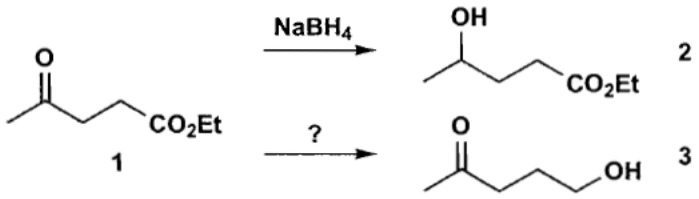
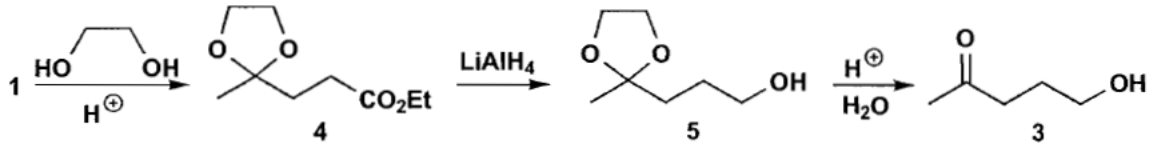
Lecture # 10-1

Strategy IV: Protecting Groups

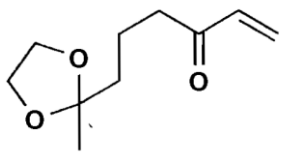
Protecting groups have been mentioned occasionally in previous chapters: in this chapter the ideas behind their use are systematically presented and a collection of protecting groups suitable for a range of functional groups is tabulated. Protection allows us to overcome simple problems of chemoselectivity. It is easy to reduce the keto-ester **1** to the alcohol **2** with a nucleophilic reagent such as $NaBH_4$ that attacks only the more electrophilic ketone.



Making alcohol **3** by reducing the *less* electrophilic ester is not so easy but protection of the ketone as an acetal **4**—a functional group that does not react with nucleophiles—allows reduction of the ester with the more nucleophilic $LiAlH_4$.

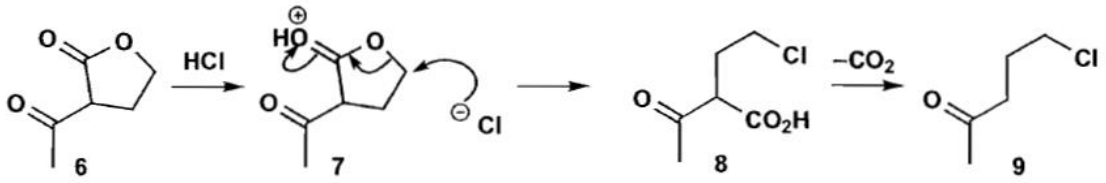


Another important function of protecting groups is to prevent a reagent from attacking itself. In the last chapter, when we discussed the synthesis of the bicyclic amine monomorine, we used the protected enone **12** but did not say how it was made.

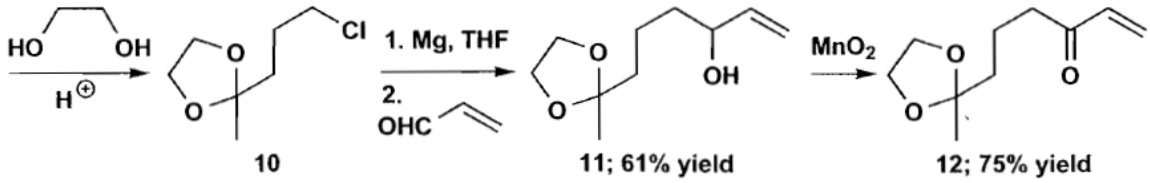


12; 75% yield

The chloroketone **9** is first made[1]
in 89–93% yield from the ketolactone **6** simply by reaction with HCl. Chloride displaces the protonated ester group **7** and the product **8** decarboxylates under the conditions of the reaction.



Any attempt to make a Grignard reagent from **9** is doomed because the nucleophilic Grignard would immediately attack the ketone. We need to protect the ketone with an easily added group that is not attacked by Grignard reagents and the acetal **10** is the answer. Addition of the Grignard from **10** to acrolein (CH_2=CHCHO) gives the allylic alcohol **11** which is oxidised to the enone **12** with manganese dioxide.[2] If you look back to chapter 8 you will see that the acetal was retained until it was very easily removed almost at the end of the synthesis.



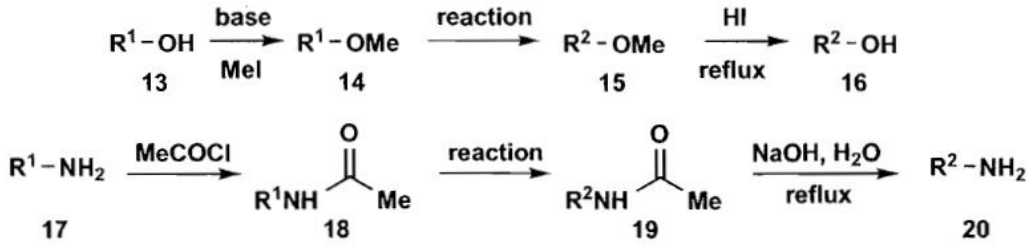
Qualities Needed in a Protecting Group

1. It must be easy to put in.
2. It must be resistant to reagents that would attack the unprotected functional group.
3. It must be easily removed.

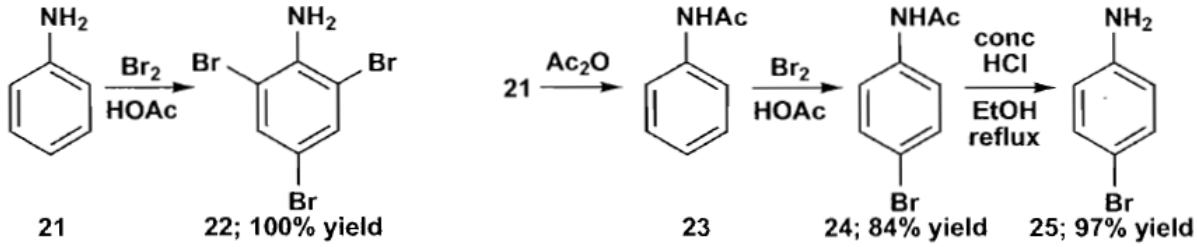
The last point may not be so obvious but it is the most difficult to achieve. Many syntheses fall down right at the end because a protecting group cannot be removed without destroying the molecule. The next section looks at ways to make removal of protecting groups easier.

Ethers and Amides as Protecting Groups

Protection of alcohols and amines might look simple. Methyl ethers and simple amides are easy to make and are very resistant to a wide variety of reagents. So there is no problem in carrying out the required reaction elsewhere in the molecule i.e. turning R^1 in **13** and **17** into R^2 in **16** and **20**. But sadly they are almost useless as protecting groups because such violent conditions are needed to remove them: cleavage of methyl ethers requires good nucleophiles under acidic conditions and the hydrolysis of amides needs refluxing 10% NaOH or concentrated HCl in a sealed tube at 100 °C overnight.

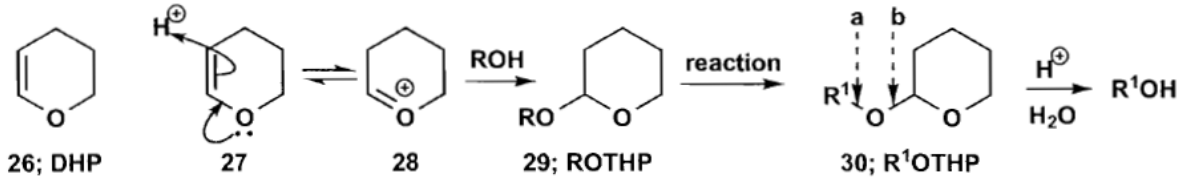


These protecting groups are used when the molecule is robust enough to take the de-protection conditions. If aniline **21** is brominated the 2,4,6-tribromo derivative **22** is formed. The yield is quantitative but we are more likely to want mono-bromination. Protection is needed against over-reaction. The amide **23** is easily made, bromination goes only in the *para* position (the *N*-acetyl group is larger than NH_2) and the hydrolysis does not destroy the benzene ring.[3]

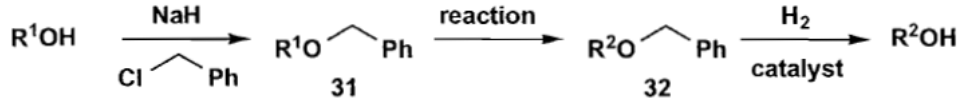


The Achilles Heel Strategy

A way round these difficulties is to use an ether or an amide that has a built-in weakness so that the over-vigorous conditions are not needed. This 'Achilles heel' for an ether is commonly the THP group that makes the ether into an acetal. Dihydropyran, DHP **26**, is protonated on carbon **27** to give the cation **28** that captures the alcohol to give the mixed acetal **29**, usually referred to as 'the THP derivative'. After the reaction the hydrolysis needs only the weak aqueous acid used for acetals. The secret is that the weak acetal bond (**b** in **30**) is cleaved[4] rather than the strong ether bond (**a** in **30**).



Another way to make an ether easier to remove is to make it benzylic **31** as σ-conjugation of the C–O bond with the benzene ring weakens it enough for it to be cleaved by catalytic hydrogenation using various transition metals.[5]



This is also the key to the weakening of amides as protecting groups for amines. The amine is acylated with benzyl chloroformate **33** (as described in chapter 5) to give urethane **34**. This is still an amide on the left but a benzyl ester on the right. Then the reaction is carried out. Hydrogenation cleaves the weak benzyl-O bond to give unstable carbamic acids **36** that decarboxylate **37** spontaneously to give the altered amine R^2NH_2. Though the C–N bond is cleaved, no nucleophilic attack on the carbonyl group is needed. This protecting group is so popular it has its own abbreviation Cbz (Carbobenzyloxy-) or even just Z.