

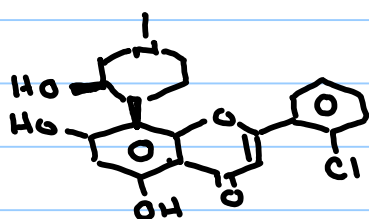
ORGANIC SYNTHESIS

Note Title

1/28/2017

- CONSTRUCTION OF LARGER MOLECULES FROM SMALLER (ULTIMATELY COMMERCIALY AVAILABLE) ONES

CONSIDER FLAVOPIRIDOL (ALVOCIDIB)



CDK9 KINASE INHIBITION
(LEAD CPD FOR MYELOID LEUKEMIA)
TREATMENT

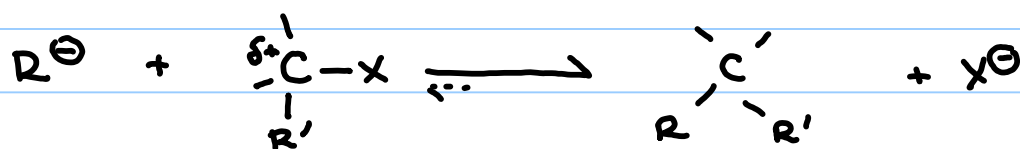
NOT NATURALLY OCCURRING

∴ MUST MAKE IT, AND SIMILAR CPDS (ANALOGUES)

- MOST IMPORTANT CONSIDERATION C-C BOND FORMING RXNS.
- WE'VE SEEN A FAIR AMOUNT OF AROMATIC CHEMISTRY (59-235), BUT NOT THAT MUCH ALIPHATIC CHEM.
- HOW CAN THIS BE DONE?
 - ACID INDUCED RXNS i.e. $\overset{\ominus}{\text{C}}^+$ HAVE SEEN SOME, WILL SEE MORE
 - BASE INDUCED RXNS i.e. $\overset{\oplus}{\text{C}}^-$ HAVE SEEN V. LITTLE
 - BIG FOCUS HERE
 - RADICAL RXNS i.e. $\overset{\cdot}{\text{C}}$ - HAVE SEEN 1 OR 2
 - CONCERTED / ELECTROCYCLIC RXNS - A COUPLE IN THIS COURSE

BASE INDUCED RXNS

- IN IT'S MOST GENERAL TERMS, WHY WE MEAN IS....



TO DO THIS, ONE NEEDS

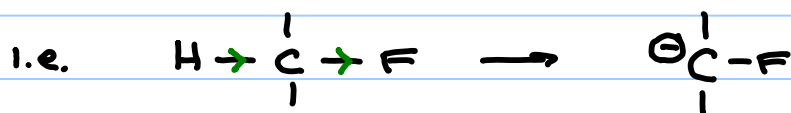
- i) COMPOUND WITH AN ACIDIC H (STABILIZED CARBANION)
- ii) STRONG ENOUGH BASE TO ABSTRACT THIS H⁺
- iii) ELECTROPHILIC CENTRE (C^{δ+}) FOR R[⊖] TO ATTACK
- iv) A WAY OF ELIMINATING THE "−" CHARGE

THESE LAST TWO DEPEND ON THE INDIVIDUAL RXN, SO WE'LL FOCUS ON THE FIRST TWO INITIALLY.

I) HOW IS AN ORGANIC COMPOUND MADE ACIDIC?
- OR HOW IS A CARBANION STABILIZED?

a) INDUCTIVE EFFECTS (−I GROUPS)

- IF YOU CAN REMOVE SOME OF THE ELECTRON DENSITY FROM A CARBANION WITH AN ELECTRONEGATIVE (EN) GROUP THAT ANION IS STABILIZED



- EXAMPLES HALOGENS, −OR, −NR₂, −C≡C−H

NOTE SP HYBRIDIZED C'S ARE MORE EN THAN SP³

- OPERATE THROUGH σ BONDS

- OFTEN 'FIELD EFFECT' USED AS SYNONYM; TERM ACTUALLY HAS A BIT MORE EXPANSIVE MEANING.

b) RESONANCE (MESOMERIC) EFFECTS (-M GROUPS)

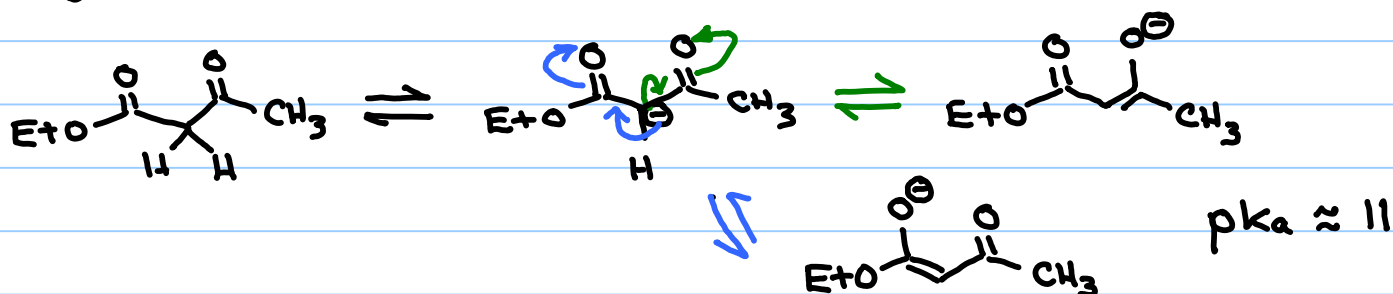
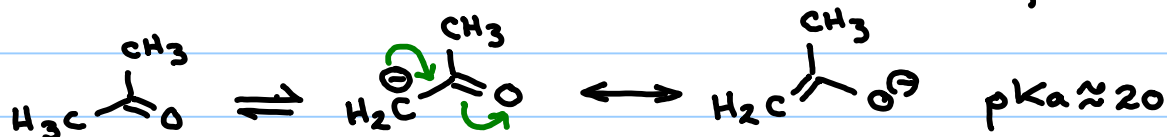
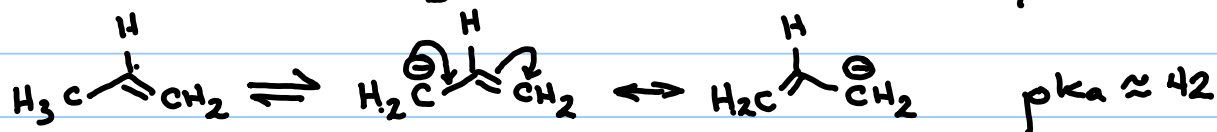
- A MUCH GREATER EFFECT

- OPERATES THROUGH THE π -SYSTEM

- EFFECTIVELY SPREADS "-" CHARGE OVER MORE ATOMS, AND IN DOING SO MAKES THE ANION MORE STABLE

- ANY RESONANCE FORM THAT PUTS "-" CHARGE ON AN ELECTRONEGATIVE (E_N) ATOM - I.E. O, N, S - IS ESPECIALLY STABILIZING.

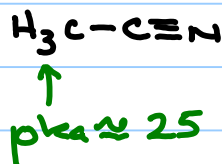
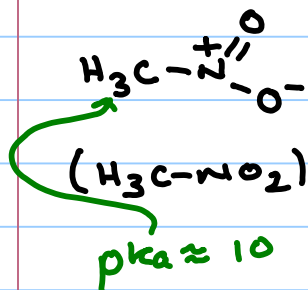
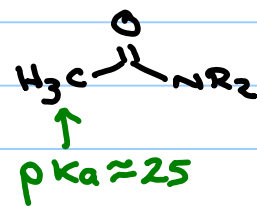
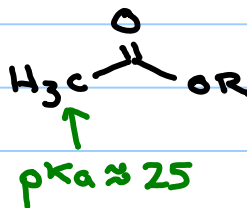
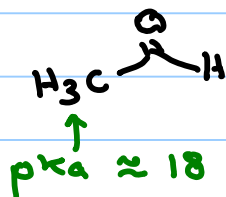
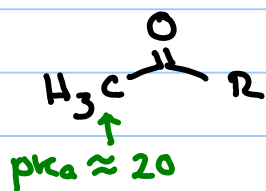
EXAMPLES



- GROUP THAT STABILIZE ANIONS BY RESONANCE ARE CALLED -M GROUP (WITHDRAWING BY MESOMERISM)

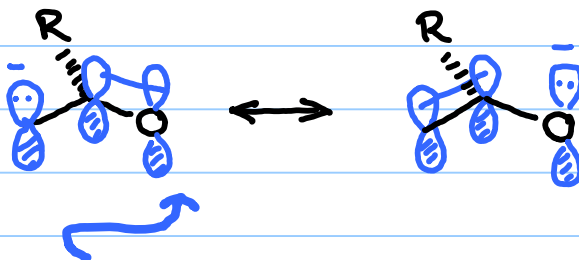
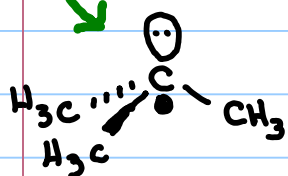
- WE SAW A LOT OF +M GROUPS IN 59-235

TABLE GIVEN OUT, BUT SOME TYPICAL EXAMPLES



- A NOTE ON CARBANION STRUCTURE

- SIMPLE ALKYL CARBANIONS ARE sp^3 HYBRIDIZED, ALTHOUGH THE BARRIER TO GOING TO sp^2 IS NOT LARGE



- IF THEY ARE NEXT TO A π -SYSTEM THOUGH, THEY ARE sp^2 , IN ORDER TO TAKE ADVANTAGE OF CONJUGATION

- C-H'S ACIDIFIED IN THIS WAY ARE SOMETIMES CALLED 'ACTIVATED' H'S

BASES FOR MAKING CARBANIONS

Note Title

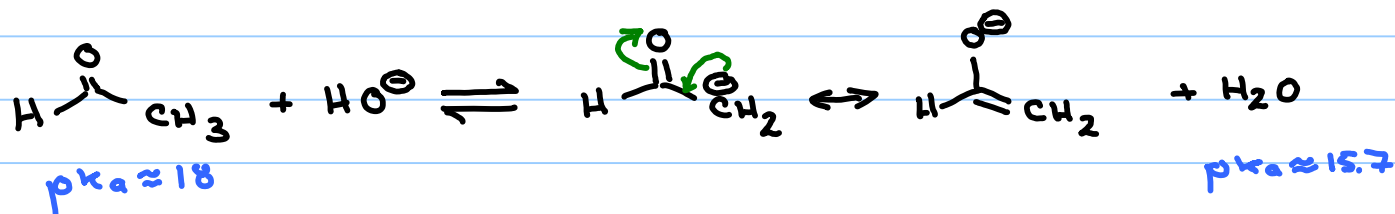
1/30/2017

- SINCE WE ARE WORKING MOSTLY WITH $pK_a \geq 20$ COMPOUNDS HERE, OH^- (pK_a OF CONJUGATE ACID = 15.7) IS ALMOST THE WEAKEST WE'LL USE
- SLIGHTLY STRONGER BASES CAN BE HAD BY REPLACING THE 'H' OF HO^- WITH AN ELECTRON DONATING GROUP BUT FOR A MUCH STRONGER BASE, ONE NEEDS AN ANION ON A LESS ELECTRONEGATIVE ATOM
- KEEP IN MIND THAT ANY BASE IS POTENTIALLY A NUCLEOPHILE, SO GOOD BASES ARE OFTEN STERICALLY HINDERED, TO LIMIT THEIR NUCLEOPHILICITY

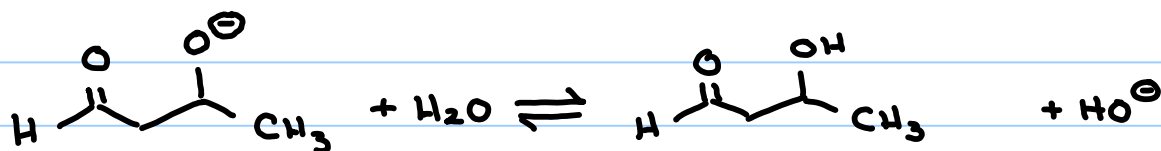
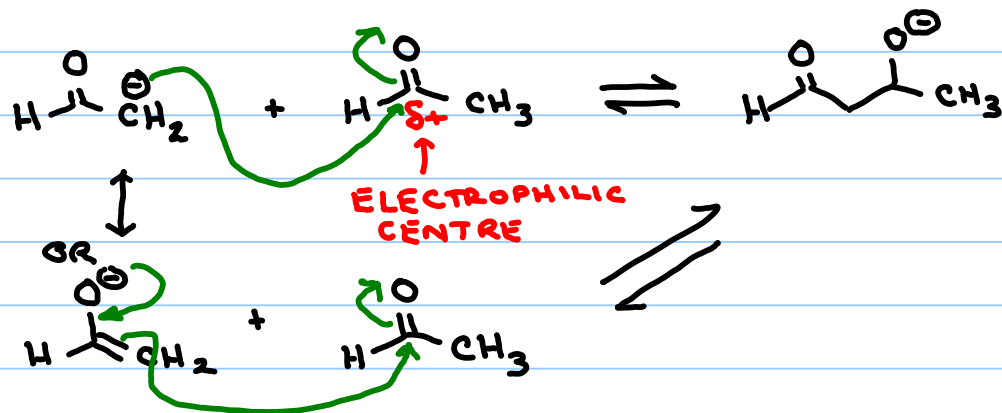
BASE	pK_a	CONJ ACID	COMMENTS
HO^-	15.74		
$H_3C-CH_2-O^\ominus$ (= EtO^\ominus)	16		
$\begin{matrix} H_3C \\ \\ H_3C-C-O^\ominus K^\oplus \\ \\ H_3C \end{matrix}$ (= $tBuO^\ominus$)	17		POOR NUCLEOPHILE DUE TO BULKY NATURE
$\begin{matrix} \\ N^\ominus Li \\ \end{matrix}$ \equiv LDA	35.7		V. STRONG BASE LIMITED NUCLEOPHILICITY - OUR FAVOURITE
$H_3C-CH_2-CH_2-CH_2-Li$ \equiv $nBuLi$	≈ 51		KILLER BASE, BUT TOO NUC

ALDOL CONDENSATION

- LET'S TRY THE SIMPLEST COMBINATION POSSIBLE
 - ACETALDEHYDE AND HO^\ominus



- NOTE: ONLY DEPROTONATION TO AN EQUILIBRIUM EXTENT ($K_{eqn} < 1$) \therefore MANY UNDEPROTONATED ACETALDEHYDE MOLECULES LEFT

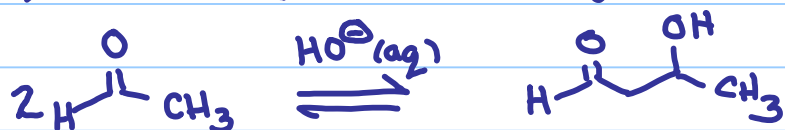


NOTES:

1) OLD NAME FOR THIS IS ALDOL, SO THIS IS KNOWN AS AN ALDOL ADDITION REACTION

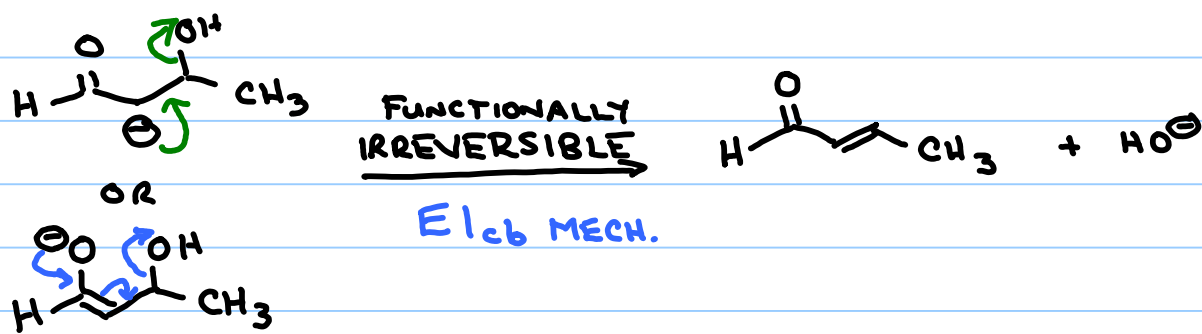
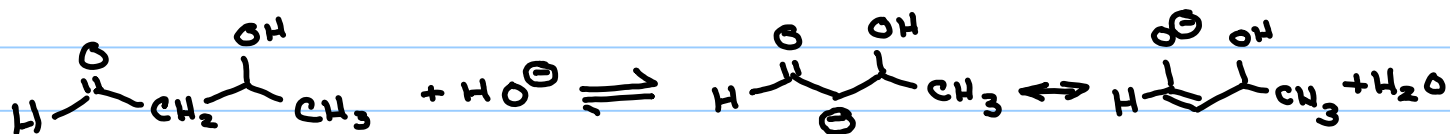
2) HO^\ominus IS REGENERATED AT THE END, SO IT IS A TRUE CATALYST

3) OVERALL REACTION IS AN EQUILIBRIUM



- THIS LAST POINT IS A PROBLEM, SINCE THE OVERALL K_{eq} IS NOT ALWAYS GREAT

- AS A RESULT, THE WAY THIS RXN IS NORMALLY RUN IS WITH EXCESS HO^\ominus AND ELEVATED TEMP. THE RXN THEN GOES FURTHER

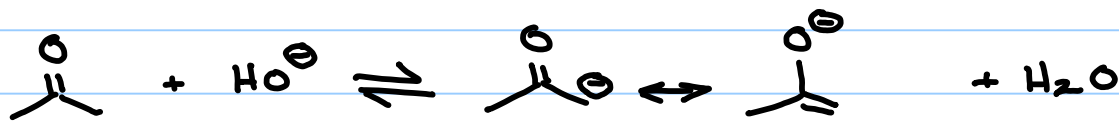


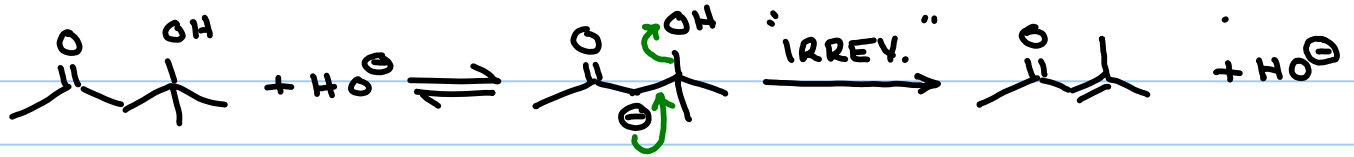
- SINCE THE LAST STEP IS 'PRACTICALLY' IRREVERSIBLE, IT IS EASY TO PUSH ALL MOLECULE TO THE PRODUCT

- REACTION NOW CALLED ALDOL CONDENSATION

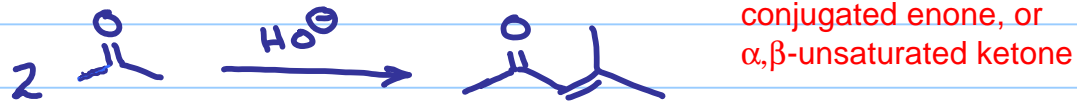


- WORKS ON A PRETTY WIDE VARIETY OF ALDEHYDES AND KETONES - LET'S TRY ACETONE

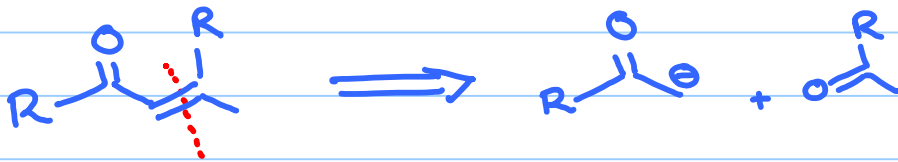




OVERALL:



RETROSYNTHETICALLY - ANY TIME YOU SEE AN α, β -UNSATURATED ALDEHYDE OR KETONE, THERE'S A GOOD CHANCE IT CAN BE MADE BY AN ALDOL



- SO FAR, WE HAVE DONE V. SIMPLE ALDOLS

- WHAT IF a) WE HAVE TWO DIFFERENT SITES THAT ARE ACIDIC ON A KETONE

b) A CROSSED ALDOL, WHERE THE ACIDIC CARBONYL AND THE ELECTROPHILIC CARBONYL ARE DIFFERENT

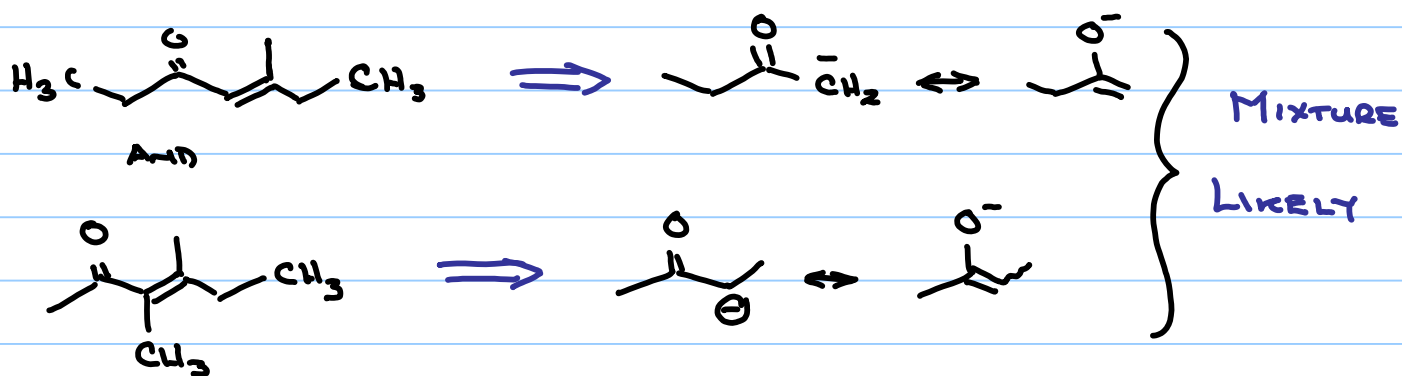
ALDOLS - UNSYMMETRICAL AND CROSSED

ALDOLS - UNSYMMETRICAL KETONES

- ISSUE. WHAT IF WE HAVE A KETONE SUCH AS....



- FORGETTING ALKENE STEREOCHEMISTRY FOR A MOMENT THERE ARE TWO POSSIBLE PROD'S.



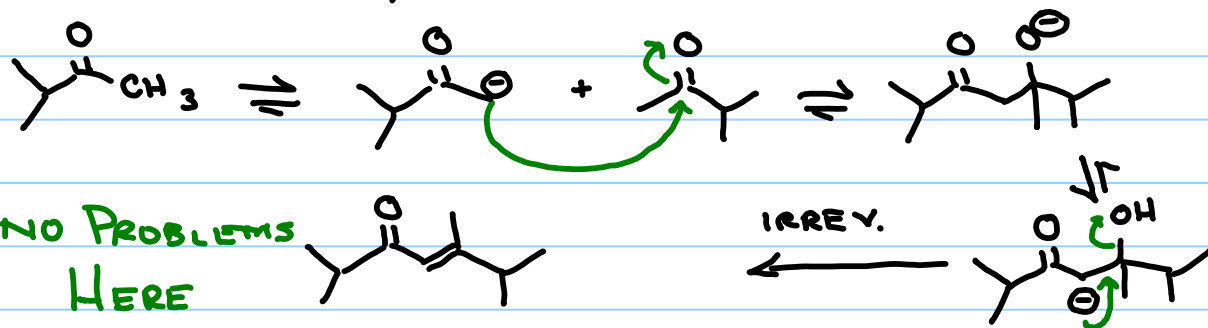
- I'D BET THAT THERE'S A BIT MORE OF THE 1ST ONE, BUT REALLY THERE MUST BE A BETTER WAY OF DOING THIS

- IT ISN'T ALWAYS ABSOLUTELY IMPOSSIBLE

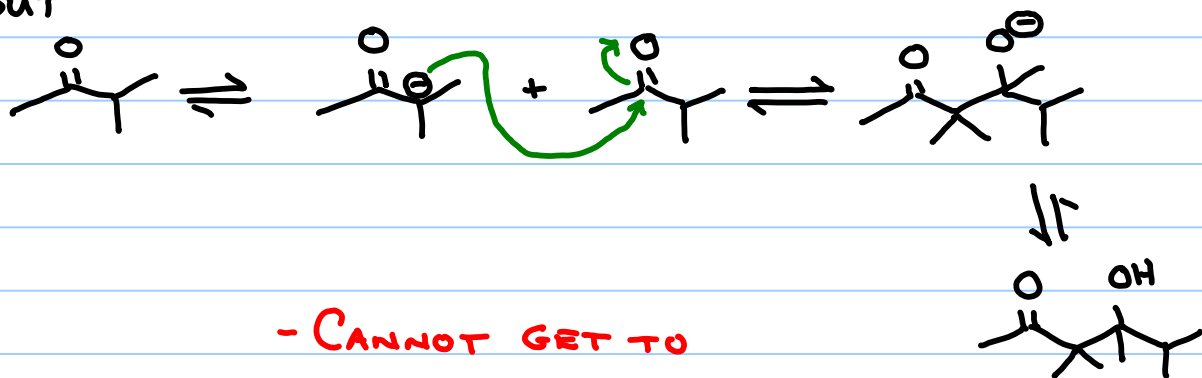
CONSIDER



AND EVEN CC(C)C(=O)C IS OK, SINCE



BUT



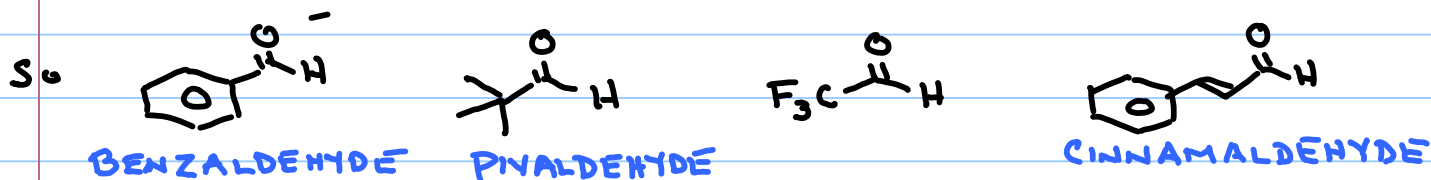
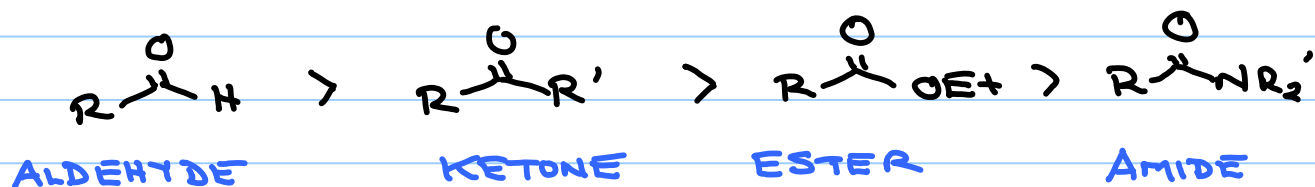
- CANNOT GET TO
IRREVERSIBLE ELIMINATION
STEP \therefore NOT FORMED

CROSSED ALDOLS

- IT IS POSSIBLE TO DO BASE 'CATALYZED' ALDOLS BETWEEN TWO DIFFERENT MOLECULES
- BUT, A COUPLE IMPORTANT REQUIREMENTS MUST BE MET

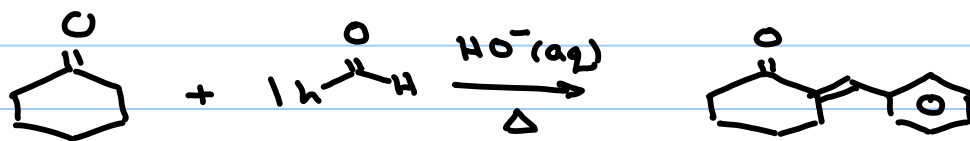
- 1) ONLY ONE OF THE CARBONYLS CAN BE ENOLIZABLE
- 2) THE NON-ENOLIZABLE ONE MUST BE MORE ELECTROPHILIC

NOTE: SINCE ORDER OF REACTIVITY TO NUCLEOPHILES IS IN THE FOLLOWING ORDER....



- ALL FIT THIS REQUIREMENT FOR ELECTROPHILE

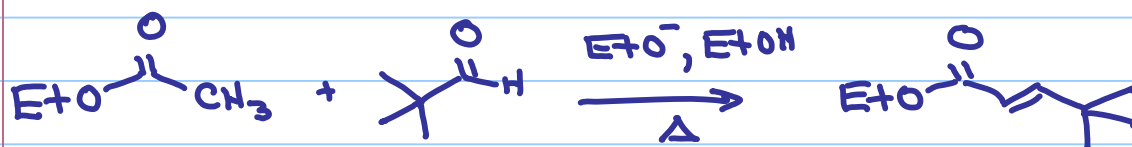
- AS A CONSEQUENCE, THE FOLLOWING WORKS FINE...



ESTERS IN ALDOLS ?

- YES, CONDITIONALLY

- PROVIDED THAT YOU ARE WISE WITH THE BASE,
ESTERS CAN BE USED AS THE ENOLATE PORTION
OF AN ALDOL ... EVEN THOUGH THEY ARE
LESS ACIDIC



(NOTE: MATCH THE BASE TO THE ESTER)

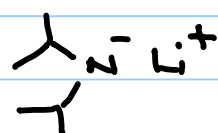
KINETIC (OR DIRECTED) ALDOL

Note Title

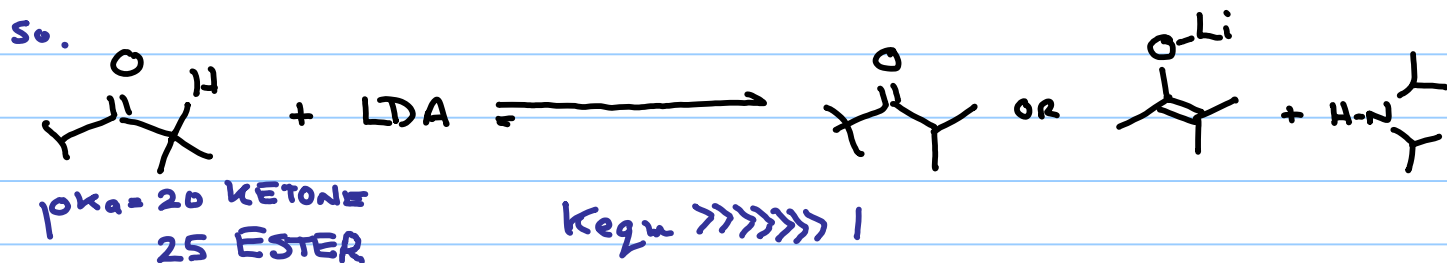
2/17/2017

THERE IS AN ALTERNATIVE TO THE BASED CATALYZED ALDOL, THAT ALLOWS YOU TO ISOLATE THAT β -HYDROXY CARBONYL RELIABLY
- FEATURES ARE SOMEWHAT DIFFERENT.

- INSTEAD OF USING A WEAK BASE SUCH AS HO^- OR EtO^- , WE'LL USE A (VERY) STRONG BASE SUCH AS $\ominus\text{NR}_2$

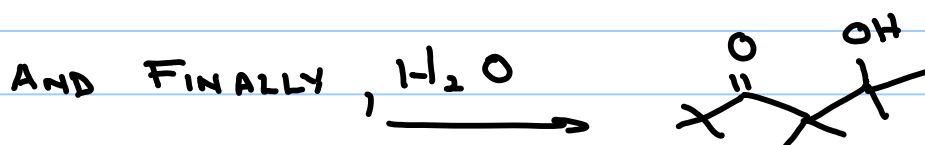
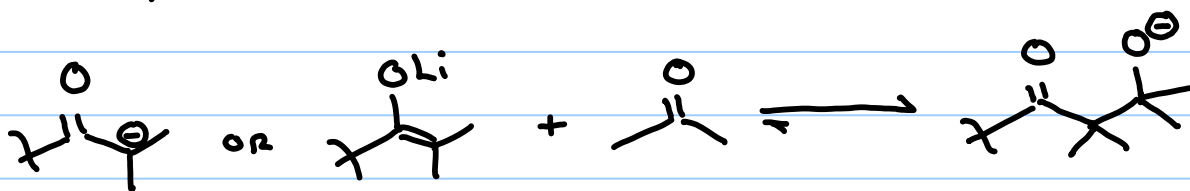
THE WORKHORSE BASE IS 

LITHIUM DIISOPROPYLAMIDE (LDA)
 $\text{pK}_a(\text{OF CONJ. ACID}) = 35.7$



- SUCH A STRONG BASE, THAT IF YOU COOL THIS DOWN TO -78°C , THE REVERSE RXN IS SO SLOW THAT IT'S ESSENTIALLY IRREVERSIBLE

- AND, IN 2ND STEP



AGAIN, IF WE KEEP EVERYTHING COLD (-78°),
THE REVERSE RXN IS SO SLOW THAT THE
ENTIRE RXN IS KINETICALLY CONTROLLED.

- AND THE ALCOHOL NEVER ELIMINATES.

- NOTE: ESPECIALLY WHEN WE'RE DISCUSSING
KINETICALLY GENERATED ENOLATES, WE'LL START
DRAWING THEM MORE OFTEN AS...



THIS IS A MUCH TRUER REFLECTION
OF THEIR ACTUAL STRUCTURE

DISTINCTIONS / ADVANTAGES OF KINETIC ALDOL FROM BASE CATALYZED PRODUCT.

- i) SOLVENT IS NOW APROTIC (NO OH'S).....



TETRAHYDROFURAN
(THF)



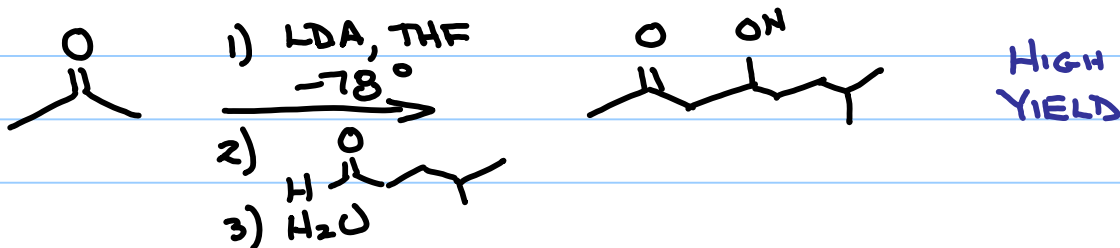
DIETHYL ETHER
(Et_2O)

- ii) RXN PRODUCT IS DIFFERENT



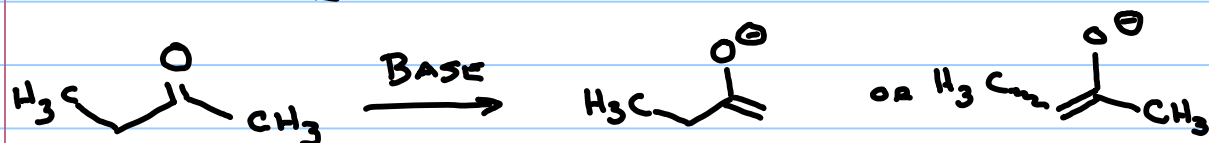
- iii) CROSSED ALDOLS ARE USUALLY MUCH MORE
STRAIGHTFORWARD

- ENOLIZABLE ALDEHYDES, KETONES ARE NOW
QUITE REASONABLE AS ELECTROPHILES



iv) ALDOLS ON UNSYMMETRIC KETONE CAN BE DONE FAIRLY PREDICTABLY

REGIOSELECTIVITY IN DEPROTONATION OF UNSYMMETRICAL KETONES



- TURNS OUT THAT OFTEN, EVEN **MUST** OF THE TIME, ONE SITE IS MORE RAPIDLY DEPROTONATED

- **KINETIC ENOLATE**

... AND THE OTHER ENOLATE IS MORE STABLE, AND THEREFORE FORMED UNDER EQUILIBRATING CONDITIONS

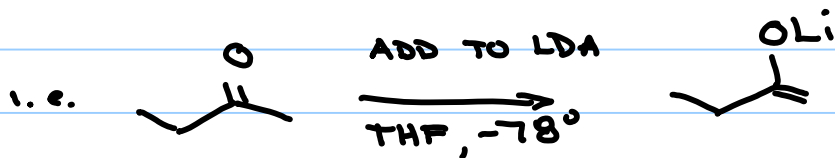
- **THERMODYNAMIC ENOLATE**

- WITH LDA (A RAPIDLY ACTING BASE) AND LOW T, WE ARE NOT EQUILIBRATING

- AND LDA HAS BEEN INTENTIONALLY DEVELOPED TO BE SOMEWHAT BULKY

FASTEST (KINETIC) SITE OF THE DEPROTONATE IS THE LESS STERICALLY HINDERED SITE

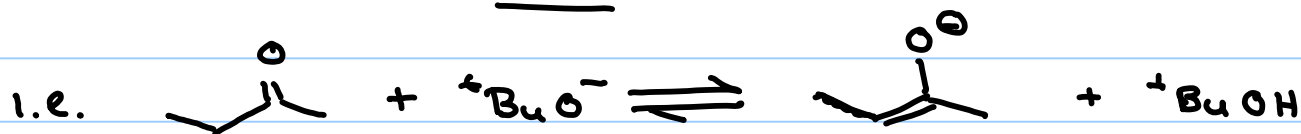
i.e. - LESS SUBSTITUTED ONE



- IF YOU CAN **EQUILIBRATE** TO FORM THE ENOLATE, YOU FORM THE MOST STABLE ENOLATE - SINCE AN ENOLATE IS REALLY A TYPE OF ALKENE, STABILITY

FOLLOWS ALKENE - TYPE RULES

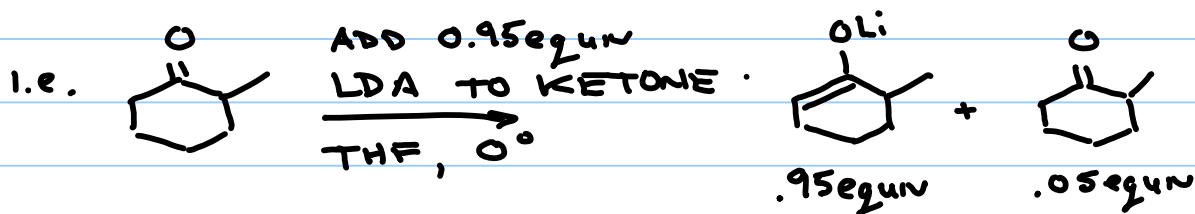
- HENCE THE THERMODYNAMIC ENOLATE IS NORMALLY THE MORE SUBSTITUTED ONE



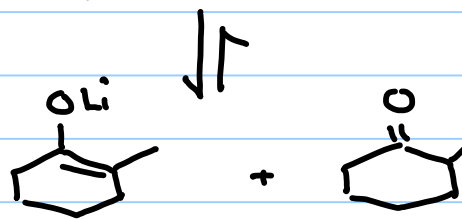
PROBLEM - THESE $t\text{BuO}^-$ OR HO^- CONDITIONS DON'T GIVE KINETIC ALDOL TYPE PRODUCTS (i.e. β -HYDROXY KETONES) RELIABLY

- SO HOW DO WE DO THIS FOR KINETIC ALDOL RXNS? CHOICES.

a) ADD LDA TO KETONE, AND KEEP THE AMOUNT OF BASE JUST UNDER 1 equiv. - I'LL ALSO KEEP TO TEMP. INITIALLY WARMER THAN WE'RE USED TO

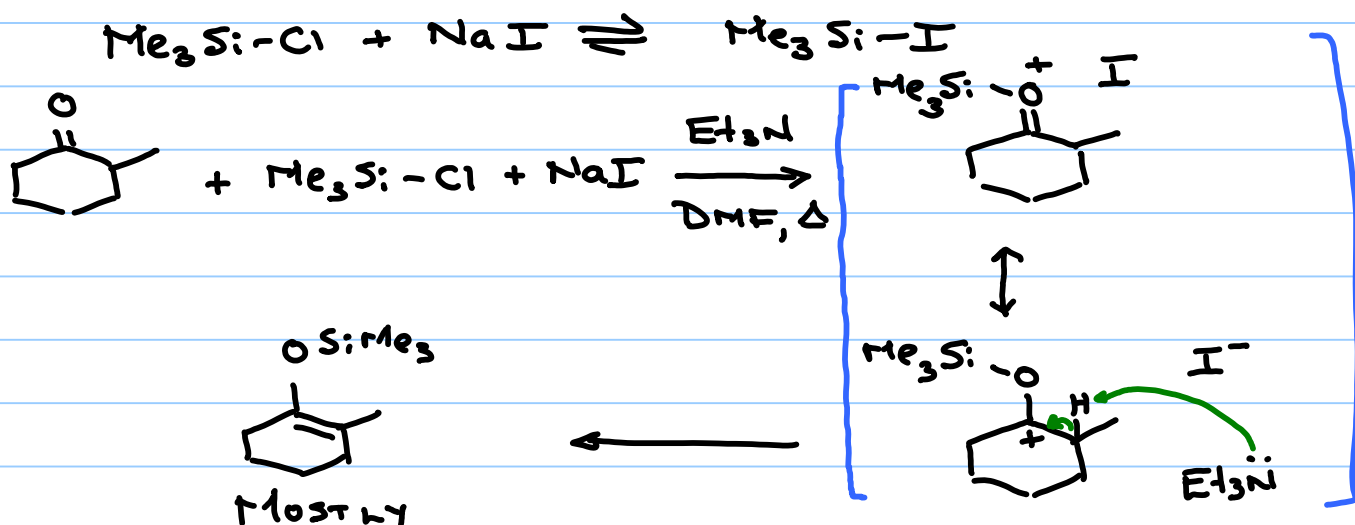


SINCE THERE'S ALWAYS SOME UNDEPROTONATED KETONE AROUND WITH ENOLATE, THE TWO WILL EQUILIBRATE BACK + FORTH

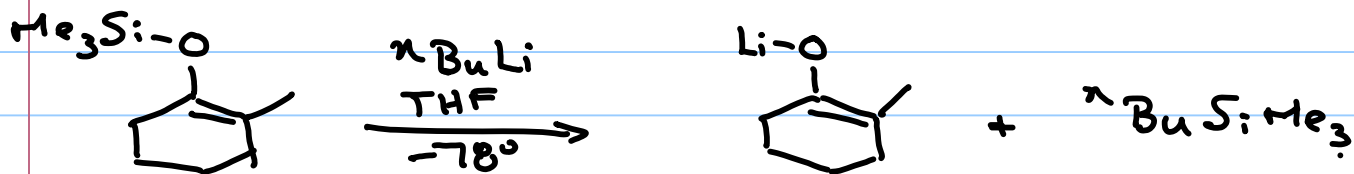


- WE THEN COOL TO -78° , AND FINISH ALDOL

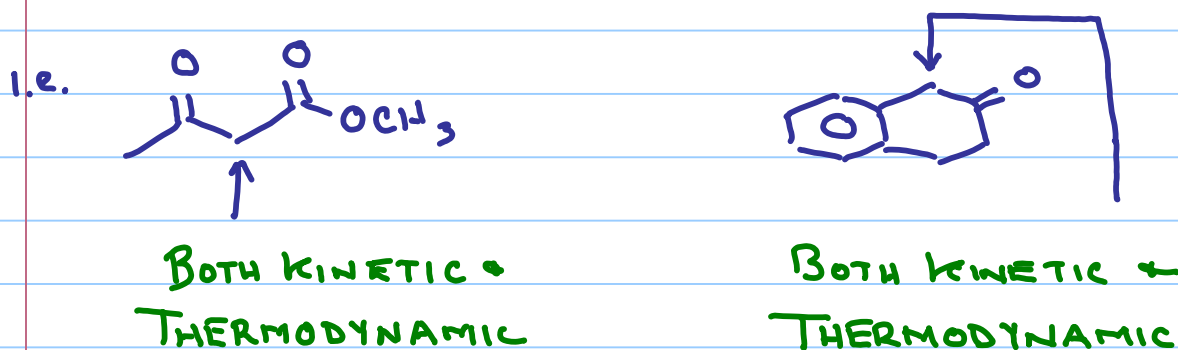
b) GENERATE SILYL ENOL ETHER USING $\text{Me}_3\text{Si}-\text{I}$ AND A WEAK BASE



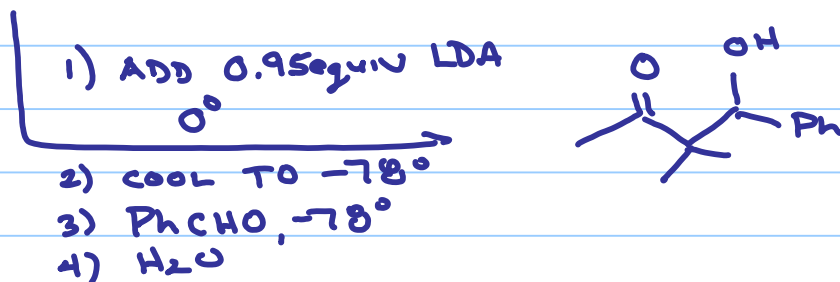
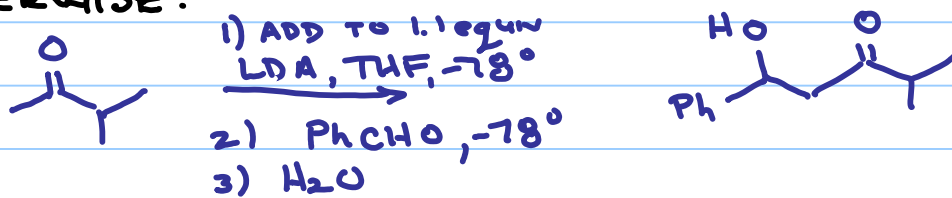
- AND ... THIS IS USEFUL SINCE SILYL ENOL ETHER CAN BE CONVERTED DIRECTLY TO THE ENOLATE



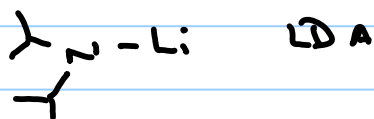
NOTE: THERE ARE SOME CASES, ESPECIALLY WITH TWO ACIDIFYING GROUPS, WHERE THE KINETIC & THERMODYNAMIC SITES ARE THE SAME,



- OTHERWISE.



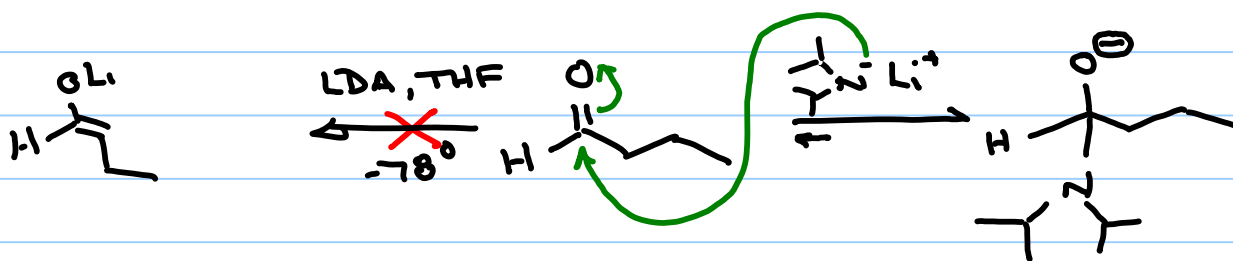
ONE DRAWBACK OF KINETIC BASES SUCH AS



- ALDEHYDES DON'T DEPROTONATE WELL

- DESPITE LDA BEING DESIGNED WITH FAIRLY BULKY R GROUPS ON N, TO MAKE IT LESS NUCLEOPHILIC

- ALDEHYDES ARE JUST TOO EASY TO ATTACK



STEREOCHEMISTRY OF ALDOL REACTIONS

Note Title

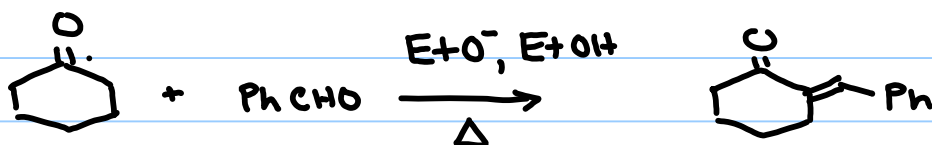
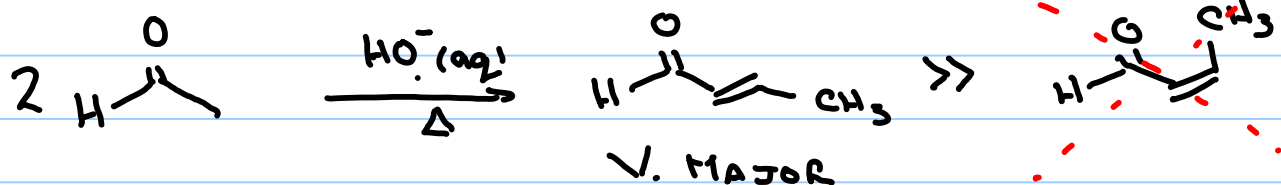
1/18/2017

- WE HAVE NOT ADDRESSED THE STEREOCHEMICAL ASPECTS OF ALDOL CONDENSATION / ADDITIONS SO FAR

- WEAK BASE INDUCED ALDOLS

- FROM A PRACTICAL STANDPOINT, THIS IS PRETTY STRAIGHT FORWARD

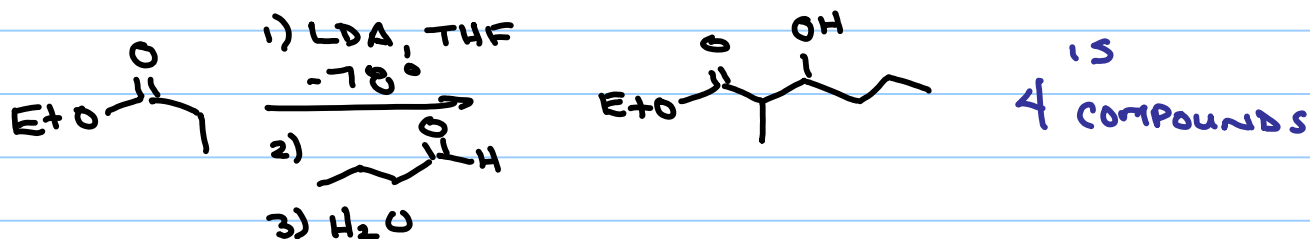
- THIS PRODUCT STEREOCHEMISTRY OBTAINED IS NORMALLY THE MORE THERMODYNAMICALLY STABLE ALKENE (GEOMETRIC) ISOMER (i.e., E-)

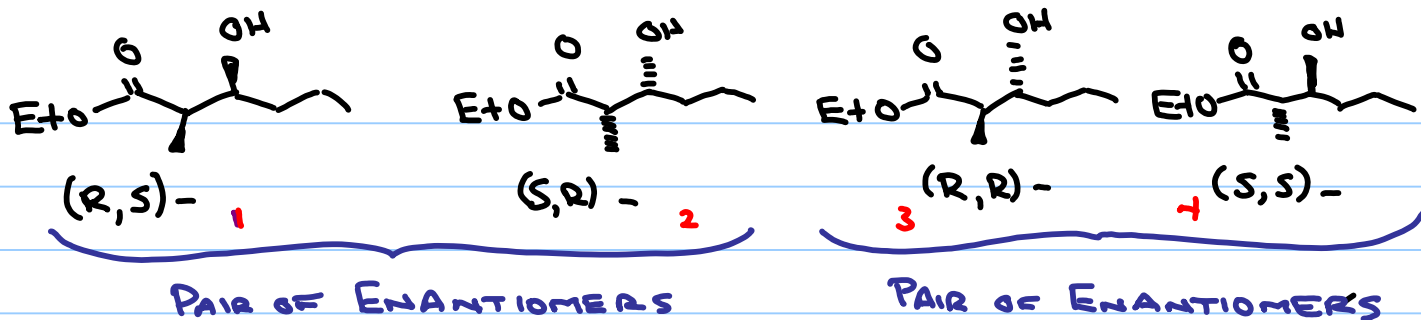


- THE REASON HAS TO DO WITH THE RELATIVE RATES OF THE ELIMINATION STEP, BUT THE PRODUCT IS V. PREDICTABLE:

KINETIC ALDOLS

- THE FIRST THING TO NOTE IS THE NUMBER OF THEORETICALLY POSSIBLE STEREOISOMERS HERE





1 + 3 } ARE DIASTEREOMERS
 2 + 4 }
 2 + 3 }
 1 + 4 }

- SINCE NONE OF OUR STARTING MATERIALS OR REAGENTS ARE ENANTIOMERICALLY ENRICHED / PURE (OR IN THIS CASE EVEN CHIRAL), OUR PRODUCTS ARE BY DEFINITION RACEMIC MIXTURES (50:50 MIXTURES OF ENANTIOMERS).
BUT, WE HAVEN'T EVEN SEEN WHAT TO CALL DIASTEREOMERS

THE PROTOCOL EVERYONE USES

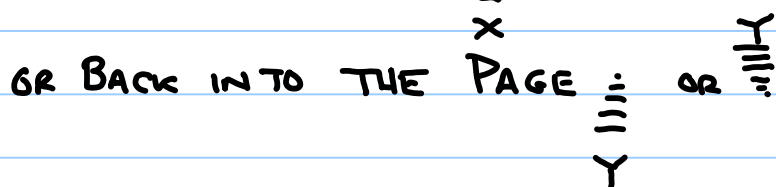
- EMPLOYS THE TERM "syn-" AND anti-

TO DETERMINE THEM:

1) WRITE OUT YOUR MAIN CHAIN IN A ZIG-ZAG FORM, I.E.,

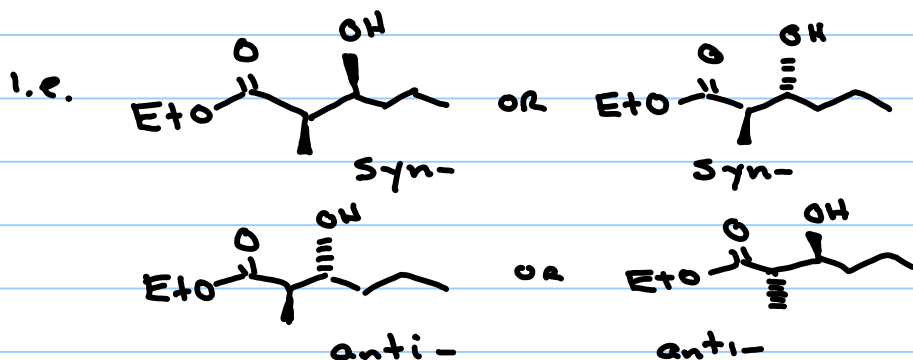


2) APPEND YOUR SUBSTITUENTS ON THE MAIN CHAIN, EITHER TOWARDS YOU



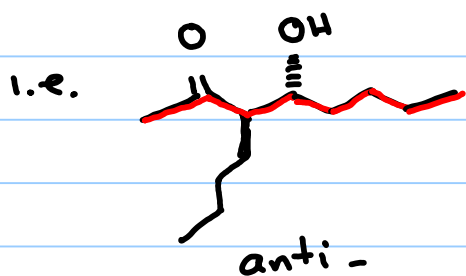
3) - IF THE TWO SUBSTITUENTS ARE BOTH TOWARDS YOU OR BOTH BACK INTO THE PAGE, YOU HAVE THE SYN-DIASTEREOMER

- IF ONE SUBSTITUENT IS TOWARDS YOU, AND ONE AWAY, IT IS THE ANTI-DIASTEREOMER



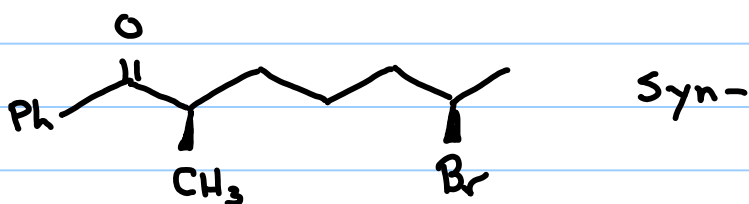
4) a) SPECIAL NOTES FOR CARBONYL / ALDOL CHEMISTRY

- SO THAT THIS APPROACH CAN BE USED IN ALDOL CHEMISTRY, THE MAIN CHAIN IS ARTIFICIALLY DESIGNATED TO INCLUDE THE CARBONYL



FOR THESE PURPOSES, MAIN CHAIN IS DESIGNATED IN RED, DESPITE IT NOT BEING THE LONGEST CHAIN

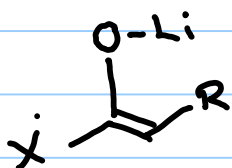
b) THERE IS NO PROBLEM IF THE CENTRES OF CHIRALITY ARE > 1 ATOM APART. JUST KEEP GOING WITH THE MAIN CHAIN IN ZIG-ZAG ORIENTATION



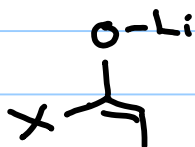
BACK TO THE QUESTION AT HAND -

WHICH ONE DOES ALDOL MAKE WHEN?

