LECTURE 5   REACTIONS HYDROXYL GROUPS PART I

NOTHING NEW OR MYSTERIOUS

The complications arise only because of there are so many of them!!

As nucleophiles, analog to non-sugar alcohols

The majority of the chemistry is related to the formation of esters and ethers.

Carboxylate esters

Acetates $–O(CO)CH_3$ or –OAc

Benzoates $–O(CO)C_6H_5$ or –OBz

Sulfonate esters

Tosylate $–O(SO_2)\ C_6H_4CH_3$ or –OTs

Mesylate $–O(SO_2)\ CH_3$ or –OMs

Triflate $–O(SO_2)\ CF_3$ or –OTf

Ethers

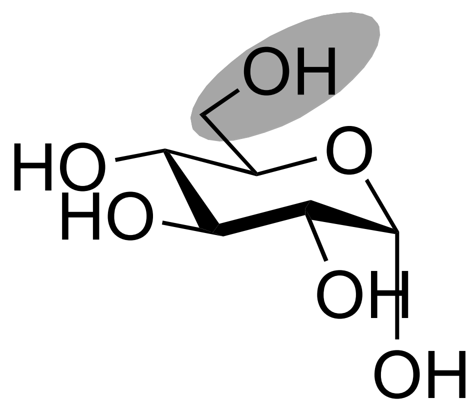
Benzyl $–OCH_2C_6H_5$ or –OBn

Trityl $–OC(C_6H_5)_3$ or –OTr

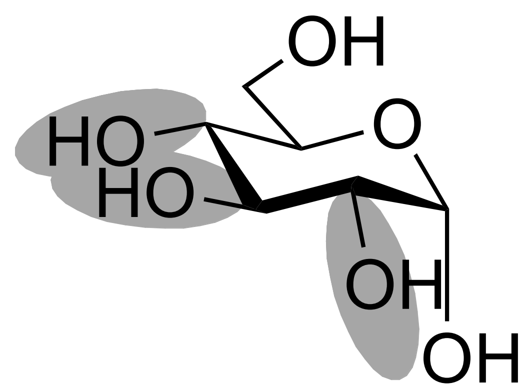
Trimethylsilyl $–OSi(CH_3)_3$ or –OTMS

Tert-butyldimethylsilyl $–OSi(CH_3)_2(C(CH_3)_3)$ or –OTBS or $–OSiMe_2Bu^t$ or -OTBDMS

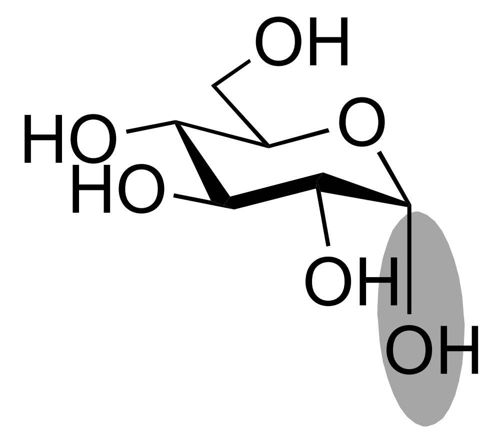
Tert-butyldiphenylsilyl $–OSi(C_6H_5)_2(C(CH_3)_3)$ or –OTBS or $–OSiPh_2Bu^t$ or -OTBDPS



primary OH-6



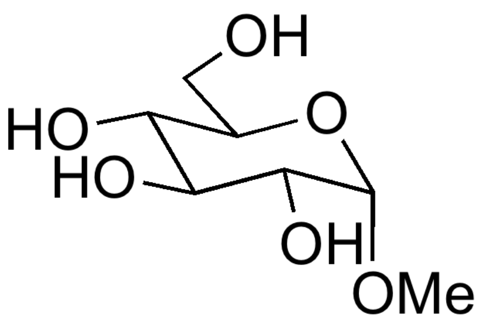
secondary OH-2,3,4

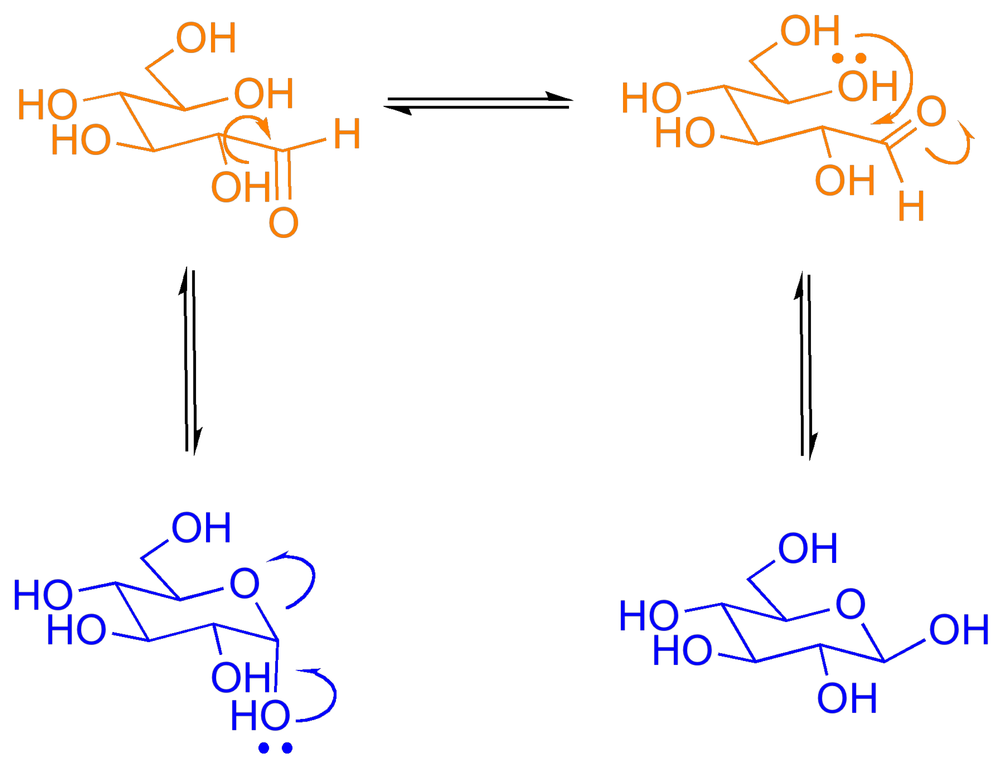


anomeric OH-1

The functionality at the anomeric center can react in two ways

as an alcohol or as an aldehyde





act as aldehyde to form acetal
Effectively protect the anomeric center and prevents further reactivity

Equilibrium of α- and β-hydroxyls at the anomeric position

Potential competing inter-conversion between α and β forms

inter-conversion between pyranose and furanose forms

Solubility: very polar in nature

very soluble in polar solvents, especially with possible H-bonding

Insoluble in non-polar solvents for organic reactions, pdt purification and manipulation

Selective protection of particular hydroxyl groups allows the regioselctive rxn of those unprotected

Common starting point: protect the majority or even all of the free -OH

- Acetylation
- Acetals
- Ether
- Ester
- Nucleophilic Substitution
- oxidation
- Reduction

Acetylation

Acetals

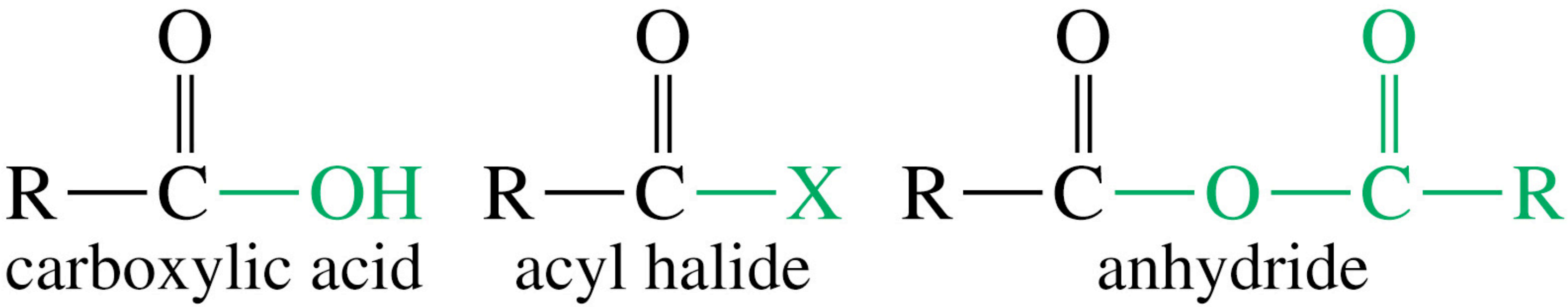
Ether

Ester

Nucleophilic Substitution

oxidation

Reduction



Esters: non-nucleophilic and stable to a wide range of Conditions

Frequently used protect groups

Less polar than the corresponding alcohols

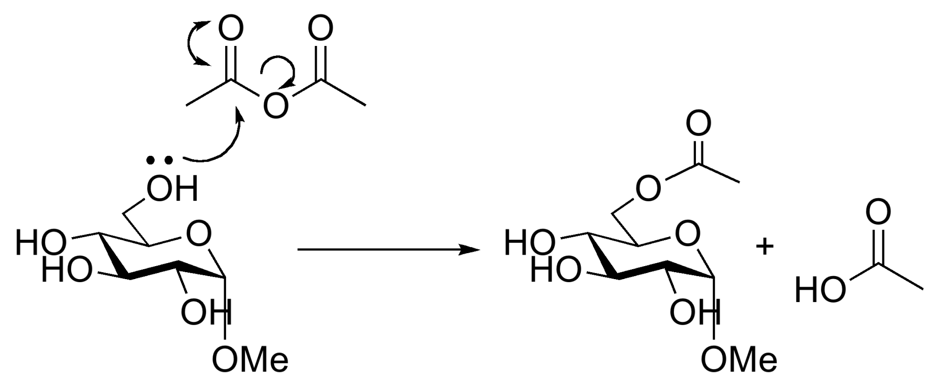
Acetylation

Most commonly used esters

Stirring the alcohol with acetic anhydride and a base

Base mop up the acetic acid generated, and catalyses the rxn itself

Nucleophilic catalysis and base



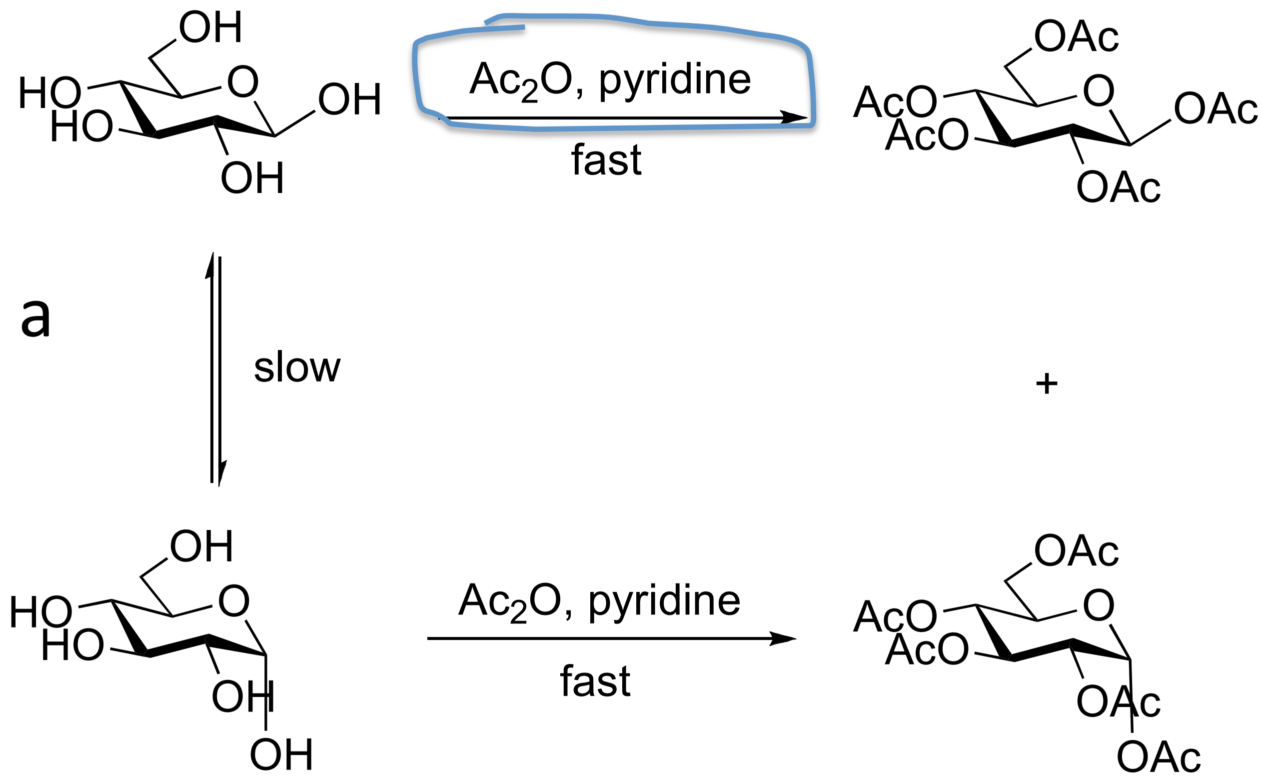
Uncatalysed rxn is very slow at rt

Lewis acid catalysis

But with possible competing process of mutarotation

1. Acetylation with acetic anhydride/ pyridine

Equal proportions as solvents



Sugars in a bottle is a mixture of α and β. /(py/fu)

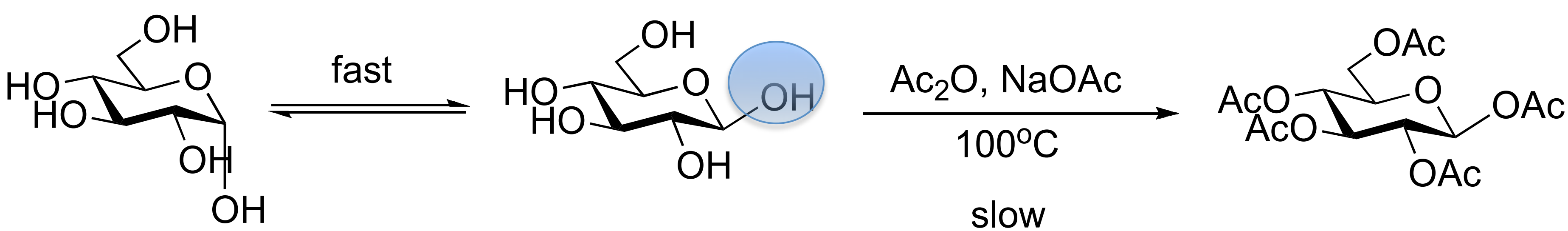
Ratio depends on particular sugars

2. Acetylation with acetic anhydride/ sodium acetate

Relatively weak base, sluggish rxn at rt

Carry out at 100°C, usually generate β-acetates

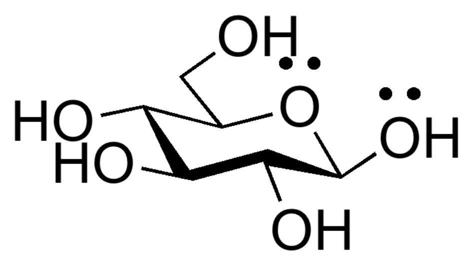
Mutarotation is much faster than the acetylation



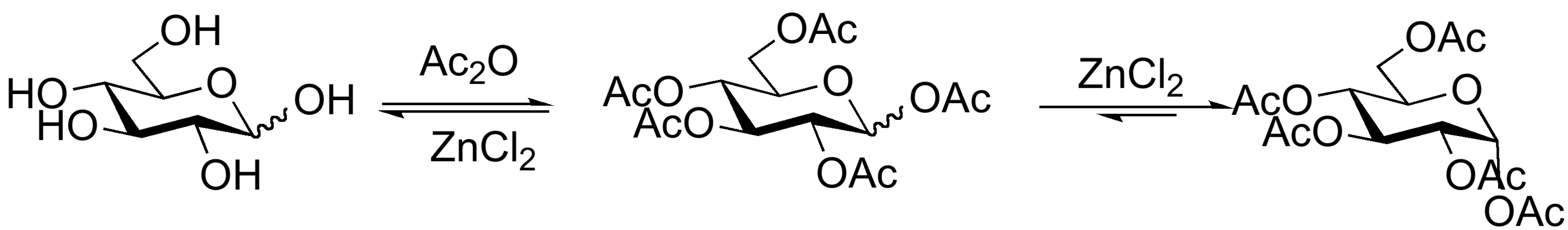
β Hydroxyl is more nucleophilic than the axial α one β- occupies a less hindered equatorial than the axial of α–

repulsive effect between the ring oxygen lone pair orbitals and the lone pair orbitals on the β-anomeric oxygen atom

Kinetic anomeric effect



3. Acetylation with acetic anhydride/ Lewis acid catalysis



Strong Lewis acid catalyses the equilibrium of α- and β-, after catalyses the rxn

Thus equilibrium of α- and β-acetates will occur after the rxn

Anomeric effect leads us α-acetates

Protecting groups

Satisfy several important criteria

1) They should be formed in good yield,

2) they should be stable to subsequent rxn conditions,

3) They should be readily removed under appropriate conditions

Acetylation

Acetals

Ether

Ester

Nucleophilic Substitution

oxidation

Reduction

Acetylation

Acetals

Ether

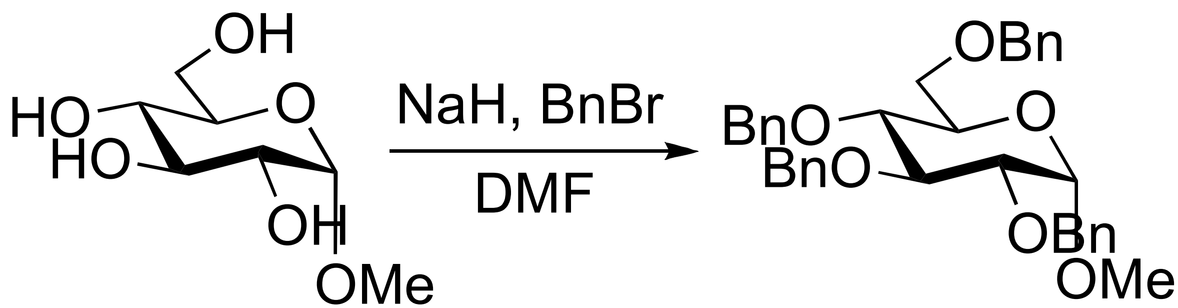
Ester

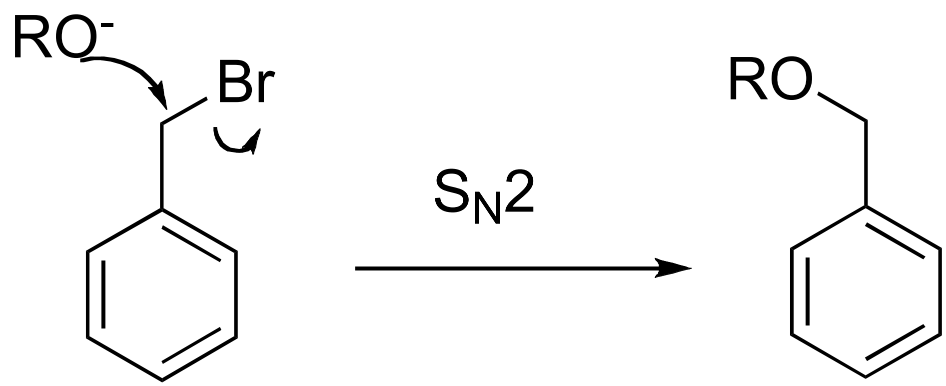
Nucleophilic Substitution

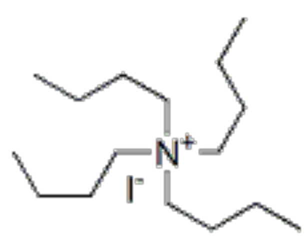
oxidation

Reduction

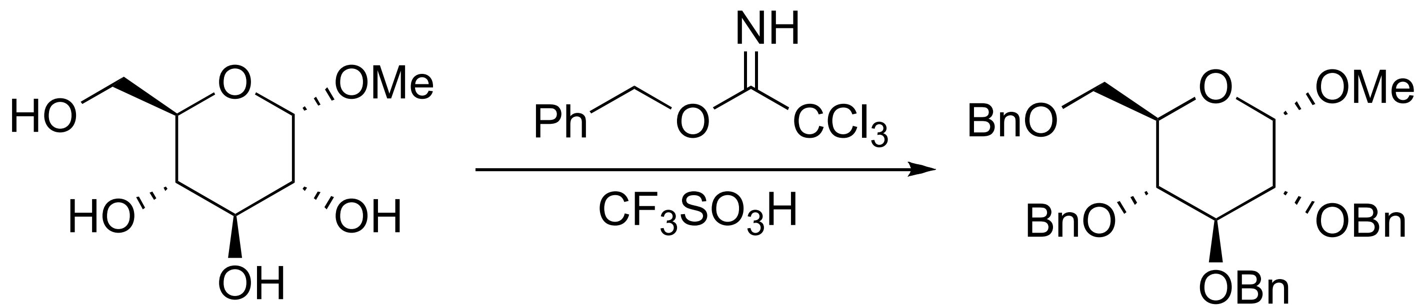
Benzyl ethers (ROBn)

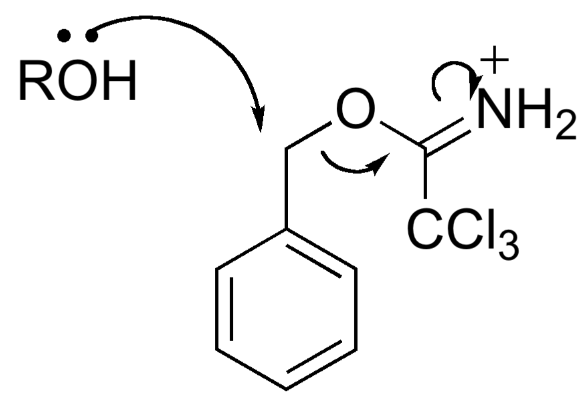






Tetrabutylammonium iodide


HO
O
OMe
HO
OH
OH
NH
Ph
O
CCl3
CF3SO3H
BnO
O
OMe
BnO
OBn
OBn


ROH
O
NH2
CCl3

Cleavage

Catalytic hydrogenation H_2

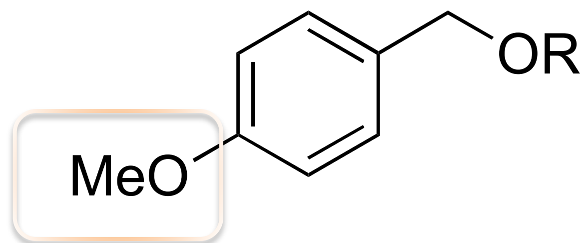
Heterogeneous catalyst

Palladium on carbon (Pd/C)

When the metal is distributed over finely-divided carbon, the surface area is larger and the catalyst is more reactive.

Palladium hydroxide (Pearlman's catalyst)

For the removal of sterically inaccessible/multiple benzyl groups

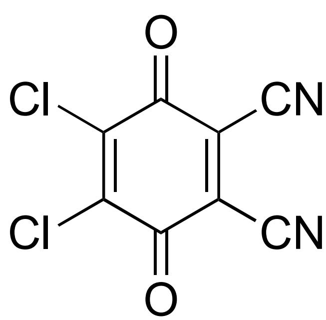


para-methoxybenzyl (PMB)

Single electron oxidising reagent

$(NH_4)_2Ce(NO_3)_6$

Ceric ammonium nitrate (CAN)



DDQ

2,3-Dichloro-5,6-Dicyanobenzoquinone

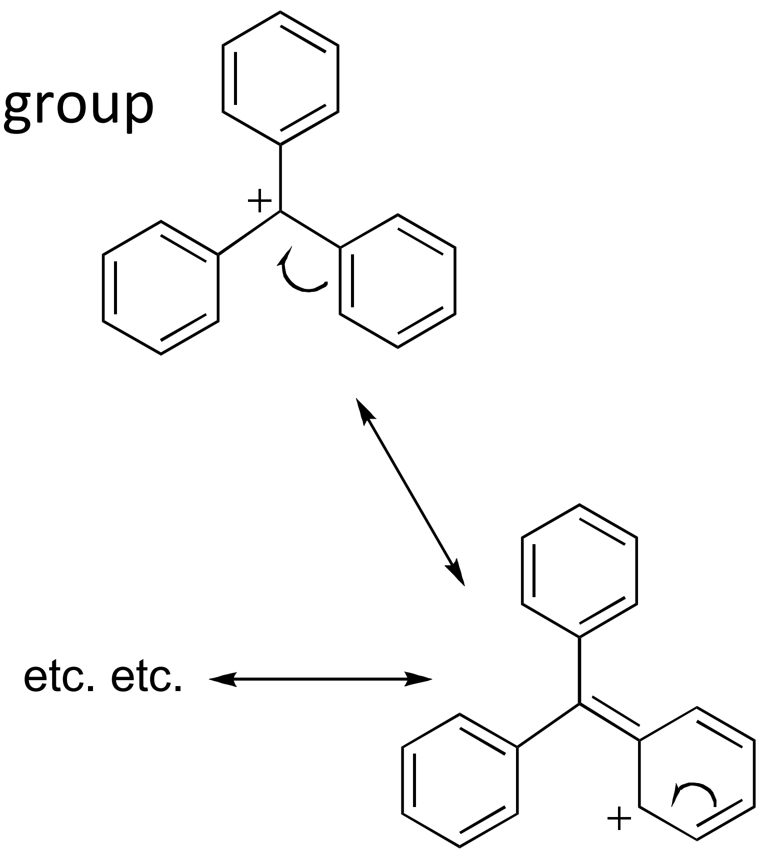
Trityl ethers

Triphenylmethyl ether

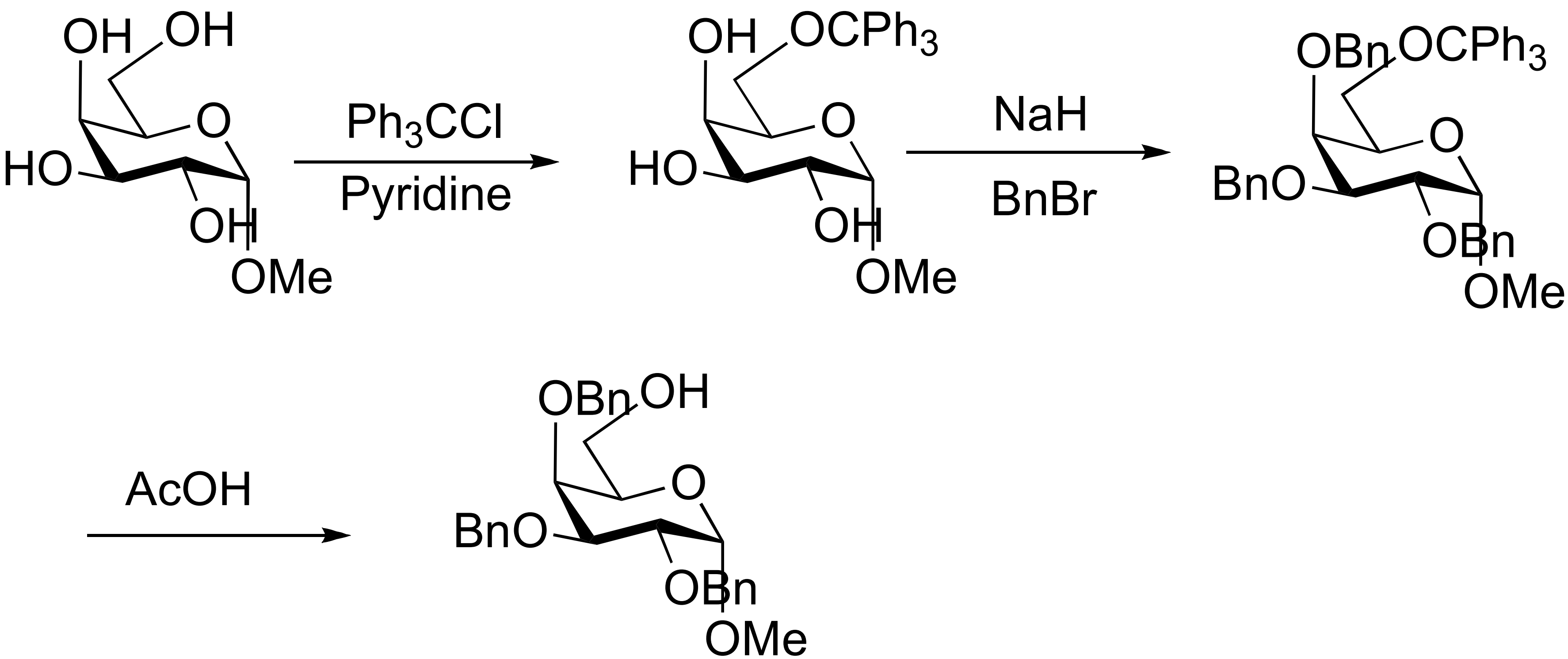
Very selective for the primary hydroxyl group

Formation via an SN1 type process

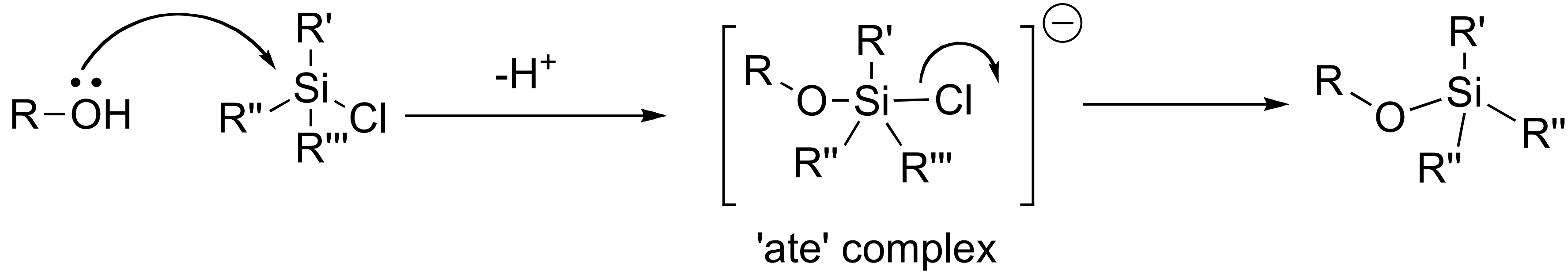
By treatment of unprotected sugar

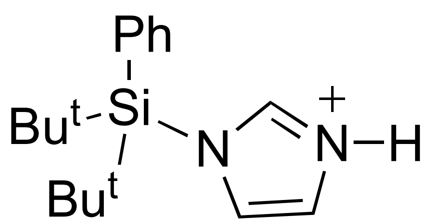


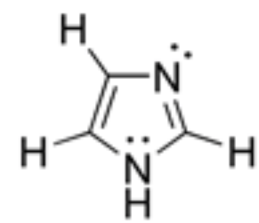
Resonance stabilisation
of the trityl cation


OH
OH
O
HO
OH
OMe
Ph3CCl
Pyridine
OCPh3
NaH
BnBr
OBn
BnO
AcOH

Silyl ethers

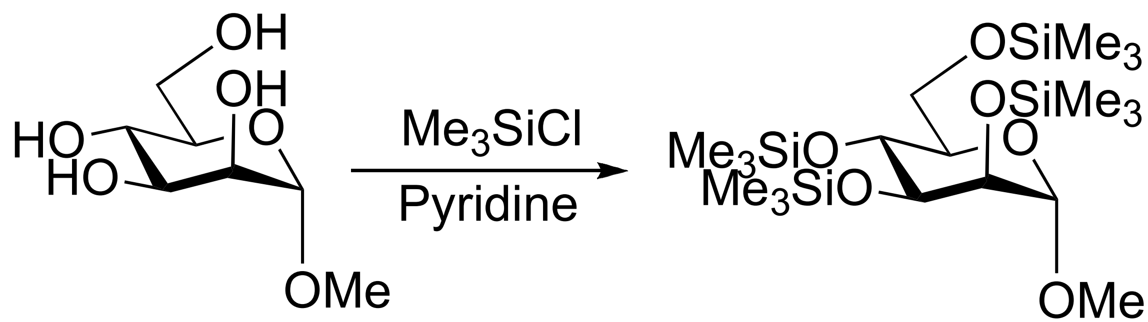




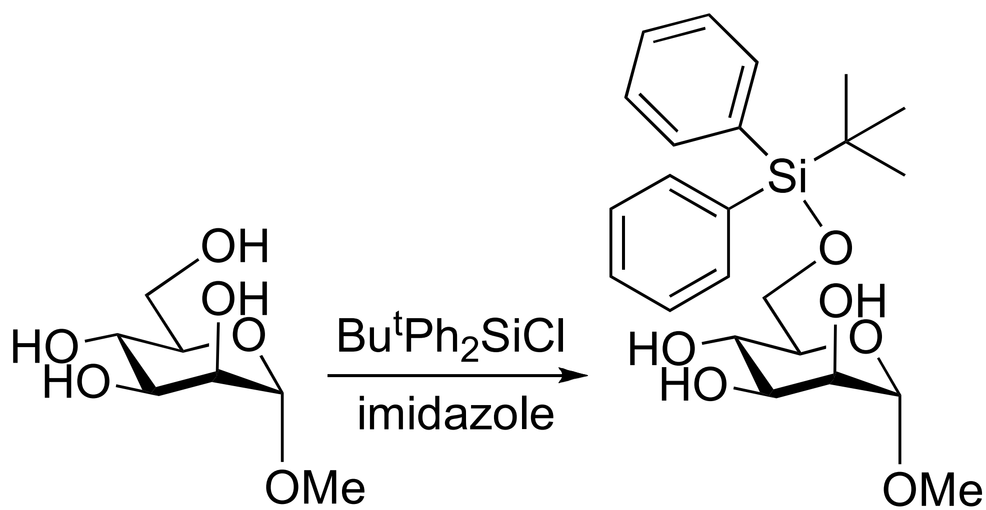


Imidazole acts as a nucleophilic catalyst and forms intermediates, e.g.

Trimethylsilyl (TMS)



Tert-Butyldimethylsilyl (TBDMS or TBS)



cleavage

acid, may also cause removal of othe racid labile protecting groups

Tetrabutylammonium fluoride (TBAF)

Relative rate of acid hydrolysis (stability increase in order)

R-OSiMe_3	1
R-OSiMe_2Bu^t	1E-3
R-OSiPh_2Bu^t	1E-5

Acetylation

Acetals

Ether

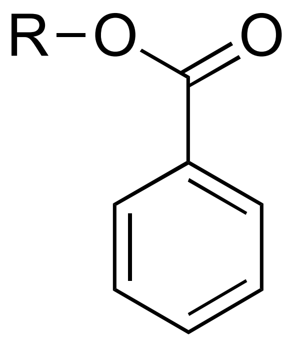
Ester

Nucleophilic Substitution

oxidation

Reduction

Acetate, and



= R---OBz

benzoyl ester

Removed by nucleophile

Most commonly methoxide in trans-esterification rxn

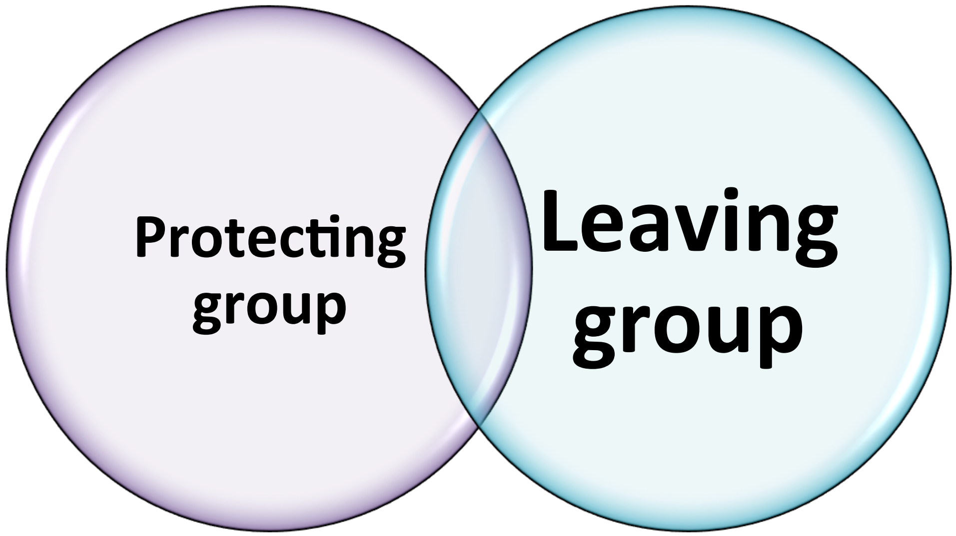
Potassium carbonate in methanol

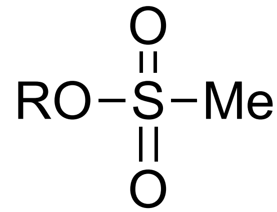
Sodium methoxide in methanol (zémplen deacetylation)

In both cases, methoxide in catalytic

Milder conditions, such as treatment with primary amines, are also effective for the removal of certain esters, and can do selective deprotection rxn

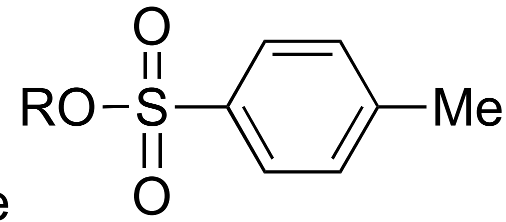
Sulfonate esters





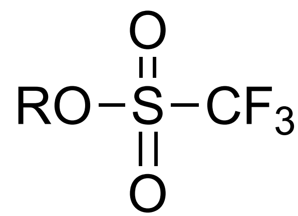
mesylate

methanesulfonate



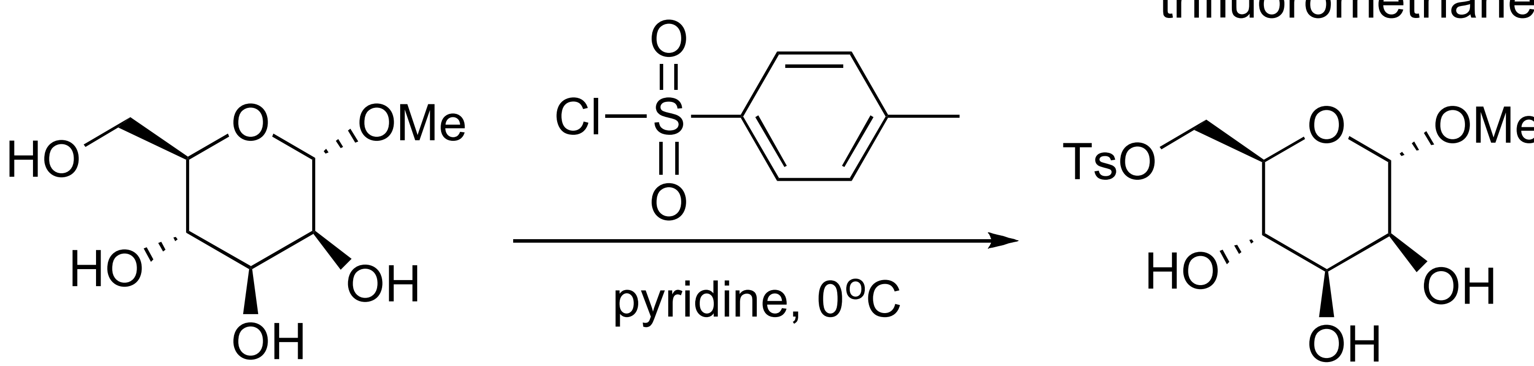
tosylate

toluenesulfonate



triflate

trifluoromethanesuflonate



Acetylation

Acetals

Ether

Ester

Nucleophilic Substitution

oxidation

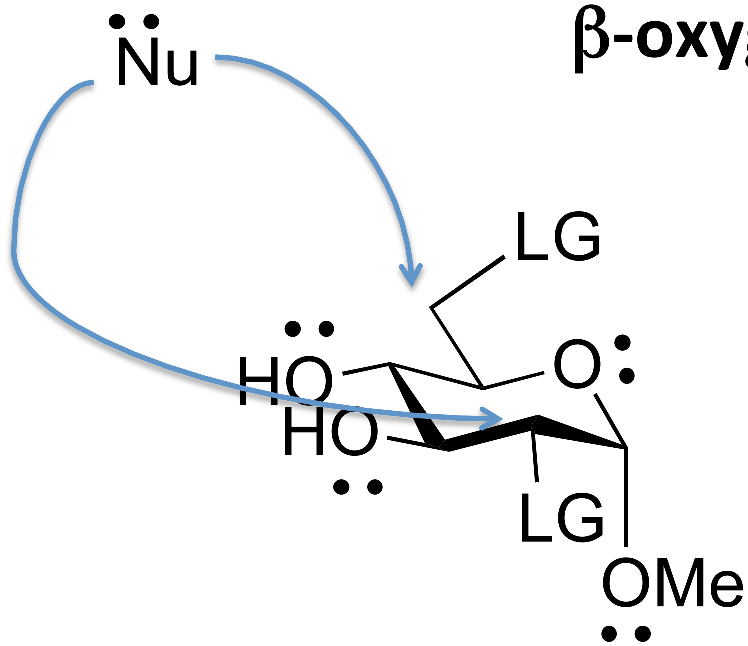
Reduction

Nucleophilic substitution RXN

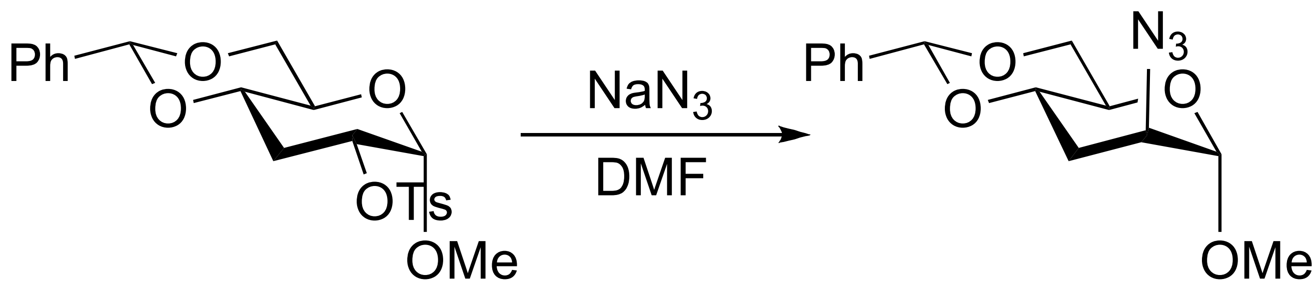
Retarded by the presence of electron withdrawing oxygen which are β to the carbon atom at which the displacement is taking place

