Synthetic Strategy – Lecture 6 (DC, 18.2.04)

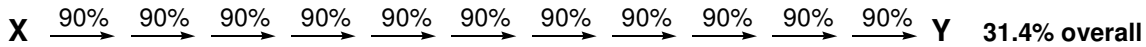
Advanced Synthetic Strategy

During the last four lectures of this part of the course, Dr Armstrong and I have presented the basic tools of retrosynthetic analysis. At this stage of the course, you should feel more or less comfortable with the fundamental aspects of the disconnection approach to designing organic syntheses, and be aware of where disconnections (how to recognise a good one), antithetical reactions, synthons and synthetic equivalents, and FGIs fit into the overall picture. We've focused the discussion largely on the synthesis of difunctional compounds, and in particular on target molecules possessing oxygen functionality with varying 'distances' between the two functional groups present. This provides a useful conceptual framework for the disconnection approach, as well as reinforcing ideas about reactivity you've met in earlier parts of this course, and indeed in earlier parts of the overall curriculum… Armed with this information and these ideas you are ready to tackle some serious retrosynthetic problems. Well, almost; here are a few more ideas, insights, tricks and tips:

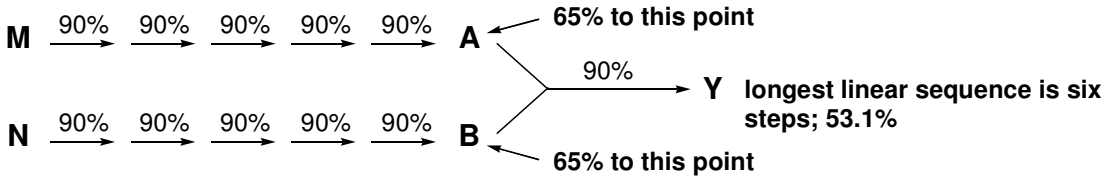
Linear versus convergent syntheses

This is based on very rudimentary number-crunching. Imagine say, an 11-step linear synthesis, in which each reaction gives a yield of 90%. The overall yield would be 0.9^{11} x 100% = 31.4%. Not bad (most likely you have ended up with a molecule with a greater molecular mass than the starting material, so probably you have a good deal more than just under a third of your original starting material mass to show for your efforts), but still a bit disappointing, given that each individual step worked pretty well… Now imagine a synthesis involving 11 synthetic steps, but with two linear, five-step sequences (90% each step) to give intermediates **A** and **B** which are combined at the end in the 11^{th} step, also in 90% yield. The longest linear step in this **convergent** route is six steps, with a corresponding yield of 0.9^6 x 100% = 53.1%. In the end the concept is more important than the numbers: by carrying out different stages of the synthesis on separate parts of the molecule you effectively avoid exposing those parts of the structure already installed to the possibility of a less-than-100% yield. (In big-molecule synthesis you will very often see the target disconnected into several major chunks (often called the 'northern hemisphere', *etc*.) which are synthesised separately and then joined together at a late stage. This approach means also that you can make structural changes in one part of the molecule independently of another part, which can be useful if you are making non-natural products for evaluating structure-biological activity relationships.)

SCHEME A



linear synthesis



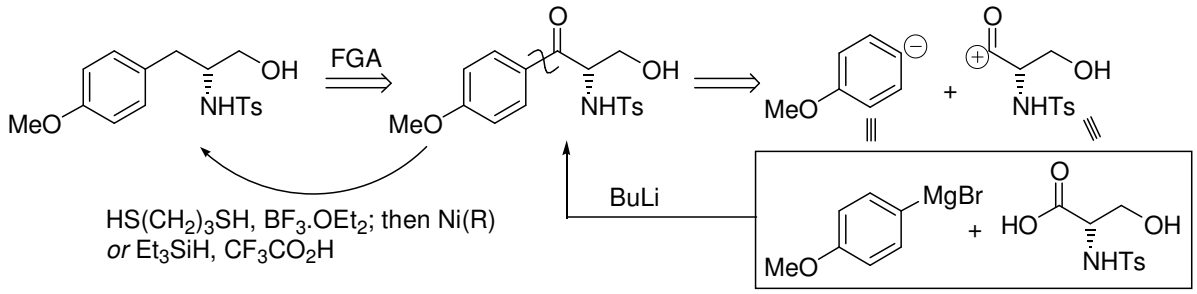
convergent synthesis

Functional Group Additions (FGAs)

This was mentioned earlier, in the contexts of enolate reactions, where an ester was retrosynthetically added to a ketone to reduce ambiguity and potential side-reactions in the enolate. Crucial to the success of any FGA-based approach is:

- The availability of the precursor indicated by the FGA – this may be a commercially available substance, or one that is easy to make
- the ability in the forward direction to remove the functionality once it has served its purpose as a control element. Also, remember that FGAs may involve addition of a functional group within the same molecule...

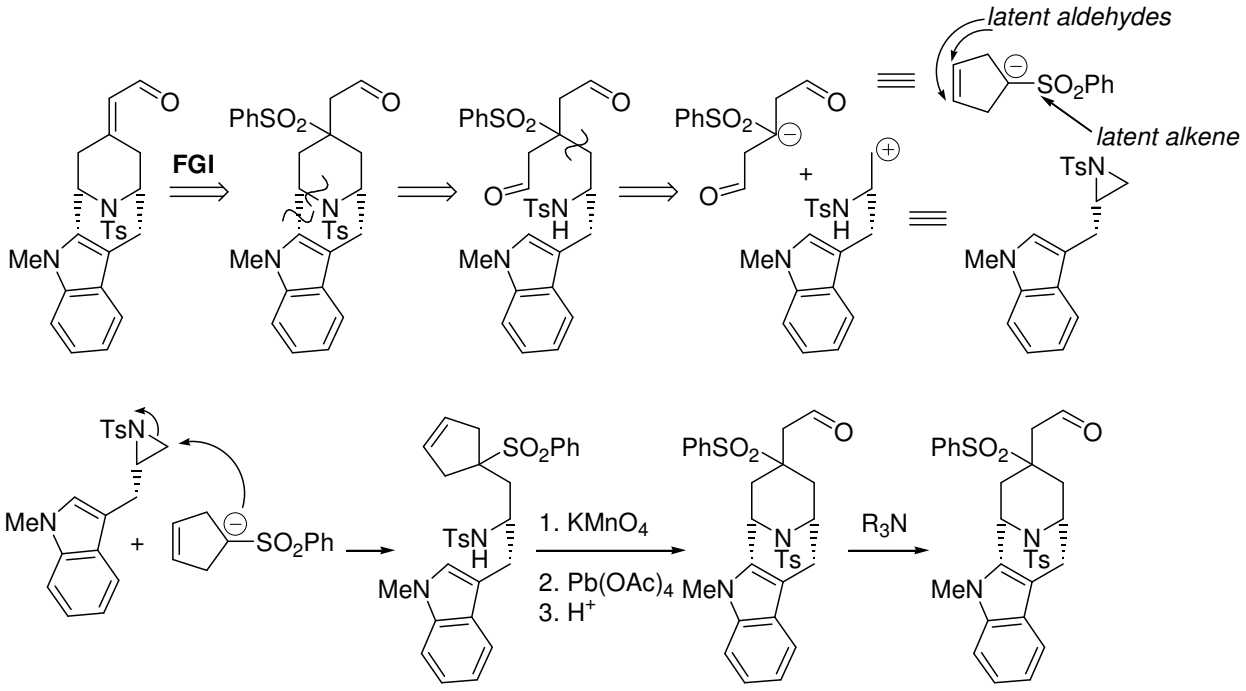
SCHEME B



Surrogate Functionality

You already know about the use of certain functional groups as polarity reversal elements (*umpolung*: AA lecture 4). These groups were masked versions of the functional groups ultimately required, which showed opposite reactivity to that of the masked group. Other groups behave as surrogate functional groups and masked structural motifs without necessarily showing this role reversal in the way they react…

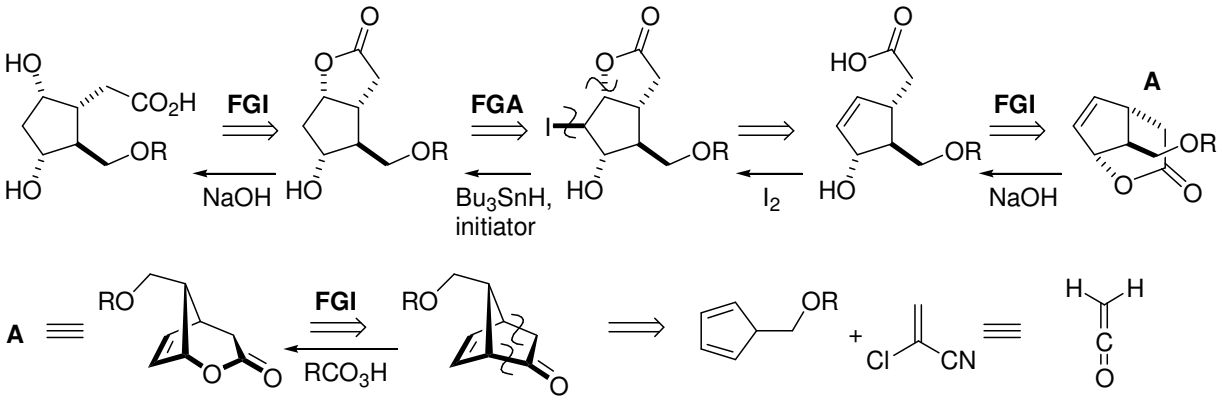
SCHEME C



The Use of Cyclic Intermediates for the Control of Regio- and Stereochemistry

The special three-dimensional structure of polycyclic systems may be exploited in syntheses which deliver target molecules which are structurally less complex than some of the intermediates. A classical example of this is in E J Corey's (sole recipient of 1990 Nobel Prize for Chemistry) synthesis of biologically active molecules called **prostanoids**…

SCHEME D



Next (and last) time (Wed 25th Feb at 11am): synthesis old and new…