

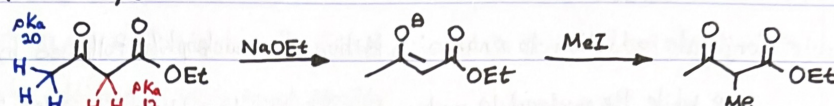
For ketones, regioselectivity can be an issue as there are protons on both sides

- this can be controlled thermodynamically and kinetically

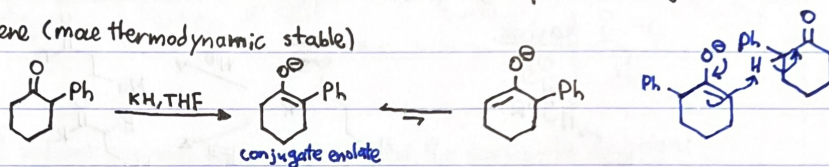
i) thermodynamic control: there are many examples, such as difference in pK_a , equilibria, etc.

- when there is a difference in pK_a for each side of a ketone, the hydrogens that is easier to protonate will be deprotonated

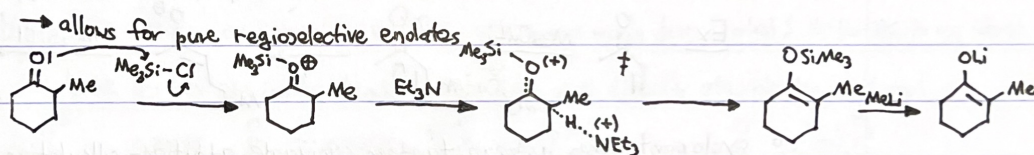
Ex. β -carbonyls



- when excess ketone is present, the enolates can equilibrate to give the most substituted alkene (more thermodynamic stable)



- using silyl enol ethers, which generally forms the more substituted enol which can be purified

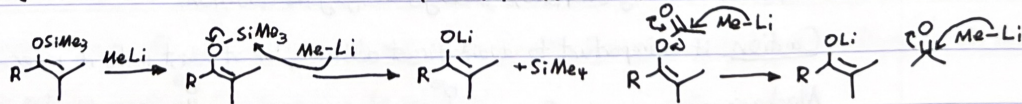


ii) kinetic control: steric hindrance is the main factor (LDA is a hindered base) and low temperature, short reaction times all help

- while thermodynamic control for methyl acetoacetate would lead to the center proton being deprotonated, formation of the dianion leads to the last anion formed reacting first

Additional Control of Regioselectivity

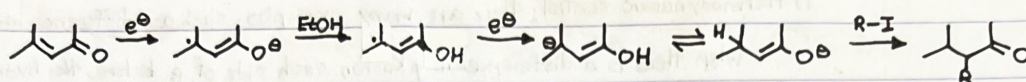
A regioselective enolate can be formed by an allyllithium w/ silyl enol ethers or enol acetates



However, sometimes there are better alternatives that also react regioselectively

- Dissolving metal reduction of enones: reduces C=C bond and alkylates

Mechanism.

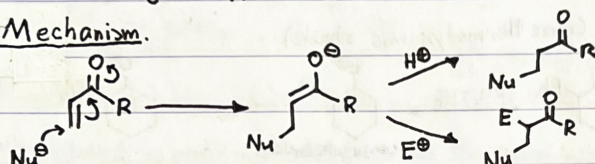


- electrons are not susceptible to steric hindrance, yielding the more thermodynamically favourable enolate

- Conjugate addition to enones: addition of a nucleophile followed by alkylation

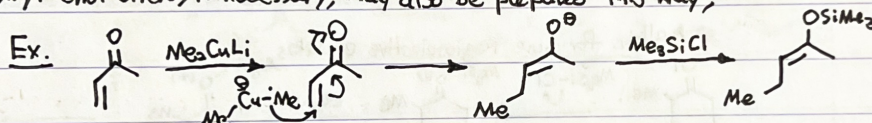
- while the nucleophile undergoing conjugate addition may be hydrogen (K-selectride), it can also be organocopper reagents, which allows for tandem reactions to be possible

Mechanism.

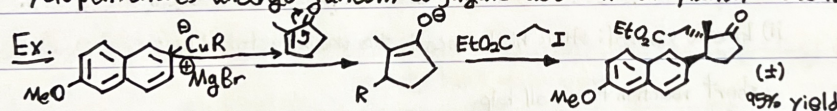


the organocopper reagent is necessary in order to prevent a direct addition to the carbonyl and to encourage conjugate addition.

- silyl enol ethers, if necessary, may also be prepared this way;



- cyclopentenones undergo tandem conjugate addition-alkylation reactions well

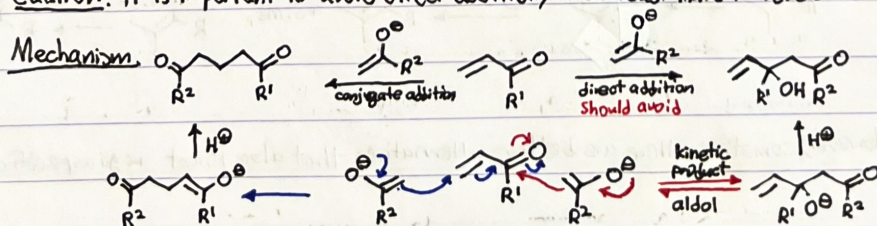


trans-addition is very preferred as alkylation prefers to occur on the less hindered face of the enolate

Michael acceptors as electrophiles

we briefly saw above how to make Michael acceptors into enolates; here, we use them as electrophiles, making enolate(s) undergo conjugate addition.

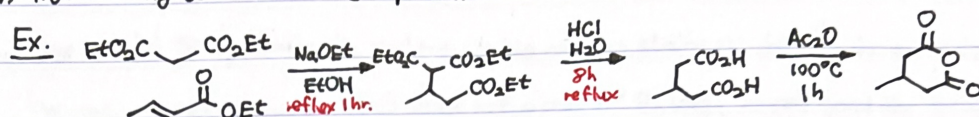
Caution. it is important to avoid direct addition; or at least make it reversible.



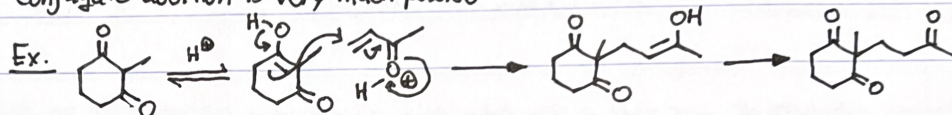
- to promote conjugate addition, make the enolate more stable & bulky

β -diesters are extremely convenient for conjugate addition reactions as well:

- stable enolate ions are formed that undergo clean conjugate addition
- hydrolysis & decarboxylation can get rid of one of the ester groups if necessary
- the remaining ester or acid group can undergo functional group interconversion



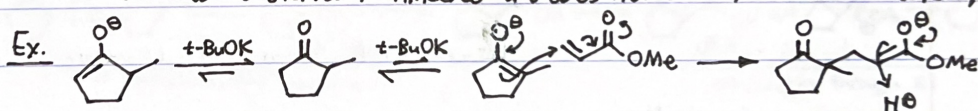
• 1,3-diketones are enolized at a significant amount in acid as well - acid-catalyzed conjugate addition is very much possible



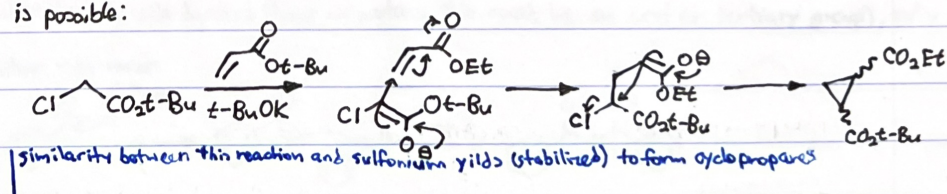
Potassium and sodium enolates are also very good for conjugate addition:

Problem: lithium binds to oxygen strongly, stabilizes aldol product.

Solution: Use sodium or potassium enolates, which are more dissociated; $t\text{-BuOK}$ is an ideal base as it is sterically hindered and does not directly attack the carbonyl.

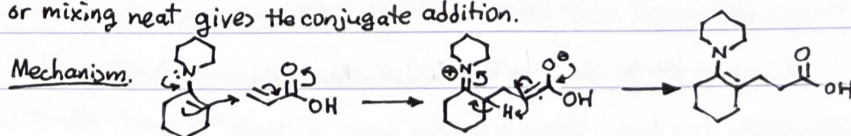


• if the enolate contains a leaving group, conjugate addition followed by intramolecular S_N2 is possible:

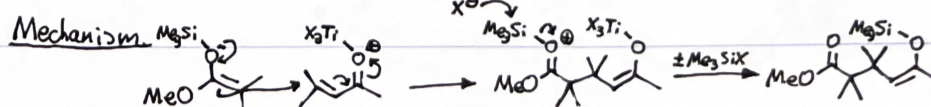


Enamines and silyl enol ethers are excellent stable enol equivalents for conjugate addition

• enamines are soft nucleophiles that are more reactive than enols; acid catalyst (sometimes), heating, or mixing neat gives the conjugate addition.

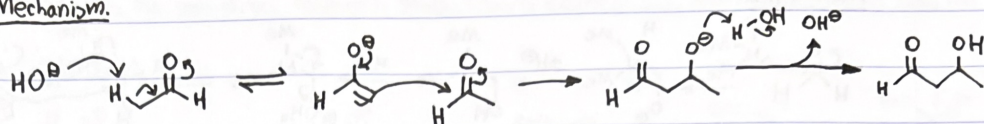


• silyl enol ethers are also great with a Lewis acid catalyst (TiCl_4)

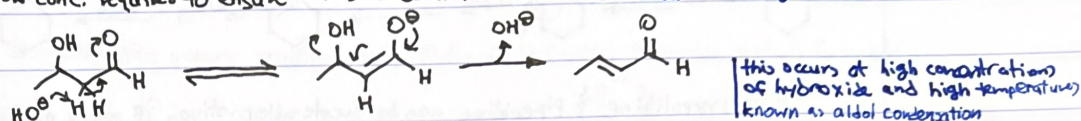


An aldol reaction is when the enolate directly attacks the carbonyl centre - leading to a hydroxy-carbonyl

Mechanism.



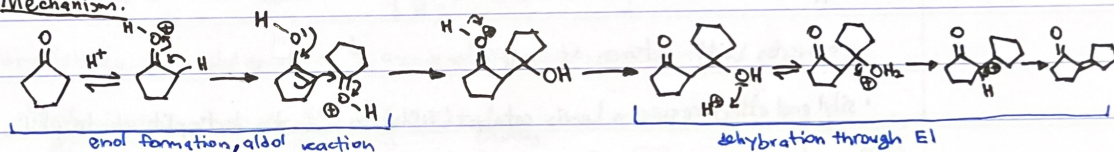
- base is needed to deprotonate the carbonyl (in this case, an aldehyde); it is truly a catalyst, but low conc. required to ensure E1cB does not occur - $\text{Ba}(\text{OH})_2$ is very good for aldol rxns



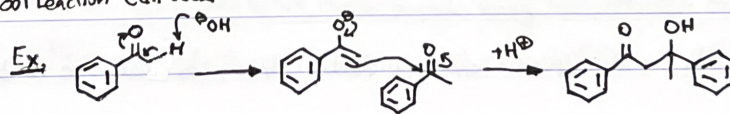
In fact, an aldol reaction may also be acid catalyzed; in that case, the dehydration product is mostly unavoidable.

- although the enol is much less nucleophilic than the enolate, the carbonyl oxygen is protonated making the species much more electrophilic.

Mechanism.



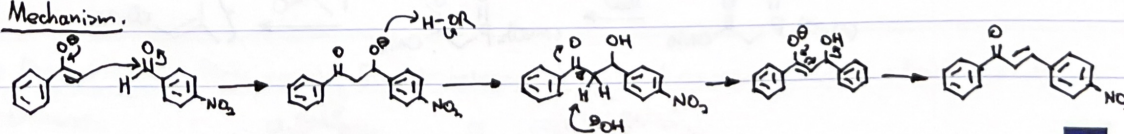
If the ketone has one side blocked (have no protons, this could be an aryl or tertiary group), only one aldol reaction can occur



Cross-condensations are extremely useful, which enables the combination of two carbonyls

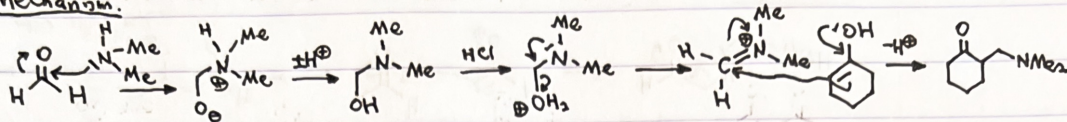
- cross-condensations must obey strict conditions in order to be successful;
 - only one "partner" must be enolizable, and on one side of the carbonyl;
 - the other "partner" should be much more electrophilic and not enolizable

Mechanism.

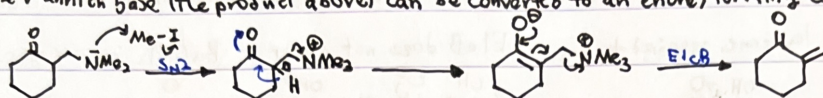


Formaldehyde can be used in aldol reactions by converting the formaldehyde into an imine:

Mechanism:



• the Mannich base (the product above) can be converted to an enone, forming α -methylene compounds

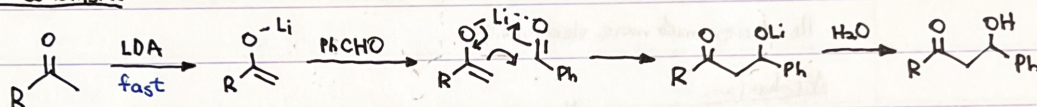


• using pyrrolidine & piperidine can be great alternatives if enone product is desired.

When the conditions for cross-condensation do not meet, specific enol equivalents can be used instead

• for lithium enolates, the coordination of the lithium cation + six-membered ring mechanism gives aldol reaction

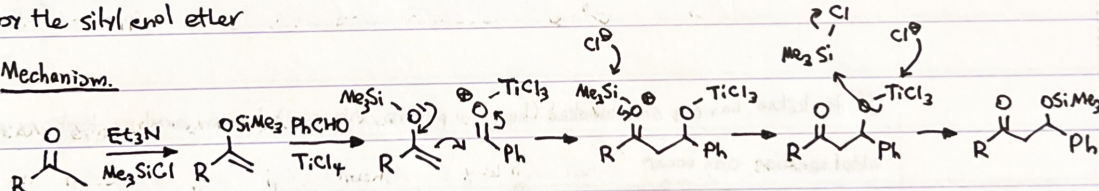
Mechanism:



• works with ketones as well

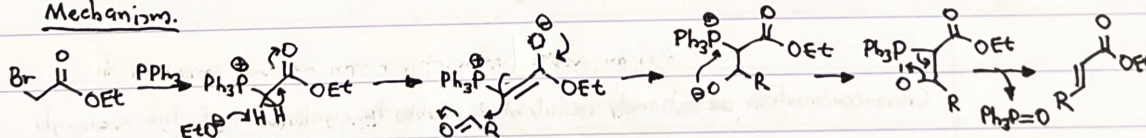
• silyl enol ethers require a Lewis catalyst (TiCl_4) to make the electrophile electrophilic enough to be attacked by the silyl enol ether

Mechanism:



• phosphonium ylids are also specific enol equivalents; only requires weak base for deprotonation

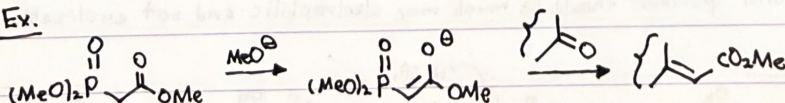
Mechanism:



• Phosphonium ylids are rather stable and only react well with aldehydes;

• for ketones, the more reactive (nucleophilic) phosphonate-stabilized enolates are required

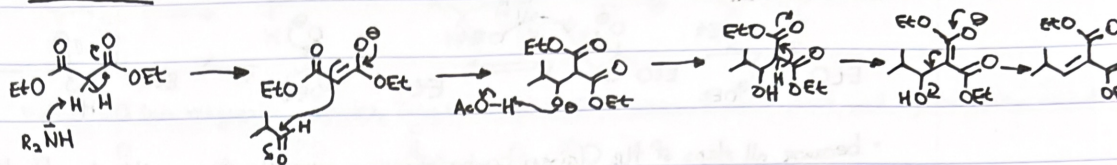
Ex.



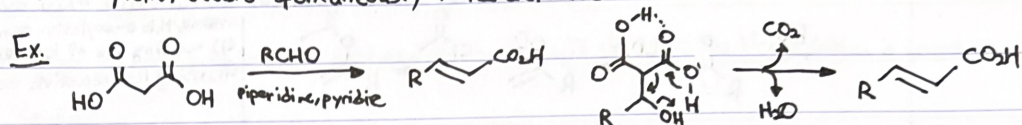
• 1,3-dicarbonyl compounds also undergo crossed aldol reactions very well

• because the unenolized carbonyl is stable (poorly electrophilic), self-condensation does not occur

Mechanism.



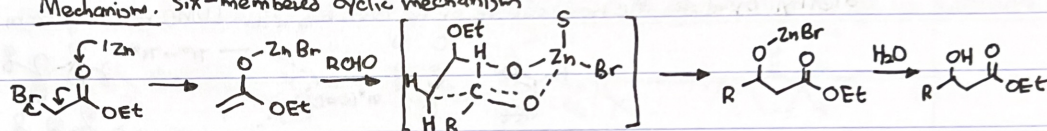
• decarboxylation occurs spontaneously if the acid (rather than the ester) is used:



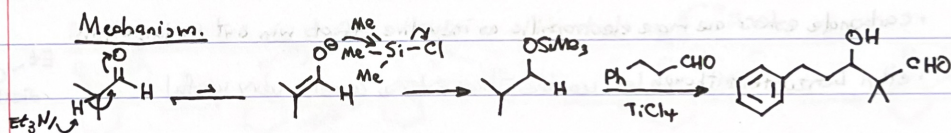
• for esters, a specific end equivalent is necessary for a successful aldol reaction

• the Reformatsky reaction involving zinc-induced reaction with α -haloesters & aldehyde/ketone:

Mechanism. six-membered cyclic mechanism



• for aldehydes, both silyl enol ether & aza-enolates work as specific end equivalents



• for ketones, the question of "kinetic" vs. "thermodynamic" enolates rises once again

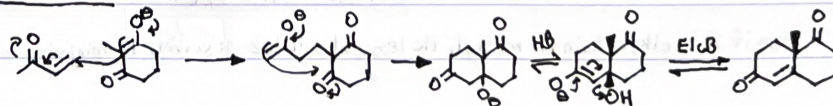
• the less substituted enolate can be prepared using LDA; although can be isolated through silyl enol ethers

• the more substituted enolate can be prepared using MeSiCl_3 w/ Et_3N ;

The Robinson annulation is an important application of the Robinson annulation to form substituted cyclohexenones

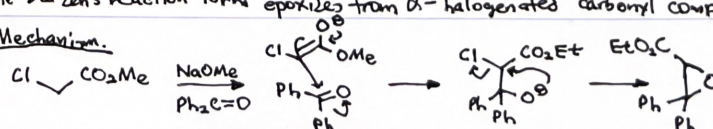
• the reaction involves three steps: (i) Michael addition (ii) intramolecular aldol reaction (iii) dehydration by Et_3B

Mechanism.



The Darzens reaction forms epoxides from α -halogenated carbonyl compounds through a tandem reaction

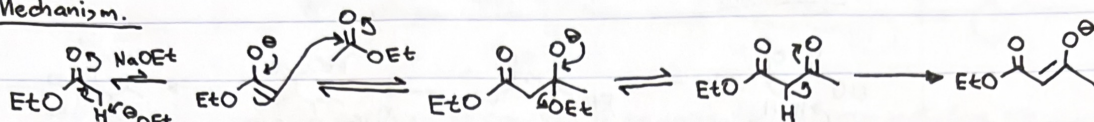
Mechanism.



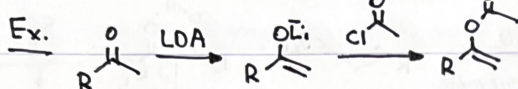
Claisen-Schmidt reaction

A similar class of reactions to the aldol reactions; however, the "completion" step is very different

Mechanism.



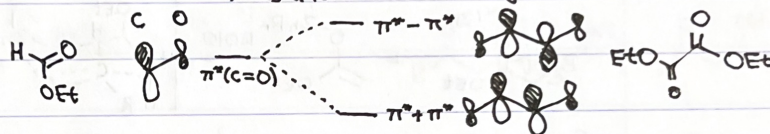
- because all steps of the Claisen condensation are reversible, irreversible deprotonation drives the reaction
- note that the Claisen condensation has another condition for success; it must avoid O-acylation



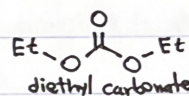
overall, this O-acylation can be avoided by
(i) making use of less reactive specific enol equivalents
(ii) using less reactive acylating reagents, such as esters

For crossed ester condensations, there are four esters that are the most important acylation reagents:

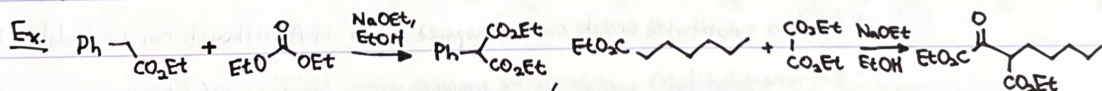
- diethyl oxalates, the most reactive of the four, has a low LUMO resulting from the sum of $\pi^* C=O$ s;



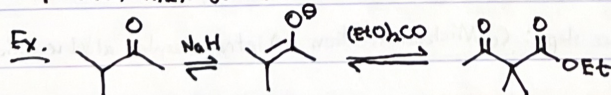
- formate esters (molecule on the left) lack σ conjugation and is therefore much more reactive
- carbonate esters are more electrophilic as inductive effects win out conjugation
- ethyl benzoate, although less reactive than esters, are also very useful



An example of Crossed Claisen ester condensation is provided below:



- Crossed Claisen ester condensations work very well for ketones and prefer the less substituted side
- the product must be able to form the stable enolate

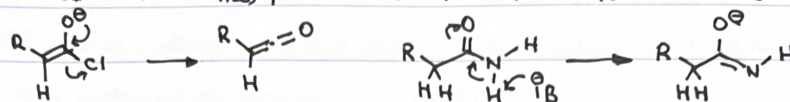


cannot form stable enolate

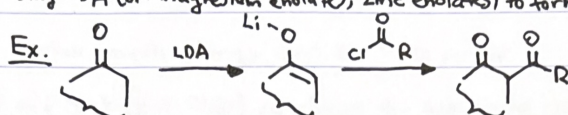
- even if it is alkyl chain vs. methyl, the less substituted side wins to minimize steric hindrance

Below are some examples of C-acylation with specific enol equivalents:

- enolization with amides & acid chlorides are not possible to use for C-acylation easily:

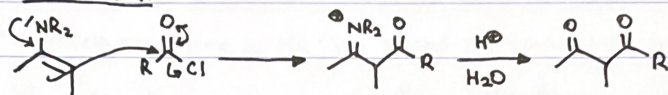


- using LDA (or magnesium enolate), Zinc enolates) to form lithium enolates react well w/ enolizable acid chlorides

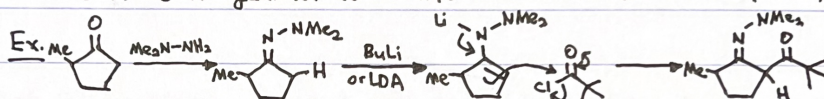


- enamines are also good specific enol equivalents for acid chlorides as N-alkylation is reversible

Mechanism:

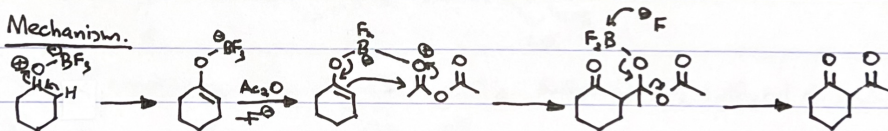


- α,α -enolates are also great for acid chlorides; recall that α,α -enolates prefer the less substituted side



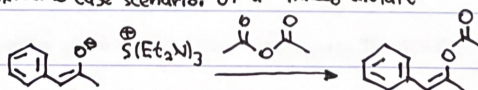
- acylation of ketone enols w/ anhydrides are catalyzed by Lewis acids such as BF_3

Mechanism:



Caution: always watch out for O-alkylation; the more "naked" the enolate is, the more likely it is for C-alkylation to occur

Ex. extreme case scenario of a "naked enolate"



- this is possible for sodium/potassium enolates; lithium or magnesium cations ^{or Mg(enol)} chelate strongly so O-alkylation is not an issue

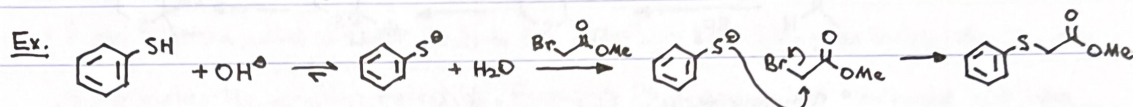
Sulfur

Some general information about sulfur:

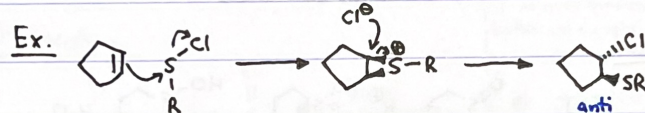
- Sulfur can be anything; it can smell good or bad, be an oxidizing or reducing agent, electrophile or nucleophile
- Sulfur's electronegativity is comparable to carbon
- C-S bonds are strong enough to be stable (362 kJ mol^{-1}) but weak enough to be selectively cleaved when much stronger C-O bonds are present
- S-S and S-X (X=F, Cl, Br) are stable bonds and can be isolated

Simple S(II) compounds can be good nucleophiles due to their high energy lone pair ($3p^3$) compared to oxygen

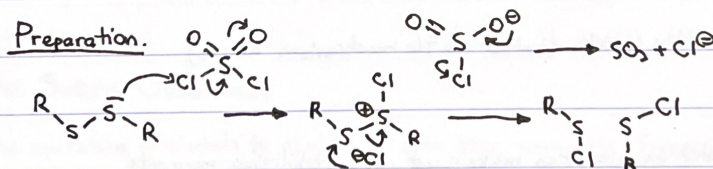
- thiols are much more acidic than alcohols, and much more softer



Sulfonyl chlorides (RSCl) are excellent soft electrophiles, reacting with carbon nucleophiles such as alkenes



- sulfonyl chlorides are prepared from disulfides (R-S-S-R) and sulfuryl chloride (SO_2Cl_2)

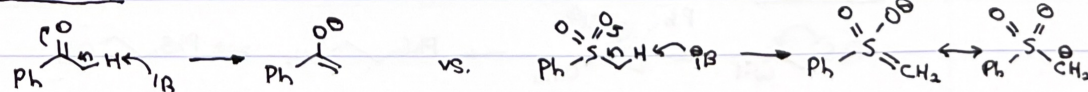


As the oxidation state of the sulfur increases, the species get harder, although high oxidative species such as sulfinate anions (S(IV)) still react at saturated carbon

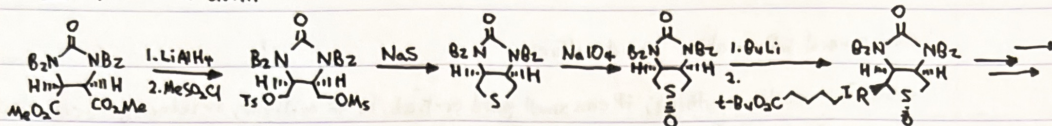
sulfur-stabilized anions, or a carbanion next to a sulfide, sulfoxide, or sulfone drastically stabilizes the anion

- deprotonation of a sulfone is comparable to an enolate; adding more oxygen atoms to the sulfur increases stabilization
- polarization of sulfur ($3s, 3p$ orbitals) also contribute to the stabilization of carbanions.

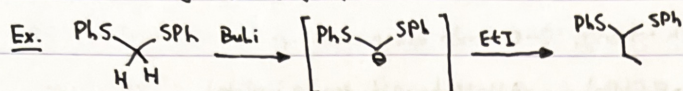
Mechanism.



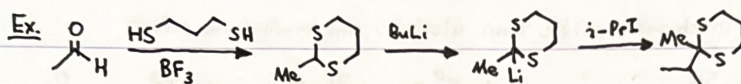
Ex. synthesis of biotin



thioacetals (having two -SR groups) further increases its acidity; alkylation is possible



- a special type of thioacetal, known as dithianes, can be made by aldehyde/ketone + Lewis acid catalyst
- very useful as they invert the polarity at the functionalized carbon atom; electrophile $\rightarrow$ nucleophile

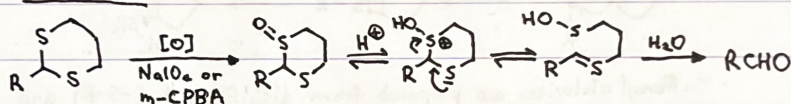


- removing the thioacetal group is tricky, and have multiple possible (but not necessarily good) ways to do it:

i) mercury $[\text{Hg}(\text{II})]$

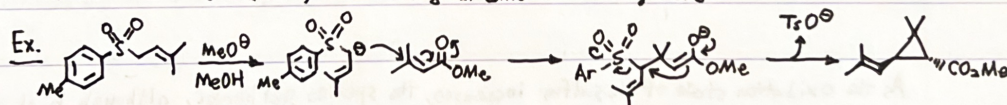
ii) oxidation of one of the sulfur atoms to sulfoxide

Mechanism:



iii) methylation (works similar to the mechanism above)

Sulfones, as illustrated earlier, can make great anion-stabilizing reagents



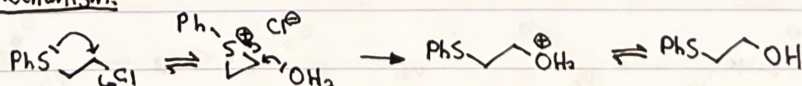
sulfides are nucleophiles and will actively attack alkyl halides to form sulfonium salts in equilibrium

- using Meerwein's salt can make this an irreversible reaction; BF_4^- is non-nucleophilic, and Me_3O^+ is a good

- the resulting sulfonium salt is an electrophile, and deprotonation leads to a ylide

- participation by sulfur, forming an episulfonium can heavily accelerate $\text{S}_\text{N}2$ reactions

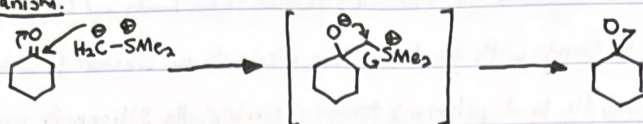
Mechanism:



sulfonium ylids are excellent tools to make epoxides & cyclopropanes from carbonyl groups

- an unstabilized ylid with an aldehyde/ketone yields an epoxide

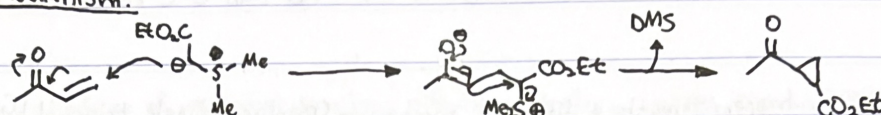
Mechanism:



notice a common theme with sulfur chemistry; they act as both anion-stabilizing groups and as excellent leaving groups.

- if the sulfonium ylid is stabilized by a conjugating group, and it reacts with a α,β -unsaturated carbonyl compound (in which conjugate addition is possible), a cyclopropane is the end product

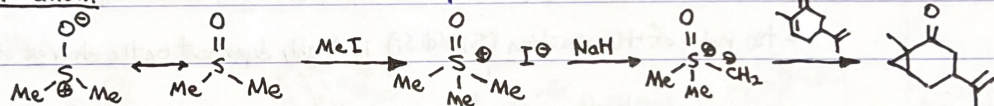
Mechanism:



- direct addition, which is faster, leads to the epoxide - but adding an extra stabilizing group makes the reaction reversible, favouring the irreversible conjugate addition

sulfoxonium ylids always yield cyclopropanes

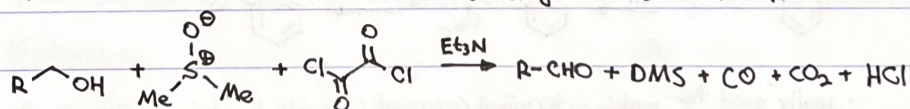
Preparation:



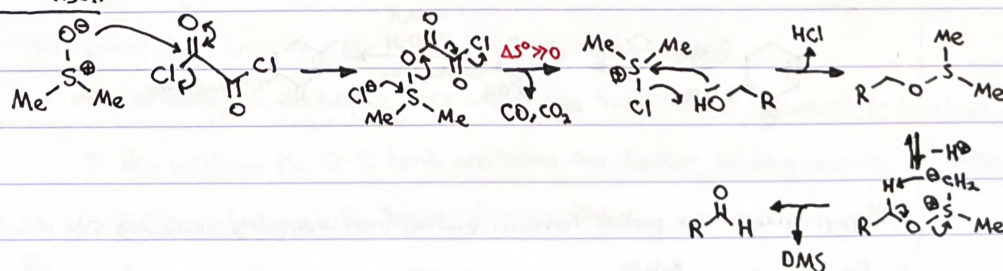
O-alkylation does not occur as sulfur's lone pair makes it the better nucleophile; S_{N2} reactions depend very little on charge attraction

The Swern Oxidation

The oxidation of alcohols to aldehydes can be done using the Swern reaction:



Mechanism:



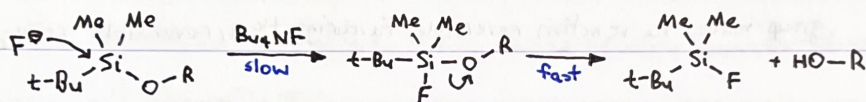
Silicon

Some general information about silicon:

- Si bonds with electronegative elements are stronger than bonds w/ carbon (Si-F bonds are 582 kJ mol^{-1})
 - conversely, Si bonds with electropositive elements are weaker than bonds w/ carbon
- a Si-C has the bond polarized towards carbon; the Silicon is susceptible to nucleophilic attack
 - the bond is strong enough to be stable but can be specifically cleaved if desired
- nucleophiles that are electronegative and can form strong bonds are the most effective for silicon
 - note that C-Si bonds are significantly longer than C-C bonds $\rightarrow$ steric hindrance $\downarrow$ role

$\text{S}_\text{N}2@ \text{Si}$ happens through a different mechanism (pentacoordinate trigonal bipyramid intermediate)

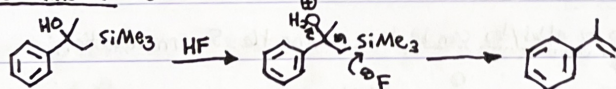
Mechanism.



