Course Chem 345 Lecturer Prof. Gellman

Day Wednesday Date 4/15/15

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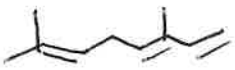
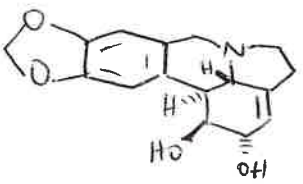
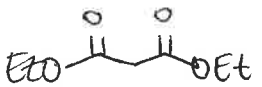
Daffodil Chemistry

 – Aroma

"Lycorine"  Poison!

Recall: How achieve α-alkylation of carbonyl compounds? Requires complete formation of enolate.

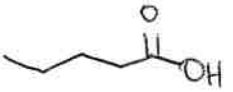
1) β-dicarbonyl – α H is now very acidic

Ex: 

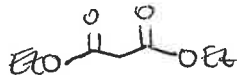
(malonate diester [pka ~ 13])

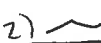
1) 1 equiv. NaOEt, EtOH
2) 

1) NaOH, H_2O
2) $H_3O^{\oplus}$, Δ

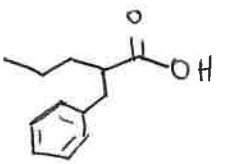
 $(+ CO_2)$

*2 alkyl groups can be added...

Ex: 

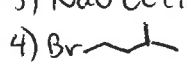
1) NaOEt (1 equiv)
2) 
3) NaOEt (1 eq)
4) 

1) NaOH, H_2O
2) H_3O^+, Δ

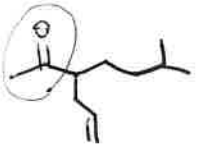


*Analogous process leads to α-substituted ketones. Start w/β-keto ester. (Available via variant on Claisen condensation - see above)

Ex: 

1) NaOEt (1 eq)
2) 
3) NaOEt (1 eq)
4) 

1) NaOH, H_2O
2) $H_3O^{\oplus}$, Δ



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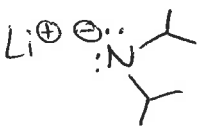
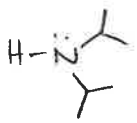
• Solution #2 – use a very strong base!

* most common

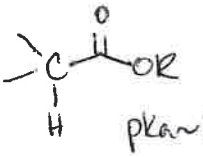


"lithium diisopropyl amide" (LDA)

(NH_2 = also termed amide)



pKa ~ 35

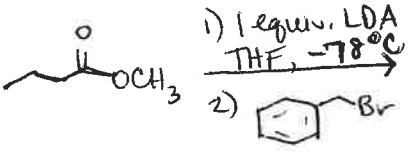


pKa ~ 25

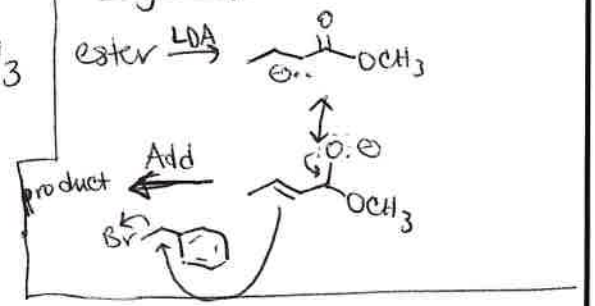
(will get quantitative deprotonation by LDA)

* Use:

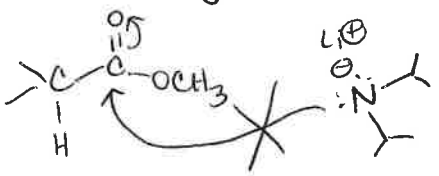
Ex:



Key step:



*Note: use "bulky" amide anion to avoid direct attack on C=O



* Generate LDA – need a very basic species!

= typically use alkyl lithium species

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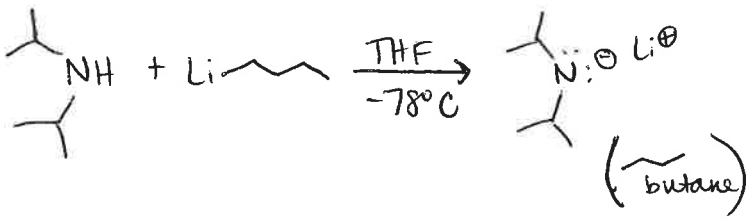
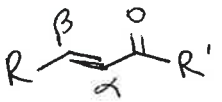
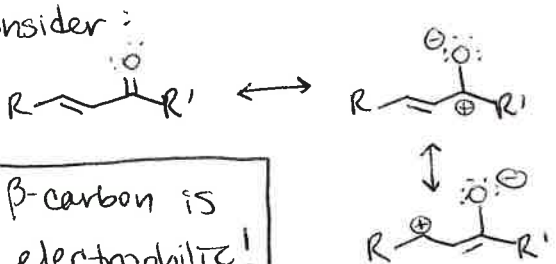


