

ORGANIC CHEMISTRY II



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TABLE OF CONTENTS

Licensing

12: Radical Reactions

- 12.1: Radical Intermediates
- 12.2: Radical Reactions
- 12.3: Organometallics

13: Conjugation

- 13.1: Allyl System
- 13.2: Dienes
- 13.3: Diels-Alder reaction
- 13.4: Diels-Alder Regio- and Stereoselectivity

14: Aromaticity

- 14.1: Conjugation vs. Aromaticity
- 14.2: Frost's Circle
- 14.3: Heteroaromaticity

15: Aromatic Substitution

- 15.1: Electrophilic Aromatic Substitution
- 15.2: Regioselectivity in Electrophilic Aromatic Substitution
- 15.3: Multiple Substituents and Heteroaromatic Rings
- 15.4: Nucleophilic Aromatic Substitution
- 15.5: Other Reactions of Aromatics

16: Nucleophilic Addition to Carbonyls

- 16.1: Nucleophilic Addition to the Carbonyl Group
- 16.2: Irreversible Nucleophilic Addition
- 16.3: Reversible Nucleophilic Addition
- 16.4: Acetal Formation
- 16.5: Nucleophilic Addition Under Neutral Conditions
- 16.6: Alcohol Oxidation

17: Nucleophilic Acyl Substitution

- 17.1: Nucleophilic Acyl Substitution
- 17.2: Reactions via Carbonyl Substitution
- 17.3: Double Nucleophilic Acyl Substitution
- 17.4: Super Leaving Groups
- 17.5: Nitriles
- 17.6: Named Reactions

18: Enols and Enolates

- [18.1: Enols and Enolates](#)
- [18.2: Consequences of Tautomerization](#)
- [18.3: Molecular Orbital Description of Enolates](#)

19: Reactions of Enolates

- [19.1: Reactions of Enolates with Aldehydes and Ketones](#)
- [19.2: Reactions of Enolates with Esters and Anhydrides](#)
- [19.3: Reactions of Enolates with Alkyl Halides](#)
- [19.4: Reactions of Enolates with \$\alpha,\beta\$ -Unsaturated Carbonyls](#)
- [19.5: Retrosynthesis with Enolates](#)

[Index](#)

[Glossary](#)

[Detailed Licensing](#)

[Detailed Licensing](#)

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CHAPTER OVERVIEW

12: Radical Reactions

[12.1: Radical Intermediates](#)

[12.2: Radical Reactions](#)

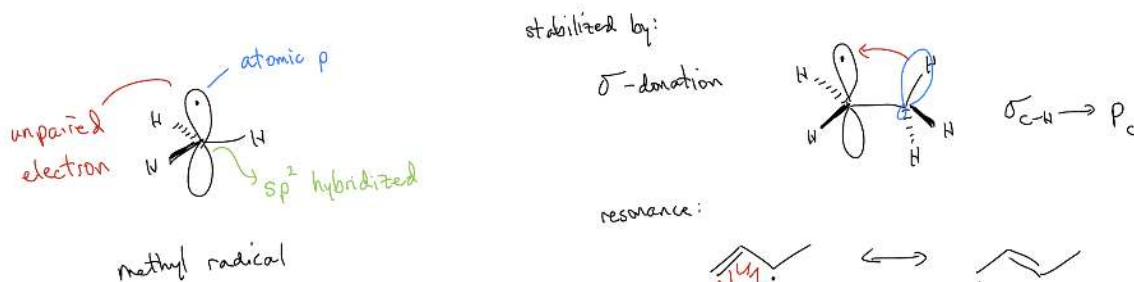
[12.3: Organometallics](#)

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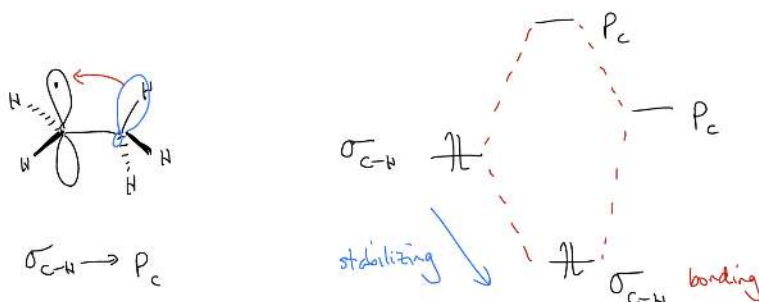
12.1: Radical Intermediates

In organic chemistry, we say that there are generally four types of intermediates: carbocations, carbanions, carbenes, and radicals. We have not said much about radicals up to this point, except that they are carbon centers that have an unpaired electron.

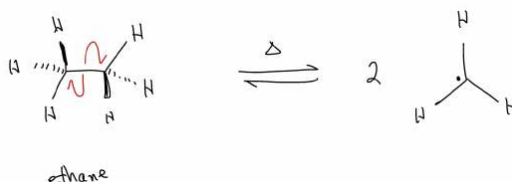
A free radical is an intermediate that is electron-deficient, but unlike the carbocation, it is overall neutral. We generally say that the carbon is sp^2 -hybridized and has a trigonal planar geometry (although in some cases it is more like a very shallow trigonal pyramid). The unpaired electron sits in an atomic p orbital perpendicular to the trigonal plane. Like carbocations, the radical can be stabilized by additional alkyl groups (σ -donation) such that 3° radicals are more stable than 2° radicals, etc. Similarly, benzylic and allylic radicals can be stabilized by resonance delocalization and are more stable than those radicals with σ -donation alone.



Why would radicals be stabilized by these effects? Let's look at the molecular orbital diagram for a radical intermediate that undergoes σ -donation. In this case, we have a three-electron system in which the unpaired electron in the atomic p orbital is overlapping with a pair of σ bonding electrons. This overlap creates two new molecular orbitals. The new bonding orbital (with two electrons) is lower in energy, and the new antibonding orbital (with one electron) is higher in energy. This is certainly destabilizing to the unpaired electron, but the overall system is still stabilized because two electrons are able to occupy the low-energy bonding orbital.



Before we talk about their reactivity, we first need to understand how radicals are formed in the first place. Recall that, according to molecular orbital theory, a σ bond is formed from the overlap of two electrons, where one electron is contributed from each atom. It might seem possible, then, that we could break a σ bond homolytically to generate two radicals. In a homolytic cleavage, a σ bond is broken equally so that each atom receives one electron, thus forming two new radicals. We use singly-headed curly arrows to describe this type of cleavage. The energy required to break a bond homolytically is called the bond dissociation energy (BDE), and is usually lower than heterolytic cleavage because no charges are generated.

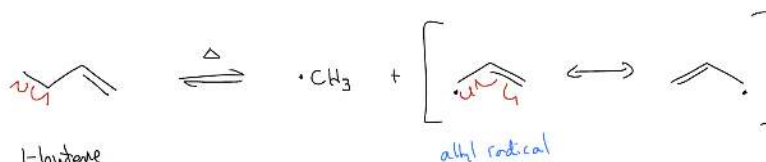


The simplest method of inducing homolytic cleavage is called pyrolysis (or thermolysis), which increases the bond vibration amplitude so much that the σ bond is broken homolytically. For ethane, the σ_{C-C} BDE is 90 kcal/mol, the result of which is two methyl radicals. Since pyrolysis involves high temperatures, some functional groups will not survive, and thus we must resort to other methods of generating radicals. These methods involve modifying the system so that the BDE is much lower.

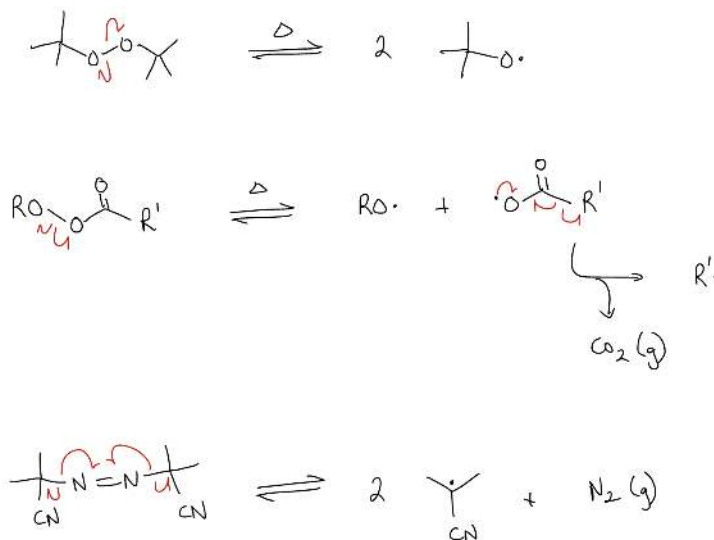
So, how can we modify an alkane in order to make the σ_{C-C} bond weaker (lower BDE)? One easy way is to introduce some strain into the alkane so that the σ_{C-C} bond is easily broken, releasing any strain energy. This happens readily for cyclopropyl rings. Pyrolysis forms a 1,3-diradical, this time with a BDE of only 65 kcal/mol. The increased strain of the cyclopropane ring made it less stable, and thus more likely to cleave homolytically.



But this is somewhat limited in scope because not all synthetically useful starting materials have cyclopropane rings. What if, instead of making the starting material less stable, we made the resulting radicals more stable? If the resulting radicals that are formed via homolytic cleavage are more stable, then the initial σ_{C-C} bond should be weaker. This is the case for allylic systems. For example, the BDE of 1-butene is 76 kcal/mol because homolytic cleavage of the σ_{C-C} bond generates a methyl radical and a resonance-stabilized allyl radical. The transition state energy is much lower, resulting in a lower BDE.



Another technique for generating radicals is to start with molecules containing especially weak bonds to begin with. You may recall that the σ_{O-O} bond is very weak. Simple peroxides have σ_{O-O} bonds with BDEs of ~38 kcal/mol, and cleave to produce alkoxy radicals. When an acyl ($C=O$) group is added to the peroxide, as in acyl peroxides, the BDE is lowered even more to ~29 kcal/mol (think *m*CPBA). The result is an alkoxy radical and a carboxyl radical, the latter of which further decomposes to produce CO_2 and an alkyl radical. Azo compounds, which contain an internal $N=N$ bond, readily produce radicals because a molecule of N_2 gas is generated. While this can be very hazardous, a more common source of radicals generated by N_2 extrusion is azobisisobutyronitrile (AIBN), which has a BDE of 31.9 kcal/mol.



Once they are generated, there are several reaction pathways available for radicals:

1. Abstraction: the process by which a radical species takes a hydrogen atom (NOT a proton) from another molecule.



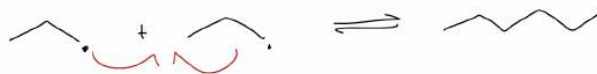
2. Disproportionation: the process by which a radical abstracts a hydrogen from the vicinal (adjacent) position of another radical to produce an alkane and an alkene.



3. β -cleavage: the process by which a radical decomposes to give an alkene and a new radical.



4. Dimerization: the process by which two radicals react with each other to create an alkane.



5. Addition: the process by which a radical adds to a π bond or cleaves a σ bond to generate a new radical.



We will see nearly all of these types of radical processes in the reactions that follow in the remainder of this chapter.

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12.2: Radical Reactions

Radical Addition to Alkenes

Recall that electrophilic addition reactions involve the reaction of an alkene with a hydrogen halide (HX) to form the more highly substituted alkyl halide by Markovnikov addition. This proceeds via protonation of the less highly substituted carbon atom of the alkene, formation of a carbocationic intermediate, and S_N1 -like attack of the atomic p orbital with the nucleophilic halide ion. While this should all seem familiar to you, when this reaction was first discovered, conflicting results were reported. In some cases, especially with HBr additions, the anti-Markovnikov product was generated! We know that this is impossible if the mechanism was truly an electrophilic addition. Well, it turns out that the quality of the HBr played an important role. While fresh bottles of HBr gave the expected Markovnikov product, older bottles of HBr gave the anti-Markovnikov product. It was discovered that older sources of HBr contain small concentrations of peroxides. Since the σ_{O-O} is weak, there is the potential for generating radicals.

Thus, the mechanism for the radical HBr addition is as follows, and can be divided into four discrete steps. Since many radical reactions are chain reactions (repeating reactions), we normally write them stepwise:

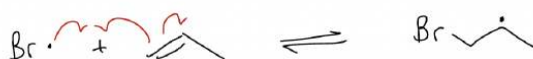
Step 1: initiation (thermolysis)



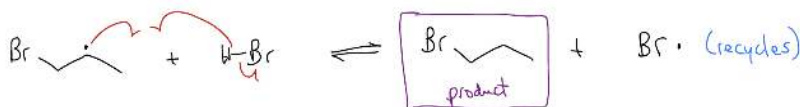
Step 2: initiation (abstraction)



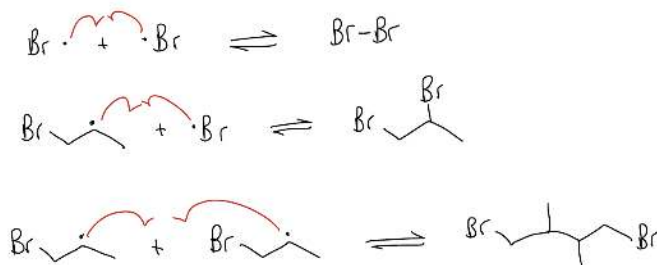
Step 3: propagation (addition)



Step 4: propagation (abstraction)

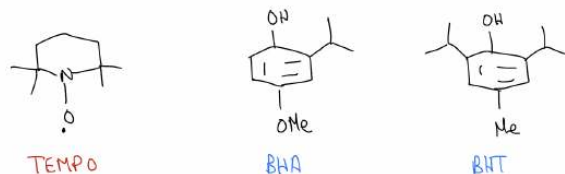


Step 5: termination (dimerization, etc.)



Steps 3 and 4 of this chain reaction are then repeated since the bromide radical can be recycled to step 3. For a chain reaction to produce the desired product, the propagation step must be more advantageous than the termination step. In a practical sense, the neutral reagents are in high concentrations and the radical intermediates are in low concentrations, so the chance of a termination step is quite rare until most of the starting materials have been consumed. Eventually, two radicals will combine to form a σ bond, ending the chain reaction, but this is so insignificant an event as to be considered inconsequential.

Sometimes, you may suspect that a reaction operates via a radical mechanism. A quick way of determining if radical are produced is to intercept these intermediates with a radical inhibitor. These reagents will act as artificial terminators, and no product will be formed. Common inhibitors are TEMPO, BHA, and BHT. Can you explain why these reagents terminate radical reactions?



While there is a radical HBr addition reaction, there is no corresponding radical addition using HCl or HI. This is peculiar, since we can write identical chain mechanisms! This can be explained by examining the thermodynamics of the two propagation steps.

In the first propagation step, a halide radical adds to a double bond. In order to determine whether this step is favorable, we would need to look at the bond strengths. The overall exothermicity or endothermicity of this step is a combination of the (π_{C-C} bond strength and the σ_{C-X} bonds strength). A π_{C-C} bond has a bond strength of 66 kcal/mol, no matter which hydrogen halide is used. But, the corresponding σ_{C-X} bond strength depends on the halide.

$$X\cdot + \text{C}=\text{C} \rightleftharpoons \text{X}-\text{C}-\text{C}\cdot$$

X	Bond strength (π_{C-C})	Bond strength (σ_{C-X})	ΔH
Cl	66 kcal/mol	85	-19 ✓
Br	66	72	-6 ✓
I	66	57	+9 ✗

For the radical HI addition, the first propagation step is substantially endothermic (+9 kcal/mol). Thus, the reaction fails. In the case of HBr and HCl, these are both exothermic for the first propagation step. But, let's take a look at the second propagation step. This step involves the abstraction of a hydrogen atom from H-X. The overall exothermicity or endothermicity of this step is a combination of the σ_{H-X} bond strength and the σ_{C-H} bonds strength. A σ_{C-H} bond has a bond strength of 98 kcal/mol, no matter which hydrogen halide is used. But, the corresponding σ_{H-X} bond strength depends on the halide.

$$\text{H}-\text{X} + \text{X}-\text{C}-\text{C}\cdot \rightleftharpoons \text{X}\cdot + \text{X}-\text{C}-\text{C}-\text{H}$$

X	Bond strength (σ_{H-X})	Bond strength (σ_{C-H})	ΔH
Cl	103 kcal/mol	98	+5 ✗
Br	87	98	-11 ✓
I	71	98	-27 ✓

For the radical HCl addition, the second propagation step is substantially endothermic (+5 kcal/mol). Thus, the reaction fails.

Free radical halogenation

Besides electrophilic additions and radical additions, another way to make alkyl halides is from alkanes themselves, even though alkanes are notoriously unreactive. Free radical halogenation is the conversion of alkanes into alkyl halides in the presence of Cl_2 or Br_2 and a source of light.



Before we discuss the mechanism of this reaction, let's first take a look at some BDE values. These values will be important when we look at the mechanism.

X_2	BDE (kcal/mol)	H-X	BDE
F-F	38	H-F	136
Cl-Cl	58	H-Cl	103
Br-Br	46	H-Br	87.5
I-I	36	H-I	71

R-H	BDE	R-X	BDE
CH ₃ -H	105	CH ₃ CH ₂ CH ₂ -Cl	85
CH ₃ CH ₂ -H	100.5	 -Cl	85
 -H	99	 -Cl	83
 -H	95		

The trends for σ_{C-H} bond strengths should make sense when we consider radical stabilities (σ -donation stabilizes radicals).

Free radical halogenation is also a chain reaction. The mechanism for the reaction of methane with Cl₂ in the presence of light has the following steps:

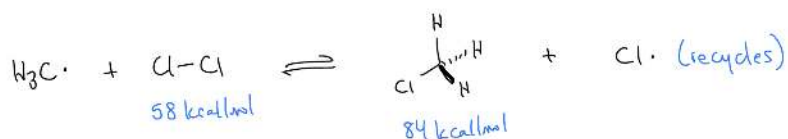
Step 1: initiation (photochemical/homolytic cleavage of Cl₂)



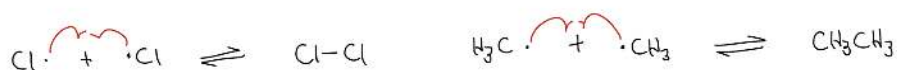
Step 2: propagation (abstraction of a hydrogen atom to generate the first carbon-centered radical)



Step 3: propagation (addition of carbon-centered radical to generate new σ_{C-Cl} and chloride radical, which recycles to step 2)

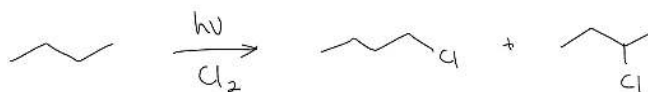


Step 4: termination (dimerization, etc.)



You can see that if we add up the bond enthalpies of all the bonds that are either formed or broken, free radical chlorination is exothermic ($\sim +24$ kcal/mol), despite the first propagation step being slightly endothermic. Free radical bromination operates by the same mechanism but is much less exothermic since the first propagation step is highly endothermic (-17 kcal/mol). This will have consequences for selectivity when using more complicated alkanes.

So, what happens when methane is not the starting substrate? Well, since there are many types of hydrogen atoms to abstract in the first propagation step, mixtures of products will result (hence, why this process may not be synthetically useful). For example, the free radical chlorination of butane gives two isomeric chlorides that arise from different hydrogen atoms being abstracted in the first propagation step. What would the ratio of these two products look like? This depends on the number of hydrogen atoms at each site.



For the primary carbon, there are six hydrogen atoms, but for the secondary carbon there are four. So, we might expect that, statistically speaking, the ratio should be 60:40 in favor of 1-chlorobutane, right? Well, the experimental ratio is actually 28:72 in favor of 2-chlorobutane. Why? Because the 2° radical is more stable! Its hydrogen atom is abstracted faster – the energy barrier to get to a 2° radical is much lower. The rate of abstraction of a hydrogen atom at a 2° center is 3.9x faster than at a 1° center. Similarly, a 3° radical is even more stable than a 2° radical, and will form a radical 5.2x faster than at a 1° center.

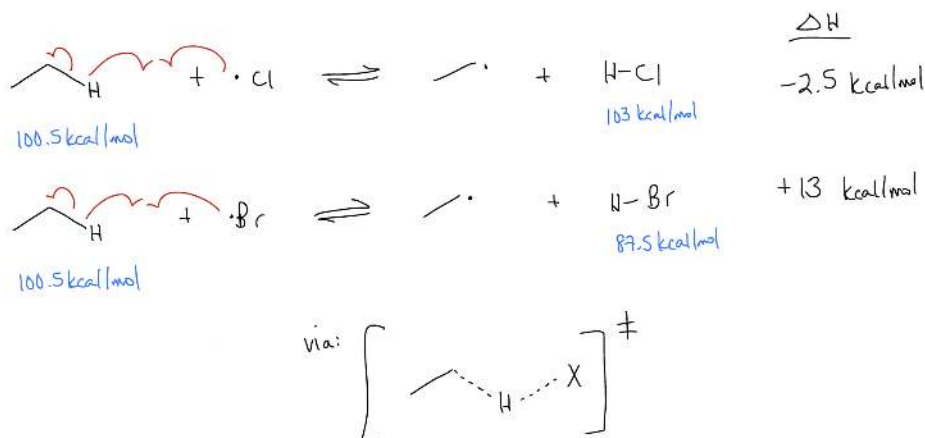
Thus, the selectivities for chlorination and bromination are as follows:

	3°	2°	1°
$\text{Cl}_2 / h\nu$:	5.2	3.9	1.0
$\text{Br}_2 / h\nu$:	1640	82	1.0

These values tell us that bromination is *much* more selective. Usually, only the 3° position is halogenated. Why? Let's look again at the BDE values.

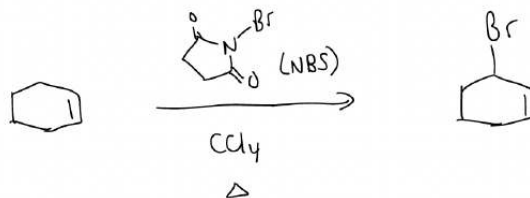
The propagation step for bromination is endothermic, meaning it is more sensitive to the stability of the free radical intermediate. Another way of thinking about this is that the transition state is much more product-like, according to the Hammond postulate, and resemble the radical intermediate more (so any way to stabilize this will be better).

Thus, chlorination of alkanes is used primarily when all hydrogen atoms are equivalent and bromination of alkanes is used to prepare 3° alkyl bromides. Neither fluorine (explosively exothermic) nor iodine (too endothermic to have any appreciable rate) undergo free radical halogenation.



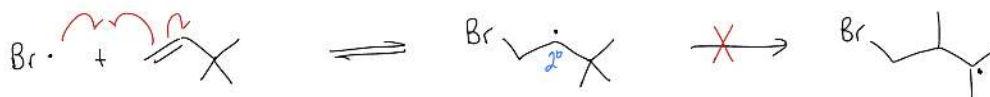
Allylic halogenation

While free radical bromination of tertiary alkanes is highly selective, an even better candidate for free radical halogenation is an allyl system. In cyclohexene, there are three types of $\sigma_{\text{C-H}}$ bonds where hydrogen atoms could be extracted: vinyl, allylic, and alkyl (methylene). Since abstraction of the allylic hydrogen would lead to the formation of a resonance stabilized allylic radical, the $\sigma_{\text{C-H}}$ bond is weaker and the BDE much lower. Thus, we can use even milder conditions for this reaction (NBS, CCl_4).

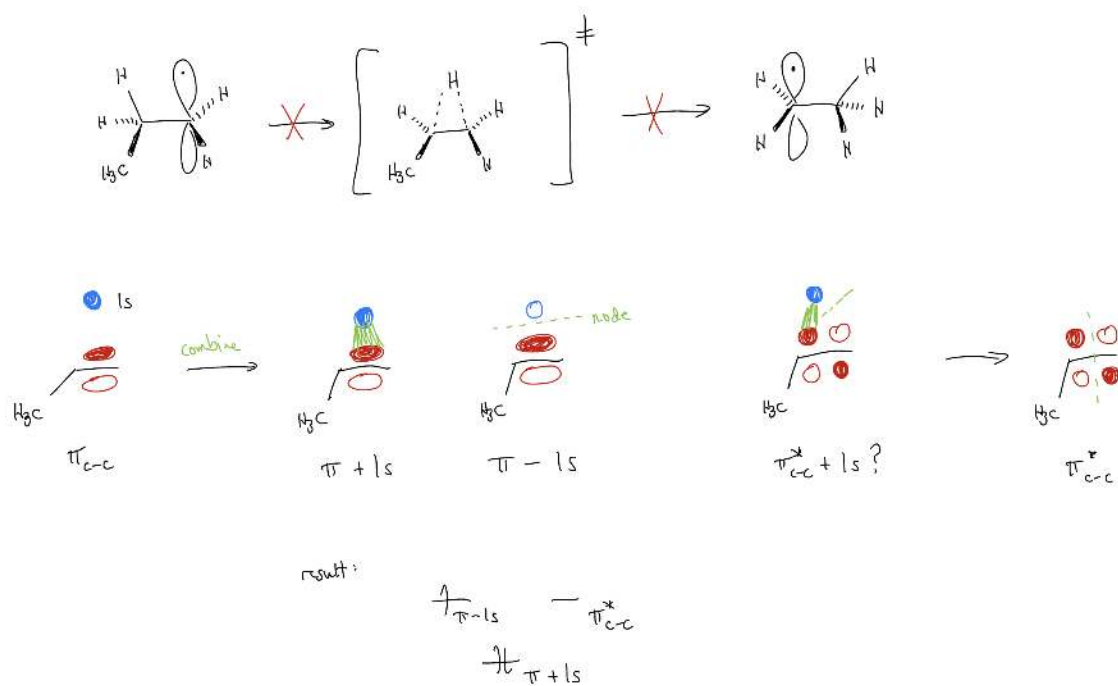


Rearrangement of Radicals

We've said that radical intermediates behave similarly to carbocations – they are electron deficient intermediates. Thus, we might think that once we form a radical, it might rearrange to generate an even more stable radical. In the case of carbocation rearrangements, this normally occurred through 1,2-hydride or 1,2-methyl shifts (which are quite fast). By contrast, the 1,2-shifts of hydrogen atoms or alkyl groups are unknown. In order to understand why, we need to look at the molecular orbital description.



Let's consider the transition state for the rearrangement, in which the hydrogen atom straddles two different carbon atoms. For this, we would need to construct the molecular orbitals for the interaction between a hydrogen 1s orbital, a $\pi_{\text{C-C}}$, and a $\pi^*_{\text{C-C}}$ orbital. This would yield three new molecular orbitals. The 1s orbital interacts with $\pi_{\text{C-C}}$ to give two new molecular orbitals, but there is no interaction with $\pi^*_{\text{C-C}}$. Why? Because there is no interaction between these orbitals in this geometry. Thus, the third molecular orbital is simply $\pi^*_{\text{C-C}}$. The energies of these new molecular orbitals can be determined by counting the nodes. The first molecular orbital has no new nodes, but the next two molecular orbitals have one new node each, and will thus be identical in energy. If we then fill the new molecular orbitals with electrons, we see that there will be an electron occupying an antibonding orbital, and this evidently unstable enough to shut down the migration entirely.

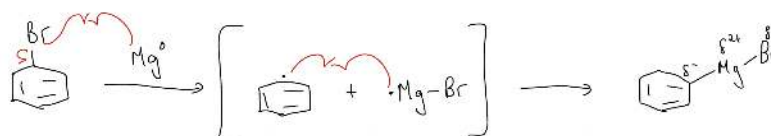


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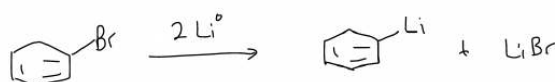
12.3: Organometallics

Organometallics are molecules that contain a carbon-metal bond which has a high degree of covalency. There are two important types of organometallic species: Grignard reagents and organolithium reagents. These molecules are stable at low temperature (some of them are even stable at room temperature). We will use them as reagents in chemical reactions later on, but for now let's talk about how to form them and what they can do as starting materials.

Let's say that we have a bromobenzene. If we were to treat bromobenzene with magnesium metal, the metal would eventually dissolve and R-Mg-Br would form at the end of the reaction. The covalent R-Mg-Br species is known as a Grignard reagent. The reaction is exothermic and occurs in THF or Et₂O (diethyl ether) as solvent. The mechanism of this reaction involves radical-transfer reactions in which a transient carbon-centered radical is formed in the presence of a magnesium-centered radical. Transfer of another electron would form the stable organometallic Grignard reagent:



If lithium metal was used instead of magnesium metal, only one electron transfer event would occur, and an organolithium reagent would form.



Both of these reagents are highly basic. One can think of the carbon atom of the C-M bond (M = metal) as being strongly negatively charged (d⁻). In turn, magnesium and lithium are positively charged (d⁺). In the presence of water (or any protic species), Grignard and organolithium reagents will protonate to give hydrocarbons. This is because the conjugate base (OH⁻) is much more stable than a negatively charged carbon species. Remember that the pK_a of H₂O is 15.7, but that the pK_a of benzene is 43. Thus, water is a much better acid than benzene. Following this logic, if D₂O is used instead of water, one can generate deuterium labeled molecules.



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CHAPTER OVERVIEW

13: Conjugation

13.1: Allyl System

13.2: Dienes

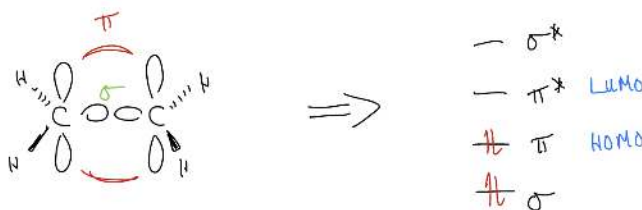
13.3: Diels-Alder reaction

13.4: Diels-Alder Regio- and Stereoselectivity

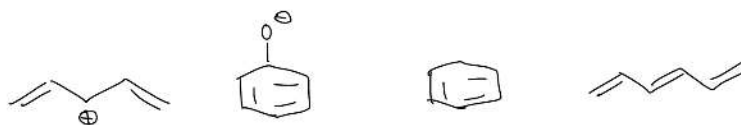
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13.1: Allyl System

We have previously described the molecular orbitals of ethylene, which contains only a single π bond. When we have consecutive double bonds (π systems), the molecular orbital description actually changes dramatically and we say that the system is conjugated.

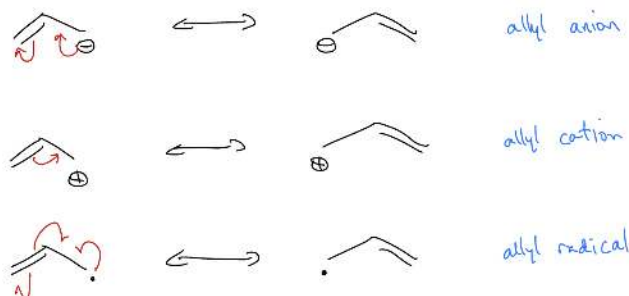


Conjugated systems are present in anything that has resonance delocalization, but it also has implications for simple neutral systems. Electrons are delocalized if π bonds are conjugated. The molecules below have electrons that can spread out over multiple atoms. Thus, our molecular orbital description must account for this.



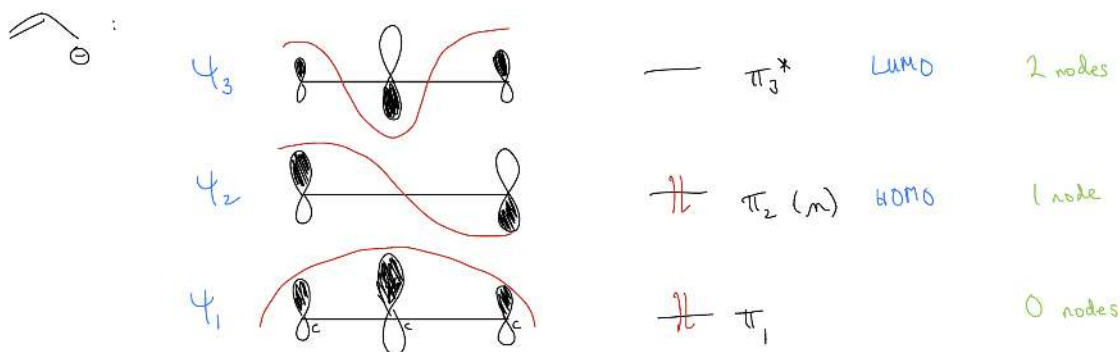
Allyl System

Let's take a look at the simplest system that has conjugation – where electrons can be delocalized over three atoms. This is known as the allyl system.



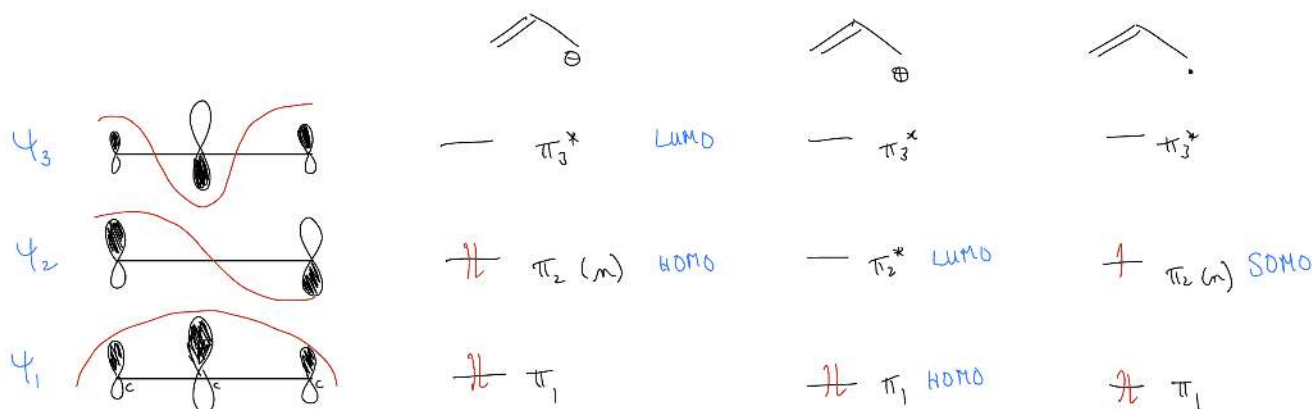
Notice that there is never any way to place the $-$, $+$, or $*$ on the central carbon atom! Why? Let's construct the molecular orbitals for the allyl group's π system.

1. n atomic orbitals combine to form n molecular orbitals
2. lowest energy molecular orbital has zero nodal planes
3. any increase in energy level results in an additional nodal plane

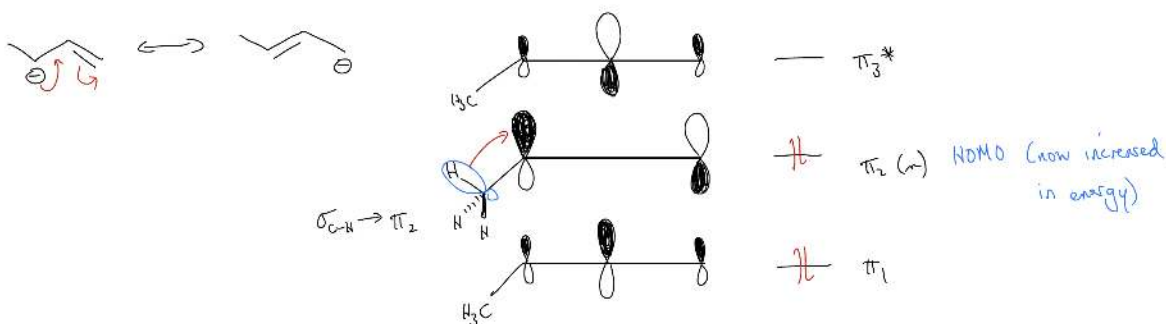


If we consider just the allyl anion, what you might notice is that in the HOMO, the coefficients are equal at the ends of the system (if symmetrical). The electron density is found at the ends, NEVER at the central carbon atom because there is a node there! This should tell you that if the allyl anion is reacting as a nucleophile, the electrons it will use will be the HOMO electrons, and the only atoms that have electron density in the HOMO are the ends!

What this means is that the molecular orbitals will tell us where all of the “chemistry” (reactivity) will occur. It is the same for the allyl cation and the allyl radical and is predicted by the molecular orbitals. All chemistry must occur in π_2 .

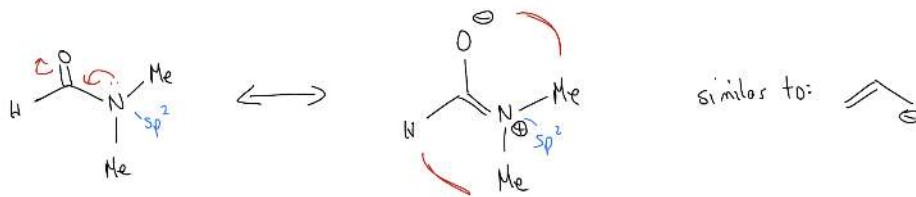


These are all examples of symmetrical systems – what about asymmetric systems? Well, the only thing that changes is the size of the coefficients in the molecular orbital diagram. Consider the asymmetric system below – which carbon would you expect to have more electron density in π_2 ? In other words, which end of the π system is more reactive? It turns out that the resonance form that contains the negative charge on the more highly substituted carbon atom is more reactive because of the extra σ -donation into the π system. This raises the coefficient on this carbon atom and makes it more reactive (better orbital overlap with an electrophile).



What about a masked allyl system? In *N,N*-dimethylformamide (DMF), the electrons on nitrogen can delocalize into the π system of the carbonyl to create a dipolar resonance form with the negative charge on oxygen (making oxygen more basic). Because this

delocalization occurs similarly to a simple allyl system, we say that the nitrogen atom is sp^2 hybridized and NOT sp^3 hybridized, and the lone pairs on nitrogen are in an atomic p orbital that can align with the π_{C-O} bond. This means that there is partial double bond character in the C-N bond and the C-O bond. What effect does this have? Well, it means that in the dipolar resonance form, the methyl groups are in different magnetic environments since there is not rotation about the C-N bond. Thus, there are two peaks for the methyl groups in the ^{13}C NMR, not one.

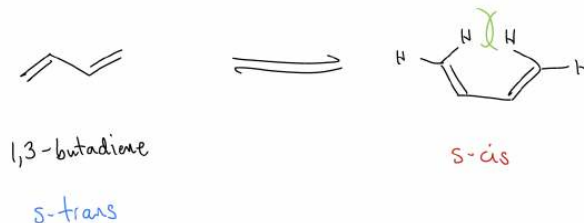


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13.2: Dienes

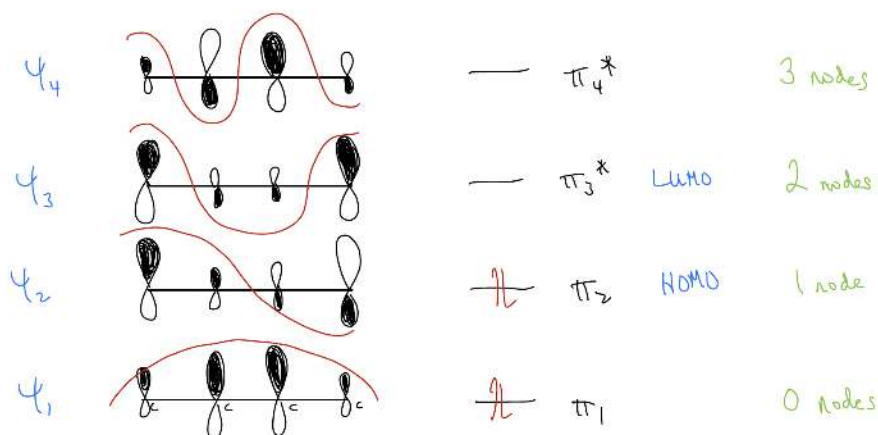
Now that we have discussed allyl systems, in which electrons are conjugated over three atoms, what if we extended the conjugation to four atoms? How would that change the molecular orbital description?

1,3-Butadiene is the simplest conjugated four-atom system. It exists in two different forms, s-cis and s-trans, with the latter more favorable by 2.8 kcal/mol because of steric strain.



One peculiar thing about 1,3-butadiene is that there is restricted bond rotation about the C₂-C₃ bond. This is odd since there is normally free rotation about the σ -bond (except, as you've seen, in cases like DMF). Well, maybe there is something similar going on. If butadiene were really just two isolated double bonds, then there should be free rotation, but because there is restricted rotation, somehow these double bonds are interacting with each other.

Let's look at the molecular orbital diagram for 1,3-butadiene.

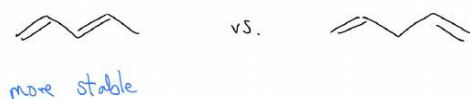


If you take a look at the ψ_1 and ψ_2 wavefunctions, you might notice that the size of the bonding interaction in ψ_1 between C₂-C₃ is stronger than the antibonding interaction between C₂-C₃ in ψ_2 . So, they don't fully cancel each other out, meaning there is net bonding between C₂-C₃. This would not be the case if the coefficients in ψ_1 were all equal – they MUST be larger at C₂-C₃. This should make sense now because the barrier to rotation between s-cis and s-trans is 6.5 kcal/mol.

Besides explaining the restricted bond rotation between C₂-C₃, why is this important? Here's a thought question: if butadiene is acting like a nucleophile, then it is the HOMO that reacts. So, which carbons react? Of course, the ones at the ends, which have greater electron density (larger coefficients).

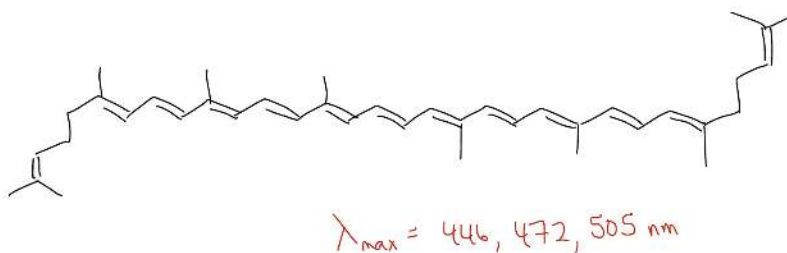
What are the effects of conjugation (or more and more conjugation)?

1. Conjugated systems have greater stability than nonconjugated systems. This is a thermodynamic effect.

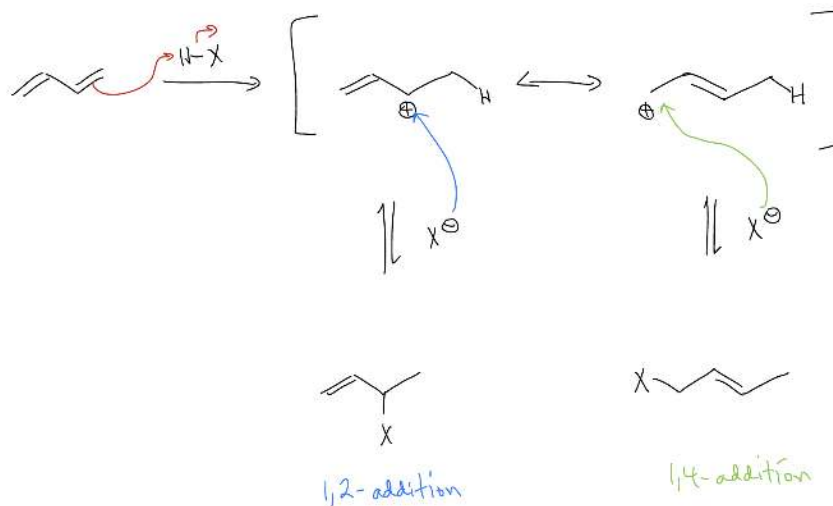


2. Conjugated systems are more reactive than nonconjugated systems. This is a kinetic effect. The LUMO of conjugated systems is lower, so it more readily reacts with a nucleophile (it is more electrophilic). The HOMO of conjugated systems is higher, so it more readily reacts with an electrophile (it is more nucleophilic).

3. As you add more and more conjugation, the HOMO goes up (kinetic effect, more nucleophilic), the LUMO comes down, but the ψ_1 always goes down (thermodynamic effect, more stable). This is the essence of UV-Vis spectroscopy. Electronic transitions occur from $\pi \rightarrow \pi^*$. As more conjugation lowers the HOMO-LUMO gap, the wavelength needed to promote that transition gets longer. Eventually, it becomes so long that it becomes visible. This gives rise to the color we see on leaves in the fall due to conjugated dienes in lycopene and carotene.



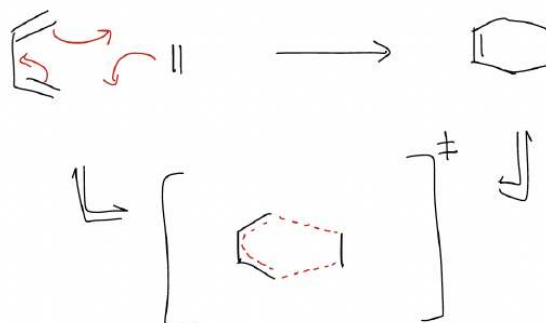
4. Dienes react with electrophiles like HX or X_2 like any normal π_{C-C} bond, but because the intermediate carbocation can undergo resonance stabilization, there is the possibility of obtaining not only the 1,2-addition product, but also the 1,4-addition product. Usually the 1,2-addition product predominates, especially under cold temperatures and short reaction time, indicating that it is under kinetic control. At higher temperatures and longer reaction time, the 1,4-product predominates, indicating that it is under thermodynamic control.



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13.3: Diels-Alder reaction

Dienes participate in a [4+2] cycloaddition reaction to generate cyclic alkenes. It is an incredibly useful way of making six-membered rings. Remember that for cycloadditions, there is a concerted movement of electrons in the transition state such that bonds are being formed and broken simultaneously.



Key features of the Diels-Alder reaction:

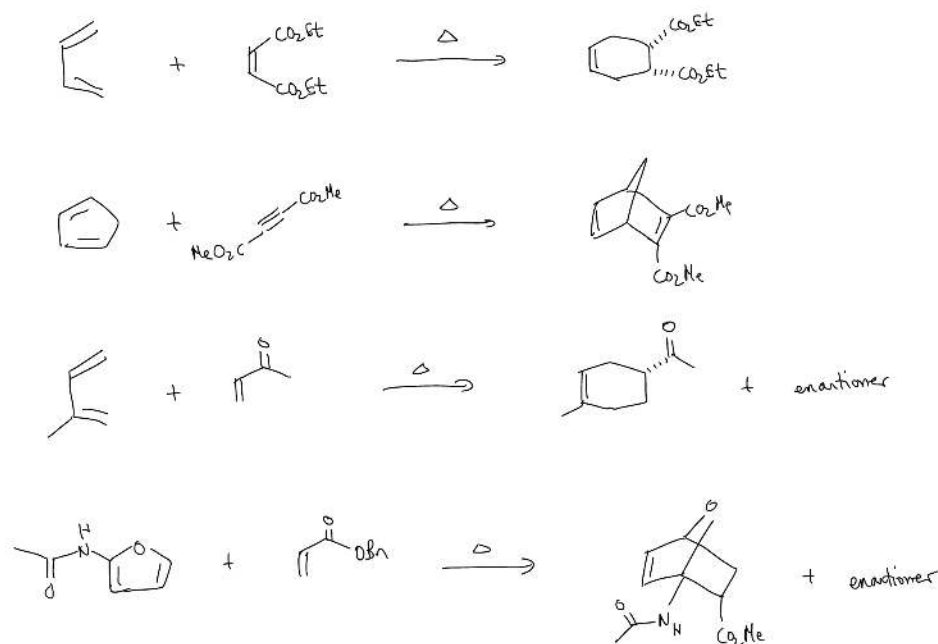
1. concerted cycloaddition
2. 6π electron transition state, which is especially stable (aromatic)
3. reversible in principle
4. thermal (Δ) or photochemical ($h\nu$)
5. stereospecific
6. thermodynamically favored (exchange 2 π bonds for 2 σ bonds), but entropically unfavorable.

The reacting partners for the Diels-Alder reaction are:

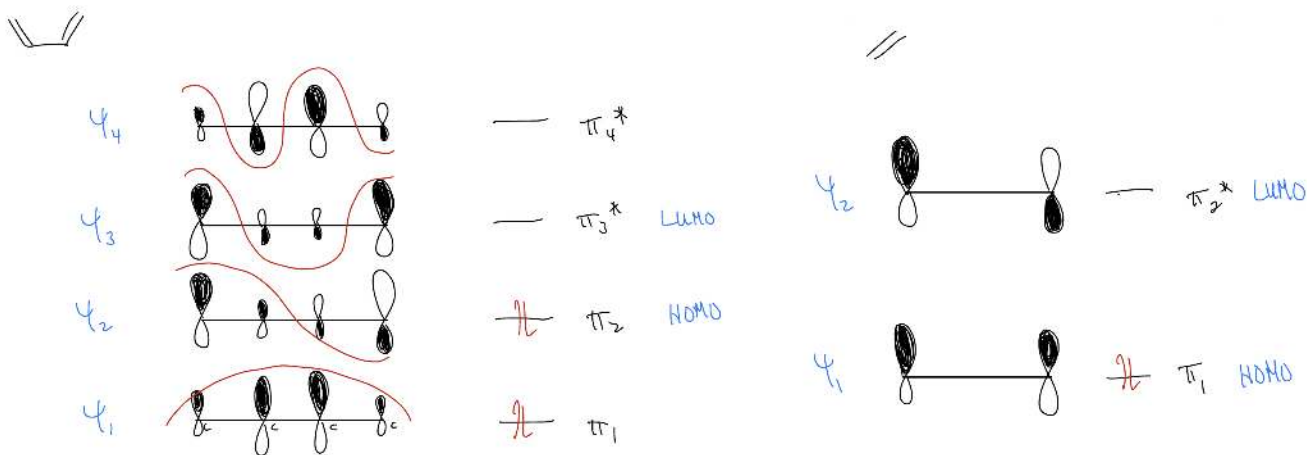
diene (4π electrons) – in order for a reaction to occur, it must be able to adopt the s-cis conformation

dienophile (2π electrons) – literally, “diene-loving,” a simple alkene

Here are several examples of Diels-Alder reactions – can you draw a mechanism?

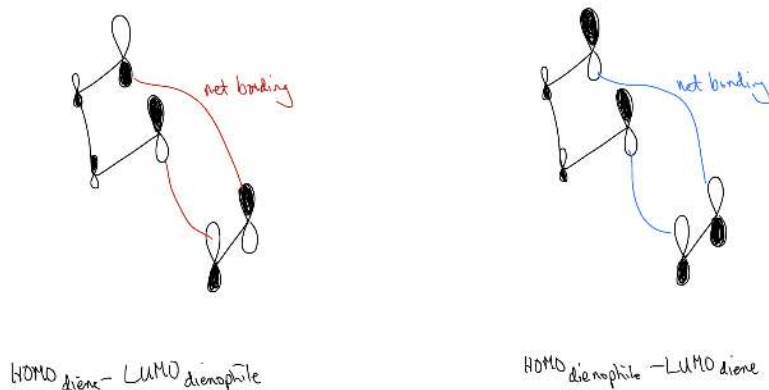


Looking at the reactions above, you may be able to draw a mechanism but are still curious why the products have the observed regioselectivity and stereoselectivity. So, let's take a look at the molecular orbital description for the simplest Diels-Alder reaction, between 1,3-butadiene and ethylene:



In order for a reaction to occur, we need orbital overlap that reinforces bonding interactions. In other words, they need to be “in phase.” We call this control by orbital symmetry and we say that the following processes are “symmetry allowed.”

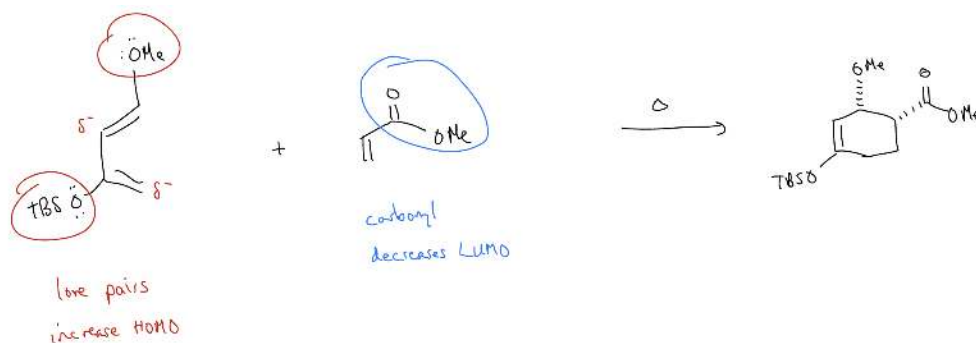
1. Normal electron demand Diels-Alder
2. Inverse electron demand Diels-Alder



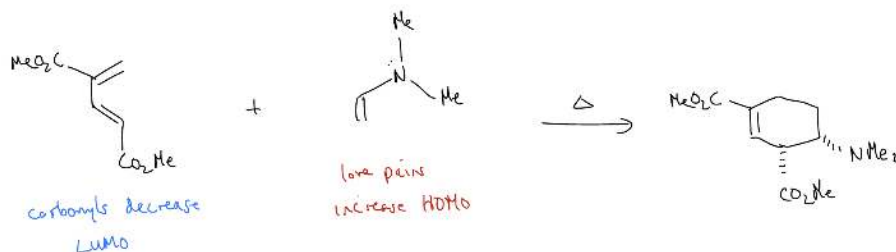
While these two processes are allowed theoretically, the energy gap between HOMO and LUMO is sometimes prohibitively larger and will require harsh conditions (high pressures and temperatures). So, how do we improve this energy difference?

Normal electron demand Diels-Alder – add electron density to the diene (raise HOMO) and remove electron density from the dienophile (lower LUMO).

- add electron-donating groups to the HOMO: -OMe, -NR₂, -R (things with lone pairs or ability to σ -donate, which push electron density into the π system, raising HOMO)
- add electron-withdrawing groups to the LUMO: -NO₂, -CN, -CF₃, -C(O)X (anything electronegative or in conjugation, which pulls electron density out of the π system, lowering LUMO)



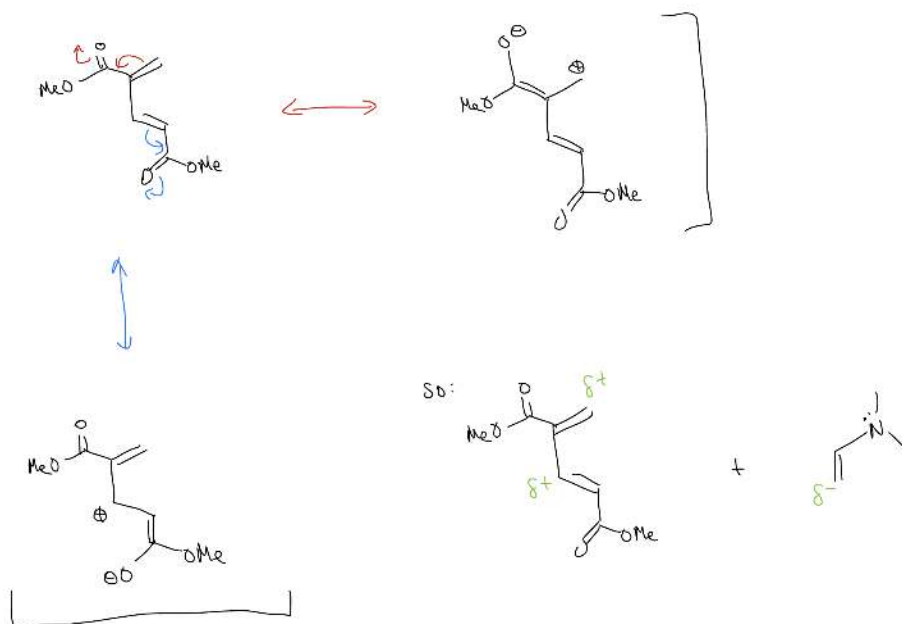
Inverse electron demand Diels-Alder – add electron density to the dienophile (raise HOMO) and remove electron density from the diene (lower LUMO). The types of electron-donating and electron-withdrawing groups are the same as above.



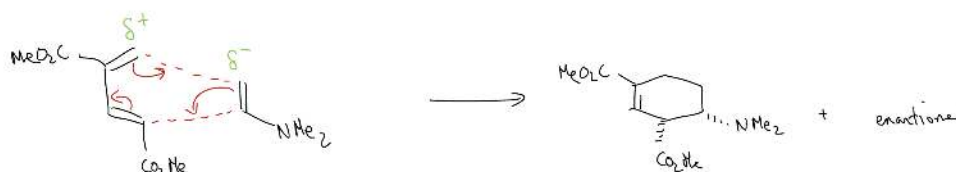
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13.4: Diels-Alder Regio- and Stereoselectivity

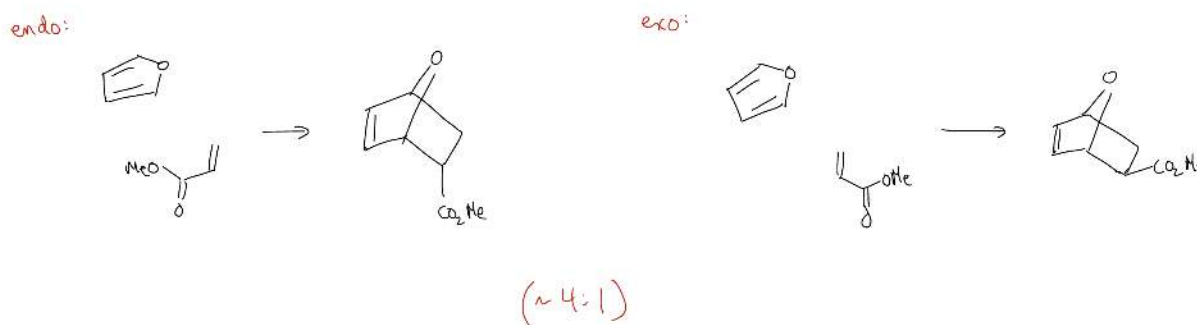
Despite all of this, it still might not be obvious why we observe the regioselectivity and stereoselectivity we do. In general, Diels-Alder reactions proceed so that an atom with the largest coefficient in the HOMO will pair with the atom with the largest coefficient in the LUMO. Take, for example, the example above. Because of resonance, the dienophile would have electron density concentrated on the terminal carbon. In the diene, the largest coefficient will also reflect important resonance structures. Since we are talking about a LUMO, we are looking for a position that has partial positive charge.



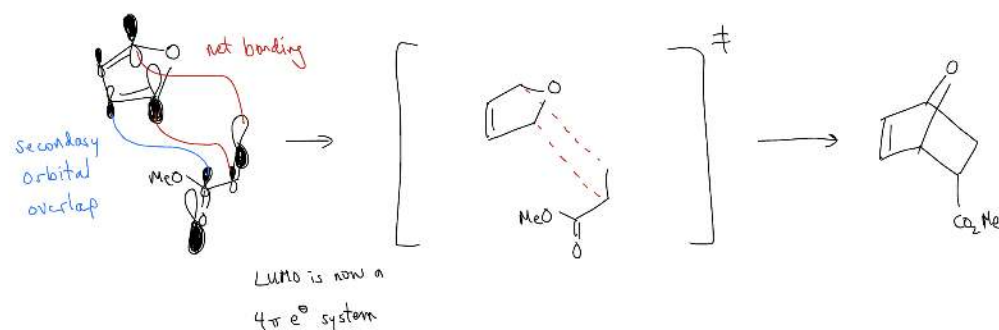
So, when you are trying to determine regioselectivity, line up the most reactive atoms:



What about stereoselectivity? In general, Diels-Alder reactions can give two products: endo and exo, which form based on the approach of the dienophile to the diene. The endo product is normally favored.

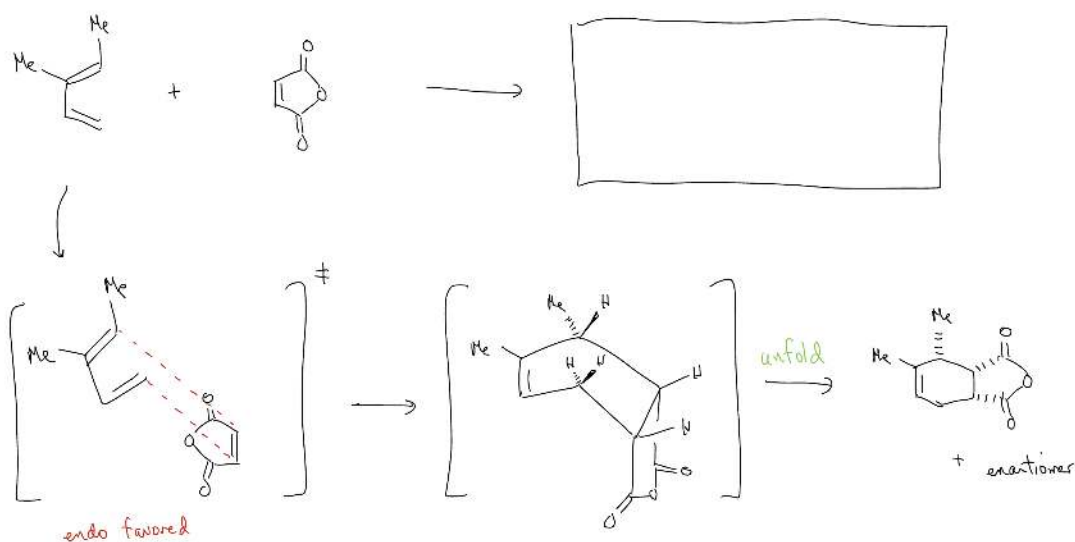


What explains the endo selectivity? Again, we must consult molecular orbital theory. Consider the following normal Diels-Alder reaction, where the Frontier molecular orbitals ($\text{HOMO}_{\text{diene}}$ - $\text{LUMO}_{\text{dienophile}}$) are drawn:

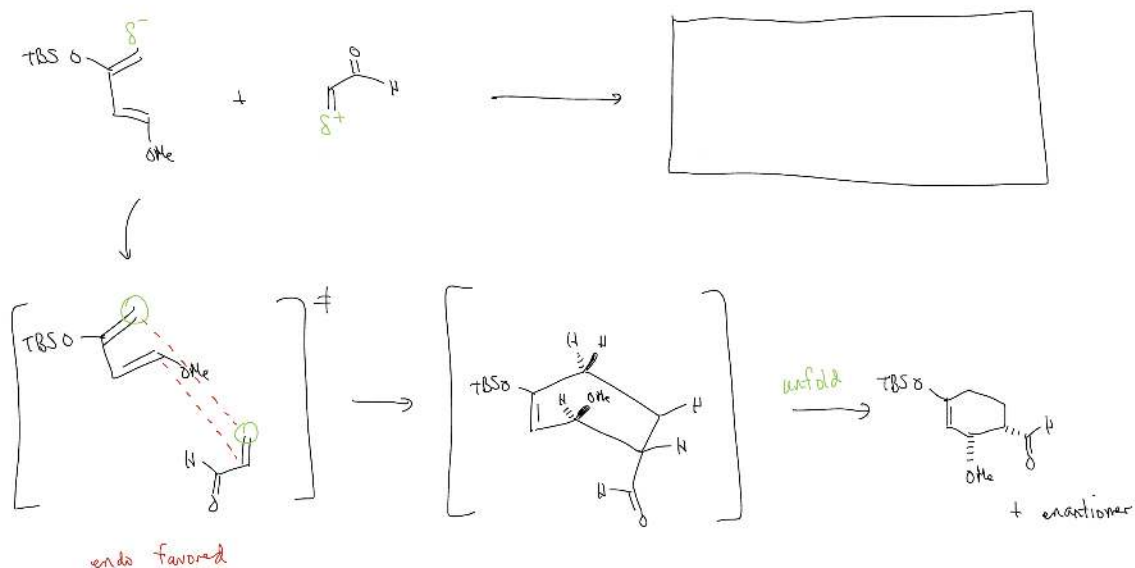


In the transition state, there is an extra bonding interaction with the carbonyl and the C_3 carbon of the diene. This interaction does not happen in the exo transition state since it is pointed in the opposite direction. This additional bonding interaction is called secondary orbital overlap, and requires the presence of a π system to overcome the steric strain of the endo transition state.

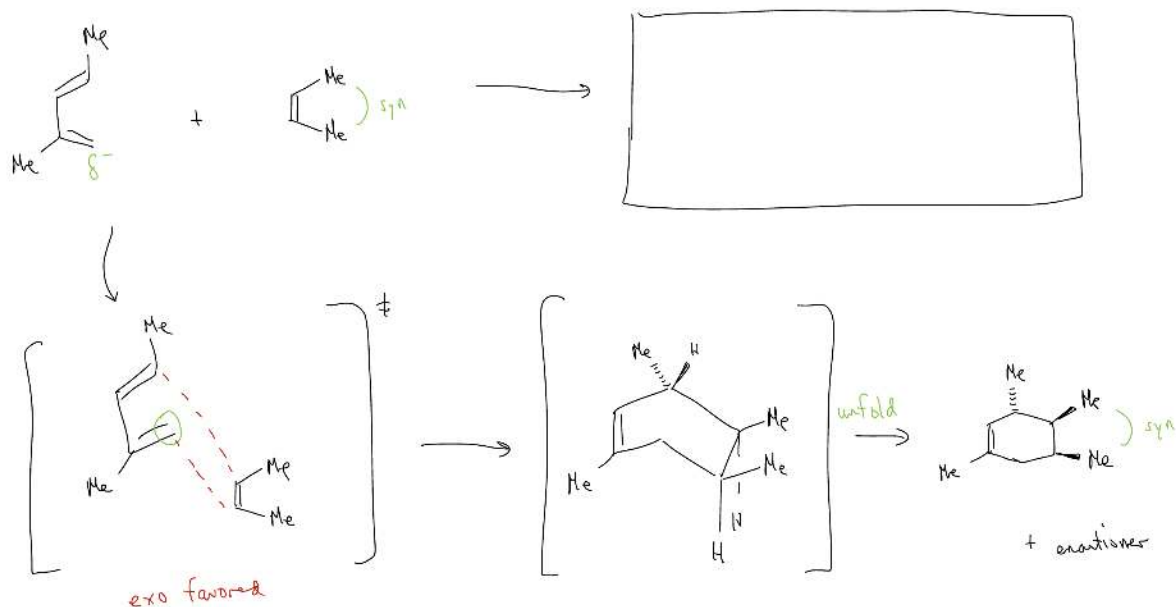
How can we predict the stereoselectivity? By drawing the transition states!



Here's an example that combines prediction of both regioselectivity and stereoselectivity:



And, finally, one last example:



This time, the exo product is favored because there is no possibility for secondary orbital overlap. Steric considerations dominate the transition state, so exo is formed. Notice also that the Diels-Alder reaction is stereospecific – the stereochemistry of the dienophile is retained in the product because the cycloaddition is a concerted process.

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CHAPTER OVERVIEW

14: Aromaticity

[14.1: Conjugation vs. Aromaticity](#)

[14.2: Frost's Circle](#)

[14.3: Heteroaromaticity](#)

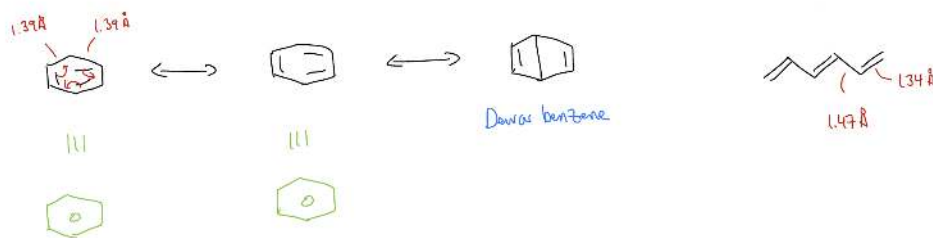
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14.1: Conjugation vs. Aromaticity

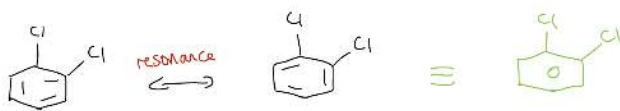
Let's recall our discussion about conjugation. Remember that as more and more p systems become conjugated, the HOMO-LUMO gap shrinks. The energy required to excite an electron from $\pi \rightarrow \pi^*$ decreases, or shifts to longer wavelengths of light. For example, hexatriene has a λ_{max} of 330 nm. Now, what if we were to place these same 6 p electrons not in a straight chain, but in a cyclic ring. Well, we get the molecule benzene. Notice that the λ_{max} of benzene (255 nm) is considerably different than hexatriene – it takes much more energy to excite an electron from HOMO to LUMO. As an aside, this wavelength of light is often used to detect quantify proteins because they contain phenyl rings in one of their amino acid side chains.



These data tell us that there is something interesting going on. Another clue comes from the bond lengths of benzene and hexatriene. In hexatriene, the double bond is 1.34 Å but the single bond is 1.47 Å. In benzene, all of the C-C bonds are identical in length. In order for this to be the case, the Lewis structure is incomplete, and we draw a resonance form that indicates the bonds are identical. We often abbreviate benzene as a six-membered ring with a circle inside to indicate that the electrons are moving throughout and all bonds are equal. There is also a third resonance form called Dewar benzene, which is only about 6% of the resonance contribution.



Given this, does 1,2-dichlorobenzene have one or two isomers? In other words, are the two structures below the same? Indeed, these molecules are the same.

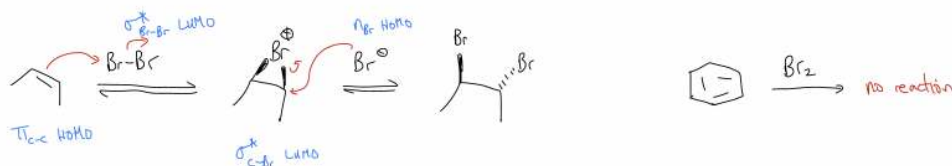


How about another example – does cyclooctatetraene (COT) have one or two isomers? One might think that since we can draw a circle of π electrons inside the ring, that there is only one isomer, but that would be incorrect. COT has two isomers, and there is an equilibrium between them ($E_a = 12\text{-}15$ kcal/mol). So, why the difference?

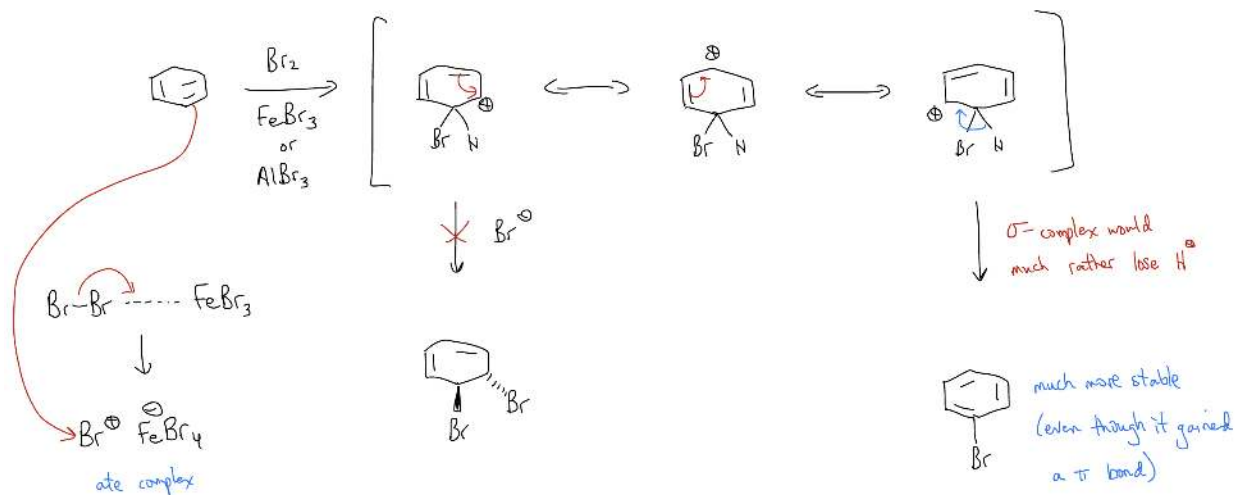


Well, the thing that makes benzene so special is a property called aromaticity. We say that benzene is aromatic (originally because these compounds smelled sweet) and that COT is antiaromatic. You might guess that the difference have something to do with benzene having 6 π electrons and COT having 8 π electrons, but that's not the whole story. We will come back to how one would predict or define aromaticity in a second, but let's look quickly at the reactive properties of aromatic compounds, for it confirms the structure of benzene we have drawn. During the bromination of 2-butene, a bromonium ion forms, followed by S_N2 attack to yield a *trans*-dibromide product. Overall, we lose a π bond (63 kcal/mol) but gain two $\sigma_{\text{C-Br}}$ bonds (2×67 kcal/mol). Overall, this is exothermic.

So, what happens when we try to brominate benzene? There is no reaction. This tells us that benzene is a worse nucleophile. Recall last time that conjugated systems were both more nucleophilic and more stable. In other words, the result with benzene completely contradicts this principle.



But when we treat benzene with Br_2 in the presence of a Lewis acid, a reaction occurs.



These results suggested to those who originally studied it that there was something “special” about benzene that made it a thermodynamic sink. This turned out to be aromaticity, which is characterized by electrons flowing in a complete circuit in a planar ring. The structure itself was first proposed by August Kekulé who dreamt that a serpent was dancing around a six-membered ring while biting its own tail.

What makes benzene so “special?” Resonance energy, or what I like to call the aromatic stabilization energy.

Aromatic Stabilization Energy

Let's consider heats of hydrogenation for various alkenes to understand aromaticity better.

a) Single isolated double bond



b) Two isolated double bonds



c) Conjugated double bonds



Overall, the starting material is more stable, so this reaction is exothermic (conjugation adds ~2 kcal/mol of stability)

d) Benzene



Benzene is aromatic, and thus much more stable than cyclohexatriene. One might predict that the ΔH_0 by the following formula: $3 \times (-28.5 \text{ kcal/mol}) = -85.5 \text{ kcal/mol}$, and if you factor in the contribution from conjugation, it should be $3 \times (2 \text{ kcal/mol}) = 6 \text{ kcal/mol}$ higher, so -79.5 kcal/mol . However, there is huge difference between this predicted value and the observed value. It tells us that mere conjugation is not enough to explain the stabilization - there is something greater, which we call the aromatic stabilization energy. How large is it? Well, $85.5 - 50 = 35.5 \text{ kcal/mol}!!!$

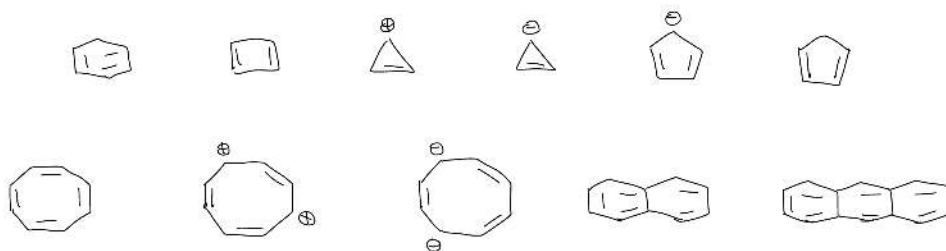
Huckel's Rule

So, how do we determine or predict aromaticity? We follow Huckel's rule - "things that are aromatic have a closed $4n+2$ loop of π electrons that are completely aligned." Essentially, there are four factors:

1. cyclic - things that are aromatic must be rings
2. fully conjugated - no intervening sp^3 hybridized atoms
3. planar - in order to align properly, these molecules must be flat
4. $4n+2$ π electrons in the system, where n is an integer or zero.

Systems that abide by rules 1-3, but have $4n$ π electrons are said to be antiaromatic.

Let's do some examples - are these molecules aromatic or antiaromatic?



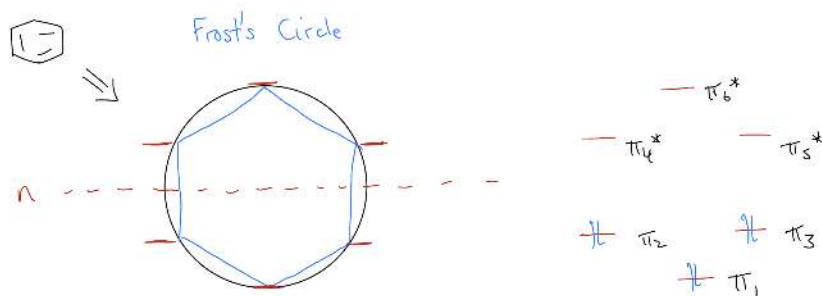
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14.2: Frost's Circle

Huckel's rule is easy to remember, but what is the reason behind the aromaticity phenomenon? For that, we need to look at the molecular orbital description. Let's take a look at benzene first.

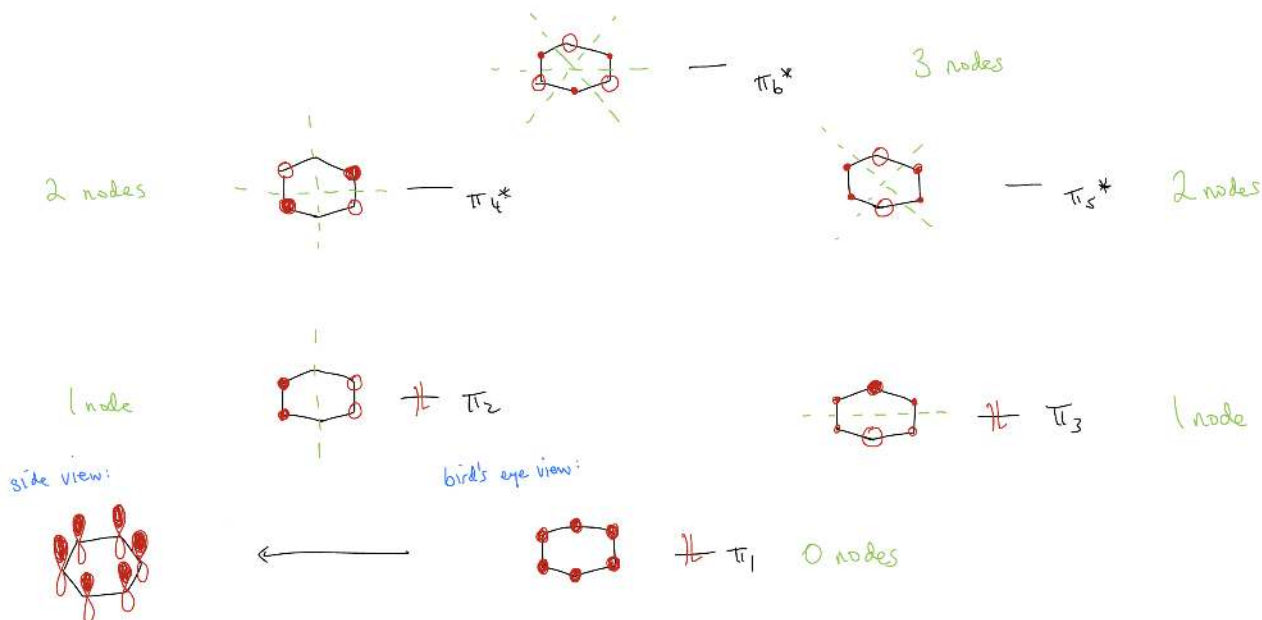
Frost's Circle

The best way to visualize the molecular orbitals for anything aromatic (or antiaromatic) is to inscribe a polygon inside a circle (Frost's circle). Draw a circle and then inscribe the polygon so that one point of the polygon touches the bottom of the circle. Then, fill in the rest of the polygon. Each point that touches the circle corresponds to a molecular orbital. The midpoint of the circle is the nonbonding orbital energy level.

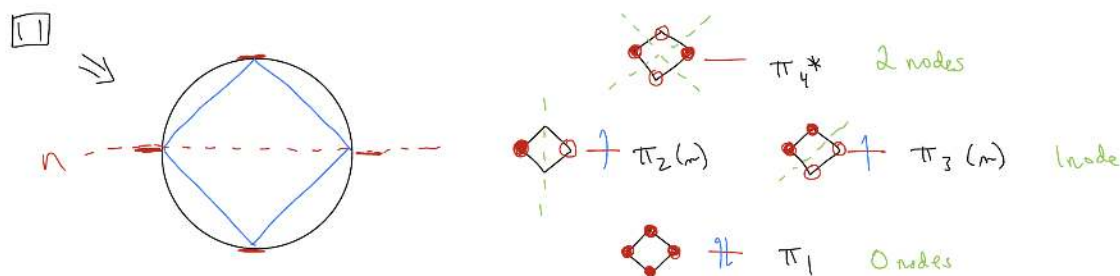


Notice that π_2 and π_3 are degenerate, as are π_4^* and π_5^* . The aromatic stabilization energy is 35.5 kcal/mol.

What do the orbitals look like? A bird's eye view is shown below (with a view from the side provided for π_1 only). Notice the increase in the number of nodes as you increase energy levels.



So, with this method, can we see why molecules are antiaromatic? Let's take cyclobutadiene.



Two orbitals in cyclobutadiene are degenerate and lie at the nonbonding energy level, so each orbital gets one electron (hence, non-bonding). This suggests that cyclobutadiene should really be drawn like a diradical. Since paired electrons are lower in energy, this makes cyclobutadiene extremely reactive. In this case, it blows itself up (decomposes) by making two molecules of acetylene, or it dimerizes.



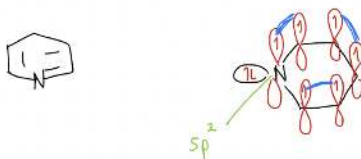
When something is antiaromatic, it will do everything in its power to break conjugation, including becoming a diradical or puckering the ring so it is no longer planar. Try these other examples and see if you can show why they are aromatic or antiaromatic.



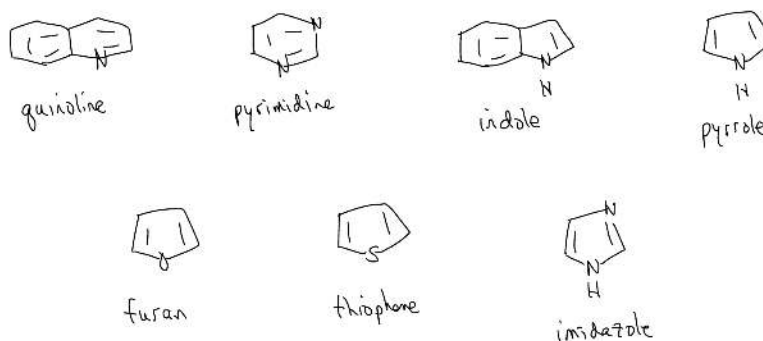
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14.3: Heteroaromaticity

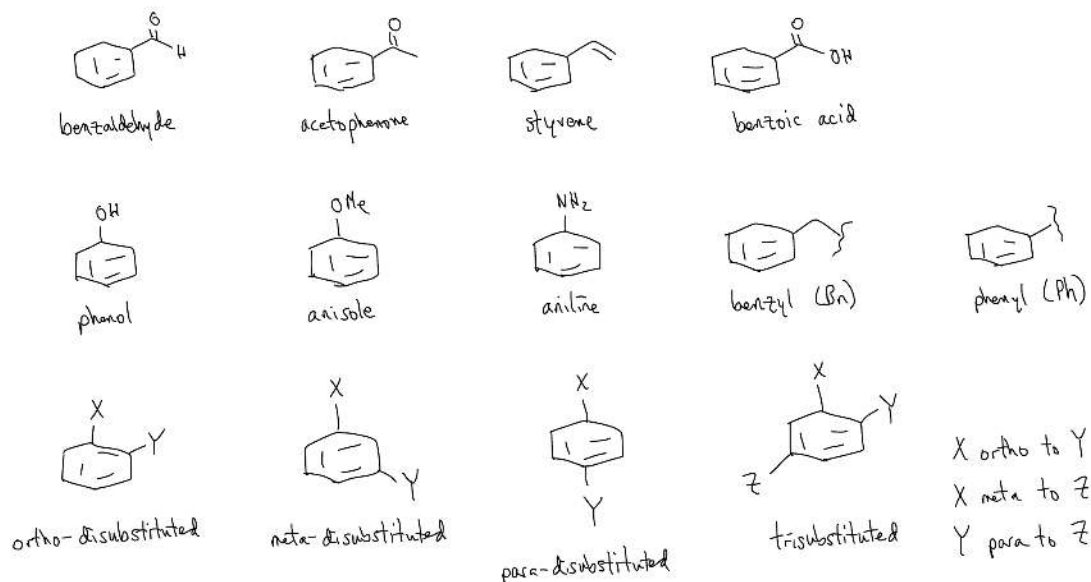
Aromaticity can also occur when atoms other than carbon are present in the ring. Pyridine is a good example. The nitrogen in pyridine is sp^2 hybridized, where the sp^2 orbital contains the lone pair and the atomic p orbital contains a single electron that is pairing with another electron in an atomic p orbital to create a π bond. The aromatic stabilization energy for pyridine is 32 kcal/mol (much less than benzene). Heteroaromatics are higher in energy than benzene. Think of it this way – heteroatoms do not like sharing their electrons because they are more electronegative.



How about other aromatics?



Here is some additional nomenclature to learn:



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CHAPTER OVERVIEW

15: Aromatic Substitution

[15.1: Electrophilic Aromatic Substitution](#)

[15.2: Regioselectivity in Electrophilic Aromatic Substitution](#)

[15.3: Multiple Substituents and Heteroaromatic Rings](#)

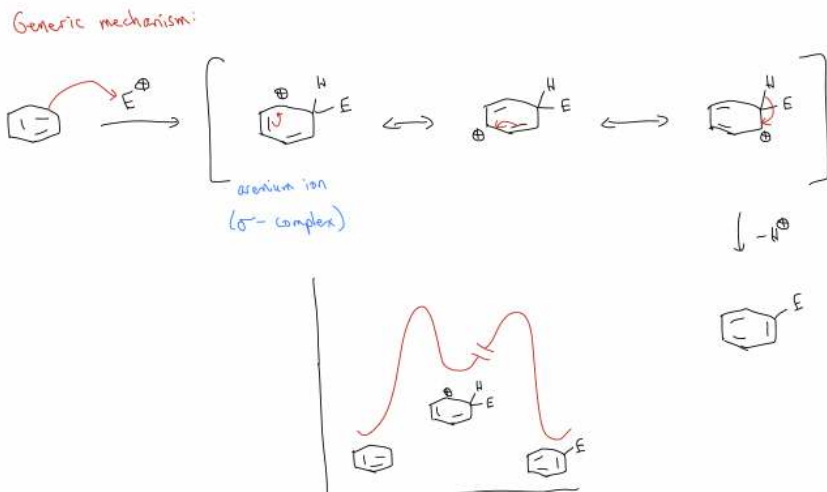
[15.4: Nucleophilic Aromatic Substitution](#)

[15.5: Other Reactions of Aromatics](#)

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15.1: Electrophilic Aromatic Substitution

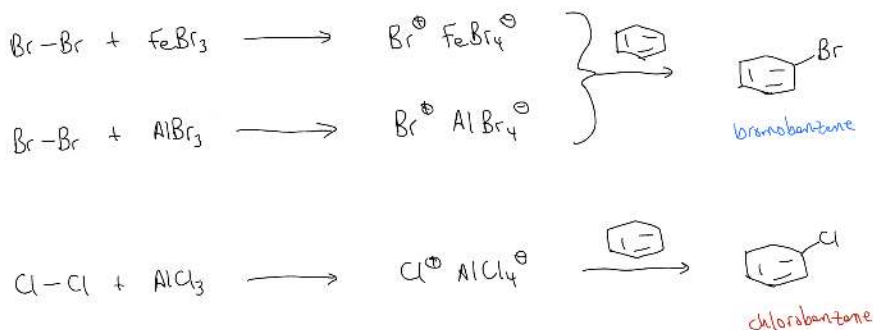
Since the π electrons in an aromatic ring are lower in energy than a simple alkene, one must overcome the aromatic stabilization energy for reaction with an electrophile to occur. Thus, one needs a very strong electrophile (one that normally has a full positive charge and thus a very, very low LUMO). Alternatively, one could add a substituent group that increases the nucleophilicity of the benzene ring, raising the HOMO. Let's do the first case – reaction between a benzene ring and a strong generic electrophile, E^+ .



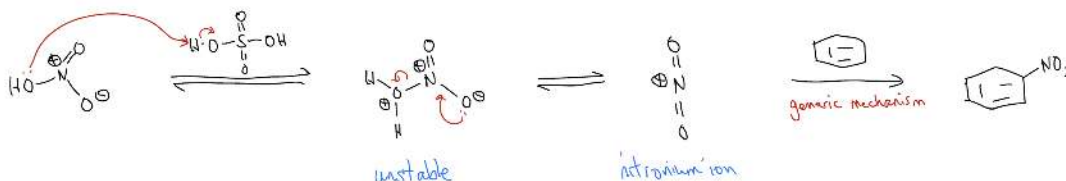
What kinds of electrophiles are used here?

1. halogenation – X^+ ($X^{\delta+}$ does not work, ie. Br_2 does not work by itself)

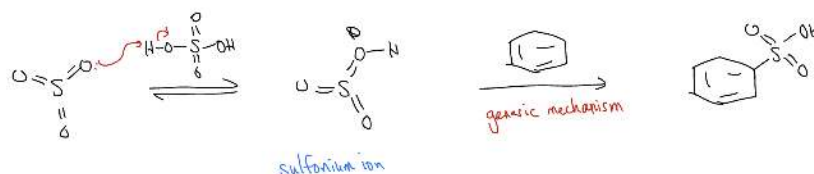
must add a Lewis acid:



2. nitration – NO_2^+ (nitronium ion); normally use HNO_3/H_2SO_4 , but there are also stable salts that are rarely used (NO_2BF_4 , NO_2PF_6).

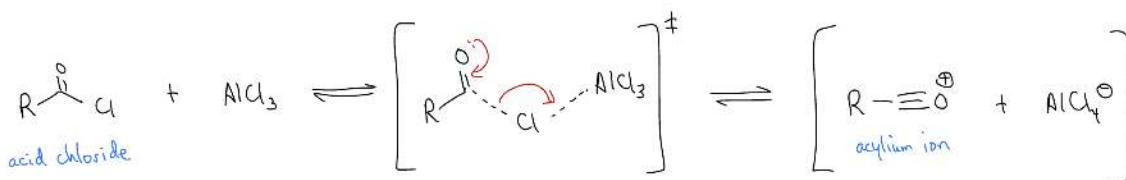


3. sulfonylation – SO_3H^+ (sulfonium ion); use H_2SO_4/SO_3 (fuming sulfuric acid)

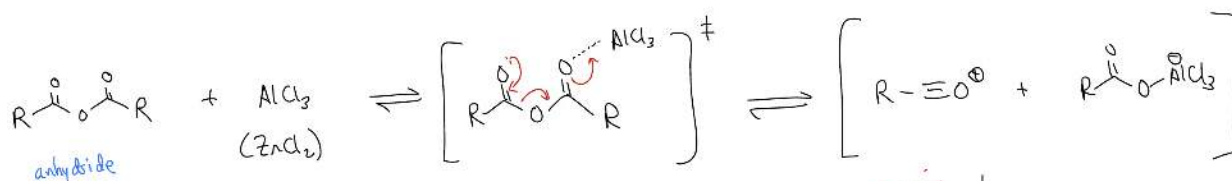


4. Friedel-Crafts acylation - (acylium ion)

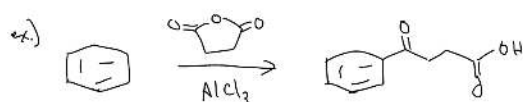
a. intermolecular processes: use Lewis acid and either acid chloride or anhydride.



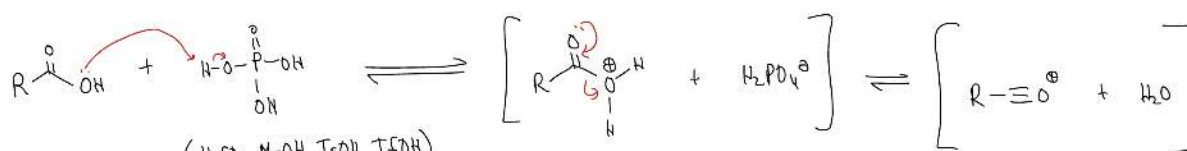
generic mechanism ↓



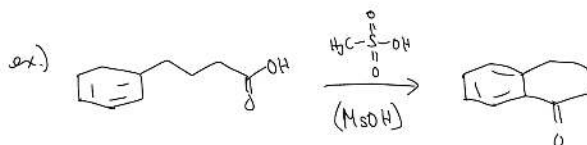
generic mechanism ↓



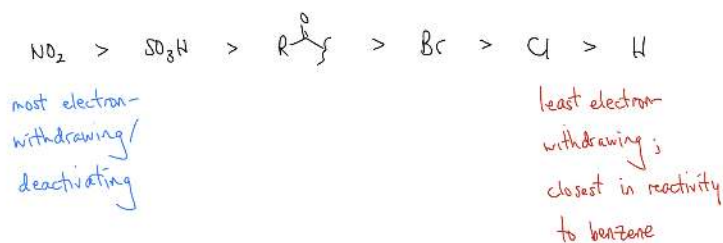
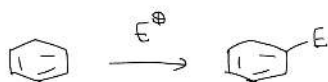
b. intramolecular processes: use a protic acid or a Lewis acid



generic mechanism ↓



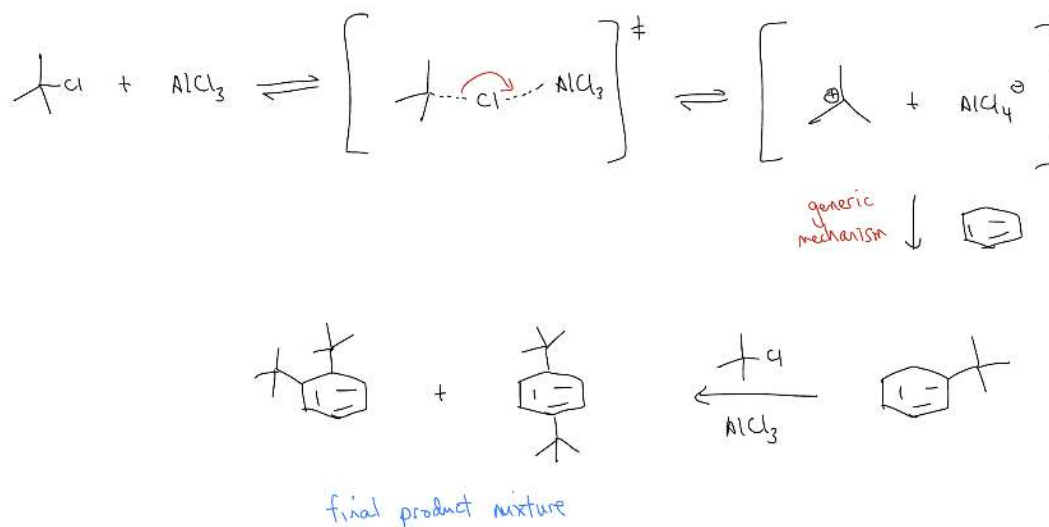
Now, so far, if we had to describe the types of groups we are adding to the benzene ring, we would say they all are deactivating. These groups are all electron-withdrawing and pull electron density from the ring, lowering its reactivity even further (lowers both HOMO and LUMO). This makes the product less nucleophilic than the starting material. Can we rank these substituents in terms of ability to deactivate (or most electron-withdrawing ability)?



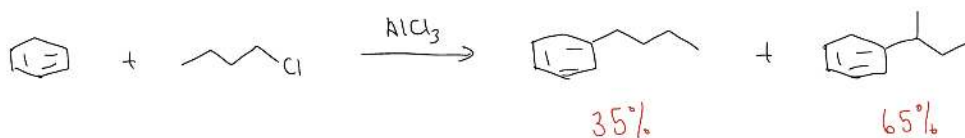
But what if we wanted to add an electron-donating group to the benzene ring?

5. Friedel-Crafts alkylation – R^+ (2° or 3° carbocation)

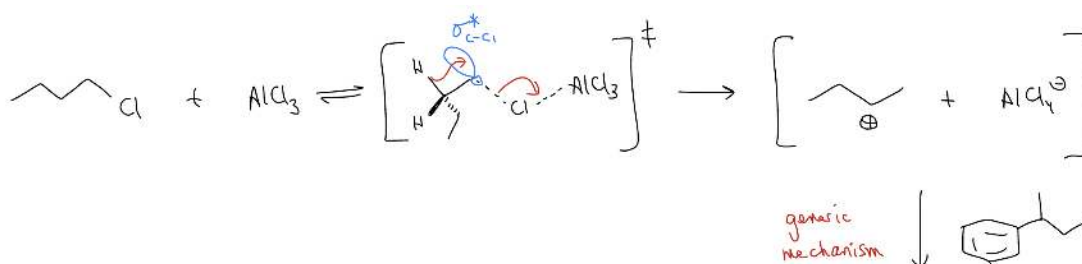
a. use alkyl halide + AlCl_3



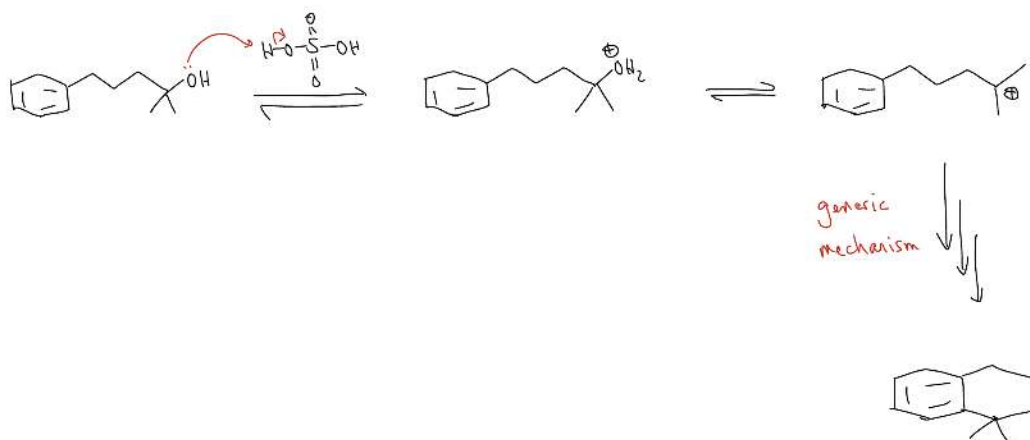
This reaction is very difficult to stop at monosubstitution because the initial product mixture is not more nucleophilic than the starting material (tBu is electron-donating, and thus activating to the benzene ring). One pitfall of this reaction is that some carbocations are subject to rearrangement. For example:



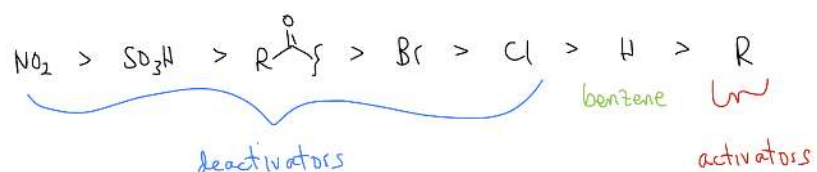
How does this occur? The major pathway proceeds through rearrangement to a secondary carbocation. Thus, better ways have been developed to add a 1° alkyl chain onto a benzene ring.



b. use alcohol + protic acid



So, now we can include alkyl groups in our reactivity series:



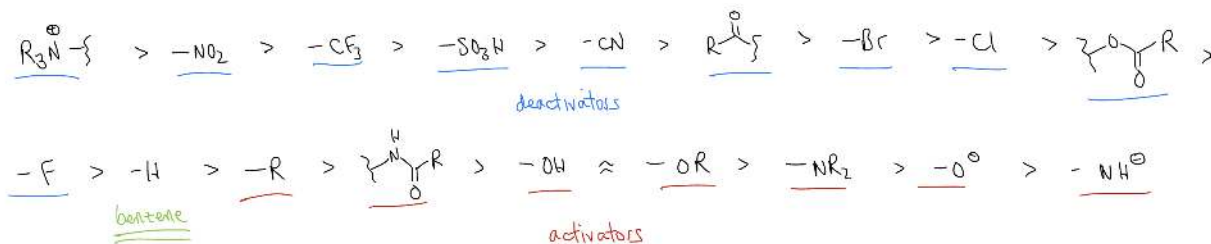
15.1: Electrophilic Aromatic Substitution is shared under a [not declared](#) license and was authored, remixed, and/or curated by LibreTexts.

15.2: Regioselectivity in Electrophilic Aromatic Substitution

We now have a good list of deactivating and activating groups that can be attached to the benzene ring, but two questions remain:

1. Are there other groups to add to this list? YES!
2. What do any of the groups in the reactivity series do to reactivity? A LOT!

Here is a longer list of substituents that may be directly attached to a benzene ring:



Why is something deactivating?

- induction through the σ -network; ex. Br, Cl, F are all electronegative
- resonance delocalization pulls electron density out of the ring; ex. NO₂, CN, R(C=O)

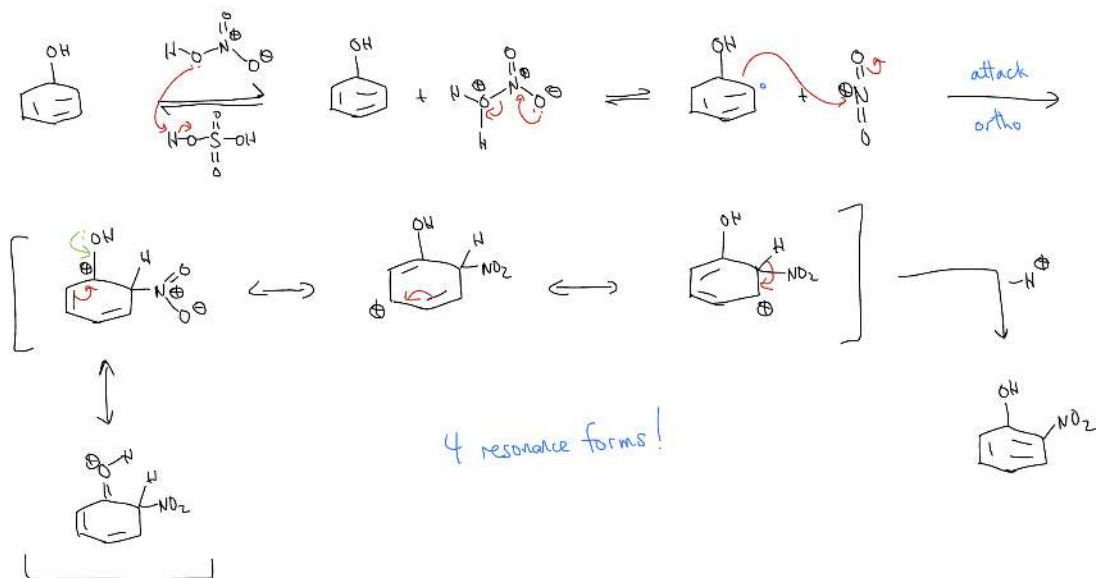
Why is something activating?

- a lone pair or π bond is directly aligned with the π system and can participate in resonance
- a σ bond is directly aligned with the π system and can participate in σ -donation

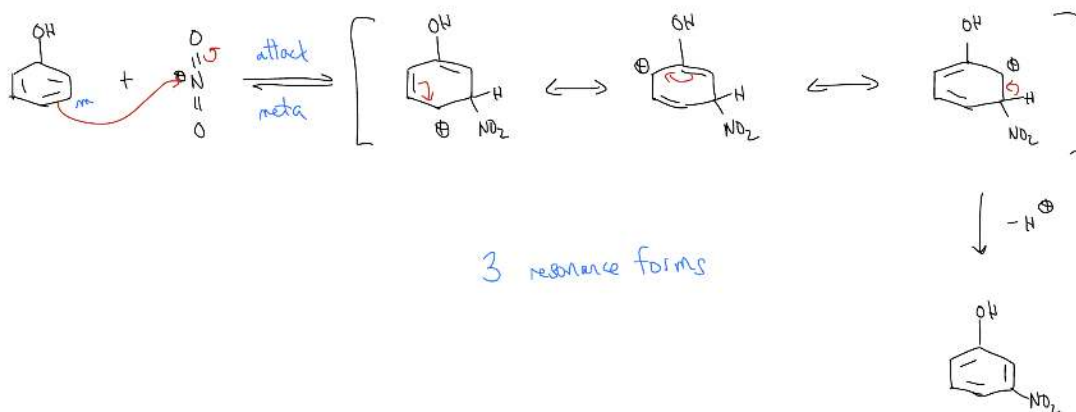
None of this tells us anything about *where* an electrophile will substitute if these groups are already on the ring. What is the *ortho*-, *meta*-, or *para*-directing ability of these groups? In other words, what is the regiochemistry of these reactions?

Let's take the nitration of phenol. One two of a possible three monosubstituted products form (*ortho* and *para*). Why not *meta*? Well, let's look at the mechanism:

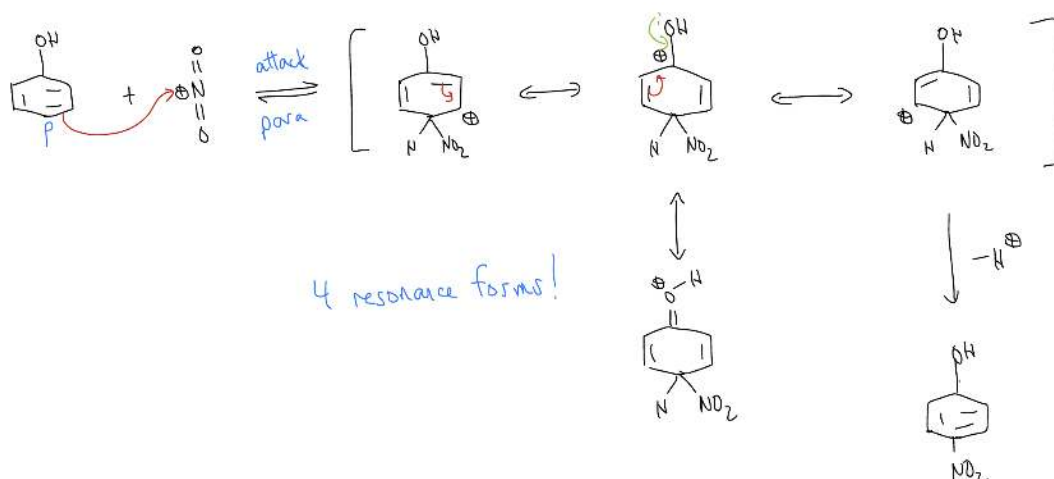
a) *ortho*-nitration



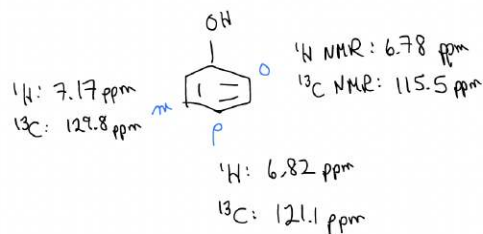
b) *meta*-nitration



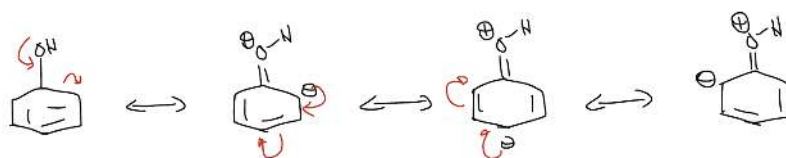
c) *para*-nitration



So, if we observed only the *ortho*- and *para*-nitrophenol products, can we devise a logical mechanistic reason for the regiochemistry? Well, since the arenium ion is more stabilized when the nitro group adds to the *ortho*- and *para*-positions, these two arenium ions will form faster. The activation energy needed to break aromaticity is smaller. Another way of looking at this is through electron density, which we can see from the ^1H and ^{13}C NMR chemical shifts.



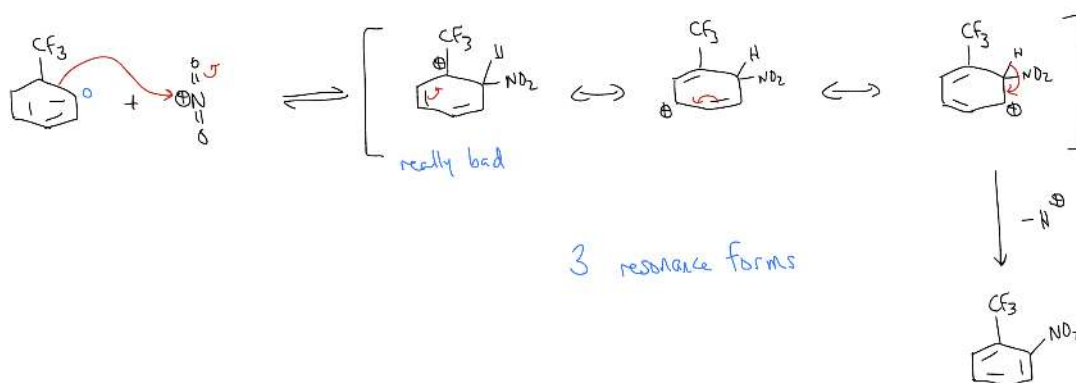
The NMR data tell you that the *ortho*- and *para*-positions have greater electron density. This should make sense because we can draw dipolar resonance forms placing negative charge at those positions.



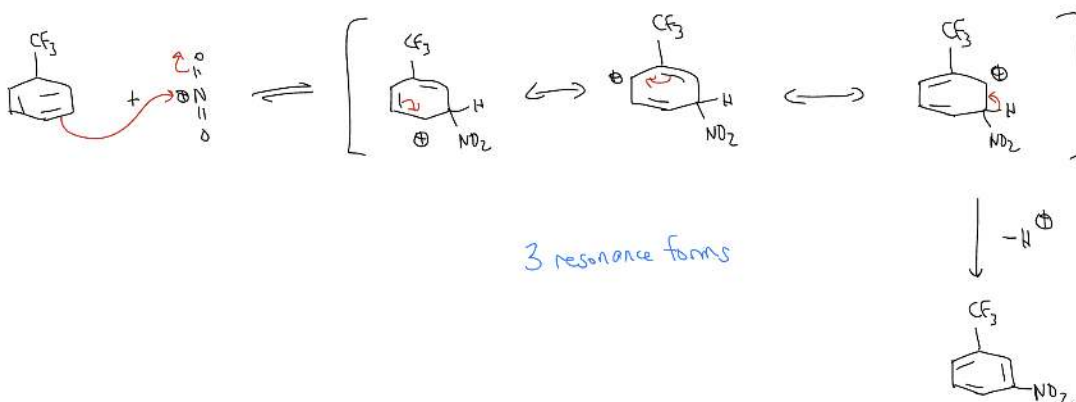
In other words, the *ortho*- and *para*-positions have greater δ^- charge. Since rate is controlled by electrostatic interactions, *ortho*- and *para*-substitution occurs exclusively.

Of course, oxygen is an activator with a lone pair aligned with the π system of the benzene ring. What would happen if a deactivator was a substituent on the ring? First, the reaction would be much slower because of the deactivating group, which lowers the HOMO. Second, the deactivator would give a set of resonance forms that favor formation of the *meta*-substituted product. Consider the nitration of trifluorobenzene:

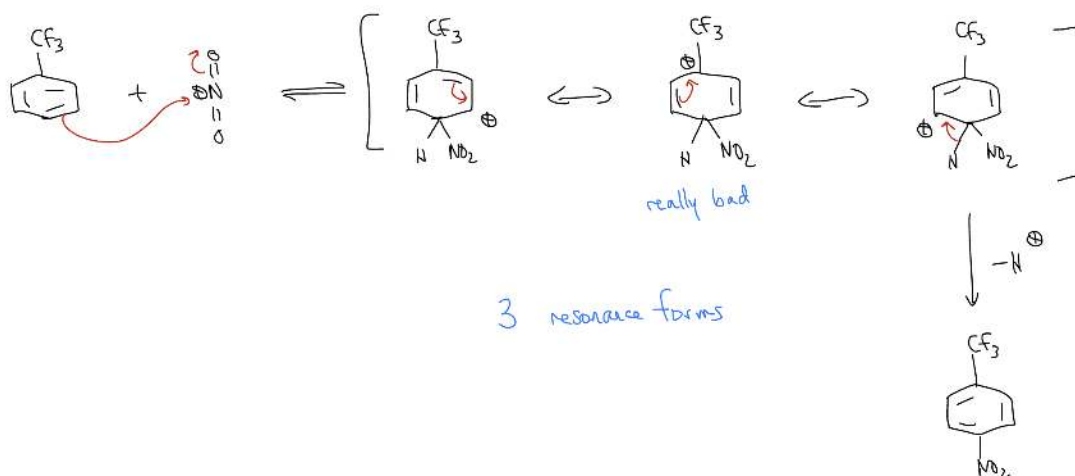
a) *ortho*-nitration



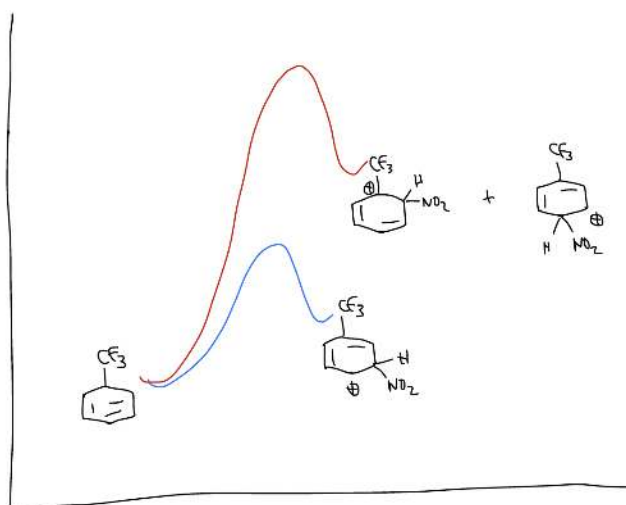
b) *meta*-nitration



c) *para*-nitration



The reaction energy diagram would look like this:



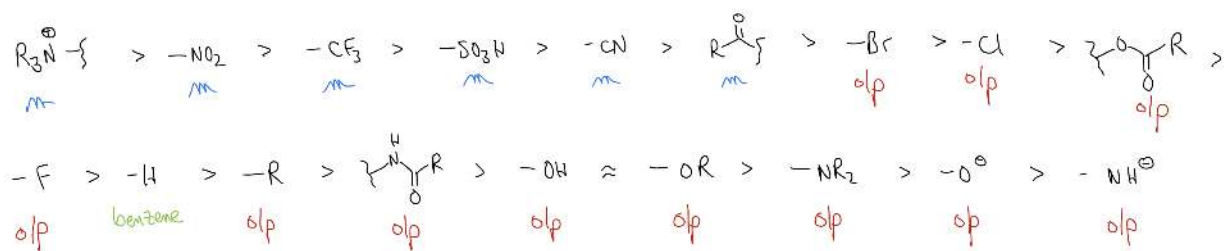
The pathway leading to the *meta*-product has a transition state that is lower in energy. Why? Because the trifluoromethyl group is strongly electron-withdrawing due to its inductive effect, and the arenium will sense this effect more strongly if the positive charge is on the carbon atom directly attached to it.

So, what does this all mean for the regioselectivity in electrophilic aromatic substitution? Can we categorize the long list of substituents not into activator/deactivator roles, but instead into *ortho*-/para- directors and *meta*-directors?

Here are some rules:

1. all activators are *ortho*-/para-directors
2. all substituents with lone pairs adjacent to the ring are *ortho*-/para-directors
3. deactivators without lone pairs adjacent to the ring are *meta*-directors

Can you assign the *ortho*-/para- or *meta*-directing ability in the reactivity series?

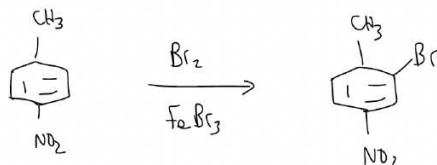


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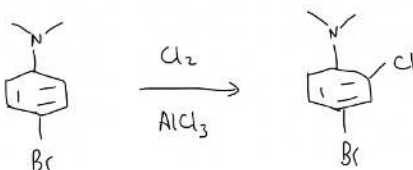
15.3: Multiple Substituents and Heteroaromatic Rings

We've described the directing effects when a single functional group is attached to the benzene ring, but what happens when more than one substituent is on a ring? Which one controls the regioselectivity? Well, there are three rules to follow:

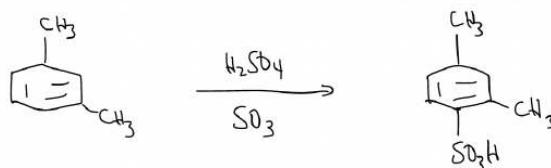
1. often the directing effects reinforce each other



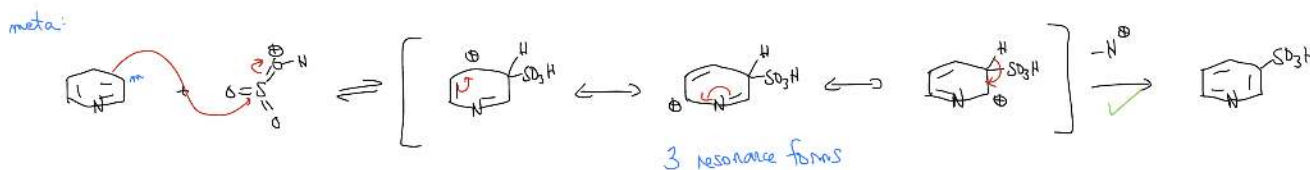
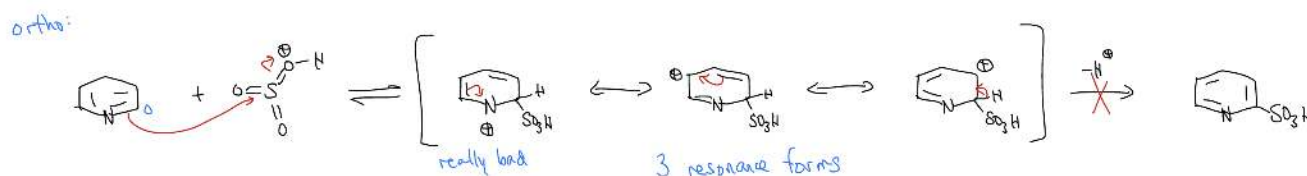
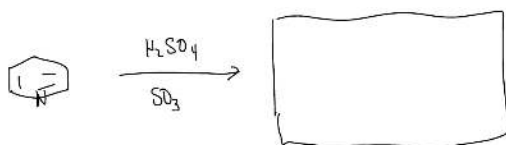
2. in cases where the effects are opposite, it is the more activating group that controls the regioselectivity.



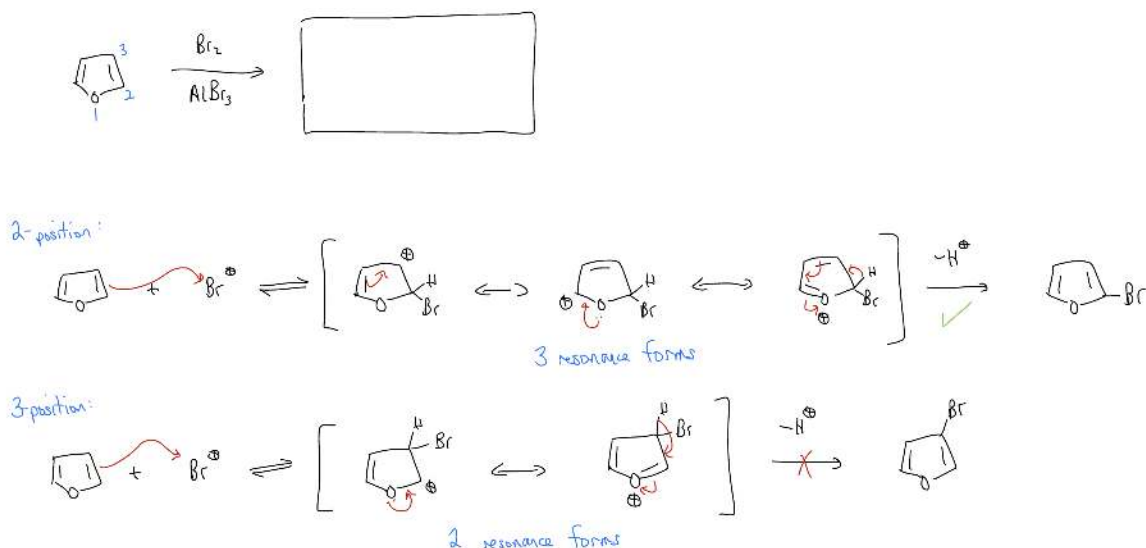
3. when two groups are similar in activation, regioselectivity is controlled by sterics, and the substitution will occur at the less sterically hindered site.



Finally, what happens in heteroaromatic rings and polycyclic aromatic hydrocarbons? It turns out that nothing changes, but you will need to draw all of the possibilities and decide based on the resonance structures you draw. Here's an example:



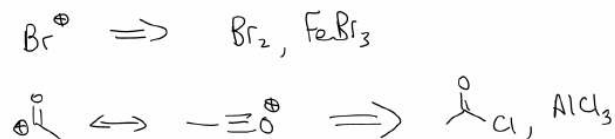
Here's another example:



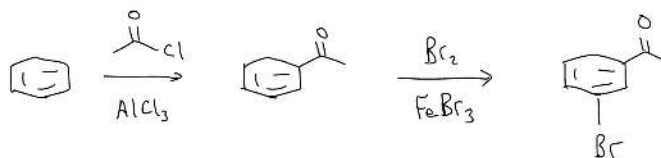
Regioselective synthesis via electrophilic aromatic substitution (S_EAr) involves a good degree of planning. Attention needs to be paid to the order of addition. Consider the retrosynthesis below.



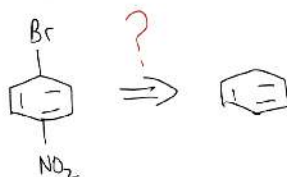
We know that we need to add an acyl group and a bromo group, but which one do we add first?



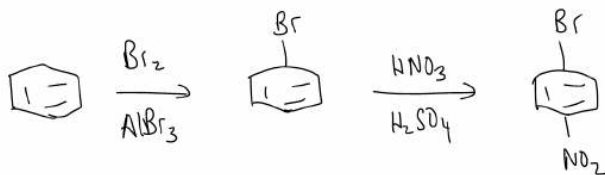
A bromo substituent is ortho-/para-directing, but the acyl group is meta-directing. In the structure, the groups are meta, so you would need to add the acyl group first.



Here's another example:



The two caveats in multistep synthesis are that an aromatic ring *more* deactivated than monohalogenes will *not* react, and that any group more than or equal in activation than -NH_2 will substitute more than once.

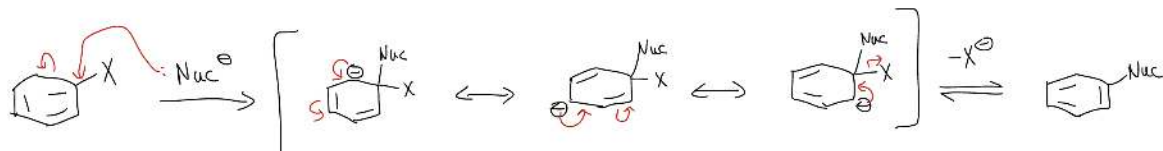


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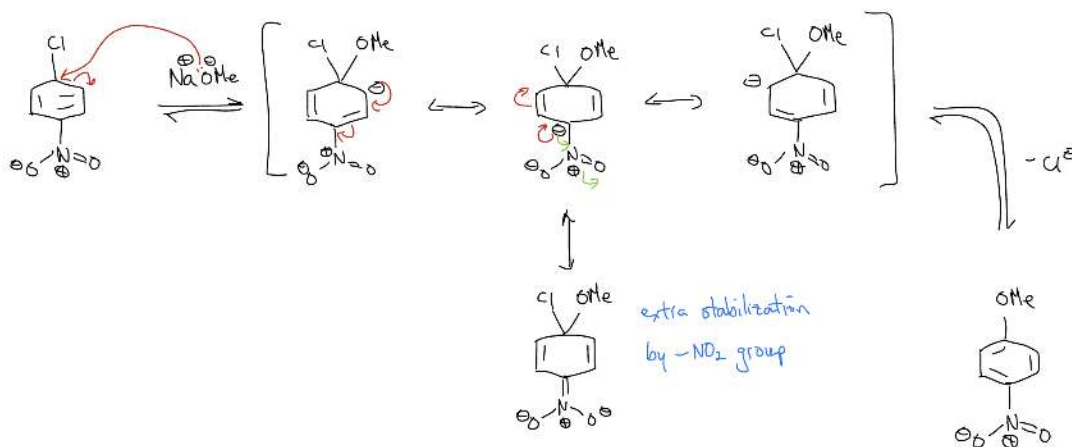
15.4: Nucleophilic Aromatic Substitution

We've said that the aromatic stabilization energy lowers the HOMO, but it also lowers the LUMO. When deactivating groups are added so that the aromatic ring is really electron-deficient, it no longer reacts with electrophiles, but instead with nucleophiles. This is called nucleophilic aromatic substitution (S_NAr).

The general mechanism for this reaction is called an addition-elimination mechanism.



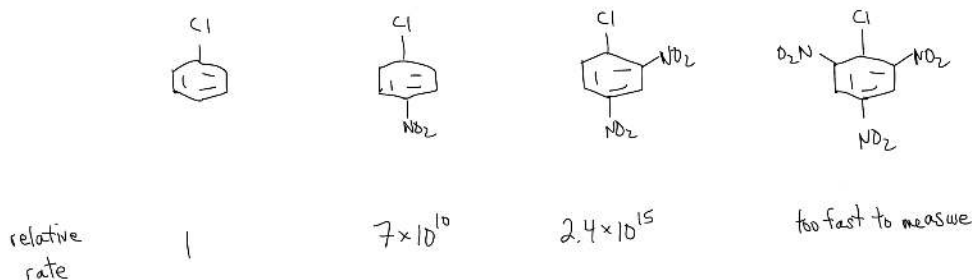
This reaction will only work if there is a pathway whereby the negative charge in the arenium ion is stabilized by an electron-withdrawing group in an *ortho*-/ *para*-position.



Note that the following reaction will not work because the nitro group is never used to stabilize the negative charge. Can you draw the resonance forms that illustrate this?

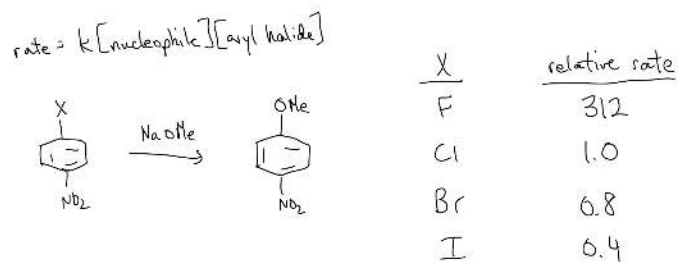


The rates of S_NAr reactions increase as the number of electron-withdrawing groups increase, due to the lowering of the LUMO even more.

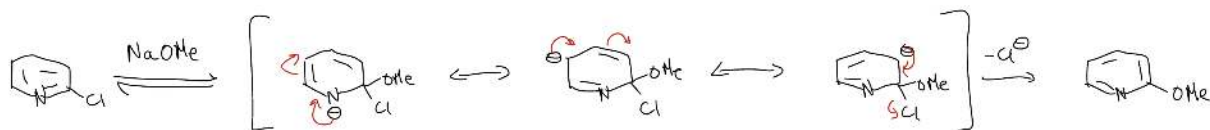


Groups that sufficiently stabilize the negative charge are R_3N^+ , NO_2 , CF_3 . Groups that are good leaving groups react on the order $F > Cl > Br > I$. This is peculiar since fluoride is not a good leaving group. However, the rate-determining step of this reaction is the

addition of the nucleophile to the arene. The fluoride is more electronegative, so it uses the inductive effect to lower the LUMO more effectively for a reaction to occur. The loss of the leaving group is fast and does not contribute to the rate law.



Another system that has S_NAr reactivity is the heteroaromatics:

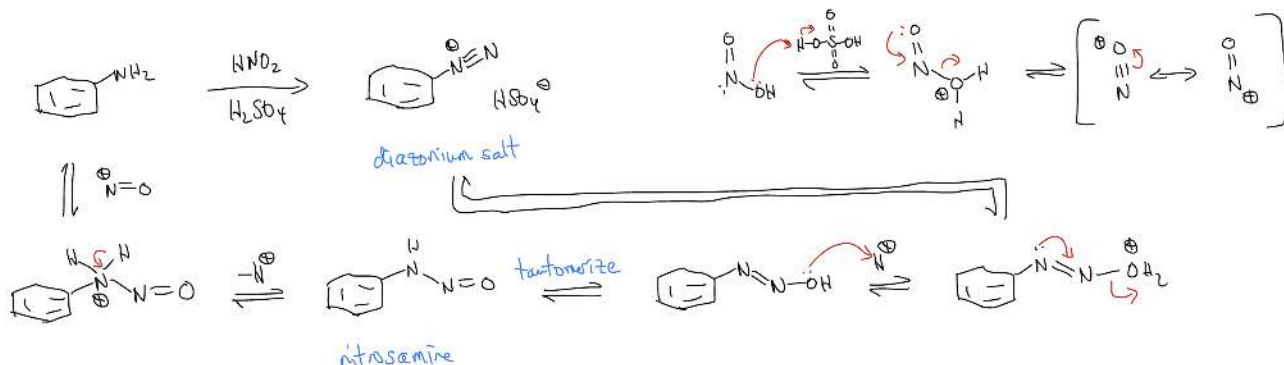


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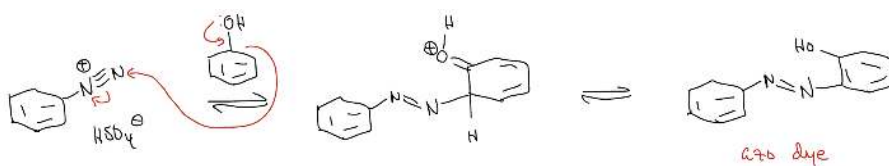
15.5: Other Reactions of Aromatics

Nitrosation of aromatic amines

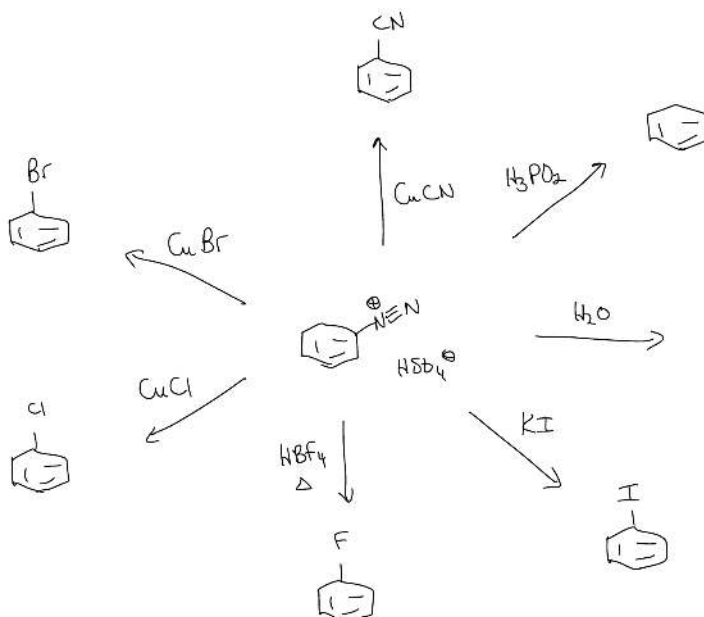
Aniline is a particularly important benzene derivative that can react with nitrous acid to produce a nitrosamine, followed by dehydration to give a diazonium salt. The reaction conditions are usually $\text{NaNO}_2/\text{H}_2\text{SO}_4$.



Diazonium salts are important synthetic intermediates because they are electrophilic – both at the aryl carbon atom *and* at the terminal nitrogen atom. For example, nucleophiles such as phenol react with diazonium salts to give deeply colored azo dyes.

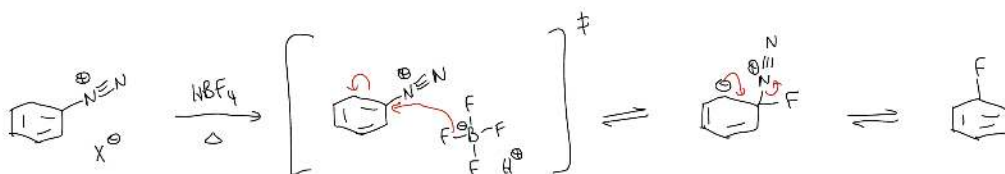


However, diazonium salts also have nucleophilic aromatic substitution reactivity that occurs at the aryl C-N bond.

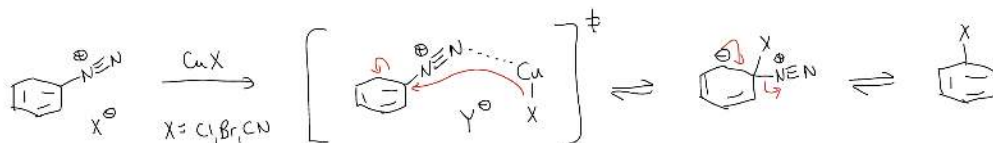


Some of these reactions have specific names:

1. Schiemann reaction – good way to make aryl fluorides



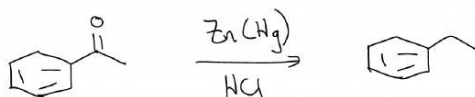
2. Sandmeyer reaction – good source of aryl chlorides, bromides, and nitriles



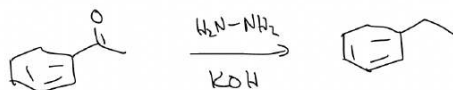
Other reactions of benzene derivatives:

Other reactions of aromatic rings that do not fit any category include:

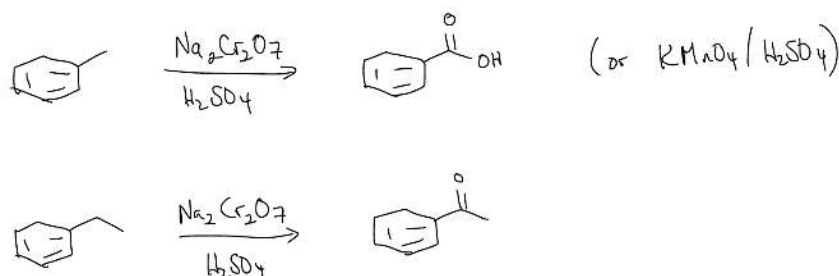
a) Clemmensen reduction – converts an aromatic ketone into an alkyl group



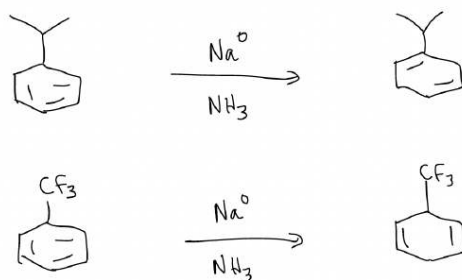
b) Wolff-Kishner reduction – converts an aromatic ketone into an alkyl group



c) Oxidation – oxidizes benzylic methyl groups into carboxylic acids or methylenes into ketones



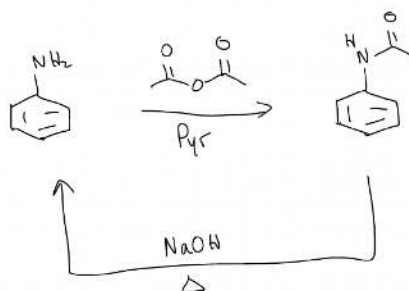
d) Birch reduction – reduces aromatic rings into 1,4-cyclohexadienes (electron-donating substituents will yield a product in which the substituent lies on a double bond, while an electron-withdrawing group will reduce so that the substituent is not directly attached to the double bond)



e) Reduction of a nitro group – reduces nitro groups to anilines



f) Acetylation of aniline – acetylated aniline will reduce the nucleophilicity of the aromatic ring so that reaction with an electrophile will only substitute once.



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CHAPTER OVERVIEW

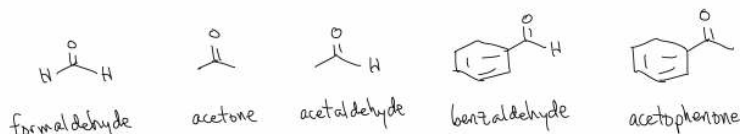
16: Nucleophilic Addition to Carbonyls

- 16.1: Nucleophilic Addition to the Carbonyl Group
- 16.2: Irreversible Nucleophilic Addition
- 16.3: Reversible Nucleophilic Addition
- 16.4: Acetal Formation
- 16.5: Nucleophilic Addition Under Neutral Conditions
- 16.6: Alcohol Oxidation

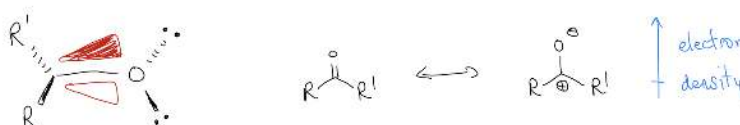
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16.1: Nucleophilic Addition to the Carbonyl Group

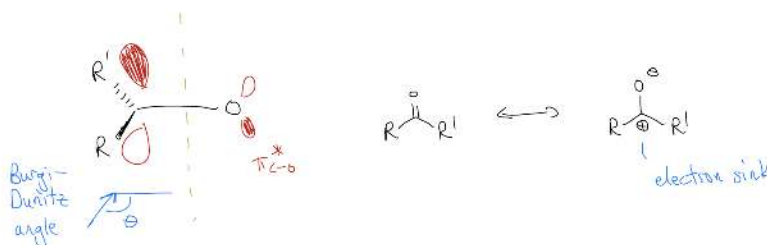
A carbonyl is any functional group that contains a C=O double bond, but we often further classify them based on what else is attached to the carbon atom. In this section of the course, we will be dealing primarily with aldehydes and ketones which contain no other heteroatoms attached to the carbonyl. Some examples are below:



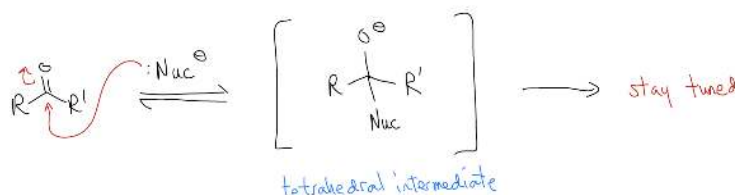
The Frontier molecular orbitals we are concerned about now are the $\pi_{\text{C-O}}$ and $\pi^*_{\text{C-O}}$. The π bond (HOMO) is polarized toward oxygen because it is more electronegative. We can draw a ketone in its dipolar resonance form to illustrate this (more δ^- on oxygen). There is a nodal plane that lies in the plane of the carbonyl; the phasing above and below this plane have opposite sign, a result of these orbitals originating from atomic p orbitals.



More important, however, is the π^* orbital (LUMO), which is strongly electrophilic at carbon (more δ^+ due to the dipolar resonance form). Most carbonyls react via their LUMO, not their HOMO, and thus carbonyls are good electrophiles. There is one nodal plane in between the carbon and oxygen atoms now, giving rise to a π^* orbital in which the biggest lobes on carbon lie at an angle of 103-107° with respect to the plane of the carbonyl. This is known as the Burgi-Dunitz angle.



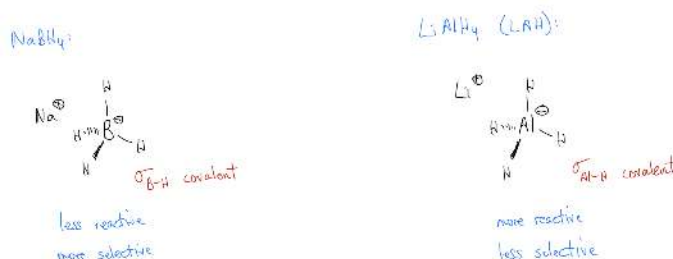
In nucleophilic addition reactions, a nucleophile will populate the π^* orbital, which breaks the π bond, resulting in rehybridization to sp^3 . A new σ bond is formed and electrons move onto oxygen as a lone pair. We call this species the tetrahedral intermediate, which then goes on to do other things (stay tuned).



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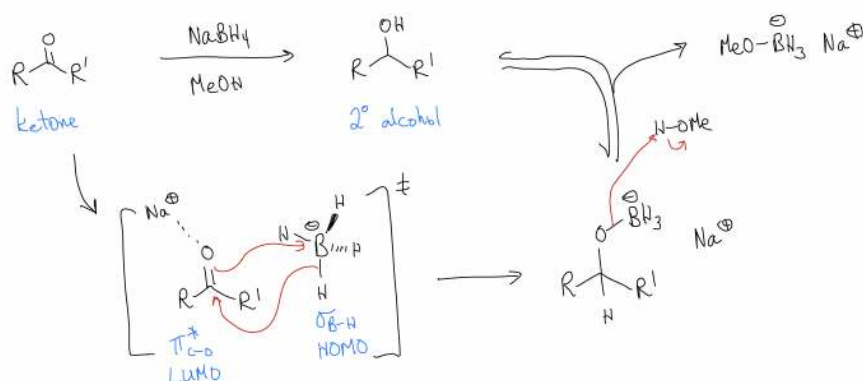
16.2: Irreversible Nucleophilic Addition

Let's first take a look at the reduction of ketones/aldehydes to produce 1°/2° alcohols. This can be performed by using a hydride equivalent. A hydride is a source of H^- , but reagents like NaH or KH are not suitable to reduce ketones/aldehydes. The reason for this is that H^- is too basic, the result of being a very hard, small point charge. It prefers to act like a base and deprotonate something than react like a nucleophile. The NaH bond is too ionic in character. Instead, we use hydride equivalents like sodium borohydride (NaBH_4) or lithium aluminum hydride (LiAlH_4 or LAH), which have $\sigma_{\text{B-H}}$ and $\sigma_{\text{Al-H}}$ bonds that are highly covalent and react by donating the hydrogen atom as a hydride equivalent, or " H^- ." These reagents act as nucleophiles and deliver hydride to a ketone/aldehyde according to the same mechanism as above, generating a tetrahedral intermediate.

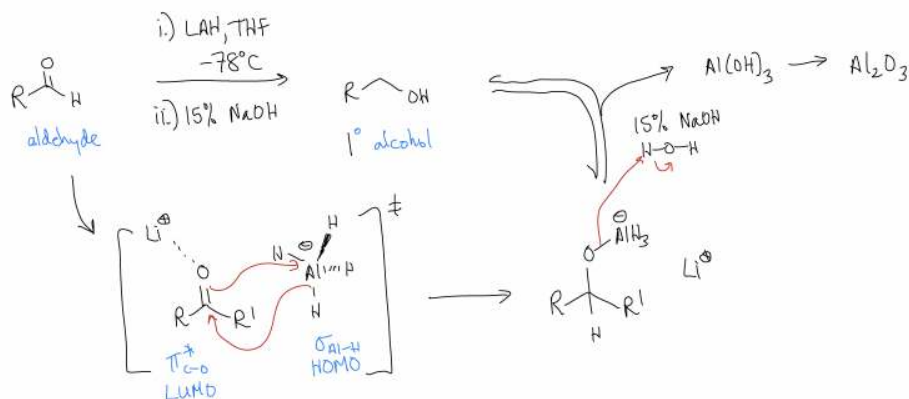


Let's take a look at the mechanism of these reactions:

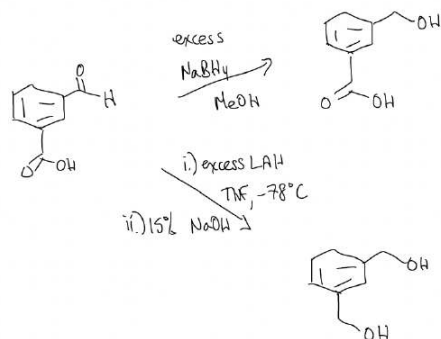
NaBH_4 reduction:



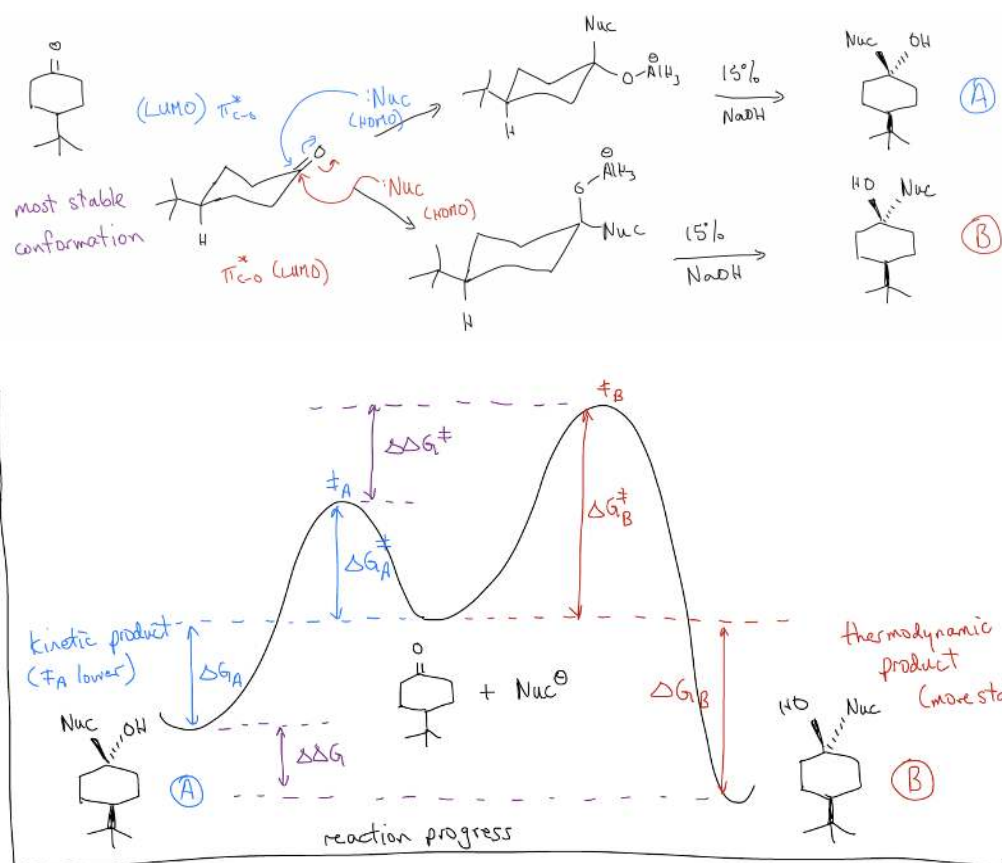
LiAlH_4 reduction:



NaBH_4 is less reactive but more selective than LAH. By analogy, LAH is more reactive but less selective. This makes for some interesting chemoselectivities. While both reagents are capable of reducing ketones/aldehydes to alcohols, only LAH is capable of reducing carboxylic acids to the corresponding alcohol (more on this mechanism later).



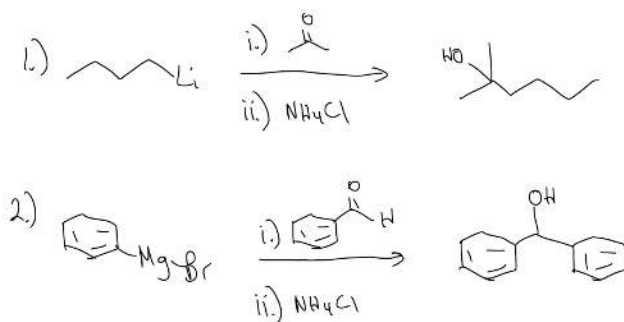
But let's take a moment to think about the transition state for this transformation. Consider the reduction of 4-*tert*-butylcyclohexanone with LAH to give two diastereomers: A and B. These reduction products have different energies, and their formation is driven by the attack of the $\sigma_{\text{Al-H}}$ bond (HOMO) onto either the top or bottom face of the carbonyl $\pi^*_{\text{C=O}}$ (LUMO). These different faces make the transition state energies diastereomeric (and thus, different in energy).



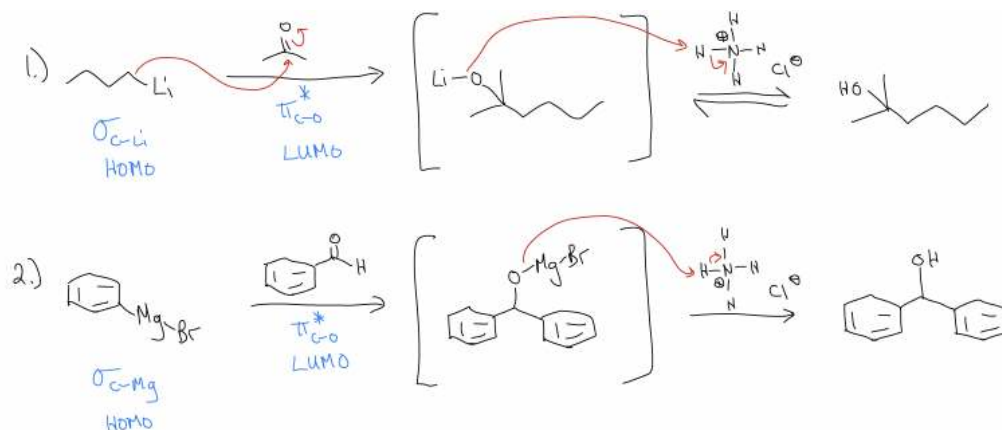
In the LAH reduction of 4-*tert*-butylcyclohexanone, the product distribution is 30:70 in favor of A. This does not change, even when heating. This should indicate to us that this reaction is irreversible (otherwise we would get B since it is lower in energy). We say that since the energies of the products have no effect on the product distribution and the energy of the transition state is controlling the reaction, that the reaction is under kinetic control.

So, why is this reaction irreversible? Let's take a look at the mechanism and see if each step is itself reversible. In order for the reaction to be under thermodynamic control, the nucleophilic addition step must be reversible. This would mean "H⁻" must be a leaving group. We know that this can't happen ($pK_aH = 32$), so this step is under kinetic control. In the second step, protonation of the alkoxide gives the product alcohol. Protonations are reversible since protons can tunnel, so this step is under thermodynamic control (normally the protonated alcohol is more stable). Overall, the reaction is under kinetic control since the first step is irreversible.

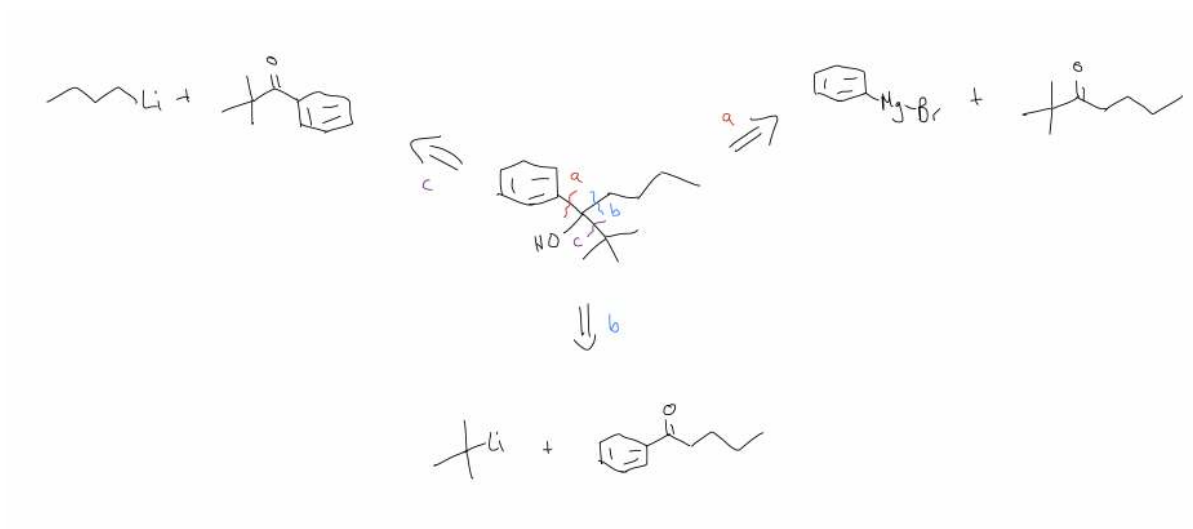
Besides hydride equivalents, there are other nucleophiles that can add to carbonyls irreversibly. Grignard reagents and organolithium reagents also add to the π^* orbital (LUMO) efficiently under kinetic control. These reactions are irreversible in the first step because the reverse reaction would require a carbon-based anion ($pK_aH > 50$) to be a good leaving group. Nucleophilic additions can only be under thermodynamic control if the incoming nucleophile is also a good leaving group (this time, the pK_a must be < 15). The difference between reduction of ketones/aldehydes ("H⁻" addition) and addition of Grignards/organolithiums is that the resulting product is a 2°/3° alcohol after quenching with a proton source (normally NH_4Cl).



How does it work? It's the same mechanism – nucleophilic addition to the carbonyl.



Tertiary alcohols (or secondary alcohols) can be made several different ways. Can you devise three different ways of making the following tertiary alcohol?

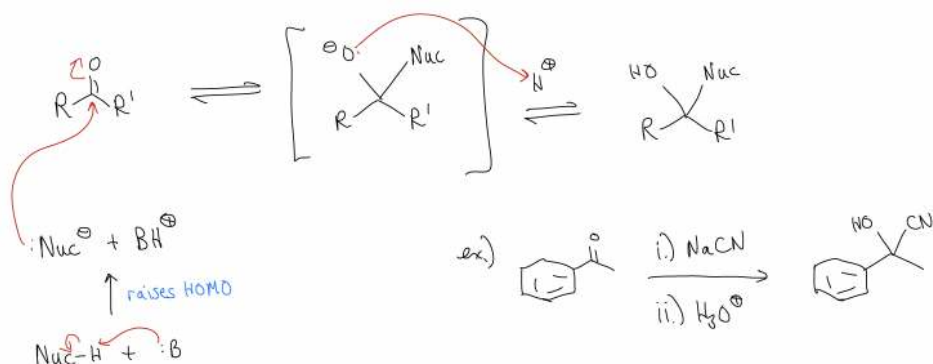


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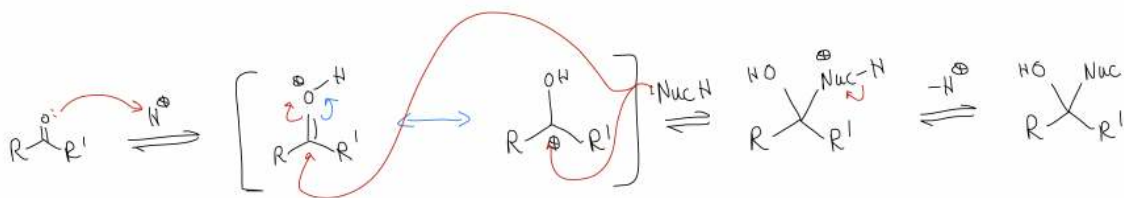
16.3: Reversible Nucleophilic Addition

So far, we have discussed the first of two primary ways for nucleophilic additions to carbonyls – irreversible reactions. Another way of classifying nucleophilic addition reactions is to base the classification on the reaction conditions: basic or acidic.

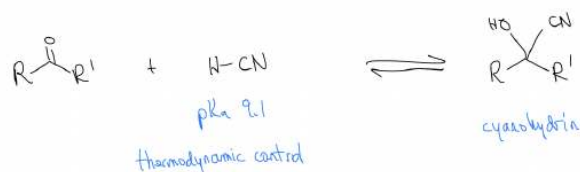
A. Basic conditions: Under these conditions, deprotonation of a nucleophile raises the HOMO, making it more reactive. Nucleophilic addition occurs to give a tetrahedral intermediate which then either 1) protonates immediately, or 2) reverses if the $pK_a < 15$ and then protonates if given enough energy (NOTE: the reverse reaction is the exact opposite set of arrows, according to the law of microscopic reversibility). An example of case #1 is the reduction of ketones/aldehydes under kinetic control. An example of case #2 is the thermodynamic addition to the carbonyl of cyanide anion to the carbonyl.



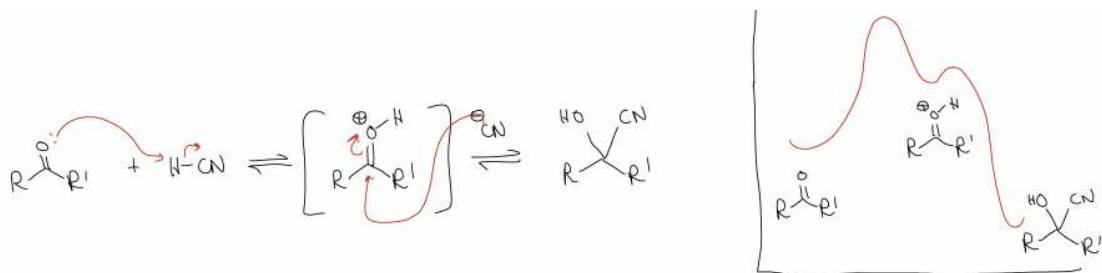
B. Acidic conditions: Under these conditions, protonation of the carbonyl (via the oxygen lone pairs) will lower the LUMO enough that a nucleophile can add. There are several more examples of this: 1) cyanohydrin formation; 2) gem-diol formation; and 3) acetal formation.



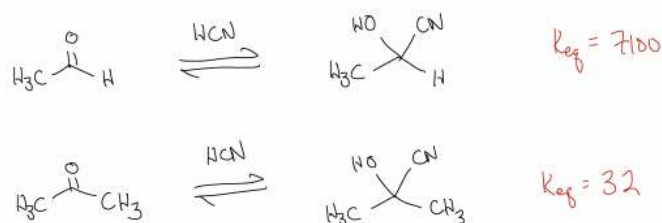
1. Cyanohydrin formation



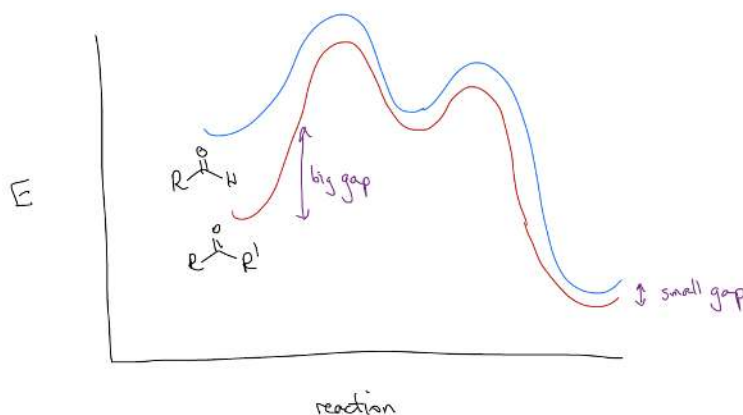
mechanism:



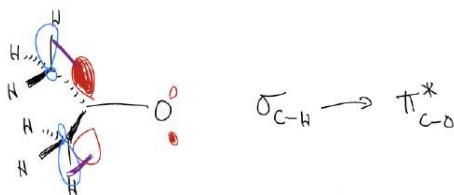
Since this reaction is reversible, there is an equilibrium constant associated with it. Consider the following two reactions:



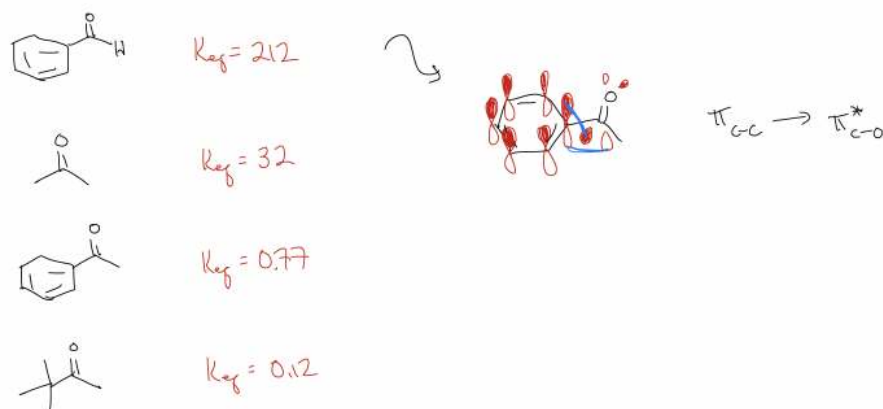
Why is there such a difference? Like most things, there is an electronic (rather than steric) explanation. The difference in the stability of the products is roughly the same, so it must arise from the stability of the starting materials. Ketones are more stable than aldehydes and since the energy of the transition states and the energies of the products are about equal, there are large differences in reactivity. We don't care how large the activation energy (E_a) is, nor how high the transition state is, because we are under thermodynamic control – there is enough energy to overcome any energy barrier.



You might be wondering why ketones are more stable than aldehydes. This is due to σ -donation. Electrons like to be spread out and this can occur more easily in ketones via σ -donation of $\sigma_{\text{C-H}}$ into $\pi^*_{\text{C-O}}$. This delocalization occurs six times, which raises the LUMO (π^*) of the ketone, making it less reactive.

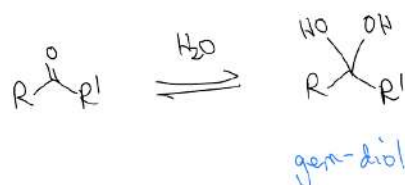


What other factors influence K_{eq} ? Consider the following data for cyanohydrin formation:

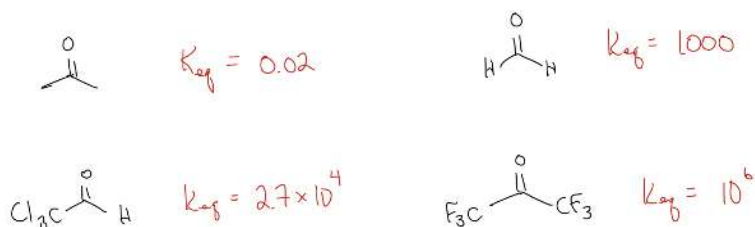


The difference between acetone and acetophenone tells us that conjugation is more powerful than σ -donation – delocalization from π_{C-C} into $\pi^*_{C=O}$ occurs because these orbitals are closer in energy (better mixing). In the case of tert-butyl methyl ketone, even though the σ_{C-C} is a better donor than σ_{C-H} due to better orbital overlap, there is steric crowding in the transition state, so the K_{eq} is lower.

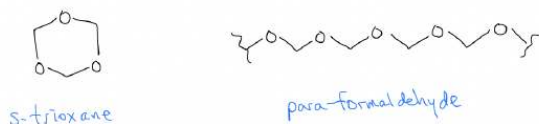
2. Gem-diol formation – geminal means “same carbon”



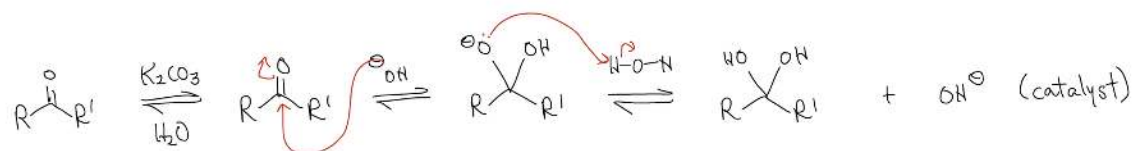
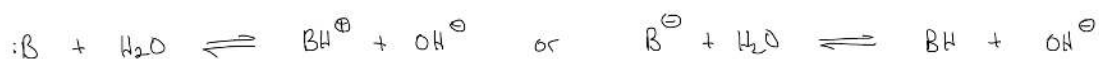
This is a very slow reaction that can be accelerated by base/acid catalysis (heat will favor the reverse direction because entropy favor bimolecular set of products). There are similar effects on K_{eq} :



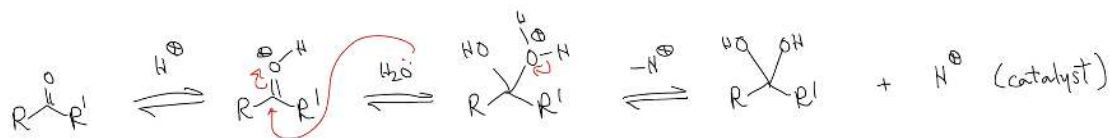
NOTE: one cannot buy formaldehyde itself, but you can access it in the following forms: 1) 40% solution in H_2O ; 2) *para*-formaldehyde and 3) s-trioxane



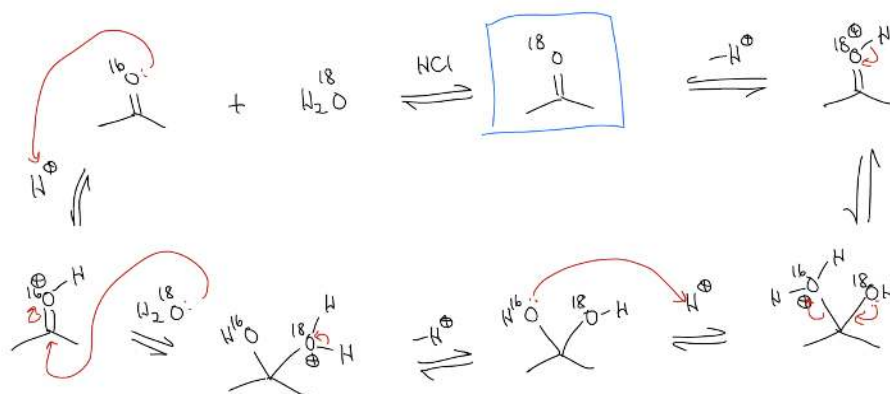
- base catalysis: Water is not a good nucleophile to attack the $\pi^*_{C=O}$ orbital. Its HOMO (n_O) is too low, but we can raise this HOMO by deprotonation with base (K_2CO_3 , $NaOH$, Et_3N , etc.)



- acid catalysis: The ketone/aldehyde is not a good electrophile to react with n_O of the incoming nucleophile. Its LUMO (π^*_{C-O}) is too low, but we can lower the LUMO by protonation with a Bronsted acid or Lewis acid.



Consider the following reaction in which ^{16}O -labeled acetone is reacted with ^{18}O -labeled water:

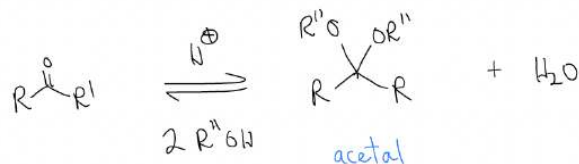


The law of microscopic reversibility states that the last three steps are just the reverse of the first three. The small amount of H_2^{16}O generated will never be able to compete with H_2^{18}O as solvent, so this reaction is pushed toward product.

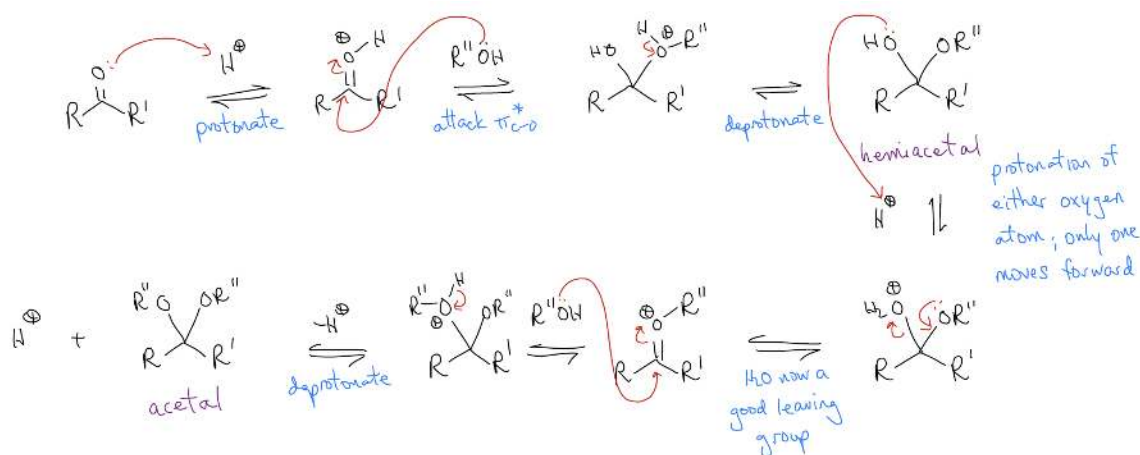
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16.4: Acetal Formation

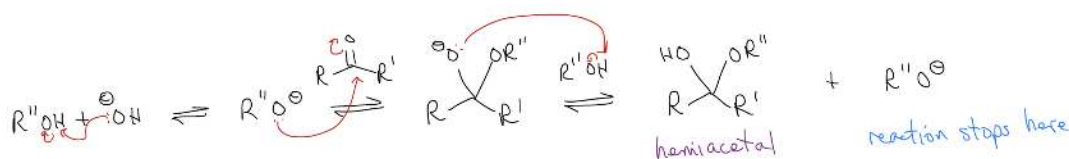
3. Acetal formation – acetal is like a gem-diol except the alcohols are ethers:



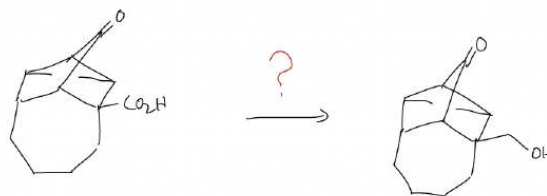
This reaction is **only** acid-catalyzed. The forward direction is acetal formation (protection) and the reverse direction is hydrolysis (driven by entropy).



In the acid-catalyzed acetal formation, the H^+ functioned to lower the LUMO of the carbonyl but also to protonate the hemiacetal and make H_2O a good leaving group. The reason this reaction cannot be catalyzed by base is because this reaction would stop at formation of the hemiacetal (there is no way to remove the hydroxyl group).

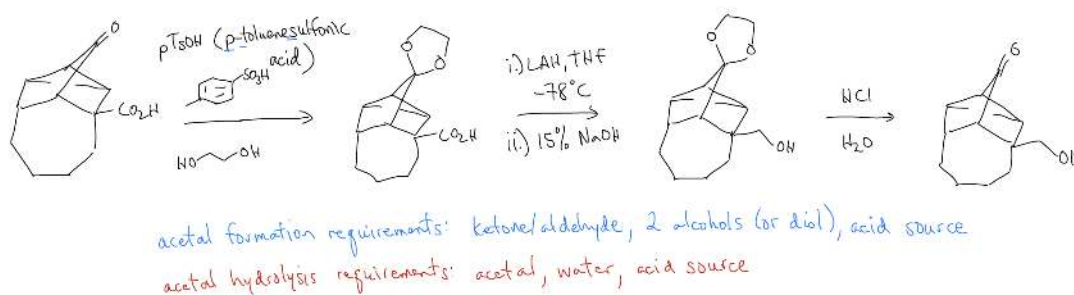


When would we want to use an acetal in synthesis? As a protecting group! A protecting group is a way to convert one functional group to another temporarily, so that its reactivity is removed and other transformations can occur. The protecting group is then easily removed to regenerate the original functional group. Consider the example below:

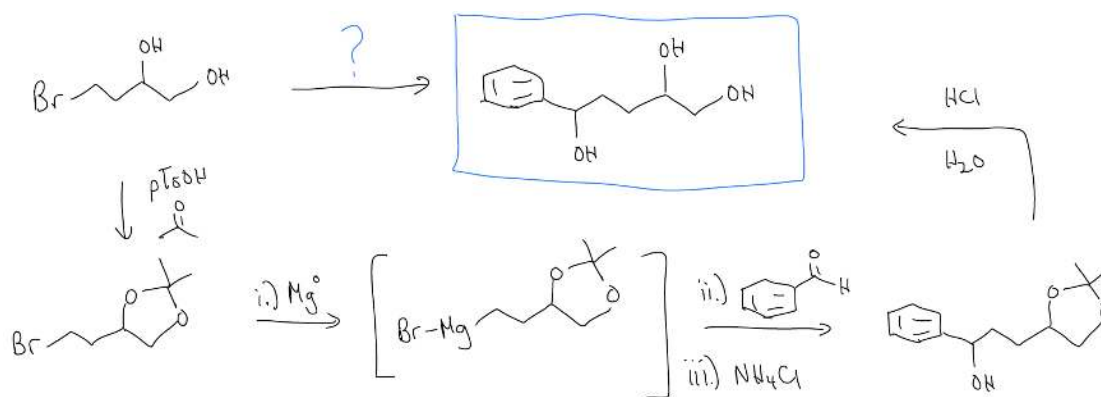


Note that we need to reduce the carboxylic acid without reducing the ketone. If we were to treat this molecule with LAH (more reactive, less selective), both the ketone AND carboxylic acid would be reduced to the alcohol. But, if we make an acetal first,

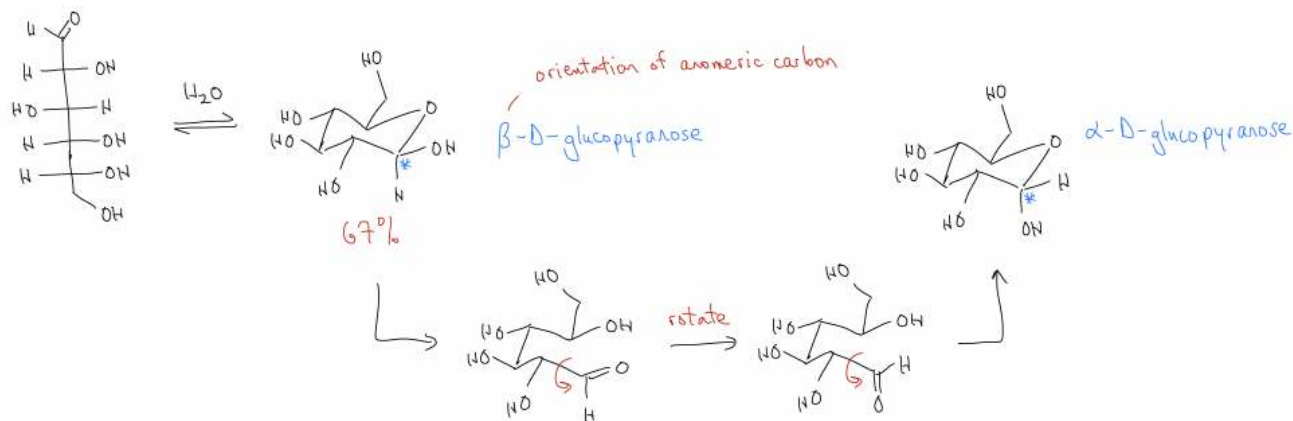
LAH will only react with the carboxylic acid functional group. The acetal will remain inert, and then you can remove the acetal (hydrolysis) to regenerate the ketone. This is known as a protection/deprotection scheme.



