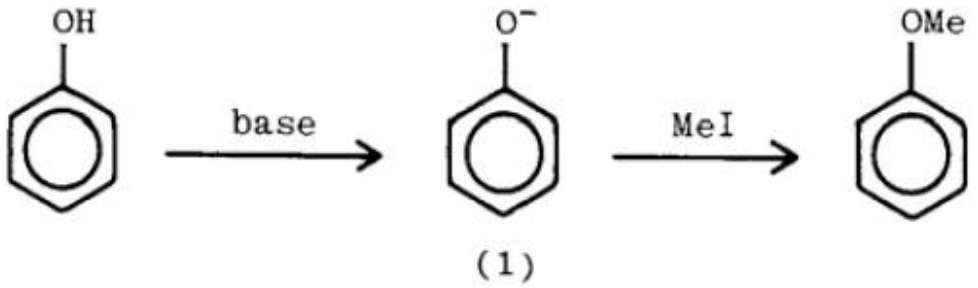
Regioselectivity

To react one specific part of a single FG

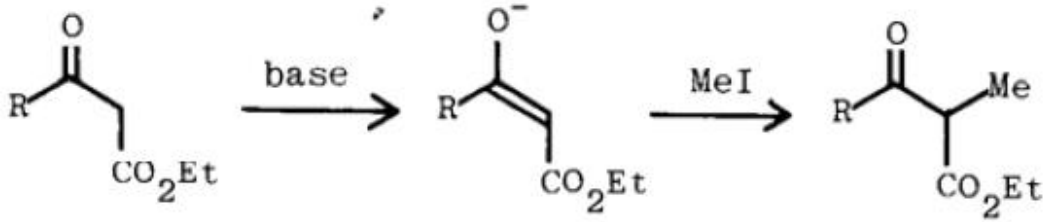
Phenolate ions react at O enolate ions at C

O-alkylation:



(1)

C-alkylation:

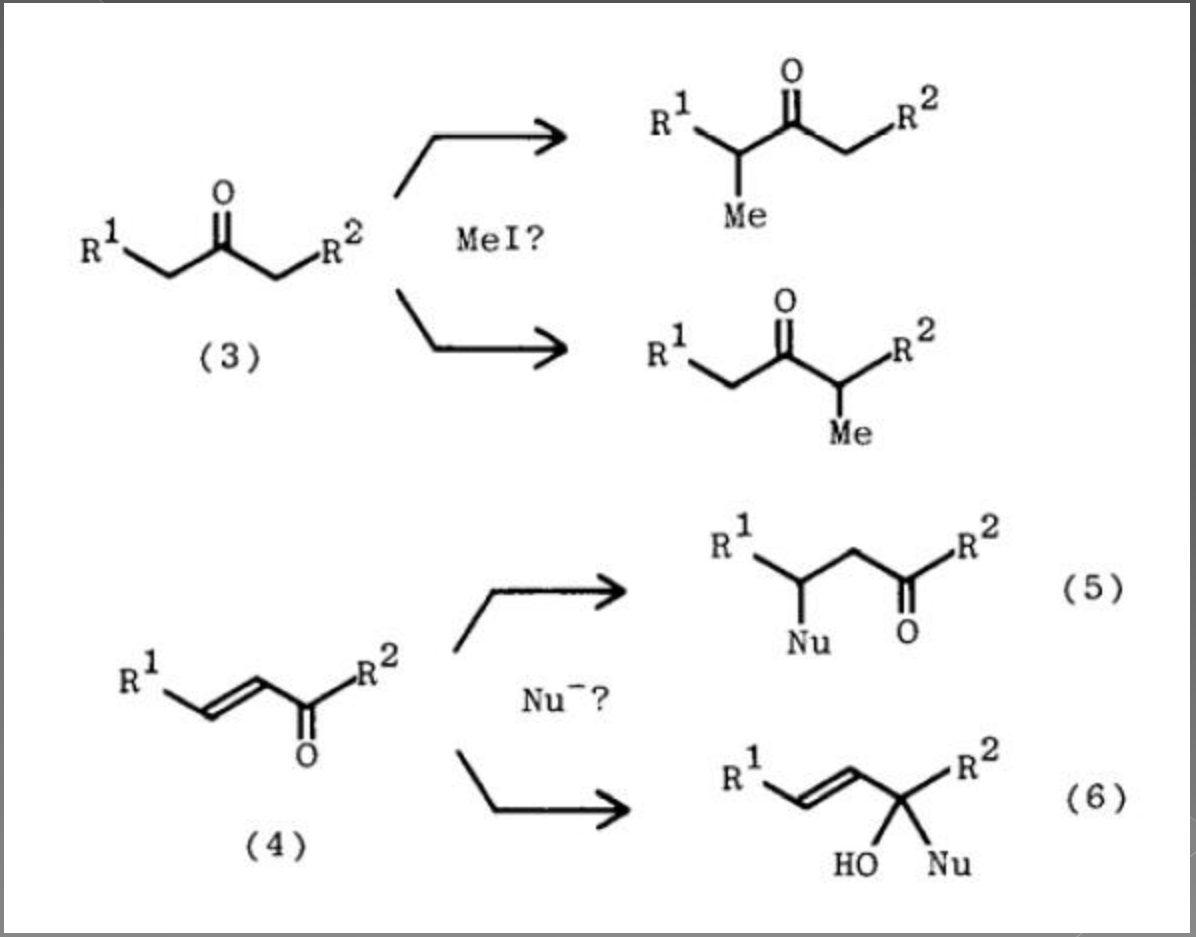


(2)

We will discuss-

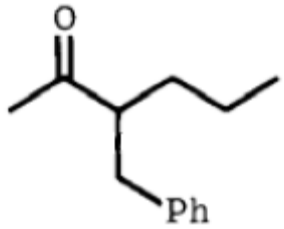
(a) how can we alkylate of brominate one side of unsymmetrical ketone

(b) how can we control addition of Nu to unsaturated C=O to get Michael or direct addition



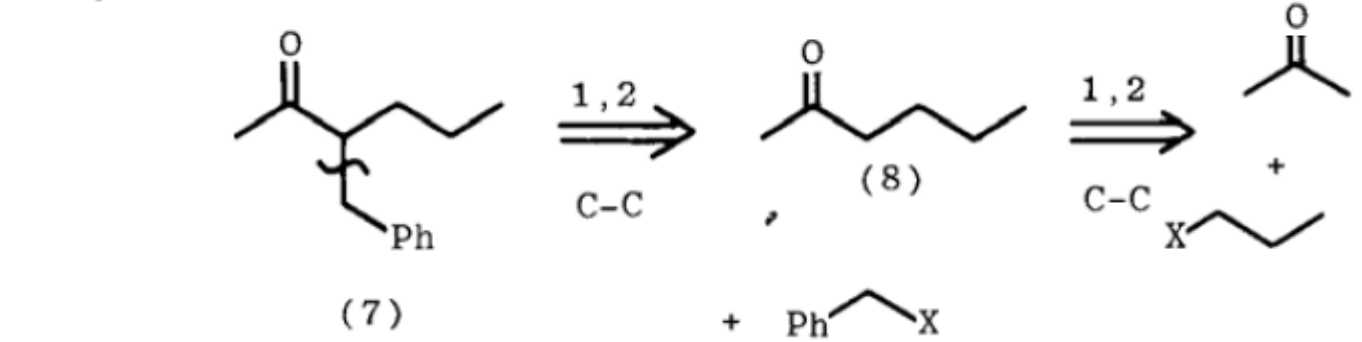
Regioselective alkylation of ketones

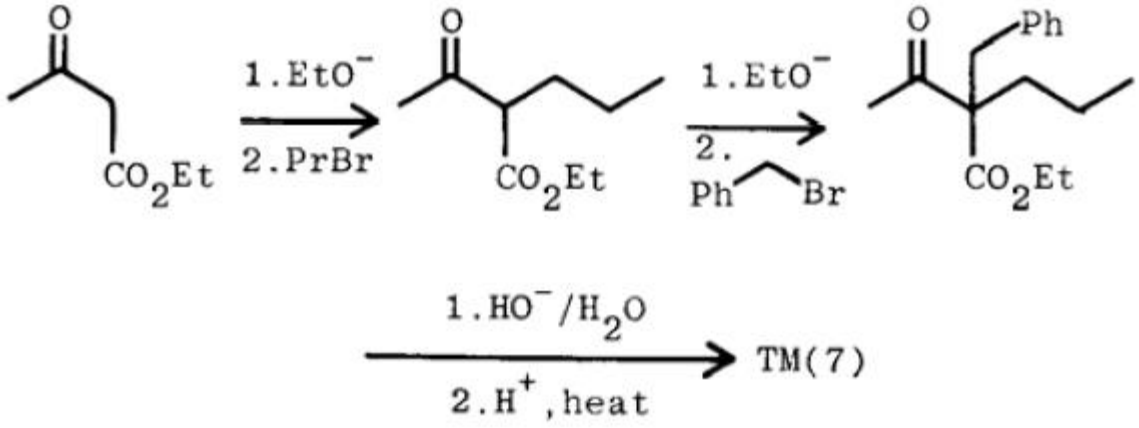
It is possible by strategy to synthesize either target molecule by alkylation

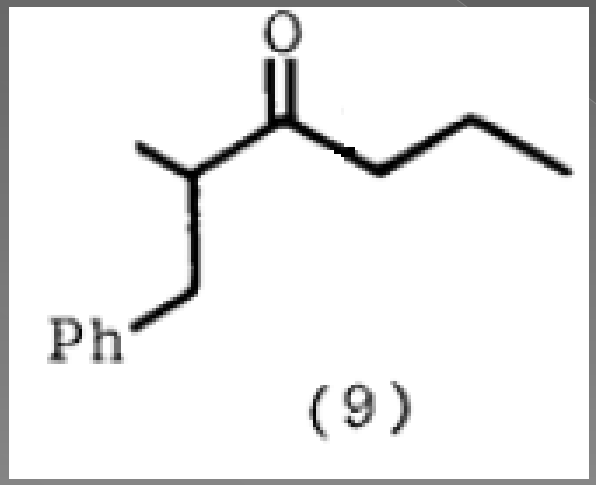


(7)

TM can be made by benzylation of ketone 8.
8 can not be selectively benzylated but if we make 8 by alkylation too, then the synthesis can be achieved
An activating gp for alkylation would be needed



