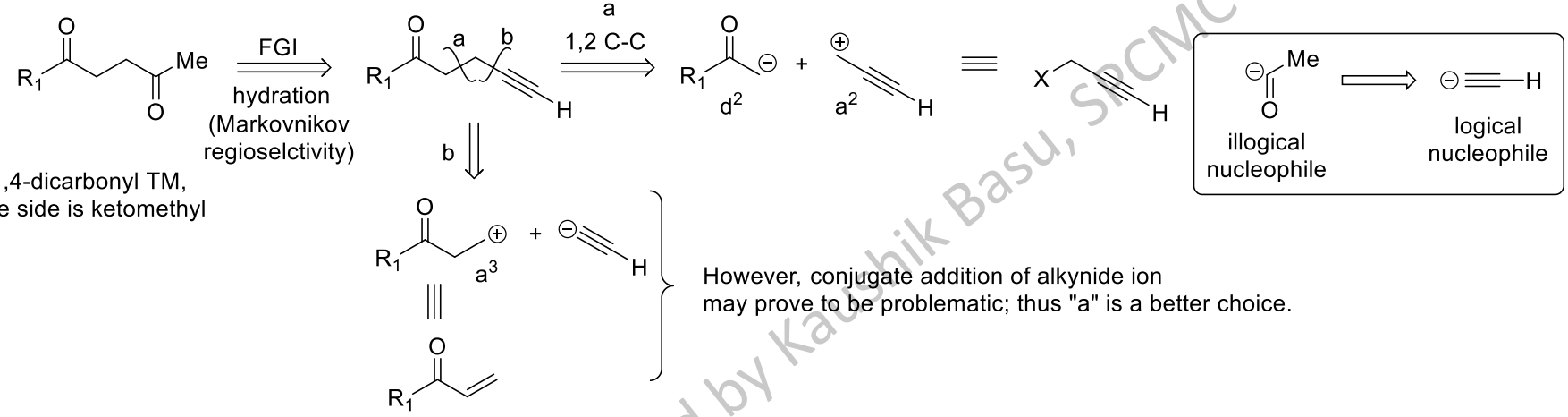

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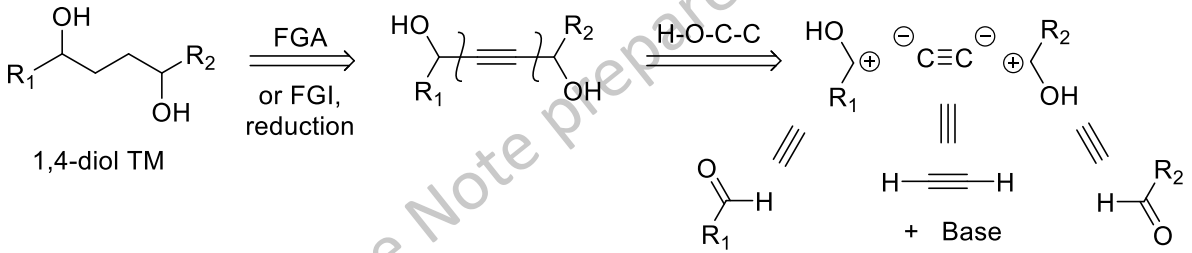
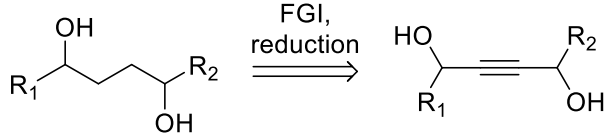


Note:

adding a triple bond - in that sense we can call this transform a functional group addition (FGA)

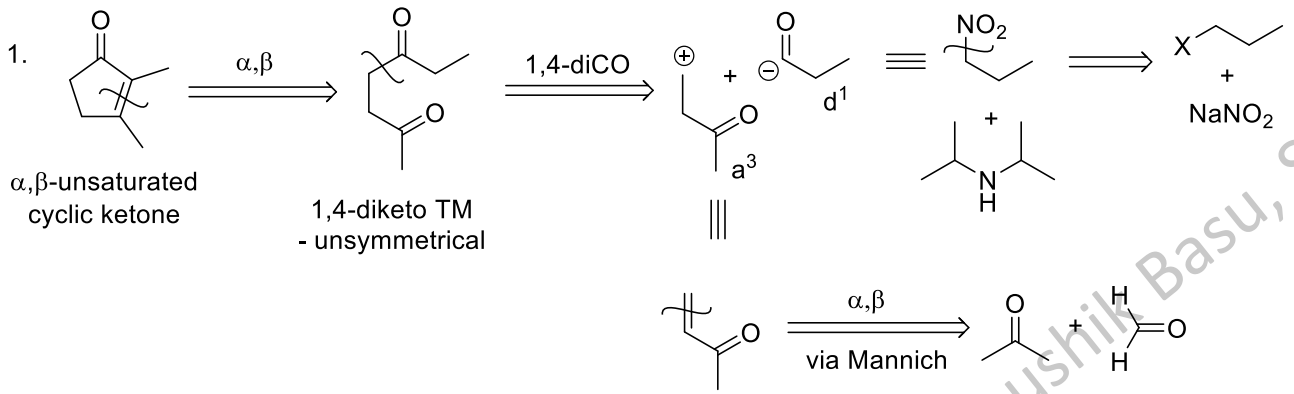


The C-C can be accessed by reducing a triple bond - in that sense we can call this transform a functional group interconcersion (FGI).

The Logic of Organic Synthesis: Analysis of bifunctional target molecules:

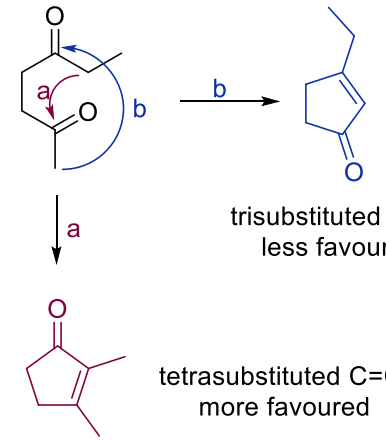
C] 1,4-bifunctional compounds (contd.):

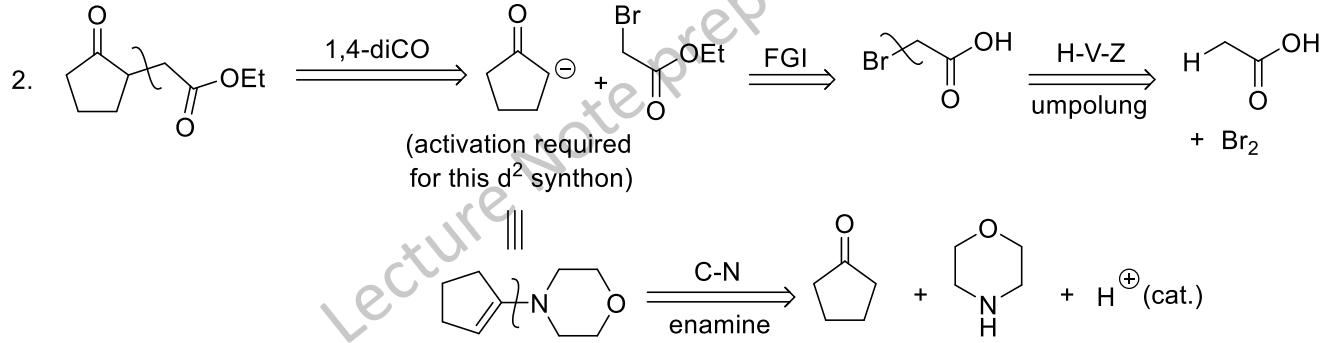
Let us now consider a few examples:



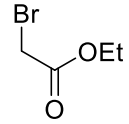
nitroalkane as acyl anion eqv.

condensation regioselectivity guided by formation of the more substituted C=C





enamines react particularly well with S_N2 reactive electrophiles

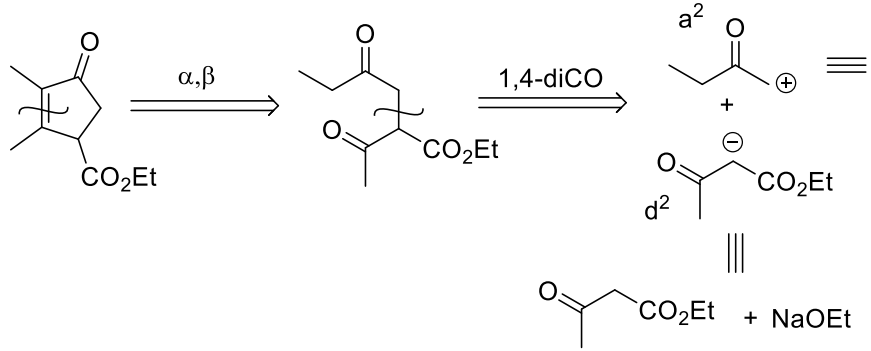


α-bromoester is very reactive in S_N2

The Logic of Organic Synthesis: Analysis of bifunctional target molecules:

C] 1,4-bifunctional compounds (contd.):

Let us now consider a few examples:

3. 

condensation regioselectivity guided by formation of the more substituted C=C

need to install the Br at the less susbt. side of the ketone, synthesis not straightforward.

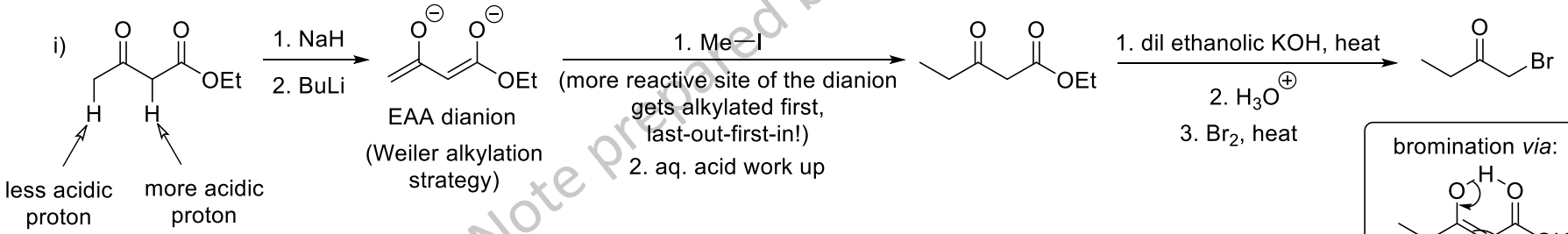
For halogenation, we can't use

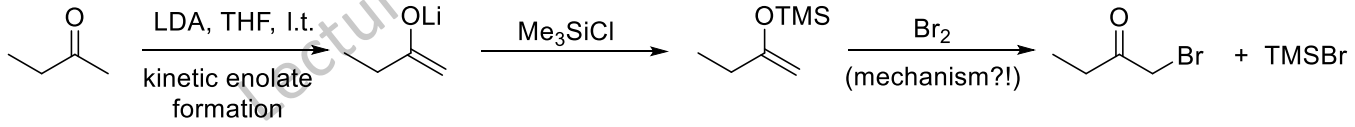
i) base - haloform!

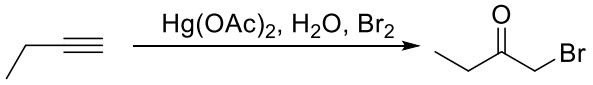
ii) acid - Br incorporated on the more substituted side!

How to solve this regioselectivity issue?

* Solutions to the regioselectivity problem:

i) 

ii) 

iii) 

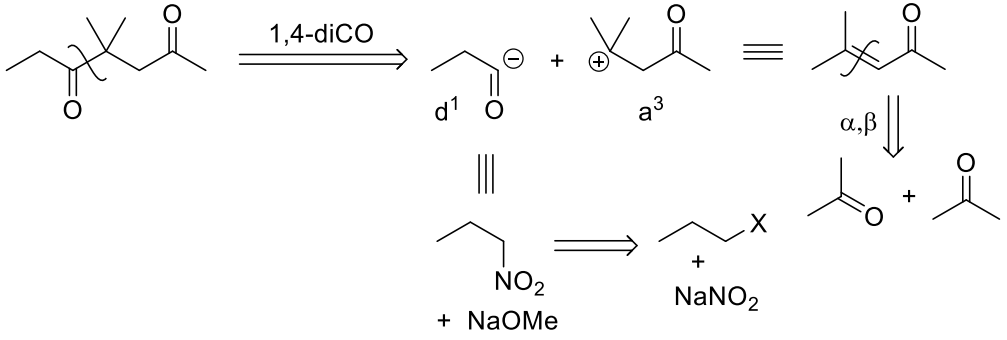
(This one is most interesting of the lot and as expected, has the most intricate mechanism. Try it; start just as you would for a Hg(II)-catalysed hydration of alkyne and then proceed from there.)

The Logic of Organic Synthesis: Analysis of bifunctional target molecules:

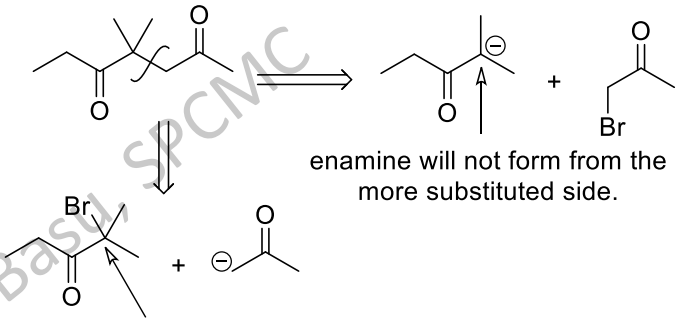
C] 1,4-bifunctional compounds (contd.):

Let us now consider a few examples:

4.



Enamine + α-haloketone strategy won't work here.