Another example of acetal use in synthesis is in the use of Grignard reagents in the presence of either carbonyls or alcohols. If we treated the starting material below with Mg metal, the resulting Grignard reagent would be destroyed by the alcohol groups' protons. So, we must protect these alcohols as the acetal first.



The most interesting example of acetals is in the chemistry of sugars, or carbohydrate chemistry. Sugars have both alcohol and aldehyde functional groups, but normally exist as cyclic hemiacetals. Compared to acyclic hemiacetals, which we've said are unstable, cyclic hemiacetals are completely stable.



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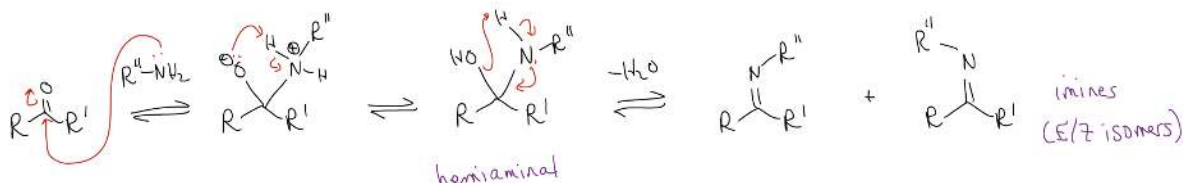
16.5: Nucleophilic Addition Under Neutral Conditions

C. Neutral conditions

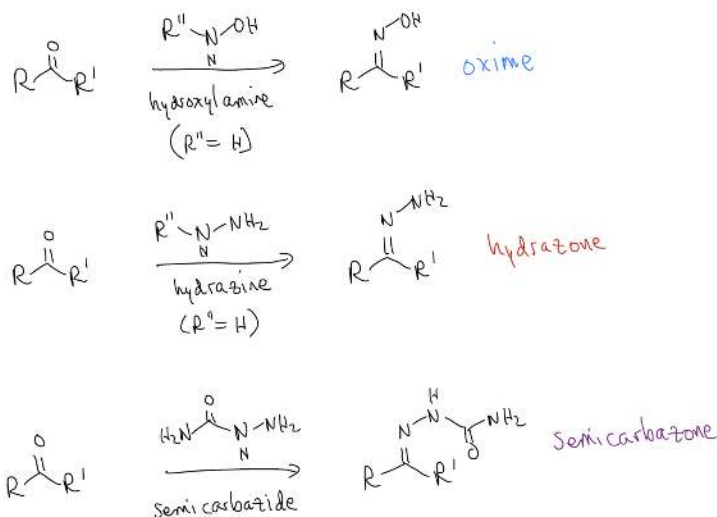
1. Imine/enamine formation

Similar in mechanism to acetal formation is imine and enamine formation, except that these reactions normally occur under neutral conditions. Like acetal formation, H_2O must be a leaving group. While this is not possible under basic conditions, strongly acidic conditions will just protonate the amine, leaving the reaction dead!

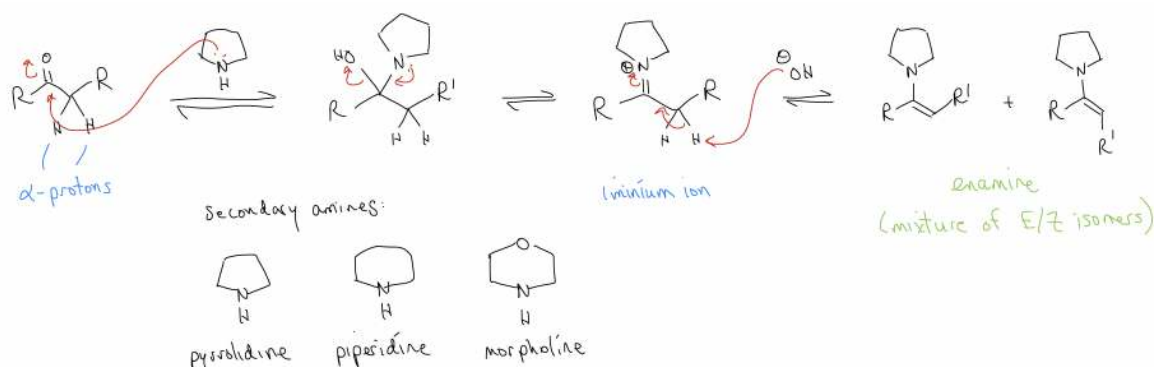
In imine formation, nucleophilic attack on the carbonyl results in a hemiaminal intermediate (carbinolamine).



This reaction is usually run at pH 4-6. Acetic acid is normally added as a catalyst. Several different types of amine can be used, whose products have special names. In each of these cases, the amine is a primary amine, and H_2O is removed. Thus, we call these reactions condensation reactions, but the mechanism is still addition to the $\pi^*_{\text{C=O}}$.



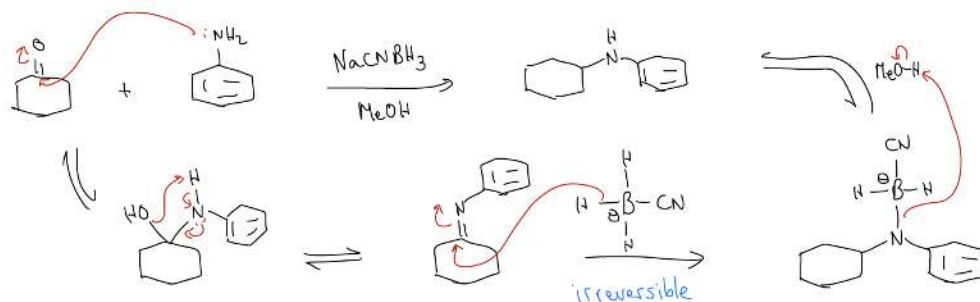
When a secondary amine is used, the resulting iminium ion deprotonates to form an enamine. The most common secondary amines are pyrrolidine, piperidine, and morpholine, but dialkylamines of all types work. In order for enamine formation to proceed, the ketone must have α -protons.



We will come back to describe the synthetic uses of enamines later, but first a brief detour on the use of imines in synthesis. Recall our discussion of the synthesis of amines during S_N1/S_N2 chemistry. We said that because of hyperconjugation, it is very difficult to stop the reaction of a primary amine with an alkyl halide at monoalkylation – the reaction keeps going because the product is more reactive than the starting material.

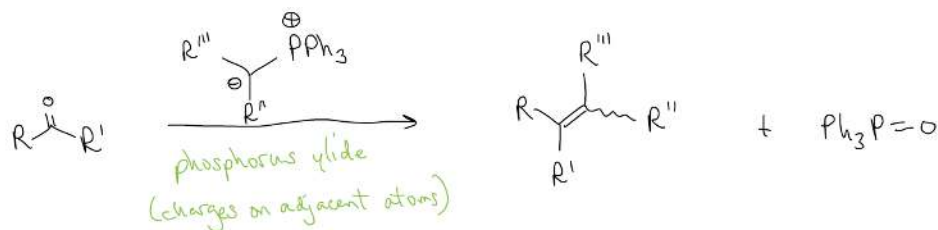
One way to circumvent this problem is to use the imine functional group as a handle. A good way to make secondary amines is by a process called reductive amination of a ketone/aldehyde. We know that a ketone/aldehyde will react with a primary amine to give an imine, so what if we could reduce the imine with a reducing agent like NaBH_4 to yield the secondary amine? It turns out that you could do this, but it would take you two steps – formation of the imine, followed by reduction with NaBH_4 . We need two steps because NaBH_4 will reduce the ketone/aldehyde to the alcohol.

But as the name of this reaction implies, you can do this all in one reaction flask by decreasing the reducing agents reactivity. There are two reagents that do this: sodium cyanoborohydride (NaCNBH_3) and sodium triacetoxyborohydride ($\text{NaBH}(\text{OAc})_3$). These reagents will not reduce the ketone/aldehyde, but are reactive enough to reduce the imine formed *in situ*. The net result: a secondary amine!

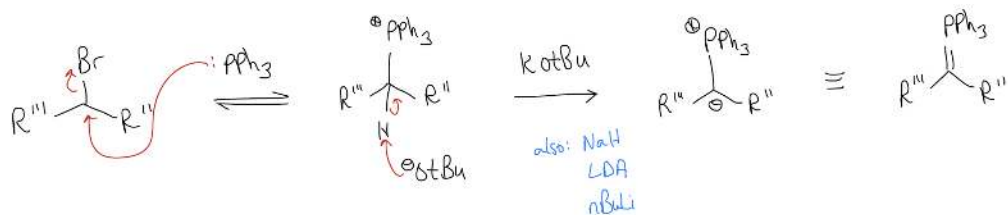


2. Wittig reaction

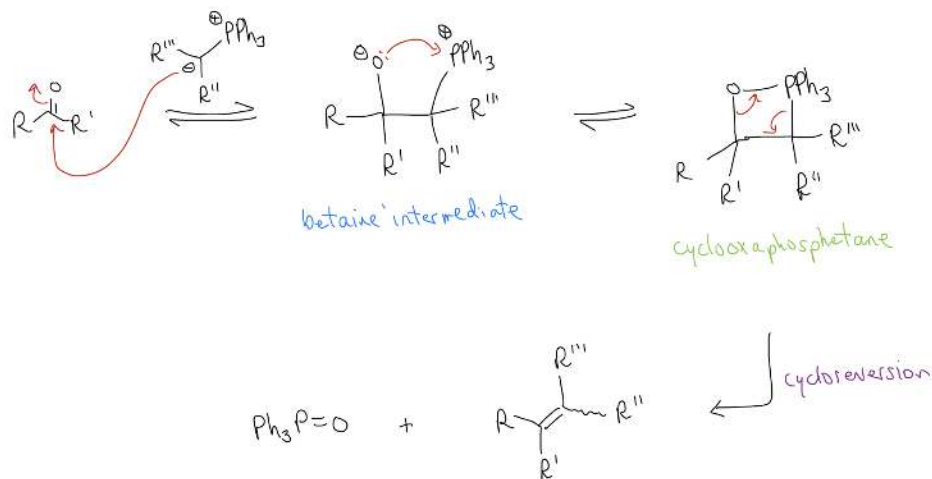
One final (and important) reaction of carbonyls is the Wittig olefination reaction. In this reaction, a ketone/aldehyde reacts with a phosphorous ylide to generate an alkene.



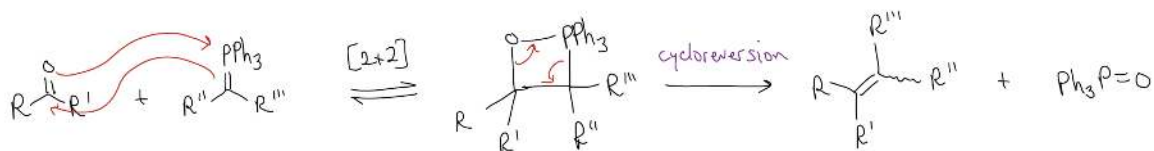
Formation of the ylide occurs by S_N2 , then deprotonation:



Treatment of the ylide (normally *in situ*) with a ketone/aldehyde results in nucleophilic addition to form a betaine intermediate, which cyclizes to give a cyclooxaphosphetane, then undergoes cycloreversion to yield the alkene and triphenylphosphine oxide.



There is debate whether the betaine actually exists, so an alternative mechanism has been proposed, which involves the direct [2+2] cycloaddition to give the cyclooxaphosphetane.



As for considerations of stereochemistry, a general rule is that stabilized ylides give E-alkenes while unstabilized ylides give Z-alkenes. Stabilized ylides normally have an electron-withdrawing group on them, making the attack on the carbonyl reversible and favoring an anti orientation of the alkyl groups (thermodynamic control).

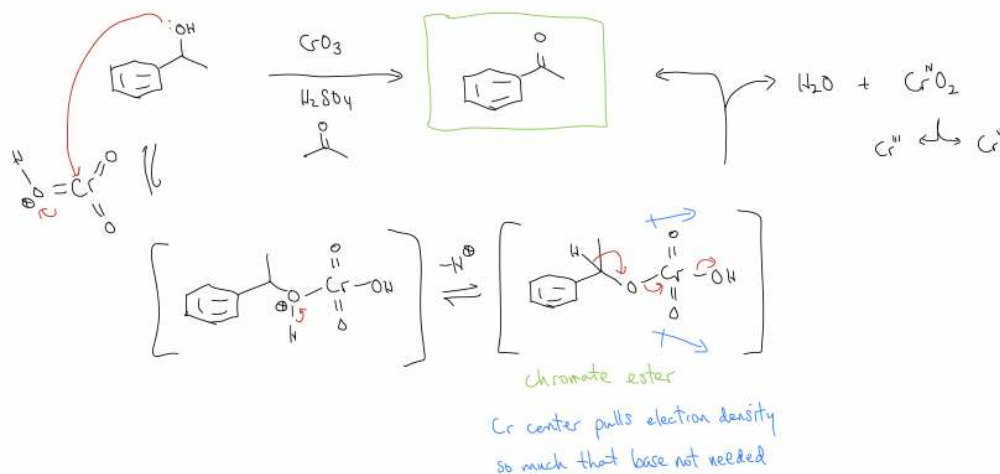
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16.6: Alcohol Oxidation

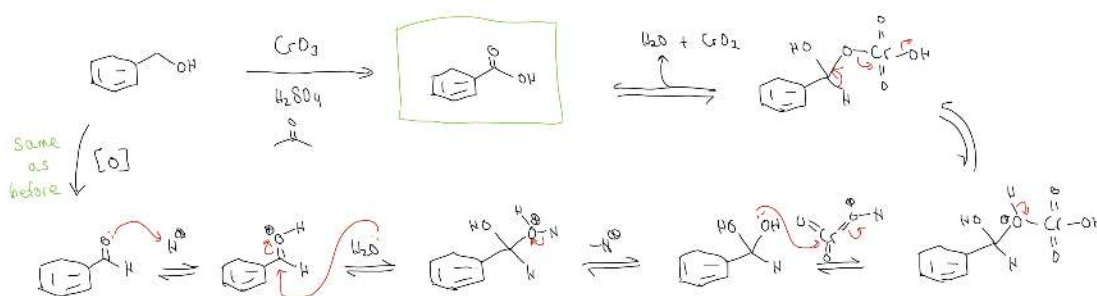
Many simple ketones and aldehydes can be purchased, but more complicated structures require reactions for their formation. Alcohols are useful functional groups for the formation of ketones (2° alcohols) or aldehydes (1° alcohols), which occurs via oxidation (the opposite of reduction). Oxidations normally occur by reacting a 1°/2° alcohol with a metal at a high oxidation state.

The two most common transformations are the Jones oxidation and the Swern oxidation.

A) Jones oxidation



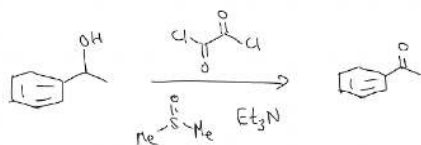
While secondary alcohols react with Jones reagents to give ketones, primary alcohols react to give carboxylic acids. Why? Well, the reaction first forms the aldehyde, but because H_2O is present in the reaction, a gem-diol can form which is susceptible to further oxidation.



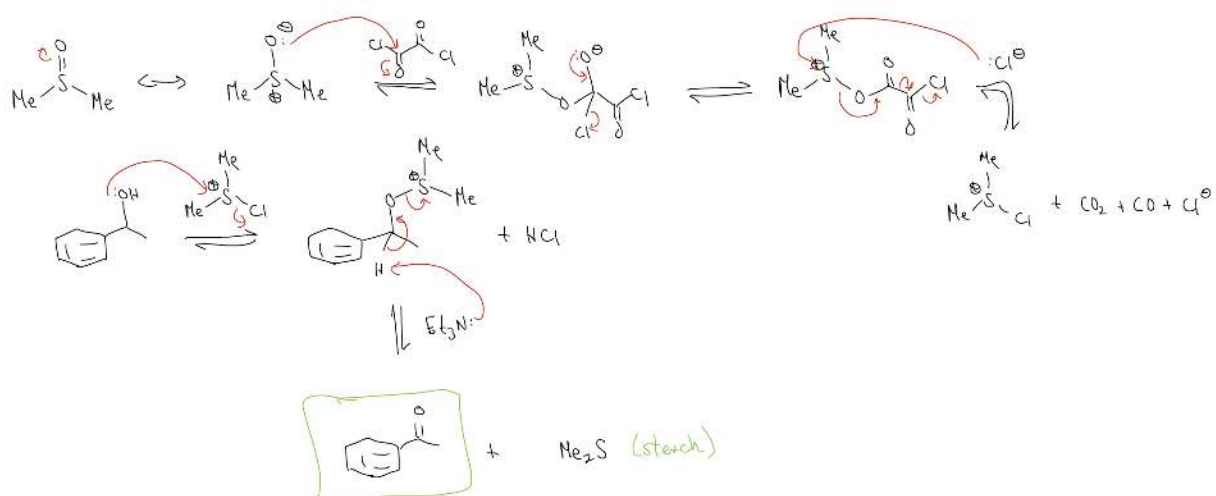
The Jones reaction generates toxic byproducts, and overoxidizes primary alcohols, so other reagents have been developed to circumvent these two problems.

B) Swern oxidation

This reaction converts 1°/2° alcohols to the aldehyde/ketone, respectively, without overoxidation. The reagents are oxalyl chloride, dimethyl sulfoxide, and triethylamine.

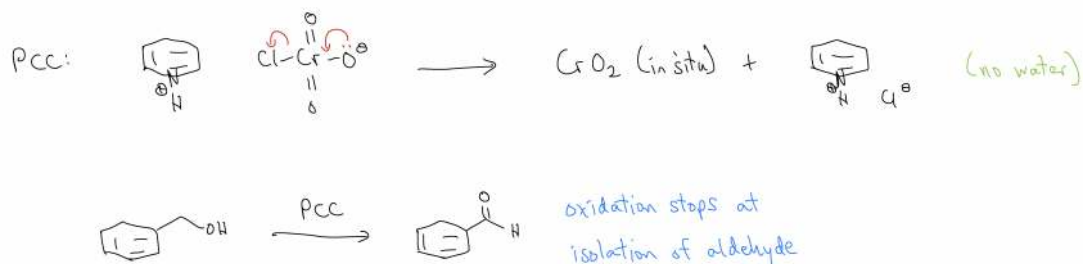


mechanism:



C) Pyridinium chlorochromate (PCC) oxidation

This is an anhydrous form of the Jones reagent, so using a primary alcohol will not result in overoxidation.



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CHAPTER OVERVIEW

17: Nucleophilic Acyl Substitution

17.1: Nucleophilic Acyl Substitution

17.2: Reactions via Carbonyl Substitution

17.3: Double Nucleophilic Acyl Substitution

17.4: Super Leaving Groups

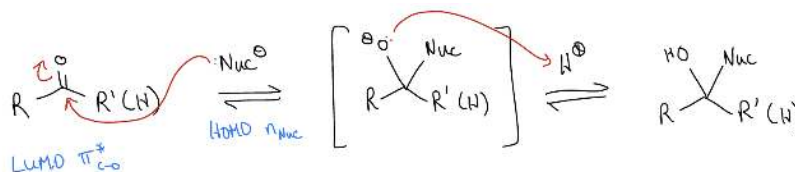
17.5: Nitriles

17.6: Named Reactions

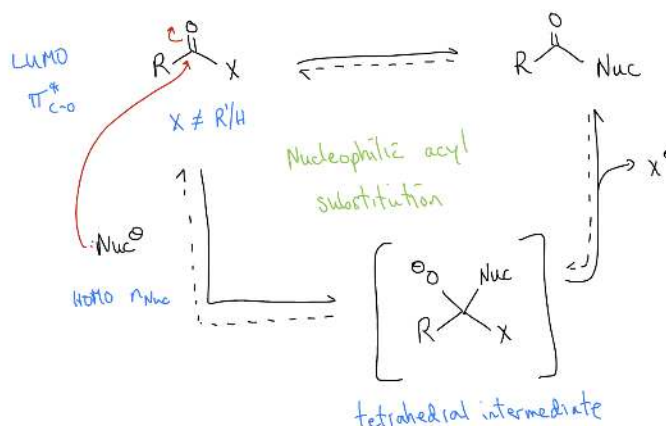
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17.1: Nucleophilic Acyl Substitution

Up until now, we have used nucleophiles to add to the carbonyl to generate a tetrahedral intermediate in a process that is reversible if the nucleophile is a good leaving group. Furthermore, the carbonyls that we have used are aldehydes and ketones, which have rather low lying $\pi^*_{C=O}$ orbitals (LUMO).

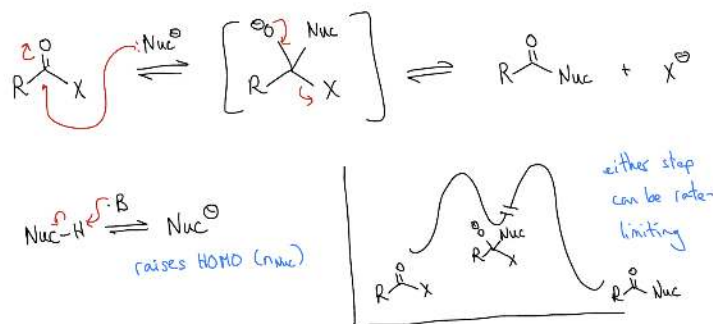


What would happen if we now had electrophilic carbonyls which were not aldehydes/ketones? Would they have the same or different reactivity? Let's take a look at a generic reaction:

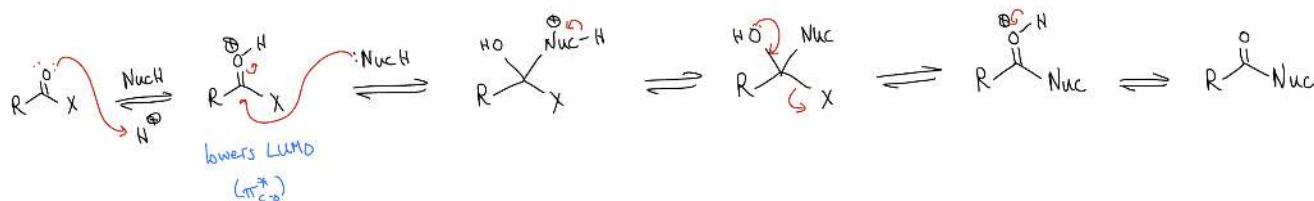


Like before, the nucleophile attacks the π^* orbital, resulting in a tetrahedral intermediate. This intermediate, however, can collapse with loss of a leaving group. This mechanism is known as a nucleophilic acyl substitution and it can occur under both basic and acidic conditions (overall, this process would be reversible if the leaving group (X^-) is a good nucleophile and the nucleophile (Nuc^-) is a good leaving group).

Basic conditions:



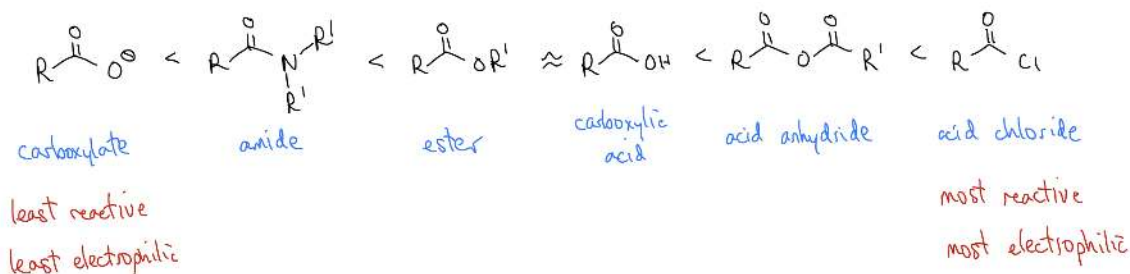
Acidic conditions:



The types of nucleophiles we will be using for nucleophilic acyl substitution are some of the same ones we used for nucleophilic additions to aldehydes/ketones, plus a few others:

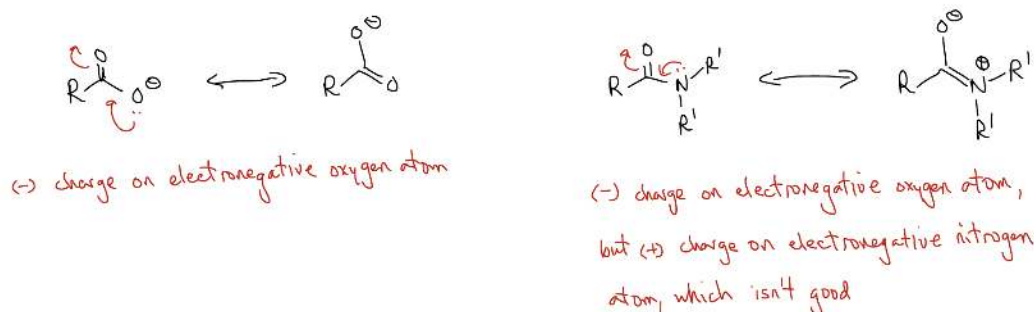


There is, of course, a diversity of electrophiles that can be used in this reaction, too. They can be arranged in order of increasing reactivity (electrophilicity) as shown below:

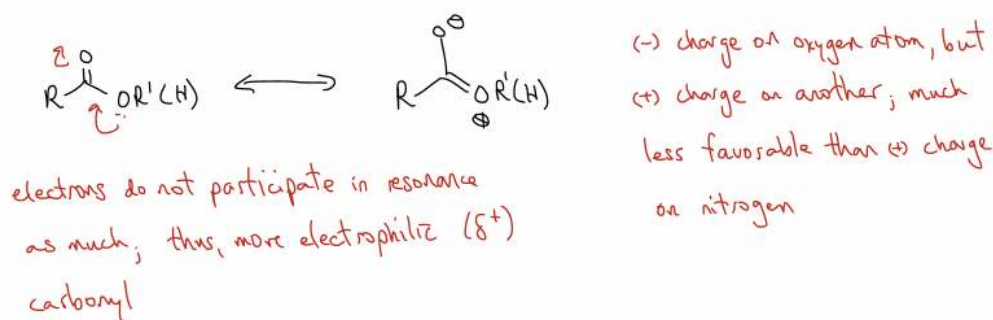


Several factors control the reactivity of these carbonyl compounds, and in each case, it is the energy level of the LUMO ($\pi^*_{C=O}$) that is impacted. By lowering the LUMO, the reactivity toward nucleophilic attack (ie. nucleophilic acyl substitution) increases. Getting to the tetrahedral intermediate requires good electrophilicity, so the carbonyl carbon should not have a lot of electron density on it. This is controlled by resonance, s-donation, inductive effects, and electronegativity.

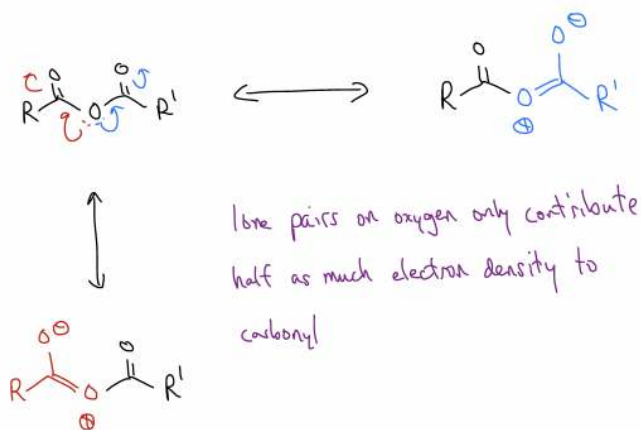
1. For carboxylates and amides, lone pair resonance increases electron density on the carbonyl, making the LUMO higher and decreasing reactivity.



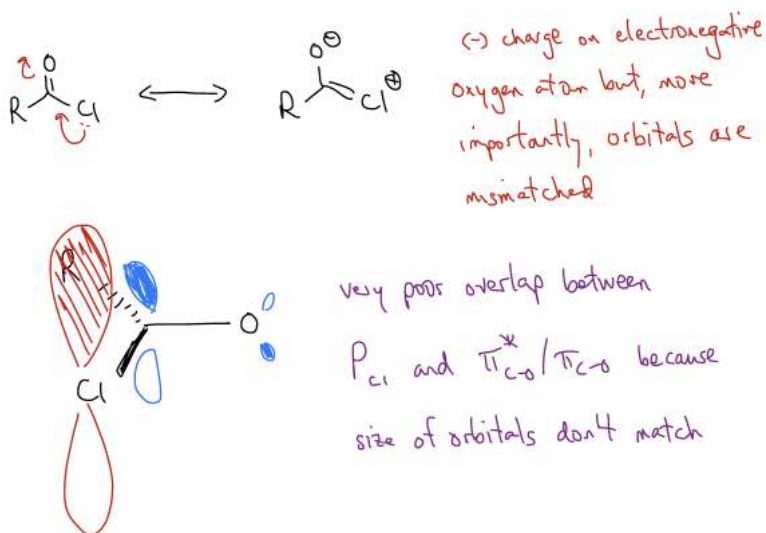
2. Esters and carboxylic acids have roughly the same reactivity and, by most accounts, are completely stable/inert. The oxygen does not like having positive charge, so it does not contribute its electrons as much to the carbonyl.



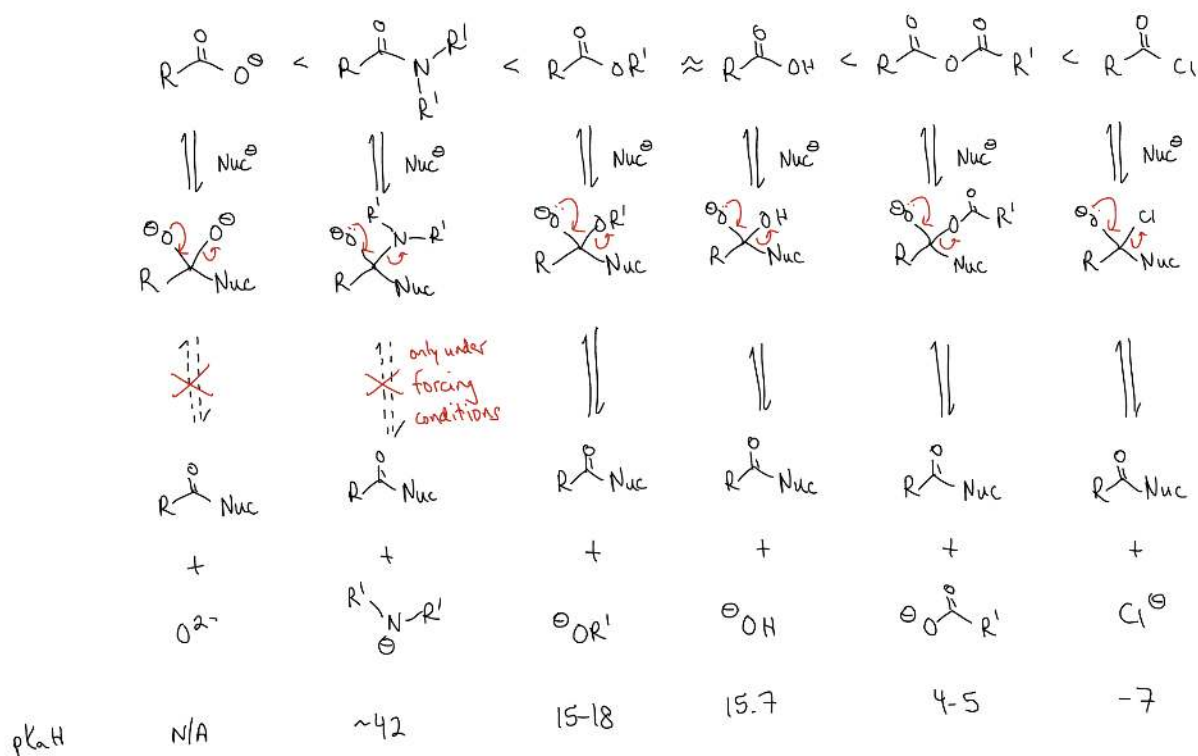
3. Acid anhydrides have lone pairs on oxygen that can delocalize via resonance, but because no single carbonyl is receiving all of this electron density, the carbonyl becomes more electrophilic. In other words, the lone pairs on oxygen are being pulled in both directions (which is different than esters/carboxylic acids).



4. Acid chlorides are most electrophilic because they suffer from orbital mismatch. Chlorine has lone pairs that are capable of delocalizing towards the carbonyl carbon, but because chlorine is in the second row, it is bigger and has poorer π overlap (resonance) with the carbonyl carbon. As a result, the lone pairs on chlorine contribute less, making the LUMO extremely low (less electron density = more electrophilic).



Let's now take each of these electrophiles and treat them with a generic nucleophile under basic conditions:

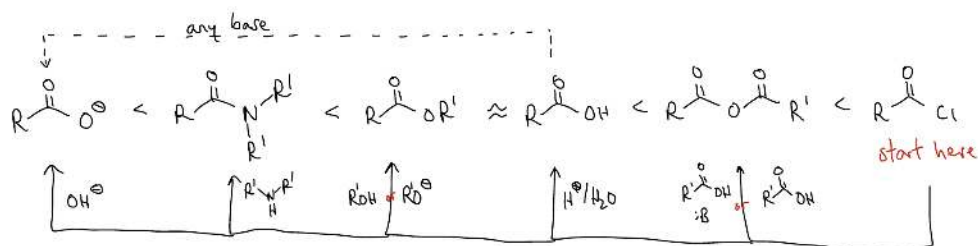


leaving group pK_aH must be < 20 for reaction to occur

What you might notice about the reactivity series is that electrophilicity also correlates with leaving group ability (pK_a).

We should be able to take each of our nucleophiles and make any of the carboxylic acid derivatives above. Some nucleophiles will be reactive enough (high enough HOMO) to react with all carbonyls, while others will only react with a few (this is known as chemoselectivity). Likewise, many electrophiles will react with all nucleophiles, while others only a few. In other words, by choosing the appropriate nucleophile, you should be able to react a carboxylic acid derivative on the right side of the reactivity series to make a carboxylic acid derivative farther to the left of the reactivity series (but not vice versa). You may use either acidic or basic conditions, but be careful – there are exceptions.

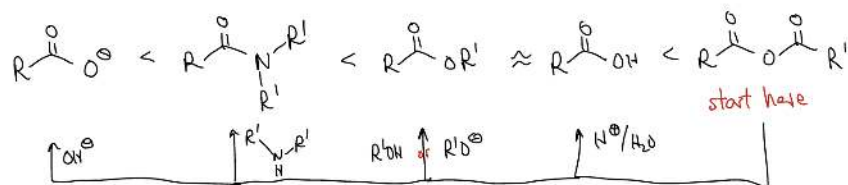
Let's start with the acid chloride:



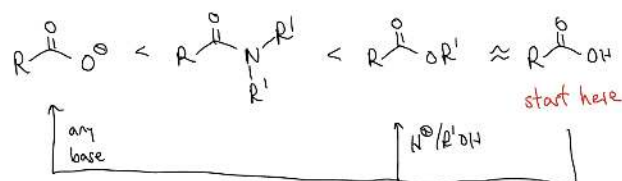
exceptions:

1. formation of carboxylic acids must occur under acidic conditions, otherwise the carboxylate will form;
2. acidic conditions are not needed for ester formation (alcohol is nucleophilic enough) or amide formation (acid will just protonate the amine).

Now, the anhydride:



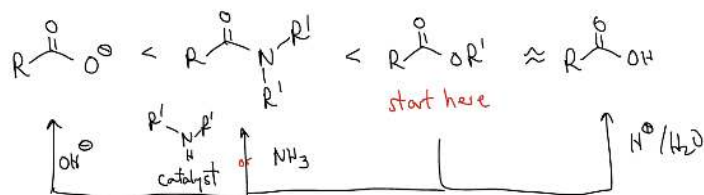
Next, the carboxylic acid:



exceptions:

1. in the formation of amides, reaction of an amine with a carboxylic acid will just protonate the amine and become unreactive (stay tuned for a better way to do this);
2. ester formation must occur under acidic conditions (Fisher estification), otherwise the carboxylate will form

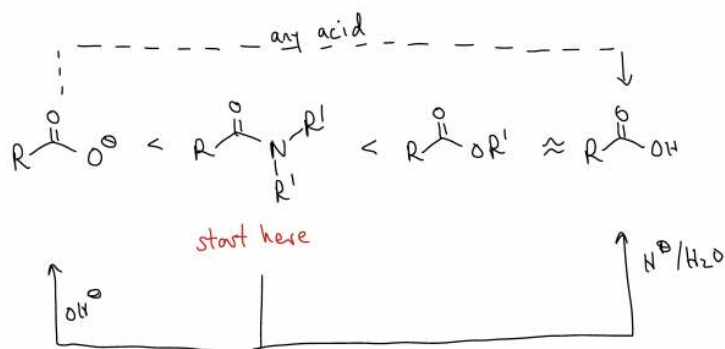
Next, the ester:



exceptions:

1. forming amides from esters is very rare and only occurs in the presence of a catalyst or using NH_3 as the nucleophile.
2. carboxylic acids can be prepared from esters via acidic or basic hydrolysis. This is the rare exception of being able to take an electrophile on the left hand side of the reactivity series and making something farther to the right.

Finally, the amide:



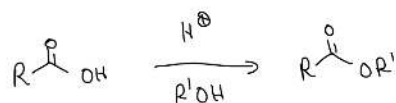
Notice that in this series, only the acid chloride cannot be made from anything else (stay tuned!).

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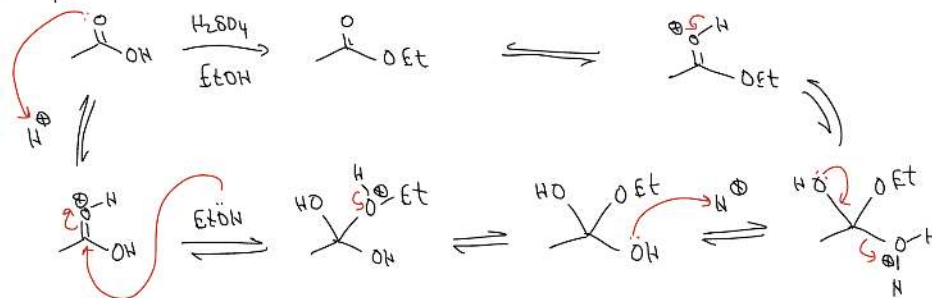
17.2: Reactions via Carbonyl Substitution

Let's now go through a few of these mechanisms to illustrate how the generic mechanism is operating:

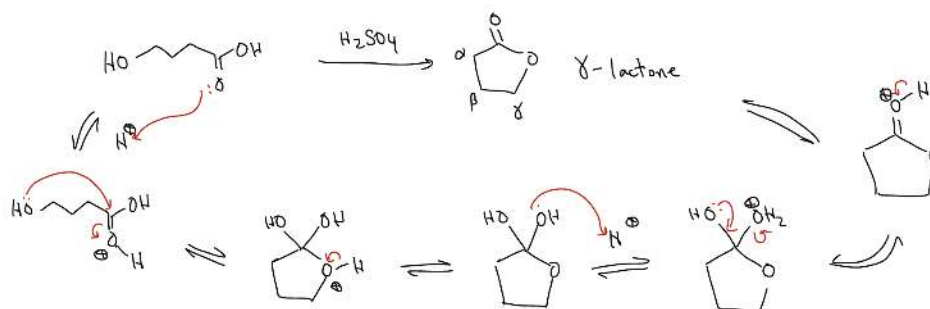
1. Fisher esterification



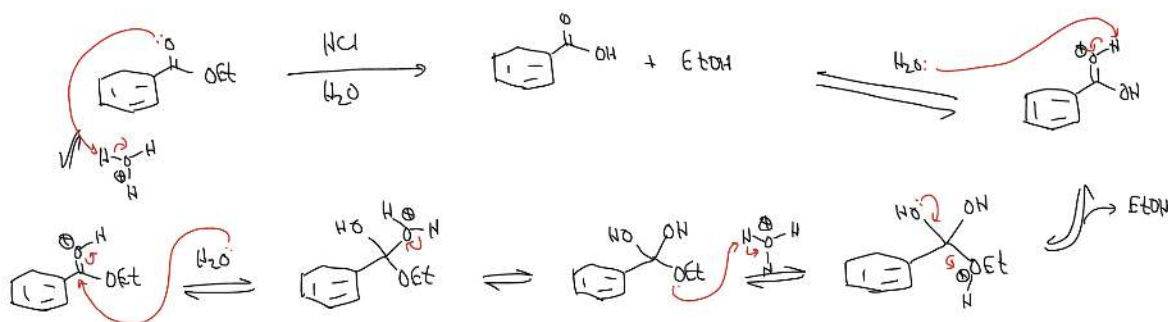
Example:



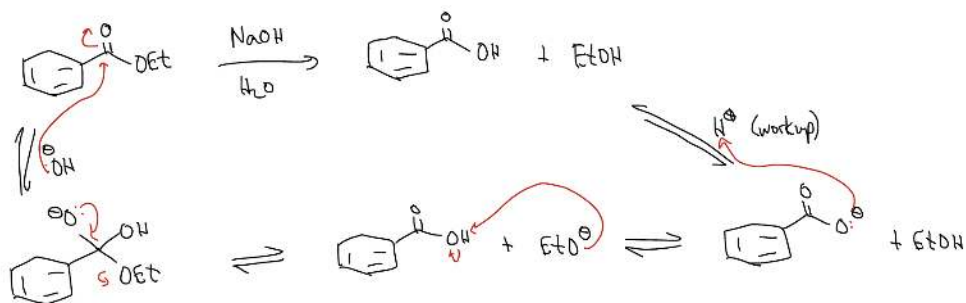
2. Lactone formation



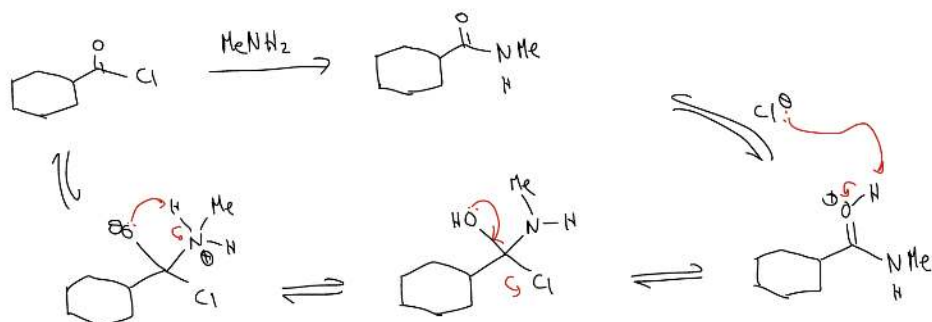
3. Ester hydrolysis (acidic conditions)



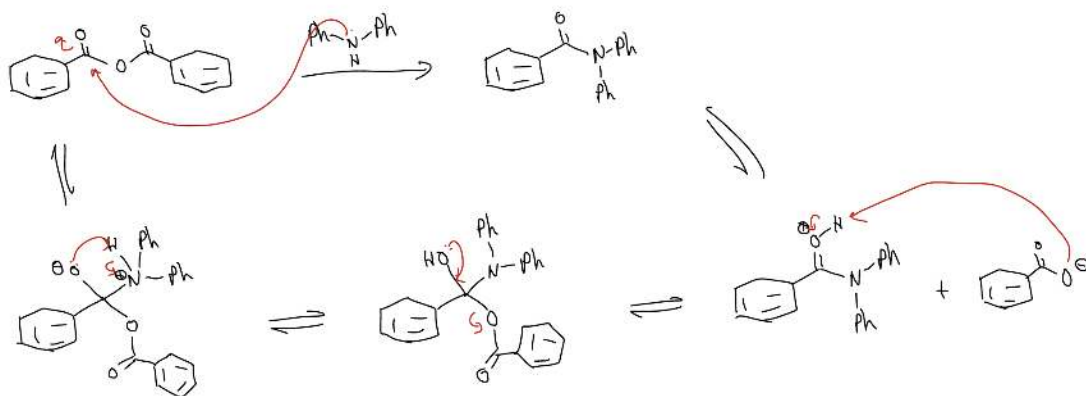
4. Ester hydrolysis (basic conditions – saponification)



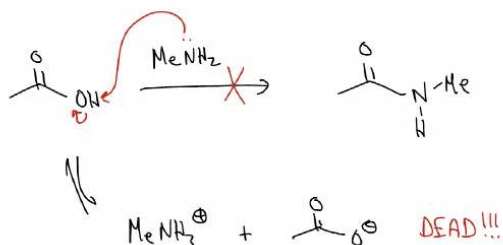
5. Amidation of acid chlorides



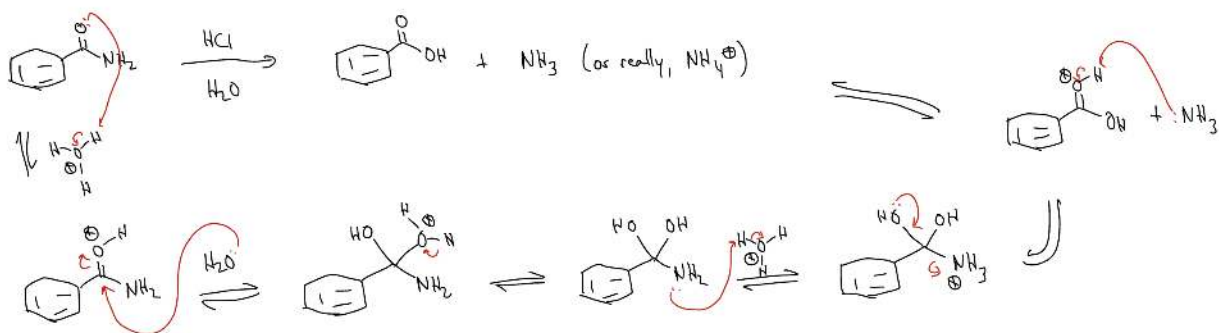
6. Amidation of acid anhydrides



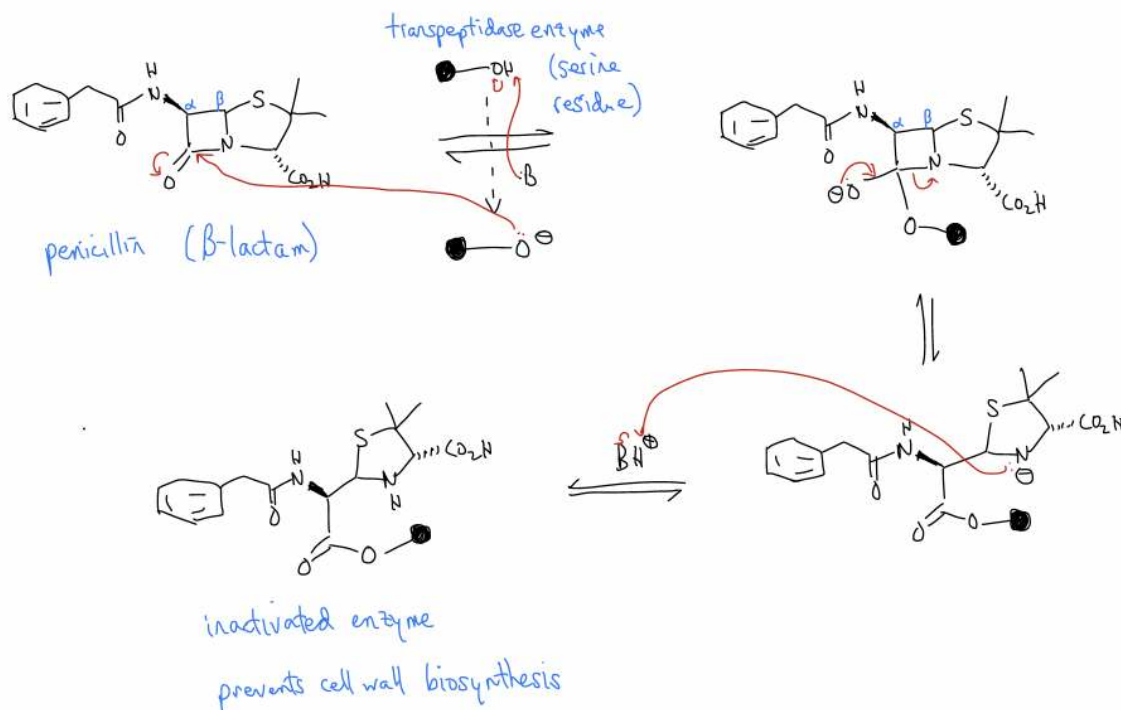
(7.) Amidation of carboxylic acids



8. Hydrolysis of amides (acidic conditions)



9. Hydrolysis of amides (basic conditions)

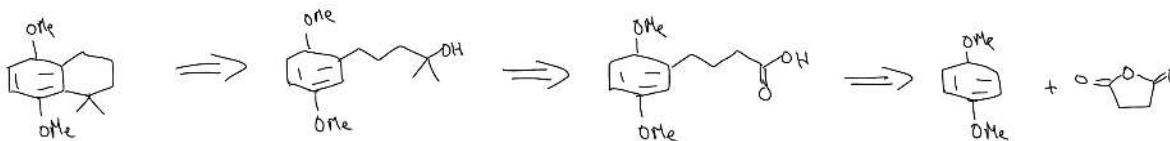


The hydrolysis of β -lactam by β -lactamases before reacting with transpeptidase is a mechanism by which bacteria become resistant to antibiotics.

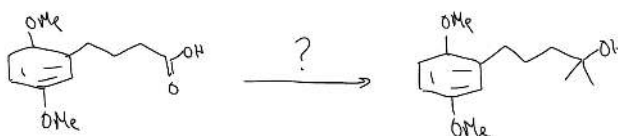
17.2: Reactions via Carbonyl Substitution is shared under a [not declared](#) license and was authored, remixed, and/or curated by LibreTexts.

17.3: Double Nucleophilic Acyl Substitution

Other nucleophiles participate in nucleophilic acyl substitution chemistry, but undergo substitution twice. Let's illustrate this concept in the context of a multistep synthesis. How would you synthesize the following molecule?

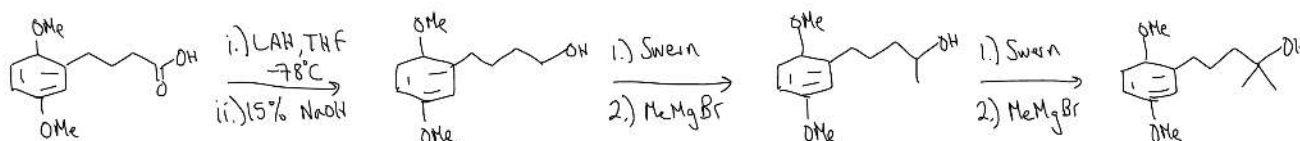


How could we convert the following compound to the tertiary alcohol?

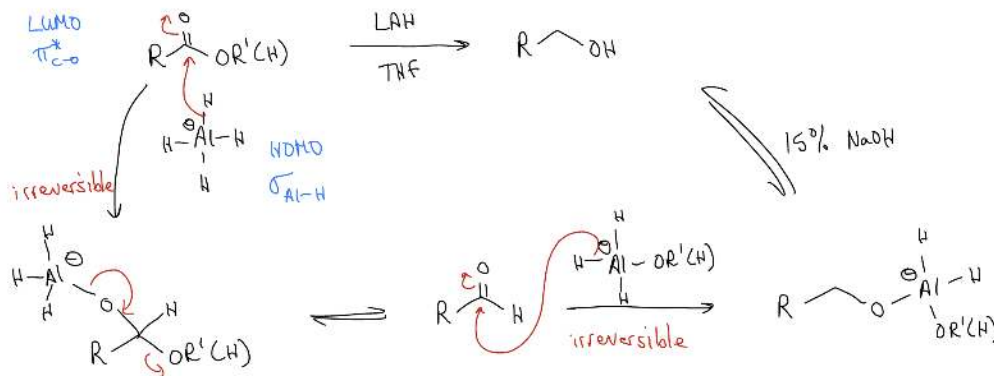


Two possibilities:

Pathway A:

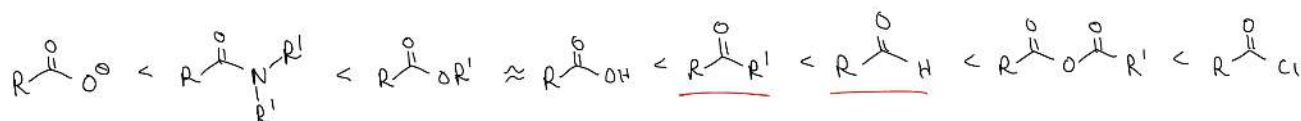


In the first step of this sequence, LAH reduces a carboxylic acid all the way to an alcohol via two successive irreversible nucleophilic acyl substitution mechanisms. This type of double reactivity can occur for both carboxylic acids and esters, or anything to the right in the reactivity series. Let's take a look:



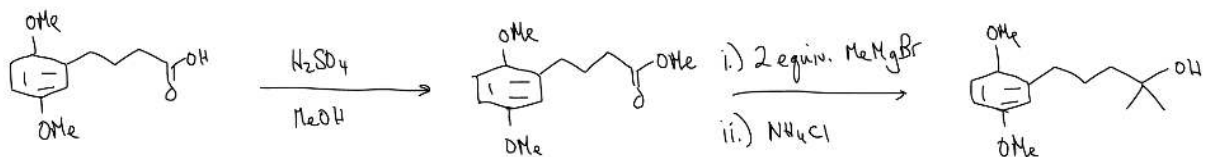
The product of the first nucleophilic acyl substitution is an aldehyde, and you already know that aldehydes react with LAH to give alcohols. Thus, the next step is also a nucleophilic acyl substitution mechanism which will yield the primary alcohol.

What this tells us is that aldehydes and ketones are *more* reactive than esters and carboxylic acids, so we can update our reactivity series. This should make sense because resonance is more strongly donating than σ -donation.

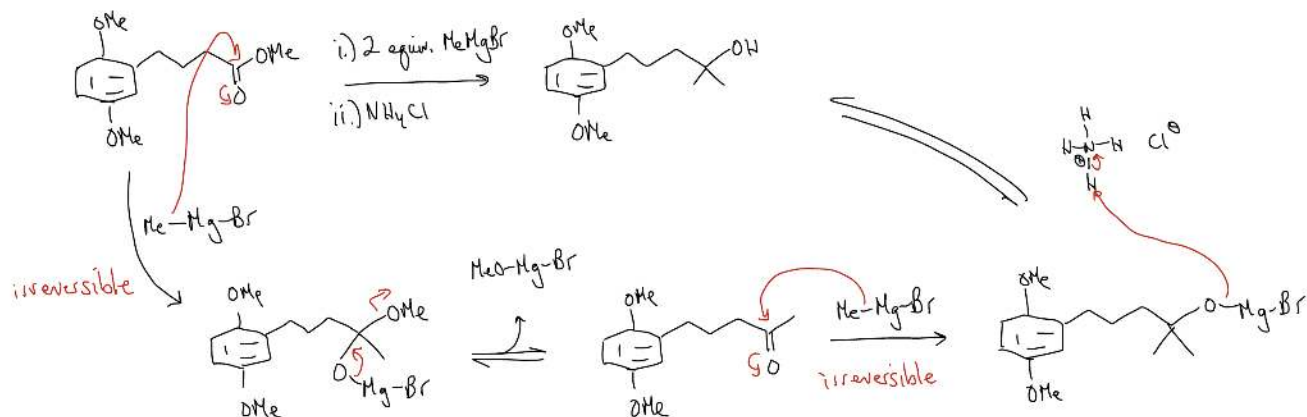


Now, let's go back to our original question. We could take LAH and reduce the acid to the alcohol, then perform a series of oxidation and Grignard reactions to arrive at the final product, but this would be quite long. Know that some nucleophiles like LAH react twice, can you think of a pathway that might be much shorter?

Pathway B:

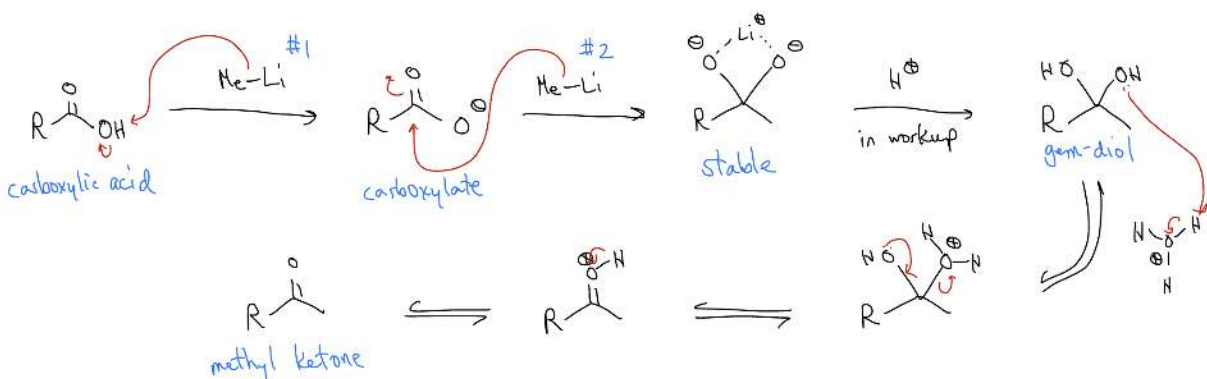


If we convert the carboxylic acid to the ester and then use two equivalents of MeMgBr, we can generate the tertiary alcohol in one reaction flask after acidic workup!



The take-home message here is that harder nucleophiles like LAH, RMgBr, and RLi perform nucleophilic acyl substitution, but the product of this step is more reactive than the starting material, so a second nucleophilic acyl substitution occurs rapidly. Overall, the nucleophile has been incorporated twice.

One more thing – MeLi and PhLi will react with carboxylic acids only once because the tetrahedral intermediate is stable. After workup, this intermediate decomposes to give a ketone.



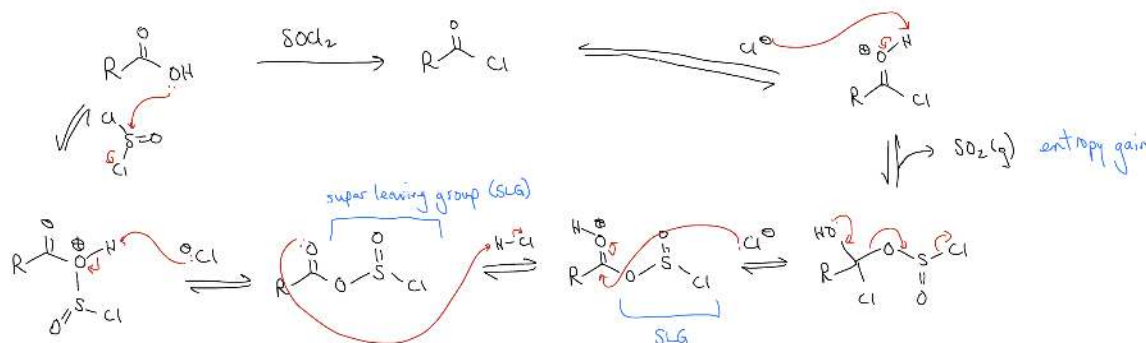
17.3: Double Nucleophilic Acyl Substitution is shared under a [not declared](#) license and was authored, remixed, and/or curated by LibreTexts.

17.4: Super Leaving Groups

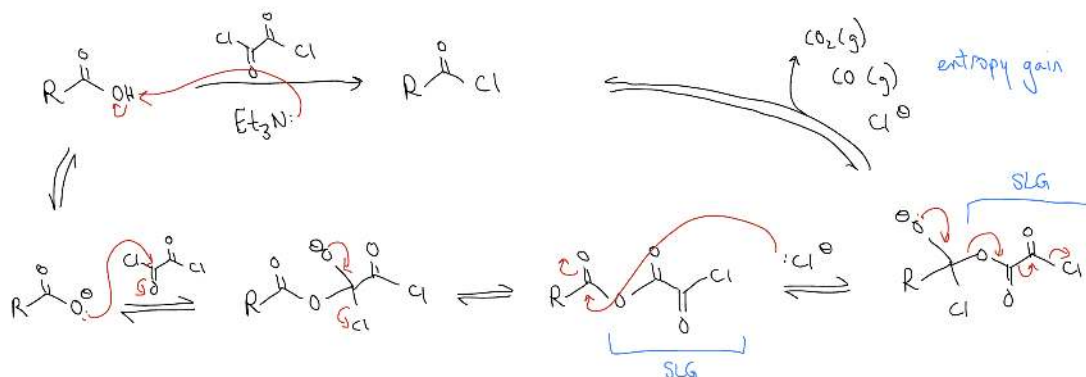
Super Leaving Groups

Now, let's go back to the reactivity series. We've said that with the appropriate nucleophile, anything to the left can be made from something on the right. This should make you uncomfortable – if acid chlorides are all the way to the right, how do we make them? The answer is that we take a carboxylic acid and then turn the $-OH$ into a “super leaving group” that then reacts with chloride. There are primarily two ways of doing this:

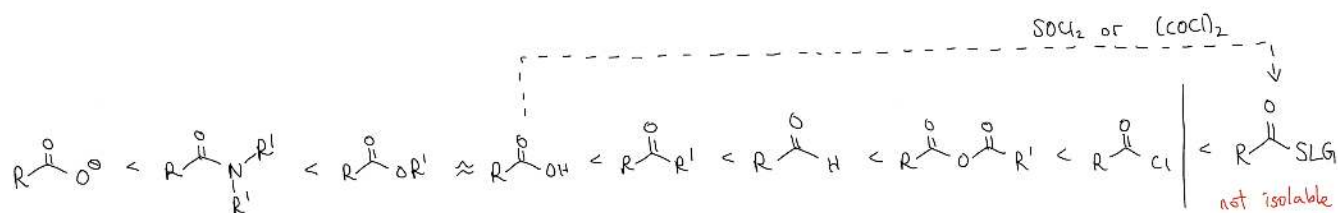
A) Reaction with thionyl chloride ($SOCl_2$)



B) Reaction with oxalyl chloride ($(COCl)_2$)



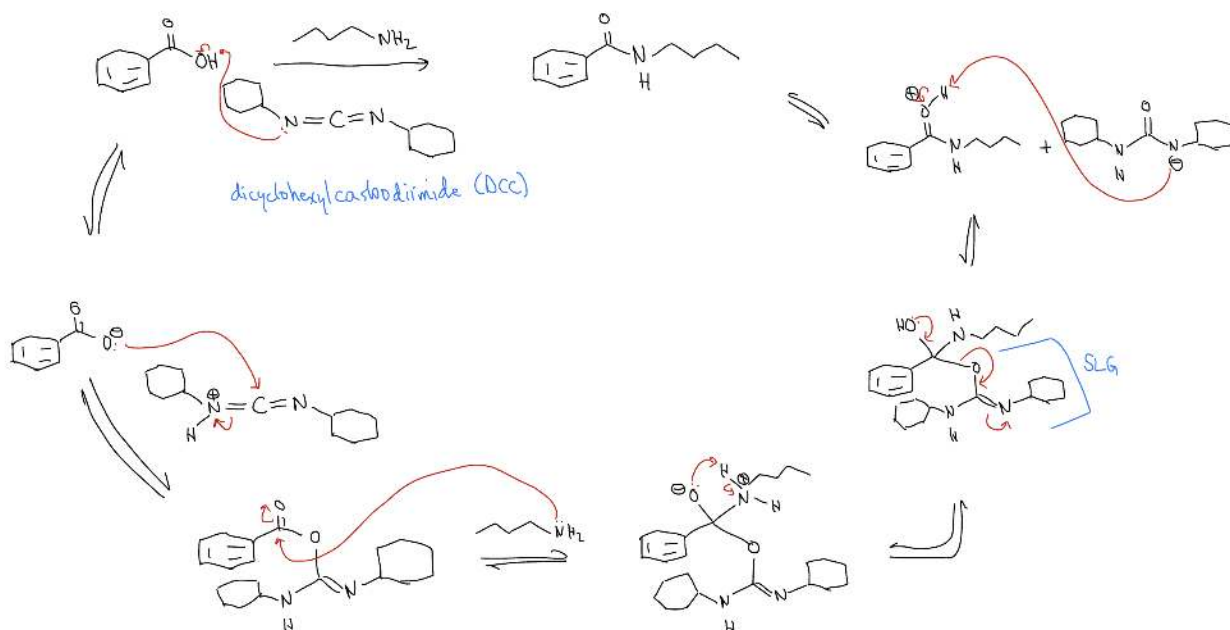
So, if we update our reactivity series, we should have the following:



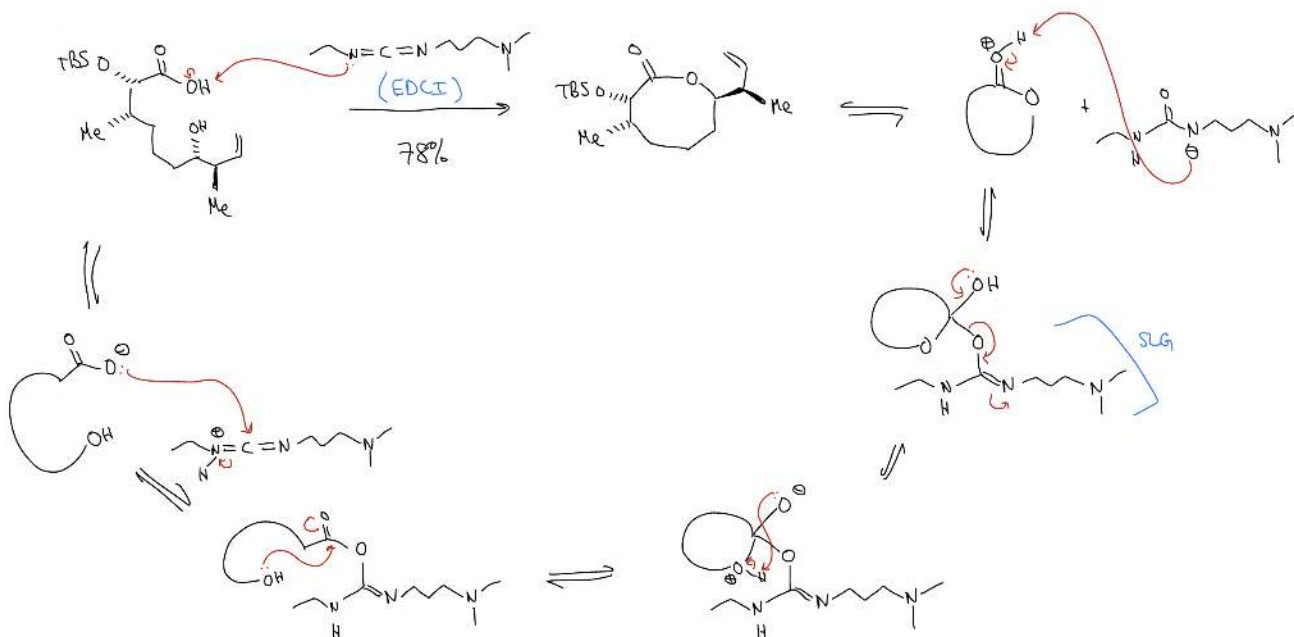
Coupling Reagents

Recall that the reaction between carboxylic acids and amines does not yield an amide because the amine simply protonates to become an ammonium salt which is non-nucleophilic and a carboxylate which is non-electrophilic. We could convert the carboxylic acid into an acid chloride, but larger, more complicated substrates may not behave well under the harsh reaction conditions ($SOCl_2$ or $(COCl)_2$). So, in order to directly promote the formation of an amide from these two substrates, which are commercially available, we use an activating agent, or coupling agent. The activating agent essentially converts the carboxylic acid into an

intermediate that has “super leaving group”-like reactivity. For example, consider the reaction sequence below with the coupling agent, dicyclohexylcarbodiimide:



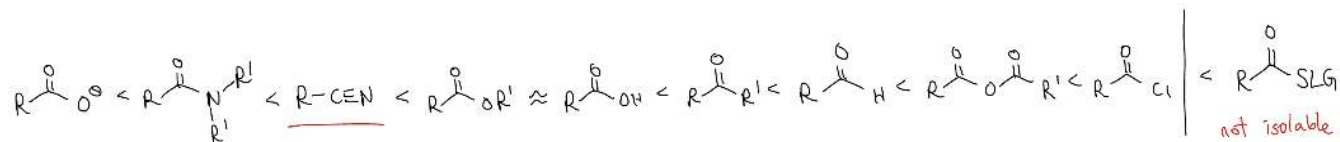
Coupling agents are also useful in the synthesis of esters, especially those that are large macrocyclic lactones. Consider the following esterification with the coupling agent EDCI:



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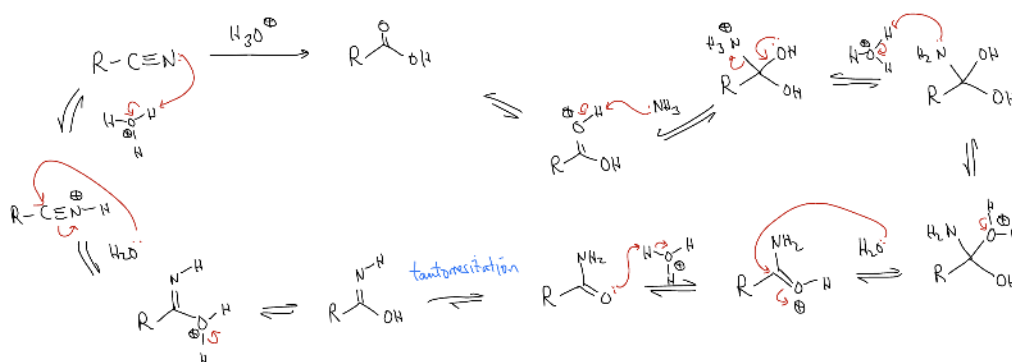
17.5: Nitriles

There is one more functional group that fits into the reactivity series. Notice that each of the electrophiles in the series (with the exception of aldehydes/ketones) has three bonds to heteroatoms. The other functional group that fits into this category is the nitrile, with three bonds to nitrogen. Its reactivity comes in between the amide and ester:

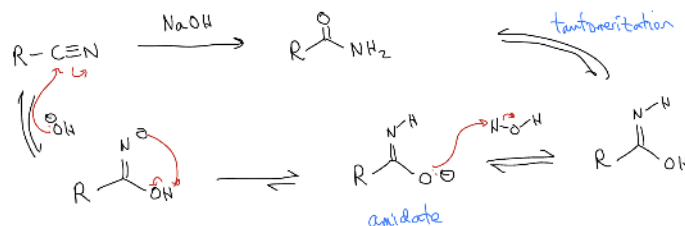


Let's look at its reactivity under acidic and basic hydrolytic conditions:

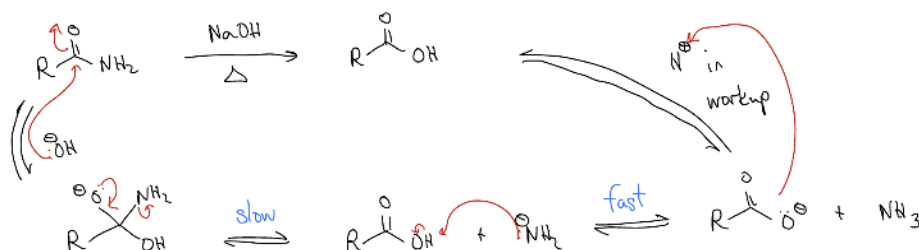
1. Acidic hydrolysis:



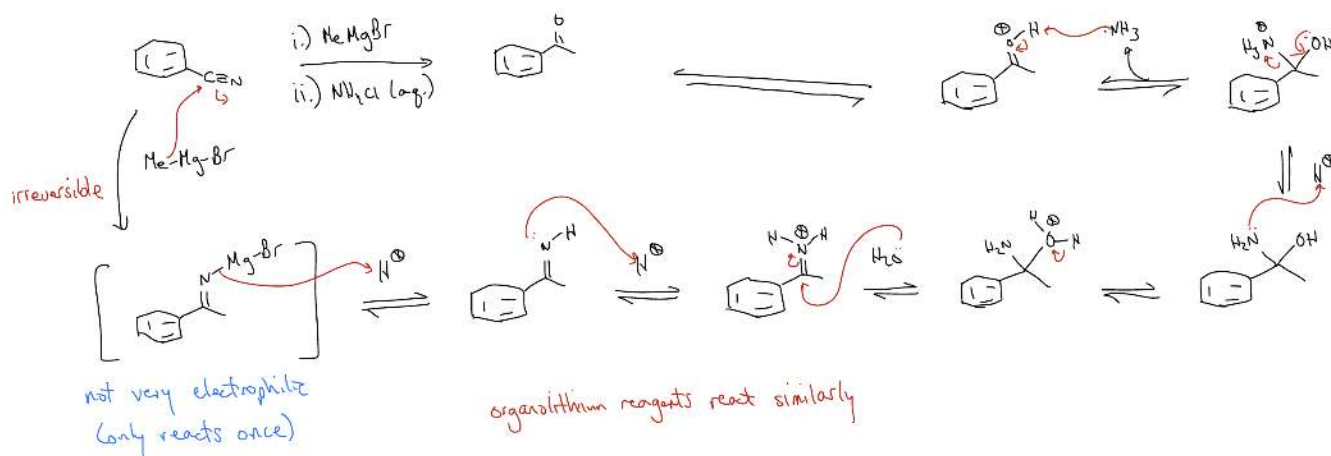
2. Basic hydrolysis



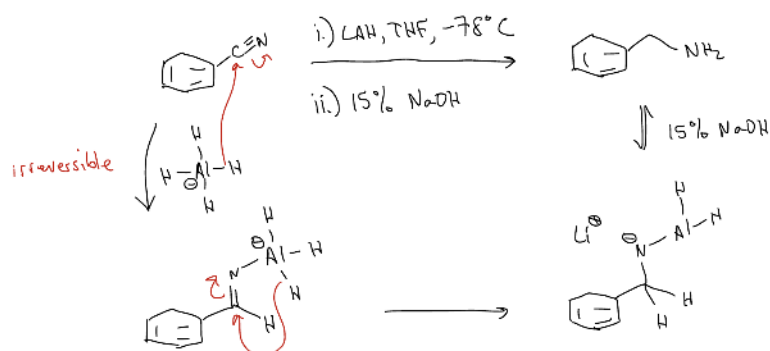
Under basic conditions, the amidate intermediate is now even less electrophilic than amides due to the negative charge. It will still react to give carboxylates (or carboxylic acids upon protonation), but more forcing conditions are needed.



What about reactions of nitriles with hard nucleophiles like organolithium or Grignard reagents?

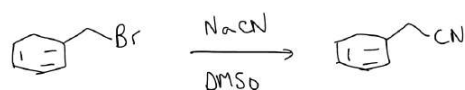


What about reactions of nitriles with reducing agents like LAH?



Finally, what methods are there to prepare nitriles?

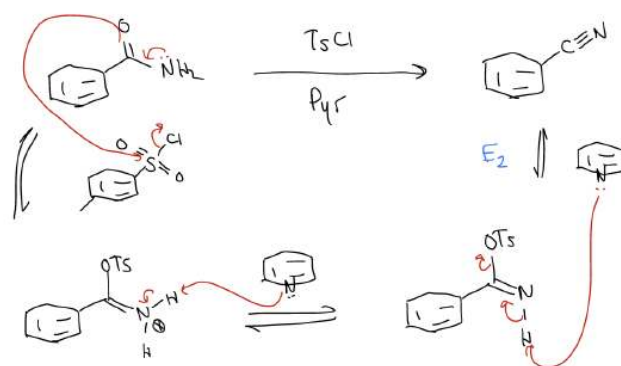
1. $\text{S}_{\text{N}}2$



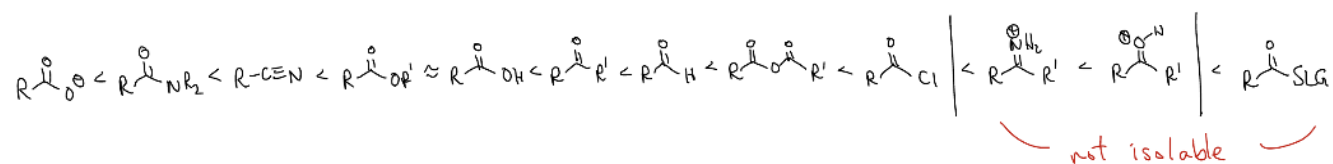
2. Cyanohydrin formation



3. Dehydration of a primary amide



Let's summarize the reactivity series one last time:

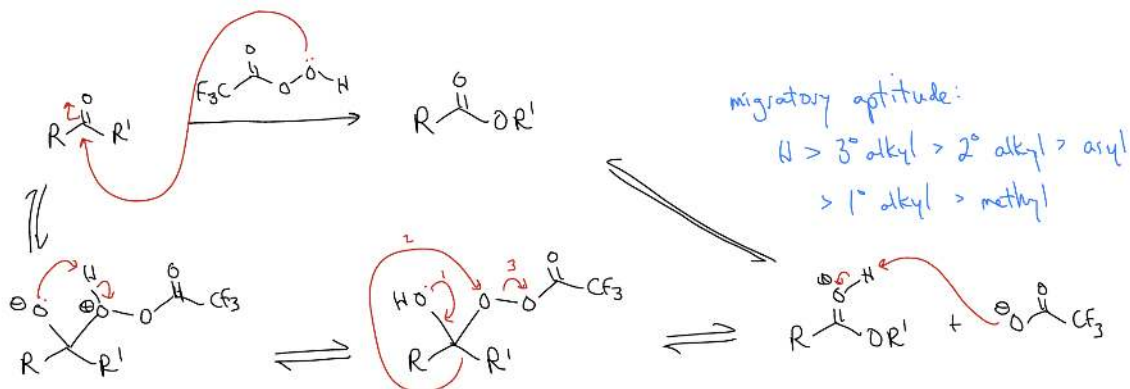


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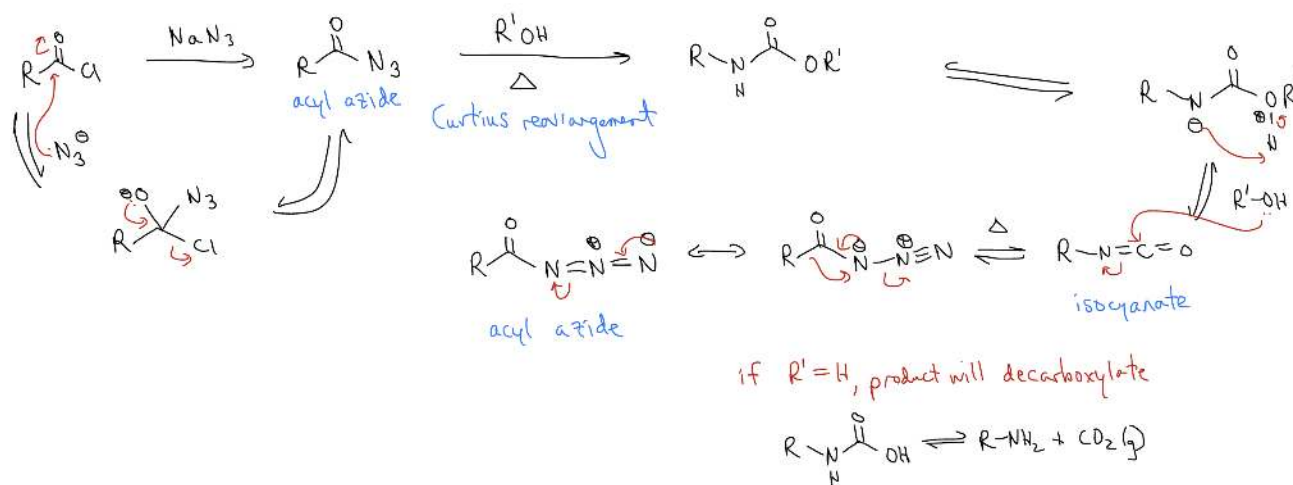
17.6: Named Reactions

There are many reactions that operate via nucleophilic acyl substitution that have specific names, known as named reactions. The mechanisms are sometimes more complicated than just substitution at the carbonyl carbon. Each reaction, listed below, provides unique ways to create common (or even rare) functional groups.

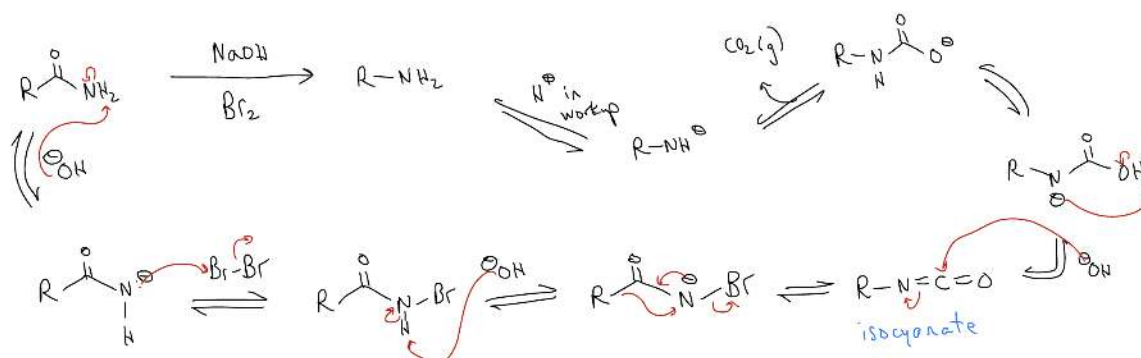
1. Baeyer-Villiger oxidation



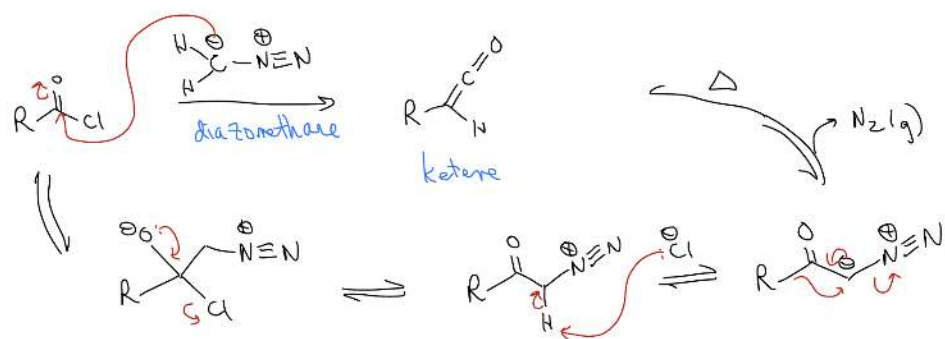
2. Curtius rearrangement



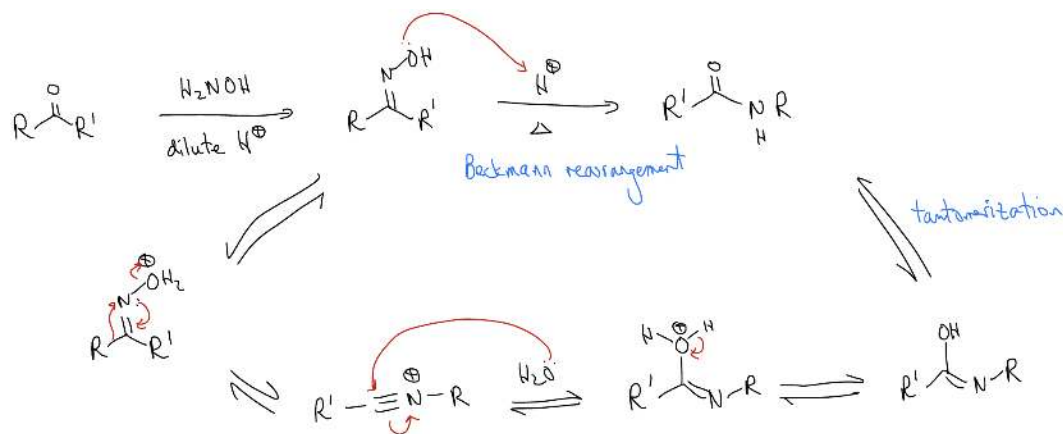
3. Hofmann rearrangement



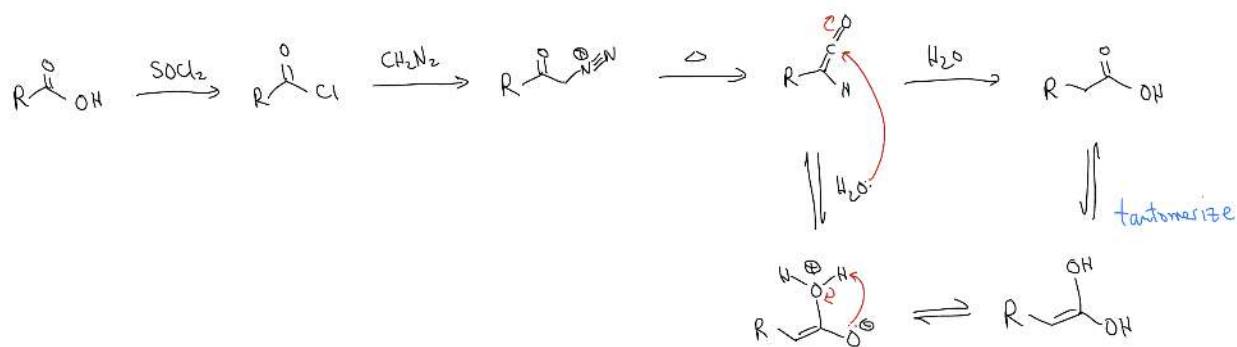
4. Wolff rearrangement



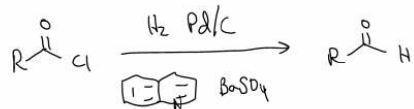
5. Beckmann rearrangement



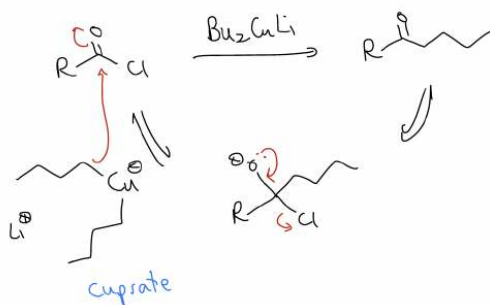
6. Arndt-Eistert reaction



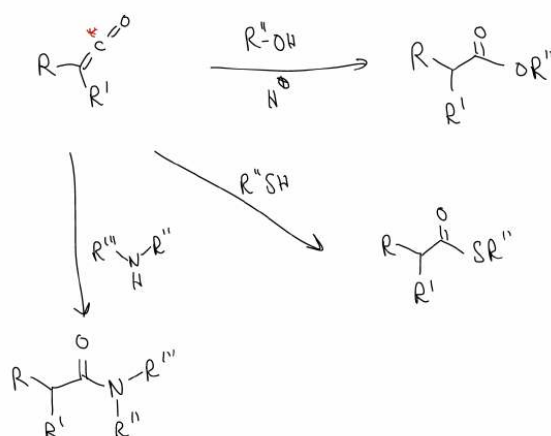
7. Rosemund reduction



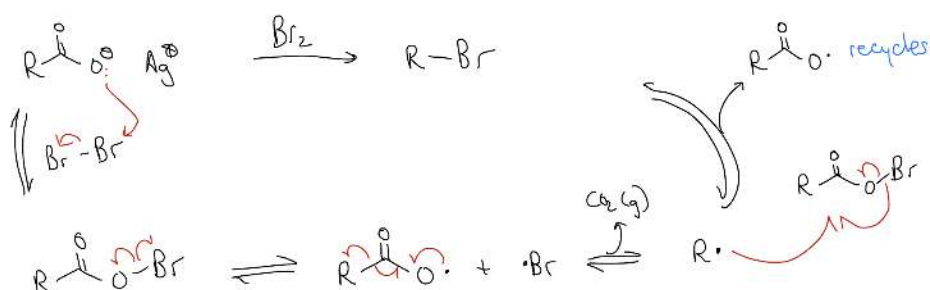
similar to Rosenmund reaction:



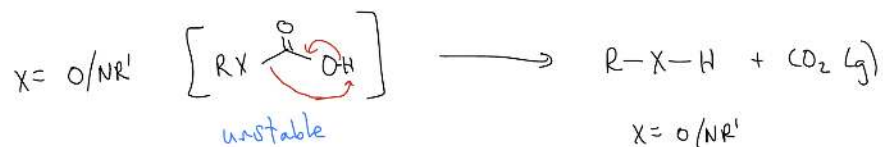
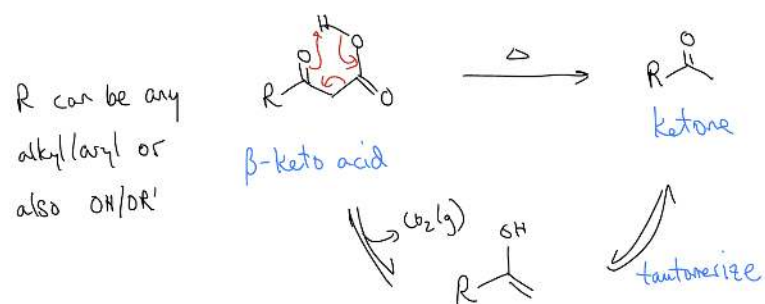
8. Reactions of ketenes



9. Hunsdiecker reaction



10. Decarboxylation of carboxylic acids



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CHAPTER OVERVIEW

18: Enols and Enolates

[18.1: Enols and Enolates](#)

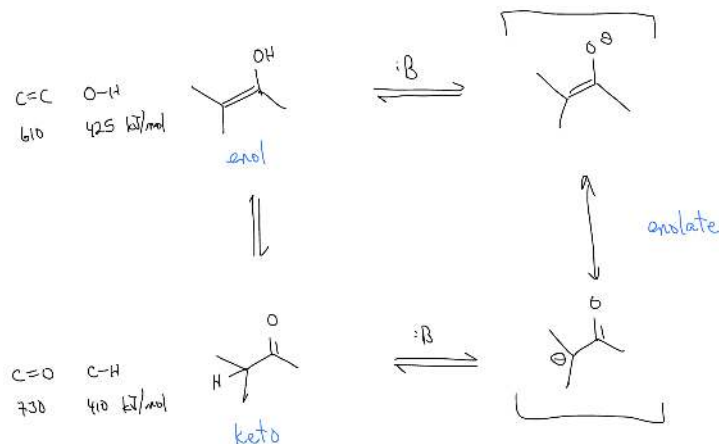
[18.2: Consequences of Tautomerization](#)

[18.3: Molecular Orbital Description of Enolates](#)

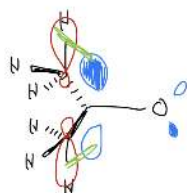
[18: Enols and Enolates](#) is shared under a [not declared](#) license and was authored, remixed, and/or curated by LibreTexts.

18.1: Enols and Enolates

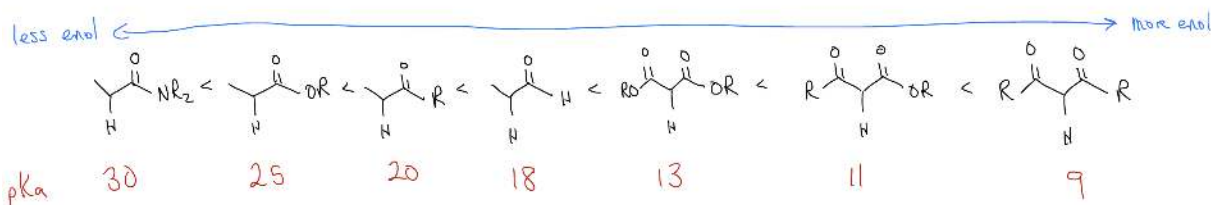
The last major class of reactions involves C-C bond formation that proceeds through an intermediate known as an enolate. An enolate is simply a deprotonated enol, which is itself a hydroxyalkene. Enols are in equilibrium with the keto form (preferred), and the enolates themselves have resonance structures that place negative charge on oxygen and carbon, respectively, in an allyl-like arrangement.



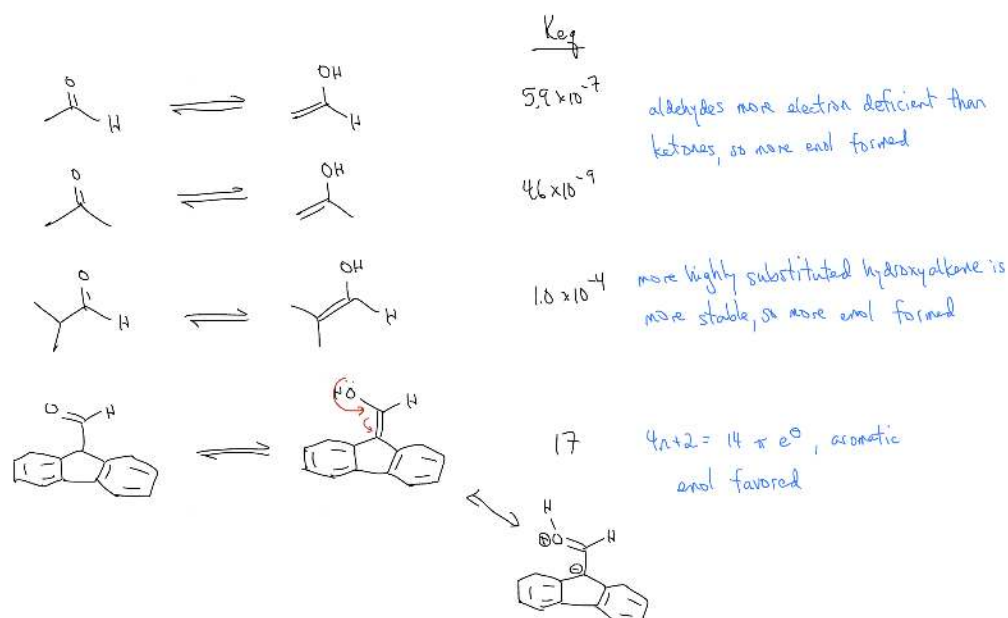
The equilibrium between keto and enol forms is not necessarily rapidly established – there could be some barrier – but the overall movement of a proton through a π system is known as tautomerization. The keto form is normally favored since the C=O bond is stronger than a C=C bond. One can promote tautomerization to the enol form by reducing the amount of electron density on the carbonyl. This would allow for better $\sigma_{C-H} \rightarrow \pi^*_{C=O}$ overlap (since $\pi^*_{C=O}$ will be lower). Thus, better σ -donation will result, more enol will be formed, and the proton that is moving will become more acidic. Another way of saying this is: as the electron deficiency of the carbonyl builds up, σ -donation is greater, and more enol forms.



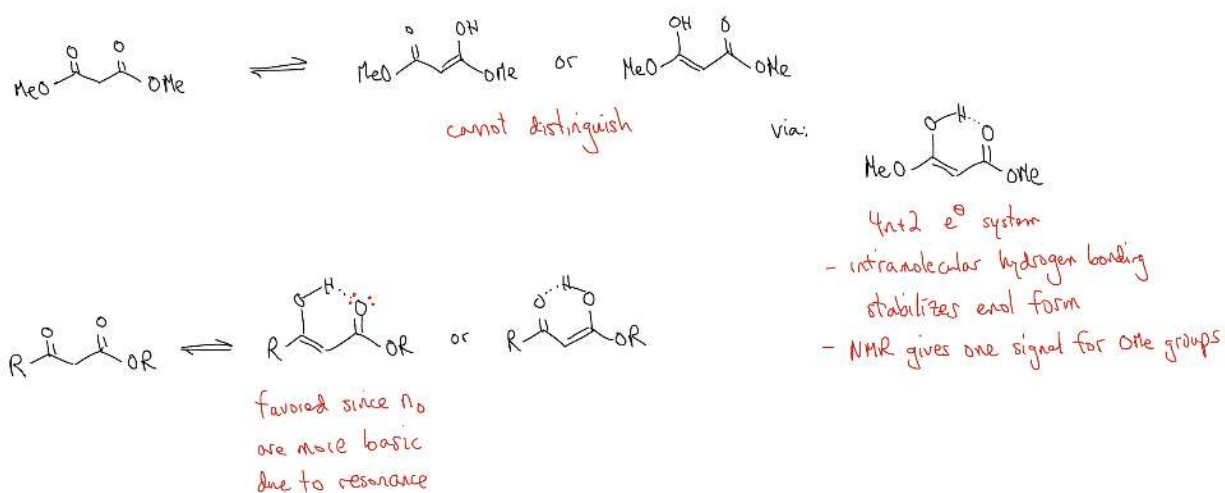
The pK_a of the enolizable proton correlates with greater stabilization of the negative charge in the conjugate base. Consider the trend for both enol and pK_a below. The cut-off for keto-enol tautomerization is roughly a pK_a of 18-20. In 1,3-dicarbonyl compounds, the central atom's pK_a is quite low due to the double resonance delocalization that can occur.



Let's take a look at how this is manifest in some K_{eq} values.

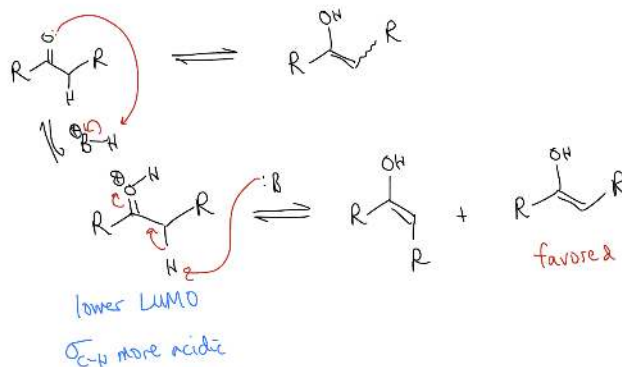


Other examples:

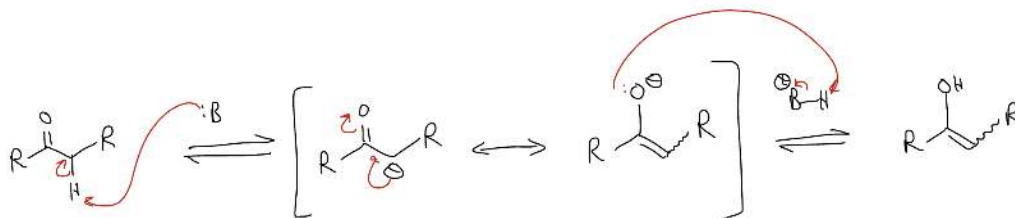


We can promote enolization under both acidic and basic conditions:

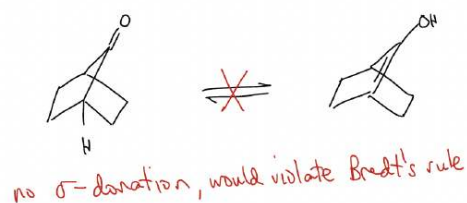
1. acidic conditions



2. basic



Remember, also, that enol and enolates only form when σ_{C-H} is aligned with π^*_{C-O} . Bredt's rule states that no enolization can occur on bridged bicyclic systems.

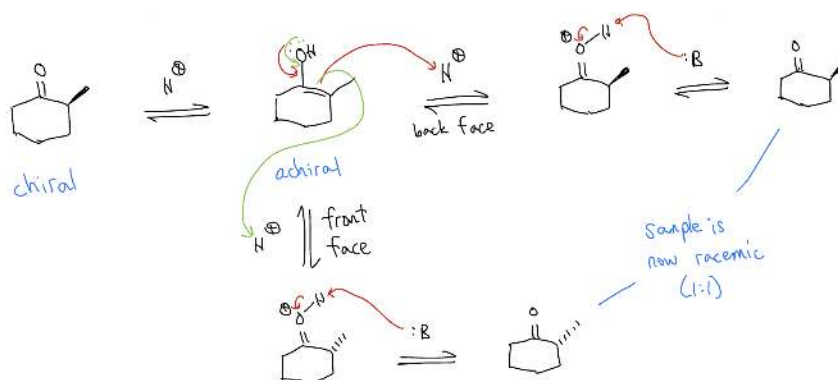


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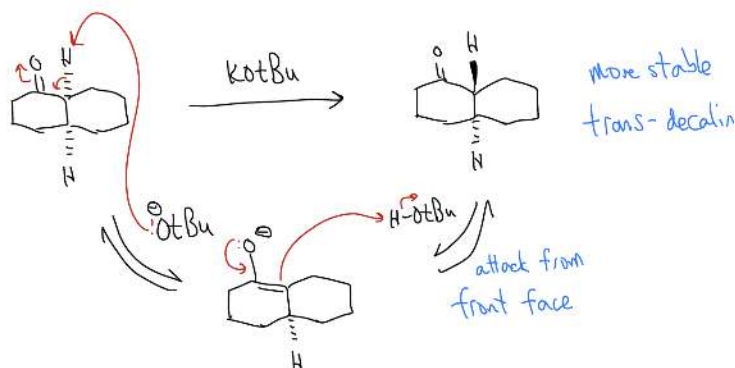
18.2: Consequences of Tautomerization

So, what are some of the consequences of keto-enol tautomerization?

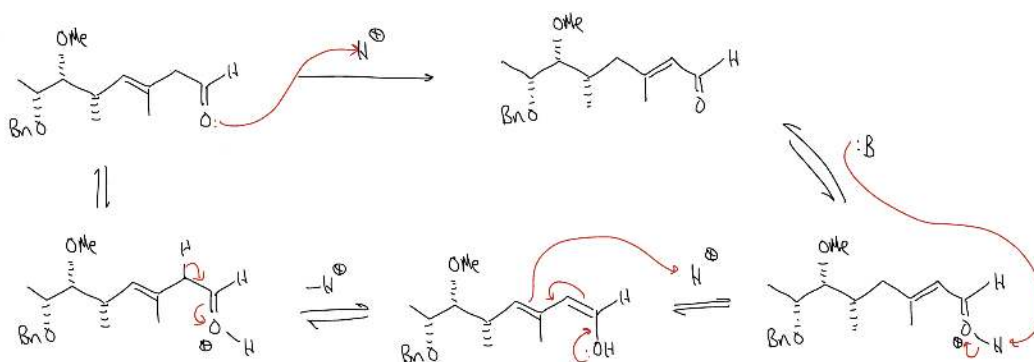
1. α -epimerization – stereochemical equilibration of a stereogenic center (either under acidic or basic conditions)



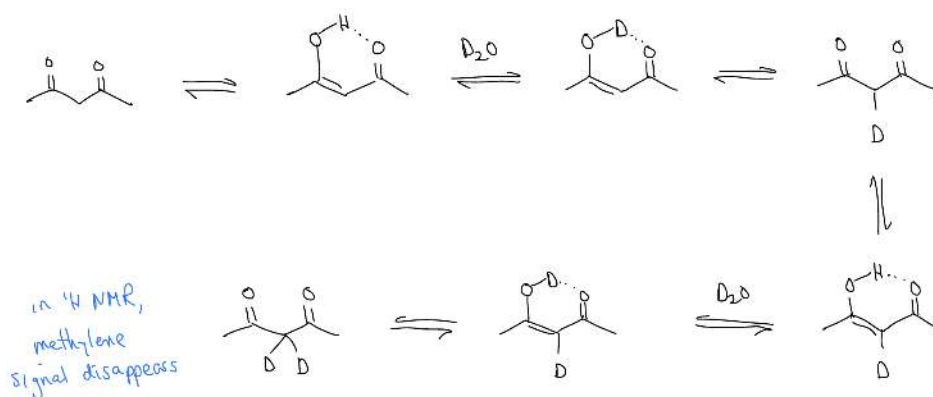
In the example above under acidic conditions, since the enol is achiral, reprotonation can occur from the opposite face, giving a racemic mixture. The same thing can happen under basic conditions:



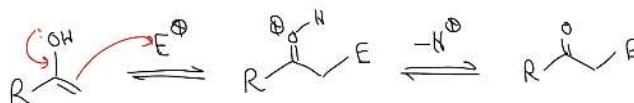
2. isomerization of nonconjugated enones into conjugated enones



3. exchange of α -protons for deuterium



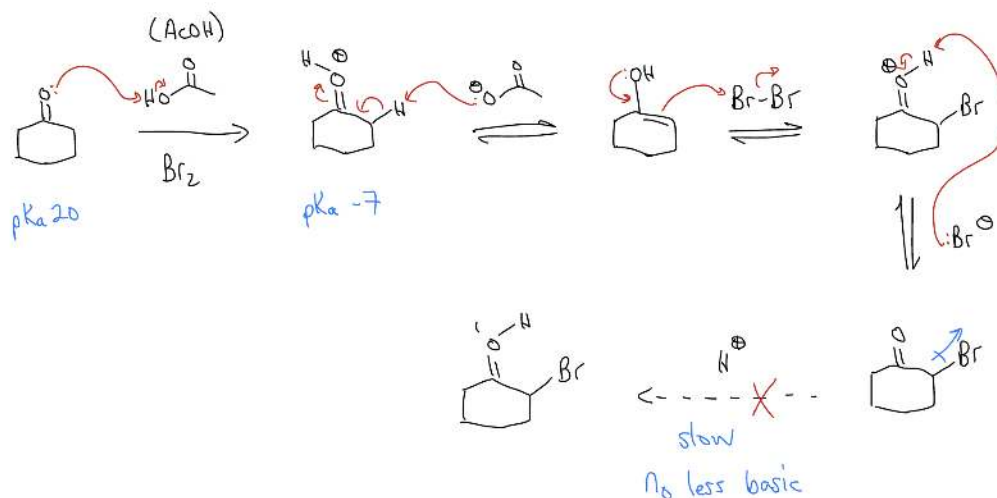
4. enols are electron-rich alkenes that undergo electrophilic addition.



Enols/enolates are nucleophiles that react through the (π bond (note the regiochemistry)). The oxygen lone pairs increase the level of the HOMO ($\pi_{\text{C-C}}$)

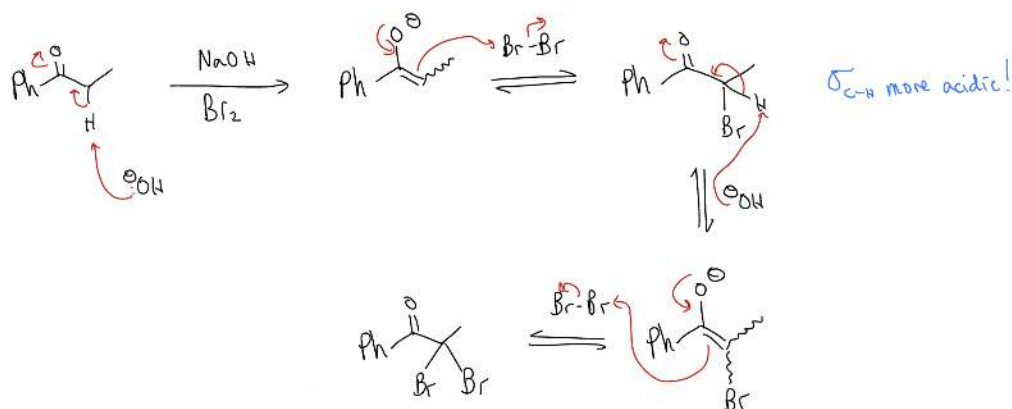
An example of this type of reactivity is the α -halogenation of ketones. This reaction can be performed under both acidic and basic conditions, but the products that form are quite different.

a) acidic conditions

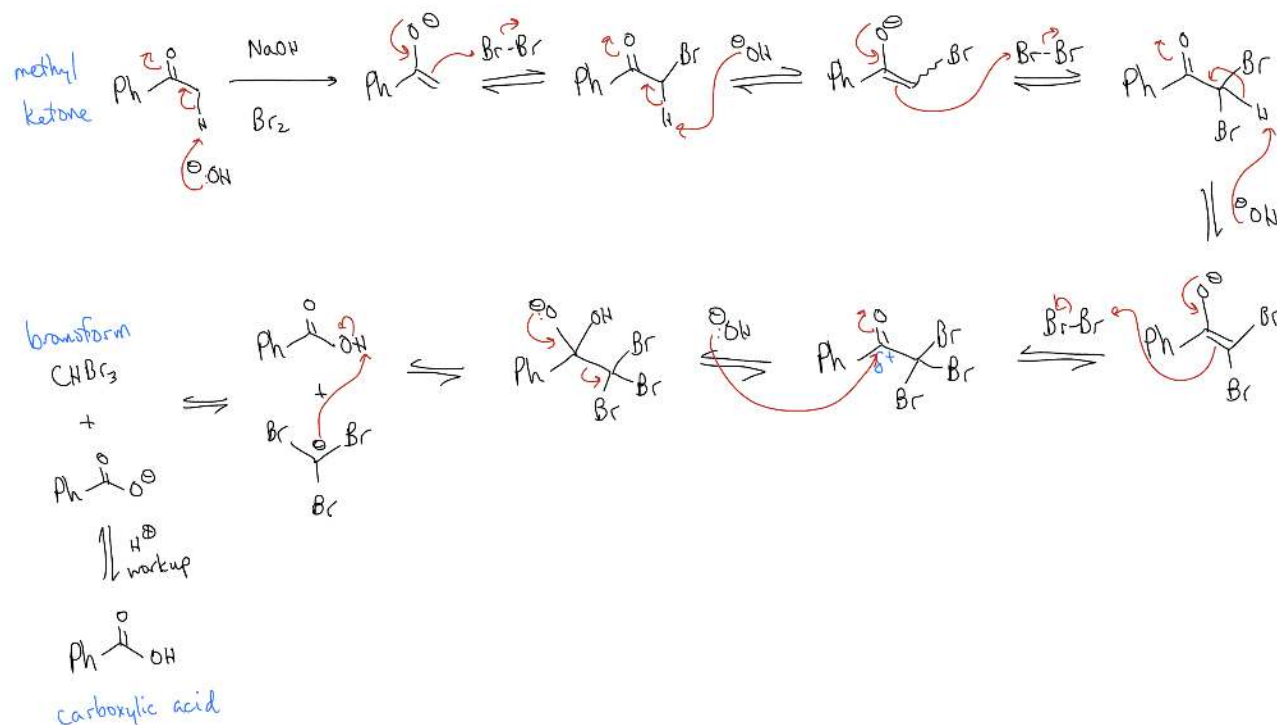


In this reaction, bromine is electronegative, so it's pulling electron density away from the carbonyl inductively, making the carbonyl lone pairs less basic and less likely to protonate and perform a second bromination. In other words, the monobrominated product is less reactive than the starting material, so the reaction stops at monobromination.

b) basic conditions



Under these conditions, the product of monobromination is more reactive than the starting material. The α C-H bond is more acidic because of the inductively withdrawing bromine atom that has been incorporated, so the reaction continues. A second and third bromination can occur, and it is very difficult to stop the reaction. When methyl ketones are treated with NaOH and Br_2 , an even different product forms:

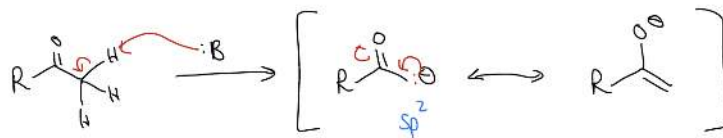


This is a good way of making carboxylic acids from ketones.

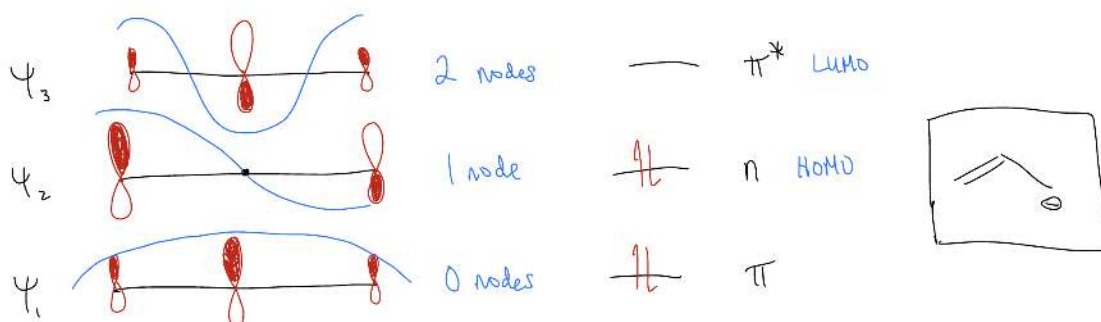
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18.3: Molecular Orbital Description of Enolates

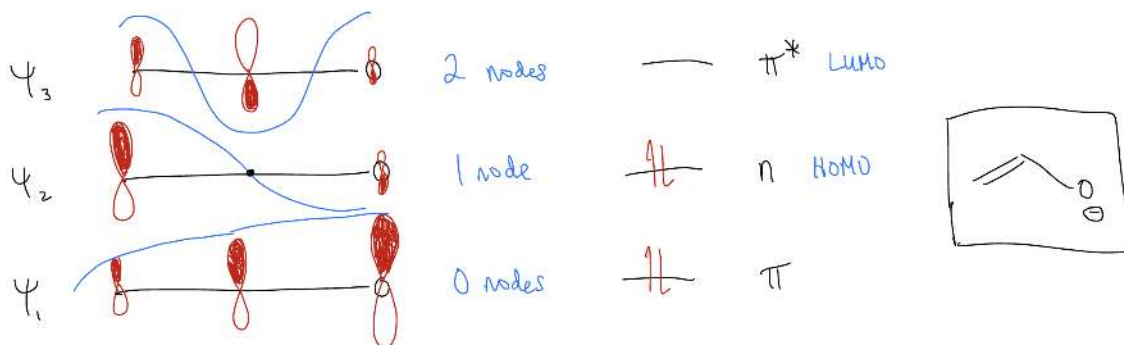
As we have previously mentioned, when a ketone that has a C-H bonds is treated with a base, deprotonation occurs to give the enolate. The α C-H bonds are rather acidic because of resonance delocalization, which arises from the allyl resonance of a 3-atom, 4 π electron system.



You might recall the molecular orbital description for the allyl anion, which is completely symmetrical.



In the enolate, the molecular orbital description changes slightly due to the presence of an electronegative oxygen atom.

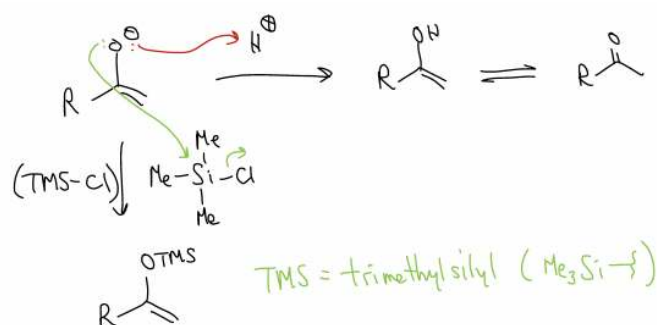


This molecular orbital description tells you a few things: 1) the total charge ($\psi_1 + \psi_2$) is greater on oxygen than on carbon, but 2) in the HOMO, the charge is greater on carbon. It should follow, then, that if an enolate is a nucleophile, it will react on either carbon or oxygen. So, how do we decide which atom reacts?

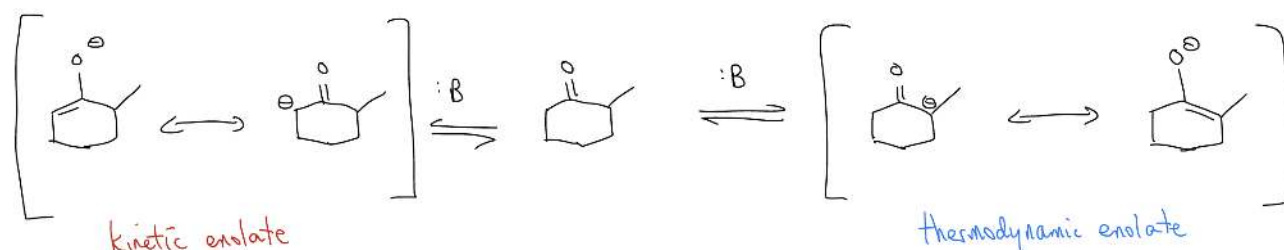
Under thermodynamic control, the reaction occurs at carbon preferentially to maintain the greater bond strength of the C=O bond.



Under kinetic control, the big lobes of electron density on either carbon or oxygen means either can react, driven by electrostatic reactions. Normally, H^+ or silicon-based electrophiles will react with oxygen.



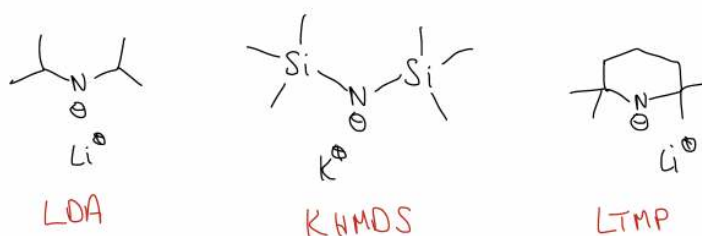
Now that we know a little more about how they react, let's take a step back and take a closer look at how enolates are formed. Say we have a molecule that bears more than one type of a C-H bond – how do we control which is deprotonated? Consider the following scheme:



Kinetic enolate – deprotonation here is less hindered and there are statistically more protons available for deprotonation ($\Delta G^\ddagger$ is lower, activation energy is lower, and transition state is more preorganized)

To favor formation of kinetic enolate, use:

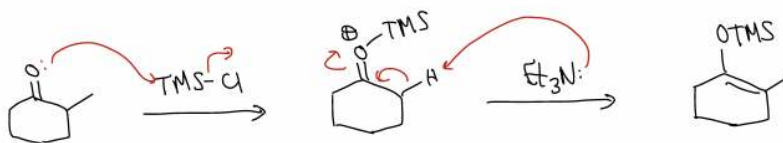
1. lower temperature (0 °C, -78 °C)
2. bulky base to disfavor deprotonation of the more hindered site
3. examples of bases:



Thermodynamic enolate – deprotonation here is sterically more congested but gives a more highly substituted enolate, which is more stable

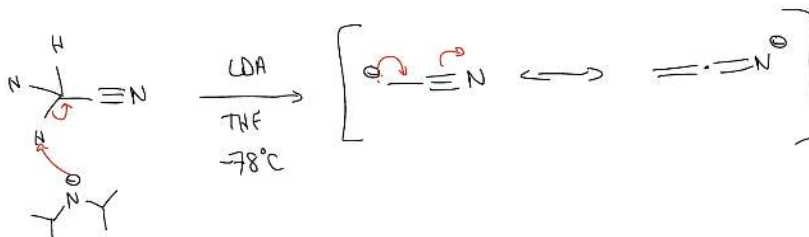
To favor thermodynamic enolate:

1. after adding base a lower temperature, allow temperature to rise to 0°C or room temperature to equilibrate
2. use less bulky base (NaOH, NaOEt, NaOMe, Et₃N, DIPEA)
3. use TMS-Cl as a Lewis acid, then add Et₃N as base (TMS group will make $\sigma_{\text{C-H}}$ more acidic due to more σ -donation)

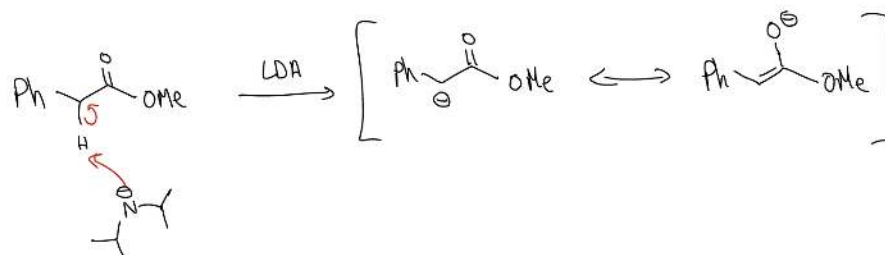


So, we can control which enolate we form by altering the reaction conditions. Enolate formation is not just an intermediate upon treatment of a ketone with a base, however. Other functional groups can also become deprotonated at the α -position, with similar reactivity.

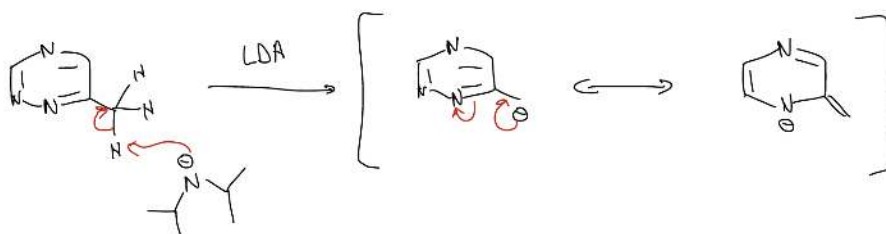
Nitriles



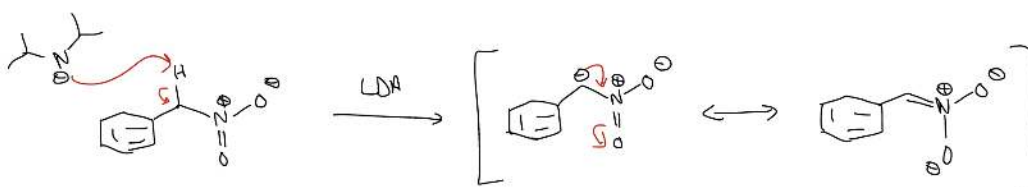
Esters



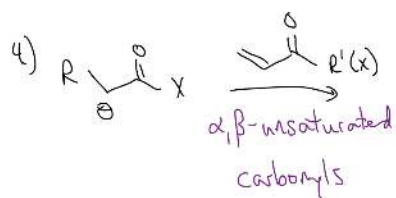
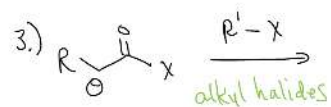
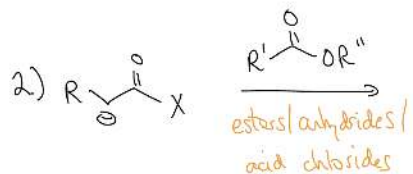
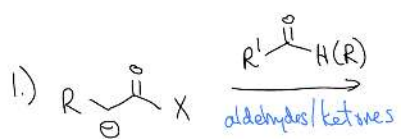
Aromatics



Nitro compounds



Each of these enolates, once formed, can react with a broad array of electrophiles. The rest of this section of the course deals with reactions of these enolates with various functional groups.



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CHAPTER OVERVIEW

19: Reactions of Enolates

[19.1: Reactions of Enolates with Aldehydes and Ketones](#)

[19.2: Reactions of Enolates with Esters and Anhydrides](#)

[19.3: Reactions of Enolates with Alkyl Halides](#)

[19.4: Reactions of Enolates with \$\alpha,\beta\$ -Unsaturated Carbonyls](#)

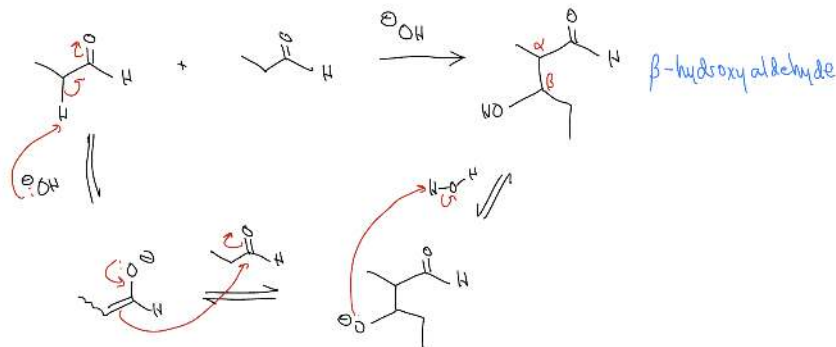
[19.5: Retrosynthesis with Enolates](#)

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19.1: Reactions of Enolates with Aldehydes and Ketones

Reactions of enolates with aldehydes/ketones

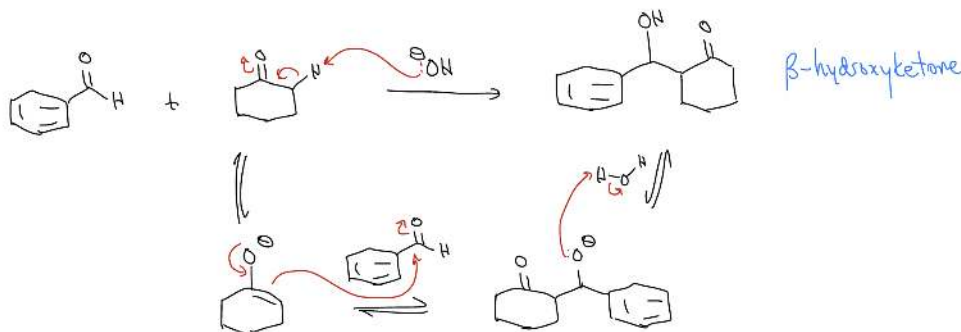
Aldol reaction – the formation of a β -hydroxycarbonyl upon reacting an aldehyde with an enolate anion. For example, treating propanal with a base (OH^-) gives an aldol product by the following mechanism:



Think of the “ β -hydroxyaldehyde” functional group as derived retrosynthetically from an aldol reaction. And remember that the enolate can be anything!



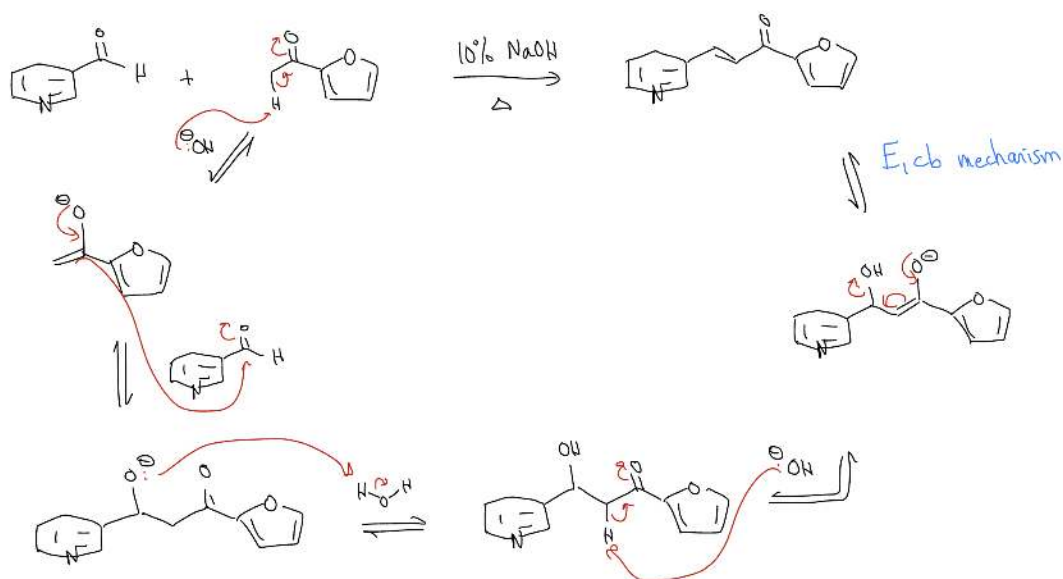
Mixed aldol condensation – an aldol reaction where the two carbonyls are not the same. Here, you must have the ability to funnel into only one product. Thus, you must limit the number of enolates you generate. We can accomplish this by using an aryl aldehyde that cannot form an enolate, according to the mechanism below:



This mixed aldol reaction works because: 1) only one enolate can form, and 2) the aldehyde is more reactive (lower π^*) than the ketone. The reaction can also occur a second time if two equivalents of aldehyde are present.

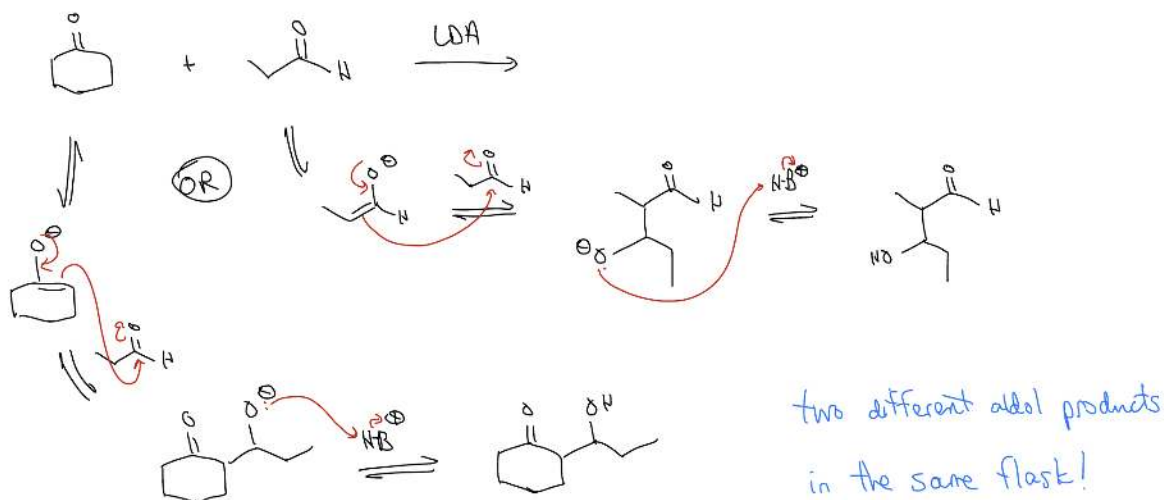
The β -hydroxycarbonyl functional group is very unstable in most cases, however, and will eliminate water to give an aldol condensation product. When using ketones and aromatic aldehydes as substrates, this is known as the Claisen-Schmidt reaction, the product of which is a chalcone.

Claisen-Schmidt reaction – aldol condensation between a ketone and an aryl aldehyde requiring more forcing conditions (excess base and heat).

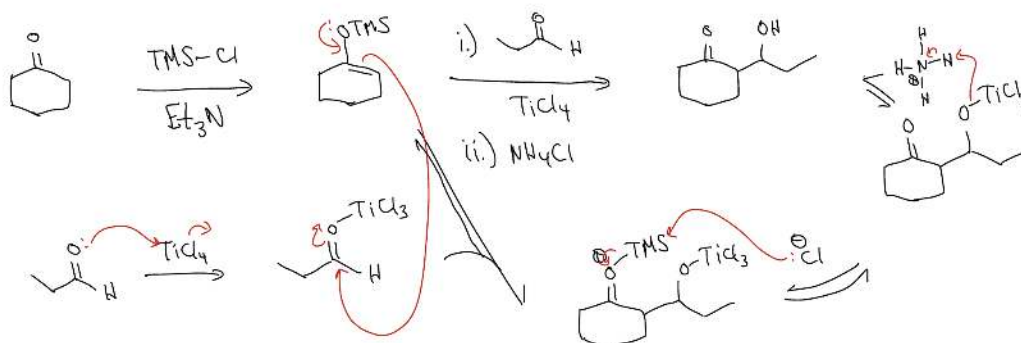


This reaction is under thermodynamic control. The α,β -unsaturated carbonyl is an important structure retrosynthetically. The last step of this mechanism is known as an E₁cb mechanism, where “cb” stands for conjugate base and the rate-limiting step is the elimination.

Mukaiyama aldol – an aldol reaction that involves an enolate-like intermediate known as the silyl enol ether. The advantage of using this reaction is that there is no risk of “scrambling.” Consider the following using LDA as the base:



We can avoid the formation of two different aldol products by using a silyl enol ether:



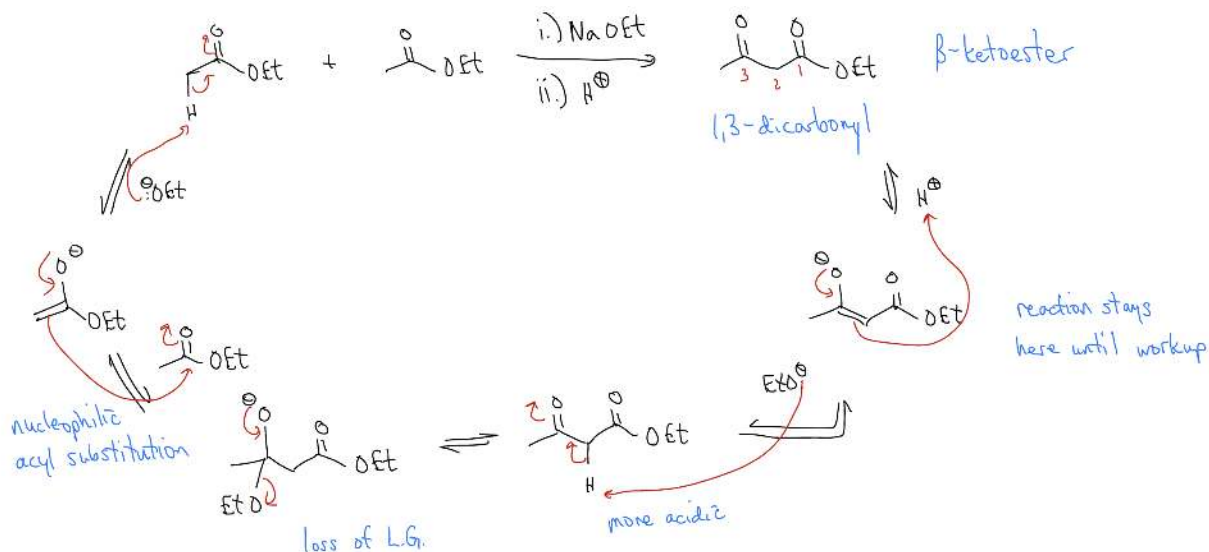
Other Lewis acids for this reaction include: BF₃, ZnCl₂, MgCl₂

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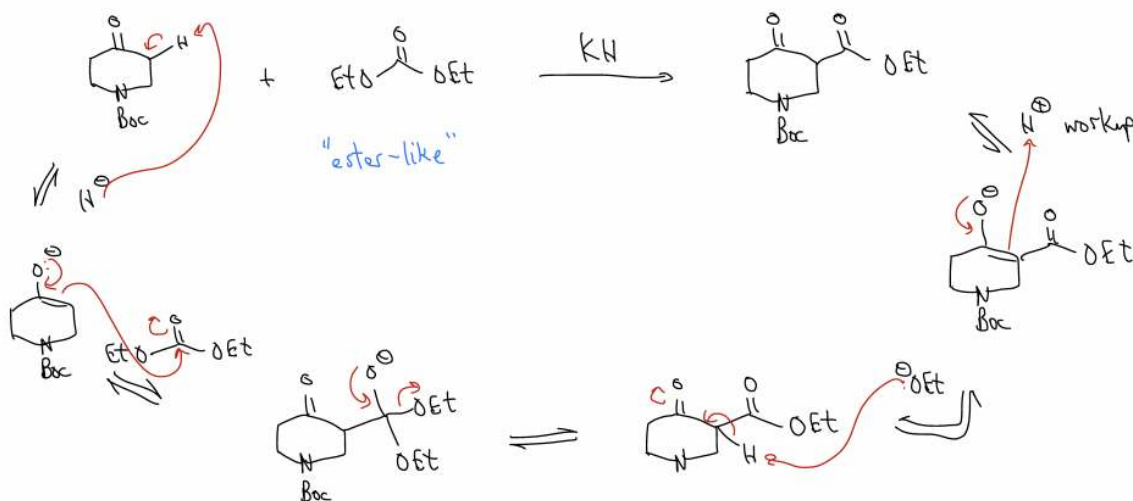
19.2: Reactions of Enolates with Esters and Anhydrides

Reactions of enolates with esters/anhydrides

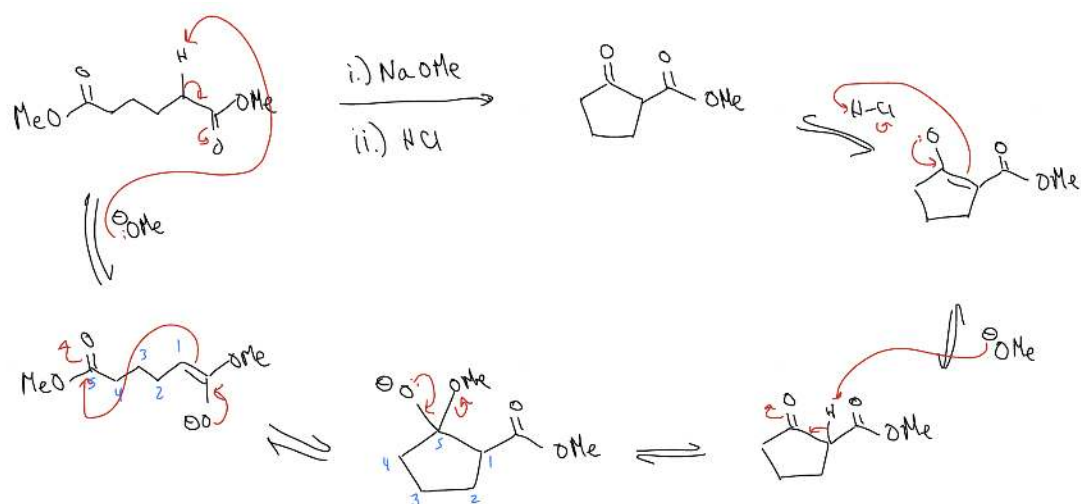
Claisen condensation – reaction of an enolate anion with an ester, anhydride, or even an acid chloride to give a 1,3-dicarbonyl. The simplest is the reaction in which the two carbonyls are the same. Retrosynthetically, the 1,3-dicarbonyl is important functional group to recognize and can come in many forms (β -ketoester, β -ketoamide, 1,3-diketone, etc.)



Mixed Claisen condensation – a Claisen condensation where the two carbonyls are not the same.



Dieckmann condensation – an intramolecular Claisen condensation

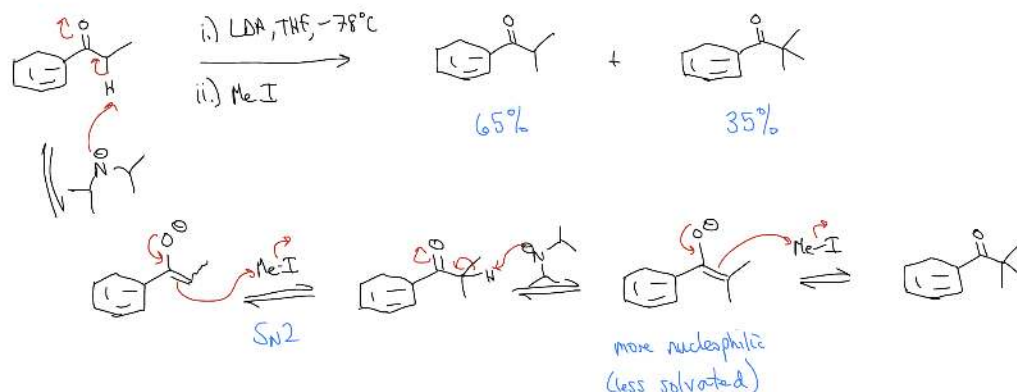


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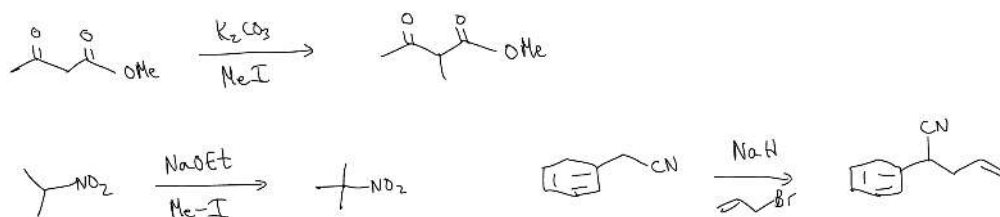
19.3: Reactions of Enolates with Alkyl Halides

Reactions of enolates with alkyl halides

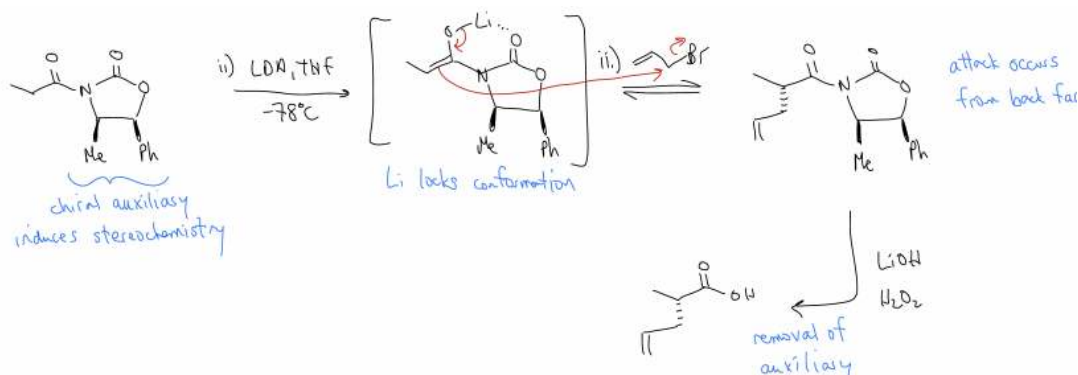
Alkylation of enolates – can occur when an enolate reacts via an S_N2 mechanism with a low-lying σ^*_{C-X} , but it is very difficult to stop at monoalkylation.



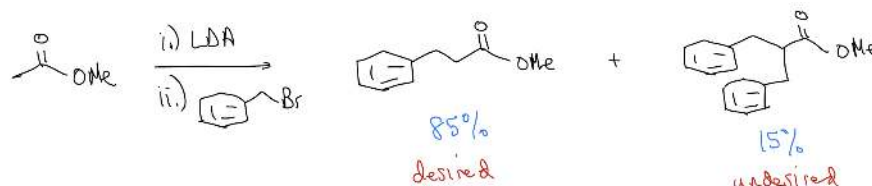
Other examples:



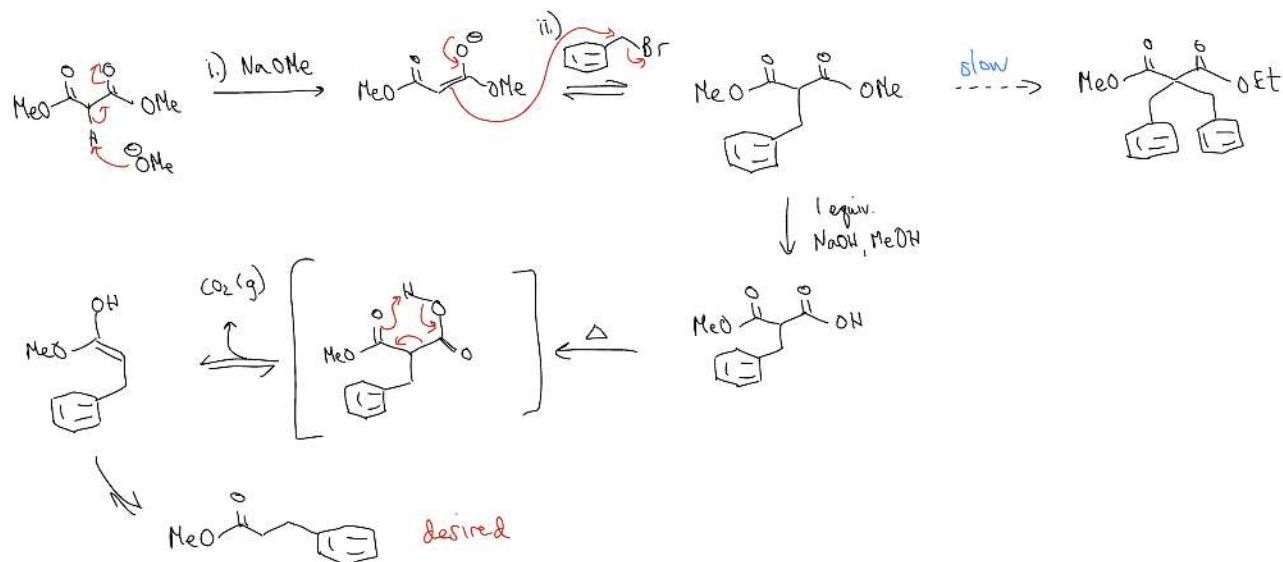
Reactions involving chiral enolates give us an opportunity to create chirality since any transition state that forms is diastereomeric. Consider the following reaction:



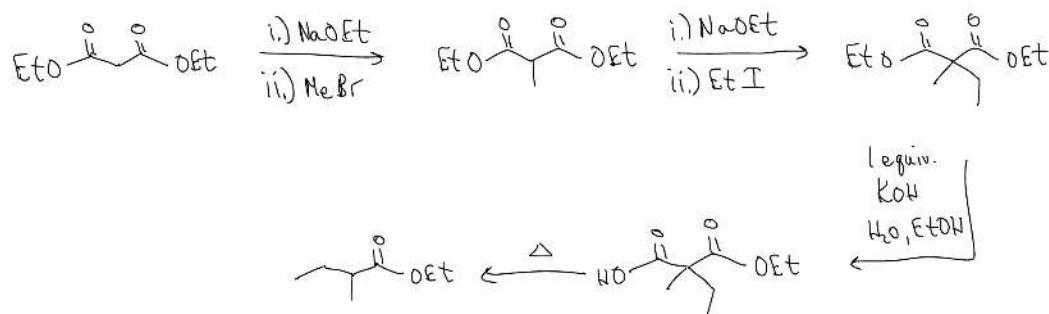
Let's come back to this issue of double alkylation. Say we wanted to create the following complex ester by double alkylation of a simple ester. The problem is that a double alkylation product is formed.



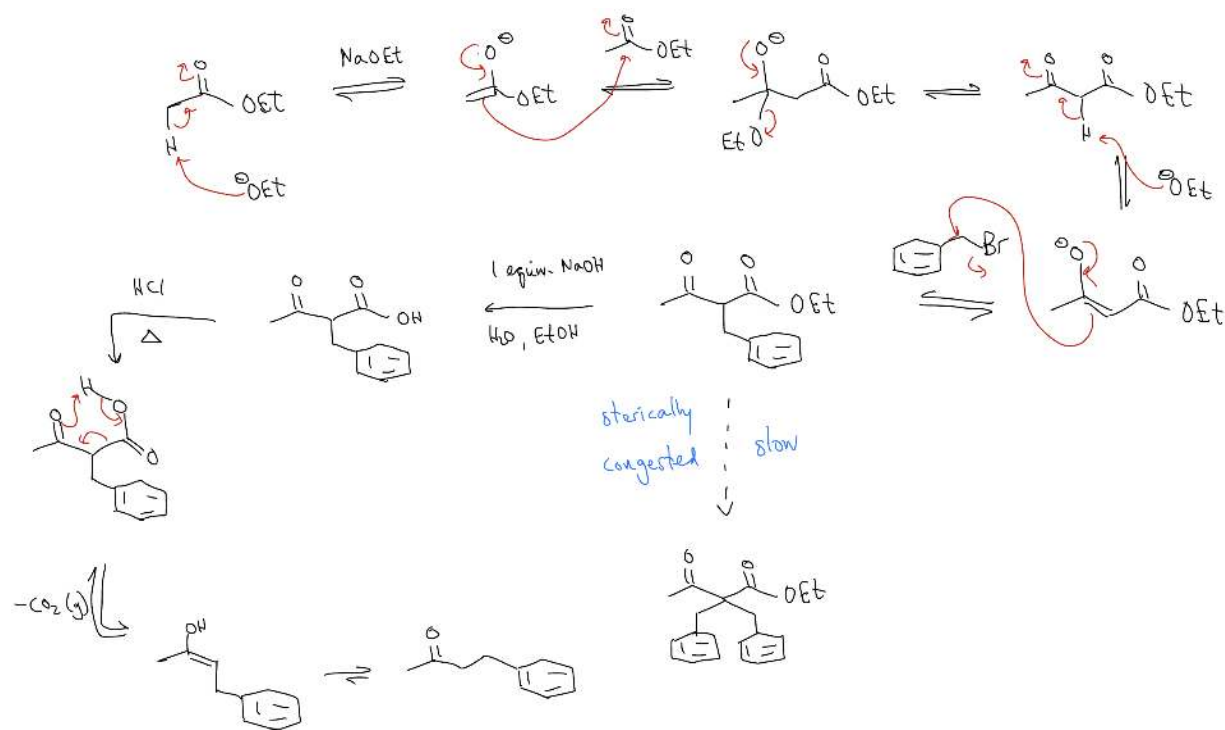
How do we avoid this? We perform a malonic ester synthesis:



The malonic ester synthesis is a good way of making α -substituted esters and can be performed successively:



What about using a similar strategy for making differentially substituted ketones? We can accomplish this by using the acetoacetic ester synthesis, the first step of which is a Claisen condensation.



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19.4: Reactions of Enolates with α, β -Unsaturated Carbonyls

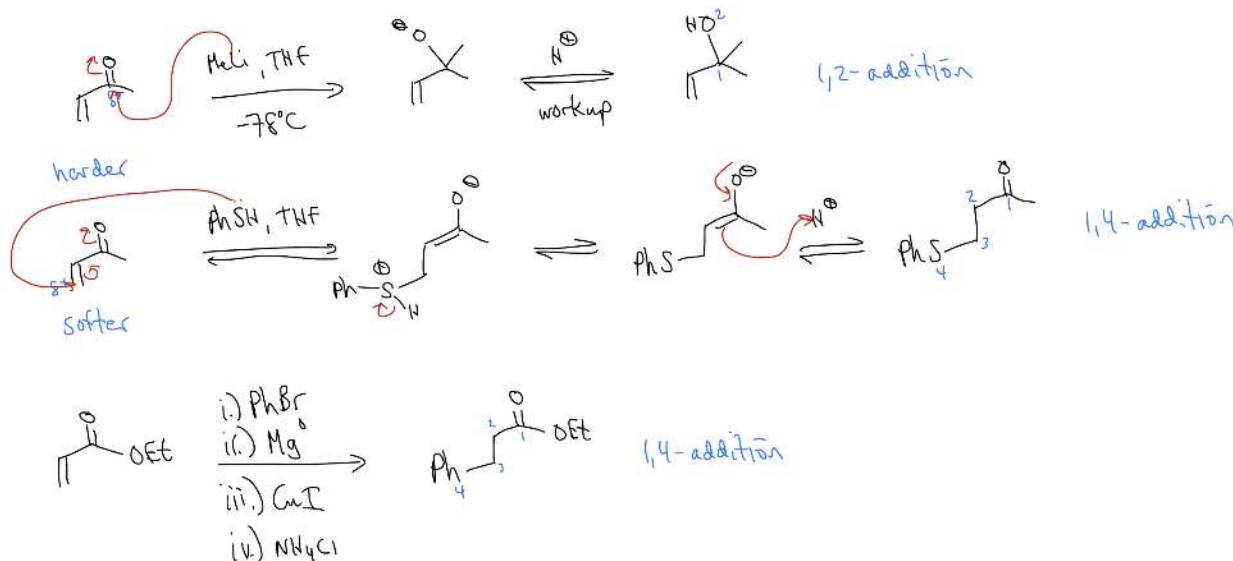
Reactions of enolates with α, β -unsaturated carbonyls

An α, β -unsaturated carbonyl has a double bond in conjugation with a carbonyl. This gives it special reactivity since it is electrophilic at two different positions – the carbonyl carbon and the β -position. Attack at the carbonyl carbon is called 1,2-addition, while attack at the β -position is called 1,4-addition. Why does 1,4-addition even occur? Because in the LUMO, the largest coefficient lies on the β -carbon. We can see this from the resonance forms below:

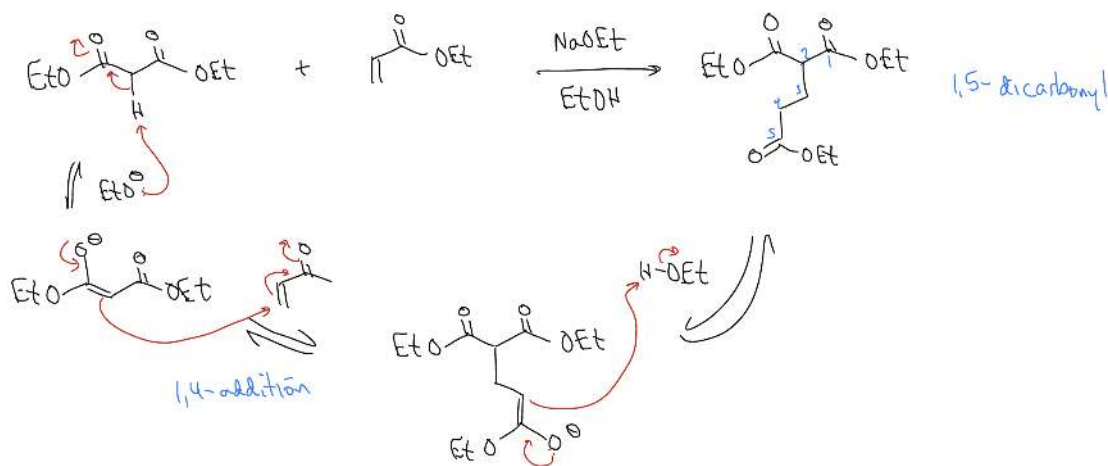


Under thermodynamic control, 1,4-addition (also known as conjugate addition) is favored (maximal orbital overlap). Under kinetic conditions, 1,2-addition is favored (electrostatic interactions dominate, and the carbonyl carbon has more positive charge).

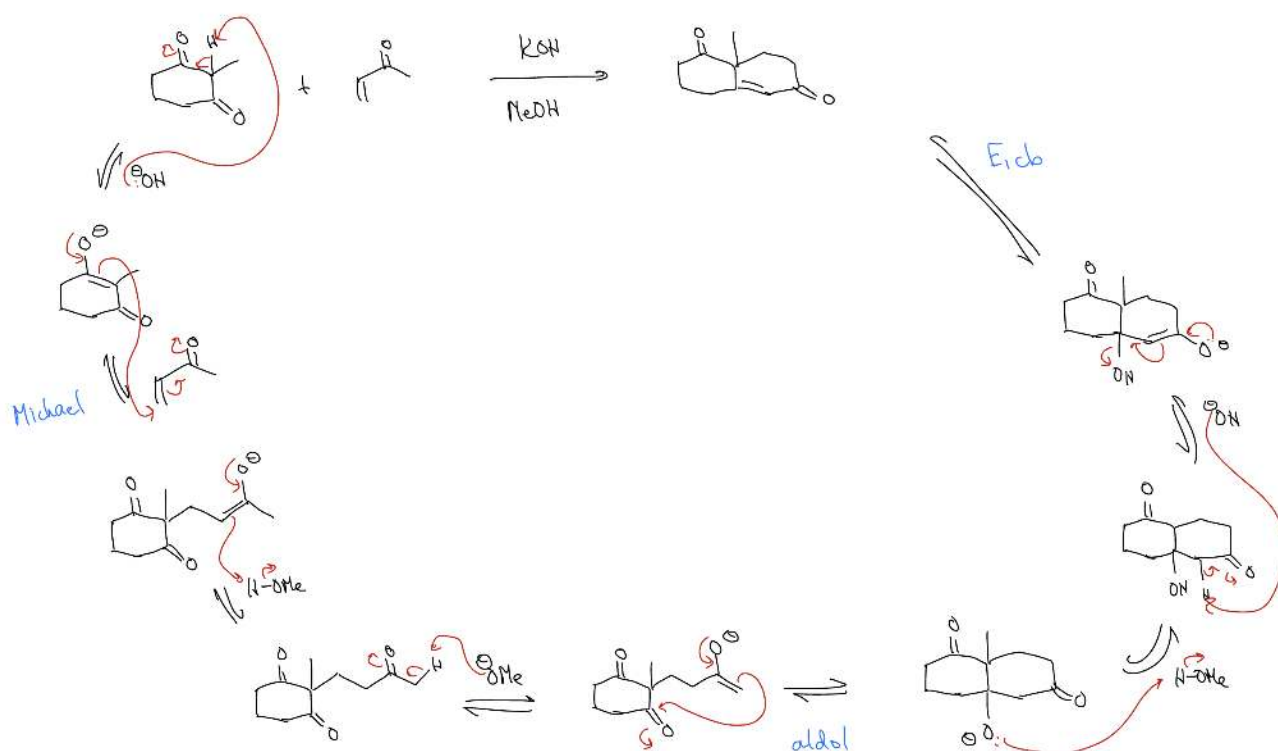
This all matters because enolates are softer nucleophiles and will attack in a 1,4-manner. Other reagents (RMgBr , LAH , RLi) are hard nucleophiles and will attack in a 1,2-fashion. Other soft nucleophiles include CN^- , RS^- , N_3^- , and RNH_2 , and will undergo conjugate addition. In addition, cuprates will add in a 1,4-manner, yielding conjugate addition products.



Michael addition – addition of an enolate to an α, β -unsaturated carbonyl with 1,4-regioselectivity. Retrosynthetically, this is an important transformation.



Robinson annulation – a three-step sequence involving Michael addition, followed by an aldol reaction, following by $\text{E}_{1\text{cb}}$ elimination. Retrosynthetically, this fused ring synthesis is important to recognize.



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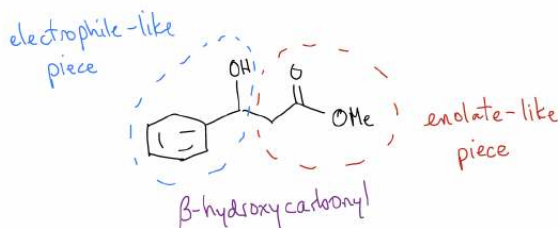
19.5: Retrosynthesis with Enolates

By now, you've seen that enolates react with a variety of different functional groups:

1. aldehydes and ketones
2. esters, anhydrides, and acid chlorides
3. alkyl halides
4. α,β -unsaturated carbonyls

The most difficult part of this section of the course is designing a synthesis. The strategy you should take is retrosynthesis, where you take a molecule and break it apart into smaller portions by making key bond disconnections. Recognizing that a particular functional groups can be made by a specific reaction will be important.

In this part of the course, the nucleophile is an enolate, so when you are making C-C bonds, one of those carbons will be capable of forming an enolate. You should simply circle this portion of the molecule so that you know that it's what forms the enolate. The other carbon will be one of the four choices above. By looking at the particular C-C bond, you should be able to identify which electrophile you need. All that is left is to break the C-C bond into these components and draw an arrow with a set of reagents. Let's do an example:



If we try to find an easy way to make this molecule, we should first try to identify where the enolate-like carbon is (it should be α to the carbonyl). There is only one choice, obviously, because there is only one carbonyl. This means that the other half is the electrophile. So, we must stitch together this molecule via C-C bond formation. Now we know that the enolate would look like this:



which can be made by deprotonating this ester with an appropriate base:



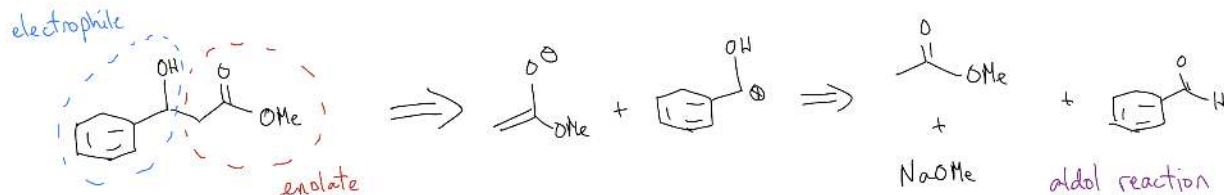
The only question we have left is – what is the electrophile? We know that our end product is an alcohol and the choices we have are: 1) aldehyde/ketone, 2) ester, 3) alkyl halide, or 4) α,β -unsaturated carbonyl. Only one of these will work – the aldehyde!

This combination would be an aldol reaction between an ester and an aldehyde to product a β -hydroxyester. You can think of the electrophile portion of the molecule having reactivity similar to the structure below, which is equivalent to a carbonyl:

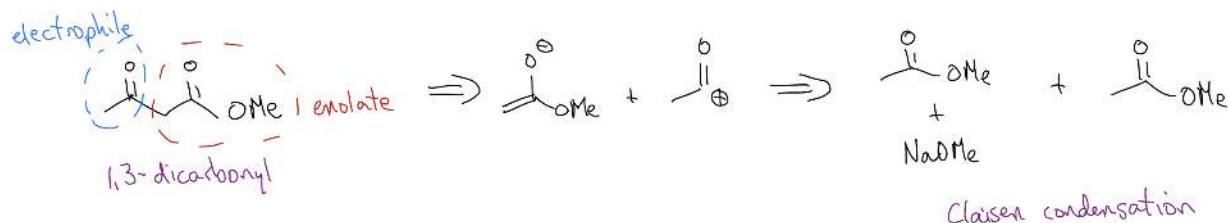


Let's see if we can identify the enolate and electrophile in each case below:

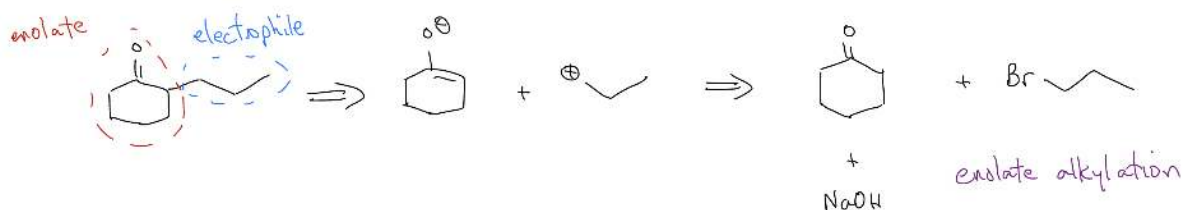
1.



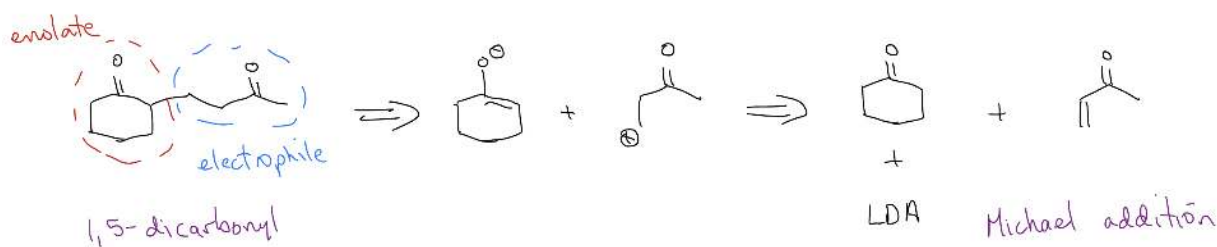
2.



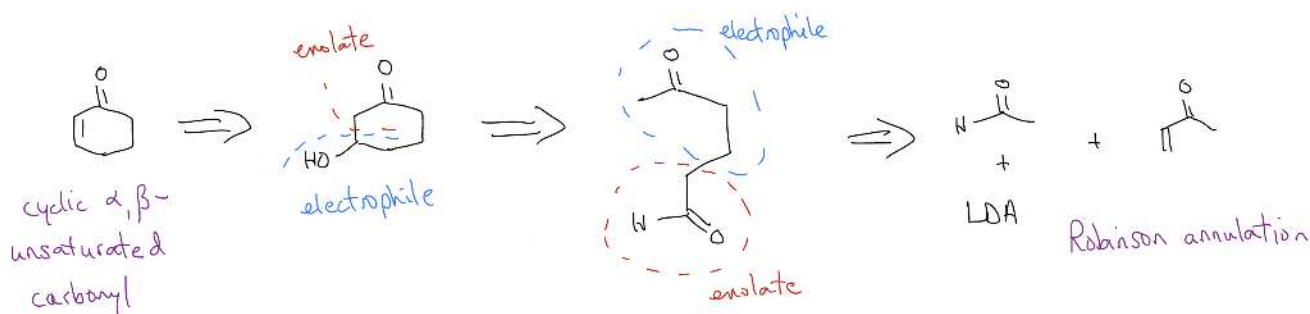
3.



4.



So, we've now developed a strategy for identifying important functional groups like β-hydroxycarbonyl (think, aldol!), β-ketoester or 1,3-dicarbonyl (think, Claisen condensation!), or 1,5-dicarbonyl (think, Michael addition). There is one other pesky functional group which gives us trouble and that's the α,β-unsaturated carbonyl – how do we form that? It's a two-step process involving E₁cb and aldol. Here's an example:



First, identify the double bond as one in conjugation with a carbonyl – this is important otherwise the rest of this doesn't work. Alkenes are formed by elimination and the specific type of elimination operative here is an E_{1cb} , or dehydration. This E_{1cb} is possible because enolate formation is quick due to resonance stabilization from oxygen. This helps to push out OH^- , so our regiochemistry should be an OH -group at the β -position. This should look familiar – isn't a β -hydroxycarbonyl formed via an aldol reaction? If we do the same sort of C-C bond disconnection, we get ring opening to provide a 1,5-carbonyl. This should also look familiar – isn't a 1,5-dicarbonyl formed via a Michael reaction? If we do a bond disconnection accordingly, we should get an aldehyde and an α,β -unsaturated ketone. Without even realizing it, you've just completed a Robinson annulation! The key is to start by identifying the functional groups that are easy to form and break bonds until you arrive at something new that suggests another key bond disconnection.

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Index

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By Page

- Organic Chemistry II - *Undeclared*
 - Front Matter - *Undeclared*
 - TitlePage - *Undeclared*
 - InfoPage - *Undeclared*
 - Table of Contents - *Undeclared*
 - Licensing - *Undeclared*
 - 12: Radical Reactions - *Undeclared*
 - 12.1: Radical Intermediates - *Undeclared*
 - 12.2: Radical Reactions - *Undeclared*
 - 12.3: Organometallics - *Undeclared*
 - 13: Conjugation - *Undeclared*
 - 13.1: Allyl System - *Undeclared*
 - 13.2: Dienes - *Undeclared*
 - 13.3: Diels-Alder reaction - *Undeclared*
 - 13.4: Diels-Alder Regio- and Stereoselectivity - *Undeclared*
 - 14: Aromaticity - *Undeclared*
 - 14.1: Conjugation vs. Aromaticity - *Undeclared*
 - 14.2: Frost's Circle - *Undeclared*
 - 14.3: Heteroaromaticity - *Undeclared*
 - 15: Aromatic Substitution - *Undeclared*
 - 15.1: Electrophilic Aromatic Substitution - *Undeclared*
 - 15.2: Regioselectivity in Electrophilic Aromatic Substitution - *Undeclared*
 - 15.3: Multiple Substituents and Heteroaromatic Rings - *Undeclared*
 - 15.4: Nucleophilic Aromatic Substitution - *Undeclared*
 - 15.5: Other Reactions of Aromatics - *Undeclared*
 - 16: Nucleophilic Addition to Carbonyls - *Undeclared*
 - 16.1: Nucleophilic Addition to the Carbonyl Group - *Undeclared*
 - 16.2: Irreversible Nucleophilic Addition - *Undeclared*
 - 16.3: Reversible Nucleophilic Addition - *Undeclared*
 - 16.4: Acetal Formation - *Undeclared*
 - 16.5: Nucleophilic Addition Under Neutral Conditions - *Undeclared*
 - 16.6: Alcohol Oxidation - *Undeclared*
 - 17: Nucleophilic Acyl Substitution - *Undeclared*
 - 17.1: Nucleophilic Acyl Substitution - *Undeclared*
 - 17.2: Reactions via Carbonyl Substitution - *Undeclared*
 - 17.3: Double Nucleophilic Acyl Substitution - *Undeclared*
 - 17.4: Super Leaving Groups - *Undeclared*
 - 17.5: Nitriles - *Undeclared*
 - 17.6: Named Reactions - *Undeclared*
 - 18: Enols and Enolates - *Undeclared*
 - 18.1: Enols and Enolates - *Undeclared*
 - 18.2: Consequences of Tautomerization - *Undeclared*
 - 18.3: Molecular Orbital Description of Enolates - *Undeclared*
 - 19: Reactions of Enolates - *Undeclared*
 - 19.1: Reactions of Enolates with Aldehydes and Ketones - *Undeclared*
 - 19.2: Reactions of Enolates with Esters and Anhydrides - *Undeclared*
 - 19.3: Reactions of Enolates with Alkyl Halides - *Undeclared*
 - 19.4: Reactions of Enolates with α,β -Unsaturated Carbonyls - *Undeclared*
 - 19.5: Retrosynthesis with Enolates - *Undeclared*
 - Back Matter - *Undeclared*
 - Index - *Undeclared*
 - Glossary - *Undeclared*
 - Detailed Licensing - *Undeclared*
 - Detailed Licensing - *Undeclared*

Detailed Licensing

Overview

Title: Organic Chemistry II

Webpages: 54

All licenses found:

- [Undeclared](#): 100% (54 pages)

By Page

- Organic Chemistry II - *Undeclared*
 - Front Matter - *Undeclared*
 - TitlePage - *Undeclared*
 - InfoPage - *Undeclared*
 - Table of Contents - *Undeclared*
 - Licensing - *Undeclared*
 - 12: Radical Reactions - *Undeclared*
 - 12.1: Radical Intermediates - *Undeclared*
 - 12.2: Radical Reactions - *Undeclared*
 - 12.3: Organometallics - *Undeclared*
 - 13: Conjugation - *Undeclared*
 - 13.1: Allyl System - *Undeclared*
 - 13.2: Dienes - *Undeclared*
 - 13.3: Diels-Alder reaction - *Undeclared*
 - 13.4: Diels-Alder Regio- and Stereoselectivity - *Undeclared*
 - 14: Aromaticity - *Undeclared*
 - 14.1: Conjugation vs. Aromaticity - *Undeclared*
 - 14.2: Frost's Circle - *Undeclared*
 - 14.3: Heteroaromaticity - *Undeclared*
 - 15: Aromatic Substitution - *Undeclared*
 - 15.1: Electrophilic Aromatic Substitution - *Undeclared*
 - 15.2: Regioselectivity in Electrophilic Aromatic Substitution - *Undeclared*
 - 15.3: Multiple Substituents and Heteroaromatic Rings - *Undeclared*
 - 15.4: Nucleophilic Aromatic Substitution - *Undeclared*
 - 15.5: Other Reactions of Aromatics - *Undeclared*
 - 16: Nucleophilic Addition to Carbonyls - *Undeclared*
 - 16.1: Nucleophilic Addition to the Carbonyl Group - *Undeclared*
 - 16.2: Irreversible Nucleophilic Addition - *Undeclared*
 - 16.3: Reversible Nucleophilic Addition - *Undeclared*
 - 16.4: Acetal Formation - *Undeclared*
 - 16.5: Nucleophilic Addition Under Neutral Conditions - *Undeclared*
 - 16.6: Alcohol Oxidation - *Undeclared*
 - 17: Nucleophilic Acyl Substitution - *Undeclared*
 - 17.1: Nucleophilic Acyl Substitution - *Undeclared*
 - 17.2: Reactions via Carbonyl Substitution - *Undeclared*
 - 17.3: Double Nucleophilic Acyl Substitution - *Undeclared*
 - 17.4: Super Leaving Groups - *Undeclared*
 - 17.5: Nitriles - *Undeclared*
 - 17.6: Named Reactions - *Undeclared*
 - 18: Enols and Enolates - *Undeclared*
 - 18.1: Enols and Enolates - *Undeclared*
 - 18.2: Consequences of Tautomerization - *Undeclared*
 - 18.3: Molecular Orbital Description of Enolates - *Undeclared*
 - 19: Reactions of Enolates - *Undeclared*
 - 19.1: Reactions of Enolates with Aldehydes and Ketones - *Undeclared*
 - 19.2: Reactions of Enolates with Esters and Anhydrides - *Undeclared*
 - 19.3: Reactions of Enolates with Alkyl Halides - *Undeclared*
 - 19.4: Reactions of Enolates with α,β -Unsaturated Carbonyls - *Undeclared*
 - 19.5: Retrosynthesis with Enolates - *Undeclared*
 - Back Matter - *Undeclared*
 - Index - *Undeclared*
 - Glossary - *Undeclared*
 - Detailed Licensing - *Undeclared*
 - Detailed Licensing - *Undeclared*