

Data-based application questions: Organic Chemistry

1 The rate of a nucleophilic substitution reaction depends on a substrate's leaving group (LG) and sometimes the nucleophile used.

(a) Fig 1.1 below shows how the LG of a halogenoalkane,  $\text{CH}_3\text{X}$ , affects the rate of its hydrolysis with  $\text{NaOH}$  in a  $\text{S}_{\text{N}}2$  reaction.

X (is the LG)	Rate	$\text{p}K_{\text{a}}$ (HX)
F	Very slow	3
Cl	Moderate	-7
Br	Fast	-9
I	Very fast	-10

**Fig 1.1**

(i) Describe the mechanism of the hydrolysis of  $\text{CH}_3\text{Br}$ , and hence state the rate law for this hydrolysis reaction. [2]

(ii) As the rate of reaction increases, the better the leaving group is. It is found that the leaving group is more stable when it's better.

Explain how **Fig 1.1** supports the second sentence in the statement above. [2]

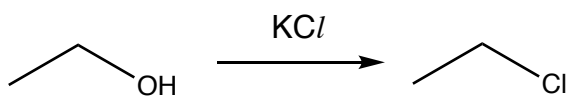
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- (iii) Hence, explain why in order for the following substitution reaction to take place, concentrated sulfuric acid is needed. [1]



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The nucleophile of the reaction affects the rate of reaction too.

Fig 1.2 below shows how the rate of substitution of  $\text{CH}_3\text{I}$  varies with different nucleophiles.

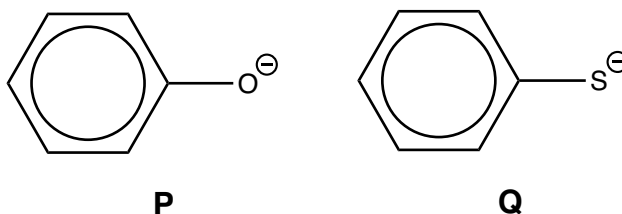
Nucleophile	Rate
$\text{OH}^-$	Fast
$\text{R}-\text{CO}_2^-$	Moderate
$\text{H}_2\text{O}$	Slow

Fig 1.2

- (iv) Suggest an explanation for the relationship between the basicity of the respective nucleophiles in Fig 1.2 to the rate of substitution. [1]

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- (v) By considering the concept of electronegativity and the availability of the lone pair on the nucleophilic site, circle the nucleophile **P** or **Q** which will yield a higher rate of substitution for a given substrate undergoing the  $\text{S}_{\text{N}}2$  reaction. [1]

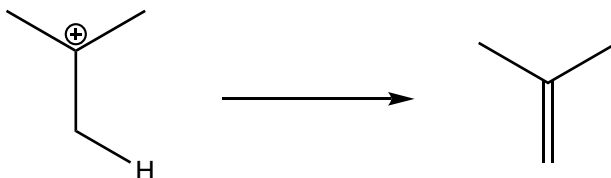




- (c) Apart from substitution reactions, elimination reactions have similar kinetics to substitution reactions.

The E1 reaction is similar to the  $S_N1$  reaction in terms of its first step.

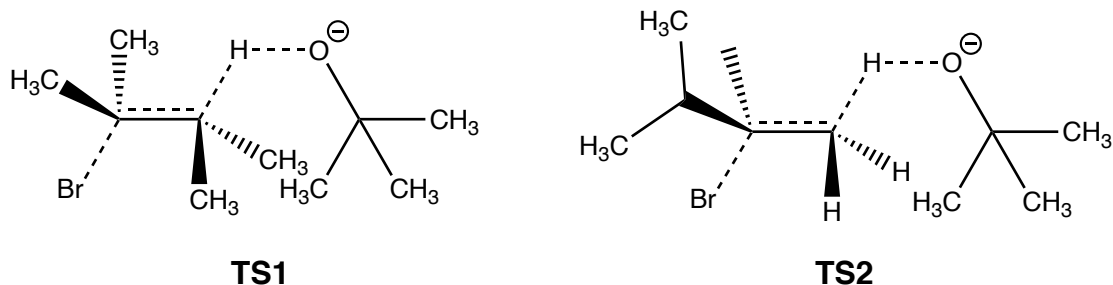
The second step of an E1 reaction is shown below in **Fig 1.3**.



- (i) Given that the  $\text{HCO}_3^-$  ion is also one of the reacting species, complete the mechanism in **Fig 1.3**. Where relevant, show the movement of electrons through curly arrows and lone pairs. [1]
- (ii) Draw an energy profile diagram for the E1 reaction of  $(\text{CH}_3)_3\text{CBr}$  with  $\text{NaHCO}_3$ . [3]

- (d) Like  $S_N2$  reactions, E2 reactions only have 1 step in their reactions. The E2 reaction is hence an overall second order reaction.

To facilitate an E2 reaction, bulky bases are used. In an E2 reaction between **X** and the bulky base  $(CH_3)_3CO^-K^+$ , the following transition states **TS1** and **TS2** are possible.

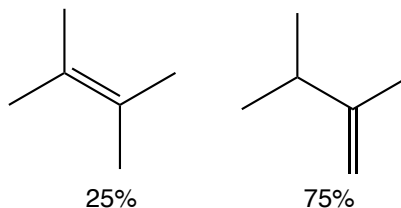


- (i) Name **X**. [1]

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- (ii) By considering the results of the E2 reaction, explain whether **TS1** or **TS2** is higher in potential energy. [2]

Proportion of elimination products formed:



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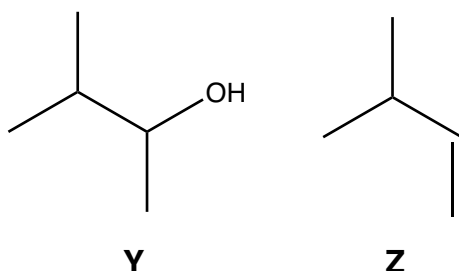
- (iii) By considering steric effects, suggest another explanation for your answer in (ii). [1]

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- (e) By considering suitable information from parts (a) to (d), suggest a synthetic pathway to synthesise **Z** from **Y**. The yield for **Z** should be as high as possible. State reagents and conditions used. [2]

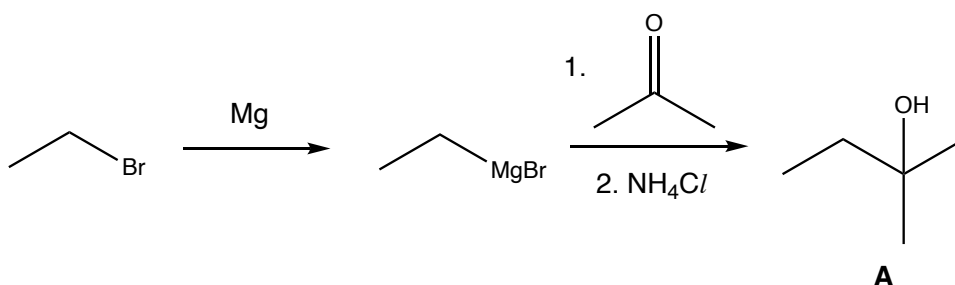


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- 2 Grignard reagents are typically used to attach an alkyl side-chain to an electrophilic carbon.

Suppose we want to make **A** from propanone. The following synthetic route can be used.



The Grignard reagent is obtained after Mg metal is added into bromoethane.

- (a) (i) Explain why bromoethane **cannot** undergo an addition reaction to propanone to form **A**. [1]

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- (ii) By considering the electronegativity of carbon and magnesium, label the atom which holds the partial positive charge and partial negative charge on the C—Mg bond of the Grignard reagent above. [1]

[1]

(iii) Given that the first step of the reaction in the second step involves a nucleophilic addition reaction, with reference to your answer in (ii),

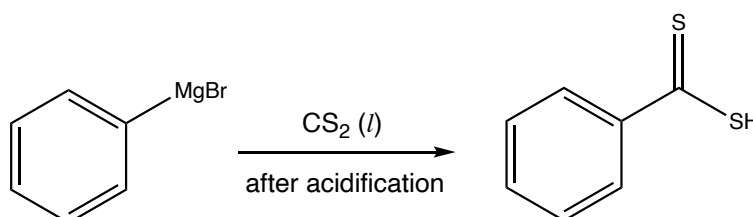
- draw the intermediate produced after the nucleophilic addition step
- and hence state the purpose of adding ammonium chloride after propanone is added.

[2]

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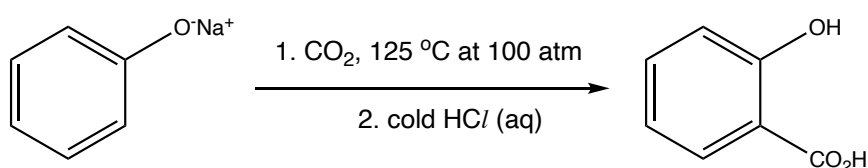
(b) Apart from adding alkyl side chains, Grignard reagents are often used to graft certain functional groups to an aromatic compound.

One example is shown in **Fig 2.1**.



**Fig 2.1**

The Kobe-Schmitt synthesis in **Fig 2.2** produces a similar product, salicylic acid. However, salicylic acid is a phenol and contains a carboxylic acid functional group.



**Fig 2.2**

Assume that sulfur analogues of their respective oxygen-containing compounds and themselves have similar chemical properties. For example,  $\text{CS}_2$  has similar chemical properties to  $\text{CO}_2$ .

(i) Which mechanism is involved in the Kobe-Schmitt synthesis, but **not** involved in the reaction in **Fig 2.1**?

[1]

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- (ii) CS<sub>2</sub> has a boiling point of 46 degrees Celsius.

Consider the conditions of the reactions in **Fig 2.1** and **Fig 2.2**. Explain why the conditions of the reaction in **Fig 2.2** are much stronger than that in **Fig 2.1** for the product to be formed. [2]

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- (iii) Explain why when benzene is reacted with carbon dioxide under the conditions in **Fig 2.2**, benzoic acid is not formed, in comparison with the fact that salicylic acid can be formed from sodium phenoxide under the same conditions. [2]

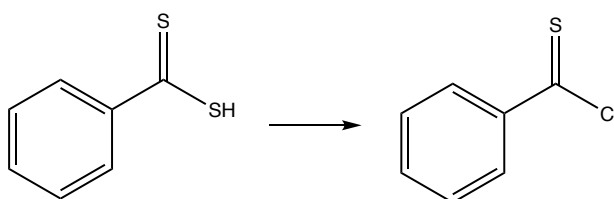
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- (iv) Suggest a sulfur-based reagent for the following transformation: [1]



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(c) Fig 2.3 illustrates a reaction scheme involving a Grignard reagent.

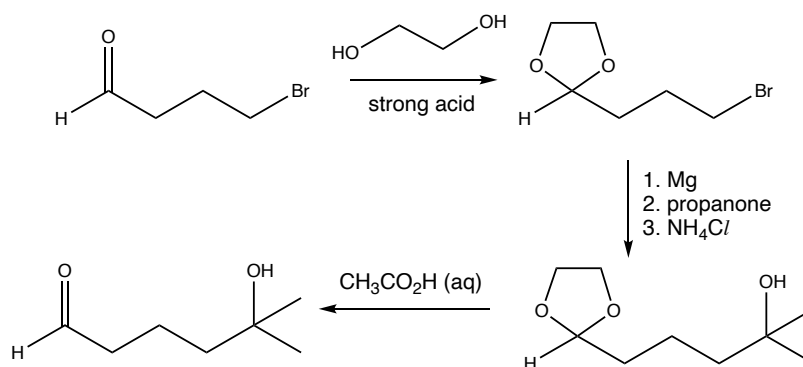


Fig 2.3

- (i) When the second step in the reaction scheme is performed on the starting compound, the expected product was **not** formed.

Instead, a 4-carbon compound was formed as the major product.

Draw the structure of this 4-carbon compound.

[1]

- (ii) Explain how you would detect the presence of the 4-carbon compound using a simple chemical test.

[1]

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- (iii) With reference to your answer in (i), explain the purpose of steps 1 and 3.

[1]

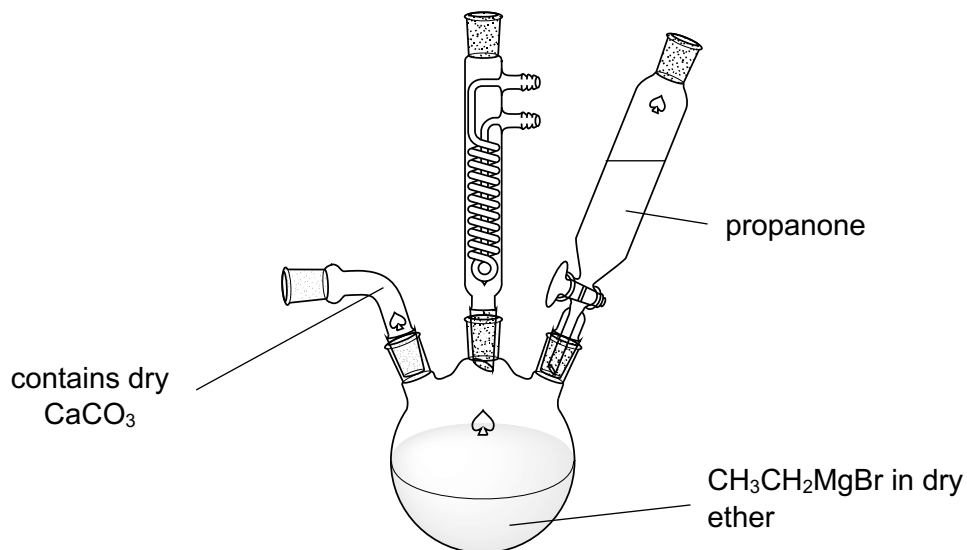
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(d) Grignard reagents are highly explosive and must be handled with care.

**Fig 2.4** shows how a typical setup looks like when a Grignard reagent is about to be reacted.



**Fig 2.4**

(i) Dry CaCO<sub>3</sub> prevents water in the atmosphere from entering the reflux setup. By considering that the Grignard reagent acts as a reactive nucleophile, suggest why water must not enter the reflux setup. [1]

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(ii) Propanone is added dropwise to the reaction mixture. In addition, the reaction mixture is maintained at a temperature of approximately 20 degrees Celsius. Suggest why propanone should be added slowly and not all at one go. [1]

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- (iii) After the reaction is done, the product needs to be separated from the dry ether. The ether used in this reaction is  $(\text{CH}_3\text{CH}_2)_2\text{O}$ .

Explain how you would separate the product from the dry ether, justifying your method. Assume that the product formed is **A** for this question. [3]

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[Total: 18]

- 3 Hydrogels are able to hold large quantities of water. Commercial hydrogels are able to hold water at least 100 times its own mass. Currently, hydrogels are used in many products from diapers to fruit spreads.

Some hydrogels used are biodegradable. This is because they are synthesised from natural cellulose found in plants.

In this question, we will study the synthesis of cellulose-based hydrogels and their properties.

- (a) Fig 3.1 illustrates the structure of cellulose. Cellulose is made up of many repeating units.

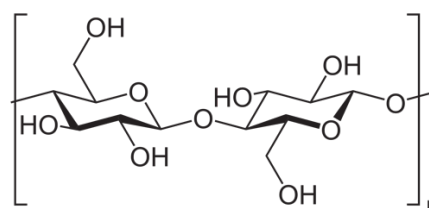


Fig 3.1

- (i) Suggest why cellulose is insoluble in water. [1]

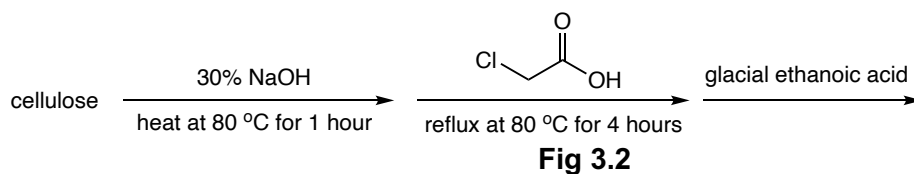
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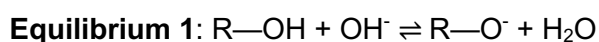
Since cellulose is insoluble in water, cellulose must undergo chemical modification in order for it to be used as a hydrogel.

This is done through a 3-step process, illustrated in **Fig 3.2**.



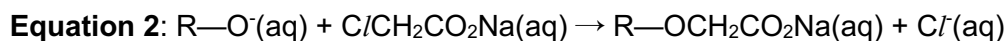
- (ii) Concentrated sodium hydroxide is added first to deprotonate the protons on the alcohol group in cellulose, R—OH.

This can be represented by equilibrium 1.



After the deprotonated cellulose is obtained, a substitution reaction occurred.

This yielded sodium carboxymethyl cellulose (CMCNa). The equation representing this reaction is shown by **equation 2**:



The reaction proceeds via  $S_N2$ .

Explain why the reaction cannot proceed via  $S_N1$ .

[2]

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(iii) In a trial run done by a group of researchers, NaOH at a concentration of 5% failed to produce the desired product. With reference to relevant information from (ii), or otherwise, suggest why a high concentration of NaOH is used in the reaction. [2]

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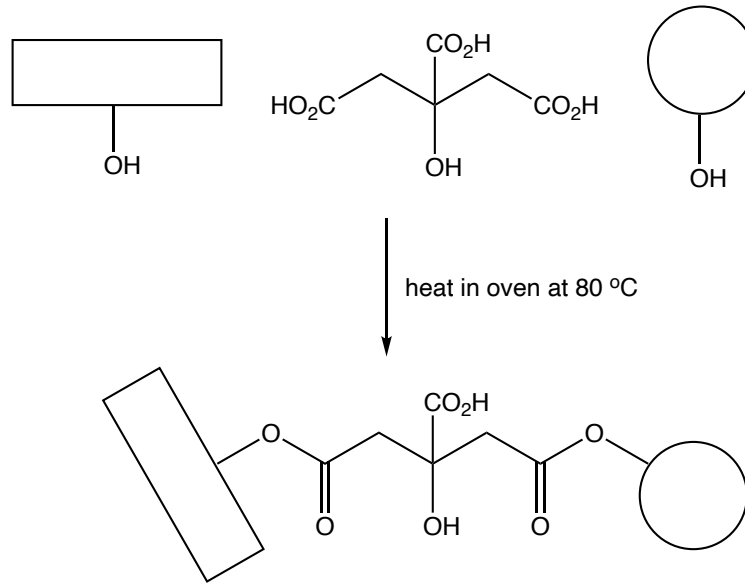
(iv) **Equilibrium 1** has an equilibrium constant  $K_1$ , while **equation 2** has a rate constant of  $k_2$ .

Derive the rate law for the formation of CMCNa from cellulose (R—OH), NaOH and C/CH<sub>2</sub>CO<sub>2</sub>H. [2]

(b) The final step to make the hydrogel is as follows.

The isolated CMCNa was dissolved in water, to which citric acid was then added. The resultant mixture was heated at 80 degrees Celsius in an oven.

The reaction occurring is schematically shown below in **Fig 3.3**.



**Fig 3.3**

The rectangle and circle represent 2 chains of CMCNa. The alcohol functional group of each chain of CMCNa polymer is shown only. Not all -OH groups were converted to the sodium carboxymethyl group during the chemical modification.

**Fig 3.3** illustrates a *cross-linking* reaction. When disparate chains of CMCNa undergo cross-linking, a longer chain of the linked CMCNa chains are able to better trap water.

(i) State the *type of reaction* occurring during *cross-linking*. [1]

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(ii) Explain how the temperature stated in the preamble facilitates the formation of hydrogel. [1]

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- (iii) Draw 2 diagrams to illustrate 2 major types of interactions between the hydrogel and water molecules. You may consider using the illustration in Fig 3.3 as a template.

[4]

- (iv) The cross-linked CMCNa chains form a matrix which are able to trap water molecules more effectively.

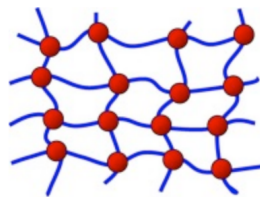


Fig 3.4

Fig 3.4 is a simplified illustration of such a CMCNa matrix. The bold circles are sites of cross-linkage.

With reference to your answer in (iii), suggest why water can be more easily trapped when CMCNa is cross-linked, compared to when CMCNa is not cross-linked.

[1]

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(c) Although hydrogels have strong ability to retain huge amounts of water, one such drawback is that salts such as sodium chloride cannot be added to it. Instead, a hydrogel holding huge amounts of water is observed to release most of it.

(i) With reference to your answer in (b)(iii), suggest why adding a salt like sodium chloride would cause the hydrogel to fail in its intended function. [1]

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(ii) However, the addition of certain salts will have a different effect. This is observed in many d-block metal salts. For example, the addition of a small amount of copper(II) sulfate will instead form a blue complex with the hydrogel.

This is because copper(II) ions have the ability to form co-ordinate bonds with the hydrogel.

Explain why copper(II) ions can form co-ordinate bonds with the hydrogel, but why the sodium ion cannot do so. [2]

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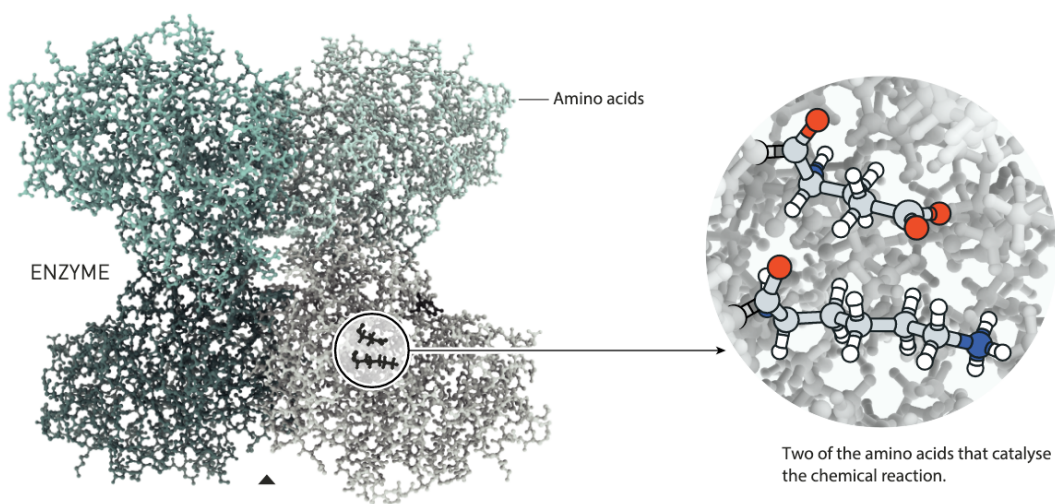
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4 [All information used in this question is taken from the *Royal Swedish Academy of Sciences*.]

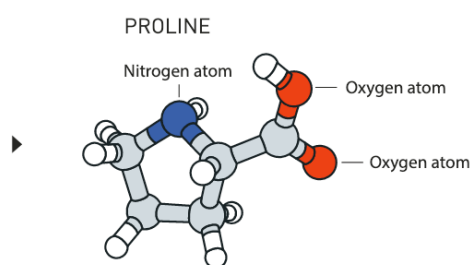
The 2021 Nobel Prize in Chemistry was awarded to Benjamin List and David MacMillan for their development of a new and ingenious tool for molecule building: organocatalysis. Its uses include research into new pharmaceuticals and it has also helped make chemistry greener.

The infographic **Fig 4.1** illustrates Benjamin List's work.





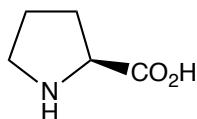
- 1 Enzymes consist of hundreds of amino acids, but frequently only a few of these are involved in the chemical reaction. Benjamin List started to wonder whether an entire enzyme was really required to obtain a catalyst.
- 2 Benjamin List tested whether an amino acid called proline – in all its simplicity – could catalyse a chemical reaction. It worked brilliantly. Proline has a nitrogen atom that can provide and accommodate electrons during chemical reactions.



©Johan Jarnestad, Agnes Moe/The Royal Swedish Academy of Sciences

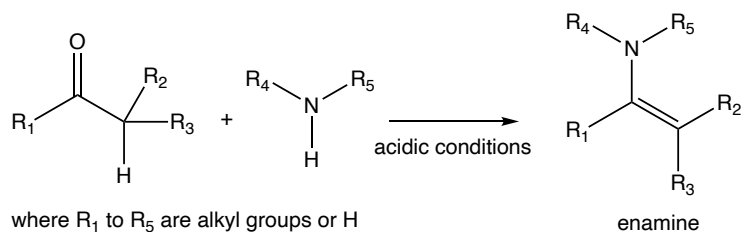
**Fig 4.1**

The skeletal formula for 1 enantiomer of proline is shown below.

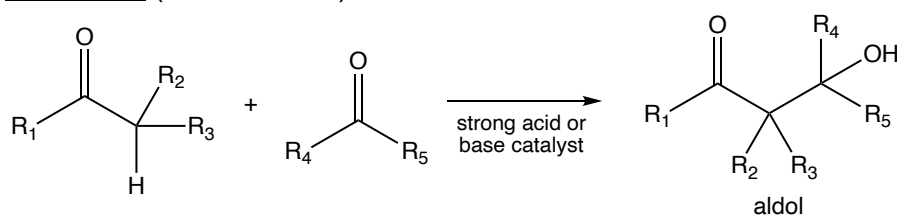


You may find the following reactions useful in the questions that follow.

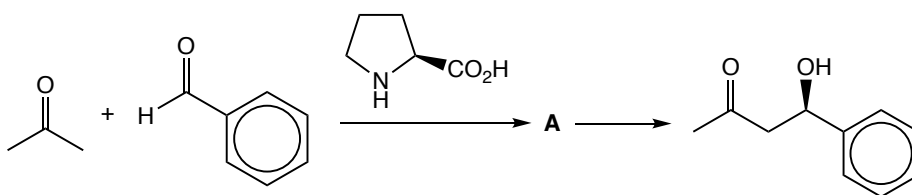
Reaction 1



Reaction 2 (aldol reaction)



- (a) In 2000, List and his team showed that the naturally occurring amino acid proline catalyses an intermolecular aldol reaction between propanone and a series of aromatic aldehydes, shown in **Fig 4.2**.



**Fig 4.2**

- (i) **A** is an enamine intermediate, formed from proline and 1 other reactant.

Draw the structure of **A**.

[1]

- (ii) The reaction leading to **A** proceeds via a nucleophilic addition.

Draw the **first** step of the reaction. Indicate lone pairs, partial charges and curly arrows representing the movement of electrons.

[1]

- (iii) Compare the  $pK_b$  values for the nitrogen atom of proline and enamine **A**. Suggest an explanation for your answer.

[2]

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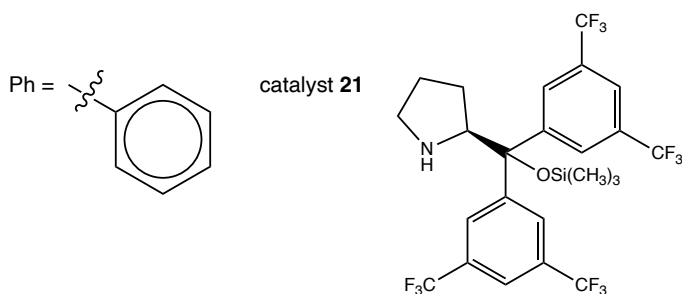
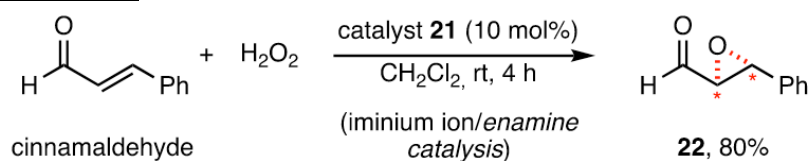
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- (iv) The reaction in **Fig 4.2** can occur without the use of the catalyst proline. Instead, a different catalyst, NaOH, is usually used. Unlike proline, NaOH is not chiral.

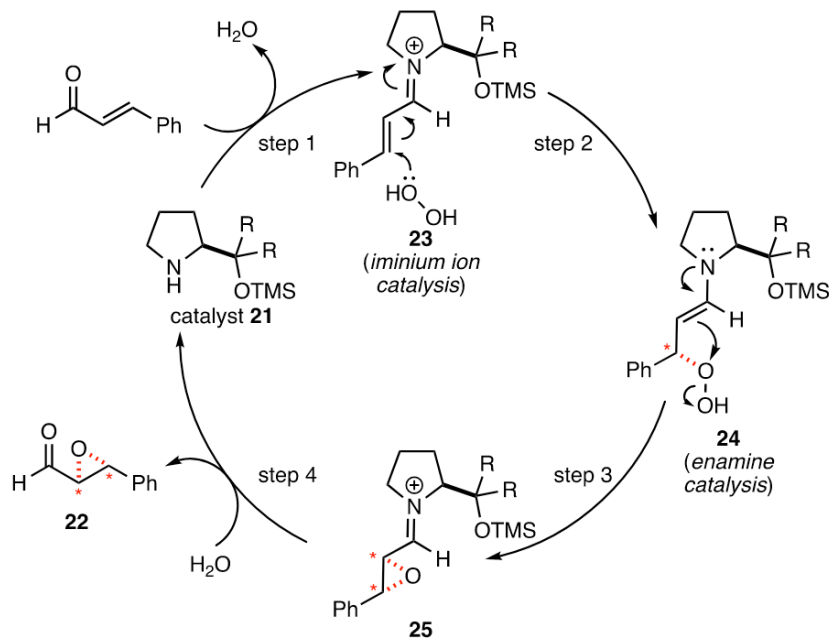
Explain why the product is a racemic mixture when NaOH is used. [1]

- (b) Following the successful synthesis demonstrated by List, other chemists worked on other catalysts to produce similar results.

**Reaction 3**



**Fig 4.3** describes the mechanism of this reaction.



**Fig 4.3**

[Abbreviations: OTMS, OSi(CH<sub>3</sub>)<sub>3</sub>]

- (i) With reference to **Fig 4.3** and **(a)(ii)**, explain why catalyst **21** can be termed as a *Lewis Base catalyst*. [2]

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- (ii) At step 2, hydrogen peroxide ( $\text{H}_2\text{O}_2$ ) attacks the  $\text{C}=\text{C}$  double bond. With reference to concepts of electronegativity and delocalisation, explain why this nucleophilic attack is possible. [2]

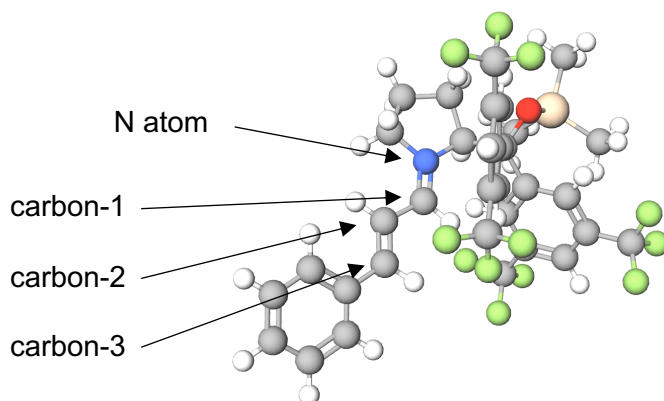
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- (iii) **Fig 4.4** shows a 3-dimensional ball-and-stick model of intermediate **23**.



**Fig 4.4**

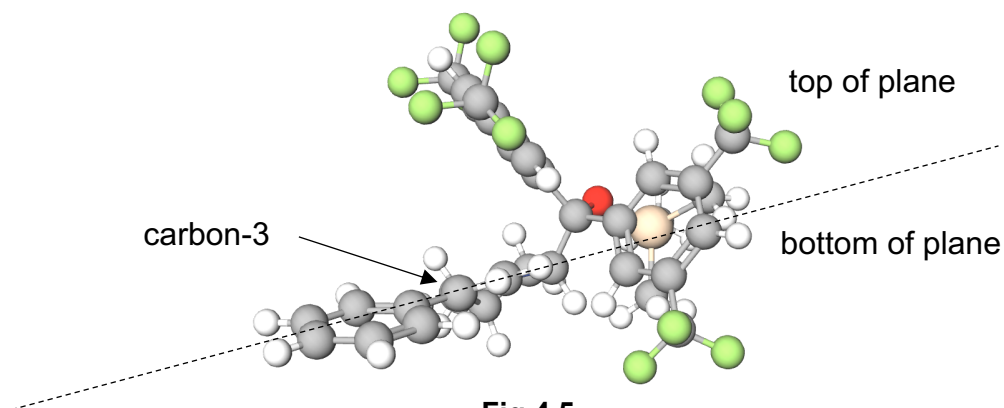
It would be helpful to identify carbon-1, carbon-2 and carbon-3 first on **23**.

- Using **Fig 4.4**, suggest a reason why hydrogen peroxide performs a nucleophilic attack at carbon-3 but not carbon-1 in step 2. [1]

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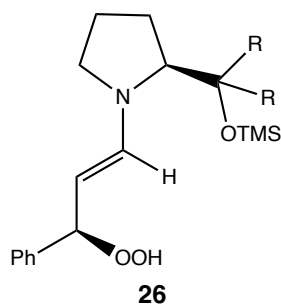
- (iv) **Fig 4.5** shows another 3-dimensional ball-and-stick model of intermediate **23** from another angle. The 'plane' referred in **Fig 4.5** is the plane formed by the N-atom, carbons 1, 2 and 3.



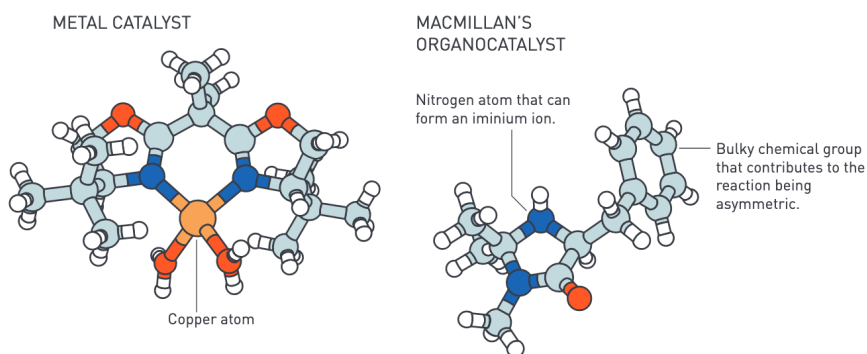
**Fig 4.5**

Using the concept of steric effects, explain why intermediate **24** is favoured over intermediate **26**.

[1]



The infographic **Fig 4.6** illustrates David MacMillan's work.



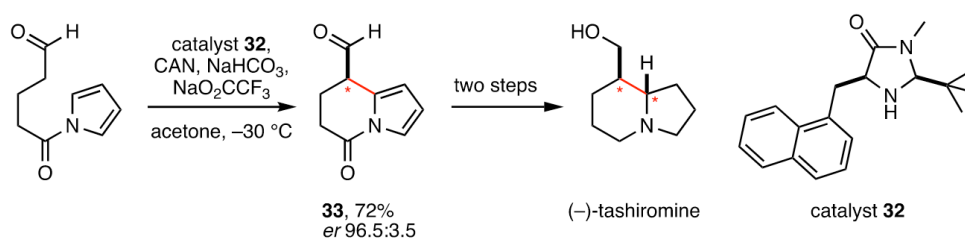
**1** David MacMillan worked with metal catalysts that were easily destroyed by moisture. He therefore started to wonder whether it was possible to develop a more durable type of catalyst.

**2** He designed some simple molecules that could create iminium ions. One of these proved to be excellent at asymmetric catalysis.

**Fig 4.6**

[In this question, asymmetric refers to the selective formation of 1 enantiomer over another.]

- (c) The synthesis of (-)-tashiromine one application of MacMillan's work. Fig 4.7 illustrates the final steps in the asymmetric synthesis of (-)-tashiromine.



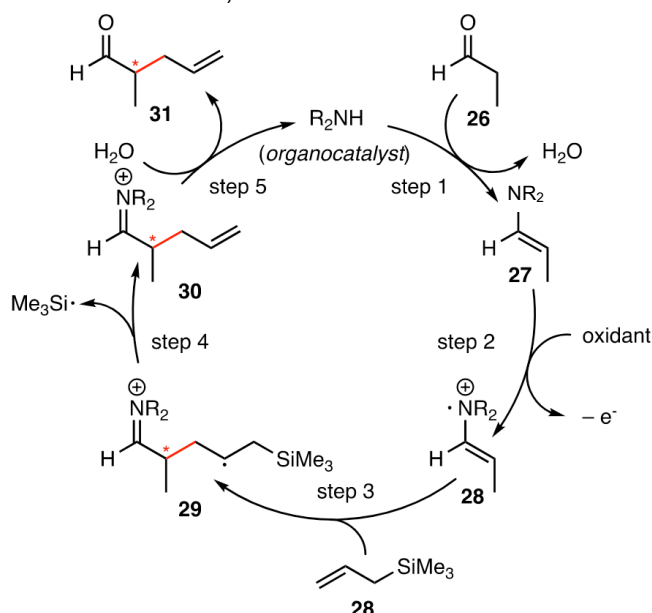
**Fig 4.7**

- (i) CAN is ceric ammonium nitrate. It has the formula  $(\text{NH}_4)_2 [\text{Ce}(\text{NO}_3)_6]$ .

State the oxidation number of Ce in CAN, and hence write the electronic configuration of Ce in CAN. [1]

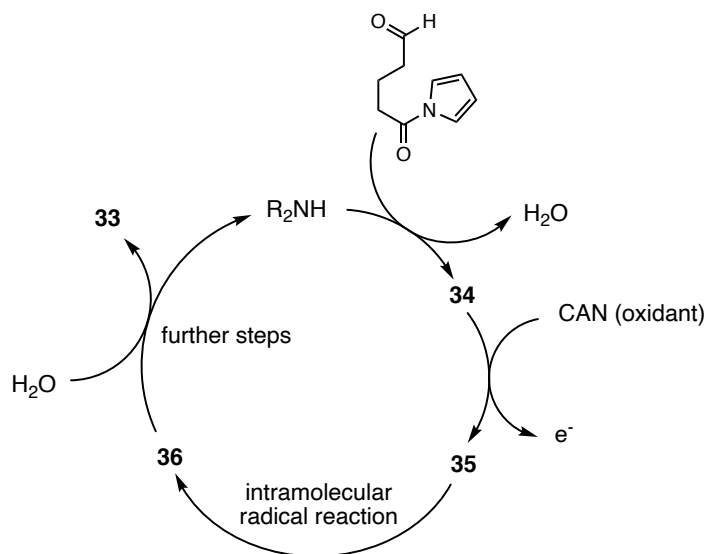
- (ii) Explain why catalyst  $\mathbf{32}$  qualifies as a MacMillan's organocatalyst. Use information in Fig 4.6 to support your answer. [1]

Fig 4.8 illustrates how an oxidant and a Macmillan's organocatalyst work together to create a C—C bond with  $\mathbf{28}$ , another reactant in the scheme. New chiral centres formed are marked with an asterisk, \*.



[Abbreviations: Me,  $\text{CH}_3$ ]

The transformation from the starting compound to **33** undergoes a similar mechanism too, shown in **Fig 4.9**.  $R_2NH$  is catalyst **32**.



**Fig 4.9**

- (iii) Draw the structures of **34**, **35** and **36** with stereochemistry in the space below. [3]  
You may use the abbreviation  $R_2N$ .

<b>34</b>	
<b>35</b>	
<b>36</b>	

(iv) Draw the mechanism describing the transformation from **35** to **36** below. [1]

(v) The transformation from **33** to (-)-tashiromine can be achieved in 2 steps.

Suggest a reducing reagent used for each step. [2]

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(d) List and Macmillan won the Nobel Prize because of their discoveries' wide applications in asymmetric synthesis. This is especially important in the production of pharmaceutical drugs.

Explain why pharmaceutical drugs must be enantiomerically pure for them to be most effective, and what can be done to test their enantiomeric purity. [2]

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[Total: 21]