

## Protecting Groups in Organic Synthesis

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### Selectivity in Organic Synthesis

Creating a complex target molecule with a sequence of reactions, including intermediary re-functionalization with a correctly placed skeleton, is often a challenging task. One of the key issues in such endeavor is chemoselectivity. Protecting groups play an important role in multistep organic synthesis to improve the chemoselectivity in subsequent steps.

### What is a Protecting Group?

As depicted in Figure 1, a protecting group (PG) is a molecular framework which is introduced onto a specific functional group (FG) in a multi-functional molecule to mask its reactivity.

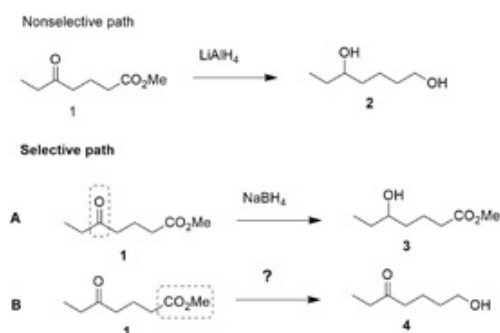


Figure 1.

A good protecting group must be readily, but selectively introduced into the specific functional group, should not be sensitive to the reagents and conditions applied in the subsequent step and should be capable of being removed under mild conditions.

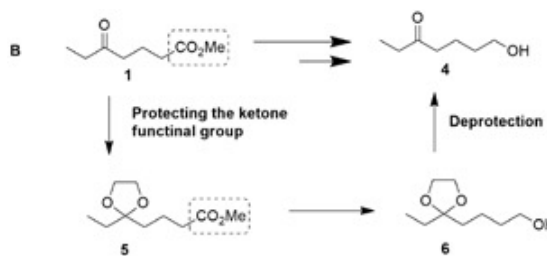
### Why use Protecting Groups?

Protecting group is a necessary tool to address the difficulty of selective manipulation of a specific functional group in a multifunctional molecule.



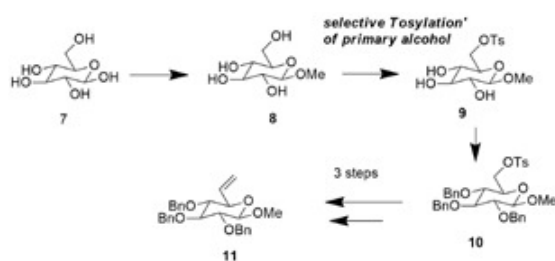
Scheme 1.

Let us consider the reduction of keto-ester 1. Keto and ester functional groups are commonly encountered electrophilic functional groups in organic chemistry. Nonselective reduction could be easily achieved using a stronger reducing agent such as Lithium aluminum hydride. With carefully manipulated reaction conditions, chemoselective reduction of the keto group could also be achieved. However, there is no reagent for the chemoselective reduction of ester group. The point of significance in the above discussion is that selective transformation in many cases are quite challenging and masking with a protecting group would only be the alternative approach. As shown in scheme 2, ketal formation under mild condition, assist the chemoselectivity in the subsequent reduction step and the de-protection of ketal could be achieved under mild acidic conditions.



Scheme 2.

While simple starting materials are often sought in a plan, chemoselective challenges associated with functional groups are not always orthogonal. Monosaccharides are among the popular starting materials in complex molecular synthesis. Protecting group manipulations are always a priority and indispensable determinant of a successful sugar based synthesis plan. As depicted in scheme 3, olefination of C6 became possible on strategic manipulation of primary and secondary alcohol groups prior to 3 steps de-protection, oxidation and Wittig sequence.



Scheme 3.

Commonly encountered functional groups and their protecting strategies are depicted in Figure 2. These functional groups often demand deactivation by masking with a protecting groups as they are reactive towards nucleophilic or electrophilic reagents.

Functional group	Protecting group

Figure 2: Commonly encountered functional groups and their protecting strategies

### Protecting-group-free (PGF) Synthesis

Over the years various parameters have been developed to quantify the efficiency of an organic synthesis. One such parameter is step economy. R. H. Grubbs, 2005 Nobel laureate in chemistry, stated that “the major challenges in synthetic organic chemistry are the construction of molecules without using protecting groups and the ability to put molecules together in fast and efficient ways”. Although multistep chemical synthesis, also known as total synthesis, was held high esteem for many decades, the current trend is shifting towards the scalability of a synthetic plan. One of the current pioneers in synthetic organic chemistry, Phill Baran recently stated that “natural product synthesis is in the scalable era”. The art of the modern day synthesis

is mostly defined by the practicality of the synthesis. One area that offers prospects along this line is minimization of the use of protecting groups in a synthesis.

In reality, protecting group manipulations involve a protection (applying) step and a deprotection (removal) step, introducing at least two steps into the synthesis while incurring the costs from additional reagents and waste disposal. Synthesis with more protecting group manipulations generally leads to a reduced overall yield. However, with the invention of novel chemoselective reaction methodologies, limited number of protecting-group-free (PGF) syntheses were spotted in the literature. Currently being limited to moderately complexed targets, PGF concept has not been fully explored.

In conclusion, protecting groups empower chemical synthesis. Although it requires some extra effort with bearing the criticism of not being the “ideal synthesis”, incorporation of protecting groups is simply unavoidable in complex molecular synthesis.