Paul Bracher
Chem 30 – Synthesis Review

Guide to Solving Sophomore Organic Synthesis Problems

Disclaimer

Omission of a topic on this handout does not preclude that material from appearing on the final exam. Any material that we have covered in lecture, in a problem set, or in the book is fair game. The exam is cumulative and may include information from previous exams and Chem 20. I have not seen the exam and the concepts discussed here are my personal choices for what I believe to be especially pertinent to synthesis on the exam. Have a nice day.

Undergraduate Organic Synthesis vs. "Real" Organic Synthesis

The synthesis problems you encounter in undergraduate organic chemistry are usually different from those tackled by academic research groups. First of all, Chem 30 problems are designed to test your knowledge of the course material. As you wind through the semester, you pick up new reactions which may be placed in your "synthetic toolbox." While a modern chemist is free to choose from all sorts of reactions, you are limited to those presented in the course. Furthermore, while a practicing organic chemist is only limited by what is commercially available, in undergraduate synthesis problems, you are often restricted to using specific starting materials or reagents. The take-home message is not to associate exam problems too closely with what chemists actually do. Nevertheless, it is important to learn basic organic reactions and the skills you learn are still very applicable to "real" organic synthesis.

Managing your Synthetic Toolbox

Your "synthetic toolbox" encompasses all of the material you've learned that is useful in constructing organic compounds. These can be single reactions that transform one functional group into another, a sequence of reactions used to construct a more complex functionality, or general techniques and methods that are universally applicable. As you come across a new reaction or technique, you should keep track of it in your notes. One of the best ways to do this is by making index cards. While there are a couple of sets of pre-made organic chemistry cards available in bookstores, they are a poor substitute for making your own. Look for reactions in:

- Problem set and exam synthesis questions
- Lecture packets, especially the reactions that are discussed in detail or given their own section
- Loudon and other undergraduate textbooks

General Advice on How to Study

- Do practice problems. Start with problems from the book (they are easier) then move on to problems associated with the course (do the practice exam, redo the problem sets, do the section practice problems, do the problems in the lecture notes, do the problems on the database).
- Focus on the interconnectivity of functional groups—know how to get from one group to another in both directions. Make "cheat sheets" that detail the reactions and transforms (how to make particular structural motifs). Please refrain from actually using the cheat sheet to cheat on an exam.

General Approaches to Synthesis Problems

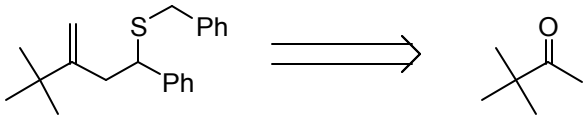
Basic Synthetic Strategies

1) See if the synthons you are given suggest an obvious forward step
2) Try "mapping" the synthons on to portions of the target. If you can figure out where a synthon "fits into the puzzle," you can then worry about properly arranging reactions to establish the connectivity.
3) If these methods don't work, take your target molecule and break it apart by going backwards one reaction at a time. With each step back, see if it is now more obvious how to work forward from the starting materials. Try to put the most complicated steps towards the end of your synthesis.

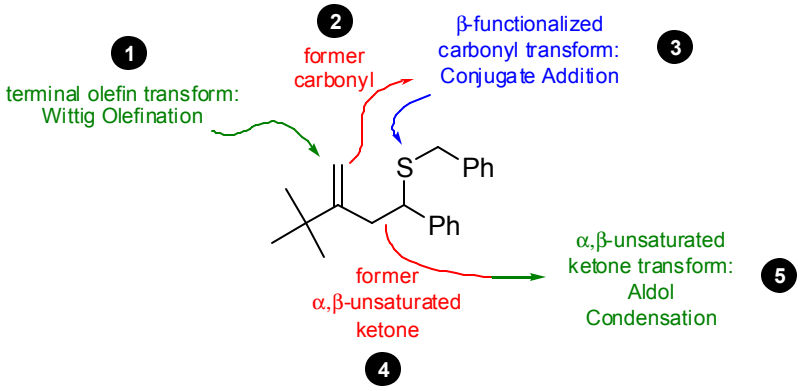
1) Trained Response / Reflex

In some cases, it is not hard to look at a target and immediately see the key functional transformations. You'll find that this "easy" approach will occur more frequently as you do practice problems and study your synthetic transforms.

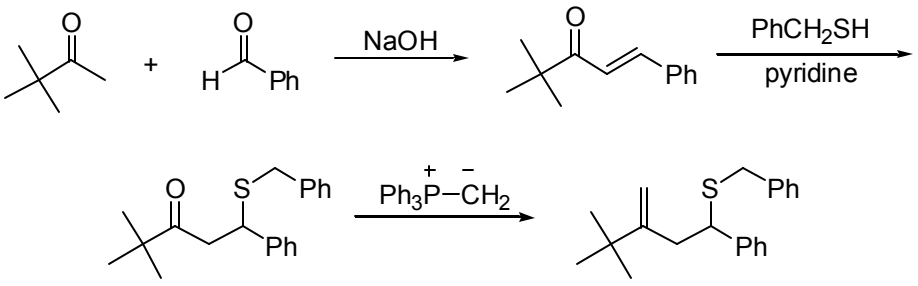
Target



Transforms

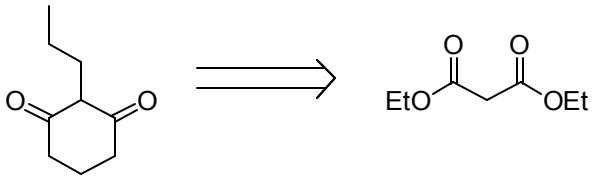


Conversion



2) Atom Mapping – The "Forward" Approach

Target

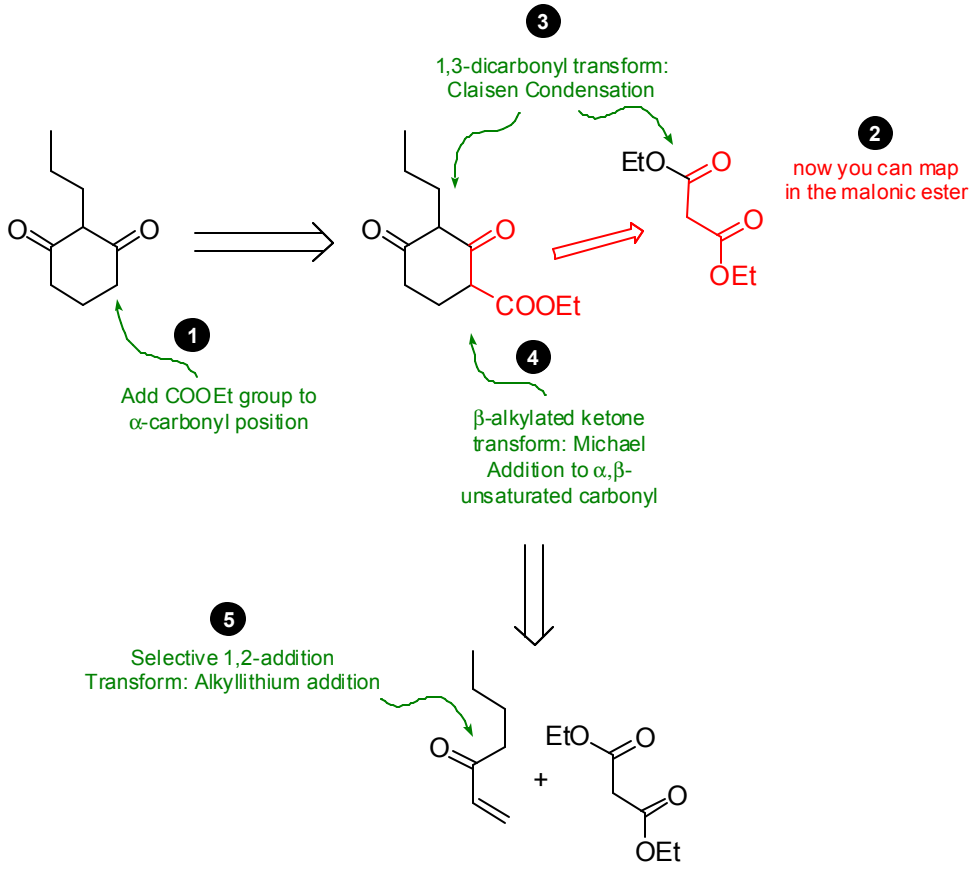


and anything else with four or fewer carbons

Approach

Whenever you are told to begin with a specific starting material, you will have to find, or "map," this compound into the product by matching atoms or functional groups. Malonic ester syntheses are particularly difficult, because you will usually decarboxylate somewhere down the line, which makes mapping harder since some atoms "disappear."

A common approach is to add a –COOR group to the α-carbonyl position in the product, which is essentially a retrosynthetic decarboxylation. After this, you can loosely apply your transforms and then write out your answer with all of the synthetic details.



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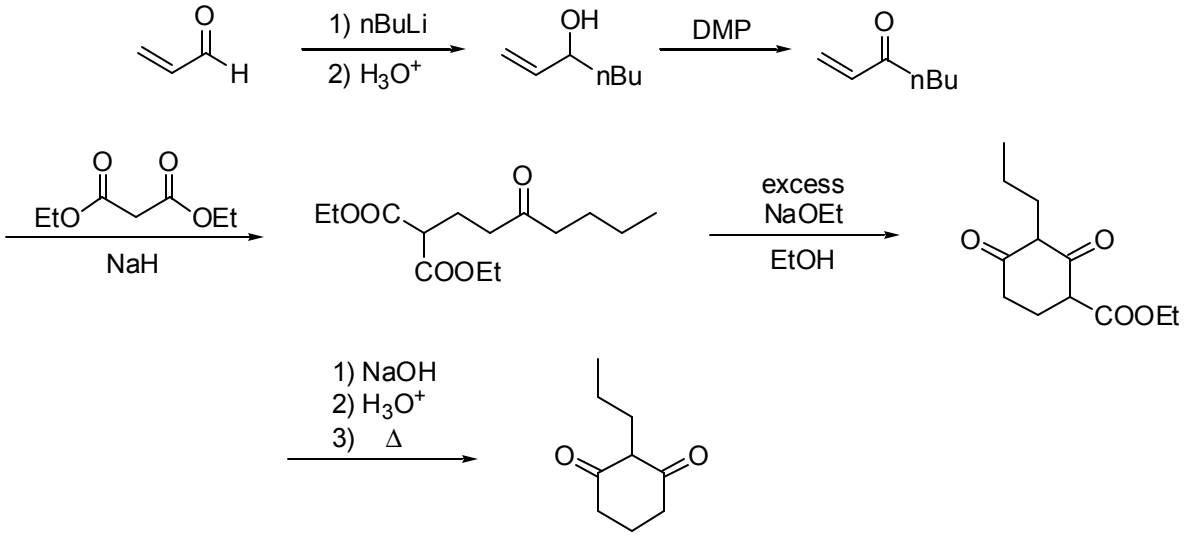
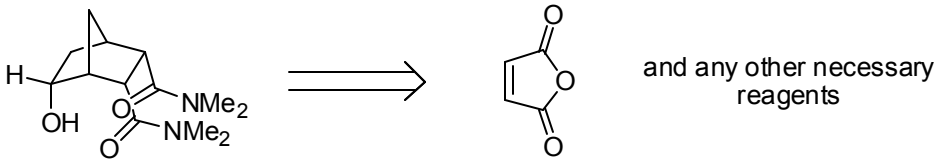

1) nBuLi
2) H_3O^+
DMP
nBu
EtO
OEt
NaH
EtOOC
COOEt
excess
NaOEt
EtOH
COOEt
1) NaOH
2) H_3O^+
3) Δ

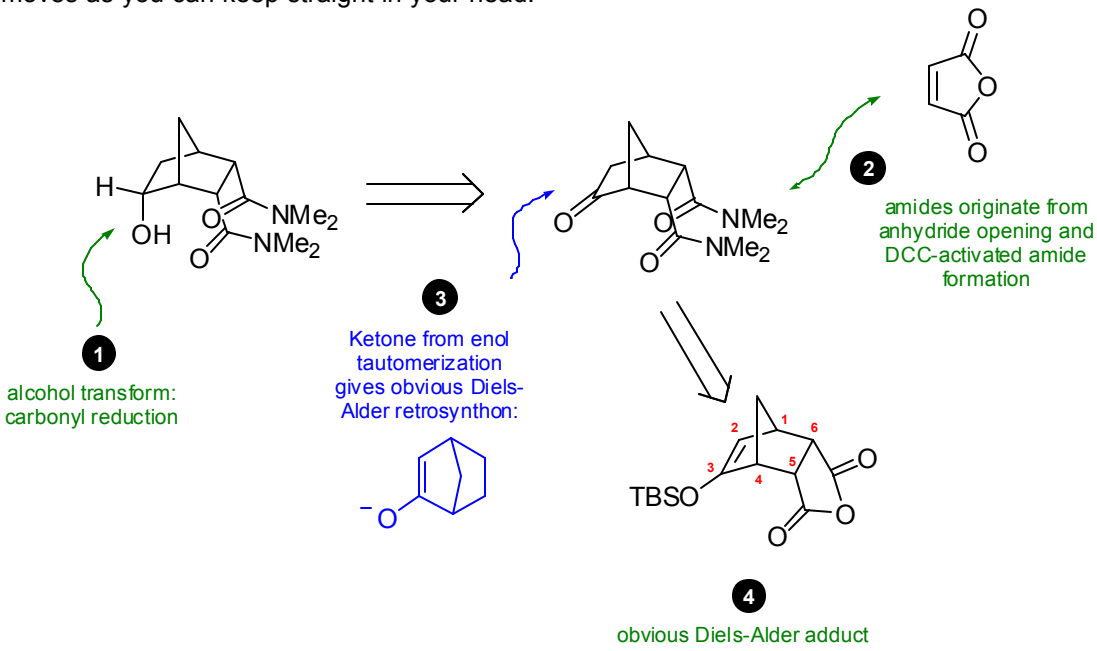
3) Retrosynthetic Analysis – The "Backward" Approach

Target



Approach

The product and starting material are giveaways for a Diels-Alder reaction somewhere in the synthesis. However, we must work backwards to get to this point. When you are initially working through the problem, don't waste time writing every specific detail in case the path becomes a dead end. Jump backwards as many moves as you can keep straight in your head.



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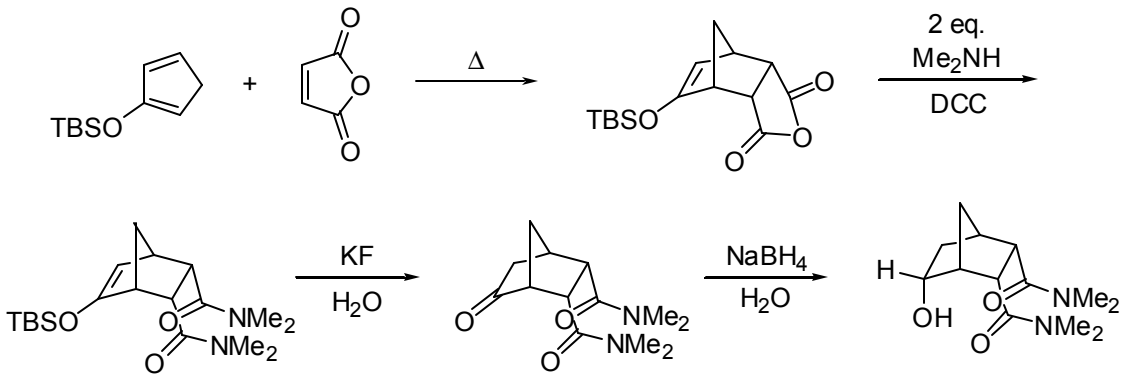
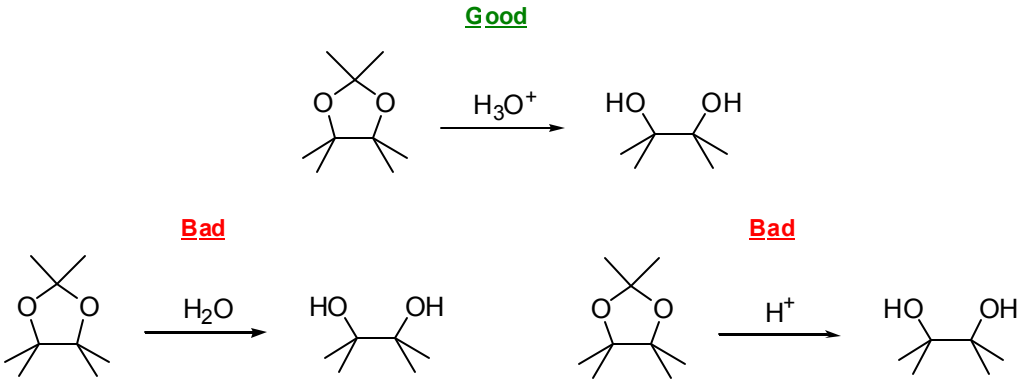


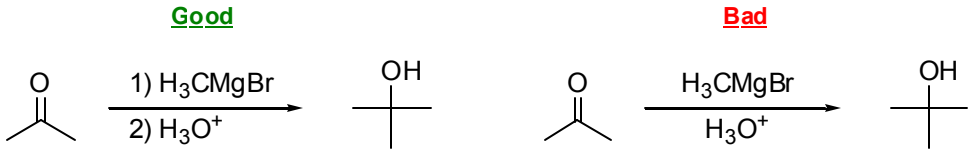
In reality, the method that you end up using will be a combination of the three. Since usually you are given starting materials that you *must* use, it is impossible to work *entirely* backwards—chances are won't arrive at the given starting material. Instead, it makes sense to work backwards, then forwards, then repeat this process until your chemical intuition sparks so that you can join the backwards and forward routes by reflex.

Synthetic Peccadilloes to Avoid

1) When applicable, include all necessary reagents

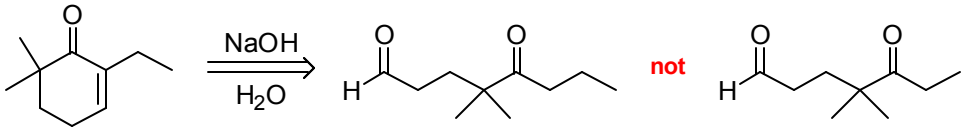


2) Pay attention to sequential addition of reagents



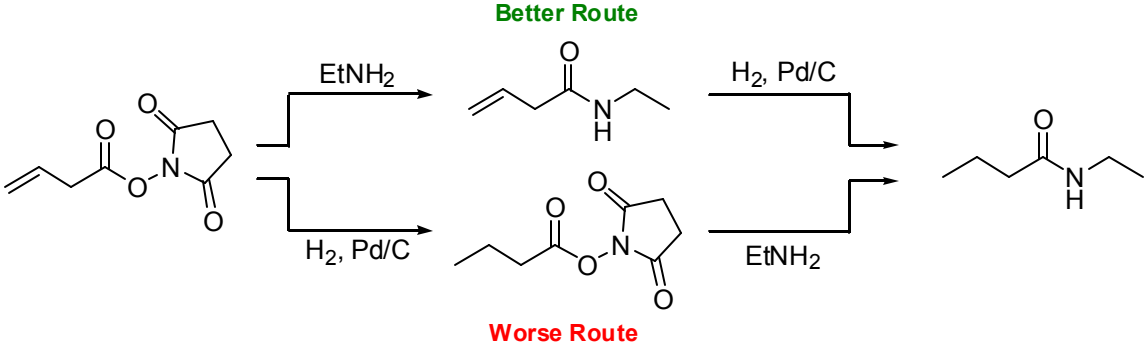
- Also, ozonolysis is 1) O_3, 2) DMS or H_2O_2/NaOH

3) Double-check your Carbon Counting

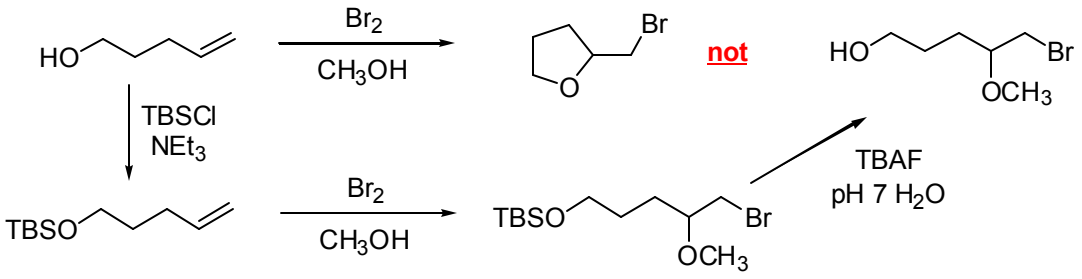


4) Use the Functional Groups of your Starting Material in Order of Decreasing Reactivity

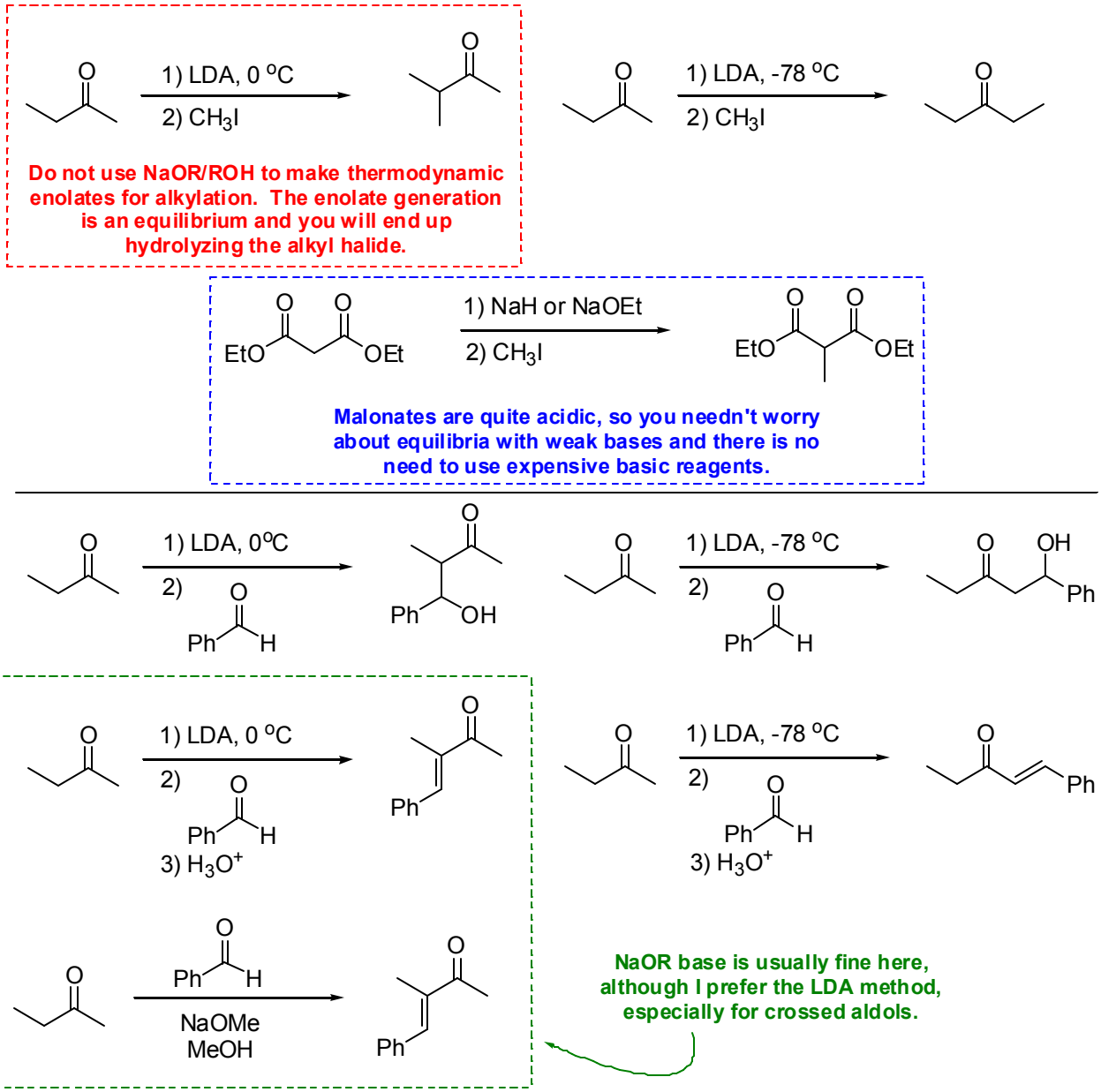
There are probably plenty of exceptions to this generalization, but when given a choice, you want to use the most reactive functionality first to minimize the possibility of deleterious side reactions



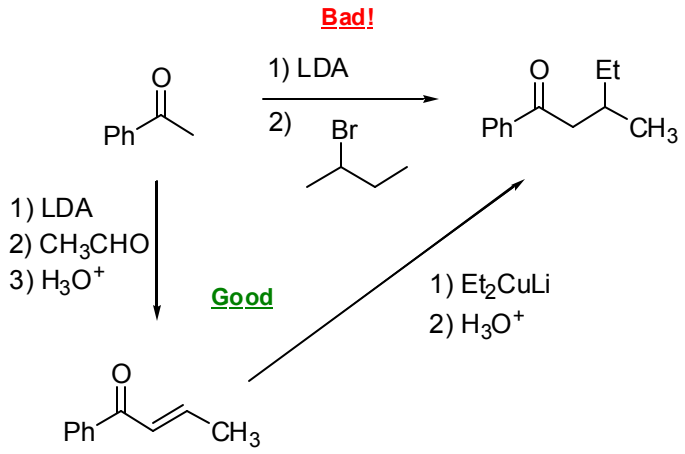
5) Protect Reactive Functionality



6) Be Careful in Deciding Upon the Conditions for Generating Your Enolate



7) It is difficult/impossible to alkylate enolates with 2° and 3° alkyl halides. Find a better way.



8) Avoid Overalkylating

Unless you want an extensively alkylated product (e.g. 4° amine), don't alkylate amines or benzene with alkyl halides. It is very hard to prevent the monoalkylated product from reacting further.

9) Play By the Rules (Read the Question)

Don't just dive in by looking at the figure—be sure to read the question prompt as well. If a synthesis problem says to use a certain starting material or to use only "compounds with *n* or fewer carbons," then abide by these rules (or face the wrath of our red pens).

Pay attention to detail—don't get nickeled and dimed for points!

Super Double Secret "Crack the System" Test-Taking Tips

1) Know Your Reactions and Synthetic Transformations

There is a list of some common synthetic transformations that we have learned this semester at the end of this packet. There is no excuse for not learning these, aside from stupidity or a desire to flounder on synthesis problems. You *will* bomb a fill-in-the-blank synthesis question if you don't know your reactions cold. This handout is nowhere near exhaustive—study the lecture notes too.

2) Look at the Point Value of the Problem

In general, more points are assigned to synthesis problems that have longer routes involving more reactions. If you arrive at a long answer for a problem that has been assigned relatively few points, think twice about your answer. Chances are that you have overlooked a more direct approach to the target.

3) Don't Dig too Deeply

From my recollection, I don't recall any extraordinarily long syntheses, either this year or in years past. If you're roaring past ten steps, chances are you'd better wrap it up soon or look for another route.

4) Lost? Try Running Through Reactions

While this approach is more useful for the midterm exams, if you are lost, try running through the reactions from a particular unit. It is highly unlikely that we would put a synthesis problem on the final exam in which all of the steps were reactions from Chem 20.

5) Don't Embarrass Yourself

This is more of a personal beef. If you are lost and can't bridge two synthetic intermediates, please don't write "magic" over the reaction arrow. It's a lame excuse, equivalent to writing "my brain doesn't work," "I didn't study enough," or "I am too lazy to think about this." Magic is for television witches and high schoolers who enjoy *Dungeons & Dragons*. If you plan on screwing up a synthesis problem, perhaps you can come prepared with witty new material that will amuse the graders.

6) Don't Leave a Synthesis Question Blank

It is a sad state of affairs when you leave a synthesis problem blank (or any problem, for that matter). At the very least, try to make some retrosynthetic cuts and identify key reactions. I always did my synthesis problems on the exam page, not scratch paper, because if I ran out of time I knew I'd have *something* down. Graders try to give partial credit—make it easy for us to justify doing so. A blank response can be given nothing but a zero.

7) Don't Panic

If you are stuck, move on to another question instead of wasting time. Some material later on in the exam may inspire you. Don't panic. Besides failing this course and ending your chances of having a successful career, what's the worst that could happen?

Common Reduction-Oxidation (Redox) Reagents

Oxidants

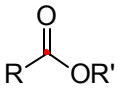
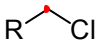
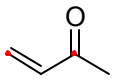
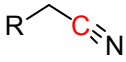
DMP	2° alcohols → ketones, 1° alcohols → aldehydes	(Swern oxidation does the same)
CrO_3	1° alcohols → aldehydes; toluenes → benzaldehydes olefins → α,β-unsaturated ketones	(basic conditions) (Allylic oxidation)
$KMnO_4$	1° alcohols → carboxylic acids, 2° alcohols → ketones 1° and 2° alkyl benzenes → benzoic acids	(fairly harsh)
O_3	olefins → aldehydes olefins → carboxylic acids	(w/ DMS or Zn/AcOH workup) (w/ H_2O_2, NaOH workup)
OsO_4	olefins → vicinal diols (glycols)	
Br_2	olefins → vicinal dibromides, olefins → bromohydrins (w/ ROH) 3° hydrocarbons → alkyl halides	(photohalogenation, w/hν)
NBS	alkyl benzenes → benzyl bromides olefins → allylic bromides	(w/hν or peroxide initiator)
RCO_3H	olefins → epoxides ketones → esters	(Baeyer-Villiger)
H_2O_2	alkylboranes → alcohols	(w/NaOH, hydroboration workup)
$I_2 + RCOO^-$	olefins → esters with neighboring alkyl iodide	(*e.g.*, iodolactonization)

Reductants

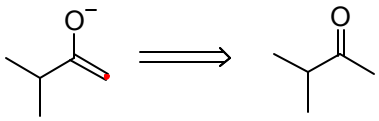
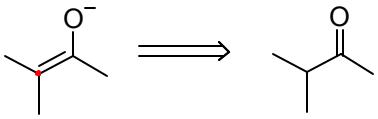
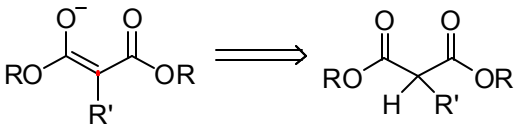
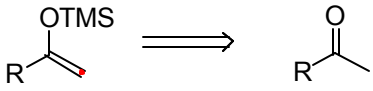
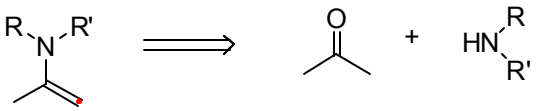
H_2	olefins → alkanes ketones → alcohols alkynes → olefins	(w/ Pd on carbon) (w/ PtO_2) (w/ Pd-$BaSO_4$, quinoline)
R_2BH	olefins → anti-Markovnikov alkylboranes	
$NaBH_4$	ketones, aldehydes → alcohols	(Felkin product)
$Zn(BH_4)_2$	ketones, aldehydes → alcohols	(chelation control product)
$NaBH_3CN$	protonated imines (at pH 5) → amines	(used in reductive aminations)
DIBAL-H	esters, nitriles → aldehydes	(relatively mild conditions)
$LiAlH_4$	carboxylic acids, ketones, aldehydes → 1° alcohols amides, imines, nitriles → amines	(relatively harsh conditions)
RLi	aldehydes → 2° alcohols; esters, ketones → 3° alcohols	
RMgBr	aldehydes → 2° alcohols; esters, ketones → 3° alcohols	(Grignard reagent)
RZnCl	acid chlorides → ketones	(reagent won't add to ketones)

Synthetic Routes to Common Nucleophiles and Electrophiles

Common Electrophiles

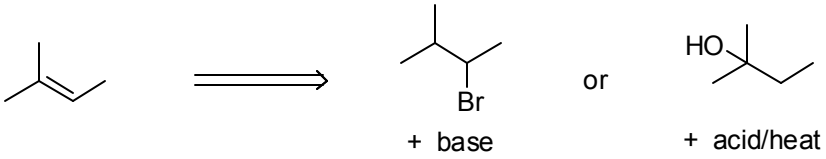
		Synthetic Preparations
aldehydes		Swern or DMP oxidation of alcohols; DIBAL-H reduction of nitriles and esters; CrO_3 oxidation of toluenes
ketones		Oxidation of alcohols; Friedel-Crafts reaction; Oxidation of Grignard products
esters		Fischer esterification of acids and alcohols; solvolysis of acid chlorides and anhydrides with alcohols; Baeyer-Villiger oxidation
alkyl halides		From alcohols with $SOCl_2$ or PBr_3; alkenes with HBr (with or w/o peroxides); alkanes by photohalogenation
α,β-unsaturated carbonyls		Aldol reactions; α-keto halogenation (Hell-Volhard-Zelinsky) then elimination of HBr
imines		Reaction of primary amines with ketones and aldehydes in acid
nitriles		Cyanide substitution of alkyl halides; dehydration of amides by P_2O_5;

Common Nucleophiles

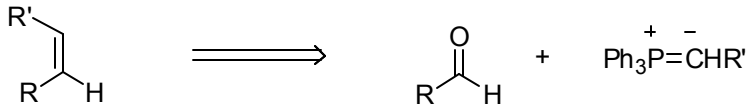
kinetic enolates		Irreversible bases at low temperature (LDA, -78 °C); bulky bases
thermodynamic enolates		Reversible bases (alkoxides, hydroxides); LDA at high temperatures (0 °C)
malonic ester enolates		Bases with $pK_a > 8$ (NaH, RO^-)
silyl enol ethers		TMSCl and an amine base in anhydrous solvent
enamines		pH = 5 catalyzed condensation

Olefins

Eliminations

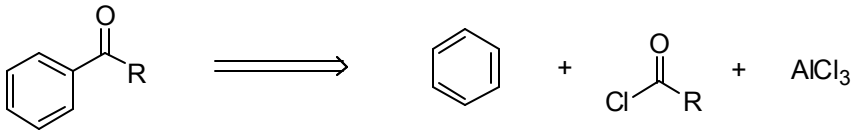


Wittig Olefination

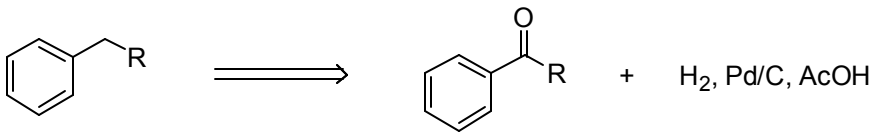


Acylbenzenes

Friedel-Crafts Acylation

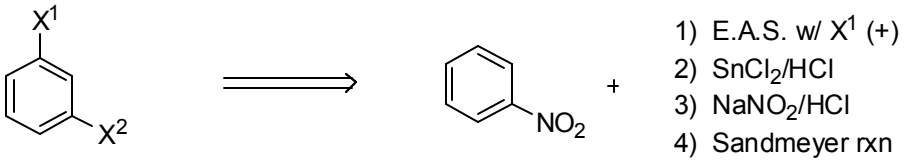


Alkylbenzenes



(aryl alkylation must be constructed via acylation to avoid overalkylation)

meta Substituted Benzene Derivatives



1) E.A.S. w/ X^1 (+)
2) $SnCl_2$/HCl
3) $NaNO_2$/HCl
4) Sandmeyer rxn for X^2

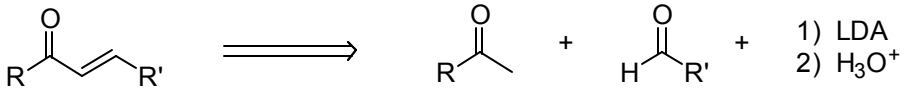
X^1 = Br, Cl, COR

X^2 = Br, Cl, I, F, OH, H

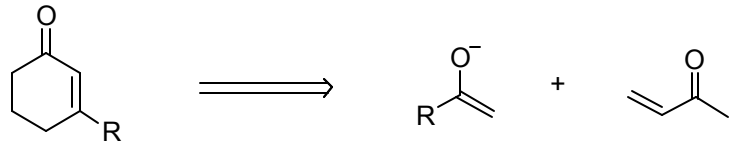
See notes and book for full list of aromatic reactions

α,β-Unsaturated Ketones

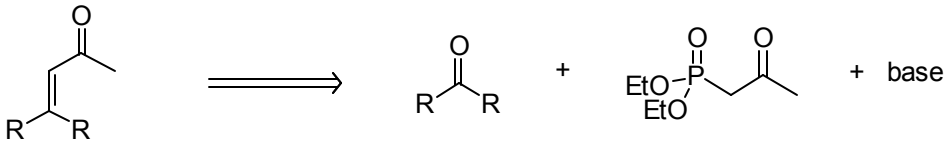
Aldol Reaction



Robinson Annulation

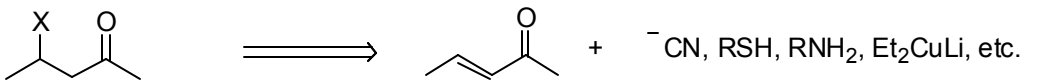


Horner-Wadsworth-Emmons



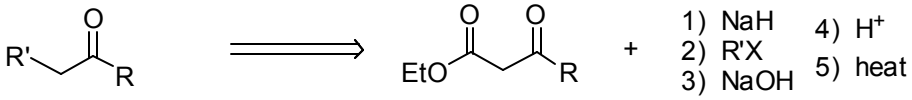
β-Functionalized Ketones

Conjugate Additions



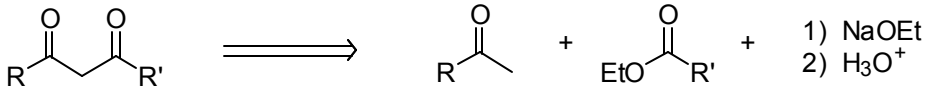
Review which nucleophiles add 1,4 vs. 1,2