- ANSWER: IT RELIES MOSTLY ON THE GEOMETRY OF THE ENOLATE CONCERNED



(Z)- ENOLATE

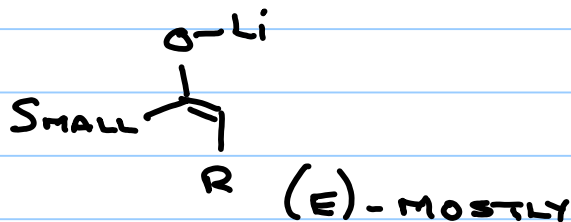
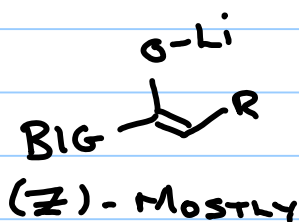


R (E)- ENOLATE

NOTE ANOTHER 'ALDOL SPECIAL RULE'

- THE OFFICIAL (Z)- AND (E)- DESIGNATIONS STAY IN PLACE EVEN IF X HAS A HIGHER C.I.P. PRIORITY THAN OLi, JUST SO AS TO AVOID CONFUSION.

- IN THIS COURSE, I WILL GIVE YOU THE ENOLATE GEOMETRY, BUT A GENERAL (APPROXIMATE) GUIDELINE IS:



BIG AND SMALL ARE MOST COMMONLY DEFINED BY CONFORMATIONAL A VALUE, A MEASURE OF



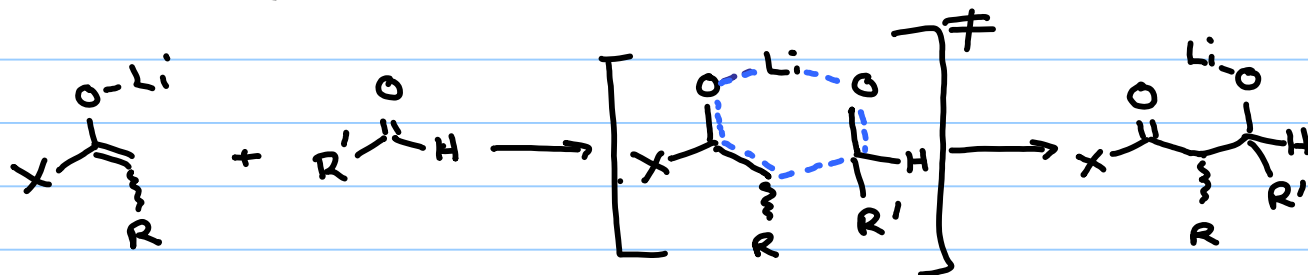
So.....

R	A VALUE	R	A VALUE
+ Bu-	> 4.5	Et-	1.8
Ph-	2.9	Me-	1.7
ⁱ Pr-	2.15	H ₂ C=CH-	1.5
-NMe ₂	2.1	-OR, -OH	~0.7
		-HALOGEN	~0.5
		-CECH	0.45
		H	0

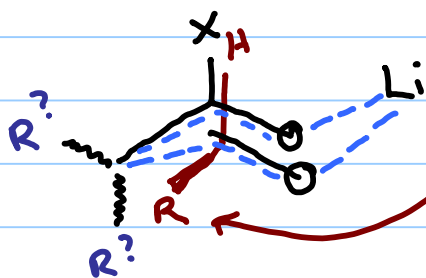
MEDIUM

SMALL

WHEN WE DO THE KINETIC ALDOL, IT BECOMES APPARENT THAT IT IS GOING THROUGH A CYCLIC SIX-MEMBERED TRANSITION STATE



- TO APPROXIMATE THIS 6-MEMBERED T.S., WE WILL USE CYCLOHEXANE

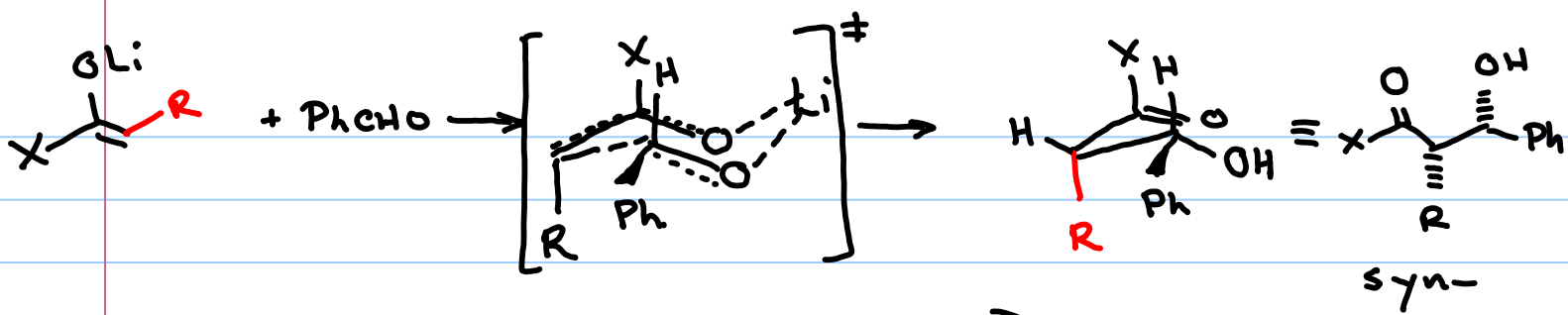


THE R' ON THE ALDEHYDE IS ENERGETICALLY PREFERRED TO BE EQUATORIAL, JUST LIKE ON ANY SELF RESPECTING CYCLOHEXANE

CALLED ZIMMERMAN-TRAXLER TRANSITION STATE.

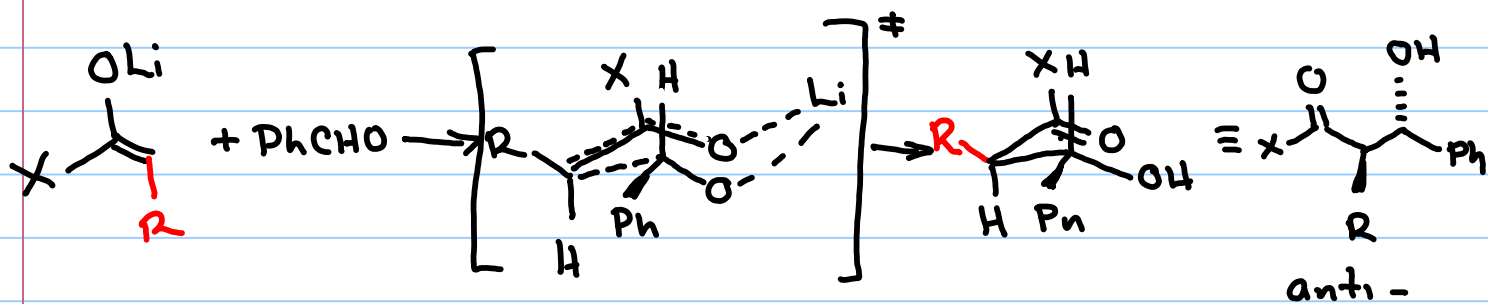
- THE R OF THE ENOLATE IS FORCED UP YOU BY THE ENOLATE GEOMETRY

- SO, FOR (Z)-ENOLATES



So (Z)-ENOLATES GIVE Syn-DIASTEREOMERS

AND FOR (E)-ENOLATES



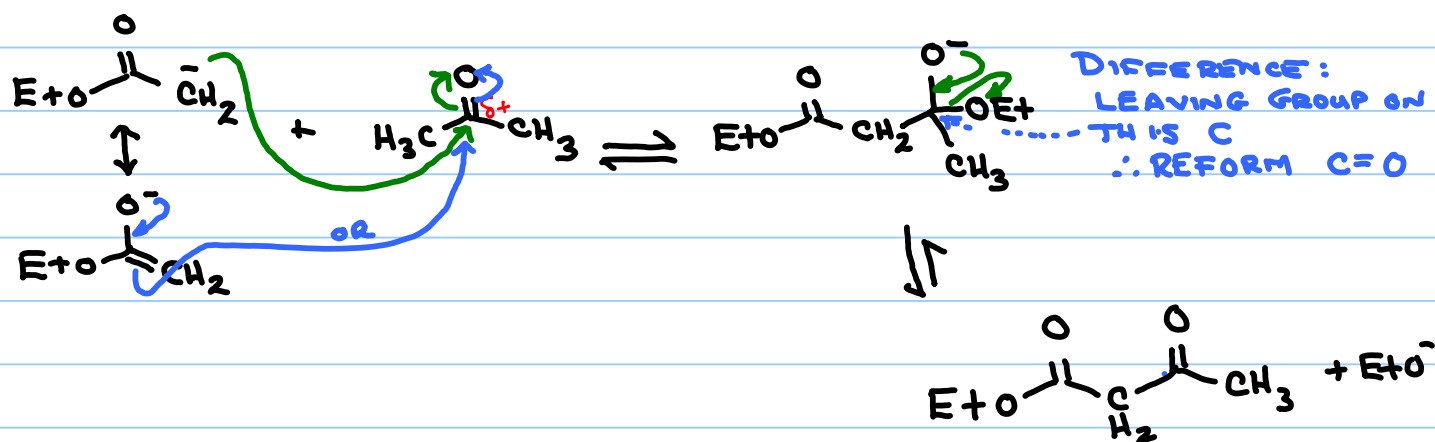
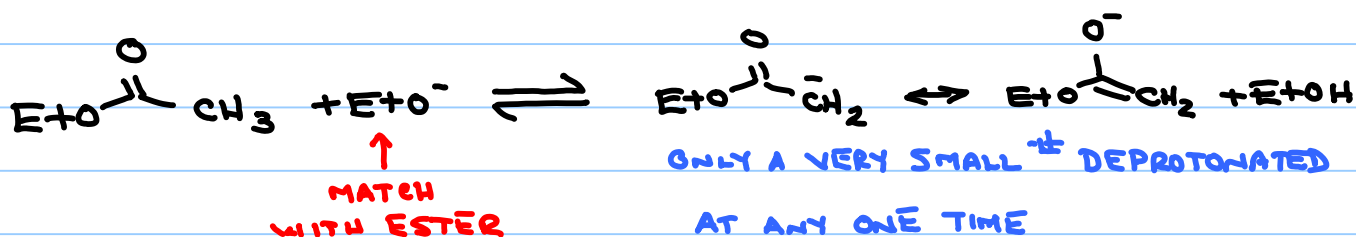
So (E)-ENOLATES GIVE anti-DIASTEREOMERS

CLAISEN CONDENSATION

Note Title

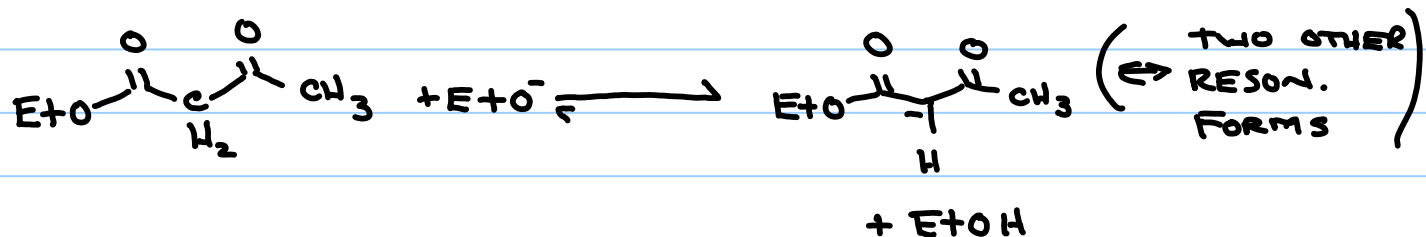
1/18/2017

- WE ARE DONE (FOR NOW) WITH ALDEHYDES OR KETONES AS E^+ IN RXNS WITH ENOLATES.
- HOW ABOUT ESTERS?
- LET'S DO THE SIMPLEST VERSION POSSIBLE

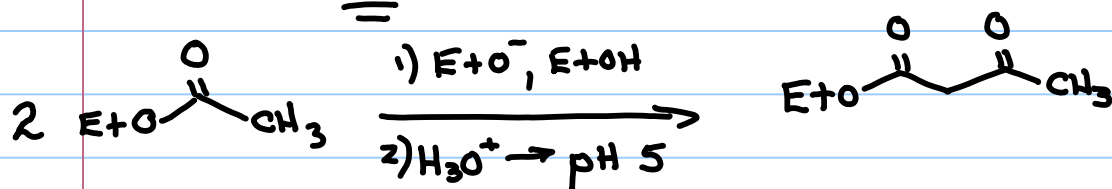


BUT, THAT CH_2 BETWEEN THE TWO CARBONYLS IS V. ACIDIC

- A LIBERATED EtO^- DEPROTONATES THERE
- THIS STEP IS FUNCTIONALLY IRREVERSIBLE, THEREFORE DRIVING RXN TO COMPLETION

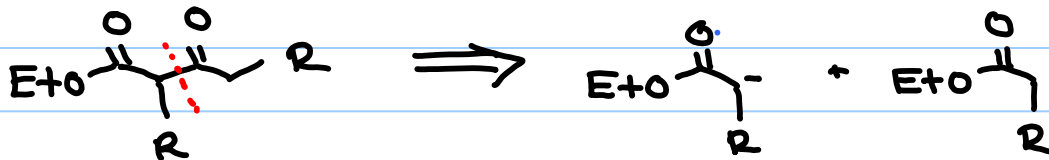


- IN V. FINAL STEP, YOU POUR THIS INTO SOMETHING ACIDIC ENOUGH TO PROTONATE THIS ENOLATE, BUT NOT TOO ACIDIC



CALLED A CLAISEN CONDENSATION

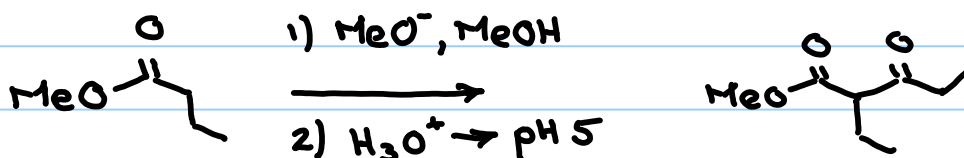
- V. WELL KNOWN WAY FOR MAKING A 1,3-DICARBONYL CPD.



- OTHER SIMPLE VARIATIONS ON CLAISEN

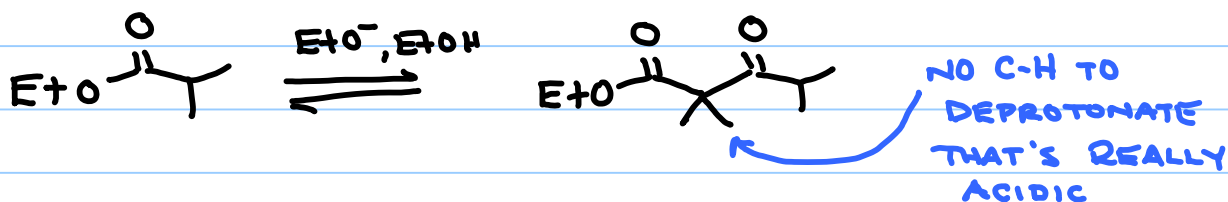
1) α -SUBSTITUTION?

- ABSOLUTELY - RXN IS COMPLETELY ANALOGOUS TO RXN WITH ETHYL ACETATE



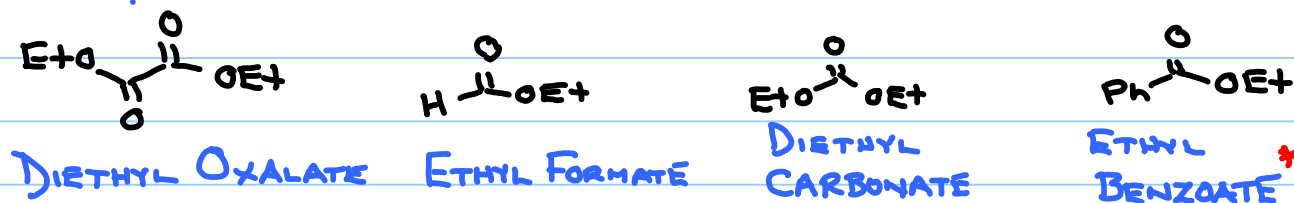
2) α,α -DISUBSTITUTION?

. NO. THE CLAISEN RELIES ON THAT FINAL DEPROTONATION TO DRIVE RXN TO COMPLETION. α,α -DISUBSTITUTED STARTING MATERIALS DON'T GIVE THAT POSSIBILITY

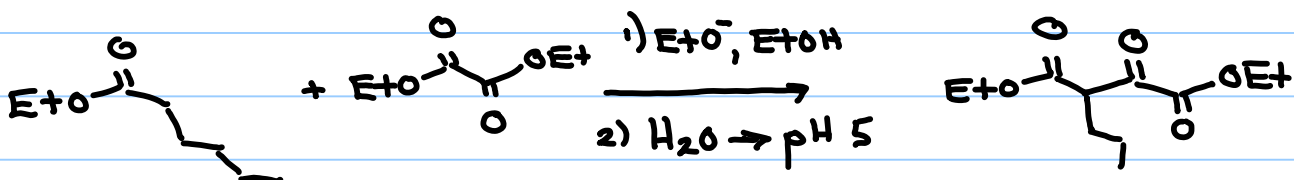


3) CAN YOU DO CROSSED CLAISENS?

- YES. THIS HAS SIMILAR RESTRICTIONS TO CROSSED ALDOLS - I.E. ELECTROPHILIC ESTER HAS NO ACIDIC H, AND TENDS TO BE AMONG THE MORE REACTIVE ONES

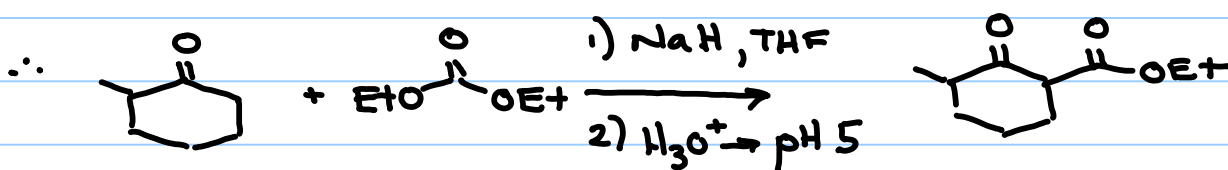


* - DOESN'T APPEAR TO BE ESPECIALLY REACTIVE ONE, BUT CLAYDEN 'SAYS' IT WORKS.



4) CAN KETONES BE THE C-H ACID IN A CLAISEN?

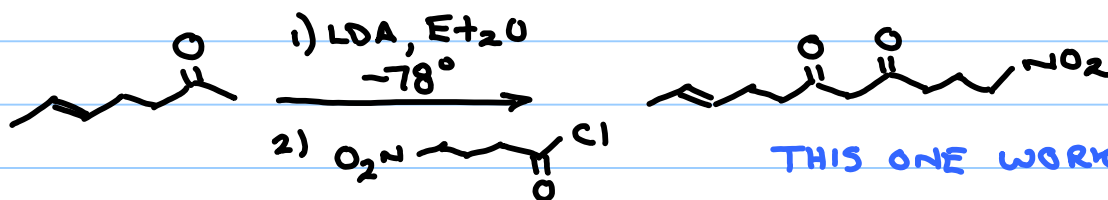
- YES, WITH SOME CONDITIONS
- ESTER ELECTROPHILE IS SAME AS CROSSED CLAISEN
- DON'T WANT SELF-ALDOL COMPETING, SO NORMALLY YOU USE A STRONGER BASE TO CONVERT 'ALL' KETONE MOLECULES TO ENOLATES - TRADITIONALLY NaH




5) DO YOU EVER DO TRUE KINETIC ENOLATE CLAISENS?

- ON OCCASION, BUT A BIT BEYOND THIS COURSE
- USUALLY USE ELECTROPHILIC CARBONYLS MORE REACTIVE THAN ESTERS - HOWEVER THE ONES YOU KNOW, ACID CHLORIDES, HAVE A BAD HABIT OF "ACYLATING" ON OXYGEN

- THERE ARE SUCCESSES, THOUGH



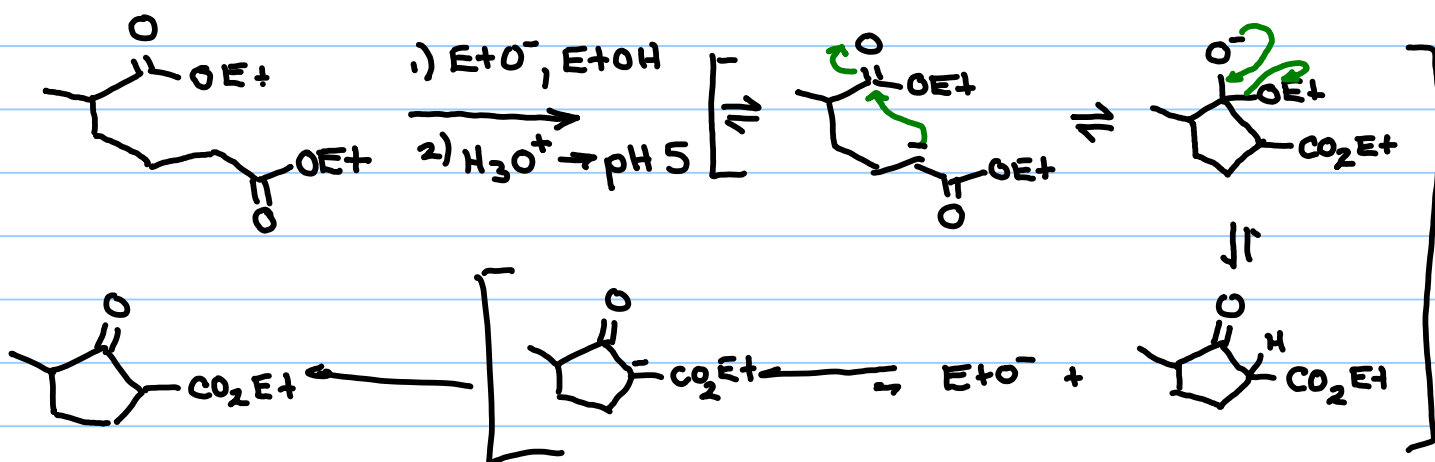
THIS ONE WORKS 'OK'

OFTEN  IS A PROBLEM

6) INTRAMOLECULAR RXNS - IS AN INTRAMOLECULAR VERSION OF THE CLAISEN KNOXN ?

- ABSOLUTELY YES

- IN FACT, IT IS COMMONLY USED TO MAKE RINGS, ESPECIALLY 5- & 6-MEMBERED ONES



- ODDLY ENOUGH, IT'S KNOWN BY A COMPLETELY DIFFERENT NAME - DIECKMANN RXN.

INTRAMOLECULAR - ALDOL?

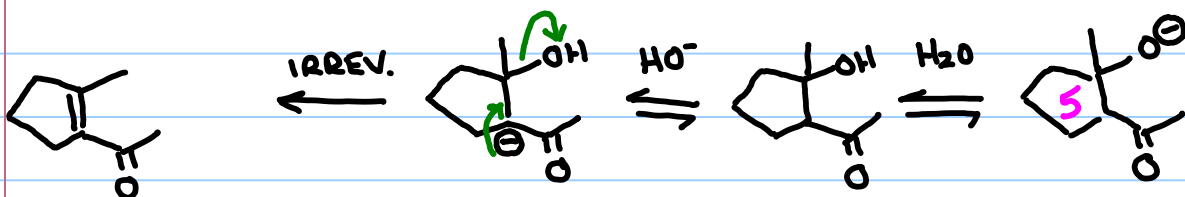
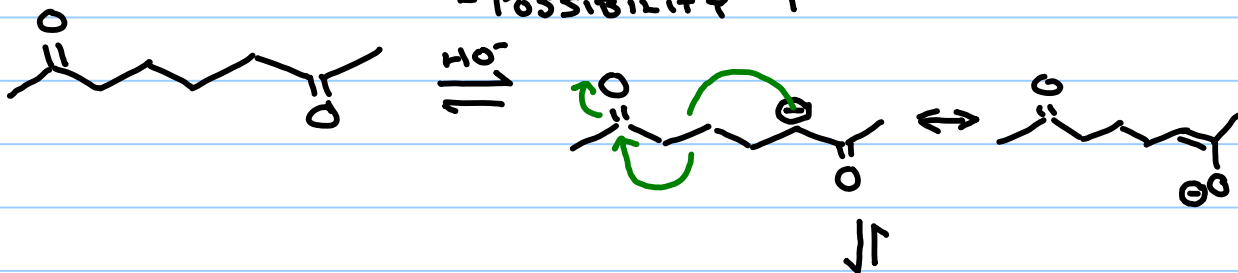
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1/18/2017

- SINCE INTRAMOLECULAR CLAISEN CONDENSATIONS (DIECKMANN'S) WORK WELL, HOW ABOUT IN ALDOLS?

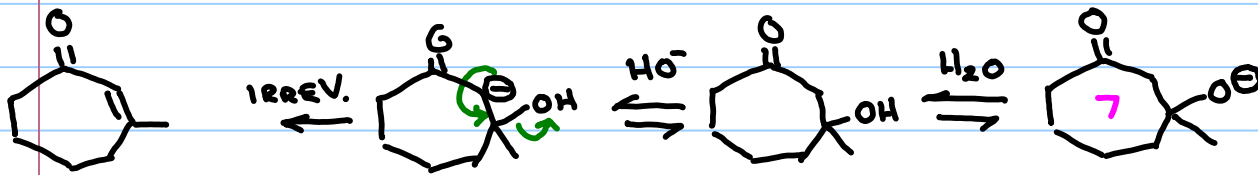
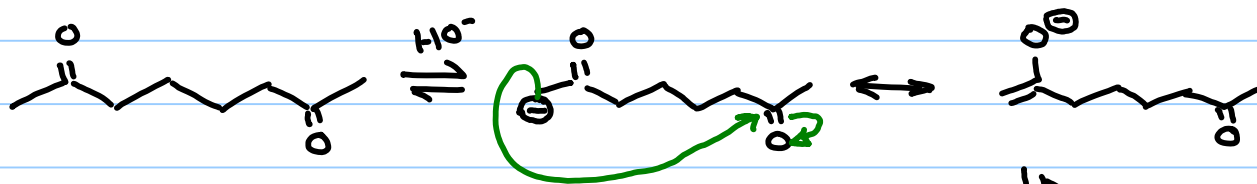
- FIRST OF ALL, YES. - BUT LET'S SET UP TWO FUNDAMENTAL EXAMPLES

- POSSIBILITY #1



5-MEMB. RING.

POSSIBILITY #2



7-MEMB. RING

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NOTE: THEY DIFFER SLIGHTLY IN VARIOUS CASES

MY FAVOURITE



RING SIZE	RATE	RING SIZE	RATE
8	1	5	1,500,000
7	97.3	4	5400
6	17000	3	21.7

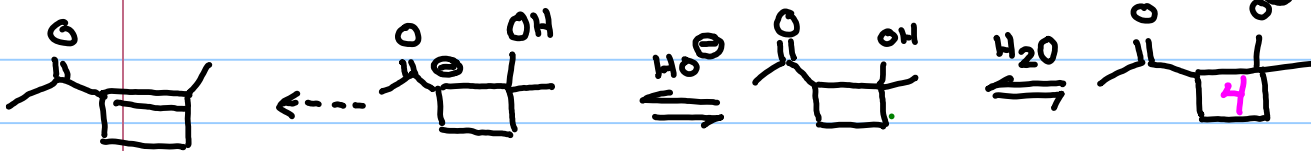
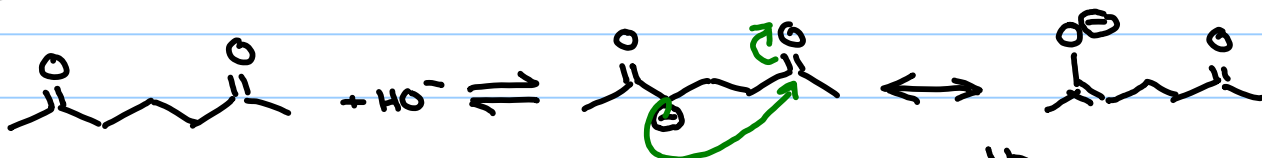
NOTE: IN OTHER CASES 7 vs. 4 vs. 3 MOVE AROUND A BIT

FOR ABOVE CASE FORMING 5 MEMB. RING IS 154,000 TIMES FASTER THAN FORMING THE 7 MEMB. RING.

∴ 5- WINS

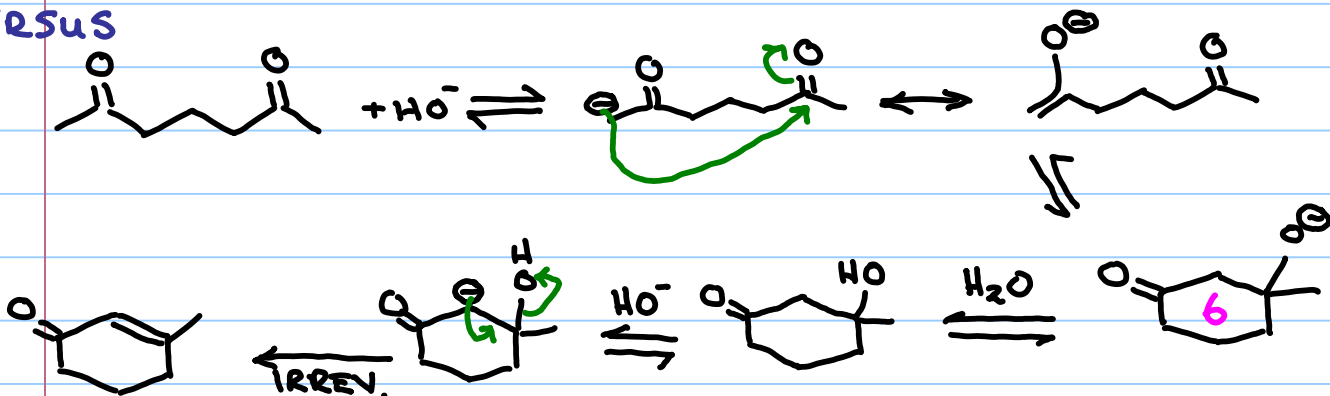
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LET'S TAKE THE 1C SHORTER CASE



FOUR MEMB. RING

VERSUS



SIX MEMB. RING

- IF WE TAKE THE RATE #'S FROM ABOVE, 6.. WINS OVER 4- BY ABOUT 3:1

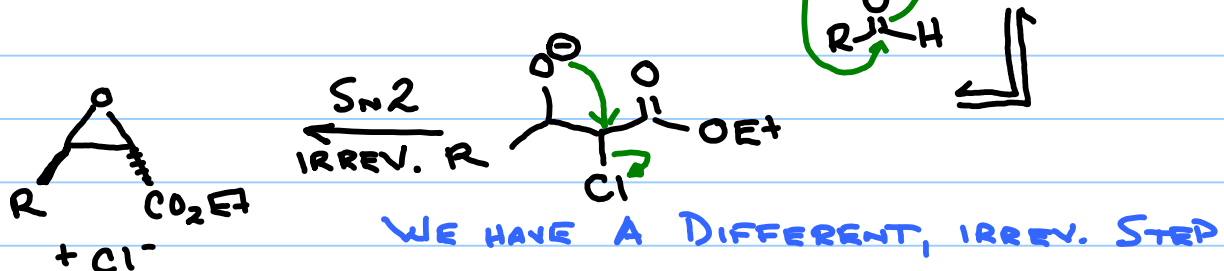
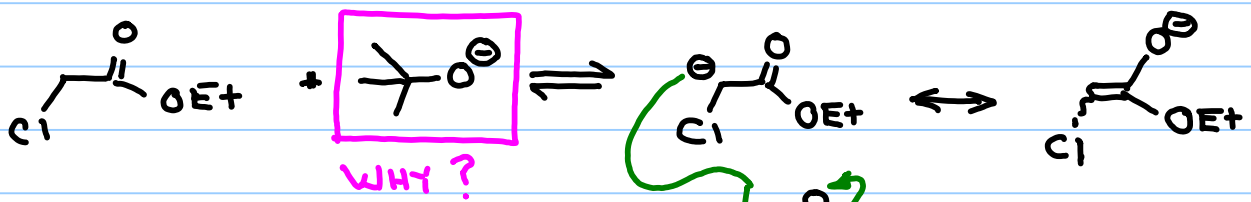
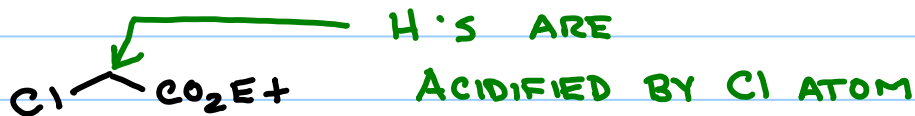
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- WE ARE FORTUNATE THAT IN THESE SIMPLE CASES SIX (2ND FASTEST AND MOST STABLE) AND FIVE (FASTEST AND 2ND MOST STABLE) DON'T COMPETE

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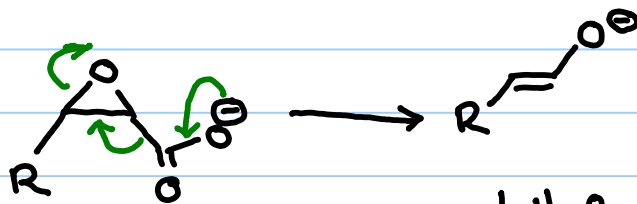
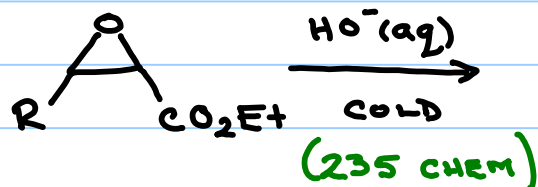


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IS GLYCIDIC ESTER

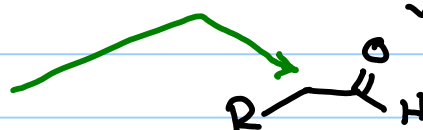
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- TREAT WITH COLD HO^\ominus



$\downarrow \text{H}_2\text{O}$
(BUT WE
NEUTRALIZE
WITH H_3O^+)

EXTRA
APPARENT CH_2



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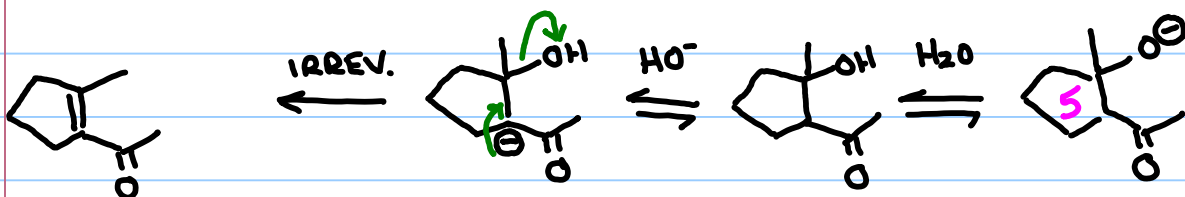
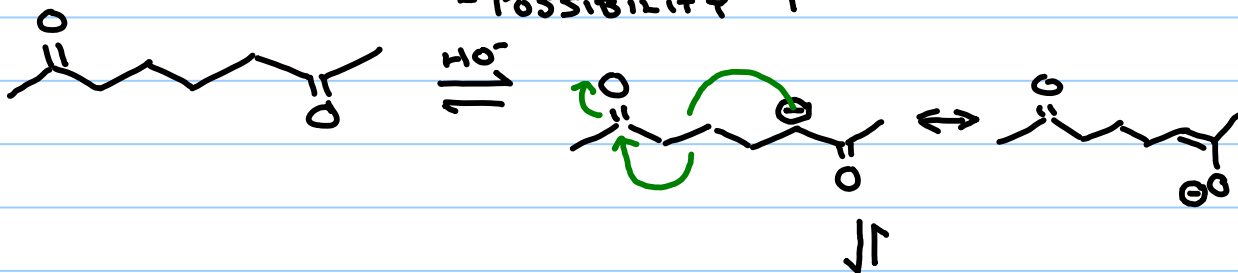
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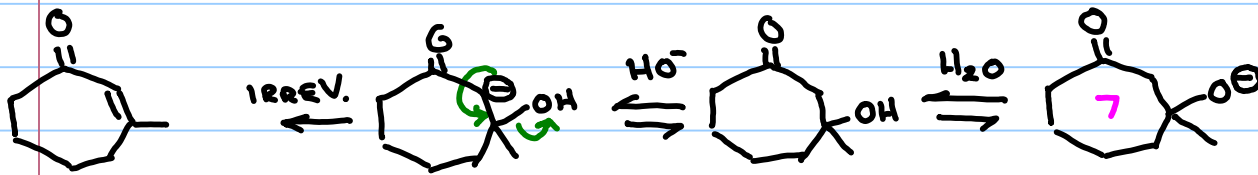
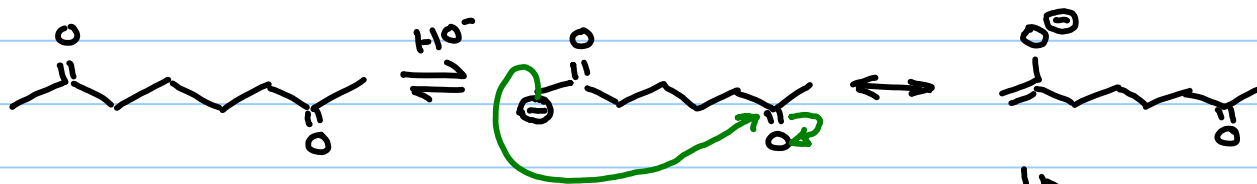
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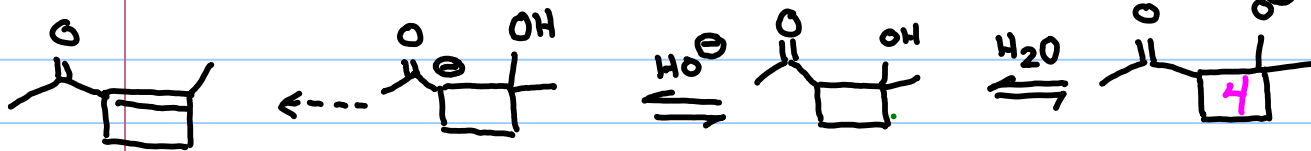
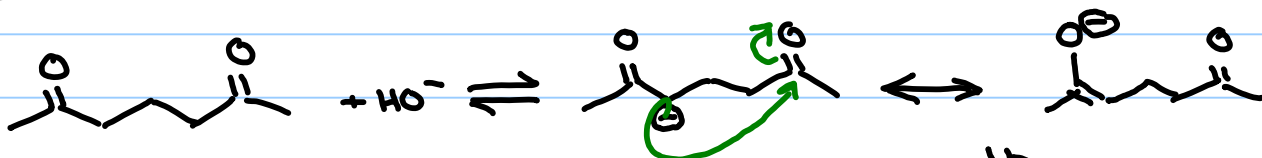
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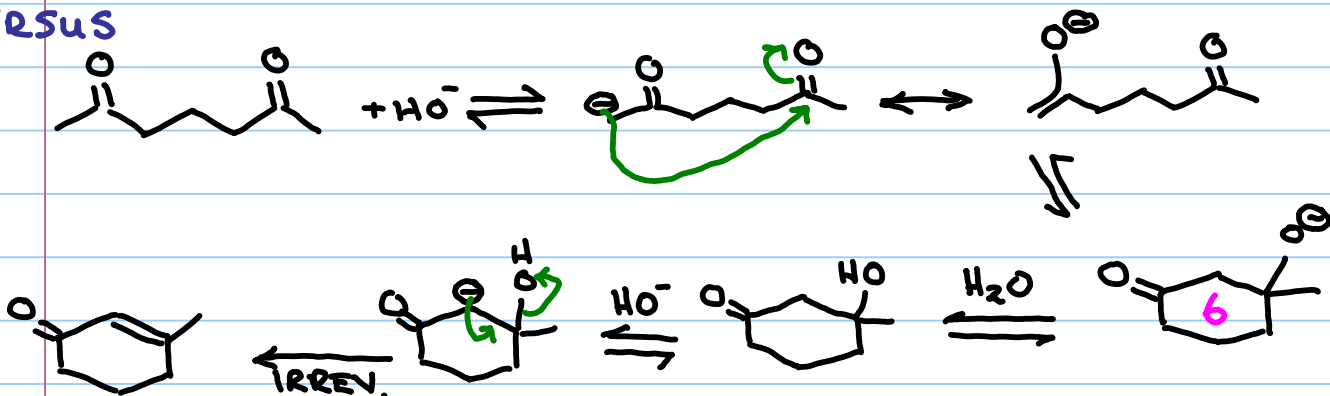
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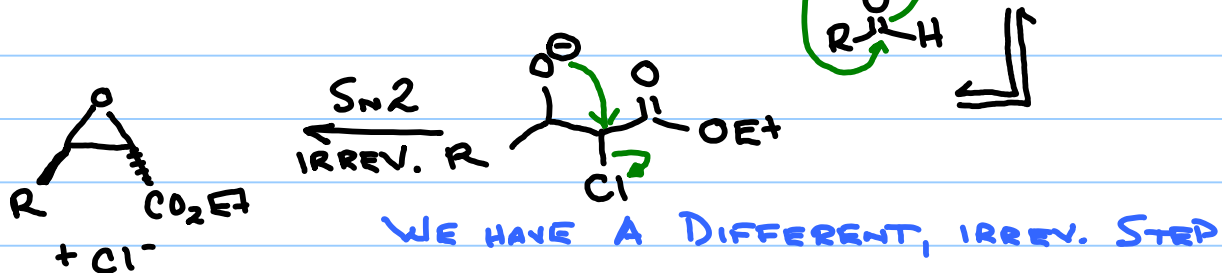
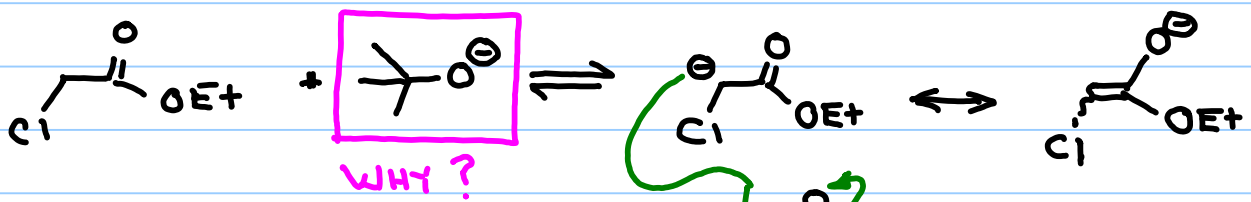
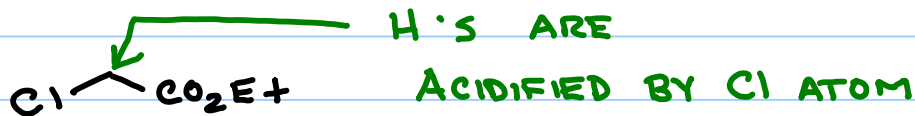
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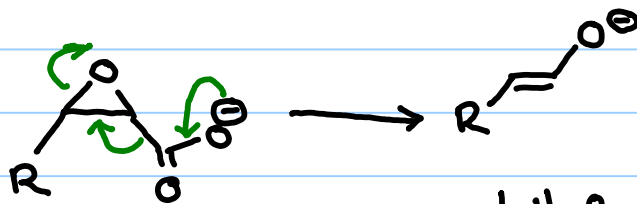
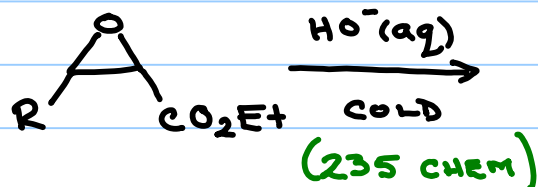


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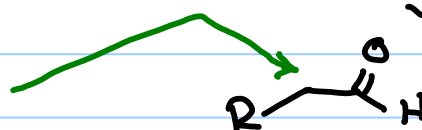
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ENOLATE ALKYLATION

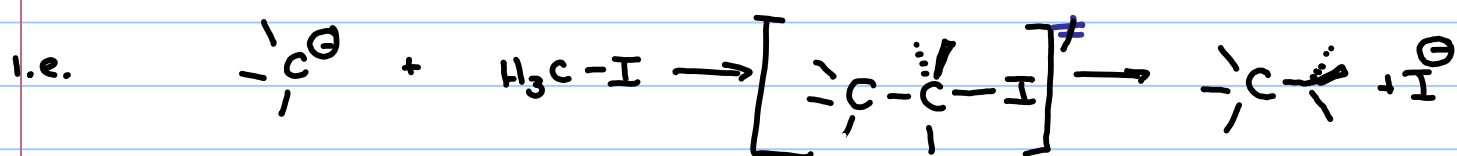
Note Title

1/22/2017

- THE ELECTROPHILE IN REACTIONS WITH ENOLATES DOES NOT HAVE TO BE A CARBONYL

- You ABSOLUTE CAN GET A RXN WHEN $C^{\delta+}$ IS DUE TO A C-X BOND (X = HALOGEN, PSEUDOHALOGEN)

IN TRUTH IT'S REALLY AN ACCEPTABLE TRANSITION STATE



MECHANISM IS ALMOST ALWAYS S_N2

THIS ALKYLATION IS FUNCTIONALLY IRREVERSIBLE

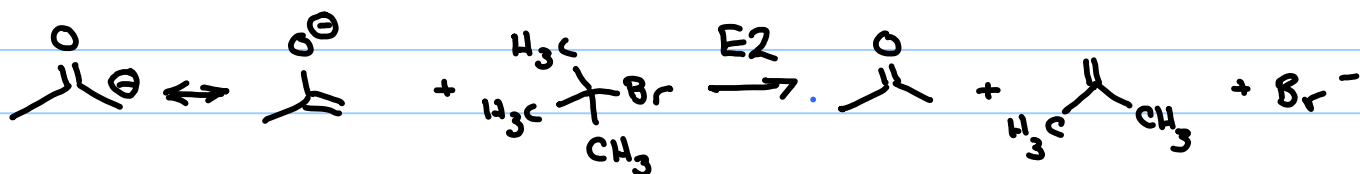
CONSEQUENCES OF S_N2 MECH.

a) FOR R-X



EXCELLENT ADEQUATE FORGET IT

3° ALKYL HALIDES NORMALLY GIVE ELIMINATION INSTEAD

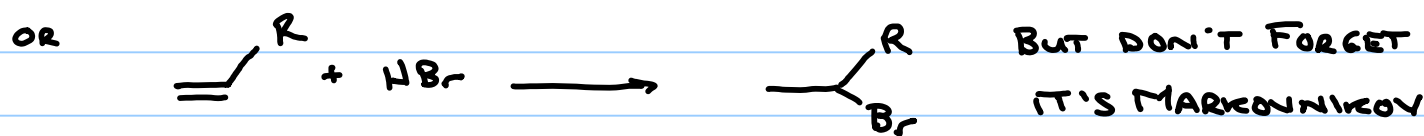
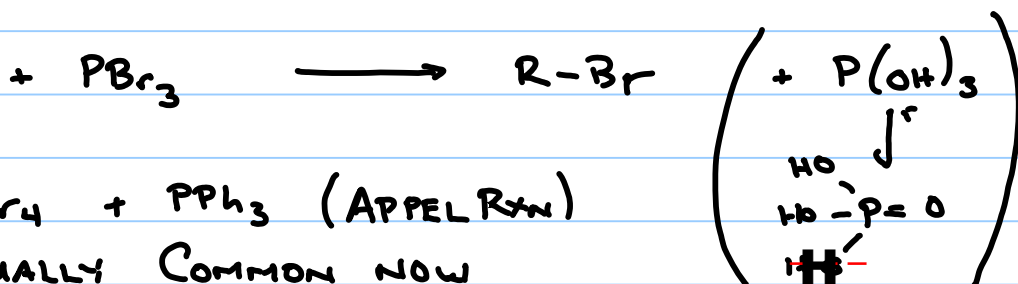
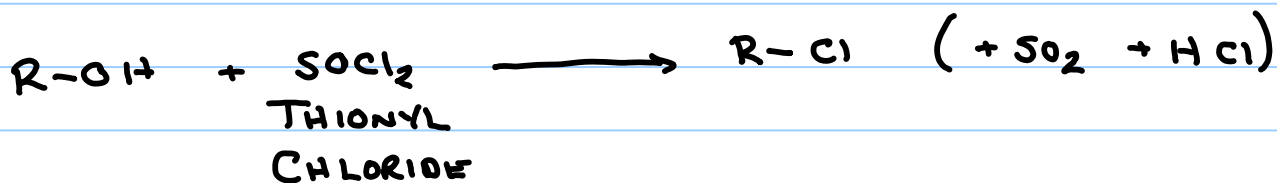


b) $\begin{array}{c} \diagup \\ \diagdown \end{array} X$, C_5H_5-X , $\equiv C-X$ ARE USUALLY UNREACTIVE

c) For HALIDES $I > Br > Cl \gg F$ ~ REACTIVITY

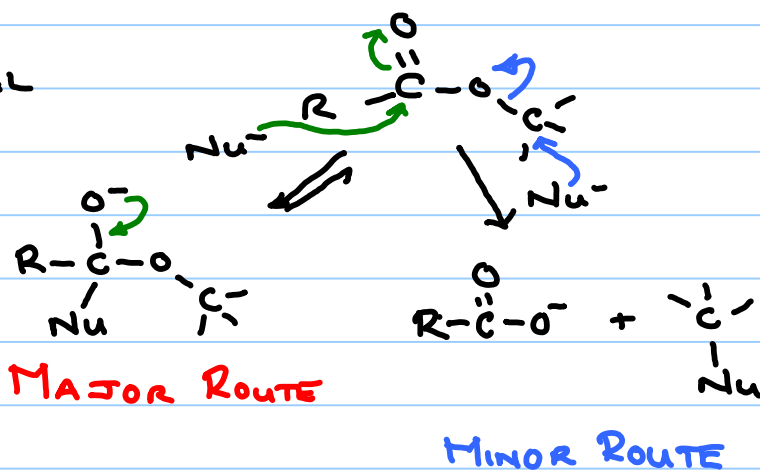
$X = Br$ MOST COMMON

RECALL PREPARATIONS

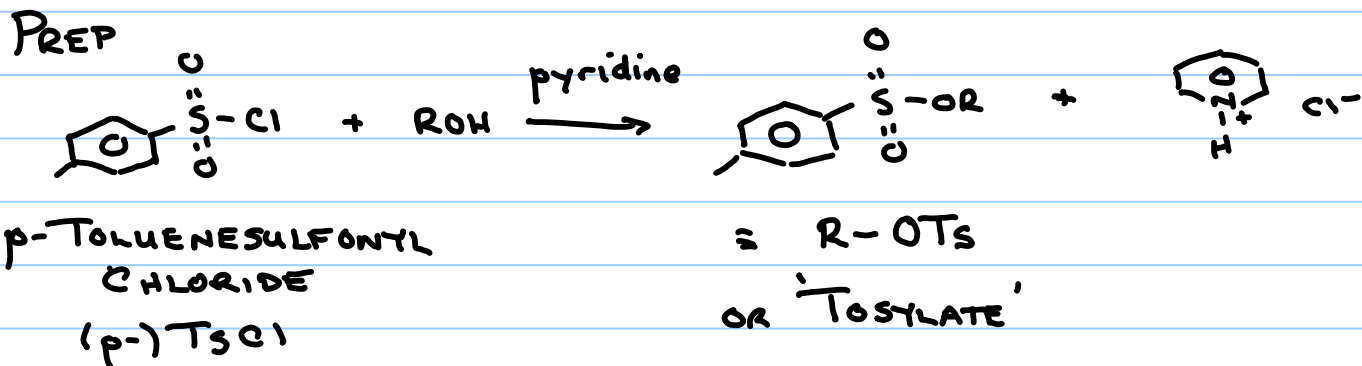
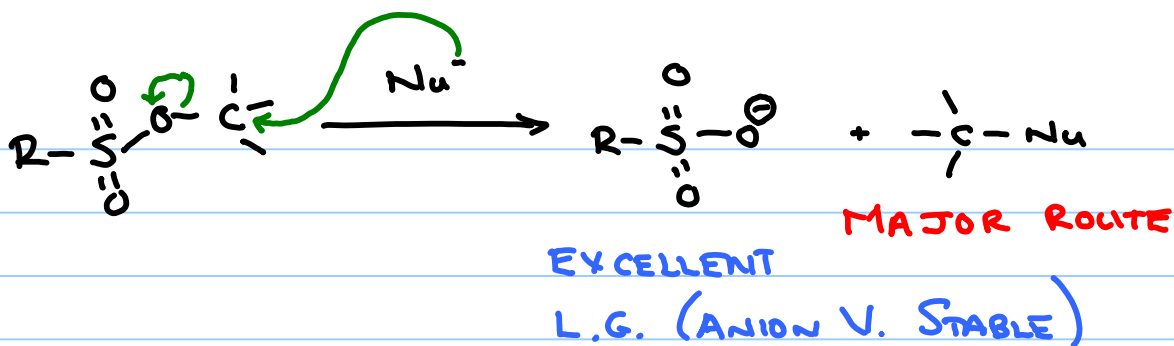


PSEUDOHALIDES - SULFONATE ESTERS
- BEHAVE MUCH LIKE HALIDES

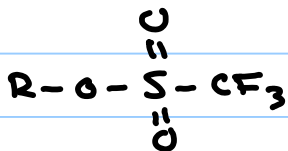
COMPARE - CONVENTIONAL ESTER



FOR SULFONIC ESTERS



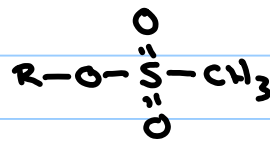
ALSO COMMON



TRIFLUOROMETHANE SULFONATE



'TRIFLATE'



METHANESULFONATE



'MESYLATE'

- EXCELLENT LEAVING GROUPS FOR $\text{S}_\text{N}2$'s

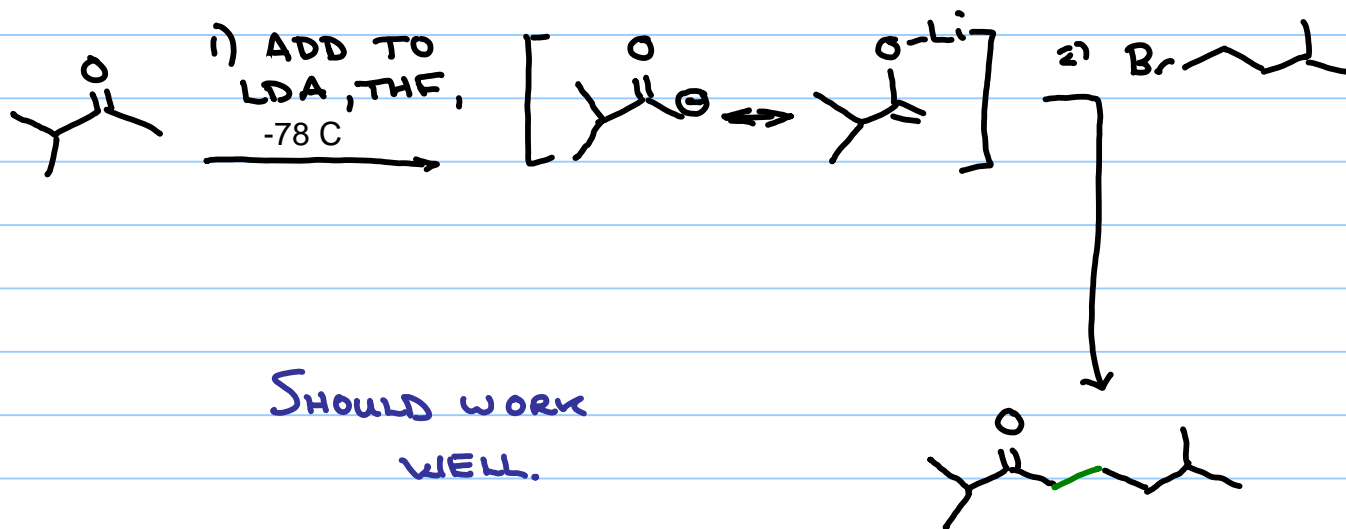
F^-	Cl^-	Br^-	I^-	Tso^-	Tfo^-
1	200	10000	30000	60000	EVEN BETTER

- AND DON'T FORGET - INVERSION OF CONFIGURATION AT A CHIRAL CENTRE.

ROLE OF BASE

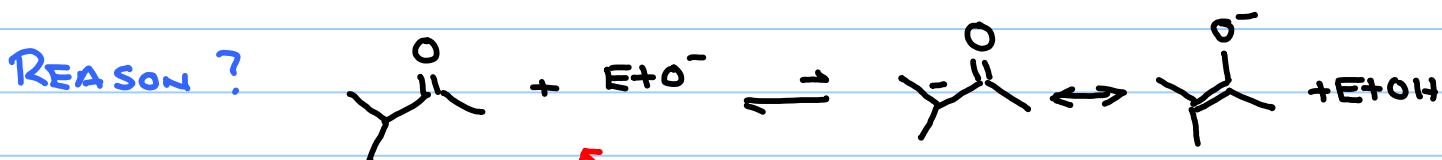
- WE HAVE SEEN BASES THAT WILL MAKE KINETIC AND ONES THAT WILL MAKE THERMODYNAMIC ENOLATES

a) KINETIC - NO CHANGES HERE - LDA AT LOW TEMP (+ USED PROPERLY) WORKS EFFECTIVELY



b) "THERMODYNAMIC" BASE

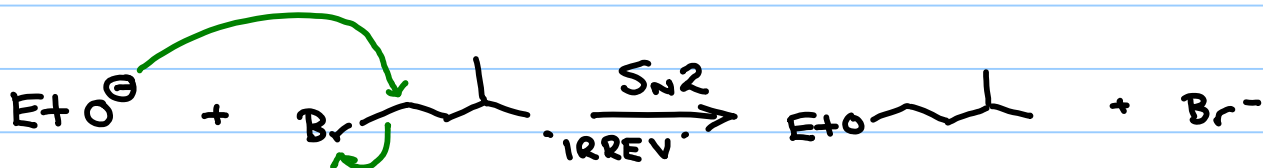
- TO THIS POINT, A WEAK BASE LIKE EtO^{\ominus} OR HO^{\ominus} HAS BEEN SUFFICIENT
- NOT A 'GO' HERE



Keqn WAY ON S.M. SIDE

\therefore A LOT OF UNREACTED EtO^{\ominus}

AND - WE HAVE A COMPETITIVE, 'IRREVERSIBLE' PROCESS



- BASE - GONE

ALKYL HALIDE - GONE

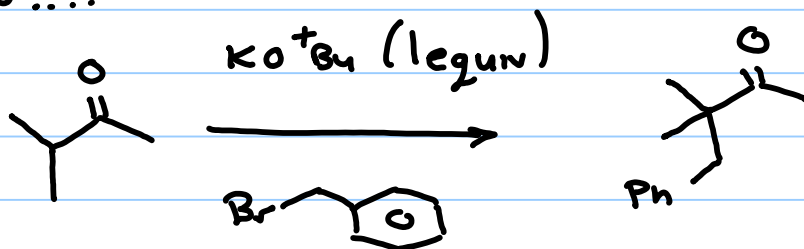
SOLUTION - THE SOLUTION ISN'T TOO DIFFICULT

- tert-BUTOXIDE $K^+ \bar{O}^+Bu$

IS HINDERED ENOUGH BY STERIC TO BE A POOR
NUCLEOPHILE

- WHILE BEING ABOUT AS GOOD (ACTUALLY A
TOUCH BETTER) AS BASE

SO



GOOD YIELDS.

ALKYLATION, CONT'D.

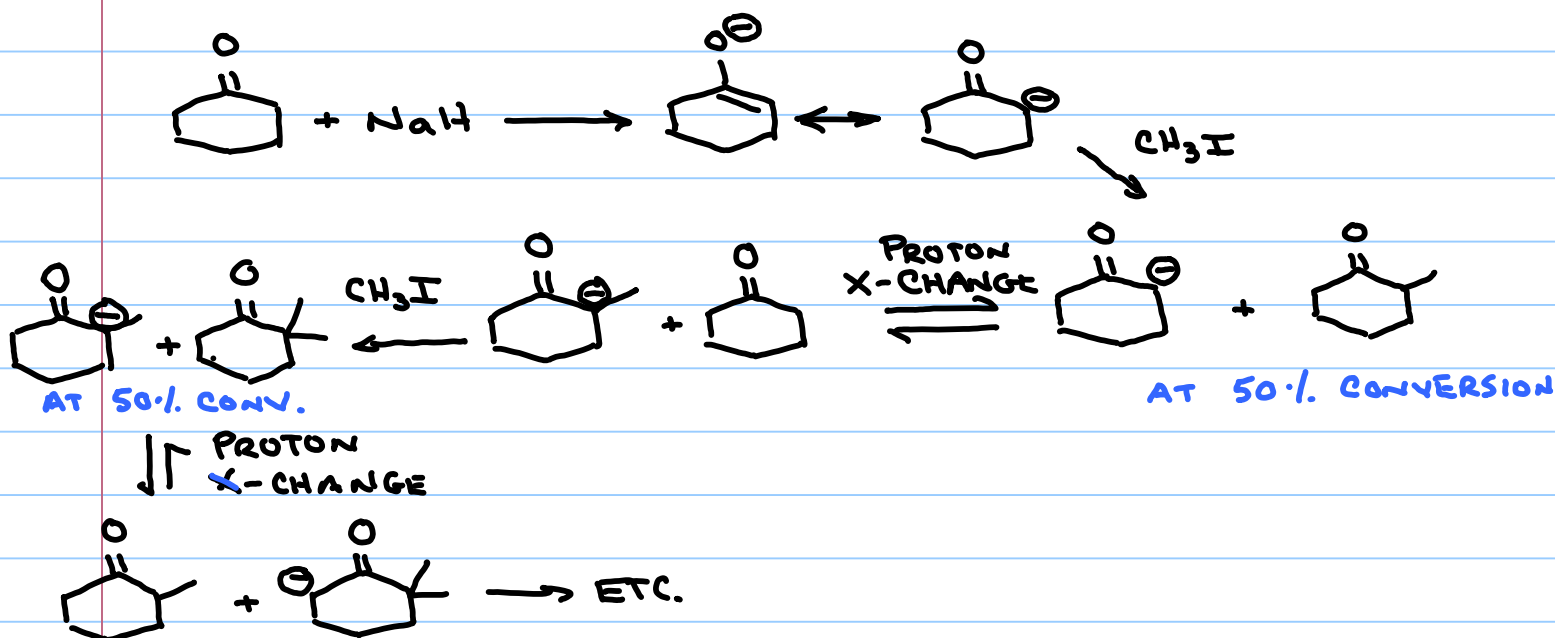
Note Title

1/24/2017

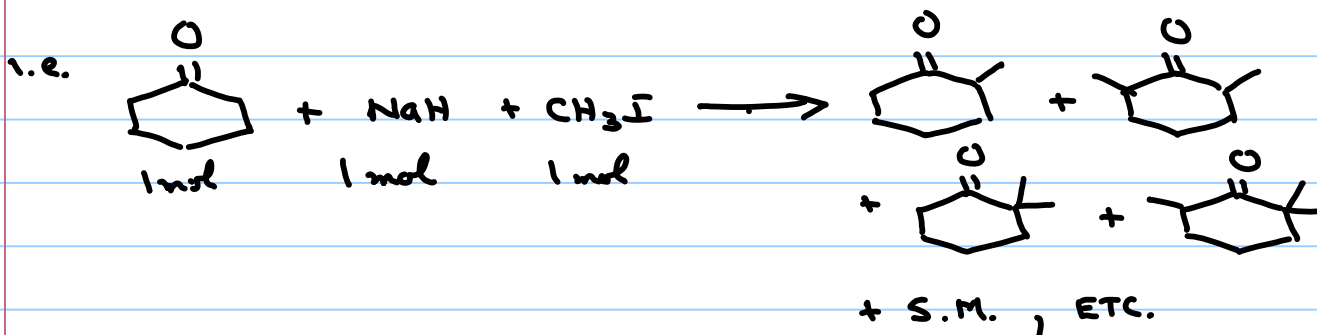
POLYALKYLATION

- POTENTIAL PROBLEM WITH ENOLATE ALKYLATION IS THAT IT IS RELATIVELY SLOW AS COMPARE TO PROTONATION AND DEPROTONATION

LET'S DO AN 'OLD SCHOOL' ALKYLATION OF CYCLOHEXANONE WITH NaH AND CH₃I



SO IT'S POSSIBLE TO GET MIXTURES OF MULTIPLY ALKYLATED PRODUCTS EVEN WITH CAREFULLY MEASURED AMOUNTS.



- DON'T WANT TO TRY TO SEPARATE THESE
- IN PRINCIPLE POSSIBLE WITH ANY ENOLATE ALKYLATION

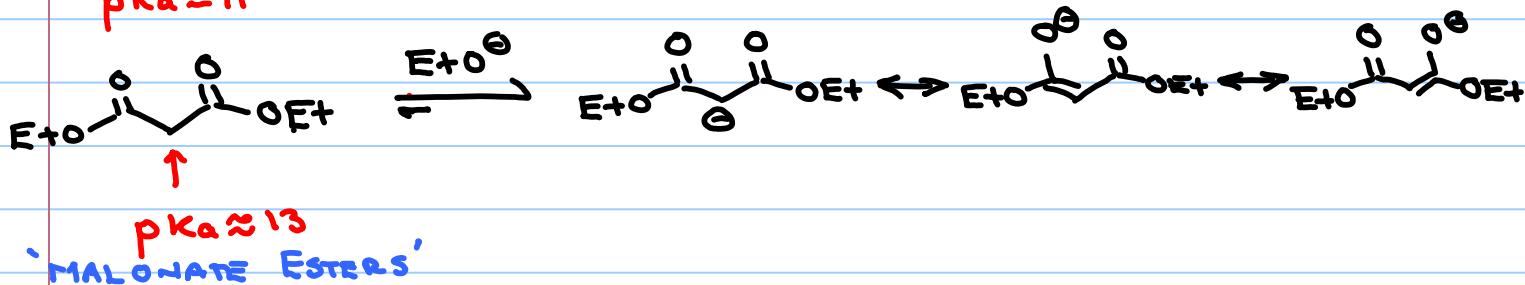
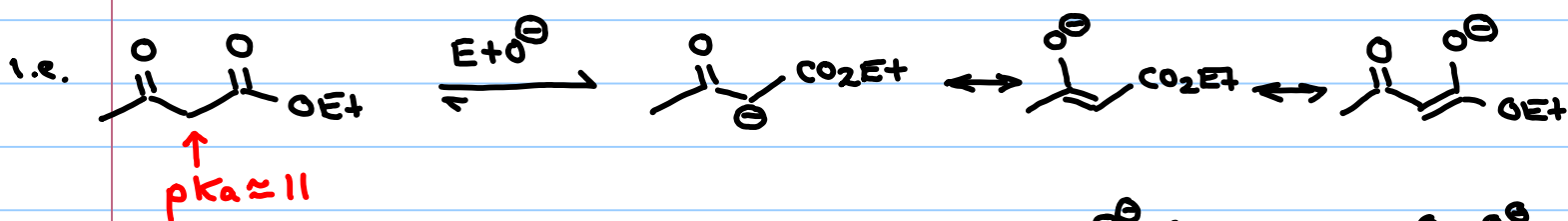
- IN PRACTICE, NOT ALWAYS

- OFFICIAL RULING FOR 59-331/333

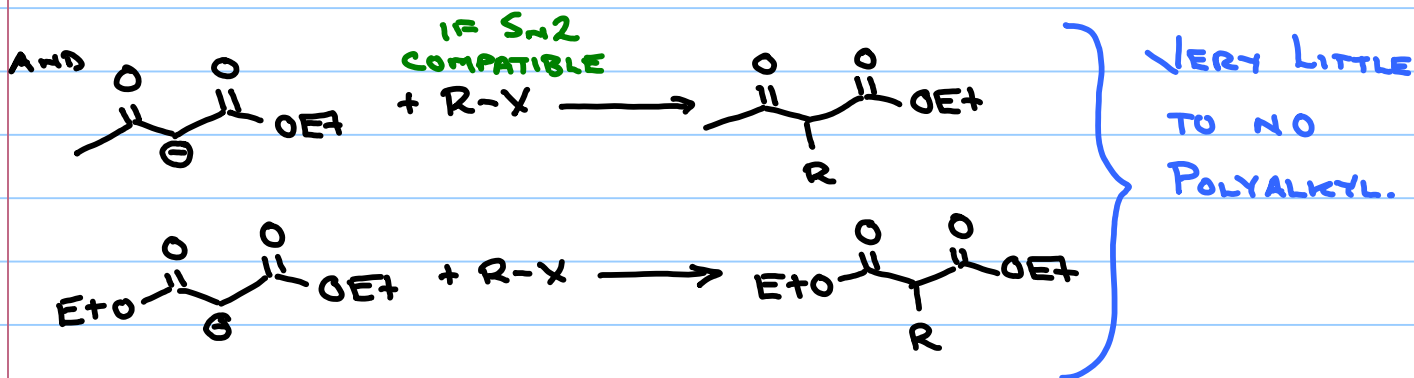
- WE'LL SAY THIS IS A PARTICULAR PROBLEM FOR
CYCLIC KETONES

SOLUTIONS?

- ONE WELL KNOWN SOLUTION IS TO GO TO ACTIVE METHYLENE 'CPS', WHICH ARE SYSTEMS W 2 CARBONYLS

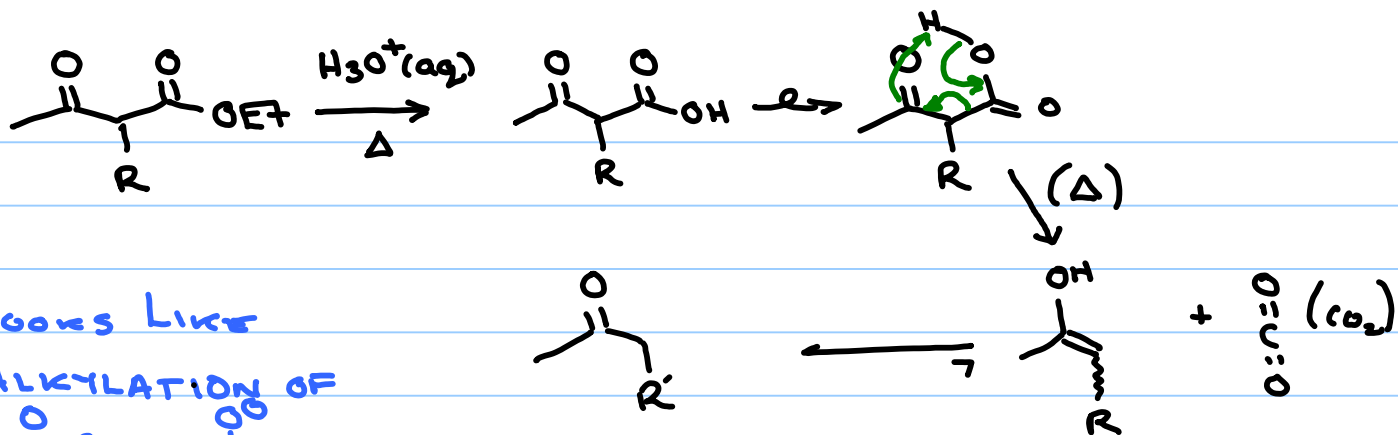


NOTE: EVEN ALKOXIDE BASES ARE NOW STRONG ENOUGH FOR 'COMPLETE' DEPROTONATION OF THESE



SO HOW DO WE GET BACK THE KETONE (OR ESTER)

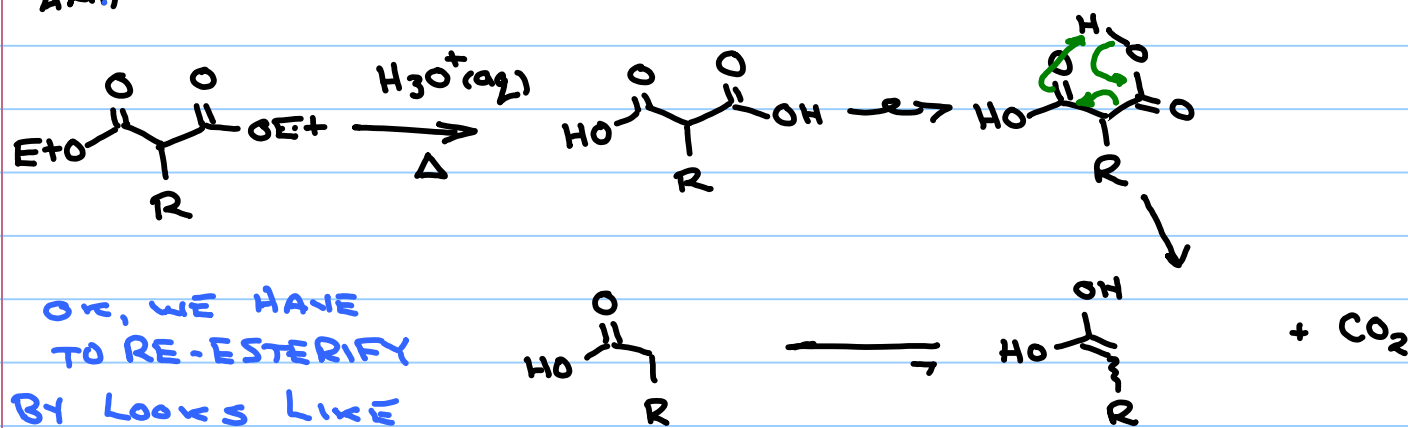
- IT TURNS OUT THAT ESTERS β - TO OTHER CARBONYLS DECARBOXYLATE RATHER EASILY, UNDER ACIDIC COND'S.



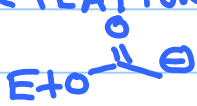
Looks Like
ALKYLATION OF



AND

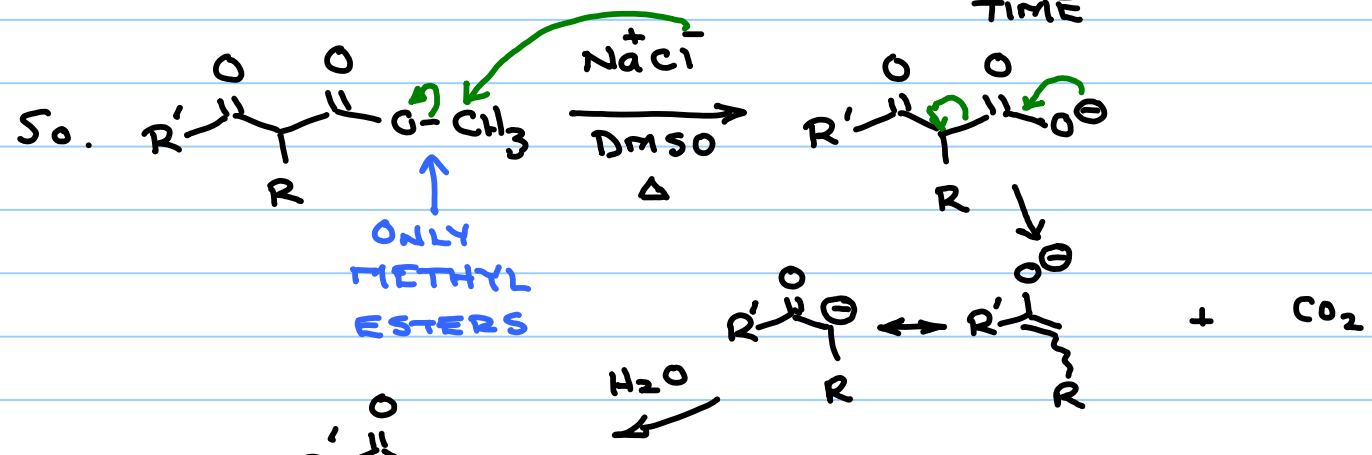


OR, WE HAVE
TO RE-ESTERIFY
BY LOOKS LIKE
ALKYLATION OF

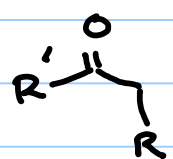


ONE ALTERNATIVE DECARBOXYLATION I'M ADDING
- KRAPCHO DECARBOXYLATION

- REMEMBER THAT STATEMENT THAT ESTER NORMALLY
ATTACK AT THE CARBONYL? - WELL NOT 100% OF
TIME



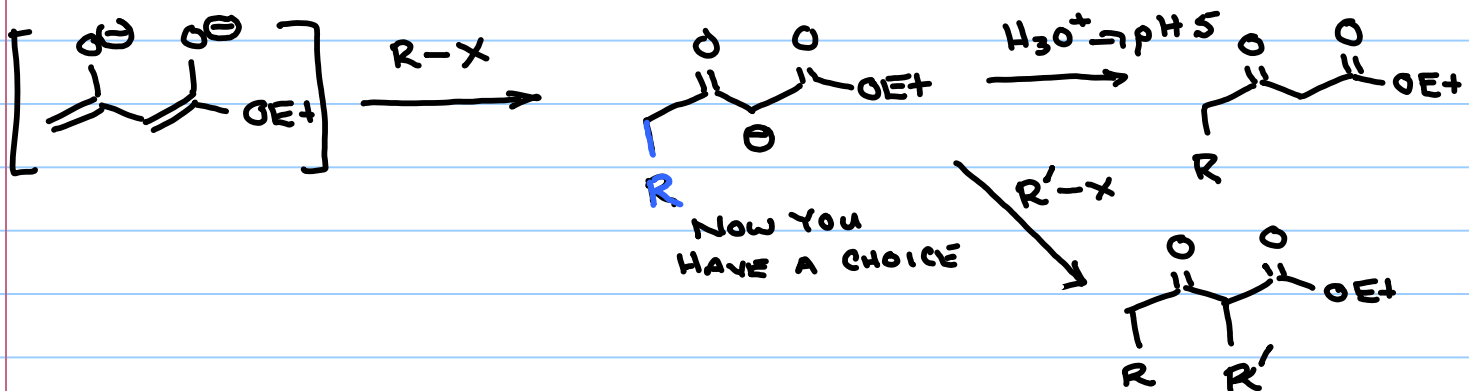
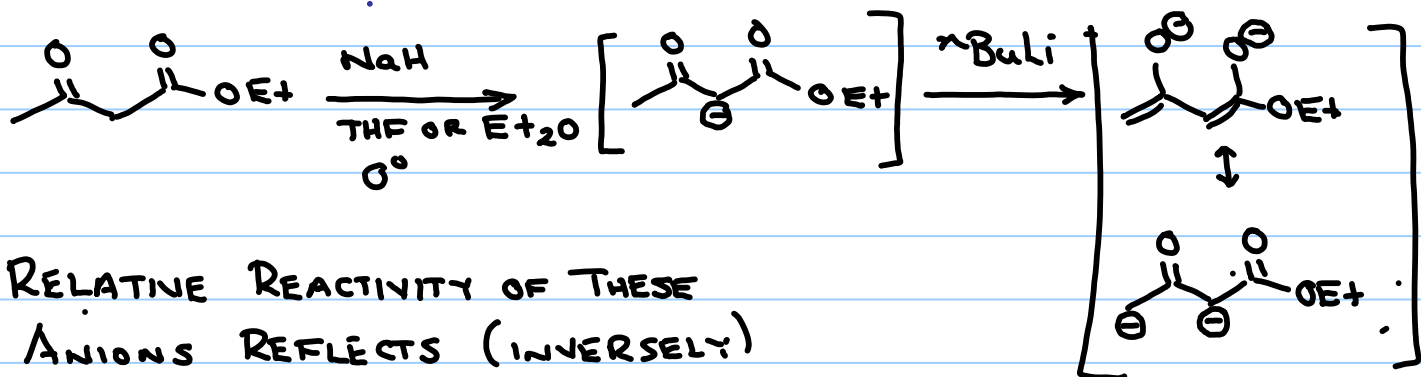
ONLY
METHYL
ESTERS



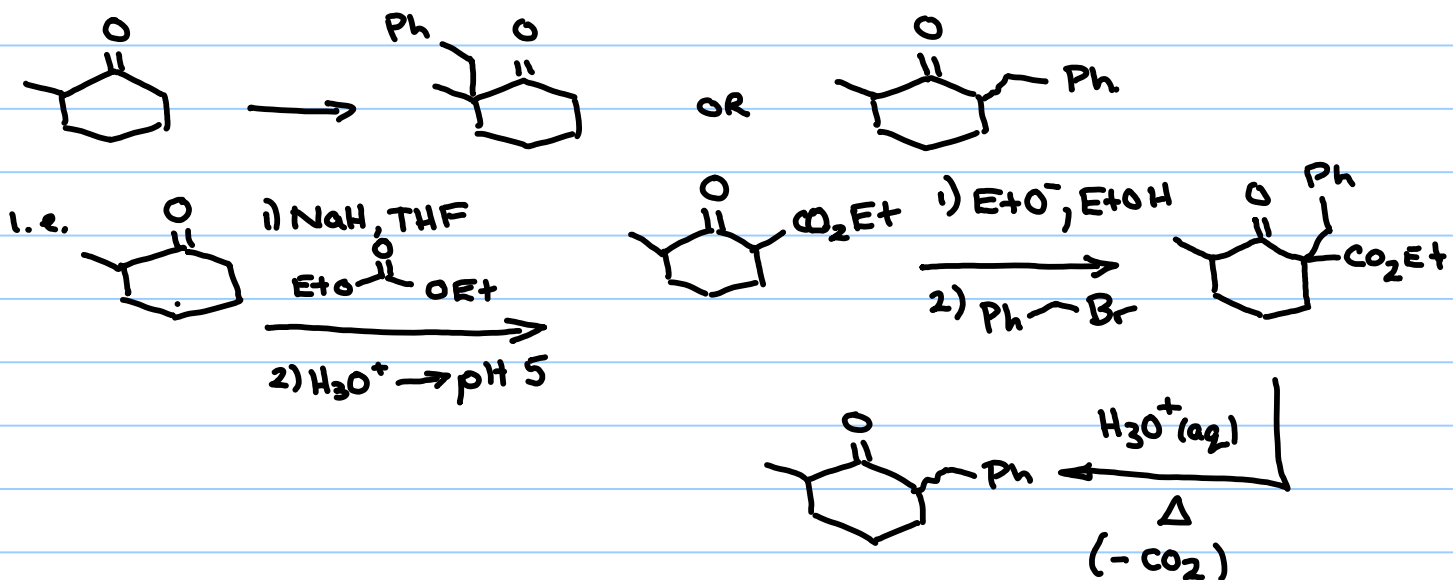
IF R' IS ESTER IT IS NOT USUALLY
HYDROLYZED

ONE ADDITIONAL USEFUL FEATURE OF β -KETO ESTER
- DIANION FORMATION

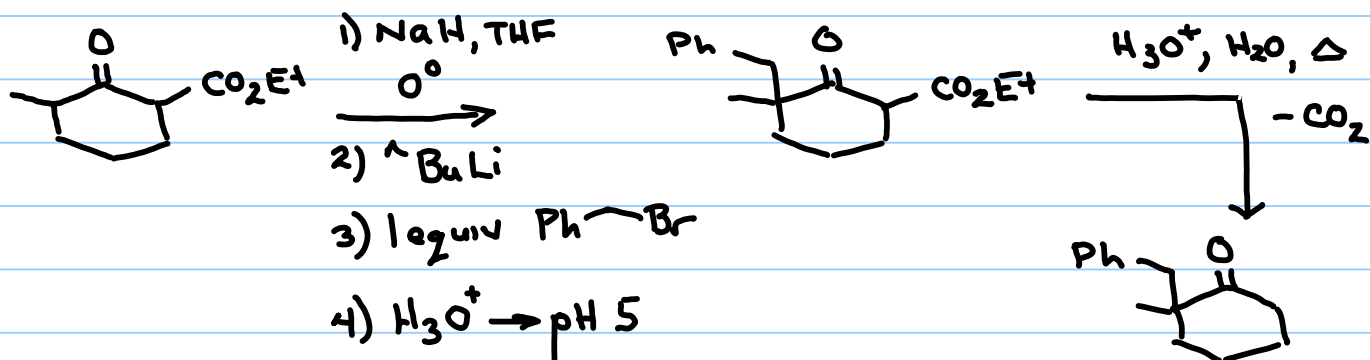
CC(=O)CC(=O)OEt ARE STABILIZING ENOUGH THAT WE CAN ABSTRACT TWO PROTONS W A GOOD CHOICE OF BASES



USE

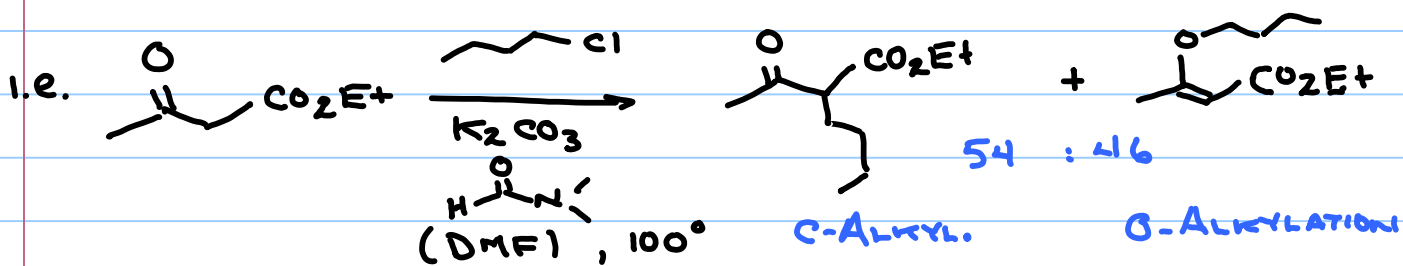


OR



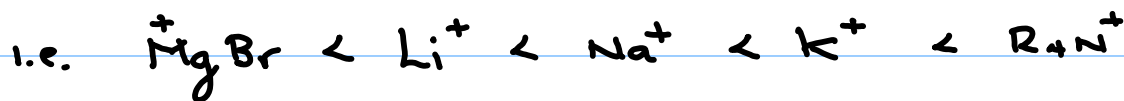
BUT THERE'S ONE PROBLEM WITH THE 'ACTIVE METHYLENE' COMPOUNDS YOU REALLY HAVE TO WATCH OUT FOR

O-ALKYLATION



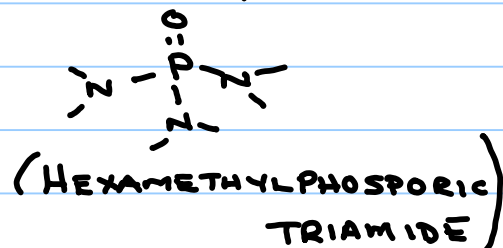
TENDS TO BE AN ISSUE PARTICULARLY WITH THESE ENOLATES

- PREVALENT WITH BIGGER COUNTERIONS, WHICH ARE NOT AS TIGHTLY ASSOCIATED WITH THE O^-



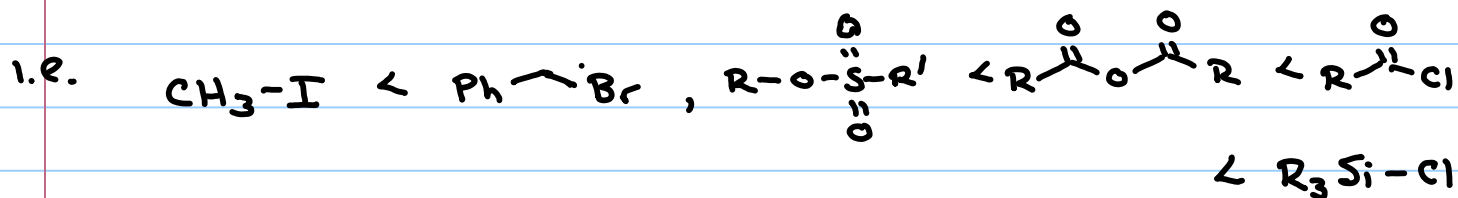
- PREVALENT IN CATION COORDINATING, V. POLAR APROTIC SOLVENTS

EtOH < THF, Et₂O < DMF, DMSO < HMPA



- WORSE WITH ELECTROPHILE WITH A GREATER δ^+ ON THE ATOM BEING ATTACKED ('HARD' ELECTROPHILE, OR CHARGE CONTROLLED INTERACTION BETWEEN ENOLATE AND ELECTROPHILE)

- NOT AS BAD WITH MORE COVALENTLY BOUND ELECTROPHILES ('SOFT' ELECTROPHILE, OR ORBITAL CONTROLLED INTERACTION BETWEEN ENOLATE AND ELECTROPHILE)



NOTE: THIS HSAB (HARD/SOFT ACID - BASE OR ELECTROPHILE - NUCLEOPHILE) APPROACH IS FAIRLY HEAVILY USED IN ORGANIC CHEMISTRY, BUT LARGELY ABANDONED IN INORGANIC CHEM.

ENAMINES:

Note Title

1/27/2017

ONE OTHER FAIRLY SELECTIVE ALKYLATION REACTION THAT STOPS POLYALKYLATION

- ENAMINES - RXN OF A KETONE W/ 2° AMINES

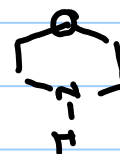
- PARTICULARLY USED W/ CYCLIC KETONES

- RELIABLE REGIOSELECTIVITY

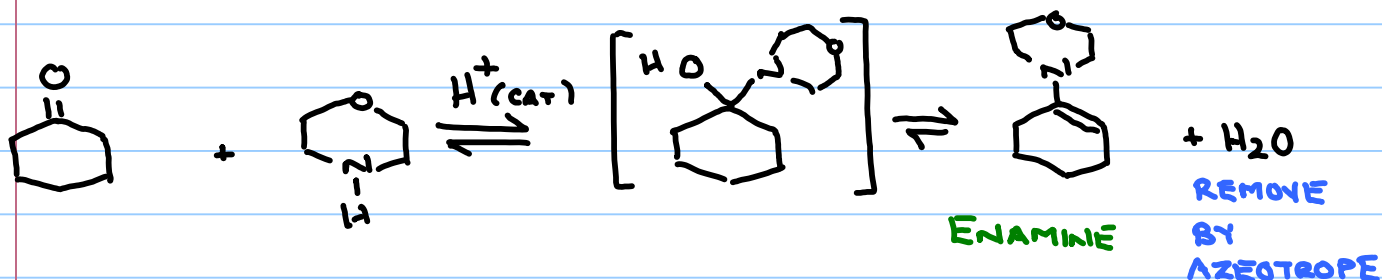
- MY FAVOURITE 2° AMINES



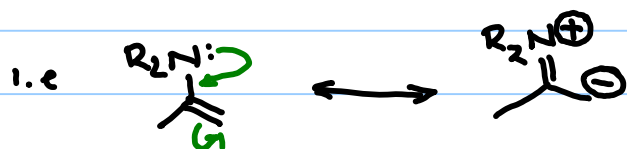
PIPERIDINE



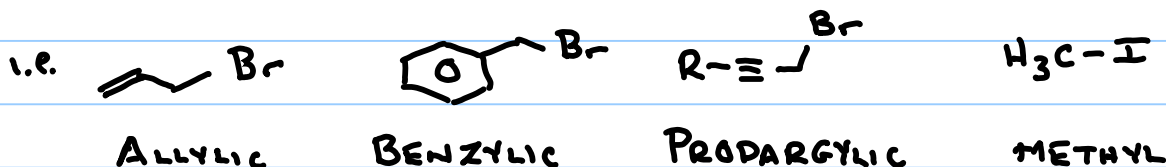
MORPHOLINE



VERY NUCLEOPHILIC FOR A NEUTRAL COMPOUND.

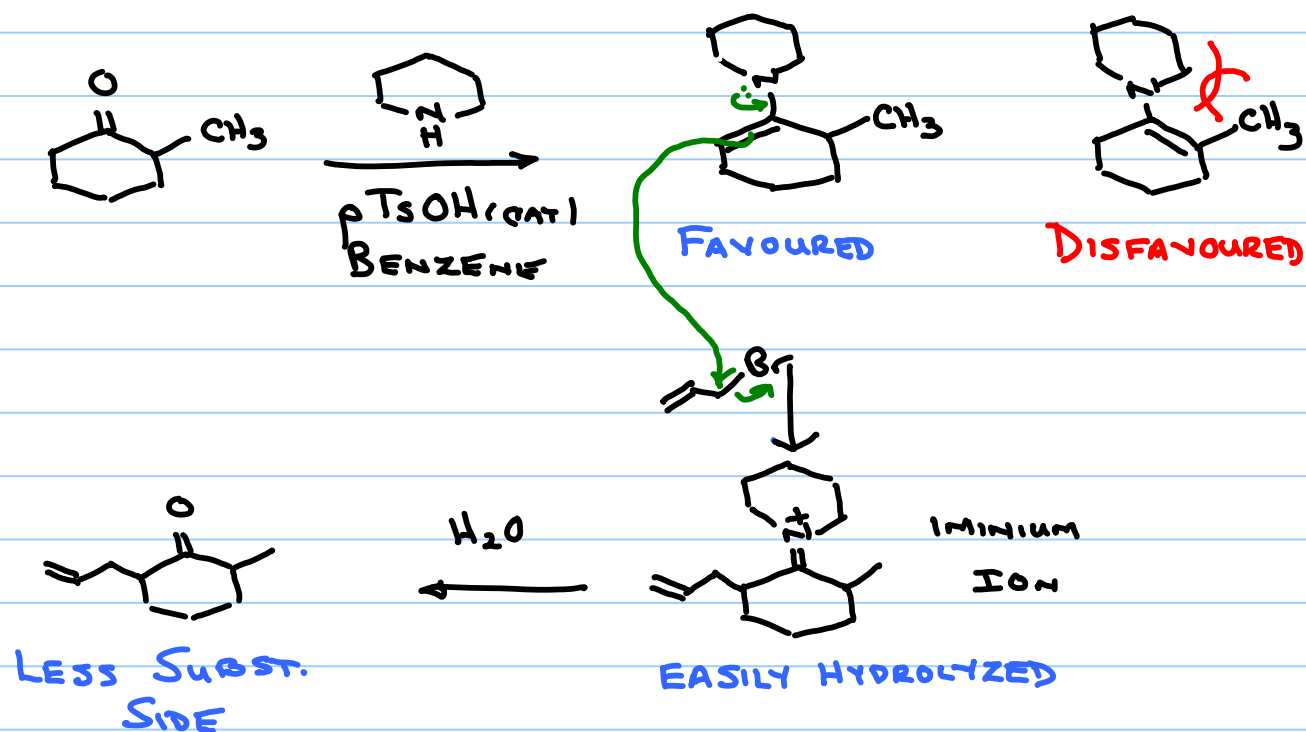


NUCLEOPHILIC ENOUGH TO DO S_N2 REACTIONS ON PARTICULARLY REACTIVE ALKYL HALIDES



- 1° ALKYL HALIDES NORMALLY NOT GOOD ENOUGH

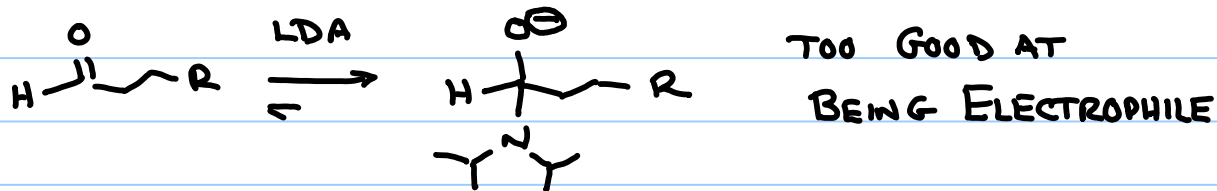
- ALSO, SUBST. IN CYCLIC KETONES IS PREDICTABLE



- NO POLYALKYLATION TO SPEAK OF.

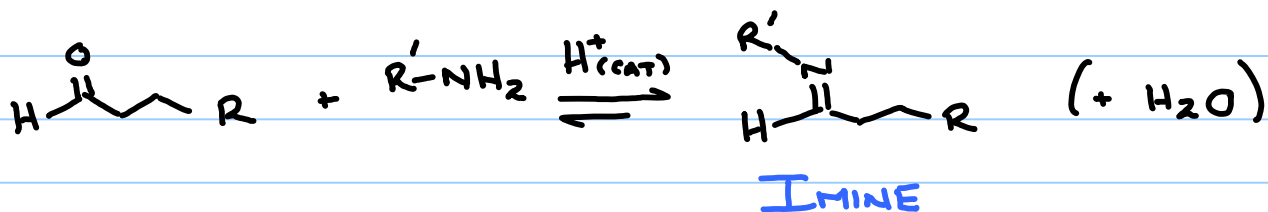
IMINES

- PROBLEM WITH ALDEHYDE ALKYLATION

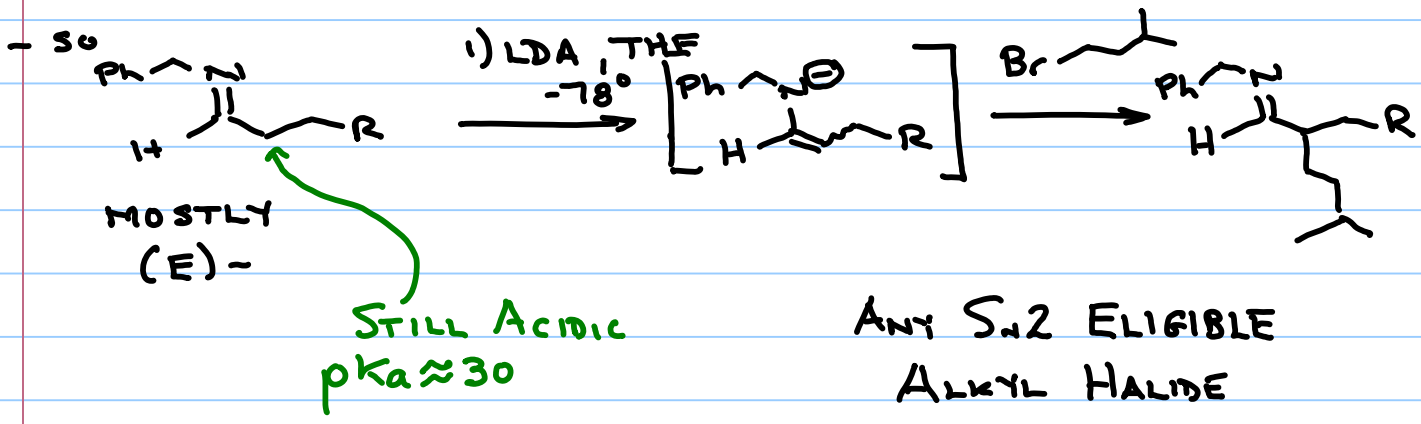
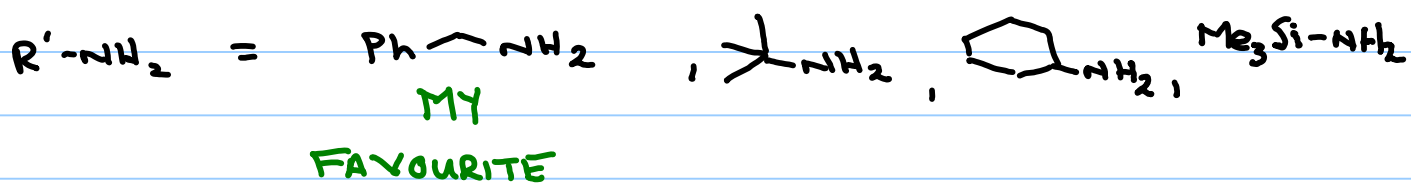


- SOLUTION - MAKE ALDEHYDE DERIVATIVE THAT IS LESS ELECTROPHILIC, BUT IS STILL ACIDIC

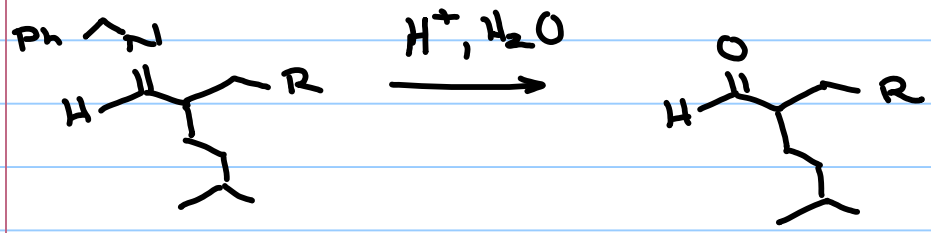
IMINE - FROM ALDEHYDE AND 1° AMINE



R' ON N NEEDS TO BE OF 'SOME' SIZE, OR ELSE THE IMINE IS TOO HYDROLYTICALLY UNSTABLE

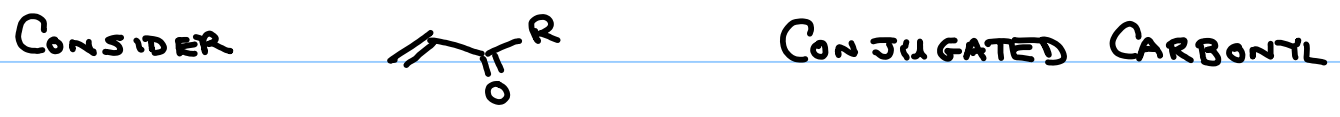


- EASY TO HYDROLYZE BACK TO ALDEHYDE

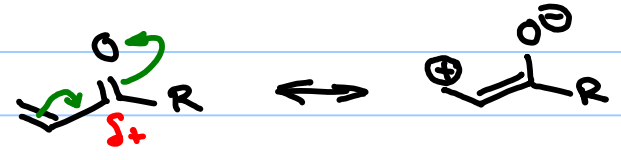


CONJUGATE (MICHAEL) ADDITIONS.

- ONE MORE C^{δ+} FOR REACTIONS WITH ENOLATES

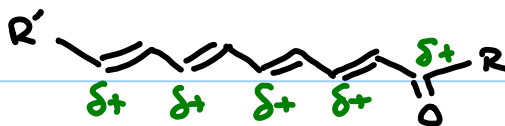


RESONANCE FORMS



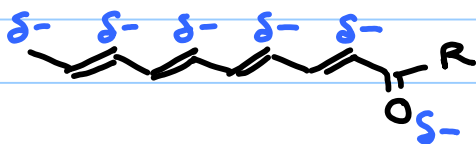
SO THE β-CARBON IS ALSO δ⁺

IN FACT...

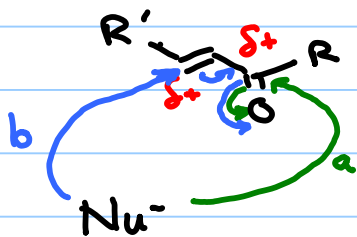


EVERY ALTERNATING CARBON, IF YOU EXTENDED CONJUGATION FAR ENOUGH, IS ELECTROPHILIC TO SOME DEGREE

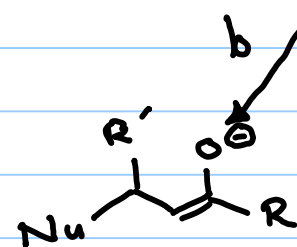
- AND IT'S BESIDE THE (CURRENT) POINT, BUT EVERY ALTERNATING ONE IS POTENTIALLY NUCLEOPHILIC (AFTER CONVERTING TO ENOLATE)



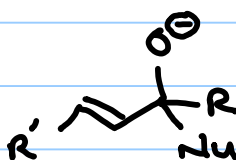
- BACK TO



SO ATTACK OF Nu^- HAS TWO POSSIBILITIES



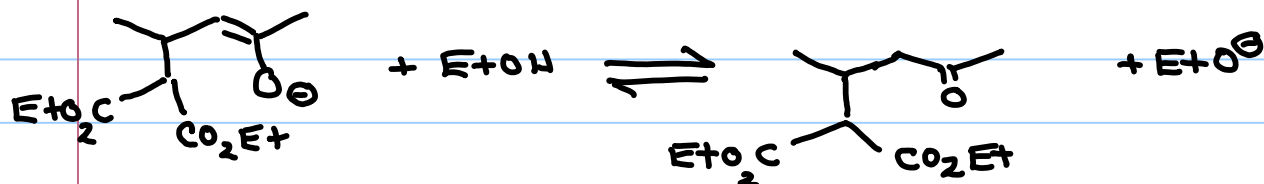
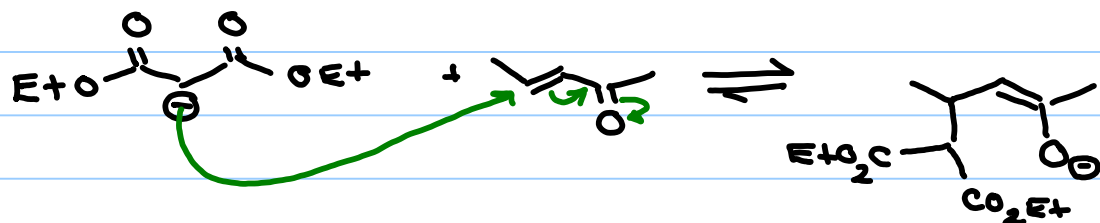
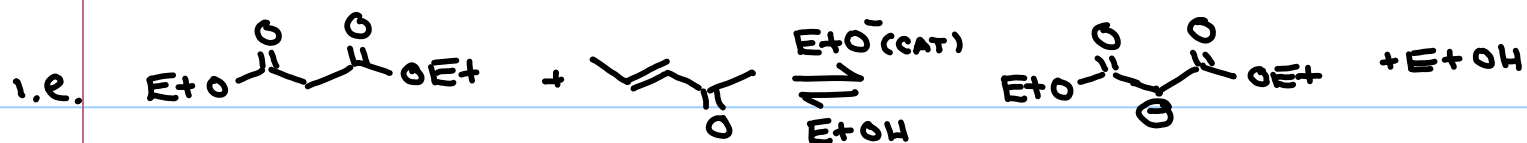
CONJUGATE, OR
1,4-ADDITION



BEGINNING OF ALDOL TYPE RXN
OR 1,2-ADDITION

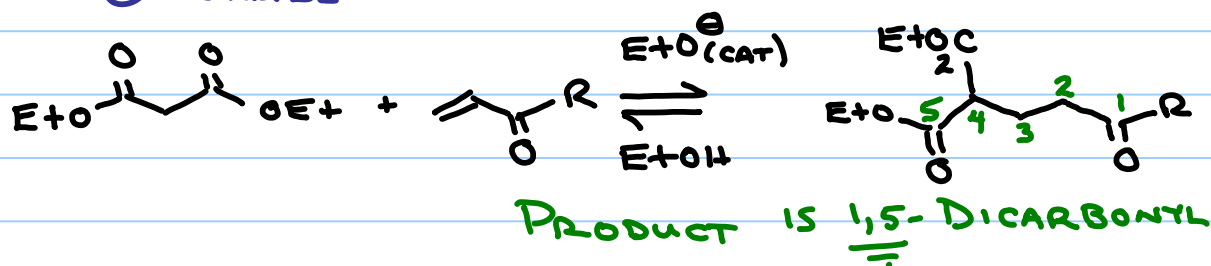
- IF Nu^- IS AN ENOLATE, THE REACTION IS CALLED MICHAEL RXN (OR MICHAEL ADDITION)

- THE TYPES OF ENOLATES THAT ARE ESPECIALLY GOOD AT DOING CONJUGATE ADDITIONS ARE THE DOUBLY STABILIZED ENOLATES DERIVED FROM 'ACTIVE METHYLENE' COMPOUNDS.



NOTICE: TOTAL RXN IS REVERSIBLE

OVERALL:

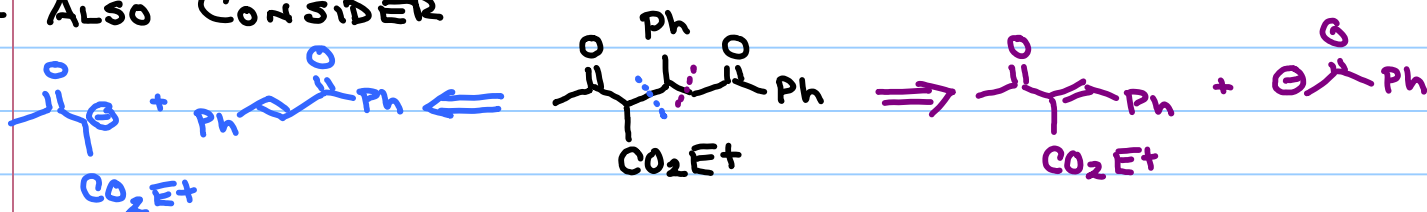


- SINCE THE MICHAEL RXN IS REVERSIBLE AND THE WEAK BASE INDUCED ALDOL CONDENSATION IS NOT...

- IF YOU USE A CATALYTIC AMOUNT OF BASE AND AMBIENT T, MICHAEL IS FAVOURED

- IF RXN IS RUN IN A WAY TO FORCE ELIMINATION OF H₂O (EXCESS BASE, REFLUX), YOU TEND TO GET THE ALDOL

- ALSO CONSIDER



- ALWAYS TWO POTENTIAL WAYS TO MAKE BY MICHAEL RXN.

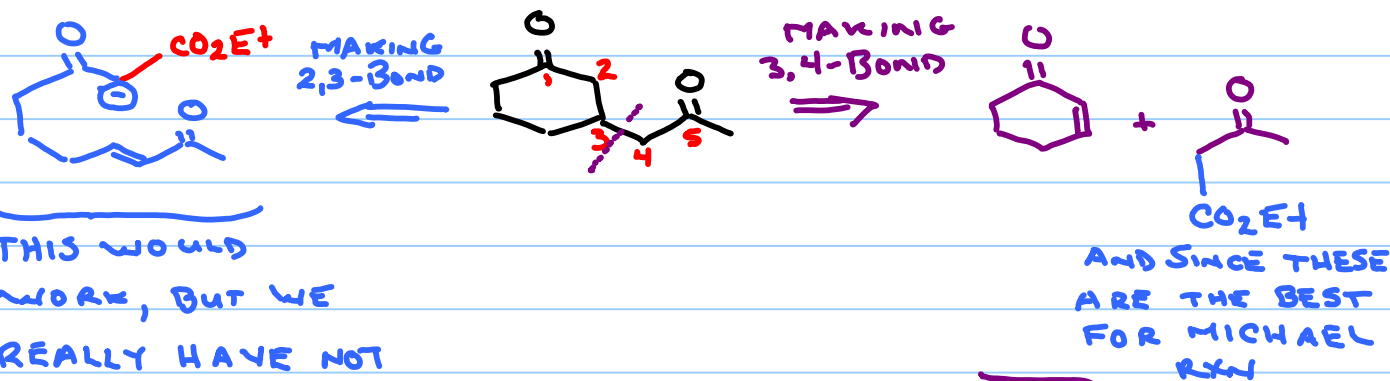
MICHAEL RXN, CONT'D.

Note Title

1/31/2017

RECALL LAST STATEMENT, THAT A 1,5-DICARBONYL IS ASKING TO BE MADE BY A MICHAEL RXN, AND THAT THERE'S IN PRINCIPLE ALWAYS 2 WAYS TO DO THIS....

EXAMPLE

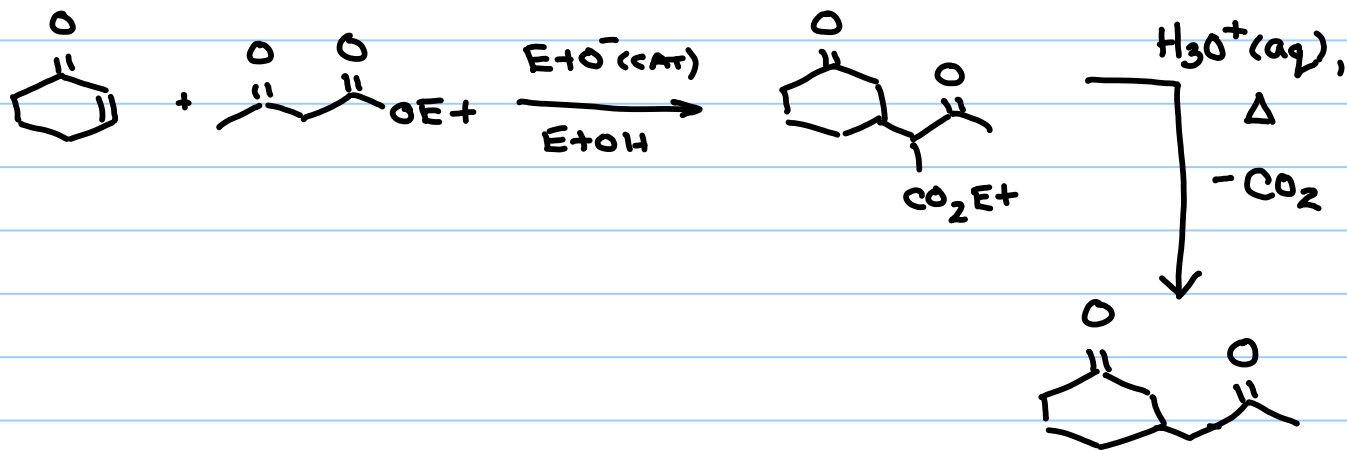


THIS WOULD WORK, BUT WE REALLY HAVE NOT

SIMPLIFIED THE MOLECULE

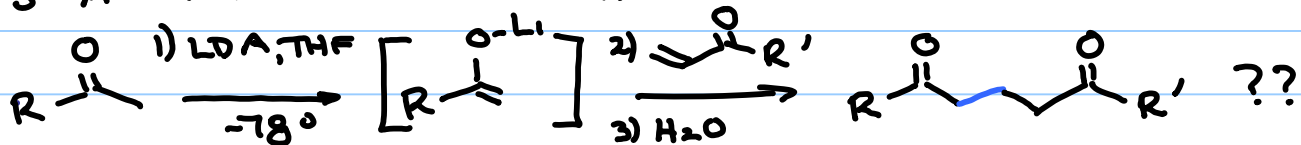
THIS LOOKS BETTER
- ALL MOLECULES AVAILABLE COMMERCIALY.

SO THE BEST PREPARATION OF THIS TARGET WOULD BE:

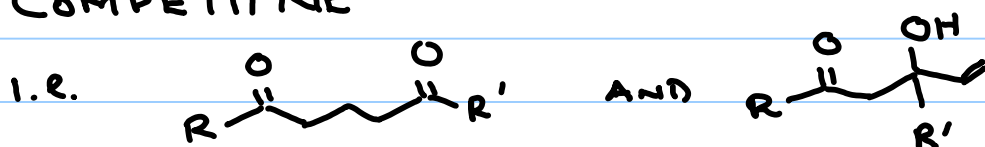


WITH KINETIC / STOICHIOMETRICALLY MADE ENOLATES?

IT'S A FAIR QUESTION ... IS THE FOLLOWING DOABLE?



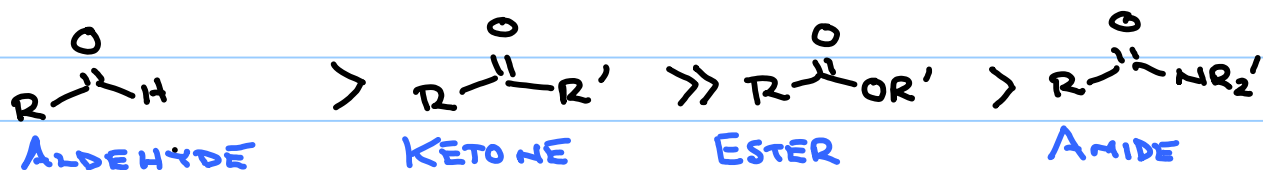
THE PROBLEM HERE IS THAT 1,2-ADDITION IS COMPETITIVE



PREDOMINATE IN SELECTED CIRCUMSTANCES

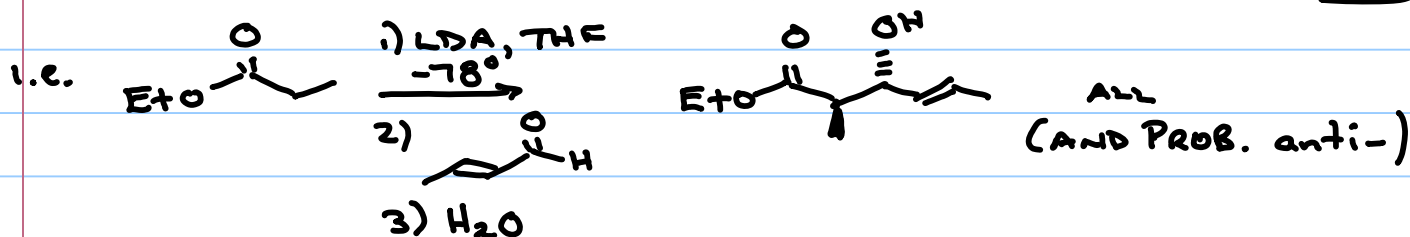
- IF YOU WANT TO TRY, HERE ARE SOME GENERAL RULES

- RECALL - EASE OF ATTACK ON CARBONYL



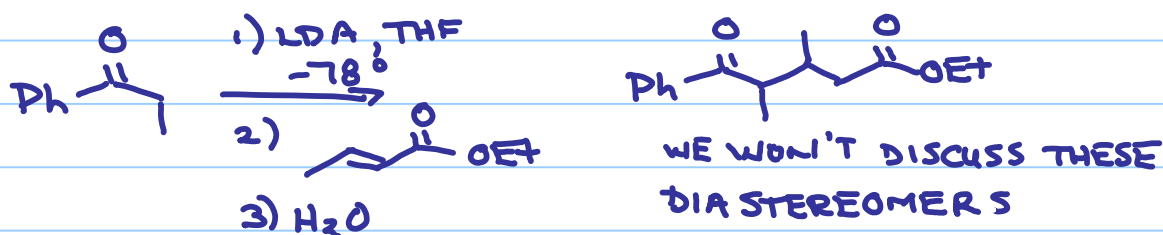
- SO ALDEHYDES? i.e. $R-CH=CH-C(=O)H$

NO GO - ALWAYS 1,2-ADDITION TO GIVE ALDOL



- ESTERS AND AMIDES (3°)? i.e. $R-CH=CH-C(=O)OEt$

VERY GOOD CHANCE - ESTERS DON'T ATTACK AS EASILY AT CARBONYL, SO 1,4-ADDITION NORMALLY WINS.

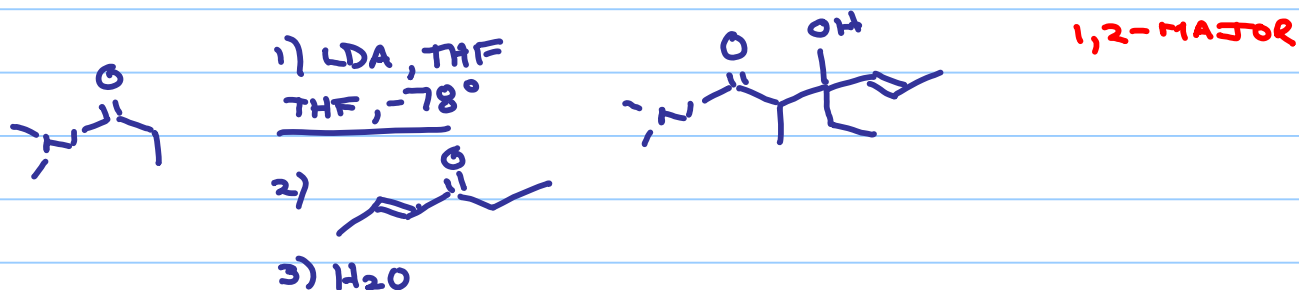
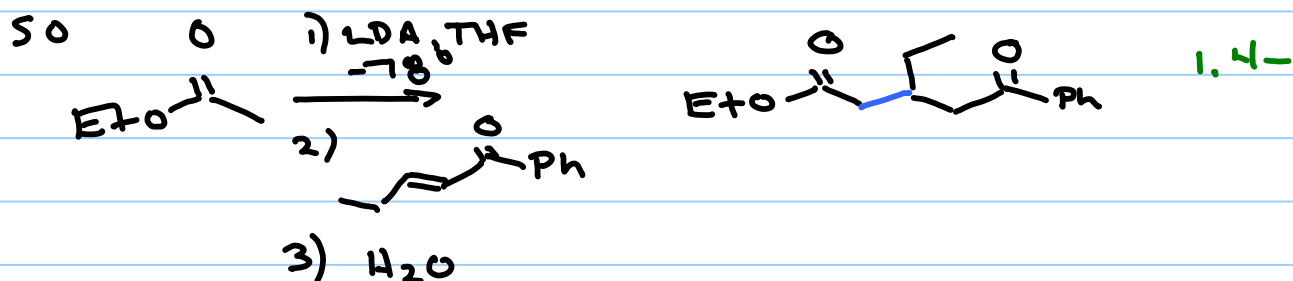


- AND KETONES? - HERE'S WHERE IT'S REALLY CLOSE, AS 1,2- AND 1,4- ADDN ARE TRULY COMPETITIVE.

- OFFICIAL RULING FOR 59-331/333

- IF THE ORGANIC GROUP ON THE KETONE CARBONYL IS LARGE (A VALUE ≥ 2) 1,4- ADDITION IS PREDOMINANT

- IF THAT ALKYL GROUP IS NOT LARGE (A < 2 ; i.e., Me, Et, α -alkyl) THE 1,2-ADDITION DOMINATES

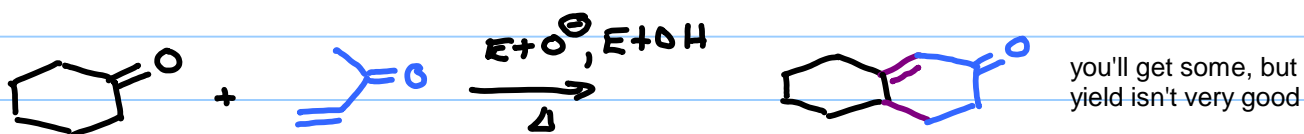


ALDOL AND 'MICHAELS' AS PARTNERS - THE ROBINSON RING ANNULATION

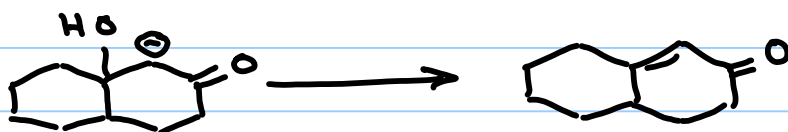
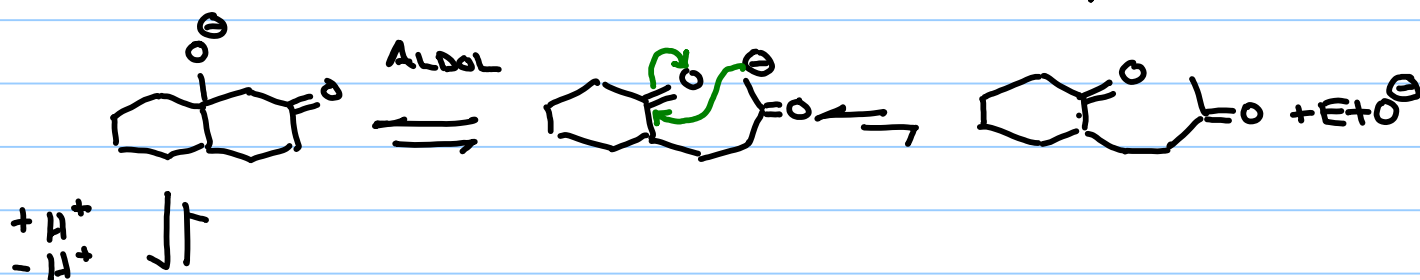
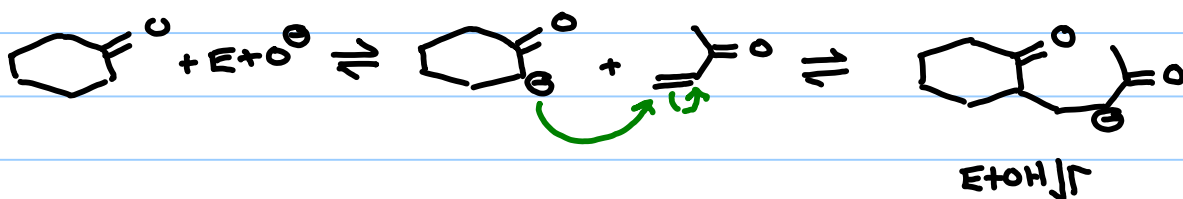
- SINCE THE ALDOL GENERATES CC(=O)C=C AND THE MICHAEL RYN. USES THEM, THERE ARE MANY, MANY INSTANCES IN SYNTHESIS WHERE THESE ARE PAIRED TOGETHER.

- THE MOST WELL-KNOWN OF THESE IS THE ROBINSON RING ANNULATION, WHICH GENERATES A NEW 6-MEMBERED RING KETONE, OFTEN (NOT ALWAYS) ONTO A CYCLIC KETONE

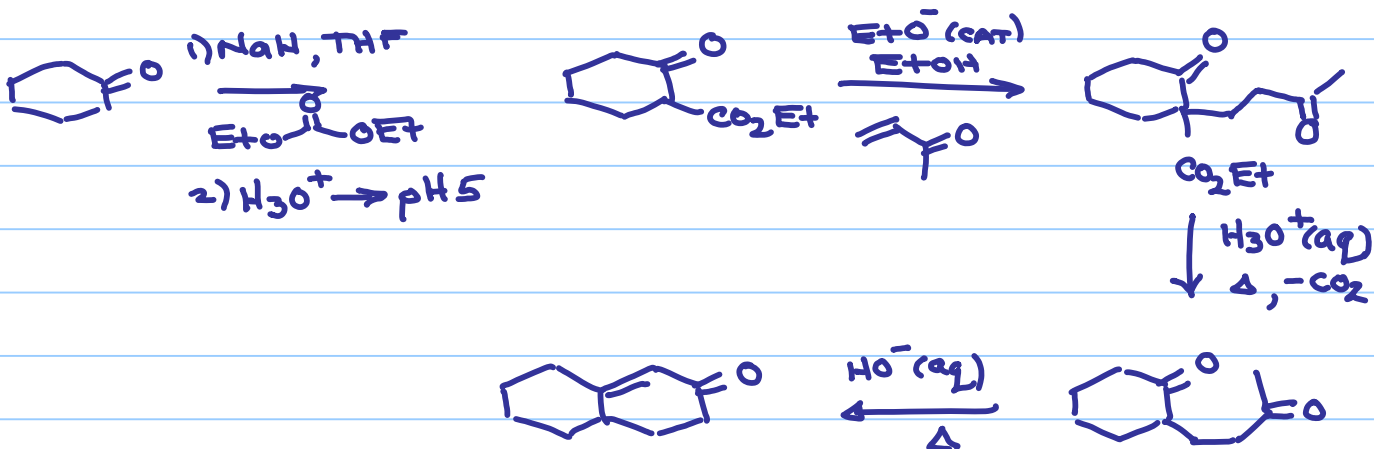
- IN ITS SIMPLEST, NOT V. HIGH YIELDING, VERSION



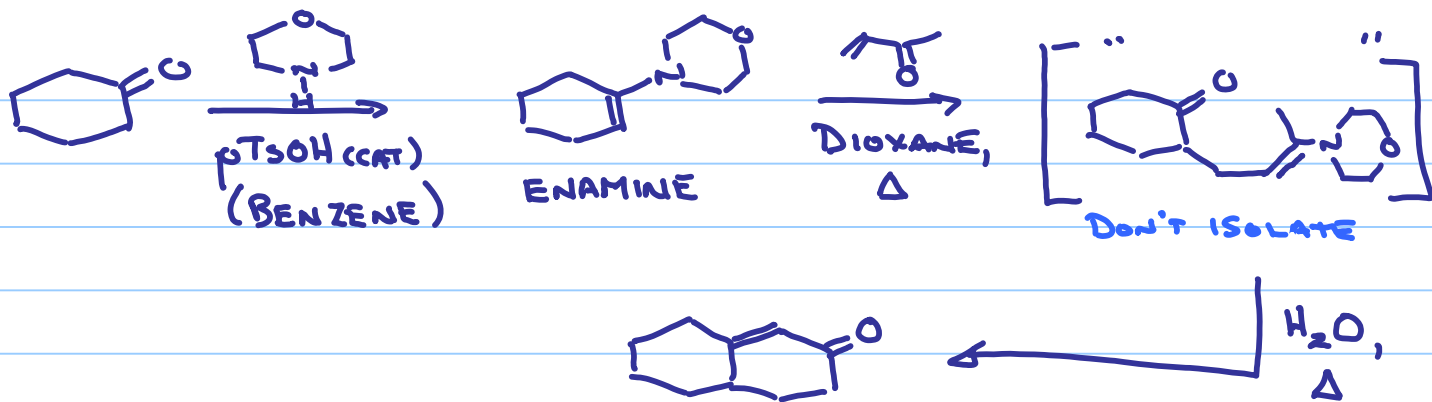
MECH.



AS WE HAVE SEEN IT, ONE OF THE PROBLEMS IS THAT THE MICHAEL STEP DOESN'T LOOK LIKE THE MOST EFFICIENT - YOU WOULD PROBABLY DO



- THIS WOULD WORK, BUT IS KIND OF LONG
- SO SEVERAL ROBINSON ANNULATION SHORTCUTS HAVE BEEN DEVELOPED - I'LL GIVE ONE



- WHEN THE ENAMINE HYDROLYZES, IT PRODUCES MORPHOLINE AND THE DIKETONE, AND THE DIKETONE IS SO 'READY' TO DO AN INTRAMOLECULAR ALDOL THAT EVEN MORPHOLINE IS A GOOD ENOUGH BASE

ACID INDUCED RXNS OF CARBONYLS

Note Title

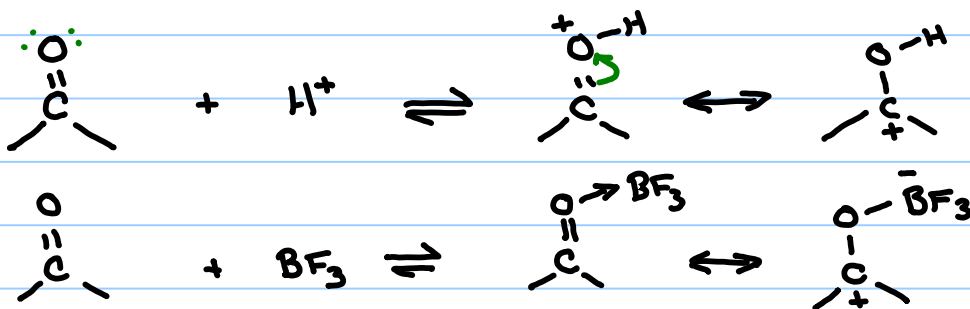
2/7/2017

- COMPLEMENTARY PROCESS TO $R_3C^{\ominus} + C^{\delta+}$
IS $R_3C^{\oplus} + C^{\delta-}$

GENERATION OF R_3C^{\oplus} in the most general possible meaning

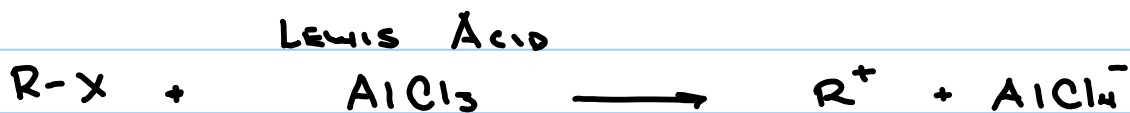
MOST COMMON

a) - CARBONYL + H^+ OR LEWIS ACID

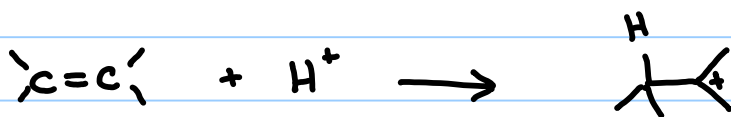


$\text{BF}_3 \cdot (\text{OEt})_2$, TiCl_4 , SnCl_4 , $\text{Me}_3\text{Si}-\text{OTf}$
SOME OF MANY COMMON LEWIS ACIDS

b) ALSO POSSIBLE - IONIZATION OF HALIDES



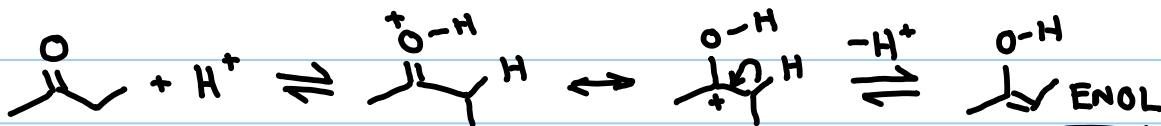
c) - ADDN TO ALKENES



REMEMBER
MARKOVNIKOV'S
RULE

NUCLEOPHILIC SPECIES

a) - VERY OFTEN THE ENOL FORM OF A KETONE

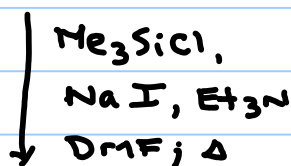
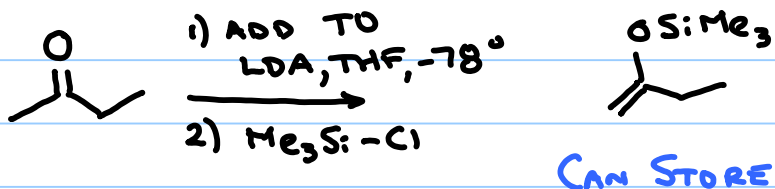


GENERALLY MORE SUBSTITUTED SIDE ENOL

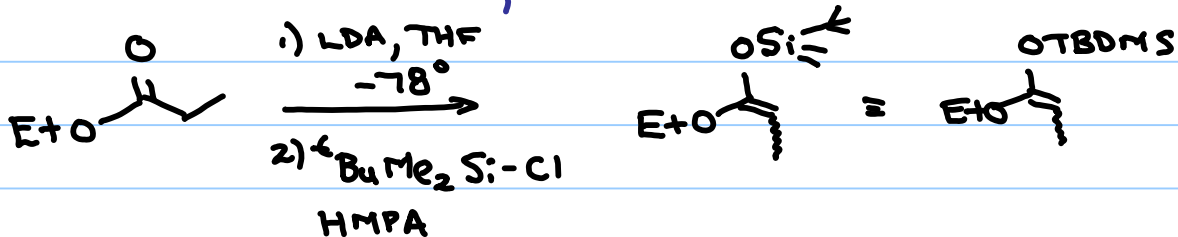
NOTE: ENOL FORM IS ONLY ONE OF $10^5 - 10^6$ MOLECULES
 - THIS IS ENOUGH

ESTERS: ONLY 1 OF EVERY $10^{18} - 10^{19}$ MOLECULES
 - THIS IS **NOT** ENOUGH

b) INCREASINGLY COMMON - ENOL SILANES / SILYL ENOL ETHERS

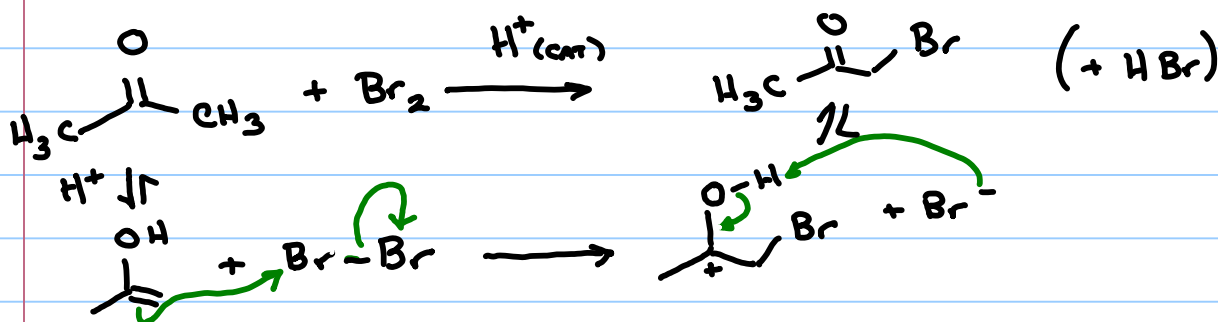


- NOW ESTERS ARE DOABLE, EXCEPT BIGGER R'S ON Si NEEDED



FIRST ACID MEDIATED RXN

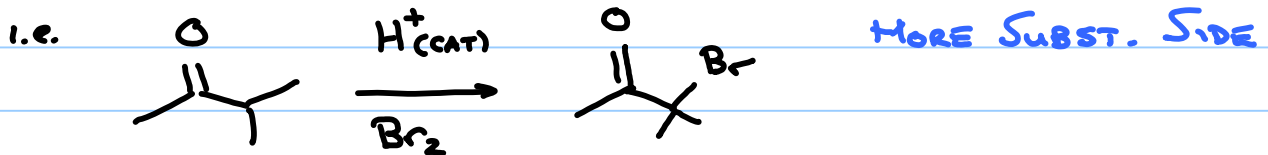
α -BROMINATION OF KETONES (AND ALDEHYDES)



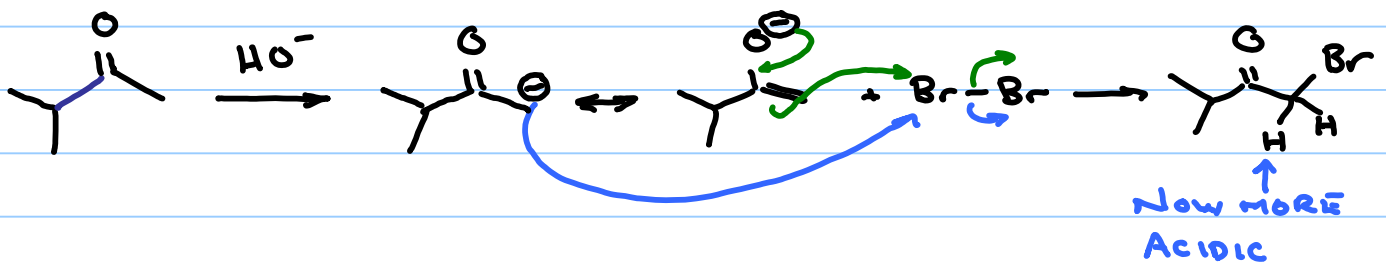
- RXN GENERATES ITS OWN CATALYST AS PRODUCT
 \therefore ACID SOMETIMES NOT PHYSICALLY ADDED.

- ENOLIZATION IS SLOW STEP

\therefore BROMINATION GOES WHERE ENOL FORMS



LET'S CONTRAST THIS WITH WHAT HAPPENS UNDER BASIC CONDITIONS

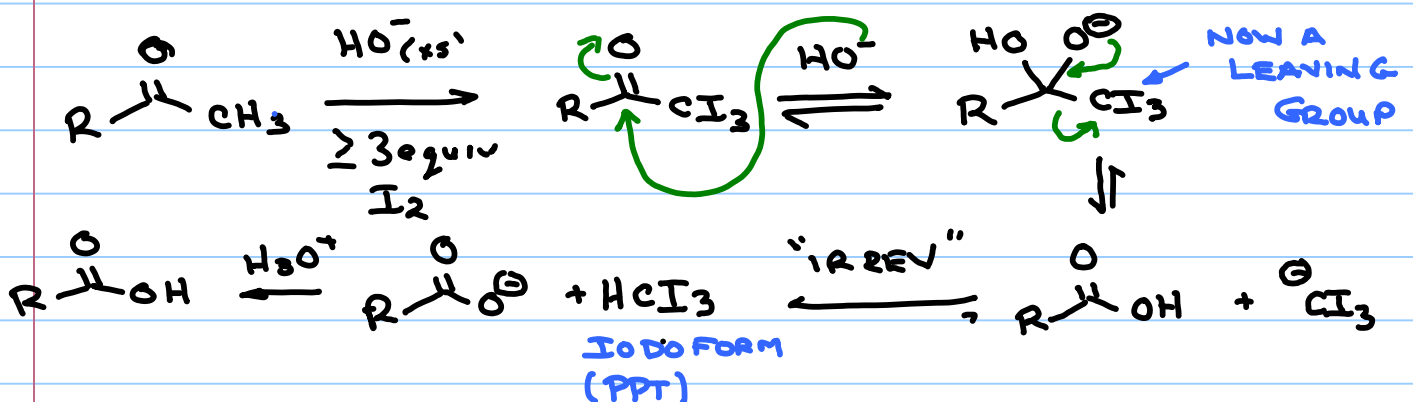


POLYBROMINATION

SO RXN
 KEEPS GOING

- SOUNDS LIKE A PROBLEM, BUT THERE IS ONE VERY USEFUL APPLICATION OF THIS - USUALLY USES IODINE
 - IODOFORM (OR HALOFORM) RXN

- FOR METHYL KETONES



- CONVERSION OF METHYL KETONE TO CARBOXYLIC ACID IS UNIQUELY USEFUL IN ORGANIC CHEM.

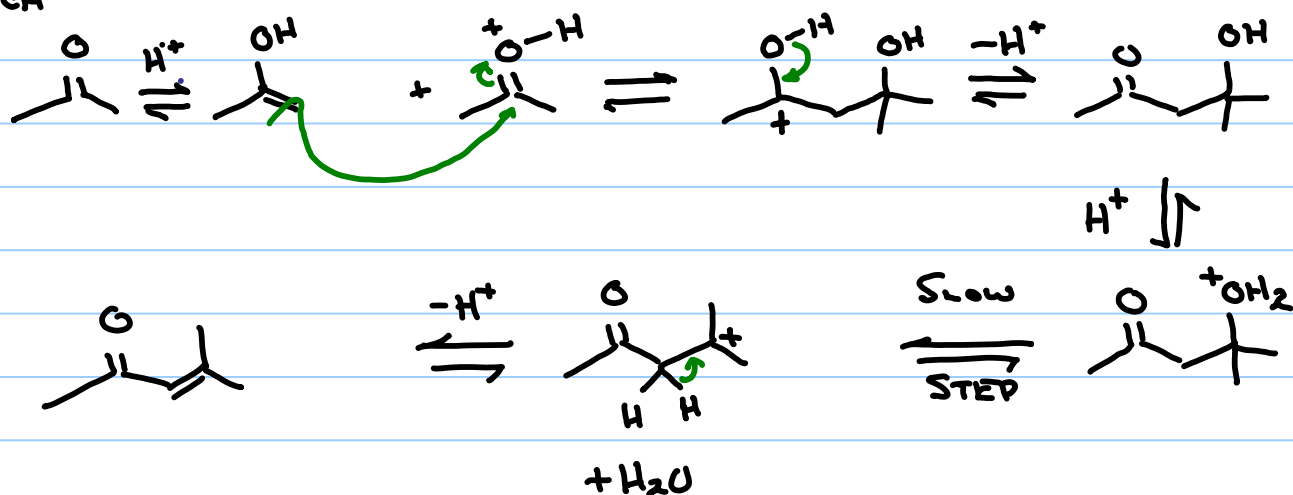
ACID CATALYZED ALDOL -

- POSSIBLE YES

- COMMON IN IT'S MOST SIMPLE MANIFESTATION?

- NOT REALLY, YIELDS TEND TO BE NOT GREAT

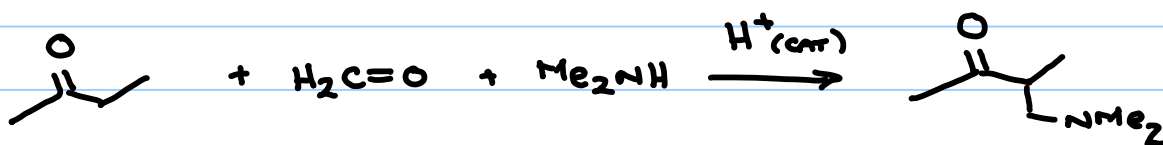
Mech



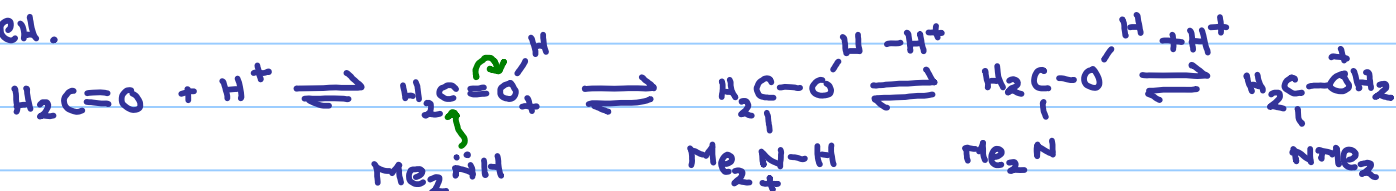
SELECTED VERSIONS THAT ARE USEFUL.

MANNICH REACTION

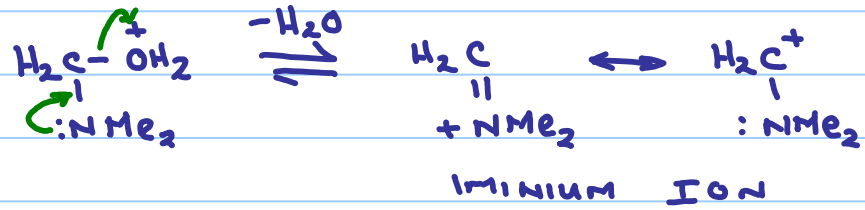
- ALDOL RXN WITH FORMALDEHYDE ITSELF WITH BASE TENDS TO BE OUT OF CONTROL
- SO COMMON REPLACEMENT FOR IT IS TO DO ACID CATALYZED VERSION, WITH Me_2NH TO MAKE IMINIUM ION



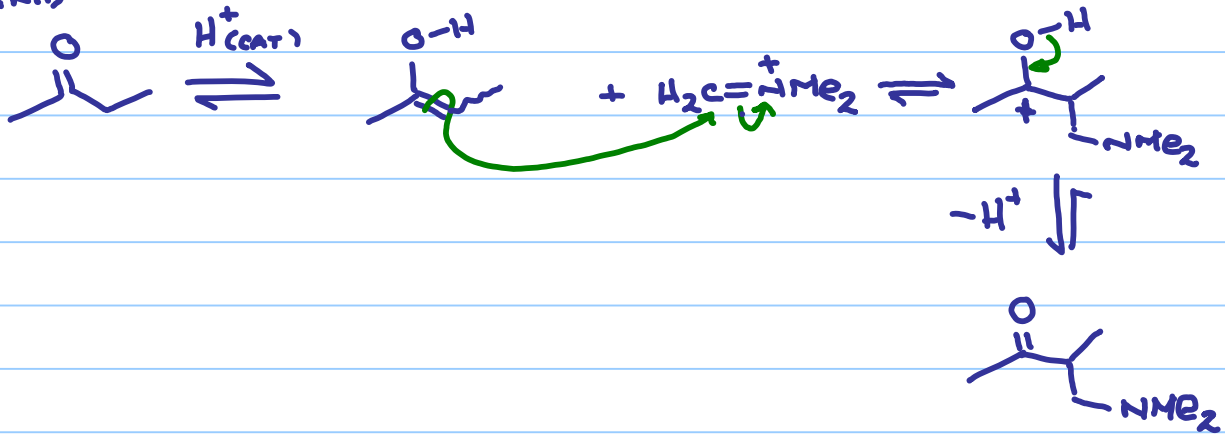
Mech.



CONT'D



ANID



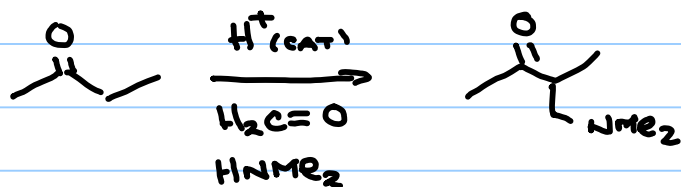
so how is this useful?.....next lecture

MANNICH RXN, CONT'D.

Note Title

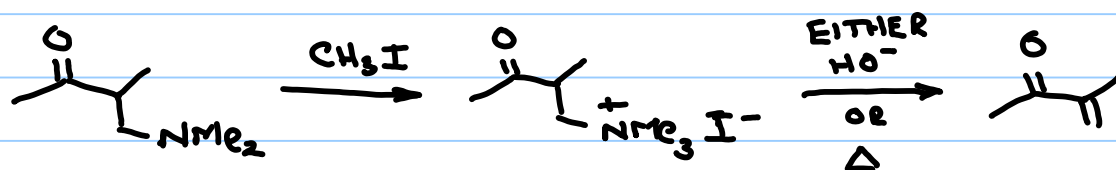
2/9/2017

- WE'VE JUST SEEN

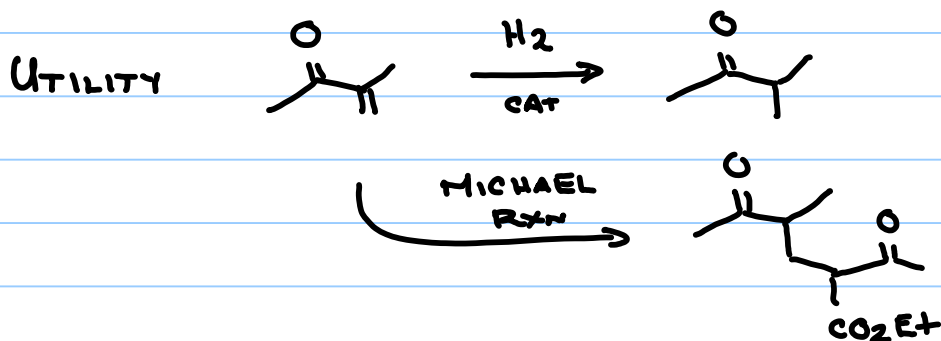


HOW IS THIS A FORMALDEHYDE ALDOL SURROGATE?

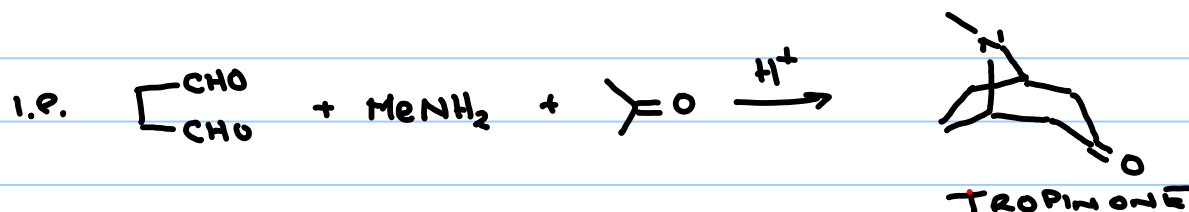
- QUATERNIZE N ATOM WITH CH_3I , THEN ELIMINATE.



LOOKS LIKE ALDOL \bar{w} CH_2O

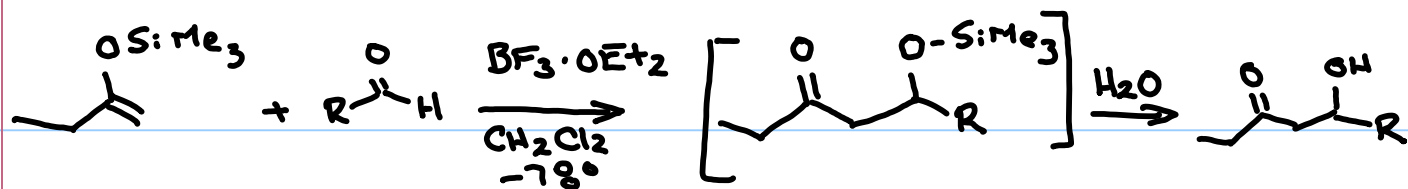


NOTE: USUALLY DONE WITH FORMALDEHYDE, BUT DOES NOT HAVE TO BE ONLY THAT ALDEHYDE

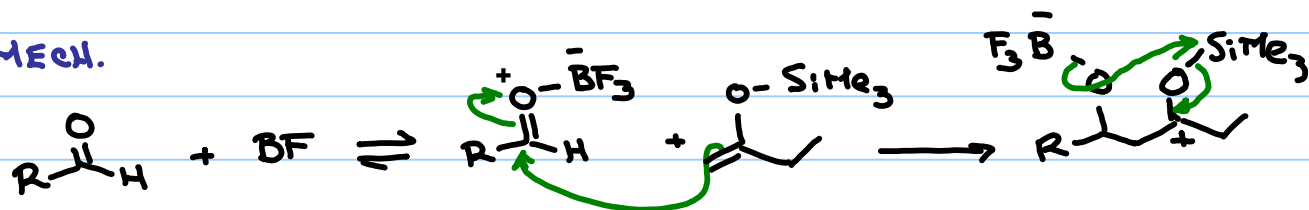


LEWIS ACID CATALYZED DIRECTED ALDOL. (MUKAYAMA ALDOL)

- IT IS VERY POSSIBLE, AND VERY COMMON, TO DO LEWIS ACID MEDIATED VERSIONS OF KINETIC ALDOLS
- USES SILYL ENOL ETHERS

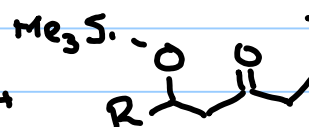


MECH.



IN PRINCIPLE
A CATALYST

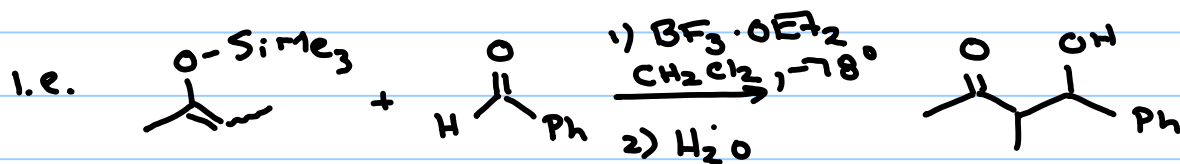
REGENERATED



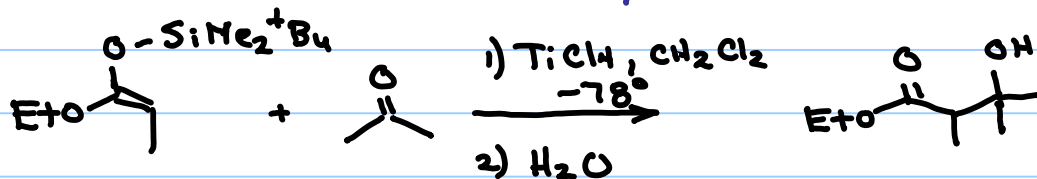
NOTES: - SOLVENT CH_2Cl_2 IS QUITE DIFFERENT FROM WHAT WE ARE USED TO - WE WANT NON-LEWIS BASIC SOLVENT SO NOTHING COMPETES WITH THE CARBONYL FOR THE LEWIS ACID

- KETONES WORK REASONABLY WELL AS ELECTROPHILES, TOO

- MORE SUBSTITUTED SILYL ENOL ETHERS, OR THOSE DERIVED FROM ESTERS, MAY ALSO BE USED



- WON'T GET INTO SYN- VERSUS ANTI- FOR THESE



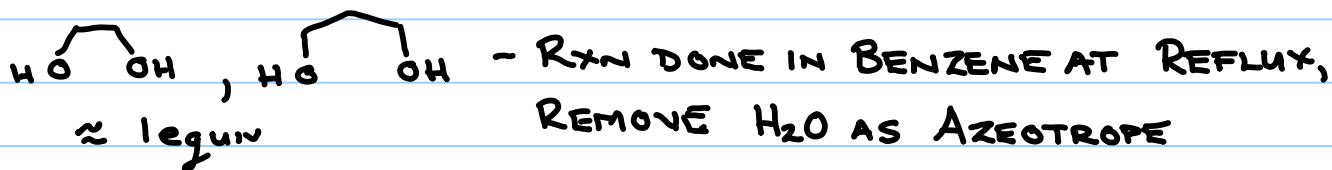
ONE OTHER ACID INDUCED RXN. OF ALDEHYDES / KETONES. ACETALS AS PROTECTING GROUPS

- OFTEN A SITUATION WHERE WE HAVE A REAGENT THAT WILL REACT WITH AN ALDEHYDE OR KETONE, BUT WE DON'T WANT IT TO.
- SOLUTION: PROTECT CARBONYL AS AN ACETAL
 - WE CAN REGENERATE THE CARBONYL LATER

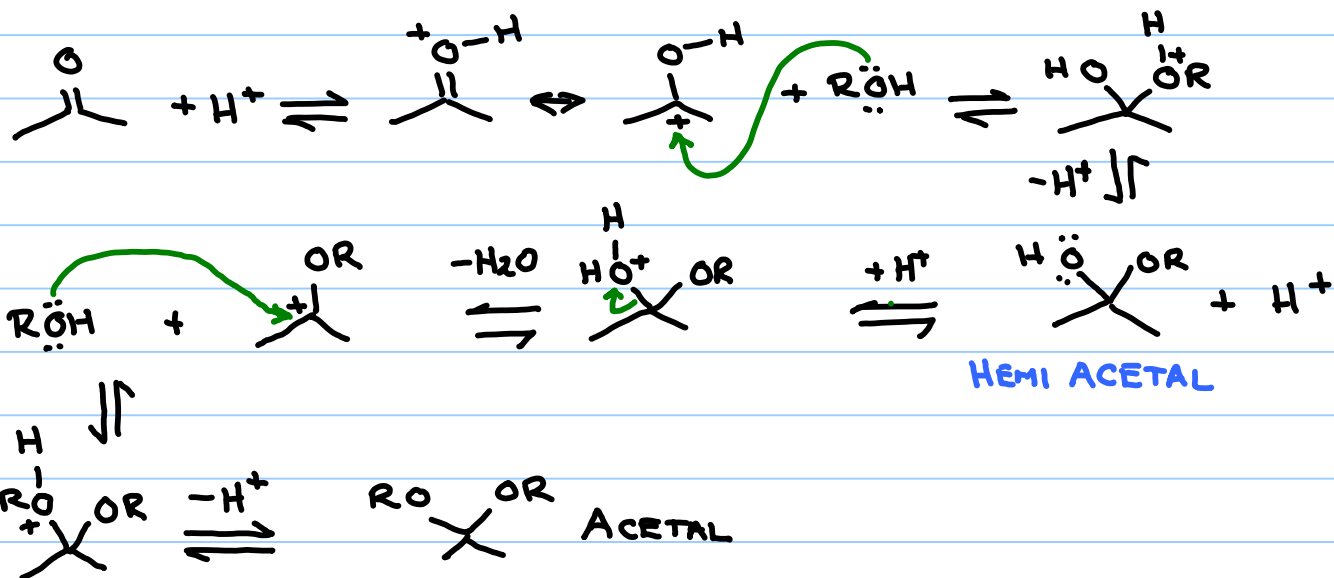


- COMMON ALCOHOLS FOR THIS

CH_3OH , EtOH - USE AS RXN SOLVENT TO DRIVE EQM TO RIGHT



MECHANISM: - QUICKLY, BECAUSE YOU SAW THIS IN 59-235

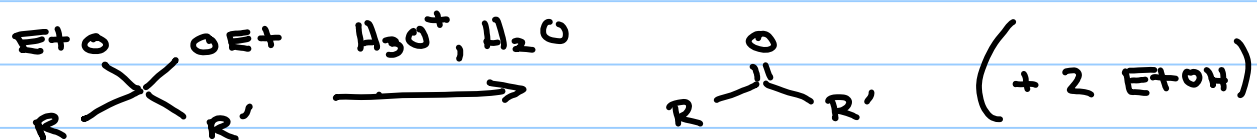


- ALL EQUILIBRIUM STEPS

AS FAR AS A LOT OF OTHER REAGENTS ARE CONCERNED,
 THIS IS NOW A TYPE OF ETHER
 - SO IT'S INERT

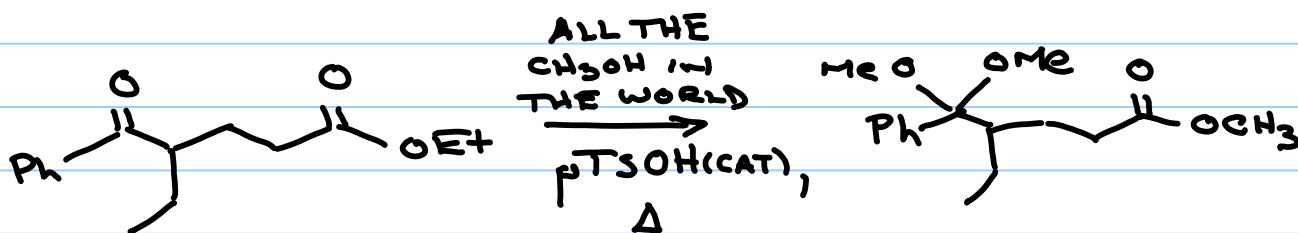
i.e. MOST BASES, "H⁻", H₂/CAT, RMgBr, R-Li

- WHEN WE WANT THE CARBONYL BACK, JUST ADD ACID
 AND H₂O, AND A SOLVENT THAT EVERYTHING IS
 SOLUBLE IN (i.e. ACETONE)

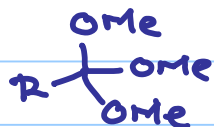


NOTE: / WARNING:

- THIS LOOKS LIKE IT SHOULD WORK FOR ESTERS, TOO
 BUT NO. THEY JUST TRANSESTERIFY.



ORTHO ESTERS



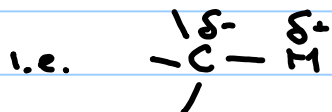
ARE KNOWN, BUT MUCH
 HARDER TO MAKE

CARBANIONS OF NON-ACIDIC COMPOUNDS

Note Title

2/12/2017

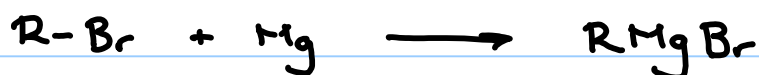
- CARBANIONS CAN ALSO BE MADE FROM NON-CARBONYLS
- ORGANOMETALLIC COMPOUNDS.



- THE MOST COMMON METALS ARE Li, MgX, AND Cu^I
- THESE ARE POLAR COVALENT BONDS, BUT TREATED VERY MUCH LIKE THEY ARE IONIC

COMMON PREPARATION METHODS

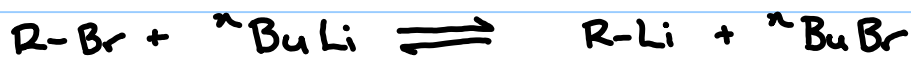
1) OXIDATIVE ADDITION



OR



2) METAL HALOGEN EXCHANGE



3) ABSTRACTION

- WILL SEE MORE IN LATER COURSES, BUT BUT IF R-H IS MORE ACIDIC THAN R'-H



MOST COMMON IN THIS COURSE - TERMINAL ALKYNES



↑ $pK_a \approx 25$

GENERAL CHARACTERISTICS

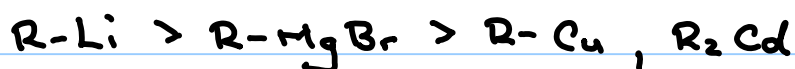
- THESE ARE V. STRONG BASES

- REACT WITH OH'S, (OFTEN) NH'S, CO₂

- PREPARE USUALLY IN ET₂O OR THF

- MORE SOLUBLE THAN YOU MIGHT THINK IN THESE SOLVENTS

- REACTIVITY TENDS TO FOLLOW RELATIVE IONIC CHARACTER

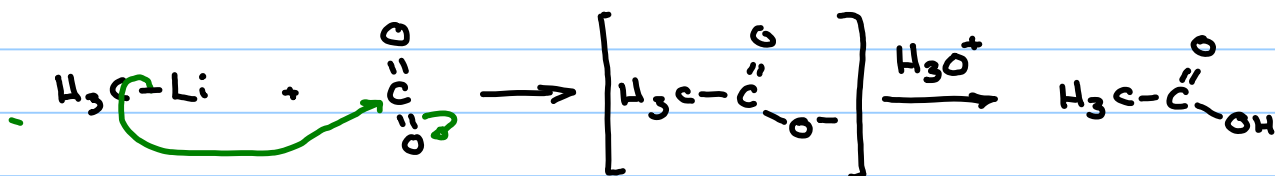


REACTIONS WITH CARBONYLS

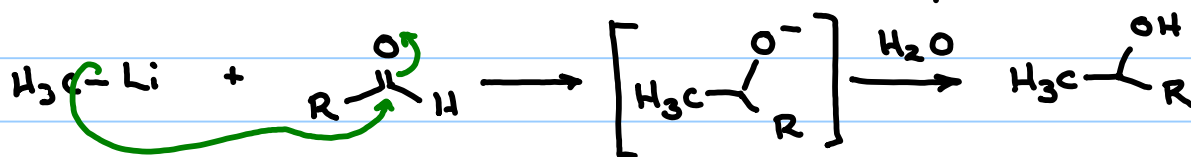
- MUCH OF THIS IS A REVIEW, EXCEPT WE'LL FOCUS MORE ON R-Li THAN R-MgBr

- I'LL USE CH₃Li AS AN EXAMPLE

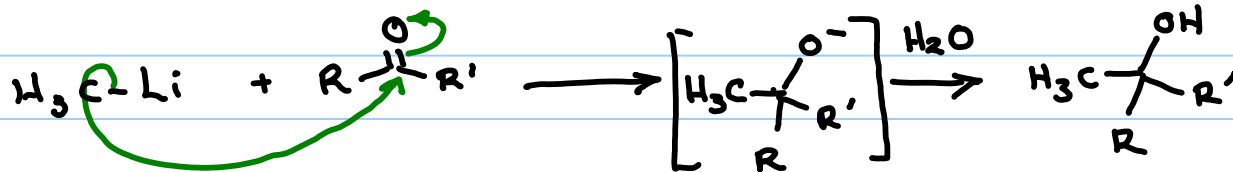
WITH CO₂ → CARBOXYLIC ACIDS



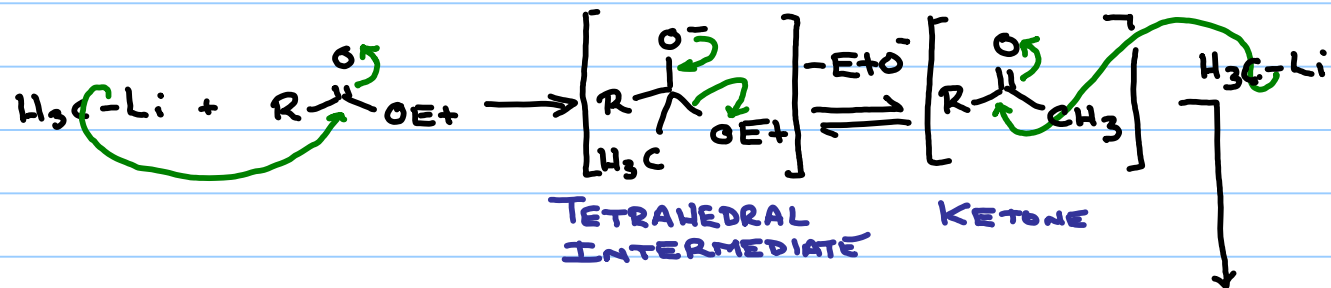
WITH ALDEHYDES → 2° ALCOHOLS



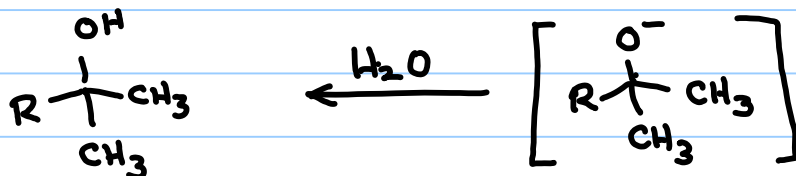
WITH KETONES → 3° ALCOHOLS



WITH ESTERS - 3° ALCOHOLS DUE TO TWO ADDITIONS



3° ALCOHOL \bar{w}
TWO IDENTICAL
GROUPS



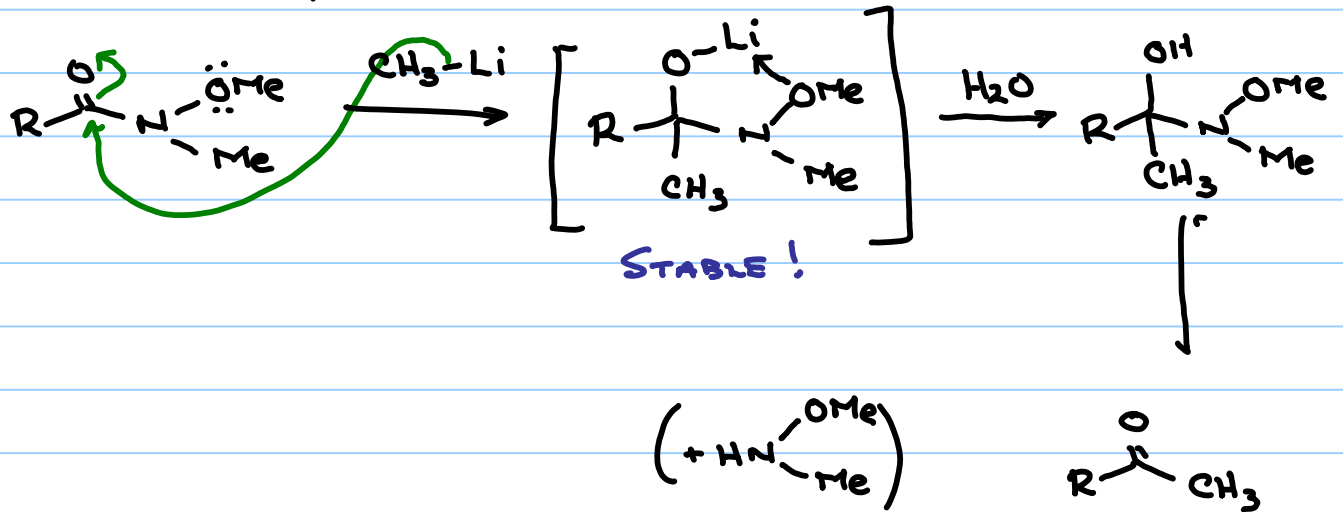
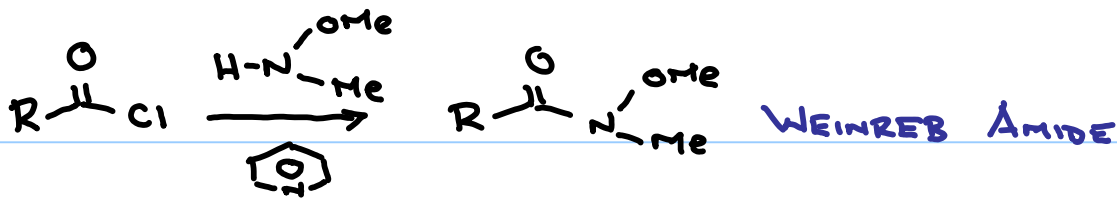
- SINCE TETRAHEDRAL INTERMEDIATE DOESN'T EXIST FOR LONG AND SINCE KETONES ARE $>$ ESTERS IN REACTIVITY, THIS IS A PROBLEM

POSSIBLE SOLUTIONS

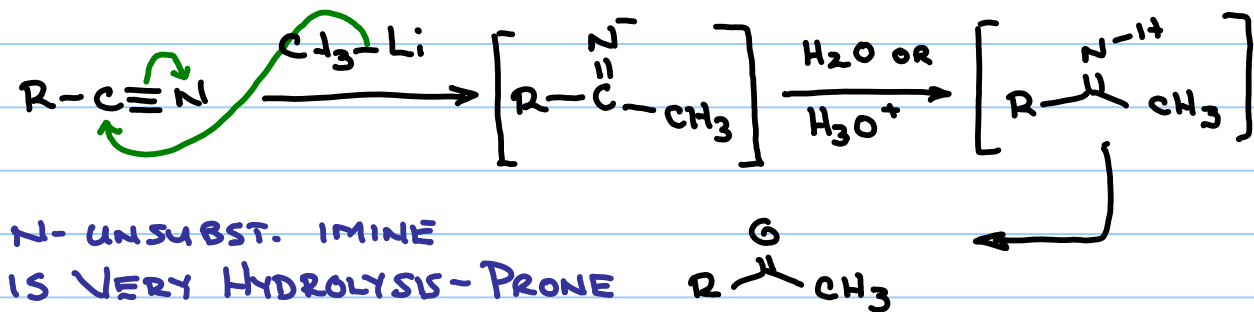
- MAKE TETRAHEDRAL INTERMEDIATE 'LIVE' LONGER
- HAVE ESTER SURROGATE THAT IS MORE REACTIVE THAN KETONE, AND R-M THAT IS SLUGGISH TO REACT WITH KETONES

PRACTICAL SOLUTIONS

- WEINREB AMIDES (MY FAVOURITE)
 - N-METHOXY-N-METHYL AMIDES ADD R-Li OR R-MgBr TO GIVE A TETRAHEDRAL INTERMEDIATE THAT IS CHELATED BY $\ddot{\text{O}}\text{CH}_3$
 - MAKES IT STABLE UP TO ROOM TEMP

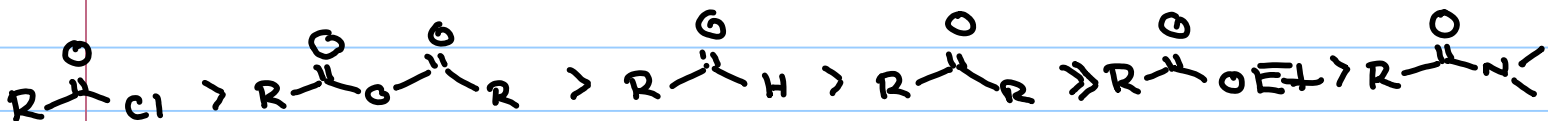


a) ii) NITRILES - $R-C\equiv N$ HAS NO LEAVING GROUP
 \therefore NO TETRAHEDRAL INT'D \therefore NO OVERADDITION

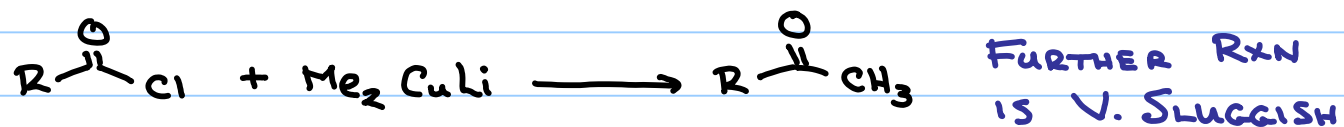
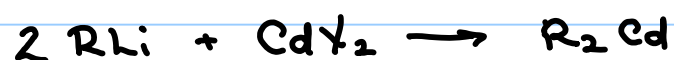


b) ACID CHLORIDES + CUPRATES / ORGANOCADMIUMS

- IF WE GO BACK TO OUR EASE OF ORDER OF ADDITION TO CARBONYLS



- SO IF WE GO TO THE LOWEST REACTIVITY OF THE SIMPLE ORGANOMETALLICS



- PROBABLY LEAST CLEAN OF THE THREE

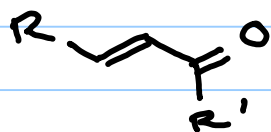
- MORE ON CUPRATES TO COME.....

ADDITIONS TO CONJUGATED CARBONYLS

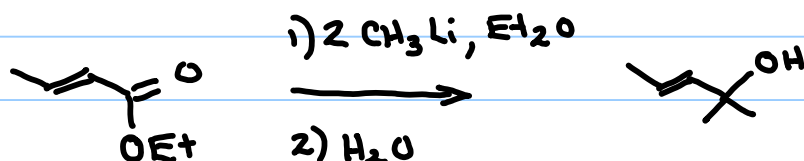
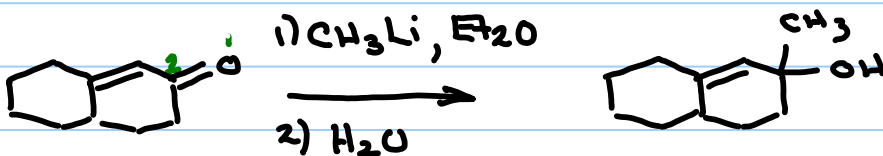
Note Title

2/14/2017

- MUCH LIKE FOR ENOLATES, THERE ARE TWO POSSIBLE MODES OF ADDITION TO AN α,β -UNSATURATED KETONE OR ESTER

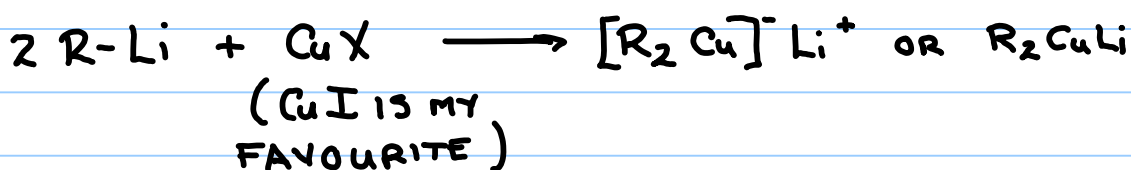


- FOR ORGANOLITHIUMS AND GRIGNARD REAGENTS, THE NORMAL PATHWAY OF ADDITION IS TO THE CARBONYL, OR 1,2-ADDITION



- IF ONE WANTS THE OTHER (ALKENE OR ALKYNE) SITE ADDED TO, WHICH IS CALLED CONJUGATE OR 1,4-ADDITION GO TO COPPER BASED ORGANOMETALLICS (SOFTER IN THE HARD-SOFT ACID-BASE REASONING, ALTHOUGH I'M NOT TOTALLY CONVINCED THIS IS THE REASON)

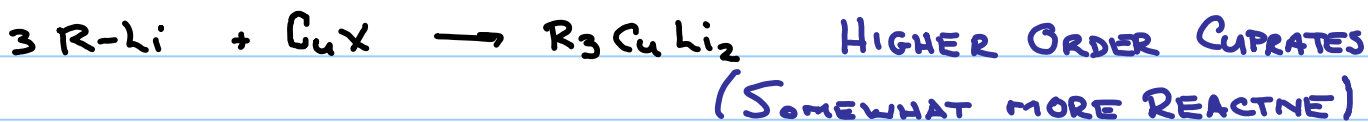
- MOST COMMON VERSION IS THE (GILMAN) CUPRATE



ALSO KNOWN

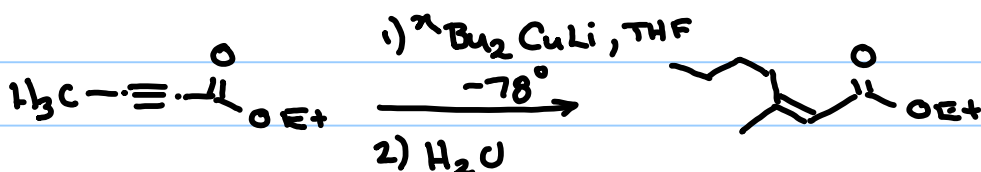
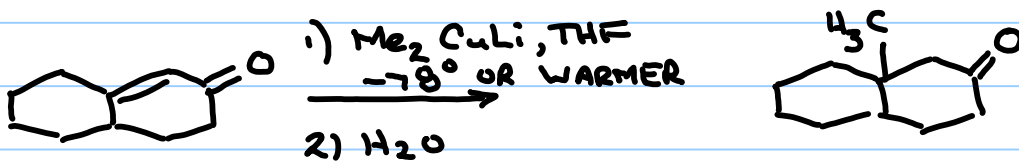


ORGANOCOPPERS
(SOMEWHAT LESS REACTIVE)



cuprates, organocoppers can be made from RMgX, but we'll focus on R-Li

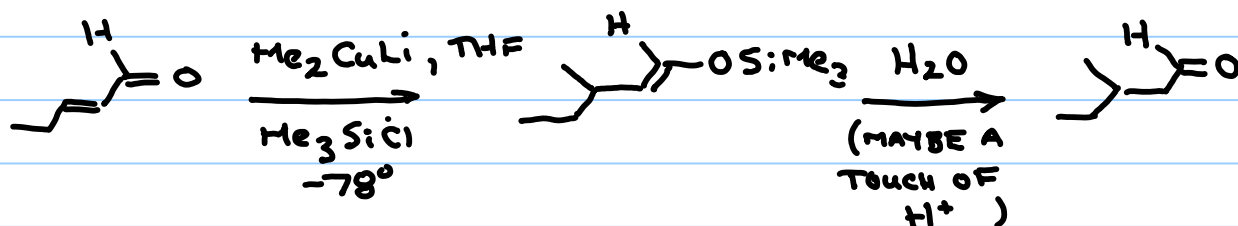
- GIVES CLEAN CONJUGATE ADDITION, EVEN WITH ALDEHYDES



J.R. GREEN PHD
DISSERTATION, 1887


- THE ADDITION OF Me_3SiCl TO THE MIXTURE OFTEN GIVES IMPROVED YIELDS BY IMMEDIATELY TRAPPING THE ENOLATE FORMED AS THE SILYL ENOL ETHER

- PARTICULARLY IMPORTANT WITH ALDEHYDES



- A COUPLE OF NOTES

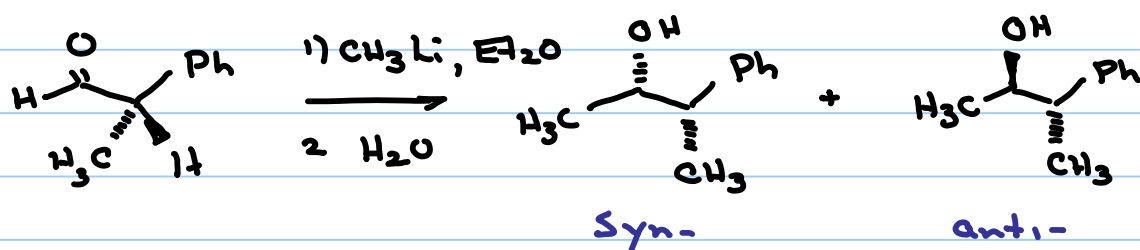
- YOU CAN USE THE ENOLATE PRODUCT (PRIOR TO WORKUP) IN REACTIONS, BUT I SUGGEST GETTING THE SILYL ENOL ETHER FIRST

- YOU CAN HAVE A 'DISPOSABLE' R' ON $RR'CuLi$ SO THAT YOU ONLY HAVE TO USE 1 EQUIVALENT OF AN EXPENSIVE ORGANIC R (i.e. , $-CN$)

- A π COMPLEX OF THE ALKENE TO COPPER HAS BEEN OBSERVED

STEREOCHEMISTRY OF ADDITION TO CARBONYLS - A

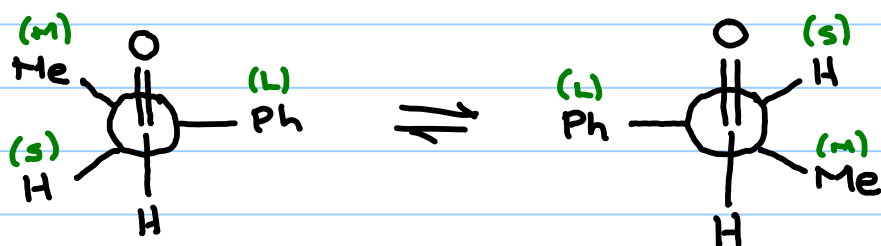
- IN MANY CASES, ADDITION OF AN ORGANOMETALLIC TO AN ALDEHYDE OR KETONE OCCURS ON ONE WITH AN α -CHIRAL CENTRE



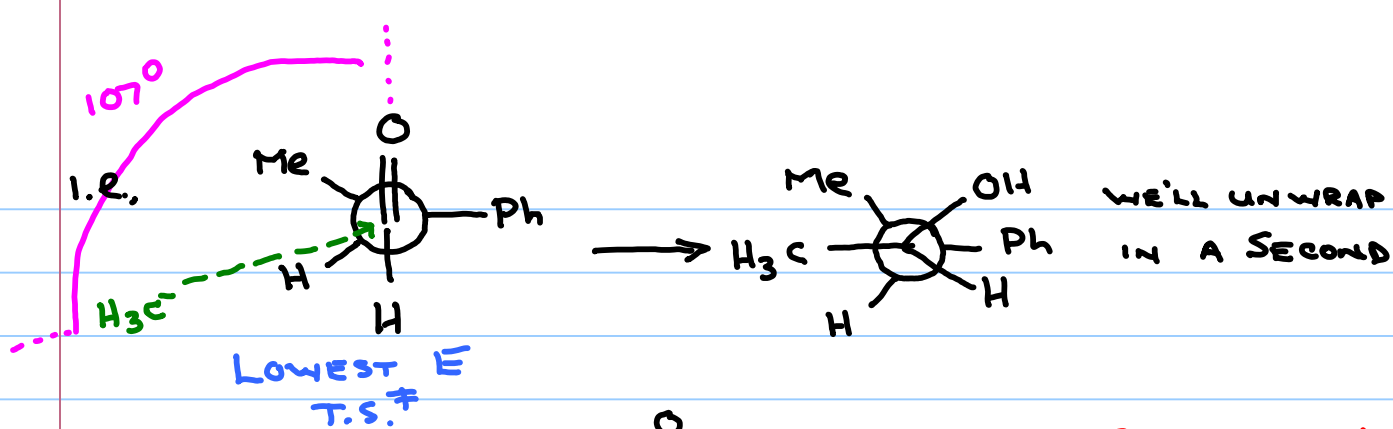
- WHICH PRODUCT PREDOMINATES IS PREDICTABLE BY FOLLOWING THE FELKIN-AHN MODEL

(NOTE: THE 'CRAM ADDITION' MODEL IS AN OUTDATED MODEL, BUT IT USUALLY GIVES THE SAME RESULT, AND YOU'LL SEE THE TERM TOSSED AROUND STILL)

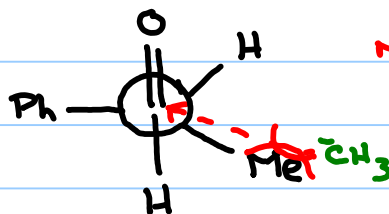
- NORMALLY, ONE GOES TO A NEWMAN-LIKE PROJECTION AND PUT THE LARGEST GROUP* PERPENDICULAR TO THE CARBONYL (AGAIN, SEE A VALUES)



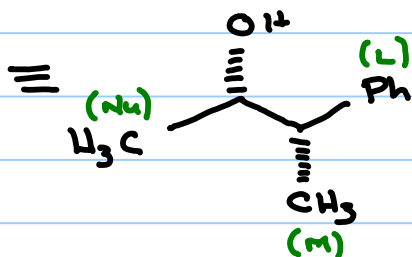
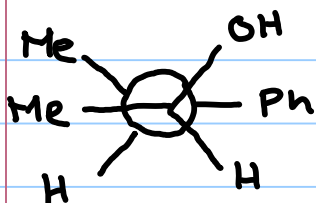
- NUCLEOPHILES PREFER TO ATTACK THE CARBONYL AT AN ANGLE OF 107° RELATIVE TO THE OXYGEN ATOM (CALLED THE BURGI-DUNITZ TRAJECTORY)
- AWAY FROM THE (L) (BIGGEST) GROUP
- ROUGHLY OVER THE (S) (SMALLEST) GROUP



IS BETTER THAN



NOT AS GOOD WHE Nu^- IS
 OVER 'M' GROUP



IF Nu^- AND (L) GROUP
 ARE PART OF THE
 MAIN CHAIN, THE
 MAJOR PRODUCT IS
 syn-

This goes a bit different when an electronegative/Lewis basic group is on the carbon next to the carbon,
 but these are also quite predictable.....that's next.

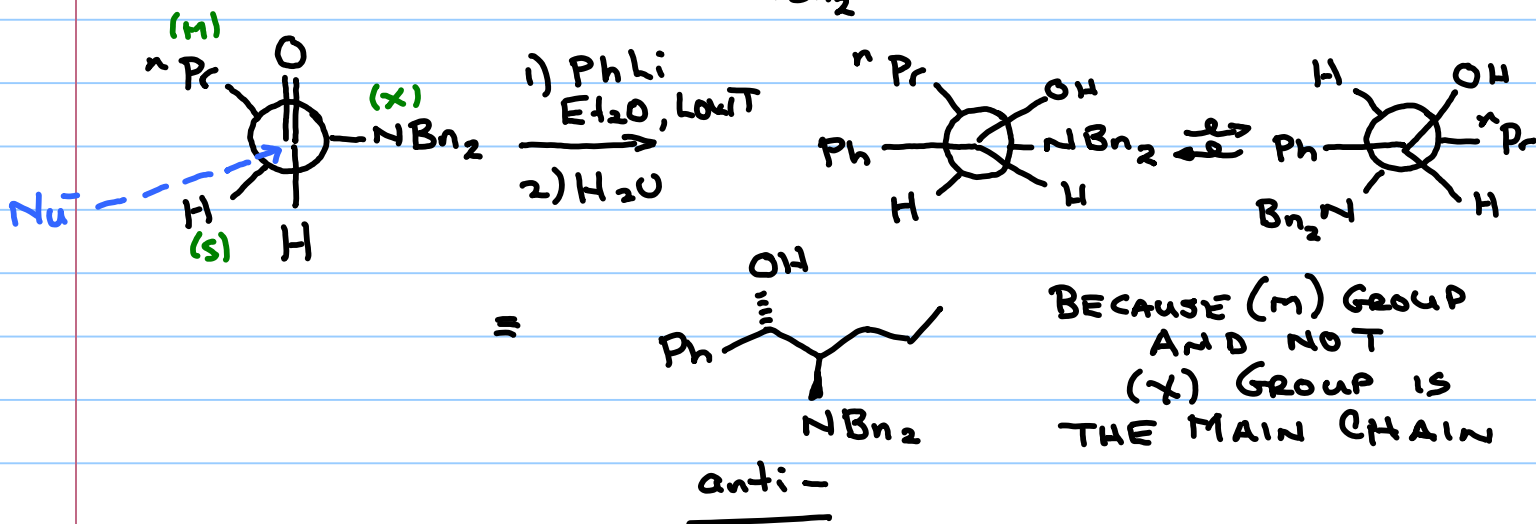
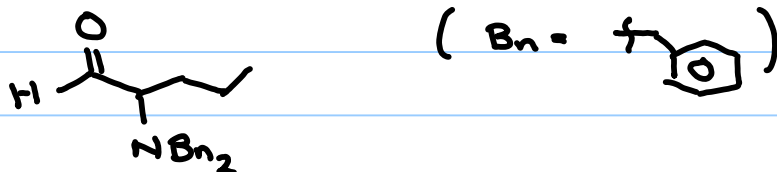
FELKIN-AUN ADDON, PT. 2

Note Title

2/16/2017

- IF THERE IS AN ELECTRONEGATIVE ATOM OR GROUP AT THE α -SITE, THE MODEL CHANGES
 $X = \text{HALOGEN, OR, } -\text{NR}_2, -\text{SR}$
- ESSENTIALLY, IT (THE X GROUP) TAKES THE PLACE OF THE LARGE GROUP
- REASON - THE σ^* ENERGY OF THE C-X BOND IS RELATIVELY LOW, AND MIXES WITH THE THE CARBONYL'S π^* ORBITAL
- THE 'MIXING' GIVES A NEW LOWER ENERGY LUMO
 - TRANSLATION - IT'S MORE REACTIVE IN THIS CONFORMATION

SO, IF WE HAVE



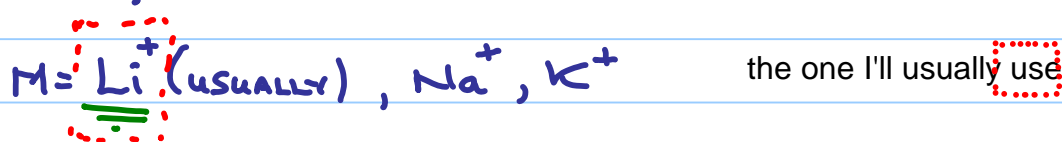
- THERE'S ANOTHER ISSUE WITH THESE ELECTRONEGATIVE GROUPS THOUGH.....

CHELATION + ADDITION - THE (CRAM) CHELATE MODEL

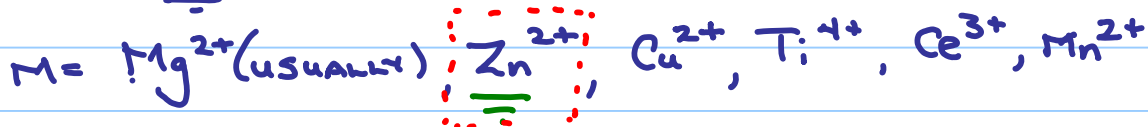
- SINCE THESE EN X GROUPS FROM ABOVE HAVE A LONE PAIR, THEY CAN SOMETIMES COORDINATE TO THE INCOMING ORGANOMETALLIC

- DEPENDS ON METAL:

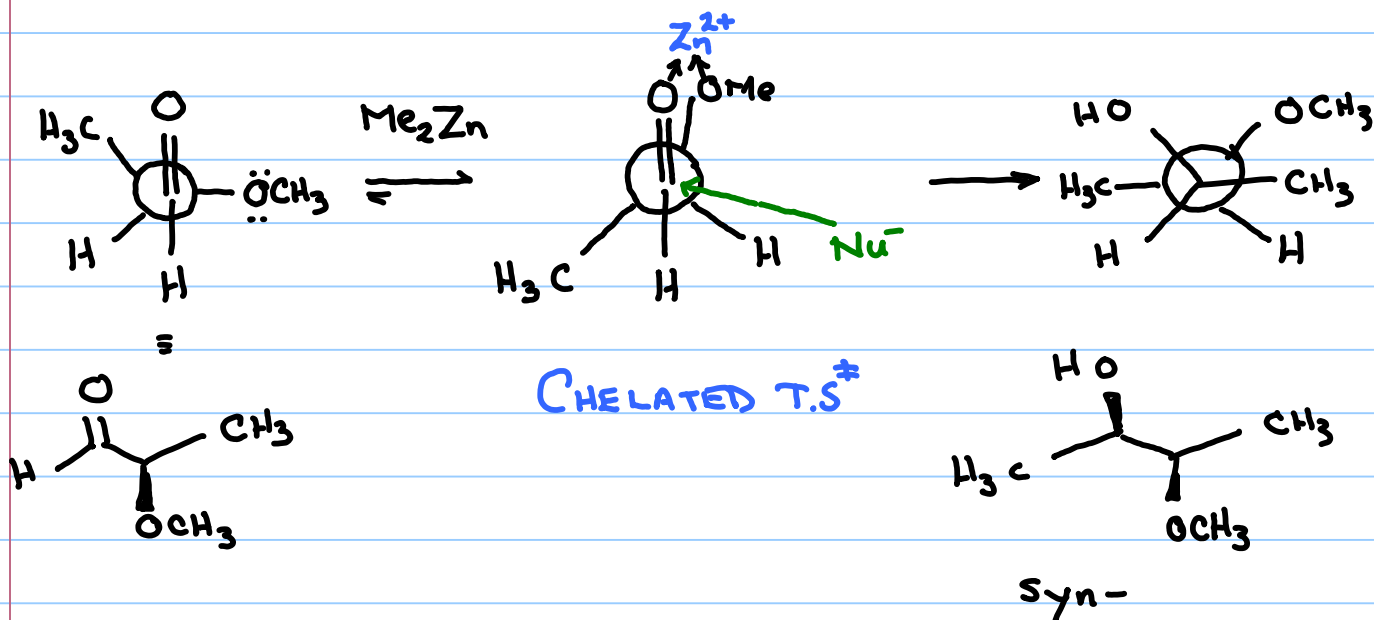
THEY DON'T DO THIS FOR R-M WHEN



- BUT THEY DO THIS COORDINATION WHEN....

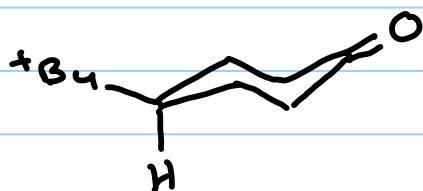


- THIS CHANGES THE MODEL OF ADDITION



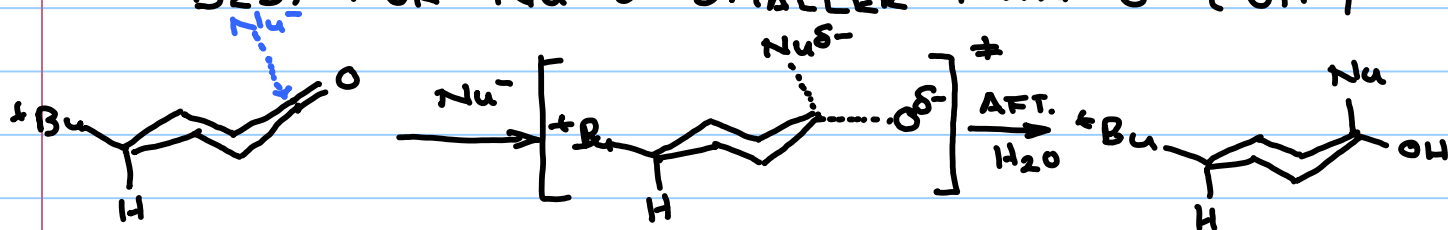
ADDITIONS TO CYCLOHEXANONES

- IT IS WORTH DISCUSSING AT THIS POINT THE STEREOCHEM. OF ADDITION OF ORGANOMETALLICS TO CYCLOHEXANONES, BECAUSE THEIR CONFORMATION IS WELL UNDERSTOOD
- WE WILL FOCUS ON SYSTEMS WITH A SIGNIFICANT BIAS, I.E. A BIG SUBSTITUENT
 - SINCE IT'S KNOWN THAT A LARGE GROUP WILL SPEND ALMOST ALL OF IT'S TIME IN EQUATORIAL CONFORMATION
- i.e. 4-*t*-Bu CYCLOHEXANONE *t*-Bu is pretty much locked equatorial

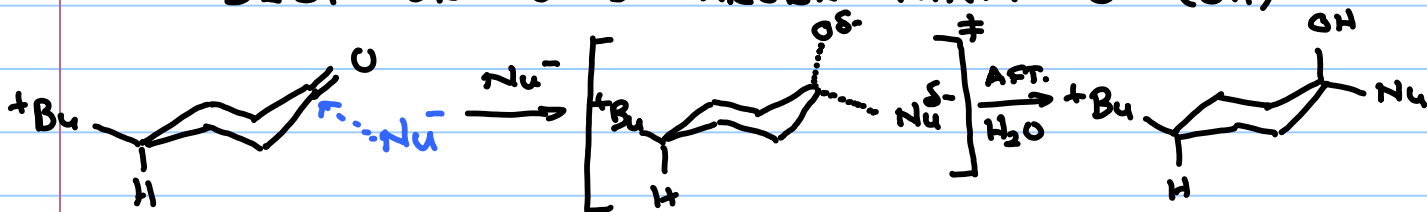


AN INCOMING NUCLEOPHILE CAN EITHER COME IN IN AXIAL OR EQUATORIAL

- IF IT COMES IN AXIALLY, THE NUCLEOPHILE'S BECOMING THE AXIAL R GROUP AND THE O⁻ (TO BECOME OH) IS BECOMING EQUATORIAL
- BEST FOR Nu⁻'S SMALLER THAN O⁻ (OH)



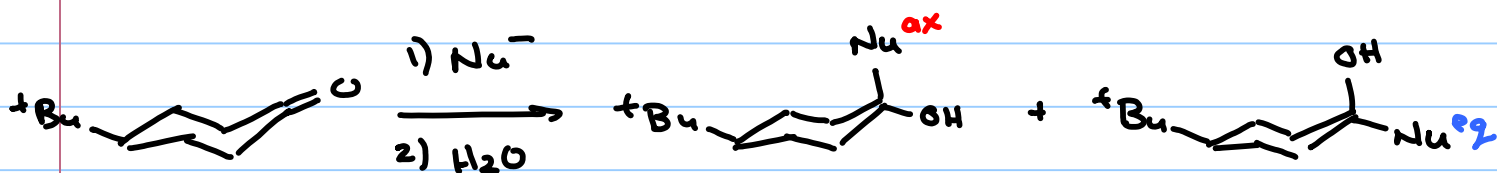
- IF IT COMES IN EQUATORIALLY, THE O⁻ (OR OH) IS BECOMING AXIAL, WHILE THE INCOMING Nu IS BECOMING EQUATORIAL
- BEST FOR Nu⁻'S LARGER THAN O⁻ (OH)



$$A \approx (\sim 0.8 - 0.9)$$

- SINCE AN OH IS A SMALLISH GROUP, WE PREDICT THAT ONLY REAL SMALL ORGANOMETALLICS WILL COME IN AXIAL, LARGER ONES WILL COME IN EQUATORIAL, WITH INCREASING SELECTIVITY.

- ACTUAL RESULTS MATCH THIS PRETTY WELL



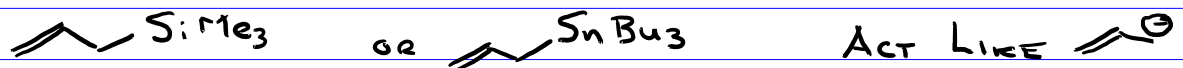
Nu.	A VALUE	% axial	% equatorial
LiAlH ₄ (H ⁻)	0	90	10
H-C≡C-Li (or Na)	0.45	88	12
Me Li	1.7	35-40	60-65
Et Mg Br	1.8	29	71
iPr Mg Br	2.1	18	82
t-Bu Mg Br	> 4.0	0	100

- ASIDE Ph⁻ DOESN'T SEEM TO FIT THIS OTHERWISE FINE TREND - PERHAPS SINCE IT'S FLAT
 - WE'LL LEAVE THAT TO OTHER COURSES

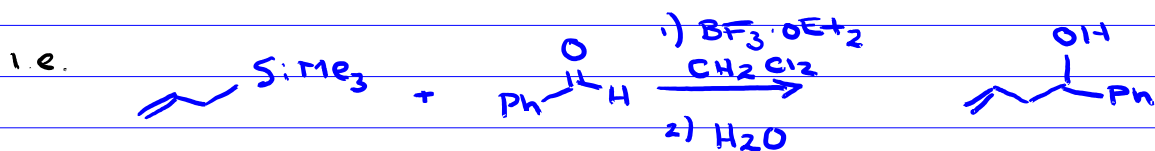
ORGANOMETALLIC ADDITIONS - FINAL EXAMPLES

ALLYLSILANES AND ALLYLSTINS

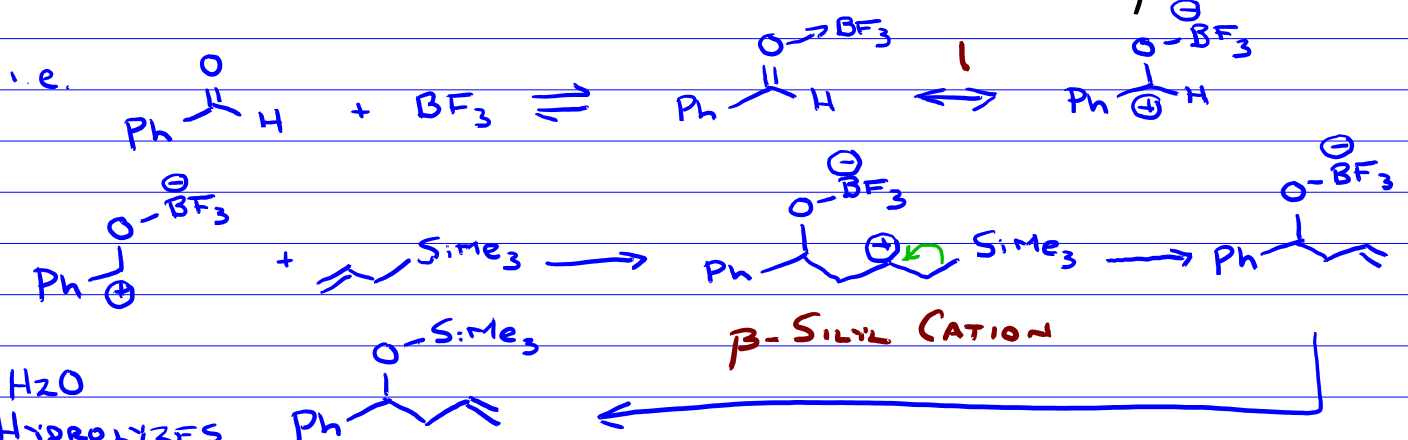
- VERY SPECIFIC NUCLEOPHILES



IN THE PRESENCE OF LEWIS ACIDS,
WITH ALDEHYDES AND KETONES



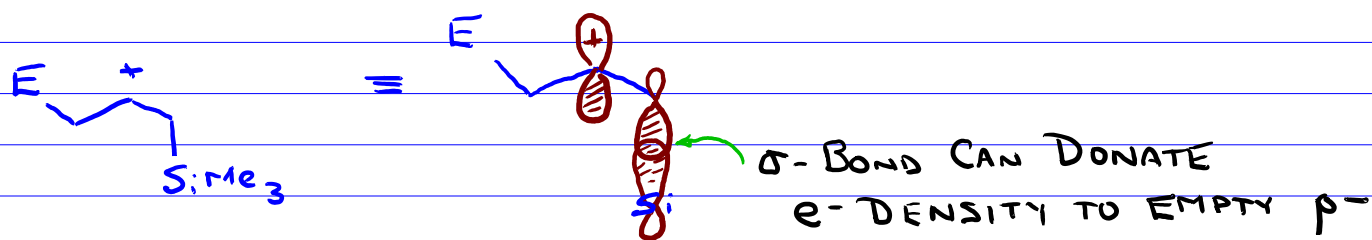
- THE REASON THIS WORKS IS DUE TO THE STABILIZATION OF CARBOCATIONS BY Si (OR Sn) IN THE β -POSITION



BF₃, IN PRINCIPLE, CAN BE A CATALYST
- NOT ALWAYS IN PRACTICE

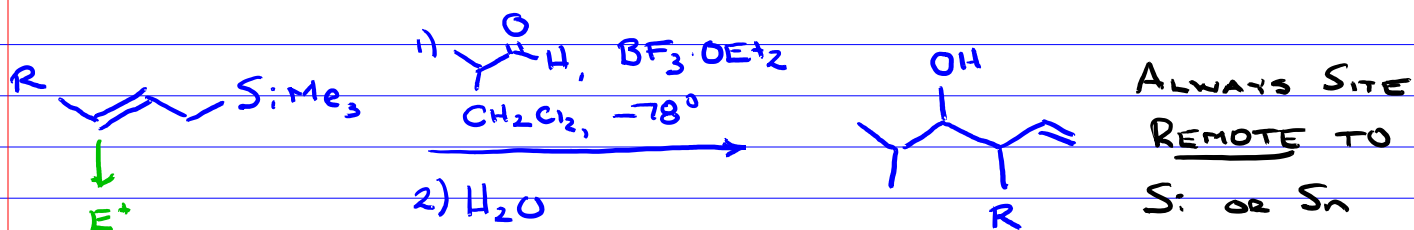
STABILIZATION OF β -SILYL CATION DUE TO EFFECTIVE OVERLAP OF EMPTY p -ORBITAL OF CATION WITH C-Si σ BOND

- REALLY A MORE EFFECTIVE VERSION OF HYPERCONJUGATION

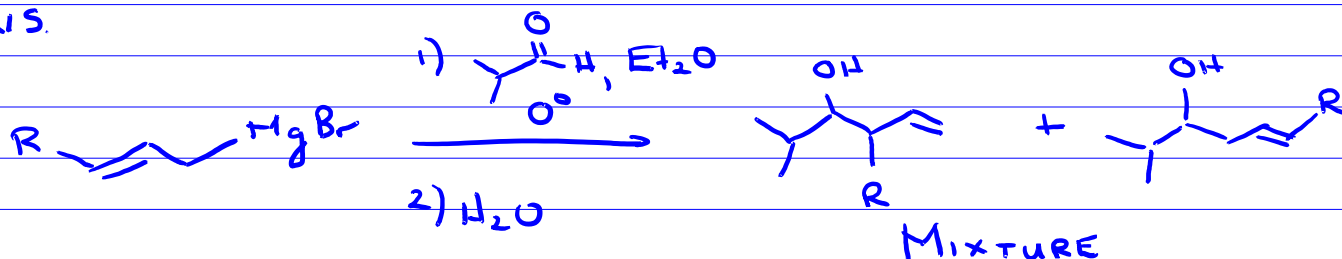


- SO WHY DOES THIS HAVE ANY ADVANTAGE OVER, SAY, A GRIGNARD?

- ALLYL SILANES AND -TINS HAVE MORE PREDICTABLE SITE OF RXN (REGIOCHEMISTRY)

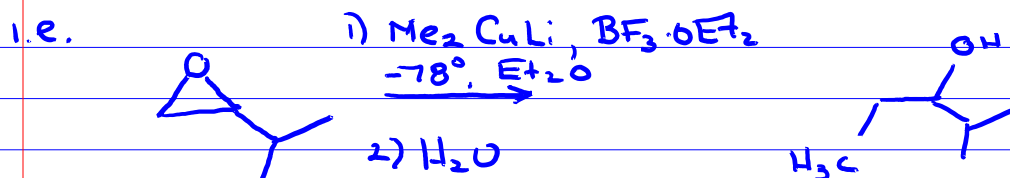


VS.

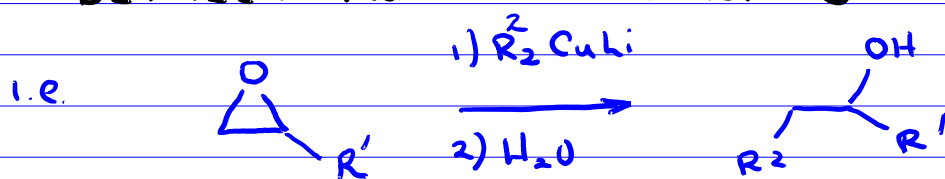


REACTIONS OF ORGANOMETALLICS WITH EPOXIDES

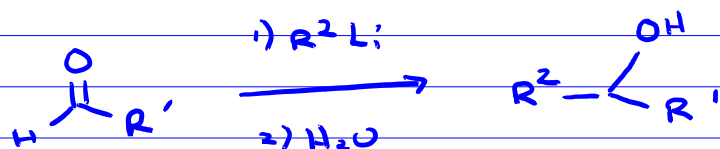
- ORGANOMETALLIC REAGENTS, ESPECIALLY CUPRATES, WILL ALSO ATTACK EPOXIDES, TO GIVE RING OPENING
- A LEWIS ACID IS OFTEN USED TO INCREASE REACTIVITY OF EPOXIDE
- S_N2 MECHANISM \therefore LESS SUBST. SIDE
 \therefore INVERSION OF CONFIGURATION



- THIS IS USEFUL DUE TO THERE BEING 1 EXTRA CARBON BETWEEN Nu^- + PRODUCT OH



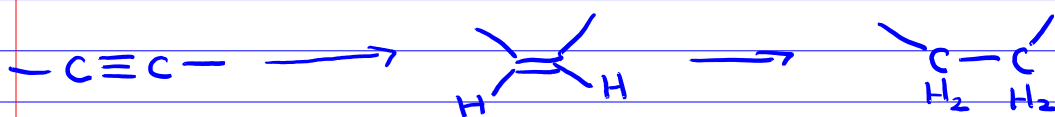
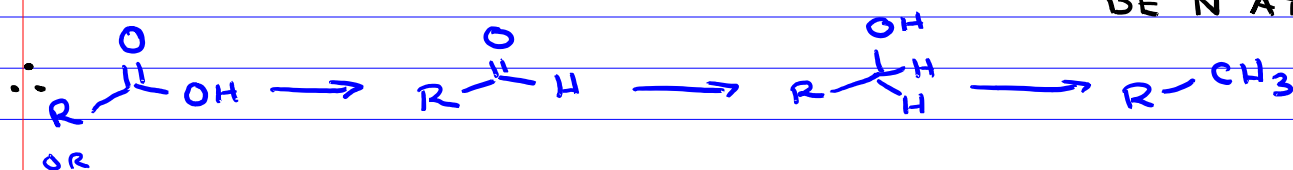
VERSUS



REDUCTION

- SO FAR, WE'VE MOSTLY FOCUSED UPON CONSTRUCTION OF CARBON SKELETON
- NOW, WE'LL FOCUS FOR A WHILE OF FUNCTIONAL GROUP MODIFICATION
- THE MOST COMMON ARE REDUCTION AND OXIDATION
 - SOME ELEMENTS HAVE BEEN COVERED IN PREVIOUS COURSES, SO WILL FOCUS MORE ON SELECTIVITY NOW.

REDUCTION - WORKING ORGANIC DEFINITION
 EITHER - ADDITION OF H ATOMS OR
 - REMOVAL OF O ATOMS (YES THIS COULD BE N ATOMS)



REDUCTIONS - CONT'D.

Note Title

2/28/2017

- WE WILL ADDRESS REDUCTIONS FROM THE MOST COVALENT TO THE MOST IONIC
- V. SIMPLE MNEMONIC IS THAT V. COVALENT REAGENTS PREFER COVALENT SUBSTRATES, AND THAT IONIC REAGENTS PREFER V. POLARIZED SUBSTRATES

1) CATALYTIC HYDROGENATION

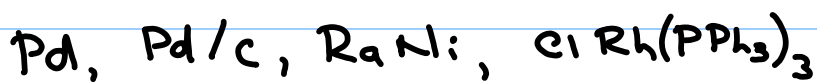
THIS IS H_2 GAS + CATALYST

- THE CATALYST TENDS TO DICTATE WHICH FUNCTIONAL GROUPS ARE REDUCED
- TEND TO BE FINELY DIVIDED METAL POWDERS, OR ONES COATED ON AN INERT SUPPORT

Pd, Pt, Ni (R₂Ni = RANEY NICKEL), Pd/C
ON CHARCOAL/CARBON

- SOLUBLE, SMALL MOLECULE CATALYSTS DO EXIST
 $Cl-Rh(PPh_3)_3$ WILKINSON'S CATALYST
- SOLVENTS - ANYTHING INERT
 $H_2O, EtOH, H_3C-\overset{O}{\underset{||}{C}}-OEt, CH_3-CO_2H$
- TOUGH ONES DONE UNDER HIGH PRESSURE AND/OR TEMPERATURE, IN A 'BOMB'
- RELATIVE REACTIVITY OF CATALYSTS

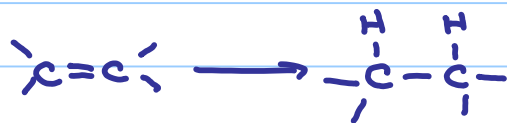
a) Low 'ish' - MOST COMMON BECAUSE YOU HAVE THE MOST SELECTIVITY POSSIBLE



b) HIGHER Pt, Ru

c) HIGHEST Rh, Ir

HIGHER REACTIVITY CATALYSTS, OR EVEN SOME OF THE LOWISH ONES AT HIGH T & P CAN REDUCE EVEN BENZENES - LET'S GO WITH THE READILY REDUCED FUNCTIONAL GROUPS

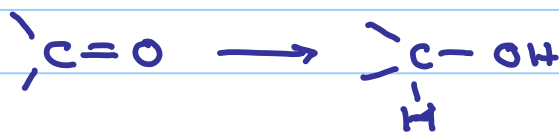


THERE CAN EVEN BE SELECTIVITY WITH ALKENE TYPE



LESS EASY

Low P_{H_2}



High P_{H_2}

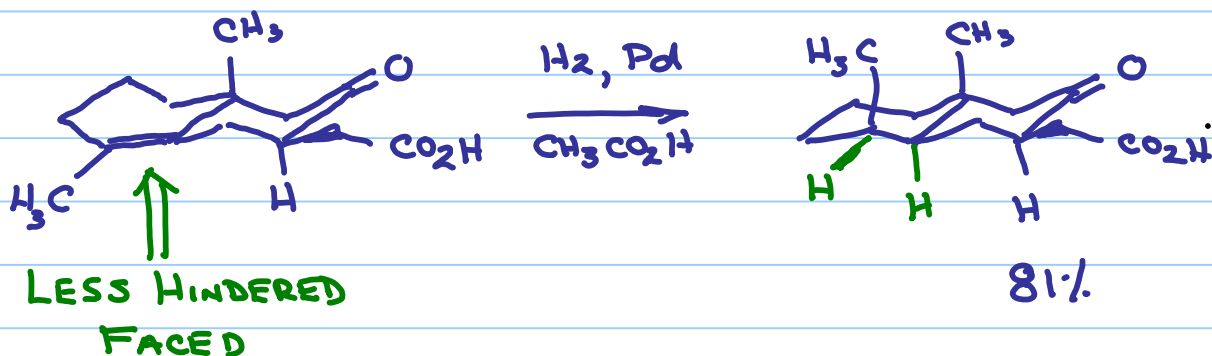


ESTERS, ACIDS, AMIDES AND AROMATICS NEED FAR MORE FORCING CONDITIONS

- OTHER CONSIDERATIONS

- H ATOMS ADD CIS - FROM THE LESS HINDERED FACE OF THE ALKENE

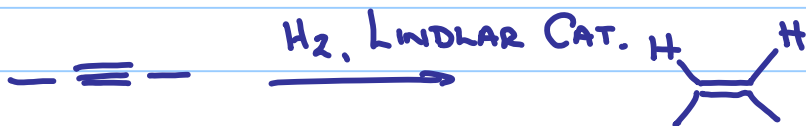
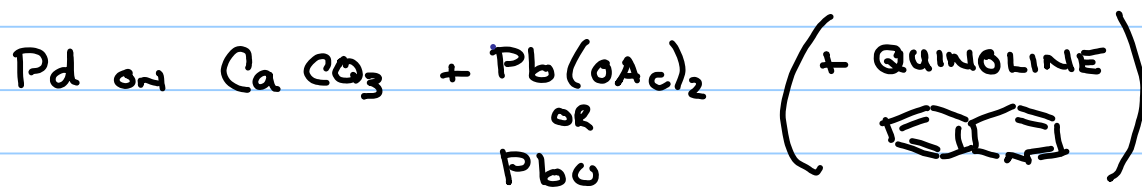
i.e.



SPECIFICALLY FOR ALKYNES

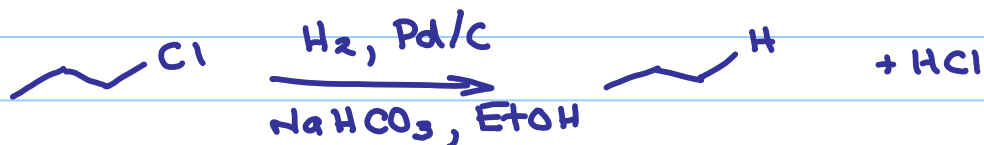
- ALKYNES AND ALKENES ARE CLOSE IN REACTIVITY SO A SPECIALIZED, LOWERED REACTIVITY (POISONED) CATALYST IS USED FOR SELECTIVE ALKYNE REDUCTION

LINDLAR CATALYST

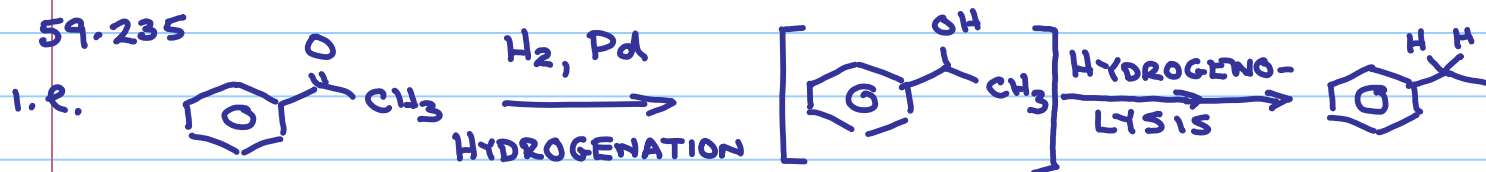


- COMPETING REACTION - HYDROGENOLYSIS

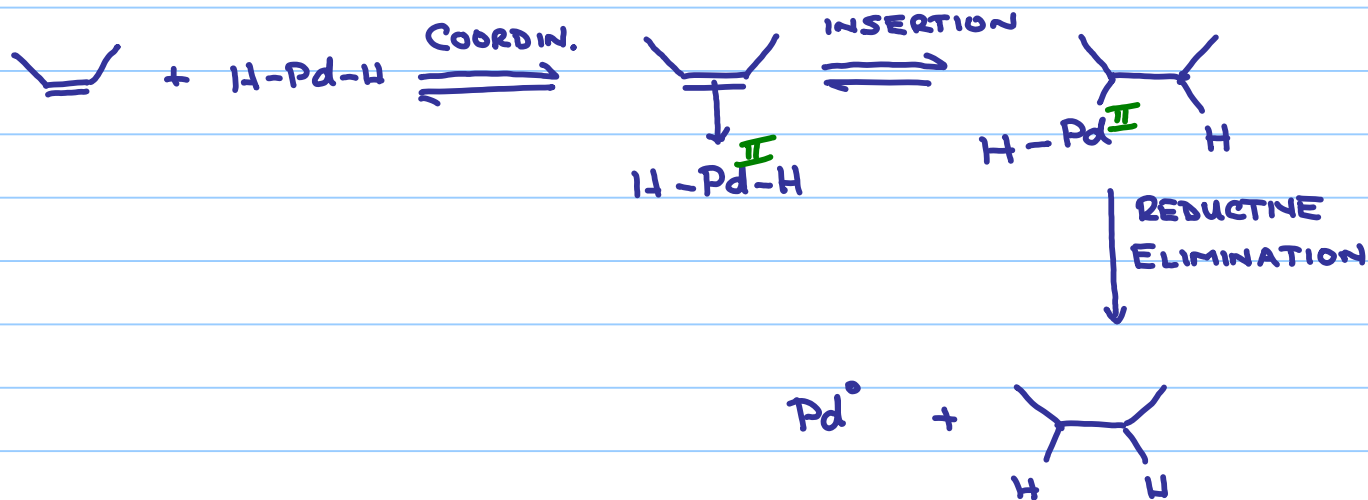
- CLEAVAGE OF A C-X SINGLE BOND



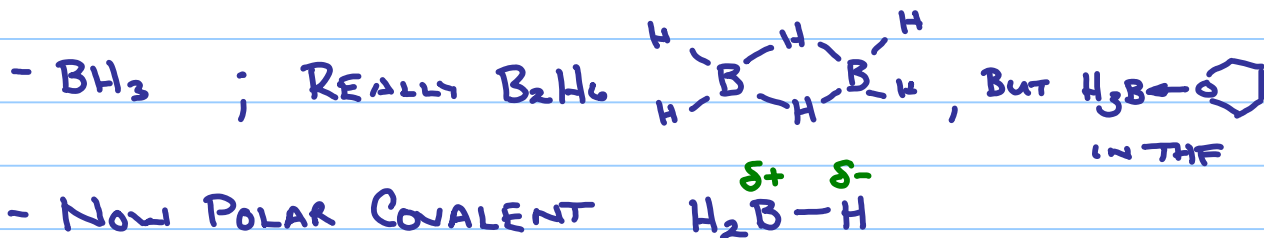
- SHOWS UP MOST WHEN X = REALLY GOOD LEAVING GROUP, OR IN BENZYLIC SUBSTRATES



HYDROGEN MECHANISM? - SOME ARTISTIC LICENSE HERE, SINCE RXN IS USUALLY ON A SURFACE, AND I'M EXTRAPOLATING TO/FROM SINGLE MOLECULES

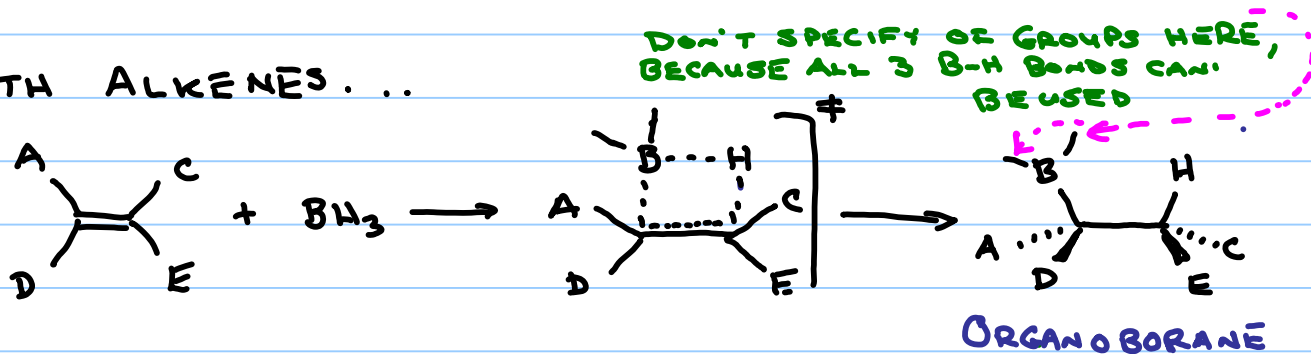


2) HYDROBORATION

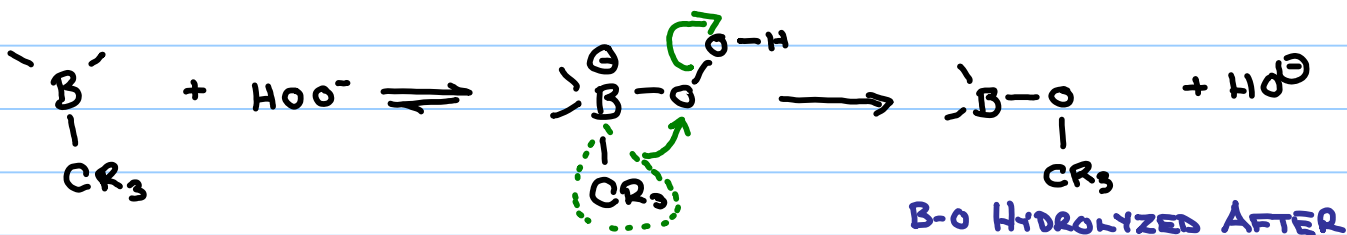
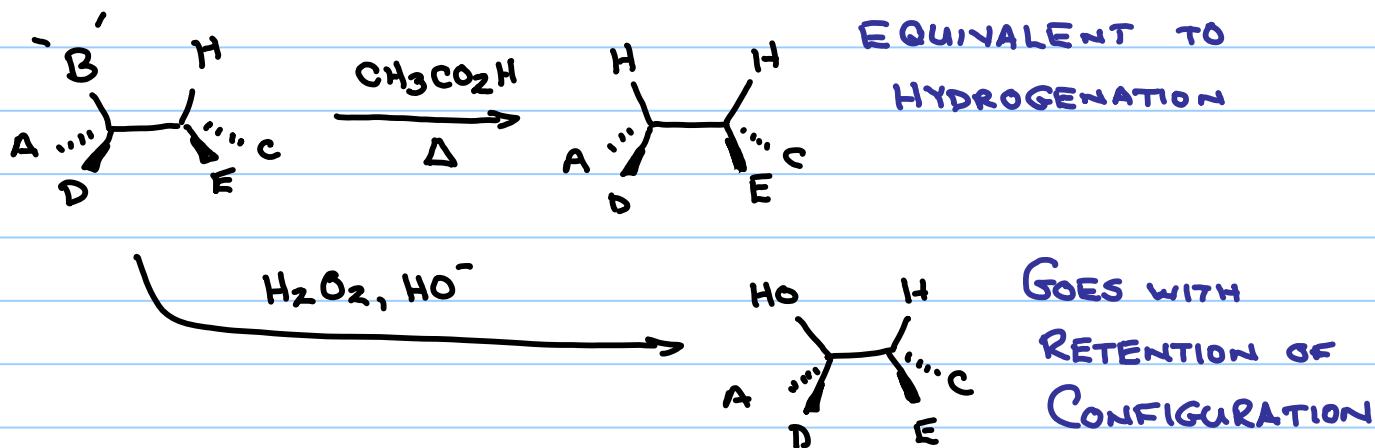


- FUNCTIONAL GROUP SELECTIVITY IS MOSTLY THE SAME AS CATALYTIC HYDROGENATION, WITH ONE BIG EXCEPTION

WITH ALKENES...

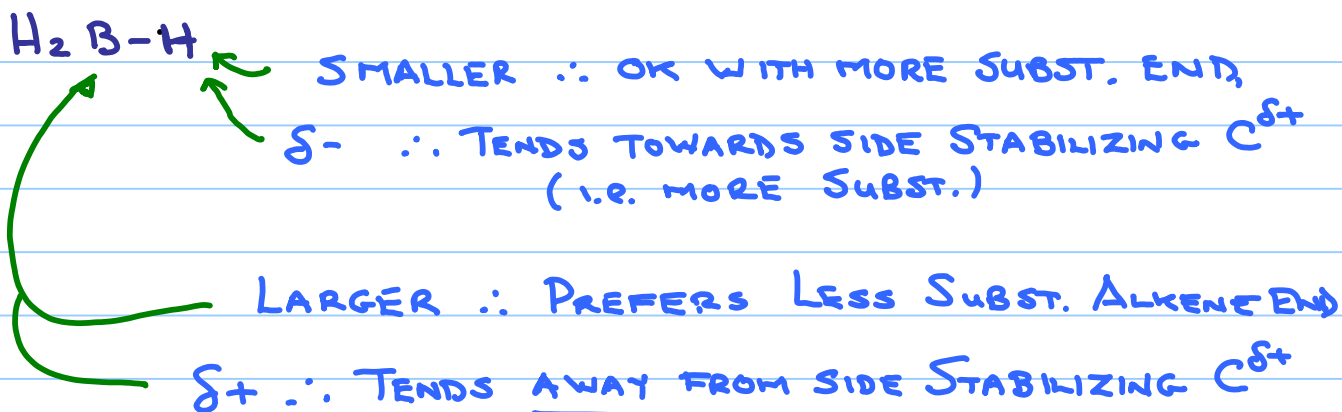


DON'T ISOLATE ORGANOBORANE, BUT INSTEAD

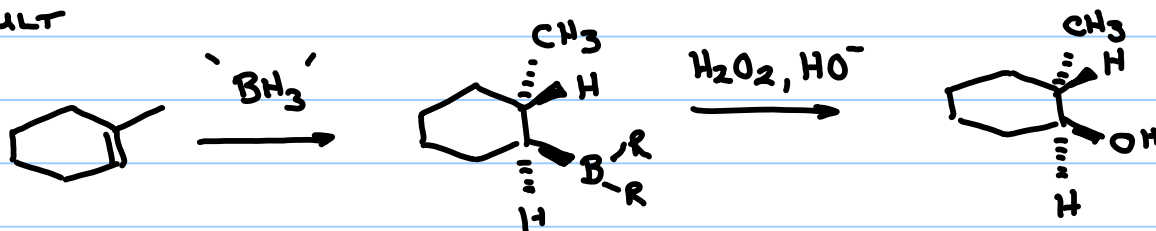


- FIRST HINT OF OUR NUCLEOPHILIC REARRANGEMENTS, AT END OF THE COURSE

RECALL: ADDN REGIOCHEMISTRY IS UNUSUAL, TOO.

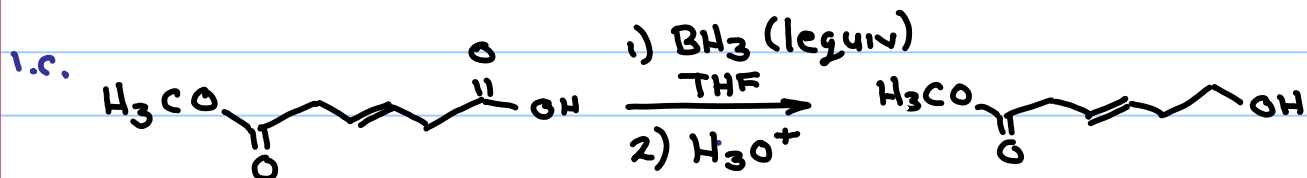


RESULT



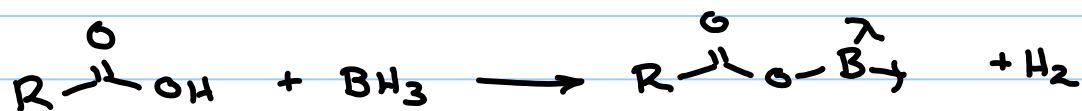
OFTEN CALLED
'ANTI'-MARKOVNIKOV

- NOW FOR THAT FUNCTIONAL GROUP SELECTIVITY REVERSAL
- NORMALLY, CARBOXYLIC ACIDS ARE AT OR NEAR BOTTOM OF GROUPS THAT COULD BE REDUCED
- WITH HYDROBORATION THEY ARE THE VERY EASIEST THINGS TO REDUCE



WHY?

- A PARTIAL ANSWER



BORON ACTS AS (-M) EWG ON O ATOM

∴ V. EWG GROUP ON CARBONYL IN TOTAL

∴ CARBONYL VERY REACTIVE

- SOME ARGUE THAT H IS DELIVERED TO THE CARBONYL FROM THE B ATOM
- SOME ARGUE NOT.

3) HYDRIDE ION $M^+ H^-$
- VERY NUCLEOPHILIC

QUICK REVIEW IONIC

∴ $\overset{\overset{\delta^-}{\mid}}{C}=\overset{\overset{\delta^+}{\mid}}{O}$ ATTACK RAPIDLY WHILE

$\overset{\overset{\delta^-}{\mid}}{C}=\overset{\overset{\delta^+}{\mid}}{C}$ IS ANYWHERE FROM LOW REACTIVITY TO NO REACTIVITY

- INVERSE TREND TO CATALYTIC HYDROGENATION
- NiH / KH ? NO. TOO GOOD AS BASES - NORMALLY NOT USEFUL AS NUCLEOPHILES
- MOST COMMON ONES

$\text{Na}^+ \text{BH}_4^-$ SODIUM BOROHYDRIDE

- Milder, more selective
- Can be used in alcohol solvents, even basic H_2O

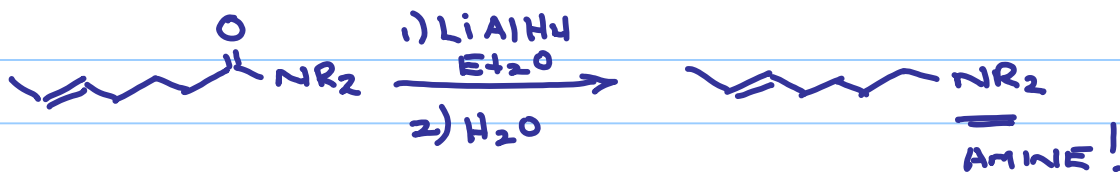
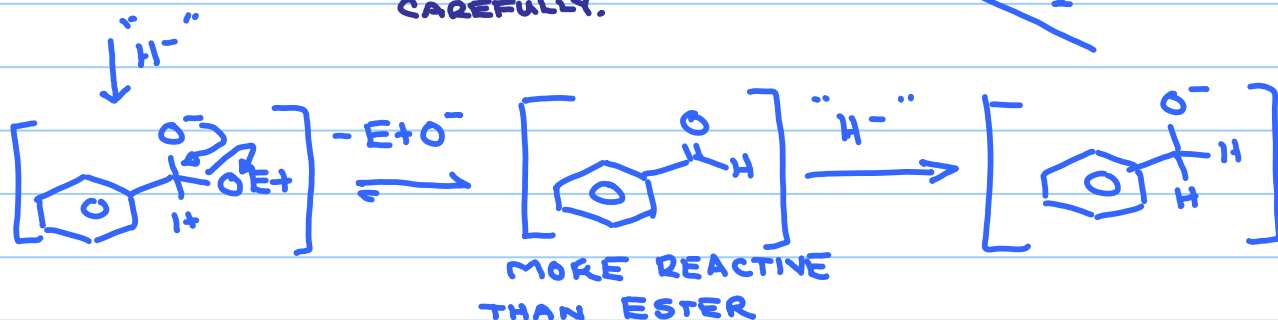
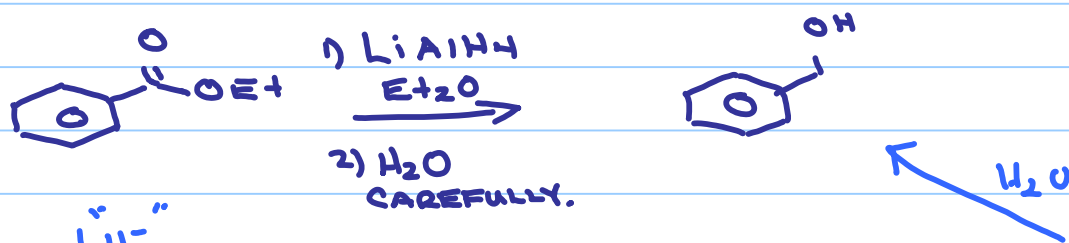
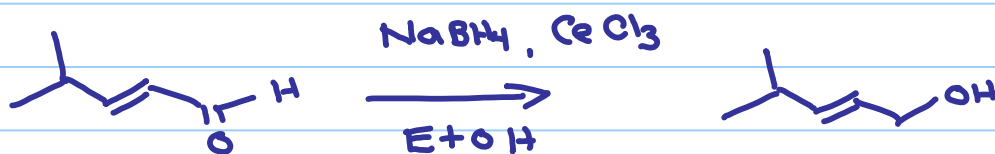
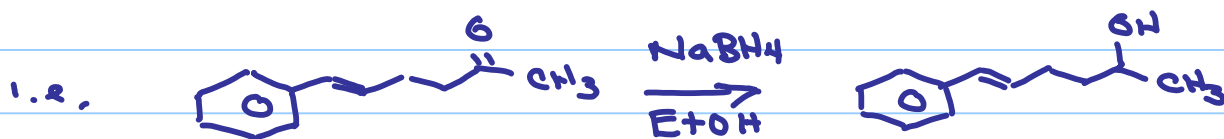
$\text{Li}^+ \text{AlH}_4^-$ LITHIUM ALUMINUM HYDRIDE

- More reactive, not selective
- Must be used in non-protic solvents i.e. THF, Et_2O

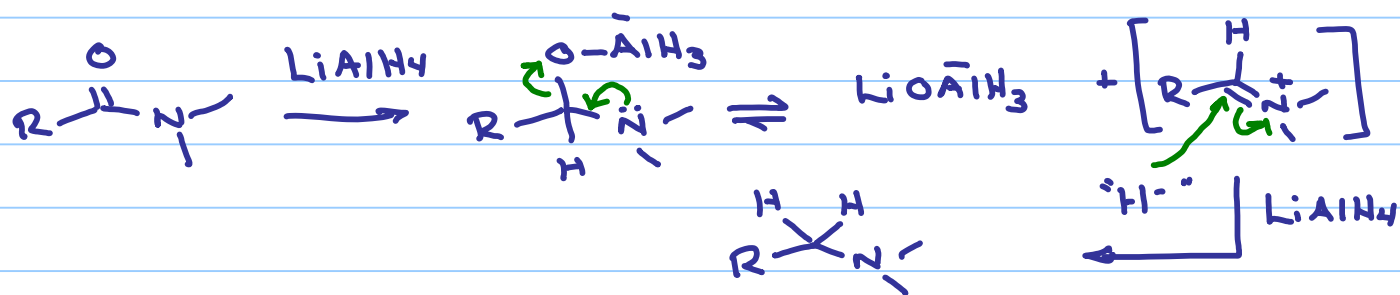
REACTIVITY

NaBH_4 REACTS WITH ALDEHYDES > KETONES > ALL ELSE

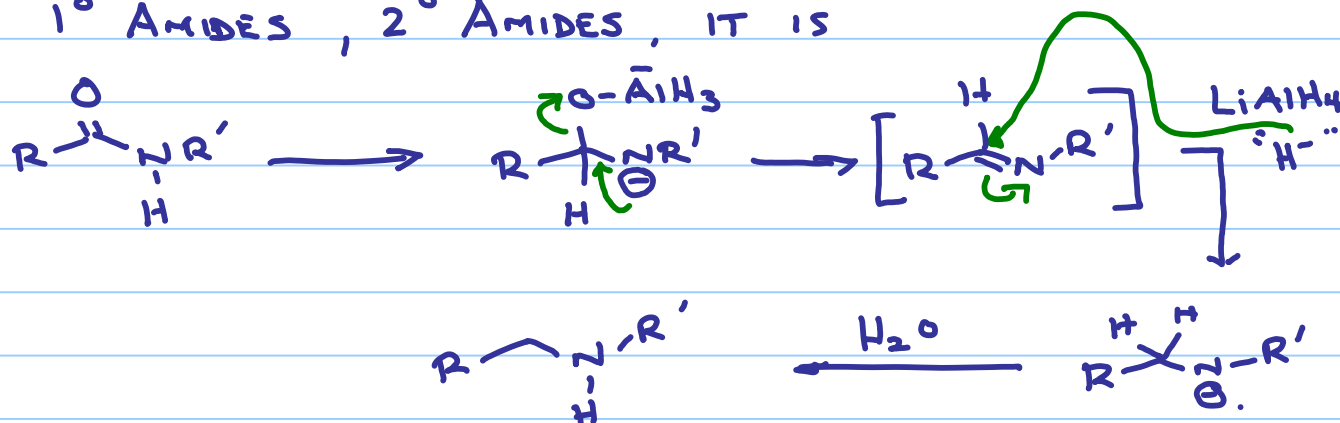
LiAlH_4 ALL CARBONYLS, EVEN CARBOXYLIC ACIDS
(ALTHOUGH A BIT MORE SLOWLY)



- AMIDES REDUCE TO AMINE, BECAUSE (BELIEVE IT OR NOT) $\text{O}^- \text{AlH}_3$ IS A GOOD ENOUGH LEAVING GROUP



W 1° AMIDES, 2° AMIDES, IT IS



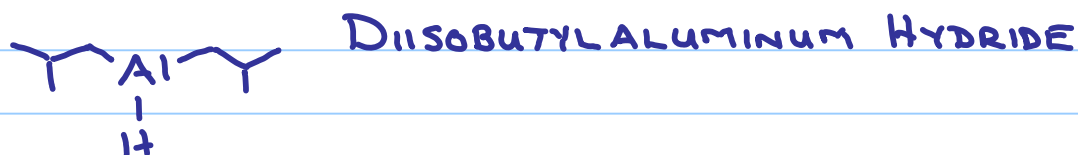
③ OVERCOMING ESTER OVERREDUCTION

- AS WE DID WITH ORGANO Li's, CAN WE DO 1 ADDN OF H^- TO ESTER (OR ANALOGUE)?



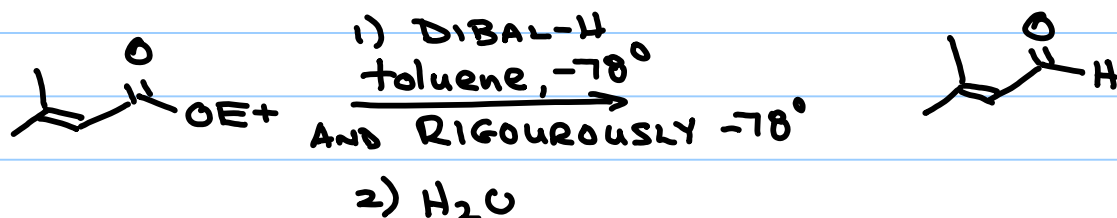
2 SOLUTIONS

1) DIBAL-H IN MANY CASES A SPECIALTY REDUCTANT



AND CAREFUL CONTROL OF LOW TEMP, AND A NON-POLAR SOLVENT

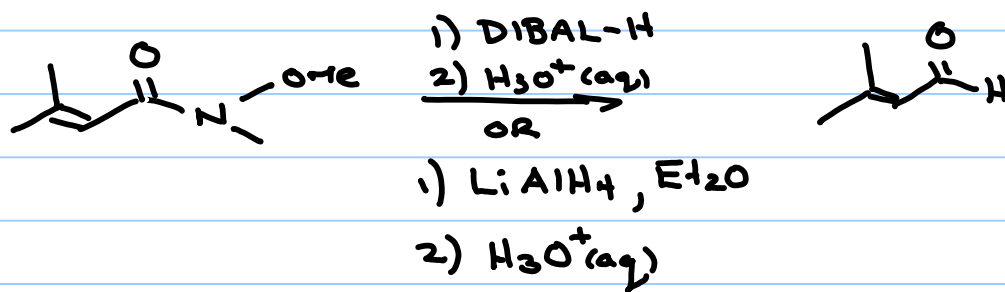
- ALLOWS THE TETRAHEDRAL INTERMEDIATE TO HANG TOGETHER LONG ENOUGH TO STOP AT 1 REDUCTION



- IF T GETS MUCH HIGHER THAN -78° , OVERREDUCTION TO ALCOHOL OCCURS

2) THE WEINREB AMIDES

- THEY WORK BEAUTIFULLY HERE, TOO



1,2- VS 1,4 - ADDITION

- H^{-} SOURCES, AND DIBAL- H HAVE A 1,2-ADDN PREFERENCE

- IN SOME CASES ADDN OF $CeCl_3$ IS NEEDED TO MAKE THAT SELECTIVITY COMPLETE

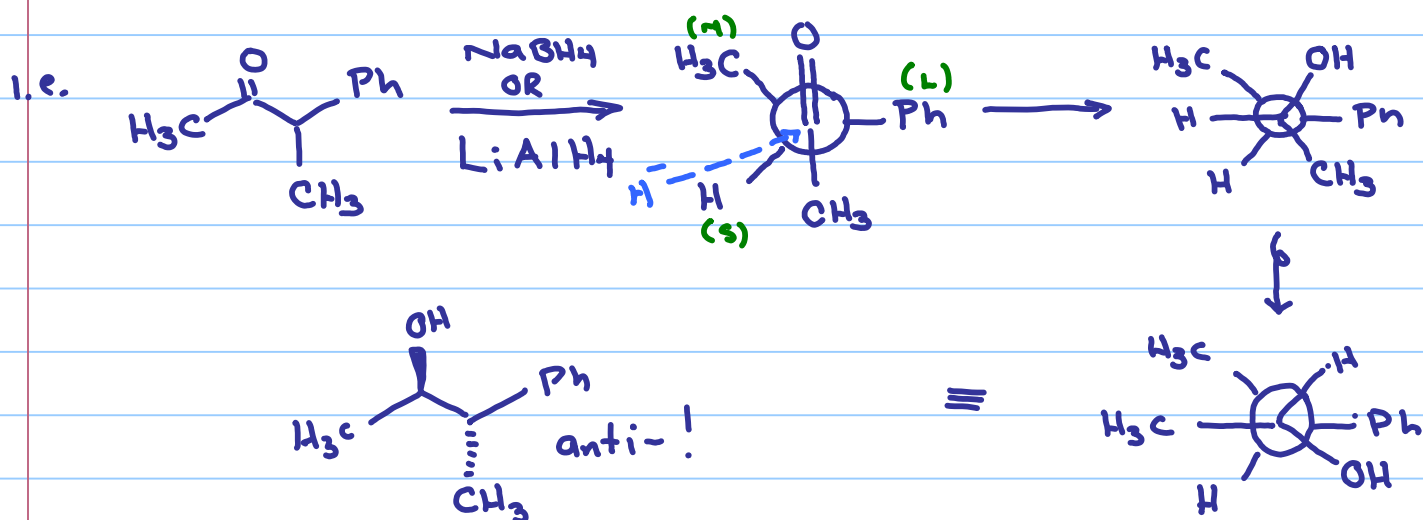
($NaBH_4 + CeCl_3$ CALLED LUCHE REAGENT)

STEREOCHEM. IN HYDRIDE REDNS.

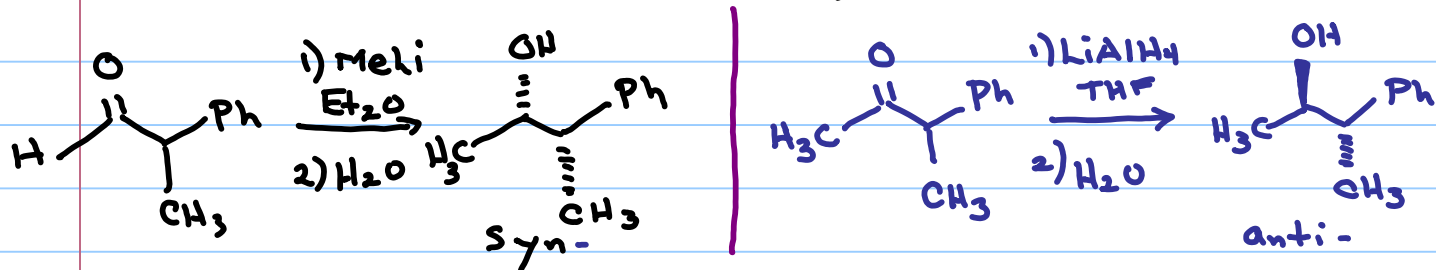
Note Title

3/5/2017

- THE REDUCTION OF CARBONYLS WITH α -CHIRAL CENTRES FOLLOWS THE EXACT SAME FELKW-ANN, OR CRAM CHELATE RULES
 - GIVES COMPLEMENTARY PRODUCT.



USEFUL SINCE YOU CAN NOW GET EITHER DIASTEROMER



CHELATE CONTROL / CRAM CHELATE

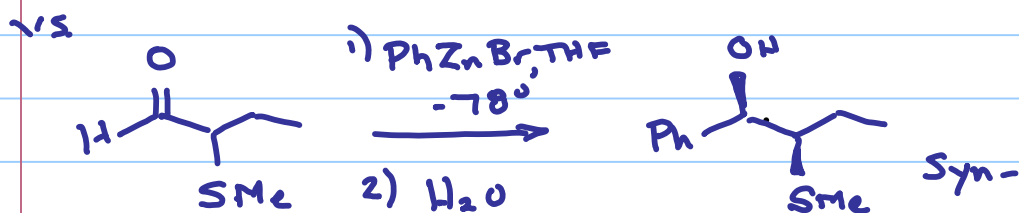
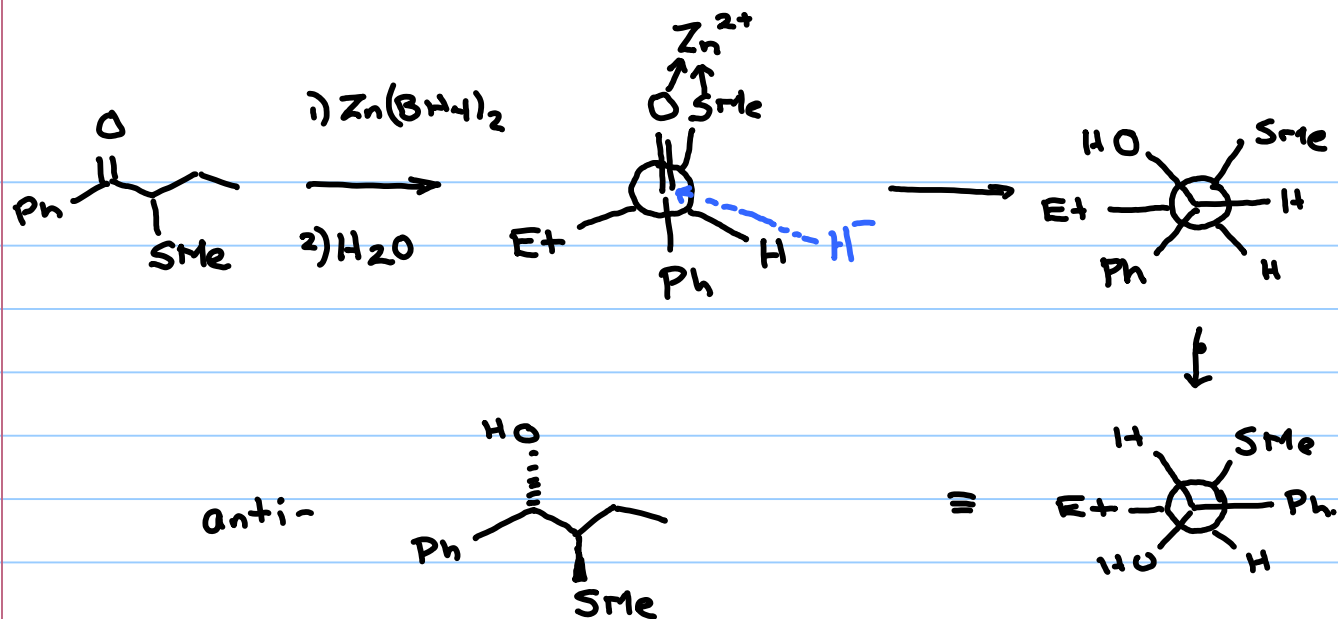
- V. SIMILAR ARGUMENTS AS BEFORE

- THE Li^+/Na^+ SALTS OF LiAlH_4 , NaBH_3 ARE NOT PRONE TO PARTICIPATE IN CHELATION CONTROL

- IF YOU DO WANT CHELATION

1) $\text{NaBH}_4 + \text{CeCl}_3$ (LUCHE REAGENT)

2) $\text{Zn}(\text{BH}_4)_2$ (Zn^{2+} COUNTERION) I'll use this one all the time in this course



REDUCTION OF CARBONYLS ($C=O$) \rightarrow CH_2

- 3 GENERAL METHODS

1 V. ACIDIC

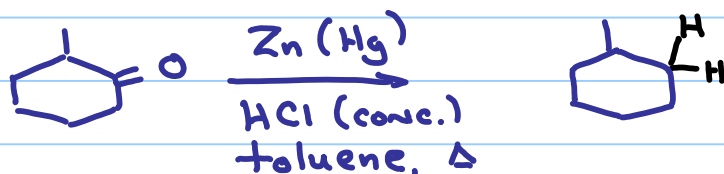
1 V. BASIC

1 HYDROGENATION LIKE

EACH HAS INSTANCES
 WHERE IT'S A PROBLEM,
 LAST IS PRETTY MILD

1) CLEMMENSEN REDUCTION

- V. ACIDIC - USES Zn-Hg ALMALGAM IN ACID



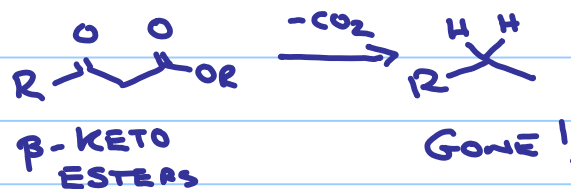
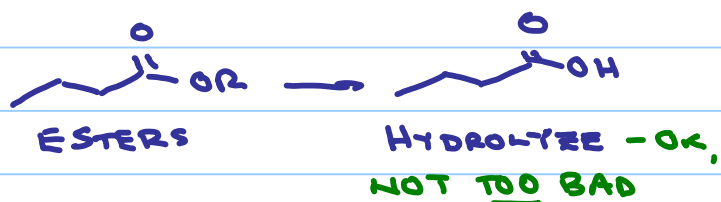
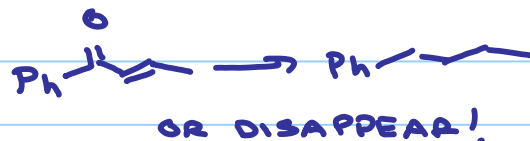
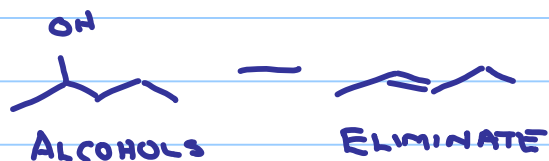
MECHANISM: NOT WELL UNDERSTOOD

- RADICAL INTERMEDIATES PROBABLY

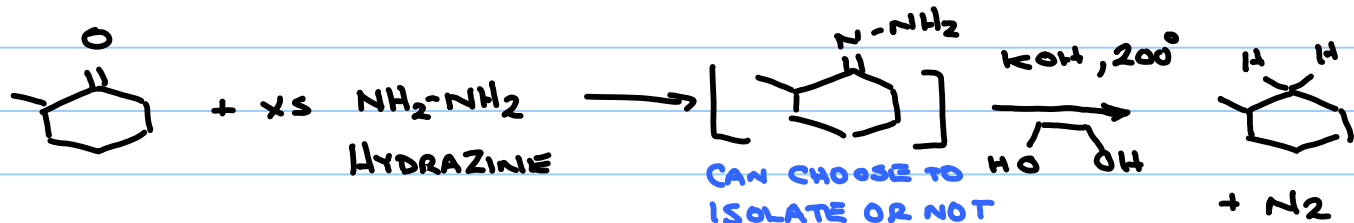
- ZINC 'CARBENE' POSSIBLE



- HINT ON MECH. DURING DISSOLVING METAL REDNS.
- SINCE IT'S SO ACIDIC, SEVERAL GROUPS DON'T SURVIVE

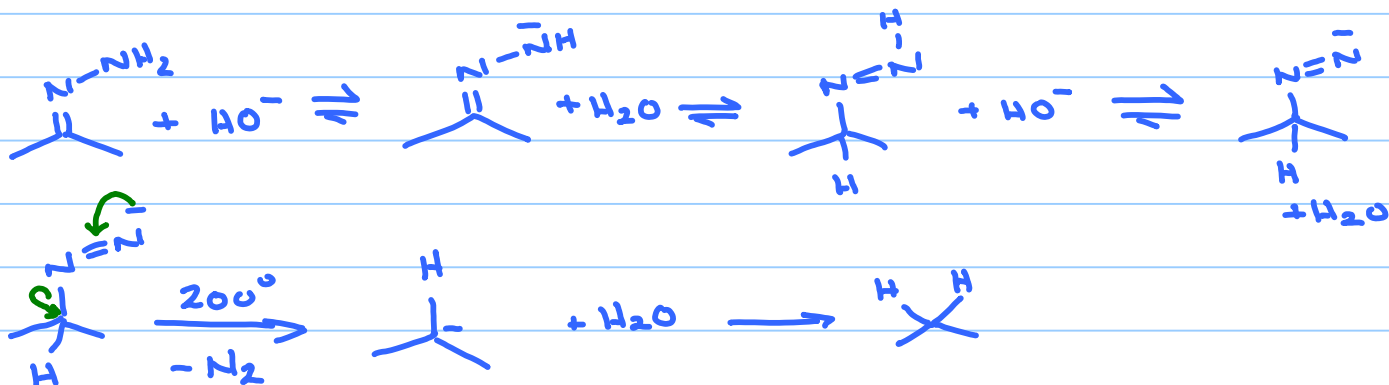


2) WOLFF-KISHNER (HUANG-MINLON MODIFICATION)



NEW MODIFICATION KO⁺Bu IN DMSO APPARENTLY GOES AT RT

MECH. IS AT LEAST UNDERSTANDABLE HERE



- FUNCTIONAL GROUP TOLERANCE ISN'T GREAT, BUT OVERALL SLIGHTLY BETTER THAN CLEMMENSEN

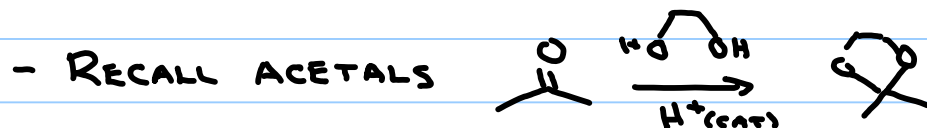
- ISOLATED ALCOHOLS, ALKENES, ACETALS ARE
PROBABLY OK

- ESTERS, AMIDES HYDROLYZE

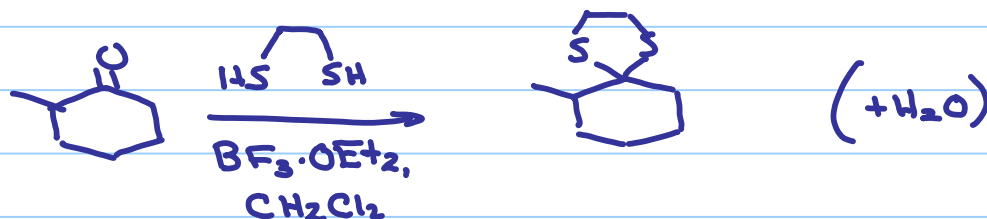
- HALIDES + NITRILES + NITRO GROUPS REACT

$\text{C}=\text{O}$ TO CH_2 , CONTD.

3. DIETHIOACETAL (1,3-DITHIANE) - MOZINGO REDUCTION



- DITHIOACETALS ARE MADE SIMILARLY, EXCEPT IT'S USUALLY A LEWIS ACID

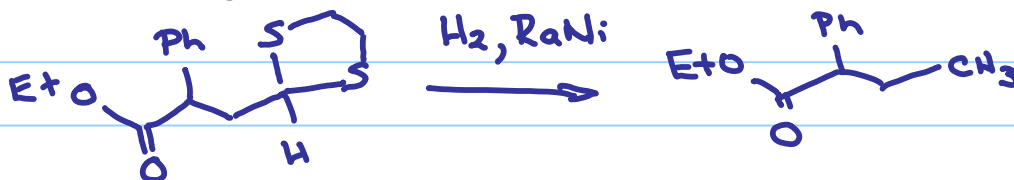


- THEY ARE SOMEWHAT SIMILAR TO ACETALS EXCEPT THAT THE C-S BONDS HAVE A HIGH PROPENSITY FOR, ESPECIALLY WHEN Ni^0 IS USED AS CATALYST

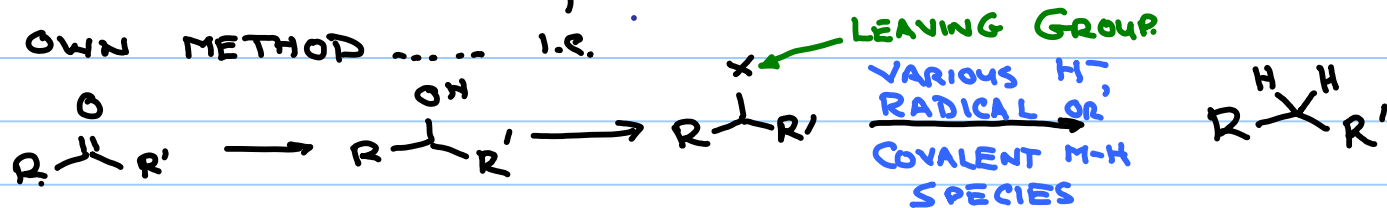
- MUCH Milder THAN OTHER REDUCTIONS

- DO HAVE TO WORRY ABOUT SURVIVAL OF EASILY REDUCED GROUPS, BUT THERE ARE EVEN REPORTED CASES WHERE ALKENES SURVIVE

- OTHERWISE



NOTE: BY THIS POINT, YOU CAN PROBABLY MAKE UP YOUR OWN METHOD I.E.



SIMPLE OXIDATIONS

- SOMETHING OF A REVIEW OF 235 COURSE

MOST COMMON - OXIDATION OF ALCOHOLS



- MOST COMMON REAGENTS Cr^{+6} CrO_3 , $\text{K}_2\text{Cr}_2\text{O}_7$
 Mn^{+7} KMnO_4

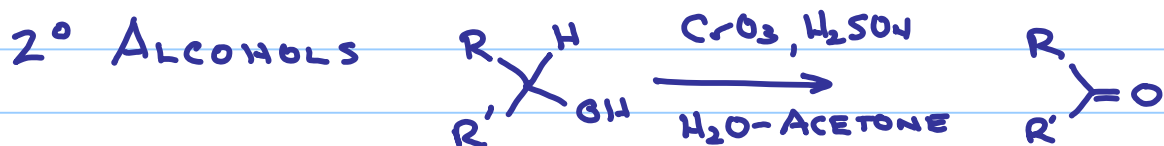
- USUALLY IN ACIDIC MEDIUM

- MOST COMMON OF ALL $\text{CrO}_3 + \text{H}_2\text{SO}_4$ IN
 $\text{H}_2\text{O} + \text{ACETONE}$

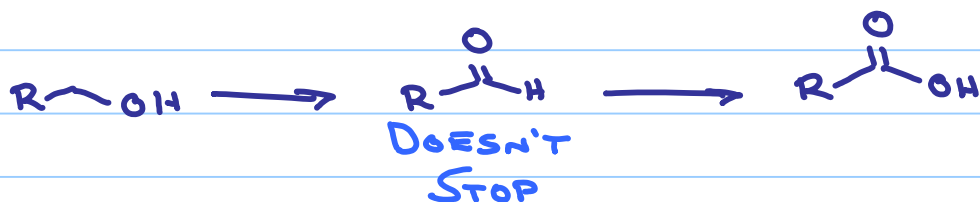
JONES
REAGENT

- PRODUCT BY ALCOHOL

3° ALCOHOL $\text{>C}(\text{OH})$ INERT, EXCEPT ACID WILL
CAUSE E1 ELIMINATION



1° ALCOHOLS - 'OVER' OXIDIZE TO ACID



- ISSUE - STOPPING OXIDATION OF 1° ALCOHOLS AT
ALDEHYDE STAGE

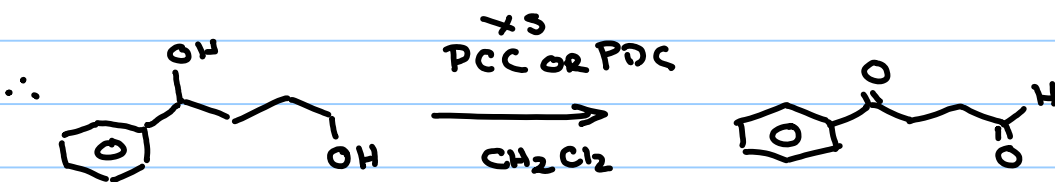
- TWO COMPARABLE REAGENTS FOR THIS PURPOSE



PYRIDINIUM CHLOROCHROMATE
PCC



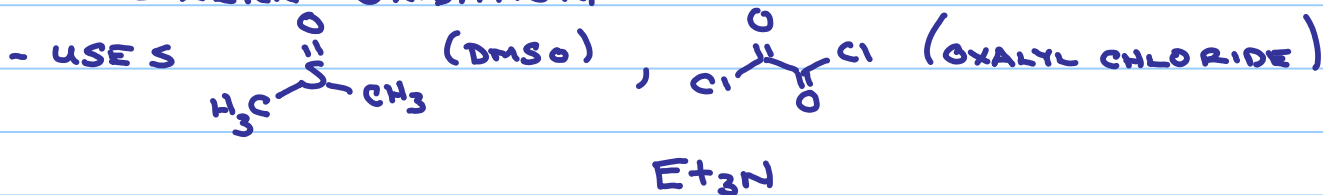
PYRIDINIUM DICHROMATE
PDC



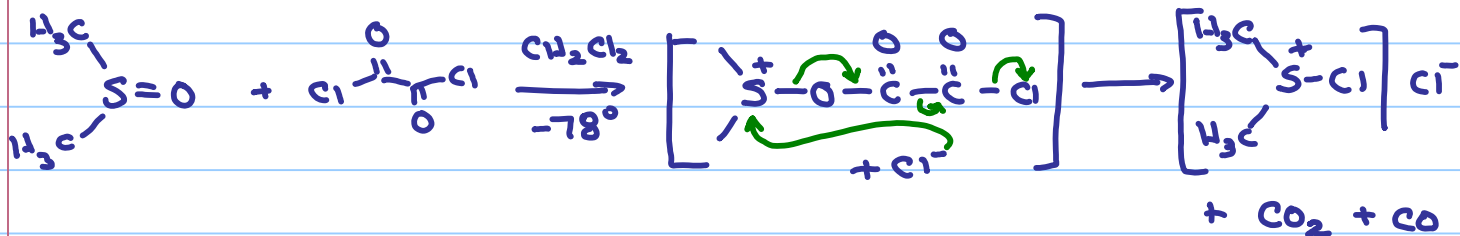
NOTICE 2° ALCOHOLS WERE FINE, TOO

- THE "BEST" REAGENT FOR THIS PURPOSE

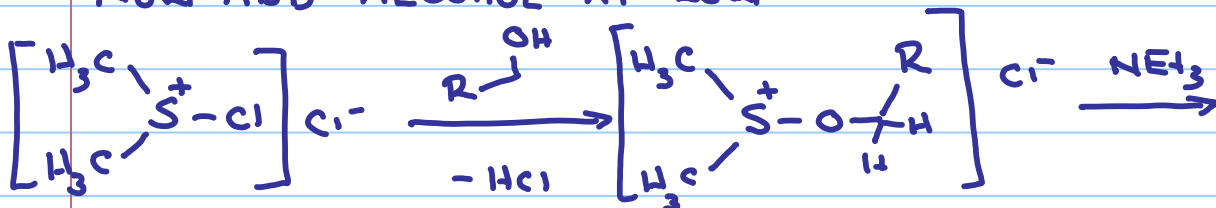
SWERN OXIDATION



- Mix. DMSO AND OXALYL CHLORIDE AT $T < -50^\circ$



NOW ADD ALCOHOL AT LOW T

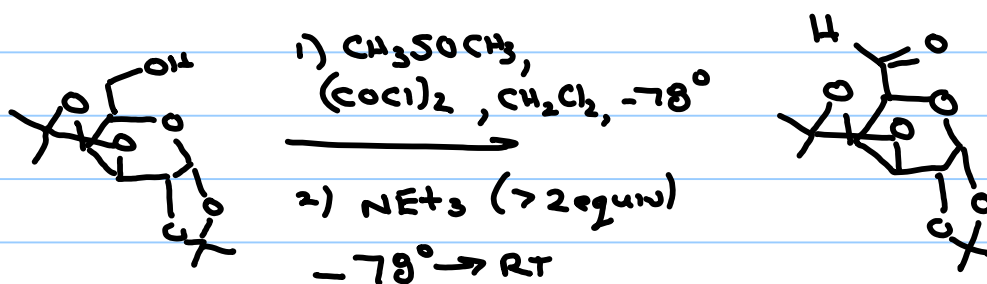


V. MILD - HCl CONSUMED BY NEt_3 ∴ ACID SENSITIVE GROUPS OK

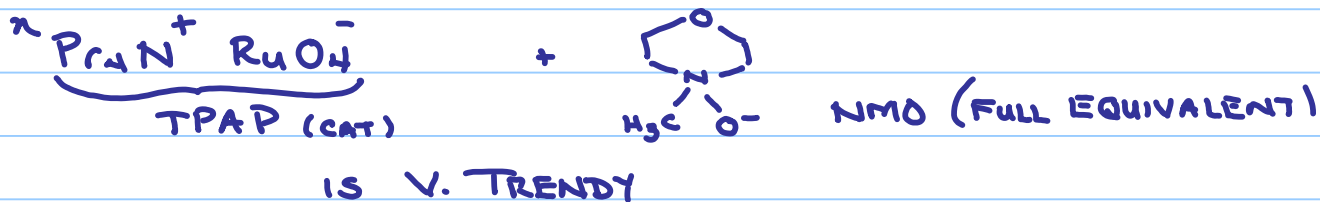
- OTHER BY-PRODUCTS EASILY SEPARATED?

- DRAWBACK (?) - Me_2S STINKS

- BUT...



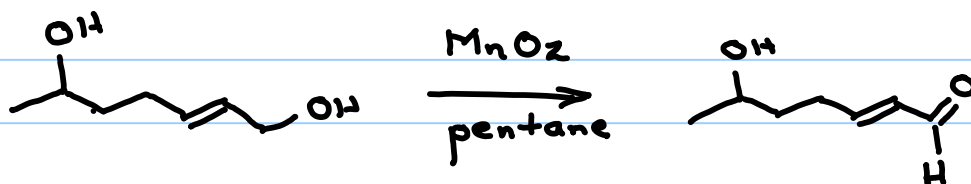
- THERE IS A CONTINUAL SEARCH FOR NEW, MORE ENVIRONMENTALLY FRIENDLY OXIDANTS



- ONE FINAL OXIDANT

MnO_2 - MANGANESE DIOXIDE

- ONLY OXIDIZES ALLYLIC AND BENZYLIC ALCOHOLS



DISSOLVING METAL REDUCTIONS

Note Title

3/9/2017

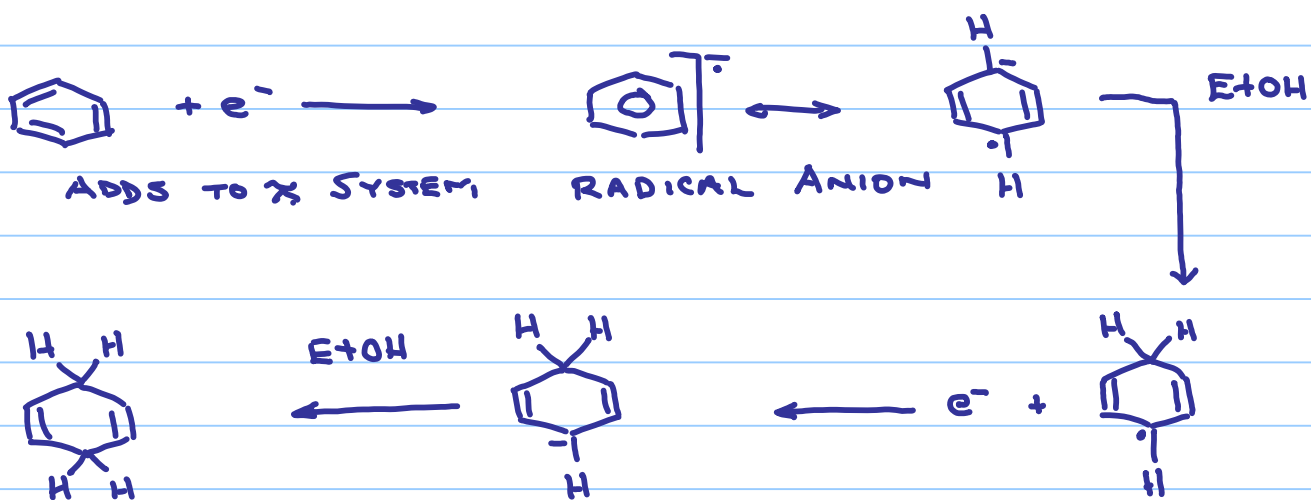
- THESE ARE REDUCTIONS DUE TO e^- 'S DONATED BY ELECTROPOSITIVE METALS



1) BIRCH REDUCTION

- Na^0 or Li^0 in $NH_3(l)$ ($-33^\circ C$) - GIVES AN INTENSE BLUE SOLUTION - $Na^+ + e^-$ SOLVATED BY $NH_3(l)$

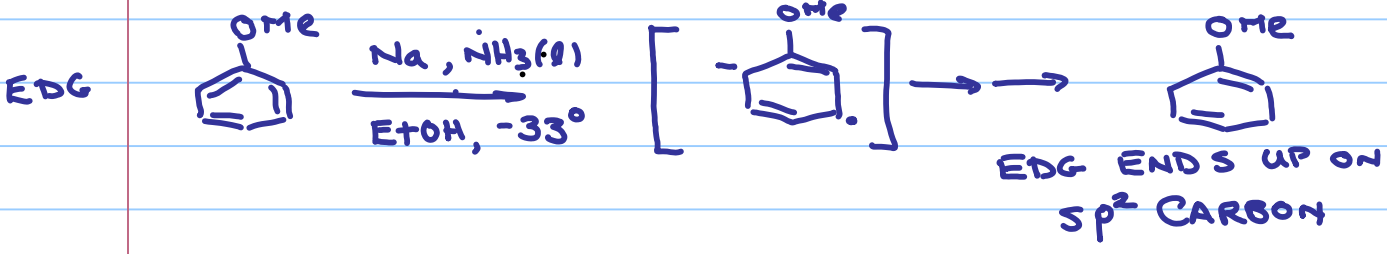
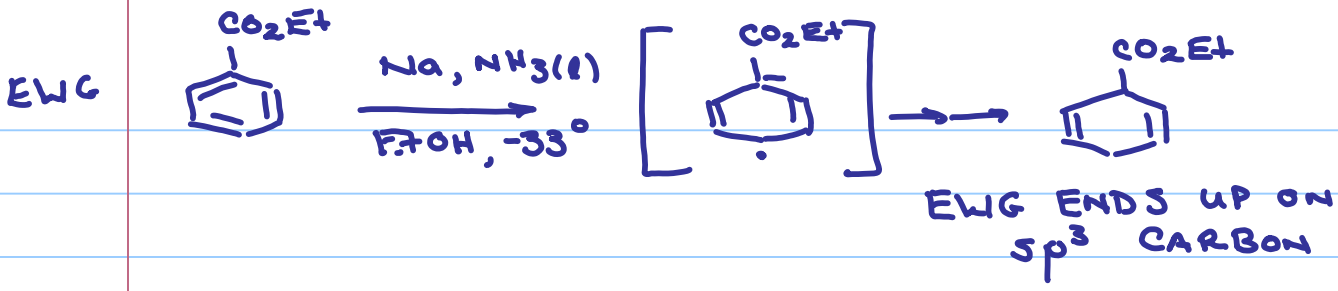
- THIS SOLUTION WILL REDUCE BENZENES, USUALLY DONE IN THE PRESENCE OF AN ALCOHOL



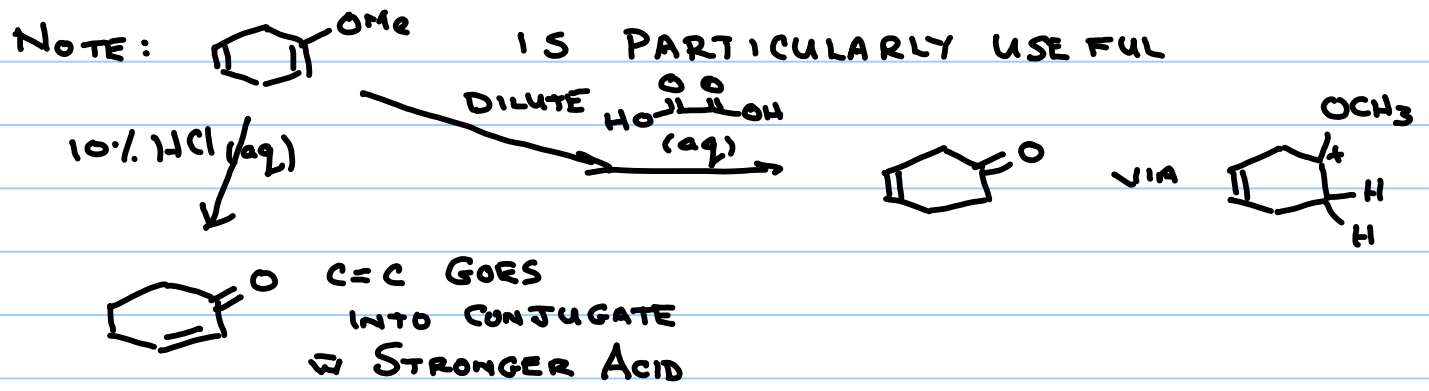
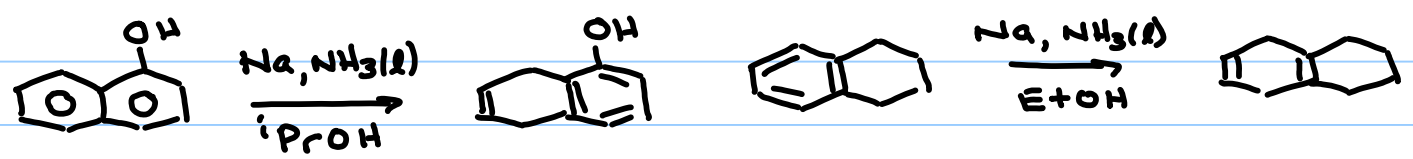
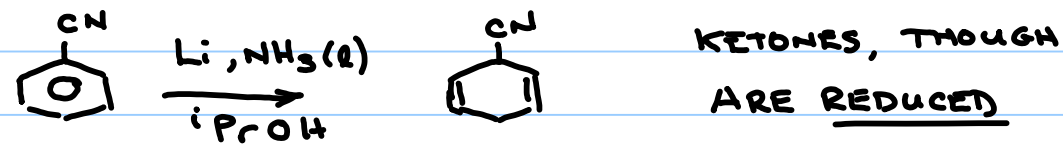
- NO CONJUGATED SYSTEM
SO RXN STOP HERE

\therefore GET NON-CONJUGATED CYCLOHEXADIENE

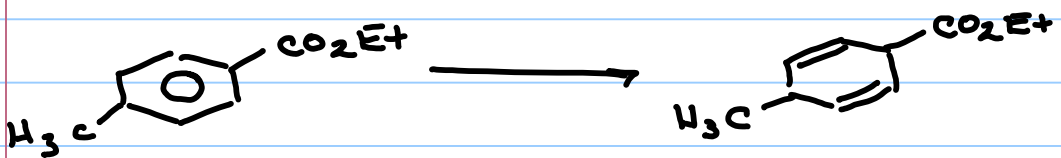
- FOR SUBSTITUTED BENZENES - PRODUCT DEPENDS ON WHETHER SUBSTIT. IS EWG ($-I, -M$) OR EDG ($+I, +M$)
- RXN FASTER WITH EWG



OTHER EXAMPLES



- WHEN AN EDG (DONATING) AND EWG (WITHDRAWING) GROUPS ARE IN COMPETITION, THE EWG ALWAYS CONTROLS THE PROCESS

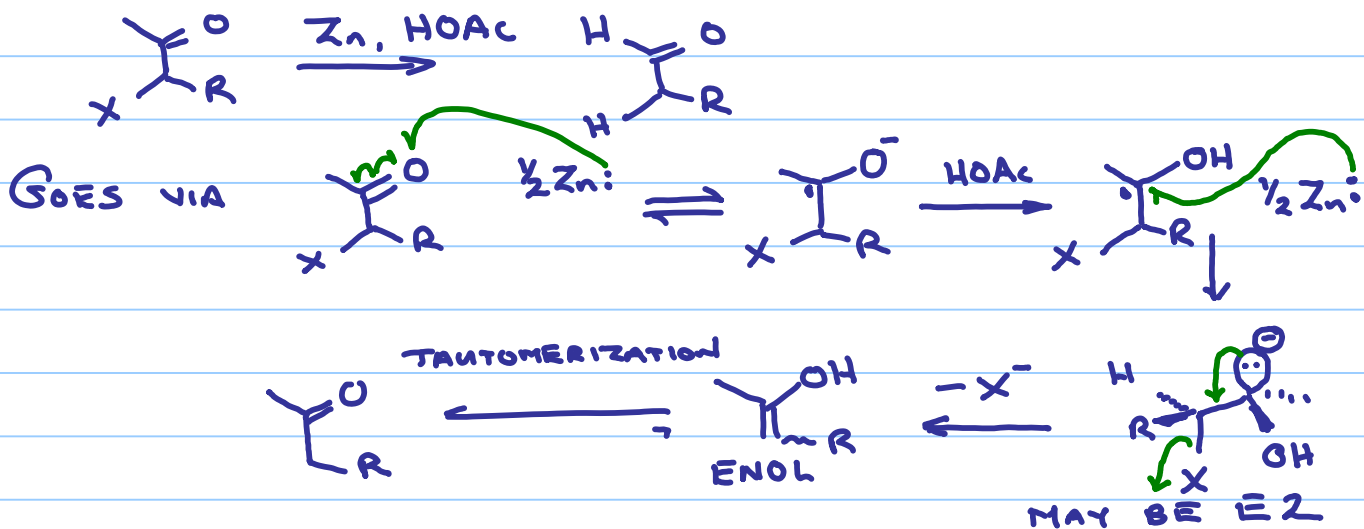


ADVANTAGE - AROMATICS ARE DIFFICULT IN CATALYTIC HYDROGENATION, AND INERT TO H^+

- V. EASILY AND PRETTY SELECTIVELY REDUCED HERE
- ISOLATED $C=C$, OH , O^- , CO_2H , CO_2R , NH_2 ARE STABLE
- CH_2OH AND KETONES ON BENZENE ARE USUALLY REDUCED, THOUGH
- ALKYNES ARE REDUCED TO TRANS- ALKENES ^{(E)-}

2. 'METAL ACID' REDUCTION

- REDUCTION OF LEAVING GROUPS ($-X$) \propto TO A KETONE
- REALLY DOES NOT HAVE TO BE A GOOD LEAVING GROUP
- $X =$ HALOGEN, $-OAc$, $-OH$, $-NR_2$
- REAGENT IS Zn IN CH_3CO_2H
- MAY GIVE A HINT TO THE INITIAL STEPS OF THE CLEMMENSEN RED.

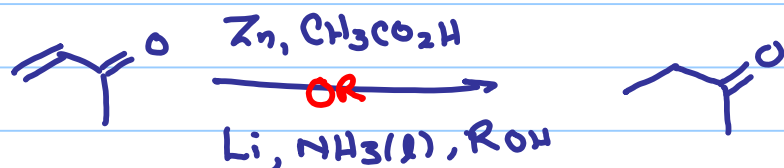


METAL ACID REDN'S CONT'D

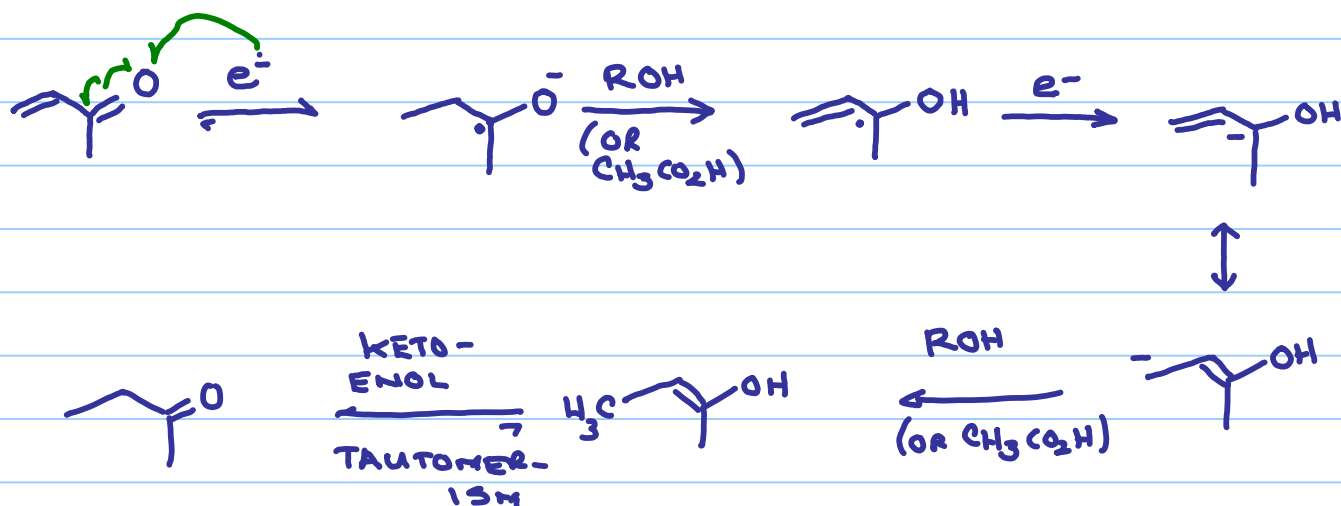
Note Title

3/19/2017

- THE Zn, CH_3CO_2H WILL ALSO REDUCE α, β -UNSAT. KETONES
- NOTE: BIRCH-TYPE CONDITIONS WILL ALSO DO THIS LATTER REDUCTION



MECH.



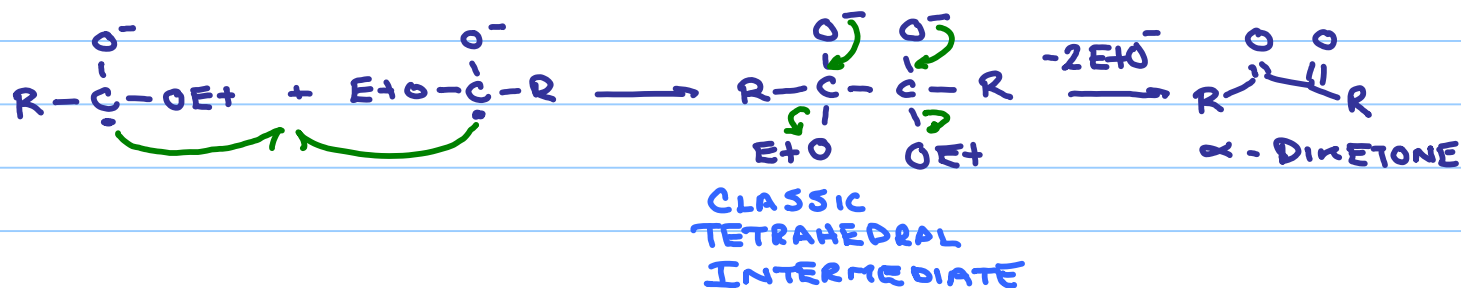
- THESE GROUPS ARE MUCH MORE EASILY REDUCED THAN THE KETONE ITSELF
- \therefore WON'T SURVIVE CLEMMENSEN EITHER

3) ACYLOIN CONDENSATION

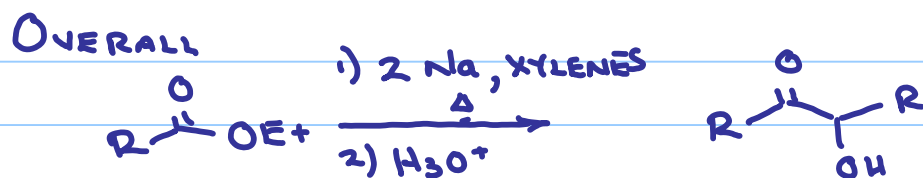
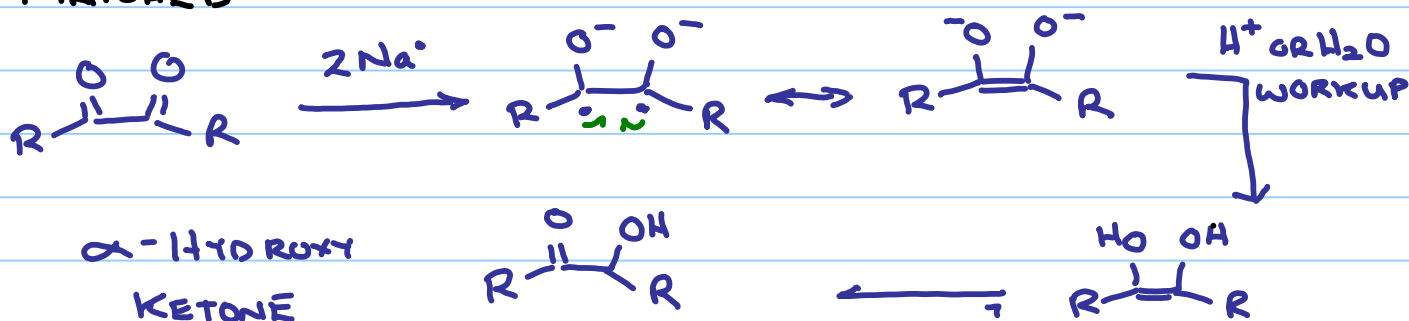
- ESTERS SURVIVED EARLIER 'DISSOLVING METAL' REDUCTIONS, BUT THEY ARE NOT INFINITELY STABLE
- UNDER SLIGHTLY MORE FORCING CONDITIONS, AND IF YOU LEAVE OUT THE PROTONATING ROH



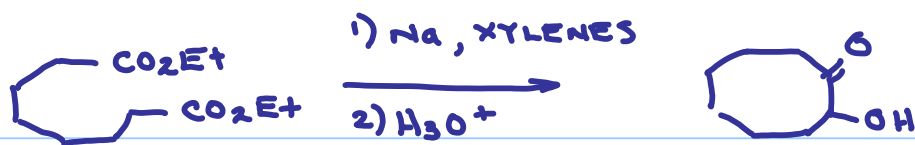
SINCE THERE'S NO PROTON SOURCE, THESE RADICAL ANIONS INSTEAD DIMERIZE



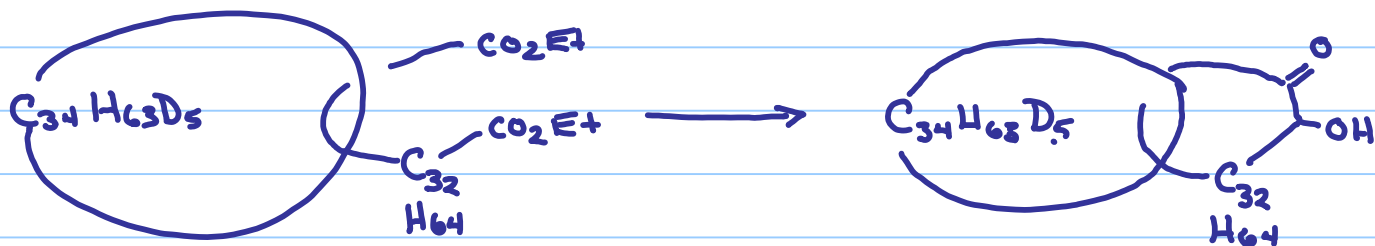
α -Diketone is unstable to rxn conds, so rxn isn't finished



- METAL - USUALLY Na OR K
- SOLVENTS - Et₂O, THF, BENZENE, TOLUENE, XYLENE
 - FOR HIGH MW ESTERS
- Me₃SiCl SOMETIMES ADDED
- TOUGH TO DO ACYLOINS BETWEEN TWO DIFFERENT ESTERS
 - ∴ R'S USUALLY THE SAME
- GOOD FOR RING CLOSING RXNS
- SINCE C-C BOND FORMING STEP IS IRREVERSIBLE, IT HAS OFTEN BEEN USED TO CLOSE UNCONVENTIONAL (LARGE) RINGS, IN ADDITION TO NORMAL SIZES

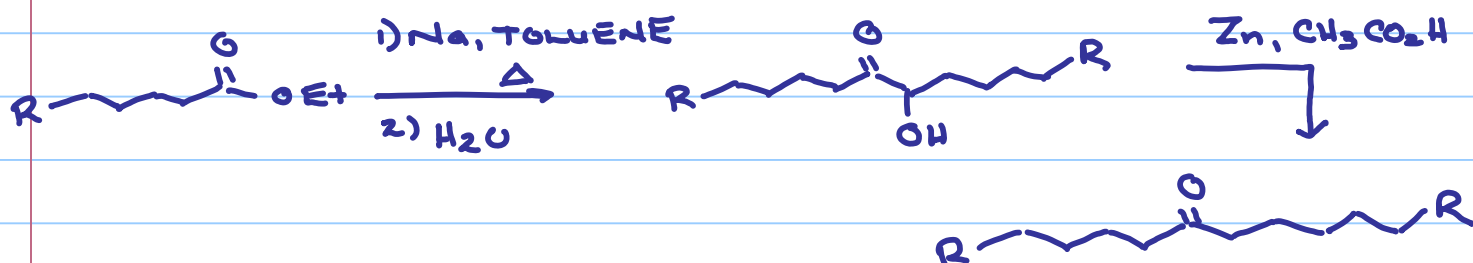


- AND ... THE FIRST CATENANE SYNTH EVER ...



WASSERMAN, U. J. Am. Chem. Soc. 1960, 82, 4433.

- AND .. THE ACYLOIN IS OFTEN PARTNERED WITH THE Zn, CH₃CO₂H METAL-ACID REDM



- FINAL COMMENTS

- WE'VE SPENT MUCH TIME ON WAYS TO MAKE 1,3- AND 1,5-DIOXYGENATED COMPOUNDS

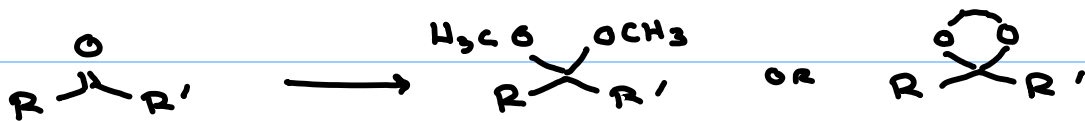
- 1,2- AND 1,4- DIOXYGENATED SYSTEMS ARE HARDER TO GET AT ...

- THIS IS OUR 1ST 1,2-DIOXO SYSTEM

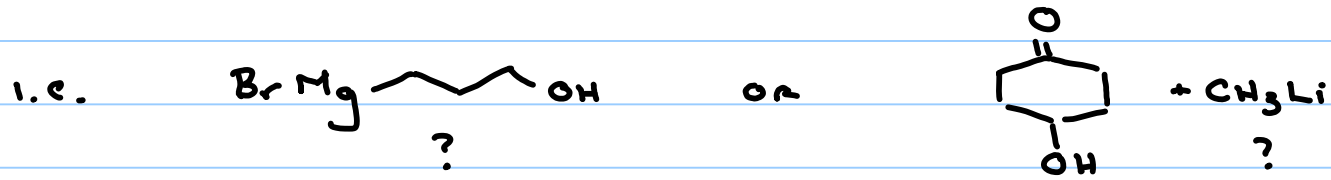
ALCOHOL PROTECTIN GROUP(S)

- A BIT OF A 'TIME OUT' FROM RED'S + OXID'S.

- RECALL HOW WE PROTECTED ALDEHYDES + KETONES FROM MANY RXNS BY MAKING AN ACETAL



- THE ANALOGOUS PROTECTING IS SOMETIMES NEEDED FOR ALCOHOL



- BOTH WOULD HAVE PROBLEMS

- MANY WAYS OF PROTECTING ALCOHOLS

- USUALLY AS A TYPE OF ETHER

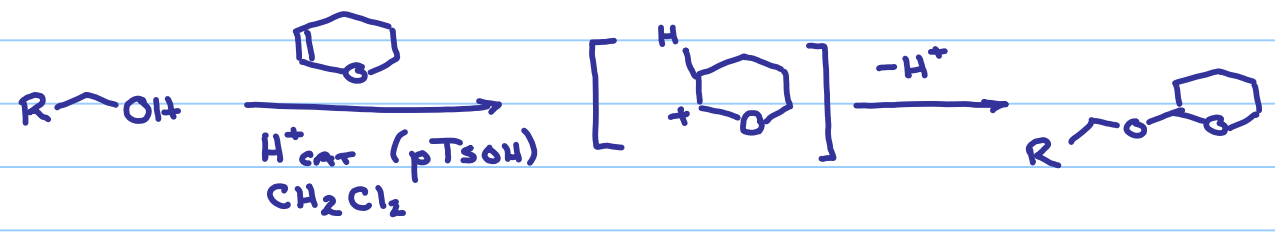
- I'LL GIVE ONE



TETRAHYDOPYRANYL (THP) ETHER

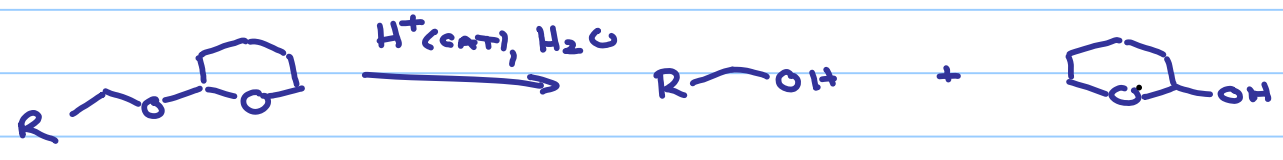
- REALLY ANOTHER TYPE OF ACETAL

- MADE BY

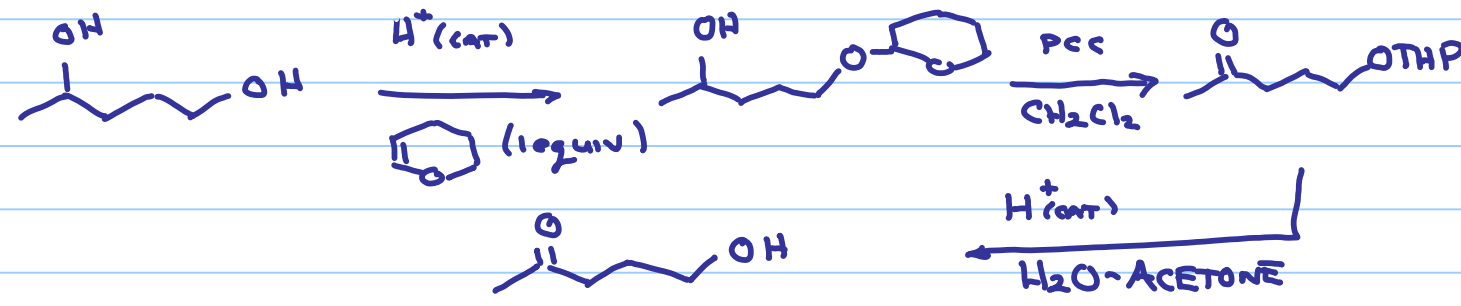


- THESE ARE LIKE MOST OTHER ACETALS - STABLE TO R-Li , R-MgBr , LiAlH_4 , BASES, NON-ACIDIC OXIDANTS

- WHEN DONE WITH IT



- ALSO, 1° ALCOHOLS FORM EASIEST, SO



OXIDATIONS - NON TRADITIONAL.

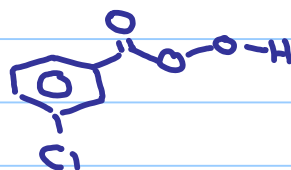
Note Title

3/21/2017

1) EPOXIDATION

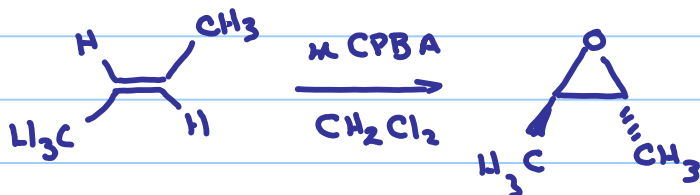
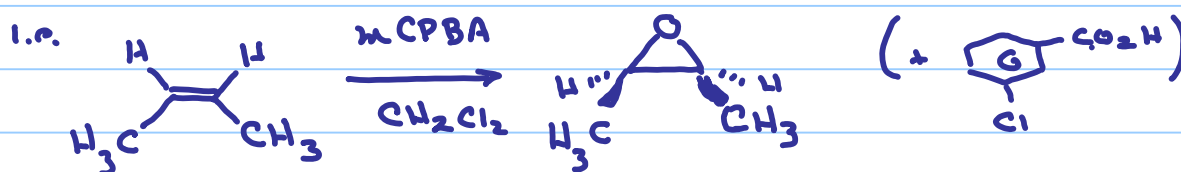
PERACIDS - HAVE THE STRUCTURE $R-\overset{\text{O}}{\parallel}{C}-O-O-H$
I.E. AN ESTER USING H_2O_2

MOST COMMON ONE

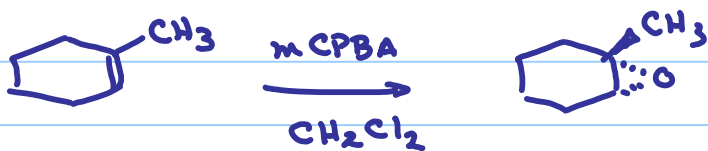


meta-CHLOROPEROXY-
BENZOIC ACID
mCPBA

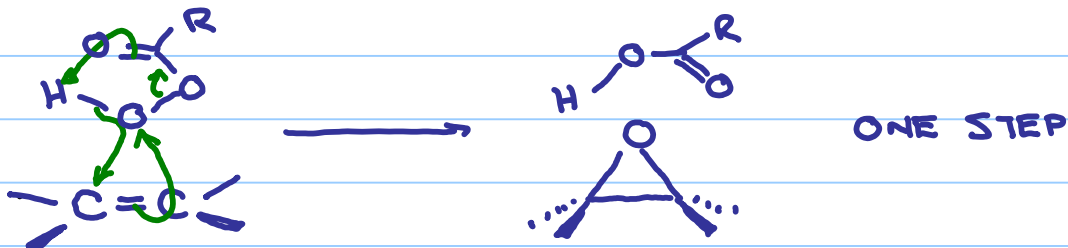
REACT \bar{w} ALKENES TO FORM EPOXIDES (OXIRANES).



NOTE: THE ADDN.
IS STEREOSPECIFIC
AND CIS.

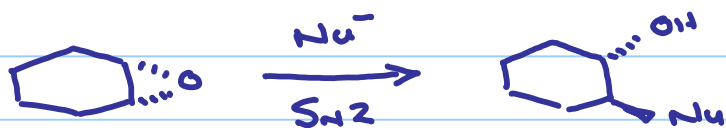


- THE MECHANISM IS CONCERTED - ALL BOND MAKING AND BREAKING EVENTS OCCUR SIMULTANEOUSLY



USE - REACTIONS OF EPOXIDES IN RING OPENINGS

1) RXNS WITH NUCLEOPHILES

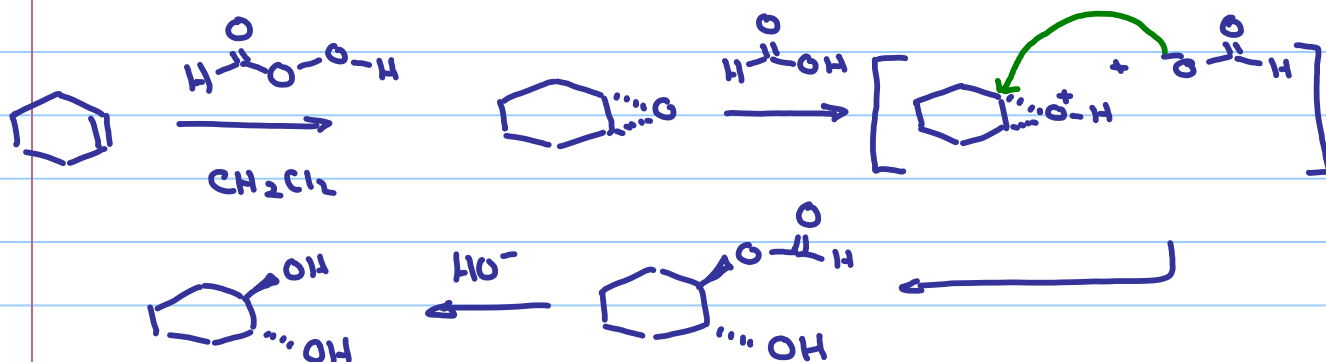


$\text{Nu}^- = \text{HALIDE ION}, \text{SR}^-, \text{H}_2\text{NR}, \text{ENOLATES}, \text{R}_2\text{CuLi}, \text{LiAlH}_4$

NOTE: RXNS WITH CUPRATES, ENOLATES OFTEN GO BETTER WITH BF_3 ADDED.

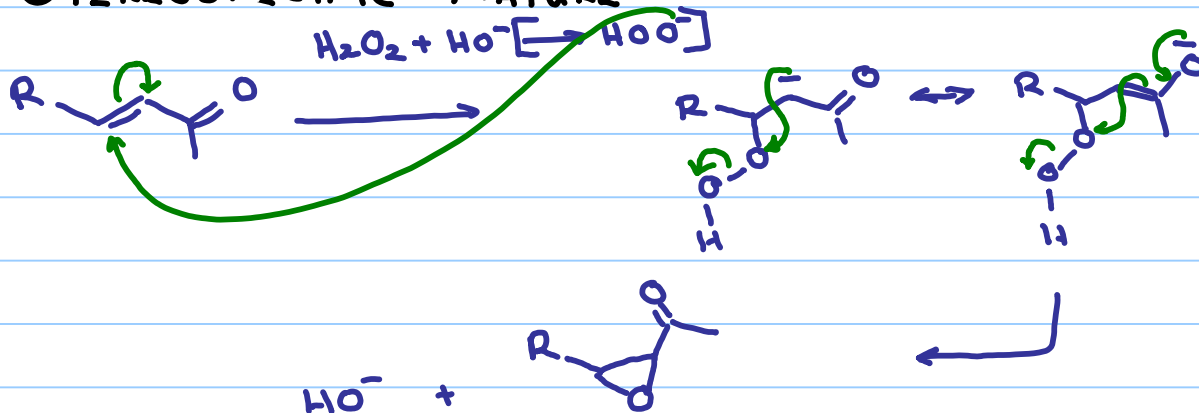
2) SPECIFIC FOR OXYGEN NUCLEOPHILES

- OFTEN DONE IN ONE STEP BY USING PERFORMIC ACID FOR EPOXIDATION



NOTE: ELECTRON DEFICIENT ALKENES OFTEN DON'T EPOXIDIZE WELL WITH mCPBA

- CAN DO IT WITH H_2O_2 AND HO^- , BUT LOSE THE STEREOSPECIFIC NATURE

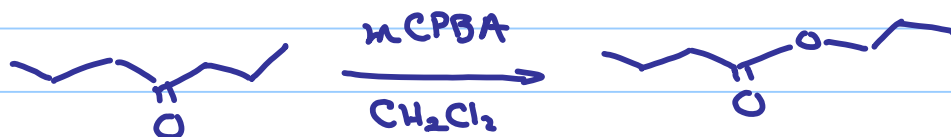
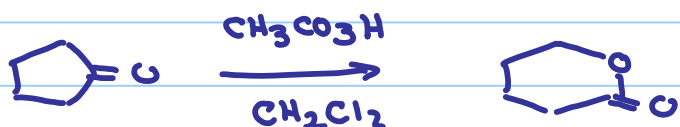


2) BAEYER-VILLIGER OXIDATION

- THIS IS SLOWER, BUT KETONES WILL ALSO REACT W/ PERACIDS

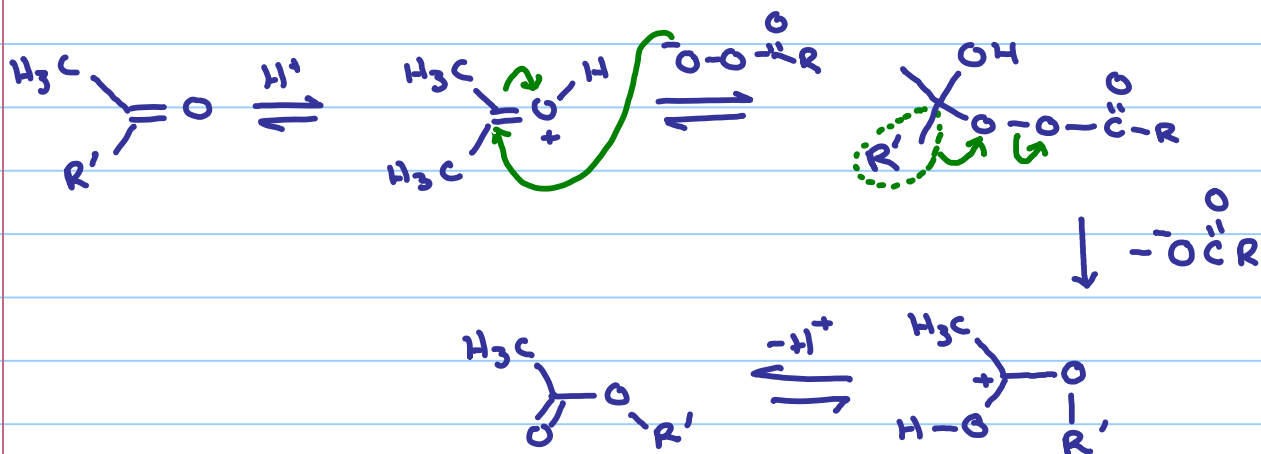
- GIVES ESTERS, OR LACTONES IN CYCLIC CASES

- RXN AMOUNTS TO STUFFING AN 'O' ATOM BETWEEN CARBONYL CARBON, AND THE α -CARBON



MECH: FORM TRANSIENT HEMI ACETAL USING THE PERACID, THEN DO A 'NUCLEOPHILIC' REARRANGEMENT

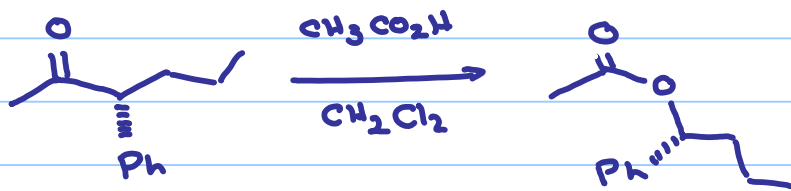
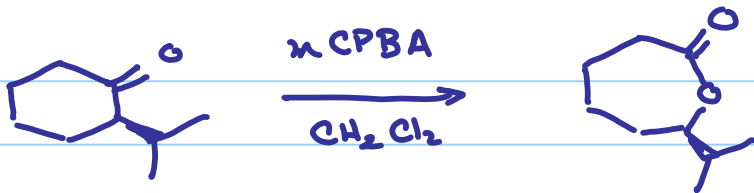
- WE'LL SEE MORE OF THESE AT COURSE'S END



- SINCE THE MI RATING R' HAS SOME δ^+ IN THE T.S.[‡] FOR MIGRATION, IT'S SPED UP BY EDG'S.

i.e. $3^\circ > 2^\circ \approx \text{aryl} > 1^\circ > \text{METHYL}$

- SINCE THE MIGRATING R' NEVER DISSOCIATES ENTIRELY DURING REARR - RETENTION OF CONFIG. IF CHIRAL



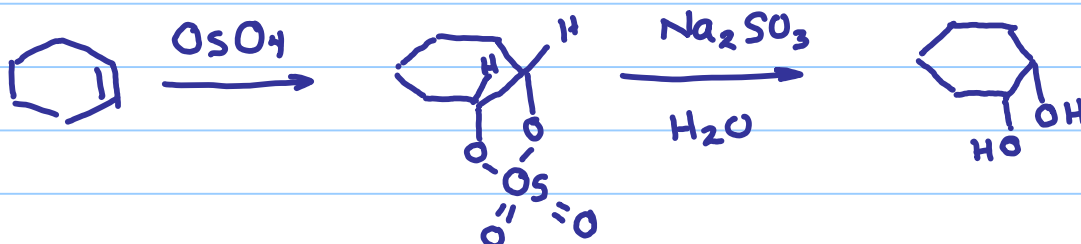
OTHER OXIDATIONS, CONT'D.

Note Title

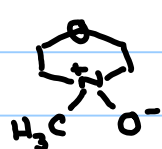
3/23/2017

OsO_4

- OSMIUM TETROXIDE ADDS TO ALKENES \Rightarrow DIOL
- ADDN IS IN A CIS FASHION



- ADDN IS FROM LESS HINDERED SIDE
- OsO_4 AMOUNT CAN BE MADE CATALYTIC BY USING



(NMO = N-METHYLMORPHOLINE N-OXIDE.)

AS STOICHIOMETRIC OXIDANT

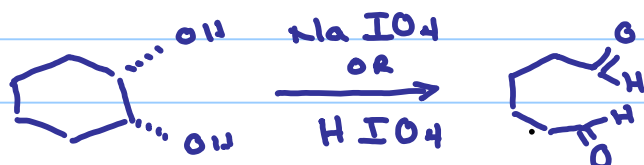
MECH. - 4th YR - BUT AN EASILY DIGESTIBLE LIE IS...

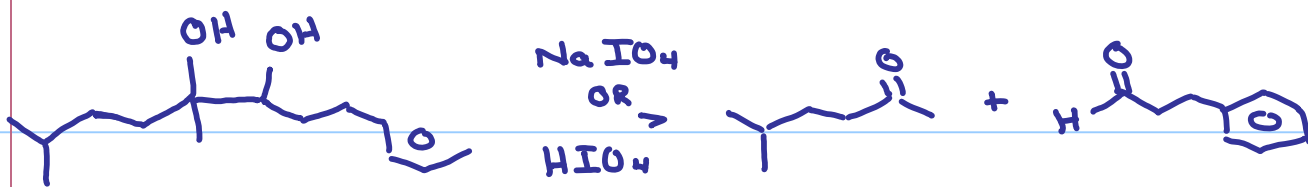


1,2-DIOLS OFTEN ENCOUNTERED IN SYNTHESIS

PERIODIC ACID OXIDATION

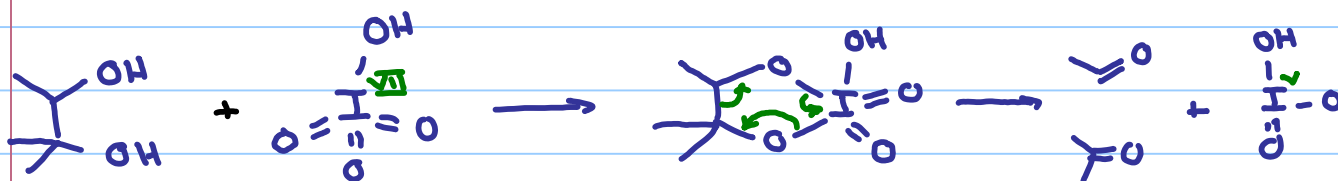
- OFTEN PAIRED WITH ABOVE OXIDATION
- USES NaIO_4 OR HIO_4 TO CLEAVE σ BOND BETWEEN 1,2-DIOL





PRODUCT 2 KETONES OR ALDS (OR 1 OF EACH)

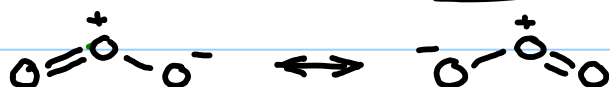
- PROBABLE MECHANISM -



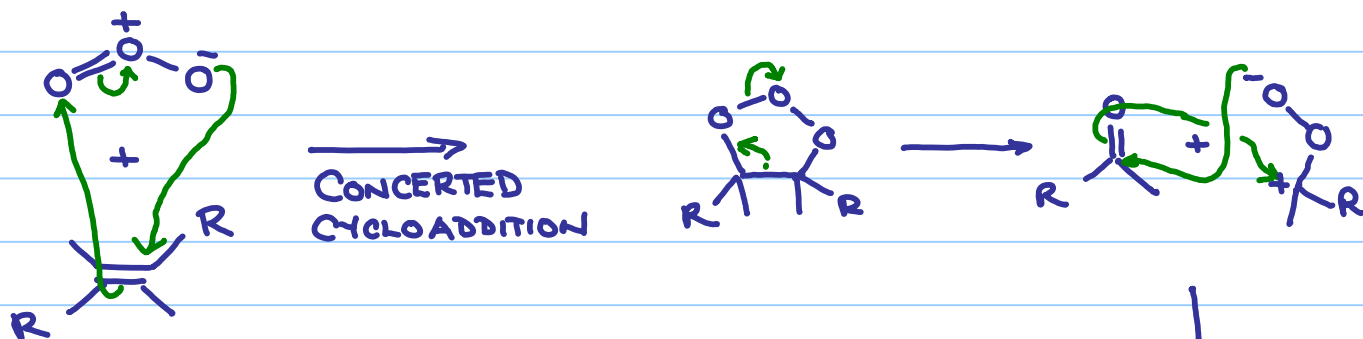
OZONOLYSIS -

- DOES THESE TWO REACTIONS (CLEAVAGE OF C=C)
ALL IN ONE OPERATION

OZONE O_3 - VERY STRONG ELECTROPHILE

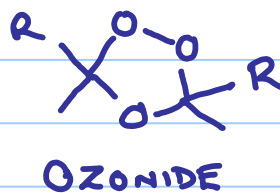


- A V. EXTENDED MECH FOR IT'S RXN W ALKENES



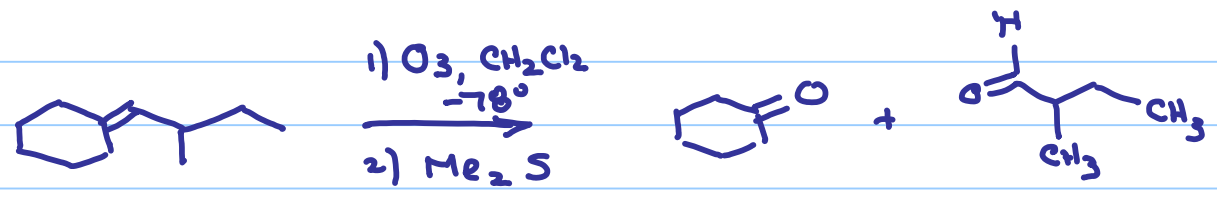
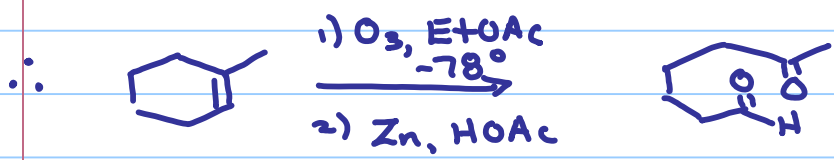
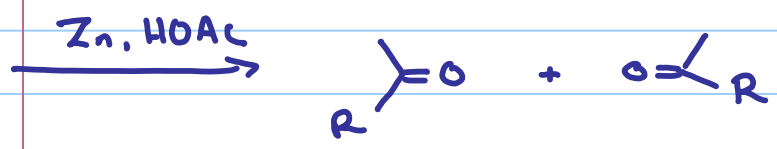
- OZONIDES ARE STABLE ENOUGH TO ISOLATE -

BARELY



- IN GENERAL THE NOT. V. STABLE O-O BOND IS CLEAVED TO GIVE 2 CARBONYLS

- NORMALLY $Zn + CH_3CO_2H$ OR Me_2S



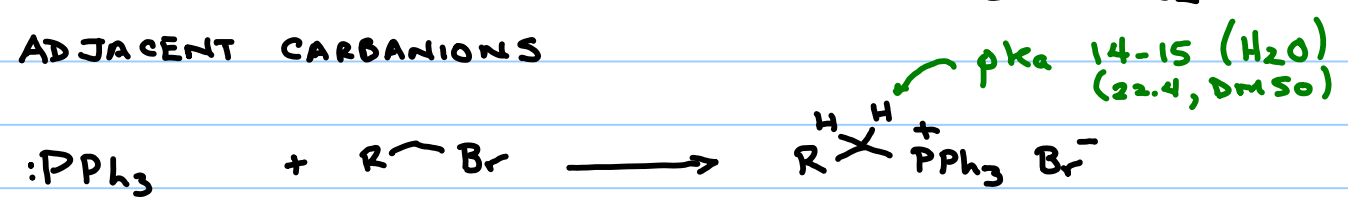
OZONE VERY REACTIVE \therefore RXN DONE AT -78° IN RELATIVELY INERT SOLVENTS (ETHYL ACETATE, CH_2Cl_2 , CH_3OH)

- STILL OXIDIZES ALDEHYDES, AMINES AT -78°
- OXIDIZES BENZENES AT ROOM TEMP.

