Conversion of Acids to Esters

The following reaction occurs in bad wine (wine containing acetic acid).

\[
\text{Acetic acid} + \text{Ethanol} \xrightleftharpoons{\text{H}^+} \text{Ethyl Acetate} + \text{H}_2\text{O}
\]

Mechanism:

Would an ester be formed under basic conditions?

\[
\text{Acetic acid} + \text{Ethanol} \xrightarrow{\text{Na}^+ \cdot \text{OH}} \text{Sodium Acetate} + \text{Ethanol}
\]

There is no ester formation from a carboxylic acid with a base. In water, a carboxylic acid is usually acidic enough to catalyze the reaction though.

Reactions at the \(\alpha\) Carbon

Compare the pKa’s of the alpha hydrogens of an ester and a ketone:
The ketone is more acidic. This can be explained by the resonance structures of the enolate (2 major forms and one minor form):

To deprotonate an alpha hydrogen a base is needed that will not attack the carbonyl (ie. act like a nucleophile). This may be achieved by using sterically hindered bases:

Electrophiles reacting with enolates:
Reaction | Electrophile | Acts as 'E⁺'
---|---|---
Halogenation | $X₂$ $X = \text{Cl, Br, I}$ | $X^+$
Alkylation | $\text{R-CH}_2\text{-X}$ | $\text{RCH}_2^+$
Aldol | $\text{R-C-H}$ | $\text{R-C-H}$
Acylation | $\text{R-C-Y}$ | $\text{R-C}$

Examples:
Halogenation

\[
\begin{align*}
\text{H-C=O-O-CH}_2
\end{align*}
\xrightarrow{\text{LDA}}
\begin{align*}
\text{H}_2\text{C=O-CH}_2
\end{align*}
\xrightarrow{\text{Cl}_2}
\begin{align*}
\text{Cl-C-CH}_2\text{O-CH}_2
\end{align*}
\xrightarrow{\text{LiCl}}
\begin{align*}
\text{N-C-CH}_2\text{-CH}_2\text{-N-CH}_2\text{CH}_3
\end{align*}
\]
Alkylation

What else could be used (instead of \( \text{ICH}_3 \))?
No, $S_n2$ reactions won't go with this reagent

Yes, in the above reaction the product would be Benzyl iodide

Aldol

1. LDA
2. $\text{O} \rightarrow \text{H}$
3. $\text{H}^+$

overall addn of
Mechanism

Acylation
Mechanism

Acylating Agents:

Above reaction would work with:

would not work
\( \beta \) Carbonyl Acids and Esters

These can be synthesized with an ester (or acid) and an acylating agent

\( \beta \) carbonyl (keto) acids decarboxylate (lose \( \text{CO}_2 \)):
The structure shown above is methyl (or dimethyl) malonate. As a reminder, you are responsible for the names of first 4 dicarboxylic acids. Methyl malonate has two alpha protons that are very acidic (pKa ~12). This is due to the presence of two carbonyls which stabilize the negative charge at the alpha carbon (resonance stabilization). The anion has three resonance structures that are shown below. The anion can be alkylated using alkyl halide through S_N2 type reaction.

The alkylation reaction can be repeated again since there is one more acidic alpha proton present.

The product from this reaction, dimethyl 2,2-diethylmalonate, can be used to perform other reactions as we will see.