Synthetic Strategy – Lecture 2 (DC, 19.1.05)

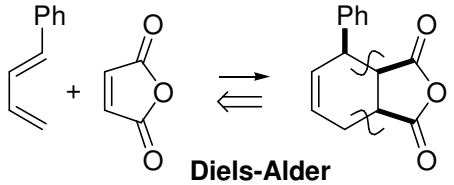
Designing organic syntheses: retrosynthetic analysis

Lectures 2 through 6 of this third part of the second-year organic synthesis course will be concerned with **designing organic syntheses**, using the **disconnection** approach, which as you probably know involves **retrosynthetic analysis** of target molecules. We will meet a number of new concepts, and encounter some new jargon, including the terms **synthon**, **antithetical reaction**, **synthetic equivalent**, **functional group interconversion** (**FGI**), **functional group addition** (**FGA**). This is in some ways a difficult body of material about which to give a conventional lecture course, since by far the best way to get to grips with the ideas, and to become adept at devising synthetic routes is to practise (and practise, and practise…). There will be an assessed problem sheet based on this joint (AA & DC) part of the course, and this takes place on Mon 21 Feb (problems set issued on Fri 11 Feb).

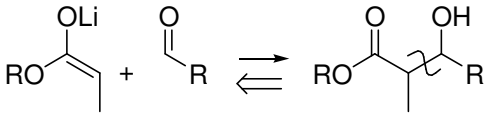
Designing organic syntheses: general issues

We met the important general issues concerning design of organic syntheses in DC lecture 1 back in October. To recap, we need to think about:

- **C-C bond formation**; this is a **strategy-level** consideration, and the decisions we make here will influence both of the other main considerations set out below. As was mentioned in lecture 1, the **Diels-Alder** and **aldol** reactions are strategy-level transformations; they result in a significant **increase in complexity** of the synthetic intermediate.

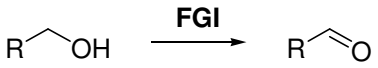


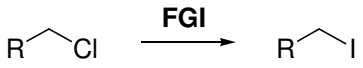
Diels-Alder



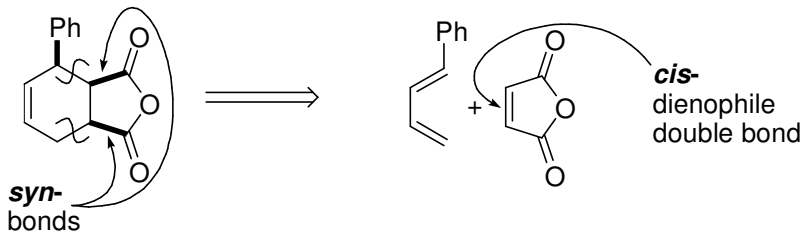
aldol

- **functional group interconversions** (**FGIs**); as stated in lecture 1, these may be regarded as largely **tactical** in nature, and in a sense are the 'glue' which holds the strategy together. For example, a functional group arising from a strategy level transformation involving C-C bond formation may have to be converted into another functional group before the next strategy-level, C-C bond-forming transformation is possible. FGIs leave the carbon skeleton unchanged (almost always!), and **usually involve exchange of heteroatoms** (*i.e.* not C or H).





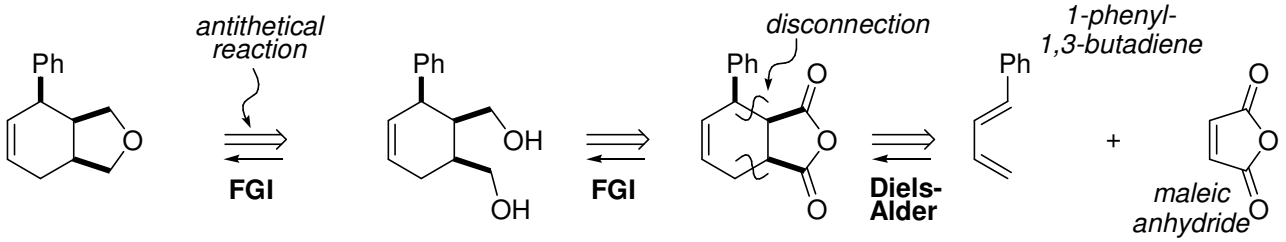
- **stereochemistry**; remember that a molecule with n stereocentres/double bonds may be in principle exist as up to 2^n stereoisomers, so we must always be aware of the likely stereochemical outcome of a transformation. As stated in lecture 1 last term, **stereochemical factors often profoundly influence decisions about strategy**.



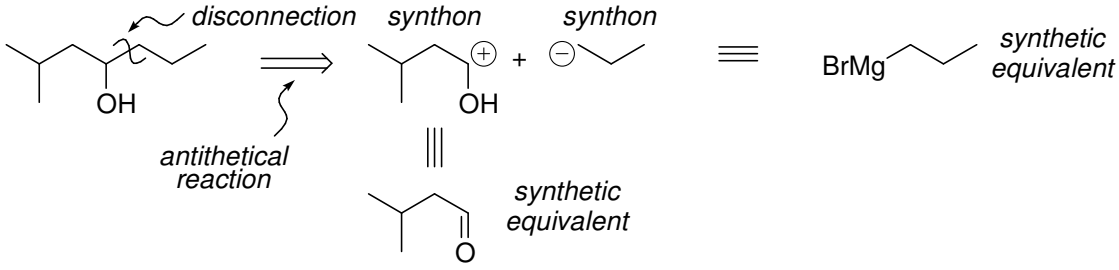
The Diels-Alder reaction is particularly suitable here, because it is **stereospecific**

Retrosynthetic analysis: the concepts

The key idea with retrosynthetic analysis and the disconnection approach is – in an imaginary way – to sequentially break bonds (*i.e.* **disconnect** atoms) within a target structure, to reveal simpler structures. These imaginary backwards reactions are termed **antithetical reactions**. The resulting simpler structures then themselves become the new target structures, and are subjected to a further imaginary bond-breaking operation, or disconnection. The idea is that after several iterations of the disconnection the newly revealed target structure will be so simple that it is recognisable either as a commercially available chemical feedstock, or something whose synthesis is straightforward and/or well-established.



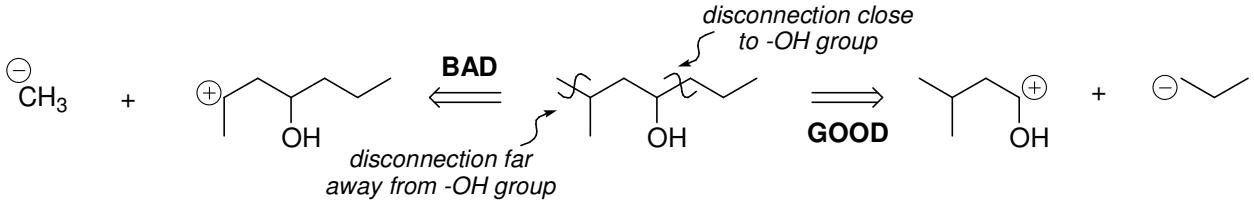
The example shown above has a cycloaddition of a symmetrical dienophile with a 1,3-diene (Diels-Alder reaction) as the strategy-level transformation, and because this is fairly readily recognised (in fact it is a **two-group disconnection**: more on this later) we didn't really need to think about the polarity of the simpler structures revealed by this disconnection. *This is not usually the case*; it is much more common for a disconnection to reveal two **imaginary fragments**, or **synthons**, which carry a **positive** or **negative charge**. Subsequently we need to identify the real (*i.e.* non-imaginary) chemicals/reactive intermediates which are the **synthetic equivalents** of the synthons identified.



Retrosynthetic analysis FAQs

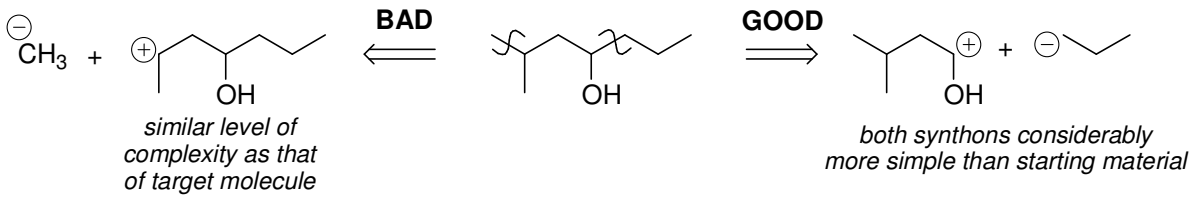
Where should I choose to disconnect?

Disconnections very often take place immediately adjacent to, or very close to functional groups in the target molecule (*i.e.* the one being disconnected). This is pretty much inevitable, given that functionality almost invariably arises from the forward reaction.



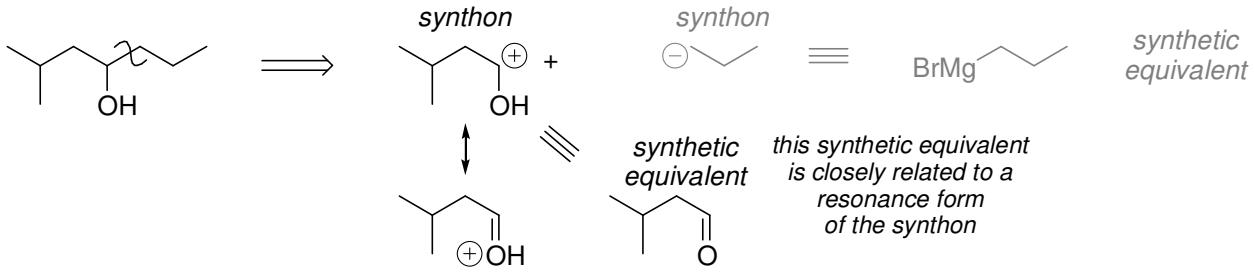
How do I recognise a good disconnection?

A good disconnection visibly simplifies the target molecule. Otherwise, the synthesis challenge doesn't get any easier!



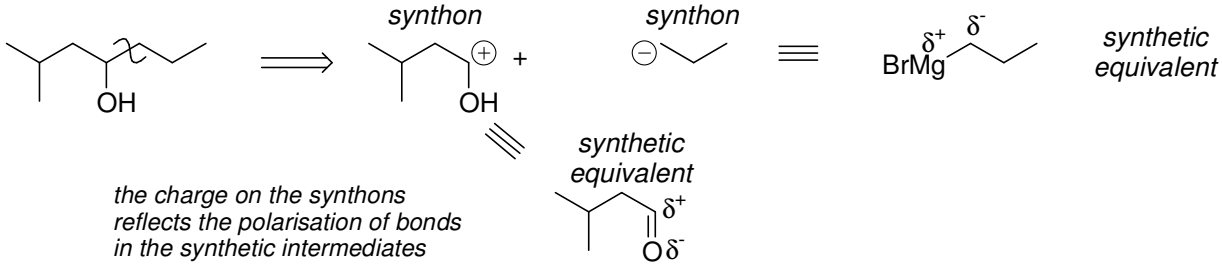
How do I decide which synthon carries which charge?

A good trick here is to consider whether you can draw a resonance form of the synthon which looks more like a *real* reactive intermediate… If it does, you've clearly made a good choice of polarity, *and* you've most likely gone a long way to identifying the synthetic equivalent!



How do I identify the synthetic equivalents of my synthons?

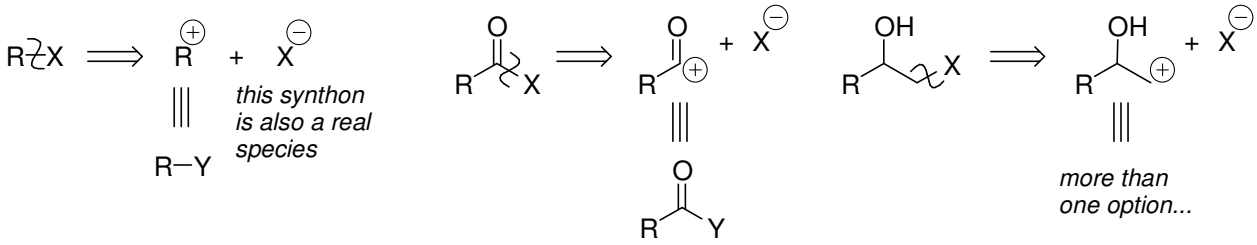
See immediately above, and consider also the inherent polarisation of the key reactive bonds within your proposed synthetic equivalent; the synthon is often just an extreme, imaginary version of the real-life situation.



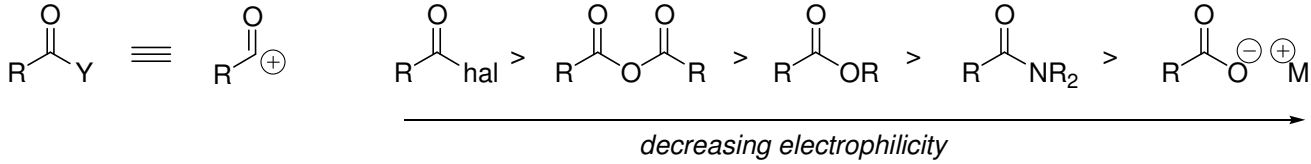
Simple disconnections and synthetic equivalents

C-X disconnections

If we need to make a C-X bond (where X is a heteroatom), a simple disconnection reveals a carbocationic synthon, and X^-. We choose this polarity because X is almost invariably more electronegative than carbon. Clearly the C-X bond could exist in many different chemical environments, which means that there will be a correspondingly wide range of carbocationic synthons and synthetic equivalents. Three major ones are shown below.



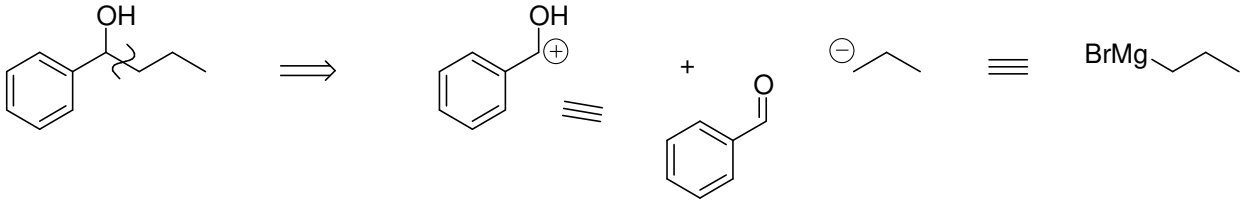
The second of these examples is hugely important: these are **acylation** reactions, and you've met these already on several occasions. We need to be aware of the pecking order of electrophilic reactivity of the various synthetic equivalents of the **acyl cation** synthon.



The third of the C-X disconnections shown at the beginning of this section is an example of a **two-group disconnection** (like the Diels-Alder example above), since it works uniquely when both of the functional groups (X and OH) are present in the target molecule. Clearly we could treat this as a simple C-X disconnection, but recognising the two groups allows us to use to highly reactive (why?) epoxide as the synthetic equivalent of the carbocationic synthon.

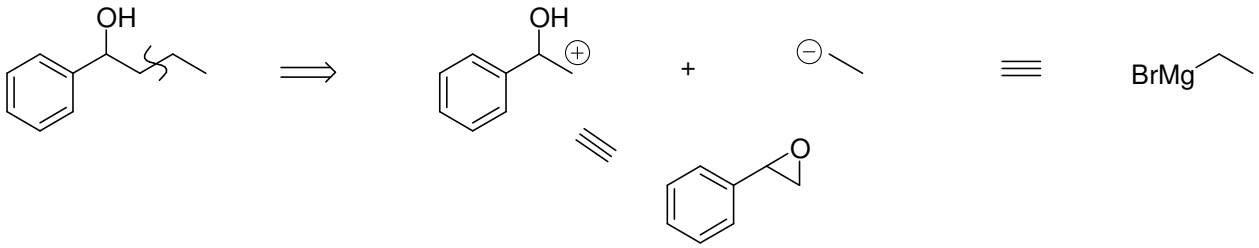
C-C disconnections: alcohols

Alcohols are a prime example of the need to disconnect right next to the hydroxyl functional group. This takes us back to a **carbanion synthon**, and an **α-hydroxyalkyl cation** synthon. The synthetic equivalent of a carbanion synthon is almost invariably an **organometallic** compound. Do the resonance form trick, and we see that the synthetic equivalent of the hydroxyalkyl cation synthon is a **carbonyl compound** (aldehyde or ketone).

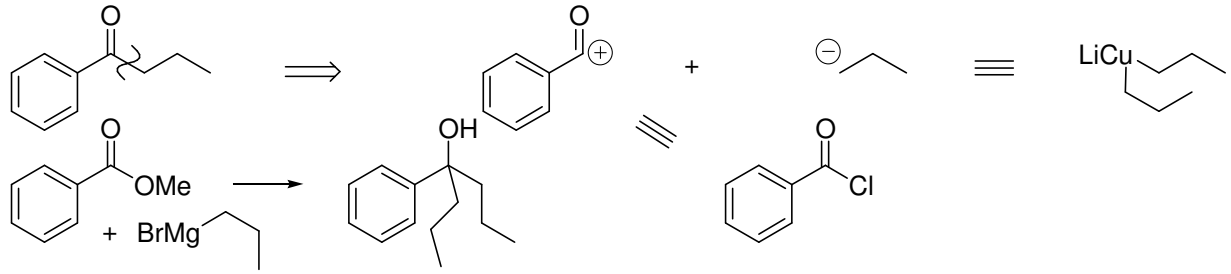


Adding an organometallic compound to a carbonyl compound very often generates a new stereocentre, and it's non-trivial to control which enantiomer of the product is formed. If we disconnect one bond further away from the alcohol in the target, we generate a **β-hydroxyalkyl cation** synthon, whose synthetic equivalent we've already seen is an **epoxide**. Epoxides are already chiral, so we have a single enantiomer of the epoxide, we form a single enantiomer of the product alcohol.

C-C disconnections: carbonyl compounds



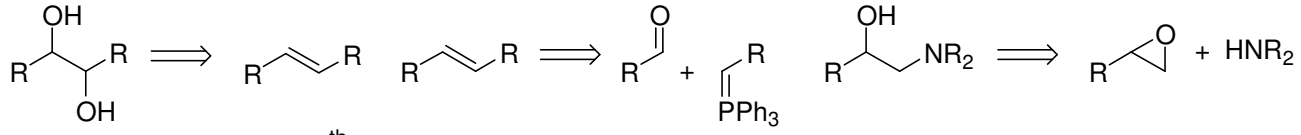
By direct analogy with the disconnection of alcohols, simple carbonyl compounds disconnect back to acyl cation synthons and carbanionic synthons, indicating the need for acylating agents and organometallic compounds. Beware the pitfalls here: as we said last term, the product carbonyl compounds are very often more reactive than the starting acylating agents (of course, this depends on which acylating agent is chosen), so double addition of the organometallic is a real danger: choose wisely!



1,2-difunctional compounds

In a way, 1,2-difunctional compounds don't lend themselves brilliantly well to the disconnection approach, in that it's quite often not particularly helpful to identify synthons. As a consequence, there is not really a unified approach to the synthesis of these compounds. Examples are:

- **1,2-diols** (the best method for their synthesis is **dihydroxylation of alkenes** (see AA lectures last term; **1,2-dihalides** are made analogously by **halogenation of alkenes**)
- **alkenes** (we met a number of methods for **olefination** in DC lectures last term)
- **1,2-diaminoalcohols**: we've seen that **ring-opening** of **epoxides** by **amines** is a highly effective strategy here



Next time (Wed 26th Jan at 11am): *1,3-difunctionality: aldol and related disconnections*