

Organic Chemistry-4
Semester-4, CBCS
Course: CEMA CC-4-8-TH

Course taught by: Kaushik Basu, Department of Chemistry, SPCMC, Kolkata
email: chiralkaushik@gmail.com

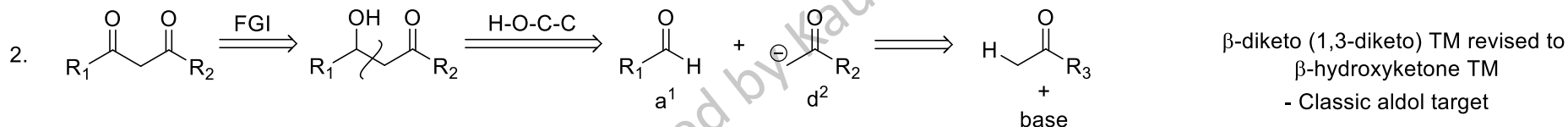
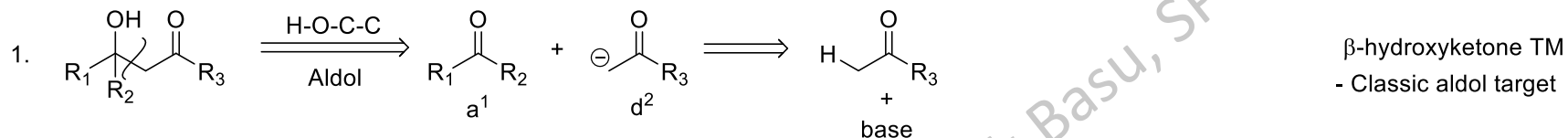
Recommended texts:

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:

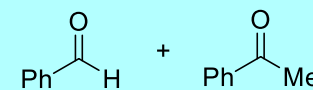
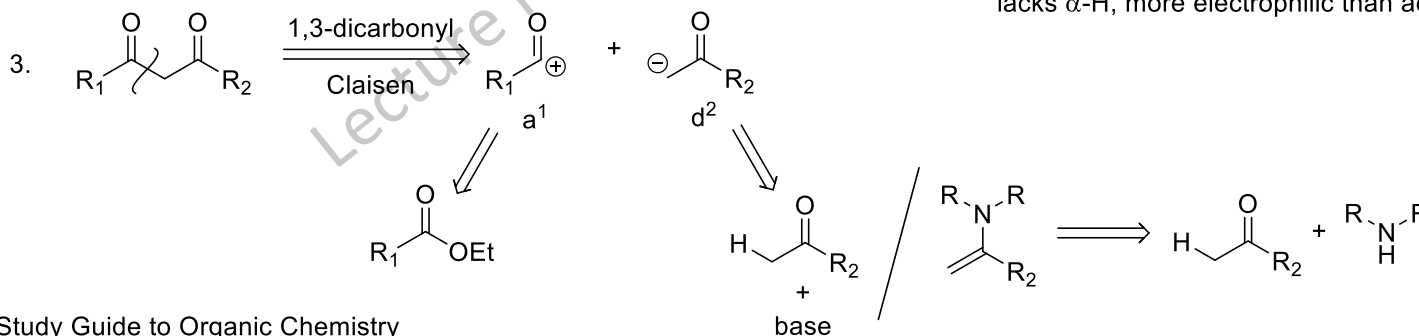
 B] 1,3-bifunctional (1,3-diX) compounds and α,β -unsaturated carbonyl compounds:

The following is a summary of the retrosynthetic strategies one can adopt commonly when the target molecule contains two heteroatom-based functional groups placed at an 1,3-relation. The α,β -Unsaturated carbonyl compounds can be traced back to 1,3-bifunctional compounds as well, so we include those here. These target molecules are conjugated systems, so umpolung strategy will not be necessary in general, but depending upon the availability of the SEs, one might adopt such a method (entry 4 and 5).



Whenever attempting cross-aldol - must take necessary precautions to avoid mixture of products. Most suitable if one component lacks α -H and is also more electrophilic than the other.

ideal combination:

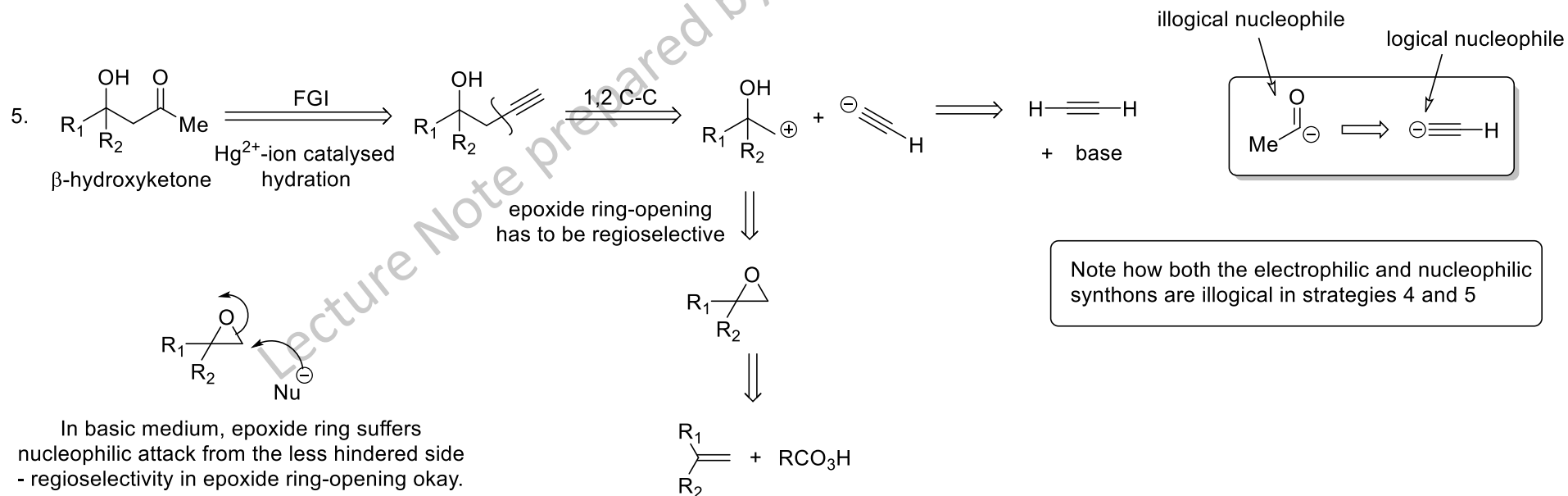
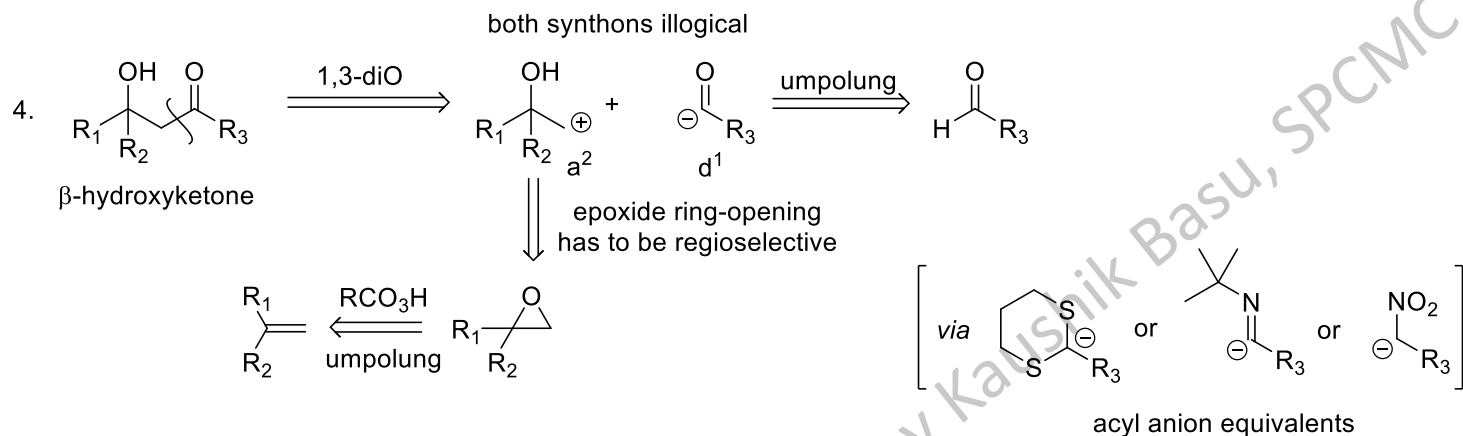