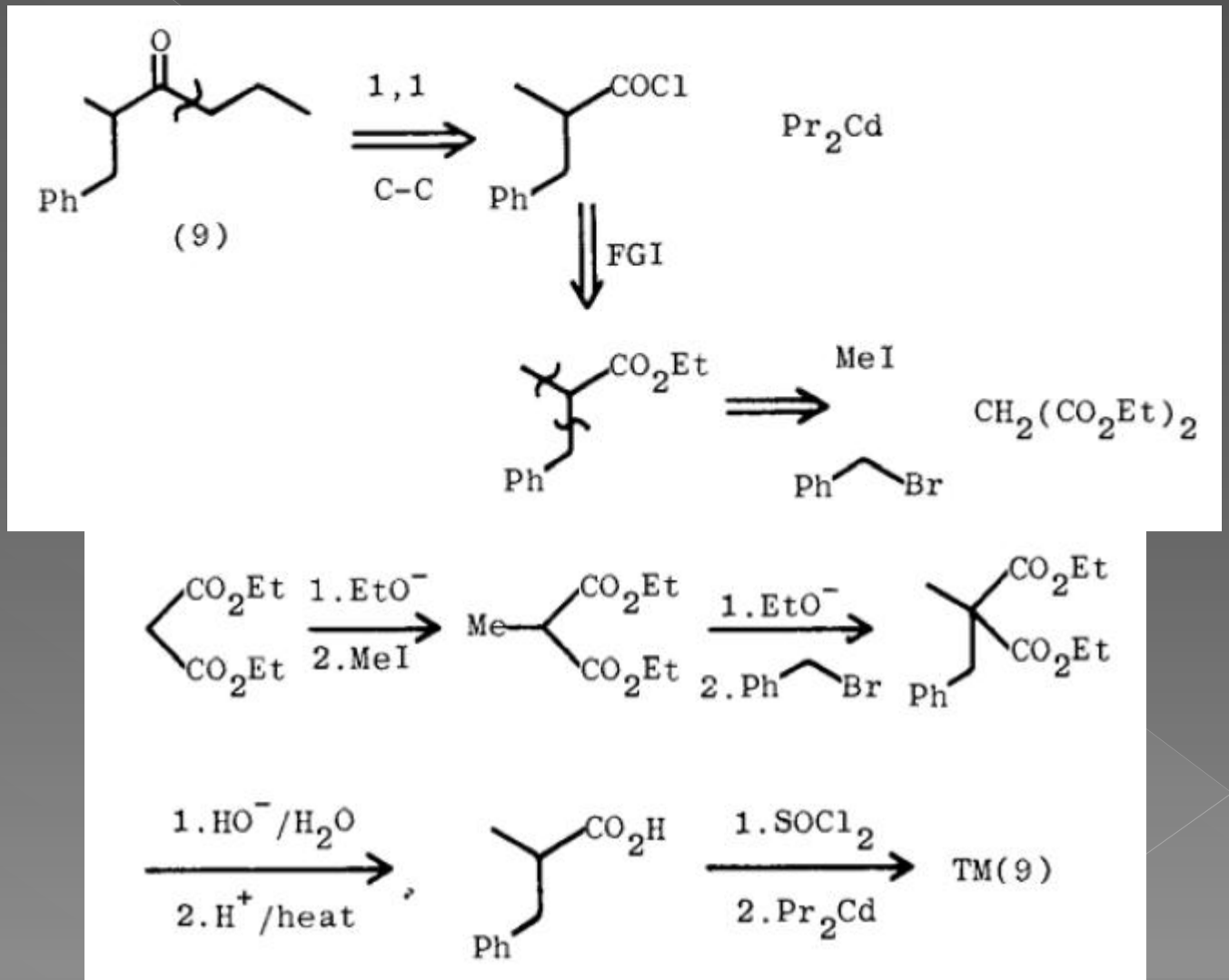




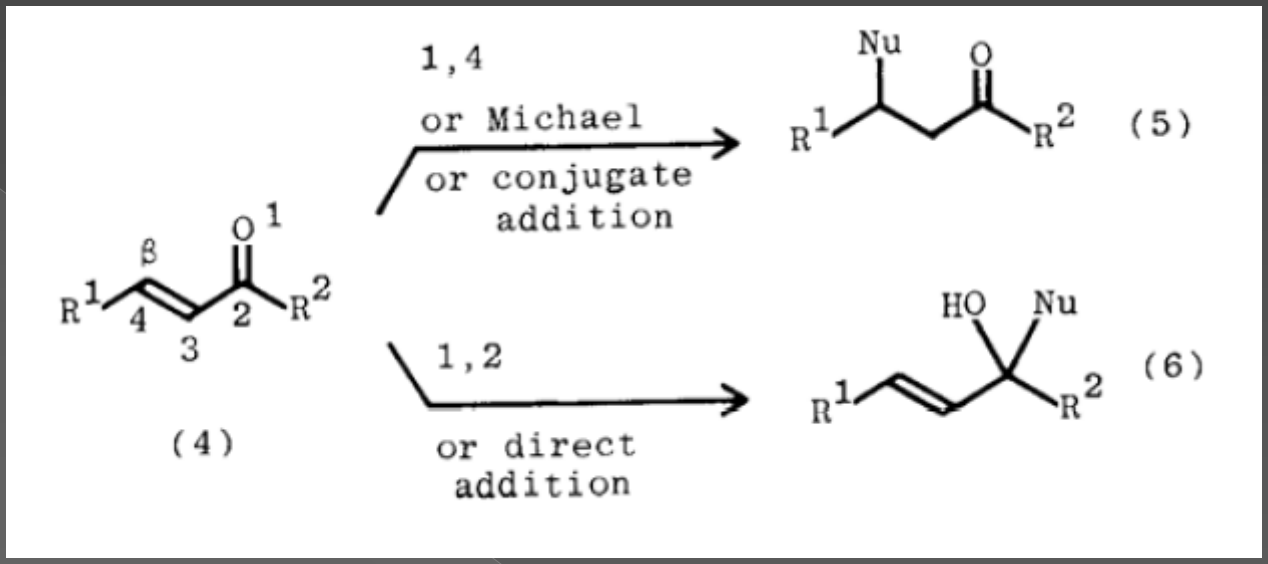
(9)

Regioselectivity problem disappears in alkylation of ester since esters can enolize on one side only

If we complete all alkylations at ester stage, we can start from malonate and make unsymmetrical ketones.



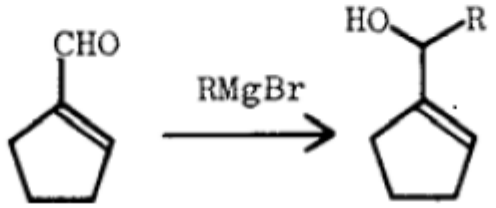
Regioselectivity in Michael Reactions



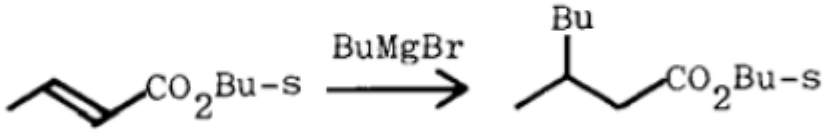
General mechanistic principles

1. The Michael product **(6)** is the thermodynamic product since the more stable C=O bond is preserved and the weaker C=C bond destroyed.
2. Direct addition is more easily reversed than Michael addition. Hence the more stable the nucleophile, or the more reversible the addition, the more Michael addition is favoured.
3. Kinetically, the C=O is the harder site and the β carbon atom the softer. Therefore strongly basic nucleophiles tend to attack directly whereas weakly basic nucleophiles tend to attack in Michael fashion.

Among Michael acceptors, direct addition is most likely with unsaturated aldehydes and acid chlorides, Michael addition most likely with ketones or esters. Hence Grignard reagents add directly to aldehyde **(10)** and Michael fashion to ester **(11)**.



(10) 85–90%



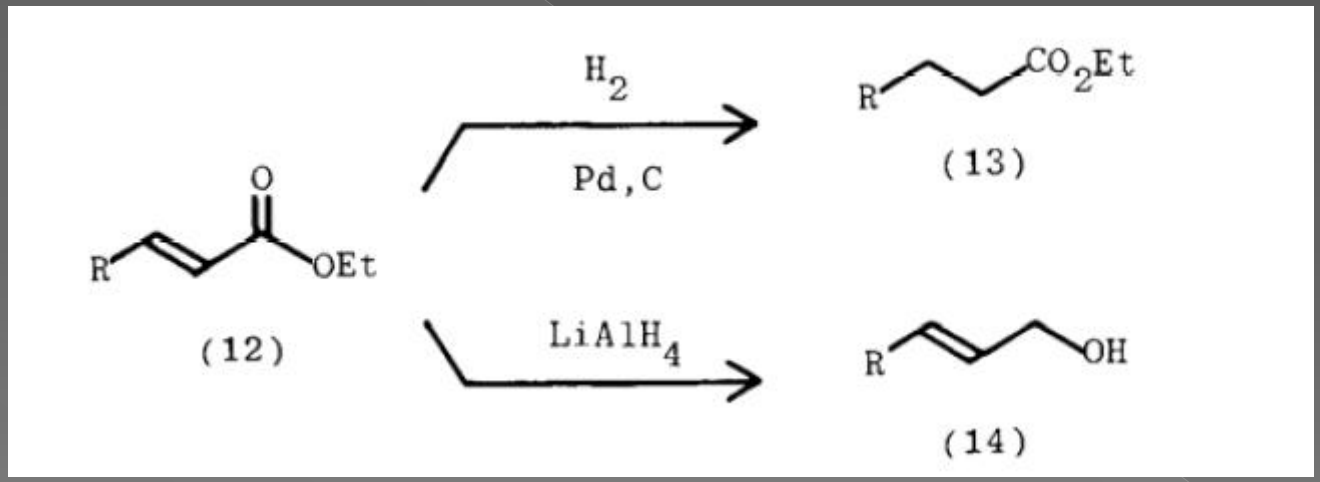
(11) 60%

Nu:

RLi, NH_2^- , RO^-, hydride reducing agents are more likely to add direct

RMgBr, neutral amines, RS^- and stable carbanions are more likely to add by Michael fashion

Hydrogenation is not ionic reaction-it selects weaker bond



Reduction of the ester should be regioselective in favour of carbonyl reduction if LAH is used