- α, β-unsaturated carbonyls – distinctive reactivity

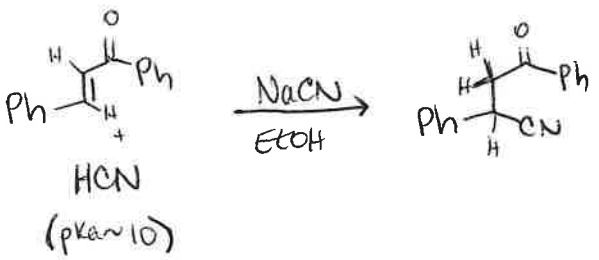


* Consider:



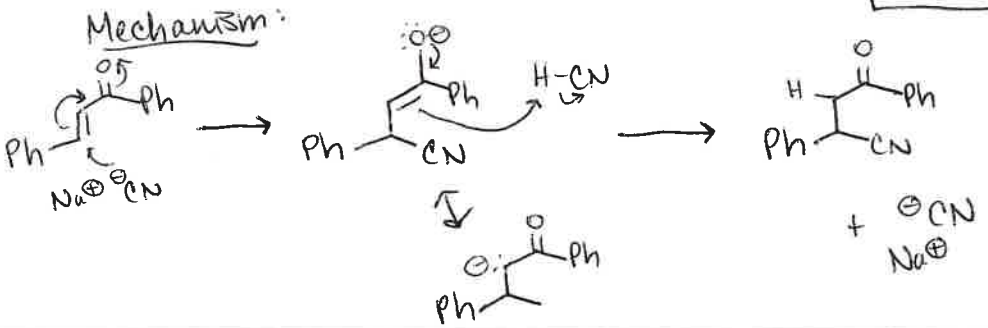
∴ β-carbon is electrophilic!

Ex:



"Conjugate addition"
↳ adding to β-carbon of α,β-unsaturated carbonyls

Mechanism:



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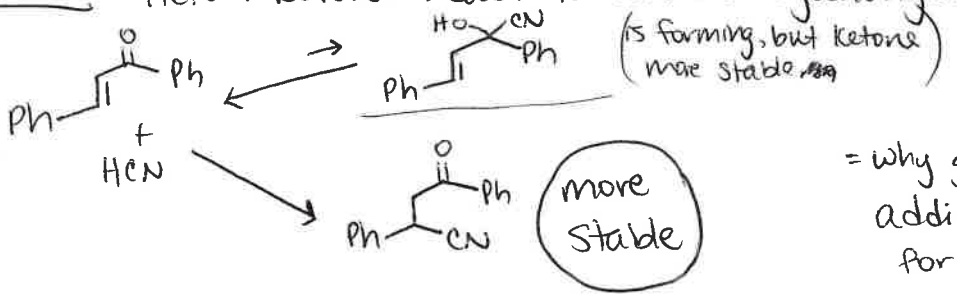
*Recall: HCN + ketone react to form a cyanohydrin (reversible)



= why get conjugate addition over cyanohydrin formation

*Note: C=C vs C=O → C=O generally preferred

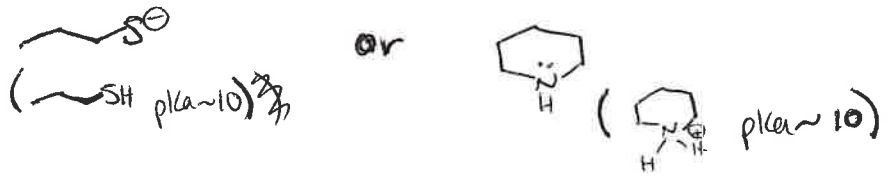
(↳ recall: enol less stable than carbonyl isomers)

$H_2C=CH-CH_2-OH$ ΔH_f -30 kcal/mol

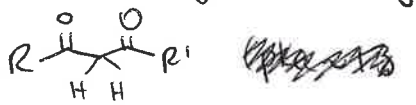
vs.

$H_3C-CH_2-C(=O)-H$ -45 kcal/mol (prefers C=O to C=C)

* In general, nucleophiles that are weakly basic undergo conjugate addition



* Most useful, synthetically, conjugate bases of β-dicarbonyls



(pKa 9~13)

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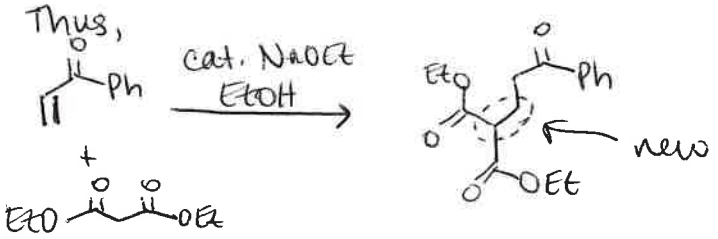
Thus,



You fill in mechanism!

"Michael additions"

-Simple Ketones react too

- Tandem Reactions
  - Michael addition, then aldol (dehydration) = "Robinson annulation"

Ex: