

# CHAPTER 1

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## NUCLEOPHILIC ADDITION TO THE CARBONYL GROUP

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### Contents

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*Concepts assumed:*

- $\sigma$ - and  $\pi$ -bonds.
- Polarisable bonds.
- Electrophile and nucleophile.
- Conjugation with  $\pi$ -bonds and lone pairs.
- Inductive effects.
- $pK_a$  values.
- Periodic table.
- Transition states.

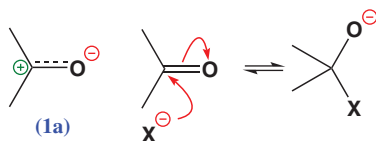
*Concepts introduced:*

- Acid catalysis.
- Instability of  $R_2C(OR)_2$  in acid solution. Driving equilibria in a chosen direction by the use of acid, solvent, etc.
- Stability of different carbonyl compounds. Stability and reactivity as two sides of the same coin.
- Effect of substituents on equilibria. Relationship between basicity and nucleophilicity.
- Organo-magnesium compounds as nucleophiles.
- Use of Grignard reagents in syntheses.
- Ease of dehydration of tertiary alcohols in acid solution.
- Sources of nucleophilic  $H^-$ .
- Use of A1 and B compounds and as anion transferring reagents.
- Drawing transition states.
- Stability of the six-membered ring.
- Use of protecting groups.
- Use of reaction mechanisms in syntheses.

Have you read the introductions explaining what help you need, what you need to know and how to use the program? It's a good idea to do this before you start.

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1. The carbonyl group (**1a**) has an easily polarisable  $\pi$ -bond with an electrophilic carbon atom at one end easily attacked by nucleophiles:



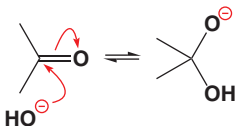
Write down the reaction (with curly arrows) between acetone and hydroxide ion.

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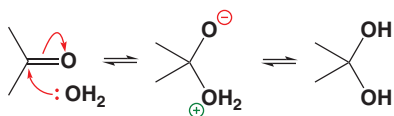
2. Have you actually written down the formulae of the reagents and drawn the arrows? The program won't be of much help to you unless you do.

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3.



A nucleophile such as water uses its lone pair electrons (:) to attack and forms a neutral addition compound by proton transfer:



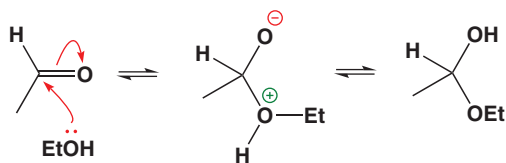
Note that only one proton is needed.

Write down the reaction between the carbonyl compound acetaldehyde and the proton-bearing nucleophile ethanol.

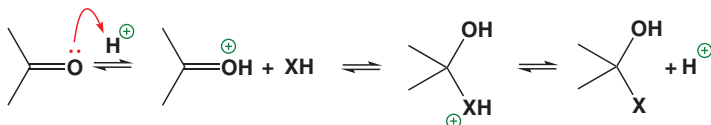
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4. If you find this difficult, use the lone pair electrons on the ethanol oxygen atom to attack the carbonyl group of acetone.

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5. Answer to *frame 3*:

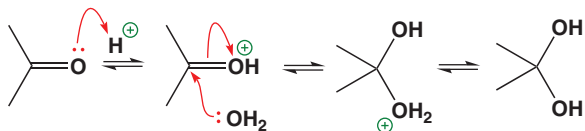
Another approach is to add the proton first, in acid solution, and to add the nucleophile afterwards:



In this case, the proton is regenerated and this is an example of acid catalysis. Show how water can be added to acetone with acid catalysis.

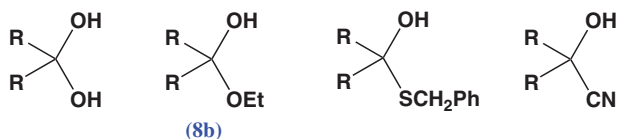
6. If you are having difficulty with this, look back at the last reaction in *frame 5*. Carry out these same steps using acetone as the carbonyl compound and water as HX.

7.



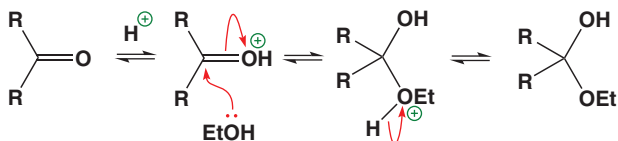
Notice that  $\text{Me}_2\text{C}=\text{O}^+\text{H}$  is much more reactive than acetone, but is still attacked at *carbon* although the positive charge is in fact on the oxygen atom. What would happen to  $\text{R}_2\text{C}=\text{O}^+\text{H}$  with water, ethanol,  $\text{PhCH}_2\text{SH}$  and cyanide ion?

8. The compounds:

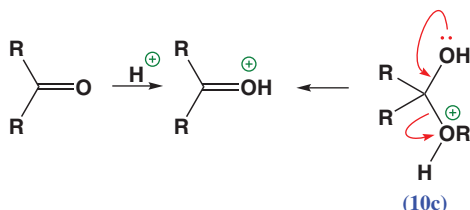


would be formed by a mechanism exactly like the one in *frame 7*. When you combined  $R_2C=O+H$  with ethanol you formed an adduct (8b), which is the product of ethanol addition to a ketone. The steps you drew are therefore part of the acid catalysed addition of ethanol to a ketone. Draw out the whole of this reaction.

9.

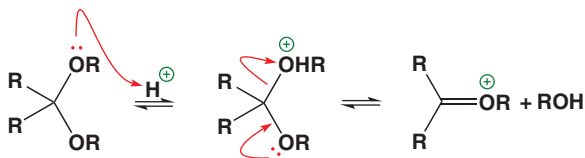


10. Look at the reactions in *frames 7* and *9* again. Note that all the steps are reversible and that therefore  $R_2C=O^+H$  may be formed from  $R_2C=O$ ,  $R_2C(OH)_2$  or  $R_2C(OH)OR$ :



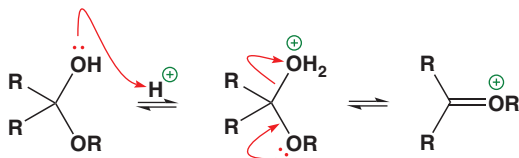
It is in fact a general rule that compounds of the type  $R_2C(OR)_2$ , having two oxygen atoms singly bonded to the same carbon atom, are unstable in acid solution. A reason for this is that both oxygens have lone pairs of electrons, and so, when one pair is protonated, the lone pair on the other can form a  $C=O$  double bond and expel the protonated atom. Draw this in detail.

11.



Look at the reactions in *frame 10* again. In the reverse reaction, we protonated and removed the  $EtO^-$  group from **10c**. What happens if we protonate and remove the  $HO^-$  group?

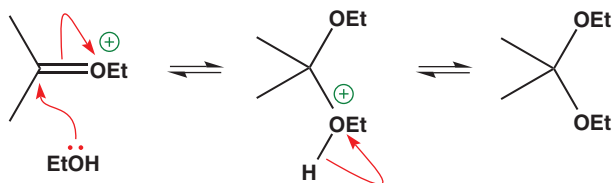
12.



This new cation,  $R_2C=O^+Et$ , is just as reactive as  $R_2C=O^+H$  and can add nucleophiles in the same way. What happens if we add EtOH to it?

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13.



This reaction sequence, added to the ones in *frames 9* and *12*, gives us the addition of two molecules of ethanol to a ketone to give  $R_2C(OEt)_2$ . Draw this sequence out in full without referring back.

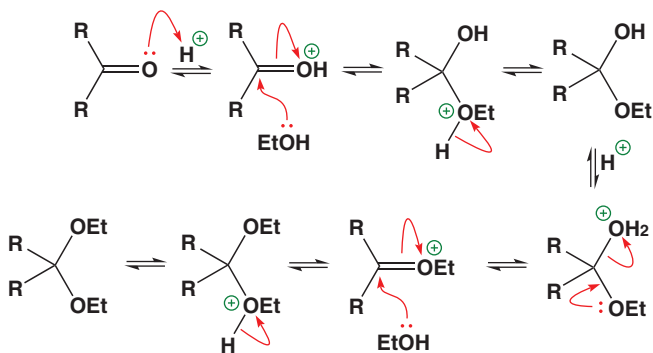
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14. If you have difficulty doing this, look at *frames 9*, *12* and *13* without writing anything down and then try again.

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15.



16. Does your reaction sequence exactly follow that in *frame 15*? If not, try to assess if the differences are trivial. If you are still in doubt, consult your adviser. It is important that you understand this reaction well.

*This is a good place to stop if you want a break.*

17. Since this whole sequence is reversible, it will go forwards in ethanol and backwards in water. What do you think would happen if acetaldehyde and *n*-butanol were dissolved together in a 1 : 3 molar ratio, and the solution refluxed for 12 hours with a catalytic quantity of toluene sulphonic acid, and the product dried and distilled?

18. This is a literature preparation of  $CH_3CH(OBu^n)_2$ . Acetaldehyde is the carbonyl component, butanol is the nucleophile and toluene sulphonic acid is the catalyst. How would you hydrolyse  $PhCH(OEt)_2$ , and what would you get?

19. Reflux  $\text{PhCH}(\text{OEt})_2$  in water with a catalytic quantity of an acid. The products would be  $\text{PhCHO}$  and  $\text{EtOH}$ . How would you make  $\text{EtCH}(\text{OMe})_2$ ?

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20. Treat  $\text{EtCHO}$  and  $\text{MeOH}$  as in *frame 17*. A glance at the reactions in *frame 15* should convince you that the *mono* adducts of carbonyl compounds and nucleophiles with lone pairs are unstable. An example is  $\text{R}_2\text{C}(\text{OH})\text{OEt}$ , which is unstable even under the conditions of its formation. What happens to it?

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21. In ethanol it gives the acetal  $\text{R}_2\text{C}(\text{OEt})_2$ , in water the carbonyl compound  $\text{R}_2\text{C}=\text{O}$ .

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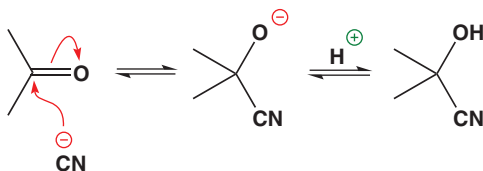
22. If we look instead at nucleophiles *without* lone pairs, we should find some stable *mono* adducts. Which of the adducts in *frame 8* should be stable?

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23. The cyanide substituent has no lone pair and so its adduct,  $\text{R}_2\text{C}(\text{OH})(\text{CN})$ , should be stable. These compounds, cyanohydrins, are made by adding excess  $\text{NaCN}$  and one equivalent of acid to the carbonyl compound. The reaction is an equilibrium. What is the role of the acid?

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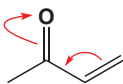
24. To drive over the equilibrium by protonating the intermediate:



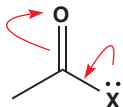
25. Since this reaction is an equilibrium, the amount of cyanohydrin formed from any given carbonyl compound will depend on the relative stabilities of the carbonyl compound itself and the product. There can be many substituents 'X' on a carbonyl compound RCOX, such as Cl, Me, NH<sub>2</sub>, Ph, OEt, H. Some have inductive effects, some are conjugated with the carbonyl group. Some stabilise RCOX making it less reactive. Others activate it towards nucleophilic attack. Arrange the compounds RCOX, where 'X' can be the substituents listed above, into an order of reactivity towards a nucleophile.

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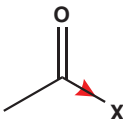
26. Before you look at the answer in the next frame, just check that you have considered each of these factors: some substituents stabilise RCOX by  $\pi$ -conjugation:



some by lone pair conjugation:



some destabilise RCOX by inductive electron withdrawal:



27. Taking RCHO as standard, we can say that Cl destabilises by inductive withdrawal, Me stabilises more by  $\sigma$ -delocalisation and  $\text{NH}_2$  and OEt by lone pair donation. ( $\text{NH}_2$  is more effective at this: compare ammonia and water as bases). Our order is

Cl ... H ... Me ... Ph ... OEt ...  $\text{NH}_2$   
*most reactive* *most stable*

These same factors could affect the product as well. Arrange the same substituents in an order for product stability.

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28. Since the carbonyl group has gone in  $\text{R}_2\text{C}(\text{OH})\text{CN}$ , we would expect very little effect from any of these substituents. There cannot be any conjugation, and inductive effects on the distant O atom will be small. What effect would an inductively withdrawing substituent have on the equilibrium for cyanohydrin formation?

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29. It will destabilise the carbonyl compound a lot and have very little effect on the product; it will therefore push the equilibrium over to the cyanohydrin side. Consider cyanohydrin formation from:

- (a)  $\text{MeCHO}$     (c)  $\text{Me}_2\text{C}=\text{O}$     (e)  $\text{Ph}_2\text{C}=\text{O}$   
 (b)  $\text{PhCHO}$     (d)  $\text{Ph}(\text{CO})=\text{Me}$     (f)  $\text{Me}(\text{CO})\text{OEt}$

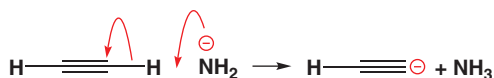
Two of these give no cyanohydrin at all. Which two? One gives 100% cyanohydrin — which? When equilibrium is established, (c) forms 10 000 times as much cyanohydrin as (d). Comment.

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30. (e) and (f) give no cyanohydrin at all: (a) gives all cyanohydrin. In (d) there is a strong  $\pi$ -conjugation from the benzene ring absent in (c) that stabilises the carbonyl compound. These results fit in with what we have said; if you don't see, consult your adviser.

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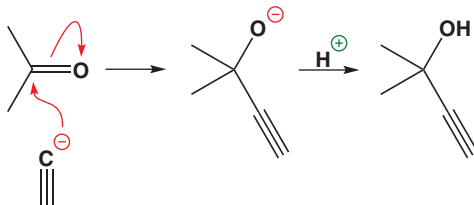
31. Another carbon anion you may have met is the acetylide ion, formed by the action of strong base on acetylene:



It adds readily to the carbonyl group. Draw out the reaction.

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32.



33. The  $pK_a$  of HCN is 9.15, that of water is 15.7 and that of acetylene is about 25. Which anion,  $\text{CN}^-$ ,  $\text{HO}^-$  or acetylide ion, would add most rapidly to acetone?

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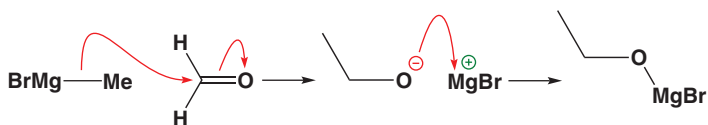
34. Acetylide fastest, then hydroxide, then cyanide slowest. Remember that if HX is a weak acid,  $\text{X}^-$  is a strong base.

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35. Another type of carbon nucleophile is the Grignard reagent  $\text{RMgBr}$  made by direct metalation of the organic halide with magnesium metal. These compounds are nucleophilic through carbon because the electrons in the  $\text{C}-\text{Mg}$  bond polarise towards carbon. Draw the attack of  $\text{MeMgBr}$  on  $\text{CH}_2=\text{O}$ .

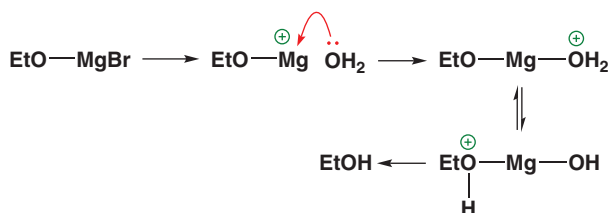
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36.



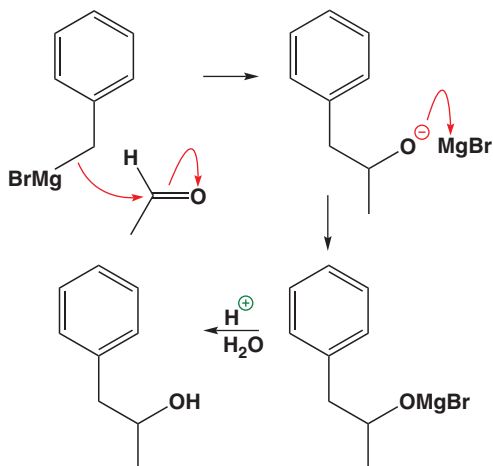
The intermediate  $\text{O-Mg}$  compound hydrolyses in acid solution by attack of water on the magnesium atom. Suggest how this might occur.

37. A possible mechanism is:



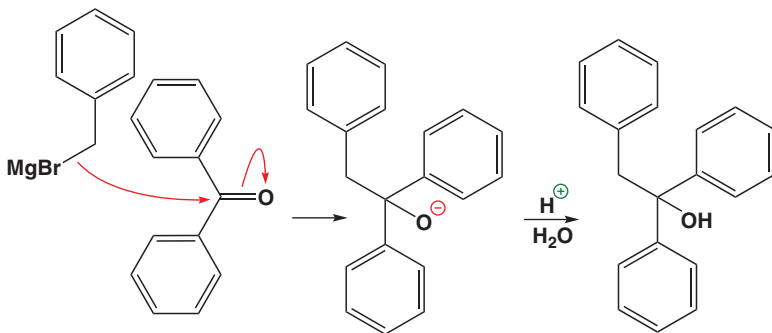
In any event, the product is a primary alcohol and is a general route from  $\text{RBr}$  to  $\text{RCH}_2\text{OH}$ . What would be the reaction between  $\text{PhCH}_2\text{MgBr}$  and  $\text{CH}_3\text{CHO}$ ?

38.



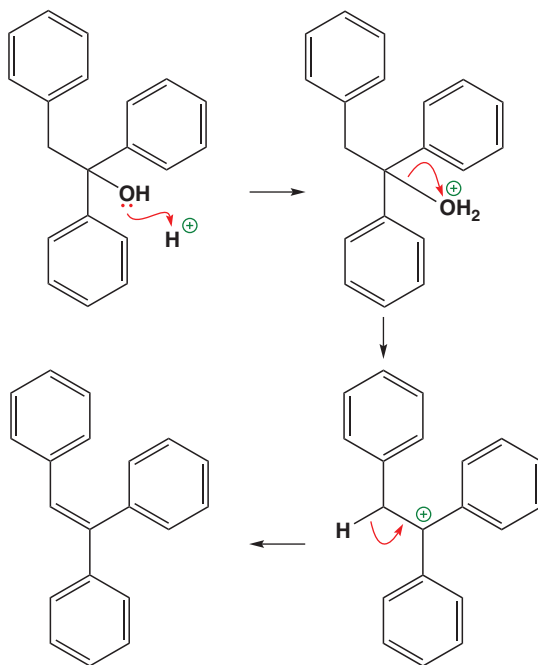
We can therefore make secondary alcohols this way. Ketones also react with Grignard reagents. Draw the reaction between  $\text{PhCH}_2\text{MgBr}$  and  $\text{Ph}_2\text{C}=\text{O}$ .

39.



The work-up is done in acid solution, and tertiary alcohols react easily with acid. What further reaction might happen here?

40. Protonation and loss of water lead to a stable tertiary carbonium ion:



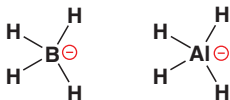
So much for carbon nucleophiles.

*This is a good place to rest.*

41. The simplest nucleophile of all is the hydride ion,  $\text{H}^-$ , but, as you may know, this ion is very basic and will not add to the carbonyl group. Sources of  $\text{H}^-$  for addition to the  $\text{C}=\text{O}$  bond are  $\text{NaBH}_4$  and  $\text{LiAlH}_4$  containing the tetrahedral anions  $\text{BH}_4^-$  and  $\text{AlH}_4^-$ . Draw out the structure of these ions.



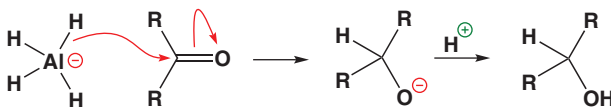
42.



Show how  $\text{AlH}_4^-$  may transfer  $\text{H}^-$  as a nucleophile to a ketone,  $\text{R}_2\text{C}=\text{O}$ .

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43.



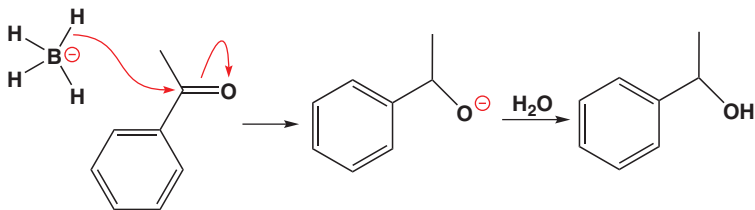
Lithium aluminium hydride,  $\text{LiAlH}_4$ , is dangerous when damp. Can you suggest why?

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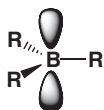
44. It gives off hydrogen in large volumes ( $\text{H}^- + \text{H}_2\text{O} \rightarrow \text{H}_2 + \text{OH}^-$ ) and evolves heat at the same time. The result is usually an impressive fire. Sodium borohydride,  $\text{NaBH}_4$ , is less reactive and can be used in alkaline aqueous solution. What would be formed from  $\text{PhCOCH}_3$  and  $\text{NaBH}_4$ ?

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45.



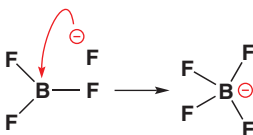
These reagents demonstrate two important properties of boron and aluminium compounds. If you are uncertain of the Periodic Table, just check to see where these two elements come. Neutral trivalent B and Al compounds are electron deficient: only six valency electrons: no lone pair.



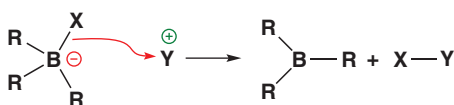
They readily accept nucleophiles to form stable tetravalent anions. Draw the reaction between  $\text{BF}_3$  and a fluoride ion,  $\text{F}^-$

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46.



Also, anions can be transferred from these tetrahedral anions to other molecules:

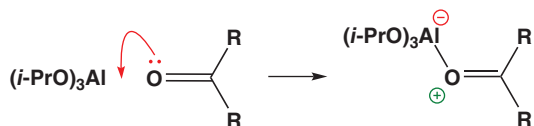


These two properties may be summarised by saying that trivalent boron and aluminium compounds will accept anions from one molecule and transfer them to another.

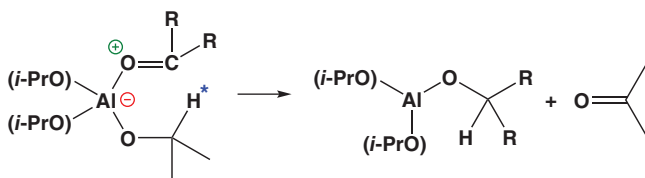
47. This is used in the selective reduction technique known as the Meerwein–Ponndorf reduction. The trivalent compound is aluminium *iso*-propoxide,  $(i\text{-PrO})_3\text{Al}$ . When a compound such as a ketone is added to this reagent, it combines with it to form a tetrahedral anion. Draw this.

48. If you are in difficulty, remember that the Al atom is electrophilic and therefore combines with nucleophiles, and think which end of the ketone molecule is nucleophilic.

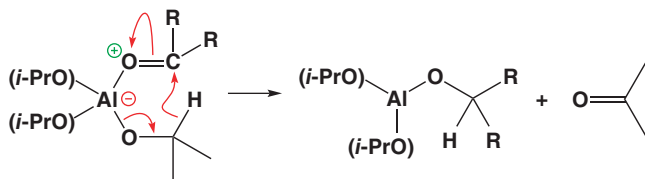
49.



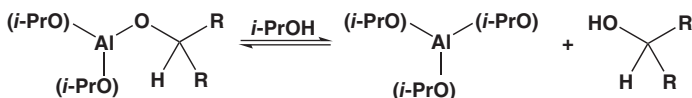
If we draw this same intermediate with one of the *iso*-propyl groups drawn out in full, we can see that the tertiary hydrogen atom in the *iso*-propyl group (\*) is geometrically placed so that it can be transferred to the ketone. Put arrows on the formula to show how this happens.



50.



**51.** The products so far are acetone and a new aluminium compound. The reaction is done in *iso*-propanol solution so that another *i*-PrO group displaces the newly formed alcohol from the Al atom:



The reaction is done at a high enough temperature for the acetone to distil off and the equilibrium is kept over to the right.

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**52.** In the hydrogen transfer reaction (*frame 50*), how is the hydrogen actually transferred – as an atom, a proton or a hydride ion?

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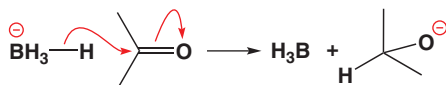
**53.** As a hydride ion – that is, with the pair of electrons from the C—H bond. This type of reaction is called a hydride transfer. You may have noticed that the transfer was done *intra*-molecularly within a six-membered ring, and therefore it has a six-membered transition state. Draw it.

---

**54.** If you do know how to draw transition states, skip to *frame 59*. If you don't know, read on. The transition state for a reaction is the state of highest energy along the reaction path. To draw it, one must first know the reaction mechanism in detail. If there are more than one step, then there will be a transition state for each step. We shall go through the process for a one-step reaction,  $\text{BH}_4^-$  and acetone. Draw the mechanism for this reaction.

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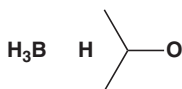
55.



Now draw the formulae again, but put in only those bonds that remain unaffected by the reaction. Don't draw charges or arrows.

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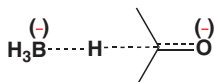
56.



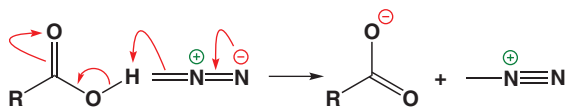
Now 'dot' in all bonds that are formed or broken during the reaction and mark all appearing or disappearing charges in brackets to show that they are partial charges. (Don't use  $\delta+$  or  $\delta-$  as these mean very small charges and here the total charge must add up to unity.)

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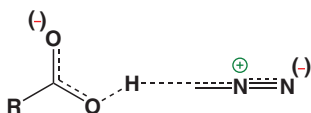
57.



Now draw the transition state for this reaction:



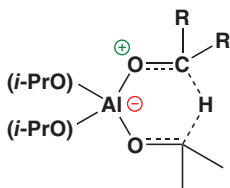
58.



If this wasn't clear, consult your adviser. If it was clear, you ought to be able to do the original problem so go back to *frame 53*.

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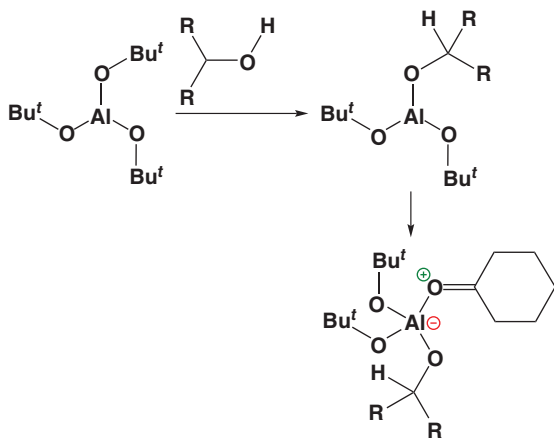
59.



The reason that this reaction goes so well is that six-membered rings are very stable, and so an intramolecular reaction going through a six-membered transition state will be the most favourable.

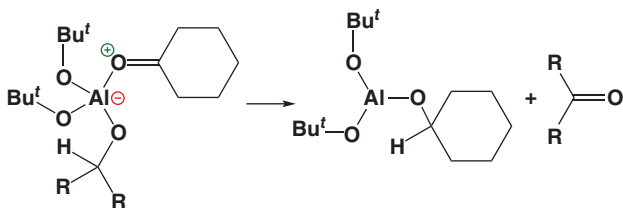
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60. The reverse reaction is known as the Oppenauer oxidation. Here, aluminium-tri-*tert*-butoxide and an involatile ketone such as cyclohexanone are used to oxidise any secondary alcohol to the corresponding ketone.



Show how a hydride transfer in this intermediate leads to the oxidation of the alcohol.

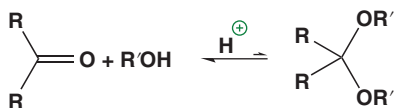
61.



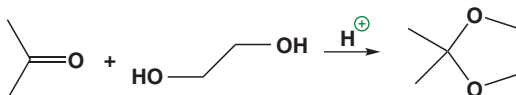
We can reduce a ketone to an alcohol or oxidise an alcohol to a ketone by using (*i*-PrO)<sub>3</sub>Al and acetone in the one case and (Bu<sup>t</sup>O)<sub>3</sub>Al and cyclohexanone in the other. By their mechanism you can see that these reactions will have no effect on other functional groups such as C=C double bonds.



**62.** This is nearly the end of the first part of the program, so here are some general problems. You will remember that acetal formation (*frames 7–17*) is a reversible reaction. It turns out that the equilibrium constant for acetal formation from a ketone is unfavourable:



and poor yields are obtained. However, cyclic acetals can be made from ethylene glycol. Draw out the mechanism for this reaction:

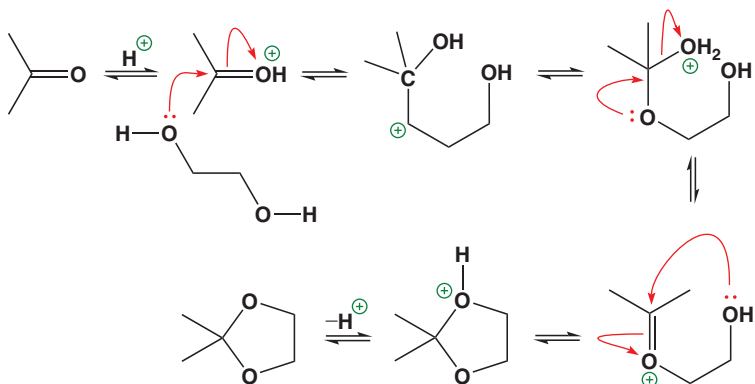


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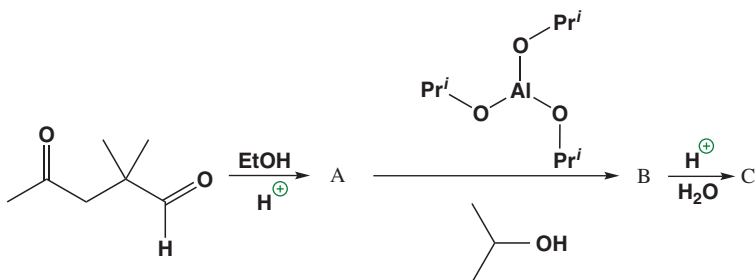
**63.** If you need some help, begin by adding one OH group of HOCH<sub>2</sub>CH<sub>2</sub>OH to the protonated ketone, just as you did with ethanol in *frame 5*.

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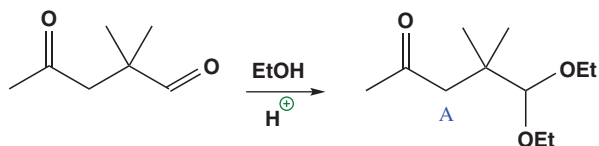
64.



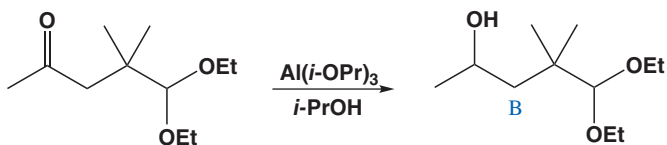
Predict what happens in this reaction sequence:



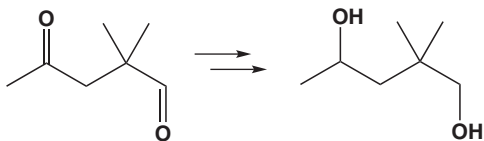
65. In the first step, the acetal from the aldehyde group but not from the ketone group (*frame 62*) is formed:



Only one carbonyl group is now available for Meerwein–Ponndorf reduction (*frames 47–61*).



Finally, the acetal is hydrolysed by standard means. The result of all this is that we have reduced a ketone in the presence of an aldehyde:



*This is the end of the first part of the program.*

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