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**PLEASE COMPLETE NOTES IN INK AND DO NOT STAPLE.**

Recall: Acidity of H on the  $\alpha$ -carbon  $\rightarrow$  enols & enolates can act as nucleophiles in a variety of reactions.

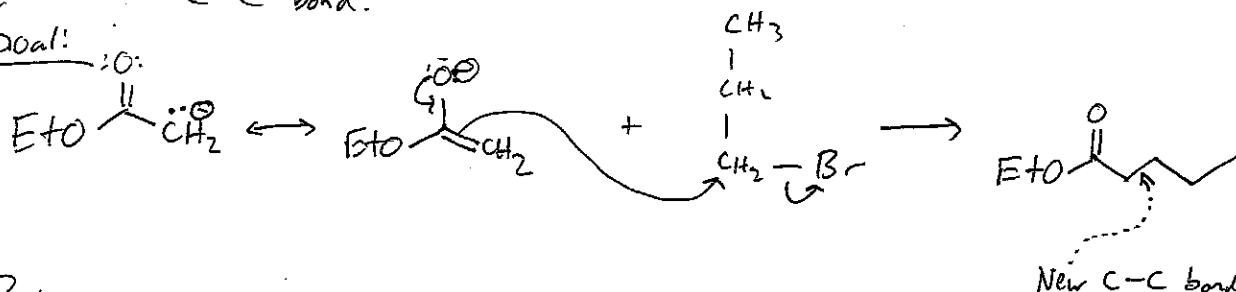
Aldol, Claisen involve a carbonyl as the electrophile. Other electrophiles are possible, too....

$S_N2$  reactions of enolates

Goal: introduce alkyl groups to the  $\alpha$ -carbon

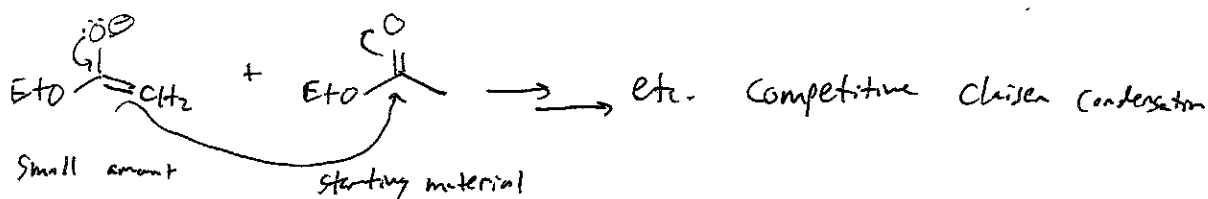
\*New C-C bond\*

Goal:



But not so easily achieved in practice

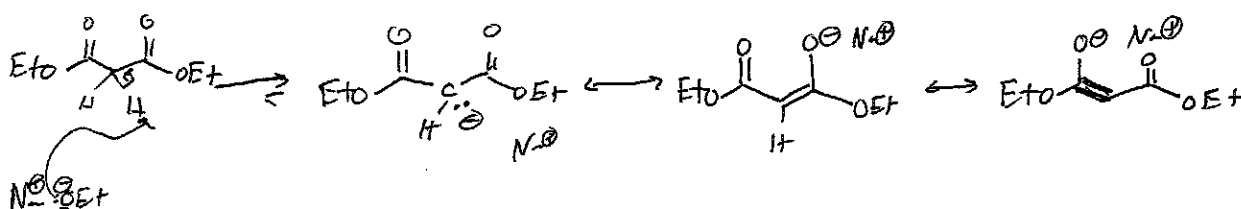
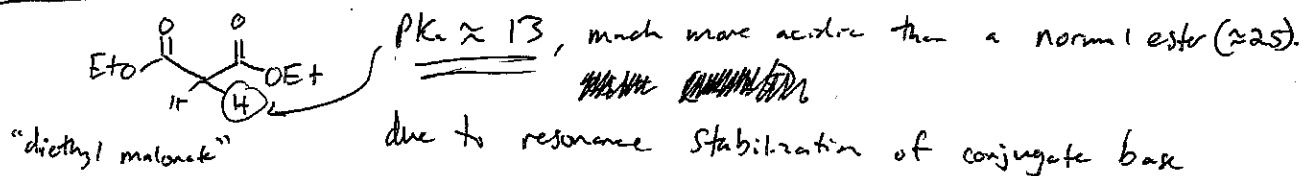
Problems bases like NaOH, NaOEt generate only a small amount of the enolate. So the remaining carbonyl compound will compete with the alkyl halide as an electrophile.



