Friday 1/24

Sometimes chemist want to convert a carbonyl to a compound where a nitrogen can be converted to an amine group in subsequent steps. If they start with an alkyl amine, the N of the amine will attack the carbonyl C. ∴ $^{\ominus}CN$ (cyanide) is used strategically to at the C of $^{\ominus}CN$ to the C=O and the N can be modified later.

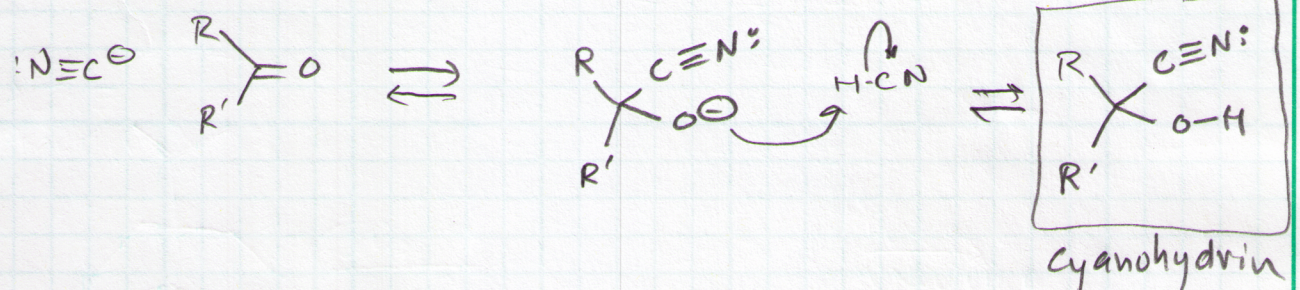
$^{\ominus}CN$ is added as HCN (gas) via $Na^{\oplus}\,^{\ominus}CN$ + (conc HCl)

moderately basic — pKa ~9.2

not as acidic as HCl(g) −6.3 !

$H^{\oplus}$ $^{\ominus}CN \rightleftharpoons HCN$

Present! at equilibrium

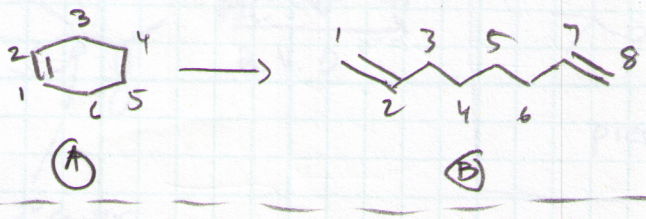


Cyanohydrin

Wed 1/22

We saw in earlier chapters how to make alkenes via E1 and E2 reactions on alkyl chains harboring a good leaving group and a base. The rxns were driven by the proper stereoisomers in the E2 rxn (anti periplanar H and Leaving group) and by double bond stability in the E1 rxn. Carbonyl compounds provide access to C=C products with great specificity via ylide ('ill-lid') rxns.

Complete the synthesis



(A) (B)

① How do you ring-open (A)?
② How do you add 1 C to each end while keeping C=C at ends?

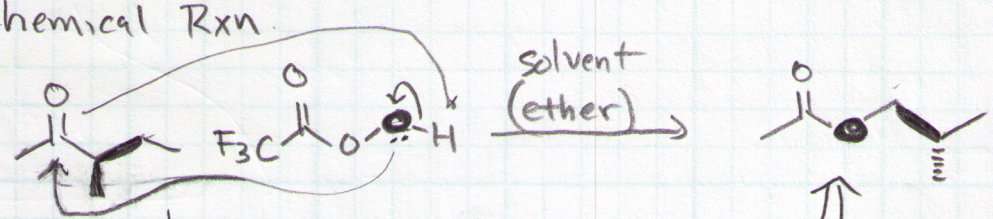
This problem was strategy practice

Baeyer-Villiger Oxidation

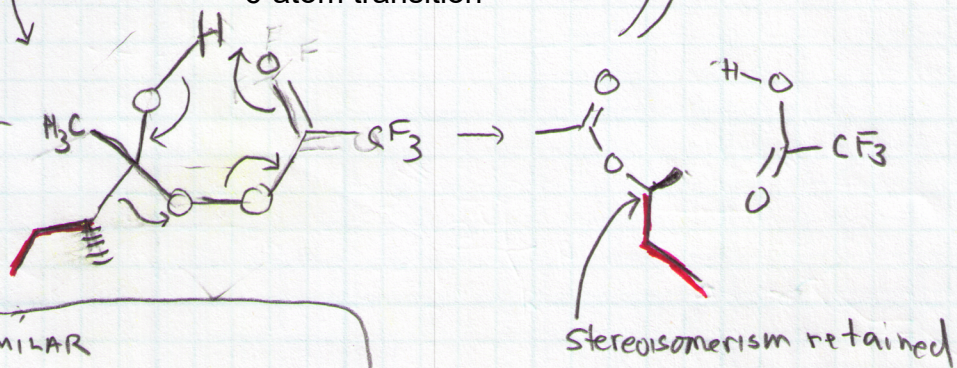
↳ converts ketones to esters and cyclic esters (lactones) that provide a feed stock for synthetic chemists to build biologically active and pharmaceutically relevant compounds in addition to those used in the fragrance sector.

An enzyme called Baeyer-Villiger monooxygenase converts ketones to biodegradable esters.

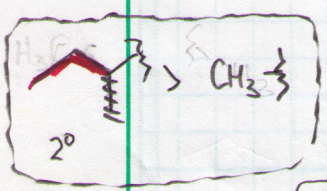
Chemical Rxn



6-atom transition

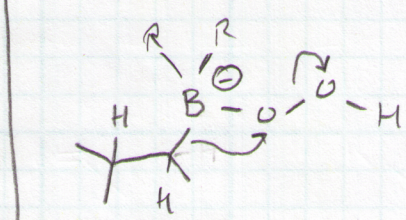


migration preference



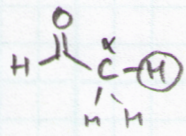
Stereoisomerism retained

SIMILAR

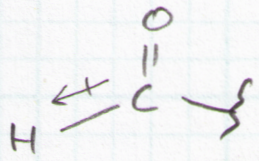


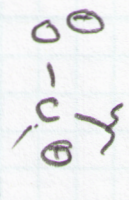
Recall that a similar reaction occurred during the oxidative deborylation reaction when converting alkenes and alkynes to alcohols and carbonyl prods.

ENOLS ENOLATES and ALDOL CONDENSATION

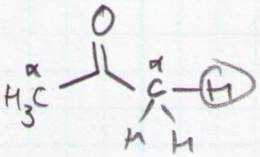


pKa 17



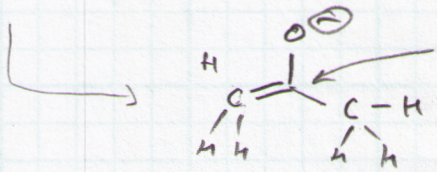
H does not stabilize 

∴ deprotonation of acidic proton (α-H) of aldehyde occurs at greater rate over ketone deprotonation



pKa 20

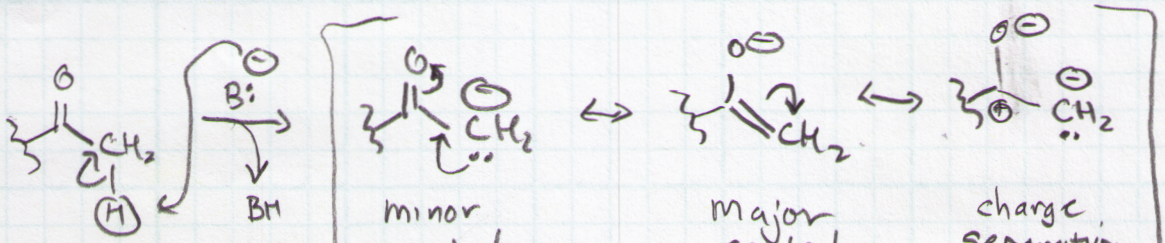
recall hyperconjugation donates e^- toward carbonyl C.



notice the δ+ here is reduced by this effect.

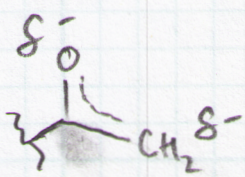
hyperconjugate

Deprotonation is stabilized by resonance

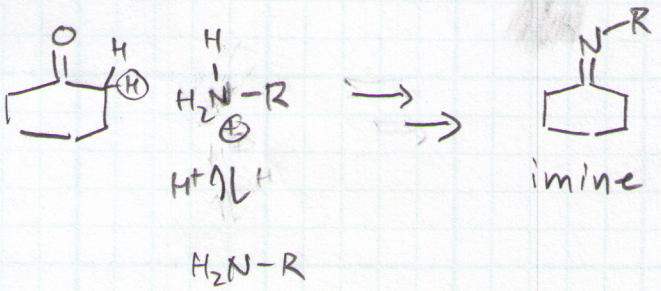


(-) prefers more e(-) atom

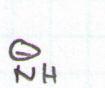
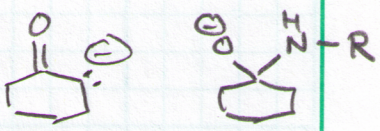
very Minor contrib

Resonance Hybrid 

We know

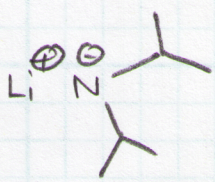


H_2N-R

if  small base is used to remove α-H THEN COMPETITION 

(Need a base whose conj acid has higher pKa than α-H of ketone)

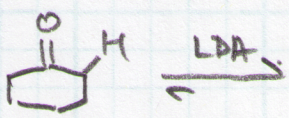
Need bulkier base that's not nucleophilic or non-nucleophilic base



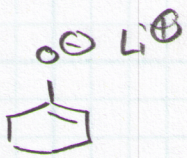
DA

Lithium diisopropylamide

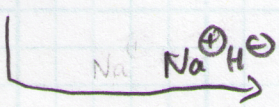
- chrg amine

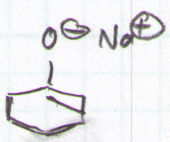


pKa 20



H-DA protonated pKa 36





H-H (g) pKa 38

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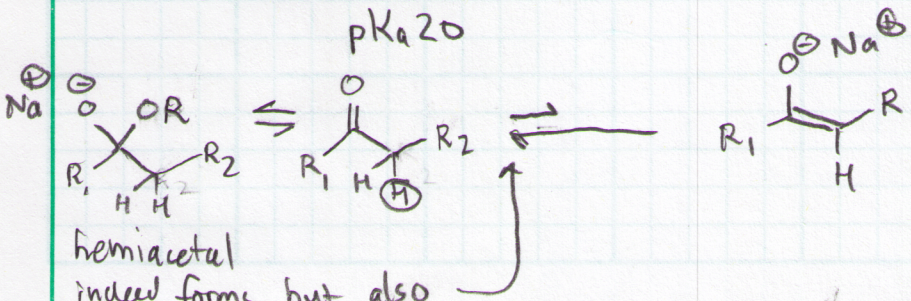
often ROH/$RO^{\ominus}Na^{\oplus}$ mixtures are used

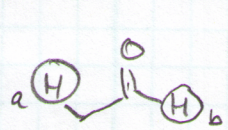
pKa 20

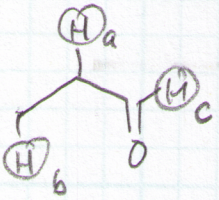


hemiacetal indeed forms but also

H-DR pKa 16

NOTE pKa values equilibrates to left



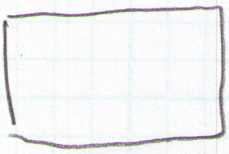


which is the most acidic α-H?

LDA

LDA

enolate salt



enolate salt

If you were in lecture, you will know the solution to this problem

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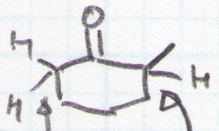
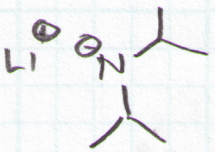
Kinetic vs Thermodynamic control of enolate production

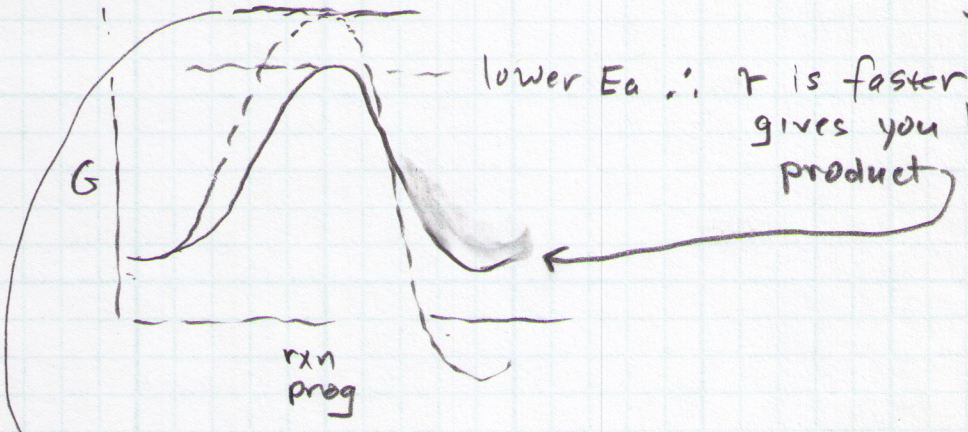


sterically hindered

less steric site

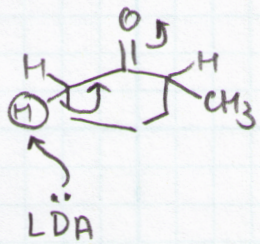


large-ish base prefers to access less steric site intrinsically



higher Ea ∴ r is slower, need more E to overcome barrier, but product is more stable along this pathway

prevents equilibration

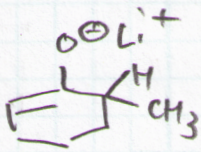


LDA

XS
LDA
THF −78°C
cold

v. little E in system

Lower Ea pathway preferred



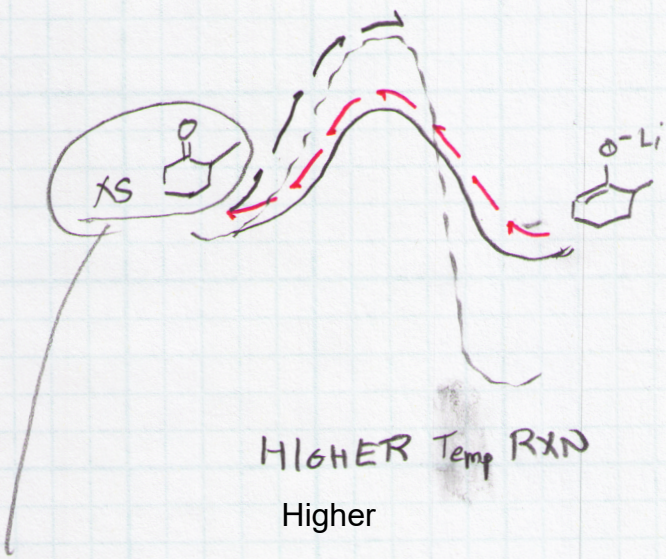
lesser substituted alkene
MAJOR

XS ketone - promotes equilibration

LDA
THF 23°C

significantly higher T than −78°C

XS Means 1.5 equiv



HIGHER Temp RXN

Higher

maintains EQUILIBRium w/ KINETIC ENOLATE, When kinetic enolate returns to ketone, then it can pass over higher Ea and go to the thermodynamic product.