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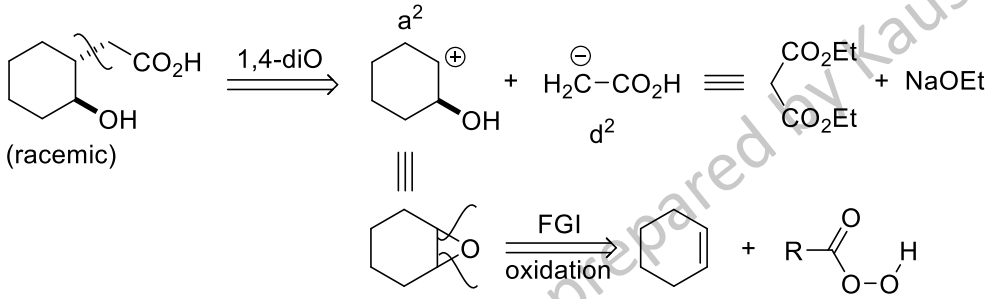
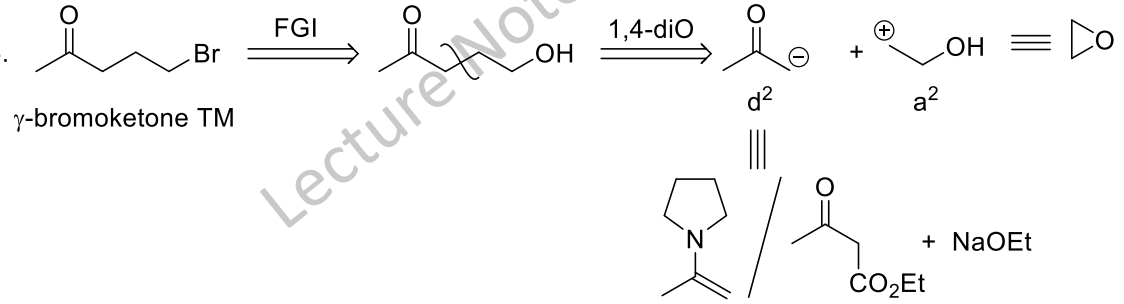
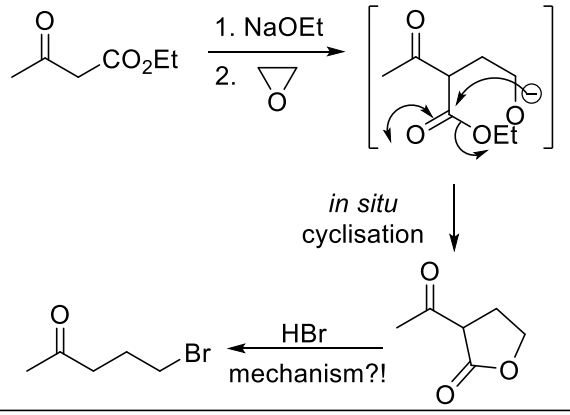


epoxide ring-opening is in *trans*-orientation

6.



Using EAA route we have the following observation:



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C] 1,4-bifunctional compounds (contd.):

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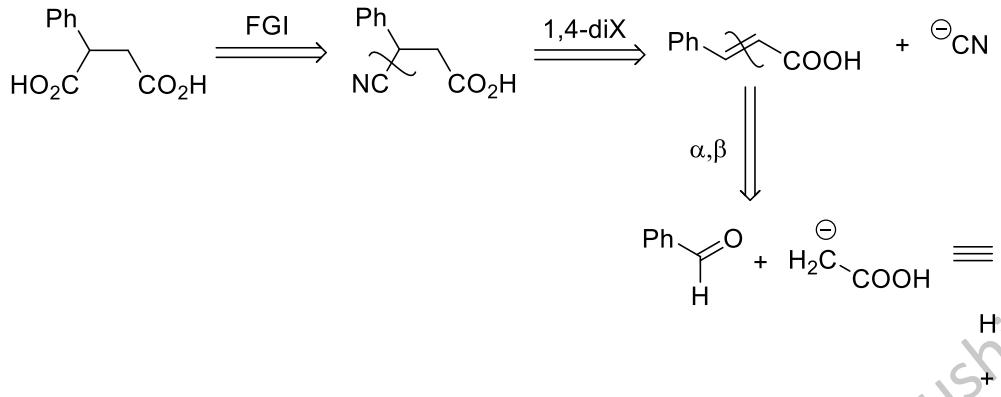
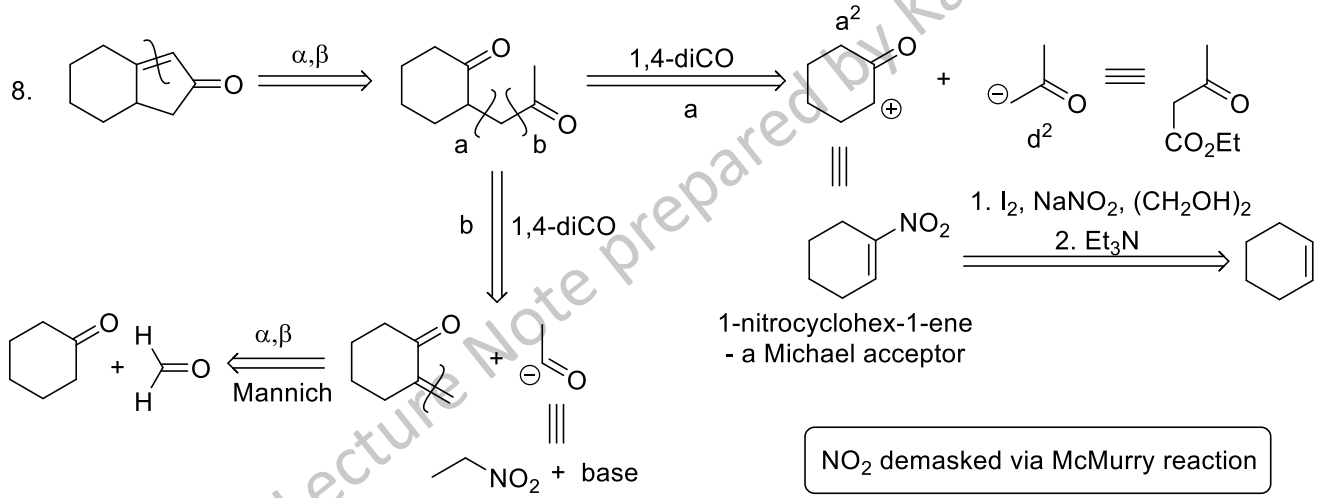


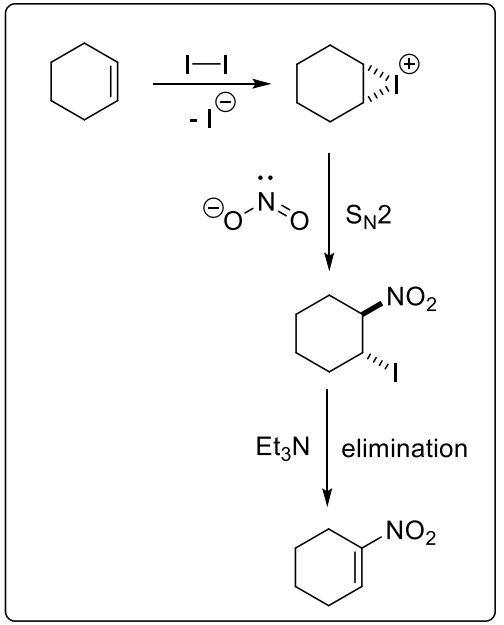
conjugate addition of cyanide is inevitable as it cannot add to COOH.

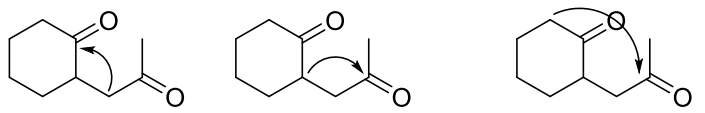
Use Perkin or Knoevenagel to access the aromatic α,β-unsaturated acid

8.



NO_2 demasked via McMurry reaction





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C] 1,4-bifunctional compounds (contd.):

Let us now consider a few examples:

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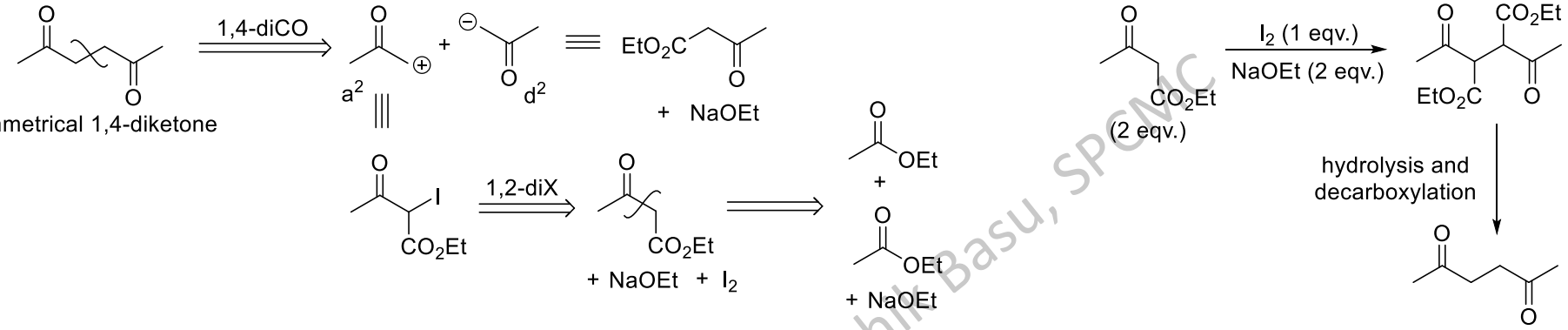

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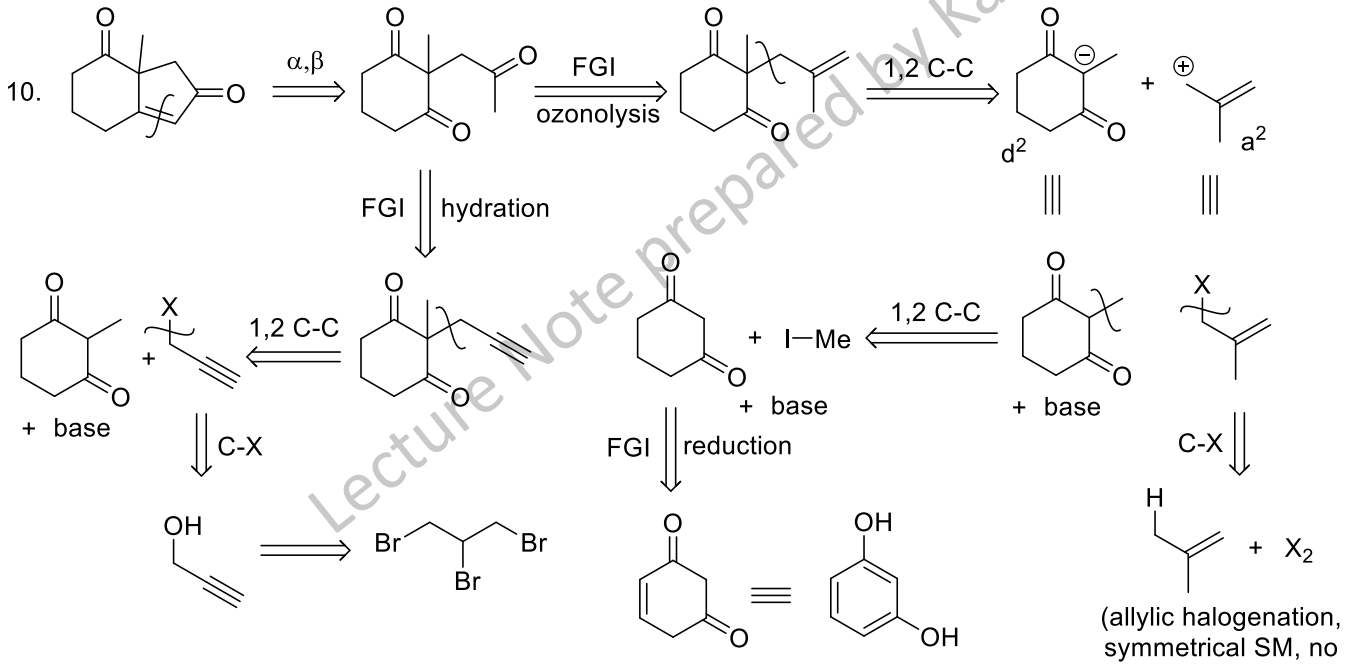
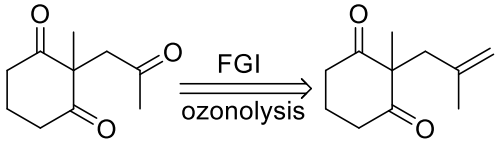




One of the strategies used here is quite unique - the ozonolysis of a C=C to install a C=O group. In terms of retrosynthesis, this implies replacing a =O with $=CH_2$. That's not a disconnection *per se*. When this analysis is carried out to approach the dicarbonyl target, we are in fact using the *reverse of a disconnection* - we are joining up a bond in the revised target which will be broken during the synthesis.

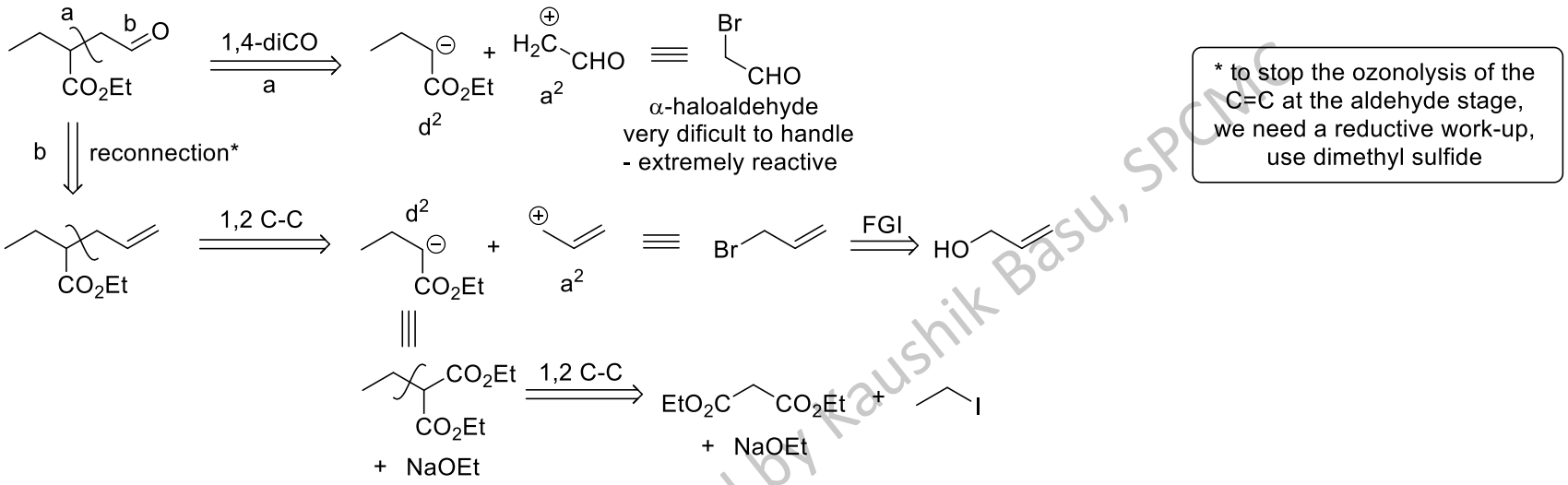
This is called the *strategy of reconnection*.

