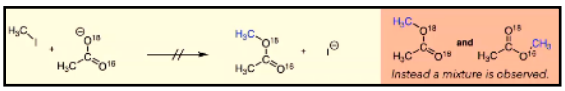
Carbonyl and Mechanism (W1)

Carbonyl polarity and mechanism (L1)

Recapping Resonance

- Resonance is a model that can be used to explain the **structure and reactivity** of molecules
  - It is used when a single Lewis structure cannot adequately represent a molecule
- Consider the following example

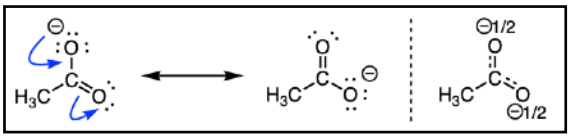


Resonance provides insight into:

1. The **stability** of starting materials/intermediates and products (greater the resonance greater the stability)
2. **Sites** of **reactivity**

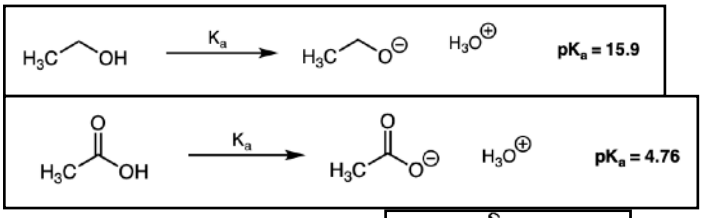
Notes on resonance

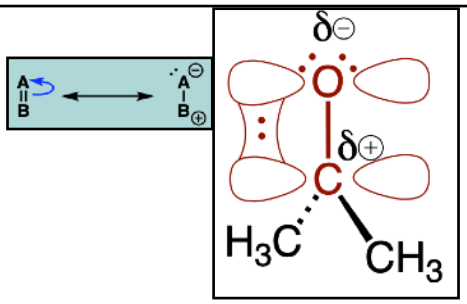
1. These are structures related through resonance (**resonance structures**) (left)
2. They are hypothetical
3. Neither is real, a **mix** can be useful to explain reactivity (the **resonance hybrid**) (right) (put **δ-** for partial negative charge)



Resonance of carboxylate accounts for acidity

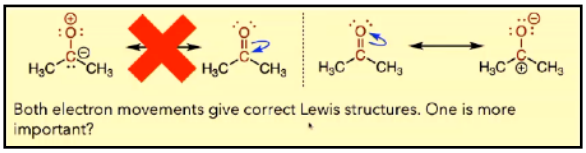
- Consider the difference in acidity of ethanol and acetic acid
- Ethanol - pKa = 15.9
- Ethanoic acid - pKa = 4.76
- A conjugate base with resonance stabilisation will be more stable, hence makes the conjugate acid more acidic





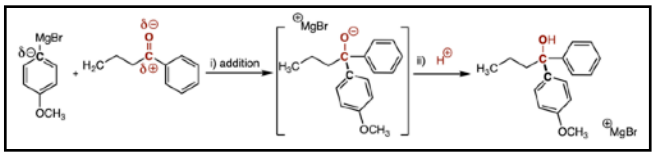
Resonance across **2 atoms**

- **Scenario #1**
- Resonance structures can be considered with any **double bond**
- A=B <—> :A(-)—B(+)
- A carbonyl is a double bond between an **sp2 C and an sp2 O**
- The bond is polar due to
  - The difference in electronegativity between oxygen (3.44) and carbon (2.55)
  - The resonance structures shown below
- Both electron movements give correct Lewis structures. One is more important? Carboanion not involved



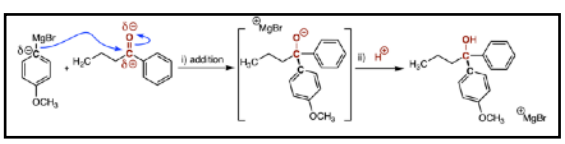
A reaction explained by resonance across 2 atoms

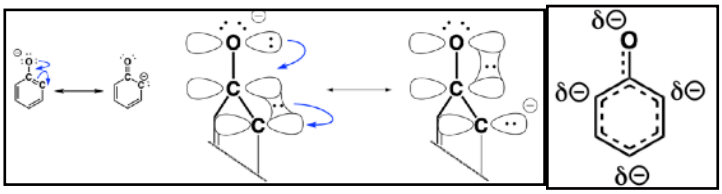
- Grignard reaction + carbonyl group
  - Addition reaction (breaks C=O double bond)
- Carbon is more δ- (more electronegative) so more nucleophilic
- C-O(-) (+)MgBr intermediate
- After acidic H+ is added
- Produces alcohol



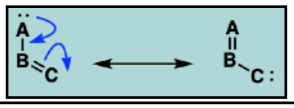
Adding the arrows

- Rule #1: Arrows always start at the nucleophile and go towards the electrophile
- Rule #2: An arrow cannot result in an impossible Lewis structure
- Rule #3: Charge is conserved in each step of a mechanism (A handy rule for checking for mistakes, consider example)

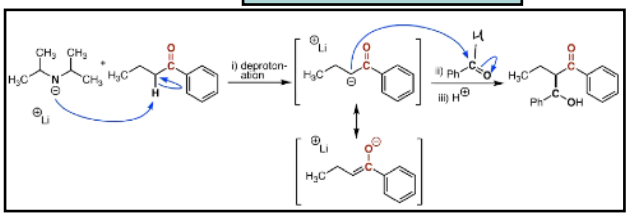




Resonance across **3 atoms**
- **Scenario #2**
- An atom with a **lone pair** (:A) attached to a **double bond** (B=C)
- Empty orbital present for double bond electrons
- The resonance hybrid of phenoxide is useful in considering aromatic chemistry, taught later

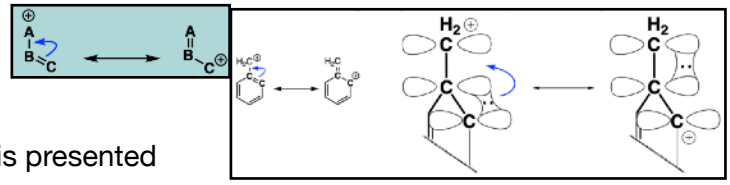


Enolates form because they are resonance stabilised
- LDA + carbonyl
- (-)C-C=O or HC-C-O(-)
- Enolate intermediate is stabilised by resonance
- Electrophile attacked by more reactive form (carboanion more reactive than oxyanion)

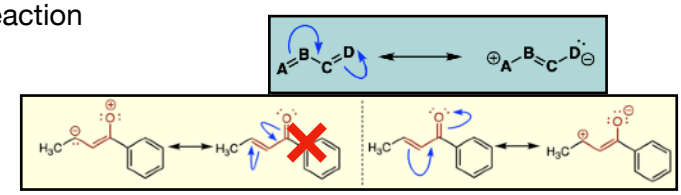


Enolates add to carbonyls in the Aldol reaction
- Enolate intermediate can be reacted with electrophile and can form carbonyl product

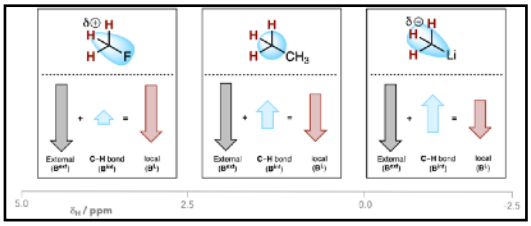
Resonance across **3 atoms (cations)**
- **Scenario #3**
- An atom with an **empty orbital** (A) attached to a **double bond** (B=C)
- This will not feature significantly in this course but is presented for completeness
- Primary carbocation is most unstable and will be in reaction



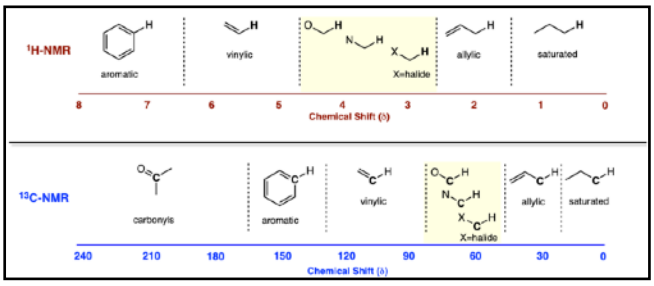
Resonance across **4 atoms**
- **Scenario #4**
- **Two π-bonds separated by a σ-bond**
- Both electron movements give correct Lewis structures. Which one is more important?
- **Double bond conjugated to carbonyl group**
- Electron arrows always move towards more electronegative atoms in resonance



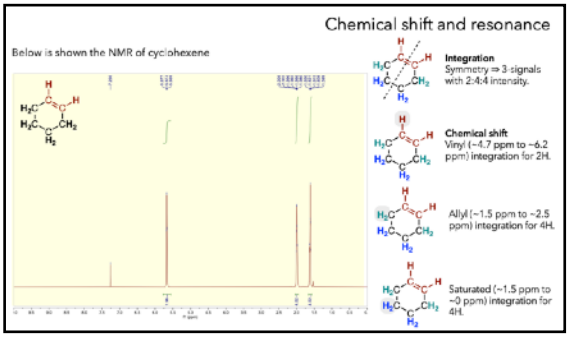
Chemical shift is determined by local electron-density
- Evidence for the effect of resonance on polarity can be obtained by considering the 1HNMR
- Consider the impact of inductive polarisation in the following series
- More electronegative the group is, the more downfield the H group is (more deshielded of electrons)

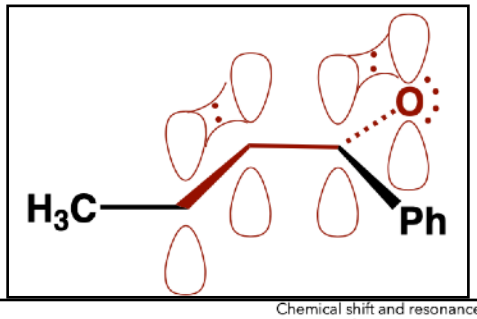


Different chemical shifts:

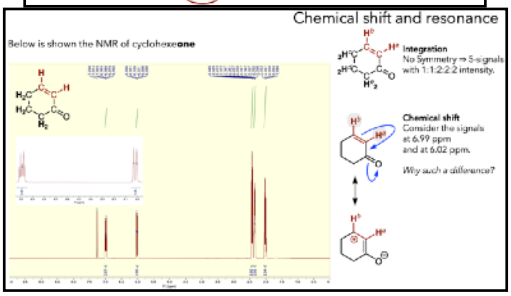


NMR of cyclohex**e**ne
- Integration
  - Symmetry -> 3 signals
  - 2:4:4 intensity
- Chemical shift
  - Vinyl (~4.7ppm to ~6.2ppm) integration for 2H
    - **H**C=C**H**
  - Allyl (~1.5ppm to ~2.5ppm) integration for 4H
    - **H2**C-CH=CH-C**H2**
  - Saturated (~1.5ppm to ~0 ppm) integration for 4H
    - **H2**C-CH2

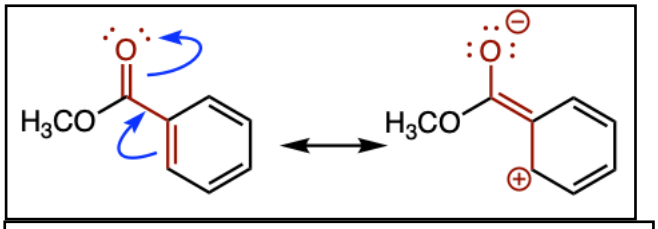




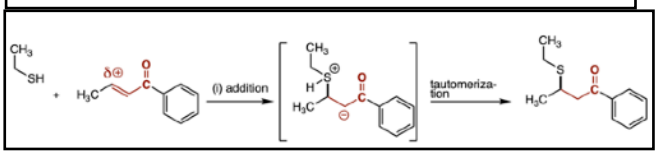
NMR of cyclohex**one**
- Integration 5 signals (1:1:2:2:2)
- Ha more deshielded than Hb (Ha more downfield)

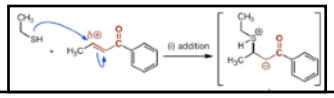


Resonance with 4 atoms
- Scenario #4
- Two pi-bonds separated by a sigma-bond
- The 4-atom resonance of electron-poor aromatic rings will be spoken about later

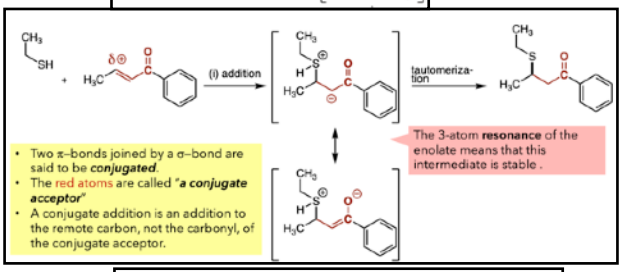


The conjugate addition
- Scenario #4
- (-)C=C-C=O
- Nucleophilic addition (CH3CH2SH)
- Tautomerisation

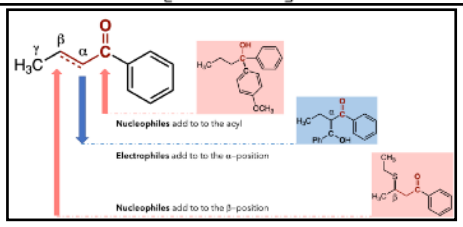




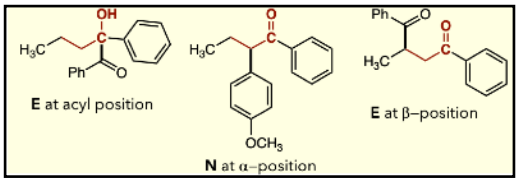
The conjugate addition
- **Two π-bonds joined by a σ-bond** are said to be **conjugated**
- The **red atoms** are called "**a conjugate acceptor**"
- A **conjugate addition** is an addition to the **remote carbon, not the carbonyl**, of the conjugate acceptor
- The 3 atom resonance of the **enolate** means that this intermediate is stable



Summary of Normal Polarity Reactions of the Carbonyls
- The previous 3-examples illustrate the natural polarity reactions of the carbonyl and surrounding atoms
- **Nucleophiles** add to the **acyl** (C=O) (carbon is electropositive)
- **Electrophiles** add to the **alpha-position** (carboanion less stable than oxyanion - enolate resonance) - acidic H
- **Nucleophiles** add to the **beta-position - conjugate addition**



Most reactions involving the carbonyl follow this pattern of reactivity
- By identifying nucleophiles/electrophiles and looking for these patterns it becomes more simple to predict reaction outcomes and mechanisms
- What about when you want an electrophile at the acyl or beta-position, or a nucleophile at the alpha position? (Reverse of mentioned before)
- These are called Reverse Polarity Reactions (Week 3)

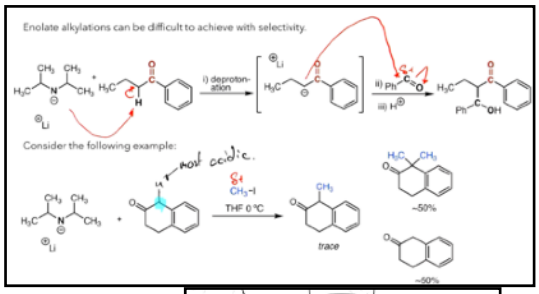


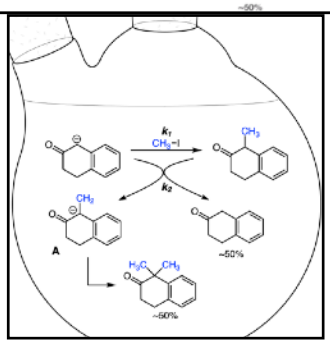
Organocatalysis 1 (W2)

Organocatalysis Part 1 (L1)

Background enolate alkylations

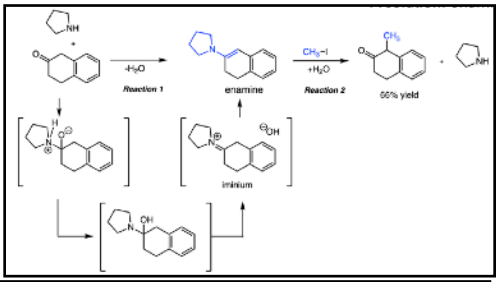
- Enolate alkylations can be difficult to achieve with selectivity
  - LDA + ketone —(Deprotonation)—> enolate
  - Carboanion is more reactive than oxyanion
  - Lone pair on carbon attacks electrophile
- Consider the following example:
  - LDA + ketone -> enolate + CH_3I -> alkylation of enolate carbon
  - Dont achieve expected product





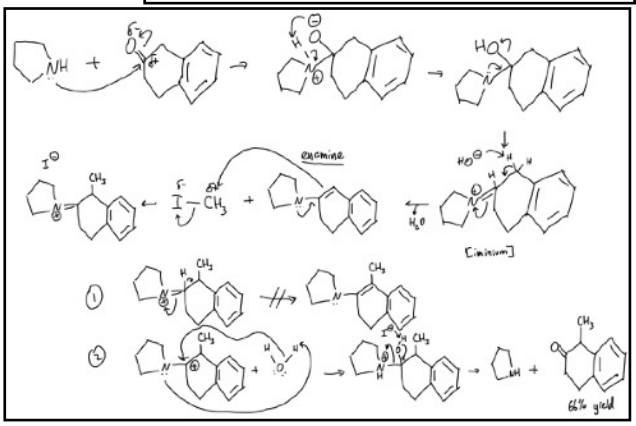
Why doesn't this reaction work?

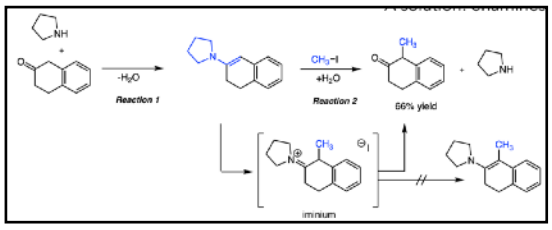
- If the rate of **alkylation (k_1)** is **less** than the rate of **proton transfer (k_2),** then enolate **A** will be favoured —> leads to **di-alkylation**
  - Would this be expected?
- **Second acidic H can be removed from another enolate**
- Enolate —(k1)—> Methyl group on enolate carbon
- Enolate —(k2)—> CH2 swaps with H or H group on enolate carbon
- A: produces two methyl groups on enolate carbon

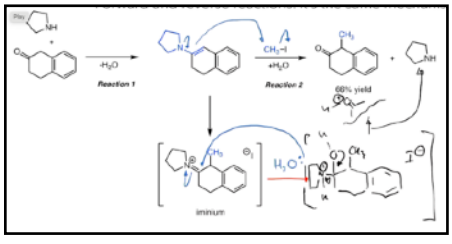


A solution: **enamines**

- **Secondary NH + ketone** —> **enamine** (loss H2O)
- Enamine + CH3-I + H2O —> cyclic NH + ketone (with methyl group)
- Consider **Reaction 1**
  - Nitrogen adds to carbonyl
  - Proton transfer from NH (tautomerisation)
  - Elimination of hydroxide (to give iminium)
  - Hydroxide acts as a base to generate enamine
- Consider Reaction 2
  - Alkylation at the nucleophilic carbon of the enamine vies a new iminium
  - But there is **no base to regenerate the enamine** so the **reaction stops ((1) doesn't proceed)**
  - Water cleaves the iminium and returns the carbonyl





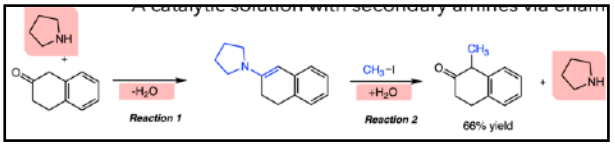


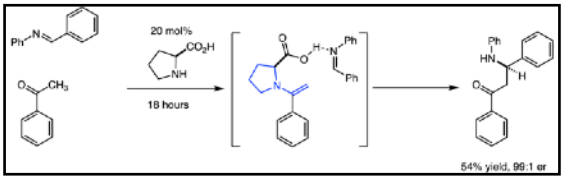
Forward and reverse reactions. It's the same mechanism

- Secondary amine + ketone —> enamine + H2O
- Enamine + CH3-I + H2O —> iminium —> methyl on alpha carbon of ketone

A catalytic solution with secondary amines via enamines

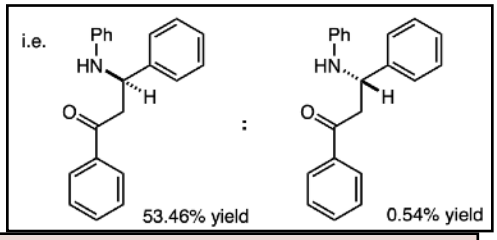
- The conditions to form the **enamine** (Reaction 1) and for its **alkylation** on alpha carbon (Reaction 2) are compatible, allowing **catalytic reactions to be achieved**
- Example:





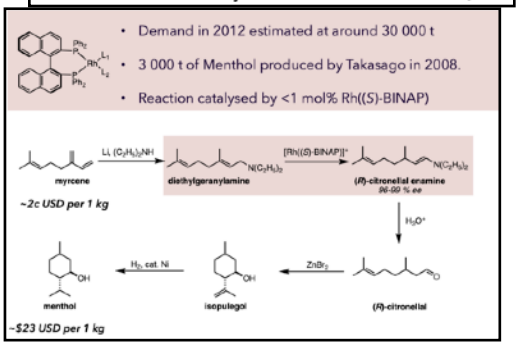
Defining some terms used in catalysis

- The **efficiency** and **selectivity** of a reaction can be quantified. Some common terms are introduced below
- **Catalytic loading** is the **amount of catalyst** needed for the reaction
  - 20 mol% means that "For every mol of substrate you need 20% the amount of catalyst (in moles)" (smaller = less enzyme needed)
- **Turnover number (TON)** is a measure of **efficiency** and is defined as **mol(product)/ mol(catalyst)**
  - 54% yield means "for every mol of substrate you generate 0.54mol of product"
    - TON = 0.54/0.2 = 2.7 turnovers (**each catalyst molecule makes 2.7 molecules of product**)
- **Turnover frequency (TOF)** is a measure of **reaction rate** and is defined as **TON/time**
  - If 2.7 turnovers are achieved in 18 hours then the TOF = 2.7/18 = 0.15 turnovers per hour
- **Enantiomeric ratio (er)** is the ratio of the two enantiomers. The major one is drawn, the minor is assumed. Determines **selectivity**



Catalysis enables good chemical synthesis

- Demand in 2012 estimated at around 30,000 t
- 3,000t of menthol produced by Takasago in 2008
- Reaction catalysed by <1 mol% Rh((*S*)-BINAP) (tautomerisation)
- Relieving minor pain caused by conditions such as arthritis, bursitis, tendonitis, muscle strains or sprains, backache, bruising, and cramping



Menthol will soon be made via 4 competing routes

- Myrcene: takasago (five steps)
- m-Cresol: symrise (six steps)
- (Z)-Citral (neral): BASF (four steps)
- Mentha arvensis: producers in India and China (distillation, crystallisation)
- All produce (-)-Menthol

How important is catalysis economically?

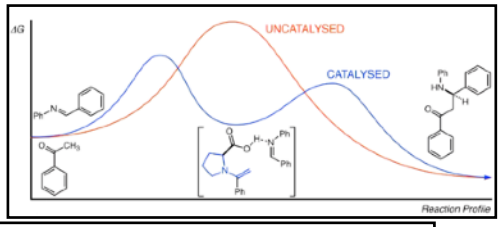
- In 2017 sales of catalysts in the US were estimated at 7.8 billion USD
- Global sales estimated at 33.9 billion USD
- In 2019 chemical manufacturing revenue estimated at 3.94 trillion USD
- Most of this manufacture involves at least one catalytic reaction

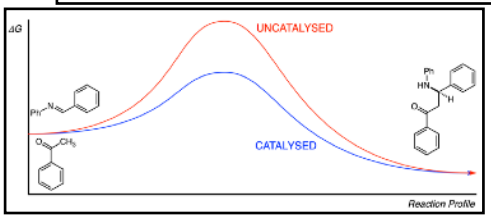
Catalysis and thermodynamics

- Definition: "The action of a material (catalyst) to increase the rate (k) of a chemical reaction"
  - The **rate of a reaction (k)** is defined by the **activation energy** for its slowest step thus the catalyst acts to decrease this activation energy
  - The **thermodynamics (K)** of the reaction are unchanged. K = [C]/[A][B]
- A catalyst changes the rate by which something happens, not whether it will happen or not
- But in life and chemistry **how long something takes** is often the most important thing

Catalysis and Thermodynamics

- Catalysis of reactions is generally achieved by one of the two following ways
- **Option 1**: The catalyst creates a **new** reaction pathway involving **lower energy transition states**
- **Option 2**: The same reaction pathway is used but the **transition state** of the rate determining step is **stabilised** (solvent base catalysis)





Main types of homogenous catalysis

	efficiency	generality	toxicity	Operational ease	General utility
Biocatalysis	✓✓✓	-	✓	✓	✓✓✓✓
Organocatalysis	✓	✓✓	✓	✓✓✓✓	✓✓✓✓
TM Catalysis	✓✓	✓✓✓	✓✓✓	✓	✓✓✓✓

- The three main types of **homogenous catalysis** are
  - **Biocatalysis - low generality, very efficient**
  - **Organocatalysis - high operational ease**
  - **Transition Metal catalysis - toxic, high generality**
- They all have strengths and weaknesses, a summary of these is shown
- Efficiency: how effective is it?
- Generality: is it universal, or is a solution to a specific problem?
- Operational ease: how easy is it to perform:
- General utility: can it be used to solve a problem of chemical synthesis

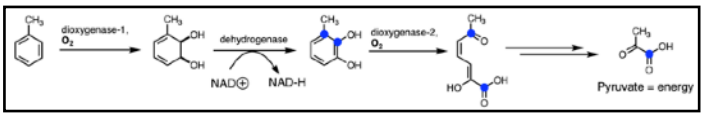
Biocatalysis **[1]**

- Biocatalysis uses **enzymes** to achieve chemical reactions valuable **outside of the biological context**
- Most commonly performed as either

1. Whole cell transformations
2. Using isolated enzymes

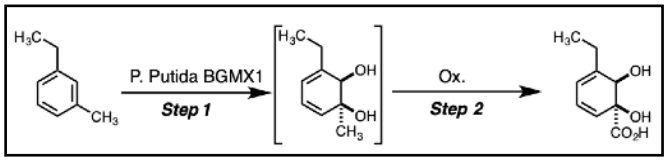
Whole cell transformations

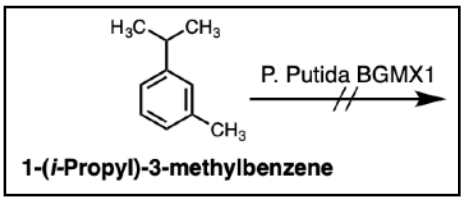
- The use of whole cells to perform chemical reactions, often evolved yeast or bacteria
  - **Limited** to **substrates tolerant of biological systems**
  - Requires specialised isolation steps
- For example: various bacteria have evolved to exploit toluene as an energy source
  - Toluene —> pyruvate



Whole cell transformations

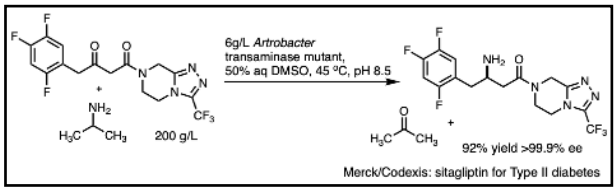
- If the **dioxygenase-1 enzyme** is cloned into an expression system, recombinant bacteria capable of performing a "useful" reaction can be developed
- An example is the reaction of P. Putida BGMX1 bacterial strain shown below
  - This reaction uses cheap and readily available starting materials
  - **Unusual reactivity**: there is no chemical reaction equivalent to the one shown above (unique reactions)
  - **Limited generality**: for example 1-(*i*-propyl)-3-methylbenzene does not react





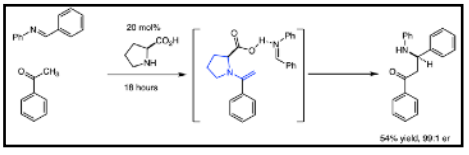
Isolated enzymes

- The use of **enzymes**, normally evolved using directed evolution, **expressed and isolated** to achieve a chemical reaction
  - Approach in protein engineering in which mutagenesis is followed by selection that mimics natural selection



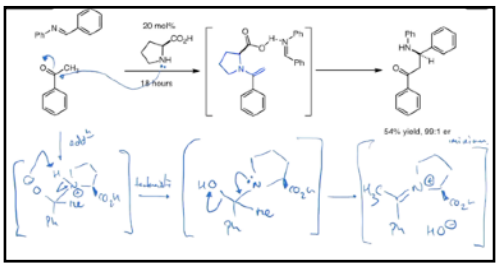
Organocatalysis **[2]**

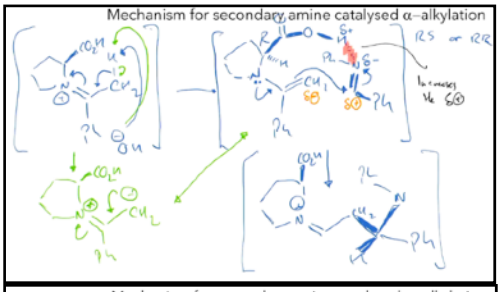
- Organocatalysis is defined as: "The use of **small organic molecules** to **catalyse reactions**."
- In this case the catalyst is the amino acid **proline**
- Often organic catalysts are:
  - Cheap, sustainable (naturally occurring materials easily isolated)
  - Easily handled as catalysts (air and moisture insensitive)
  - While organocatalysis has received significant attention since around 2000 it is actually a very old field of catalysis (1958)

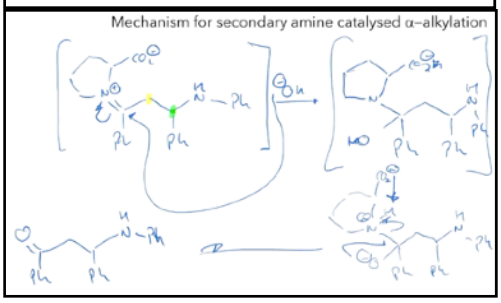


<u>Returning to secondary amine catalysis (Via enamines)</u>

- Mechanism for secondary amine catalysed alpha-alkylation
- Both enantiomers will have different activation energy pathways, so one enantiomer will have lower energy and be more favourable





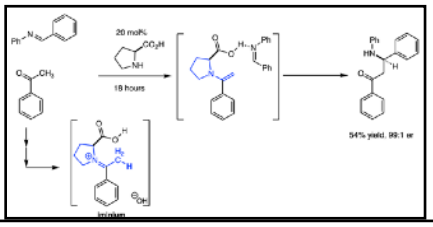


Organocatalysis 2 (W3)

Organocatalysis Part 2 (L1)

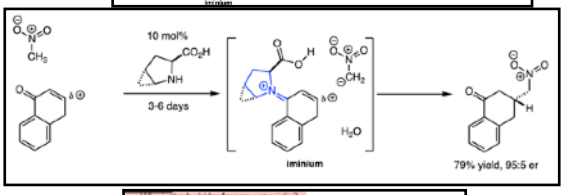
Secondary amine catalysts also allow reactions of the iminium

- Previously we discussed the formation of the enamine using proline as a catalyst



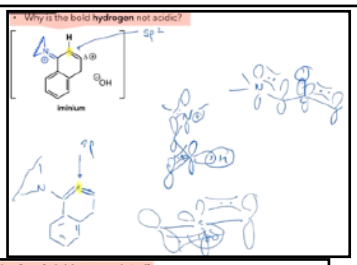
Enantioselective conjugate addition using the iminium

- Consider an example which **lacks an acidic proton**
- Secondary amine catalyst (act same way as Proline)
- Why is the bold hydrogen not acidic?
  - Can't resonance stabilise the carbon



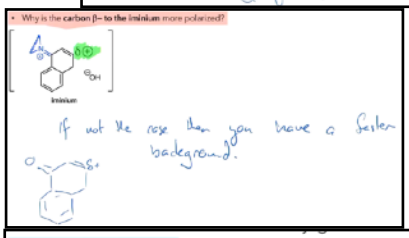
Why is the hydrogen not acidic:

- Removal of H cannot be resonance stabilised



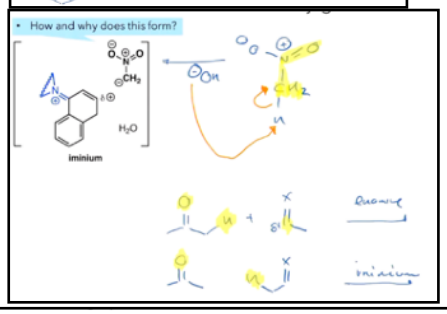
Why is the carbon beta- to the iminium more polarised:

- If not the case then you have a faster background



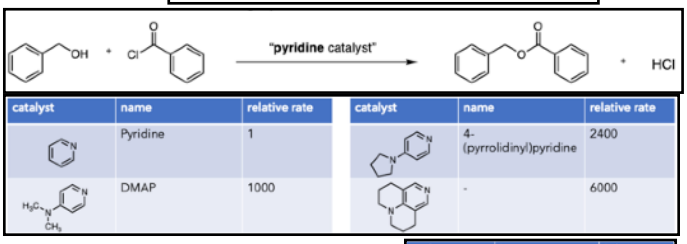
How and why does this form?

- Nitromethane



Esterification by Pyridine catalysts

- One of the most common organocatalyst is **4-dimethylaminopyridine (DMAP)** which is used for **esterification** (and related) reactions
- Consider the following equation

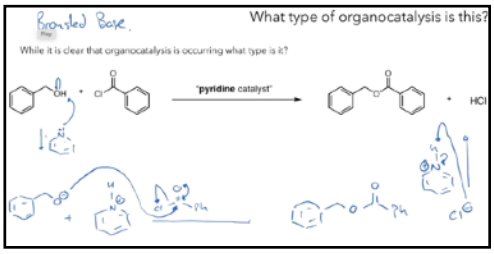


catalyst	name	relative rate	catalyst	name	relative rate
	Pyridine	1		4-(pyrrolidinyl)pyridine	2400
	DMAP	1000		-	6000

catalyst	Name	Relative rate
	2-methylpyridine	0.05
	2,4-dimethylpyridine	0.01

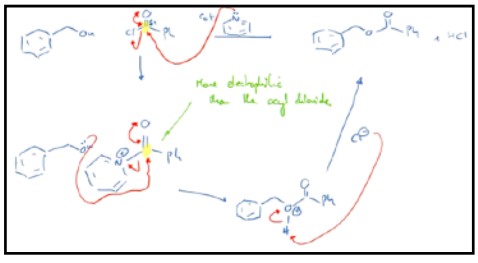
Esterification by Pyridine catalysts

- Relative rate of different pyridine catalysts
  - Pyridine: 1
  - DMAP: 1000
  - 4-(pyrrolidinyl)pyridine: 2400
  - "No name": 6000
    - **Planarity** makes it so good: orbital alignment
    - For resonance to occur, needs to be planar (other versions have bonds free to rotate)
    - The annulation forces the p-orbital on N to be in "plane"
- What type of organocatalysis is occurring?
  - Clear that its organocatalysis, but…
  - **Bronsted Base mechanism (1):**
  - Sensitive to **sterics unlikely**

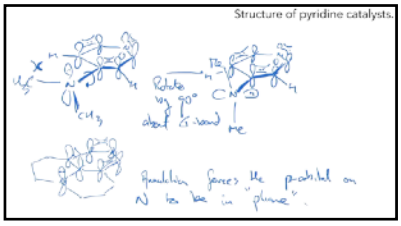


Mechanism for DMAP catalysed esterification

- **Lewis base mechanism (2):**
- Carbonyl carbon is more electrophilic than acyl chloride due to N+
- **Sterics are more important** in lewis base mechanism which

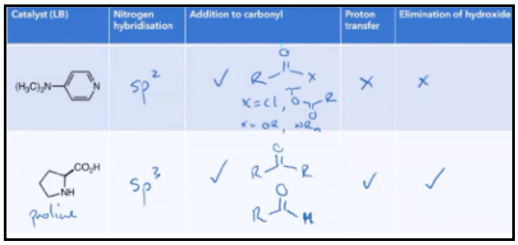


explains the lower rate of reaction of steric catalysts



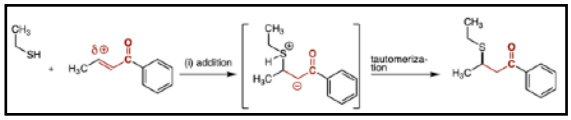
Structure of pyridine catalysts

- **Planarity** makes it so good: orbital alignment
- For resonance to occur, needs to be planar (other versions have bonds free to rotate)
- The annulation forces the **p-orbital on N to be in "plane"**
- By considering the kinetic data is was possible to rule out the Bronsted base pathway in favour of Lewis base pathway



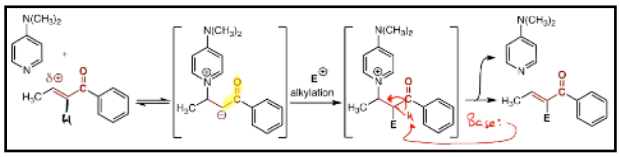
Two organocatalysts: DMAP and proline

- We examine two nitrogen Lewis base catalysts this year. What are their similarities and differences?
- Lone pair of N + ketone —> ?
- **Pyridines**: R-C=O-**X** (X=leaving group, O-R) (**no H+ transfer**)
- **Proline**: aldehyde, Ketone, R-C=O-R (**H+ transfer**)



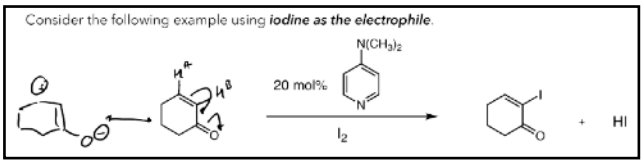
Pyridine catalysis with conjugate acceptors

- Previously we discussed the addition of thiols into the b-position (conjugate position), see below:
- Carbonyl carbon is direct position
- Pyridine catalysts can undergo **conjugate addition** and enable reactions of the resulting **enolate**
- Transient access to a hidden enolate



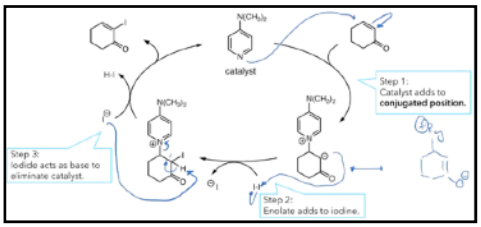
Pyridine catalysis with conjugate acceptors

- Consider the following example using iodine as the electrophile:
- Ha is more downfield than Hb because of resonance
  - Results in +ve charge



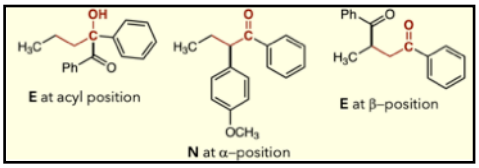
Catalytic mechanism:

1. Catalyst adds to conjugated position
2. Enolate adds to iodine (electrophile)
3. Iodide (nucleophile) acts as base to eliminate catalyst



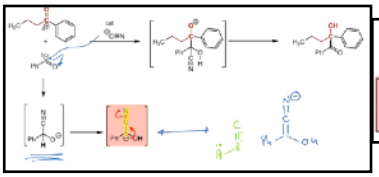
Reverse polarity reactions of the carbonyl

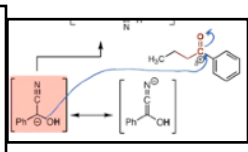
- Next we examine the introduction of electrophiles (E) at the acyl position (which is a delta+ carbon)
- What about when you want an electrophile at the acyl or beta-position, or a nucleophile at the alpha-position?
- Question: how do we get two electrophiles to add to each other?
- We introduce a catalyst that inverts the carbonyls polarity



Reverse polarity addition to the carbonyl - mechanism

- **Cyanide** can be used as a catalyst to **invert the polarity of the carbonyl**
- The formerly electrophilic carbonyl is now a **nucleophile**
- Proton transfer and elimination of the catalyst returns the carbonyl





Preparation of kinamycin

- A family of antibiotics isolated in the 1970s and first prepared in 2007
- They have both potential anti-cancer and antibiotic activity
- Kinamycin D is representative of the family
- Kinamycin synthesis mechanism: