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

B] 1,3-bifunctional compounds and $\alpha,\beta$-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. $\alpha,\beta$-Unsaturated carbonyl compounds can be traced back to 1,3-bifunctional compounds as well, so we include those here. 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).

1. $\text{H-O-C-C} \xrightarrow{\text{H-O-C-C}} \text{R}_1\text{R}_2\text{R}_3 \xrightarrow{\text{Aldol}} \text{R}_1\text{R}_2 + \text{R}_3\text{d}^2 \xrightarrow{\text{base}} \text{H} + \text{R}_3\text{a}^1 \beta$-hydroxyketone TM - Classic aldol target

2. $\text{OH} \xrightarrow{\text{FGI}} \text{R}_1\text{R}_2\text{R}_3 \xrightarrow{\text{H-O-C-C}} \text{R}_1\text{R}_2\text{R}_3 \xrightarrow{\text{base}} \text{H} + \text{R}_3\text{a}^1 \beta$-diketo TM revised to $\beta$-hydroxyketone TM - Classic aldol target

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

3. $\text{R}_1\text{R}_2\text{R}_3 \xrightarrow{1,3\text{-dicarbonyl}} \text{R}_1\text{R}_2\text{R}_3 \xrightarrow{\text{Claisen}} \text{R}_1\text{R}_2\text{R}_3 \xrightarrow{\text{base}} \text{R}_1\text{R}_2\text{Et} \xrightarrow{\text{Claisen}} \text{H} + \text{R}_3\text{N}^+\text{R}$

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

Study Guide to Organic Chemistry
- Saha et al. Volume 5 (ISBN 9788193853085)
The Logic of Organic Synthesis: Analysis of bifunctional target molecules:

B) 1,3-bifunctional 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).

Note how both the electrophilic and nucleophilic synthons are illogical in strategies 4 and 5.
The Logic of Organic Synthesis: Analysis of bifunctional target molecules:

6. \[ R_2\text{CO} \rightarrow \text{FGI} \rightarrow \text{HOC-C} \rightarrow \text{Aldol} \rightarrow R_1R_2\text{CO} + R_1\text{CO} \]

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

7. \[ H\text{C} = \text{C}R \rightarrow \text{FGI elimination} \rightarrow \text{C-N amine} \rightarrow \text{Mannich} \]

Never use formaldehyde in a cross-aldol, it is super-electrophilic, will react multiple times leading to misery. For TMIs like MVK that bear the \( \text{H}_2\text{C} = \text{C} = \text{O} \) fragment, always adopt Mannich.

8. \[ R_2\text{CO} \rightarrow \text{FGI elimination} \rightarrow \text{HOC-C-C} \rightarrow \text{Reformatsky} \rightarrow R_1R_2\text{CO} + \text{EtCO} \]

For \( \alpha,\beta \)-unsaturated carboxylic acids, we can use Perkin or Knoevenagel reactions as well; Perkin can be used with aromatic variant only.

Accessing 1,3-dioxgenated 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 \( \alpha,\beta \)-unsaturated carbonyl compounds.
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:

1. \[
\text{HOOC} \quad \text{EtO} \quad \xrightarrow{1,3\text{-diCO}} \quad \text{O} \quad \text{CO} \quad \text{EtO} \quad \text{EtO} \quad \text{H} \quad \text{EtO} \quad \text{O}
\]

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

2. \[
\text{Ph} \quad \text{O} \quad \text{O} \quad \text{EtO} \quad \xrightarrow{1,3\text{-diCO}} \quad \text{Ph} \quad \text{CO} \quad \text{EtO} \quad \text{EtO} \quad \text{O} \\
\text{Ph} \quad - \quad \text{H} \quad + \quad \text{Cl} \quad \xrightarrow{\text{Friedel-Crafts}} \quad \text{Ph} \quad \text{O} \quad \text{C} \quad \text{H} \quad \text{EtO} \quad \text{EtO} \quad \text{O}
\]

aromatic ketone

1,3-dicarbonyl, β-diketo TM

Claisen condensation b/w ketone enolate and ester
- must avoid self-condensation of ester

Aldol reaction b/w ketones can be easily reversed, but reaction b/w ketone enolate and ester cannot.

\[
\text{HOOC} \quad \text{EtO} \quad \xrightarrow{1,3\text{-diCO}} \quad \text{O} \quad \text{CO} \quad \text{EtO} \quad \text{EtO} \quad \text{O} \\
\text{EtO} \quad \text{O} \quad \text{CO} \quad \text{EtO} \quad \text{EtO} \quad \text{O} \quad \text{HO} \quad \text{HO} \quad \text{O}
\]

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

Two 1,2-diO relationship in TM route 'a' is better, greater simplification, lesser number of steps

Study Guide to Organic Chemistry
- Saha et al. Volume 5 (ISBN 9788193853085)
**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:

4. α-alkylated ketone
   (not a 1,3-dicarbonyl, so why are we dealing with this here?!) Let's see... alkylation of ketone is not a synthetically viable reaction, unless one uses very strong base, like LDA)

5. Enamine strategy would also work:

   ![Diagram](image-url)
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:

6. Ph-RCO-Ph
   \[ \xrightarrow{F GA} \] EtO₂C\_RCO\_Ph \]
   \[ \xrightarrow{1,3-di CO} \] Ph + EtO₂C\_RCO\_Ph
   same ester
   \[ \xrightarrow{Et O^{-}} \] Ph
   (bad idea! why?)

7. 1,2-dicarbonyl TM
   \[ \xrightarrow{F GA} \] EtO₂C\_RCO\_CO₂Et \]
   revised TM is 1,3-dicarbonyl
   \[ \xrightarrow{1,3-di CO} \] EtO₂C\_RCO\_CO₂Et
   \[ \xrightarrow{1,5-di CO} \] EtO₂C\_RCO\_CO₂Et
   \[ \xrightarrow{F GA} \] EtO₂C\_RCO\_CO₂Et + EtO⁻
   + EtO⁻
   + EtO⁻
   + EtO⁻

Strategy a does not work as it involves...

and requires a nucleophilic substitution on an unactivated aryl halide
- not a general reaction

Study Guide to Organic Chemistry
- Saha et al. Volume 5 (ISBN 9788193853085)
The Logic of Organic Synthesis: Analysis of bifunctional target molecules:

B) 1,3-bifunctional compounds and $\alpha,\beta$-unsaturated carbonyl compounds (contd.):

Let us now consider a few examples:

1. 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.

2. 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.

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

4. 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.
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:

10. β-hydroxy carbonyl

\[
\begin{align*}
\text{OH} & \quad \text{Ph} \\
\text{O} & \quad \text{1,3-diO} \\
\text{cross-aldol} & \quad \text{Ph} \\
\text{OH} & \quad \text{1} \\
\text{reduction} & \quad \text{FGI} \\
\text{H} & \quad \text{O} \\
\text{O-C-C} & \quad \text{via Grignard} \\
\text{Br} & \quad \text{CO}_2 \\
\text{H} & \quad \text{OH} \\
\text{OH} & \quad \text{H}_2\text{C-CO}_2\text{H} \\
\text{CO}_2\text{H} & \quad \text{EtO}_2\text{C-CO}_2\text{Et} \\
\end{align*}
\]

11. benzil

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph} \\
\text{O} & \quad \text{aldol} \\
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph} \\
\text{EtO}_2\text{C-CO}_2\text{Et} & \quad \text{as demonstrated in example 6} \\
\end{align*}
\]

12. tertiary allylic alcohol

\[
\begin{align*}
\text{OH} & \quad \text{H-O-C-C} \\
\text{Ph} & \quad \text{Me-Li} \\
\text{(need regioselective} & \quad \text{1,2-addition)} \\
\text{IM aldol} & \quad \text{1,5-dicarbonyl - ?!} \\
\text{symmetrical TM} & \quad \text{FGA} \\
\text{EtO}_2\text{C-CO}_2\text{Et} & \quad \text{1,2-C-C} \\
\text{EtO}_2\text{C-CO}_2\text{Et} & \quad \text{(2 eqv.s)} \\
\end{align*}
\]

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.
**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:

13. 

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.

Doing the cross-aldol with enamine strategy:
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:

14. PhCHO $\xrightarrow{\alpha,\beta}$ \(\text{PhCO} + \text{CHO} \rightarrow \text{HO} + \text{HO} \xrightarrow{1,2 \text{ C-C}} \text{HO} + \text{HO} \xrightarrow{a^2 - \text{ illogical}} \text{BrMg} \xrightarrow{\text{O}}

Control necessary as the more reactive aldehyde can enolise in this case, so we must minimize self-condensation. This is done here by using an excess of benzaldehyde.

15. CO$_2$Et $\xrightarrow{\alpha,\beta}$ aldol with ester enolate

Forward reaction:

EtO$_2$C$\xrightarrow{\text{HOAc, Me$_2$NH}}$ Me-CHO reaction condition as mild as possible

This is the Knoevenagel reaction

Alternatively,

$\xrightarrow{\text{FGI dehydration}}$ β-hydroxy ester $\xrightarrow{\text{Reformatsky}}$ MeCHO $\xrightarrow{\text{H$_2$C-CO$_2$Et}}$

H$_2$CO$_2$H $\xrightarrow{\text{H-V-Z}}$ BrCO$_2$H $\xrightarrow{\text{FGI}}$ BrCO$_2$Et (via zinc-enolate)

Control necessary as the more reactive aldehyde can enolise in this case, so we must minimize self-condensation. DEM is the preferred enolate equivalent here, as it enolises completely under the reaction condition.
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:

16. \( \text{Ph-} \text{COOH} \xrightarrow{\text{FGI reduction}} \text{Ph-} \text{CO}_2\text{H} \)

\( \text{cis-cinnamic acid} \)

\( \xrightarrow{\text{H-O-C-C}} \)

\( \text{Ph}\xrightarrow{\text{+ base}} \text{Ph} \text{-H} \)

\( \text{phenylpropionic acid} \)

\( \xrightarrow{\text{FGI elimination}} \text{phenylacetylene} \)

Final step of synthesis requires stereoselective reduction.

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

17. \( \text{Ph-} \text{CO}_2\text{H} \xrightarrow{\text{FGI bromination}} \text{Ph-} \text{Br} \text{COOH} \)

\( \xrightarrow{\text{FGI elimination}} \text{Ph} \xrightarrow{\text{Perkin}} \text{H}_2\text{C}-\text{COOH} \)

\( \xrightarrow{\text{Perkin}} \text{Ph} \text{CHO} + \text{H}_2\text{C}=\text{COOH} \)

\( \xrightarrow{\text{FGI}} \text{Ph} \text{H} + \text{H}_2\text{C}=\text{CO}_2\text{H} + \text{AcO}^\ominus \)

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.
**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:

1. **18.**
   - **1,3 C-C**
   - **Me**
   - **2-cyclohexenone**
   - **MeCuLi**
   - **MeLi**
   - **Cul**
   - **(conjugate addition required)**
   - **TM is a β-functionalized cyclohexanone**

2. **19.**
   - **FGI**
   - **Birch**
   - **enol ether hydrolysis**
   - **OMe**
   - **Ph**
   - **Se**
   - **Seleno-Cope sequence**
   - **1,2 C-Se**
   - **Cl**
   - **Se**
   - **Li**
   - **N**
   - **in THF**
   - **tandem conjugate addition-alkylation, functionalising both β- and α-position; the two methyls would be *trans* to each other.**

3. **20.**
   - **seleno-Cope strategy to install a double bond between α- and β-carbon**
   - **Me**
   - **Ph**
   - **Se**
   - **regioselective selenylation**
   - **Me**
   - **LDA, DME, low temp. (kinetic enolate formation)**

---

*Study Guide to Organic Chemistry*
- Saha et al. Volume 5 (ISBN 9788193853085)
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:

21. \[ \text{\chem{\text{CH}_2\text{C} = \text{CH}}}} \quad \text{\chem{\alpha,\beta}} \quad \Longrightarrow \quad \text{\chem{\text{CH}_2\text{C} = \text{O}}} + \text{\chem{\text{CHO}}} \]

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 CH₂O directly as well, lest Tollens condensation intervenes. Way out??

Revised strategy:

a) \[ \text{\chem{\text{CH}_2\text{C} = \text{CH}}} \quad \xrightarrow{\text{FGI, elimination}} \quad \text{\chem{\text{CH}_2\text{C} = \text{O}}} + \text{\chem{\text{C} = \text{Cl}}} \]

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

b) \[ \text{\chem{\text{CH}_2\text{C} = \text{CH}}} \quad \xrightarrow{1,1 \text{ C-C}} \quad \text{\chem{\text{CH}_2\text{C} = \text{O}}} + \text{\chem{\text{C} = \text{Cl}}} \]

(just a ketone synthesis!)

\[ \text{\chem{\text{C} = \text{Cl}}} \quad + \quad \text{\chem{\text{Li}}} \quad \xrightarrow{\text{H}^+} \quad \text{\chem{\text{CH}_2\text{C} = \text{Li}}} \]

\[ \text{\chem{\text{C} = \text{Cl}}} \quad + \quad \text{\chem{\text{Li}}} \]

\[ \text{\chem{\text{CH}_2\text{C} = \text{CH}}} \quad \xrightarrow{1,1 \text{ C-C}} \quad \text{\chem{\text{CH}_2\text{C} = \text{O}}} + \text{\chem{\text{C} = \text{Cl}}} \]

(c) \[ \text{\chem{\text{CH}_2\text{C} = \text{CH}}} \quad \xrightarrow{\text{FGI, chemoselective reduction}} \quad \text{\chem{\text{CH}_2\text{C} = \text{CH}}} \quad \xrightarrow{\text{rev. TM is an allylic alcohol}} \quad \text{\chem{\text{CH}_2\text{C} = \text{H}}} \]

\[ \text{\chem{\text{HO-C-C}}} \quad \xrightarrow{\text{H-O-C-C}} \quad \text{\chem{\text{MgI}}} \quad + \quad \text{\chem{\text{HO-C-C}}} \quad \xrightarrow{\text{pinacol-pinacolone}} \quad \text{\chem{\text{HO-C-C}}} \quad \xrightarrow{\text{glycerol}} \]
The Logic of Organic Synthesis: Analysis of bifunctional target molecules:

B) 1,3-bifunctional compounds and $\alpha,\beta$-unsaturated carbonyl compounds (contd.):

Try these yourself:

[B.1] \[
\text{Ph} - \text{CO} - \text{CO} - \text{Et} \]

[B.2] \[
\text{CH}_2 - \text{CH}_2 - \text{C} = \text{C} - \text{Ph} \]

[B.3] \[
\text{CH}_2 - \text{CH}_2 \text{CO} - \text{Et} \]

(this one's imp. for exam, think dianion from EAA)

[B.4] \[
\text{CH}_2 \text{OH} - \text{CO} \]

[B.5] \[
\text{C} = \text{C} - \text{Ph} \]

[B.6] \[
\text{Ph} - \text{CO} - \text{CO}_2 \text{Et} - \text{CO}_2 \text{Et} \]

[B.7] \[
\text{Cl} - \text{C} = \text{O} - \text{Cl} \]

[B.8] \[
\text{Me} - \text{O} - \text{C} = \text{O} \]

[B.9] \[
\text{O} - \text{C} = \text{O} \]

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