Lecture # 6

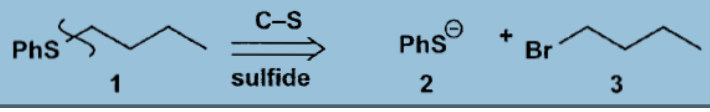
Two-Group C–X Disconnections

Background Needed for this Chapter

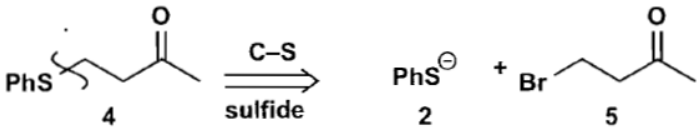
Conjugate Addition.
Formation and Reaction of Enols and Enolates.

One-Group and Two-Group C–X Disconnections

Asked to make the sulfide **1** you would not hesitate to disconnect a C–S bond, choosing the one between the sulfur and the aliphatic part of the molecule to ensure a good S_N2 reaction. There is only one functional group in the target molecule **1** so you have to choose a one-group C–X disconnection.



If you were asked to make the sulfide **4** you might very reasonably take the same decisions, proposing the same sulfur compound **2** as nucleophile and the alkyl bromide **5** as electrophile.



There is nothing wrong with this suggestion except that it ignores the other functional group—the ketone—in the target molecule **4** and so misses an opportunity for a two-group disconnection. Our message in this chapter is going to be that two-group disconnections are better than one-group disconnections. Reverting to synthons for a moment, the sulfur synthon **2** is the same as the reagent but the carbon synthon **6** might make you think of a different reagent.

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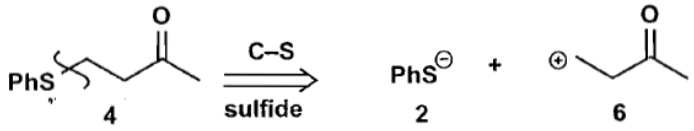
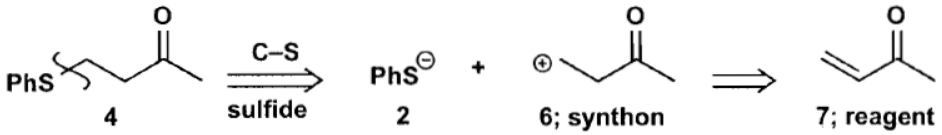
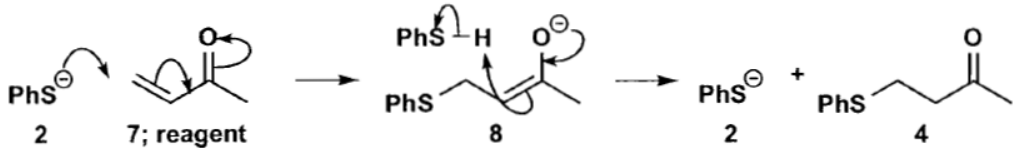


The idea with two-group disconnections is that we recruit the other functional group to help us discover a better reagent. Here the carbonyl group can make the cationic centre in **6** electrophilic if we simply add a double bond to the structure.



The reaction is conjugate addition of the thiolate anion **2** to the enone **7** making an enolate intermediate that captures a proton from PhSH **8** to give the target molecule **4** and regenerate the nucleophile **2**.

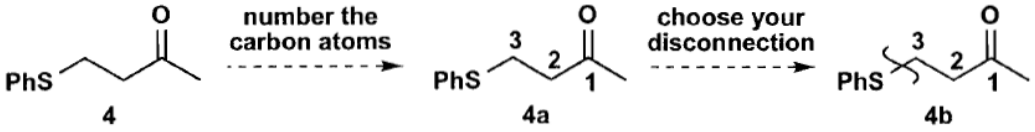


This route using **7** is better than the first suggestion using **5** for several reasons.

1. There is no need to waste an atom of bromine to provide a leaving group: the enone **7** is naturally electrophilic at the right carbon atom.
2. The two functional groups in the target molecule co-operate in making the new C–S bond.
3. No strong acids, bases or high temperatures are needed as the enolate intermediate regenerates the reagent **2** so only catalytic weak base is needed.
4. The bromide **5** is likely to eliminate under the reaction conditions to give **7** anyway.

Recognising a Two-Group C–X Disconnection

The key step is recognising the *relationship* between the two functional groups. To do this, number the *carbon atoms* bearing the functional groups. It doesn't matter which you call 1—only the relationship matters. Here we see **4a** that we have a **1,3-diX** relationship. That means that the two functionalised carbon atoms have a 1,3-relationship. Knowing that, we can choose conjugate addition as our reaction and do the disconnection **4b** we have already done and reveal **2** and **7** as our reagents.

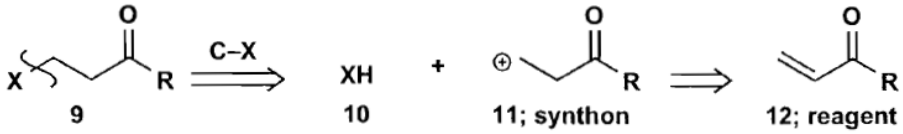


4 4a 4b

To start with you may like to draw the synthons and, by inspecting the carbon synthon, decide which electrophilic reagent to use. But as this chapter develops, you will see that there is a particular chemistry used to make each different relationship (e.g. a 1,3-relationship suggests conjugate addition) and you may soon not bother with the synthons but write the reagents directly. This is a matter for personal choice.

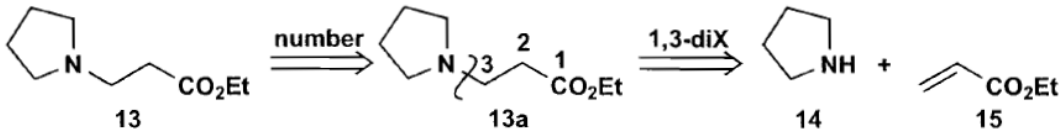
The 1,3-diX Relationship

Since we are using conjugate addition, it is essential to have an electron-withdrawing group, usually a carbonyl group but it could be CN for example, in the right position. The disconnection in general terms is this:



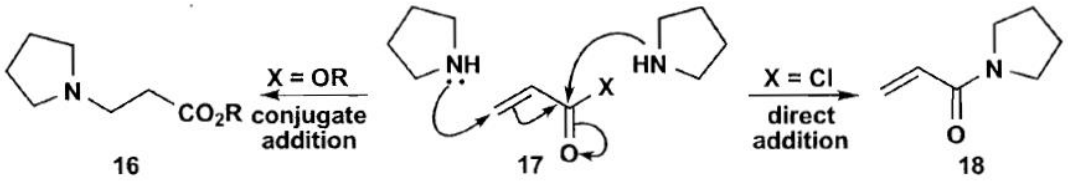
9 10 11; synthon 12; reagent

The nucleophilic reagent will depend on the heteroatom. If X=O or S, base will probably be necessary, but if X=N, the amine itself should be nucleophilic enough to do conjugate addition. An example would be the amino ester **13**. Numbering the carbon atoms **13a** reveals the 1,3-relationship and C–N disconnection gives the secondary amine **14** and ethyl acrylate as reagents.



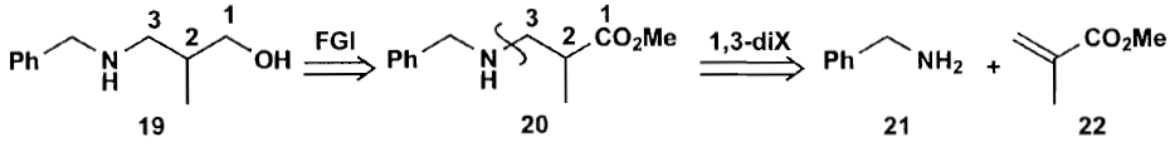
13 13a 14 15

This is the time to reveal a potential problem. In this synthesis we want conjugate addition. But we might on another occasion want to make the amide **18** so how do we control whether the nucleophile adds direct to the carbonyl group or by conjugate addition **17**? In general the reactivity of the electrophile is crucial. Very electrophilic compounds such as acid chlorides or aldehydes tend to prefer direct addition while less electrophilic compounds such as esters or ketones tend to do conjugate addition.

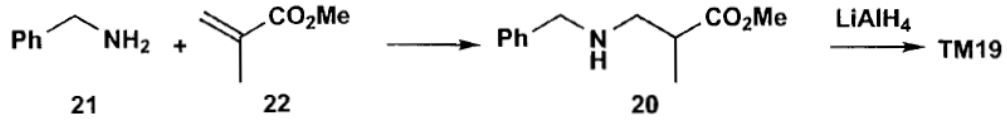


What if There Is No Carbonyl Group?

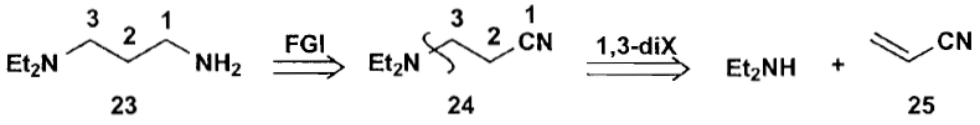
The amino alcohol **19** has a 1,3-diX relationship but no carbonyl group. So we introduce one by FGI. We could have an ester or an aldehyde. An aldehyde would be easier to reduce but there is a danger of direct addition. So we choose an ester (it doesn't matter which).



The synthesis is straightforward and we shall need $LiAlH_4$ to reduce the ester.

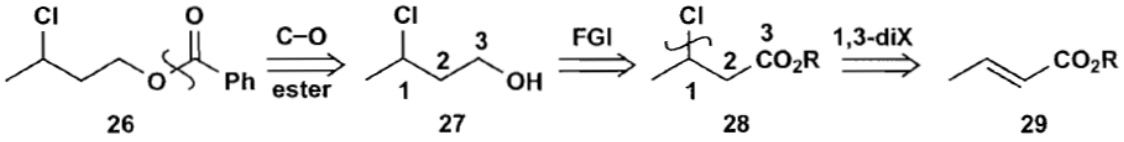


Supposing there is no oxygen-based functionality at all, as in the diamine **23**? It is not necessary to have a carbonyl group for conjugate addition, in fact a nitrile is much better. So we do FGI on the primary amine and disconnect the secondary amine Et_2NH from acrylonitrile **25**. The synthesis is to mix those two and reduce **24** catalytically or with $LiAlH_4$.



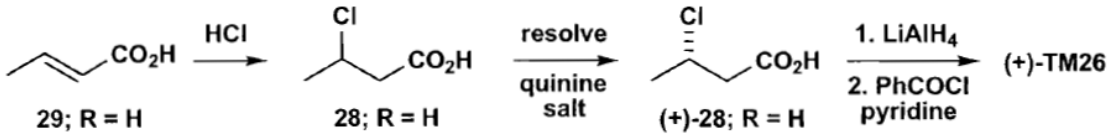
Examples of 1,3-Difunctionalised Compounds

Enantiomerically pure chloro-ester **26** was needed for an investigation into the stereochemistry of the Friedel-Crafts reaction. Disconnecting the ester we reach the one piece of carbon skeleton and see that it has a 1,3-diX relationship **27**. However we need a carbonyl group and an ester **28** should ensure conjugate addition of chloride to **29**.



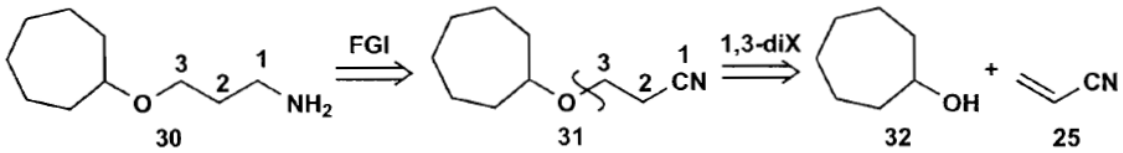
26 **27** **28** **29**

The acid itself was chosen for the conjugate addition as the intermediate can then be resolved by crystallisation of the quinine salt. Conjugate addition of HCl was successful and the acid was reduced to the alcohol with $LiAlH_4$ before esterification in the usual way.[1]



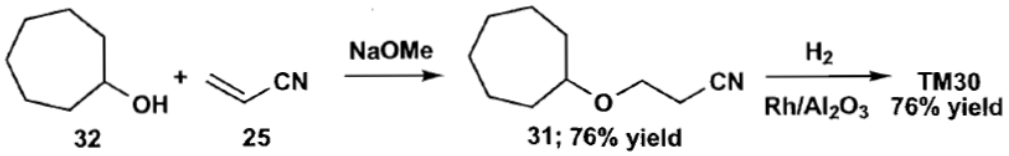
29; R = H **28; R = H** **(+)-28; R = H**

The aminoether **30** containing a seven-membered ring has a 1,3-relationship but no carbonyl group. We could remove the seven-membered ring and put a carbonyl group at C-3 but a shorter synthesis comes from the nitrile **31** as we can add the alcohol **32** in one piece to acrylonitrile **25**.



30 **31** **32** **25**

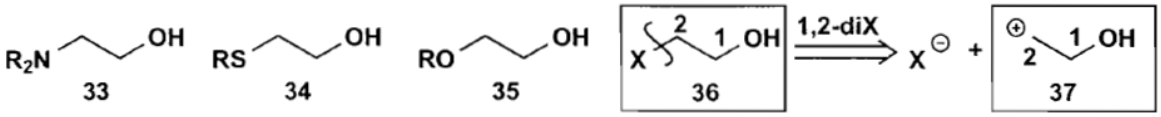
The synthesis is a simple two-stage process with catalytic hydrogenation used for reduction of the nitrile.[2]



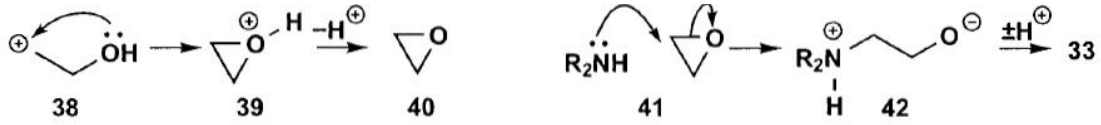
32 **25** **31; 76% yield**

The 1,2-diX Relationship

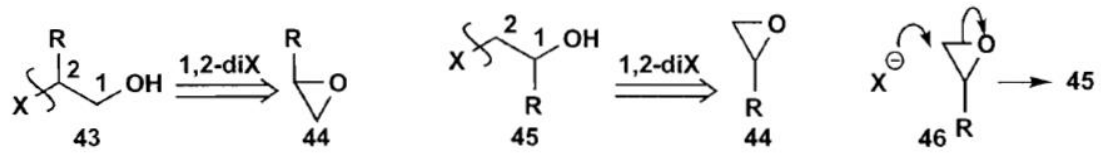
The 1,2-diX relationship presents a different series of opportunities in which we use the second functionality to make the right carbon atom electrophilic. The amino, thio- and alkoxy- alcohols **33** to **35** all fit the pattern **36** and can be disconnected to the usual heteroatom nucleophile and the synthon **37**.



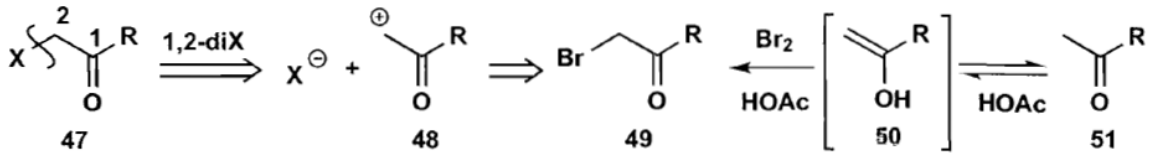
If you don't see at once what reagent will be used for the synthon **37**, you are not alone. How can we use the other OH group at C-1 to make C-2 electrophilic? One way to visualise the answer is to imagine what would happen if you actually made the cation **37**. It would instantly cyclise **38** to form a three-membered ring **39** that could lose a proton to give the epoxide **40**. Epoxides are strained ethers and react with nucleophiles such as amines **41** to give **42** and hence the aminoalcohol **33**.



It doesn't matter which end of the symmetrical epoxide is attacked by the nucleophile—the same product **42** is formed. If there is a substituent at either end of the molecule **43** or **45** we can still make the 1,2-diX disconnection but the 'two' epoxides **44** are the same. This is clearly a problem. In fact the nucleophile will prefer to attack the less substituted end of the three-membered ring **46** so we can make **45** but not **43** this way.

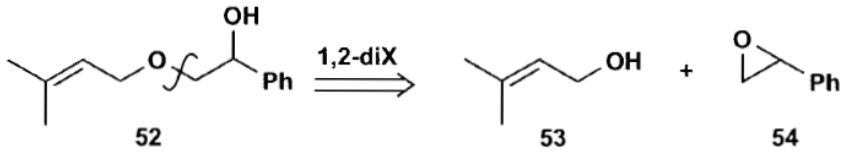


The disconnection **47** gives a different synthon **48** at the carbonyl oxidation level and the best reagents are the α-halo carbonyl compounds **49**. At first this looks like a one-group disconnection but there are two reasons why it isn't. The presence of the carbonyl group makes the S_N2 displacement of halide enormously faster and the α-halo carbonyl compounds **49** are made from the ketone **51** by acid-catalysed halogenation of the enol **50**.

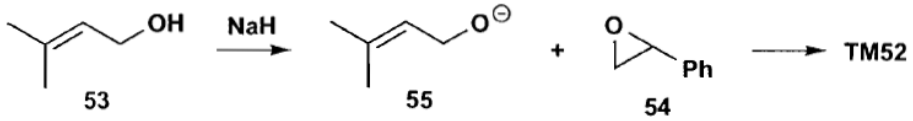


Examples of 1,2-Difunctionalised Compounds

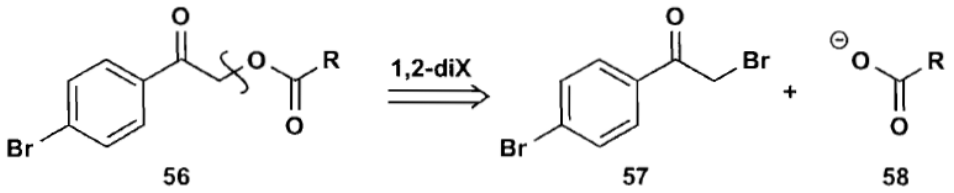
The ether **52** was needed to study the Claisen rearrangement and can be disconnected in 1,2-diX fashion as the epoxide **54** will be attacked at the less hindered end by the anion of **53**.



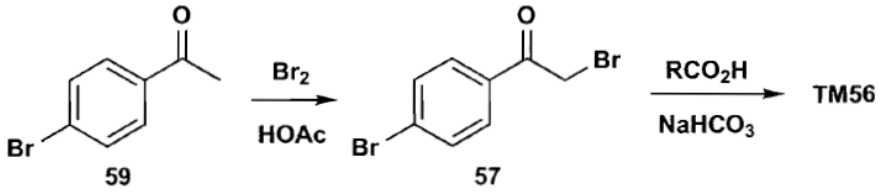
The synthesis involves treating the allylic alcohol **53** with NaH to make the anion **55** and combining that with the epoxide **54** easily made from styrene.[3]



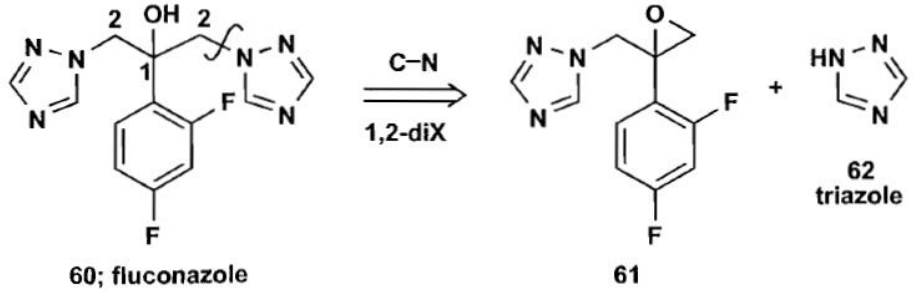
Compounds like the ester **56** were briefly mentioned in chapter 4 and we can now show how they can be made by a two-group disconnection. The electrophile will be the α-halo carbonyl compound **57** and the nucleophile the anion of a carboxylic acid.



The bromide **57** is made by direct bromination of the ketone **59** and only the very weak base $NaHCO_3$ is needed to make the anion of the carboxylic acid. This reaction shows just how electrophilic such α-halo carbonyl compounds must be as carboxylate anions are very weak nucleophiles. Compounds **56** are therefore derivatives of carboxylic acids. They are highly crystalline and can be used to characterise and purify such acids.[4]



The Pfizer anti-fungal compound fluconazole **60** is a more advanced example of such disconnections.[5] It has two identical 1,2-diX relationships between nitrogen and the OH group. You might think that we can make both the same way, but not so. The first disconnection is easy: we want the aromatic amine triazole **62** to combine with the epoxide **61** at its less substituted end.



But how are we to make the epoxide **61**? The obvious route is by epoxidation of the alkene **63**. The alkene **63** could be made by a Wittig reaction (chapter 15) on the ketone **64** or directly by sulfur ylid chemistry (chapter 30).