α-Functionalized Ketones



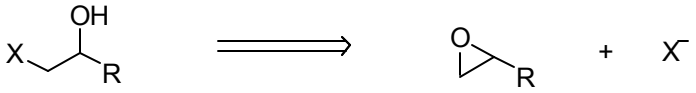
1,3-Diketones

Claisen Condensation



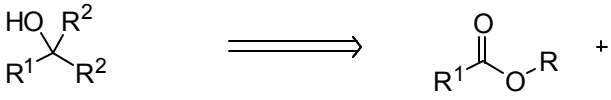
α-Functionalized Alcohols

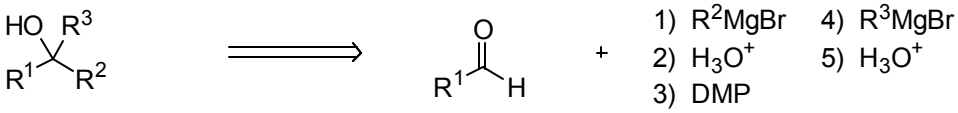
Epoxide Opening



Substituted Alcohols

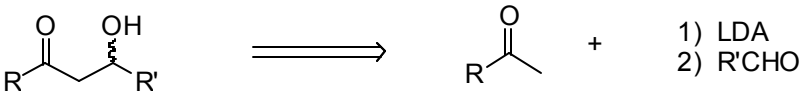
see reductions list earlier in packet





β-Keto Alcohols

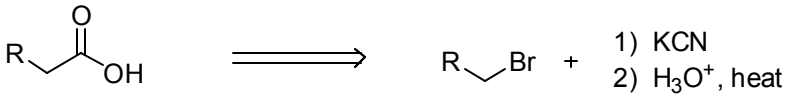
Aldol Reaction



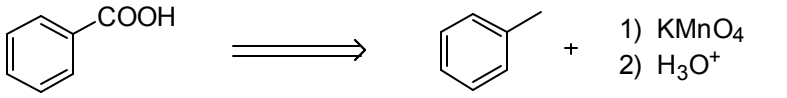
Carboxylic Acids

See Oxidations Earlier in Packet

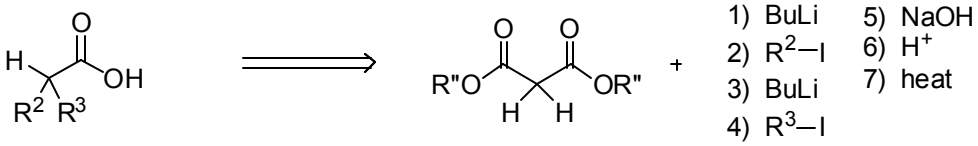
Nitrile Hydrolysis



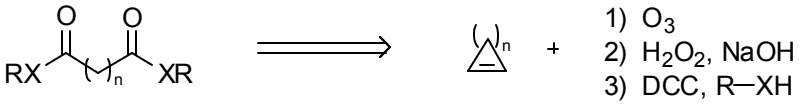
Oxidations of Aryl Hydrocarbons



Malonic Ester Alkylation

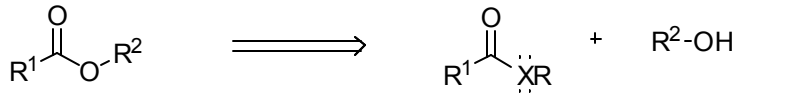


Symmetric Carboxylic Acid Derivatives

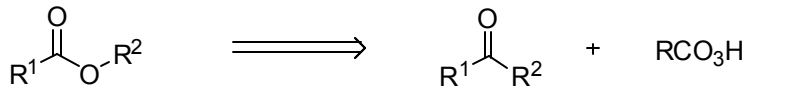


Esters

Acid Derivative Substitution

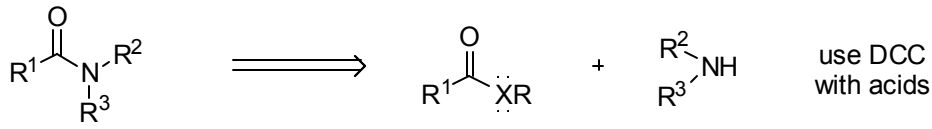


Baeyer-Villiger

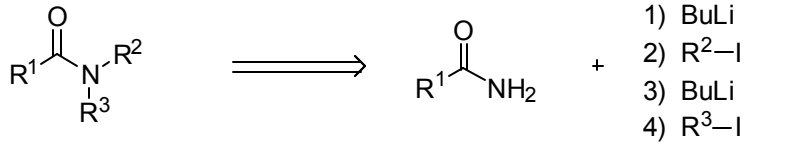


Substituted Amides

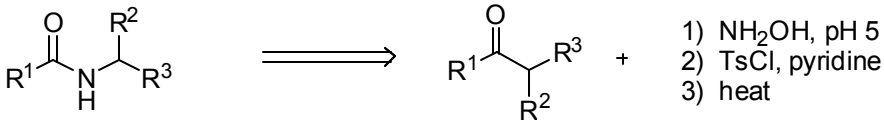
Acid Derivative Substitution



Amide Alkylation

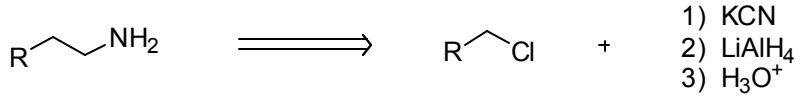


Beckmann Rearrangement

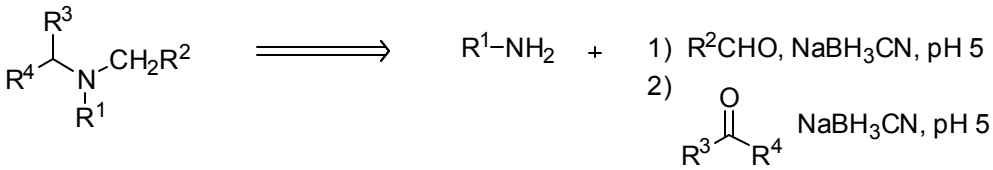


Substituted Amines

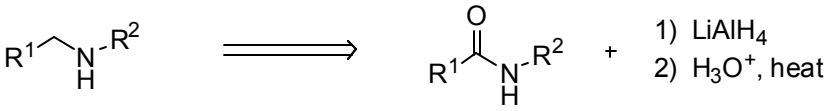
Cyanide Reduction
(extends chain by 1 carbon)



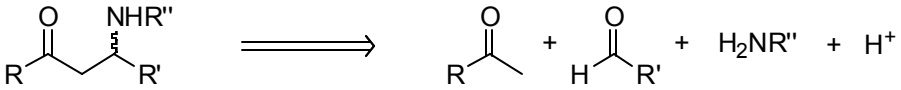
Reductive Amination



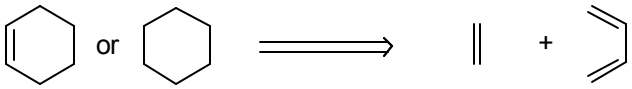
Amide Reduction



β-Amino Ketones
Mannich Reaction

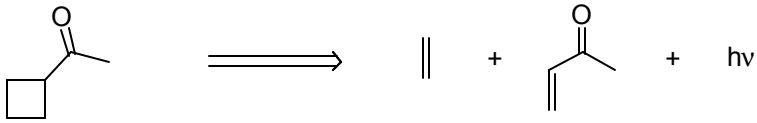


Cyclohexanes
Diels-Alder

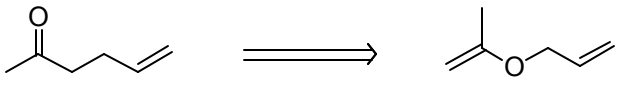


follow with H_2/Pd/C for cyclohexanes

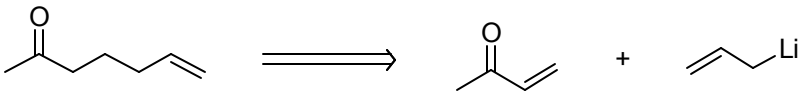
Cyclobutanes
[2+2]



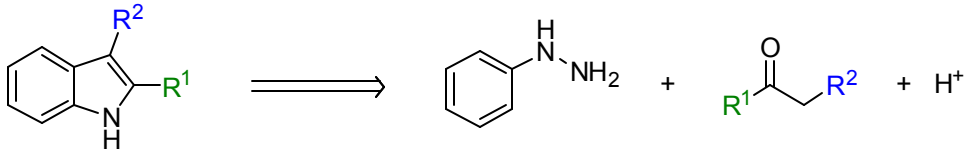
γ,δ-unsaturated carbonyls
Claisen rearrangements



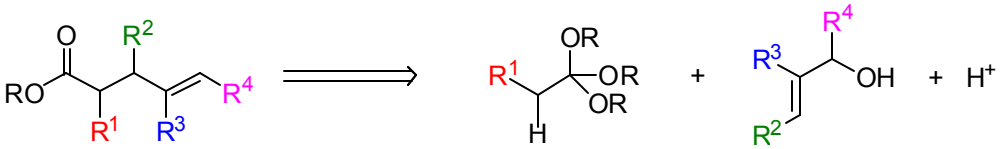
δ,ε-unsaturated carbonyls
oxy-Cope rearrangement



Indoles
Fischer Indole Synthesis



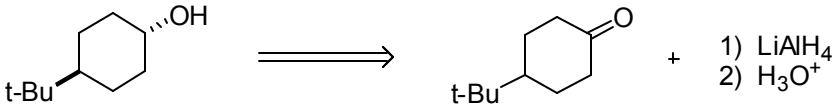
γ,δ-unsaturated carbonyls
ortho ester Claisen



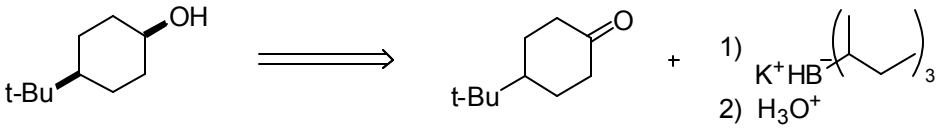
Important Stereoselective Reactions

Cis/*Trans* Cyclohexanes

Axial Attack

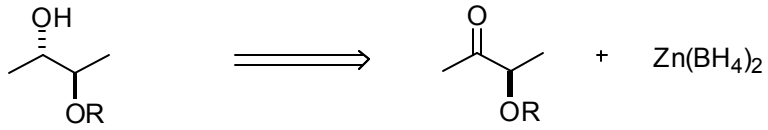


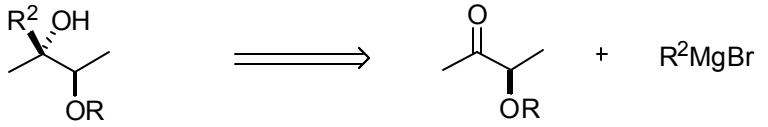
Equatorial Attack



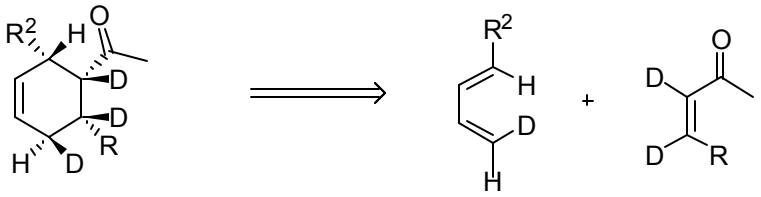
Chiral Alcohols

Chelate Controlled Reductions

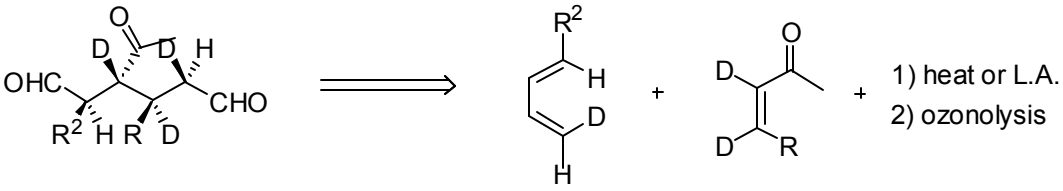




Chiral Cyclohexanes and 1,6-Dicarbonyl Derivatives

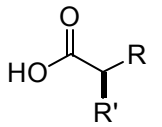


Diels-Alder Reactions

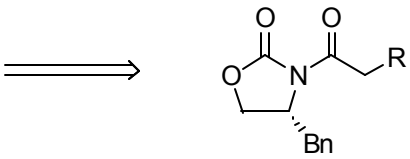


Chiral α-Alkyl Acids

Alkylation with Chiral Auxiliaries



Use LAH or $LiBH_4$ to get terminal alcohols

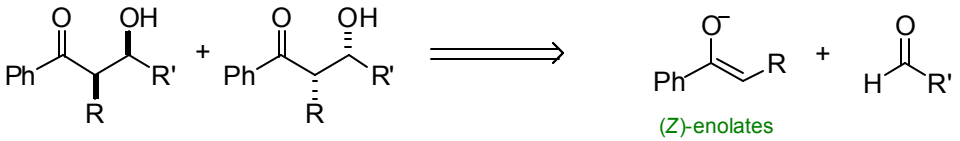


via (*Z*)-enolate

1) LDA
2) R' Cl
3) LiOOH
4) H^+

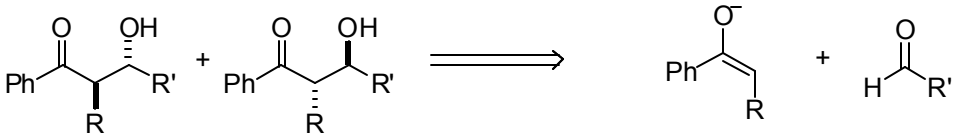
Chiral α-Alkyl-β-Keto Alcohols

Syn Aldol Products



(*Z*)-enolates

Anti Aldol Products

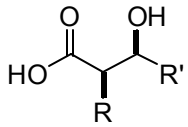


(*E*)-enolates

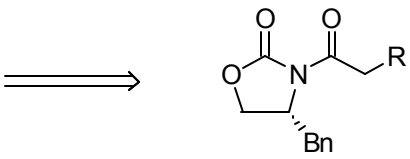
soft enolizations
(*Z*)-enolates: use Bu_2BOTf, NEt_3
(*E*)-enolates: use Cy_2BCl, NEt_3

Chiral 1-Alkyl-2-ol Acids

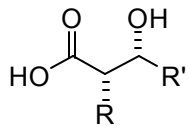
Evans' Aldol Reaction



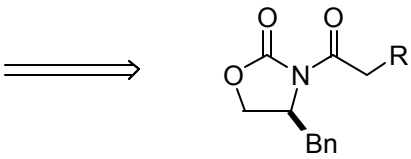
via (*Z*)-enolate



1) Bu_2BOTf, NEt_3
2) R'CHO
3) LiOOH
4) H^+

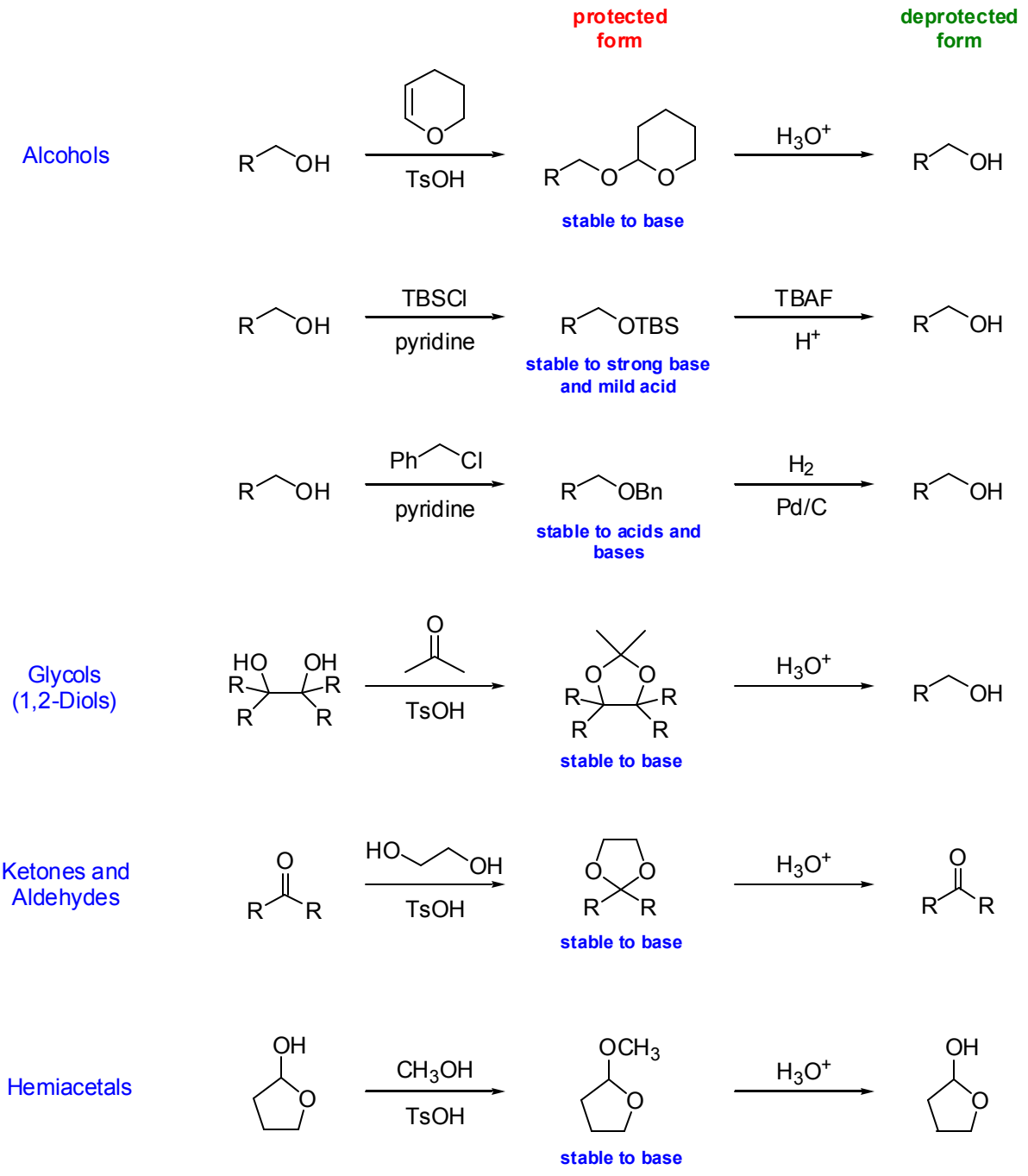


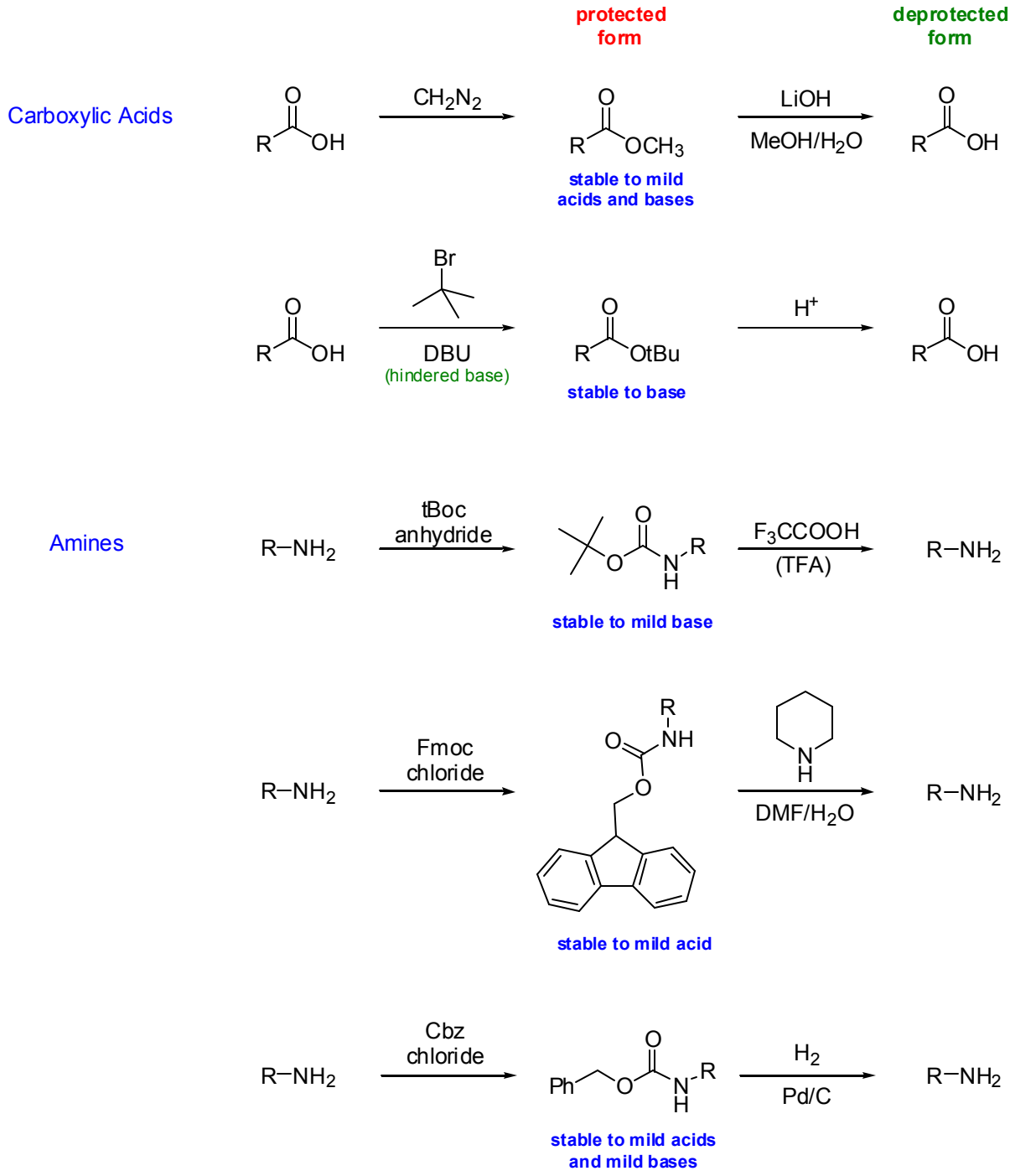
Cannot generate (*E*)-enolates of oxazolidinones



1) Bu_2BOTf, NEt_3
2) R'CHO
3) LiOOH
4) H^+

Protecting Groups





Take note of orthogonal protecting groups that are removed with different conditions so you can selectively deprotect one group at a time