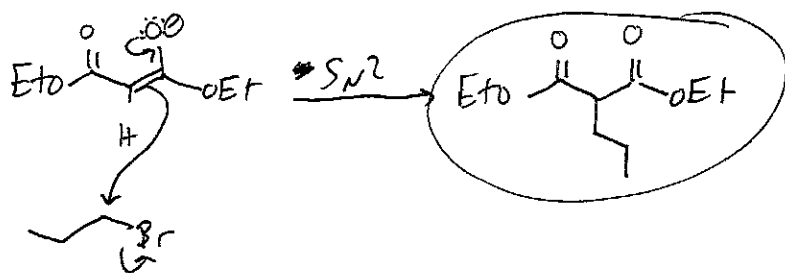
Solution #1: Make the  $\alpha$ -proton more acidic so that NaOEt can quantitatively deprotonate the molecule, i.e. complete enolate formation.

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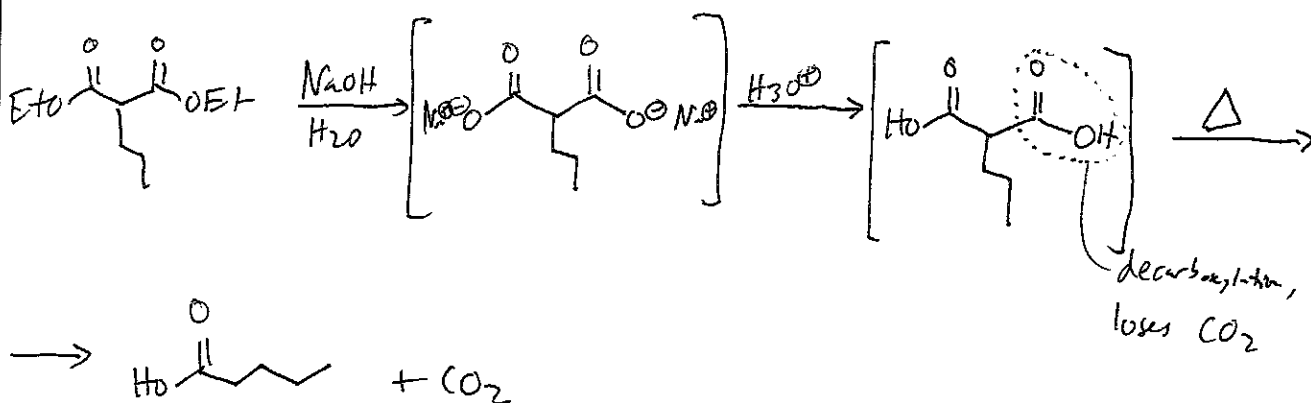
For example:



Then,



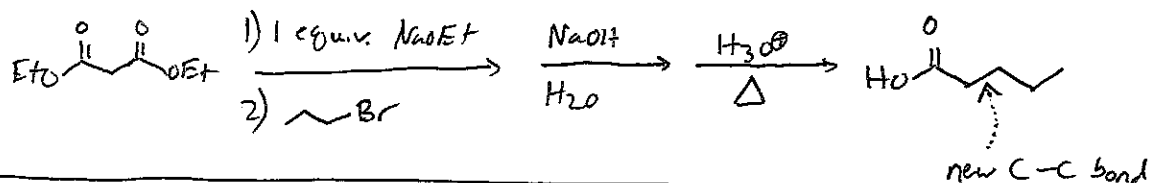
This resulting ester can be hydrolyzed to the diacid, then heated to promote decarboxylation.



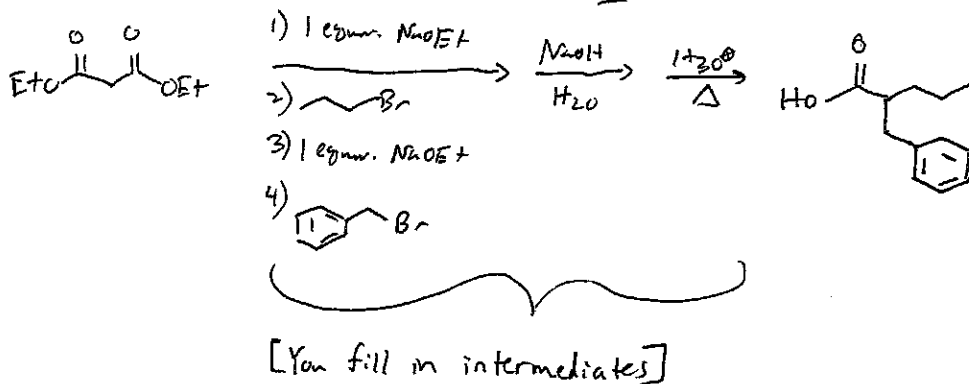
Review Luder (pp. 977-978) on decarboxylation.

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Overall: can introduce alkyl groups to a carboxylic acid starting from the malonate diester and following this series of steps.

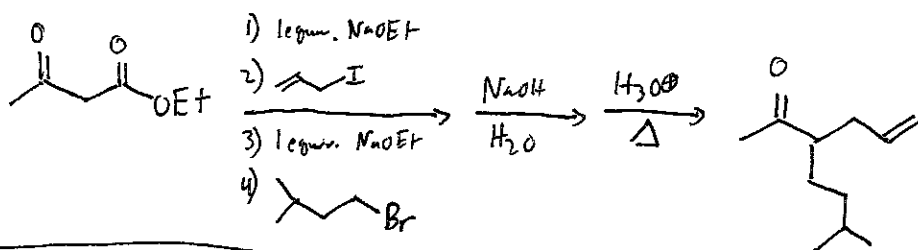


Modified Approach: can be used to introduce 2 alkyl groups.



Overall this is called the "malonic ester synthesis of carboxylic acids"

Similar strategy: to create ketones from  $\beta$ -keto esters

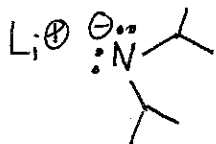


Remember, goal: introduce alkyl groups to  $\alpha$ -position.  
 Problems: bases such as NaOEt are not strong enough to completely deprotonate simple esters.

Solution #2: use a stronger base for quantitative deprotonation.

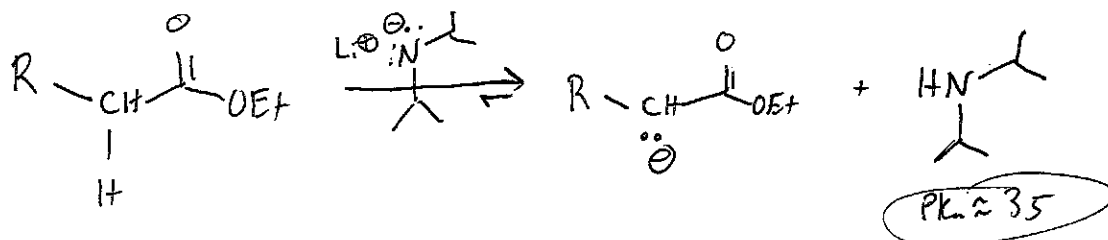
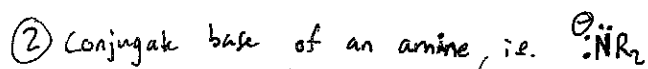
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Common example:



Lithium diisopropyl amide (LDA)

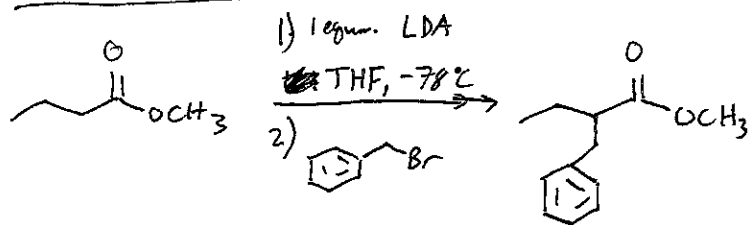
Note: "amide" has two meanings in organic chemistry. Unfortunate historical artifacts



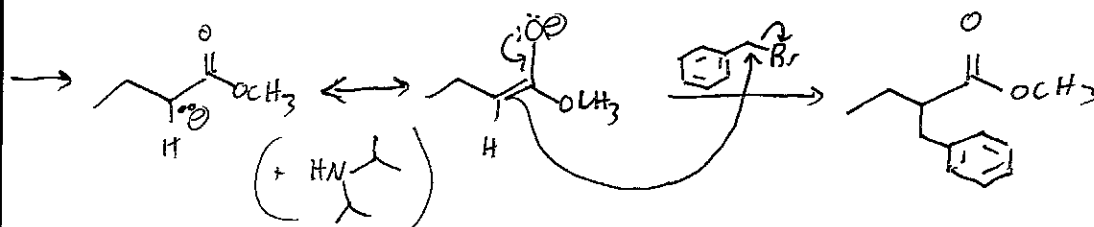
$\text{pK}_a \approx 25$

So favored by  $10^{10}$ , very product-favored. Quantitative deprotonation.

Synthetic example:



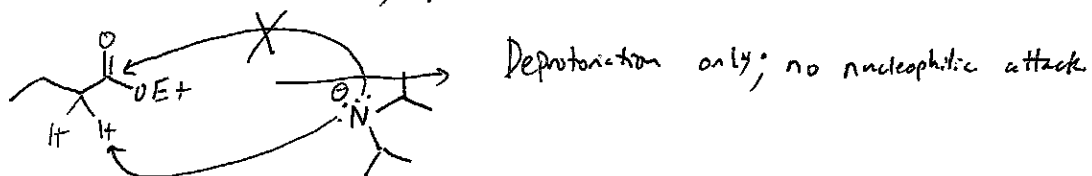
Key Step:



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### Notes about LDA

- 1) Avoid Claisen condensation by slowly adding the ester to the LDA solution. Thus, the solution never contains very much neutral ester.
- 2) LDA could potentially react as a nucleophile (rather than a base) and attack the carbonyl carbon of the ester. But the isopropyl groups are bulky, and prevent this from taking place.



- 3) Formation of LDA requires an even stronger base

