

# Protection of OH group of alcohol

طالبة الماجستير

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Alcohols represent a cornerstone class of functionalized molecules essential to the basics of organic chemistry. A wide range of chemical and biochemical processes involve transformations of alcohols into valuable products and building blocks.

In this context, development of flexible tools to facilitate selective transformations of alcohol derivatives in multistep synthetic procedures is of great importance in organic and pharmaceutical chemistry.

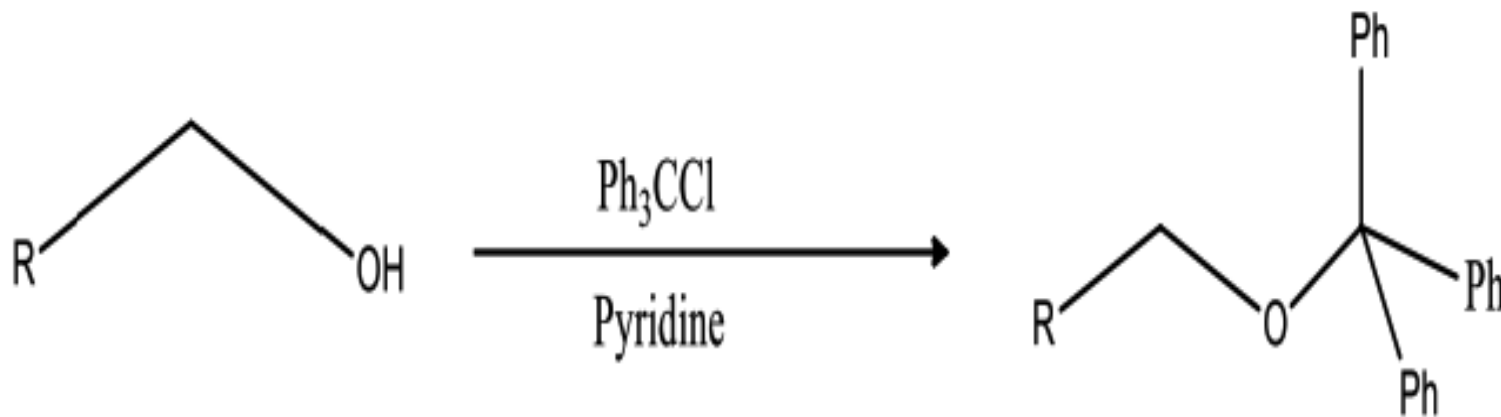
protection strategy eliminates the acidic proton on the alcohol, and also reduces the nucleophilicity and basicity of the oxygen atom by steric hindrance and / or electronic effects.

When we choose a suitable protection group, the following features must be considered :-

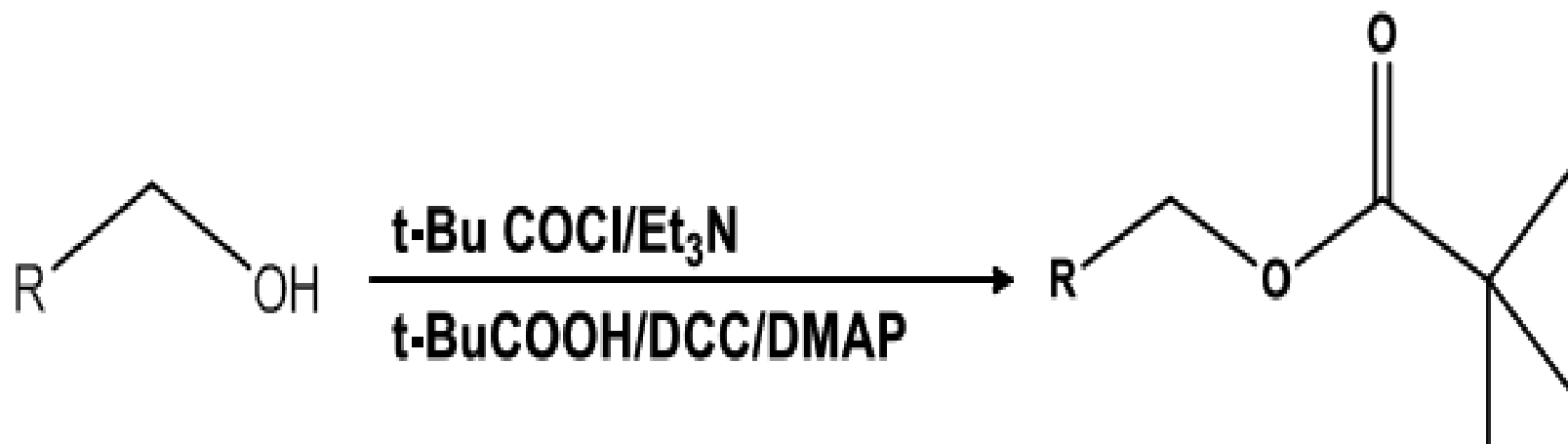
- Cheap and commercially available.
- Simple to put in high yield .
- Stable to reaction conditions .
- Easy to remove in high yield .