- the significant difference between $\text{S}_\text{N}2@ \text{Si}$ and $\text{S}_\text{N}2$ is that silyl halides are hard electrophiles
 - the best nucleophiles for silicon are charged, highly electronegative atoms (F, Cl, or O)
 - the rate of the reaction ($\text{S}_\text{N}2@ \text{Si}$) is highly dependent on the charge of silicon

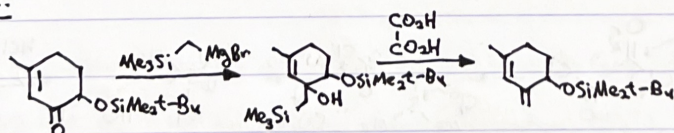
The Me_3Si group can act as a "super proton"; a regioselective reaction to give alkenes

Mechanism. Peterson elimination

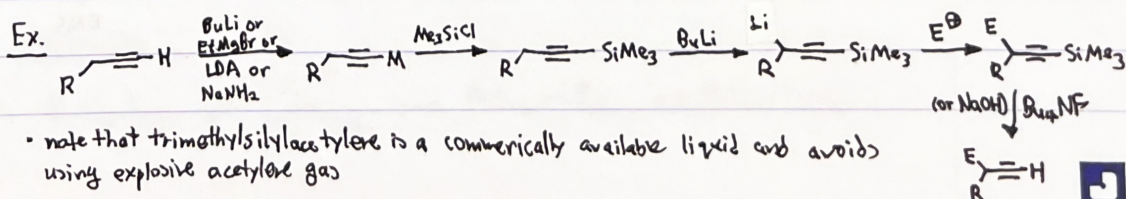


- really good for making terminal/exocyclic double bonds; $\text{Me}_3\text{SiCH}_2\text{Br}$ is widely available!

Ex.



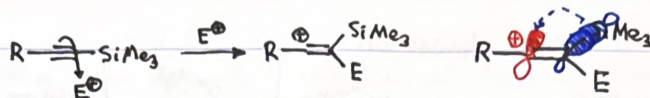
Alkynyl silanes can protect terminal protons from undergoing unwanted side reactions



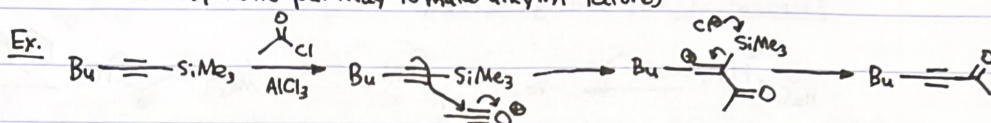
- note that trimethylsilylacetylene is a commercially available liquid and avoids using explosive acetylene gas

- electrophilic addition on alkynyl silanes are regioselective, due to σ donation by the C-Si bond

Mechanism.

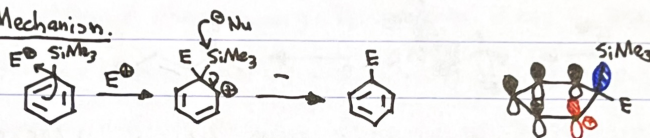


- this also weakens the C-Si bond (due to σ donation) and allows the bond to be more easily broken
- allows a synthetic pathway to make alkynyl ketones



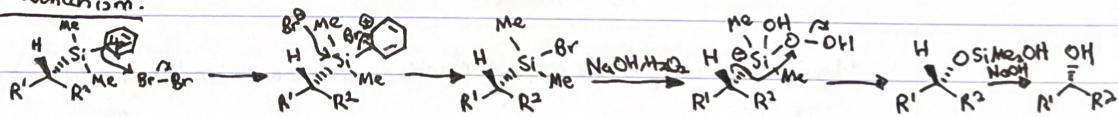
Similar (interns of reasoning) to alkynyl silanes, aryl silanes undergo ipso substitution (β -stabilization)

Mechanism.



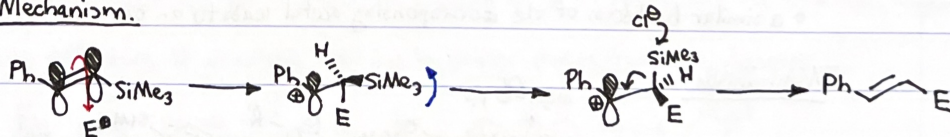
- the Fleming-Tamao oxidation makes use of this mechanism that is stereospecific reaction with retention of configuration at the C-Si bond, converting it into a C-O bond

Mechanism.



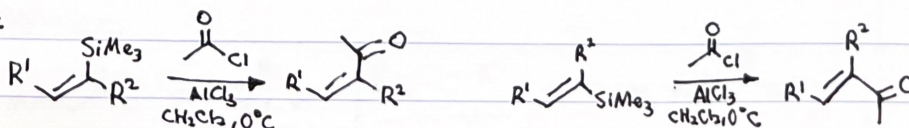
Vinyl silanes also react with electrophiles at the ipso carbon atom with retention of geometry

Mechanism.



- the mechanism is driven by β -stabilization by σ donation;
- after attacking the electrophile, rotation of the SiMe₃ group increases σ donation;
- this weakens the C-Si bond, and before any further rotation occurs, the Me₃Si group is removed to give the preserved geometry

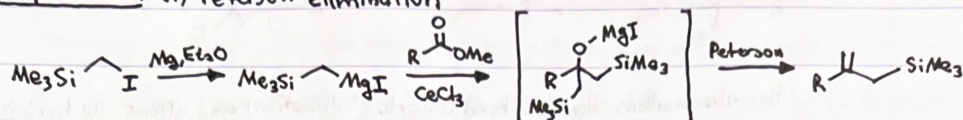
Ex.



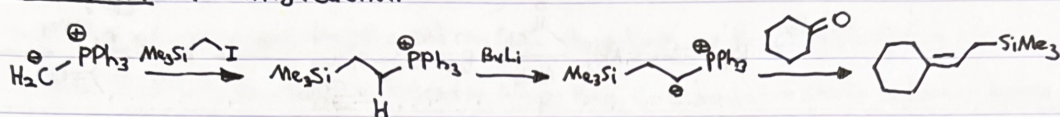
allyl silanes are a much more reactive version of alkenes with β -silyl cation stabilization in addition

• there are two ways to prepare allyl silanes; (i) Peterson elimination (ii) Wittig reaction

Preparation. (i) Peterson elimination

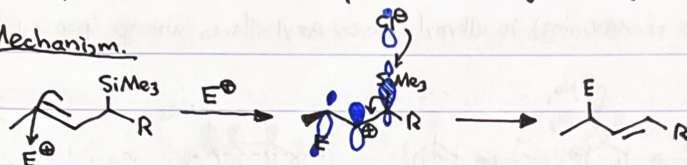


Preparation. (ii) Wittig reaction



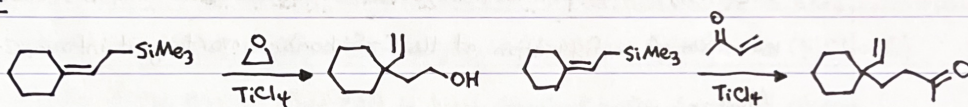
• these allyl silanes react with electrophiles with even greater regioselectivity than vinyl silanes

Mechanism.



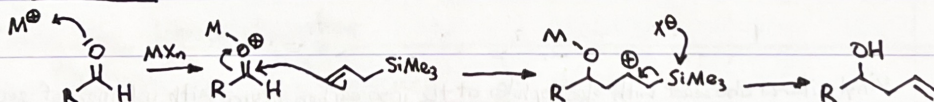
• reactions occur similar to silyl enol ethers; activation w/ Lewis acid (BF_3 , TiCl_4 , AlCl_3) allows for rxns

Ex.



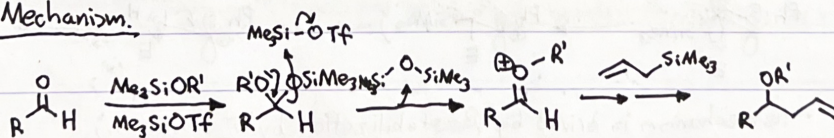
• Lewis acids can promote coupling reactions between carbonyl compounds and allyl silanes:

Mechanism.



• a similar breakdown of the corresponding acetal leads to an oxonium cation

Mechanism.

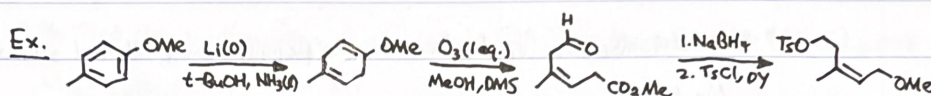
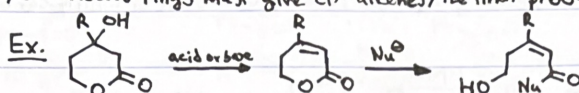


Here, we illustrate the selective synthesis of alkenes, putting emphasis on geometry:

There are many ways to control the geometry of algebras, four of which are illustrated below:

(i) exploiting cyclic compounds → which can only form cis-alkenes

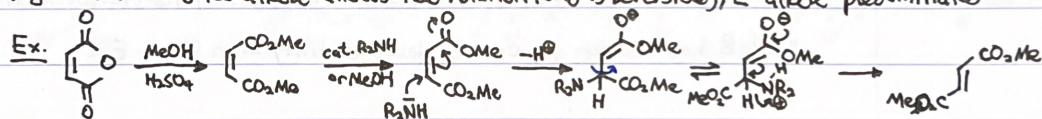
- 5, 6-membered rings must give cis-alkenes; the final product does not necessarily have to be cyclic as...



(ii) equilibration of alkenes causes the (generally more) stable E alkenes to form over time

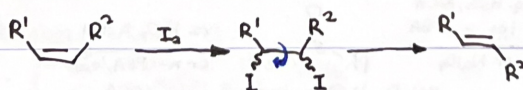
- although π bonds are rather strong (260 kJ mol^{-1} to rotate) to prevent rotation, if a reaction, such as

conjugate addition to the alkene allows free rotation (and is reversible), E-alkene predominates



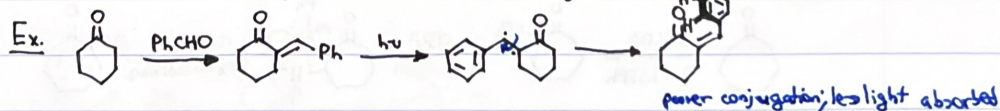
- iodine adds to alkenes reversibly; this can be useful for equilibrating alkenes

Mechanism.



- sometimes, just UV light can force the broken π bond to rotate into the Z-alkene, which should be

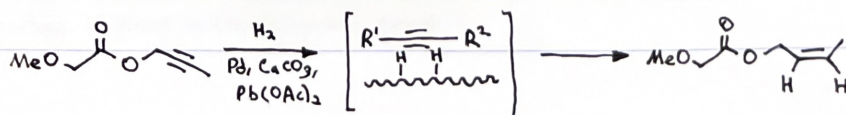
less effective at absorbing light due to poorer conjugations on whatever



(iii) stereoselective addition to alkyne, yield either E or Z alkenes by kinetic control.

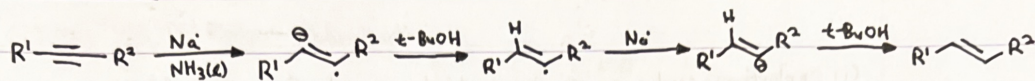
- Z-selective reduction can be done using Lindlar's catalyst

Mechanism.

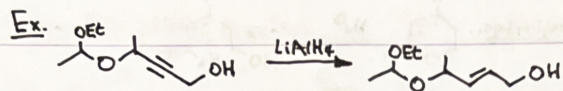


- E-selective reduction can be achieved through Birch reduction

Mechanism.

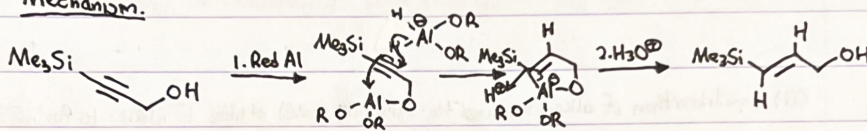


- if there is a hydroxy/ether group near the alkyne, $RO-Al$ or $LiAlH_4$ can be used alternatively



- geometrically pure vinyl silanes can be prepared using alkynyl silanes. For E-selective reduction:

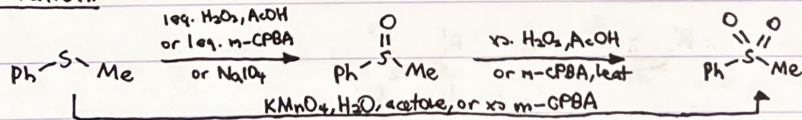
Mechanism.



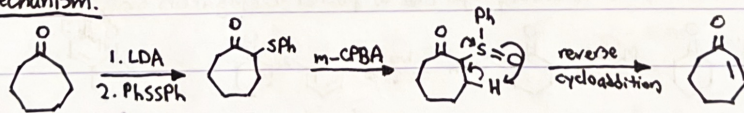
- for E1 and E2 (that have a choice of protons to be removed) are stereoselective and are kinetically controlled
- E1cB has better regio- and stereoselectivity than E1 or E2

Going back to sulfone chemistry momentarily, sulfoxides can act as both a good anion-stabilizing group and leaving group through reverse cycloaddition

Preparation.



Mechanism.

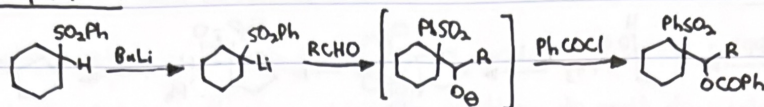


- rather than sulfur, selenium (selenoxides) can be used and elimination occurs spontaneously at SATP.

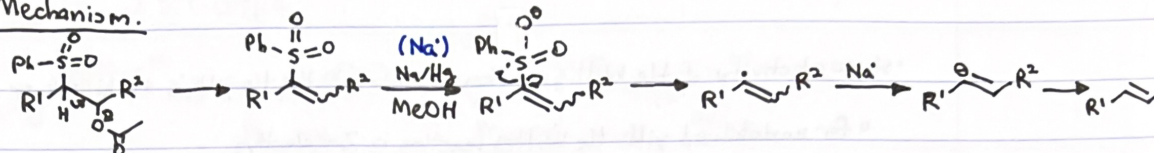
→ coupling reaction!

The Julia olefination is connective and gives E-alkenes stereoselectively and regioselectively

Preparation.

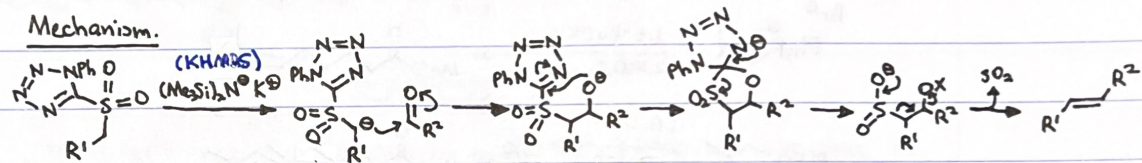


Mechanism.



- the first step is elimination of an acetate (OAc^-) or benzoate ester (OBz^-) group to give a vinyl sulfone
- the second step is fairly similar to a Birch reduction, but the first electron goes into sulfone
- a modified one-step refined version, known as the Julia-Kocienski reaction, utilizes a tetrazole

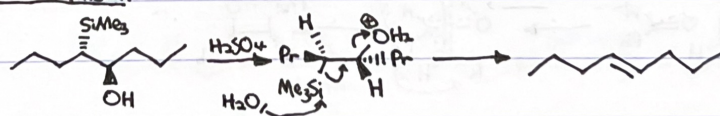
Mechanism.



The Peterson elimination is stereospecific; given any single diastereoisomer of hydroxy silane, both E, Z geometric isomers can be prepared

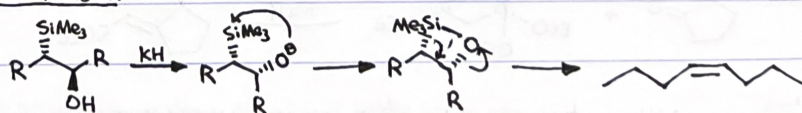
- when acid (H_2SO_4) is used, anti-periplanar elimination occurs stereospecifically

Mechanism.



- when base (KH , NaH) is used, syn-periplanar elimination occurs stereospecifically

Mechanism.

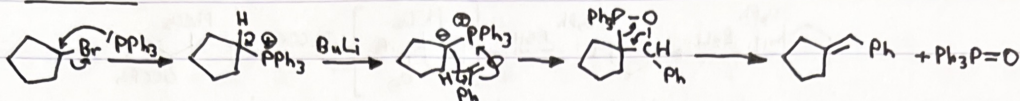


The Wittig reaction is another connective (coupling) reaction; its mechanism is somewhat similar to above

- the phosphorus group, which carry an electronegative substituent or positive charge, increases the acidity of the carbon adjacent to the phosphorus group

- ylids can be isolated, but are commonly used ^{and prepared} in situ and attack aldehydes/ketones

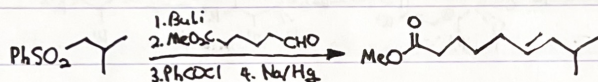
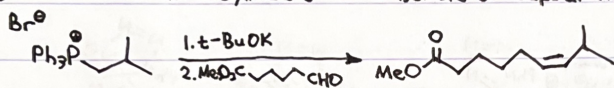
Mechanism.



- stereoselectivity of the Wittig reaction depends whether the ylid is stabilized or not;
 - for unstabilized ylids, the Wittig reaction is Z-selective
 - for stabilized ylids (aldehyde, ketone, or ester group), the Wittig reaction is E-selective.

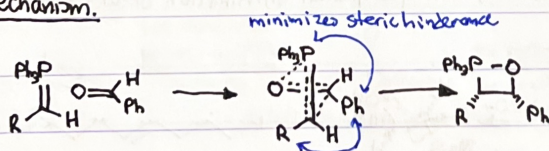
the Z-selectivity of the Wittig reaction w/ unstabilized ylids complement well w/ the Julia olefination

Ex. intermediates in the synthesis of E/Z isomers of capsaicin.



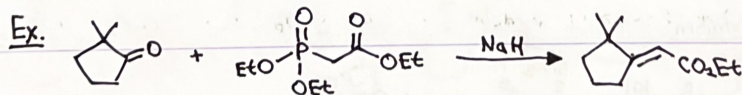
- the mechanism of preferring Z-alkene relies on the formation of oxaphosphetane, as its decomposition is stereospecific. By orbital symmetry rules, the ylid & carbonyl approach perpendicularly to each other

Mechanism.

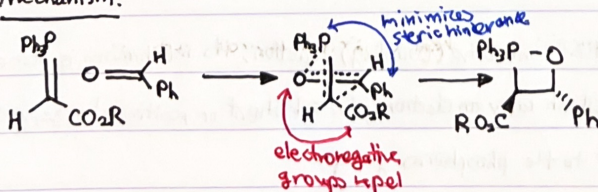


→ Horner-Wadsworth-Emmons reactions

- stabilized ylids are often too stable - phosphonate esters are used more frequently



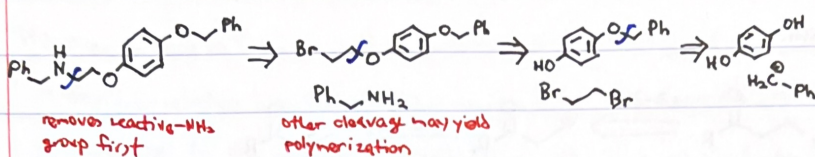
Mechanism.



Some basic guidelines for retrosynthetic analysis is as follows:

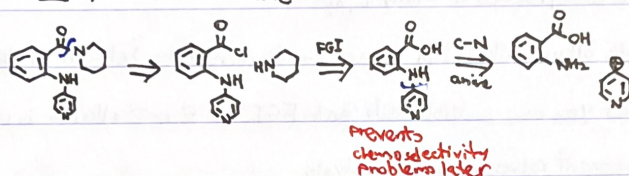
- i) disconnections must correspond to known, reliable reactions
- ii) when a heteroatom connects two parts of a compound, disconnect next to the heteroatom
- iii) try to introduce reactive groups late in the synthesis to avoid chemoselectivity issues

Ex. synthesis of ICI-D7114



iv) when possible, utilize functional group interconversions to avoid chemoselectivity issues

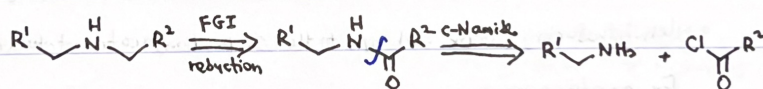
Ex. synthesis of ofornine



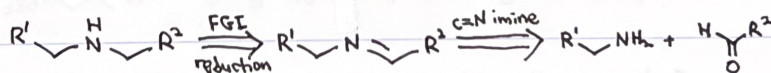
• amine synthesis can always be an issue as multiple alkylation can take place

Solution. (i) convert to amide, use LAH or borane (ii) convert to imine, use NaCNBH₃ or H₂/cat. reductive amination

(i) Mechanism:



(ii) Mechanism:



• word of note: if the starting material is less reactive (for example, an inductively electron-withdrawing group is present) or there is significant steric hindrance, simple alkylation by S_N2 may work

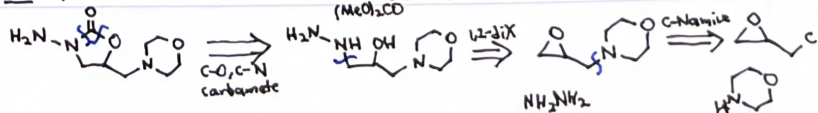
v) two-group disconnections are always better than one

• 1,2-diX synths

• epoxides are a great tool for adding adjacent hydroxyl groups

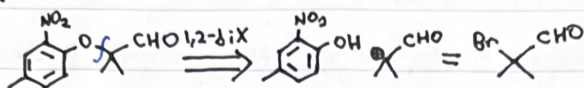
- epichlorohydrin in particular is a great tool

Ex. synthesis of moxidazole intermediate



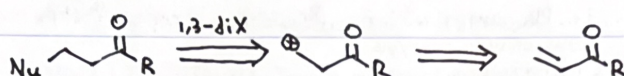
- α -halo carbonyl compounds are good synthons for when we want an adjacent carbonyl group

Ex.



- 1,3-diX for carbonyl groups – use α,β -unsaturated carbonyl compounds

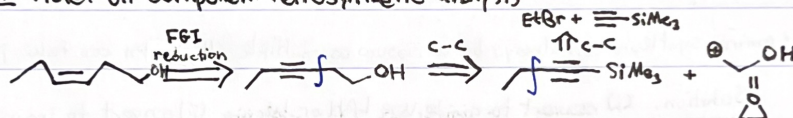
Mechanism.



C-C bond disconnections can be approached in many ways

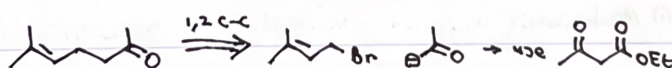
- utilizing the very reliable alkyl alkylation is good – disconnections between triple bonds are good
- even more useful as you can control easily and FGI to E or Z alkenes is very easy

Ex. violet oil component retrosynthetic analysis



- when there is an alkyl group two carbon atoms away from a carbonyl group, utilize enolates
- when introducing simple carbonyls to the 1,2 position, acetoacetate and malonate esters are good

Ex. carotene precursor



if $RO-C(=O)-R$ is the synthon required, then just utilize $EtO_2C-CH_2-CO_2Et$ and do decarboxylation

- when in question, utilize oxygen-based groups versatility and facilitate C-C disconnections that way
- for 1,1 C-C disconnections, utilize carbon nucleophiles, such as Grignard reagents
- if there are two identical groups in a tertiary alcohol, use an ester + Grignard reagent

For searching up available starting materials, use a supplier's catalogue; but as a general rule of thumb:

- compounds w/ up to six carbon atoms + one functional group is generally available
- for straight-chain compounds, the carbon count increases to eight or more

donor synthons (d) are negatively polarized and acceptor synthons (a) are positively charged

• the number (superscript) illustrates the position the functional group is w.r.t the reactive site

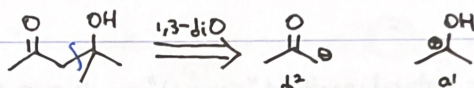


We now go back to two-group disconnection, but for C-C bonds:

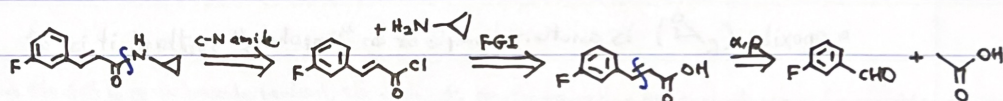
• for 1,3-relationships the aldol reaction can be a useful tool; ($d^2 + a^1$)

• applies to α,β -unsaturated carbonyls as well; it could easily be the dehydration product!

Mechanism.

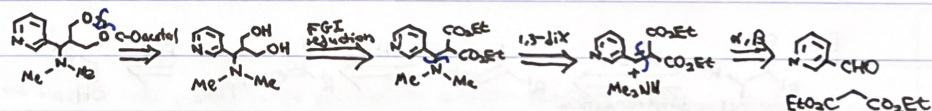


Ex. retrosynthetic analysis of cinnulide



• always look out for concealed functional group relationships

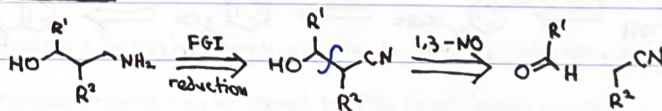
Ex. retrosynthetic analysis of doxipicoline



• when N and O are in a 1,3-relationship, there are two ways to approach this problem:

• aldol-style reactions with nitriles yield a feasible pathway:

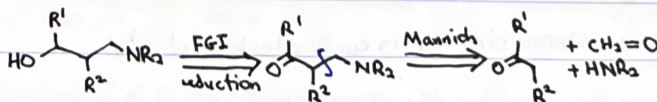
Mechanism.



as a side note - 1,2-NO relationship can also utilize nitriles by reduction of cyanohydrins
 $HO-CH(R^1)-CN \xrightarrow{1,2-NO} O=CH(R^1)-H + CN^-$

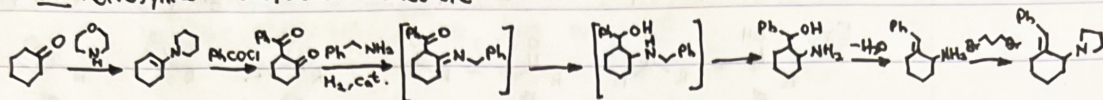
• the Mannich reaction also works here

Mechanism.



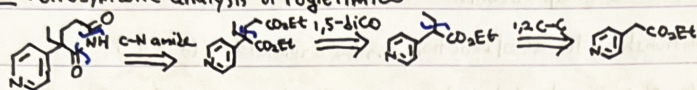
- for two carbonyl groups, use the Claisen ester condensation

Ex. retrosynthetic analysis of tazadolene



- for 1,5-relationships, use an enone (α^2) to do Michael addition of enolates

Ex. retrosynthetic analysis of rosetimide

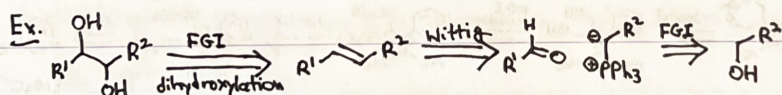


The "natural reactivity" of carbonyl compounds results in odd-number acceptor synthons and even-number donor synthons;

- synthons that have their natural reactivity "reversed" are known as "umpolung" synthons
 - cyanide anion (CN^-) is one type of an "umpolung" synthon; it is δ^+
 - epoxide ($\text{R}_2\text{C}_2\text{O}$) is another example of an "umpolung" synthon; it is α^2

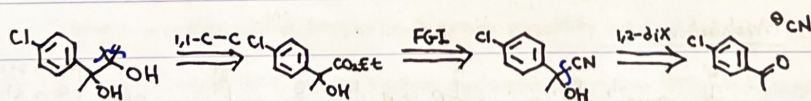
For 1,2-difunctionalized compounds, there are many ways to approach the issue (epoxides being one example)

- electrophilic addition to alkenes can result in 1,2-difunctionalized compds; alkene made by the Wittig reaction



- cyanide (δ^+) can be a very useful reagent, especially since it can undergo FGI to carbonyl group

Ex. retrosynthetic analysis of phenaglycodol



For 1,4-difunctional compounds, there are lots of possible strategies: $\delta^3 + \alpha^1$, or $\delta^1 + \alpha^3$, or $\delta^2 + \alpha^2$

- for $\delta^2 + \alpha^2$, using enamines + α -bromo carbonyl compound is an excellent strategy
- for $\delta^1 + \alpha^3$, using enones + cyanide is an excellent strategy

replacing one of the carbon atoms in a benzene ring yields pyridine

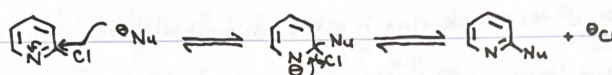


- this imine is incredibly stable due to its aromaticity - however has three different shifts

- the molecule (nitrogen lone pair) is also incredibly basic as the lone pair is not a part of the π system and nucleophilic
- an addition of a nitrogen atom lowers all of the MOs; a lower LUMO = better electrophile, but worse nucleophile
- electrophilic aromatic substitution DO NOT occur; the nitrogen lone pair is nucleophilic
- notably, bromination & chlorination work very well for pyridine

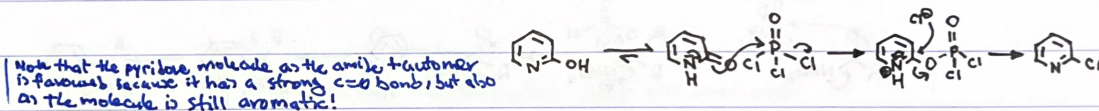
When there is a leaving group in the 2- or 4- position of pyridine, reactions occur almost similar to carbonyl substitution

Mechanism:



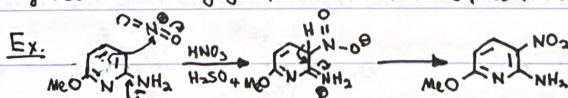
- amines & thiols are good nucleophiles for this reaction. For leaving groups, chloride, methoxide, and hydroxide work best

When the LG is a hydroxide (anion), the molecule can tautomerize to a much more favourable amide tautomer



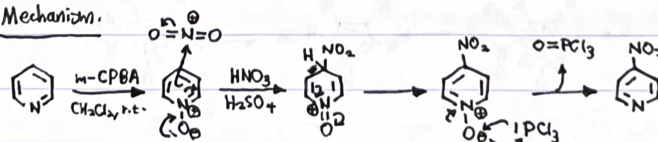
There are ways to make pyridine to do electrophilic aromatic substitution if you activate the ring

- using electron-donating groups (EDG) donates lone pairs to raise the HOMO of the ring



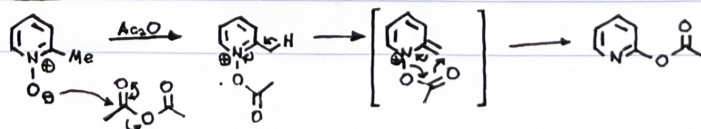
- oxidizing pyridine by adding an oxygen atom to the nucleophilic nitrogen (m-CPBA or H₂O₂/AcOH) raises the HOMO
- the pyridine N-oxide can be reduced by PX₃ (X=Cl, OMe) species which act as both nucleophile & electrophile:

Mechanism:



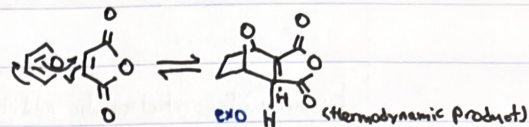
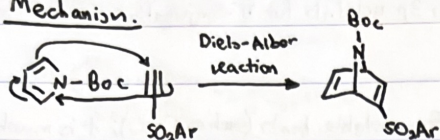
- functionalization of the side-chain is possible with participation of pyridine N-oxides

Mechanism:



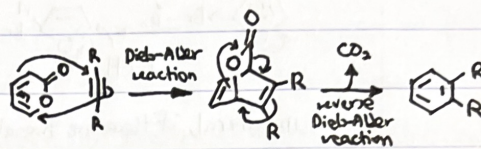
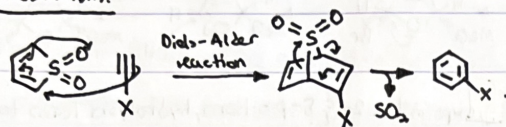
Five-membered heterocycles (and α -pyrones) undergo Diels-Alder reactions

Mechanism.



• for thiophene (which must be oxidised to sulfone) & α -pyrones, release of gas (SO_2, CO_2) results in hetero ring

Mechanism.



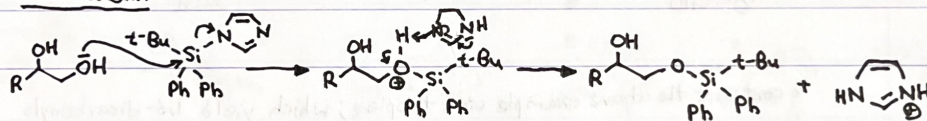
Both prazole (1,2-diazole) and imidazole (1,3-diazole) have one pyrrole-like Nitrogen and one that is pyridine-like

• imidazole in particular, due to its 1,3-relationship, shares charge equally amongst the two nitrogen atoms

• this makes imidazole much more basic than pyrrole/pyridine ($\text{pK}_a \sim 7.0$) and more acidic than pyrrole ($\text{pK}_a \sim 14.5$)

• imidazole is common in nature and a popular catalyst as it can do nucleophilic catalysis & base catalysis:

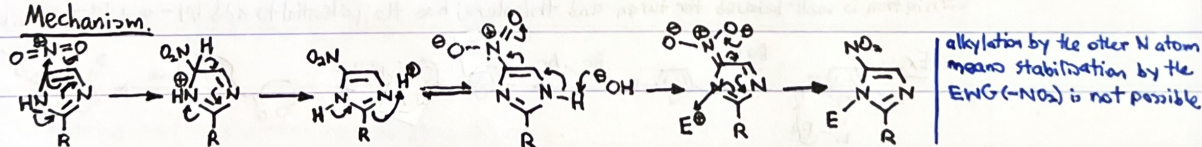
Mechanism.



• Carbonyl diimidazole (CDI) can act as a double electrophile, replacing COCl_2 which is incredibly toxic

imidazoles can undergo tautomerism (and does spontaneously); if alkylated, tautomerization stops and occurs on the NO_2 side.

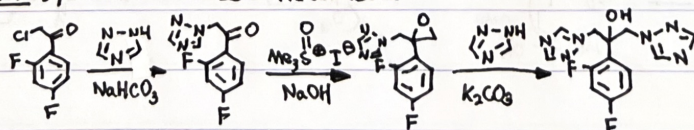
Mechanism.



For the triazoles, there is one pyrrole-like nitrogen and two pyridine-like nitrogens with the possibility of tautomerism

• the addition of pyridine-like nitrogen atom makes it less basic much more acidic than imidazole (anion is easier to make)

Ex. synthesis of Pfizer's fluconazole



tetra-zoles are great substitutes for carboxylic acids as their pK_a s are similar

Indoles are important in biological systems and prefers 3-substitution unlike pyrrole in electrophilic substitutions

- cross-conjugation is inevitable - however, 2-substitution disrupts the aromatic benzene ring

when 3-substitution is not possible, 2-substitution may occur and often occurs through migration

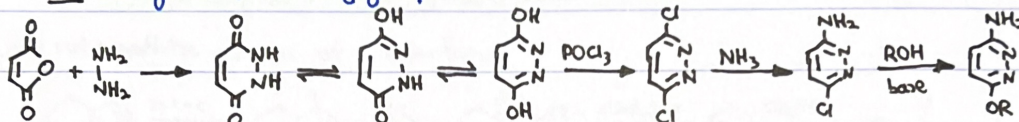
Mechanism.



When we add two nitrogen atoms to a six-membered ring, both nitrogen atoms act as the pyridine type

- it will only do well, will focus on nucleophilic substitution as the ring is very electron-deficient

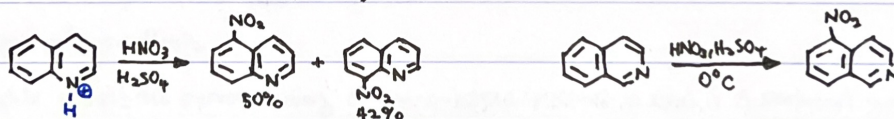
Ex. adding electron-donating groups slows down the nucleophilic substitution



iso
quinolines and quinolines are pyridines that are fused into a benzene ring

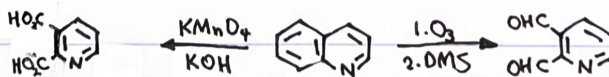
- electrophilic substitution tends to favour the benzene ring, while nucleophilic substitution favours the pyridine
- however, most reactions for quinoline tends to be unsatisfactory

Ex. nitration of quinoline $\frac{1}{2}$ isoquinoline



- with vigorous oxidizing reagents, the benzene rings are destroyed:

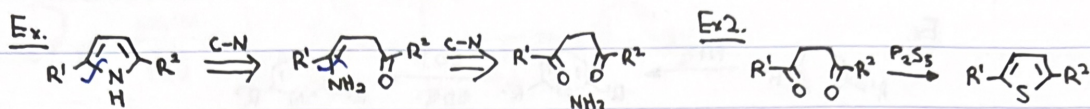
Ex. vigorous oxidation of quinoline



Synthesis of aromatic heterocycles is approached slightly different from our familiar benzene derivatives

- approach is: have the substituents already in place, use heteroatom as nucleophile to make the ring
- very favourable as C-X bonds are easy to make, and end product is very stable (aromatic)

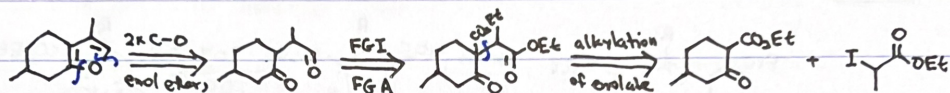
five-membered heterocycles can be easily approached by disconnecting the C-X bonds (enolequivalents, kind of)



- furan, can be made by dehydrating the 1,4-diketone (base leads to intramolecular aldol reaction)

We illustrate some examples of furan synthesis below:

Ex. retrosynthetic analysis of menthofuran



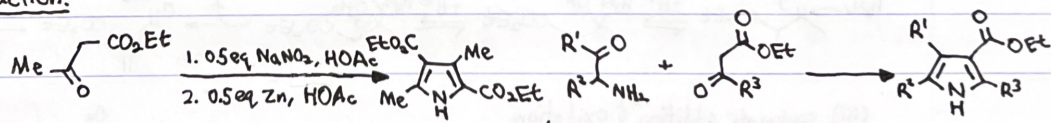
Synthesis:



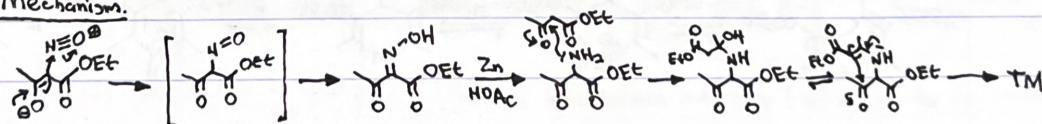
Knorr pyrrole synthesis

Creates highly substituted pyrroles using α -amino-ketone (prepared in situ) & a carbonyl group (w/ an α -EWG)

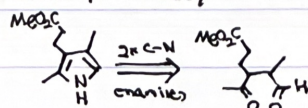
Reaction:



Mechanism:

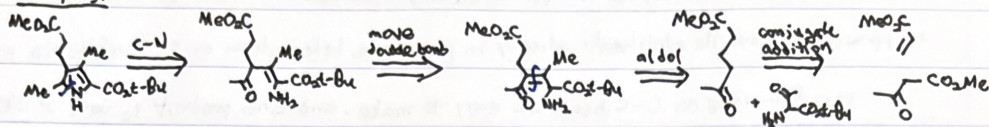


We attempt retrosynthetic analysis for one of the components of porphyrin in haemoglobin



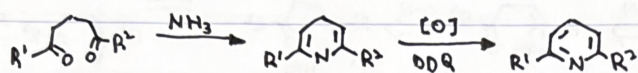
this starting material is bad because the aldehyde is too reactive (e.g. t-BuOAc protecting group seems necessary) and too difficult to make, considering there is a better way

Analysis:



six-membered heterocycles utilize a similar strategy, but with 1,5-dicarbonyls & an oxidizing reagent

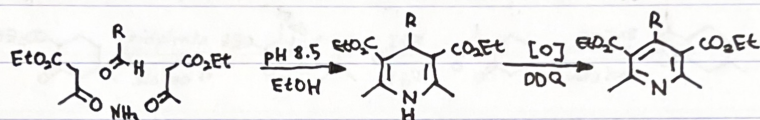
Ex.



Hantzsch pyridine synthesis

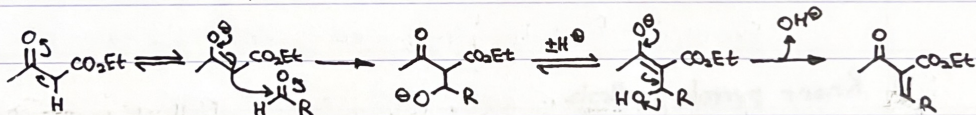
A one-pot synthesis involving two β -keto esters, a nitrogen donor, and an aldehyde.

Reaction:

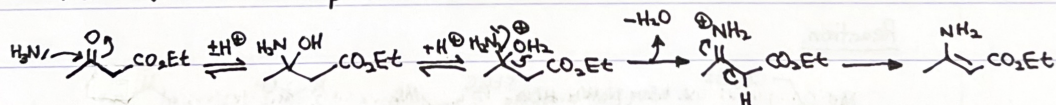


Mechanism: As a multi-step reaction with a variety of components & possible mechanisms:

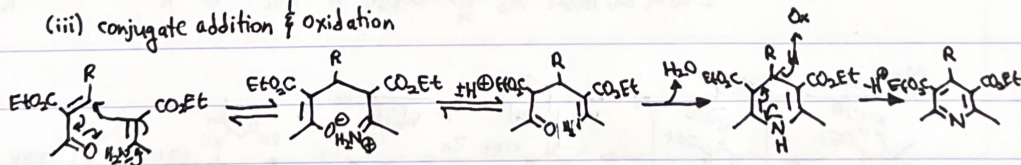
(i) aldol reaction between β -keto ester & aldehyde



(ii) enamine formation from β -keto ester



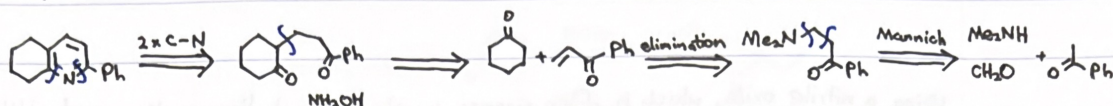
(iii) conjugate addition & oxidation



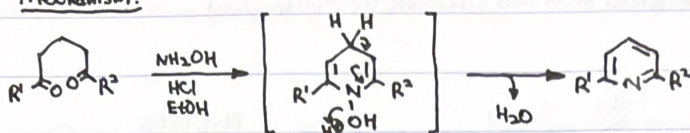
• If step (ii) is done different place from (i), asymmetric pyridines can be synthesized

Pyridines can be directly made from 1,5-dicarbonyls if hydroxylamine (NH_2OH) is used instead of ammonia

Analysis:

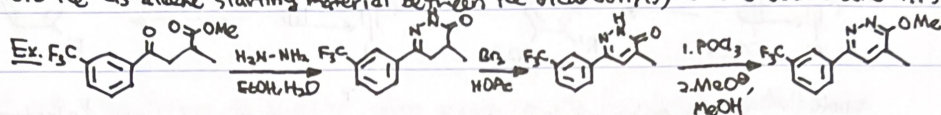


Mechanism:

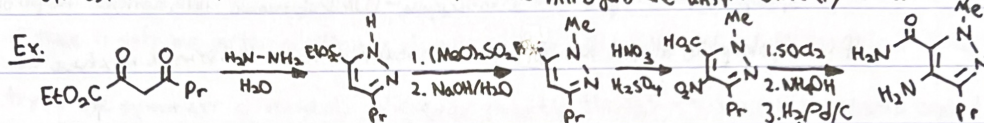


Pyrazoles and pyridazines can be made with hydrazine & dicarbonyl compounds

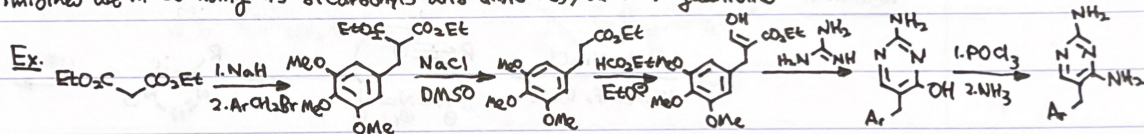
• avoid the cis alkene starting material between the dicarbonyls; remove double bond first



• sometimes, selectivity issues can arise when the two nitrogens are unsymmetrical; in that case, just alkylate them

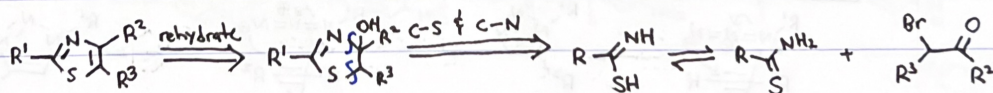


pyrimidines are made using 1,3-dicarbonyls and amidines, such as guanidine



thiazoles can be synthesized using thioamide (from amide + Lawesson's reagent) and an α -haloketone

Analysis:



• always consider that soft-soft and hard-hard interactions are very favourable for disconnections

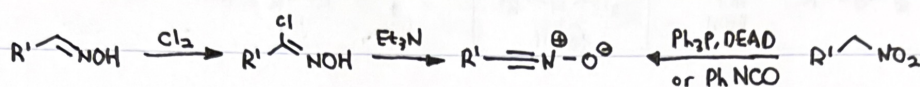
isoxazoles can be synthesized in two ways:

- using hydroxylamine & 1,3-dicarbonyls
- cycloaddition reactions

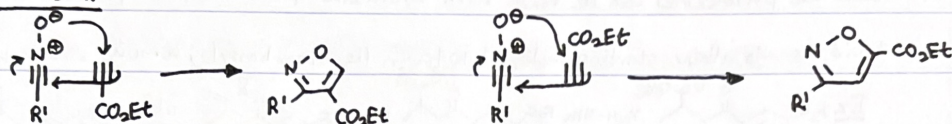
With the hydroxylamine route, the more nucleophilic atom of the hydroxylamine can be controlled by pH;
 • the starting material can also be modified to ensure the more electrophilic carbonyl is attacked first

Using a nitrile oxide, which is often prepared in situ to avoid dimerization, cycloaddition occurs with an alkyne (acts as the dienophile, or in this situation, the dipolarophile)

Preparation.



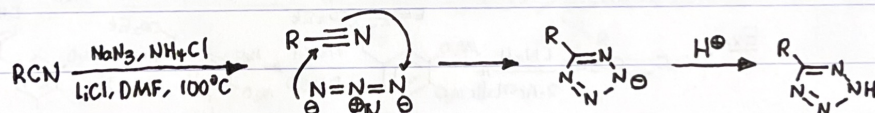
Mechanism.



• note that nitrile oxides are linear 1,3-dipoles; they are both nucleophilic & electrophilic, so both HOMO_{dipolarophile} - LUMO_{dipole} and HOMO_{dipole} - LUMO_{dipolarophile} interactions are possible, and especially if the dipolarophile alkyne has an EWG, the reaction tends to form a mixture of isomers

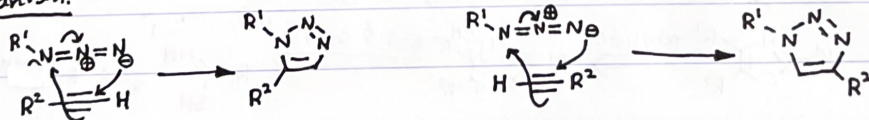
tetrazoles are made through 1,3-dipolar cycloadditions w/ an azide anion & a nitrile (preferably w/ an EWG)

Reaction.



triazoles are very similar, except we use an ordinary alkyne as the dipolarophile & we get two regioisomers

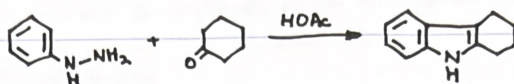
Mechanism.



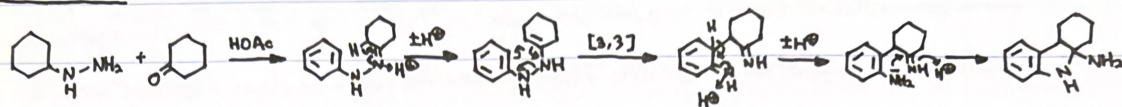
• adding Cu(I) (made in situ by Cu₂O + mild reducing agent) accelerates the reaction & favours 1,4-product

Fischer indole synthesis

Reaction.



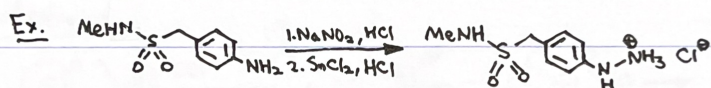
Mechanism.



- after animal formation, acid-catalyzed decomposition occurs and expels NH_3 leading to the indole
- A C-C bond is established at the expense of a weak N-N bond

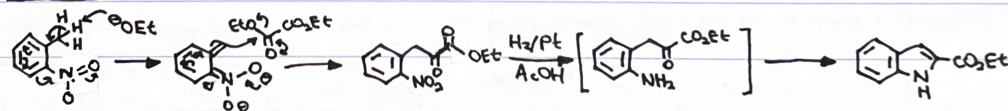
There are some things to consider when preparing the Fischer indole synthesis:

- if the phenylhydrazine attacks an aldehyde instead of a ketone, only one product is possible
- if there is only one ortho position available, attack will occur only at that position of the benzene ring
- try to use symmetric reagents whenever possible though - unless regioselective control is possible
- phenylhydrazine can be made from a $-\text{NH}_2$ group by nitrosation + reduction w/ SnCl_2 & HCl

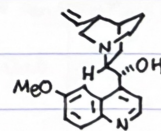


The Reimer synthesis is another method of preparing indoles

Mechanism.

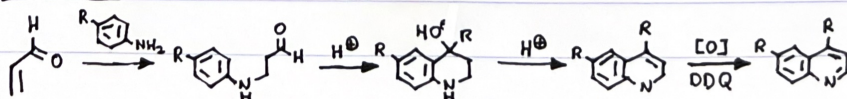


Quinine is a quinoline w/ $-\text{OMe}$ group on C6 & a large side-chain on C4



- many other anti-malarial drugs share this structure (substituent positioning)
- the modern Skraup synthesis creates dihydropyridine from an aniline + Michael acceptor and oxidizes it

Mechanism.



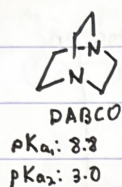


saturated heterocycles have two important properties:

- i) synthesis and ring-opening reaction are somewhat easy to do
- ii) stereoelectronic effects (chemical consequences of the arrangement of orbitals in space) fix the orientation of lone pairs in space.

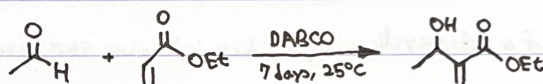
saturated nitrogen heterocycles are amines that are much more nucleophilic, as they lack any hindrance from substituents

- the substituents are "tied back" to the ring; allows the lone pair to exert its full nucleophilicity
- a proton (acidity) is barely (if at all) affected by steric effects; how electron-rich the nitrogen is does.
 - DABCO is a bridged piperazine, which by inductive effect, makes the nitrogen atom less nucleophilic & basic
 - especially when comparing pK_a , vs. pK_a of the protonated nitrogen with low density from the unprotonated one

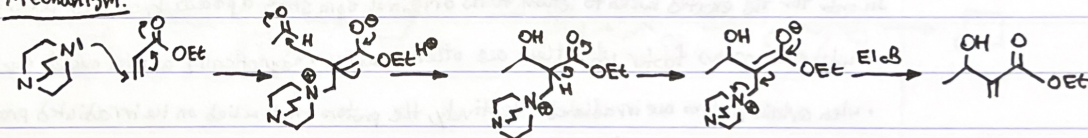


Because DABCO is cyclic and has a relatively low pK_a , it is a decent nucleophile and an excellent leaving group — it is very good as a nucleophilic and base catalyst for the Baylis-Hillman reaction

Reaction.



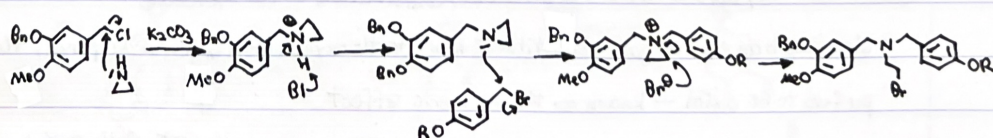
Mechanism.



Aziridine () and azetidine () are stable rings that are strained; have significantly different chemistry

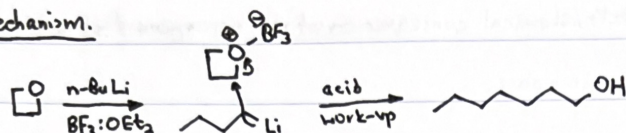
- because these rings have significant angle-strain, the nitrogen atom has much more s character than usual
 - leads to a much less nucleophilic & basic molecule
- when these nitrogen heterocycles attack an acyl chloride, if protonated, a nucleophile can open the ring
 - in base, deprotonation occurs swiftly and the N-acetyl heterocycle can be isolated

Ex.



oxygen heterocycles tend to be more stable as cyclic ethers, although epoxides are reactive and oxetane ($\square^{\text{O}}$) can undergo a ring-opening reaction with a Lewis acid

Mechanism.



- cyclic ethers like THF or dioxane are stable solvents that can also solvate organometallics with electron-deficient cations by the oxygen's lone pair

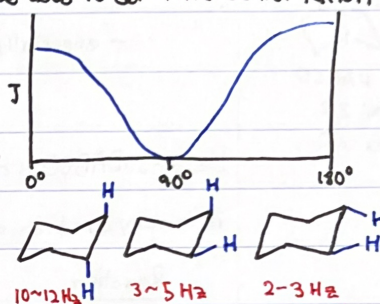
Because coupling constant vary depending on dihedral angle, NMR can be used to determine conformation

- the relative values of coupling constant vs. dihedral angle shown on the right is known as the Karplus relationship

- coupling constant is greatest at 180° and almost as great at 0°

- orthogonal protons have 0 Hz coupling; note that small coupling

constants are often overlooked

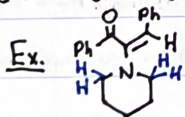


- formation of a heterocyclic ring can help determine stereochemistry using coupling constants

In order for the excited nuclei to return to its original spin state, a process known as relaxation must occur

- relaxation occurs faster when there are other nearby magnetically active nuclei such as protons
- when certain protons are irradiated selectively, the protons that relies on the irradiated protons to relax show a slightly more intense peak $\rightarrow$ known as the nuclear Overhauser enhancement (NOE)

- the NOE effect is very sensitive to distance between the protons - about $\propto 1/r^6$



The four blue hydrogens are identical; when irradiated, the hydrogen atom connected to the alkene has a slightly more intense peak due to the NOE effect; this confirms that this must be an E alkene

Heteroatoms in heterocyclic molecules have axial or equatorial lone pairs, which may play an important role in reactions, but they can also affect the structure/conformation of the molecule

- when there is an electronegative substituent next to the oxygen atom in tetrahydropyran, the substituent prefers to be axial - known as the anomeric effect

- this is because the O lone pair can donate electron density to the σ^* of the C-X bond, weakening it

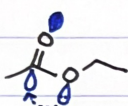
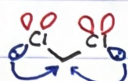


spiroketals have stereochemistry that is highly influenced by the anomeric effect

- three conformations exist for the chiral spiroketal; the conformation in which both C-O bonds are axial is the most stable as a lone pair can donate to the σ^* C-O orbital



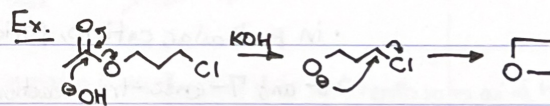
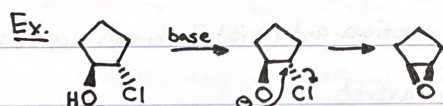
In general (not just heterocycles), if a lone pair is anti-periplanar to a low-energy antibonding orbital, the conformation will be extra stable by a stereoelectronic interaction.



- dichloromethane always has a lone pair from Cl anti-periplanar to the other C-Cl bond
 - benefits from a "permanent anomeric effect", making it a great solvent
- acetals prefer to adopt the gauche conformation (methyl groups 60°) as that allows stabilization by stereoelectronic effects;
- esters also prefer a cis conformation as it allows the oxygen lone pair to donate to the C=O σ^*
 - because cyclic esters (lactones) are forced into a trans conformation, this makes lactones much more reactive than normal esters

Synthesis of heterocycles

ring-closing reactions are essentially the opposite of ring-opening reactions; some examples are shown below:

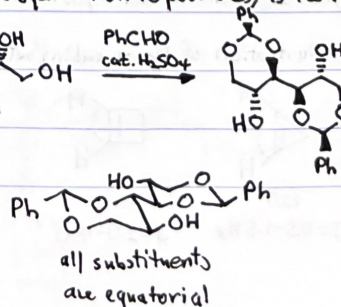
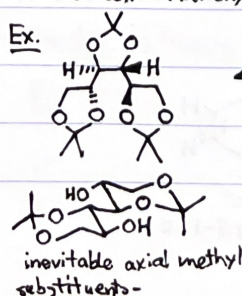


To determine the relative rate of the formation of rings, we must look at activation energy: $\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$

- ring sizes 5-7 suffer from little to no ring strain; $\Delta H^\ddagger$ is small
 - ring sizes 3-4 have very few conformations it can have, so $\Delta S^\ddagger$ is small
- $\Rightarrow$ the relative reaction rates are therefore: $5 > 6 > 3 > 7 > 4 > 8-10$.

Of course, just because a ring forms fast does not mean it is the most stable; thermodynamics is a thing

- whichever conformation, if given a choice (and equilibration is possible), is the most stable will be predominant



The Thorpe-Ingold effect states that more substituents on the product ring increases the rate of ring formation

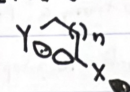
- for small rings, additional substituents causes steric repulsion, decreasing the bond angle and therefore becomes much closer to the ring angle
- for larger rings, additional substituents decrease the possible conformations of the starting material; $\Delta S^\ddagger \uparrow$.

We can classify cyclization reactions by (i) ring size being formed (ii) endo/exo (iii) the hybridization

• using Baldwin's rules, we can determine whether a reaction is favoured or disfavoured

i) all exo-tet or exo-trig cyclizations are favoured

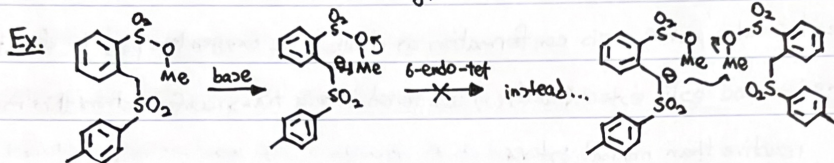
[n+3]-exo-tet



[n+3]-exo-trig



ii) all endo-tet reactions (does not make a ring) are disfavoured



iii) 3-, 4-, and 5-endo-trig are disfavoured as the nucleophile has a hard time interacting w/ π^* orbital

• note that Baldwin's rules are kinetic arguments; if there is no other stable product, it may do disfavoured reactions

• in particular, cations, pericyclic reactions, and Period 3 elements may be exceptions

• 6- and 7-endo-trig reactions are favored.

iv) all endo-dig cyclizations are favored as one $\pi^*C=O$ bond must lie in the plane of the ring

v) 3 & 4-exo-dig are disfavoured; 5 to 7-exo-dig are favored.

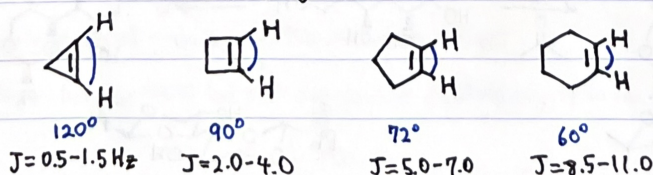
• to determine w/ Baldwin's rules, see its transition state

By principle of macroscopic reversibility, Baldwin's rules also apply to ring-opening reactions

Going back to NMR, in addition to the dihedral angle, the angle between how two C-H bonds are spread out also affects the coupling constant

• a larger angle (the further apart the two hydrogens are) results in a smaller coupling constant

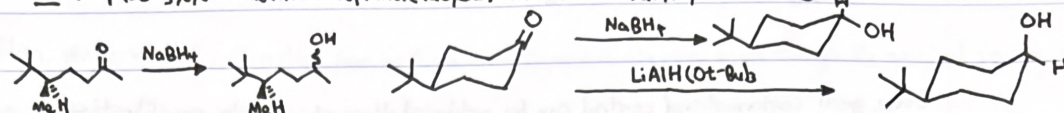
Ex. illustration of the 'spreading out' effect



with acyclic compounds, there are a bunch of conformations the molecule can take $\rightarrow$ reactions tend to be not stereoselective

- with cyclic compounds there are a very limited number of possible conformations; substituents on the ring heavily influence the stereoselectivity of the reactions (making them potentially diastereoselective)

Ex. compare 5,6,6-trimethyl-2-heptanone (acyclic) with 4-tert-butylcyclohexanone (cyclic)

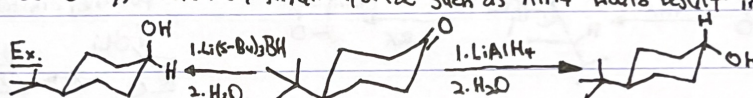


substituents prefer an equatorial position for cyclohexanes; this becomes more true as the substituents get bigger

- this essentially "locks" (favors) a single conformation, making reactions much more stereoselective

When only one out of the six carbon atoms in cyclohexane is sp^2 hybridized, it does not affect the chair conformation

- when discussing axial vs. equatorial attack for cyclohexanones, it depends on the relative size of Nuc vs. OH group
 - for example, by having the conformation locked by a t-Bu group, a bulky hydride such as L-selectride would yield an equatorial attack
 - conversely, a relatively small hydride such as AlH_4^- would result in axial attack

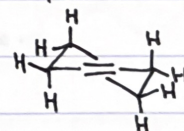
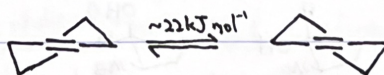


- the reasoning is that (although not the only proposition) the transition state that results in an axial hydrogen is much more unfavourable for smaller reagents ($\ddagger$ is high)

- sometimes stereoselectivity can be poor, and in those situations, equilibration can be sometimes favourable

We now introduce the scenario where there are more than two sp^2 atoms in the ring - for example, cyclohexene

- cyclohexene adopts a flattened chair conformation, which can flip rapidly



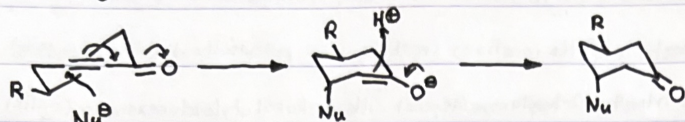
- this half-chair conformation is much more unstable than the chair conformation, so most reactions' stereoselectivity is dependent on turning this half-chair conformation into a chair rather than a twist-boat



axial attack is necessary to approach & interact with the π orbital

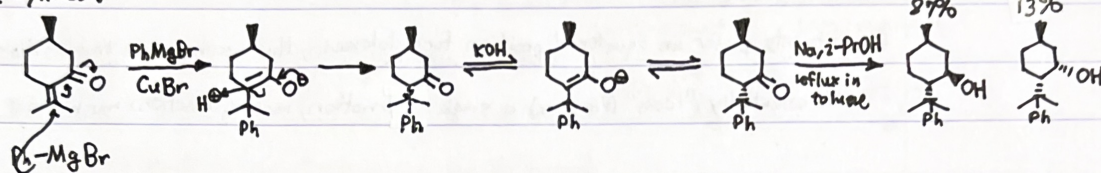
cyclohexenones are even flatter, but drawn similarly for convenience.

Ex. conjugate addition w/ cyclohexenone



Some great conformational control can be achieved through enolate equilibration

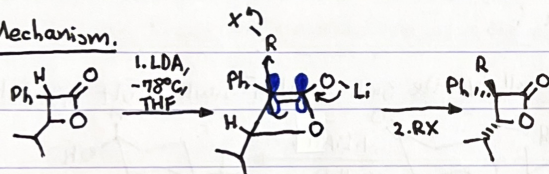
Ex. synthesis



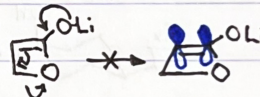
saturated four-membered rings are slightly bent, although four-membered lactones are flat

• with lactones, it will attack from the side that does not have bulky substituents

Mechanism.



Note: E1cB w/ four-membered β -lactones is not possible; orbitals are orthogonal

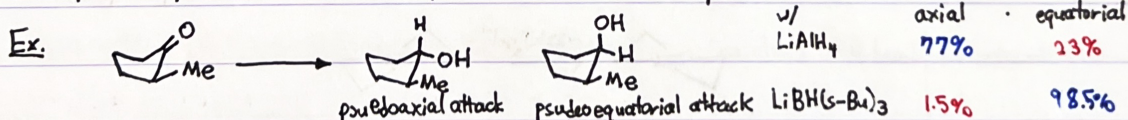


• with cyclobutanones, attack on the less hindered side is always favored



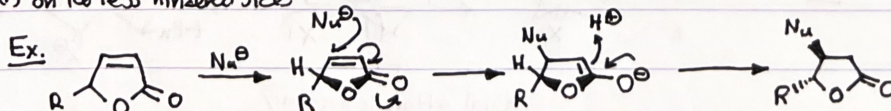
Saturated five-membered rings are flexible, so all five atoms can be higher than the rest at a given instant

• an example of a pseudoaxial vs. pseudoequatorial attack for cyclopentanone is shown below:

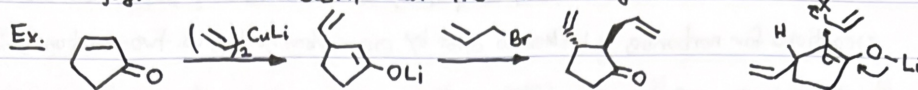


With two or three sp^2 Cs on the ring, five-membered rings become completely flat and nucleophilic attack

occurs on the less hindered side

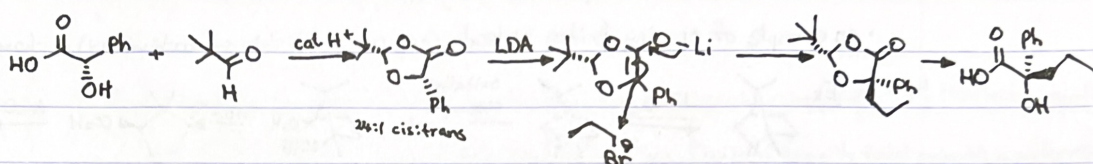


Tandem conjugate addition can easily create two new stereogenic centres:



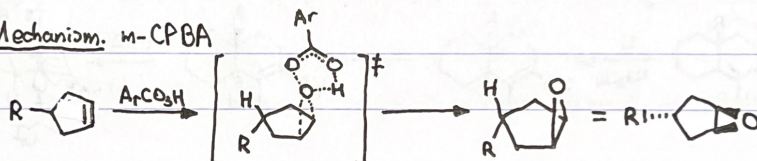
Often, stereochemical information can be transmitted across the ring even though the original source of that information may be lost during the reaction

Ex.

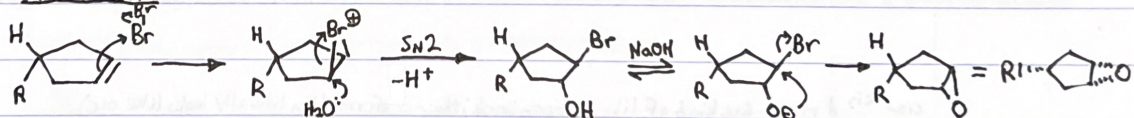


Compare the different methods of epoxidation on a five-membered ring:

Mechanism. m-CPBA

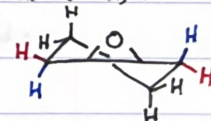


Mechanism. 1. NBS 2. 30% NaOH



To form epoxides in cyclohexenes from a S_N2 reaction, (i) the leaving group & nucleophile must be trans & diaxial

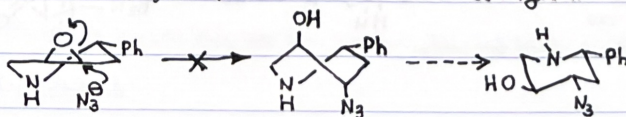
- the resulting cyclohexene oxide results in sort-of a half-chair conformation
- coloured hydrogens are considered pseudo; black hydrogens are not



- the transition state of ring-opening & ring-forming reactions are the same
- ⇒ the initial product (or reactant, if it is a ring-forming reaction) must be diaxial

- note that as we saw with cyclohexenes, the nucleophile (for ring-opening) can only attack on one side, as attack on the other side yields the twist-boat configuration

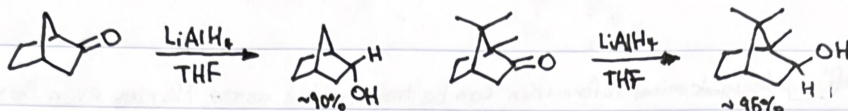
Ex.



We now take a look at bridged bicyclic compounds, which often only stay in their one conformation

- reactions for norbornane, is influenced a lot by one-carbon bridge vs. two-carbon bridge

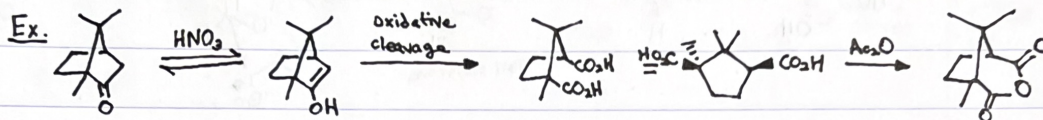
Ex. reduction of norbornanone vs. camphor



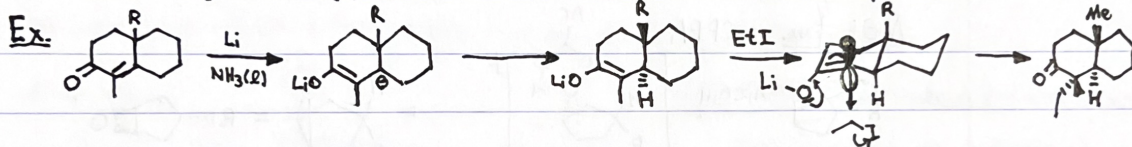
- for the two vastly different structures, the exo approach is favoured if it is less hindered (like the 1st ex.)

for molecules like camphor, the endo approach is favoured

- an example of opening bridge molecules (and preserving their stereochemistry) is shown below:

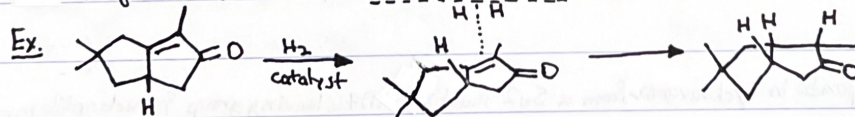


For fused bicyclic rings, 6,6-ring junctions prefer trans, while for smaller systems (5,6)/(5,5), (6,4) it is not

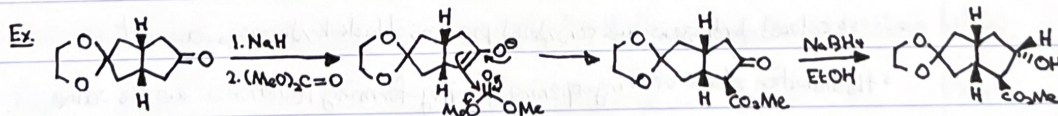


- as always, if there are any substituents on the junction (like R in the example above) axial approach is disfavoured as there is a bad 1,3-diaxial interaction in its transition state, so equatorial approach is favoured

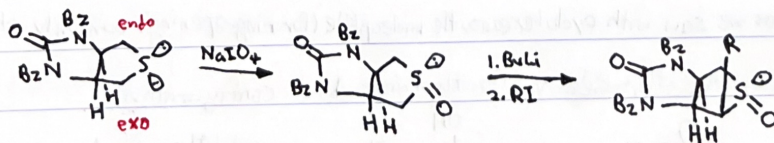
cis-fused rings are kind of like a open book (their conformation literally looks like one).



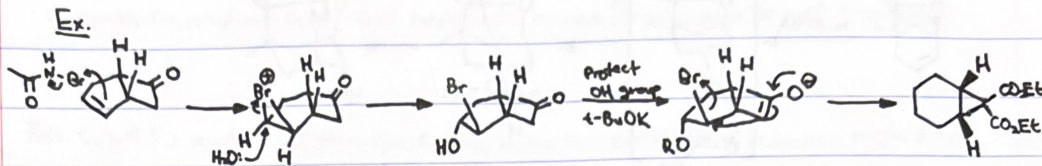
- because the other ring is folded away from the junction, most reactions tend to occur on the junction substituent side



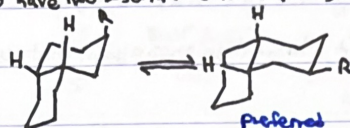
- we saw the synthesis of biotin earlier in Chpt. 27; its diastereoselectivity is illustrated here:



Here is some interesting synthesis of a 3,5-system;

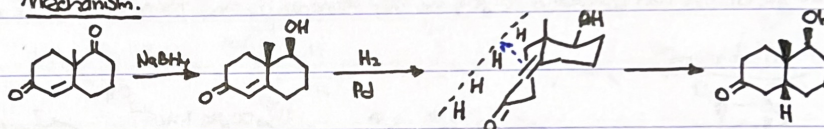


cis-decalins have two resonable conformations it can flip back & forth; both are chair-conformations:



- the Wieland-Miescher ketone (common product from Robinson annelation) can be reduced/protected & then hydrogenated
- when the intermediate product is hydrogenated, the "flatter" side ("inside" of the partly folded molecule) is preferred

Mechanism.

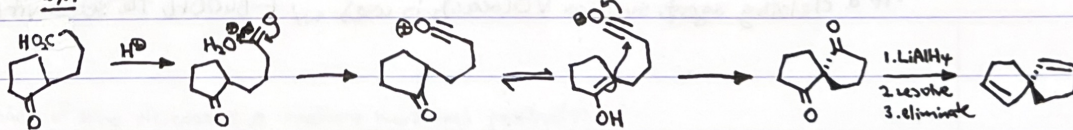


- with base, this can form an enolate and undergo intramolecular alkylation

Many spirocyclic compounds that seem symmetrical on paper can be chiral - we want to look for planes of symmetry

- since the two groups in a spiro centre are orthogonal to each other, stereochemical info is often not retained
- however, some reactions can be surprisingly stereoselective.

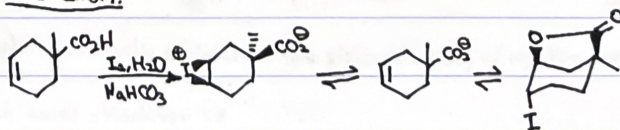
Ex.



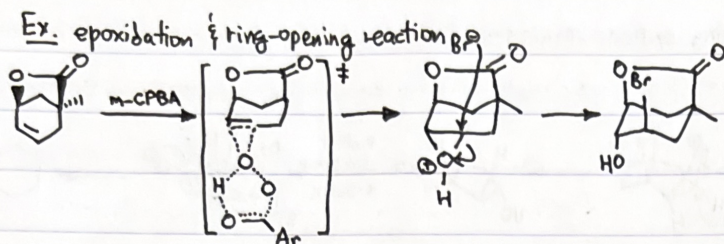
Using cyclic intermediates or transition states can yield great stereocontrol

- iodolactonization can be a useful way to make temporary rings; and is especially interesting for cyclic molecules

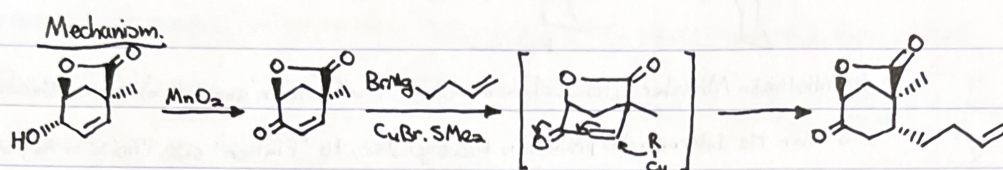
Mechanism.



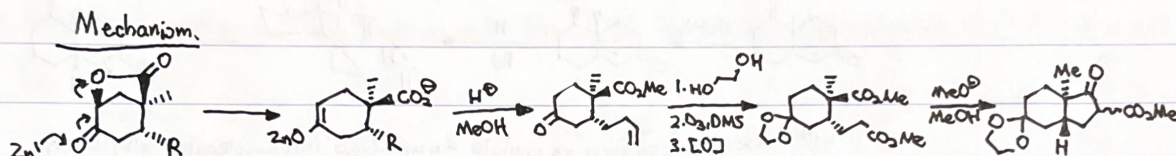
- because the lactone fixes the ring into one conformation, and blocks one side of the ring, the stereochemistry becomes controlled



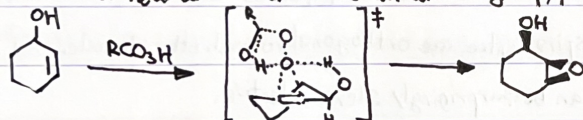
- our goal is to make trans-fused 6,5 rings w/ a quaternary carbon at the junction; to proceed, we first protect the alcohol, and undergo a $E2$ elimination once again (net result: move the double bond)



- as the lactone has completed its job we now remove it, and then cyclize the righthand side;



If there is a tether near an alkene, such as an alcohol group, peroxidation forms a syn peroxide;



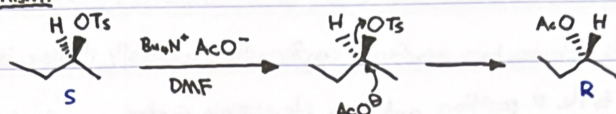
- if a chelating agent, such as $\text{VO}(\text{acac})_3$ is used w/ $t\text{-BuOOH}$, the selectivity increases to great yields

- stereospecific reactions: the stereochemistry of the reactant determines the stereochemistry of the product
- stereoselective reactions: one product predominates because its pathway is the most favourable

Both S_N2 & $E2$ reactions are stereospecific; this makes them excellent tools to make a single diastereoisomer

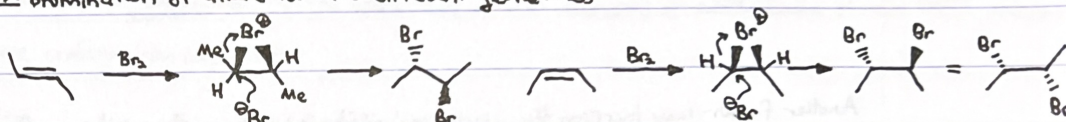
- the S_N2 reaction occurs with an inversion of configuration

Mechanism:



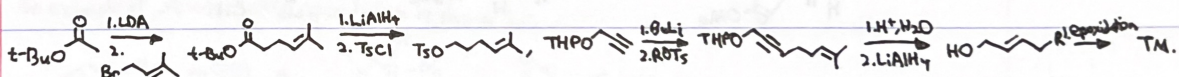
- most electrophilic additions to alkenes are also stereospecific, as they involve a lot of S_N2 reactions
- by preparing a specific geometry of the double bond we can make a specific diastereoisomer

Ex: bromination of alkenes for two different geometries



- epoxidation, iodolactonization are all examples of stereospecific reactions; epoxides, especially, are useful reagents
- this is because epoxides also react (S_N2) stereospecifically; inversion of configuration occurs

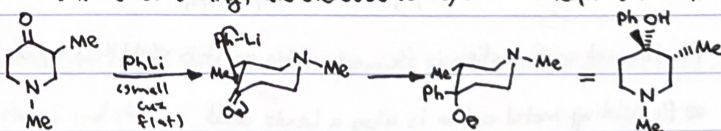
Ex: synthesis of Leukotriene C_4



Review of some stereoselective reactions mentioned previously:

- $E1$ reactions are pretty stereoselective, forming the more stable alkene
- ketone attack on six-membered rings are stereoselective; small nucleophiles attack axially, vice versa.

Ex:



- alkylation of cyclic enolates are also stereoselective, w/ reaction preferring less hindered face (for 4-5 membered-rings) and axial attack for six
- epoxidation of cyclic alkenes are stereoselective as well, as directed epoxidation (or less hindered face) is possible

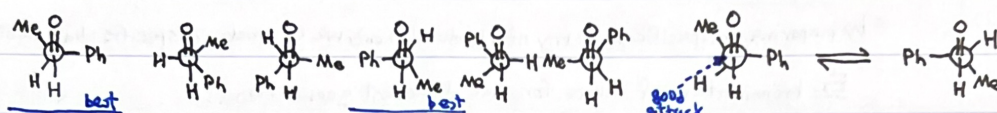
A prochiral carbon centre is one that forms a stereogenic centre after the trigonal planar centre has reacted

- many stereoselective reactions involve a prochiral centre w/ diastereotopic faces distinguishable by steric hindrance or a nearby hydrogen-bonding group (local epoxidation)

- some molecules, may not be diastereoselective even if the molecule has two diastereotopic faces if the stereogenic centre is far away from the prochiral centre

Carbonyl groups, like cyclic molecules, have a preferred conformation, especially if there is a huge difference in size of the substituents bonded to the α position and is a stereogenic centre

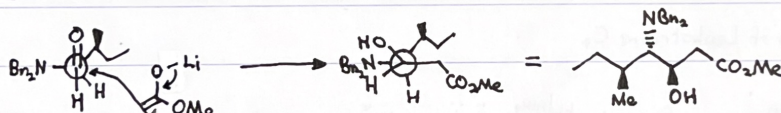
Ex. conformations of a chiral aldehyde, and its stereoselective reaction



Electronegative atoms may increase the diastereoselectivity (or perhaps change it as well)

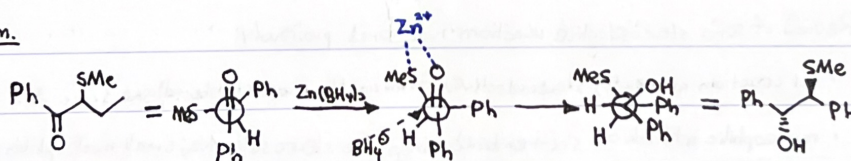
- If the C-X (where X is the electronegative substituent) is perpendicular to the C=O bond, the π^* & σ^* align to form a much more reactive, lower-energy LUMO

Ex.



Chelation may reverse the stereoselectivity of the reaction; chelation causes a different conformation to be favoured

Mechanism.

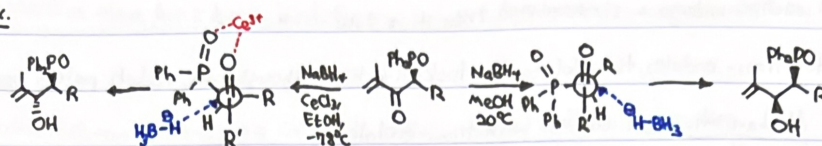


- the favoured conformation is the most stable as it is stabilized by chelation, but also the most reactive as the chelating metal cation is also a Lewis acid

- this leads to a huge increase in reaction rate & diastereoselectivity

An example of utilizing delation is shown below:

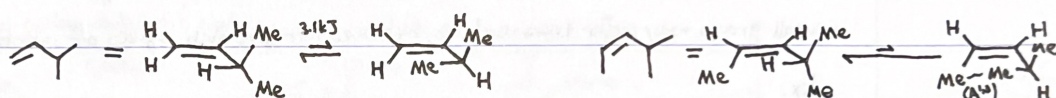
Ex.



Although electrophilic addition reactions such as epoxidation are stereospecific, if the alkene itself is already a stereoisomer (contains a chiral centre) there is an additional stereoselective element in terms of which diastereotopic face it attacks.

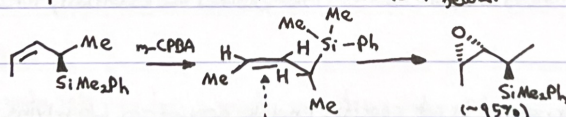
- before we consider anything, we must take a look at the most favourable conformation of each alkene
- for chiral alkenes, the lowest conformation will be the one which H eclipses the double bond
- if the alkene is trans, there may be two conformations in equilibrium; if cis, allylic strain (A^{13}) makes only one conformation important

Ex.



- of course, if the eclipsing group is larger than methyl group, it becomes increasingly unfavourable.

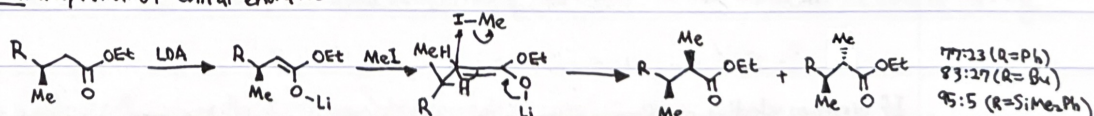
An example of stereoselective epoxidation is shown below:



- without the cis substituent, the diastereoselectivity is much lower as there are two low-energy conformations
- note that an addition of a hydroxyl group (hydrogen-bonding substituent) can still increase diastereoselectivity

Alkylation of chiral enolates can also be stereoselective; there is only one conformation to consider to avoid A^{13}

Ex. alkylation of chiral enolates



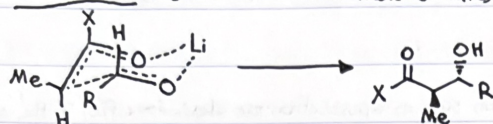
- if the minor diastereoisomer is desired, simple enolate formation + protonation helps

aldol reactions are also potentially stereoselective, although this depends heavily on cis/trans enolates,

- aldol reactions undergo a six-membered transition state

- for trans-enolates, the aldol reaction looks like this (although note, aldehydes prefer pseudo-equatorial for its R group)

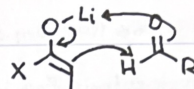
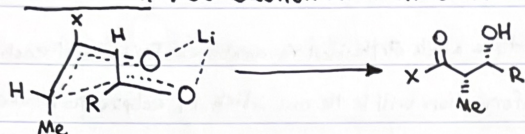
Mechanism: aldol reaction with trans-enolates



Reaction:

- for cis-enolates, on the other hand, look very familiar:

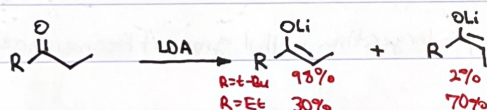
Mechanism: aldol reaction with cis-enolates



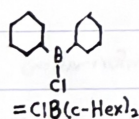
If we rely on the way of making enolates from before, the size of the group that is not enolized plays a huge role

- large groups force cis-enolates $\rightarrow$ may give high diastereoselectivity
- small groups may prefer trans-enolates, but does not give high degrees of selectivity

Ex.



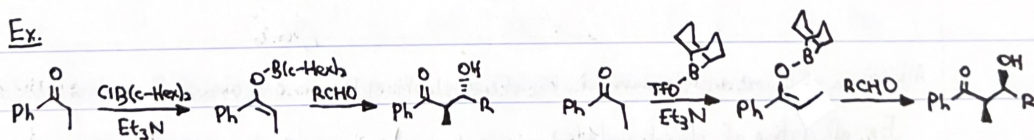
- notably, if the enolizable ketone is a cyclic ketone, trans-enolates are essentially forced and therefore yeah



Boron enolates can be reliable alternatives to get specific enolate geometries w/o relying on the size of group

- the trans-enolate can be made by using really bulky boranes, such as chlorodicyclohexylborane
- the cis-enolate can be made by using 9-BBN or di-n-butylboron triflate (Bu_2BOTf)

Ex.



If diastereoselective reactions are done with a racemic starting material, a racemic product is formed;

- in other words, if the starting material is enantiomerically pure, diastereoselective reactions will lead to one enantiomer of the product

reactions where electrons move around in a circle are known as pericyclic reactions

- a reaction where two π bonds break to form two σ bonds are known as cycloaddition reactions

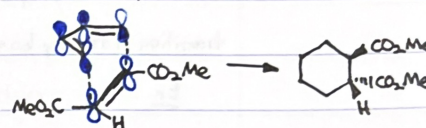
A reaction between a diene and a dienophile is known as the Diels-Alder reaction

- the diene must be in the s-cis configuration
 - cyclic dienes are rapid w/ Diels-Alder because it is locked in s-cis conformation
- the dienophile must have a conjugating group attached to the alkene (Ph, Cl, carbonyls, CN, sulfones, etc)



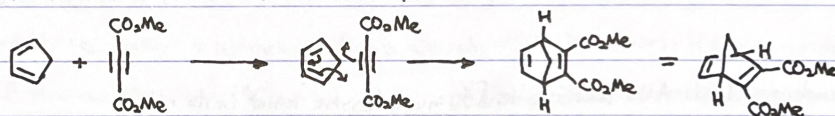
The reaction occurs by the diene coming down on top of the dienophile; stereochemistry of the reactants "transfer" to its products

- for dienophiles, cis-groups will remain cis; trans-groups will remain trans (see Mechanism on the right)



- for dienes, BOTH cis, cis or trans, trans results in cis substituents; cis-trans results in trans substituents

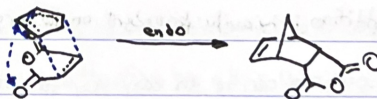
Ex. cyclopentadiene & acetylene dicarboxylate



formation of predominantly endo product results from kinetic control; predominantly exo product from thermodynamic control.

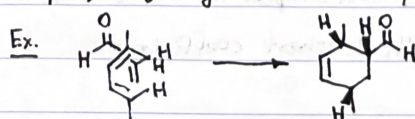
- endo pathway has a much lower transition state as there is a favourable interaction between the $C=O$ bond and the developing π bond on the diene centre

Mechanism:



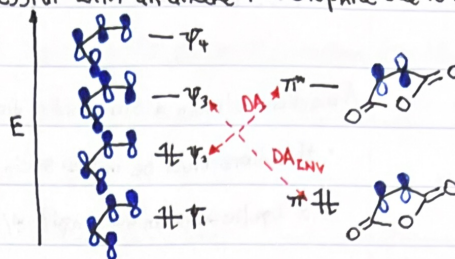
- if the Diels-Alder reaction is reversible, the exo product is formed predominantly as there is less steric hindrance between the axial anhydride & the newly formed alkene at the back of the ring.

For simplicity (of guessing the stereochemistry correctly) just tuck the carbonyl under the diene



Frontier orbitals show that not only do the HOMO-LUMO energies have to match, but also their symmetries

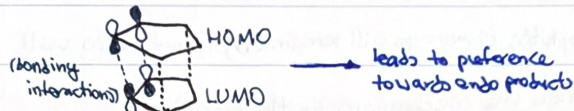
- attempt at cycloaddition by test is found to be unsuccessful with an alkene & dienophile due to orbital mismatch
- adding electron-withdrawing groups lower the LUMO while electron-donating groups raises the HOMO
- the Diels-Alder reaction becomes much more favourable as the energy gap decreases



- if $\text{HOMO}_{\text{dienophile}} - \text{LUMO}_{\text{diene}}$ has a smaller energy gap, inverse electron demand Diels-Alder occurs instead

Frontier orbitals may be used to explain the general preference for endo products; orbital symmetry leads to a lower transition state by bonding interaction

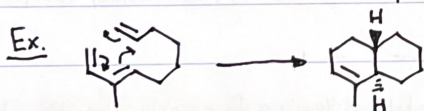
Ex.



Water is a very good solvent for nonpolar Diels-Alder reactions as they force them to be in close proximity.

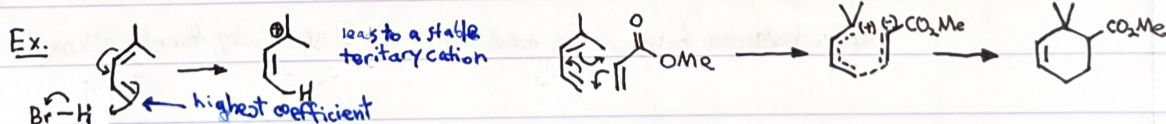
Intramolecular Diels-Alder reactions tend to be much more lenient in its rules;

- a lot of times the dienophile doesn't necessarily need an electron-withdrawing group for intramolecular reactions
- the molecule folds in the most sterically favourable way; may not lead to endo preference



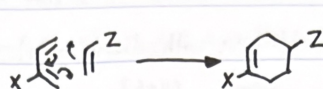
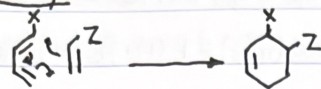
The regioselectivity of cycloaddition is heavily dependent on the largest coefficients of the HOMO/LUMO

- using example ionic reactions can be an easy way to determine the largest coefficient in an asymmetric molecule



- in the transition state, bond formation is almost complete between the carbons with highest coefficients while little bond formation is done with the lowest coefficients

Summary:

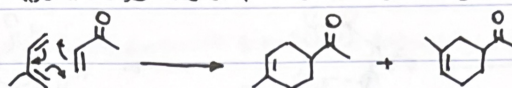


X = EDG (alkyl, aryl, AD, Me₃SiO, R₂N)
Z = EWG or conjugating group
(CHO, COR, CO₂H, CO₂R, CN, NO₂, halogen, alkenyl, aryl)

Lewis acids can increase both the regioselectivity & rate of the reaction;

- if Lewis acid can bind to the electron-withdrawing group of the dienophile, decreases LUMO $\rightarrow$ $\uparrow$ rate
- Lewis acids also increases the difference of coefficients in the LUMO

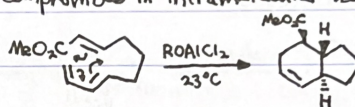
Ex.



71:29 $\rightarrow$ 93:7 if Lewis acid catalyst is added to the mixture

Again, regioselectivity may be compromised in intramolecular reactions

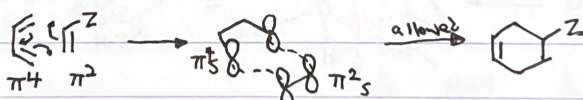
Ex.



In order to see whether a pericyclic reaction is allowed, utilize Woodward-Hoffmann rules:

- If there are $(4q+2)_s$ & $(4r)_a$ components, and if the sum of all components are odd, thermal is allowed.
- 's' stands for suprafacial (same face) & 'a' stands for antarafacial (opposite face)

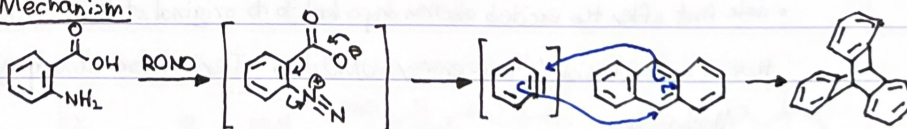
Ex. using Woodward-Hoffmann rules for cycloaddition



Reactive intermediates can be trapped by cycloaddition; two examples are provided below:

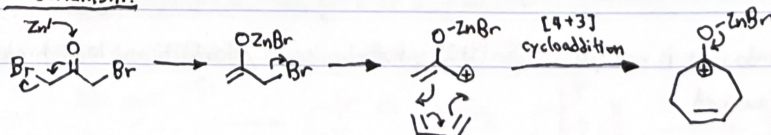
- benzyne is a very reactive (and therefore has a low LUMO) electrophile that can undergo Diels-Alder

Mechanism:



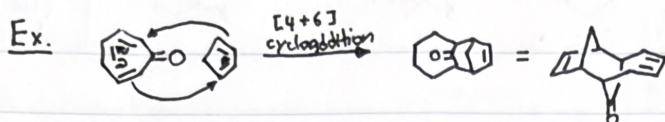
- oxyallyl cation intermediates can undergo [4+3] cycloaddition and are made from α,α' -dibromo ketones

Mechanism:



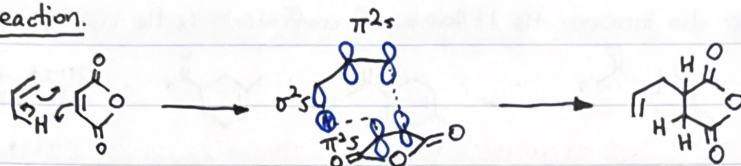
There are other cycloadditions besides $[4+2]$ (Diels-Alder) that comply with Woodward-Hoffmann rules

- $[4+6]$ cycloadditions with diene ($\pi 4_s$) + triene ($\pi 6_s$) = 1 ($4q+2$)_s component (the triene)

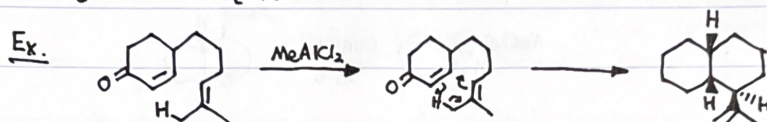


- if a ene (alkene) replaces a diene, an analogous reaction known as Alder-ene reaction may occur

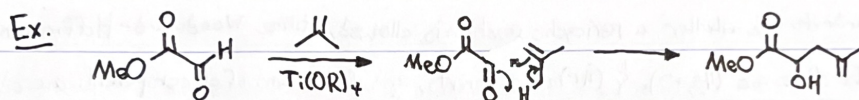
Reaction.



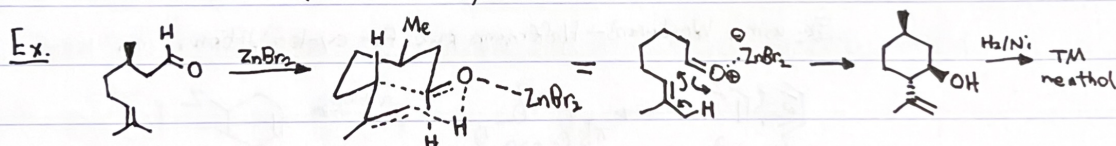
- often times, the Alder-ene reaction does not occur very efficiently; Lewis acid catalysis or intramolecular reactions are often required



- if the enophile is a carbonyl group, the reaction occurs well and is referred to as a carbonyl-ene reaction



- Lewis acids can further catalyze the reaction;

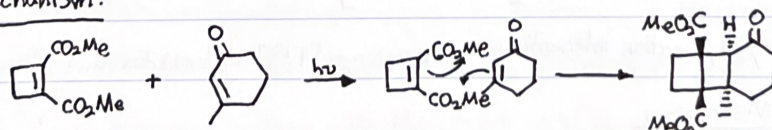


We now introduce $[2+2]$ cycloadditions, which can be done photochemically and thermally under special conditions

- if you excite an electron of an alkene to be HOMO $\rightarrow$ (old) LUMO, the new HOMO can react with the LUMO and undergo cycloaddition

- note that after the excited electron drops back to its original state, it cannot absorb electrons; there is no mechanism (a low-energy LUMO does not exist) for absorbing photons

Mechanism.

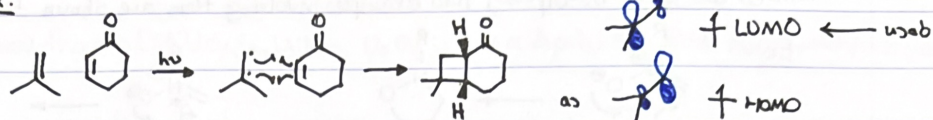


- endo rule is not present for $[2+2]$ photochemical cycloadditions; least hindered transition state is favoured

The opposite regioselectivity expected from thermal [2+2] cycloadditions is observed

- as the (old) HOMO & LUMO have opposite coefficient distributions, the new HOMO has a larger coefficient on the other carbon

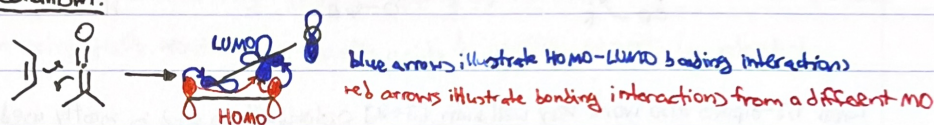
Ex.



Thermal [2+2] cycloadditions are possible given that the electrophile (w/ lower energy LUMO) has two p orbitals

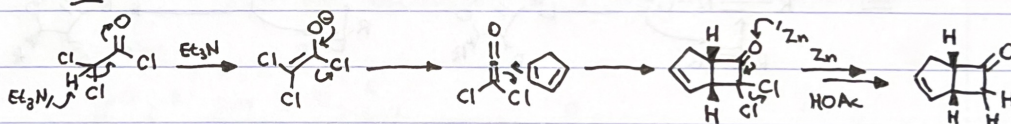
- having the two orbitals to be orthogonal to each other leads to two antibonding interactions, but four bonding interactions if there is an extra p orbital (for ketenes or isocyanates)

Mechanism.



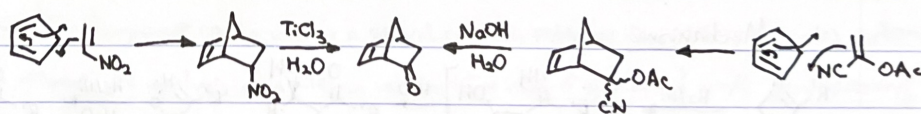
- for ketene [2+2] cycloadditions, dichloroacetyl chloride is commonly used to create ketenes

Ex.



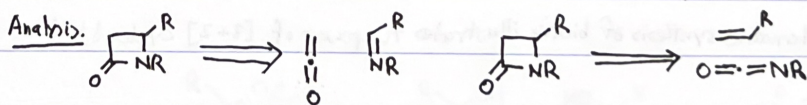
- note: for [4+2] cycloadditions, a masked ketene can be used to achieve similar results

Ex.

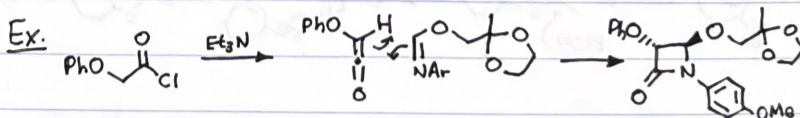


- β -lactams can be made in two ways; a ketene + imine or an isocyanate + alkene.

Analysis.

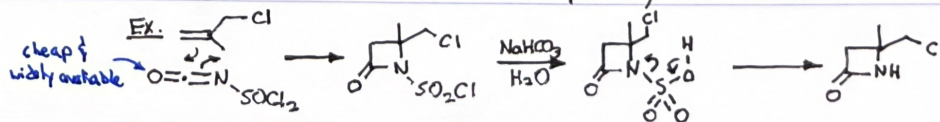


- for the imine pathway, N-aryl imines can help the stability of the imine



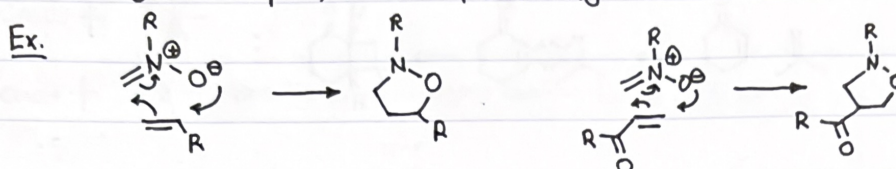
- for the isocyanate pathway, an EWG must be on nitrogen to make the isocyanate very electrophilic

to accommodate for the alkene's moderate nucleophilicity

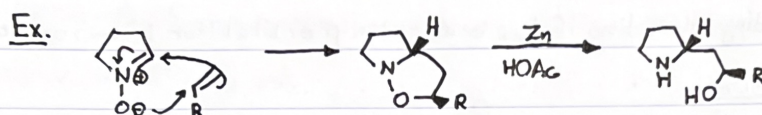


[3+2] cycloadditions can occur with 1,3-dipoles & a dipolarophile

- 1,3-dipoles are three-atom, four-electron species that can act as both a nucleophile & electrophile
- because of this, the dipolarophile can be both an electron-deficient or electron-rich alkene
- nitrones are great 1,3-dipoles; two examples involving them are shown below:

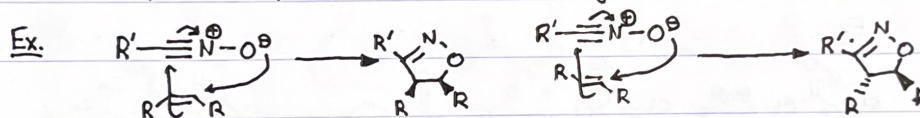


- in terms of its stereochemistry, the approach with the least steric hindrance is favoured
- because N-O bonds are weak, they can be selectively cleaved to give a 1,3-relationship b/w NH & OH



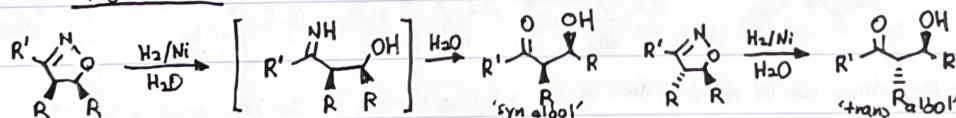
Linear 1,3-dipoles also work very well with [3+2] cycloadditions and is mostly used to form isoxazole

- stereochemistry of the dipolarophile is retained during the cycloaddition

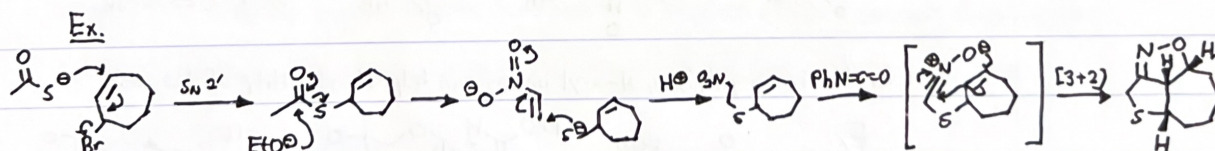


- if the dienophile is an alkyne, the product results in a molecule known isoxazole (Chpt. 30)
- reduction of the products from the example above leads to retention of stereochemistry

Mechanism.

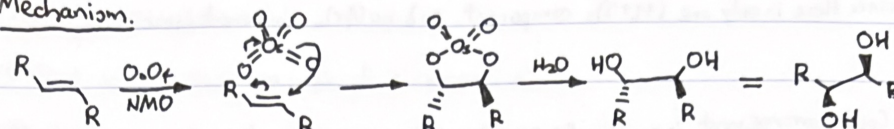


- an alternative synthesis of biotin illustrates the power of [3+2] cycloadditions:



syn dihydroxylation of alkenes w/ OsO_4 also occur through [3+2] cycloaddition:

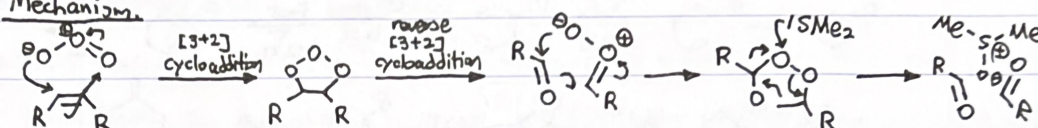
Mechanism.



- because this is a [3+2] cycloaddition, OsO_4 is also a dipole; can attack electron-rich/deficient alkenes

Ozonolysis involves multiple [3+2] cycloadditions and reverse [3+2] cycloadditions;

Mechanism.

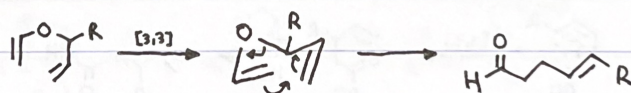


- using different oxidizing agents & reducing agents result in different compounds
- using H_2O_2 results in carboxylic acids & NaBH_4 results in alcohols

sigmatropic rearrangement is another class of pericyclic reactions that involve no net change of σ bonds

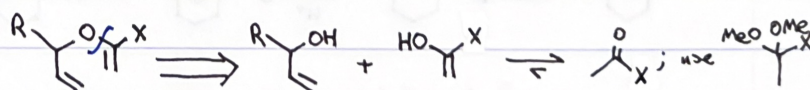
- the Claisen rearrangement is the first recorded [3,3]-sigmatropic rearrangement with a chair conformation

Mechanism.

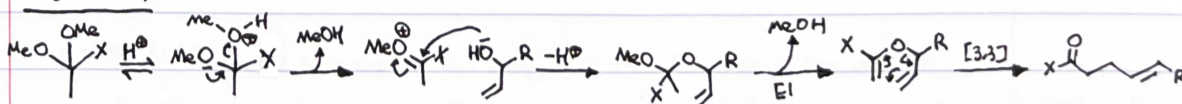


- geometry of resulting alkene is most often trans because the resulting substituent prefers to be equatorial
- the Claisen rearrangement can be used as a general synthesis pathway for γ,δ -unsaturated carbonyls
- by retrosynthetic analysis of a Claisen reactant (an ether of one allylic & vinylic group necessary), the vinyl alcohol can be substituted for its carbonyl acetal equivalent.

Analysis.

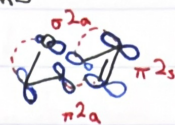


Mechanism.



Woodward-Hoffmann rules can illustrate the nature of [3,3]-sigmatropic rearrangements

- since there is only one $(4q+2)s$ component, and no $(4r)a$ component, reaction is allowed

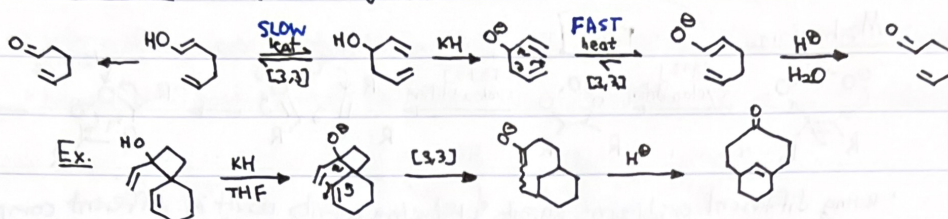


The Cope rearrangement is another [3,3]-sigmatropic rearrangement involving all carbon atoms

- the oxy-Cope rearrangement occurs by forming a stable $C=O$ bond

- this reaction can be accelerated by adding a strong base (KH), forming the much more (relatively) stable enolate

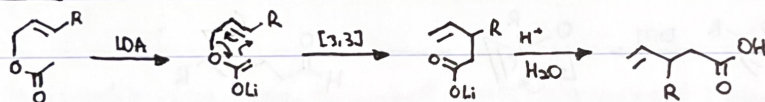
Mechanism. oxy-Cope rearrangement



- if the starting materials are very unstable, this can be a huge driving factor in the Cope rearrangement

The Ireland-Claisen rearrangement, which has an oxygen atom both inside & outside the ring, results in a γ,δ -unsaturated carboxylic acid

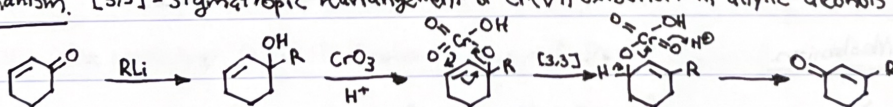
Reaction.



- yield may improve if lithium enolate is converted to silyl enol ether; E selectivity is preferred

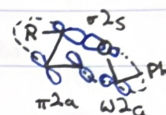
[3,3]-sigmatropic reactions are present outside of oxygen atoms; the Fischer indole synthesis & Cr(VI) oxidation of allylic alcohols

Mechanism. [3,3]-sigmatropic rearrangement of Cr(VI) oxidation in allylic alcohols

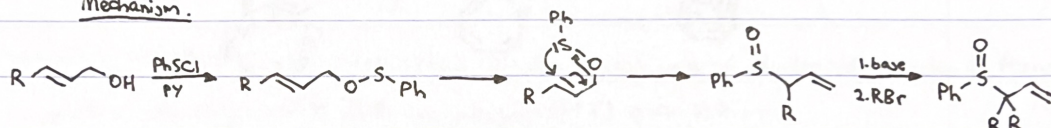


- we first begin with the example of a carbanion;

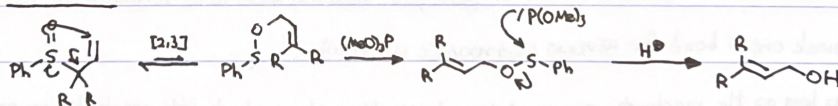
CC(=C)C(R)OPh + BuLi >> [c-]1C=CC(R)OPh1 + BuH >> [2,3] >> CC(=C)C(R)OPh + BuH >> CC(=C)C(R)O + PhH



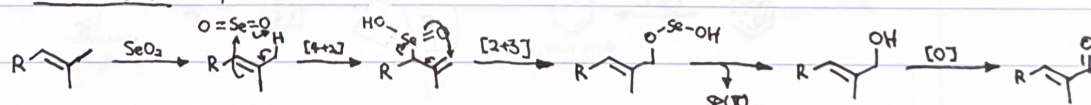
- Mechanism.



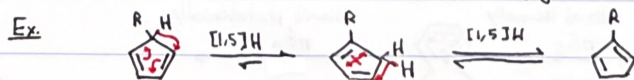
- Mechanism.



- Mechanism. Riley oxidation (allylic)



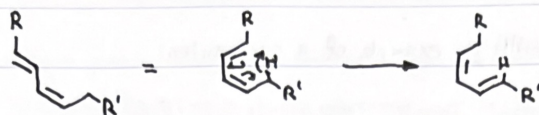
- [1,5]-sigmatropic hydrogen shifts causes more stable conjugated diene to form



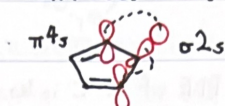
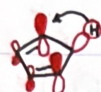
- often, [1,5]H shifts occur rapidly and may ruin attractive Diels-Alder reactions
- by adding conjugating groups to the diene, you can ensure Diels-Alder occurs before a [1,5]H shift

- [1,5]H shifts are also the main reason E, Z dienes are hard to form i.e. because they tend to undergo [1,5]H shifts

Mechanism.



- both the frontier orbital approach & Woodward-Hoffmann rules work; [1,5]H shift occurs suprafacially



- by symmetry & Woodward-Hoffmann rules, [1,3]H & [1,7]H shifts are allowed if it occurs antarafacial

- [1,3]H shifts are essentially impossible as the H atom cannot reach; [1,7]H shifts are possible

Reaction.



- with photochemical reactions, all suprafacial reactions occur antarafacially and vice versa.

Electrocyclic reactions are the last class of pericyclic reactions; leads to the formation of one single σ bond (or break one σ bond for reverse electrocyclic reactions)

- as long as the reactants are much less stable than the products (the reactant has some kind of reason to become products) electrocyclic reactions occur

Ex.



500°C



form new σ bond, stronger

Ex.



200°C



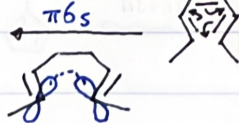
removes ring strain

Woodward-Hoffmann rules are extremely valuable for electrocyclic reactions.

- $(4n+2)\pi$ electron systems are disrotatory for thermal reactions and conrotatory for photochemical reactions
- $4n\pi$ electron systems are conrotatory for thermal reactions and disrotatory for photochemical reactions

Ex.

allowed thermally

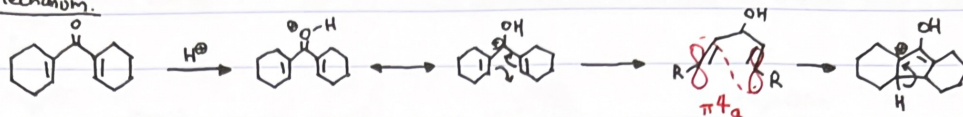


allowed photochemically



Nazarov cyclization is an example of a 4 electron, 5-membered electrocyclic reaction

Mechanism:



- as the reaction is conrotatory, the hydrogen atoms must be trans of each other

small rings, such as cyclopropane or aziridine are likely to be unintentionally opened by electrocyclic reactions

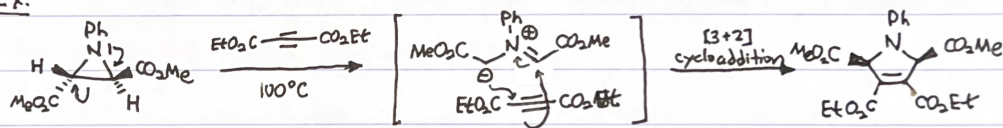
- any reaction that attempts to form the cyclopropyl cation will spontaneously undergo reverse electrocyclic reaction

Mechanism:



- aziridines with electron-withdrawing groups are unstable and undergo electrocyclic reaction to form azomethine ylides, a dipolarophile which can undergo [3+2] cycloaddition

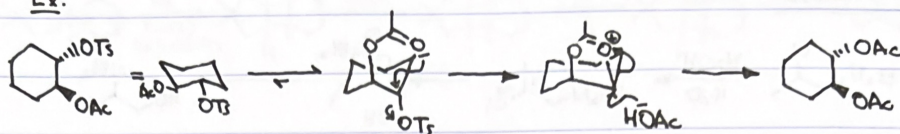
Ex.



When neighbouring group participation occurs, in most cases it occurs by a cyclic intermediate

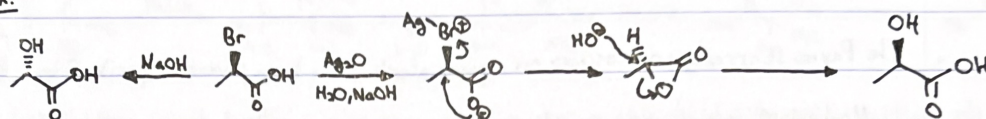
- stereochemistry can be crucial (especially in cyclic compounds) as it can determine whether NGP is possible

Ex.



- with the syn diastereomer, NGP is not possible as the acetoxy group cannot reach the orbital of the OTs group
- retention of stereochemistry only occurs because S_N2 occurs twice $\rightarrow$ most likely NGP

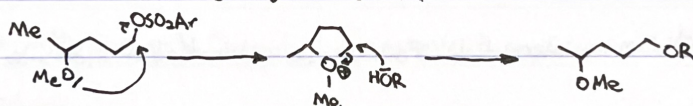
Ex.



Neighbouring groups only participate if it speeds up the reaction; often, electron-rich hetero atoms are best participants

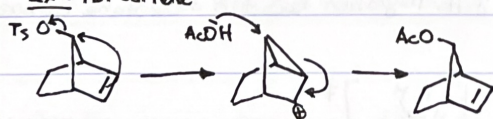
- sulfides tend to be much more better at increasing the rate compared to ethers
- three- and five-membered rings are the most common; six-membered rings are pretty uncommon

Ex. five-membered ring neighbour group participation

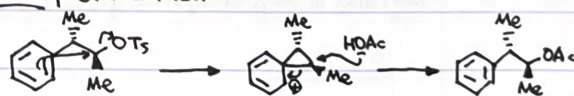


π electrons can also participate; two primary examples are with phenyl group & norbornene

Ex1. norbornene

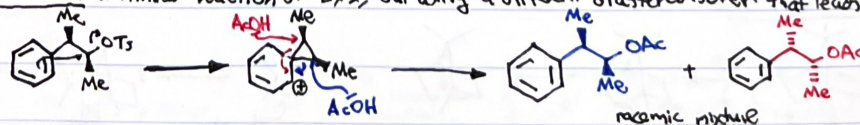


Ex2. phenonium ion



Although S_N2 reactions are stereospecific (relative stereochemistry is retained from reactants $\rightarrow$ products), if neighbouring group participation does occur, it may lead to loss of absolute stereochemistry

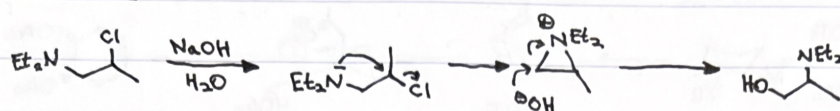
Mechanism: a similar reaction of Ex2, but using a different diastereoisomer that leads to a racemic mixture



intramolecular reactions that form 3/5/6-membered rings are usually faster than intermolecular reactions

• this means that neighbouring group participation can cause rearrangement to sometimes occur

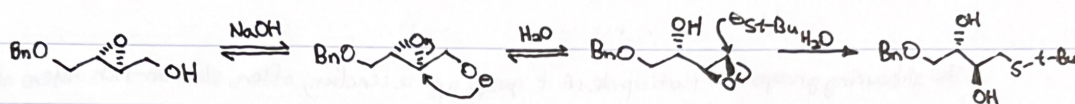
Mechanism.



• "NEt₂" is a good nucleophile, and because Cl⁻ is a moderate LG on a secondary centre, the internal nucleophile reacts first to form the aziridinium ion. 2° = both S_N1 & S_N2 are meh

The Payne rearrangement occurs on epoxy alcohols in base; moves epoxide from secondary to primary

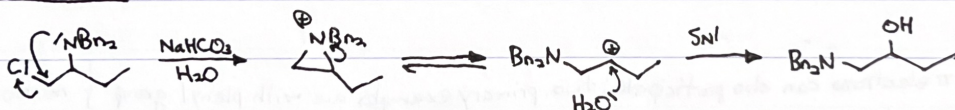
Mechanism. secondary migration origin, primary migration terminus



because epoxide attack is slow on secondary (which reactant epoxide has), and with a bulky nucleophile, the Payne rearrangement occurs first to give a primary epoxide

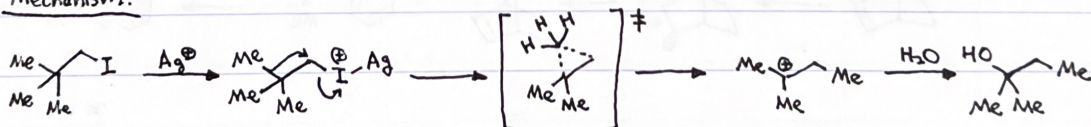
Going back to the aziridinium ion intermediate, if water was used instead of hydroxide, a different product results;

Mechanism.



Migration of alkyl or hydride group will occur if its migration leads to a more stable carbocation

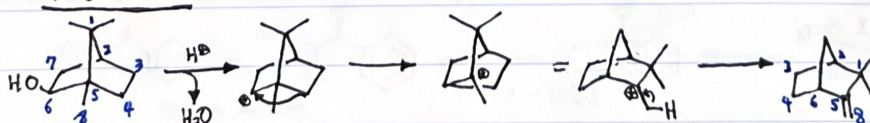
Mechanism.



• especially with rearrangements, numbering the carbons can be very helpful in finding the mechanism

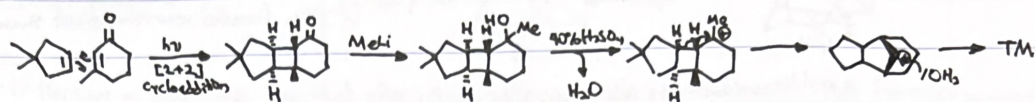
• the Wagner-Meerwein rearrangement involves a simple alkyl migration that looks awfully complex

Mechanism.



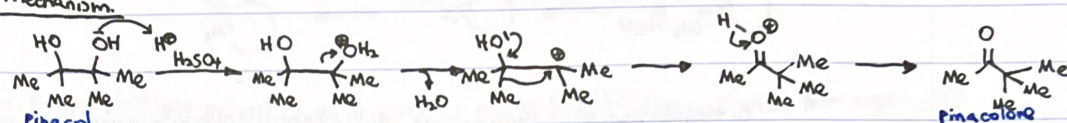
If there is a small ring nearby a cation, ring expansion may occur to relieve ring strain

Ex.



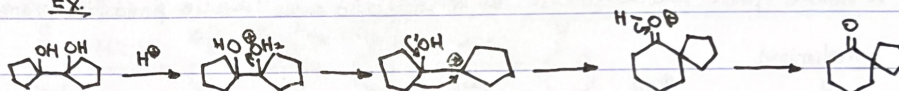
The pinacol rearrangement involves 1,2-diols, forming a carbonyl by alkyl migration

Mechanism.



- mechanism driven by the lone pair on oxygen being able to stabilize the positive charge
- spirocycles can be easily made by the pinacol rearrangement

Ex.



Epoxides with Lewis acids (in particular magnesium) rearrange in a pinacol fashion

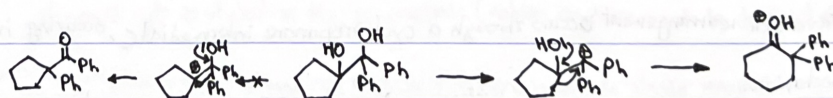
Mechanism.



- if a Grignard reagent is used instead of MgBr_2 , rearrangement occurs first, then adds to the carbonyl.

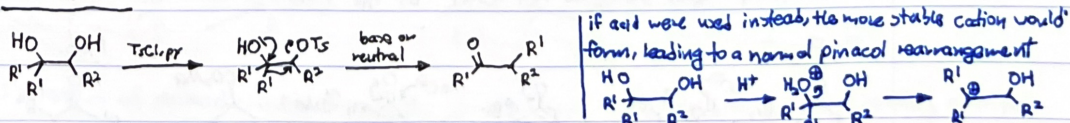
When the migrating group has a choice, the more stable carbocation is formed

Ex.

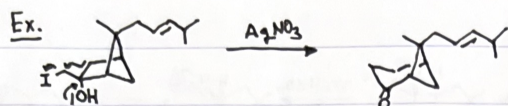


- if there is only one way for the pinacol rearrangement to occur, but the leaving group (formation of cation) is not favourable, the hydroxy group can be converted to a better leaving group and is known as semipinacol rearr.

Mechanism.



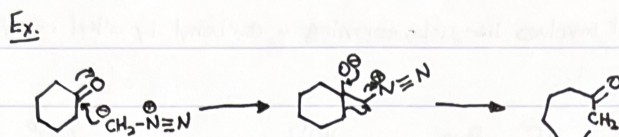
- the leaving group can be a halide or nitrogen gas (N_2) from the diazonium ion



the silver ion improves iodine's leaving ability while unaffected the nucleophilicity of the hydroxyl group; this favours rearrangement than epoxide formation.

- aryldiazonium salts are stable, but alkyl diazonium salts are not

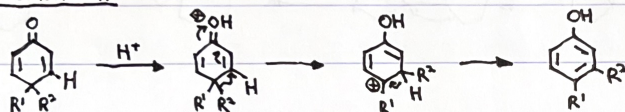
- instead, the conjugate base of alkyl diazonium, known as diazoalkanes can be used for semipinacol rearrangement



- of course diazotation of 1-amine methyl-cycloalkanol results in a semipinacol rearrangement; this particular reaction is known as the Tiffeneau-DeMjanov rearrangement (TDR)

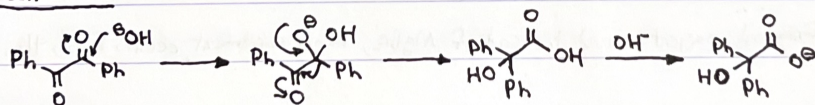
The dienone-phenol rearrangement can be considered as a "reverse pinacol rearrangement"

Mechanism.



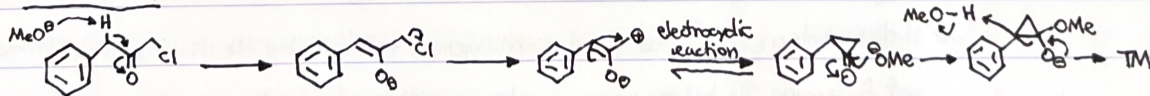
The benzilic acid rearrangement resembles the semi-pinacol rearrangement; although carbonyl formation (at migration origin) and carbonyl destruction (at migration terminus) occurs at the same time

Mechanism.

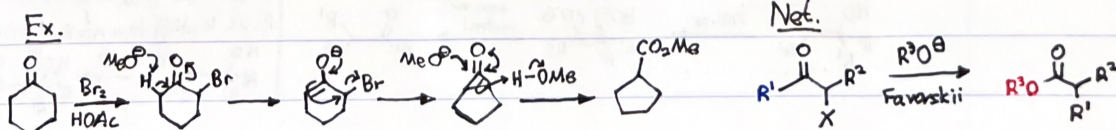


The Favorskii rearrangement occurs through a cyclopropanone intermediate, occurring in α -halo ketones

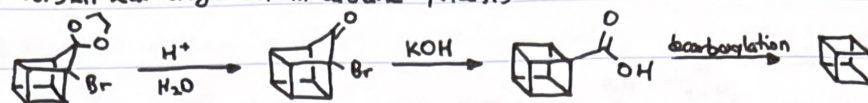
Mechanism.



- the example below shows the "net result" of the Favorskii rearrangement:

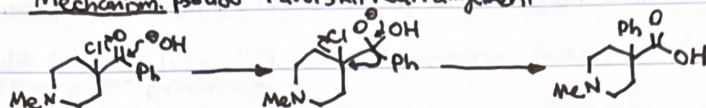


Ex. Favorskii rearrangement in cubane synthesis



• if there are no acidic hydrogens, that allow endolization, an alternative benzylic-type Favorskii rearrangement occurs

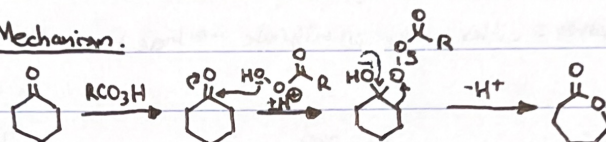
Mechanism: pseudo-Favorskii rearrangement



The Baeyer-Villiger oxidation is an oxygen analogy to TDR (semi-pinacol rearrangement)

- similar to diazoalkene, which has a nucleophilic component + carrying a good leaving group
- peroxy acid is used as this equivalent for ketones

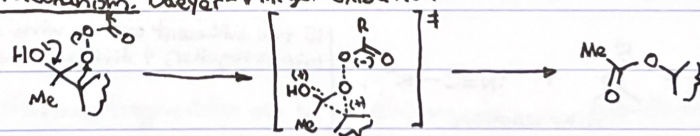
Mechanism:



The migrating group which can stabilize the transition state is the best group, although there are "exceptions"

- transition state stabilization is the main factor, σ -conjugation or π -participation can all make that group much more favourable to migrate

Mechanism: Baeyer-Villiger oxidation

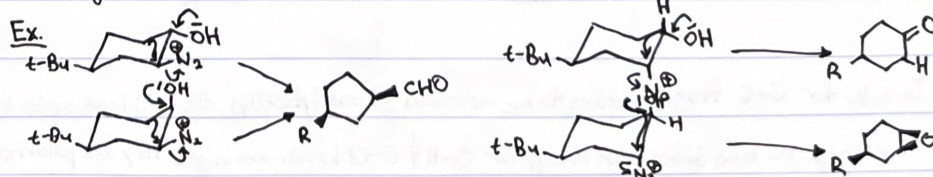


$t\text{-Bu} > \text{sec-alkyl} \approx \text{Ph} > \text{Et} > \text{Me} > \text{H}$
in order of migration

- note: if an electron-withdrawing group is a choice, it may migrate (if it is a strong EWG) so that it would not destabilize the intermediate (cation carbon next to destabilising group = BAD!)

• stereochemistry can also play a huge role (especially if there is only a single reasonable conformation) in migration,

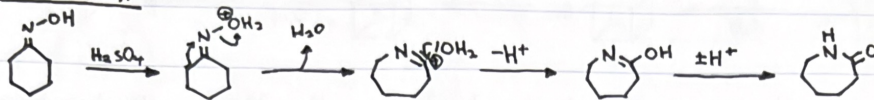
in that the group that is anti-periplanar to the C-X σ^* of the LG



- note: retention of stereochemistry occurs with 1,2-migrations; the sp^3 orbital of the migrating atom just shifts one position

The Beckmann rearrangement utilizes an oxime to rearrange into an amide, using $-OH$ in oxime as a leaving group

Mechanism.



Note of warning:

The Beckmann rearr.

runs rather vigorously

conditions ($>160^\circ\text{C}$)

H_2SO_4

- note that for acyclic Beckmann rearrangements, the product cation is more often represented as a nitrilium ion
- acid is not necessary like the pinacol rearrangement; SOCl_2 , PCl_5 , acyl/sulfonyl chlorides are all OK
↳ for converting $-OH$ group to be a suitable LG
- to determine which group migrates in the Beckmann rearrangement, you need to consider two cases:

i) $\text{C}=\text{N}$ bonds can exert cis/trans isomerism; bulky group anti to $-OH$ in oxime is favourable

• by allowing equilibration (using a $\text{S}_\text{N}2$ nucleophile such as TsOH), you can cause the oximes to interconvert

ii) because the σ^* of the bond of the leaving group must be anti-periplanar to the migrating carbon, the migration is stereospecific with respect to the geometry of the oxime

• equilibration of oximes = either group can migrate $\rightarrow$ more favourable group migrates

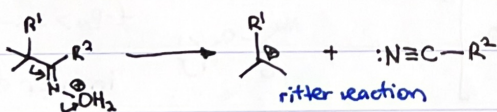
Ex.



If the migrating group for the Beckmann rearrangement is "too good" fragmentation (release of carbocations)

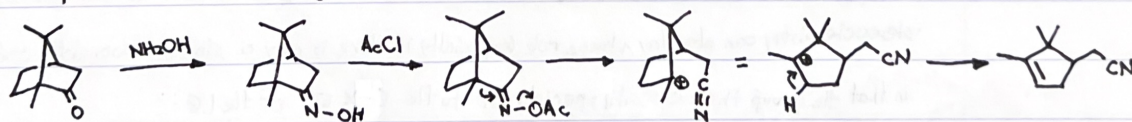
may occur

Ex.



if two different oximes with an α -tertiary centre are mixed together, 4 different coupling products are observed

Ex2. camphor - Beckmann fragmentation



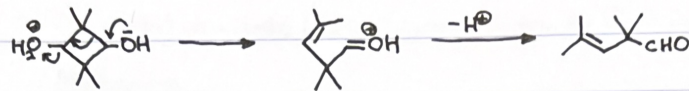
In order for C-C fragmentations to be successful (heterolytically), the C-C bond needs to be heavily polarized

- although the bond dissociation energy for $\text{O}-\text{H}$ & $\text{C}-\text{O}$ bonds are high, they are polarized & hard nucleophiles and bases do the trick. For C-C bonds (or C-H), they are usually not polarized so much harder to break

Fragmentations require electron push & electron pull; it needs a source (electron-rich) & a sink (electron-deficient)

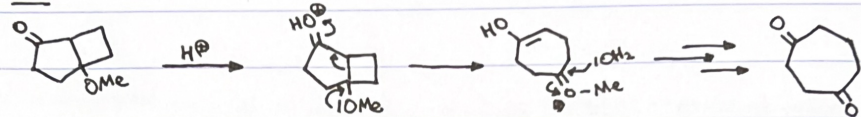
- migrations also require a "push & pull", except for migrations it occurs on the adjacent atom rather than being one atom apart

Ex. fragmentation of a cyclic diol

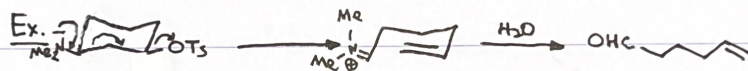


- protonated carbonyls ($C=O^+$) can function as "sinks"

Ex.



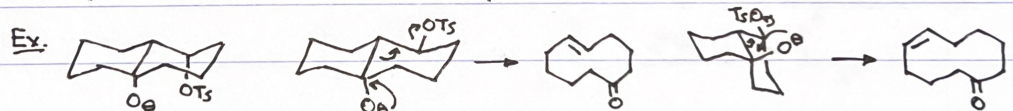
- of course, a leaving group can act as a pull (sink), and elimination reactions may function as a sink (push)
- stereochemistry of the reactants control fragmentations as well; key being anti-periplanarity



other diastereomer undergoes simple E2 rather than a fragmentation reaction

Medium rings can be synthesized through fragmentation of fused rings;

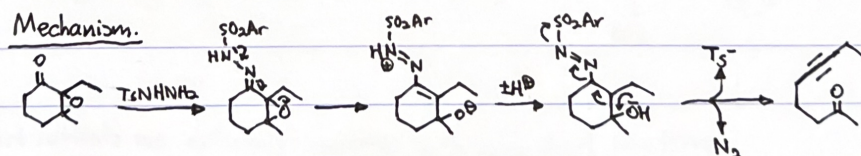
- an example of how the 4 diastereoisomers of a particular decalin can fragment is shown below:



- the bonds that break (in a 1,2,3,4 electron source-sink arrangement) must be anti-periplanar to work!

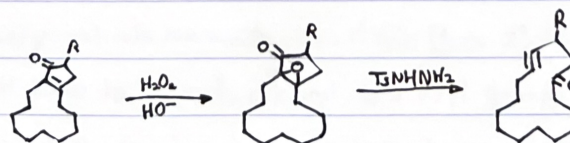
The Eschenmoser fragmentation can be a useful way to make keto-alkynes (or expand rings!)

Mechanism.



- as long as you have a ketone & epoxide in the 1,2,3,4 electron source-sink arrangement, works fine

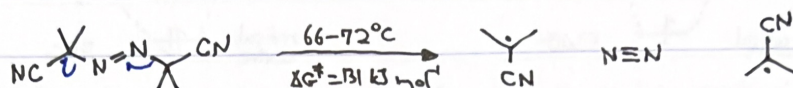
Ex.



Radicals form by homolytic cleavage; this can be induced by heat or light

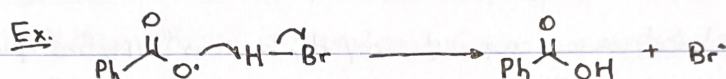
- although temperatures of $>200^{\circ}\text{C}$ will homolyse most bonds, weaker bonds (BDE is small) will have a tendency to homolyse at much lower temperatures than usual
- dibenzoyl peroxide, $(\text{PhCO}_2)_2$, has a tendency to homolyse at $60-80^{\circ}\text{C}$ to form two radicals
- azobisisobutyronitrile (AIBN) is very similar to $(\text{PhCO}_2)_2$ but for different purposes

Mechanism

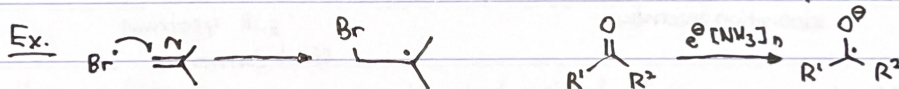


Radical abstraction are substitution reactions in which a radical + spin-paired molecule forms a new radical + spin-paired molecule (kind of like double replacement)

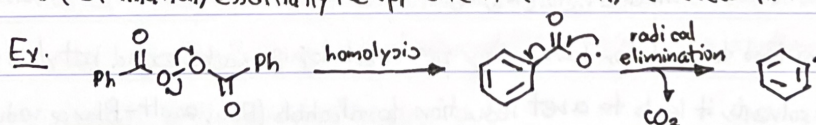
- Hydrogen abstraction can help form radicals even for strong bonds



Radical addition occurs when a radical attacks (adds) to a double or triple bonded species;

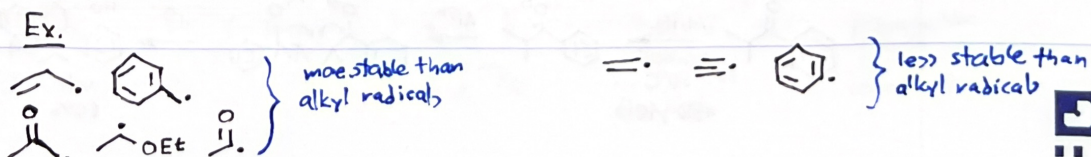


Radical elimination, essentially the opposite of addition, can occur in the radicals formed by $(\text{PhCO}_2)_2$



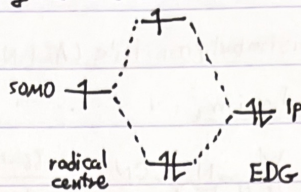
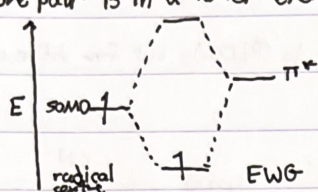
Most radicals are extremely reactive with very short lifetimes

- A higher ΔG (E required to homolyse the bond) illustrates a more unstable radical
- tertiary radicals are much more stable than 2° , 1° or methyl
- C-H bonds to alkynyl, alkenyl, and aryl groups are very strong (less stable radical formed)
- adjacent functional groups or C-H bond connected to a carbonyl form less reactive radicals



Radicals are stabilized by both electron-donating & electron-withdrawing groups (& conjugation as well!)

- for EWGs that have a low-energy LUMO (usually π^*), the new SOMO formed is much lower in energy
- for EDGs that have relatively high-energy lone pairs, the new SOMO is much higher in energy, but the lone pair is in a lower energy state, making the overall radical more stable

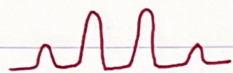


Radicals can be stable due to electronic effects (above) but steric effects can play a huge role as well

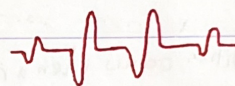
ESR (electron spin resonance) is used to analyse structure of radicals;

- unpaired electrons function analogously to protons in $^1\text{H NMR}$ but their magnet moment is much larger
- these unpaired electrons can couple w/ nearby Hs; known as "hyperfine splittings" (au)

Ex. a methyl radical ($\text{CH}_3^\bullet$)



absorption spectrum



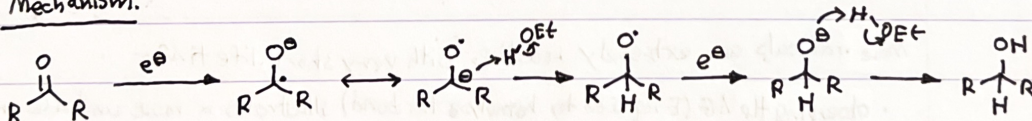
ESR spectrum
(first derivative)

- delocalization, angles can also be determined through ESP although beyond the scope of the text

Dissolving metal reduction, which a metal ($\text{Na}, \text{Mg}, \text{Zn}, \text{Al}$) releases an electron that is solvated

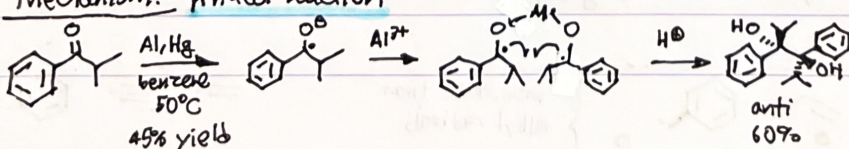
- these electrons tend to look for low-energy π^* orbitals; for ketones, a ketyl is formed
- in protic solvents, it leads to a net reduction to alcohols (Bouveault-Blanc reduction)

Mechanism.



- in aprotic solvents in which ketyl radicals can build up, using a metal that can form strong covalent bonds w/ oxygen are used to reduce electrostatic repulsion (chelation)

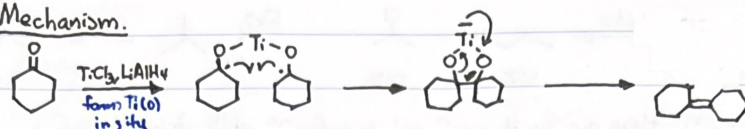
Mechanism. pinacol reaction



syn
40%

When $Ti(O)$ metal is prepared in situ by $TiCl_3 + LiAlH_4$ (or Zn/Cu), pinacol radical-radical coupling occurs but also deoxygenates to form an alkene (known as the McMurry reaction)

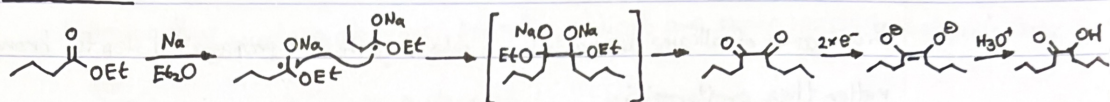
Mechanism.



- coupling reactions between two different ketones are rarely successful

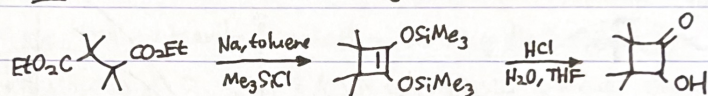
Esters can also undergo pinacol-type coupling, known as the acyloin reaction;

Mechanism.



- competing side-reactions due to the reactivity of the enolate can hinder its performance;
- addition of Me_3SiCl improves yield of the acyloin reaction

Ex: intramolecular reactions are great too!



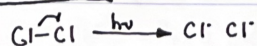
The three reactions above are exceptional; radical-radical reactions are rare as radicals are so reactive they can react with essentially everything (solvent, some other molecule)

- radical chain reactions, in which a new radical is formed while one is consumed throughout the cycle, begin by forming radicals through the initiation step, continues through the propagation step, and ends by the termination step

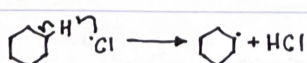
- as termination step kills radicals, the initiators such as peroxide needs to be (>10% mol%) to have sufficient yield (although these radical initiators are technically catalytic)

Chlorination of alkanes are done in presence of light, and can be potentially explosive in sunlight (lol)

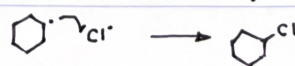
Mechanism.



initiation



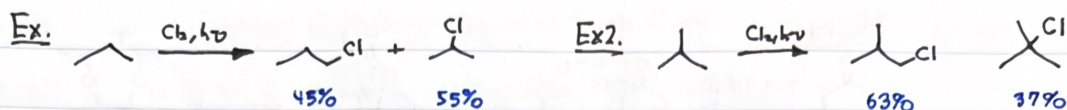
propagation



termination

The product can be single (as in the case of cyclohexane which all 12 protons are equivalent) or mixture

- the ratio of products are determined by statistics and stability of the radical



• for Ex₁, there are six Hs on 1° and two for 2°; still, stability wins

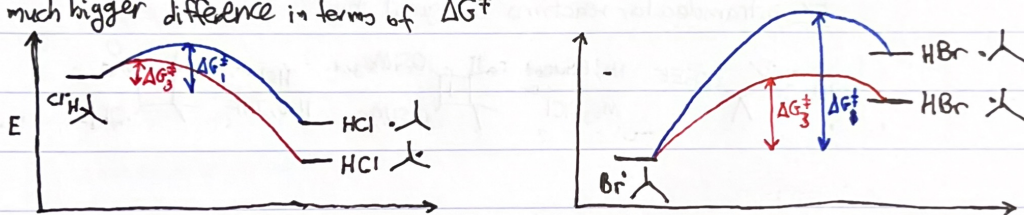
• for Ex₂, although relative reactivity of C-H (3°:1°) is 5:1, probability wins here

- not only are the product radicals in the reaction more stable for 3°, but the $\Delta G^\ddagger$ is lower as well

• as the transition state has significant radical character, more groups = more stability

Bromination of alkanes are much more selective; the first propagation step for bromination is endothermic rather than exothermic;

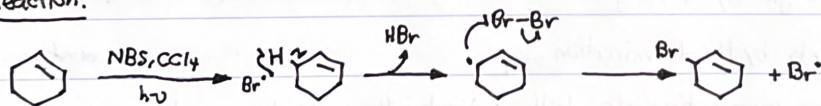
- by the Hammond postulate, the transition state for the alkane has much more "radical character", or characteristic of the product than the reactant (which was the case for chlorination) which means a much bigger difference in terms of $\Delta G^\ddagger$



- note that fluorination is too dangerous (explosive) as it is too exothermic and iodination doesn't work

Allylic bromination can be a very useful tool to make allylic bromides; the allylic C-H bond is weaker

Reaction.

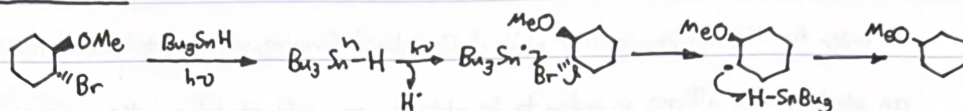


- the competing reaction(s): dibromination by bromonium cation (polar addition), and dibromination by radical reaction (where a bromine radical attacks π^*) can be controlled by low concentrations of Br_2 (use NBS) and using a nonpolar solvent (CCl_4) to destabilize bromonium cation
- note that this reaction is very sensitive to steric bulk; regioselectivity can be controlled

halogens (Cl, but especially Br & I) can be substituted by hydrogen through tin radicals

- tributyl tin hydride (Bu_3SnH), in which the Sn-H bond is weak, is the suitable radical indicator for this reaction.

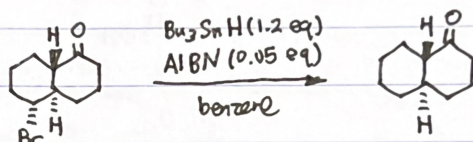
Mechanism.



- AIBN can help promote homolysis of Bu_3SnH ; this may be necessary for alkyl chlorides/bromides that require a rather high concentration of $\text{Bu}_3\text{Sn}^\bullet$ to work well

as AIBN forms radicals that are rather stable, they are rather picky in terms of which hydrogen they want to abstract; peroxide radicals are super reactive and pick any

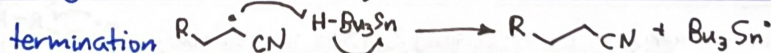
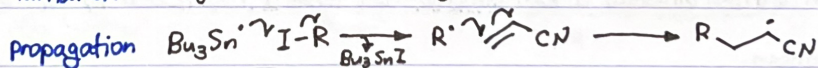
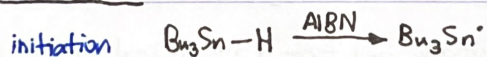
Ex.



Radical reactions are heavily dependent on breaking the "weakest bond";

- A combination of $\text{Bu}_3\text{Sn-H}$ & AIBN can be used to induce coupling reactions

Mechanism.



there are four radicals in one mixture, yet the reaction is very clean. Why?

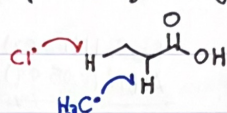
- The tin radical ($\text{Bu}_3\text{Sn}^\bullet$) does not react with the alkene as the Sn-C bond is weak; only occurs if:
 - the concentration of the alkene is too high
 - the starting alkane (which the $\text{Bu}_3\text{Sn}^\bullet$ is supposed to react) is rather unreactive (R-Cl or R-Br)
- the rate constant of $\text{R}^\bullet$ abstracting H from Bu_3SnH is about as similar as addition to alkene;
 - in order for the reaction desired to occur, the conc. of acrylonitrile is ≈ 10 times more than Bu_3SnH
 - note that too high of conc. can lead to side rxns; Bu_3SnH can just be added slowly w/ syringe pump
- the better method of control is to use small catalytic amount of Bu_3SnBr , and a hydride reducing agent
 - NaBH_4 is most common as a stoichiometric reductant, but NaCNBH_3 is also an alternative

The concept of nucleophilicity and electrophilicity also applies to radicals as well;

- radicals that are stabilized by EWGs are electrophilic with a low-energy SOMO.
- radicals that are stabilized by EDGs are nucleophilic with a high-energy SOMO.

In order for the intermolecular radical C-C bond forming reaction to occur, the "radical trap" must be an electrophilic alkene in order to be able to properly stabilize the nucleophilic ^{alkyl} radicals

- with this in mind, consider other reactions as well, such as chlorination of functional groups:
- because chlorine is electronegative, it has a low-energy SOMO and likes to abstract Hs that have the highest-energy HOMO
- the methyl group is rather nucleophilic (high-energy SOMO) so abstracts the α hydrogen

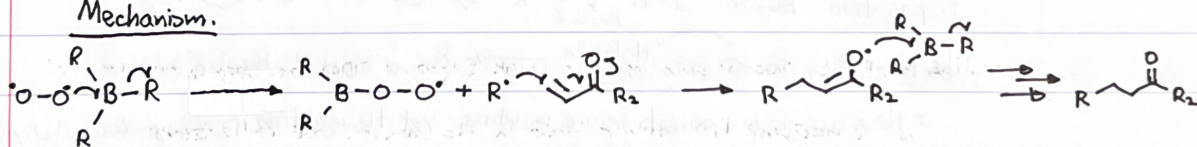


Reactivity patterns for polar reactions & radical reactions are very different; radicals are the ultimate soft species that only care about frontier orbitals

Intermolecular C-C bond forming reactions with tin can be done with boron as well; much less toxic

- dioxygen (a triplet diradical) is the "initiator" that forms a alkyl radical by S_H^2 or boron (2nd order homolytic displacement)

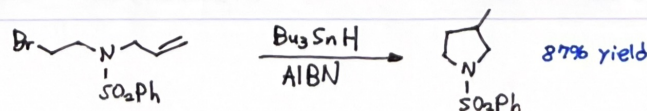
Mechanism.



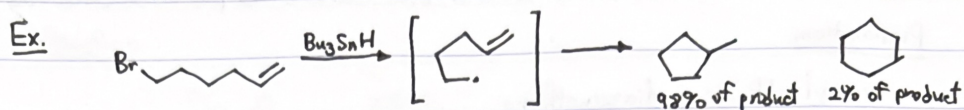
Intramolecular radical reactions are much more efficient and less strict in its conditions;

- the double bond does not need to be activated as the double bond is always held close to the radical
- cyclization resulting from intramolecular radical reactions are extremely rapid
- hydride donor (Bu_3SnH , for example) can be present at higher concentrations as competing reactions for intramolecular radical reactions is too fast they can't compete
- a good leaving group is not necessary; Cl , SPh , and $SePh$ are all acceptable

Ex.

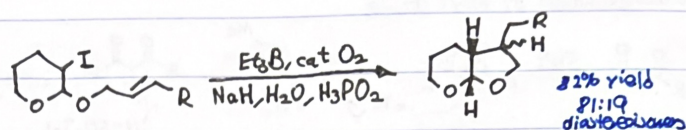


Baldwin's rules apply to radical reactions just as equally well as ionic reactions;

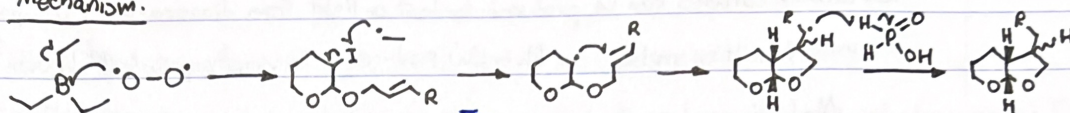


Intramolecular radical cyclisations can be catalysed by boron as well;

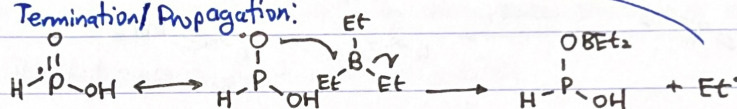
Reaction.



Mechanism.



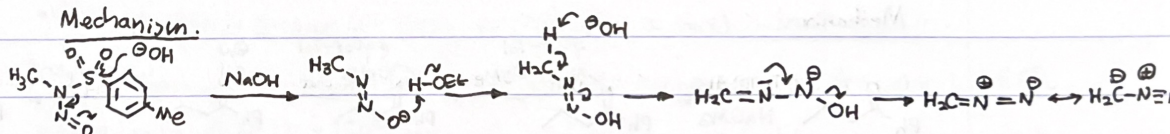
Termination/Propagation:



diazomethane is an interesting compound that is frequently represented as a dipole

- prepared with N-methyl-N-nitrosourea or N-methyl-N-nitrosofluorenesulfonamide

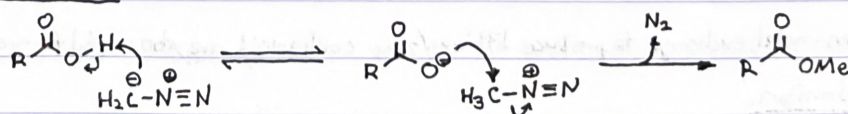
Mechanism.



- diazomethane is toxic, very explosive at high concentrations, and has a boiling point at -23°C
- useful reagent but mostly used in the small-scale laboratory
- diazomethane, when irradiated with light, becomes a source of carbene
- carbene in reactions tend to be dominated by "insertion" reactions

Without light, diazomethane can be a methylating reagent for acidic -OH groups

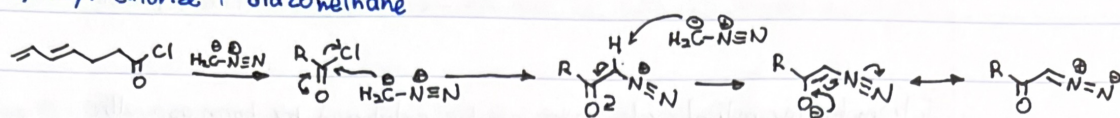
Mechanism.



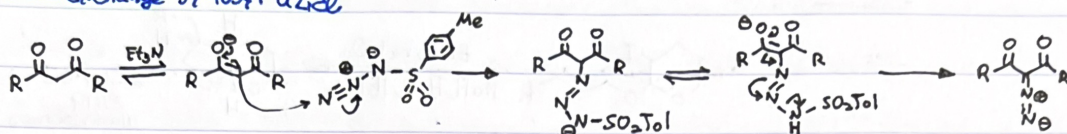
Because diazoalkanes are so explosive, the safer diazocarbonyl is preferred (stabilized by carbonyl group)

Preparation.

by acyl chloride + diazomethane

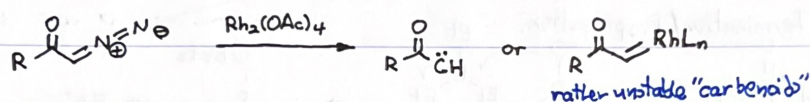


diazotransfer by tosyl azide



- these carbonyl carbenes can be produced by heat or light from diazocarbonyl compounds
- using transition metals (esp. Rh or Cu) produces a "carbene equivalent" known as carbenoids

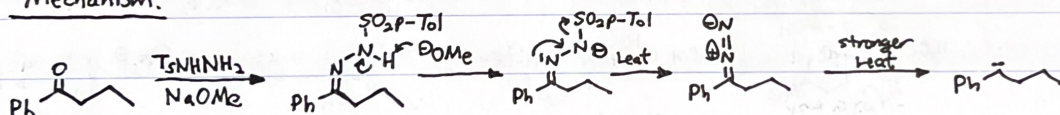
Mechanism



There are other alternative ways to make carbenes that don't have a carbonyl group:

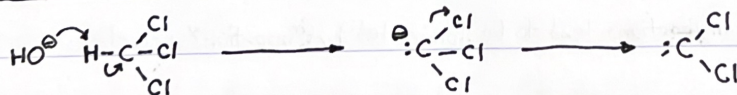
- tosyl hydrazones can make some useful carbenes while using diazoalkanes as an intermediate, more safety

Mechanism.



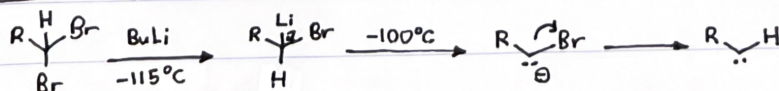
- α elimination, where the proton & leaving group is on the same carbon, also leads to carbene formation
- hydroxide/alkoxides can promote α elimination for trihalomethanes

Mechanism.



- for dihalomethanes, a stronger base (LDA) is needed; for primary alkyl chlorides, one of the most powerful base mixtures, Schlosser's base (t-BuLi/t-BuOK) is used
- halogen-metal exchange to produce lithium/zinc carbenoids are also useful for making carbenes

Mechanism.



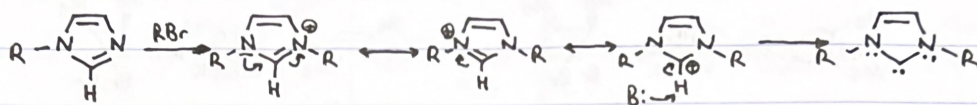
- if the reactant is base-sensitive, decarboxylation of trichloroacetate can be an option w/ heat

Reaction.



- deprotonation of a stable cation (by lone pairs) is another good way to produce stable carbenes

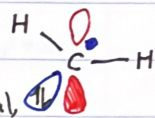
Mechanism.



There are two types of carbenes; one which the two electrons are paired and the other unpaired.

- if the two electrons are paired, they are known as singlet carbenes and are not observable by ESR

- has a bond angle of $100-110^\circ$; the carbene species possesses a sp^2 hybridization with both of its electrons in the non-bonding sp^2 orbital

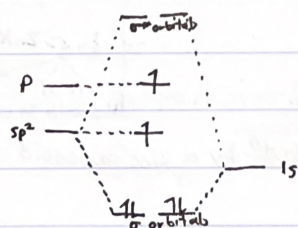


- although the energy of the sp^2 orbital is lower than the empty p orbital, pairing requires a significant amount of energy and singlets form if the difference in energy between sp^2 & p is greater than pairing energy.

- electron repulsion is greater for two - resulting in a smaller bond angle

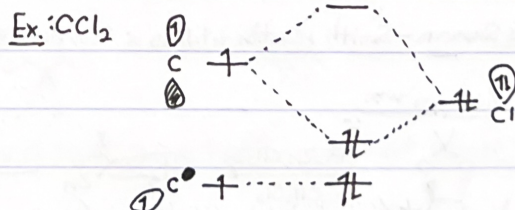
- if the two electrons are unpaired, they are known as triplet carbenes and are observable by ESR.

- has a bond angle of $130-150^\circ$; same hybridization since unpaired there is much less repulsion



- if stabilization is not given (e.g. lone pair), triplet state is more common

- an example of lp donation that makes singlet more favorable is below:



- if carbenes form by ionic reaction, they must form a singlet (electrons "travel" in pairs)

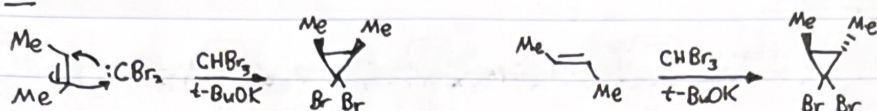
Carbenes are very soft and electrophilic; it is electron-deficient and reacts with any HOMO (C-H, alkene, lp, etc.)

- carbenes tend to undergo insertion reactions

Carbenes tend to form cyclopropanes from alkenes

- singlet carbenes undergo a concerted mechanism; yields a stereospecific reaction

Ex.



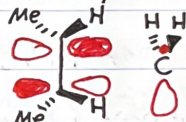
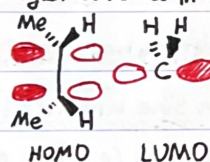
- for triplet carbenes, the mechanism cannot be concerted, and slow spin inversion must occur to form a C-C bond

Mechanism.

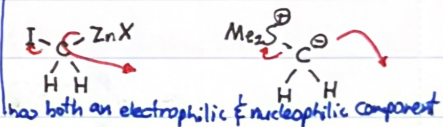


- while "waiting" for a collision (must often solvent) by a molecule to induce spin-flip, the bonds can rotate to produce a mix of diastereoisomers
- note that in general, ring-flipping is relatively slow compared to how fast carbene reactions occur

Addition of singlet carbenes into an alkene is actually a [1+2] cycloaddition:

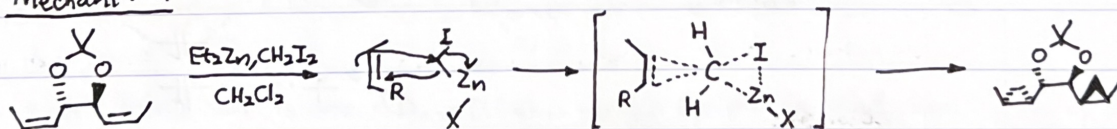


Note: see the similarity between a Simmons-Smith reagent & another cyclopropane making reagent, the sulfonium ylide;



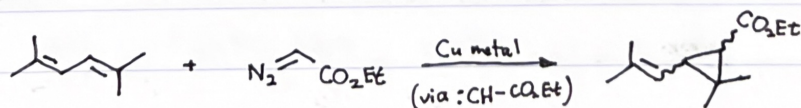
The Simmons-Smith reaction utilizes a "carbene equivalent" by a zinc carbenoid

Mechanism.



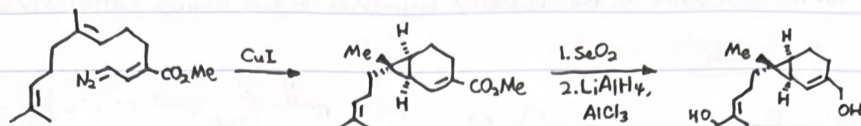
- note that allylic alcohols undergo this reaction magnitudes faster + much better stereoselectivity
- carbenoids can be used (metal-catalyzed decomposition of diazocarbonyls)

Ex.



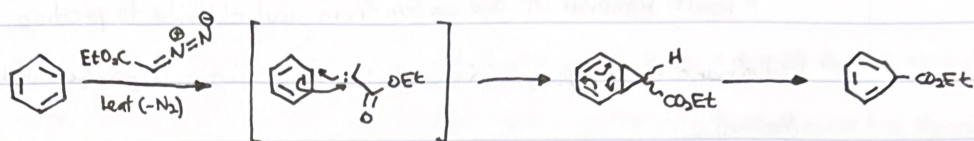
- Intramolecular reactions are much more reliable, allowing for highly-substituted cyclopropanes

Ex.



- with carbones that have EWGs (making it even more reactive), it can even insert to benzene

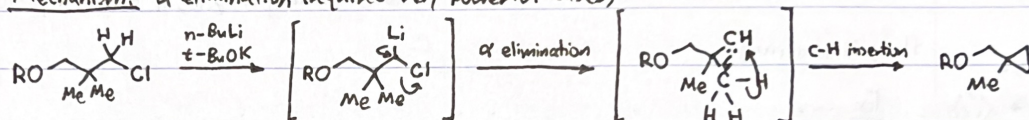
Ex.



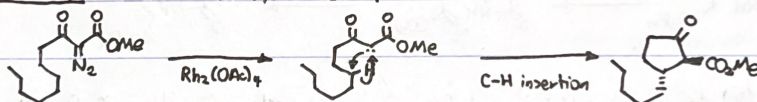
Alkyl-substituted carbones rarely undergo intermolecular reactions (including forming cyclopropanes)

- instead, C-H insertion intramolecularly is much more common by either α elimination or carbeneoids

Mechanism. α elimination (requires very powerful bases)



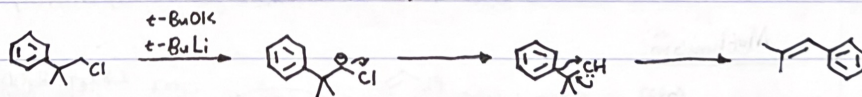
Mechanism. rhodium-catalyzed decomposition to carbones



- although the mechanism for insertion into C-H bonds are similar to alkenes (differs for singlet vs. triplet), triplets were never observed to undergo C-H bond insertion; just assume mechanism is concerted

Rearrangement reactions do occur for carbene species; they are electron-deficient after all

Ex.



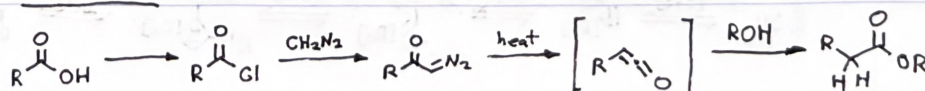
- when the carbene is adjacent to a carbonyl group, Wolff rearrangement proceeds to form ketenes

Mechanism.



- when one more carbon needs to be added between the carbonyl & the rest, use the Arndt-Eistert reaction

Mechanism.



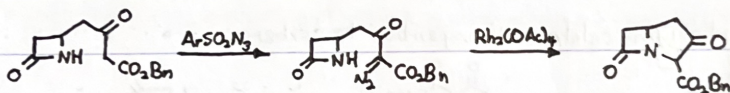
- forms isocyanates, but are easily hydrolysed to give amines & attacked by alcohols to give carbamate

$$R-C(=O)Cl \xrightarrow[N_2]{NaN_3} R-C(=O)N_3 \rightarrow R-N=C=O \xrightarrow[ROH]{H_2O} R-NH-C(=O)OH \rightleftharpoons R-NH-C(=O)O^- \xrightarrow{-CO_2} R-NH_2$$
 (if $R = BnCH_2$ then it is Cbz-protected amine)

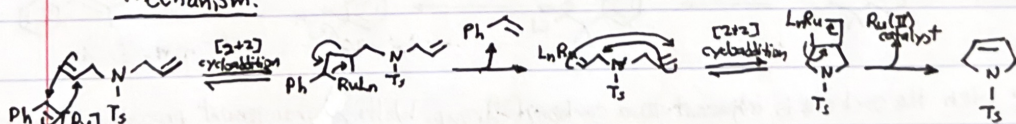
- the Hofmann rearrangement is very similar to the Curtius rearrangement, but starts from amides

$$R-\overset{\overset{O}{\parallel}}{C}-NH_2 \xrightarrow{NaOH} R-\overset{\overset{O^-}{\parallel}}{C}-NH^- \xrightarrow{Br-Br} R-\overset{\overset{O}{\parallel}}{C}-N(Br)-Br \xrightarrow{NaOH} R-\overset{\overset{O^-}{\parallel}}{C}-N(Br)=O \xrightarrow{H^+} R-\overset{\overset{O}{\parallel}}{C}-N(Br)=O \xrightarrow{H_2O, CO_2} R-NH_2$$

$$\text{EtO}_2\text{C}-\overset{\text{N}_2}{\text{C}}-\text{CO}_2\text{Et} + \text{Cyclopentadiene} \xrightarrow{\text{AlH}_3(\text{OAc})_3} \text{EtO}_2\text{C}-\text{C}(\text{Cyclopentadienyl})-\text{CO}_2\text{Et}$$

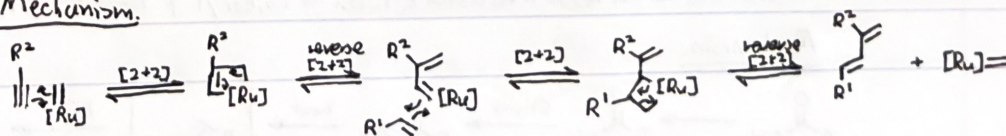
Ex.
$$\text{N}=\text{N}=\text{Ph} \longrightarrow \left[\text{HC}^{\ddot{}}-\text{Ph} \right] \xrightarrow[\text{PCl}_3]{(\text{Ph}_3\text{P})_3\text{RuCl}_2} \text{Cl}-\text{Ru}(\text{PCl}_3)_2=\text{CH}-\text{Ph}$$

Mechanism.



- cross metathesis works if the two coupling partners have very different electronic/steric properties

Mechanism.



When determining organic reaction mechanisms, several aspects of the reaction must be identified:

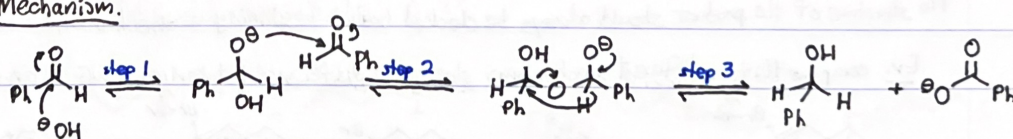
- the 'true' product of the reaction
- how many steps in the reaction are present and any structures of intermediates
- finding the rate-determining step
- finding any catalysis present in reaction

Like all sciences, a hypothesis (proposed mechanism) is constructed and evidence is sought for and against these proposed mechanisms. If the experiment does not fit the hypothesis, the old is thrown away and the new is proposed.

We will be using the Cannizzaro reaction as an example:

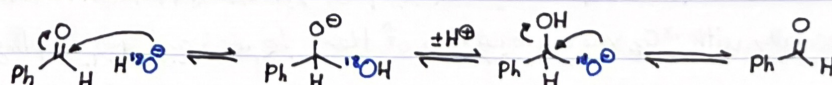
- a radical mechanism was proposed in the early stages; addition of radical initiators & inhibitors had no effect
 $\Rightarrow$ the lack of change of rate leads to the conclusion that the reaction is not a radical reaction
- as the concentration of base increased, the order of the reaction changes;
 - for low concentrations, an overall third order is observed - $\text{rate} = k_4 [\text{PhCHO}]^2 [\text{OH}^-]$
 - for higher concentrations, transition towards a fourth order overall reaction is observed; $\text{rate} = k_4 [\text{PhCHO}]^2 [\text{OH}^-]^2$ $\Rightarrow$ as the rate law is directly affected by the concentration of base, this points towards a polar mechanism.
- when isotope labelling was conducted (solvent as D_2O), no C-D bonds were observed in the product
 $\Rightarrow$ the newly formed C-H bond must come from the aldehyde, not the solvent itself

Mechanism 'B' that seems to fit all of the evidence above involves an adduct + intramolecular hydride transfer
Mechanism.



- once again by isotope labelling (^{18}O), the rate of the first step can be determined by seeing if isotope exchange occurs faster than the main reaction itself
- in this situation, it indeed does;

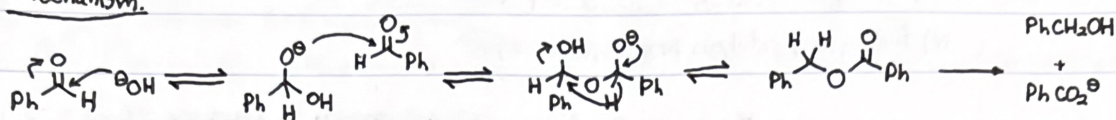
Reaction.



since step 2 is very similar in nature to step 1, we can assume step 3 is likely the RDS

- disproving the mechanism occurred when a different nucleophile (OMe^-) was used
- another mechanism, which also took into consideration of the fact that cooling + avoiding excess alkali allowed some benzyl benzoate to be isolated during the reaction rather than being hydrolysed

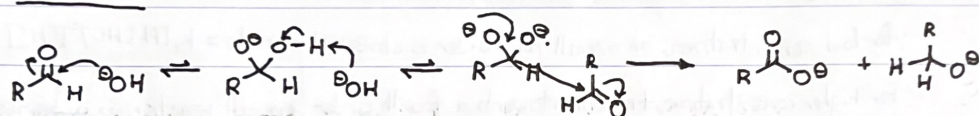
Mechanism.



- if this mechanism were to be correct, that would mean the ester intermediate is the only way to make products; comparing the rate at which products to the amount of ester present in the Cannizzaro reaction & the rate at which a pure sample of the ester hydrolyses, it was confirmed this mechanism was x

The only 'correct' mechanism of the Cannizzaro reaction is the one below:

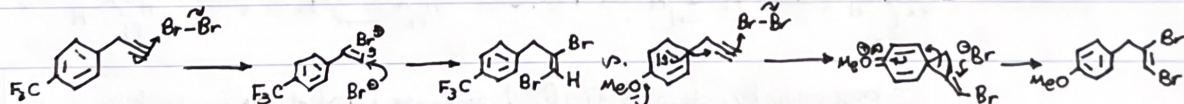
Mechanism.



- by varying the structure of the substrate (e.g. add EWG or EDG to the ring), and comparing their relative rates, a lot of information can be derived
- for example, for aromatic aldehydes in the Cannizzaro reaction, EWGs on the arene actually speeds up the reaction by a large factor as it stabilizes the monoanion/dianion

The structure of the product should always be checked before beginning a mechanistic investigation

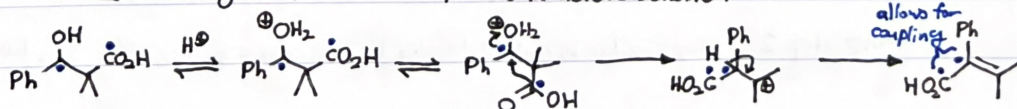
Ex: compare the two different mechanisms due to the difference between an EWG & an EDG



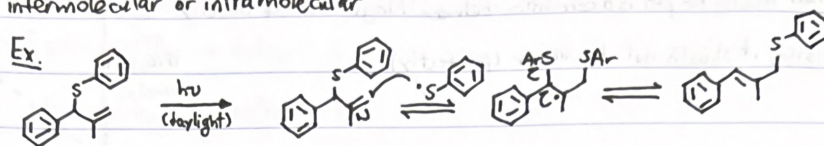
Labelling experiments give key evidence where atoms from the starting material ended up;

- D and ^{13}C are common isotopes to use for labelling; they are detectable by NMR
- especially with ^{13}C , you can have two of them be used and use coupling to your advantage

Ex: rearrangement of a hydroxy-acid in acidic solution

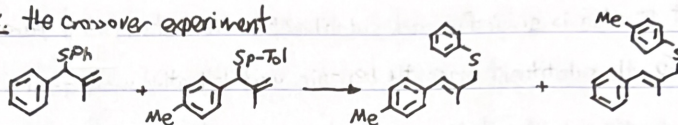


crossover experiments involving double labelling (does not have to be isotopic) can illustrate whether a reaction is intermolecular or intramolecular



• while above was the true mechanism, another potential intramolecular reaction, a [1,3]-sigmatropic shift, was dismissed by a crossover experiment:

Ex. the crossover experiment

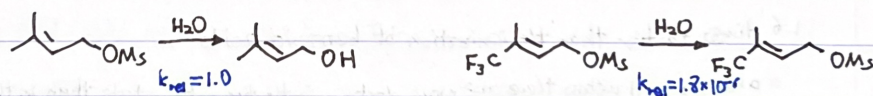


• here, it is crucial for the para-methyl group to have barely any steric or electronic effect to significantly impact the outcome

Systematic structural variation can give strong evidence about a mechanism by seeing its rate

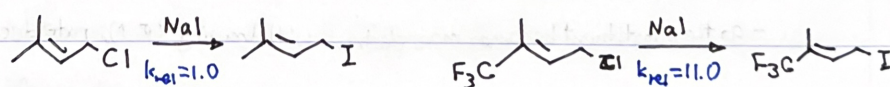
• for example, in the case of some allylic compounds:

Ex1. allylic mesylate: S_N1 or S_N2 ?



• in this example, the mechanism must be S_N1 ; the trifluoromethyl group destabilizes carbocation

Ex2. allylic chloride: S_N1 or S_N2 ?



• this time, it must be S_N2 as the rate is relatively unaffected;

The Hammett relationship quantifies the effects that EWG/EDG have on the transition state or intermediate during the course of a reaction

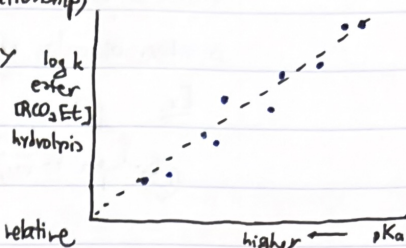
• Hammett used pK_a s of a lot of acids to illustrate the rate of hydrolysis for its corresponding esters

• for esters that had substituents (R) which could have steric effects affect the reaction, they were removed
e.g.: ortho-substituted aromatics, aliphatic substituents



Plotting the meta- & para-substituted isomers gives a relatively linear relationship;

- note that because the plot is a correlation between things that are directly not related, it should not be linear (perfectly)

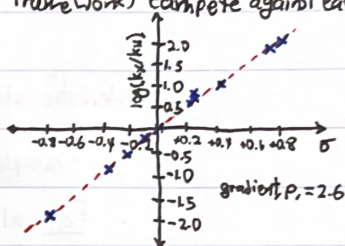


σ illustrates how electron-donating (or withdrawing) a substituent is relative to H as a difference between the pKas of a benzoic acid derivative w/ the substituent & benzoic acid itself

$$\sigma_x = \log \left(\frac{K_a(XC_6H_4COOH)}{K_a(C_6H_5COOH)} \right) = pK_a(C_6H_5COOH) - pK_a(XC_6H_4COOH)$$

- a different σ value is given for each substituent in the meta (σ_m) & para (σ_p) positions
- if $\sigma > 0$, the substituent makes the benzoic acid derivative more acidic, so withdraws electron density
- if $\sigma = 0$, the substituent has no electronic effect overall; acidity is the same
- if $\sigma < 0$, the substituent makes the benzoic acid less acidic, so donates electron density
- always, note that a combination of conjugation & induction effect (σ framework) compete against each other

The gradient of the best-fit line (ρ) illustrates the sensitivity of the reaction to substituent effects in comparison w/ the ionization of benzoic acid

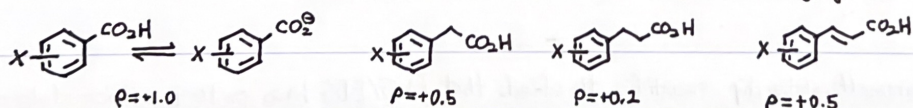


- since the gradient is 2.6, the reaction responds to substituent effect

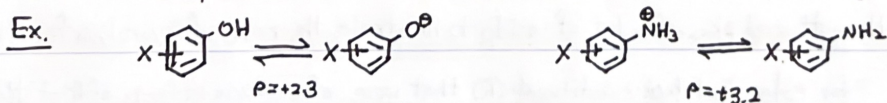
$10^{2.6}$ times faster than the ionization of benzoic acid

- when $\rho > 0$, it means there are more electrons in the transition state than in the starting material
 - as the substituent becomes more electron-withdrawing ($\sigma \uparrow$), rate increases ($k_x \uparrow$)
- when $\rho < 0$, it means there are less electrons in the transition state than in the starting material
 - as the substituent becomes more electron-withdrawing ($\sigma \uparrow$), rate decreases ($k_x \downarrow$)

Hammett ρ values are affected (in magnitude) by how relevant the changing substituents are to the reaction



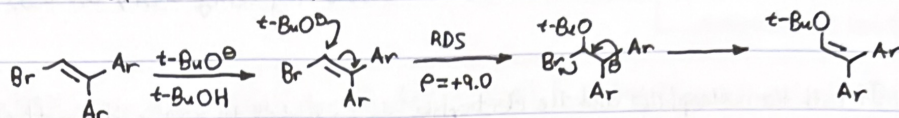
- unlike these carboxylic acids, if the oxygen anion can delocalize into the ring, ρ increases



Both the sign & magnitude of the Hammett ρ value illustrate what happens in the rate-determining step of the rxn

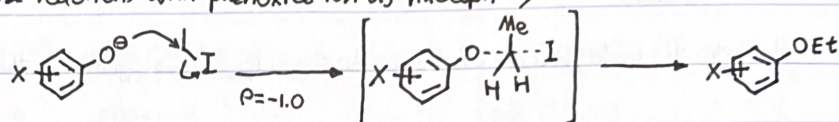
- if the RDS is nucleophilic attack on a carbonyl group, the ρ is around 2~3
- if extra electrons are delocalized into the ring, this ρ value increases further

Ex. addition-elimination mechanism

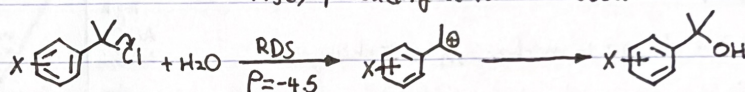


Negative ρ values result when electrons are flowing out of the ring

Ex. S_N2 reactions with phenoxide ion as nucleophile;

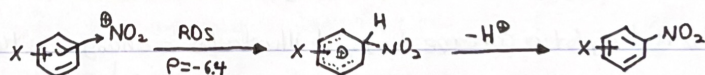


Ex. S_N1 reactions are even worse, producing a full carbocation



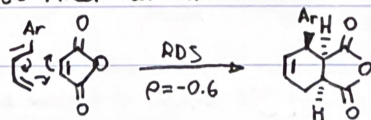
- in order to have large negative ρ values, they must flow out of a ring (e.g. electrophilic aromatic substitution)

Ex. electrophilic aromatic substitution



Low ρ values are expected if the reaction involves little to no charge accumulation/dispersion in its mechanism

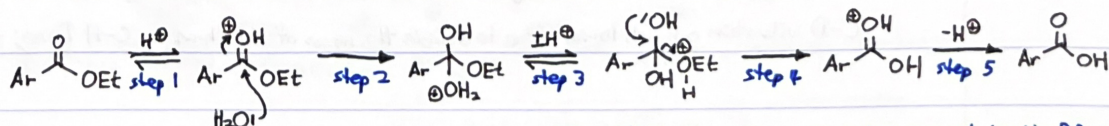
Ex. Diels-Alder reaction



The negative sign of ρ is because raising the HOMO by making the ring more electron-donating increases the rate of the Diels-Alder reaction

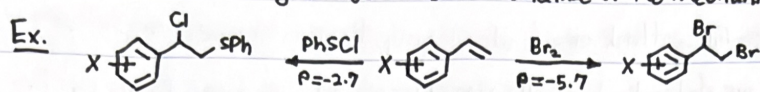
Sometimes the ρ value can be close to zero because ρ values of certain steps of the reaction cancel each other out

Ex. hydrolysis of benzoic ester in acid



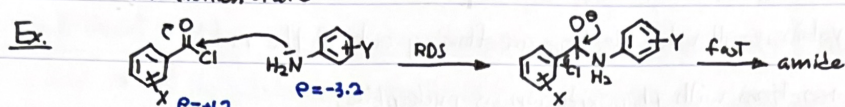
Proton transfers, especially to electronegative atoms, are extremely fast; so steps 1, 3, and 5 cannot be the RDS; step 2 is probably the RDS, and the reaction ρ value for step 2 is probably +2.5; since the protonation of the carbonyl oxygen in step 1 has electron density flowing outside the ring, the equilibrium $\rho = -2.5$ giving $\rho \approx 0.1$.

The Hammett ρ values can give huge clues to the nature of the mechanism:



- we can expect the Br_2 to have the aromatic ring being heavily involved, unlike the sulfonyl chloride

If both the nucleophile and the electrophile can be probed to give a Hammett plot, we can get the complete picture of the transition state

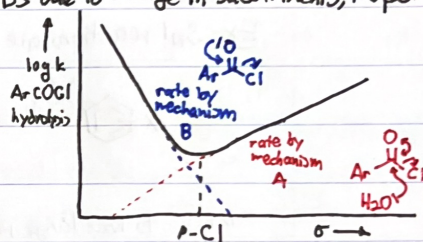


- illustrates the nucleophilicity of the amine is 100 times more significant than the electrophilicity for rate

If the reaction has an alternative pathway, or a change in RDS due to change in substituents, the plot becomes non-linear

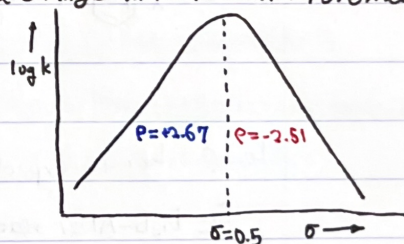
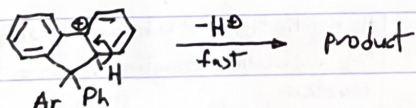
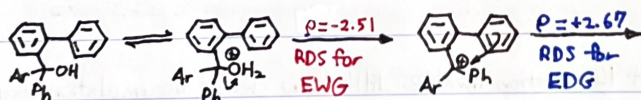
Ex. hydrolysis of acid chlorides

- there is a change in mechanism as σ changes
- $\rho = -4.4$; suggests a formation of a cation in the RDS
- $\rho = +2.5$; expected from nucleophilic carbonyl attack



- if the plot is concave up, it illustrates a change in mechanism
- conversely, if the plot is concave down, it illustrates a change in the RDS within one mechanism

Ex. intramolecular Friedel-Crafts alkylation

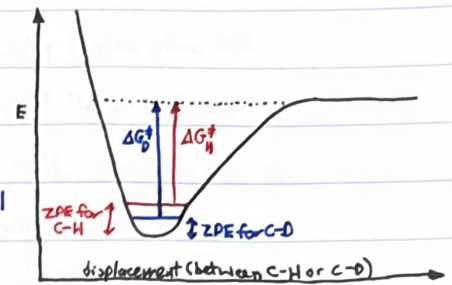
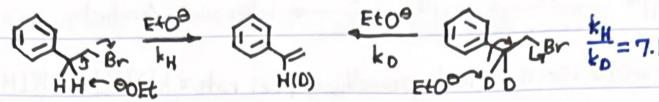


Kinetic isotope effects (KIE) is the changes in rate when a H atom is replaced with deuterium (D); k_H/k_D

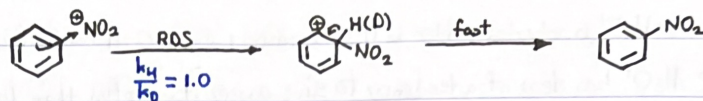
- hydrogen and deuterium differ chemically as the bond between C-D is much more stronger than C-H
- assuming the C-H/C-D breaking is involved in the rate-determining step, the zero-point energy of C-D vibration is much lower (due to double the mass of H) than a C-H bond; the $\Delta G_D^\ddagger \gg \Delta G_H^\ddagger$

At room temperature, the theoretical maximum value of KIE ~ 7 .

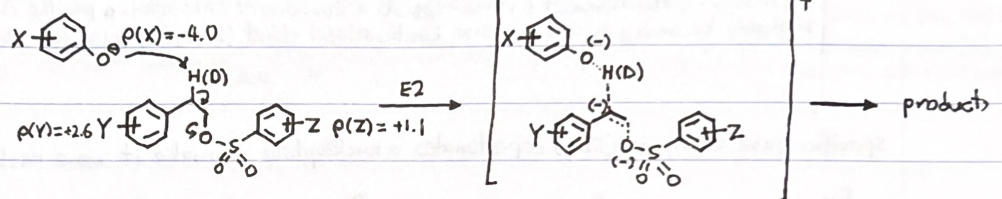
Ex. An E2 elimination



Ex. The KIE can be a great indicator of whether C-H bond breaking is involved in the RDS;



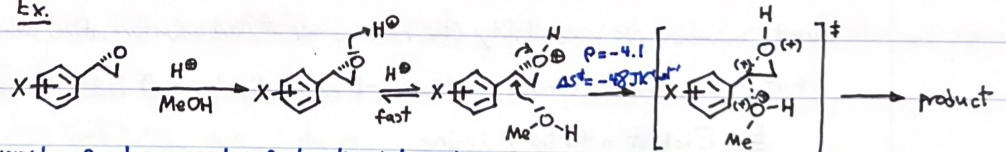
Ex. KIE information can be extremely valuable in addition to Hammett plots:



$\Delta S^\ddagger$ (entropy of activation) provides additional information about the reaction; the change in order from the starting material to the transition state

- $\Delta S^\ddagger > 0$ if there are more products than reactants; e.g., fragmentation reactions
- $\Delta S^\ddagger < 0$ if there are more reactants than products; e.g., Diels-Alder reactions
- in the extreme end, $\Delta S^\ddagger$ is very negative if in a bimolecular reaction, neither reagent is in great excess
- $\Delta S^\ddagger$ is less negative if in a bimolecular reaction, one of the reagent is a solvent or just in large excess

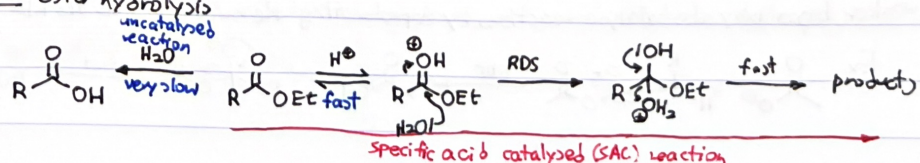
Ex.



a very low ρ value suggests a carbocation intermediate & the regioselectivity of the reaction on the benzylic position, but a moderately negative $\Delta S^\ddagger$ suggests it's probably S_N2 (attng w/inversion of configuration) w/ a loose TS(?)

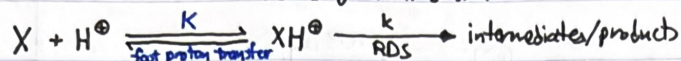
Specific acid catalysis protonates electrophiles before the RDS, making them more electrophilic

Ex. ester hydrolysis



SAC works only if $pH \leq pK_a(\text{conjugate acid of the substrate})$, and is only dependent on pH (H_3O^+ is the only catalyst)

- most, if not all SAC reactions share some general characteristics:

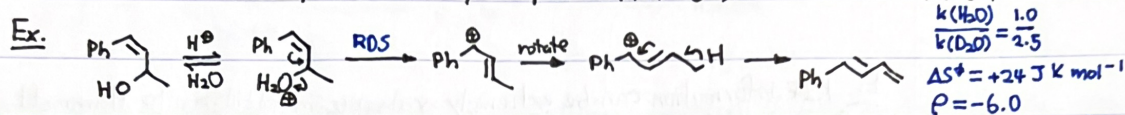


- therefore, the rate of the reaction looks something like: $\text{rate} = k[XH^+] = kK[H^+][X]$

If D_3O^+ is used instead of H_3O^+ and the rate increases, this is known as the inverse solvent isotope effect

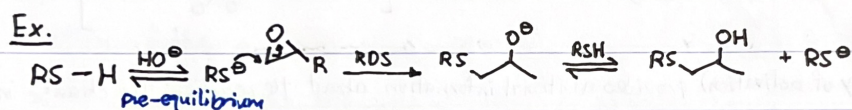
- because H_3O^+ is solvated better in H_2O because longer O-H bonds (higher ZPE) results in stronger H bonds

- H_3O^+ has less of a tendency to give away its proton than D_3O^+ , which is less solvated in D_2O



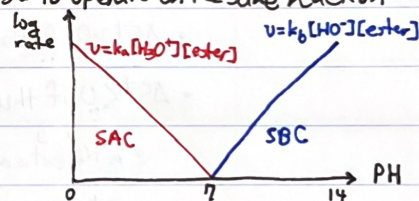
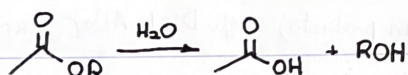
The strongly negative Hammett ρ value suggests a formation of carbocation, a positive $\Delta S^\ddagger$ illustrates one molecule probably becoming two. The inverse kinetic solvent effect ($k_H/k_D < 1$) indicates SAC.

specific base catalysis (SBC) deprotonates a nucleophile to make it more nucleophilic before RDS



- the reaction depends on the pH of the solution; this makes SAC & SBC to operate on the same reaction

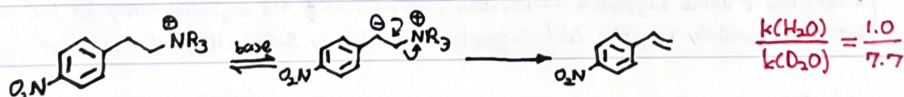
Ex. ester hydrolysis v/ pH



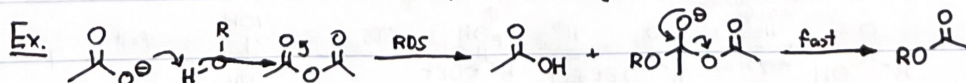
- removal of protons from carbon can be the RDS; this is illustrated by the inverse kinetic isotope effect due to microscopic reversibility (the reverse step of carbocation formation, which is protonation)

- if done in D_2O , the reverse reaction (C-D heterolytic cleavage) is done more slowly, so E1cB is faster

Ex. E1cB of a tertiary amine



weaker bases may also catalyze reactions by deprotonating the nucleophile as the RDS occurs



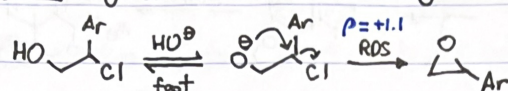
one huge downside to the GBC is a trimolecular step; $\Delta S^\ddagger = -168 \text{ J K}^{-1} \text{ mol}^{-1}$

- for GBC, at least one of the three molecules must be in large excess (e.g., ROH is the solvent)
- since a bond to H is being formed & broken, the normal kinetic isotope effect applies: $k_H/k_D = 2.4$

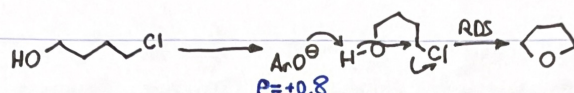
To differentiate between SBC and GBC, just set the pH constant and change the concentration of weak bases

- we introduce two different but very similar-looking reactions:

Case. ring formation: 3-membered ring



Case. ring formation: 5-membered ring



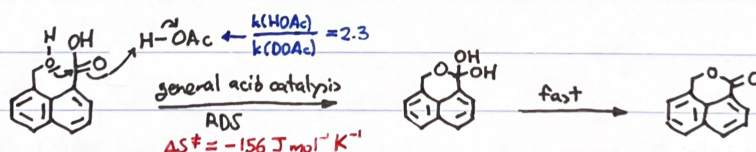
In both cases, increasing pH increases the rate of the reaction; however, the epoxide is very strained and the starting material must be raised in energy to ensure cyclization can occur. GBC is not possible - purely SBC reaction. Inverse solvent isotope effect is expected as the reverse reaction of deprotonation is slower in D_2O ; these two results in an overall faster reaction for D_2O .

For the 5-membered ring, the transition state is unstrained and only a small push is needed to get the reaction going; we expect a small normal kinetic isotope effect.

GAC occurs when a proton from a weak acid is transferred during the RDS

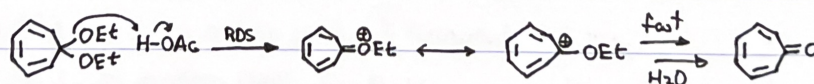
- also a termolecular step that depends on the acid (weak) present
- an intramolecular ester formation can utilize GAC!

Mechanism.



- if an acid-catalyzed acetal hydrolysis results in some sort of stability for the intermediate $\Rightarrow$ GAC

Mechanism.



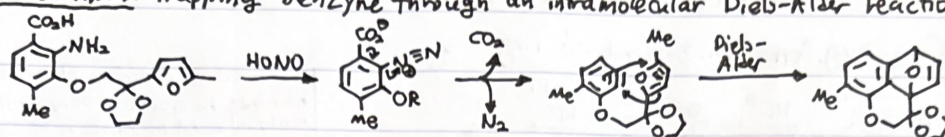
- if mechanism undergoes GAC, normal KIE should be observed

Intermediates can be key to determining the mechanism of reactions; but they may not be involved in an actual reaction in other cases

In order for intermediates in a reaction to be convincing,

- i) detection of intermediate in the reaction, perhaps by a trapping rxn
- ii) intermediate must give product when added to reaction mixture
- iii) kinetic evidence that rate of formation & consumption are adequate.

Mechanism: trapping benzyne through an intramolecular Diels-Alder reaction



The 18-electron rule is a good indicator for stability; ideally, we want a catalyst that is stable in its resting state but can be quickly activated in solution, most commonly through a loss of a ligand

- there are common exceptions to this rule; especially if one of the d orbitals are much higher in energy in comparison to others (e.g. 16-electron complexes)

A single ligand can be attached in more than one place; this count is illustrated by the haptic number η

- more points of attachment means more donation of electrons;
- there are two ways to bond to the metal; σ bonding forms σ complexes and π bonding (containing usually no σ bonds) form π complexes

Ex. examples of bonding



- neutral ligands such as cyclooctatetraene can also bond in a variety of ways ($\eta^2, \eta^4, \eta^6, \eta^8$)
- the electrons provided by the ligands often provide 2 electrons per each "source"; can be up to 8 (η^8) to make up the 18-electron rule
- this is independent of formal charge
- for determining oxidation states of the metal, do not bother unless σ bonds to ligands are involved

Mainly, there are two types of bonding interactions;

- when a filled lone pair from the ligand bonds with a vacant $s d^n$ orbital, this forms a conventional σ bond
 - this donates electron density from the ligand to the metal
- if the ligand has an empty orbital w/ an appropriate symmetry, the filled d orbitals of the metal may back-bond and reduce electron density of the metal
 - this donates electron density from the lone pair to the ligand
- with ligands such as alkenes, both σ & π donation (from π orbital & π^* orbital of the alkene respectively) is OK

Oxidative addition occurs by breaking a σ bond; this adds two extra ligands w/ a negative formal charge

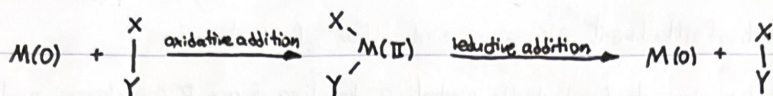
- increases the oxidation state of the metal by II; also increases the ligand count by two
- frequently occurs on complexes w/ low oxidation states & has an empty site for a ligand (coordinatively unsaturated)

- both non-polar and electrophilic species (H_2 , $C-H$, $C-SiR_3$, $H-X$, $R-X$, $X-X$)

Although neutral ligands such as alkenes and phosphines can simply dissociate, other species require a more active process known as reductive elimination

- essentially a reverse process of oxidative addition; $(II) \rightarrow (0)$, removal of two ligands

Mechanism. oxidative addition and reductive elimination

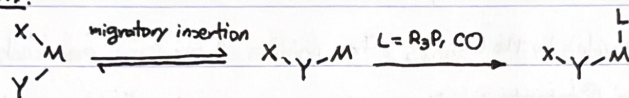


- ligands that are to be eliminated must be cis to one another (concerted process)

Migration can occur in metal complexes; requires cis arrangement w/ retention of stereochemistry

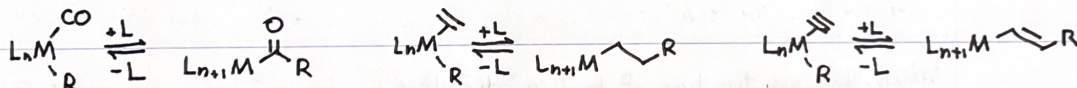
- this leads to a net (os) of one ligand; often, migration is driven by the addition of another ligand

Mechanism.

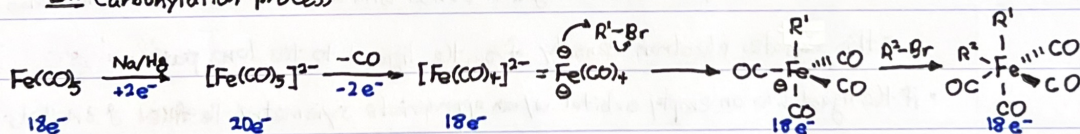


- migratory insertion can help "build up a chain" before elimination

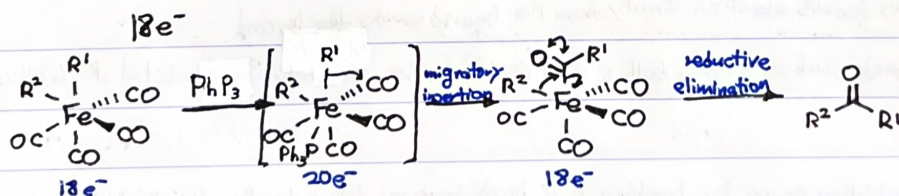
- usually driven by external ligands such as increased pressure of CO or higher presence of PPh_3



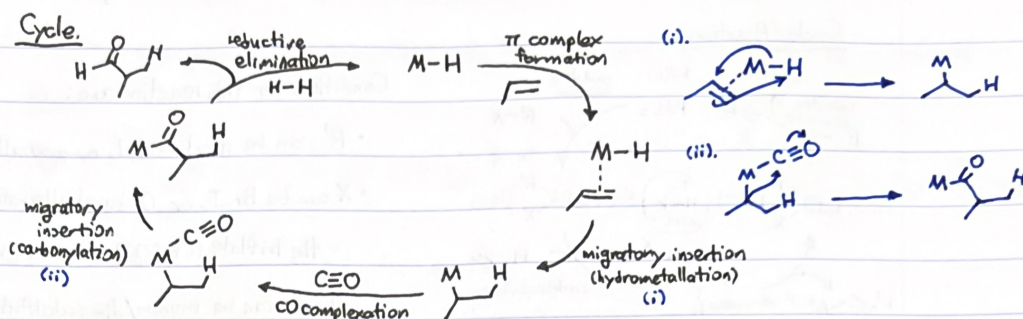
Ex. carbonylation process



- keep in mind that $20e^-$ complexes can form, but are just reactive and prefers to go down to

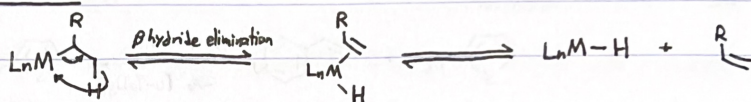


The OXO process is a method of carbonylation to alkenes such as propene, making aldehydes



- if the CO partial pressure is somewhat low, the reverse reaction (decarbonylation) may dominate
- the final step of decarbonylation is β hydride elimination; alkyl group bonded to metal becomes allyl

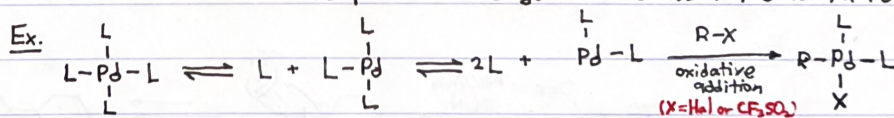
Mechanism.



- requires a vacant ligand site; metal & hydride must be syn to each other
- β -hydride elimination is a very fast process (intramolecular) so original substrate must be considered with care in many reactions

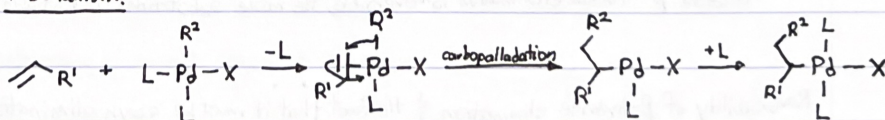
Palladium is a very popular organometallic catalyst and dominated primarily by two Oxidation states, 0 & (II)

- palladium(0) is electron-rich and prefers to undergo oxidative addition to form a Pd(II) complex



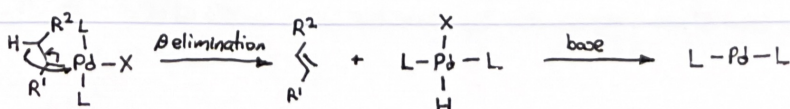
- Pd-R σ bonds are very reactive; alkyl groups are poor ligands and migratory insertion is common

Mechanism.



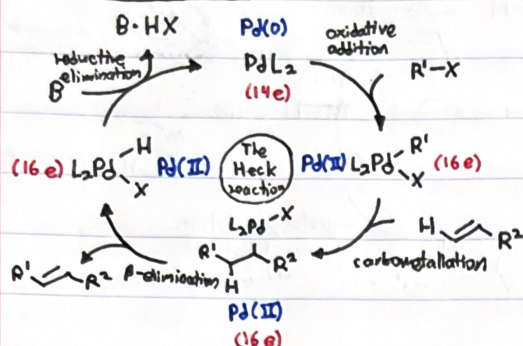
- although polymerization could occur by continuing insertion, palladium expels to product by β elimination
- to finish the catalytic cycle, the catalyst is renewed by reductive elimination of HX by base

Mechanism.



The Heck reaction couples an organic halide & an alkene w/ a Palladium catalyst

Cycle/Reaction.

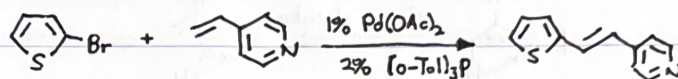


Conditions for this reaction are:

- R' can be aryl, vinyl, or any alkyl group w/o β H
- X can be Br, I, or O-based alternative LG triflate anion
- the triflate (CF₃SO₃⁻) LG is an excellent non-basic LG
- alkene can be mono-/di-substituted and be electron-rich, poor, or neutral
- base can be Et₃N, NaOAc, or Na₂CO₃ (aq)

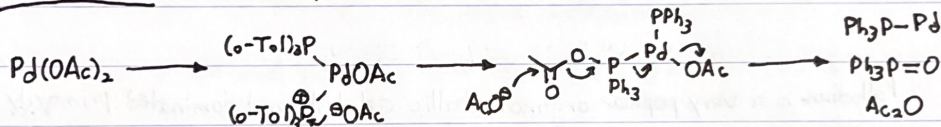
• the Heck reaction has high regioselectivity; alkenes w/ a EWG forms trans alkenes w/ aliphatic group on opposite end

Ex.



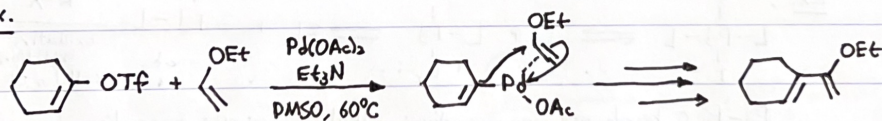
• Pd(0) can be prepared in situ by reduction of Pd(II); this reduction can be done by amines, phosphines, alkenes and many organometallics

Mechanism. (o-Tol)₃P in the reduction of Pd(II) to Pd(0)



• with EDGs, 1,1-disubstituted product is favoured

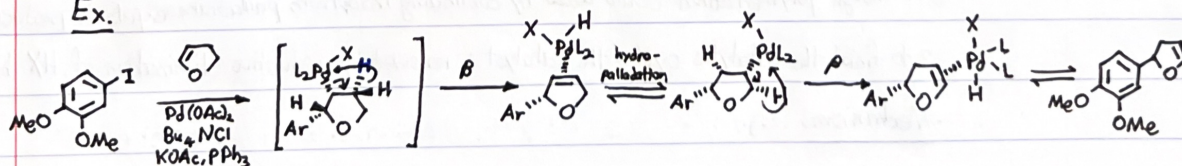
Ex.



• because β-hydride elimination is reversible, the more substituted and stable product results

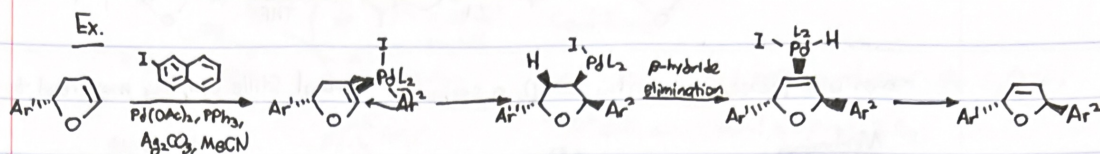
Reversibility of β-hydride elimination & the fact that it must be a syn elimination can be exploited

Ex.



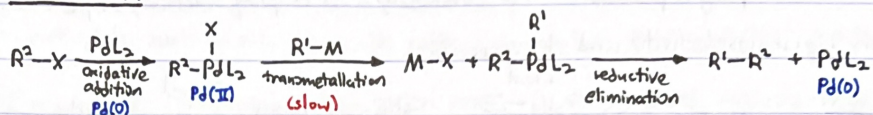
The product can undergo a second Heck reaction, which forms an anti product

* Palladium is very sensitive to steric effects; the less hindered diastereotopic face is preferred



Cross-coupling reactions, which an organometallic reagent and halide compound reacting to give the coupled product, can be done if organometallic catalysts are involved

Mechanism.



