Lecture # 3

Strategy I: The Order of Events

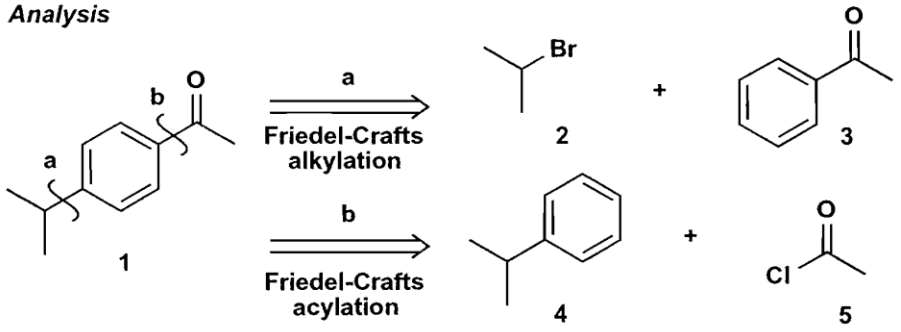
Background Needed for this Chapter

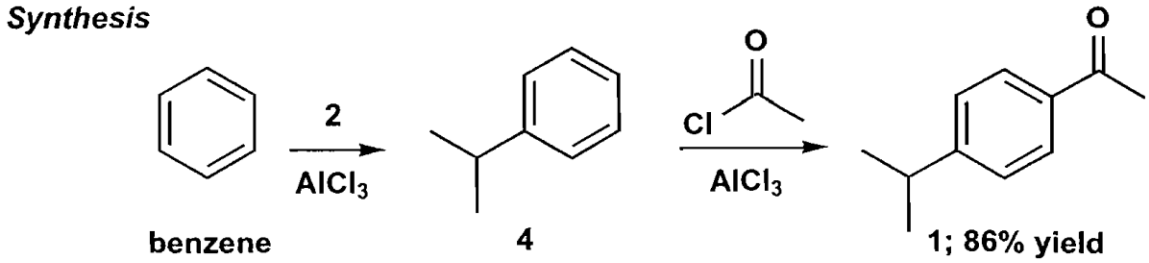
Electrophilic aromatic substitution

Alternating with instructional chapters, like the last one, will be strategy chapters, like this one, which discuss reasons for choosing one route rather than another: in other words the overall plan rather than the individual steps. In this chapter we shall examine the order of events, using the synthesis of aromatic compounds as examples. The details are specific but the guidelines general.

Guideline 1: Consider the effects of each functional group on the others. Add first (that is disconnect last) the one that will increase reactivity in a helpful way. So, for aromatic compounds, introduce first that group that helps, by reactivity or direction, the introduction of the others.

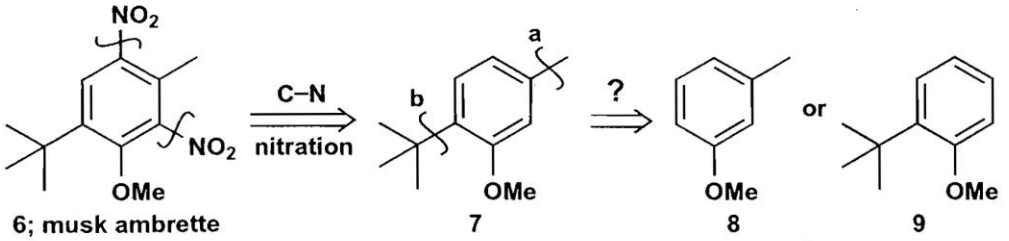
The analysis of the perfumery compound **1** could be tackled by two possible first disconnections. Friedel-Crafts alkylation **a** would work reasonably well with the secondary alkyl halide **2** but the ketone in **3** is *meta*-directing and would give the wrong product. Friedel-Crafts acylation **b** would give the right product as the alkyl group in **4** is *ortho,para*-directing. Further the alkyl group in **4** is activating while the ketone in **3** is deactivating.



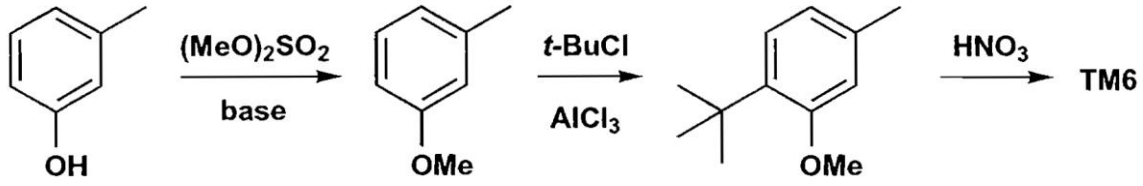


Our next example emphasises one aspect of guideline 1. Some functional groups are so deactivating that it is difficult to do any further chemistry once they have been inserted. In other contexts it may be that they are so unstable that we would not wish to risk any further reactions.

Musk ambrette **6** is a synthetic musk, essential in perfumes to enhance and retain the fragrance. It has five substituents round a benzene ring. Two of these, the nitro groups, are so deactivating that we want to add them last. So we disconnect them first.



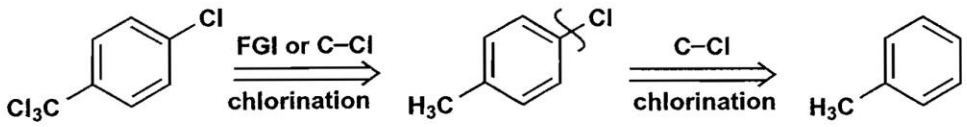
6; musk ambrette 7 8 9



10 8 7

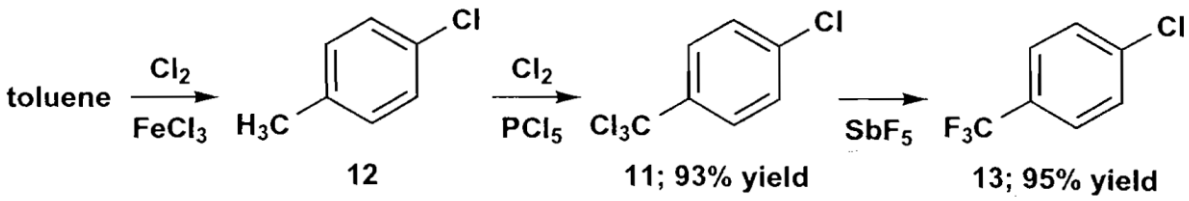
Guideline 2: Changing one functional group into another may alter reactivity dramatically. Changing an alcohol or phenol to a *t*-Bu ether increases steric hindrance. Alcohols and aldehydes or ketones are easily interconverted by redox reactions. The carbonyl compounds are electron-withdrawing, alcohols weakly electron-donating. Most dramatically for aromatic compounds, the nitro group is powerfully electron-withdrawing, deactivating and *meta*-directing while the amino group, often made by reduction of a nitro group, is strongly electron-donating, activating and *ortho,para*-directing. In an analysis featuring FGI, it may pay to consider at which stage to carry out some other reaction.

A simple example is the tetrachlorocompound **11** clearly made from toluene by some form(s) of chlorination. In fact we must change the *meta*-directing CCl_3 group into a *ortho,para*-directing methyl group before we disconnect the Ar-Cl bond.



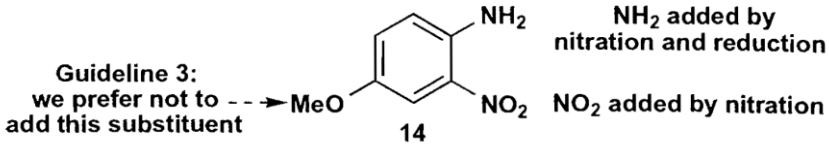
11 12 toluene

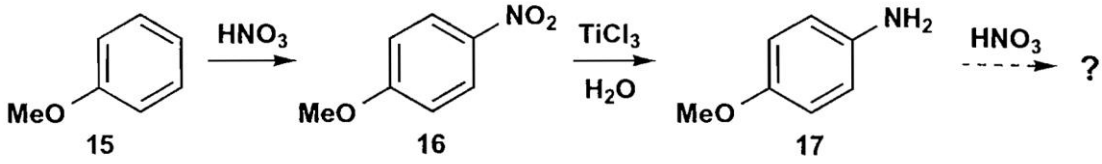
This compound **11** was actually used[3] to make the trifluorocompound **13**. The chlorination of toluene with Lewis acid catalysis gives mostly **12** and chlorine and PCl_5 does the, probably radical, chlorination of the methyl group.



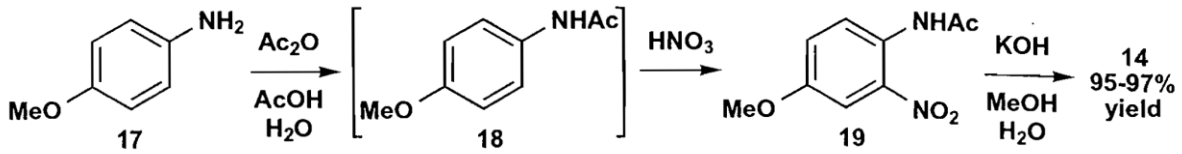
Guideline 3: Some substituents are difficult to add so it is best to start with them already present. It is not necessary to start all syntheses of aromatic compounds from benzene: a glance at any supplier's catalogue will show the great range of aromatic compounds available. The chief examples of such substituents are phenols and the ethers derived from them as there is no simple reagent for electrophilic oxygen. But a methyl group and primary alkyl groups in general, are also difficult to add as Friedel-Crafts alkylation with primary alkyl halides leads to rearranged products.[4]

The trisubstituted benzene **14** was used by Woodward as a starting material for his synthesis of the natural product reserpine.[5] It too has to be made. We shall not add the MeO group but buy anisole (methoxybenzene) as starting material. Both nitrogens will be added by nitration but in which order?

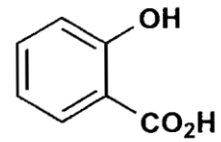




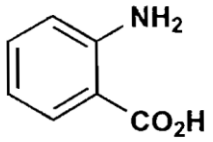
In practice, there is too much activation in **17** and attempted nitration oxidised the molecule. The amine must be acetylated first and then, without isolation of **18**, can be nitrated (with nitric acid alone) to give **19**. Hydrolysis of the amide gives **14** in excellent yield.[8]



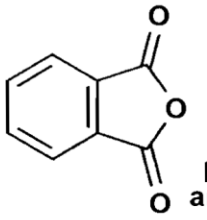
Guideline 4: Some disubstituted compounds are also readily available and they may contain a relationship (especially *ortho*) that is difficult to achieve by electrophilic substitution. Here is a selection: a supplier's catalogue will reveal more.



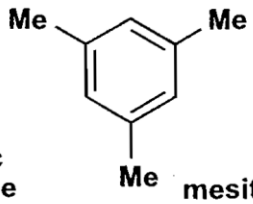
salicylic acid
(also aldehyde)



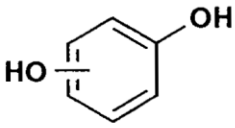
anthranilic acid



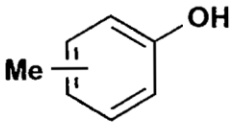
phthalic anhydride



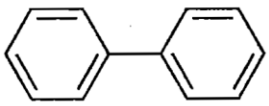
mesitylene



ortho (catechol)
meta (resorcinol)
para (quinol)

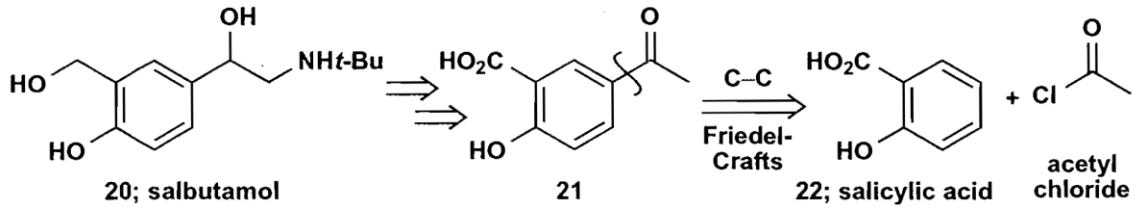


ortho, *meta* and
para cresols



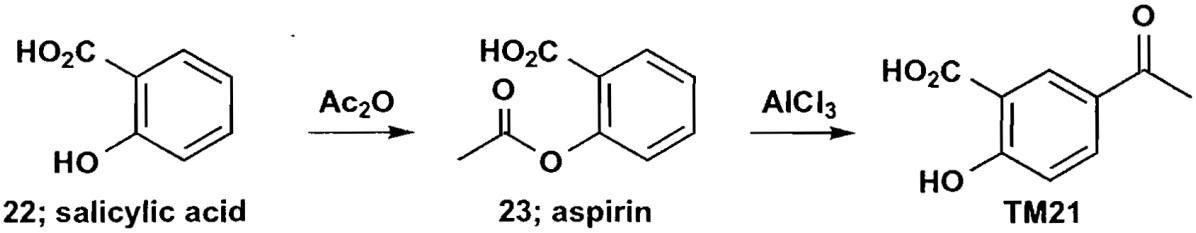
diphenyl

A good example is **21** needed for the synthesis of the GSK anti-asthma drug salbutamol **20**. This ketone **21** could be made by a Friedel-Crafts acylation of **22**, which turns out to be salicylic acid, with acetyl chloride.



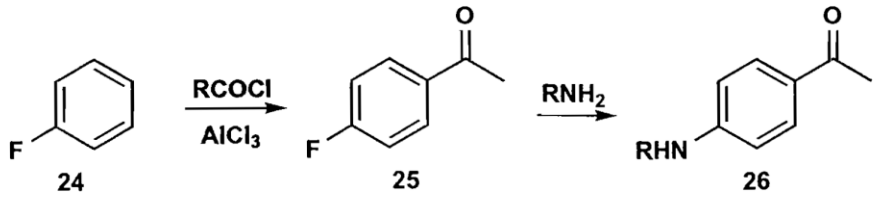
20; salbutamol 21 22; salicylic acid acetyl chloride

This synthesis is easier than it may seem as the free phenol, rather then interfering, can be acylated to give the ester **23** which rearranges with $AlCl_3$ to give **21** directly.[9] Even the intermediate **23** is available and cheap–it is aspirin.



22; salicylic acid 23; aspirin TM21

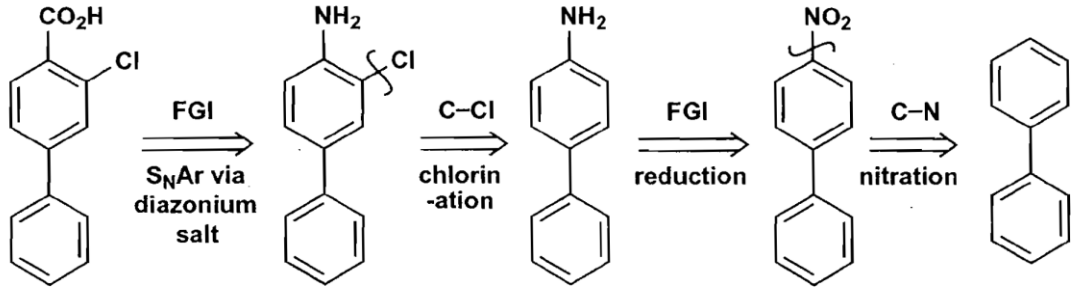
Guideline 5: Some groups can be added to the ring by nucleophilic substitution. This is mechanistically more difficult than electrophilic substitution and requires an electron-withdrawing activating group such as nitro or carbonyl *ortho* or *para* to a normal leaving group such as a halide (chapter 2). Fortunately nitration or Friedel-Crafts acylation of halocompounds puts the activating group in the right position for nucleophilic substitution. So Friedel-Crafts acylation of fluorobenzene **24** gives the ketone **25** and displacement of fluoride by the addition–elimination mechanism[10] gives the amine **26**.



24 25 26

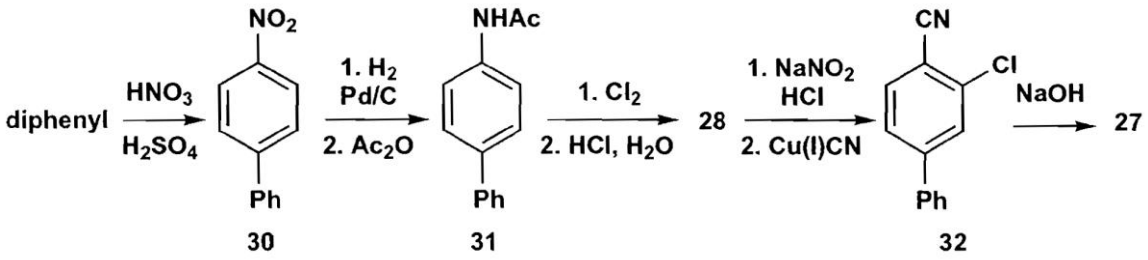
If this kind of activation is not available, nitrogen can be displaced from diazonium salts by the S_N1 mechanism. The acid **27** was needed at Hull University in work on liquid crystals.[11]

The skeleton is diphenyl (Guideline 4) which reacts in the *para*-positions with electrophiles. The chlorination is difficult therefore and we need to replace the CO_2H group with a group more electron-donating than the phenyl ring. An amine is the answer **28** and that soon takes us back to diphenyl.



27 28 29 30 diphenyl

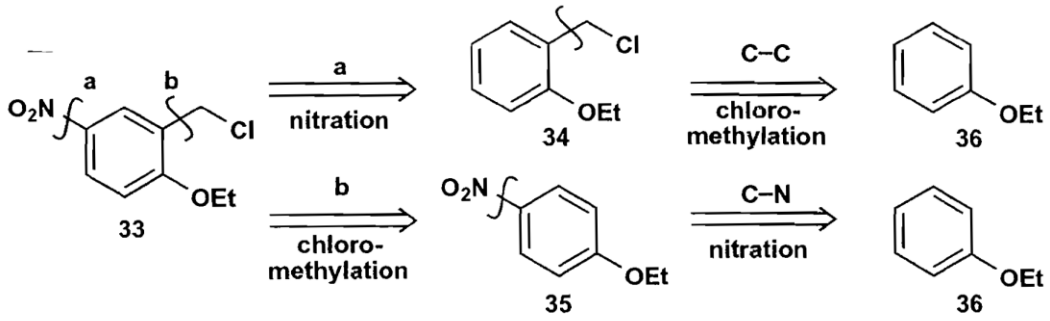
The nucleophile to introduce the CO_2H group is cyanide ion, used as its Cu(I) salt, and the amine in **29** must be acylated to prevent over-chlorination (compare **18**).



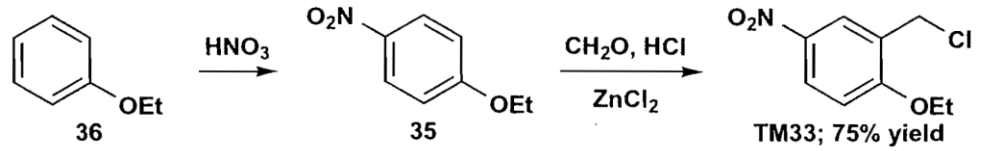
30 31 32

Guideline 6: If a series of reactions must be carried out, start with one that gives a single product unambiguously and not one that would give a mixture. With aromatic compounds if you need to add both *ortho* and *para* substituents, putting in the *para* substituent first may be less ambiguous than the reverse.

Compound **33** was needed to make some antimalarial drugs.[12] We prefer not to disconnect the OEt group (Guideline 3) and there are good reactions–nitration and chloromethylation–that would go in the right position (*ortho* or *para*) to the activating OEt group. Either disconnection **a** or **b** could be tried first.



We expect the *para* product to be the major product from either reaction on ether **36** (steric hindrance) so it makes sense to nitrate first. There is also a danger that nitration of **34** might oxidise the CH_2Cl group to CHO or even CO_2H. The synthesis works well if nitration is carried out first.[12]



It should be obvious that not all of these six guidelines will be relevant in every synthesis–indeed some may even contradict others. It is a matter for judgement and then laboratory trial to select a good route. As always, several different strategies may be successful.