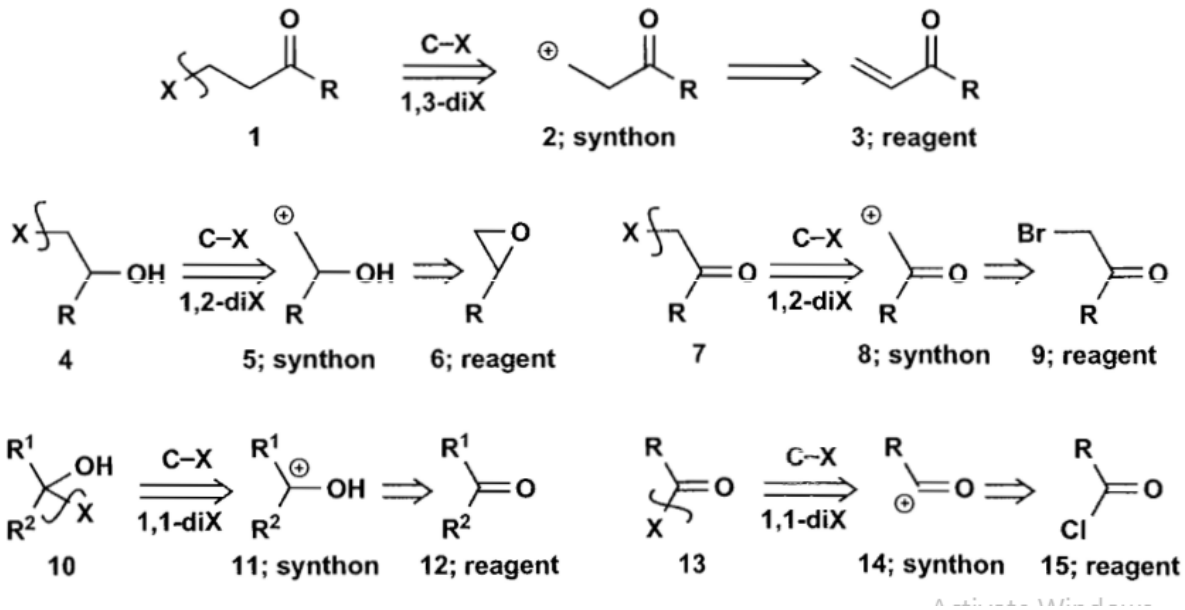
Lecture # 8

Strategy III: Reversal of Polarity, Cyclisations, Summary of Strategy

This chapter considers in more depth two strategic points that emerged from the discussion of C–X disconnections in chapters 4–6.

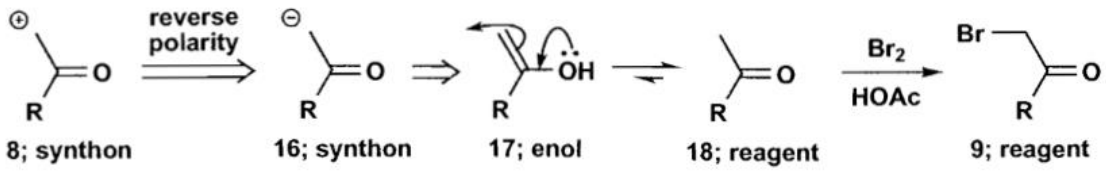
Reversal of Polarity
Synthesis of Epoxides and α-Halo-Carbonyl Compounds

In chapter 6 we needed three types of synthon depending on the di-X relationship in the target molecule. For the 1,3-diX relationship we used just one synthon **2**, for the 1,2-diX we used related synthons **5** and **8**, and for the 1,1-diX two more **11** and **14**. The synthons for the 1,3-diX and 1,1-diX relationships could be turned into reagents **3, 12** and **15** simply by using the natural electrophilic behaviour of the carbonyl group. The synthons **5** and **8** for the 1,2-diX relationship could not be turned into reagents so easily: reagent **6** does not resemble synthon **5** while synthon **8** looks very unstable and such intermediates cannot be made.

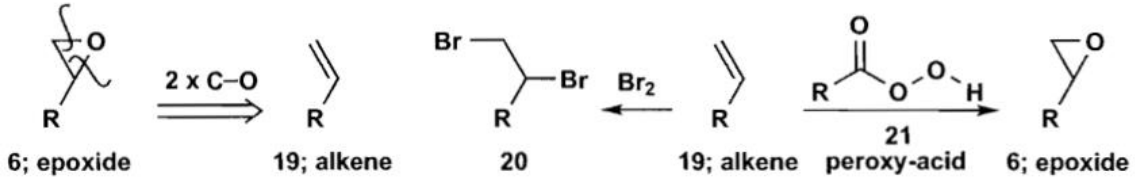


We solved those problems by using an epoxide **6** for synthon **5** and an α-haloketone **9** for **8**: two apparently different devices that actually rely on the same principle—one that is the subject of this chapter. It is easy to see with the synthon **8**: if we simply reverse the polarity to the anion

16 we discover a synthon that again uses the natural reactivity of the carbonyl group as an enol **17** (or enolate) in equilibrium with the ketone **18** by tautomerisation.[1] Treatment of the ketone **18** with bromine in acidic solution gives the α-haloketone **9** with an electrophilic carbon atom in the right place.

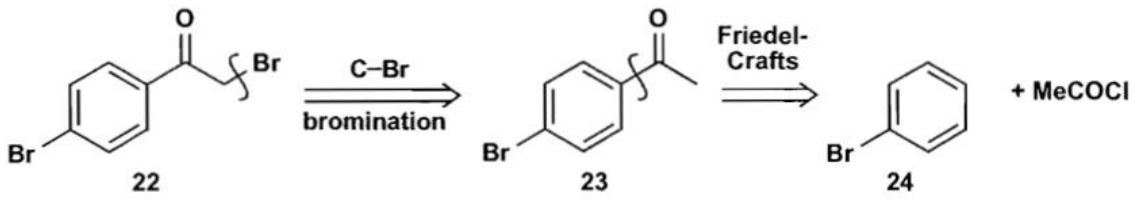


The epoxide **6** is naturally electrophilic, but where does the epoxide come from? By far the most important method of epoxide synthesis is the treatment of alkenes **19** with peroxy acids RCO_3H **21**. Alkenes are naturally nucleophilic:[2] they react with bromine to give dibromides 20 and with electrophilic peroxyacids **21** to give epoxides. Again, these reactions convert nucleophilic alkenes into electrophilic derivatives. A very popular reagent for epoxidation is *m*CPBA (*meta*-chloro-perbenzoic acid) **21**; R = 3-chlorophenyl but many other compounds are used.

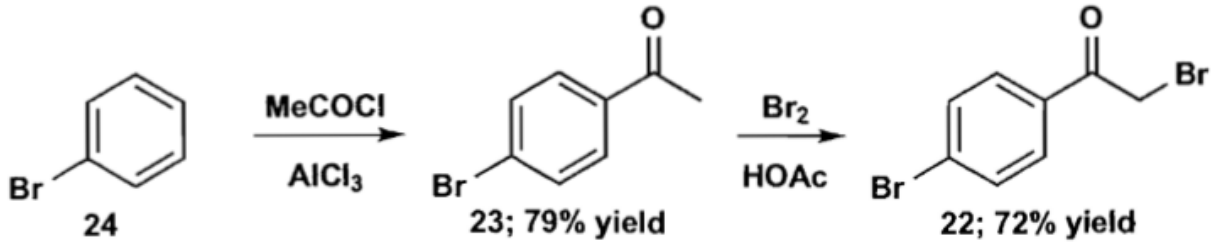


The Halogenation of Ketones

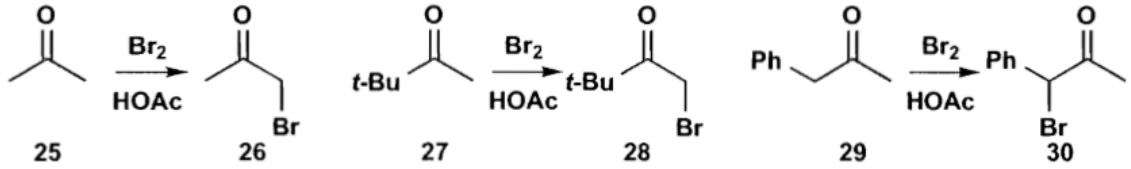
The halogenation of ketones must be carried out in acid solution to avoid polyhalogenation.[1] So the synthesis of reagent **22**, used to make derivatives of carboxylic acids in chapter 6, is simple providing that we notice the directing effects of the two groups on the benzene ring in **23** and disconnect with Friedel-Crafts in mind.



The synthesis is very straightforward: no bromination occurs on the ring as would be expected in the absence of a Lewis acid. Enols react with bromine without the need of any catalysis.[3]

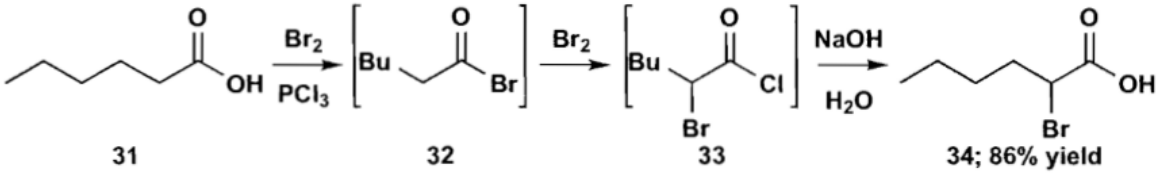


This bromination was unambiguous as the ketone could enolise on one side only. In general the reaction is suitable only for ketones that are symmetrical[4] (e.g. **25**), blocked on one side[5] (e.g. **23** or **27**) or which enolise regio-selectively[6] (e.g. **29**).

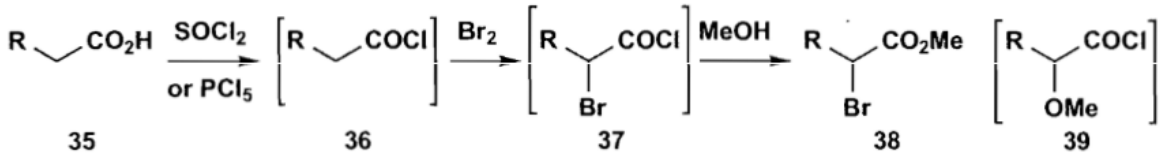


Halogenation of Acids

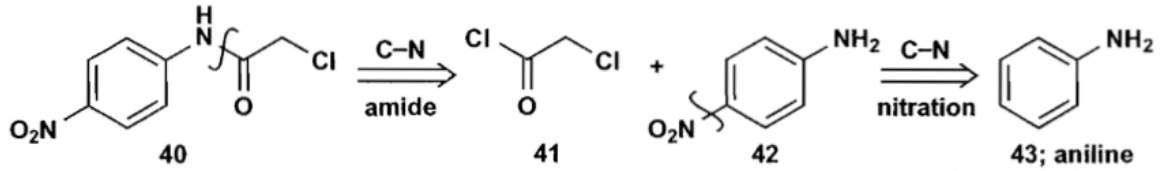
There is no ambiguity in the halogenation of acids as they can of course enolise on one side only. Reliable methods are bromination with PCl_3 and bromine or red phosphorus and bromine. The acid is converted into the acyl chloride with PCl_3 or the acid bromide by PBr_3, formed in the reaction mixture from red phosphorus and bromine. Bromohexanoic acid **34** can be made in good yield if the reaction mixture is worked up with water.[7]



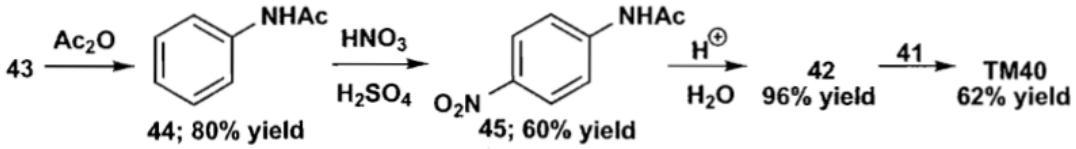
If the reaction is quenched with an alcohol, only the acyl halide reacts and this is a simple way to make α-bromoesters **38**. The alternative product **39** is not formed. Water and alcohols are poor nucleophiles in the S_N2 reaction but better with carbonyl groups.



Many α-chloroacids are available commercially (chloro-acetic, propanoic, etc.) and chloroacetyl chloride **41** is made on a very large scale industrially.[8] The α-chloro amide **40**, needed to make some analeptic tetrazoles, is best disconnected as an amide as **41** is cheap.[9]

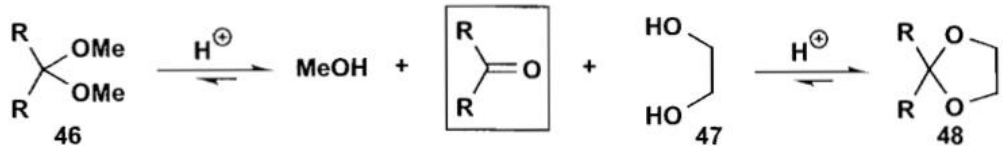


It is better to acylate aniline before nitration to prevent oxidation or over-nitration and reduce the proportion of *ortho*-nitration. The yield of **45** is after separation from the *ortho* isomer.[10] Notice that in the last step nitrogen, like oxygen, prefers to attack the acyl rather than the alkyl chloride.

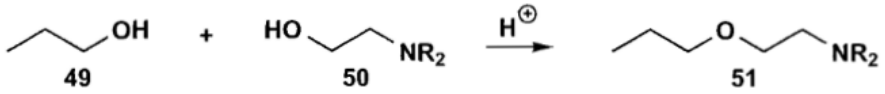


Cyclisation Reactions

Generally intramolecular reactions are easier than intermolecular reactions: entropy being a major factor. If you want to make an acetal from a ketone (chapter 6) it is better to use a diol **47** rather than, say methanol. The equilibrium is in favour of the cyclic acetal **48** but not in favour of the methyl acetal **46**. Two molecules—one of each—go into **48** but three—two alcohols and one ketone—go into **46**. Entropy is a thermodynamic factor.

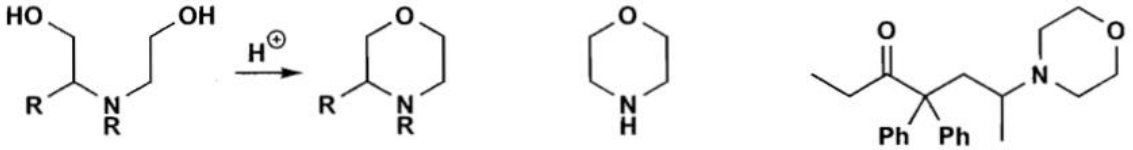


But the rates of cyclisations to form 3-, 5-, 6- and 7-membered rings are greater than the rates of corresponding bimolecular reactions. This is kinetics but the smaller loss of entropy (fewer degrees of freedom lost in the cyclisation) is also a factor. We should not expect a good yield in an acid-catalysed ether formation from two alcohols. If the reaction worked at all, we should get dimers of each alcohol as well as the mixed ether **51**.



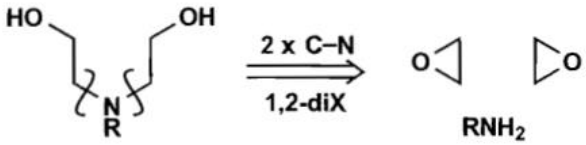
49 **50** **51**

But if the reaction were a cyclisation of the diol then things would be very different. The rate of the cyclisation will be much greater so even this unpromising reaction should go well. And no regioselectivity problems would arise. If the side chains on nitrogen were different **52** we should still get the same product **53** regardless of which OH group were protonated and which acted as the nucleophile. The parent compound **54** is morpholine and this unit is present in many drugs such as the analgesic phenadoxone[11] **55**.



52 **53** **54; morpholine** **55; phenodoxone**

The necessary diol for such compounds comes, by two 1,2-diX disconnections **56**, from the amine RNH_2 and two molecules of ethylene oxide. Now we want the epoxide to react twice so an excess is used and the diol **56** cyclised in acid.[12]



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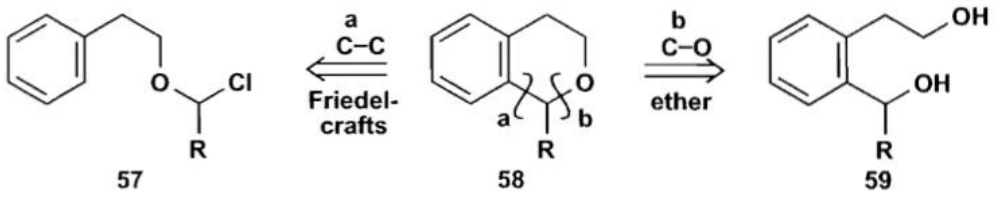
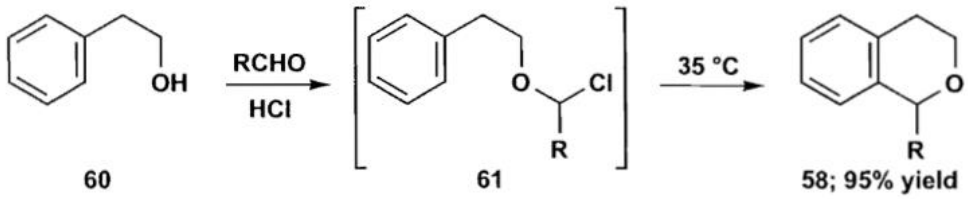
Choosing cyclisation reactions can make possible syntheses we should certainly reject if a bimolecular reaction were required. The ether disconnection **58b** gives a perfectly reasonable

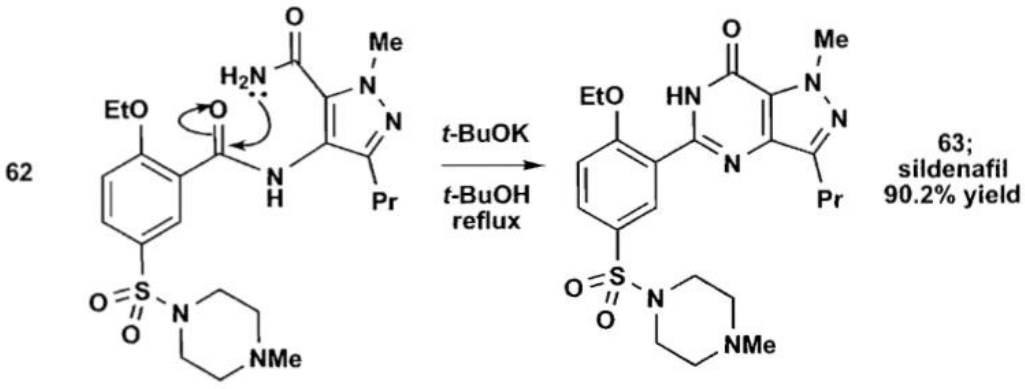
diol **59** that would certainly cyclise as we wish. But making **59** would involve creating an *ortho* relationship with the unwanted *para* relationship probably preferred.



We should not normally consider the Friedel-Crafts alternative **58a** as the intermediate **61** would be unstable. But what that means is that **61** will cyclise rapidly to **58**. Indeed it is difficult to isolate[13] **61** as it gives **58** even at 35 °C.



A dramatic example occurs in the last stage of the production of sildenafil **63** the Pfizer treatment of male erectile dysfunction better known as Viagra™. The cyclisation of **62** must involve the attack of the nitrogen atom of one amide on the carbonyl atom of the other (arrows show first stage). This is an exceptionally difficult reaction: amides are very poor nucleophiles and very poor electrophiles. Yet this reaction goes in over 90% yield.[14] It does so because it is intramolecular.



The diamide **62** is heated under reflux for several hours in *t*-butanol with the base *t*-BuOK as catalyst so it may be that the anion of the nucleophilic amine is involved. Afterwards, dilution with water and neutralisation to pH 7.5 with HCl gives pure **63**.

Summary of Strategy

In chapter 1 we gave the bare bones of synthetic strategy. We can now add life to those bones by adding the main points from chapters 2–7. There will be fuller outlines as the book progresses.

Analysis:

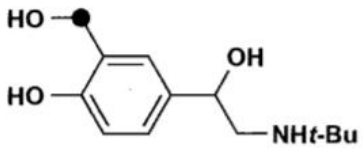
1. Recognise the functional groups in the target molecule.
2. Disconnect with known reliable reactions in mind, using FGI as needed to give the right FG. Disconnect:
   (a) Bonds joining an aromatic ring to the rest of the molecule, whether Ar–X or Ar–C (chapters 2 and 3);
   (b) Any C–X bond (chapter 4) especially:
      (i) Bonds next to carbonyl groups RCO–X (chapter 4);
      (ii) Using two-group disconnections (chapter 6);
      (iii) Bonds in saturated rings as cyclisations are so good (chapter 7).
3. Repeat as needed to reach available starting materials.

Synthesis:

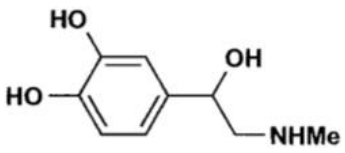
1. Write out the plan in the forward direction adding reagents and conditions.
2. Check that a rational order of events has been chosen (chapter 3).
3. Check that chemoselectivity is favourable (chapter 5). Use protection if necessary (chapter 9).
4. Modify the plan from points 2 and 3 (and later from unexpected failures or successes in the laboratory).

Example: Salbutamol

The anti-asthma drug salbutamol **64**, better known as GSK's Ventolin™, is closely related to adrenaline **65**. The extra carbon atom, marked with a black blob in **64**, prevents dangerous side effects on the heart and the *t*-butyl group makes the drug longer lasting.

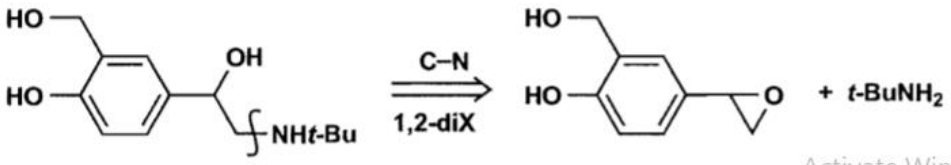


64; salbutamol



65; adrenaline

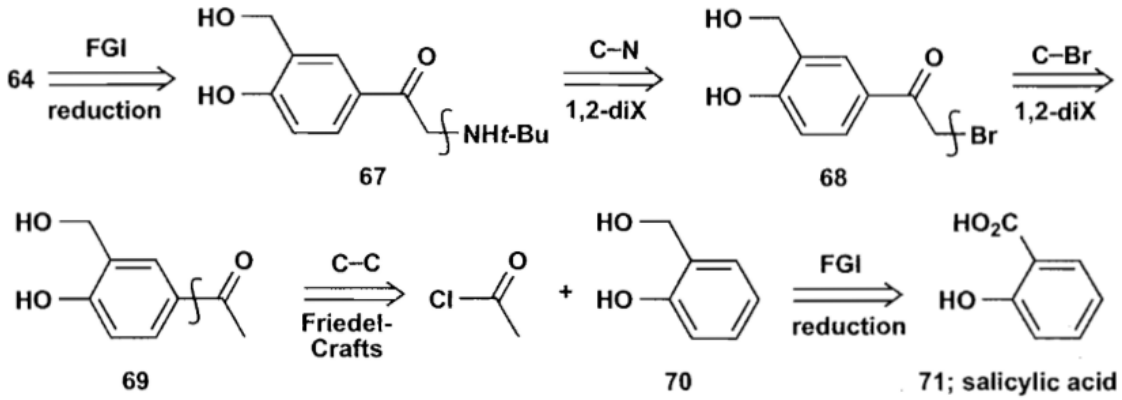
Salbutamol has three hydroxyl groups and an amine but the only two-group C–X disconnection is of the C–N bond **64a** revealing the epoxide **66** as a starting material. This approach is successful but it involves chemistry we encounter in chapter 30 so we shall discuss it there.



64a 66

An alternative is FGI back to the ketone **67** and hence the α-bromoketone **68** that can be made from the ketone **69** itself by methods discussed earlier in this chapter. The ketone **69** is clearly made by some sort of Friedel-Crafts acylation, but how are we to make the diol **70**? In chapter 3 we said that a good strategy to make *ortho*-disubstituted aromatic compounds was to start with an

available compound with that relationship already present. Here the obvious candidate is salicylic acid **71**.



67 68 69 70 71; salicylic acid

Further consultation of chapter 3 reveals the synthesis of the related ketone **73** by a Friedel-Crafts style reaction on aspirin **72**. As we have two reductions (of the acid and the ketone) it makes sense to do them both at the end. The plan is now: