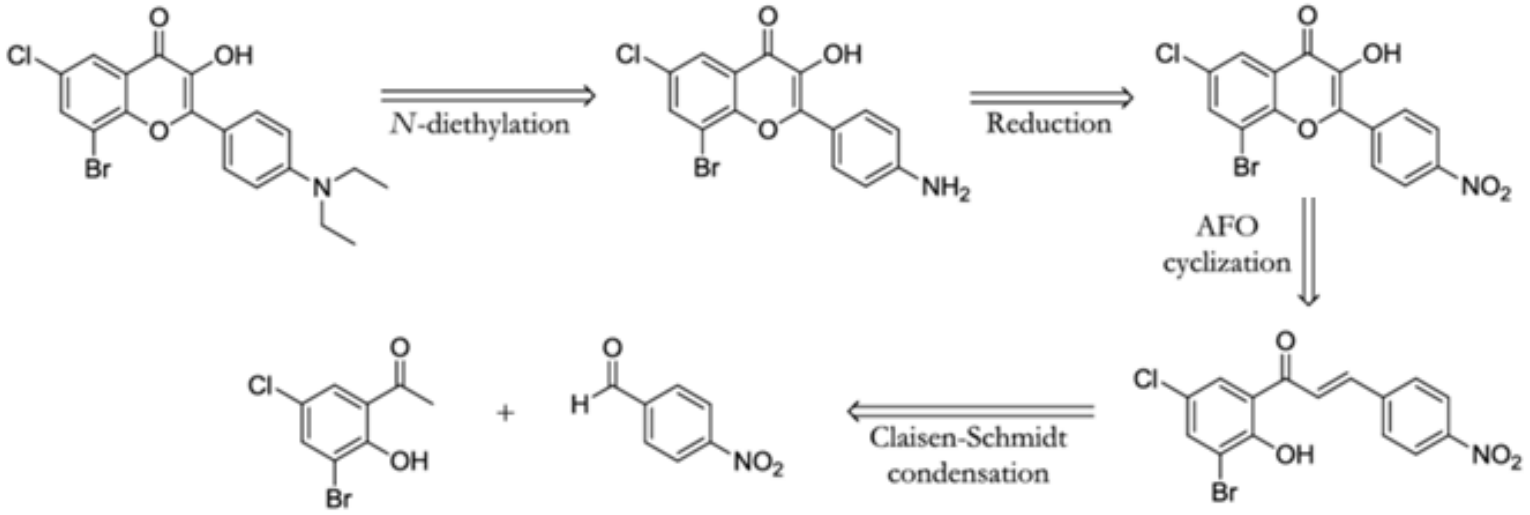
2302774 – Advance Organic Synthesis

Lecture 5

Retrosynthetic Analysis

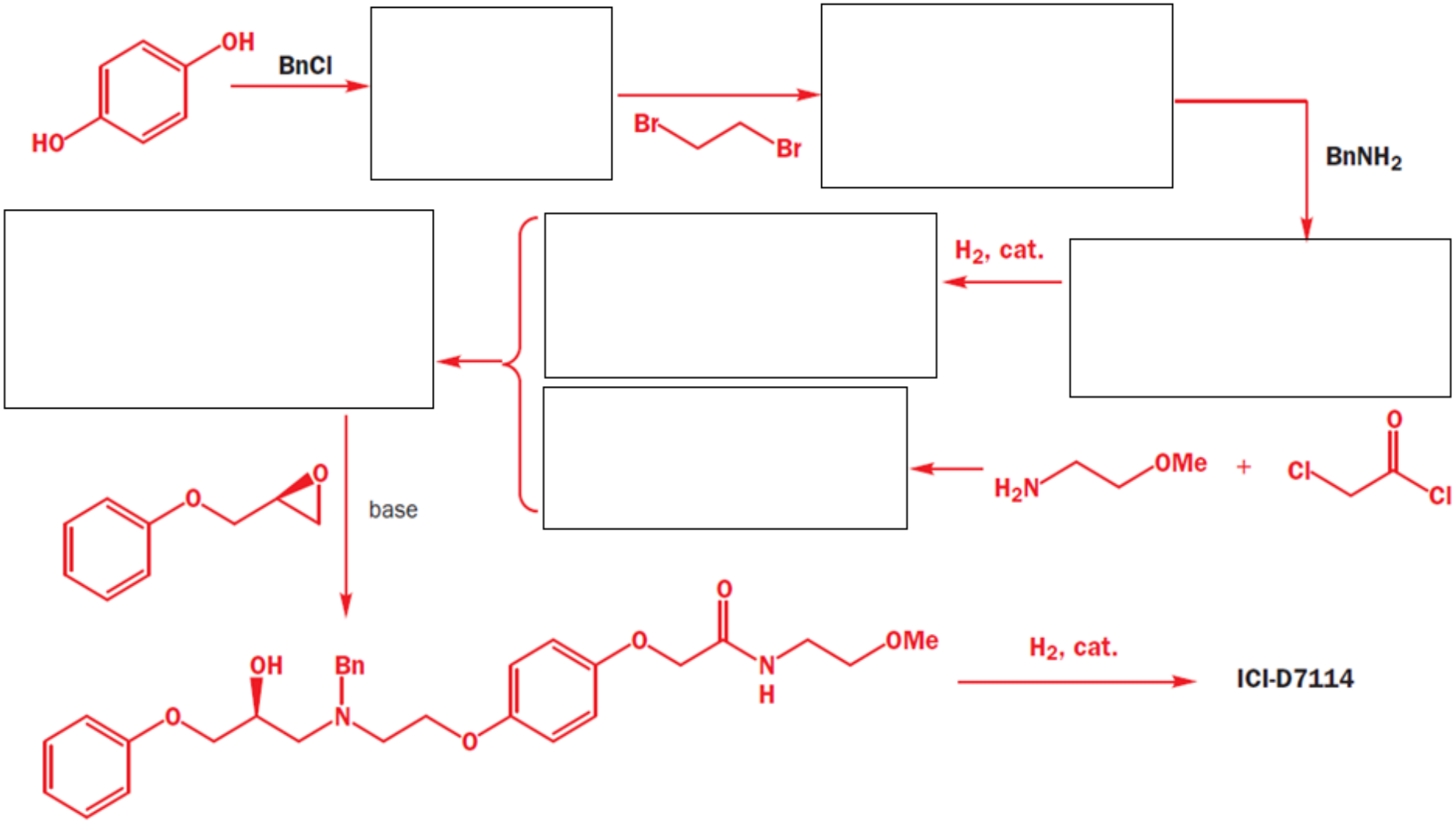


Instructor: Asst. Prof. Dr. Tanatorn Khotavivattana
E-mail: tanatorn.k@chula.ac.th

Recommended Textbook:

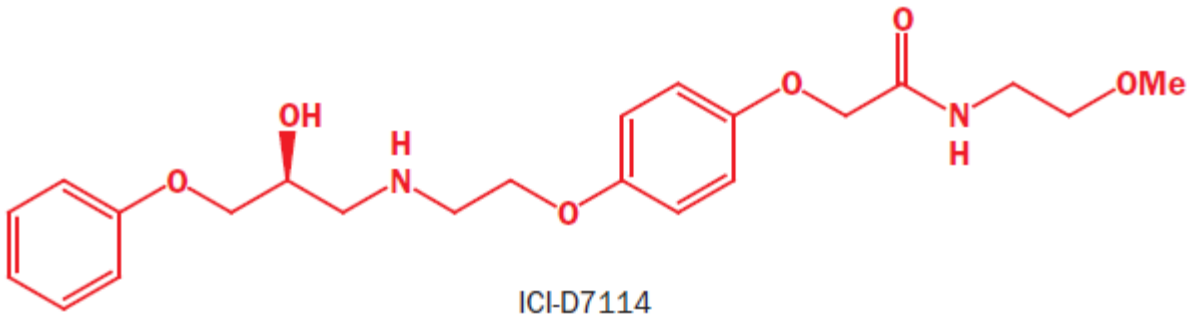
Chapter 30 in *Organic Chemistry*, 1st Edition, J. Clayden, N. Geeves, S. Warren, **2001**, Oxford University Press

Example: Synthesis of ICI-D7114



Synthetic Planning

ICI-D7114, and was identified as a possible anti-obesity drug. To test its efficacy, several hundred grams of it had to be made



ICI-D7114

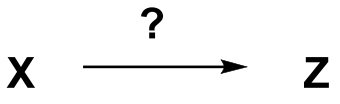
Target molecule

Synthetic planning starts with the product, which is fixed and unchangeable, and works backwards towards the starting materials. This process is called **retrosynthesis**

The art of planning the synthesis of a target molecule is called **retrosynthetic analysis**

Retrosynthetic Analysis: synthesis backwards

Most of the chemistry you have learned so far has concentrated on **reactions** (questions like 'what do you need to add to **X** to get **Z**?')

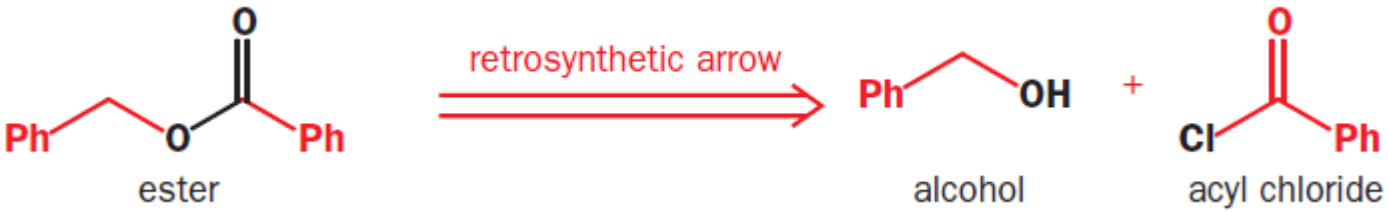


or on **products** (questions like 'what will happen if **X** and **Y** react together?')

Now we're looking at **starting materials** (questions like 'what X and Y do you need to react together to make Z?'); We have a special symbol for a reverse reaction called a **retrosynthetic arrow**

a retrosynthetic arrow

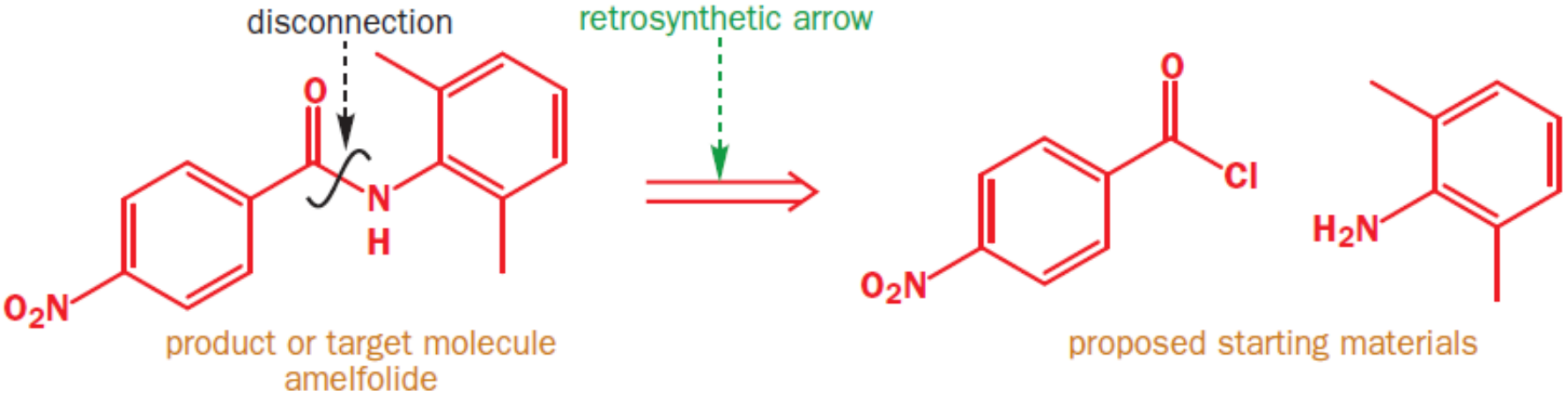
This scheme means '**Z** could be made from **X** plus **Y**'



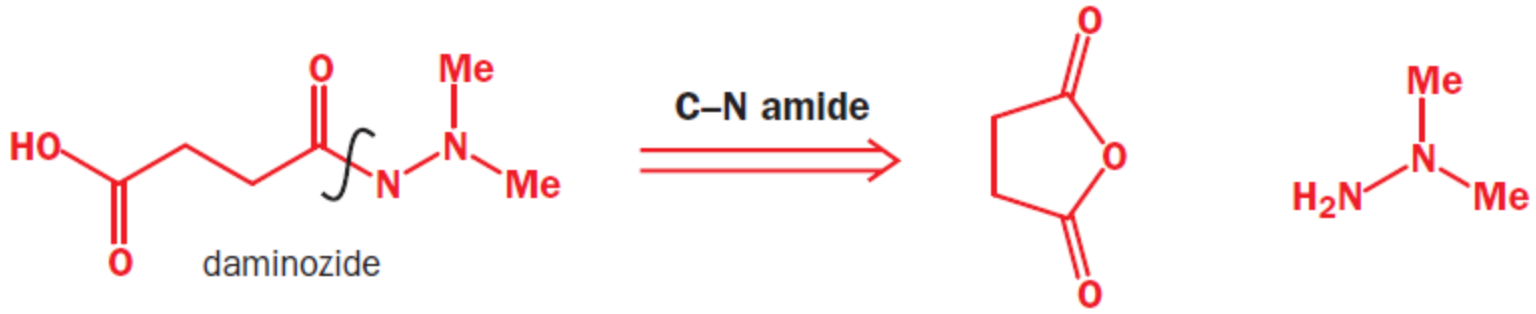
ester alcohol acyl chloride

Disconnection

Mentally breaking a molecule into its component parts is known as **disconnection**, and it's helpful to indicate the site of the disconnection with a wiggly line as we have here

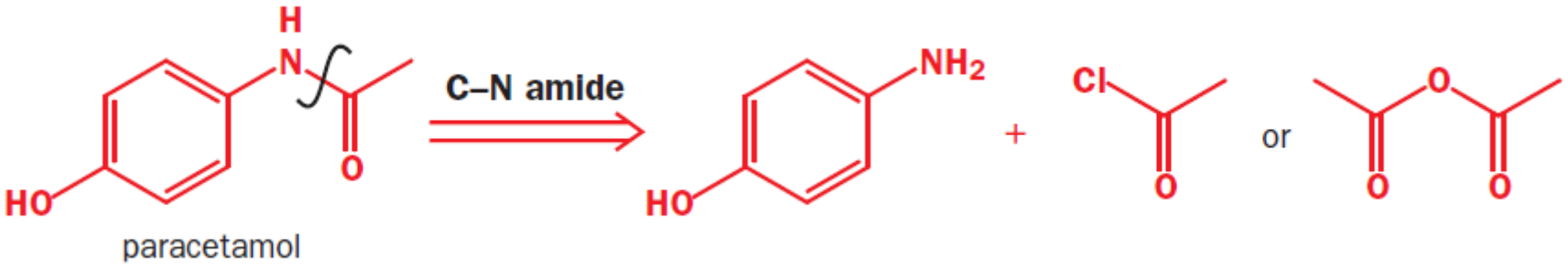


Daminozide is again an amide, so the best disconnection is the C–N bond. This time we've written '**C–N amide**' above the retrosynthetic arrow as a reminder of why we've made the disconnection and we advise you to follow this practice.



Synthons

There are several alternative reagents all corresponding to the same disconnection. Paracetamol, for example, can be disconnected either to [amine + acyl chloride] or [amine + anhydride]



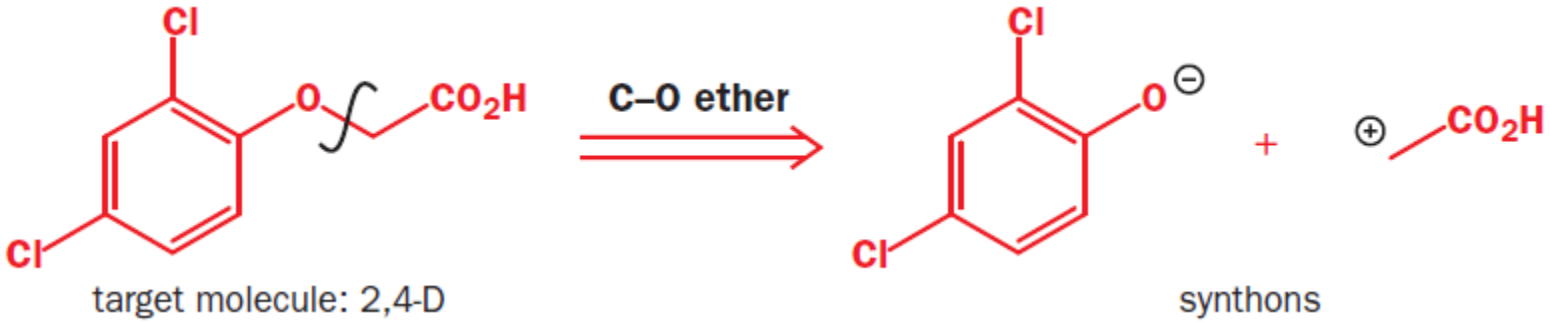
Which reagent is best can often only be determined by experimentation; In a retrosynthetic analysis, we don't really want to be bothered by this sort of decision, which is best made later, so it's useful to have a single way of representing the key attributes of alternative reagents.

We can depict both anhydride and acyl chloride in this scheme as an '***idealized reagent***'—an electrophilic acetyl group $MeCO^+$. We call such idealized reagents **synthons**

synthon

Synthons

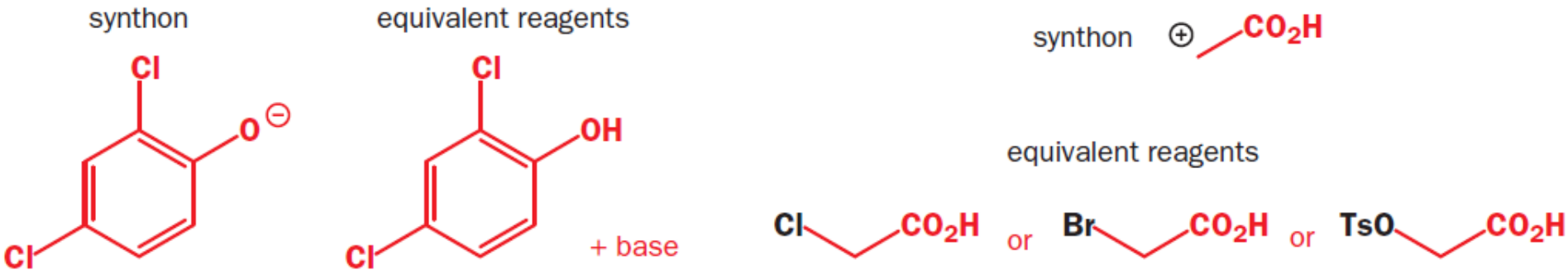
Synthons are fragments of molecules with an associated polarity (represented by a '+' or '–'); They are not themselves reagents, though they may occasionally turn out to be intermediates along the reaction pathway



target molecule: 2,4-D

synthons

By disconnecting bonds to synthons rather than to actual reagents we can ***indicate the polarity of the bond-forming reaction without having to specify details of the reagents***; Once the retrosynthetic analysis is done, we can go back and use our knowledge of chemistry to think of reagents corresponding to these synthons.



Summary

The overall aim of retrosynthetic analysis is to get back to starting materials that are **available** from chemical suppliers, and to do this as **efficiently** as possible

Some definitions of terms used in synthesis

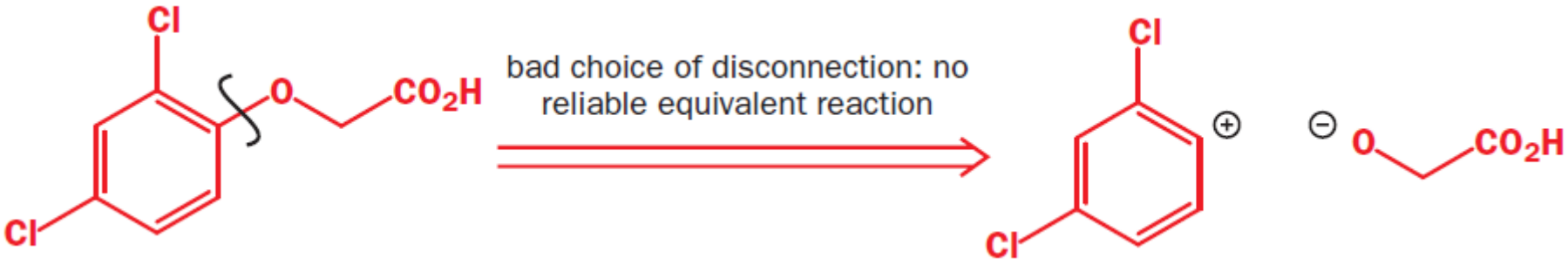
target molecule (or TM)	the molecule to be synthesized
retrosynthetic analysis or retrosynthesis	the process of mentally breaking down a molecule into starting materials
retrosynthetic arrow	an open-ended arrow, $\Rightarrow$, used to indicate the reverse of a synthetic reaction
disconnection	an imaginary bond cleavage, corresponding to the reverse of a real reaction
synthon	idealized fragments resulting from a disconnection. *Synthons* need to be replaced by *reagents* in a suggested synthesis
reagent	a real chemical compound used as the equivalent of a synthon

Choosing a Disconnection

The hardest task in designing a retrosynthetic analysis is spotting where to make the disconnections. The followings are rough ***guidelines***, but the best way to learn is through experience and practice

Guideline 1

Disconnections must correspond to known, reliable reactions



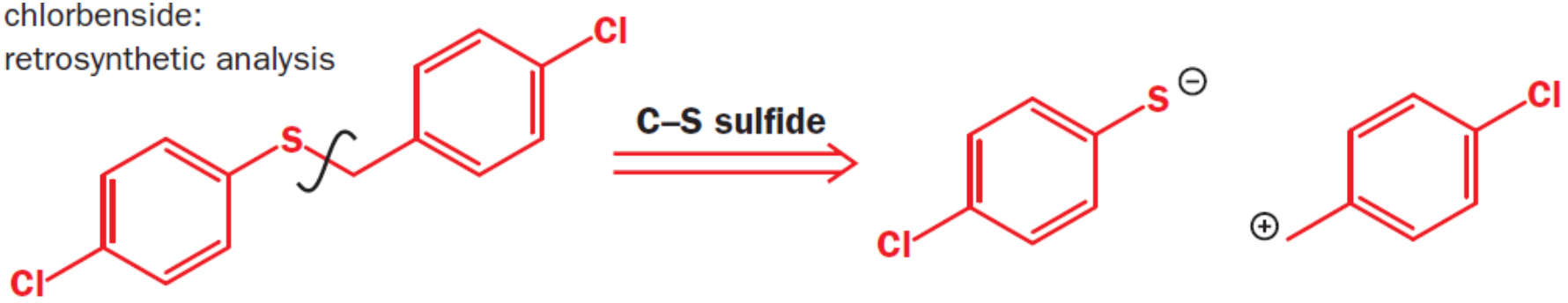
We chose not to disconnect on the aryl side of the oxygen atom because we know of **no reliable reaction** corresponding to nucleophilic attack of an alcohol on an unactivated aromatic ring

Guideline 2

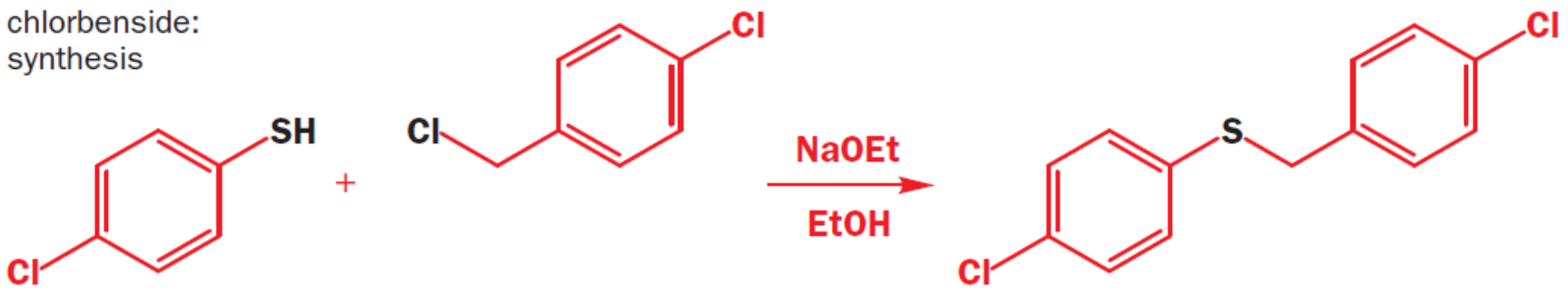
For compounds consisting of two parts joined by a heteroatom, disconnect next to the heteroatom

This guideline works for esters, amides, ethers, amines, acetals, sulfides, and so on, because these compounds are often made by a **substitution** reaction.

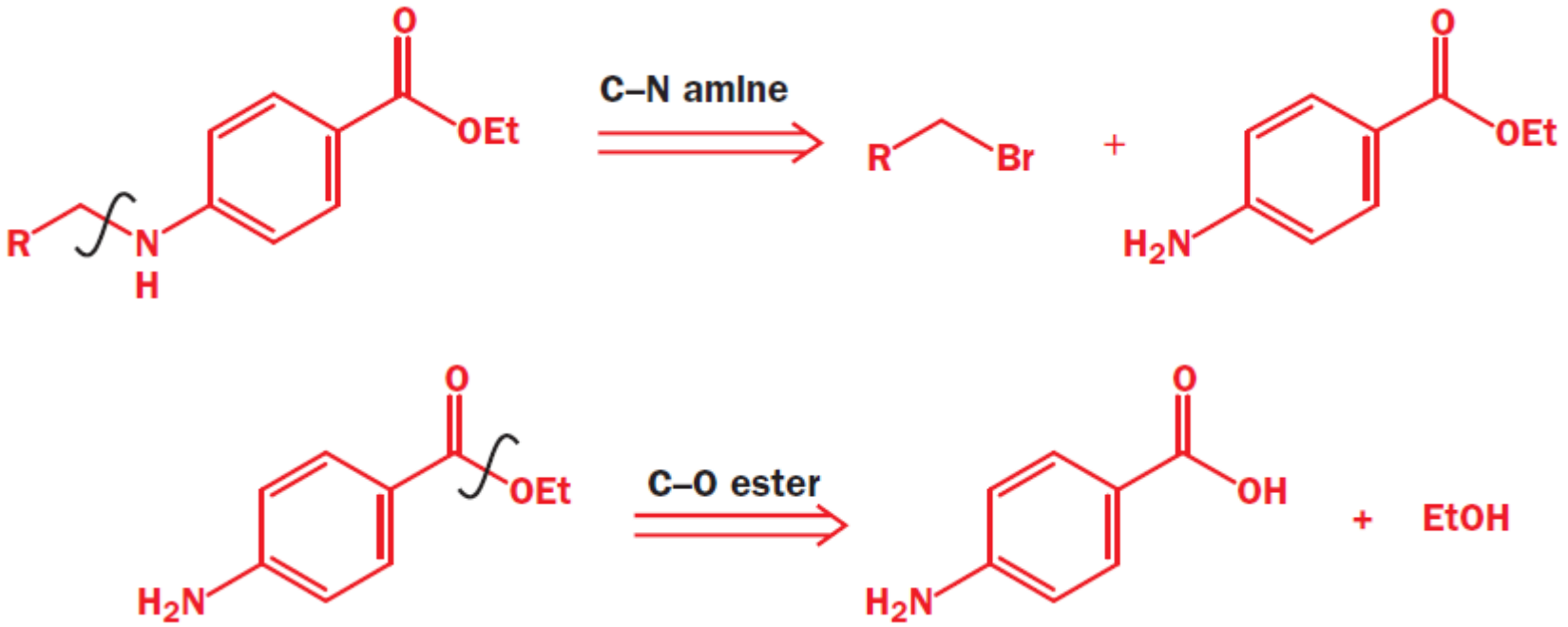
chlorbenside:
retrosynthetic analysis



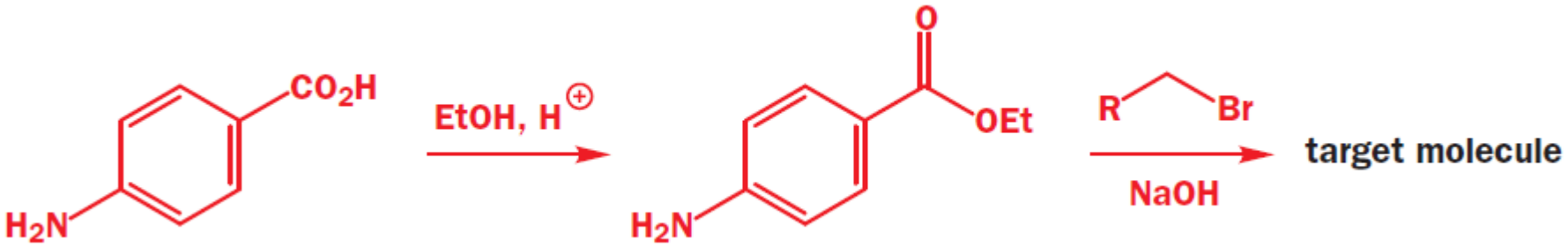
chlorbenside:
synthesis



Example: Retrosynthetic analysis of cetaben ethyl ester:

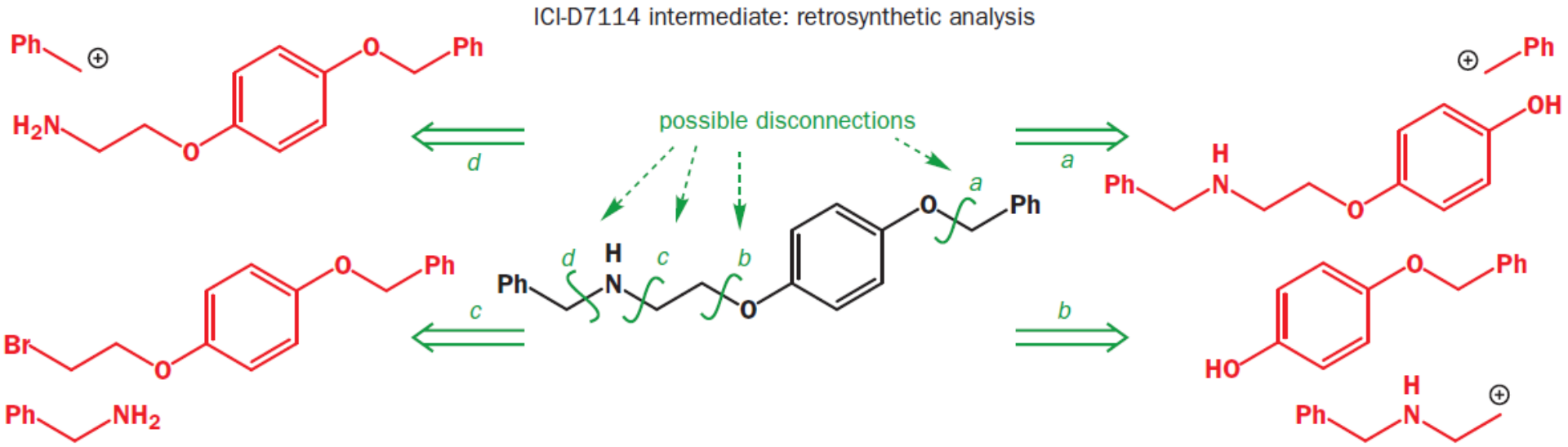


Synthesis of cetaben ethyl ester:



Multiple Step Syntheses

For the synthesis of a more complex target molecule with many functional groups, it requires several disconnections to take it back to simple compounds. The question is **which do we do first?** One way to solve the problem is to **write down all the possibilities**

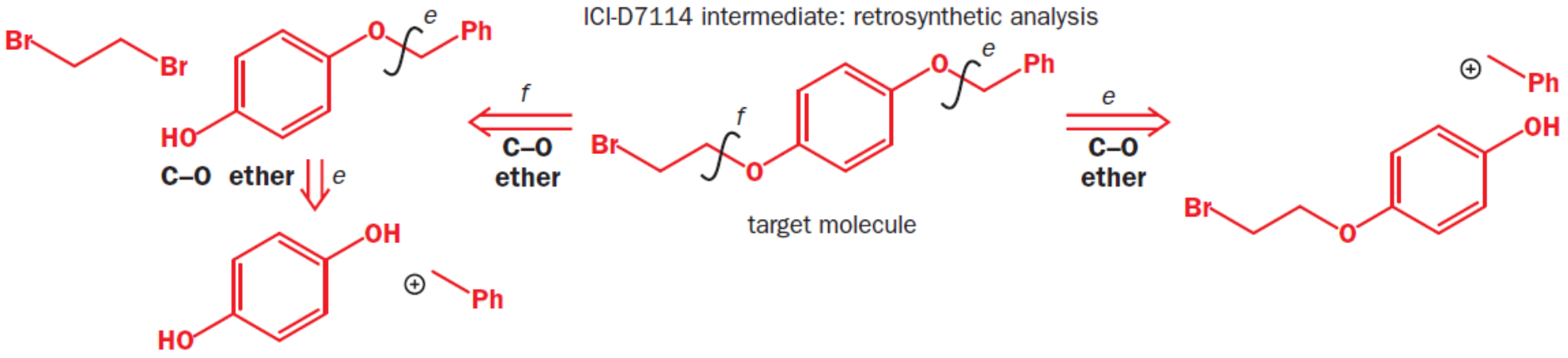


Both **(a)** and **(b)** pose problems of chemoselectivity as it would be hard to alkylate the phenol in the presence of the basic nitrogen atom.

(c) appears to be the better choice because the next disconnection after **(d)** will have to be an alkylation of O in the presence of an NH_2 group.

Guideline 3

Consider alternative disconnections and choose routes that avoid chemoselectivity problems—often this means disconnecting reactive groups first



Disconnection **(e)** requires alkylation of a compound that is itself an alkylating agent

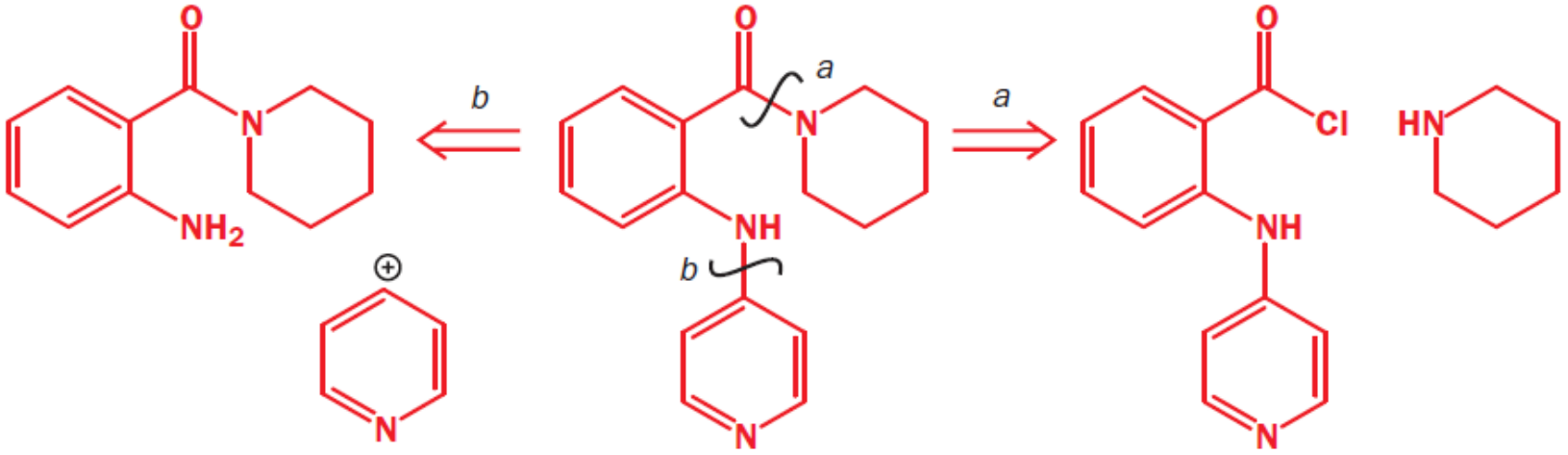
Disconnection **(f)** is much more satisfactory, and leads to a compound that is easily disconnected to *4-hydroxyphenol* and *1,2-dibromethane*

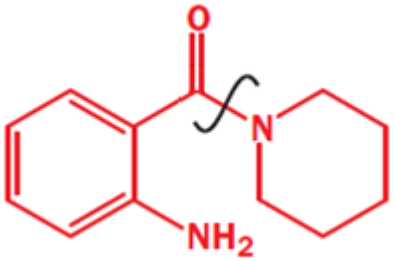
Using Guideline 3, we can say that it's best to disconnect the *bromoethyl group* **(f)** before the *benzyl group* because the *bromoethyl group* is more reactive and more likely to cause problems of chemoselectivity

Functional Group Interconversion

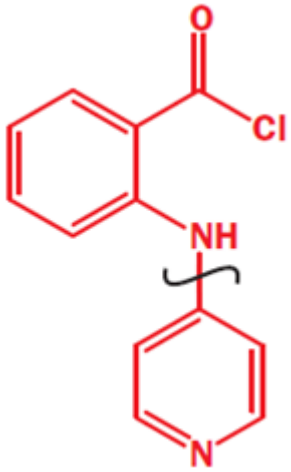
The antihypertensive drug ofornine contains an amide and an amine functional group

ofornine: retrosynthetic analysis





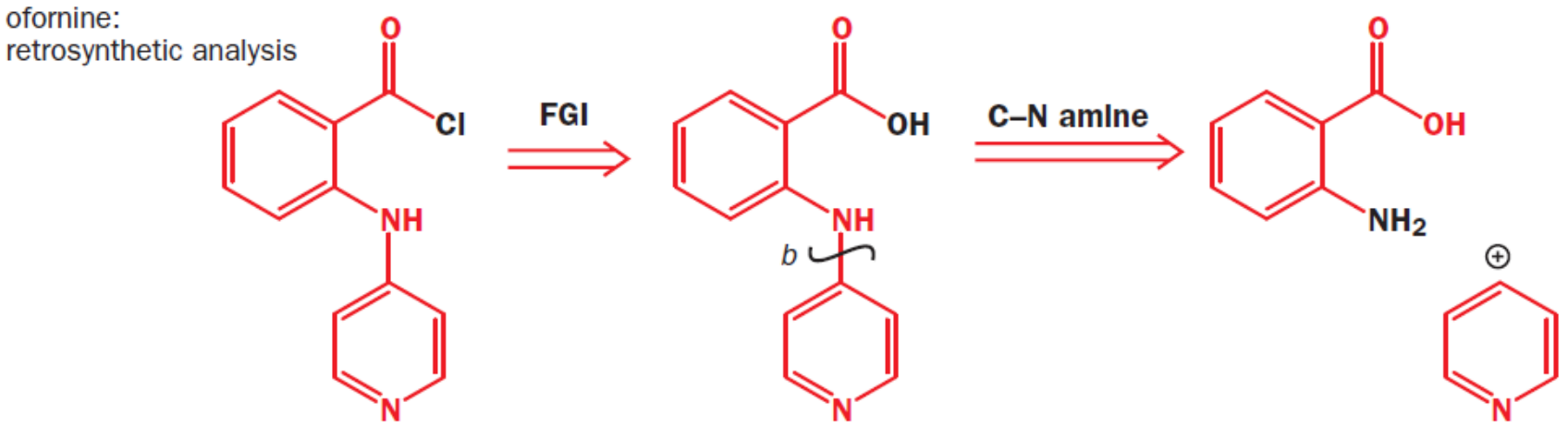
If we disconnect the secondary amine first (b), we will have chemoselectivity problems constructing the amide in the presence of the resulting NH_2 group



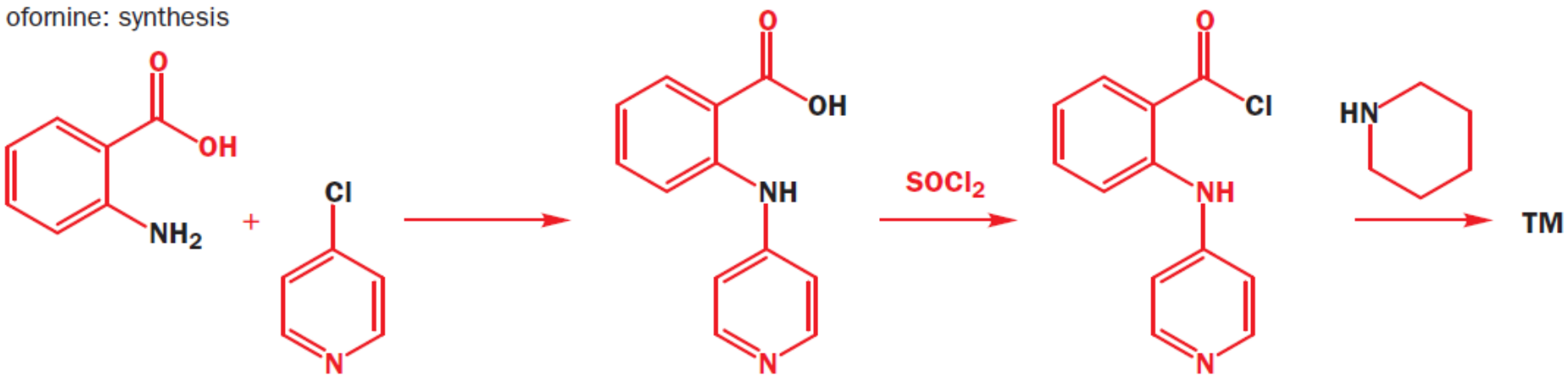
Yet disconnection (a), on the face of it, seems to pose an even greater problem because we now have to construct an amine in the presence of an acyl chloride!

Functional Group Interconversion

However, we shall want to ***make the acyl chloride from the carboxylic acid***, which can then easily be disconnected to 2-aminobenzoic acid and 4-chloropyridine

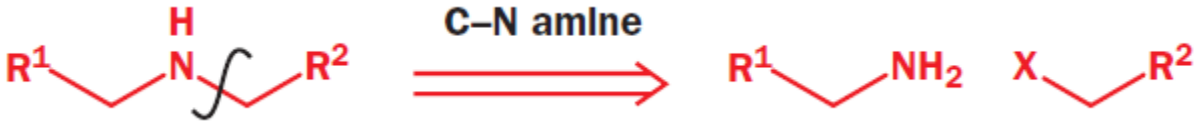


The retrosynthetic transformation of an acyl chloride to a carboxylic acid is not really a disconnection because nothing is being disconnected. We call it instead a **functional group interconversion**, or **FGI**, as written above the retrosynthetic arrow

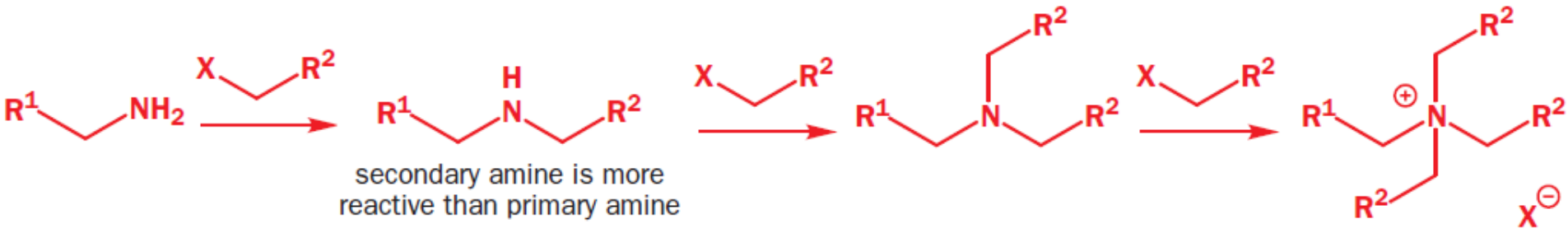


FGI: Amine Synthesis

The synthesis of amines poses a special problem because only in certain cases is the obvious disconnection successful



The problem is that the ***product is usually more reactive than the starting material*** and there is a danger that ***multiple alkylation*** will take place

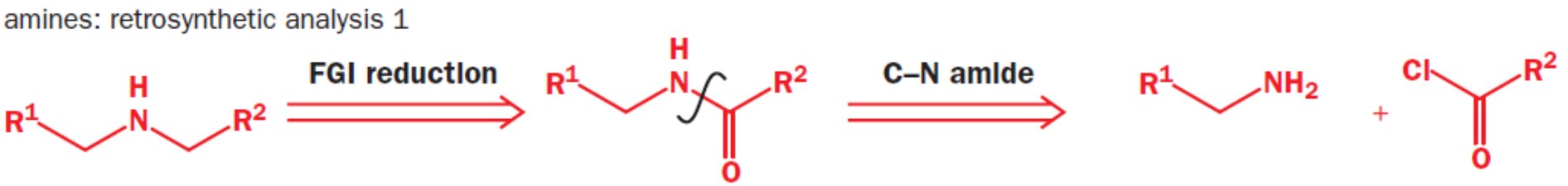


There are few successful examples using this disconnection; these are due to either for steric or electronic reasons. However, it is better to **avoid disconnecting an amine in this way**

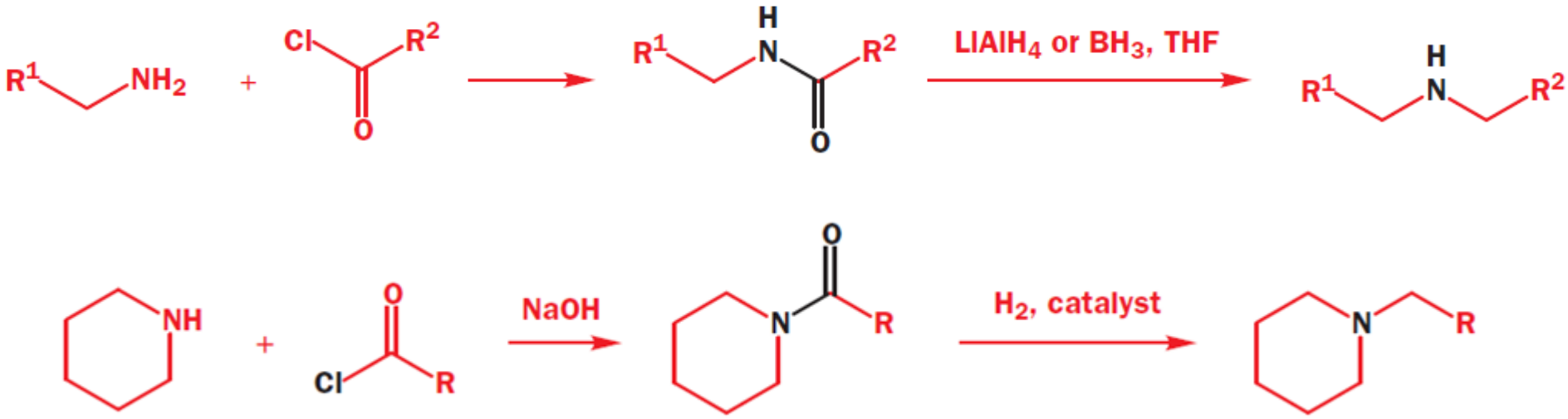
FGI: Amine Synthesis

What are the alternatives? There are two main ones, and both involve functional group interconversion, with the **reactive amine being converted to a less reactive derivative** before disconnection

1. Convert amine to **amide** (**FGI reduction**) and then disconnect the C-N amide

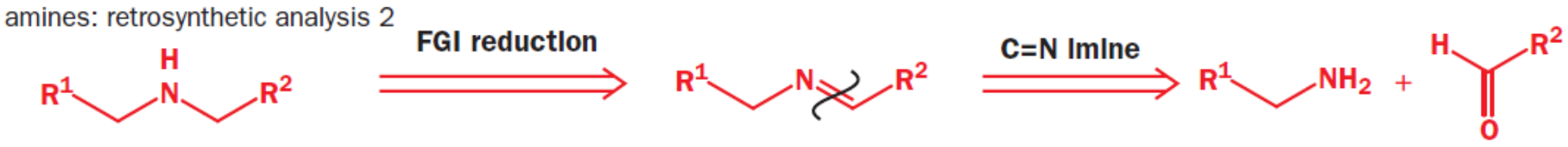


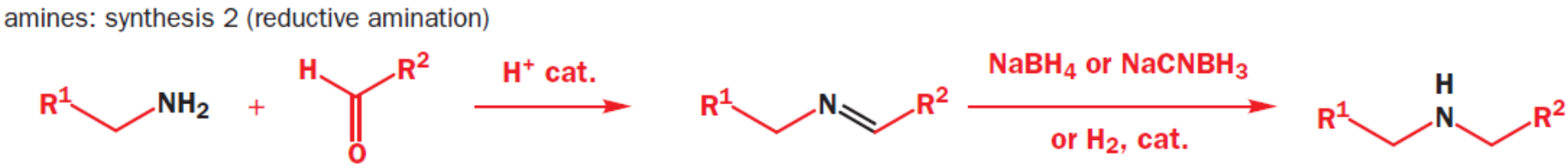
Examples:



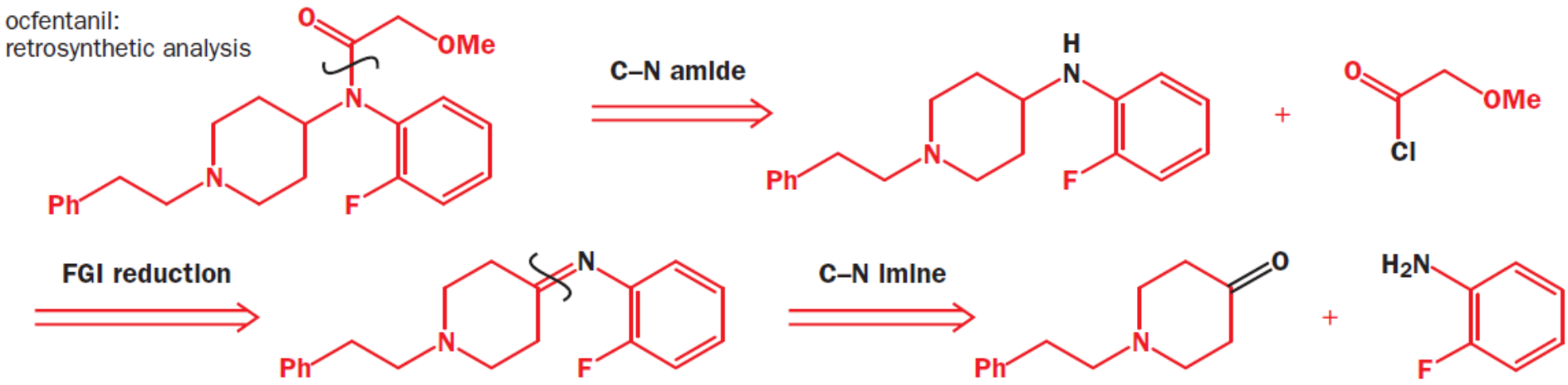
FGI: Amine Synthesis

2. Convert amine convert to an **imine** (**FGI reduction**), which can be disconnected to amine plus carbonyl compound : **reductive amination**



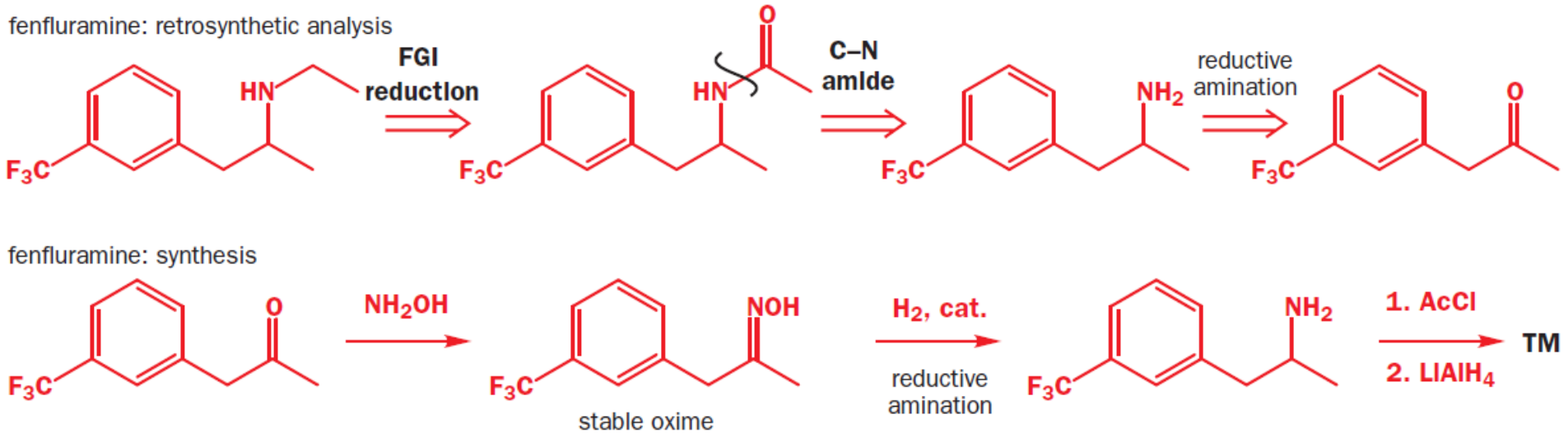


Examples:

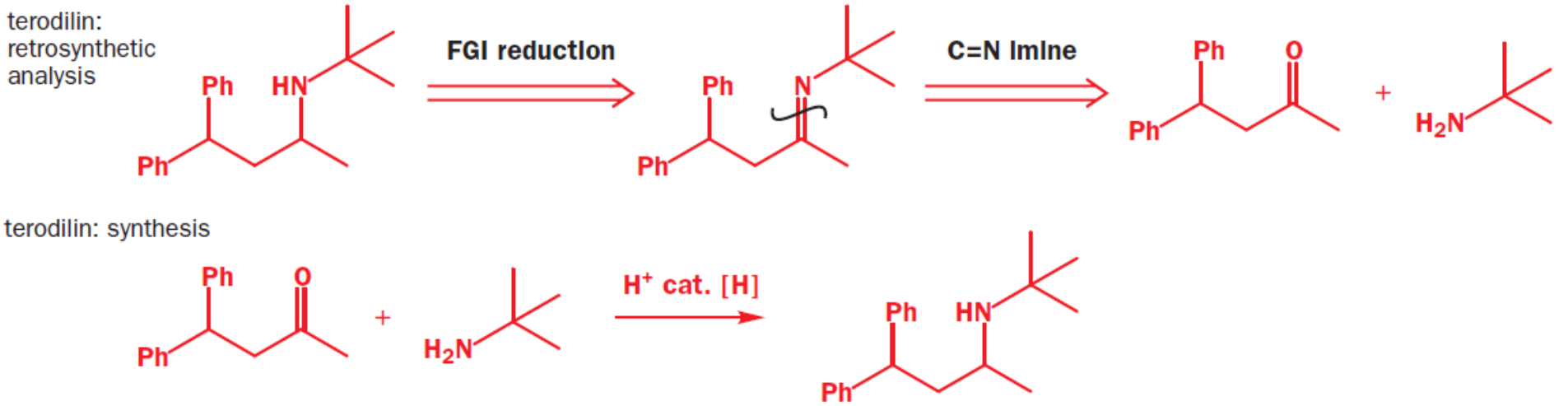


FGI: Amine Synthesis

Example 1:

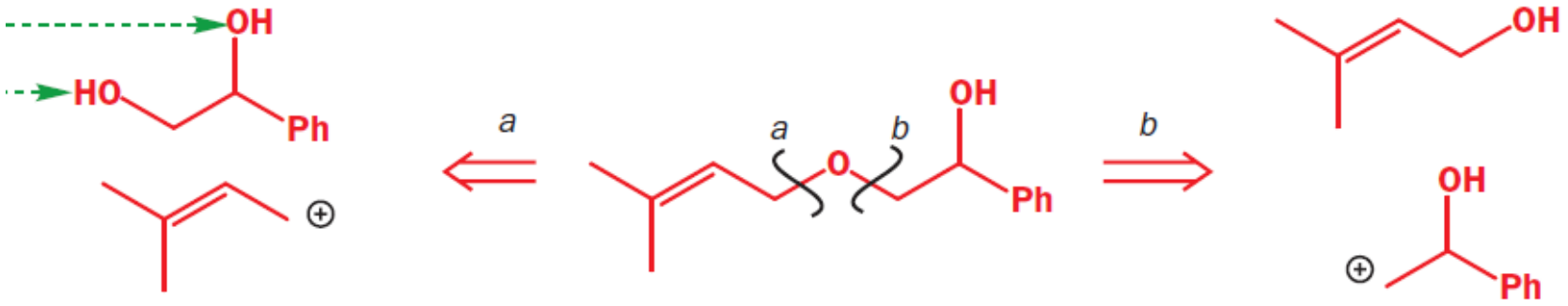


Example 2:



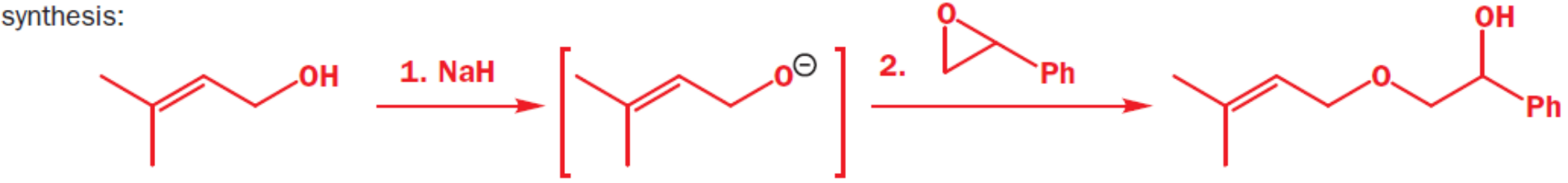
Guidelines for good disconnections

4. Use two-group disconnections wherever possible



We can disconnect on either side of the ether oxygen atom, but **(b)** is much better because it might be hard to control selective alkylation of the primary hydroxyl group in the presence of the secondary one in **(a)**

Nucleophile attack on the less hindered terminal carbon atom of the **epoxide** gives us the type of compound we want

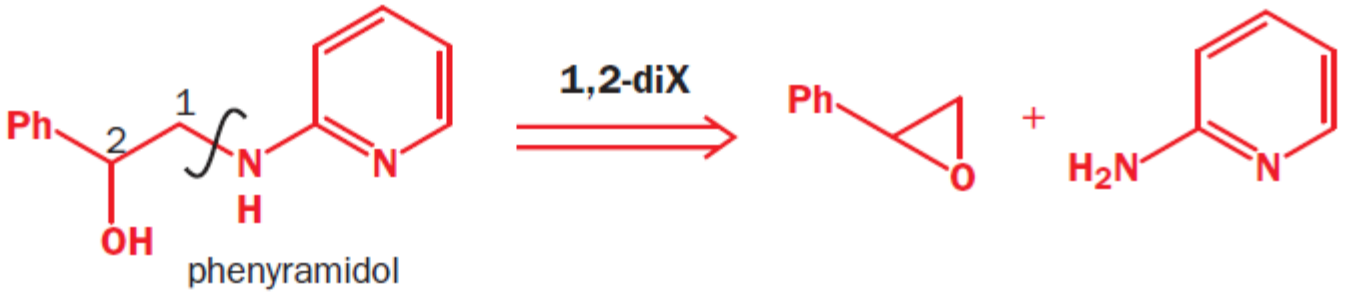


In using the epoxide, we have used ***one functional group to help disconnect another***, Such disconnections are known as **two-group disconnections**

1,2-Disconnections – Epoxides

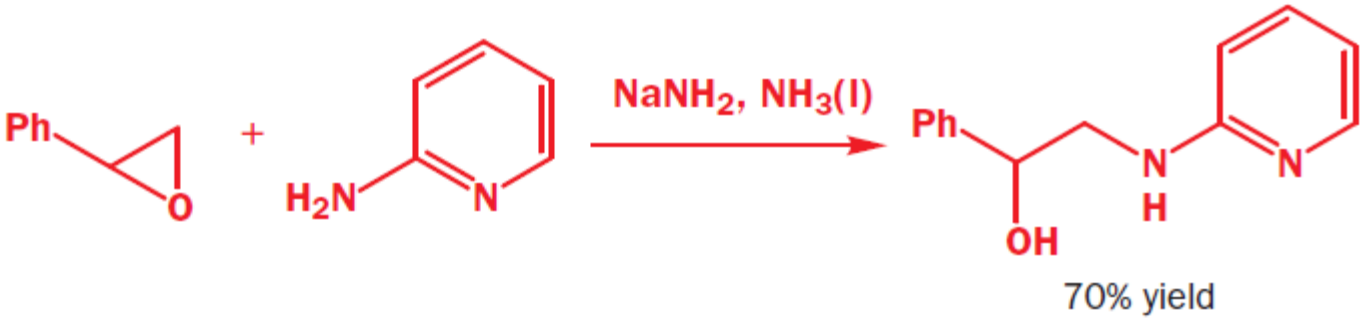
We call this epoxide disconnection a **1,2-disconnection** because the two functional groups in the two-group disconnection are in a ***1,2-relationship***

phenyramidol:
retrosynthetic analysis



phenyramidol

phenyramidol:
synthesis

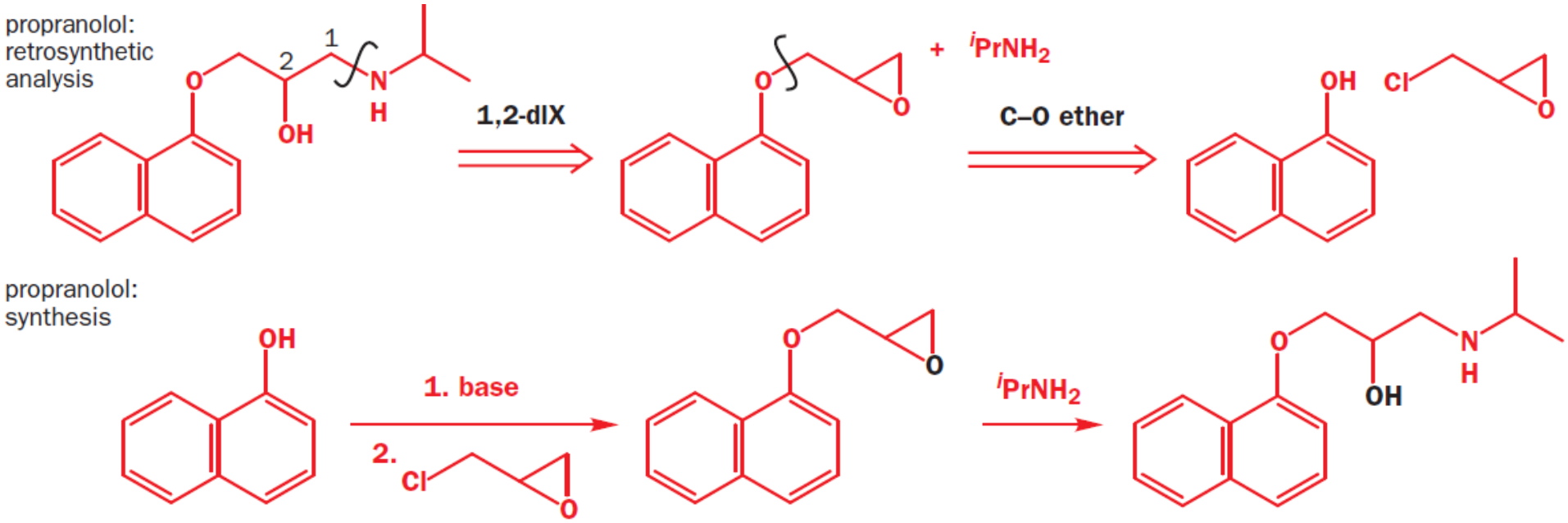


70% yield

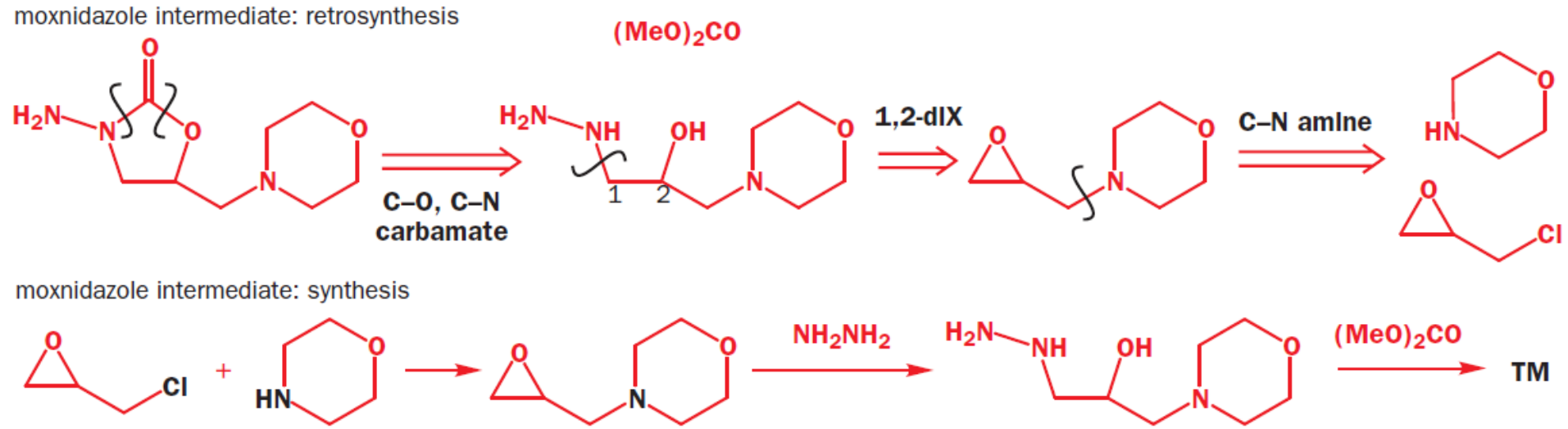
Notice that we have written '**1,2-diX**' above the arrow to show that it's a two-group ('diX') disconnection

You should always be on the look-out for opportunities of using two-group disconnections because they are an **efficient** way of getting back to simple starting materials

Example 1:

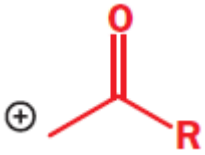


Example 2:



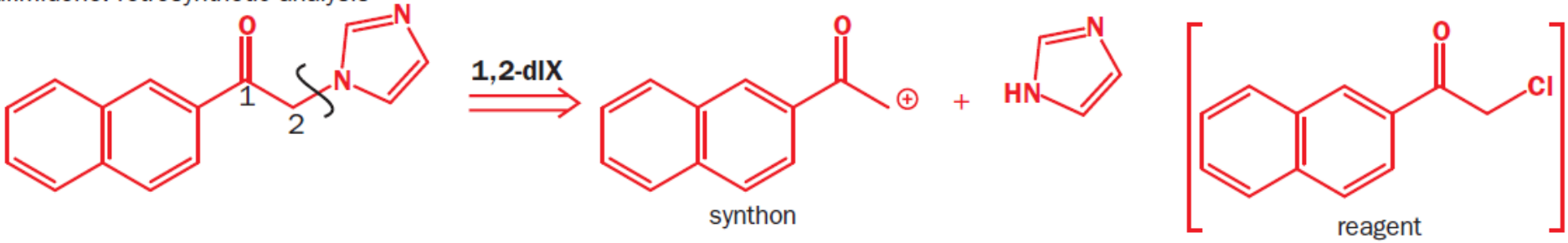
1,2-Disconnections – α-halocarbonyl

α-halocarbonyl compounds are useful reagents for the carbonyl equivalent:



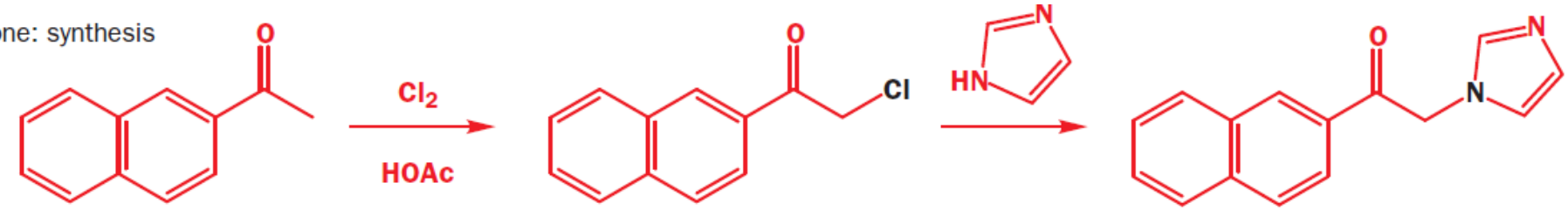
We can consider disconnection to this synthon to be a two-group disconnection because the α-halocarbonyl equivalents are ***easily made by halogenation of a ketone, ester, or carboxylic acid*** and the ***carbonyl group adjacent to the halide makes them extremely reactive electrophiles***

nafimidone: retrosynthetic analysis



The α-chloroketone is simply made by chlorination, and substitution is rapid and efficient even with the weakly basic heterocyclic amine

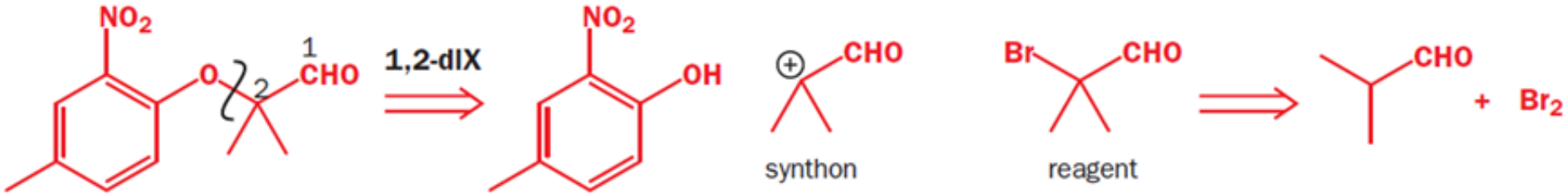
nafimidone: synthesis



1,2-Disconnections – α-halocarbonyl

Example:

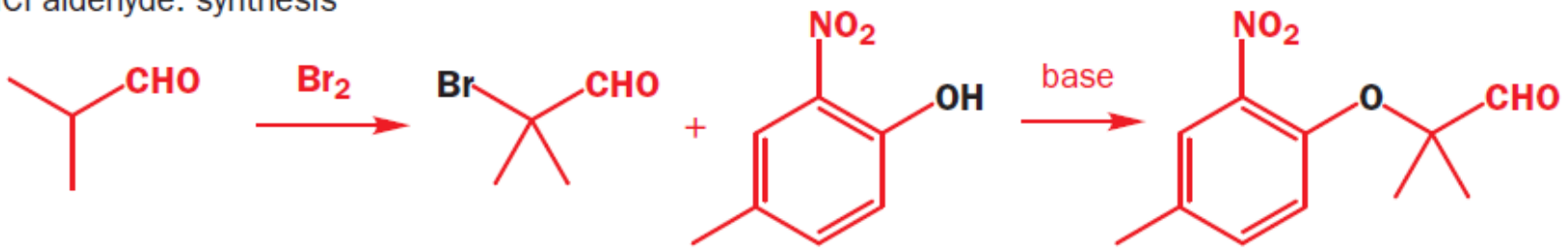
ICI aldehyde: retrosynthetic analysis



Two-group disconnection gives a 2-halo-aldehyde that can be made from the corresponding aldehyde

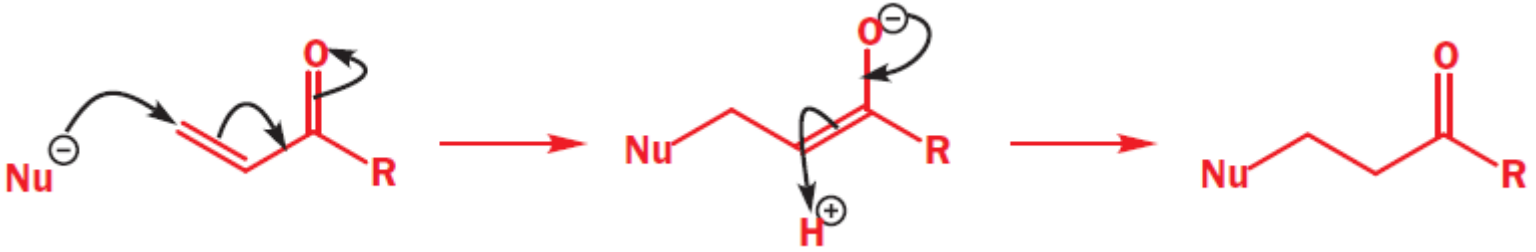
The synthesis requires a normal bromination of a carbonyl compound in acid solution but the next step is a most unusual ***S_N2 reaction at a tertiary centre***. This happens because of the ***activation by the aldehyde group*** and is further evidence that the functional groups must be thought of as working together in this type of synthesis.

ICI aldehyde: synthesis

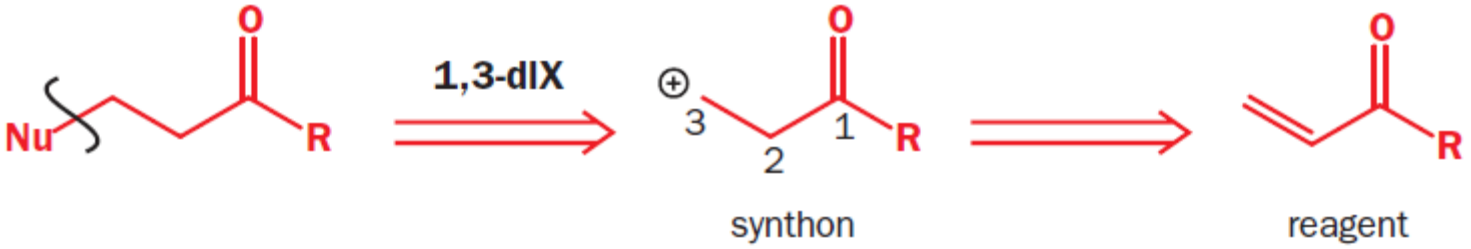


1,3-Disconnections – conjugate additions

***α,β*-unsaturated carbonyl compounds** can undergo **conjugate additions**



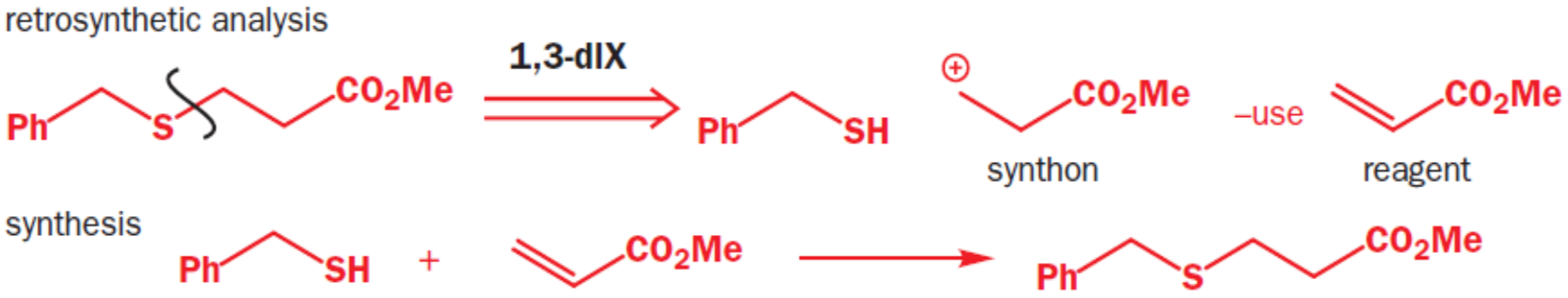
Two-group 1,3-disconnections are therefore possible because they correspond to this forward reaction. These **Michael acceptors** have an ***electrophilic site two atoms away from the carbonyl group***, and are the reagents corresponding to this synthon



This type of reaction is available only when the alkene is conjugated to an electron-withdrawing group – usually **carbonyl**, but it can be **nitro**, **cyanide**, etc.

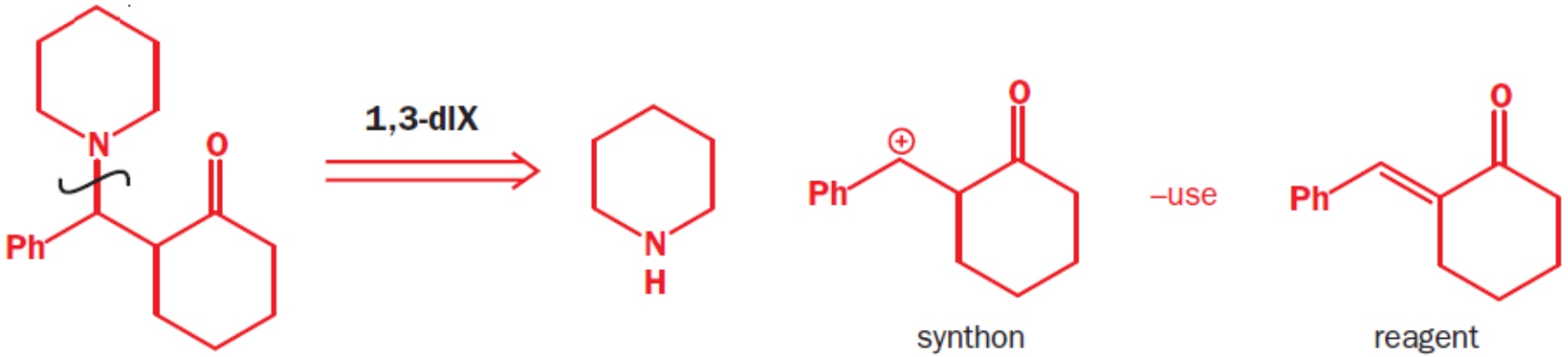
1,3-Disconnections – conjugate additions

Example 1:



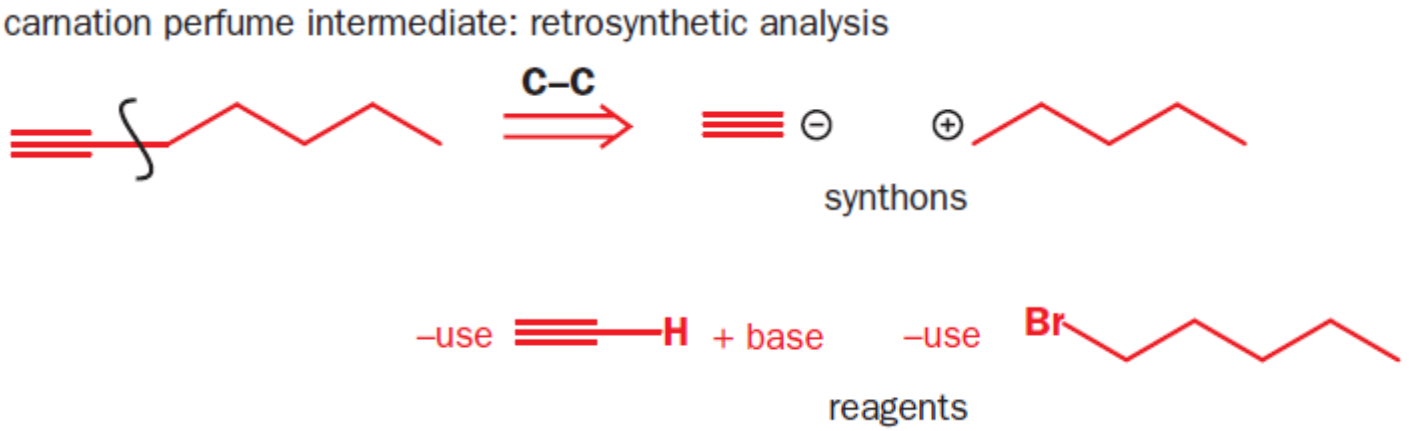
Remember that **not all nucleophiles will successfully undergo Michael additions**; you must bear this in mind when making a 1,3-disconnection of this type. Most reliable are those based on nitrogen, sulfur, and oxygen

Example 2:

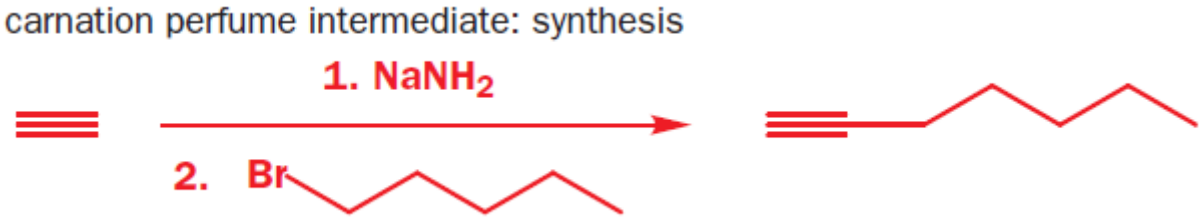


C–C disconnections – Alkynes

The disconnections we have made so far have all been of C–O, C–N, or C–S bonds, but, of course, the most important reactions in organic synthesis are those that form **C–C bonds**



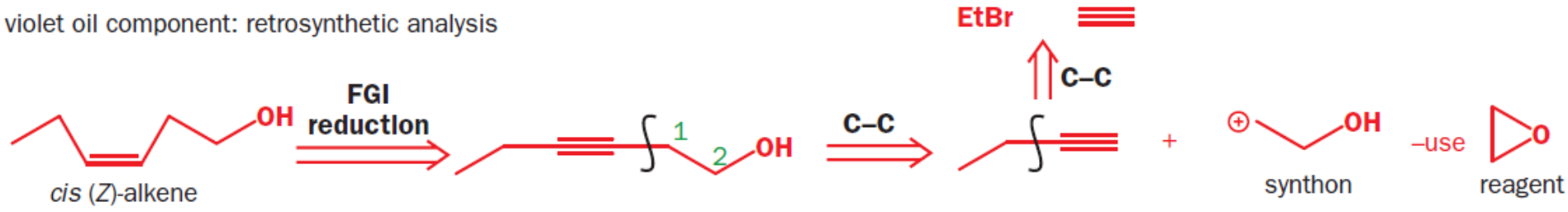
The only functional group is the triple bond, and we shall want to use the chemistry of alkynes to show us where to disconnect. You know that **alkylation of alkynes** is a reliable reaction, so a sensible disconnection is **next to the triple bond**



C–C disconnections – Alkynes

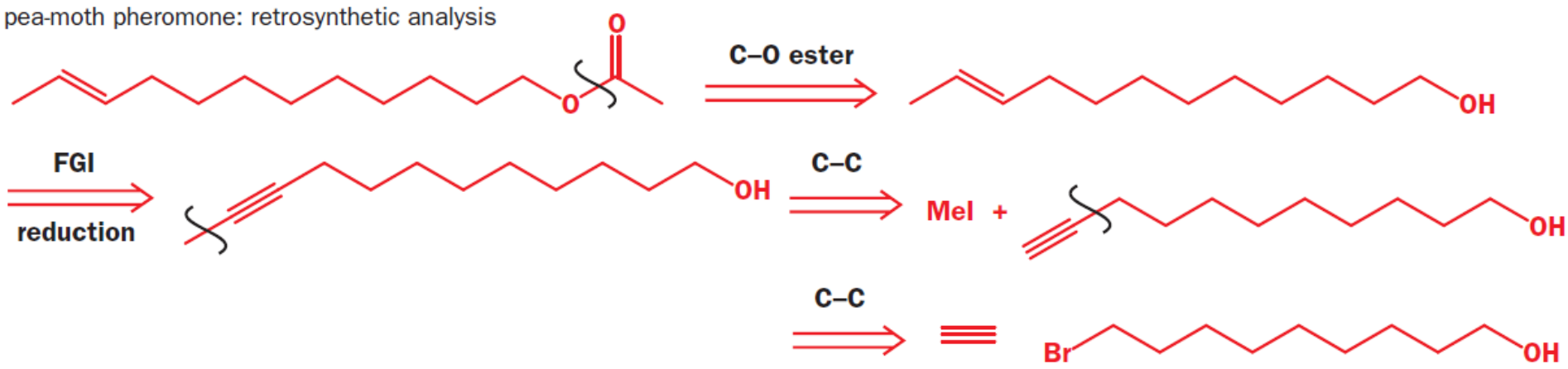
Alkynes are particularly valuable as synthetic intermediates because they can be **reduced either to *cis* or to *trans* double bonds**

It's often a good idea to start retrosynthetic analysis of target molecules containing **isolated double bonds** by considering **FGI to the alkyne** because C–C disconnections can then become quite easy

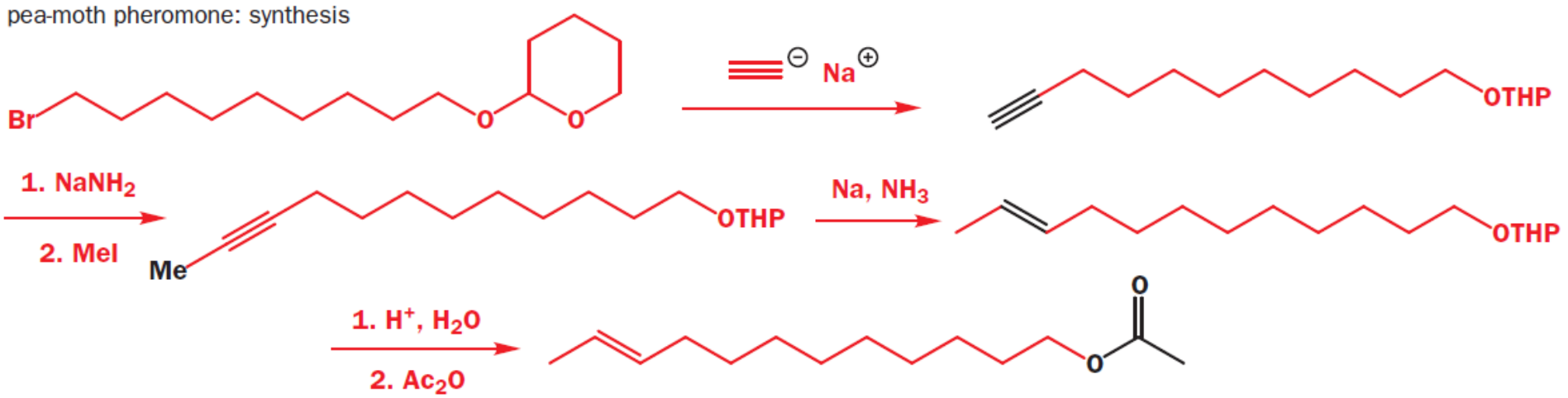


C–C disconnections – Alkynes

Example:



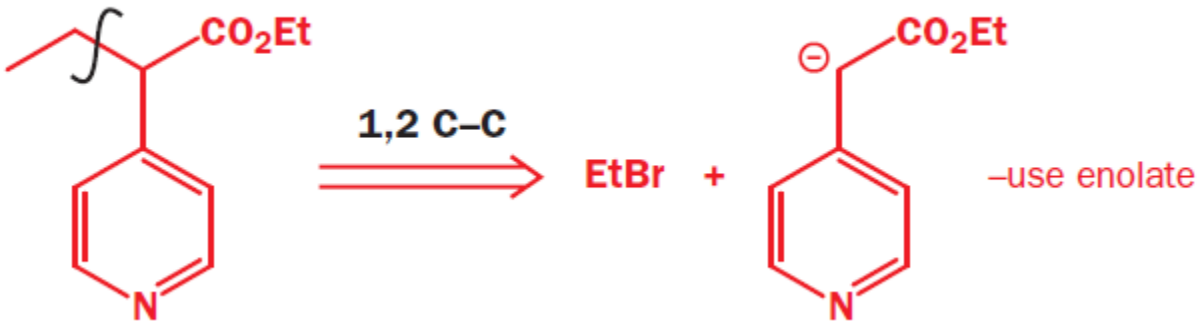
After disconnecting the ester, **FGI on the *trans* double bond** gives an alkyne. Disconnection on either side of the alkyne leads us back to a bromo-alcohol alkylating agent. In the synthesis of the pheromone, it turned out to be best if the hydroxyl group was **protected as its THP ether**



1,2 C–C disconnections – Enolates

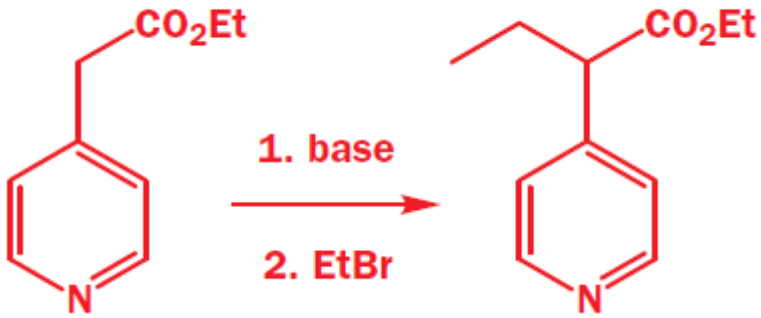
The **alkylation of enolates** of esters or ketones provides a reliable way to make C–C bonds; another good basis for a C–C disconnection

rogletimide intermediate: retrosynthetic analysis



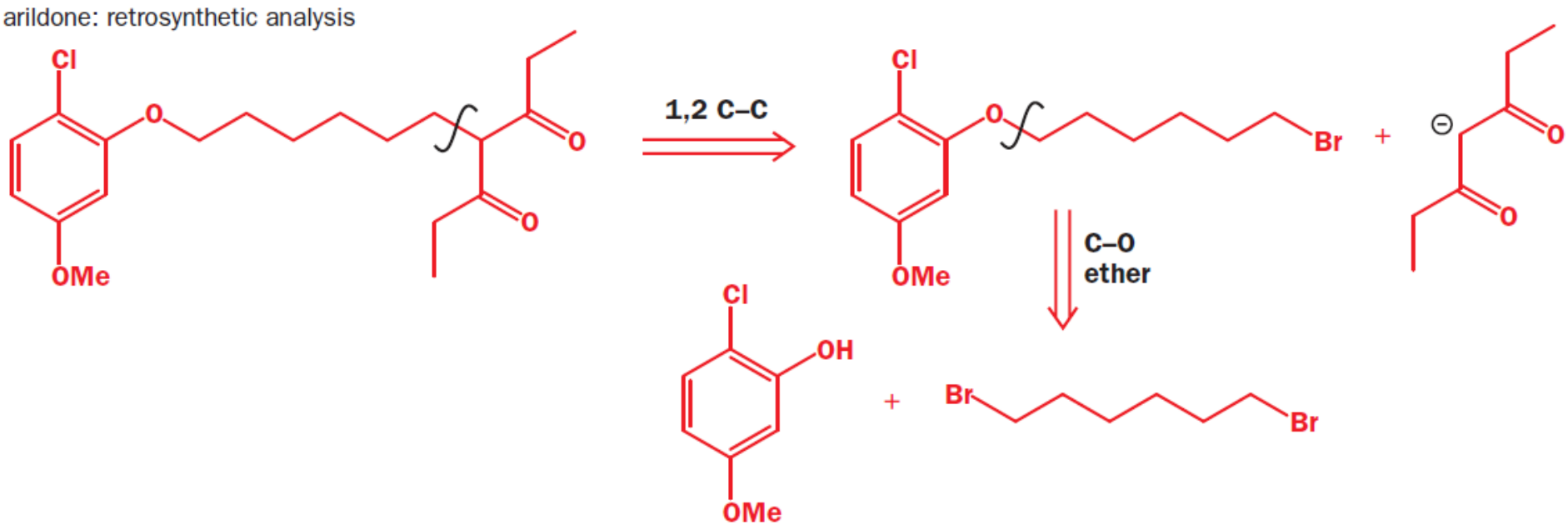
We have labelled the disconnection '**1,2 C–C**' because the new C–C bond is forming two atoms away from the carbonyl group. To spot disconnections of this sort, you need to look for ***alkyl groups in this 2-position***

rogletimide intermediate: synthesis

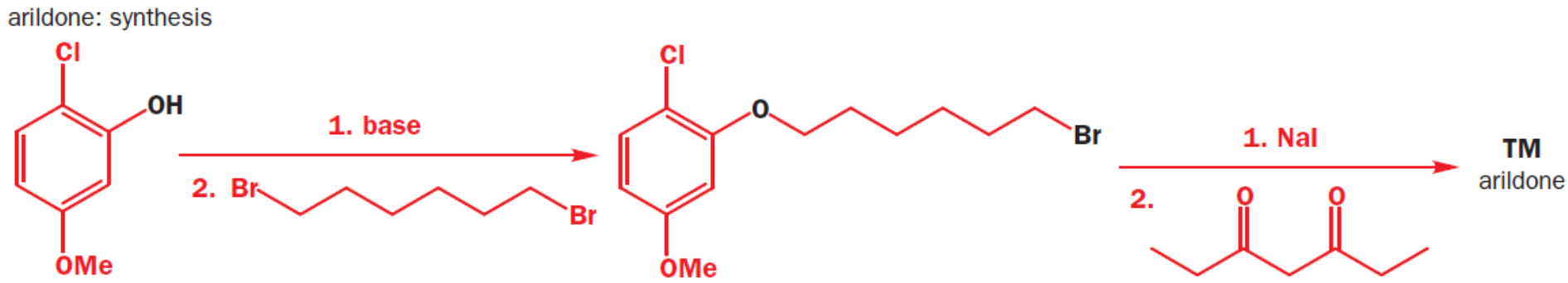


1,2 C–C disconnections – Enolates

Example:

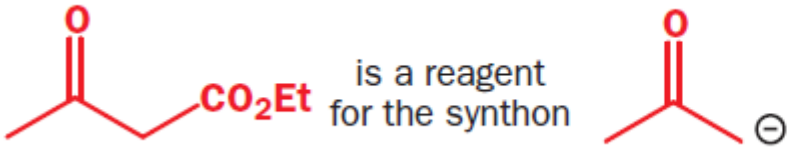


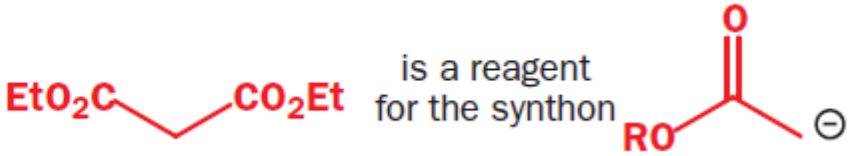
With **two carbonyl groups**, the alkylation should be particularly straightforward since we can use a base like methoxide



1,2 C–C disconnections – Enolates

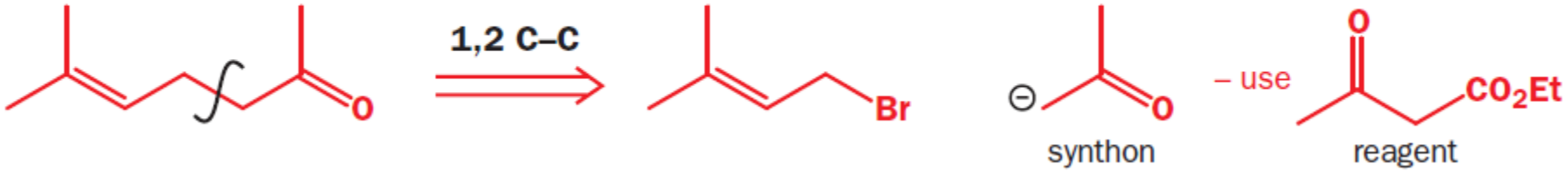
Chemistry of malonate esters as a useful way of controlling the enolization of carbonyl compounds. **Alkylation followed by decarboxylation** means that we can treat acetoacetate and malonate esters as equivalent for these synthons



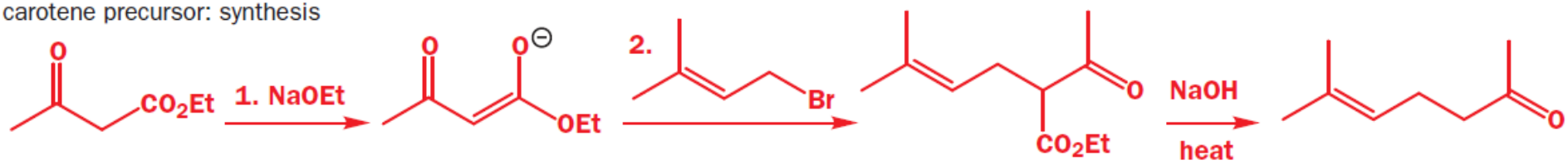


Example:

carotene precursor: retrosynthetic analysis



carotene precursor: synthesis

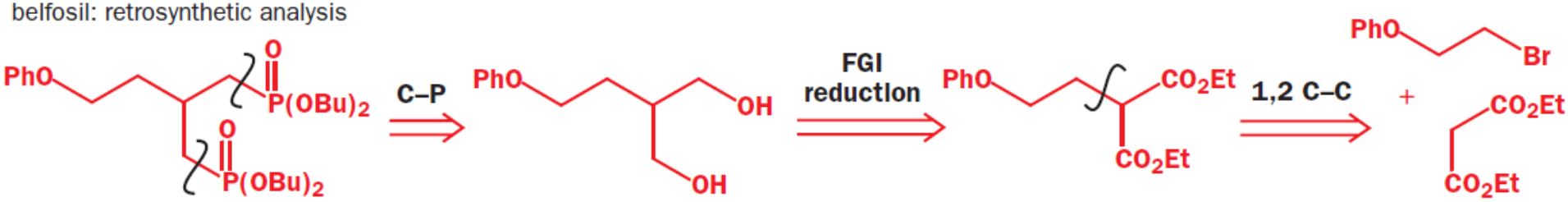


Guideline 5

Convert to oxygen-based functional groups to facilitate C–C disconnections

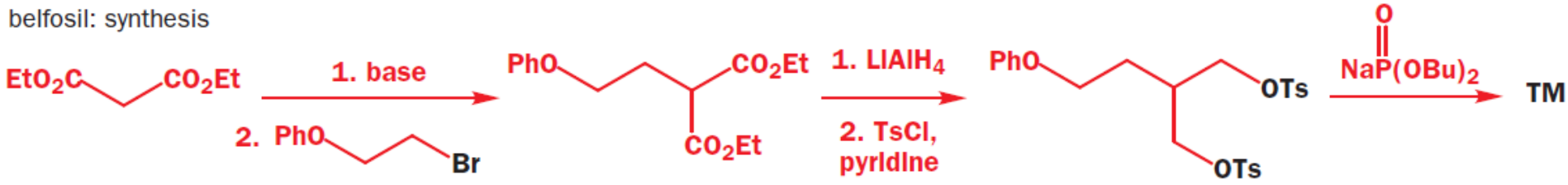
This organophosphorus compound, belfosil, is a Ca^{2+} channel blocker. You should be able to reason that a good disconnection will be the **C–P bond** by analogy with the sulfides

belfosil: retrosynthetic analysis



Alkyl bromides are inconvenient to disconnect further, so we go back to the **more versatile diol** – the diol was converted to the **bis-tosylate**. **FGI to the ester oxidation level** reveals a malonate derivative

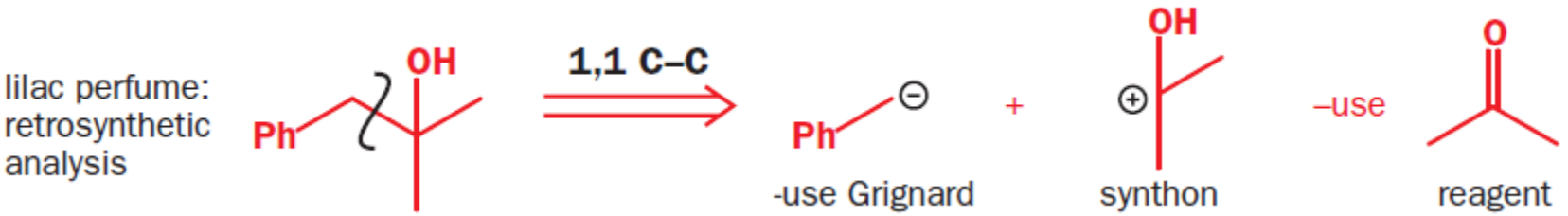
belfosil: synthesis



Oxygen-based functional groups (alcohols, aldehydes, ketones, esters, and acids) have one important property in common – **versatility**

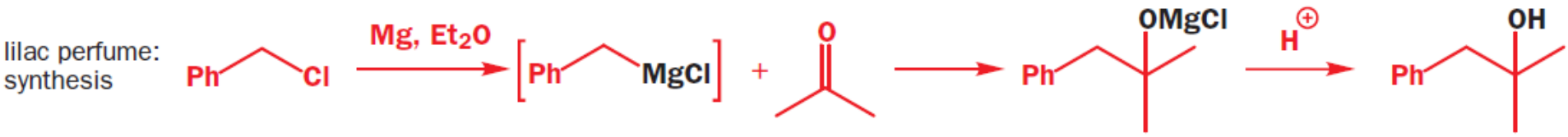
1,1 C–C disconnections – Grignard

The alternative, reaction of a carbon nucleophile (such as a **Grignard reagent**) with an electrophilic functional group, allows us to do C–C disconnections on alcohols



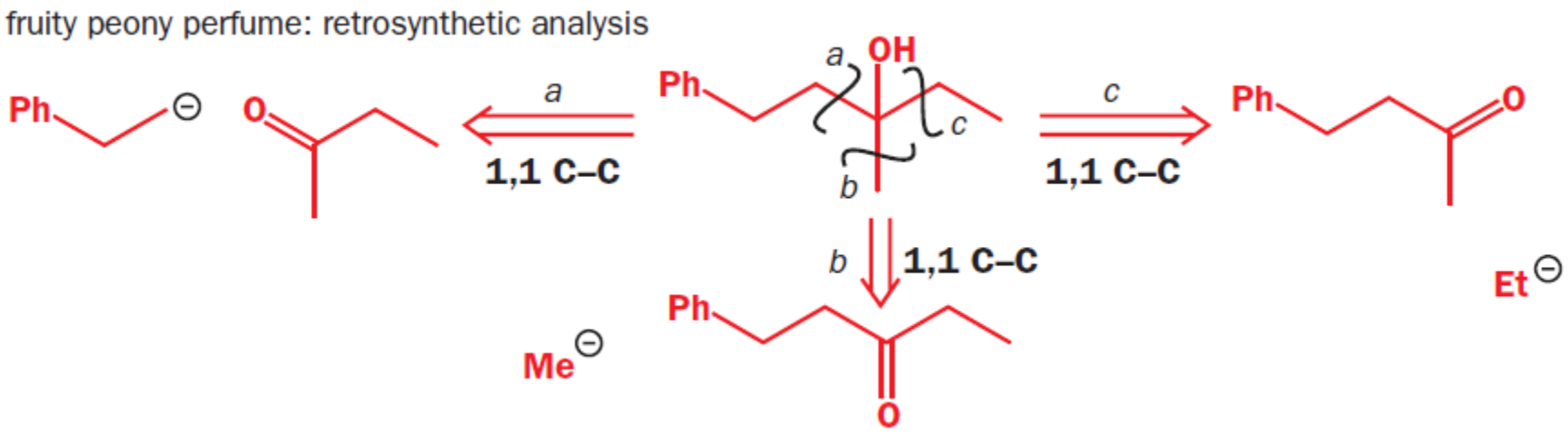
We look to the one functional group, the hydroxyl, to tell us where to disconnect, and **disconnection next to the OH group** gives two synthons for which sensible reagents are a Grignard reagent and acetone

Notice that we label these disconnections **1,1 C–C** because the bond being disconnected is attached to the same carbon atom as the hydroxyl functional group

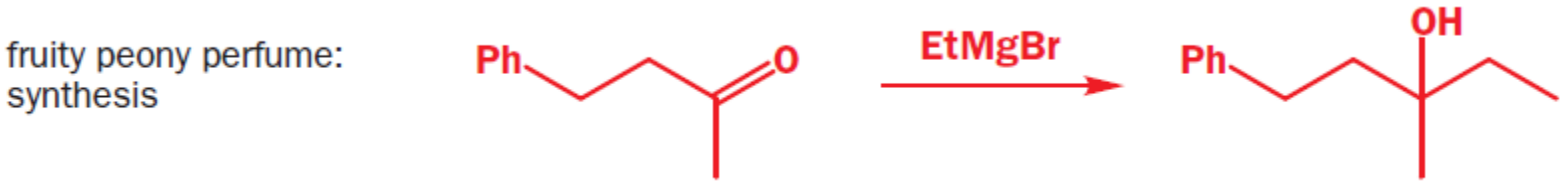


1,1 C–C disconnections – Grignard

This similar alcohol has a ‘peony-like fruity odour’ and could be disconnected in three ways



Disconnection **(c)** leads back to a ketone, which is cheaply made starting from acetone and benzaldehyde, and this was the route that was chosen for the synthesis



Available starting materials

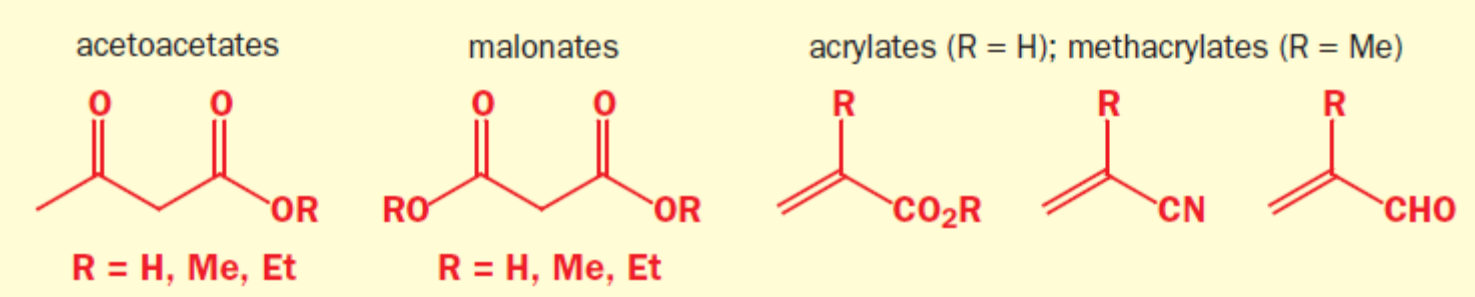
How can we know which materials will be available?

The only way to be absolutely sure what you can buy is to look up a compound in a **supplier's catalogue**, and this is what a chemist would do when assessing possible alternative synthetic routes

A good rule of thumb is that compounds with up to about **six carbon atoms and with one functional group** (alcohol, aldehyde, ketone, acid, amine, double bond, or alkyl halide) are usually available

This is less true for heavily branched compounds, but most straight-chain compounds are available up to eight or more carbon atoms

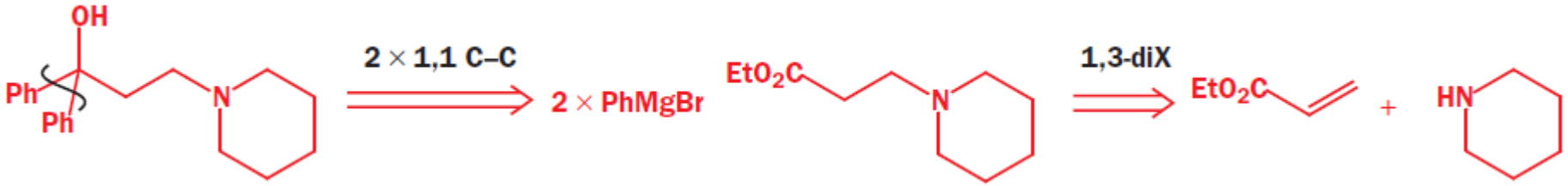
Many other compounds are available too, including some **difunctional compounds**



Double disconnections can be a short cut

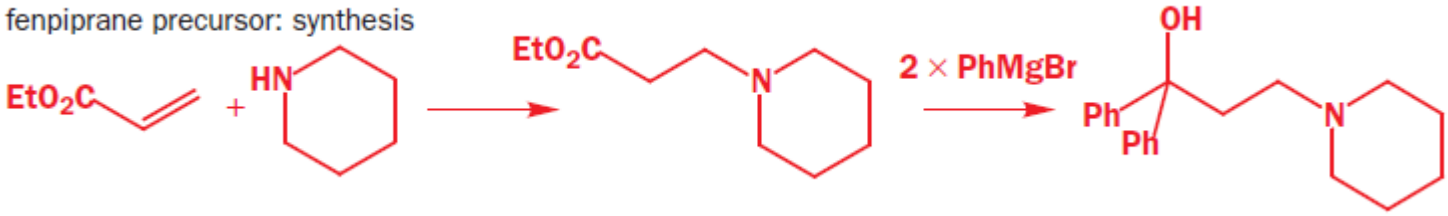
Tertiary alcohols with two identical groups next to the hydroxyl group are often made by attack of **two equivalents of a Grignard reagent** on an ester

fenpiprane precursor: retrosynthetic analysis



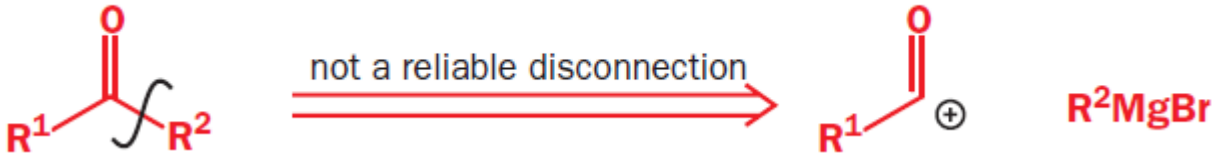
The tertiary alcohol is a precursor to the drug and can be disconnected to ester + Grignard reagent because of the two Ph groups. The ester required has a 1,3 functional group relationship, and can be disconnected to amine plus Michael acceptor

fenpiprane precursor: synthesis

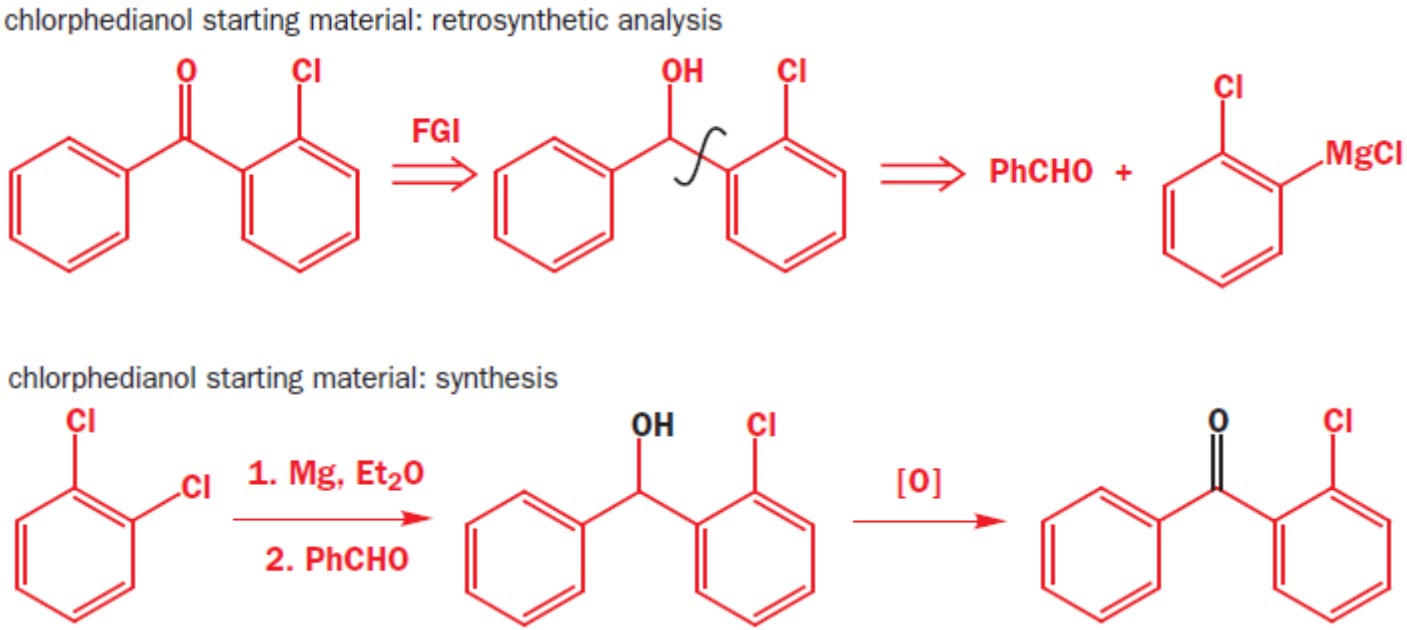


Double disconnections can be a short cut

The fact that Grignard reagents add twice to esters means that disconnection of a ketone in this way is often **not reliable**

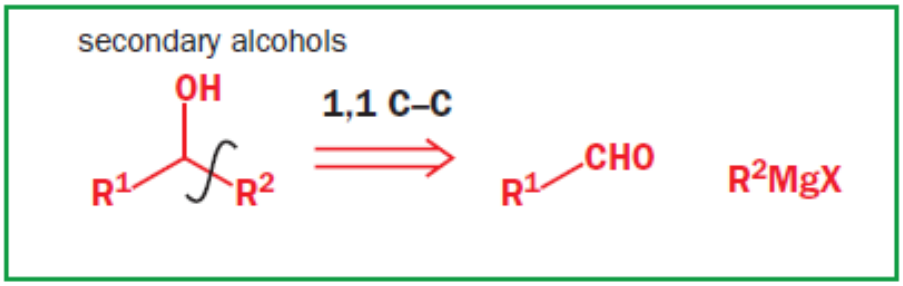


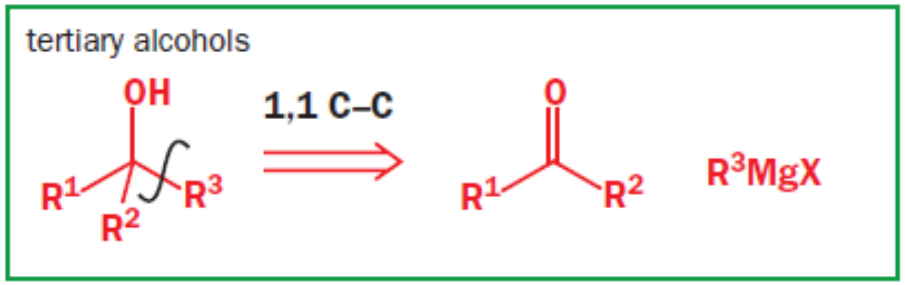
An alternative is to first **convert to the alcohol oxidation level**, then disconnect

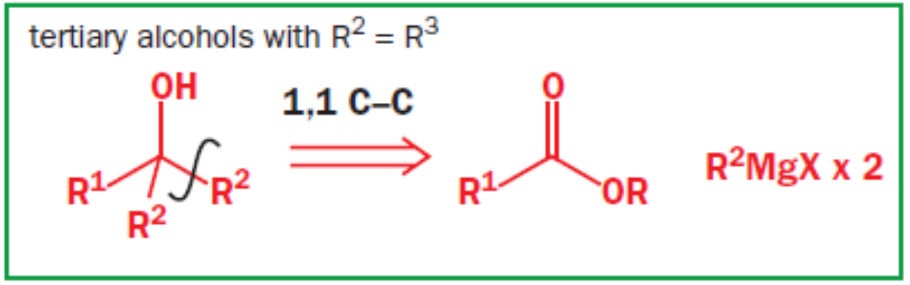


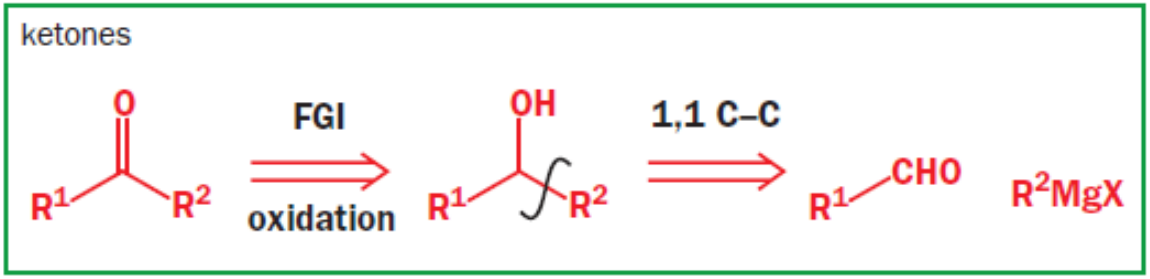
1,1 C–C disconnections – Grignard

Summary:









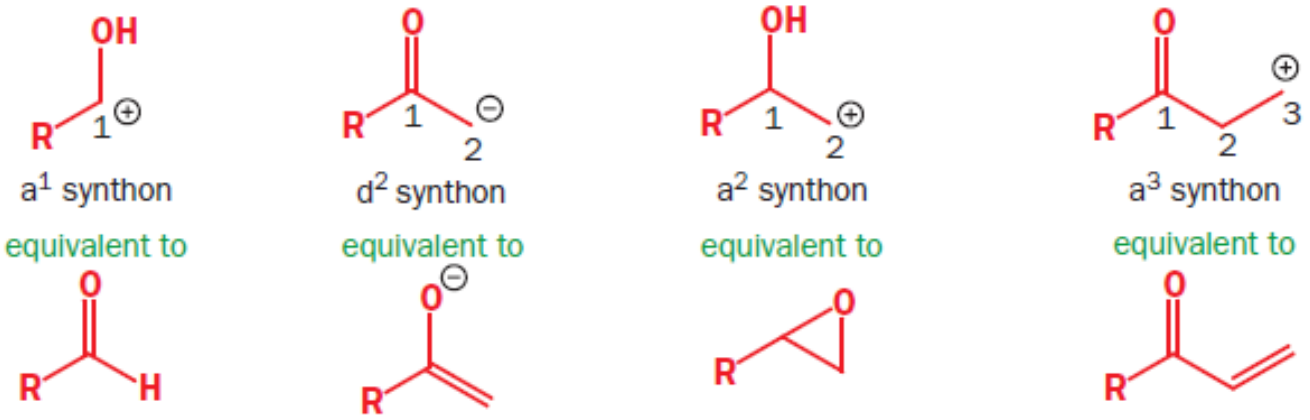
Donor and acceptor synthons

We've now met a variety of synthons and it's useful to be able to classify them:

We call a **negatively polarized** synthon a **donor synthon** and give it the symbol '**d**'

Positively polarized synthons are called **acceptor synthons** and are given the symbol '**a**'

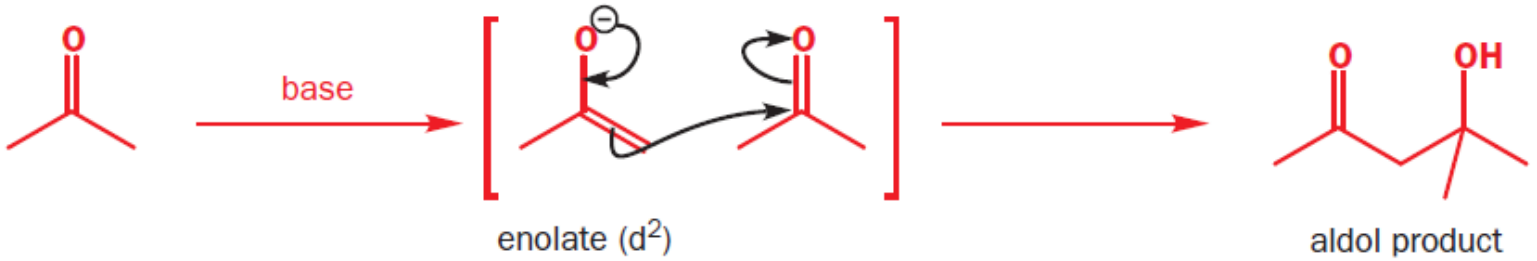
We can classify the synthons further according to ***where the functional group is in relation to the reactive site***



We call an **aldehyde** an **a^1** synthon, because it is an acceptor that carries a functional group on the same carbon as its reactive centre

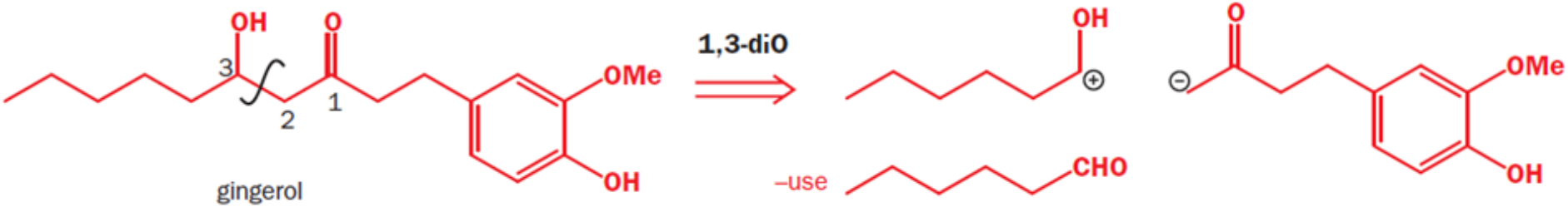
Enolate is a **d^2** synthon because it is a donor whose reacting site is in the 2-position relative to the carbonyl group

Two-group C–C disconnections – 1,3-diO



The **aldol reaction** is extremely important in organic synthesis because it makes compounds with two functional groups in a **1,3-relationship**

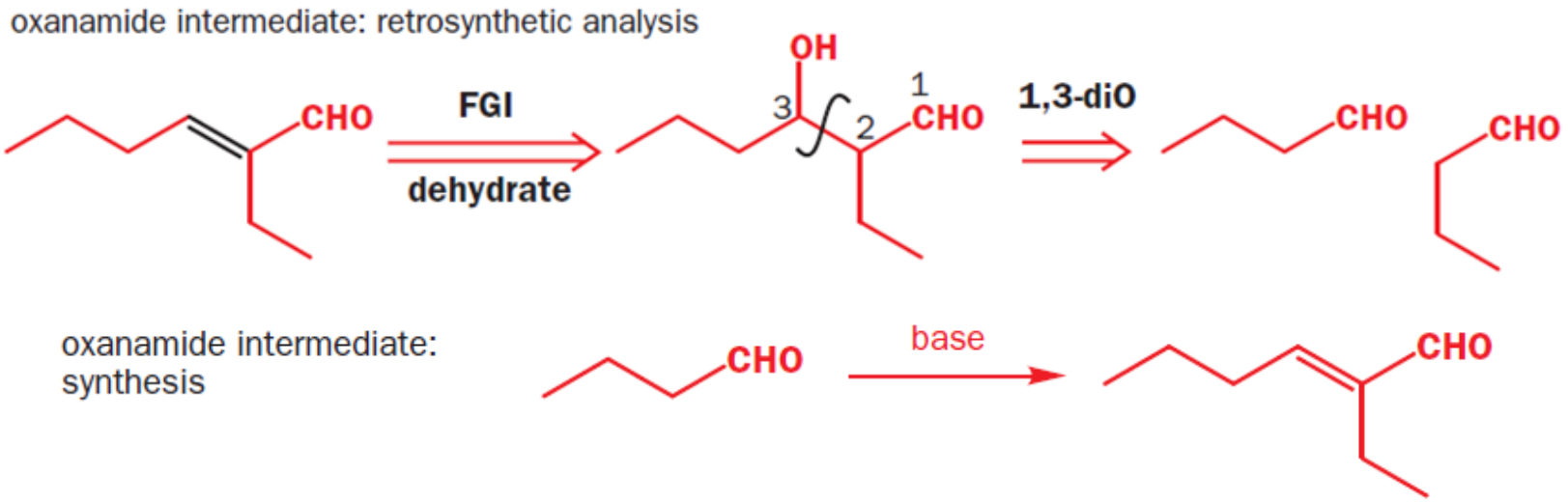
We call this disconnection a **two-group C–C disconnection**, because we are using the **OH and the C=O groups together** to guide our disconnection. The disconnection gives us a d^2 synthon for which we shall use an enolate equivalent, and an a^1 synthon, for which we shall use an aldehyde or a ketone.



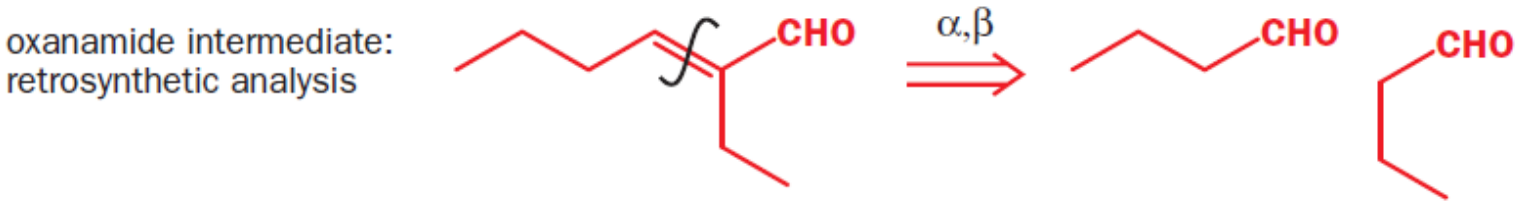
Two-group C–C disconnections – 1,3-diO

The ***β*-hydroxy carbonyl products** of aldol reactions are often very easily **dehydrated to give *α*,*β*-unsaturated carbonyl compounds**

If you spot an *α*,*β*-unsaturated carbonyl group in the molecule, you should aim to make it by an aldol reaction. You will first need to do an **FGI to the *β*-hydroxy carbonyl compound**, then disconnect as before



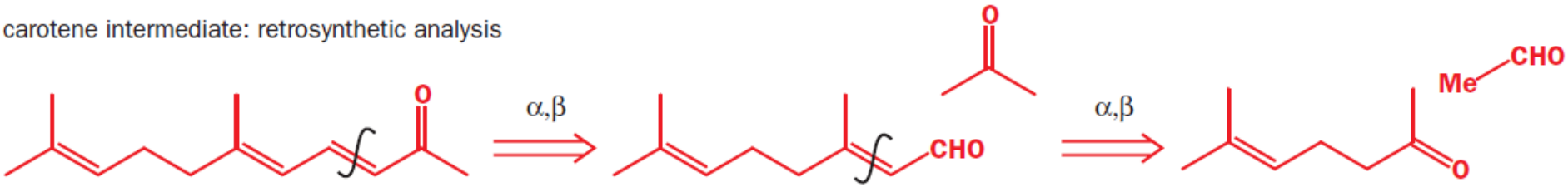
Because this disconnection of unsaturated carbonyl compounds is so common, it's often written using a **shorthand expression**



Two-group C–C disconnections – 1,3-diO

Example 1:

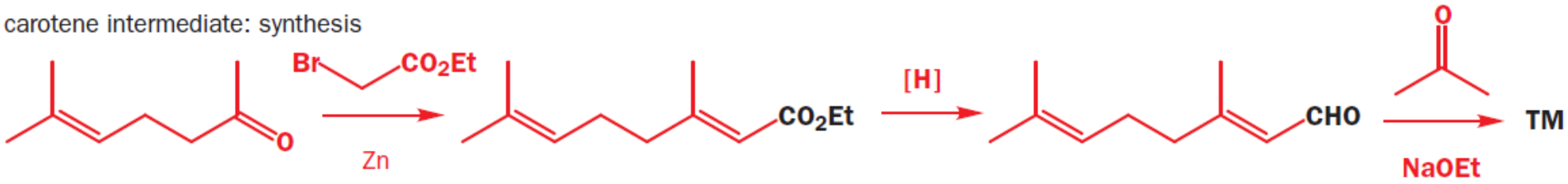
carotene intermediate: retrosynthetic analysis



The aldehyde generated by this first disconnection is also *α*,*β*-unsaturated, so we can do another *α*,*β*-disconnection, back to a ketone

An aldol reaction using the **enolate of acetaldehyde** and requiring it to react with a ketone is doomed to failure: acetaldehyde itself is far **too good an electrophile**. In the forward synthesis, therefore, this first step was carried out at the ester oxidation level (using a **Reformatsky reaction**), and the ester was subsequently converted to the aldehyde by a **reduction**

carotene intermediate: synthesis

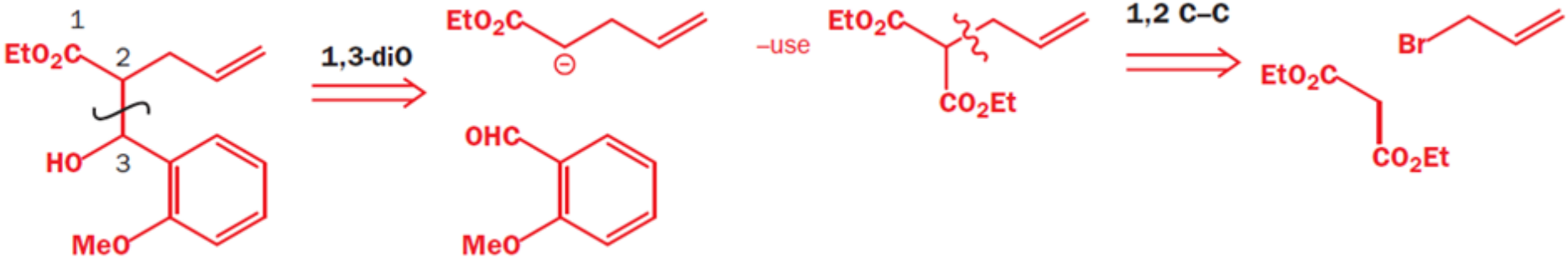


You should equally look to disconnect ***β*-hydroxy or *α*,*β*-unsaturated esters, acids, or nitriles** in this way

Two-group C–C disconnections – 1,3-diO

Example 2:

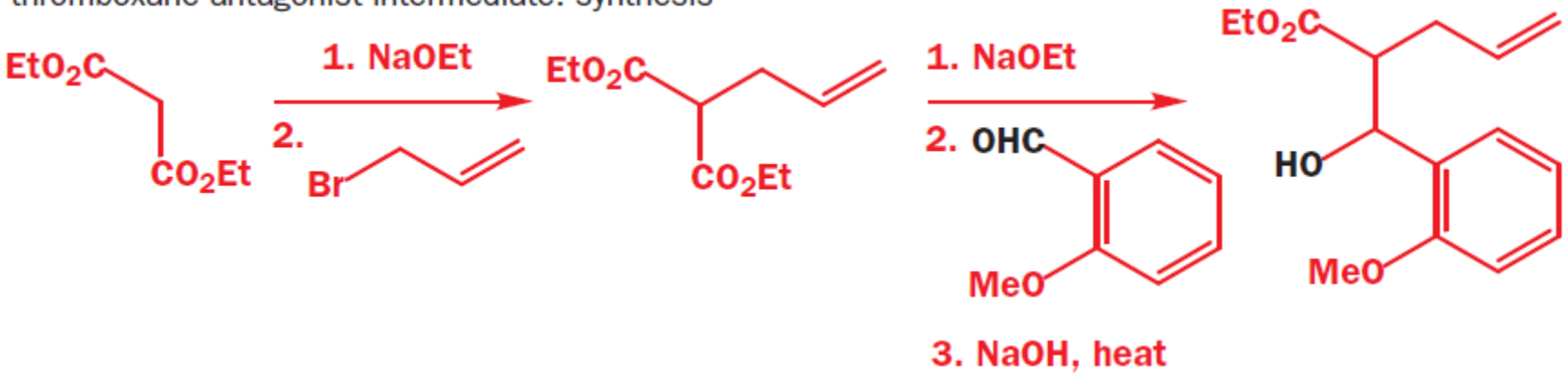
thromboxane antagonist intermediate: retrosynthetic analysis



We can immediately spot the **1,3-relationship** between the ester and the hydroxyl group, so **1,3-diO** disconnection is called for

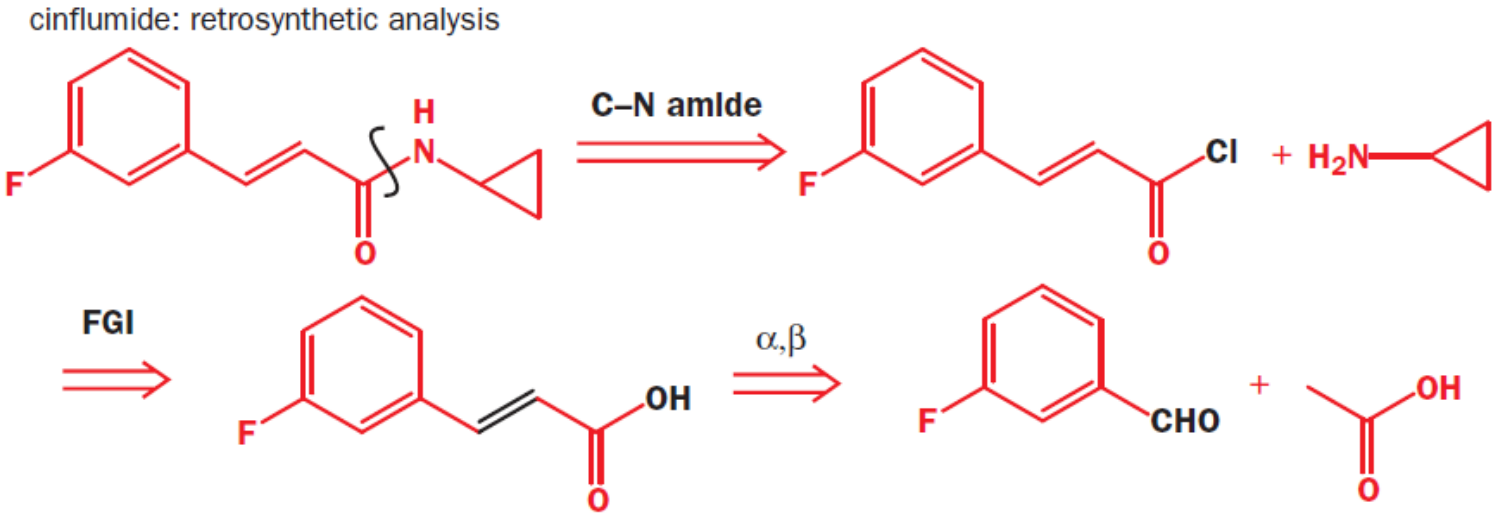
A good equivalent for the **'ester enolate' d^2 synthon** is a ***β*-dicarbonyl compound**, because it can easily be disconnected to diethyl malonate and an alkylating agent

thromboxane antagonist intermediate: synthesis

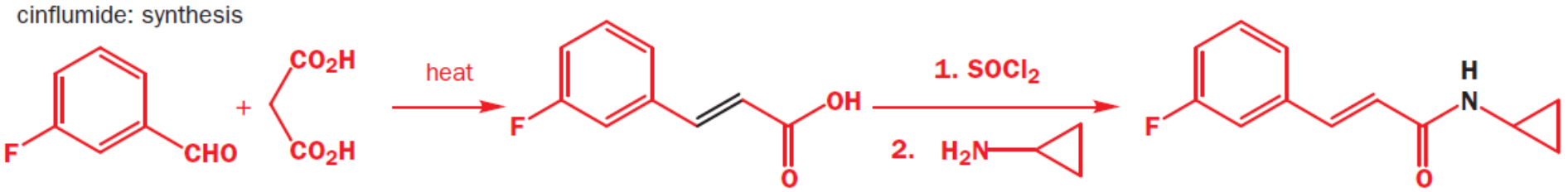


Two-group C–C disconnections – 1,3-diO

Example 3:

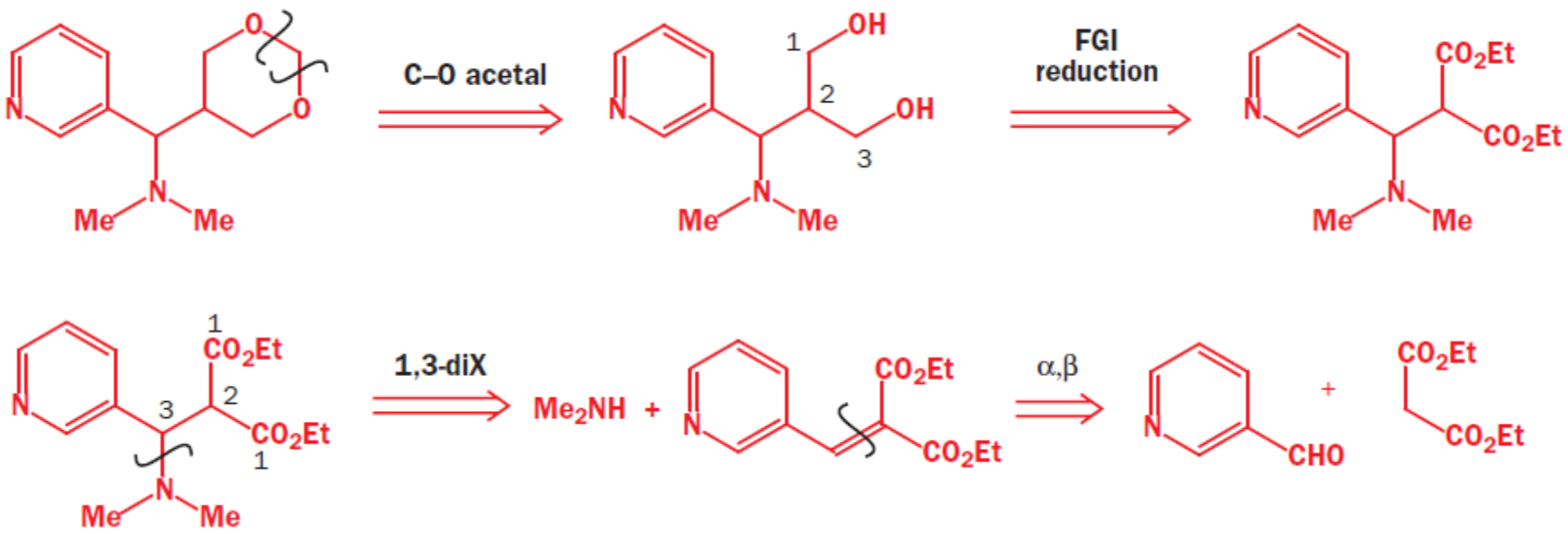


Disconnection of the amide gives an acid chloride that we can make by FGI from the acid. You should then spot the ***α,β*-unsaturated carbonyl disconnection**, a masked 1,3-diO disconnection, back to *m*-fluorobenzaldehyde.



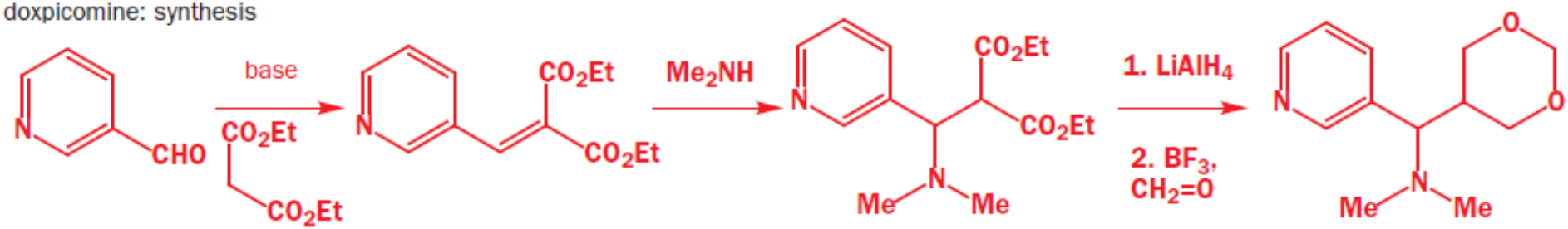
Functional group relationships may be concealed by protection

doxpicomine: retrosynthetic analysis I

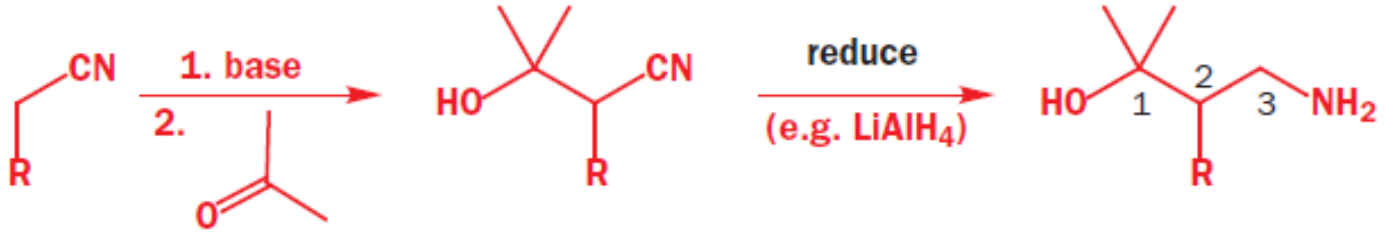


Removal of the acetal reveals a 1,3-diol that could be formed by reduction of a much more promising diester which has a **1,3-diO** relationship

doxpicomine: synthesis

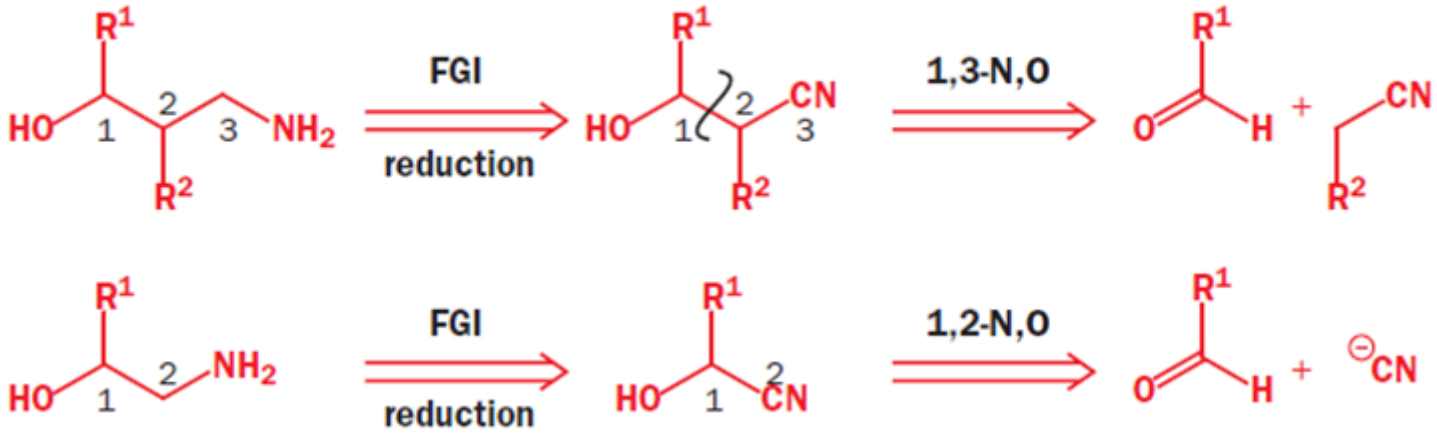


1,2- and 1,3-N,O Disconnections – Reduction of Nitriles



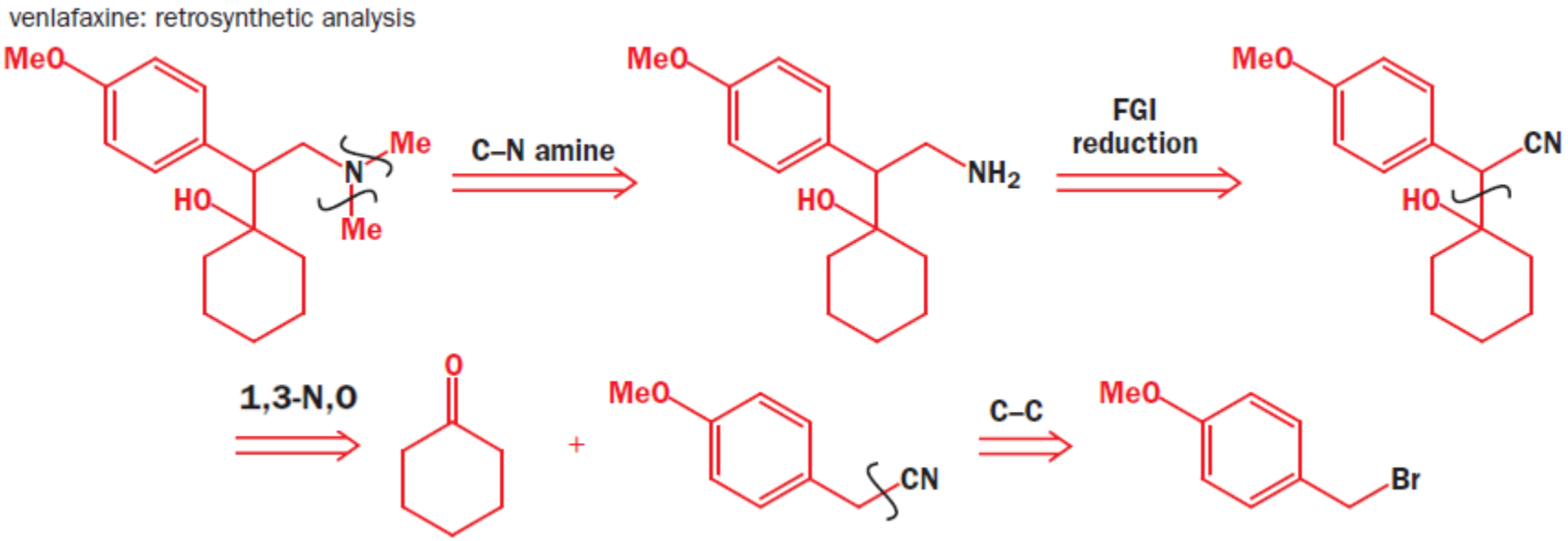
Another important class of compounds that undergo aldol-type additions to aldehydes and ketones is **nitriles**. Because nitriles can be **reduced to amines**, this reaction provides another useful route to **3-amino-alcohols**

This reaction, coupled with the **reduction of cyanohydrins**, means that compounds with either a **1,3-** or a **1,2-**relationship between N and O can be made from cyanides

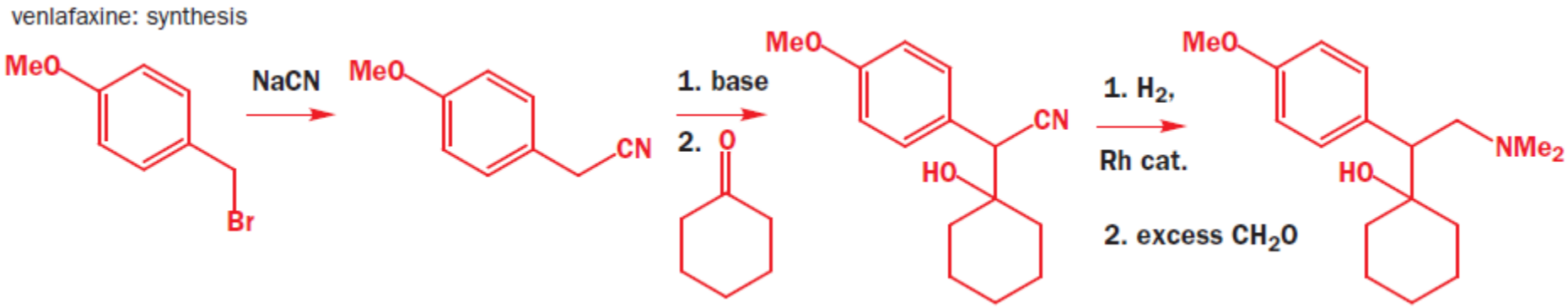


1,2- and 1,3-N,O Disconnections – Reduction of Nitriles

Example:

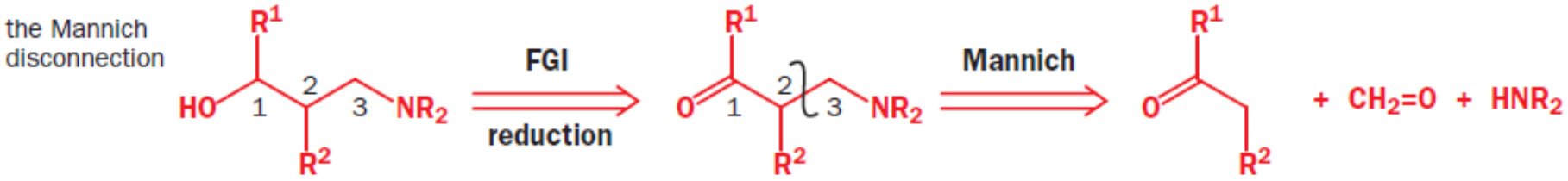


Venlafaxine is an antidepressant and, like many neuroactive agents, it is an amino-alcohol which are 1,3-related, so we aim to use a **1,3-NO** disconnection



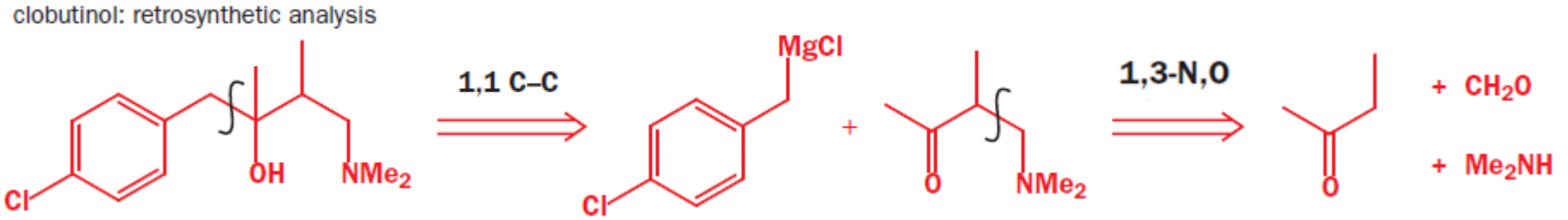
1,3-N,O Disconnections – Mannich Reaction

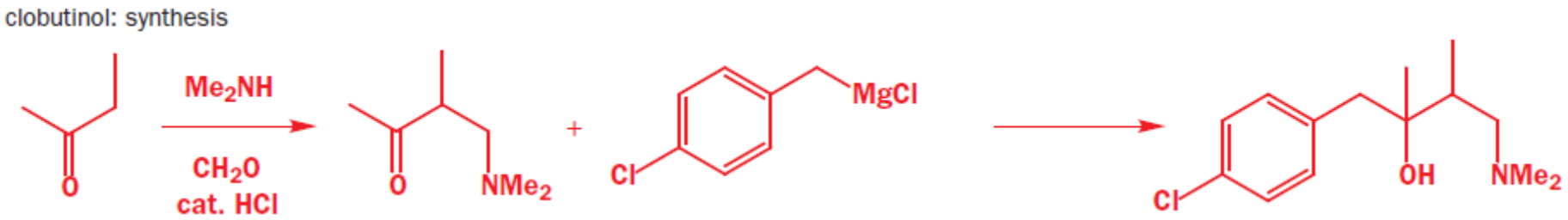
Another important reaction for making amines with a **1,3-relationship to a carbonyl** group is the **Mannich reaction**



Because the amine is introduced directly and not by reduction of a nitrile, it can have **up to two alkyl groups from the start**

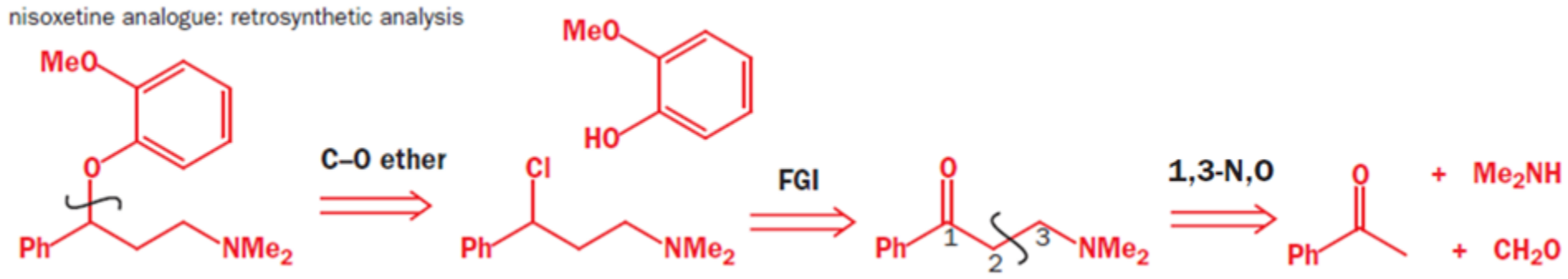
Example 1:





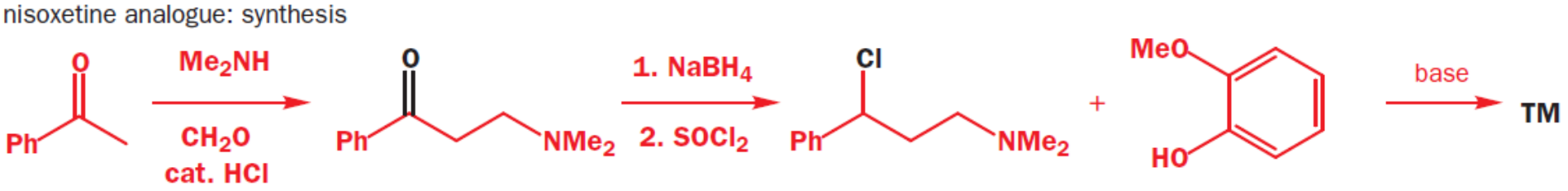
1,3-N,O Disconnections – Mannich Reaction

Example 2:



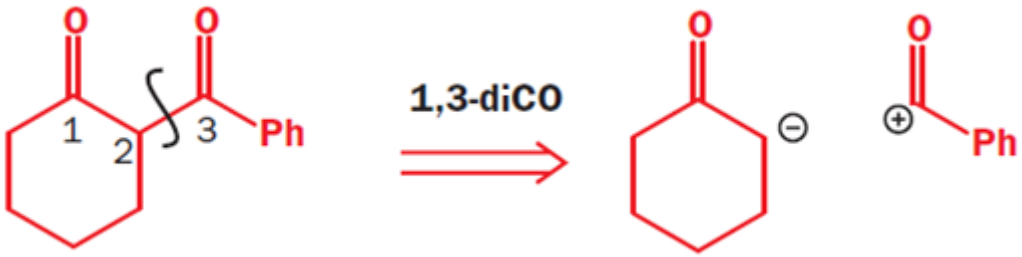
You can immediately spot the 1,3 relationship in this analogue of the antidepressant, nisoxetine. It can't be disconnected straight back to an amino-alcohol because that would require **nucleophilic substitution on an electron-rich aromatic ring**. We have to disconnect the ether on the other side, giving an alkyl chloride

Using guideline 5 we want to **convert the halide to an oxygen-based group**, and a sensible solution is to choose the ketone. 1,3-Disconnection of this compound corresponds to a **Mannich reaction**



1,3-diO Disconnections – Claisen condensation

1,3-Diketones can be disconnected in a similar way: this time the disconnection corresponds to a **Claisen condensation**, but it's still 1,3-diO; The synthons are still **d^2** plus **a^1** but the **a^1** synthon is used at the **ester oxidation level**

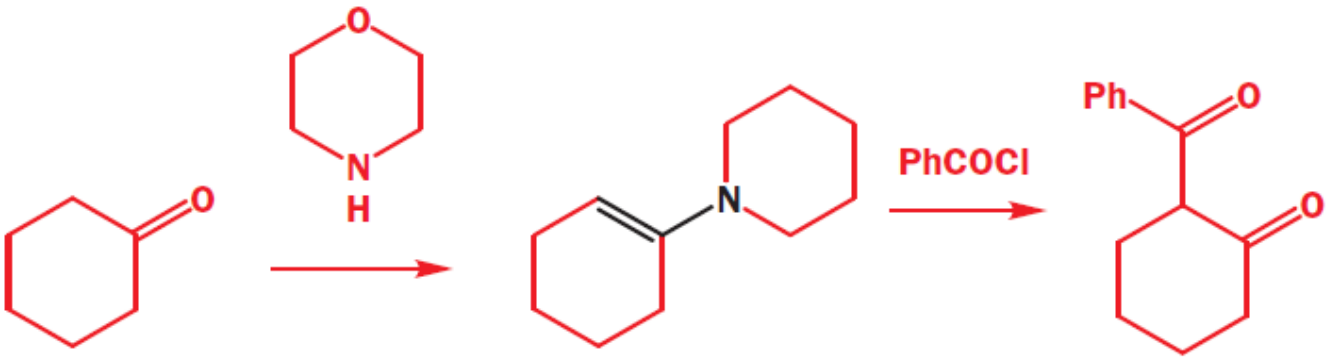


With 1,3-diketones, there's always a choice where to disconnect, and you should be guided by which disconnection

(1) corresponds to the most reliable reaction

(2) gives the simplest starting materials

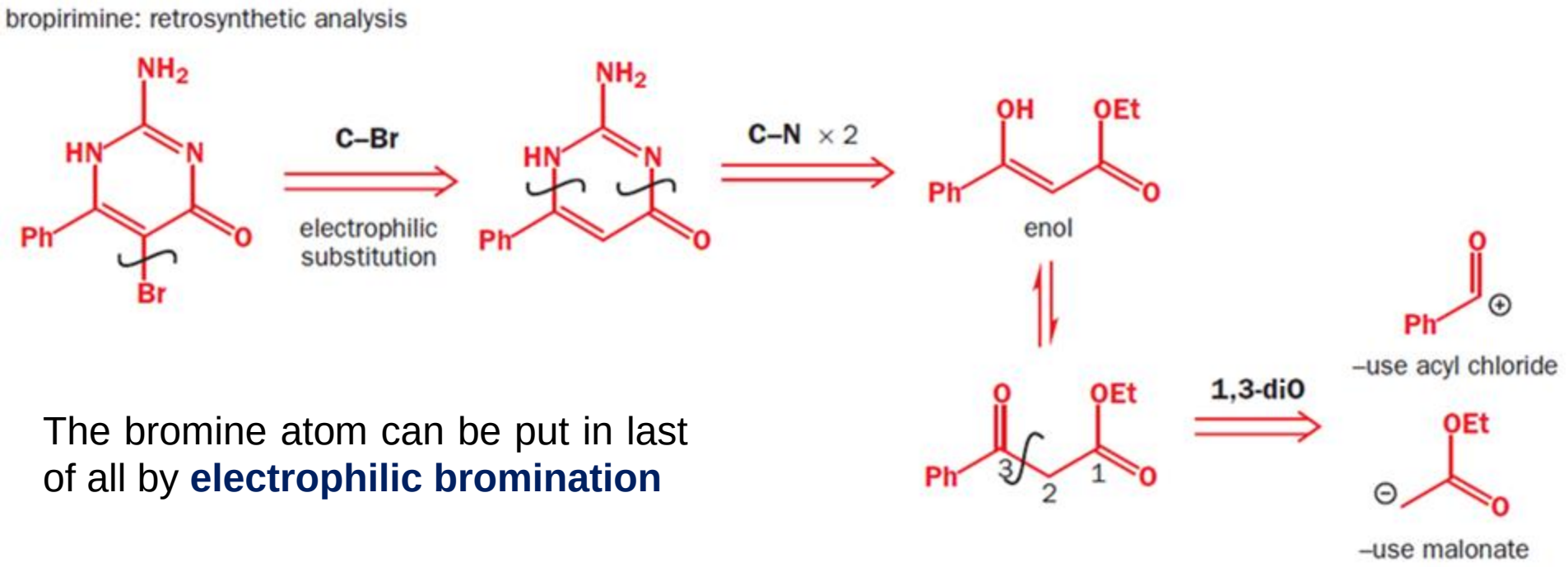
In this case, it's much better to disconnect back to cyclohexanone



1,3-diO Disconnections – Claisen condensation

Example:

The 1,3-dicarbonyl relationship may not be revealed in the target molecule



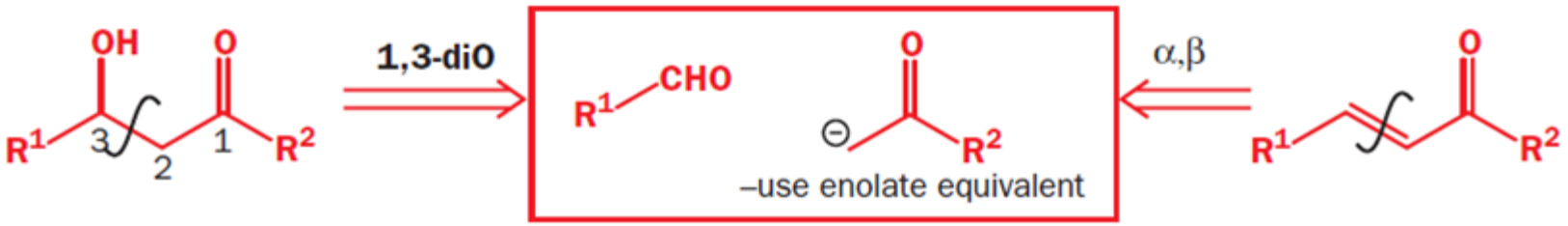
The bromine atom can be put in last of all by **electrophilic bromination**

Disconnection of two C–N bonds removes a molecule of guanidine and reveals a **1,3-dicarbonyl relationship** with a straightforward disconnection.

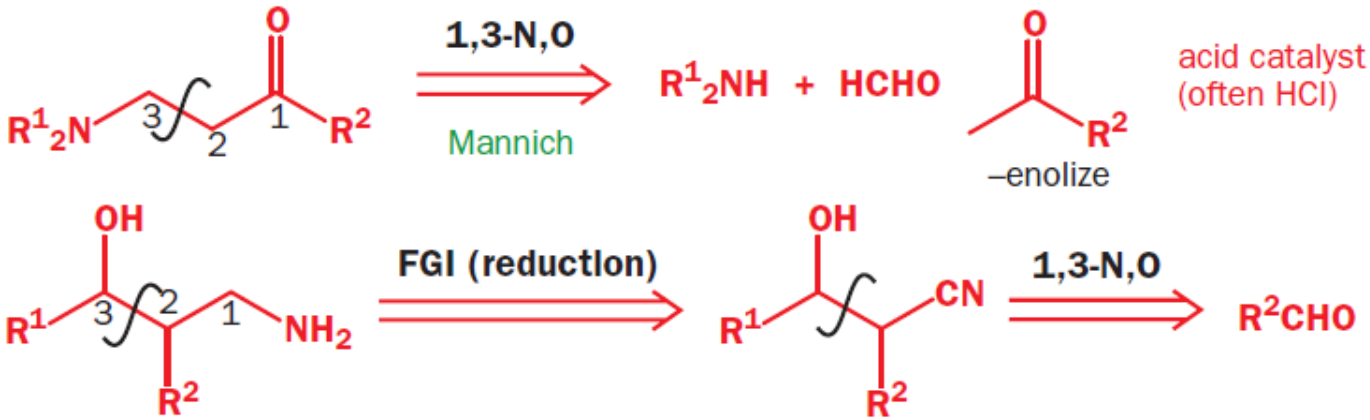
1,3-diX Disconnections

Summary:

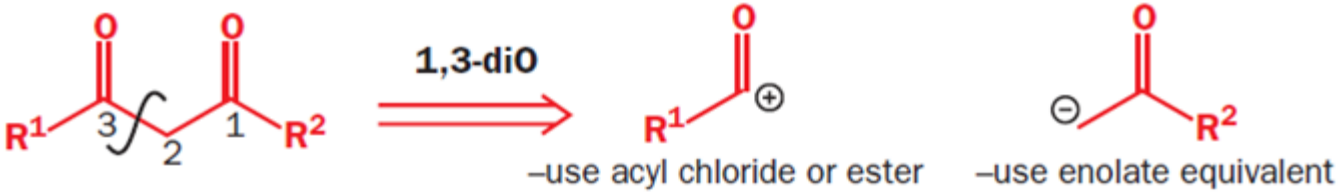
3-hydroxy carbonyls and α,β-unsaturated carbonyls: use the aldol reaction



3-amino ketones and alcohols: use Mannich or nitrile aldol

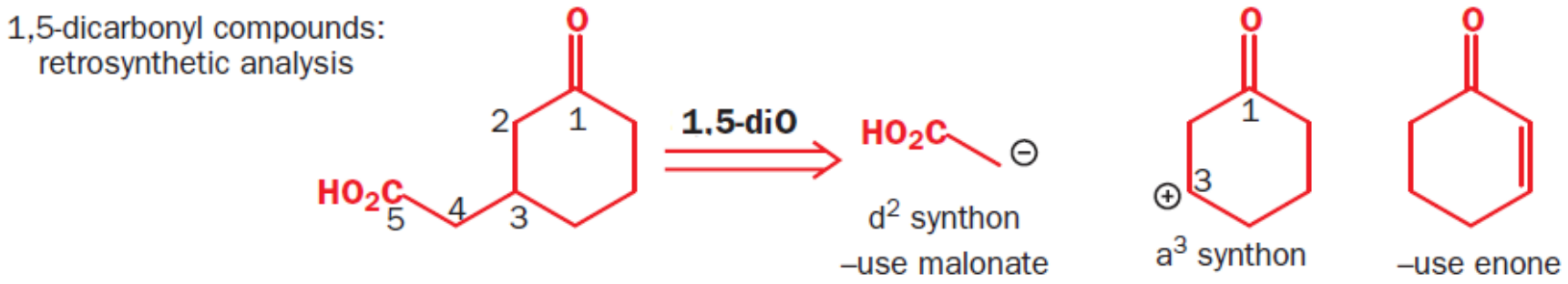


1,3-diketones: use the Claisen condensation



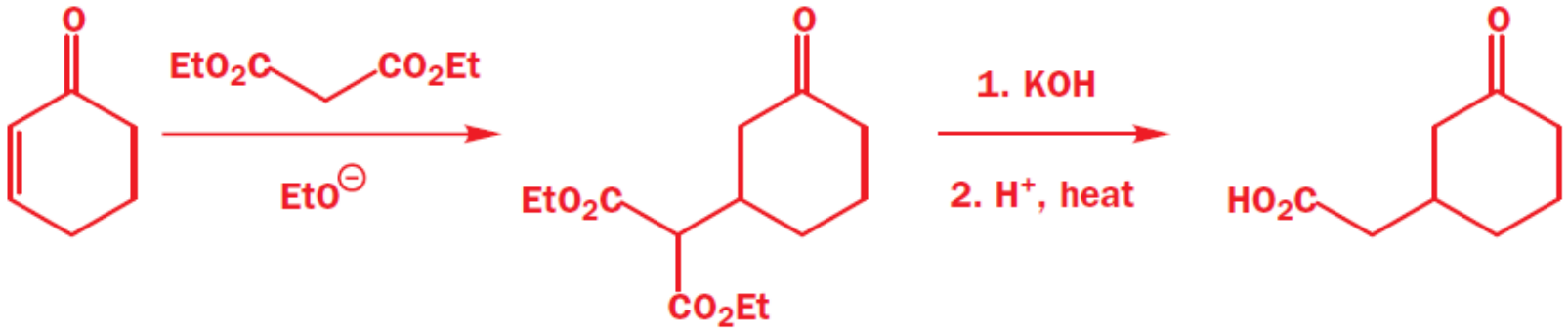
1,5-diO Disconnections

This compound has a **1,5 relationship between two carbonyl groups**. Disconnection to give an enolate as one reagent therefore requires an **a^3 synthon**: in other words a **Michael acceptor**



The synthesis will be successful only if **(1) the right reagent enolizes** and **(2) the nucleophile undergoes conjugate (and not direct 1,2-) addition** to the unsaturated carbonyl compound

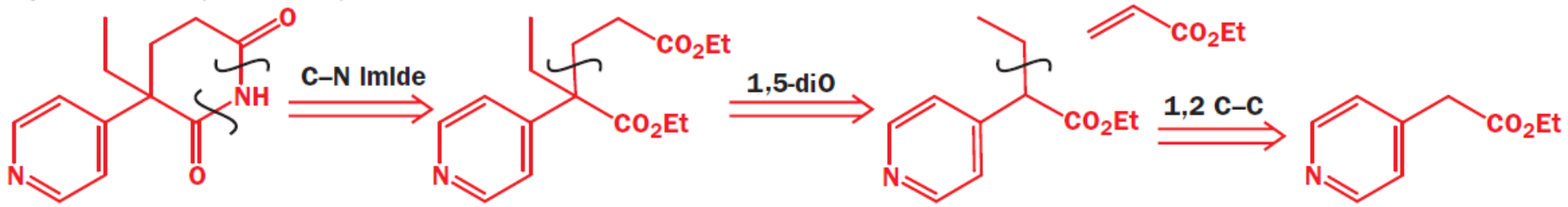
Malonate derivatives **enolize easily** and **do Michael additions** and are therefore a good choice for this type of reaction



1,5-diO Disconnections

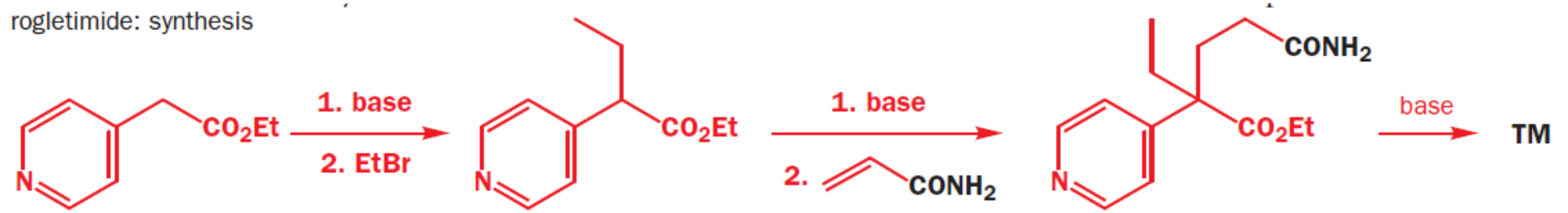
Michael addition of enolates to *α*,*β*-unsaturated compounds is a good way of making **1,5-difunctionalized compounds**, and you should look for these **1,5-relationships in target molecules** with a view to making them in this way

rogletimide: retrosynthetic analysis



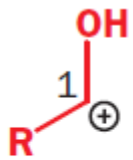
The synthesis was most efficient with an unsaturated amide as Michael acceptor

rogletimide: synthesis

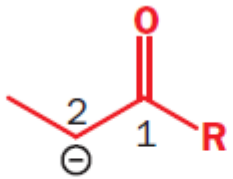


‘Natural reactivity’ and ‘umpolung’

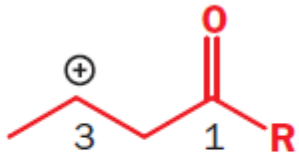
So far, we have encounter the following synthons



a^1 (equivalent to aldehyde or ketone)



d^2 (equivalent to enolate of ester or ketone)



a^3 (equivalent to α,β-unsaturated carbonyl compounds)

Notice that the **acceptor synthons have odd numbers**; the **donor synthon has an even number**: donor and acceptor properties **alternate along the chain** as we move away from a carbonyl group

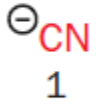
This ‘**natural reactivity**’ of carbonyl compounds explains why we find it easy to discuss ways of making **1,3-** (from $a^1 + d^2$) and **1,5-**difunctionalized compounds (from $a^3 + d^2$)

Reagents corresponding to synthons like d^1 or a^2 are rarer, and therefore compounds with **1,2-** or **1,4-** related functional groups require special consideration retrosynthetically

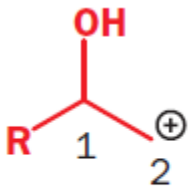
‘Natural reactivity’ and ‘umpolung’

You have in fact met one example of each of the ‘**unnatural**’ synthons with **a²** and **d¹** reactivity

two umpolung reagents

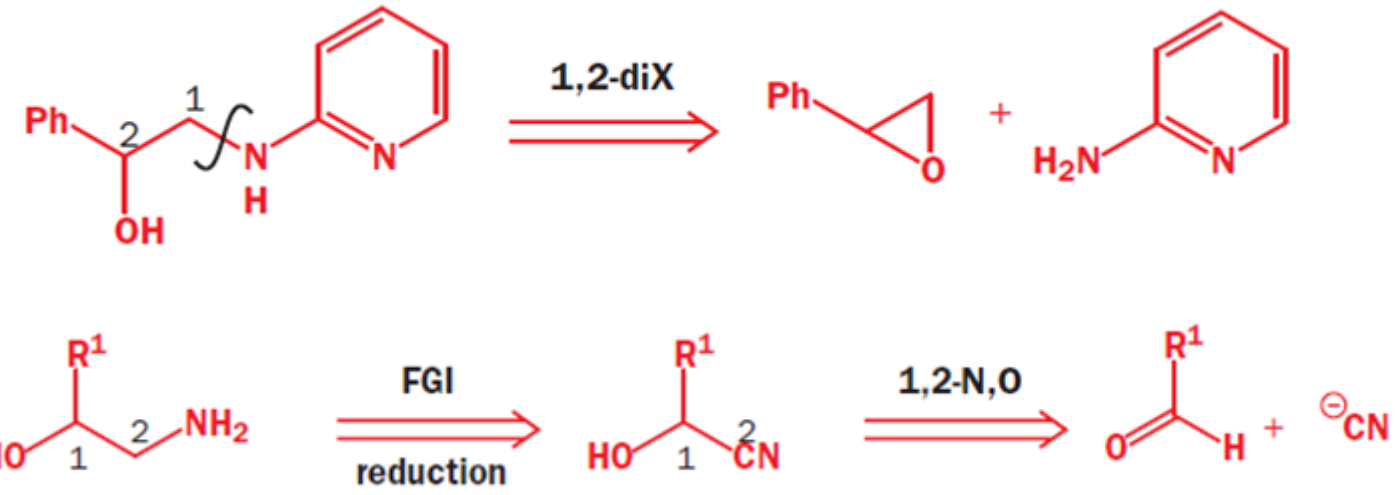


d^1 synthon
(cyanide anion)



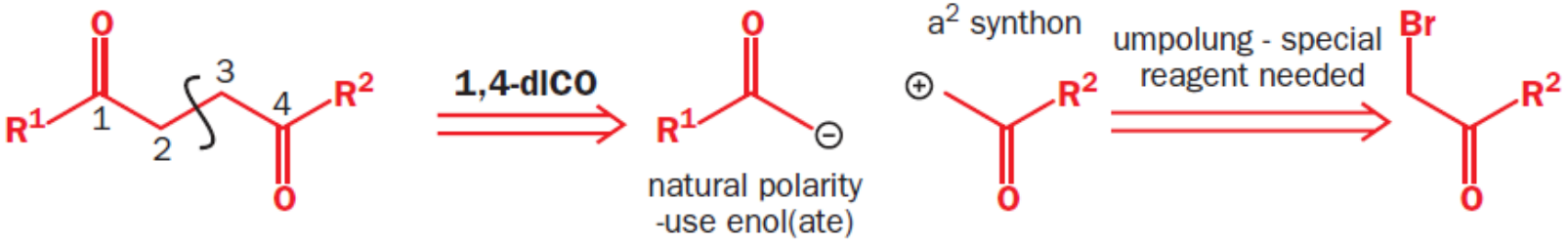
a^2 synthon
(equivalent to epoxide)

Such synthons are given the German name ***Umpolung***, meaning ‘**inverse polarity**’ because their **natural reactivity is reversed**, and umpolung reagents are the key to the synthesis of 1,2- and 1,4-difunctionalized compounds

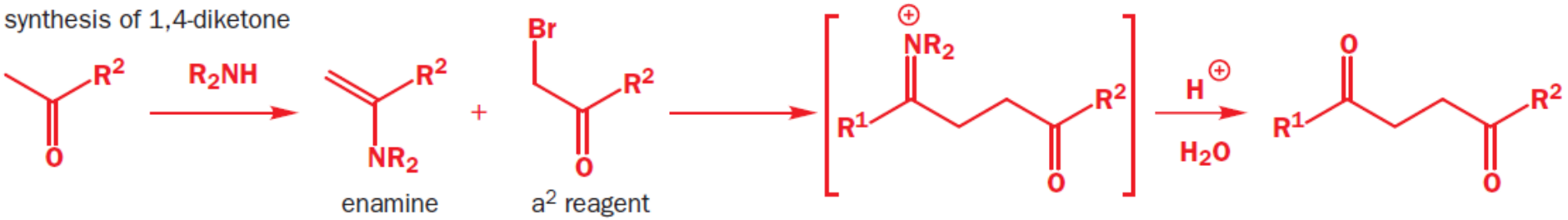


1,4-Difunctional compounds

If we start with a **1,4-dicarbonyl compound** we might consider first disconnection of the **central bond**

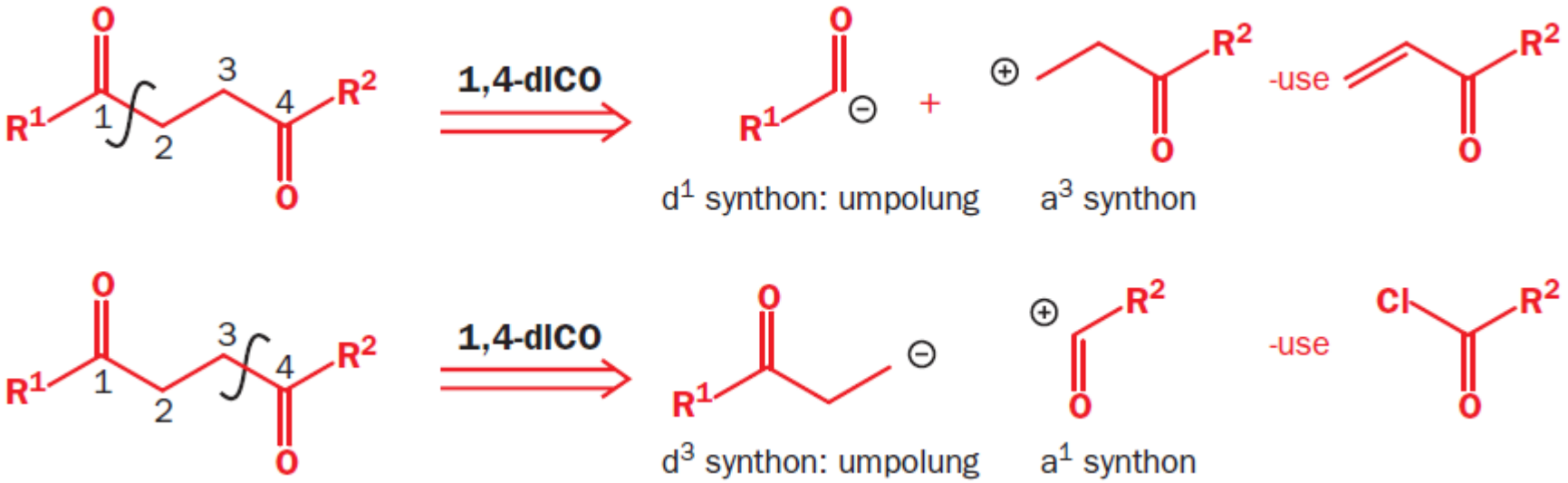


We can use an **enolate** for one reagent but the other will have to have umpolung. This is not a very serious kind of umpolung as an ***α*-bromo carbonyl compound** will do the job nicely if we select our enol(ate) equivalent carefully; **enamines** are the most suitable enolate equivalent



1,4-Difunctional compounds

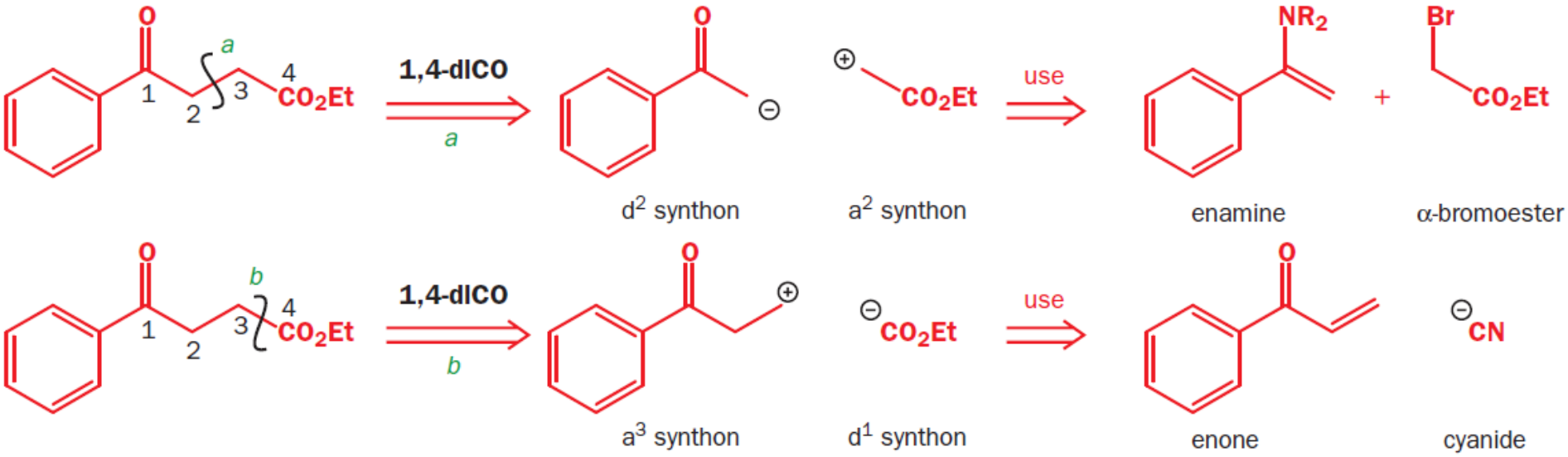
If we attempt the disconnection of one of the other bonds, two possibilities are available because the two fragments are different. We can use either a **d^1** + **a^3** strategy or an **a^1** + **d^3** strategy. In each case we have one natural synthon and one with umpolung



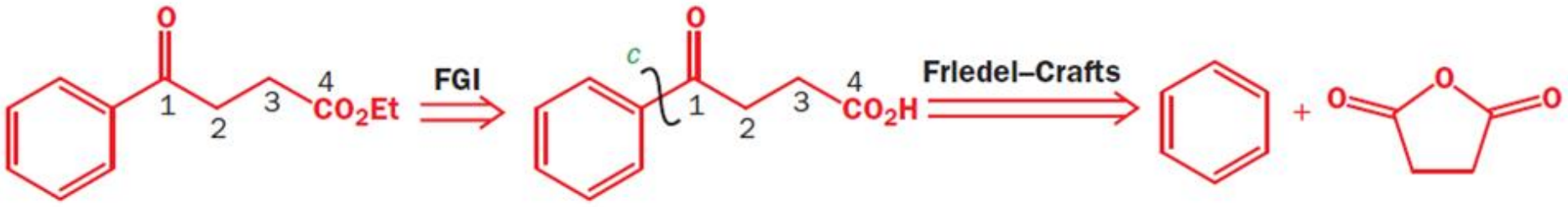
Conjugate addition of a **cyanide** to an **unsaturated carbonyl compound** would be an example of the **d^1** + **a^3** strategy

1,4-Difunctional compounds

Summary: using Umpolung chemistry



There is one way to avoid umpolung and that is to make the **disconnection outside the 1,4 relationship**



This strategy is available only if there happens to be a starting material available to suit any particular case