

Organic Synthesis Part 2 - Functional Group Interconversions

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6 lectures

Recommended texts:

General: “Organic Chemistry” by Clayden, Greeves, Warren and Wothers, OUP, 2001
“March’s Advanced Organic Chemistry”, M.B. Smith and J March, Wiley, 5th edn (£50, but a good investment!)

“Oxidation and Reduction in Organic Synthesis”, T.J. Donohoe, OUP primer

Aims of course: To build on the lectures by Donald Craig and introduce students to the 'tactical' aspects of functional group interconversions. To provide students with the synthetic armoury which, in combination with the first part of the course, will allow the design and execution of simple organic syntheses which are chemo, regio-, and (where required) stereoselective.

Course objectives: At the end of this course you should be able to:

- Select an appropriate reagent for a given transformation covered within the course, in the context of molecules which you may not have met in the course (ie apply your knowledge)
- Be able to explain, at the level of your colleagues, the mechanistic rationale underpinning any issues of selectivity in the reaction (chemo, regio-, stereo- and enantioselectivity);
- Be ready to apply this knowledge with that from Donald Craig's course to tackle problems in small molecule total synthesis.

Course content:

1. Introduction to FGIs. Introduction to classes of reducing agent. Reduction of C=X bonds.
2. Reduction of CO₂R and related functions.
3. Reduction of C-C multiple bonds.
4. Reduction of C-X bonds.
5. Oxidation of C-H bonds bearing no heteroatom.
6. Oxidation of CH-OH groups.
7. Oxidation of olefins.

Notes for the course are available at: <http://www.ch.ic.ac.uk/local/organic/tutorial/>
There is also a link here to useful resources such as lists of definitions of acronyms!

Functional Group Interconversions - Lecture 1

Background and general principles

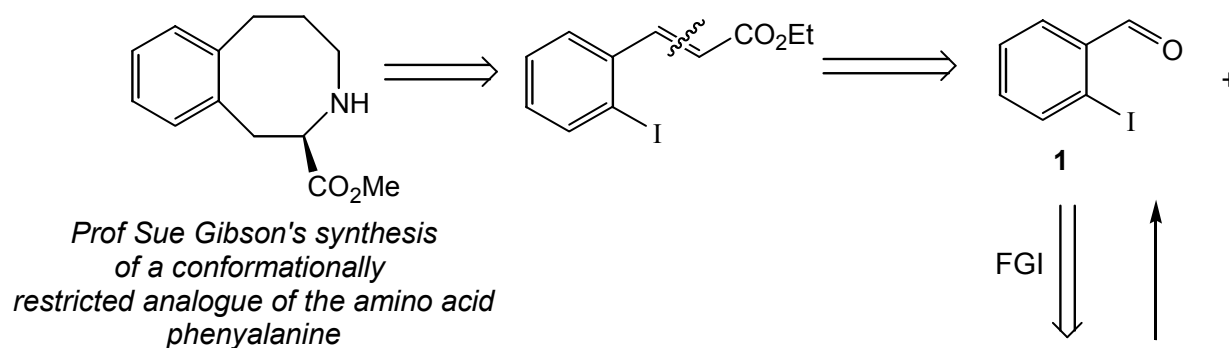
What is a functional group interconversion?

It was defined by Stuart Warren as *"the process of converting one functional group into another by **substitution**, **addition**, **elimination**, **oxidation** or **reduction**, and the reverse process used in (retrosynthetic) analysis."*

We can easily think of examples of each of these categories. So that's what FGIs are; the next question is why might we want to bother? There are four common reasons for carrying out FGIs (and including them in retrosynthetic analysis):

1. Unavailability of starting materials

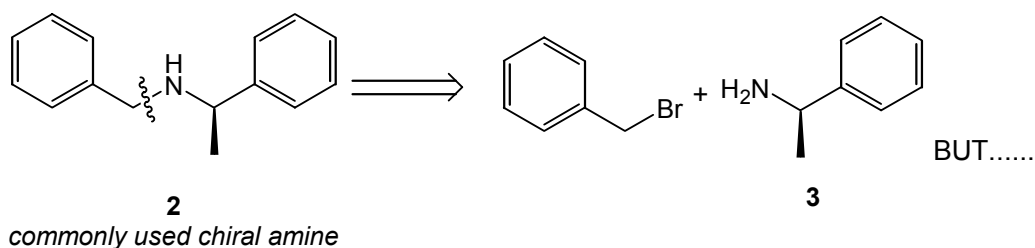
FGI's are often needed to convert commercially available compounds (e.g. from Aldrich) into desired synthetic intermediates. For example, in the synthetic scheme below, the required iodoaldehyde **1** was not (at the time) commercially available. However, the corresponding alcohol was, and this could be oxidized to give **1**.



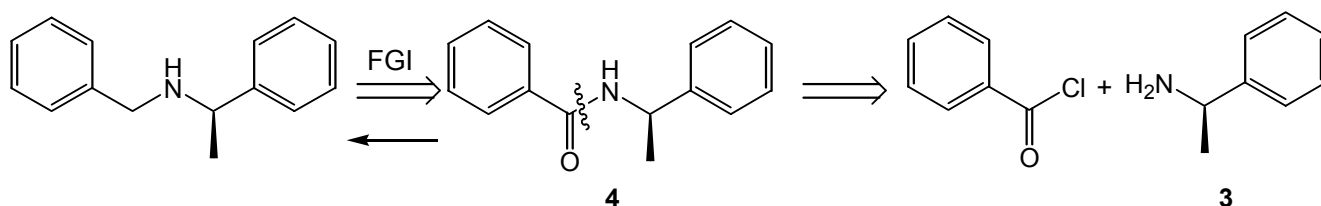
2. Adjustment of functionality after use of a known, reliable reaction

Sometimes, direct preparation of a desired FG is not possible or is inefficient, and so FGI's are often needed to convert the products of reliable reactions into the desired FG.

For example, the "obvious" disconnection to make the useful chiral amine **2** is shown below, and involves alkylation of the amine **3**. Unfortunately, amine alkylations of this type are often difficult to control and over-alkylation results. A much better synthesis can be achieved using FGI, namely reduction of the amide **4** which in turn can be prepared by acylation of the amine **3**. Acylation of amines is much more reliable than alkylation because amide nitrogens are much less nucleophilic than amine nitrogens, and so over-reaction does not occur.

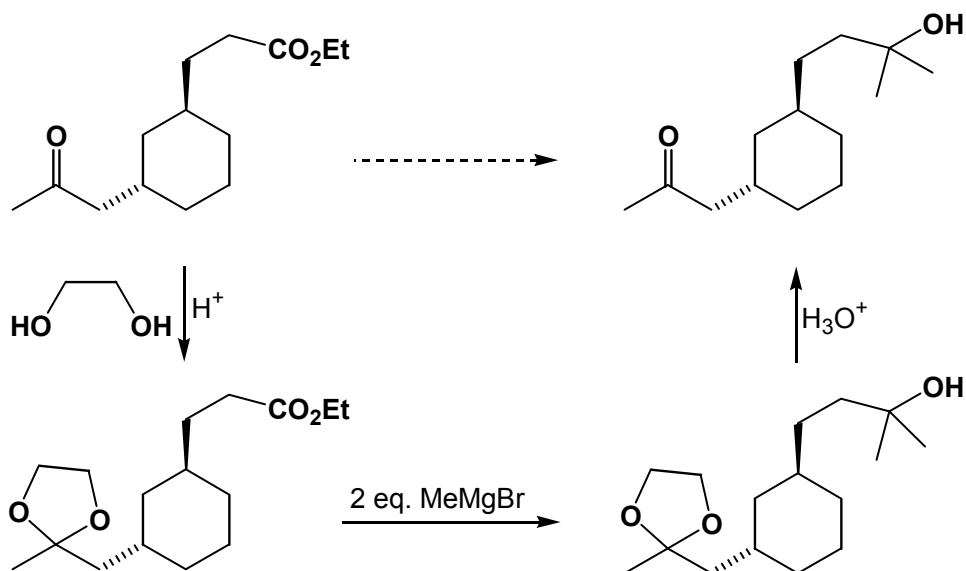


A much better route involves TWO steps:



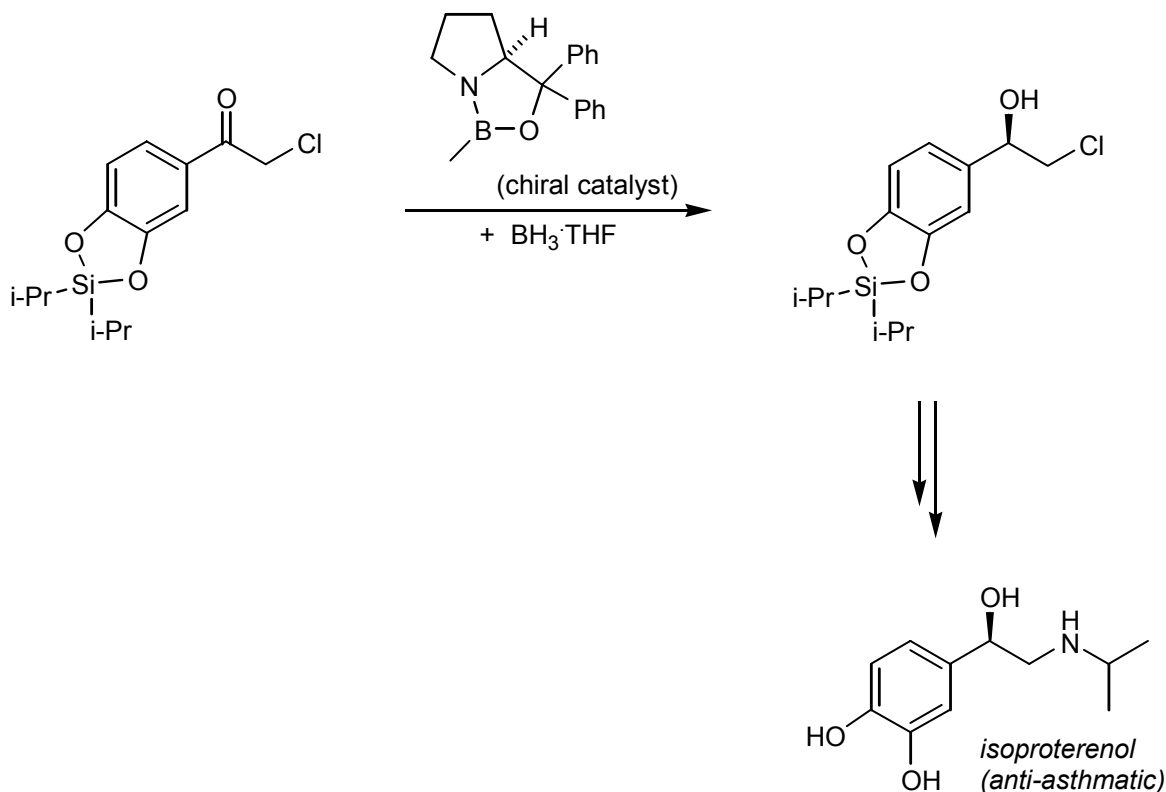
3. To mask reactive functionality in a molecule

Often, reagents are not available to effect the desired selective reaction of one FG in the presence of another. A common tactic to get round this is to temporarily mask or protect one FG. (We will look at this concept in more detail later in the course.) For example, if we want to add Grignard reagent to the ester in the molecule below without reacting the ketone group, we can't do this directly since the ketone is more reactive towards Grignards than the ester. One solution is to temporarily *protect* the ketone as an acetal, which can later be hydrolyzed under acidic conditions to unmask the ketone.



4. (**VERY** important nowadays!)- To introduce asymmetry into molecules

FGI reactions – especially oxidations and reductions – are some of the most important and efficient reactions currently available for what's called asymmetric synthesis, which requires the control of stereochemistry. This is crucial for the synthesis of many important molecules, particularly pharmaceuticals where two enantiomer (mirror image) forms may have quite different biological activities.



So that's what FGI's are and why we do them. In this course we'll be concentrating on oxidation and reduction (although some of the oxidations of olefins could equally well be regarded as additions), since the addition, elimination and substitution chemistry is pretty well taken care of from first year. We'll start our tour of FGI's by looking at reduction processes. Here are the main classes of reducing agents:

Main classes of reducing agent

Three main classes of reducing agent are commonly used in organic synthesis: Hydrogen itself; hydride reagents; and dissolving metals. Each has associated advantages and disadvantages, as well as useful selectivity that we will try to understand mechanistically.

1. Catalytic hydrogenation

Hydrogen is **CHEAP!!!** Its reductions are also often what's called "atom efficient", since the two H atoms are often transferred to the organic molecule being reduced with no waste. Hydrogenation of alkenes (to alkanes) and of aldehydes/ketones (to alcohols) are especially important industrial processes.

Hydrogen is not a good reducing agent on its own - apart from combustion, H_2 alone is pretty unreactive. So we need a catalyst to weaken or break the H-H bond to make it reactive. The catalysts we use fall into two categories, heterogeneous and homogeneous:

- (a) *Heterogeneous* - usually transition metals or their salts (e.g. Pd, PtO_2), often supported on an inert carrier (e.g. charcoal, alumina, clay). A key advantage of heterogeneous catalysts is in the ease of separation of the insoluble catalyst at the end of the reaction. Vigorous stirring of the reaction may be needed to speed up reaction at the liquid-solid interface.
- (b) *Homogeneous* - The latter are often soluble transition metal complexes. A classic example is Wilkinson's catalyst, $(Ph_3P)_3RhCl$, discovered in this Department (Wilkinson received the Nobel Prize in 1973 for his pioneering contributions to organometallic chemistry). The advantage of homogeneous catalysts is that we can tune the ligands and the metal to achieve selective reductions (chemo- and enantioselectivity). Of course, separation of the catalyst may be more difficult than with heterogeneous systems.

2. Hydride transfer reagents

Essentially transfer "H" as a nucleophile, although be aware that H^- is **NOT** a nucleophilic species and NaH, LiH, KH etc are **NOT** good reducing agents (they are used as bases). There are two subclasses of hydride transfer reagents: ones which act as nucleophiles directly, and those which are electrophilic and require activation by a Lewis base before they donate hydride. This mechanistic difference can lead to very useful differences in reactivity and selectivity!

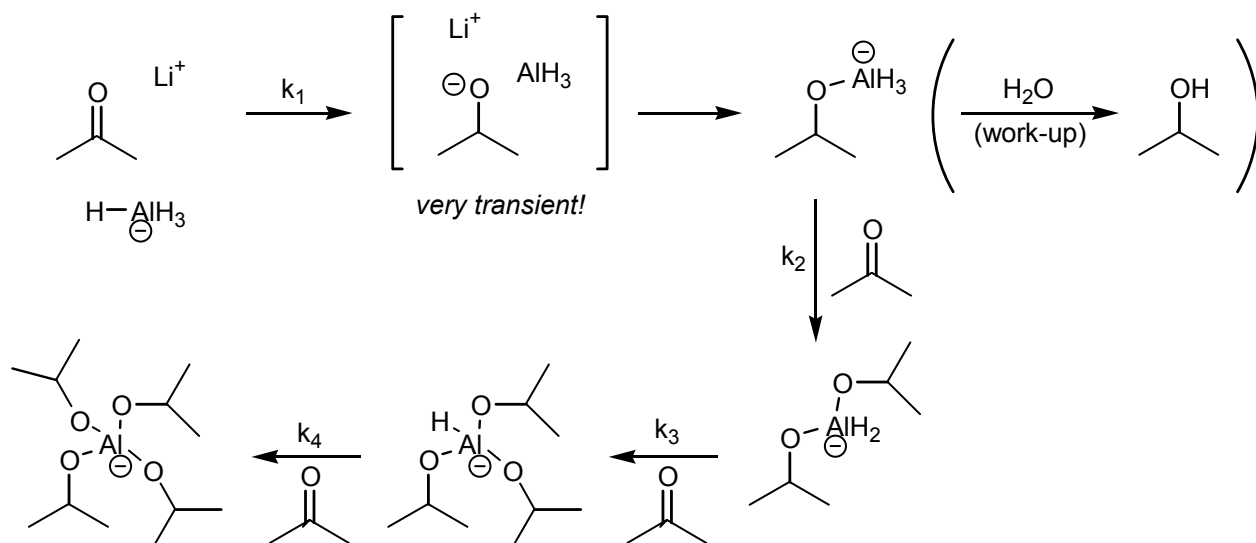
(a) 'Nucleophilic' hydride reagents

(i) Lithium aluminium hydrides

The parent compound is $LiAlH_4$ (lithium aluminium hydride, LAH or 'lithal'). It is a **VERY** moisture sensitive grey compound which reacts violently with water and other protic solvents. It is therefore used in **DRY**, aprotic solvents. Ethereal solvents such as Et_2O , THF and DME are best, giving usable suspensions of the reagent.

LAH is a **VERY** reactive reducing agent and reduces most functional groups relatively indiscriminately.

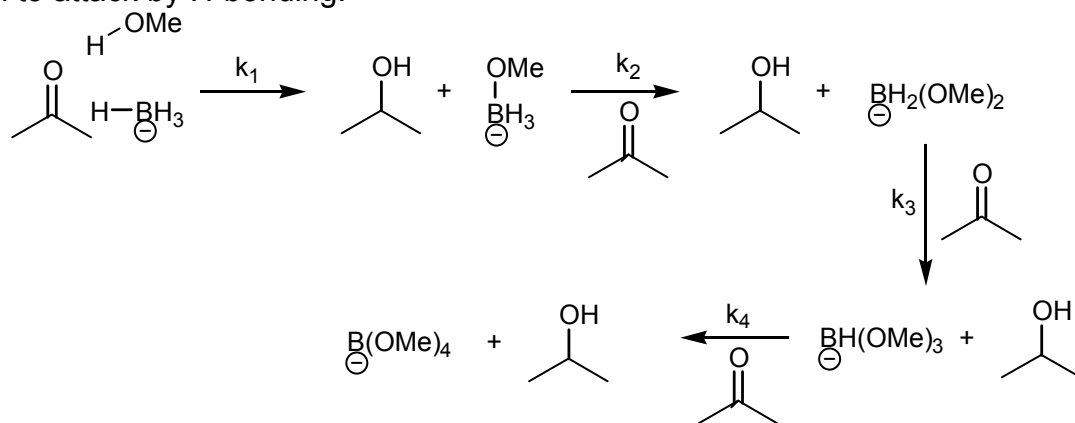
The mechanism for $LiAlH_4$ reduction of carbonyl compounds is shown below and involves donation of hydride, to give a transient alkoxide/alane pair which combines to give an alkoxytrihydroaluminate. This can go on to donate the remaining three hydrides in the same way, although at a reduced rate (*i.e.* $k_1 > k_2 > k_3 > k_4$). We can exploit this by deliberately making and using trialkoxyaluminiumhydrides (e.g. $LiAlH_4 + 3^tBuOH$ gives $LiAlH(O^tBu)_3$, which is a relatively mild and selective reducing agent).

**(ii) Sodium borohydrides**

The parent compound is NaBH_4 (sodium borohydride) which is available as a white powder. It is only moderately reactive towards protic solvents ($\text{H}_2\text{O} > \text{MeOH} > \text{EtOH}$) and is usually used in ethanolic solution.

It is less reactive than LAH; **for example, it reacts only slowly with esters, making it possible to reduce ketones or aldehydes in their presence.**

The mechanism involves the solvent (MeOH in the Scheme below), which helps to activate the carbonyl to attack by H-bonding:



Unlike LAH, substitution of the hydrides by alkoxy groups ($-\text{OR}$) **INCREASES** the rate of addition (*i.e.* $k_1 < k_2 < k_3 < k_4$). However, substituting the hydrides by electron withdrawing groups such as acetate or cyanide can give rise to more selective reducing agents, *e.g.*

- $\text{NaBH}(\text{OAc})_3$ sodium triacetoxymethylborohydride (can sometimes give useful selectivity for reduction of aldehydes over ketones)
- NaBH_3CN sodium cyanoborohydride (stable at low pH....see later for its use in imine reduction!)

Next time (Thurs 27th Nov at 9am): other reducing agents and $\text{C}=\text{X}$ reductions.

AA 13.11.03