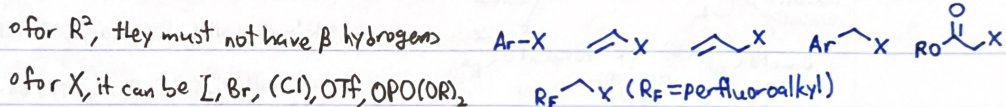
• transmetalation occurs when the nucleophile (R') switches places with the counterion (X)

• for conditions to allow this reaction to proceed smoothly:

◦ for R' , there are essentially no restrictions put into place;

◦ for M , MgX , ZnX , Cu , SnR_3 , SiR_3 , $ZrCp_2Cl$, $AlMe_3$, $B(OR)_2$, BF_4^- are all possible

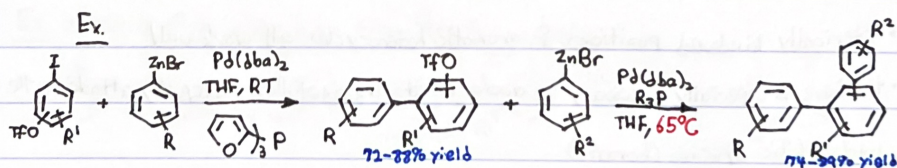
◦ for R^2 , they must not have β hydrogens



◦ for X , it can be I, Br, (Cl), OTf, OPO(OR)₂ R_F-X (R_F = perfluoroalkyl)

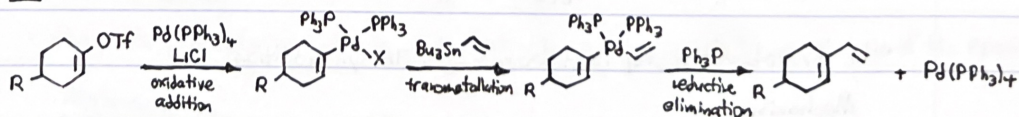
• for B: Suzuki coupling, Mg: Kumada coupling, Sn: Stille coupling, Zn: Negishi coupling

• the difference in reactivity of aryl iodides & triflates can be exploited:



Stille coupling: using stannanes (organotin reagents) for coupling

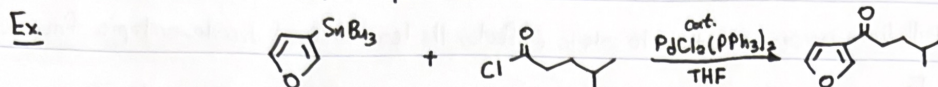
Ex.



• a source of halide (e.g., LiCl) is generally required since OTf may not be able to bind to metal complex

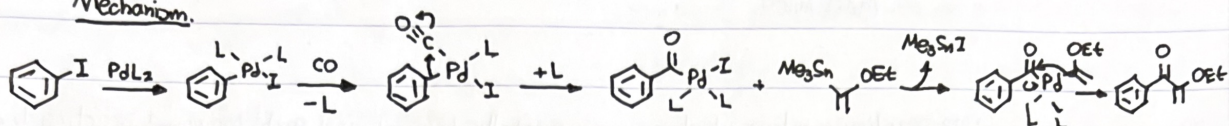
• generally, R' tends to be alkenes (vinyl triflates), but alkynes (sp) can be used as well

Stille coupling can form carbonyl-coupled products w/ acid chlorides & an atmosphere of CO to prevent decarbonylation

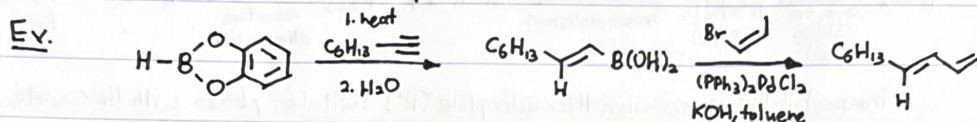


• even with presence of 1 atm CO(g), a seemingly normal Stille coupling may lead to carbonylated products

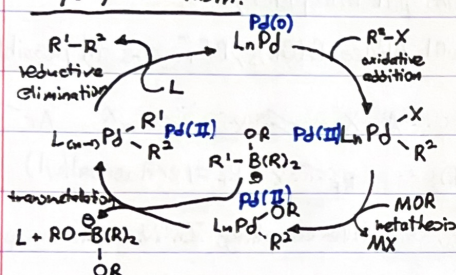
Mechanism.



The Suzuki coupling is probably the most commonly used coupling reactions; simple and mild reactants with very high regioselectivity and stereospecific



Cycle/Mechanism.

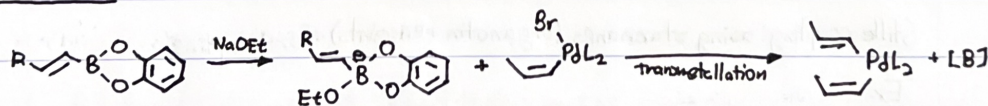


Conditions required for this reaction:

- R^1 = alkyl, allyl, alkenyl, aryl; R = alkyl, OH, O-alkyl; R^2 = alkenyl, aryl, alkyl; X = Cl, Br, I, OTf; Base = Na_2CO_3 , $Ba(OH)_2$, K_3PO_4 , Ca_2CO_3 , K_2CO_3 , $TIOH$, KF , CSF , Bu_4F

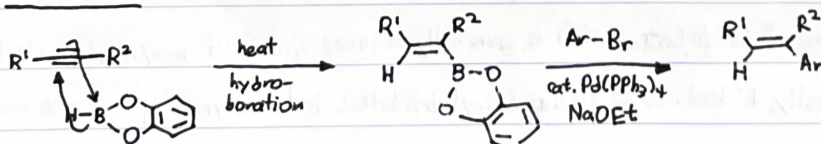
- sterically hindered positions & aromatic heterocycles all work well
- the base is especially necessary to accelerate the transmetalation step, by attaching the boron making it more nucleophilic species (borate)

Mechanism.



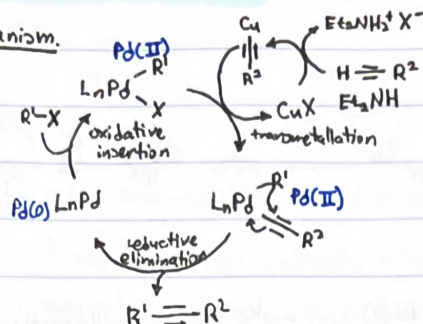
- the hydroboration step is stereospecific with syn addition

Mechanism.



The Sonogashira cross-coupling reaction is a method to couple aryl/alkenyl/heteroaryl & alkynes together

Mechanism.



Conditions:

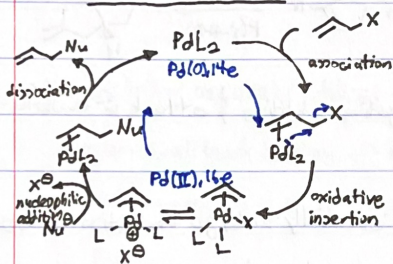
- $R' = \text{aryl, alkenyl, heteroaryl}; X = \text{Cl, Br, I, OTf};$
- $R^2 = \text{H, alkyl, aryl, alkenyl, SiR}_3;$
- both Pd(0) or Pd(II) catalysts are acceptable as Pd(0) can be made in situ

• geometry for the Sonogashira reaction is usually preserved

Allyl electrophiles such as allyl bromides suffer from the lack of regioselectivity due to competing S_N2 & S_N2' reactions; however, Pd complexes allow control over both stereo- and regiochemistry

• leaving groups that are not as good also works; $\text{AcO}^-, \text{OPO}(\text{OR})_2, \text{Cl}^-, \text{Br}^-, \text{OPh}$ all work

Cycle/Mechanism.

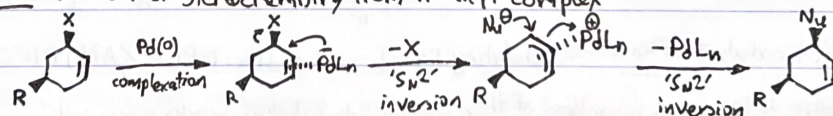


• the reaction (nucleophilic attack) becomes regioselective; will attack whatever results in the more thermodynamically stable product

• with intramolecular reactions, its regioselectivity usually depends on the length of the chain

• reaction usually undergoes retention of configuration; a double inversion occurs

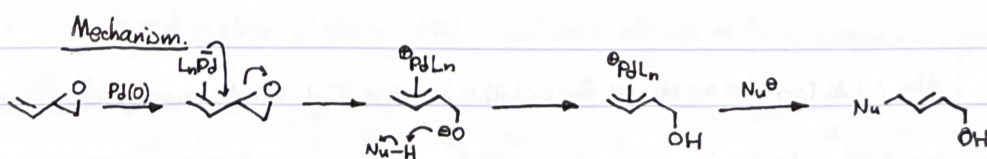
Ex. retention of stereochemistry from π -allyl complex



Vinyl epoxides can undergo an overall 1,4-addition of NuH by Pd(0) catalysis and formation of base from the vinyl epoxide

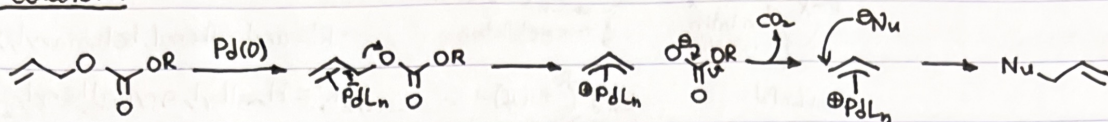
• also undergoes retention of stereochemistry by Pd(0) adding to the opposite side of the epoxide

Mechanism.

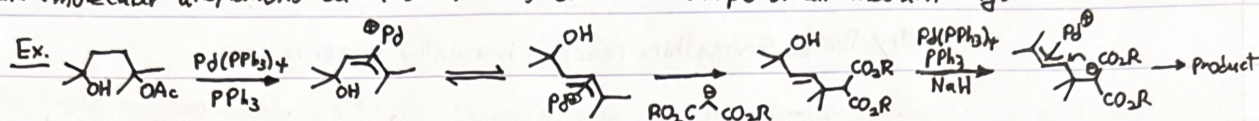


Allylic carbonates w/ Pd(0) catalysis & nucleophile (NuH) results in a net overall S_N2' reaction with retention of stereochemistry

Mechanism.

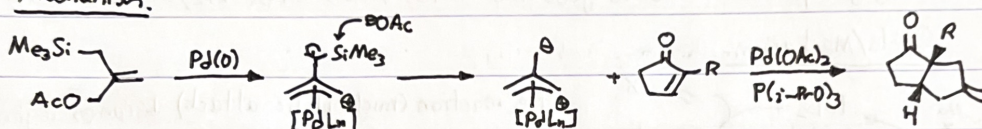


Intramolecular alkylations catalyzed by Pd(0) can make simple small-medium rings



A [3+2] 'cycloaddition' with trimethylethene is catalyzed by Pd(0);

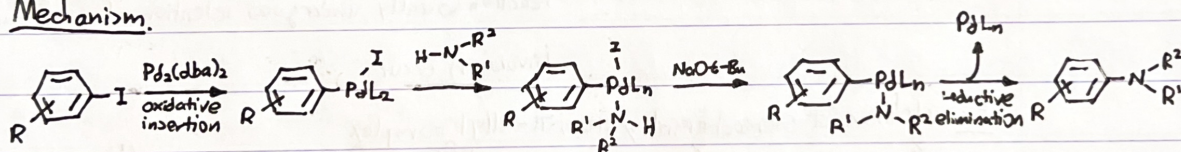
Mechanism.



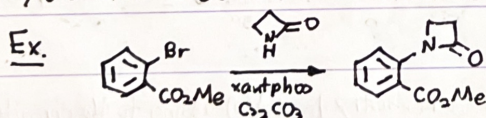
• in reality, the mechanism is stepwise with conjugation addition & attack of enolate to π-allyl unit

The Buchwald-Hartwig cross-coupling utilizes Pd(0) to essentially undergo amination of aromatic rings

Mechanism.

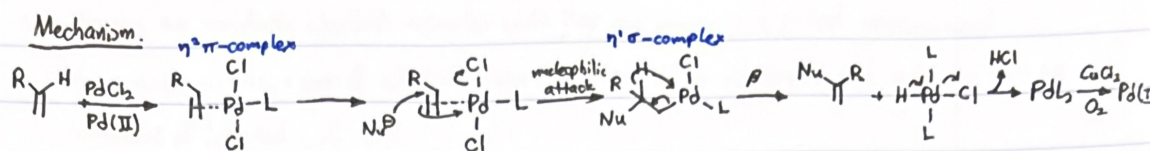


- The Pd(0) catalyst often utilizes chelating ligands such as dba, DPBP, XANTPHOS, BINAP, etc.
- aromatic heterocycles regardless of their electron distribution work very well
- independent of "nucleophilicity" of the amine; amides and even azetidines work well
- they just have to be able to function as a ligand for the Pd complex



Although aryl iodides are the best for oxidative insertion, aryl chlorides are perfectly fine and cheaper

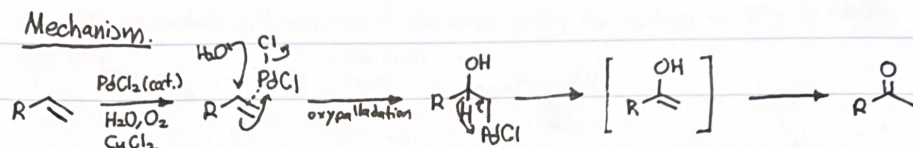
When alkenes are coordinated to Pd(II), it has electron density drawn towards the metal and allows nucleophilic attack



• at the end of the reaction, Pd(0) must be oxidized back to Pd(II); can be done by either:

- just use Pd(II) stoichiometrically, although only appropriate in small scale
- use an external oxidant such as O_2 w/ $CuCl_2$

The Wacker oxidation oxidizes terminal vinyl groups to methyl ketones by oxy-palladation

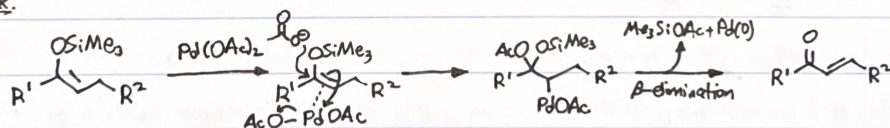


• contrast to the Heck reaction; internal nucleophiles from Pd prefer the terminal position

Oxy-palladation can also be utilized in the oxidation of silyl enol ethers to enones

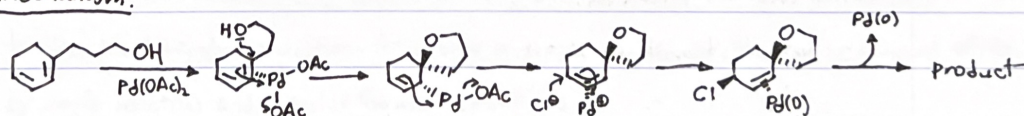
- requires at least half eq. of Pd(II), even w/ reoxidation by benzoquinone
- reaction process is very E-selective, forming trans bonds

Ex.



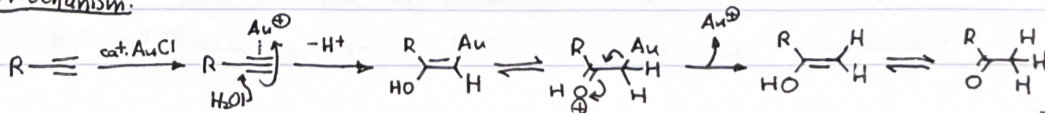
Cyclic ethers/amines can be made intramolecularly w/ Pd(II) catalysis; uses internal amine/alcohol Nuc

Mechanism.



Gold can be used in place of Mercury(II) to activate alkynes to form ketones in water

Mechanism.

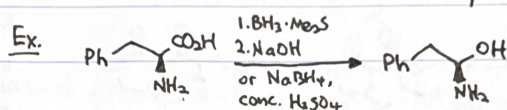


Asymmetric synthesis controls the absolute chemistry to make single enantiomers

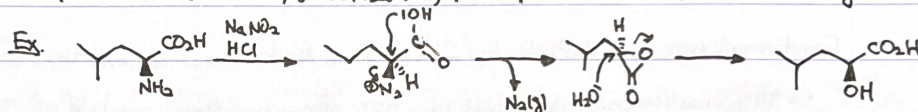
- enantiomers are essentially identical molecules until they are placed in a chiral environment
- this includes nature; a pair of enantiomers can have totally different smell, and medicine can be a difference of life and death

There are many options to choose from when undergoing asymmetric synthesis;

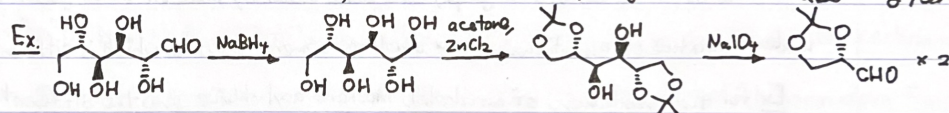
- use the chiral pool - these are enantiomers (pool from nature that can be used as starting materials)
 - all of the amino acids found in proteins
 - simple derivatives of amino acids
 - amino alcohols with retention of stereochemistry can be done w/ BH_3 & NaOH ;



- hydroxy acids can be made by diazotization; participation causes retention of configuration



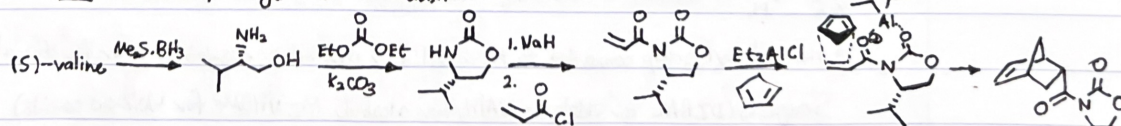
- carbohydrates & their derivatives; D-mannose is the most useful as it can make (S)-glyceraldehyde



- resolution can be a great option for large-scale processes, esp. if both enantiomers are necessary
 - by using a cheap, readily available compd from nature, and for example, allowing it to act as a protecting group, the two enantiomers have different b.p.s or crystalline properties
 - when resolution is used, a maximum theoretical yield of 50% is possible per enantiomer

- chiral auxiliaries are essentially enantiomerically pure compounds, that can act as sort of a "catalyst" to allow diastereoselective reactions form only a single enantiomer; they can be removed afterwards by simple reactions and recycled for more reactions

Ex. formation & usage of a chiral auxiliary

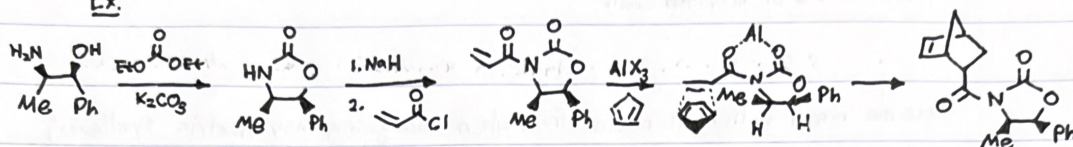


- at the end of a reaction, a simple nucleophilic attack can remove the chiral auxiliary

although it is ideal for both enantiomers for the chiral auxiliary to be available, in this case with Evan's oxazolidinone auxiliary with (S)-valine, it is not

instead, (-)-norephedrine can be used instead to act as an auxiliary made with (R)-valine

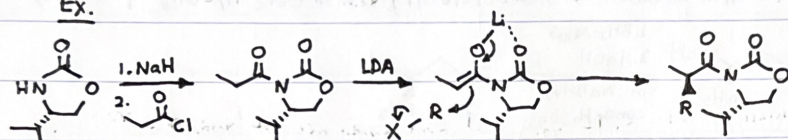
Ex.



Chiral auxiliaries, especially with Evan's oxazolidinone auxiliaries are good for alkylation of enolates

here, the coordination of the lithium ion is crucial to fix the structure and prevent attack on the wrong face

Ex.



R-X diastereoisomeric ratio (d.r.)

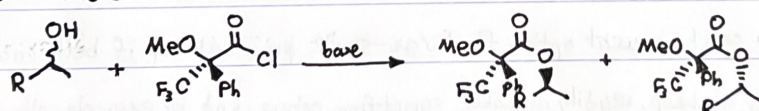
BnBr	99:1
AllylBr	98:2
EtI	94:6

Enantiomeric excess (ee) illustrates how much more one diastereoisomer has over the other

a 94:6 enantiomeric ratio would have 88% of one enantiomer and 12% of mixture (racemate); the 88% ee

in order to determine ee, chromatography on a chiral stationary phase (HPLC or GC) or making a derivative that makes a mixture of enantiomers into a diastereoisomeric mixture, which is differentiable by NMR

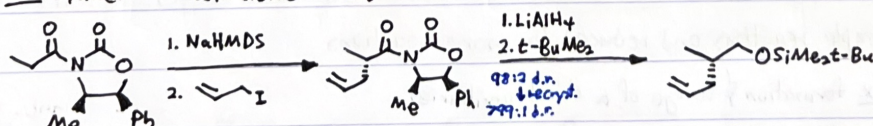
Ex. for two enantiomers of an alcohol, Mosher's acyl chloride gives two different diastereoisomers



integration of ^1H and ^{19}F NMR gives us the ratio of diastereoisomers

Chiral auxiliaries can function as a resolving agent; as the compounds are a pair of diastereoisomers, they are much easier to separate by recrystallization

Ex. synthesis of antibiotic X-206



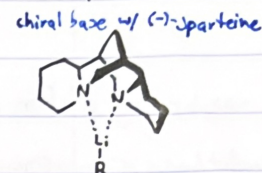
the carbonyl group connected to the auxiliary can be converted to other functional groups with typical reagents (DIBAL for aldehyde, LiAlH_4 for alcohol, MeNHOMe for Weinreb amide)

acid/base hydrolysis needs more attention; risks epimerization (interconversion of one chiral centre) so using hypervalent iodine or LiOH is recommended to form carboxylic acid

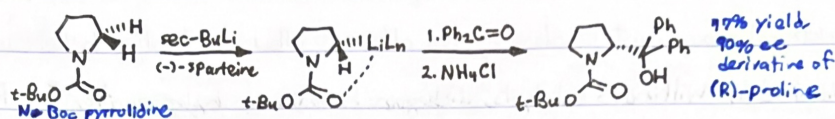
Unlike previous methods which rely on substrate control (e.g. using the chiral pool), chiral reagents can be used to undergo enantioselective reactions

- an enantiomerically pure chiral base can selectively choose one of the two enantiotopic protons and must form a chiral product

- chiral organolithiums can be made; enantioselective planar enolates cannot



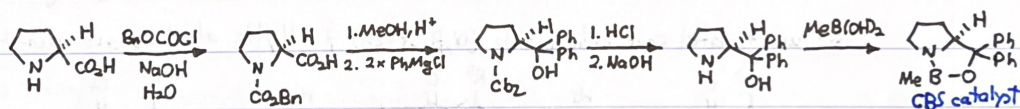
Ex. sparteine-mediated lithiation



- in order for asymmetric catalysis (or just to create a few chiral centre in general) to work, you need the carbon centre to be prochiral; one step away from becoming chiral

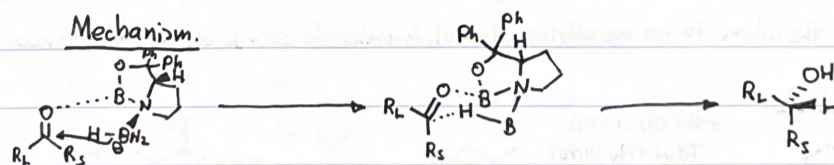
The CBS catalyst utilizes a boron heterocycle which complexes with borane, enantioselectively transferring a hydride to a ketone by a six-membered transition state

Preparation.



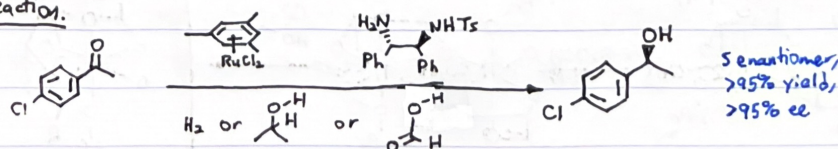
- given that the ketone's two substituents differ greatly in terms of steric effects, the reaction works well
- borane (BH_3) cannot reduce ketones; when it is complexed w/ the CBS catalyst, the boron atom functions as a Lewis acid to make the ketone more reactive, and the basic nitrogen donates electron density to BH_3 to persuade the hydride transfer

- undergoes a six-membered cyclic transition state, with the large substituent at pseudoequatorial

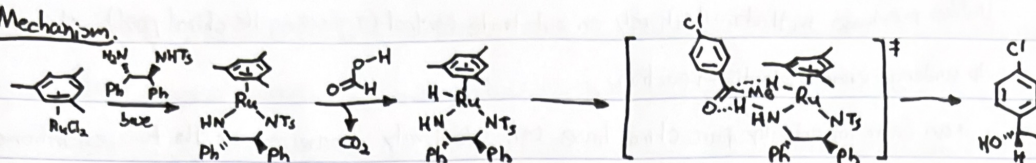


Another way to undergo asymmetric hydrogenation of ketones is through this ruthenium catalyst:

Reaction.



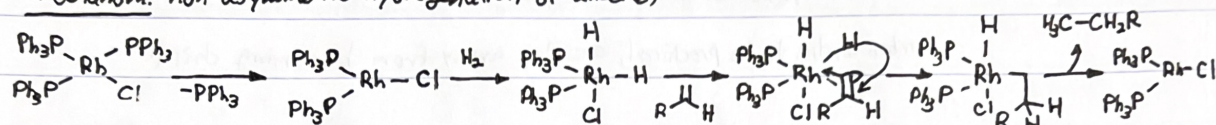
Mechanism.



For asymmetric hydrogenation of alkenes, a soluble complex (esp. Rh & Ru) as a homogeneous catalyst is commonly used

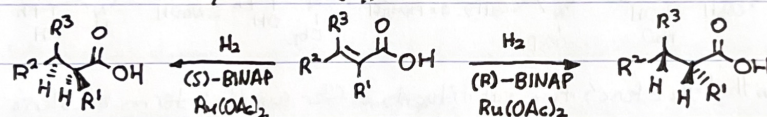
- a functional group must be close by the alkene to allow coordination to the complex
- first inspired by Wilkinson's catalysts, undergoes homogeneous hydrogenation w/ $\text{RhCl}(\text{PPh}_3)_3$

Mechanism. non-asymmetric hydrogenation of alkenes



- by changing the phosphine ligands w/ something chiral (BINAP in particular), the complex must transfer hydrogen on one of the two possible enantiotopic faces of the alkene during migratory insertion
- coordination substituents are best done with N -acyl enamines, giving excellent results

Ex: unsaturated carboxylic acids (α, β often) & allylic alcohols are great too

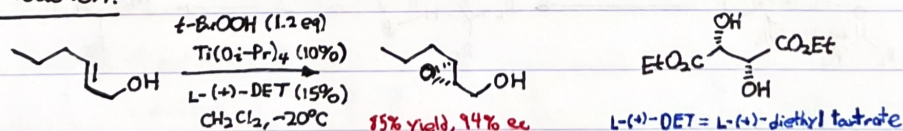


- the right combination of metal & ligand can enantioselectively reduce any unsaturated carboxylic acid derivative.

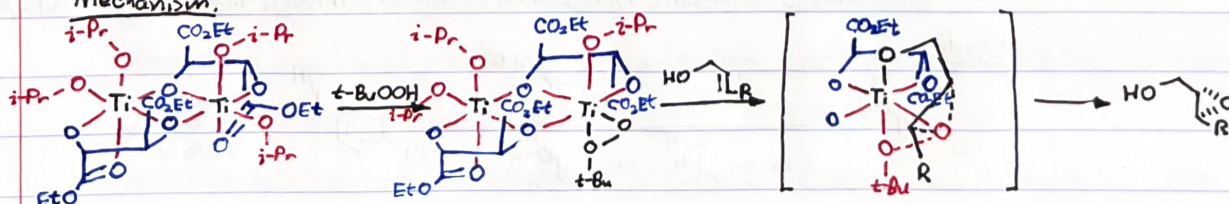
Asymmetric epoxidation is done best using Sharpless epoxidation, using titanium catalysis

- requires the alkene to be an allylic alcohol in order to coordinate to the titanium complex

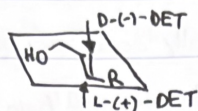
Reaction.



Mechanism.

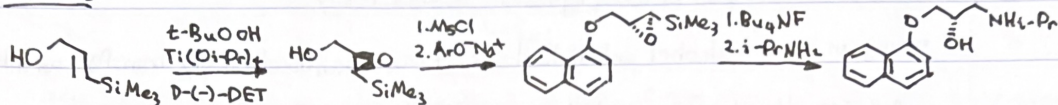


predicting how the different enantiomers of the chelating ligand would lead to which enantiomeric product can be rather difficult, but the following mnemonic can be used as a rough guide:



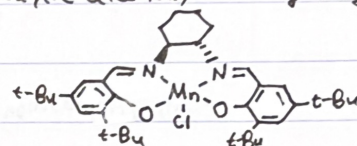
very good synthon for enantiomerically pure 1,2,3-functional group patterns; starting material can be an allylic alcohol (although warning: a silicon-substituted allylic alcohol was used as the epoxide is hard to handle)

Synthesis.



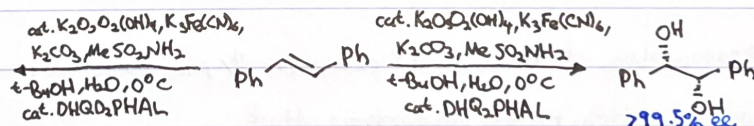
The Jacobsen asymmetric epoxidation can be used for alkenes w/o allylic alcohols, utilizing a ligand w/ C₂ symmetry known as a "salen" derivative

- mechanism is not well understood, probably a concerted mechanism involving the Mn(V) oxo species

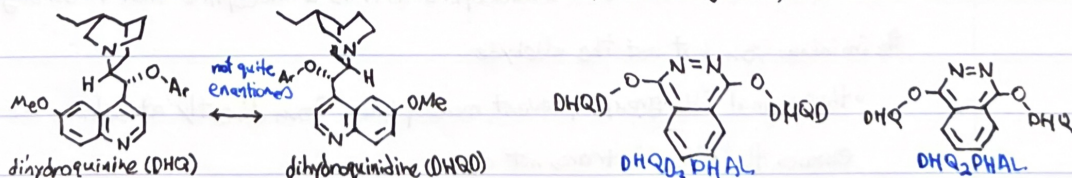


The Sharpless asymmetric dihydroxylation is one of the greatest asymmetric reaction of all

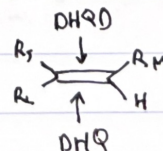
Reaction.



- OsO₄, the reagent typically used in normal dihydroxylation is often created in situ as it is volatile & toxic
- K₃Fe(CN)₆ functions as oxidant for OsO₄ after dihydroxylation
- K₂CO₃ & MeSO₂NH₂ increases the rate of the reaction
- DHQD₂PHAL & DHQ₂PHAL are two chiral tertiary amine ligands; see below



- The mixture above (w/ MeSO₂NH₂) is sold commercially, DHQD₂PHAL → AD-β & DHQ₂PHAL → AD-α
- reactivity patterns are illustrated by this mnemonic:

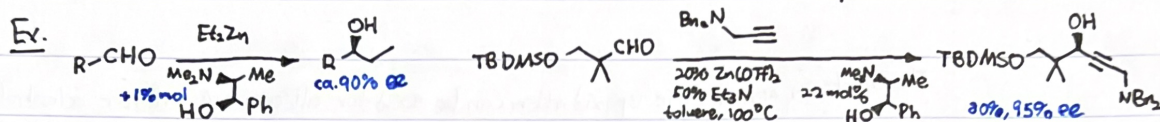


The reason why Sharpless asymmetric dihydroxylation works well is because the ligands provide a chiral environment AND accelerates the reaction (known as ligand-accelerated catalysis)

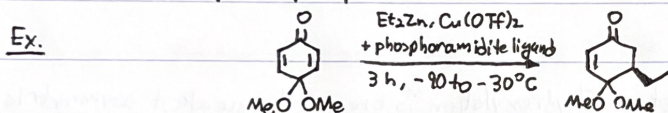
- we want reactions that don't normally occur very quickly to utilize asymmetric ligand-accelerated catalysis as if the reaction still works very well (w/o the ligand), racemic background reactions will overwhelm the "asymmetric reactions" we desire

Here are some examples of using ligand-accelerated catalysis:

- using an amino-alcohol and dialkylzinc, it can enantioselectively transfer an alkyl group to an aldehyde
- a zinc alkoxide forms, which accelerates the transfer of the alkyl group

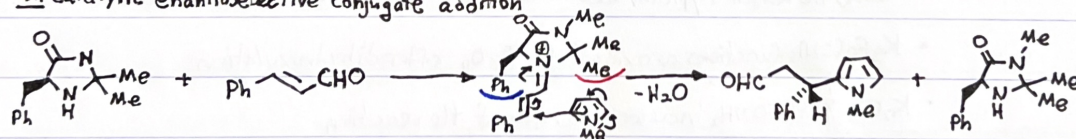


- conjugate addition can be promoted by copper, and using organozinc + chiral phosphorus-containing ligands such as phosphites/phosphoramidite made from (S)-BINOL



Organocatalysis, which uses chiral & enantiomerically pure compounds (commonly amides) provide a chiral environment and activates them towards enantioselective attack

Ex. catalytic enantioselective conjugate addition

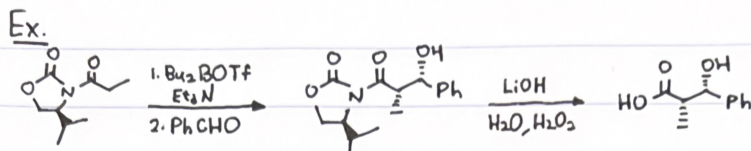


- here, pyrrolidine was chosen as the nucleophile as it is a nucleophile that is strong enough to attack the iminium ion but not the aldehyde

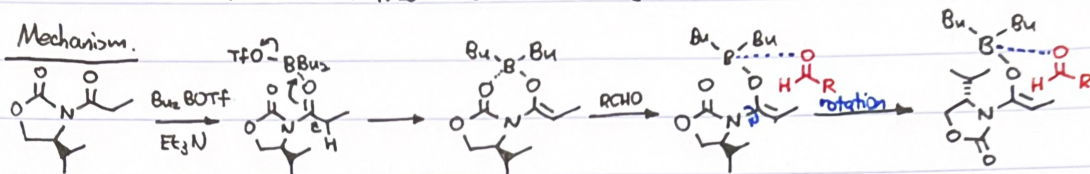
- the geminal CH_3 groups prevent nucleophiles from directly attacking the C=N bond and ensures the imine is trans, not cis

- the benzyl group shields the front of the alkene, making it enantioselective

Evan's auxiliaries are one way to undergo asymmetric aldol reactions



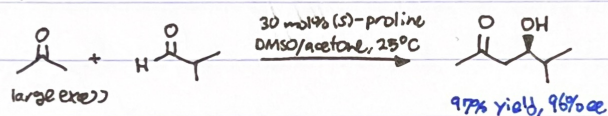
the mechanism is beautiful and involves boron coordinating to different oxygen atoms



the enolate attacks the aldehyde on the front face of the enolate; undergoes a six-membered Zimmerman-Traxler transition state with the aldehyde R group pseudoequatorial

Aldol reactions are also catalyzed by L-proline

Ex.



of the two reactants, the ketone can easily form the more reactive enamine as it is in large excess and less hindered

Mechanism.