 lacks α -H, more electrophilic than acetophenone


All cases use d^2 synthon -
make use of suitable enol equivalent

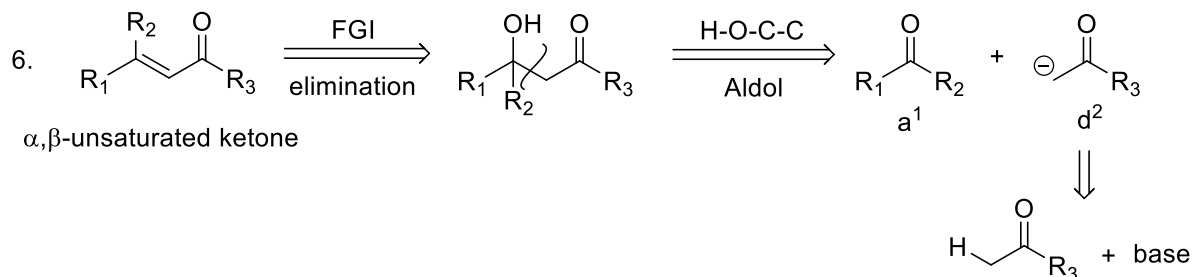
The Logic of Organic Synthesis: Analysis of bifunctional target molecules:

 B] 1,3-bifunctional (1,3-diX) compounds and α,β -unsaturated carbonyl compounds (contd.):

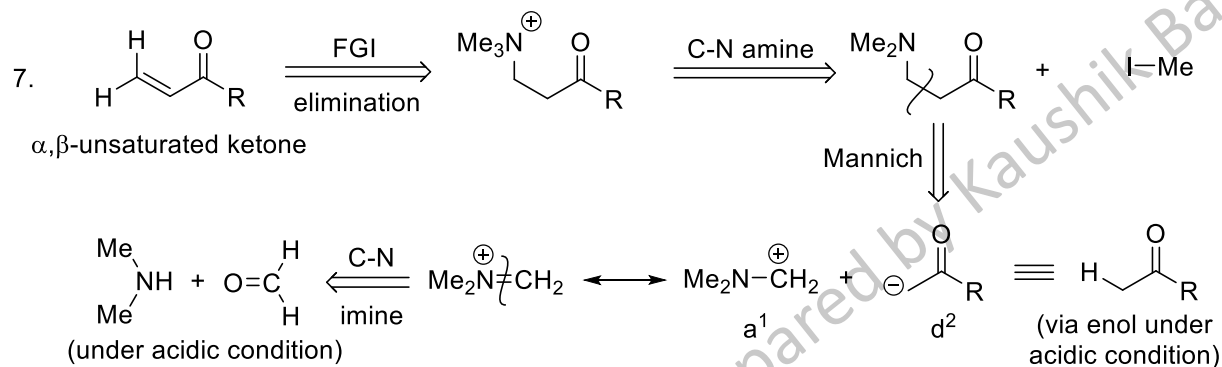
These target molecules are consonant systems, so umpolung strategy will not be necessary in general, but depending upon the availability of the SEs, one might adopt such a method (entry 4 and 5).



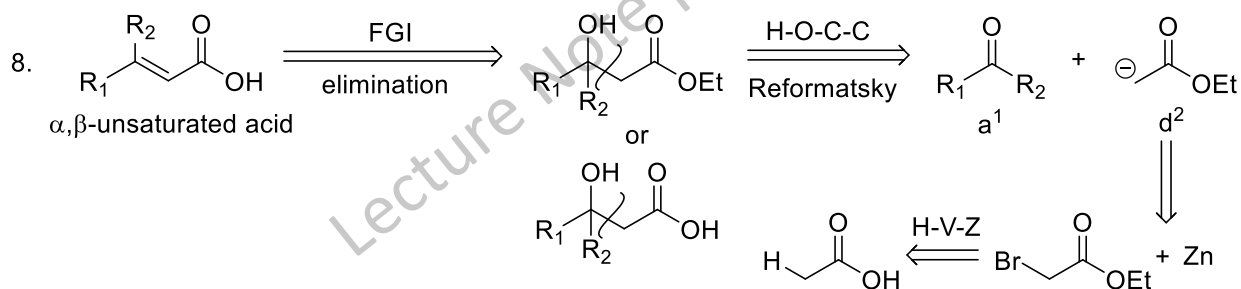
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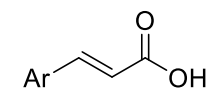
Cross-aldol - must take necessary precautions to avoid mixture of products. Most suitable if one component lacks α -H and is also more electrophilic than the other.



Never use formaldehyde in a cross-aldol, it is super-electrophilic, will react multiple times leading to misery. For TMs like MVK that bear the $\text{H}_2\text{C}=\text{C}=\text{O}$ fragment, adopt Mannich. However, there may be regioselectivity issues as the Mannich reaction proceeds through enol, which forms at the more substituted side in case of an unsymmetrical ketone.



For α,β -unsaturated carboxylic acids, we can use Perkin or Knoevenagel reactions as well; Perkin can be used with aromatic variant only:

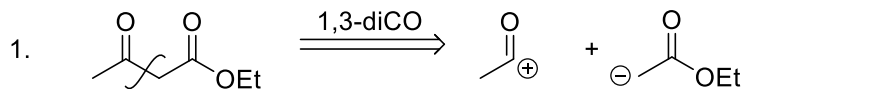


Accessing 1,3-dioxygenated target molecules depends mostly upon two important reactions, aldol and aldol-like reactions, and Claisen condensation. The product of aldol or aldol-like reaction may be transformed into α,β -unsaturated carbonyl compounds.

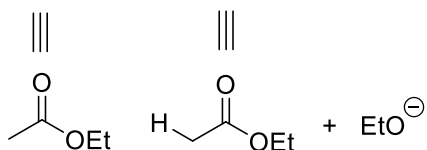
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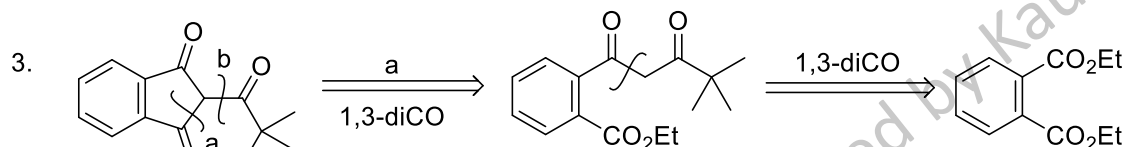
Let us now consider a few examples:



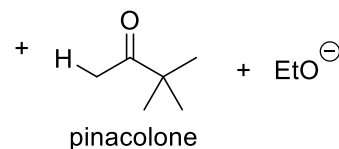
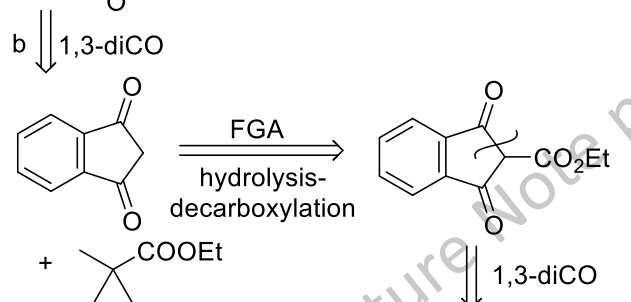
the 1,3-dicarbonyl will remain in the basic solution as the conjugate base, so acid work-up is necessary.



1,3-dicarbonyl, β -ketoester TM
Classic Claisen condensation

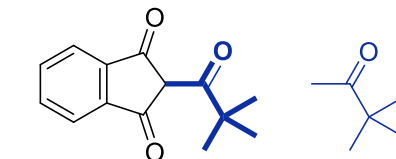
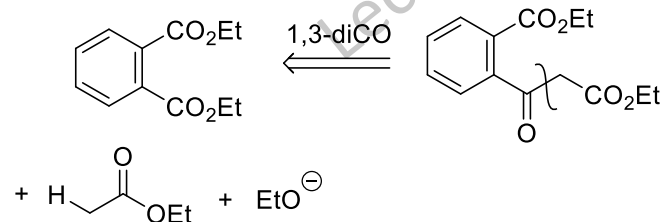


diethyl phthalate
- a symmetrical diester
- no regioselectivity issue



pinacol, an 1,2-bifunctional compound, accessed from radical coupling of two acetone molecules

Two 1,3-diO relationship in TM route 'a' is better, greater simplification, lesser number of steps

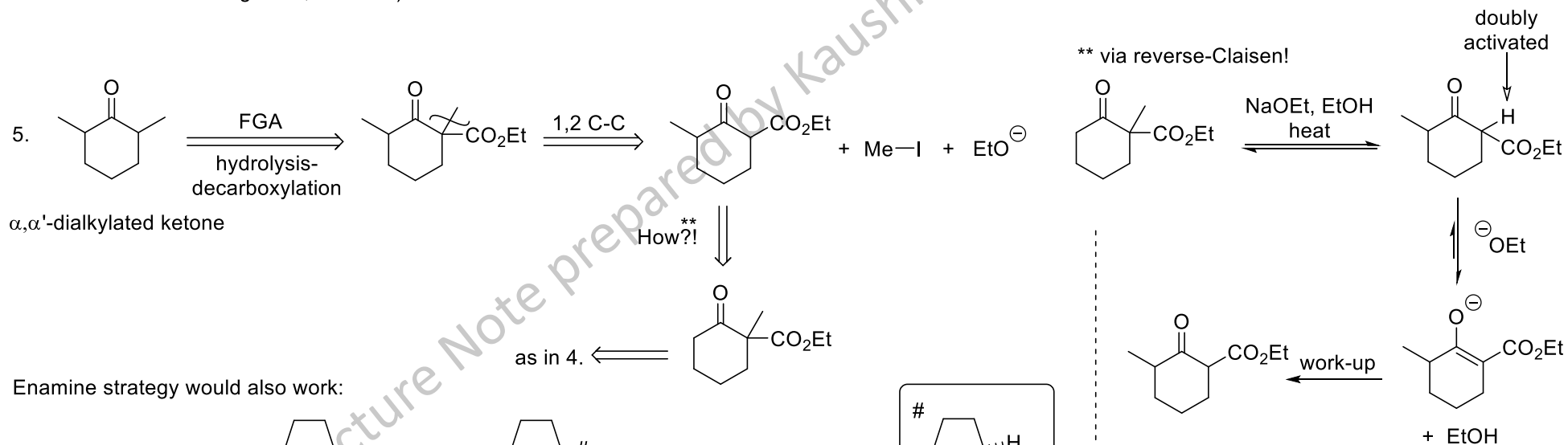
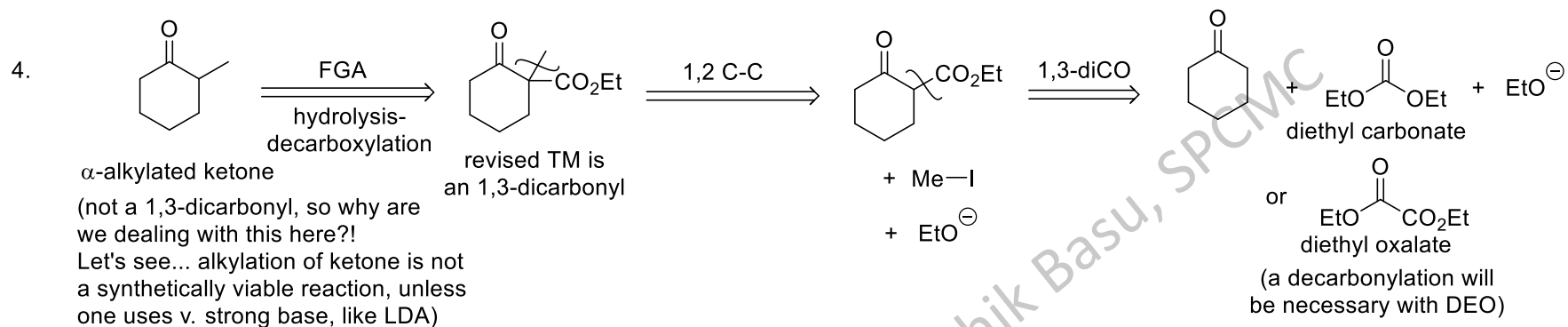


compounds containing *t*-butyl group can be accessed from pinacol-pinacolone rearrangement

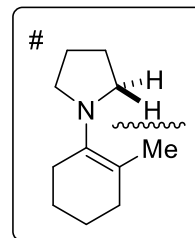
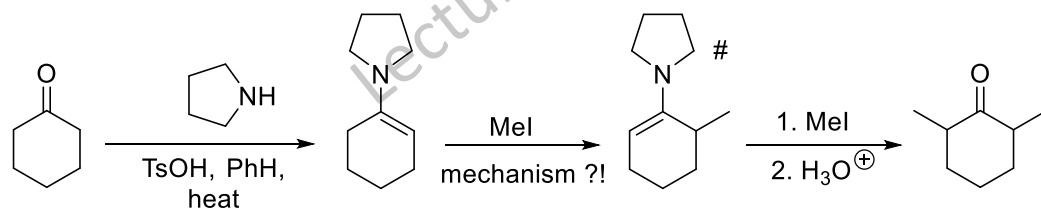
The Logic of Organic Synthesis: Analysis of bifunctional target molecules:

B] 1,3-bifunctional compounds and α,β -unsaturated carbonyl compounds (contd.):

Let us now consider a few examples:



Enamine strategy would also work:

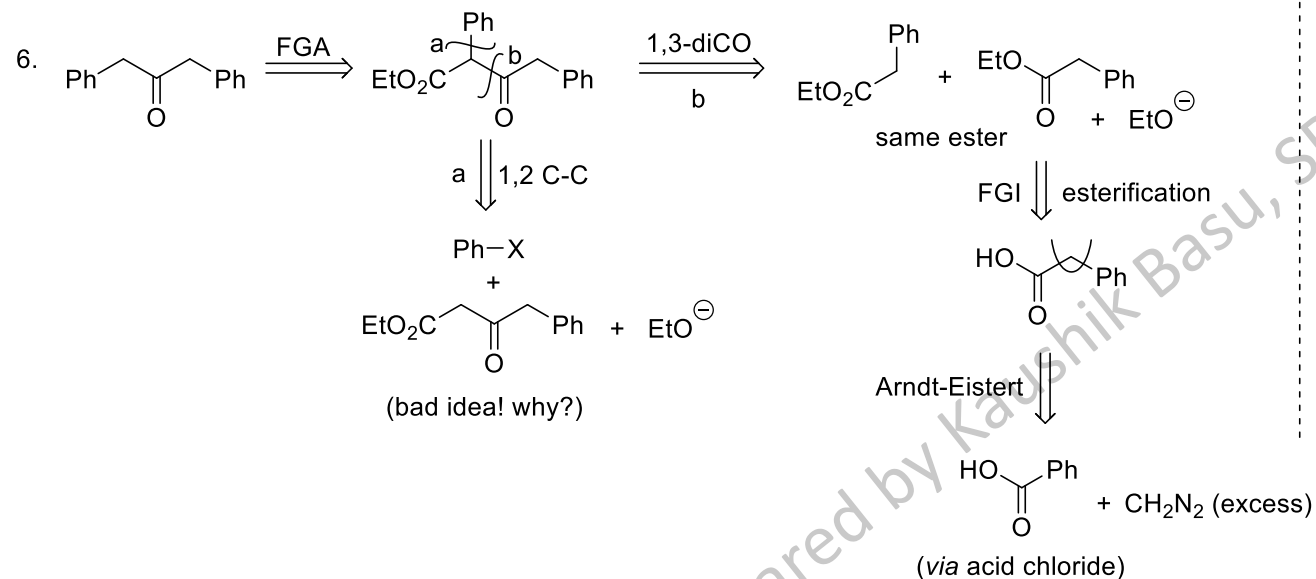


the other regioisomer suffers from 1,3-allylic strain

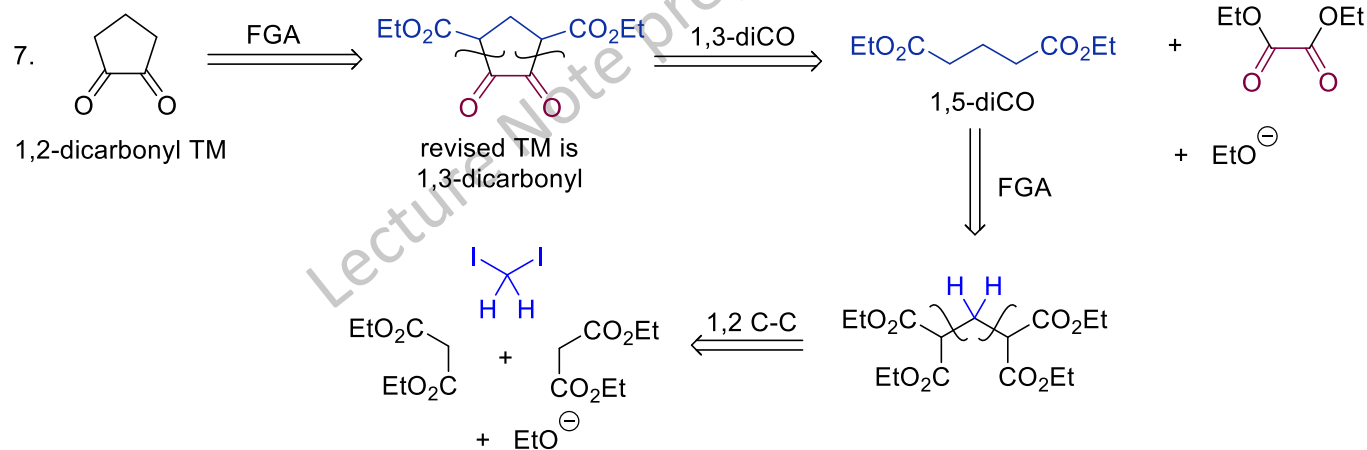
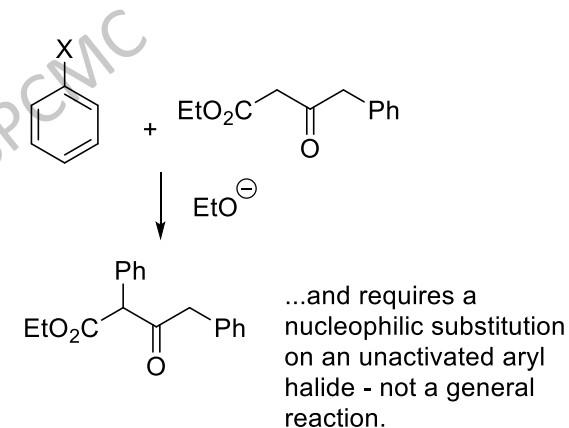
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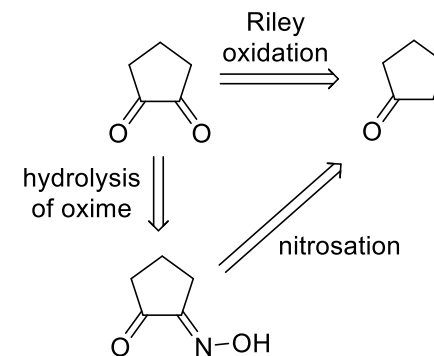
Let us now consider a few examples:



Strategy 'a' does not work as it involves...



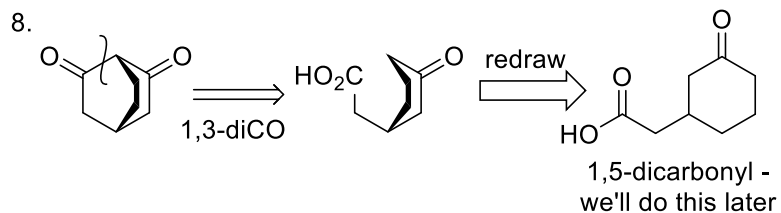
Exploiting the TM as a 1,2-dicarbonyl:



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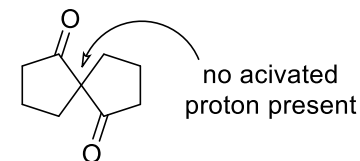
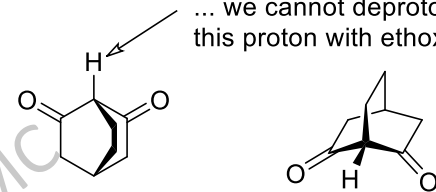
Let us now consider a few examples:



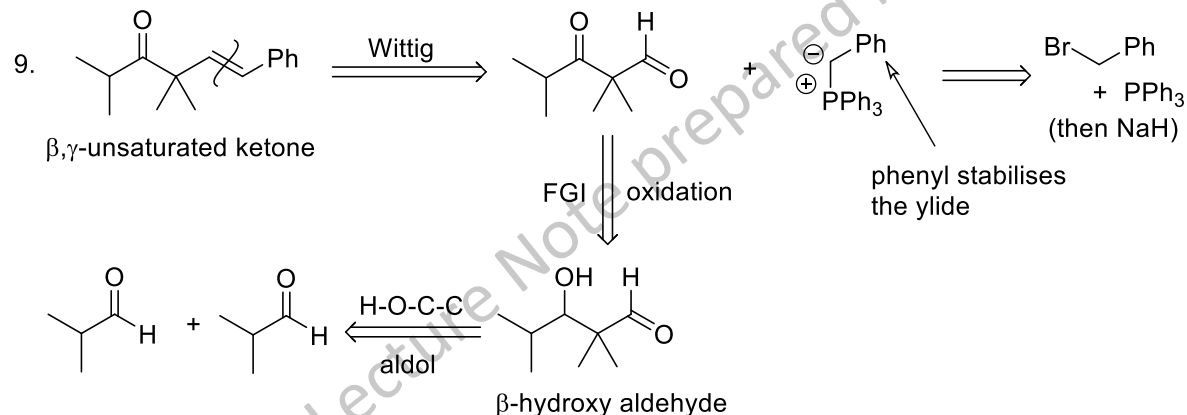
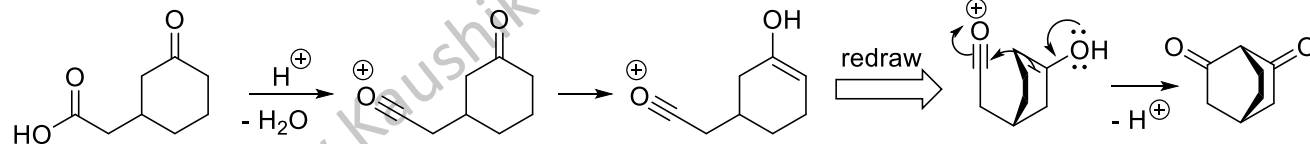
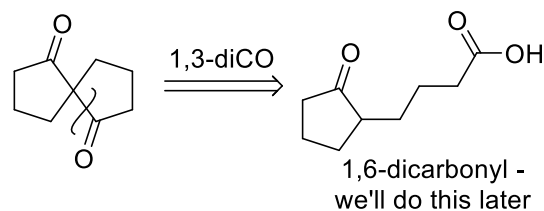
Claisen condensation with ethoxide won't work for these TMs - either lacks the activated proton or the one present cannot be abstracted by a base such as ethoxide - final step in Claisen not possible.

as the C-H s-orbital and the C=O π^* orbitals are not parallel...

... we cannot deprotonate this proton with ethoxide



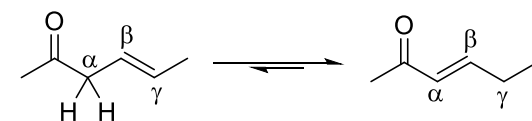
We have to use acidic condition (PPA, AcOH, heat) so that the reaction proceeds via an acylium ion. These are special cases. We will also use the keto acids as starting materials, and not the keto esters.



1. Wittig reaction is chemoselective - attacks the more reactive aldehyde, and stereoselective, gives *E*-alkene with stabilised ylide.
2. Oxidation of secondary alcohol to keto in presence of aldehyde is done chemoselectively by PCC, CH_2Cl_2

Point to be noted that it is difficult to keep a β,γ -unsaturated carbonyl compound's structural integrity intact. Given any chance, it isomerises to the more stable α,β -unsaturated carbonyl analogue. That, however, is not a problem here, as no α -hydrogen that can promote such isomerisation is available for this TM.

That is also precisely why we can safely implement the Wittig strategy. If a proton were present between the two carbonyl groups, Wittig reagent would have most likely abstracted it in an acid-base reaction.

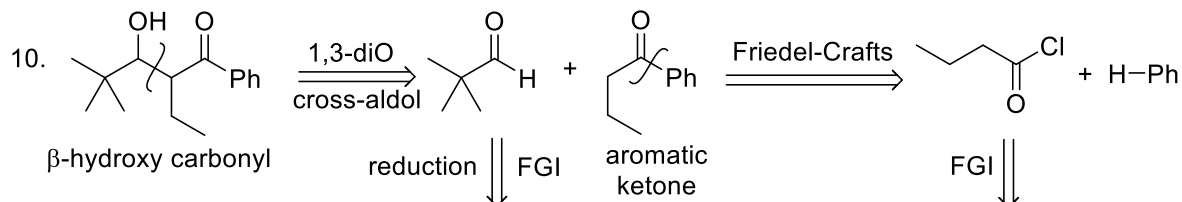


enolisable H must be present for this isomerization to happen

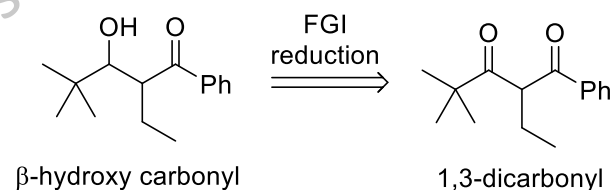
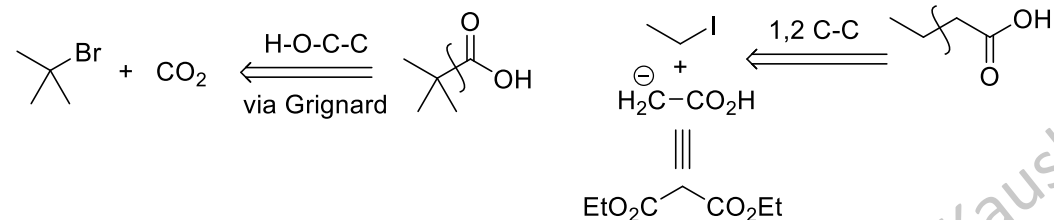
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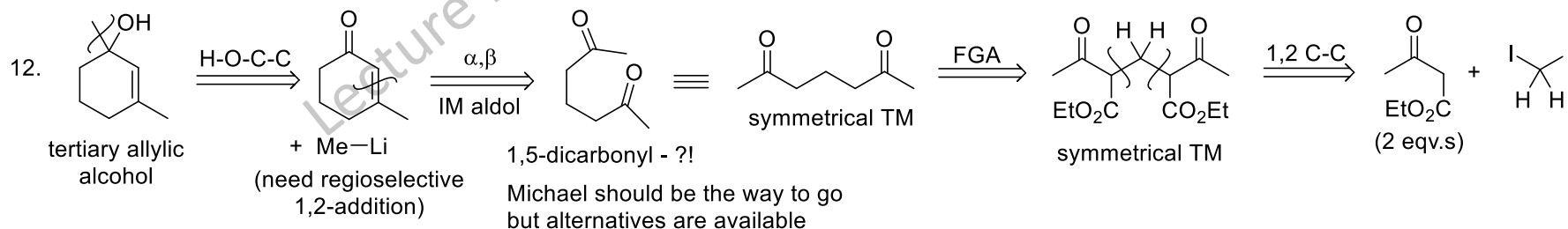
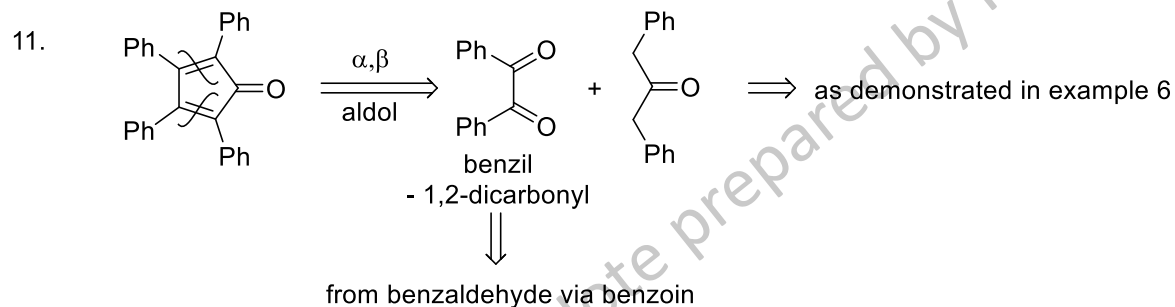
Let us now consider a few examples:



No control needed in the cross aldol, the more reactive component aldehyde cannot enolise - no self-condensation from that; moreover, the ketone enolises from one direction only, no regioselectivity issue as well



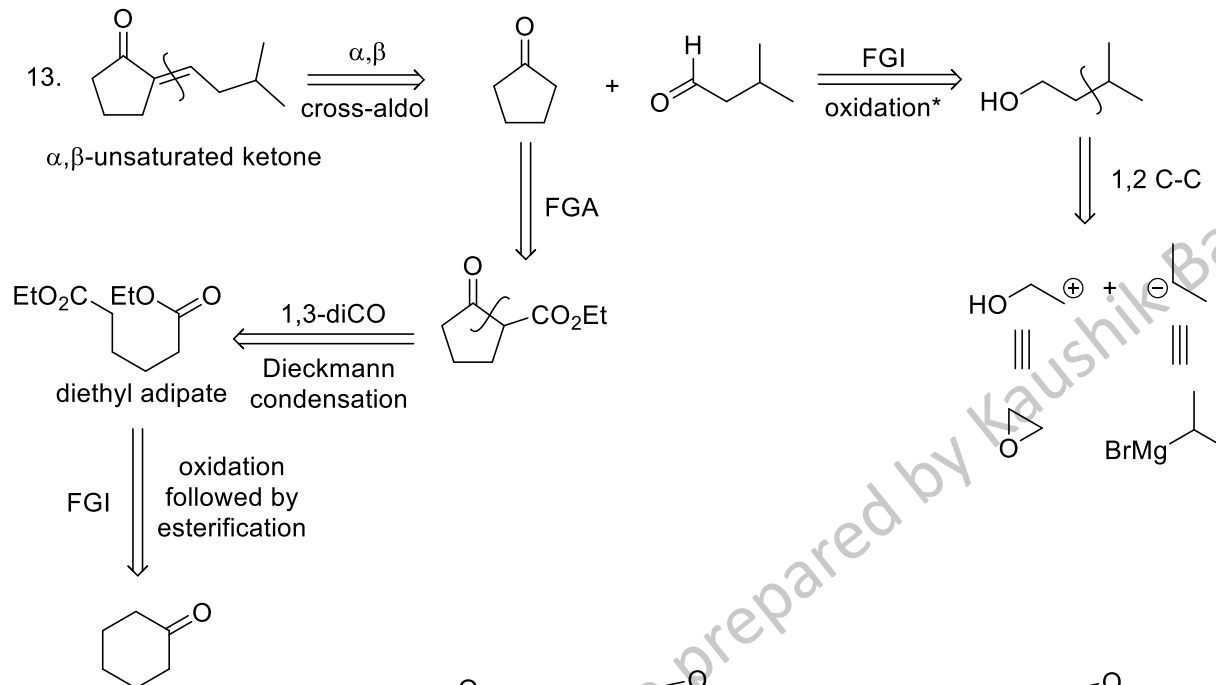
Alternative FGI strategy to revise TM to a 1,3-dicarbonyl will require chemoselective reduction of one of the C=O in the final synthesis step - problematic!



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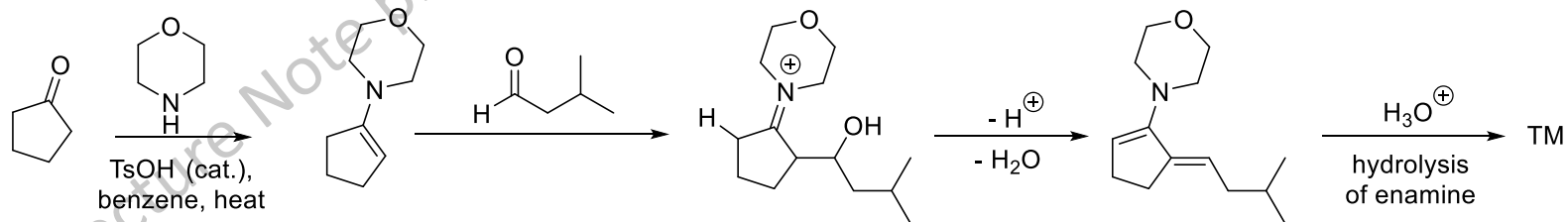
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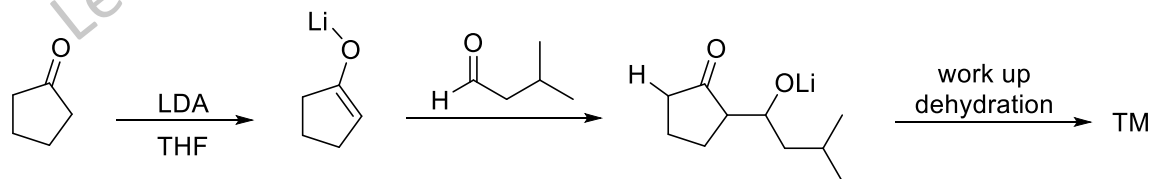
Control needed in the cross-aldol as the more reactive aldehyde can enolise in this case, so we must minimize its self-condensation. We have to use a stable enolate equivalent, enamine offers a good solution to the problem. Ketone symmetrical, no regioselectivity problem.

* Oxidation of primary alcohol to aldehyde
 - must use high-valent Cr in non-aqueous solvent to prevent over-oxidation to carboxylic acids
 - PCC in CH_2Cl_2 good option

Doing the cross-aldol with enamine strategy:



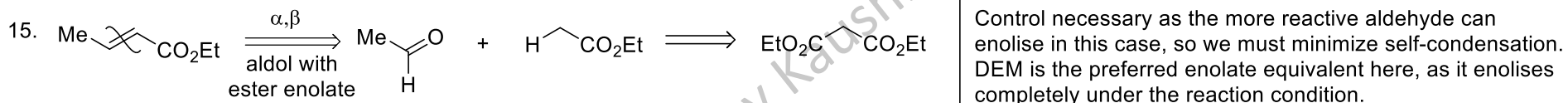
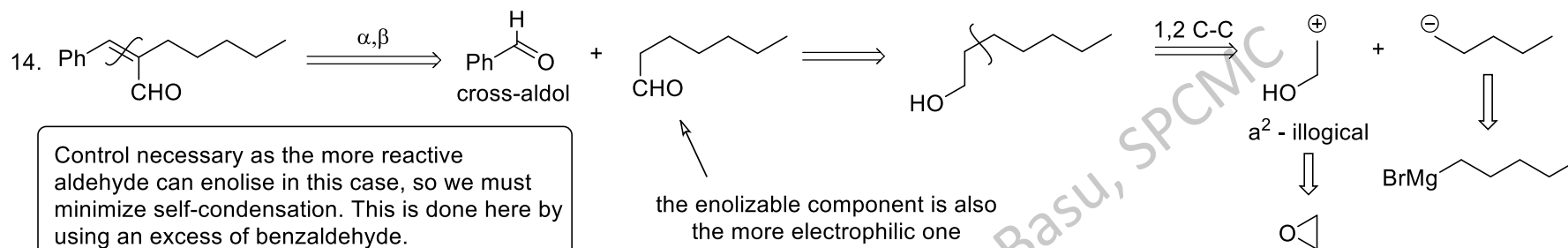
Can also use Li-enolate strategy:



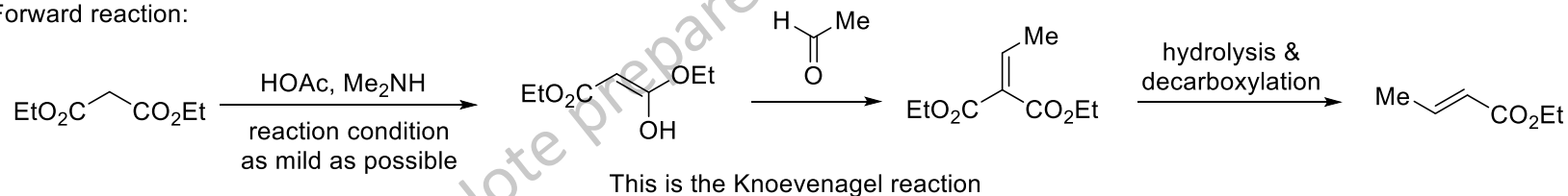
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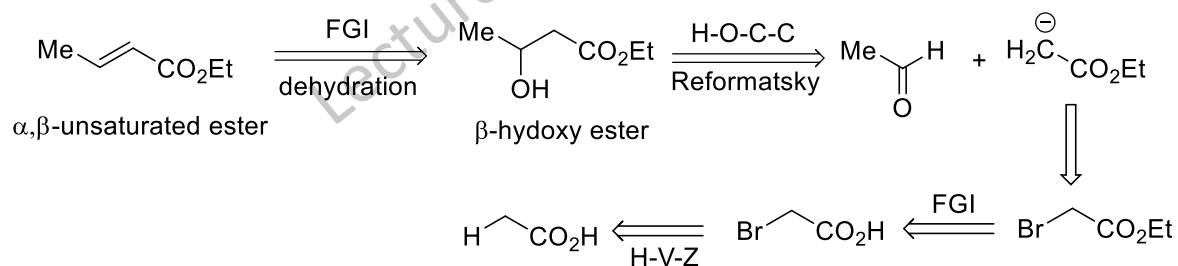
Let us now consider a few examples:



Forward reaction:



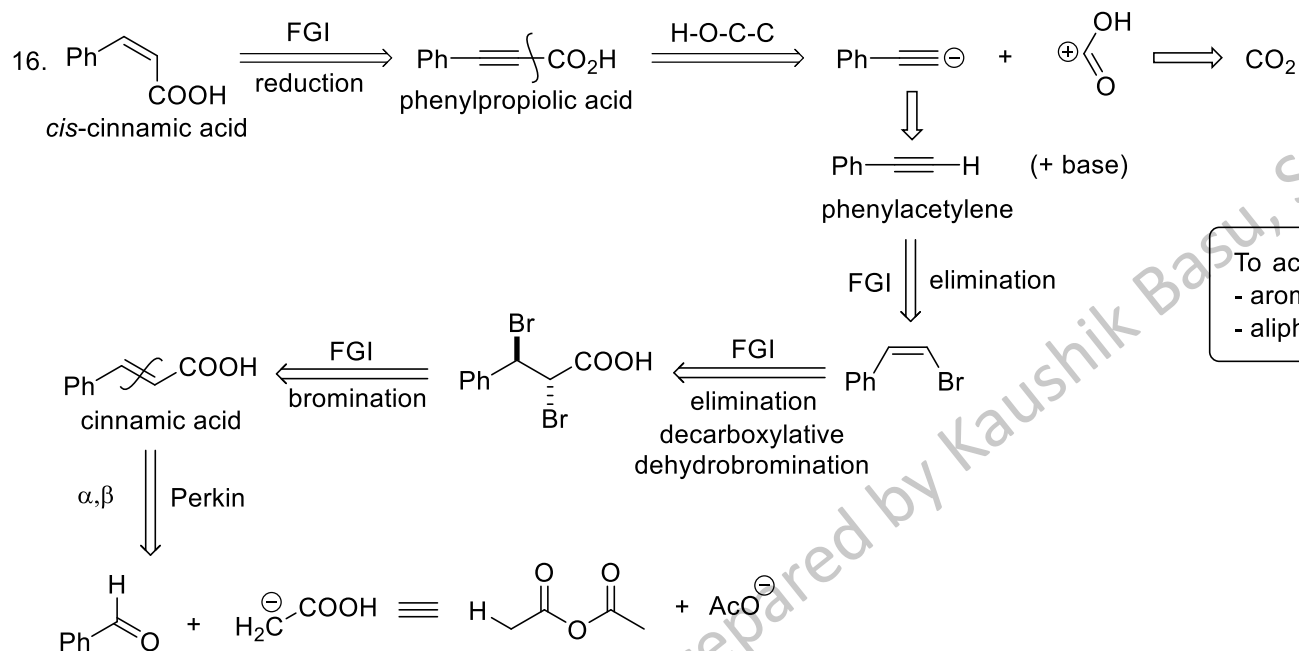
Alternatively,



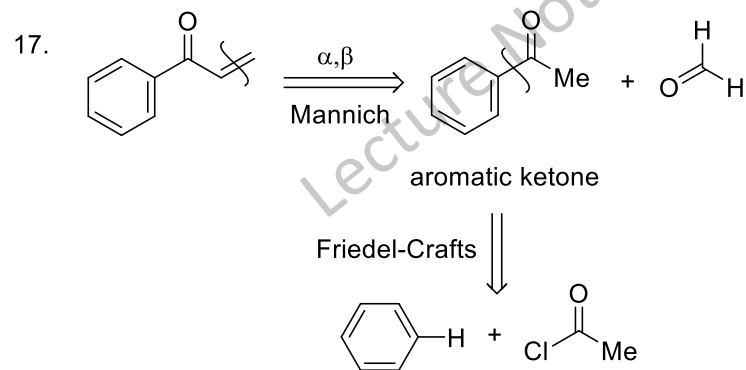
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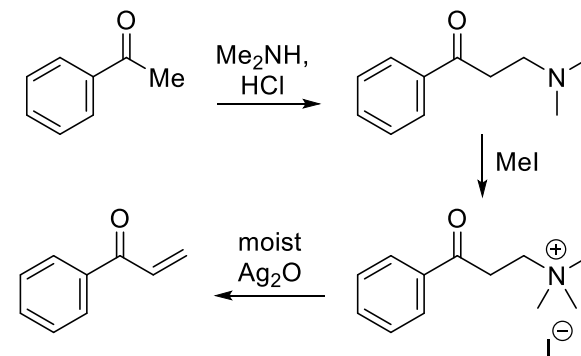
Let us now consider a few examples:



Final step of synthesis requires stereoselective reduction.

 To access α,β -unsaturated acid / derivative:
 - aromatic variant - Perkin, Reformatsky, Knoevenagel
 - aliphatic variant - Reformatsky, Knoevenagel


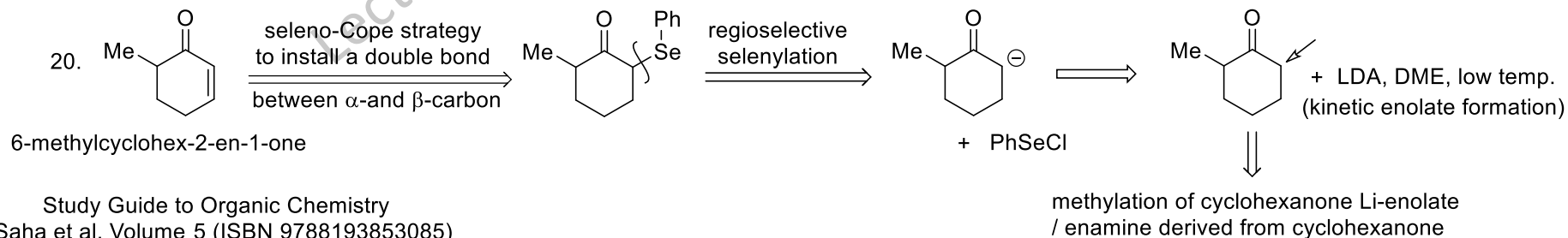
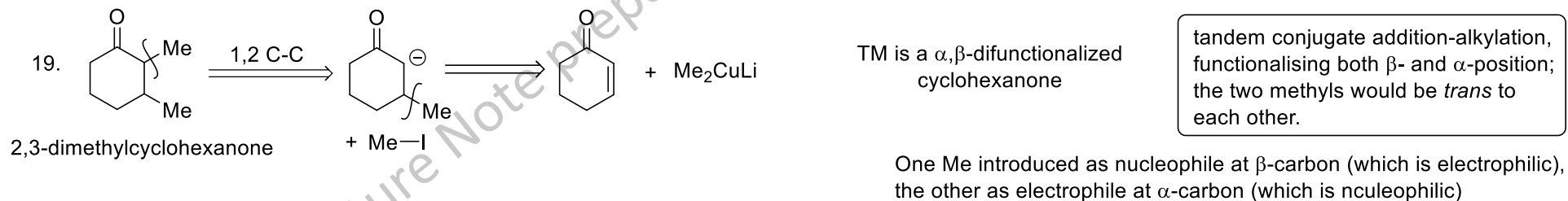
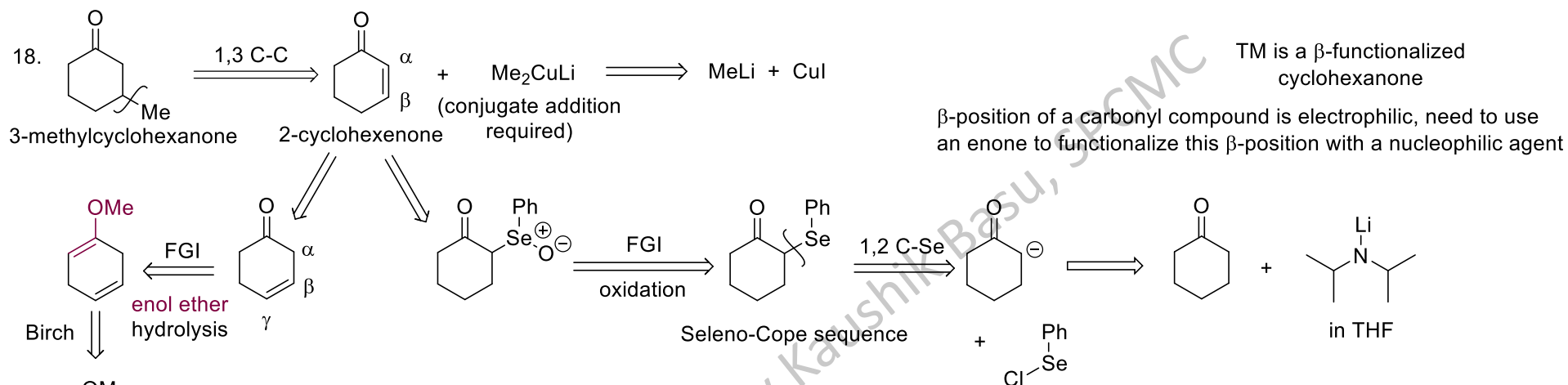
With formaldehyde as the electrophilic partner of an aldol-type condensation, the chances of Tollens' condensation is high, so better use Mannich to access that TM.



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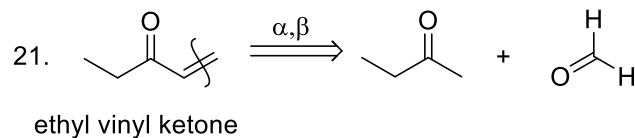
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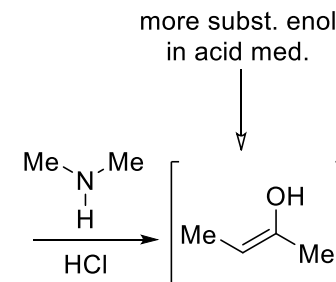
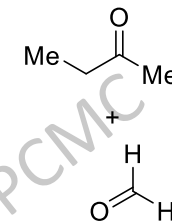
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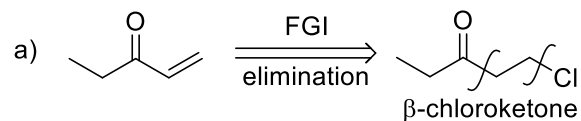
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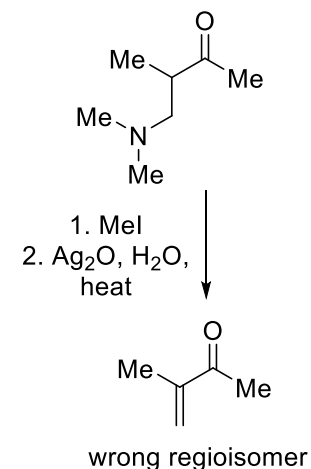
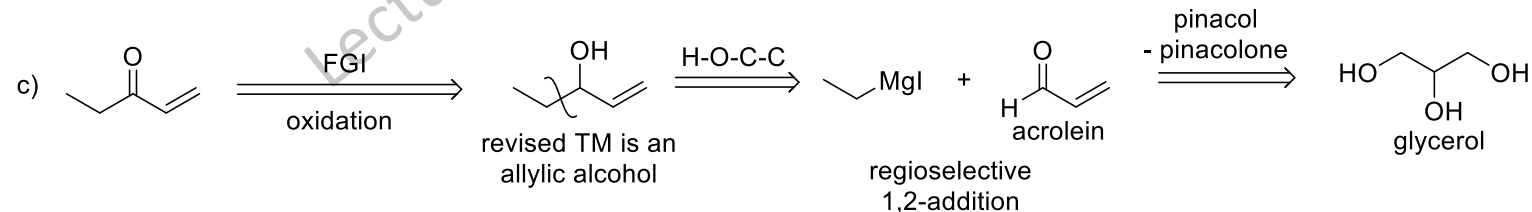
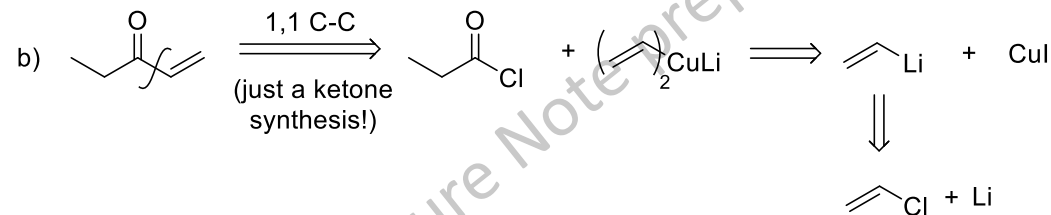
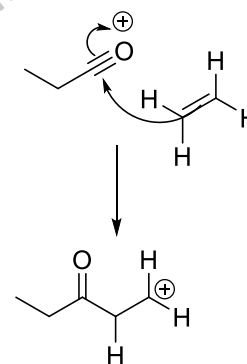
Not a good choice, as Mannich reaction would afford the wrong regioisomer because it would proceed through the more stable, more subst. enol of 2-butanone. We cannot use the CH_2O directly as well, lest Tollens condensation intervenes. Way out??



Revised strategy:



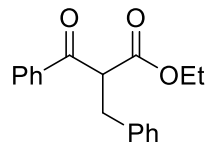
(under Lewis acid condition - just like Friedel-Crafts minus the aromatisation step!)



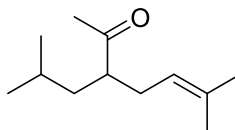
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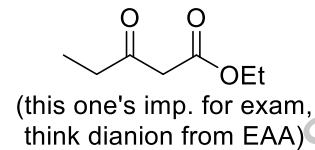
Try these yourself:



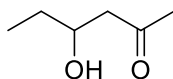
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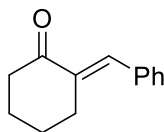
[B.2]



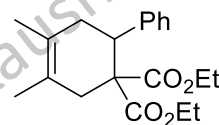
[B.3]



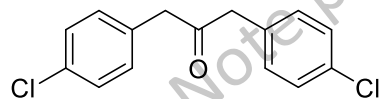
[B.4]



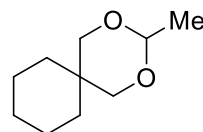
[B.5]



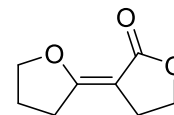
[B.6]



[B.7]



[B.8]



[B.9]

Propose another route (other than those shown!) for preparation of ethyl vinyl ketone.