The Logic of Organic Synthesis: Analysis of bifunctional target molecules:

C] 1,4-bifunctional compounds (contd.):

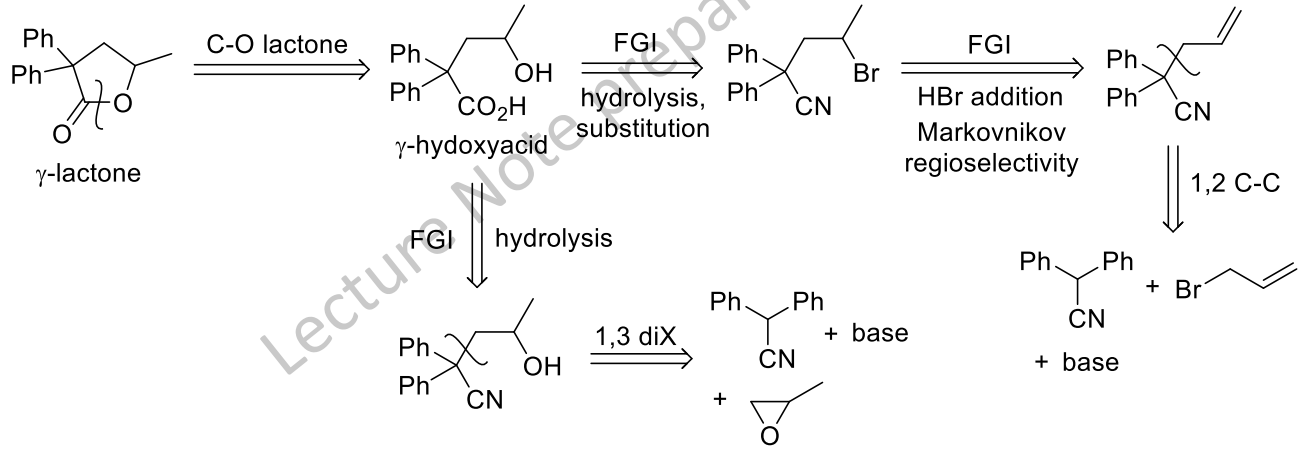
Oxidative cleavage of a C=C provides a useful route to 1,4-dicarbonyl targets. Here's another example of this concept at work:

11.



* to stop the ozonolysis of the C=C at the aldehyde stage, we need a reductive work-up, use dimethyl sulfide

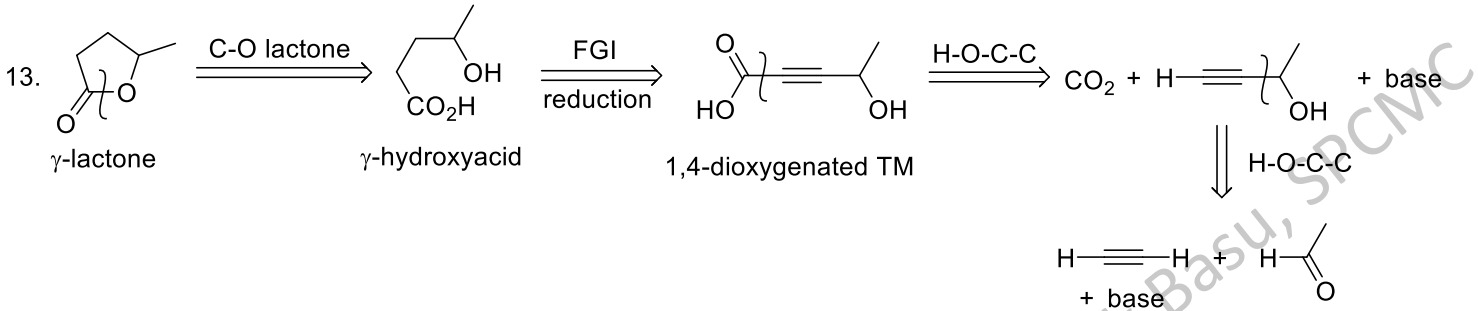
12.

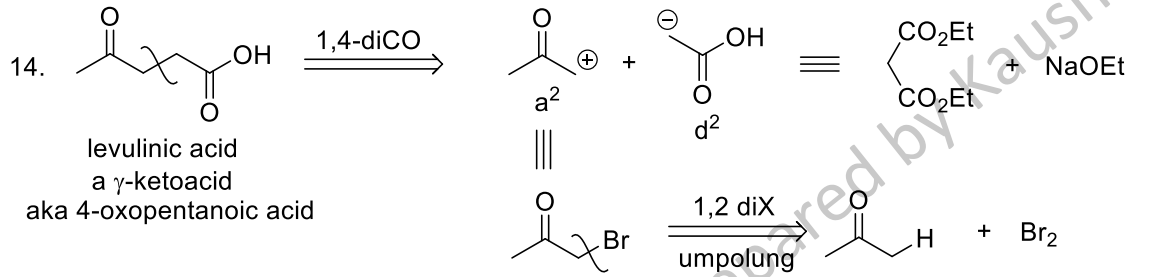


The Logic of Organic Synthesis: Analysis of bifunctional target molecules:

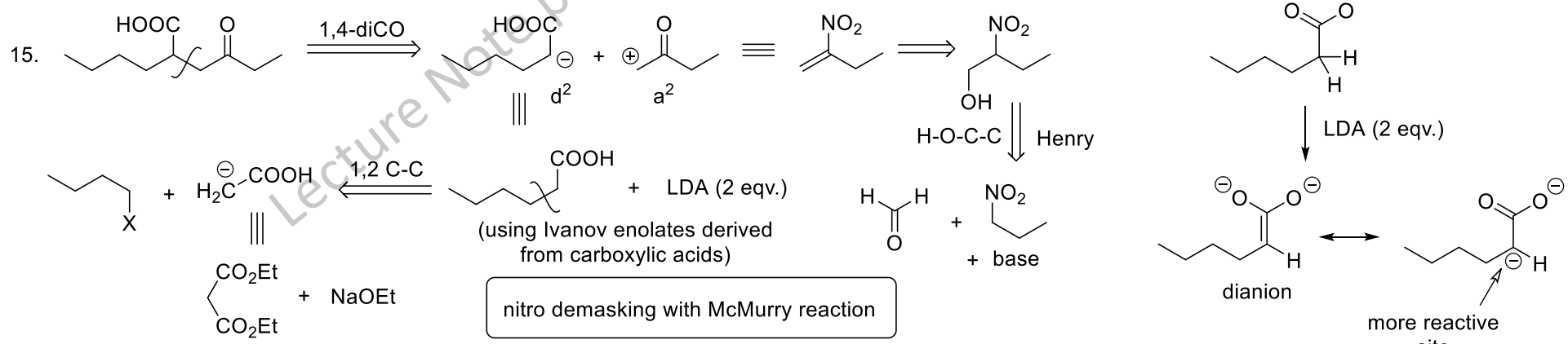
C] 1,4-bifunctional compounds (contd.):

Let us now consider a few examples:





bromination in AcOH to access the α-bromoacetone



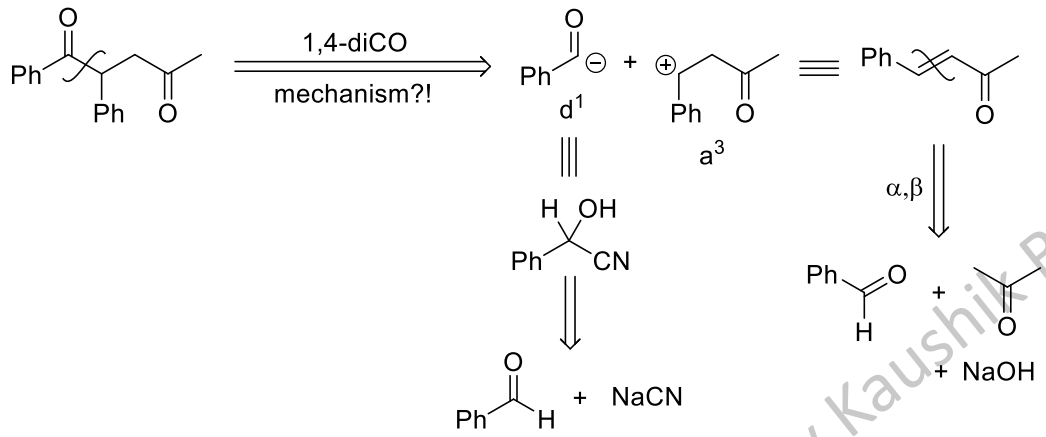
nitro demasking with McMurry reaction

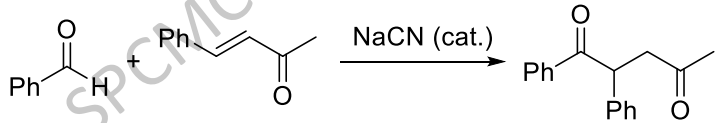
The Logic of Organic Synthesis: Analysis of bifunctional target molecules:

C] 1,4-bifunctional compounds (contd.):

And finally, let us revisit a 1,4-dicarbonyl target once more. Again we use the d^1+a^3 combination, but this time, our acyl anion equivalent is different from the one derived from nitroalkanes:

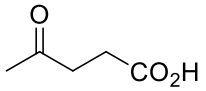
16.



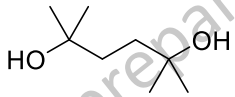


This is the Stetter reaction (mechanism?), using the cyanohydrin derived from the aromatic aldehyde as the umpoled reagent, an acyl anion equivalent. Possible side reaction is benzoin condensation which is reversible, so not a threat.

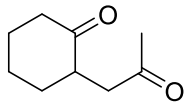
Try these yourself:



[C.1]
(two separate methods, other than the one shown)



[C.2]



[C.3]
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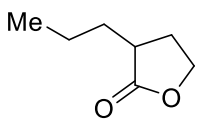
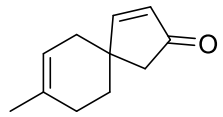
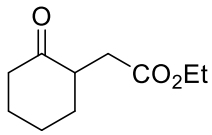


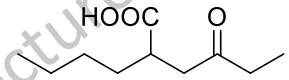
[C.4]



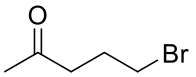
[C.5]



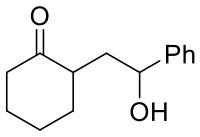
[C.6]



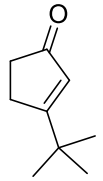
[C.7]
(other than the method shown)



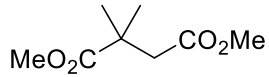
[C.8]



[C.9]



[C.10]



[C.11]