# Principle of protection of alcohol

- By putting a bulky protecting group on the hydroxyl oxygen which can sterically prevent it from competing effectively for electrophiles.



❖ By delocalizing the lone pairs of electrons by conjugation



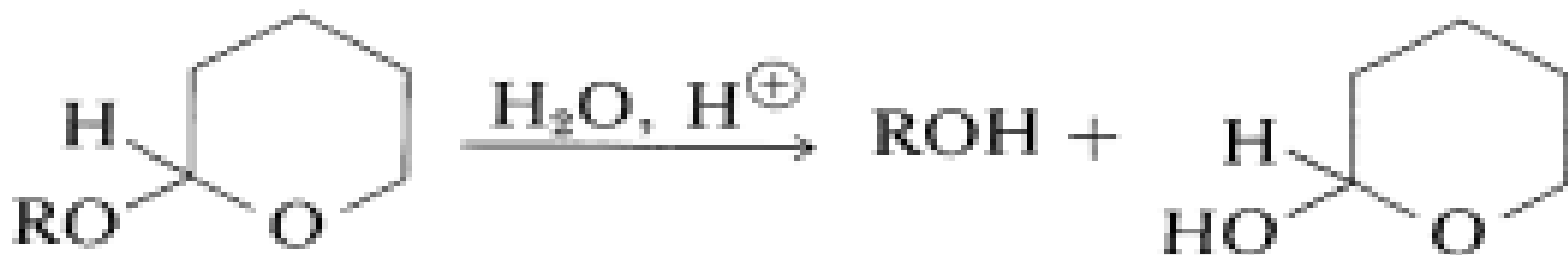
## **acetal or ketal as protecting group for alcohol**

- Commonly used ketals include :
  - Tetrahydropyranyl (THP) derivatives,
  - methoxyethoxymethyl (MEM) derivative
  - methoxymethyl (MOM) derivative

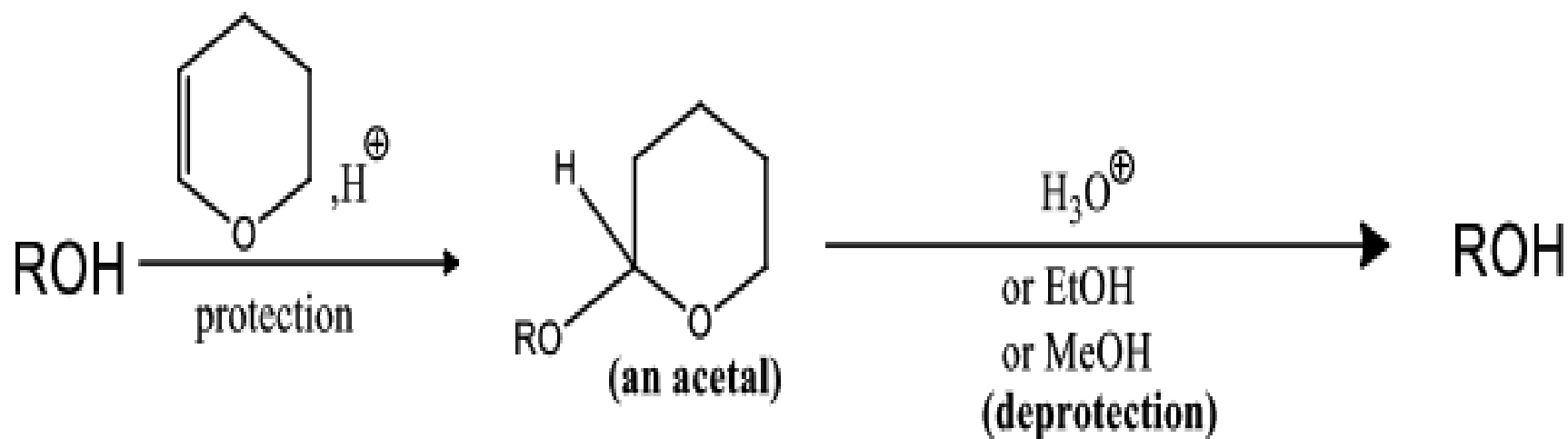
- An excellent reagent to form acetals is the unsaturated cyclic ether. This ether adds alcohols in the presence of an acid catalyst to give the acetal :



The 3-oxacyclohexene (dihhydropyran) protecting group can be removed readily by treating the acetal, with aqueous acid:

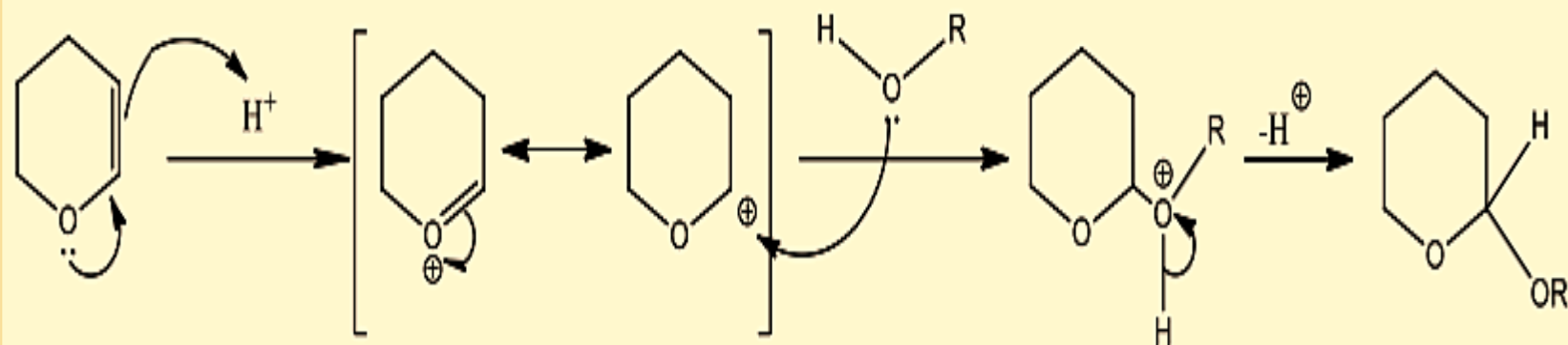


- Acetals / ketals are simply removed by treatment with aqueous acid.

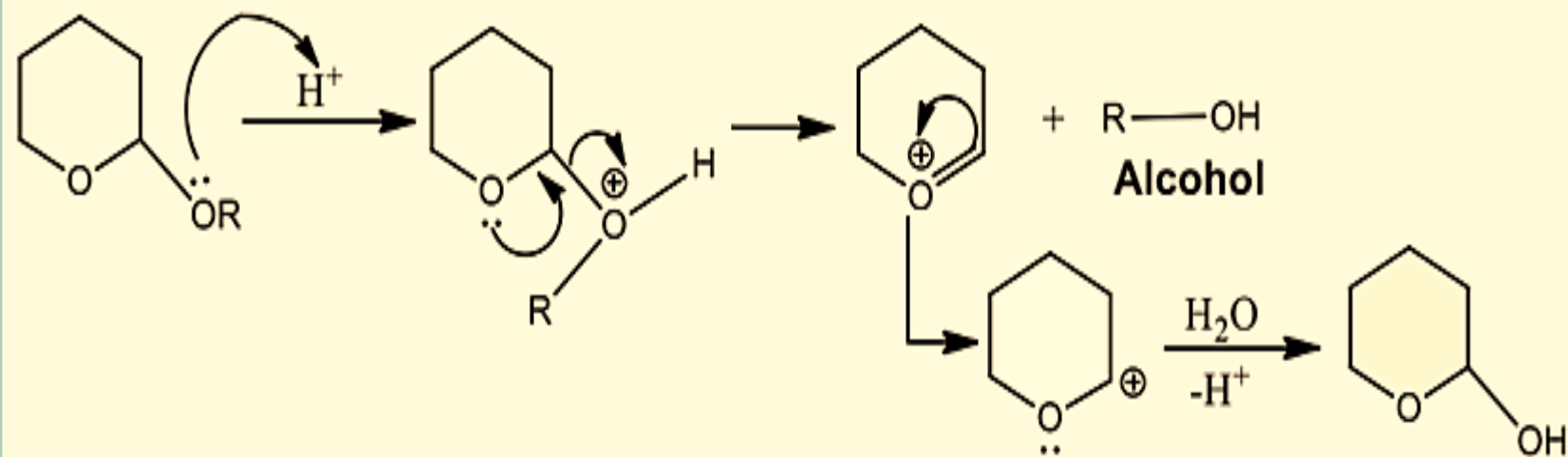




## Mechanism of Protection:-



## Mechanism of Deprotection:-

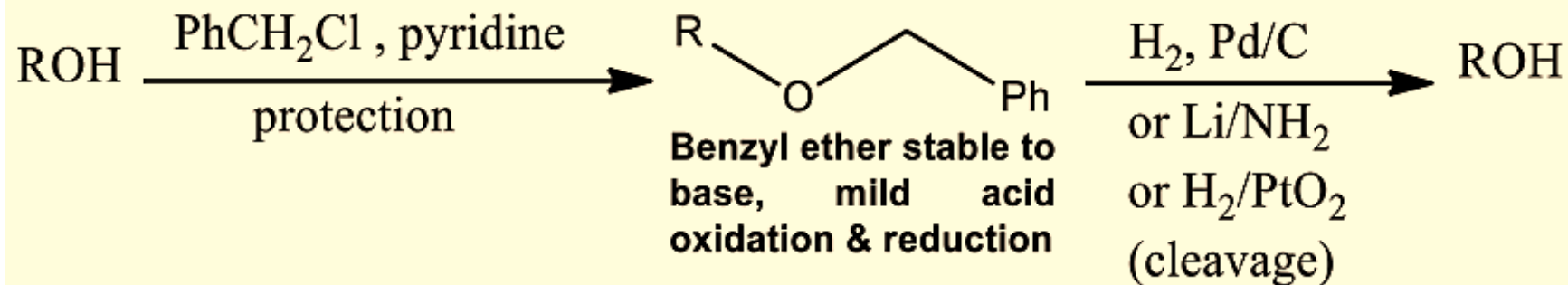


# Ether as protecting group for alcohol

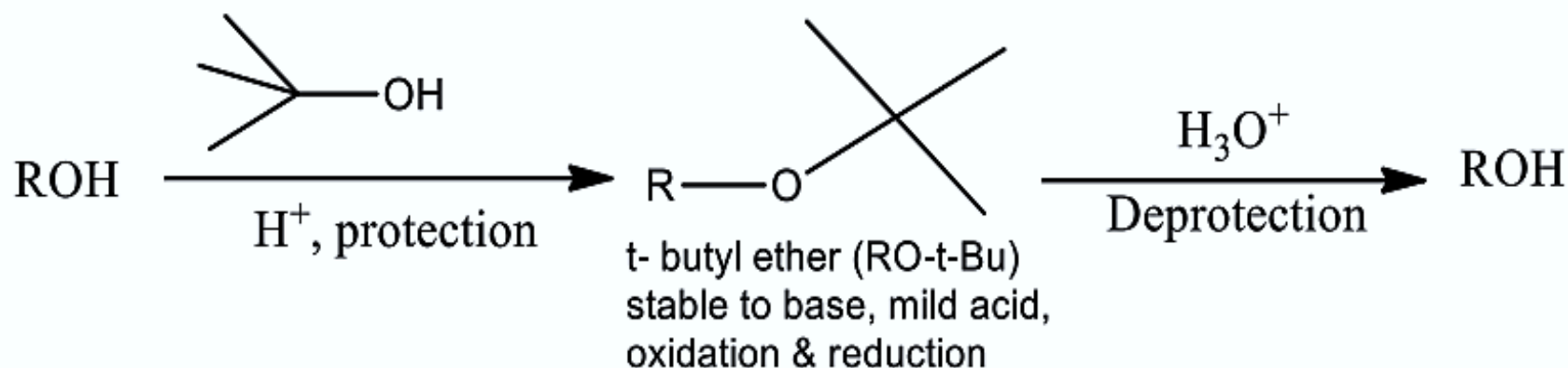
- It is relatively stable in harsh conditions (acidic, basic, reflux, etc.)
- enhance the reactivity due to electron-donating effect.
- More compatible to the conditions needed for deoxygenation or amino (azido) substitution
- Selective protection is possible
- they do not react with oxidizing /reducing agents and are inert to organometallic reagents.
- However, this stability means that many others are not easily cleaved to their parent alcohol under mild conditions. Therefore, only certain ethers, which are easily cleaved under mild conditions, are commonly used as protecting groups for alcohols.

## For example:-

**Benzyl ether** which are converted to alcohols under neutral conditions by catalytic hydrogenolysis.

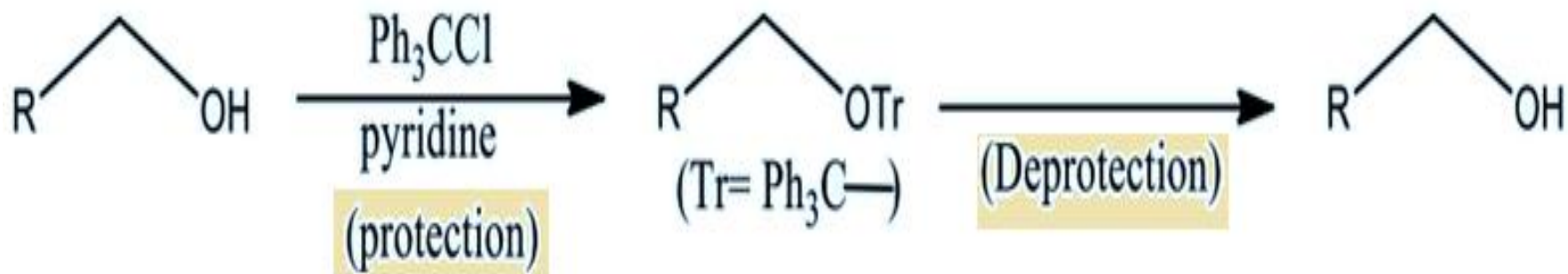


➤ **t-butyl ethers** which are readily hydrolyzed with dilute acid.



## -Tri-phenylmethyl as protecting group

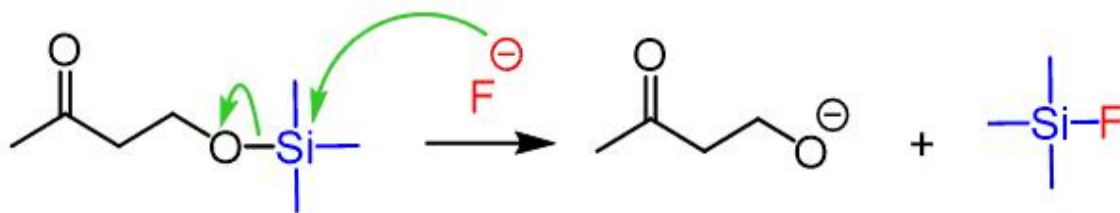
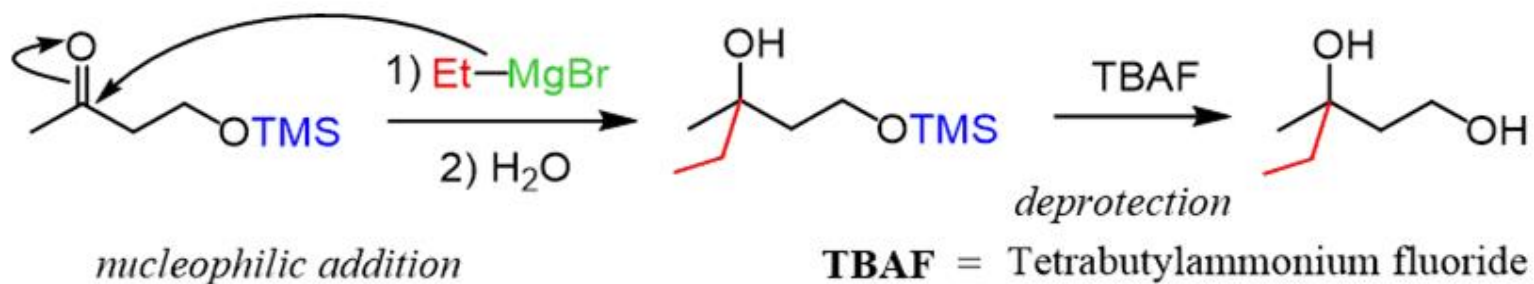
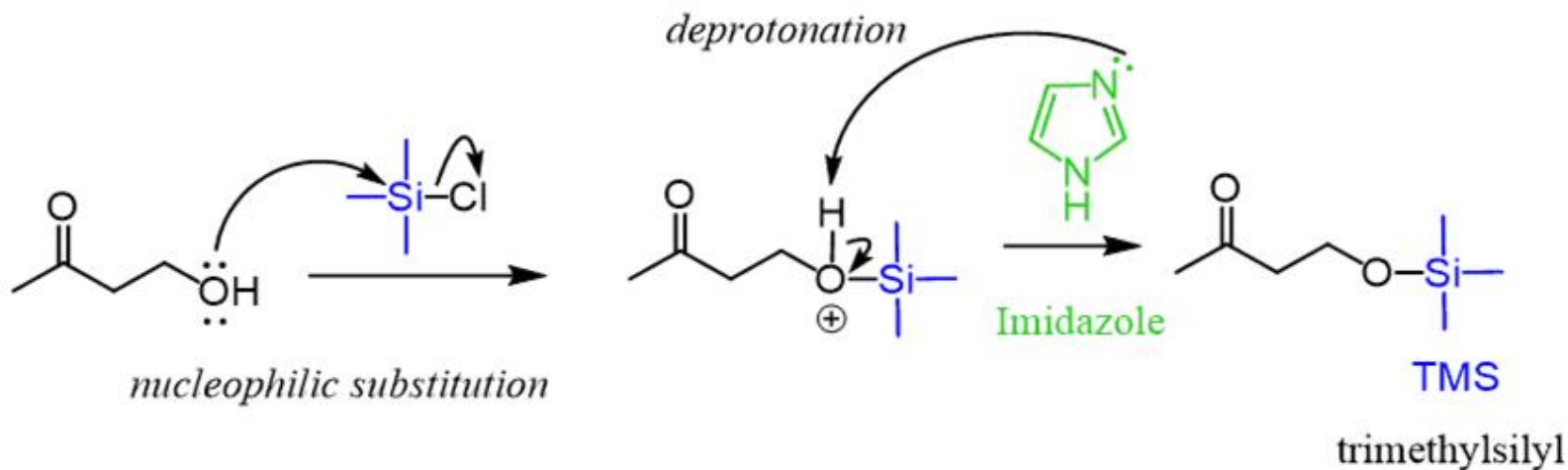
Only 1°- alcohols react at a useful rate with trityl-chloride in pyridine so selective protection of 1°- hydroxyl groups is possible. Deprotection by catalytic hydrogenation .



## -Trimethylsilyl ethers as protecting groups

- Trimethylsilyl ether (TMS)
- Triethylsilyl ether (TES)
- Triisopropylsilyl ether (TIPS)

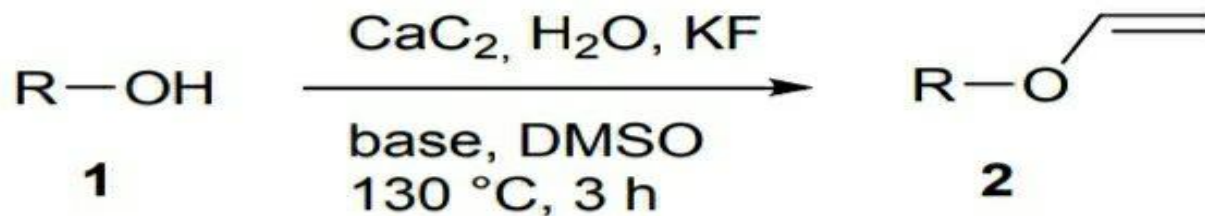
## Protection and deprotection of alcohols by a common silyl ether - trimethylsilyl (TMS)



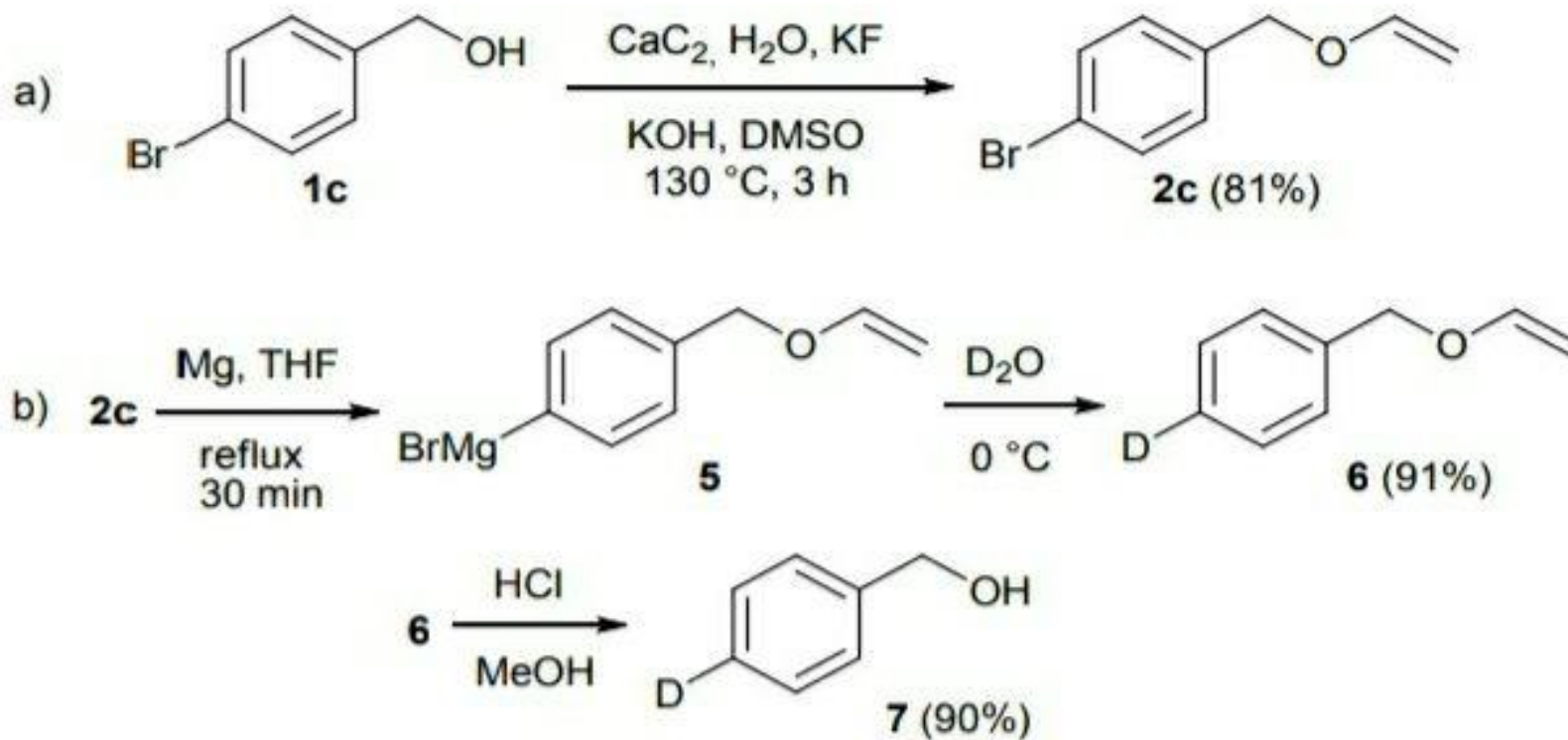
## **the vinyl moiety as a protecting group**

The vinyl protecting group (by using calcium carbide-mediated vinylation ) is base-resistant though easily removable by acidic hydrolysis.

This simple and cost-efficient protection/deprotection protocol is suitable for primary and secondary alcohols and phenols.