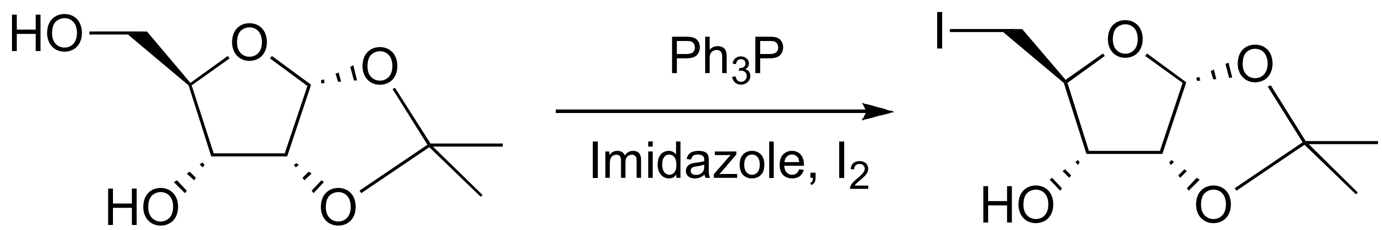
S_N2 not S_N1

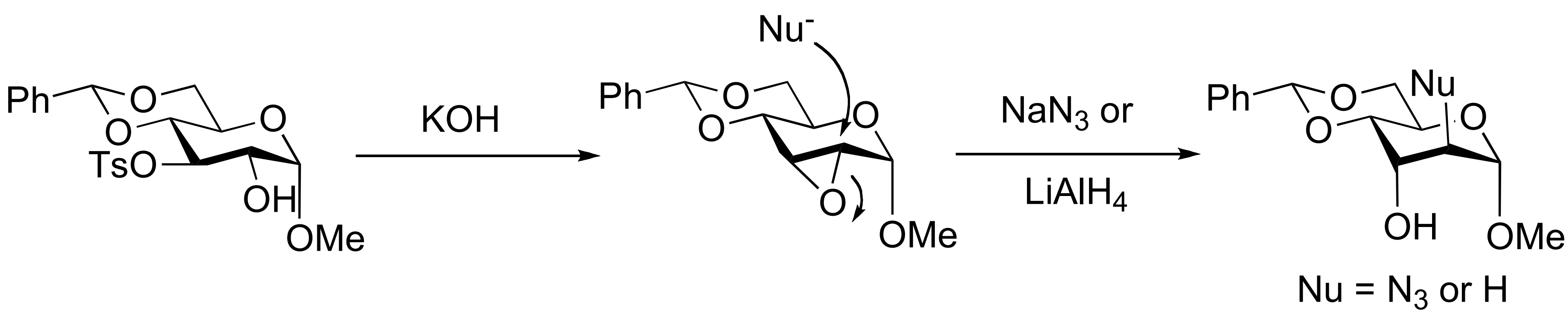
Electron withdrawing effect greatly destabilises any carbonium in in S_N1



β-oxygen effect







S_N2 trans

trans

Acetylation

Acetals

Ether

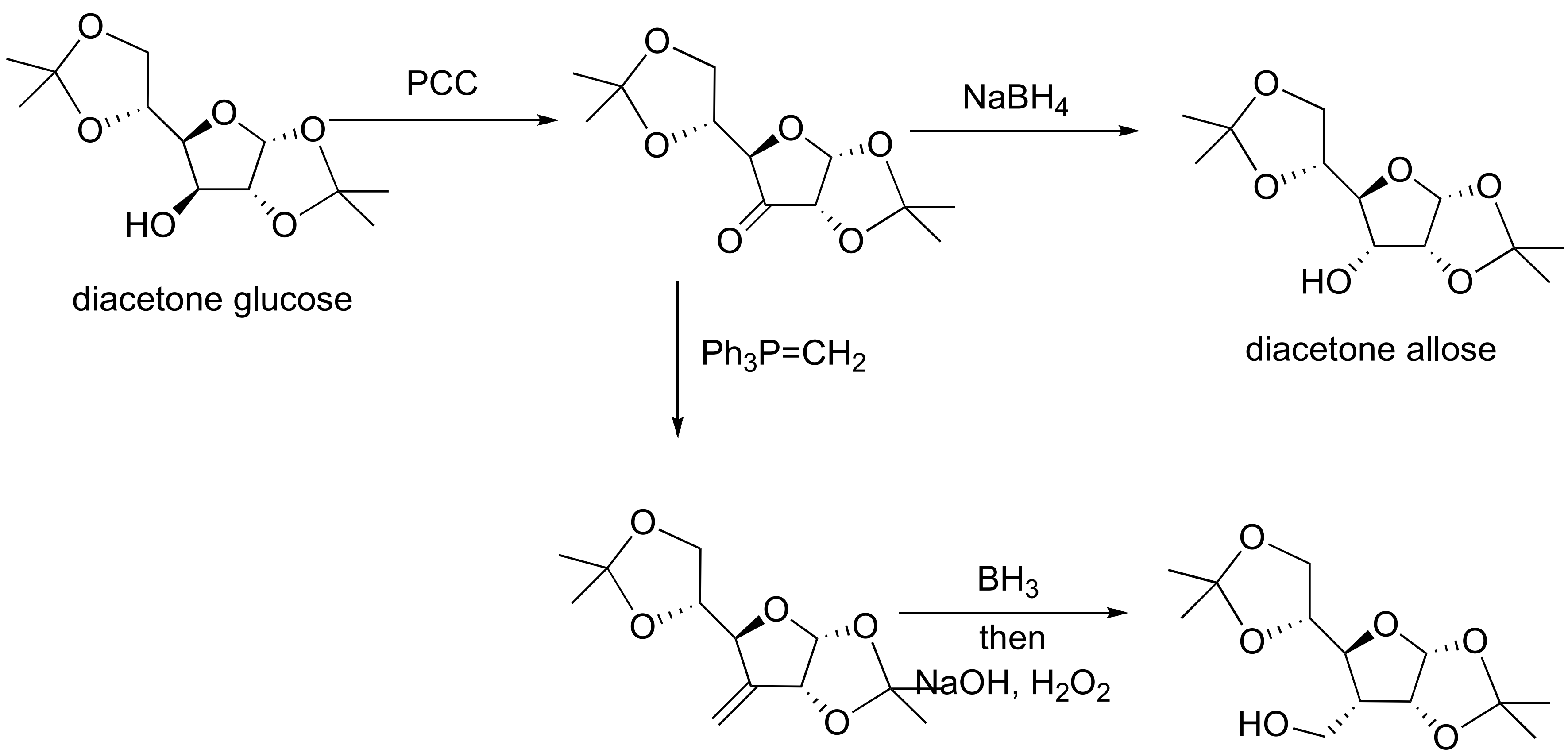
Ester

Nucleophilic Substitution

oxidation

Reduction

Oxidation



PCC
NaBH4
diacetone glucose
diacetone allose
Ph3P=CH2
BH3
then
NaOH, H2O2

The Nobel Prize in Chemistry 1990
Elias James Corey

PCC Oxidation

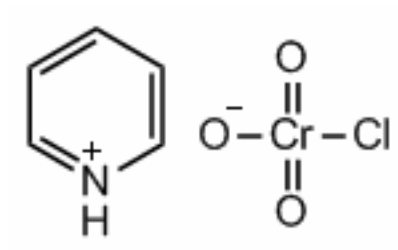
Elias James Corey

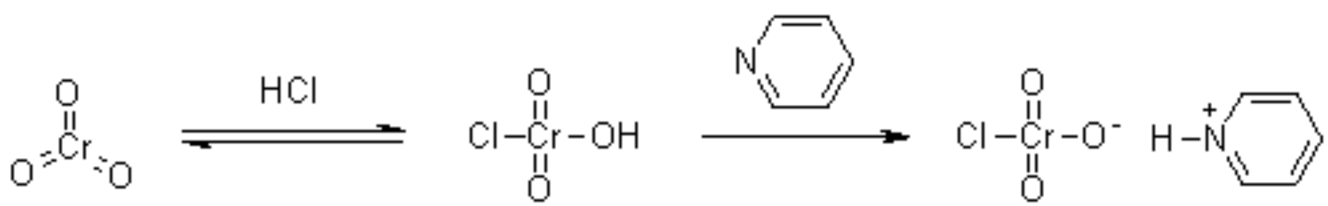
Born: 12 July 1928

Affiliation at the time of the award: Harvard University, Cambridge, MA, USA

Prize motivation: "for his development of the theory and methodology of organic synthesis"

Field: Organic chemistry

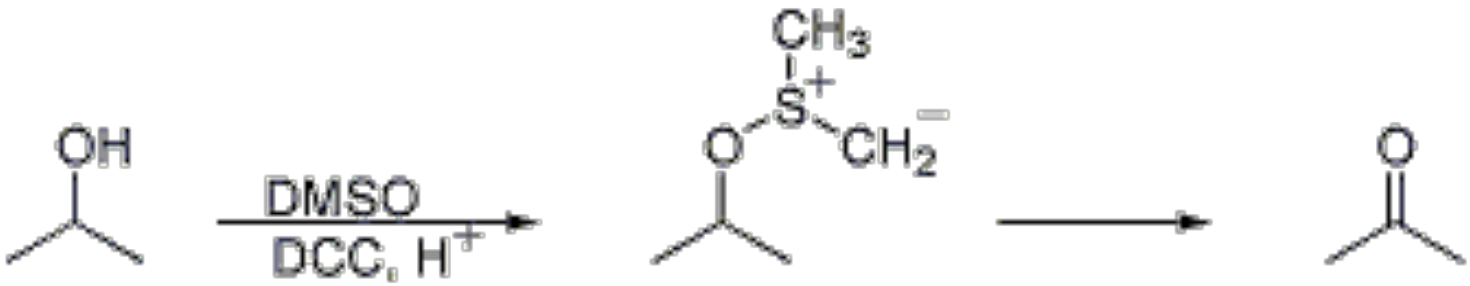




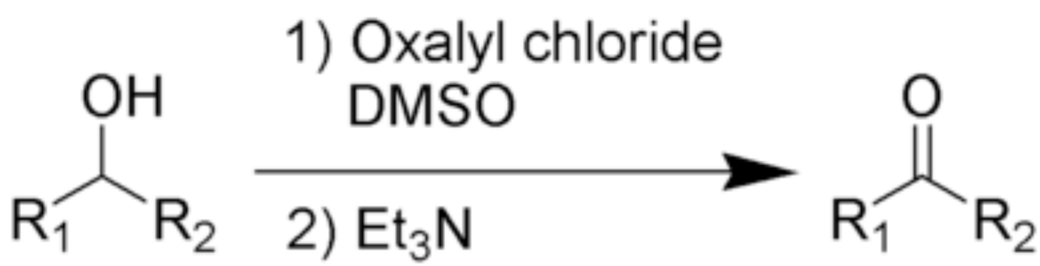
chlorochromic acid

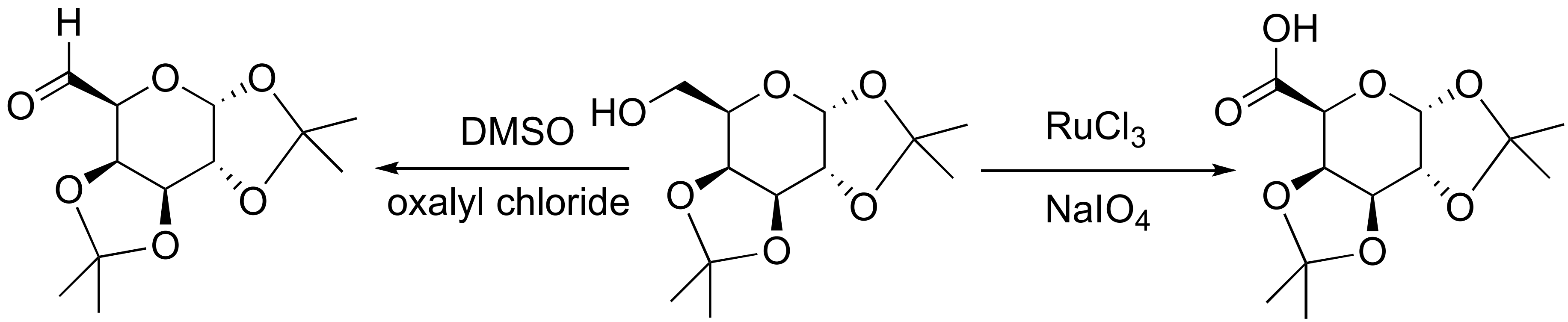
pyridinium chlorochromate

Pfitzner–Moffatt oxidation

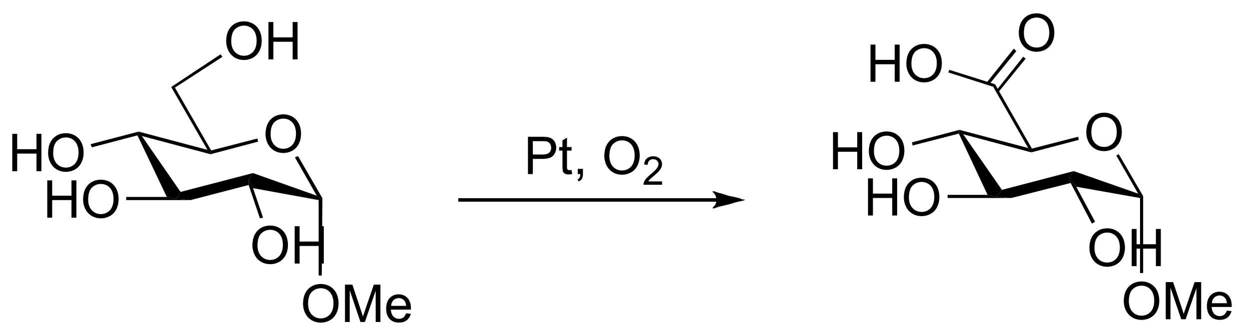


Swern oxidation

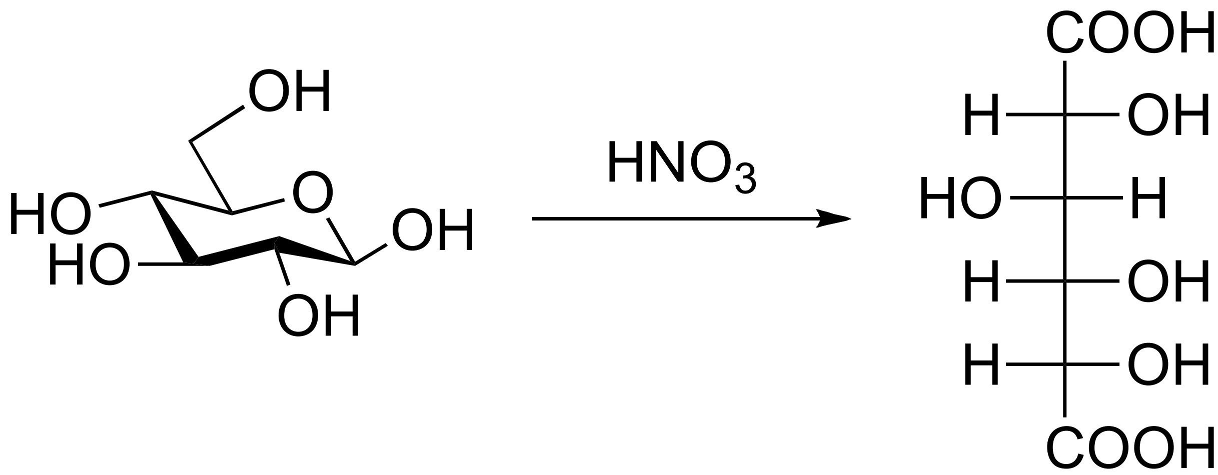




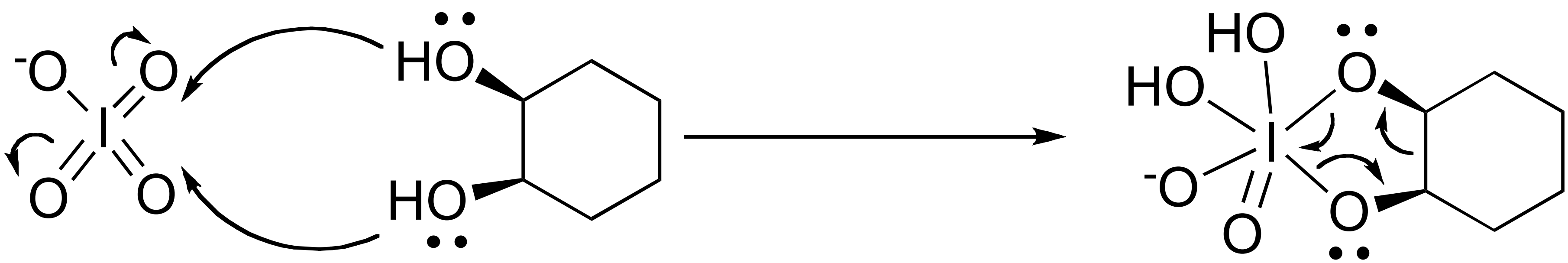
uronic acid

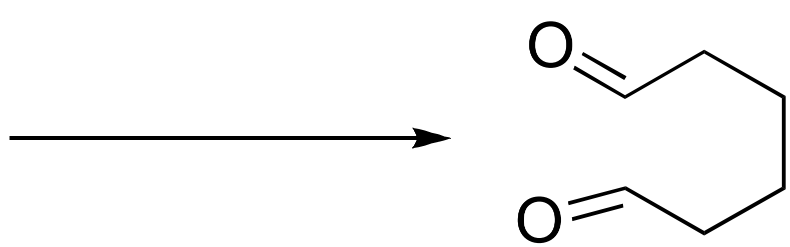


Selective oxidation to primary hydroxyl group

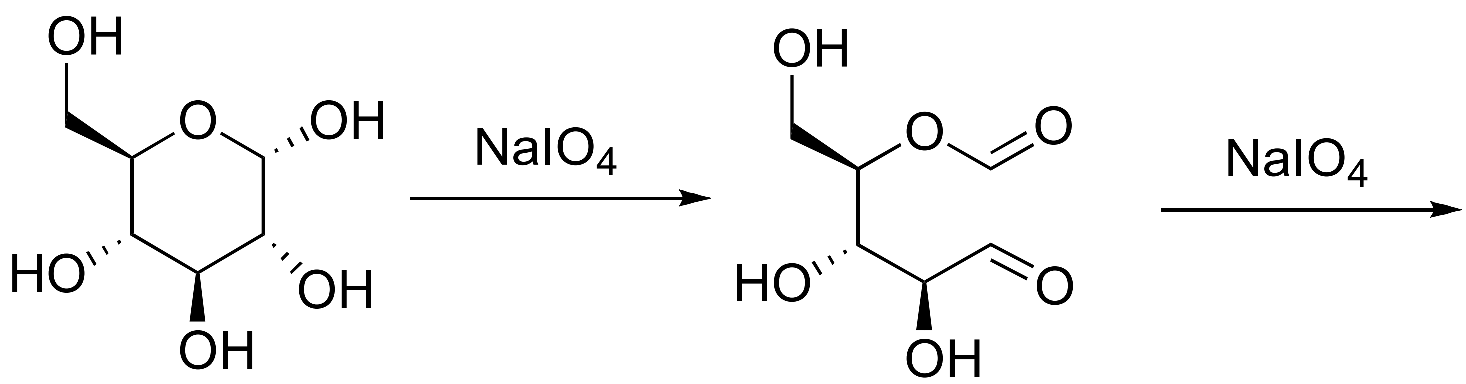


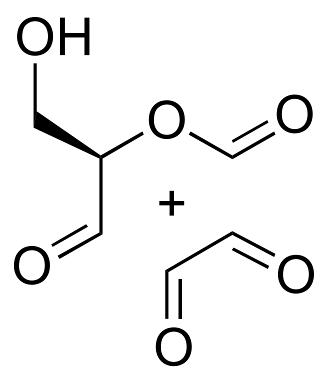
aldaric acid





Sodium periodate





Particularly useful for cleavage of the carbohydrate backbone at a specific point

Since the reagent will only cleave between two **cis** alcohol groups

Also useful for shortening of the carbohydrate chain

Acetylation

Acetals

Ether

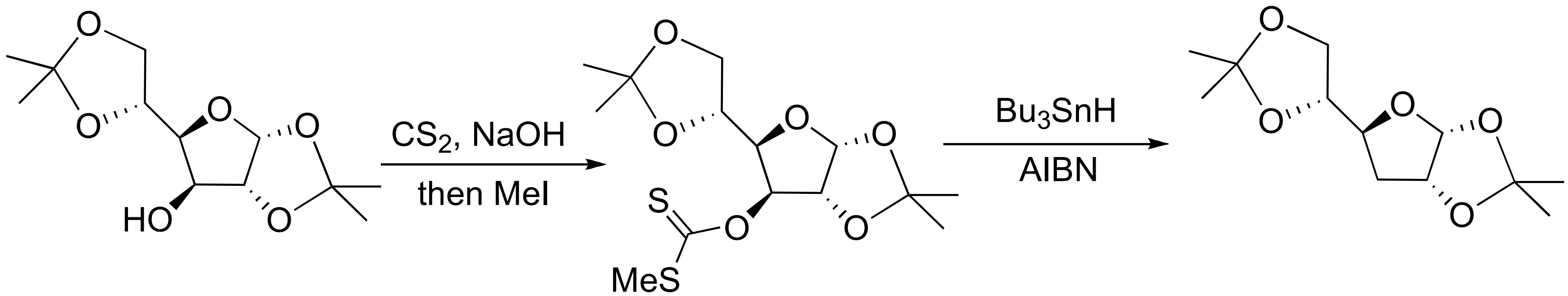
Ester

Nucleophilic Substitution

oxidation

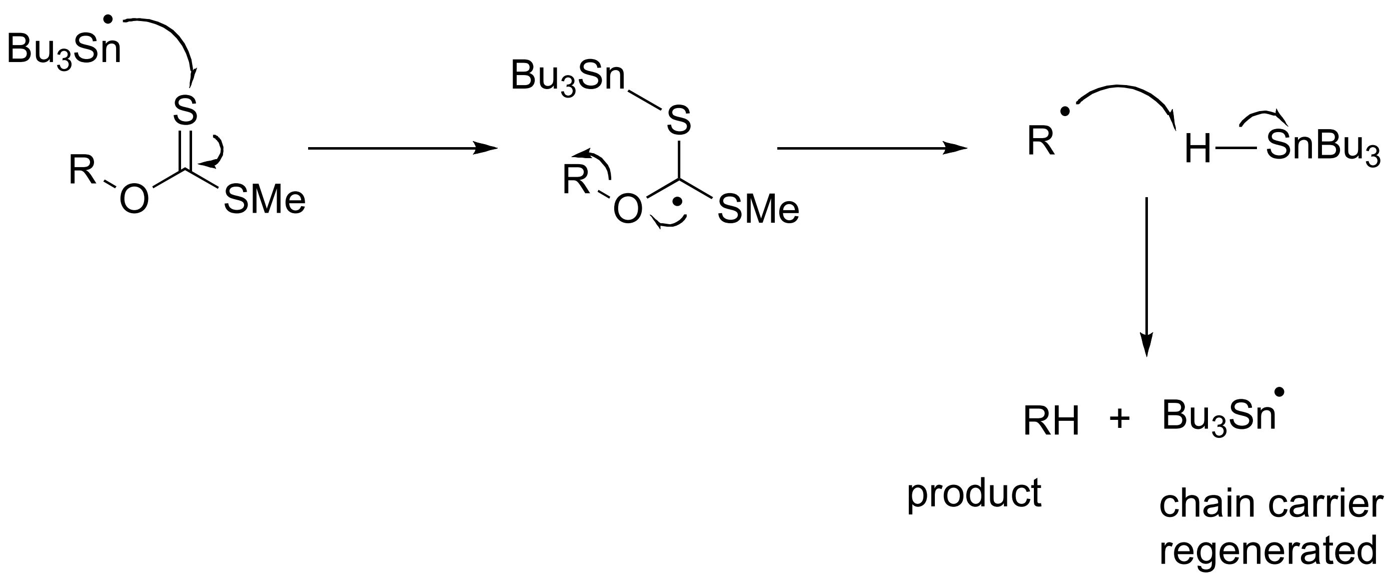
Reduction

Reduction to prepare **deoxy sugars**



Xanthate ester

Barton-McCombie deoxygenation



Other possible ways

Nucleophilic displacement of leaving groups, e.g. OMs or OTs, with hydride from reducing agents such as $LiAlH_4$ is not generally a good route

Nucleophilic substitution is much slower in carbohydrates due to the β-oxygen effect

Under basic conditions, side reactions such as elimination rxns occur preferentially with reducing agents

Hydrogenolysis of halides in the presence of mild base is prefered.

summary

Describe the three types of hydroxyl groups found in sugars

Remember anomeric center acts as an alcohol or aldehyde

Describe the three types of hydroxyl groups found in sugars

Realize the importance of protection to allow regioselective rxns of those unprotected

Explain the pdts of acetylations under different conditions

Know how to selectively protect the primary hydroxyl group

Recall the method in forming and cleaving ethers and esters