OTHER RXNS

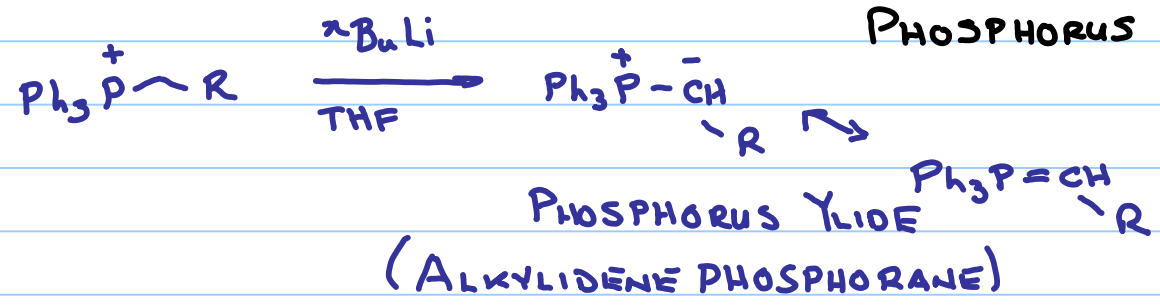
WITTIG RXN

- USES FACT THAT 3RD ROW ELEMENTS STABILIZE ADJACENT CARBANIONS



NUCLEOPHILIC

PHOSPHONIUM SALT
- ACIDIC H'S NEXT TO PHOSPHORUS

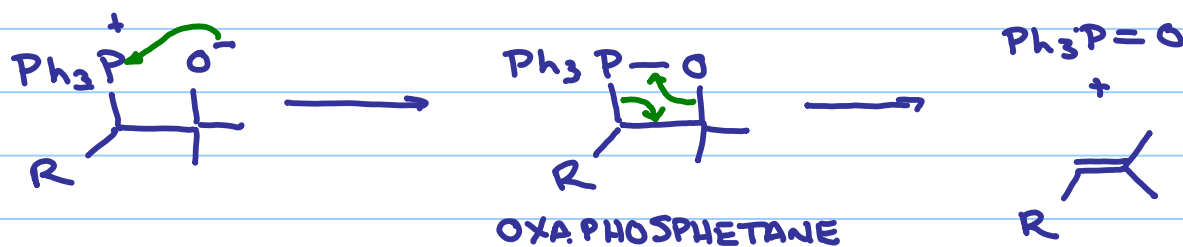


- Now, A LIE THAT WAS ACCEPTED FOR YEARS AND THAT I'LL PROPAGATE FOR A FEW MINUTES

- YLIDE NUCLEOPHILIC ENOUGH TO ATTACK ALDEHYDES + KETONES

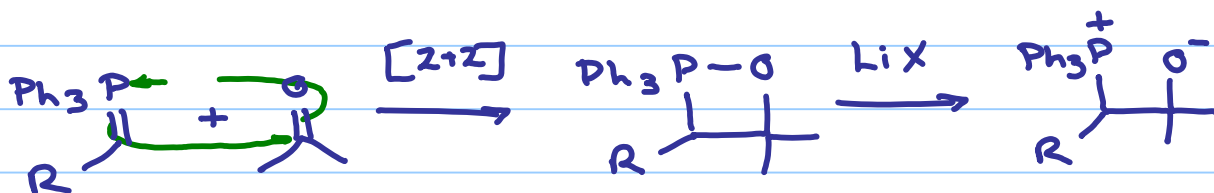


- THE CPDS ELIMINATE $\text{Ph}_3\text{P}^+ \text{---} \text{O}^- \leftrightarrow \text{Ph}_3\text{P}=\text{O}$ (TRIPHENYL PHOSPHINE OXIDE) WITH SLIGHT HEATING



OVERALL REPLACEMENT OF $\text{C}=\text{O}$ WITH $\text{C}=\text{C}$

- THE LIE ? - MOST PEOPLE NOW AGREE THAT THE 1ST STEP IS A 2+2 CYCLOADDITION TO GIVE THE OXAPHOSPHETANE, WHICH OPENS TO THE BETAINE WHEN LiX IS PRESENT



- CHEMICALLY EXTREMELY USEFUL

CONT'D

WITTIG, CONTD.

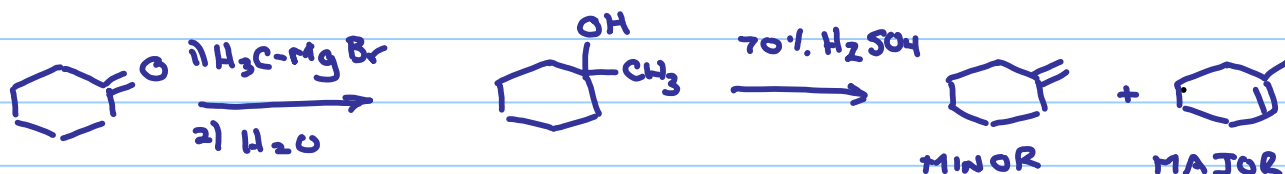
Note Title

3/24/2017

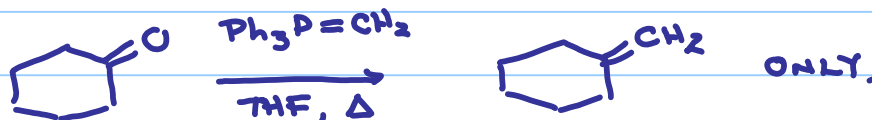
- USE OF WITTIG.

- ONE OF IT'S GREAT ADVANTAGES IS THAT ONE ALWAYS KNOWS WHERE EXACTLY THE C=C ENDS UP

- LET'S COMPARE TO GRIGNARD / E1 ELIMINATION

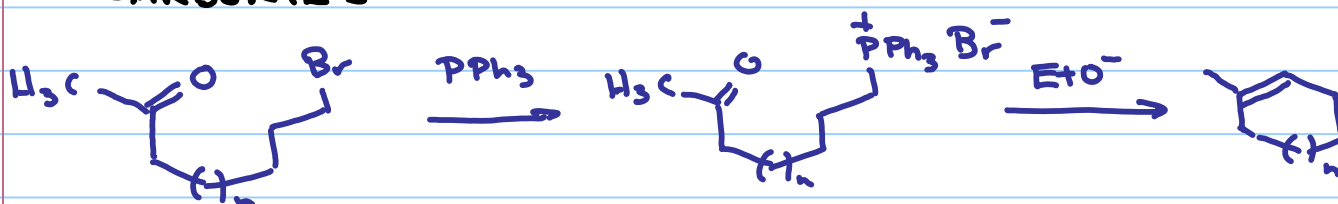


VERSUS



- A FEW TRICKS

i) - INTRAMOLECULAR RXNS ? - YES, SINCE THE PHOSPHONIUM SALT PRECURSOR IS MORE ACIDIC THAN MOST CARBONYLS

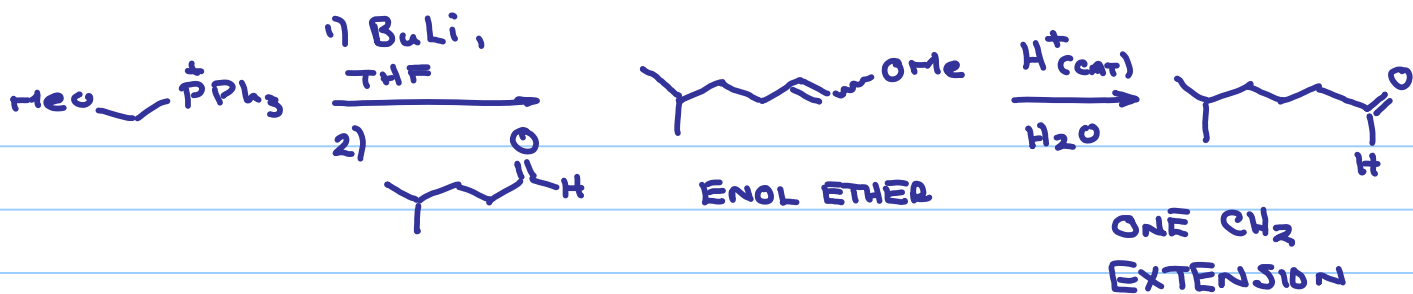


- LARGE RING SIZES CAN BE MADE, TOO

ii) A ONE CARBON EXTENSION THAT IS A DARZENS REPLACEMENT



CHLOROMETHYL
METHYL ETHER



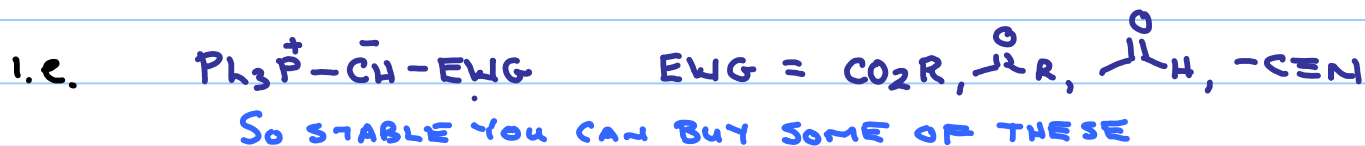
(iii) CAN WE PUT AN EWG ON PHOSPHORUS YLIDE & COMPETE W/ BASE CATAL. ALDOL?

- YES, WITH AN ASTERISK

- AS IT IS, ALDEHYDES & KETONES ARE THE PARTNERS FOR WITTIGS - ESTERS, AMIDES, ETC. AREN'T REACTIVE ENOUGH.

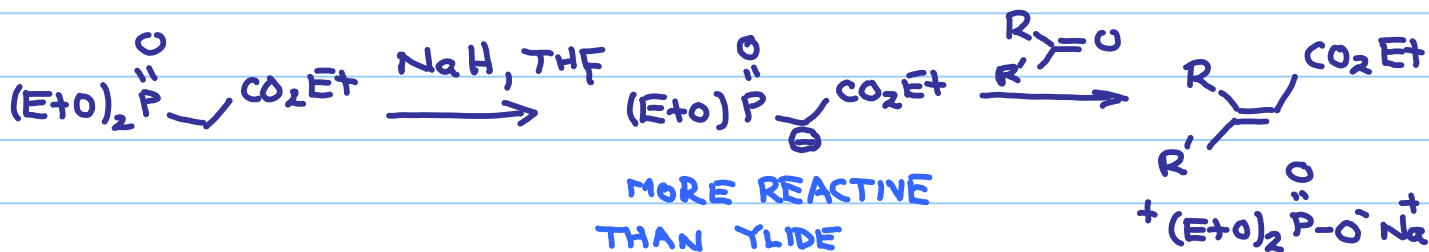
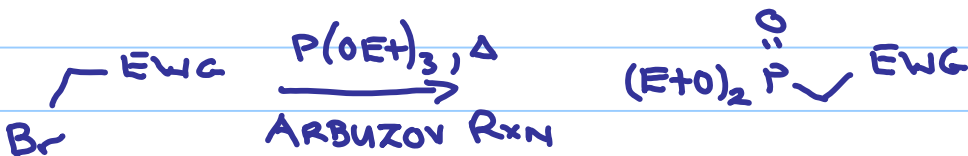
- WITH AN EWG PRESENT, ANION IS SO STABILIZED THAT REACTIVITY IS LOWERED

- ALDEHYDE USUALLY OK STILL, BUT KETONES ARE NOW JUST TOO UNREACTIVE



SOLUTION:

GO TO A SLIGHTLY LESS ANION STABILIZING PHOSPHORUS BASED GROUP
 - PHOSPHONATE ESTER

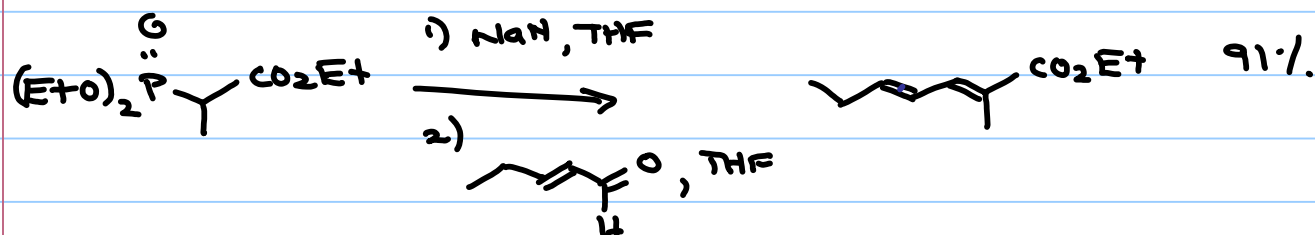


- ALDEHYDES & KETONES NOW REACT NICELY

THIS VARIATION HAS A NEW NAME.

(ANY TWO OR MORE OF...) WADSWORTH-HORNER-EMMONS RXN.
(OR HWE RXN)

- FRANKLY, IN MANY CASES, THIS IS MORE FOOLPROOF
THAN THE BASE CATALYZED ALDOL.



- A WORD ON STEREOCHEMISTRY

- THE UNSTABILIZED ONES ACTUALLY GIVE MOSTLY
(Z)-STEREOCHEMISTRY R = ALKYL

- THE STABILIZED ONES (R = EWG) OR HWE VERSION
NORMALLY GIVE (E)-ISOMERS

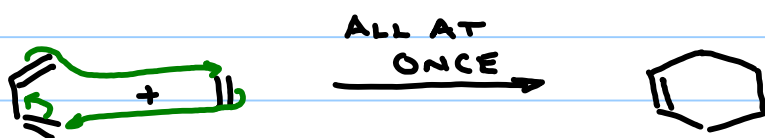
- REASONING BEYOND OUR SCOPE & TIME

DIELS-ALDER RX.

Note Title

3/28/2017

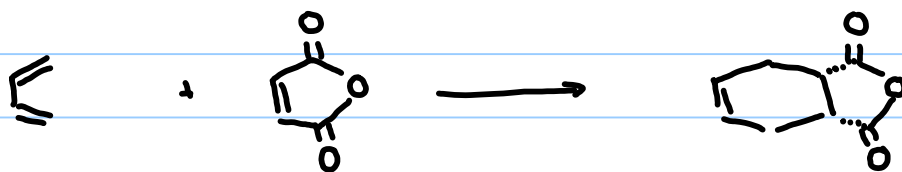
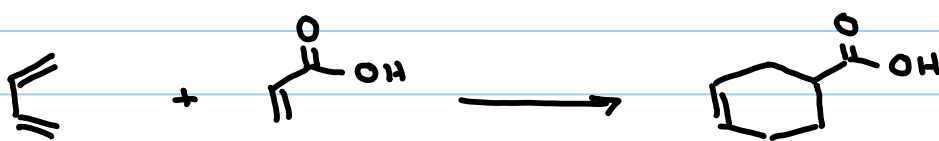
- THIS IS THE MOST WELL KNOWN AND PERHAPS THE MOST IMPORTANT OF ALL THE CONCERTED CYCLOADDN. REACTIONS.
- RXN. OF A CONJUGATED DIENE AND A DIENOPHILE (MOST OFTEN AN ALKENE) TO GIVE A CYCLOHEXENE IN ONE STEP



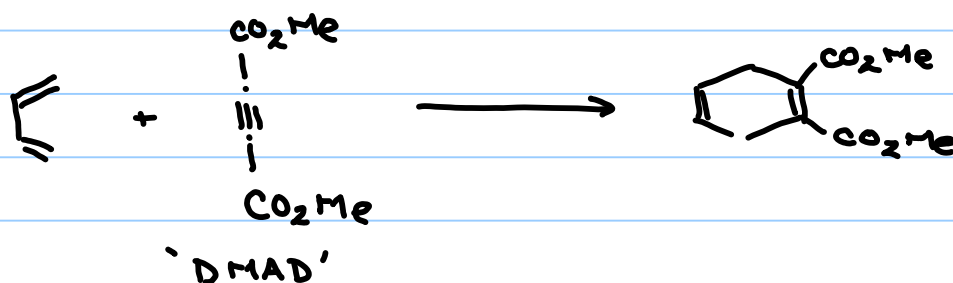
REQUIREMENTS

i) DIENOPHILE

- ETHENE ITSELF IS POOR
- NEED A CONJUGATING GROUP, USUALLY AN EWG (-M) GROUP - THEN IT WORKS WELL

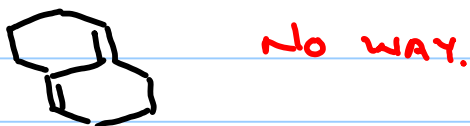
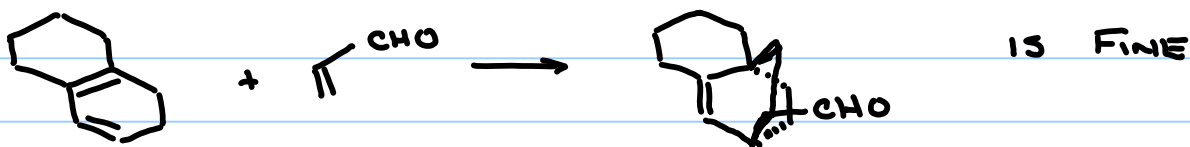
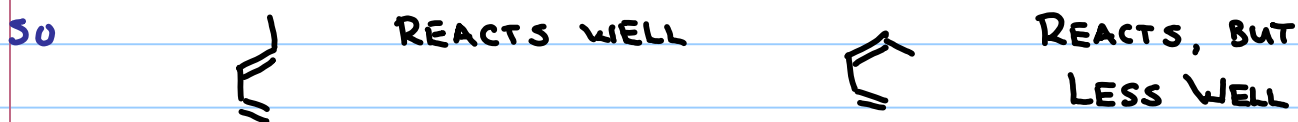
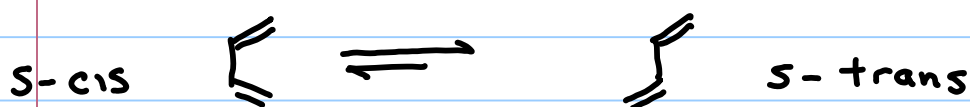


- DIENOPHILE CAN ABSOLUTELY BE AN ALKYNE




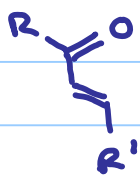
ii) THE DIENE - TWO REQUIREMENTS

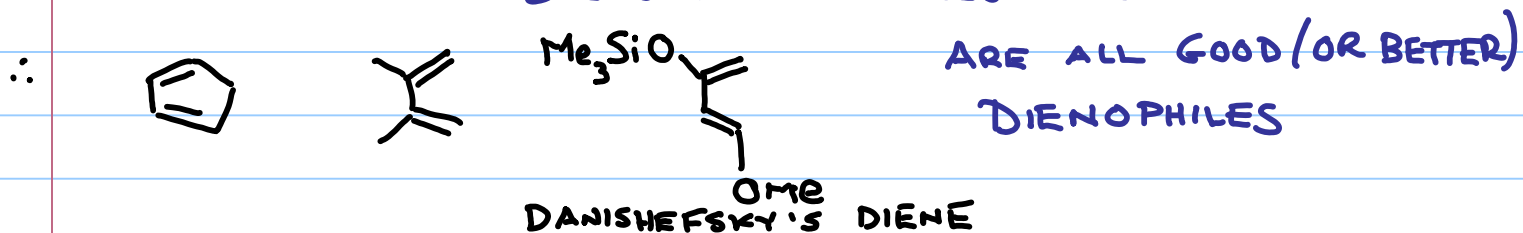
- a) - DIENE MUST BE CONJUGATED
 - MUST BE ABLE TO ATTAIN AN S-CIS CONFORMATION,
 SOME OF THE TIME
 (ENDS OF DIENE MUST BE ABLE TO REACH ENDS OF
 DIENOPHILE SIMULTANEOUSLY)
 - BUTADIENE ITSELF IS OK, BUT EDG'S (+M OR +I)
 ENHANCE REACTIVITY
 - DIENE CAN BE CYCLIC OR ACYCLIC



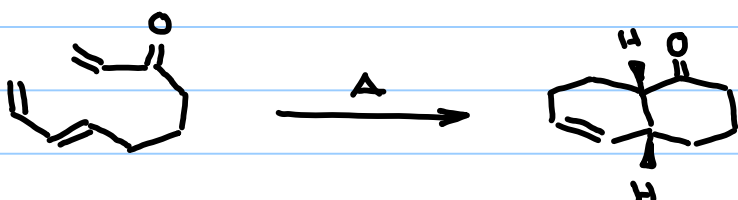
BENZENE DOES NOT REACT - TOO MUCH AROMATIC
 STABILIZATION TO OVERCOME

- FURAN  HOWEVER, IS LESS AROMATIC AND IS A
 DECENT DIELS-ALDER DIENE

 HETEROATOMS CAN BE PART OF DIENE, BUT WILL
 NOT BE PART OF OUR FOCUS
 (HETERO-DIELS-ALDER CYCLOADDN)



- MANY, MANY, MANY INTRAMOLECULAR EXAMPLES
I.E. DIENE, DIENOPHILE ARE IN SAME MOLECULE

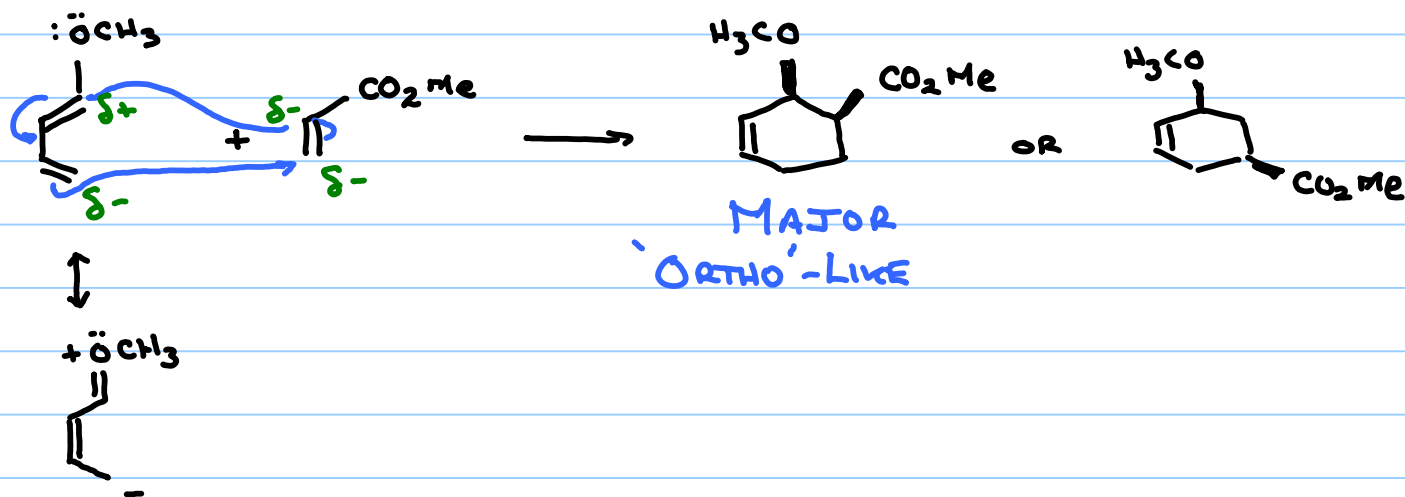


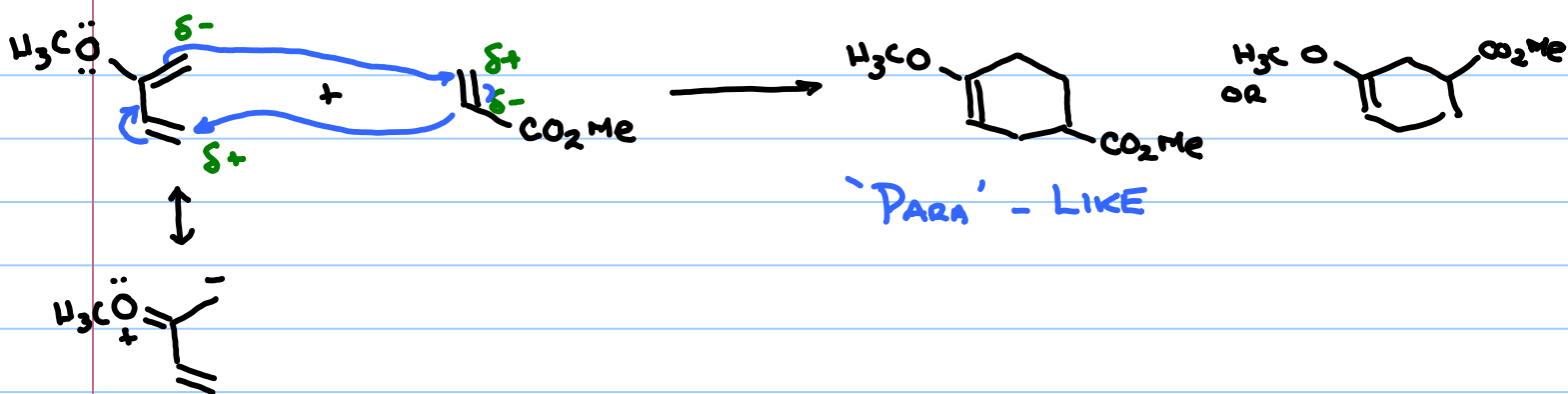
REGIOCHEMISTRY AND STEREOCHEMISTRY

- WHICH END BONDS WHICH, AND HOW THE STEREOCHEMISTRY PLAYS OUT, IS DETERMINED BY THE FRONTIER MOLECULAR ORBITALS OF THE DIENE + DIENOPHILE
- HOWEVER, WE CAN GO A LONG WAY BEFORE WE INVOKE THOSE

REGIOCHEMISTRY

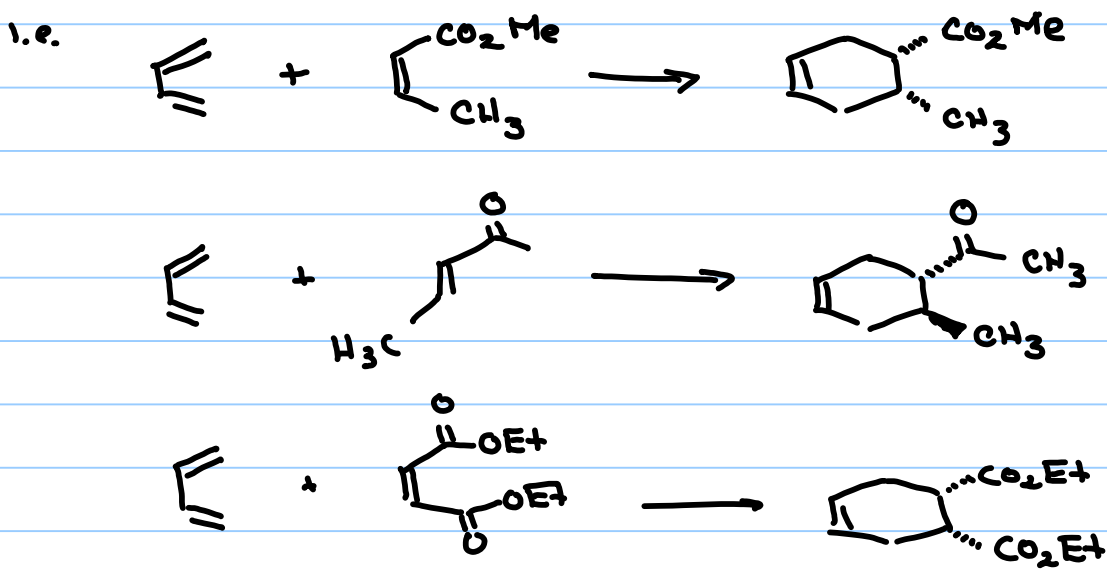
- NORMALLY FOLLOWS ORTHO/PARA RULE
- WE'LL CONSIDER THE TWO POSSIBILITIES, KEEPING IN MIND THAT DIENE NORMALLY HAS EDG
DIENOPHILE NORMALLY HAS EWG





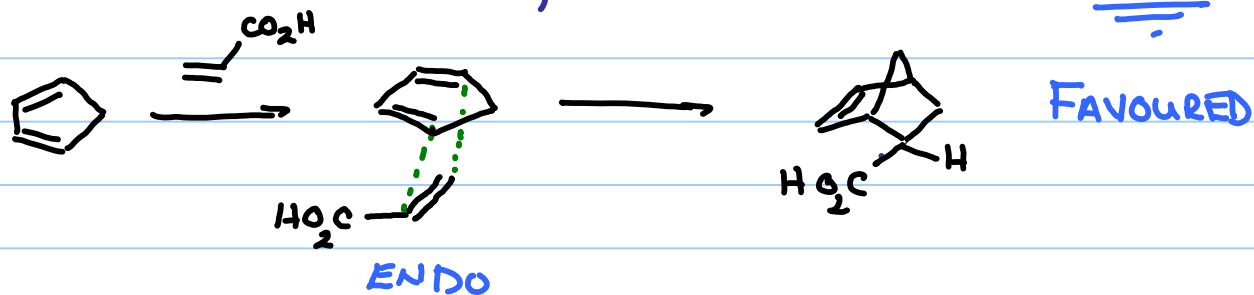
STEREOCHEMISTRY

i) WITH RESPECT TO DIENOPHILE, RXN IS STEREOSPECIFIC AND SYN-

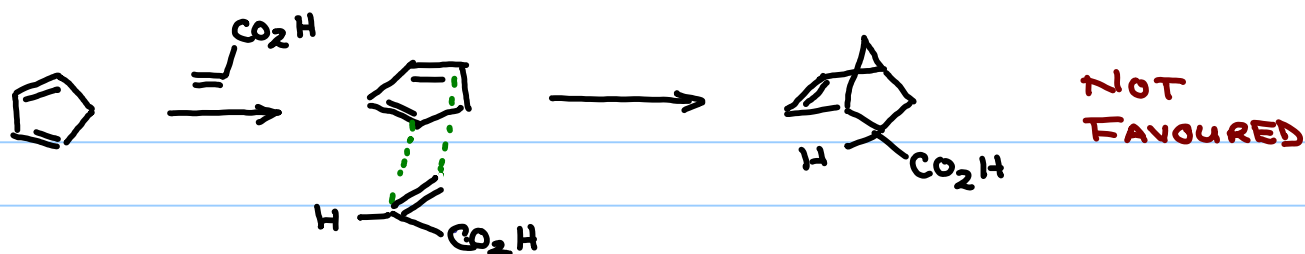


ii) ENDO VERSUS EXO ADDITION

- ASSUMING THE GROUP ON THE DIENOPHILE HAS A π -SYSTEM, IT'S PREFERENCE IS ENDO

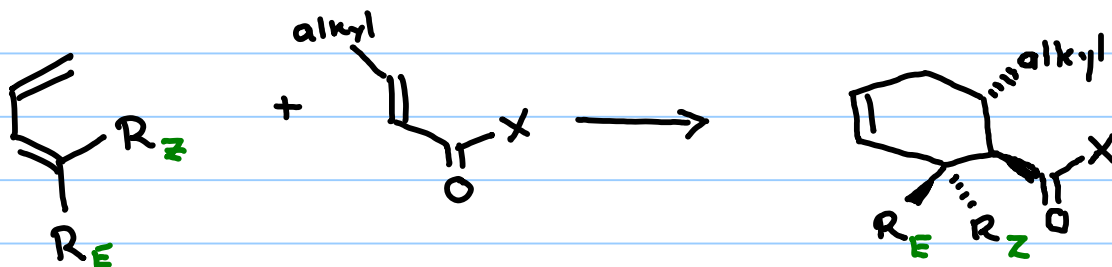


EWG is 'under' pi-system



EXO EWG 'outside', away from pi-system

- So WHAT NORMALLY RESULTS IS.....



R_E ON DIENE CIS TO EWG ON DIENOPHILE

R_Z ON DIENE TRANS TO EWG ON DIENOPHILE

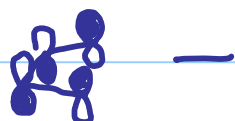
DIELS-ALDER, CONT'D.

Note Title

3/31/2017

- FRONTIER MOLECULAR ORBITALS CONTROL THE CYCLOADDITION, SINCE IT IS A CONCERTED PROCESS
- DIENE IS USUALLY e^- RICH \therefore HOMO DOMINATES
- DIENOPHILE IS USUALLY e^- POOR \therefore LUMO DOMINATES

DIENE MO'S



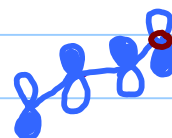
LUMO



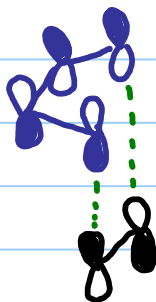
NOTE FOR



IT'S



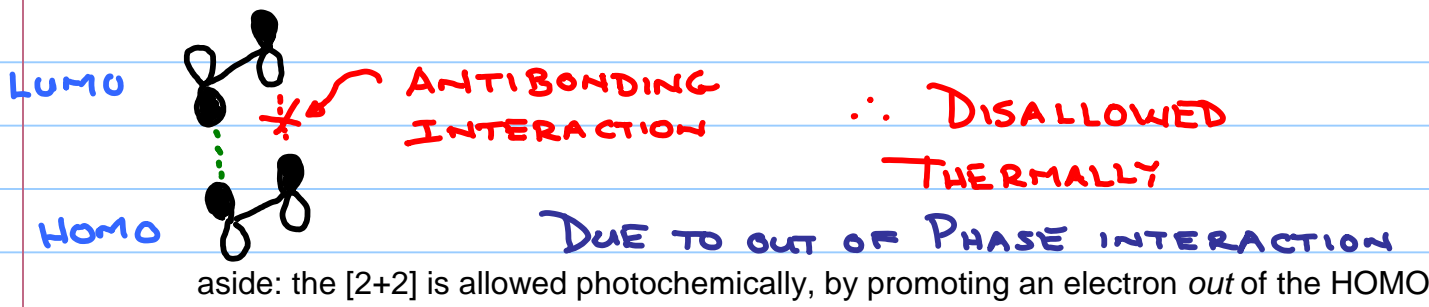
- IF WE BRING HOMO/DIENE + LUMO/DIENOPHILE TOGETHER



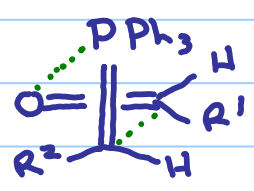
- EACH INTERACTION IS 'IN PHASE'
- \therefore BONDING / ENERGY LOWERING

\therefore CONCERTED RXN IS ALLOWED THERMALLY FOR [4+2] CYCLOADDS.

- ON THE OTHER HAND, A [2+2] CYCLOADDITION IS DISALLOWED THERMALLY



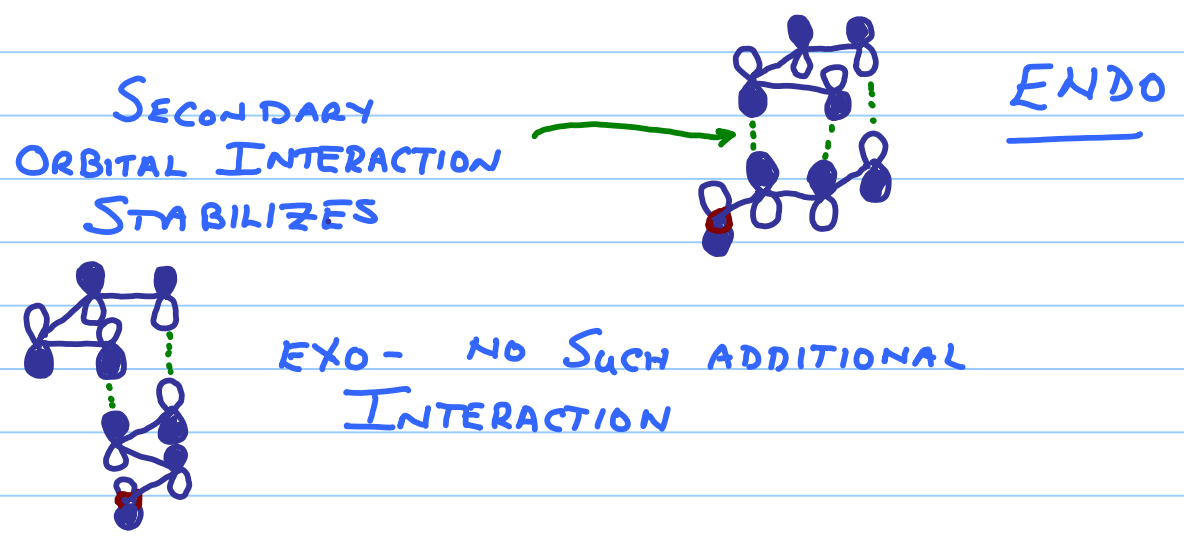
- SO WHY DOES WITTIG RXN 2+2 OCCUR?
- P 3RD ROW ELEMENT



- BOND LONG ENOUGH FOR ANTARAFACIAL PROCESS CAN OCCUR (I.E. ONE FACE OF YLIDE CAN 'REACH' BOTH FACES OF CARBONYL PARTNER)

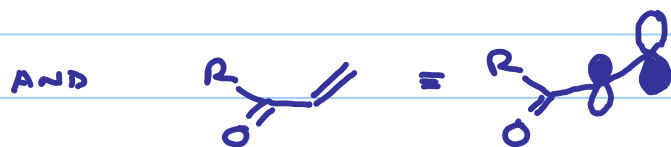
THE ENDO RULE

- FIRST OF ALL, WE MUST CONSIDER THE MORE COMPLETE VERSION OF THE DIENOPHILE, WITH THE EWG π -SYSTEM
- IF WE NOW BRING THAT LUMO UP UNDERNEATH THE 'DIENE HOMO, YOU CAN SEE A SECONDARY ORBITAL INTERACTION BETWEEN THE DIENOPHILE (AT THE 'CARBONYL' CARBON) AND C-2 OF THE DIENE. THIS IS AN IN-PHASE INTERACTION, MEANING BONDING / ENERGY LOWERING.
- THIS IS NOT AVAILABLE IN THE 'EXO'-MODE

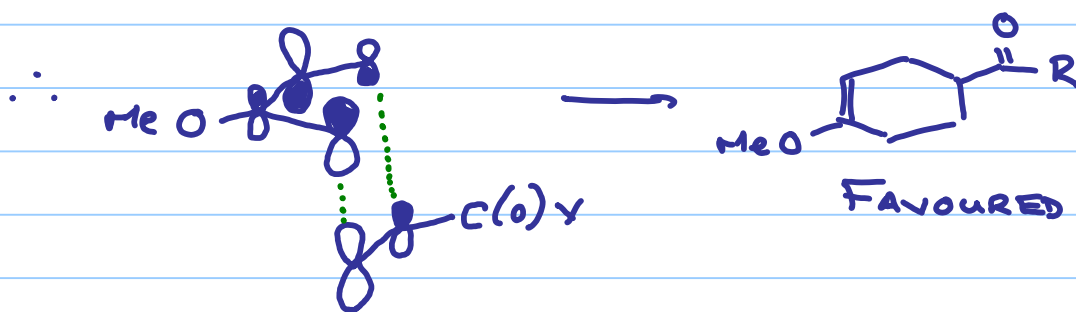


ORTHO/PARA RULE

- IN MORE DETAILED VERSION OF HOMO + LUMO ORBITALS, THE ELECTRON RICH (δ^-) ATOMS NORMALLY HAVE LARGER ORBITAL COEFFICIENTS IN THE HOMO
- THE ELECTRON POOR (δ^+) ATOMS HAVE LARGER COEFFICIENTS IN THE LUMO

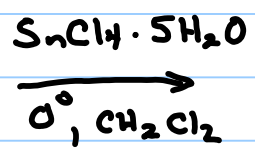
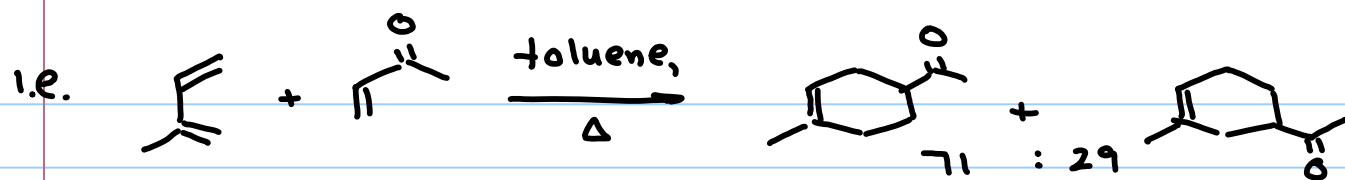


- AND IN THE TRANSITION STATE, THE LOWEST ENERGY SITUATION OCCURS WHERE THE LARGEST COEFFICIENT 'ENDS' OVERLAP.



- SOME FINAL POINTS

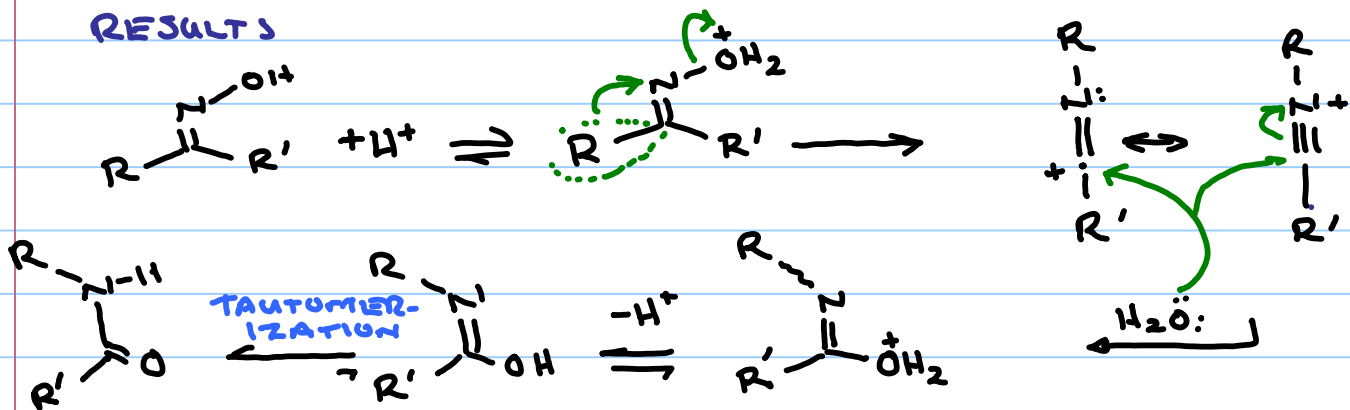
- EVERYTHING WE HAVE SAID IS ABOUT THE KINETIC D.A. RXN, BUT DIELS-ALDERS ARE OFTEN REVERSIBLE
- SOLVENT CAN BE ALMOST ANYTHING - EVEN NO SOLVENT VERSIONS ARE COMMON
- LEWIS ACIDS WILL OFTEN SPEED UP RXN VASTLY, BY MAKING THE EWG MORE e^- WITHDRAWING.



93 : 7

IN THE PRESENCE OF A STRONG ACID (H_2SO_4 , $pTSOH$) OR LEWIS ACID (PCl_5), THE OH PROTONATES, AND LEAVES - OF COURSE THIS WOULD GIVE A 6 VALENCE N^+ (EXTREMELY UNSTABLE - AND LIKELY TOO MUCH TO OCCUR) - SO AN ALKYL GROUP MIGRATES - THE MOST SUBSTITUTED ONE... SO AN AMIDE (OR LACTAM IN CYCLIC CASES)

RESULTS

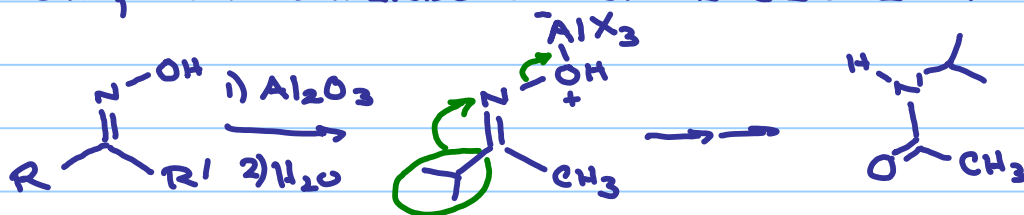


AMIDE / LACTAM

$R \quad 3^\circ > 2^\circ \approx \text{ARYL} > 1^\circ > \text{METHYL}$

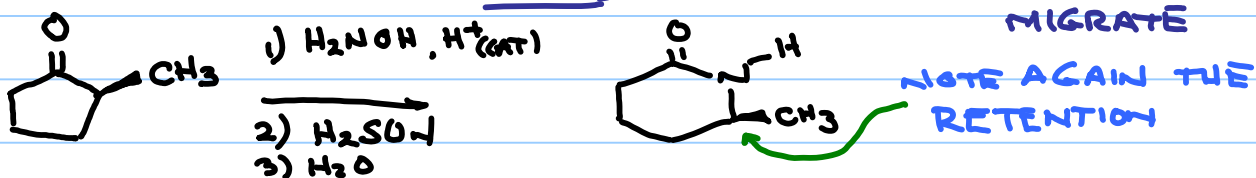
- IN STRONG ACIDS, THE OXIME IS UNDERGOING Z/E ISOMERIZATION, SO STEREOELECTRON EFFECTS ARE NOT EVIDENT

- WITH WEAKER LEWIS ACIDS, THOUGH, IT IS EVIDENT THAT THE GROUP THAT MIGRATES IS TRANS- TO THE OH, SO IT DEPENDS ON OXIME GEOMETRY



- OF COURSE IN MOST CASES THE OXIME IS MOSTLY (E)-, SO IT'S STILL NORMALLY THE LARGER GROUP MIGRATING

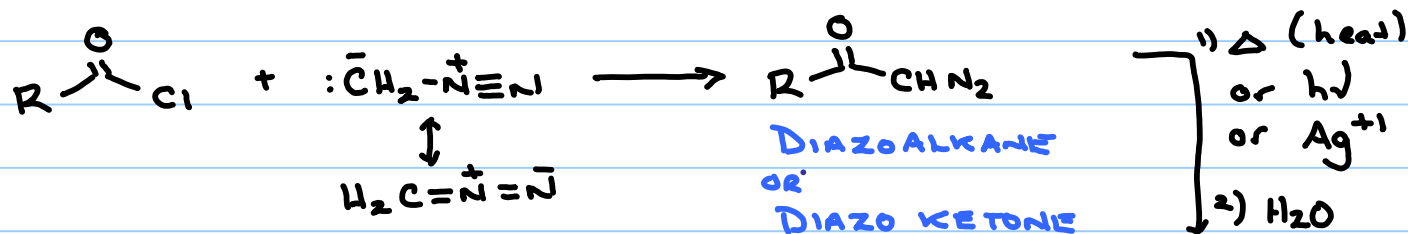
- BUT HERE YOU COULD MAKE THE SMALLER GROUP MIGRATE



ARNDT-EISSERT SYNTHESIS

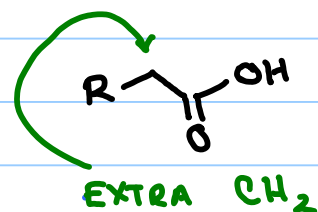
- ACTUALLY A TWO STEP PROCEDURE, WITH THE REARRANGEMENT PART CALLED THE WOLFF REARR.
- ACTUALLY IS THE EXTENSION OF A CARBOXYLIC ACID BY 1 C
- INVOLVES A CARBENE INTERMEDIATE

- WE'LL BEGIN WITH AN ACID CHLORIDE

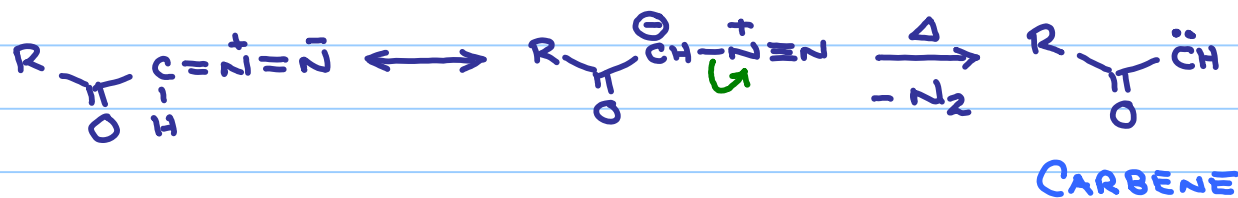


CH_2N_2 DIAZOMETHANE

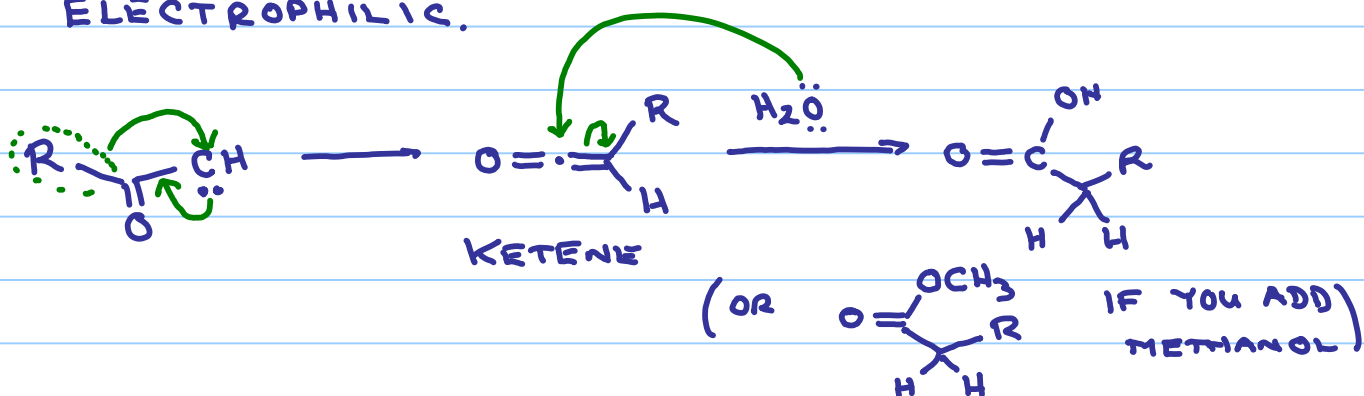
MILDLY NUCLEOPHILIC AT \underline{C}
 (OR BETTER $Me_3Si:CHN_2$)



MECH. OF REARR.



- CARBENE IS NEUTRAL, BUT 6 VALENCE C^{\cdot} CARBON
- 98% OF THEM ARE TRANSIENT INTERMEDIATES, AND ELECTROPHILIC.



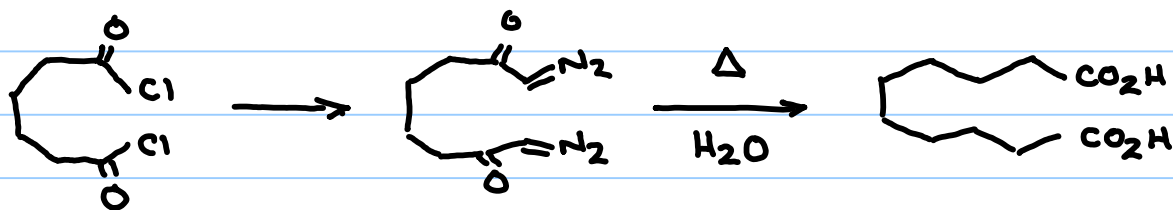
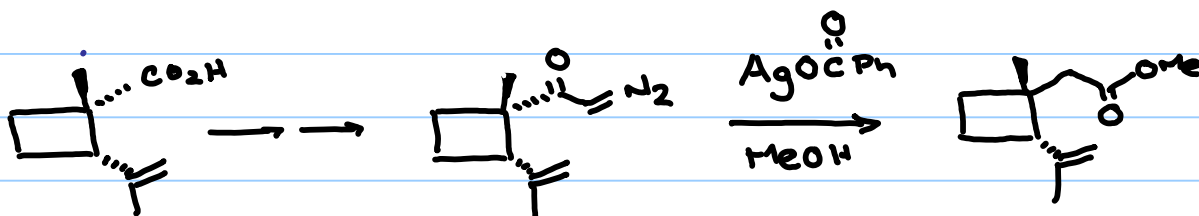
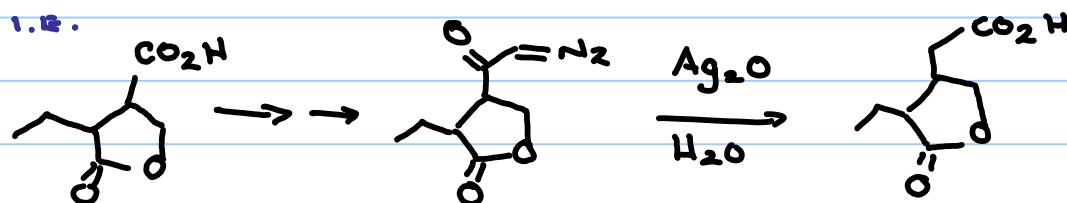
- ASIDE : THOSE 2% OF STABLE CARBENES TEND TO HAVE GROUPS DONATING AN e⁻ PAIR TO THE CARBENE CARBON, AND BULKY GROUPS



- THEN THESE TEND TO BE NUCLEOPHILIC

- PRETTY FUNCTIONAL GROUP TOLERANT

- THE MOST FUNCTIONAL GROUP SENSITIVE THING IS OFTEN MAKING THE ACID CHLORIDE



TOLERANT OF -NO₂, KETONES, LACTONES, ESTERS, OTHER REDUCTION PRONE GROUPS.

- AN OBVIOUS ALTERNATE TO DARZEN'S + WITTIG RXN WITH Ph₃P=O_{me} - JUST DIFFERENT OXIDATION LEVEL OF CARBONYL.