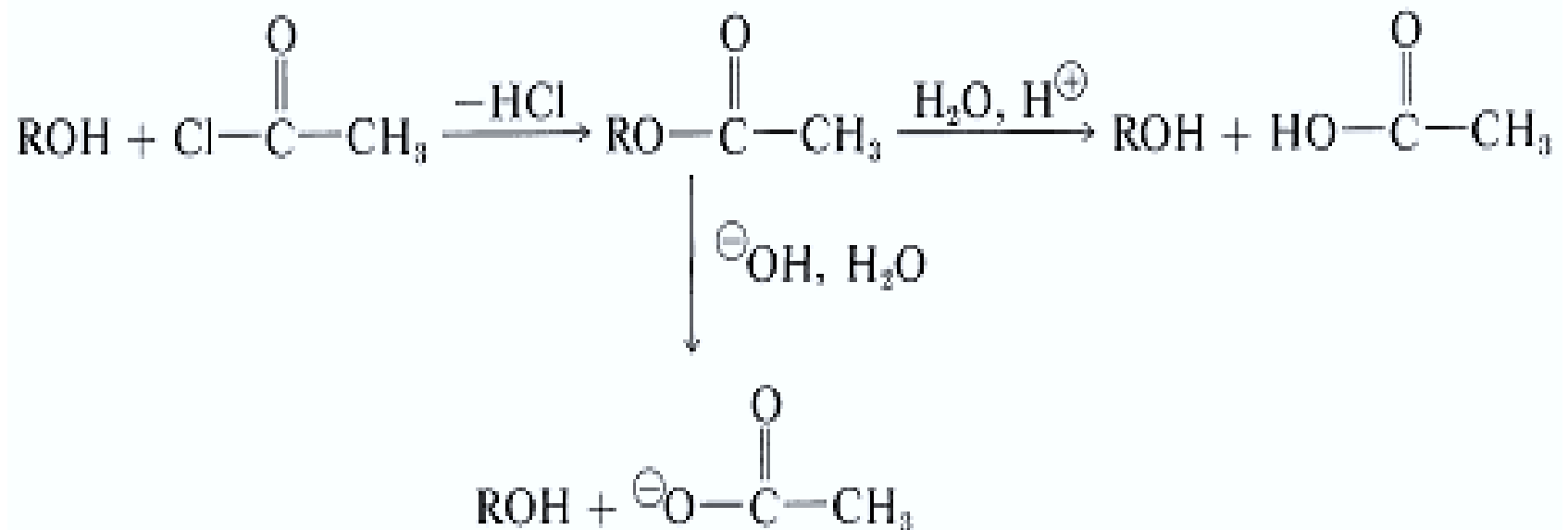


example:



## Ester as protecting group for alcohol

ester are formed from alcohol and acyl halide, anhydride, or acid, the alcohol can be regenerated easily by either acid or base hydrolysis of ester.

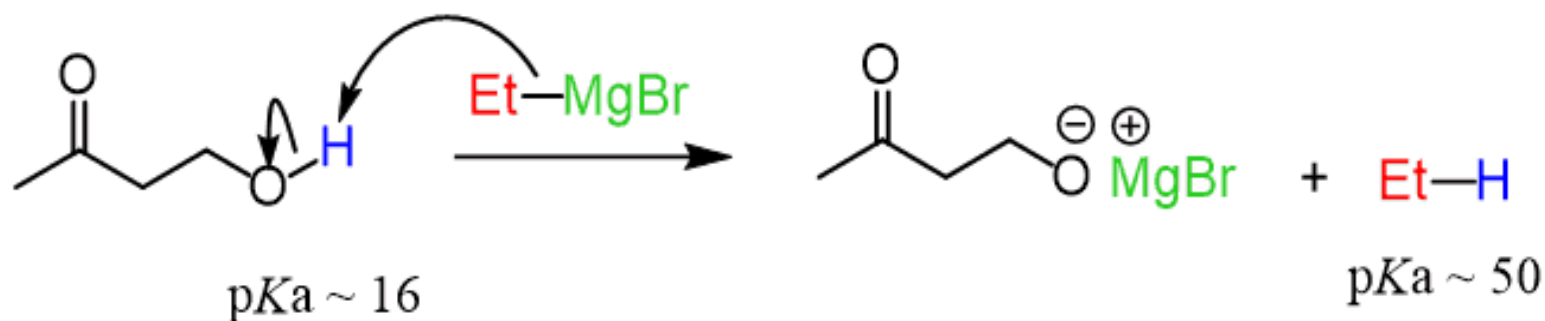




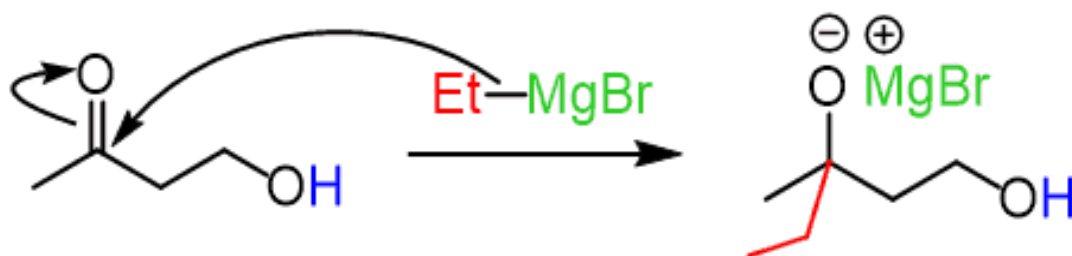
## Example of reaction when we need protection of alcohol functional group

- The problem here is that Grignard reagents are strong bases, and will react with even weak acids (like alcohols). If we try to make a Grignard on a molecule with an acidic functional group, we'll end up destroying our Grignard instead. So that one way around this problem is to protect alcohols as some kind of inert functional group (like an ether) which doesn't react with our grignard

## Grignard reagent is good nucleophiles and very strong base



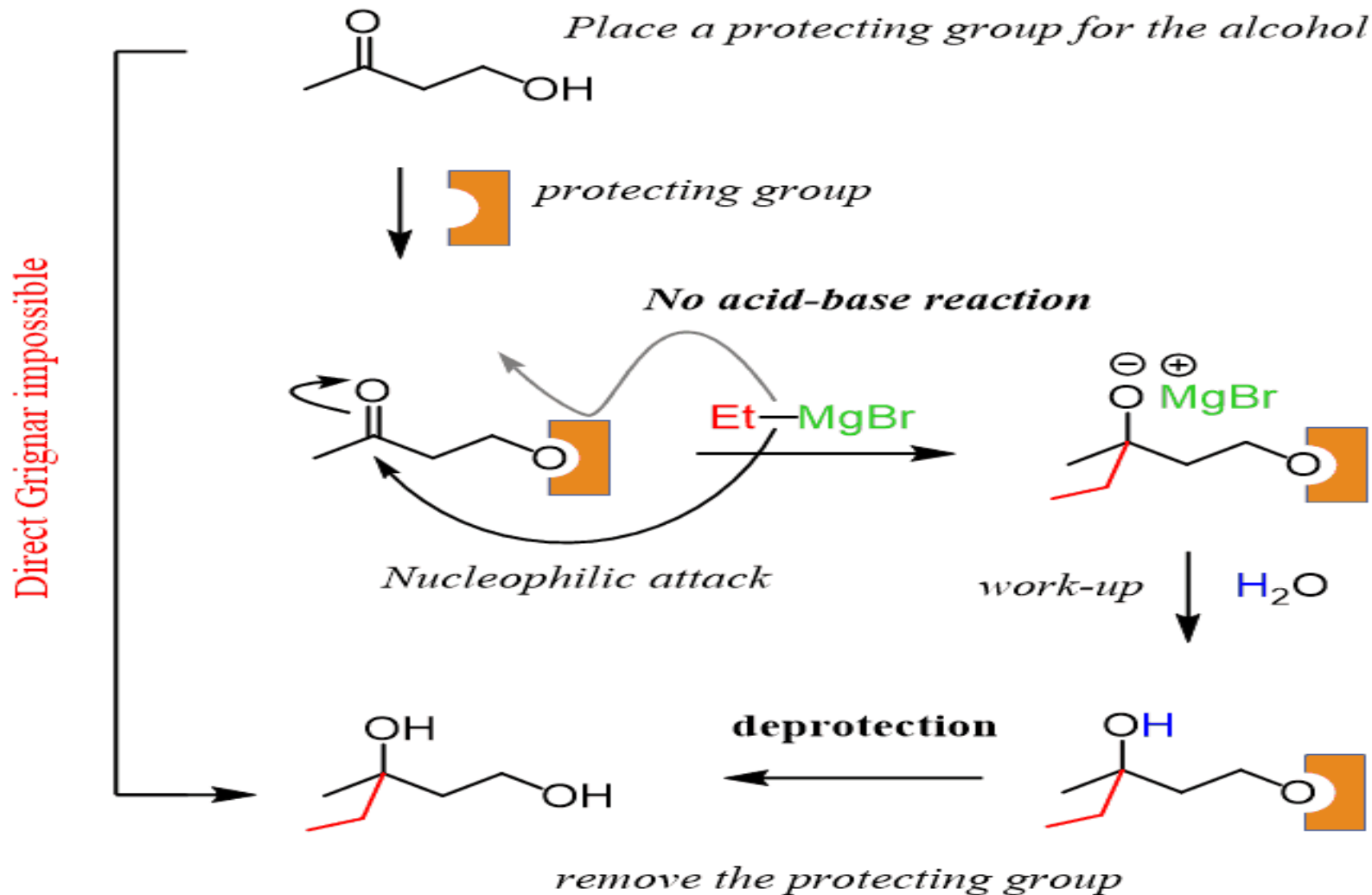
### Acid-Base reaction



### Nucleophilic addition reaction

*These two reactions compete and the acid-base reaction occurs before the nucleophilic attack*

# How the protecting group works in a Grignard reactions



# References

- Protection (and deprotection) of functional groups in organic synthesis by heterogeneous catalysis  
Giovanni Sartori, Roberto Ballini, Franca Bigi, Giovanna Bosica, Raimondo Maggi, Paolo Righi *Chemical Reviews* 104 (1), 199-250, 2004
- Carey & Sundberg Chapter 13.1 problems # 1; 2; 3a, b, c ; Smith: Chapter 7
- Issue 11, 202 From the journal: *Organic Chemistry Frontiers* Examining the vinyl moiety as a protecting group for hydroxyl (–OH) functionality under basic conditions

Thank you