



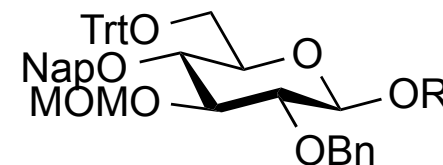
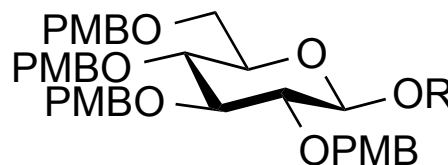
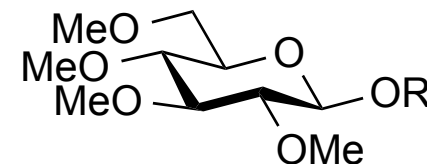
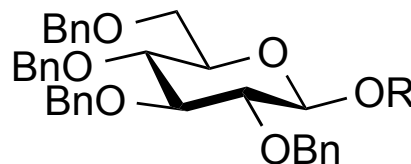
## 2. Reactions at Non-Anomeric Hydroxyl Groups



### 2.1 Ether-Type Protecting Groups

- ◆ Alkyl and aryl ethers are relatively stable to acids and bases due to the high C–O bond energy (358 KJ/mol)
- ◆ most useful ether-type protections utilize resonance stabilization (by delocalization) of the benzylic-type cation or radical to facilitate the cleavage
- ◆ The most common ethers used as protecting groups are:

- Methyl Ethers
- Benzyl (Bn) Ethers
- Substituted Benzyl Ethers
- Allyl and Related Ethers
- Trityl (Tr) Ethers
- 2-Naphthylmethyl (NAP) Ethers
- Propargyl Ethers
- *o*-Xylylene Ethers





# Alkylation Reactions: Ether-Type Protecting Groups

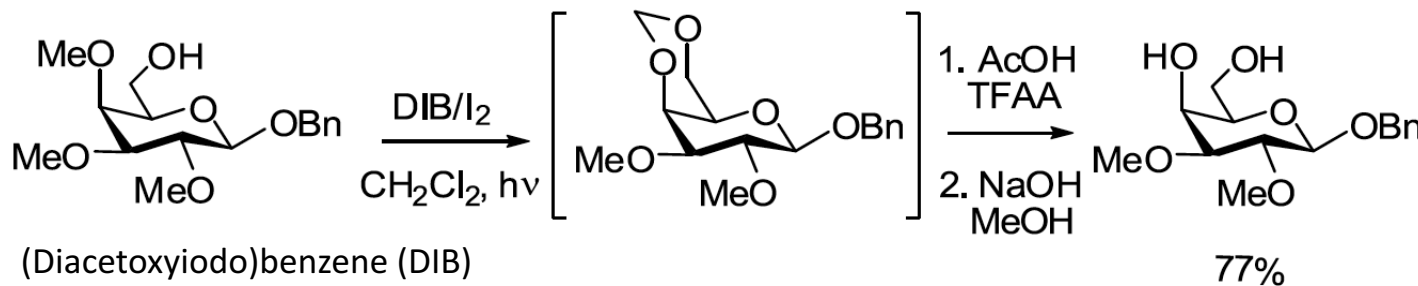


## Methyl Ethers

- Methyl ethers are not normally regarded as protecting groups
- The removal is difficult requiring conditions not compatible with other functional groups The selective removal of an ether adjacent to a hydroxyl group in carbohydrate substrates

## Selective removal of methoxy protecting groups

Boto A, et al. (2004) Org Lett 6:3785

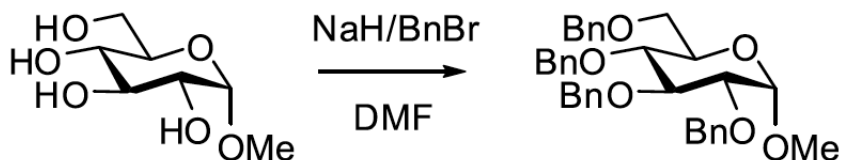


## Benzyl (Bn) Ethers

- The classical permanent protecting group for carbohydrates
- It is very stable and can be readily removed under essentially neutral conditions
- Benzyl ether formation is usually achieved by the reaction of alcohols and benzyl halides



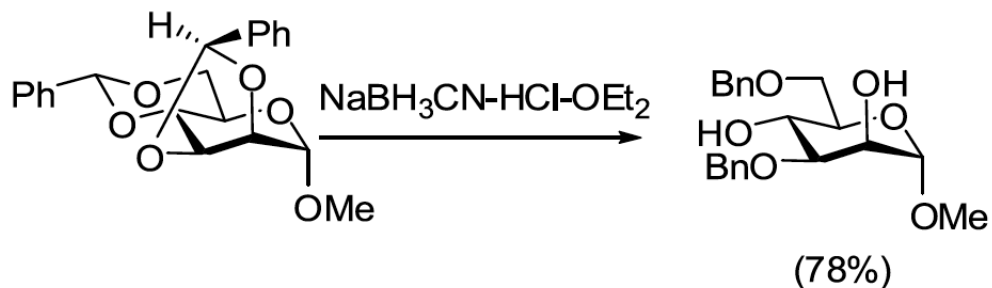
# Benzyl (Bn) Ethers



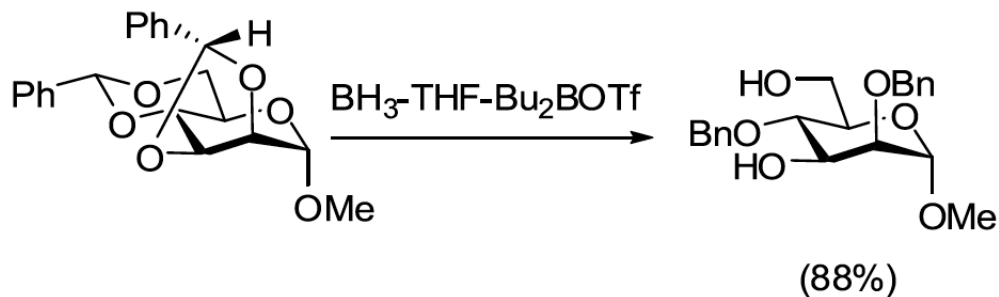
## Benylation of methyl $\alpha$ -D-glucopyranoside

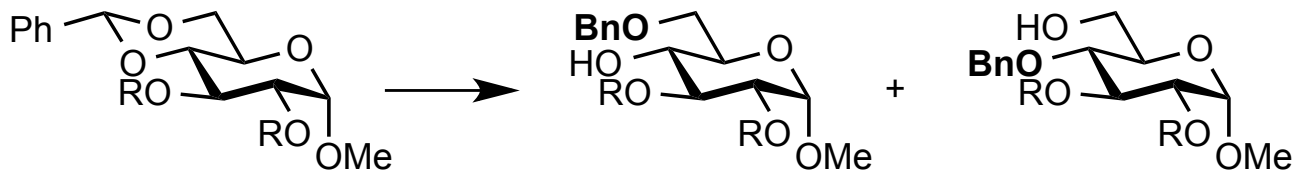
- Selective benzylation of carbohydrate hydroxyl functions by direct one-step protection is difficult to achieve
- Several techniques for the selective protection have been developed

- Generally, one of the two C–O bonds in benzylidene acetals can be selectively cleaved



- the direction of the cleavage is dependent on steric and electronic factors as well as, on the nature of the cleavage reagent





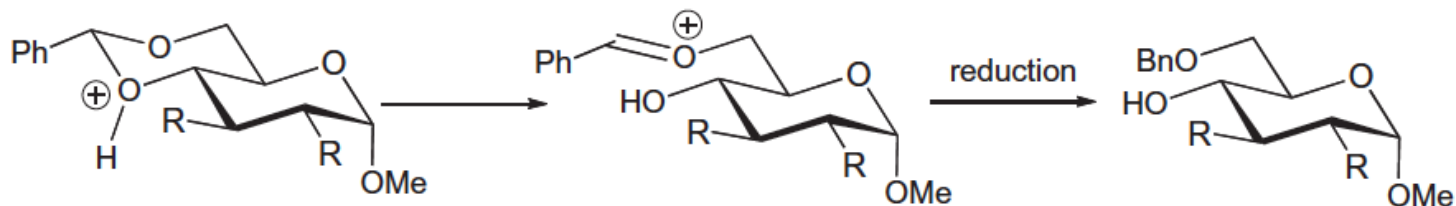
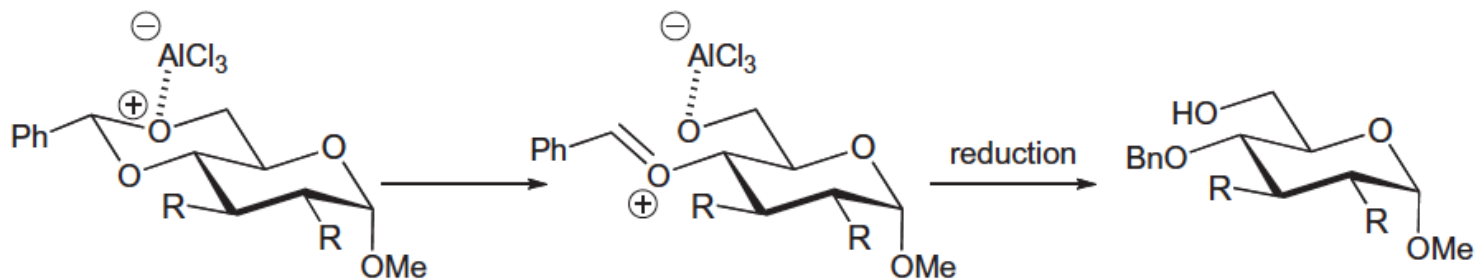
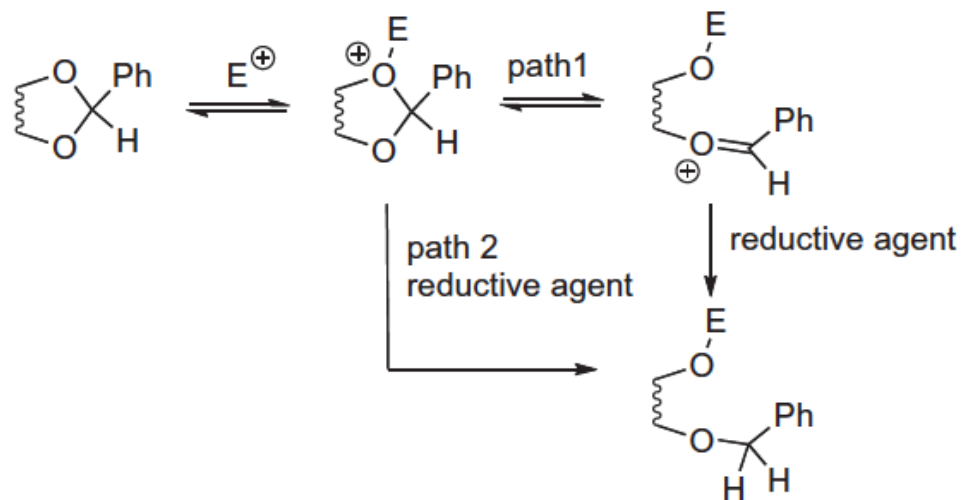
Entry	Reagent	Solvent and temperature	R	Yield (%)	
				6- <i>O</i> -Bn	4- <i>O</i> -Bn
1	NaBH <sub>3</sub> CN/HCl	THF, 0 °C	Bn	81	
2		THF, 0 °C	Bn	95	
3		THF, rt	Bn (1- <i>O</i> -Allyl)	80	
4		THF, rt	Bn (1- <i>O</i> -Allyl)	79	16
5	Me <sub>3</sub> N·BH <sub>3</sub> /AlCl <sub>3</sub>	THF, rt	Bn	71	
6		THF, rt	Bz	74	
7		Toluene, rt	Bn		50
8		Toluene, rt	Bz		40
9	Me <sub>3</sub> N·BH <sub>3</sub> /BF <sub>3</sub> ·Et <sub>2</sub> O	MeCN, 0 °C	Bn	30	55
10		CH <sub>2</sub> Cl <sub>2</sub> , 0 °C	Bn	3	73
11	Et <sub>3</sub> SiH/CF <sub>3</sub> CO <sub>2</sub> H	CH <sub>2</sub> Cl <sub>2</sub>	Bn	81	55
12		CH <sub>2</sub> Cl <sub>2</sub>	Ac	98	
13	BH <sub>3</sub> ·THF/Bu <sub>2</sub> BOTf	CH <sub>2</sub> Cl <sub>2</sub> , 0 °C	Bn		87
14	BH <sub>3</sub> ·THF/Cu(OTf) <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub> , rt	Bn		94
15	Me <sub>2</sub> EtSiH/Cu(OTf) <sub>2</sub>	CH <sub>3</sub> CN, 0 °C	Bn	84	



# Selective Opening of Benzylidene Acetals

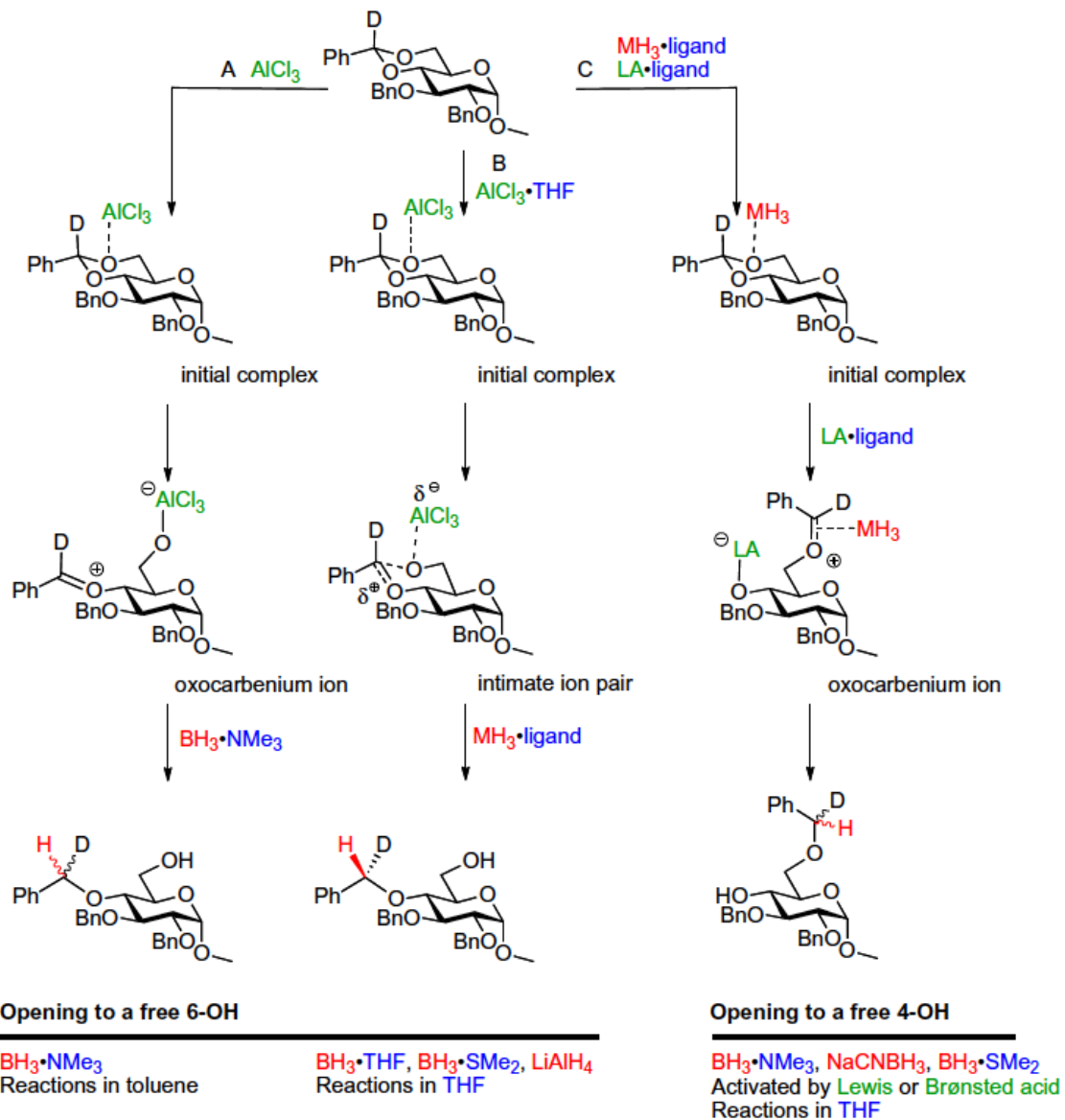


General mechanis





# Selective Opening of Benzylidene Acetals



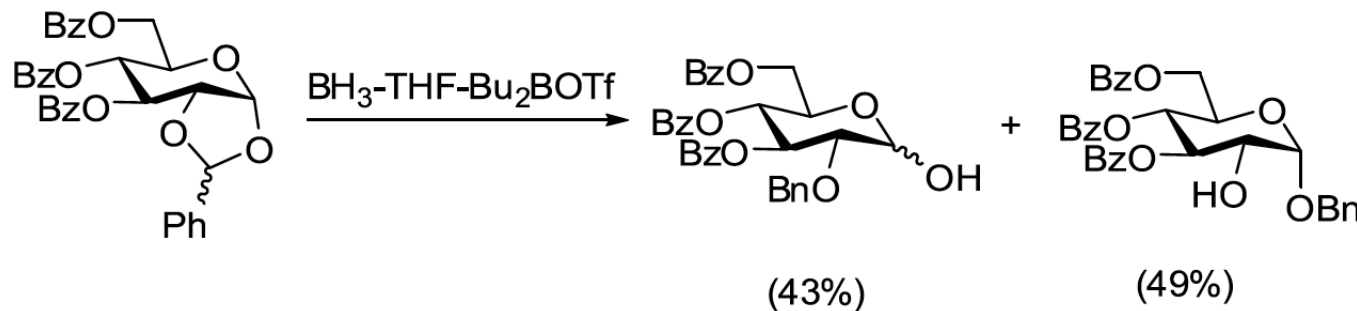
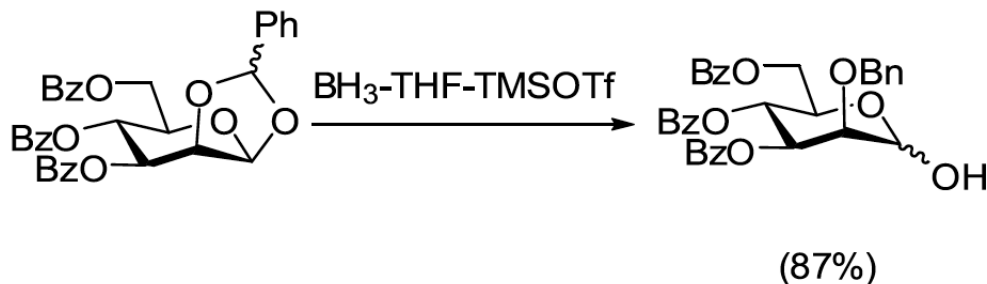


# Regioselective benzylation by opening of benzylidene acetals



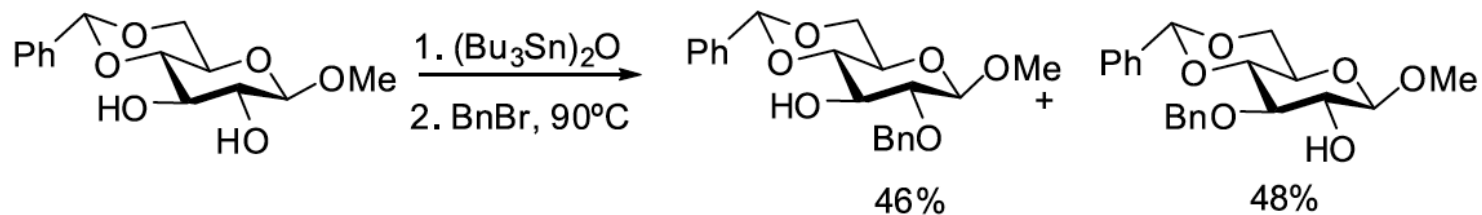
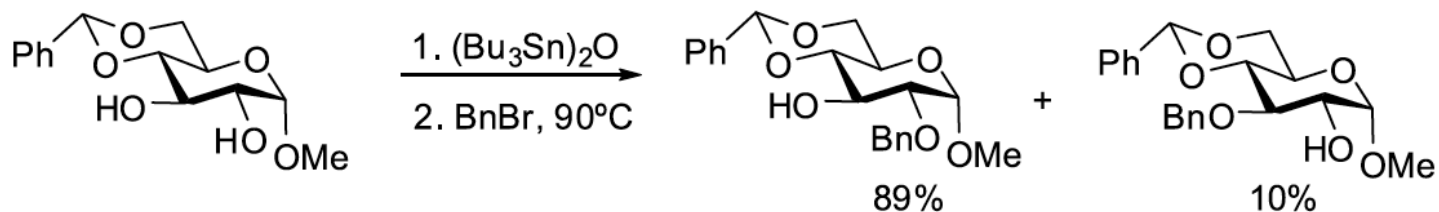
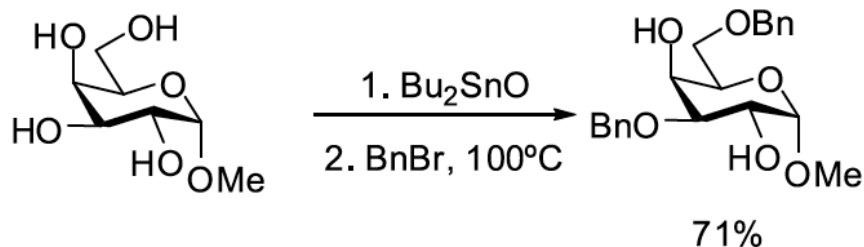
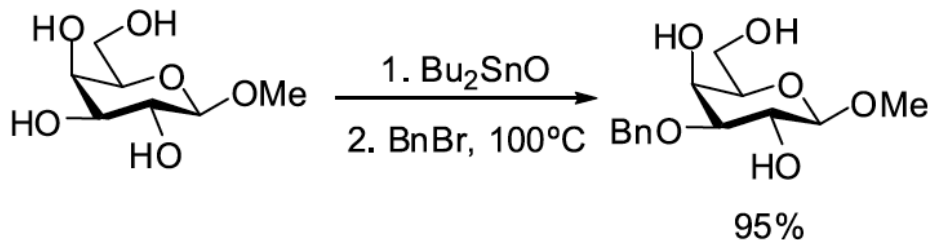
“Benzylidene acetals can also be opened under oxidative conditions, typically using NBS in CCl<sub>4</sub> “

- Substrate can be treated with the tin reagent forming one or two Sn–O bonds, enhancing the nucleophilicity of the oxygen atoms in the stannyl ether or stannylene acetal.
- The effect is different for the two oxygen atoms forming an Sn-acetal and can be used for higher regioselectivity.





# Examples of stannyl-mediated regioselective benzylation





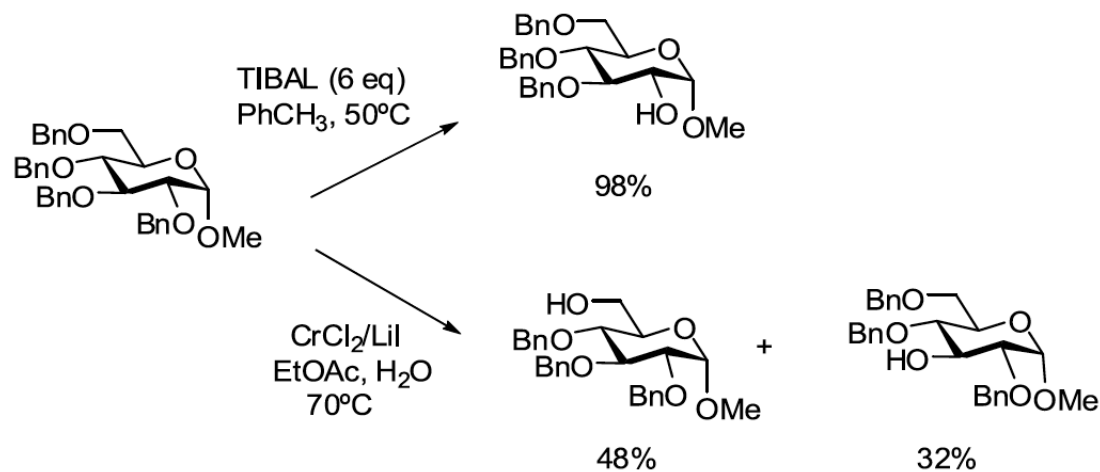
# Examples of regioselective de-O-benzylation



Selective de-O-benzylation of easily available polybenzylated precursors.

This has been achieved in limited cases by:

- catalytic hydrogenolysis
- Catalytic hydrogen-transfer cleavage
- Acetolysis
- hypoiodite fragmentation
- iodine-mediated addition-elimination sequences
- Lewis acids
- By isobutylalanes or the combination CrCl<sub>2</sub>/LiI

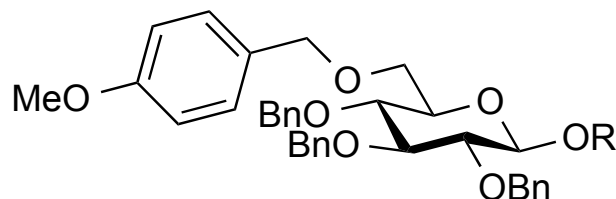




# Substituted Benzyl Ethers



- Substituted benzyl ethers can be selectively removed in the presence of unsubstituted benzyl ethers have been developed.

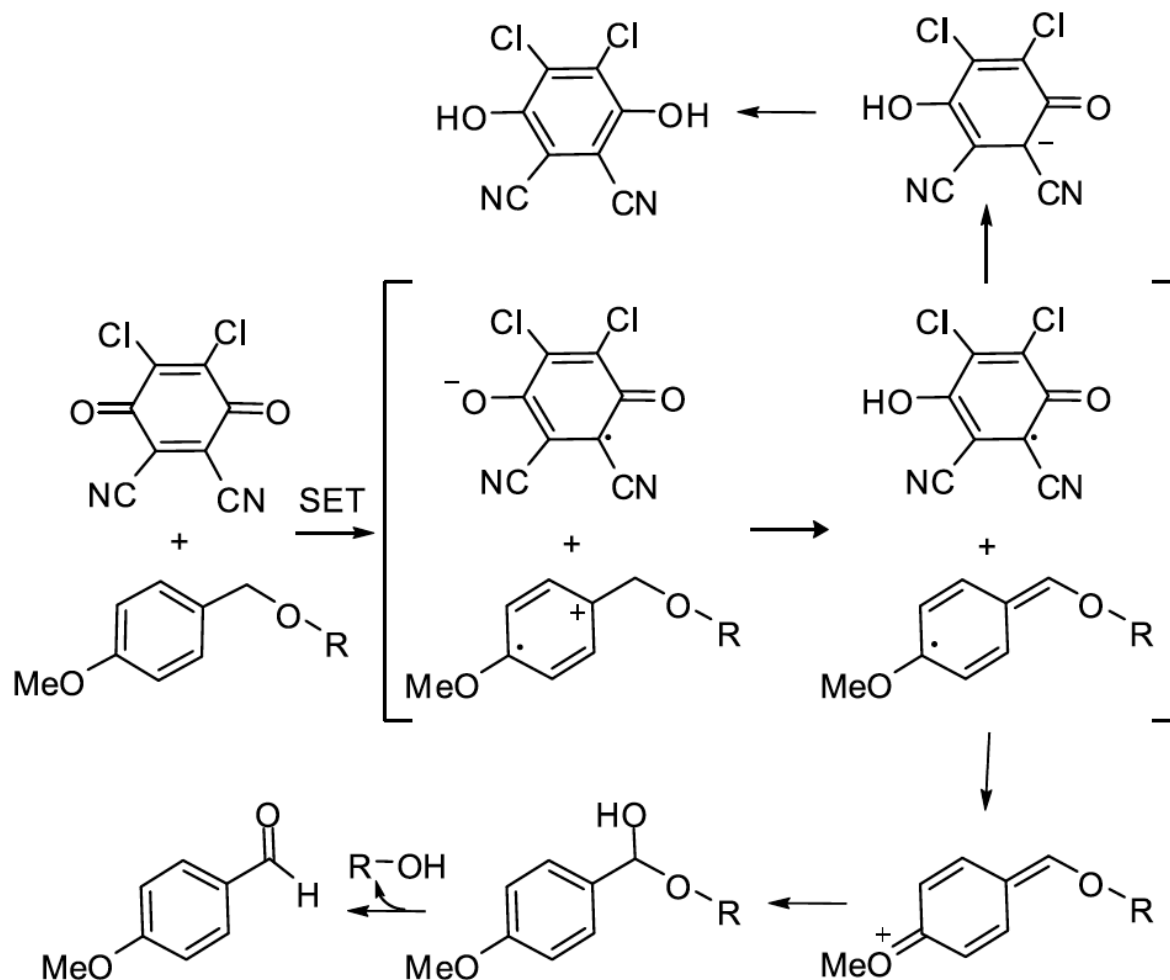


- ❖ *p*-methoxy benzyl (PMB) is an important in carbohydrate chemistry due to its easy introduction and removal.
- ❖ PMB group removal can be mediated by oxidizing agents or by Lewis acids
  - By oxidation with DDQ
  - DDQ-FeCl<sub>3</sub>
  - DDQ-Mn(OAc)<sub>3</sub>
  - CAN (Cerium Ammonium Nitrate)

PMB ethers can be cleaved with ZrCl<sub>4</sub>, SnCl<sub>2</sub>/TMS-Cl/anisole, CF<sub>3</sub>CO<sub>2</sub>H in CH<sub>2</sub>Cl<sub>2</sub>, CeCl<sub>3</sub>·7H<sub>2</sub>O/NaI, or I<sub>2</sub>/MeOH



# Removal of p-Methoxybenzyl Ethers with DDQ

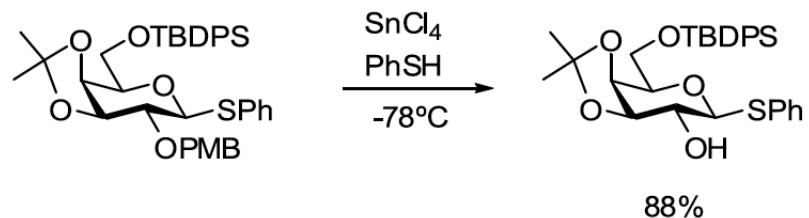
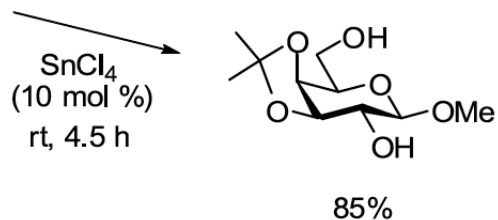
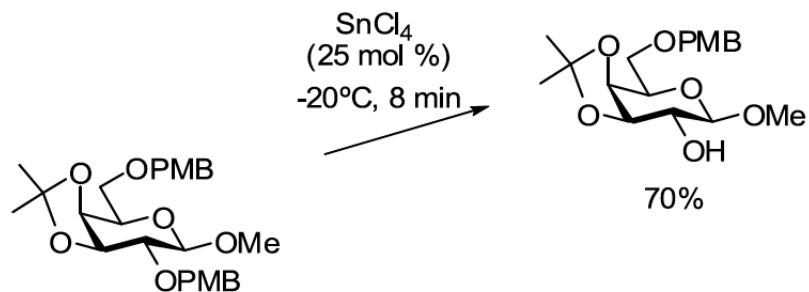




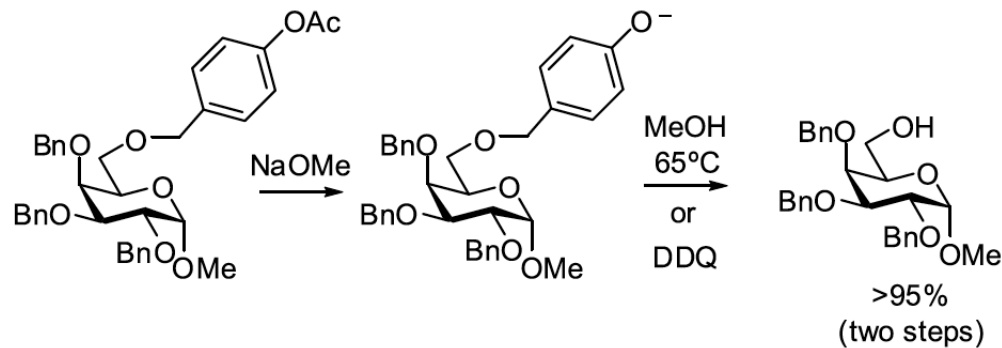
# Removal of PMB with Acids



Examples of deprotection of *p*-methoxybenzyl ethers with a Lewis acid ( $\text{SnCl}_4$ )

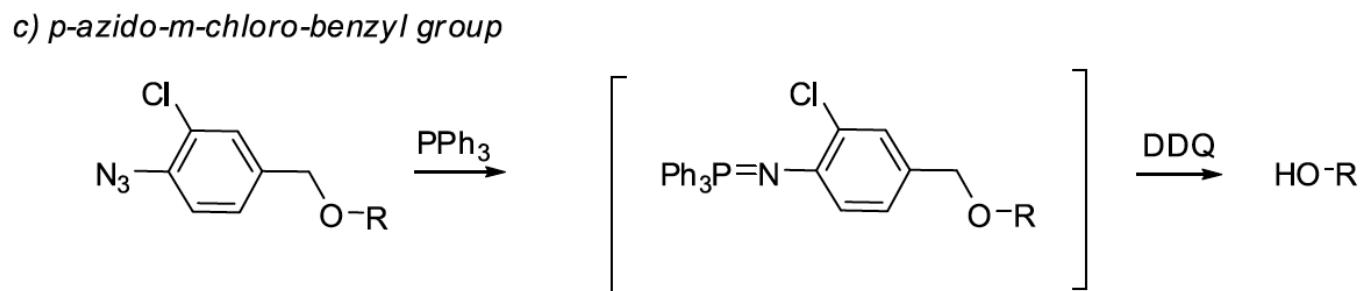
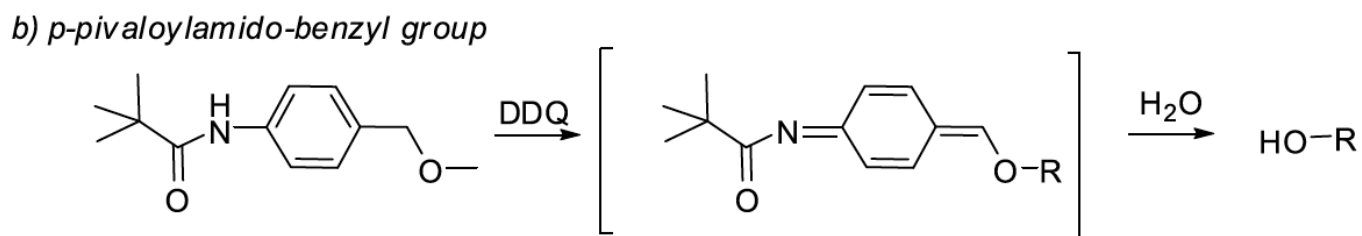
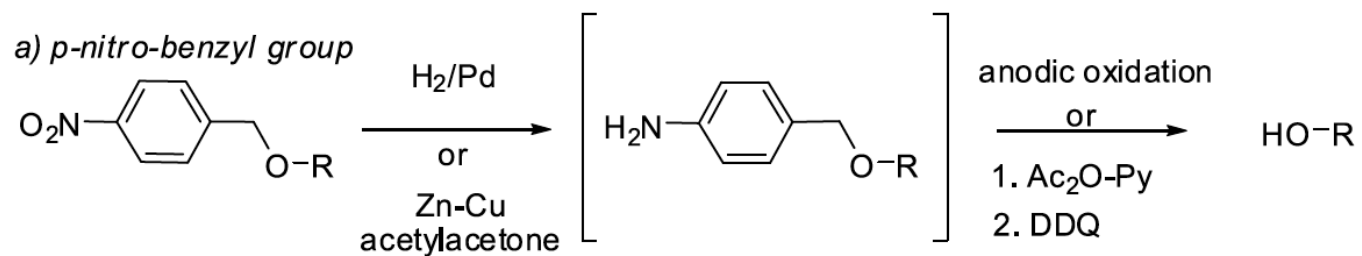


Two-step deprotection of *p*-acetoxybenzyl protecting group





# Examples of *p*-substituted benzyl-type protecting groups

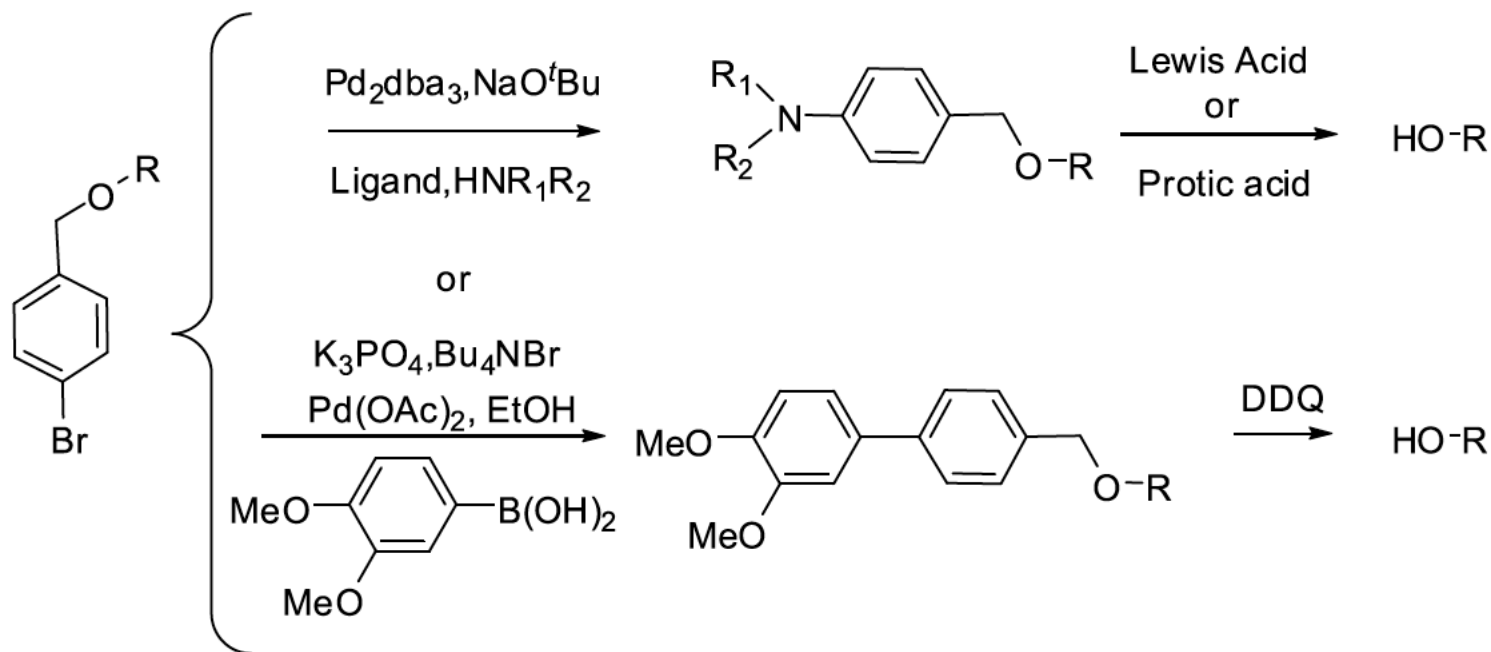




# Examples of *p*-substituted benzyl-type protecting groups



d) *p*-bromo-benzyl group



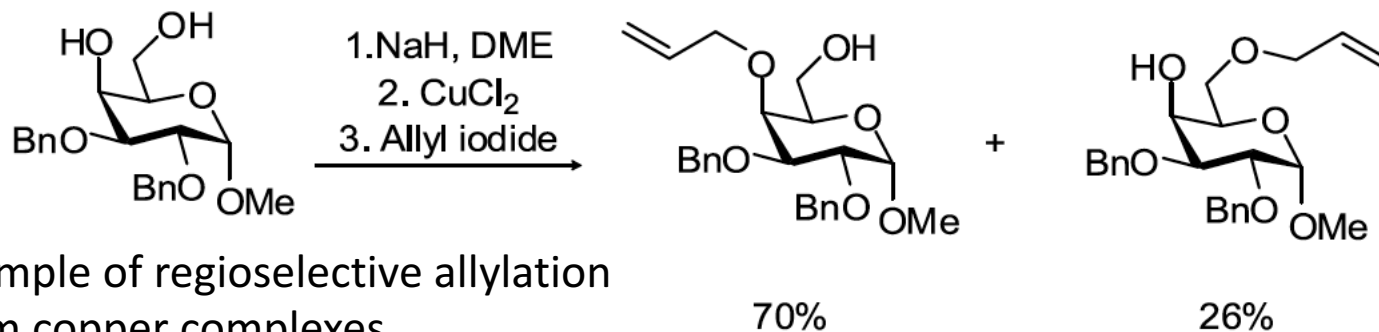
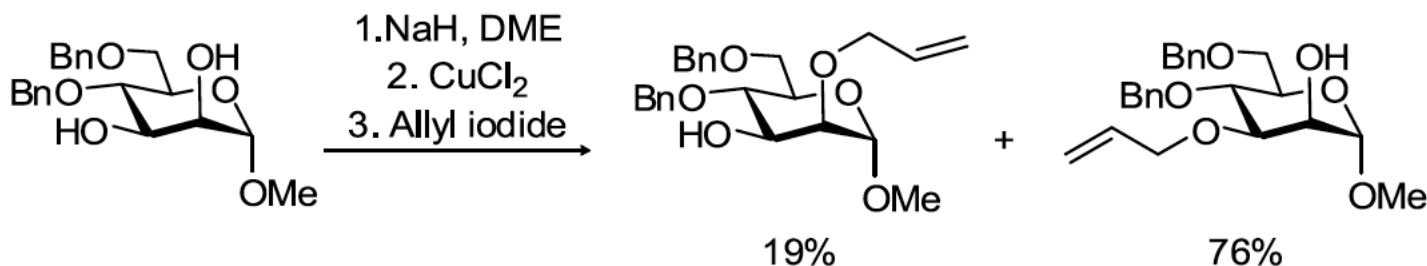


# Allyl and Related Ethers



## Allyl-ethers

- The protection with allyl and related (prenyl, methylallyl, cinnamyl, homoallyl) groups is of great importance due to their stability under the conditions required for glycoside formation.
- They are moderately stable to acids and bases, and offer the potential for selective dealkylation



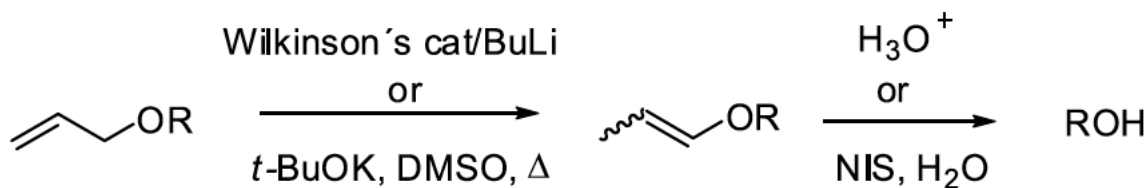
Example of regioselective allylation from copper complexes



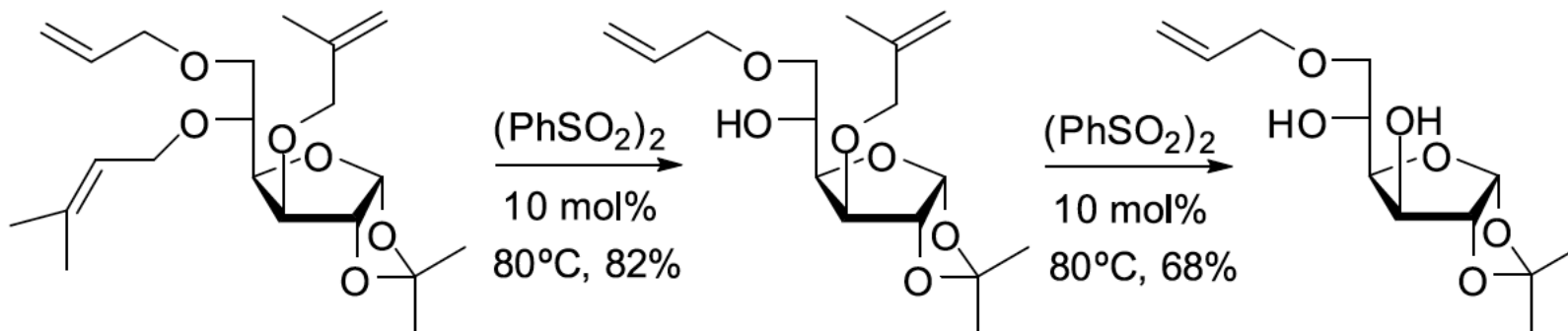
# Removal of Allyl Ethers



- Common allyl deprotection methods are two-stage procedures that include isomerization to 1-propenyl group with a variety of agents
- The most frequently employed conditions are:  
treatment with *t*-BuOK, Wilkinson catalyst, Pd/C, PdCl<sub>2</sub>, ruthenium(II), and iridium(I) complexes followed by acid hydrolysis or oxidation.



## Selective cleavage of branched allyl ethers

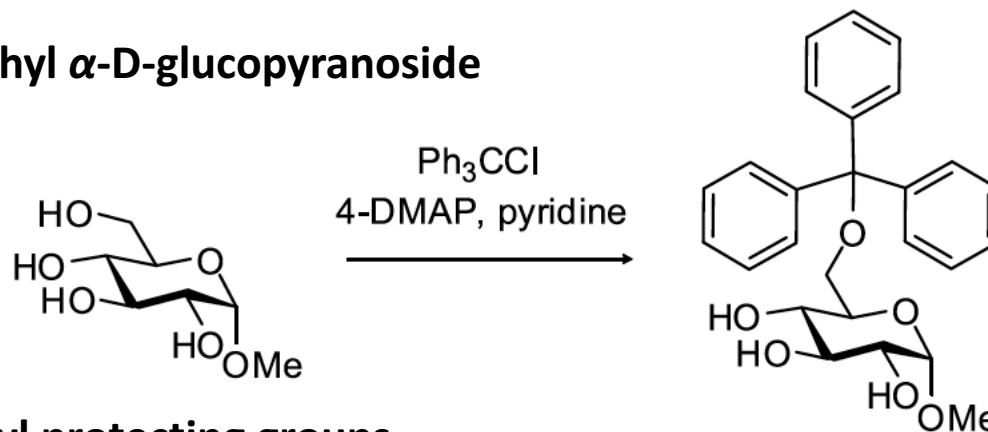




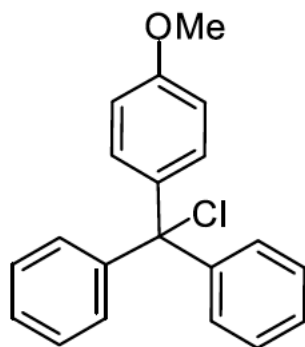
## Tryl-ethers

- Its utility is attributed to the easy preparation and removal as well as to the high selectivity for primary positions observed in polyols

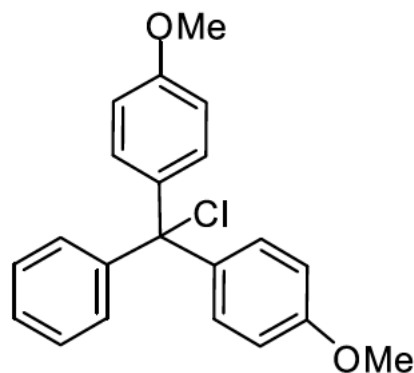
## Trylation of methyl $\alpha$ -D-glucopyranoside



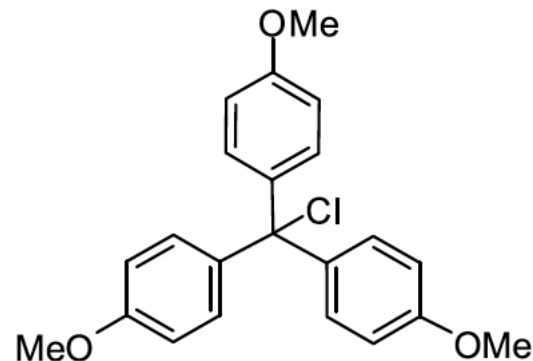
## Substituted trityl protecting groups



MMTr



DMTr



TMTr



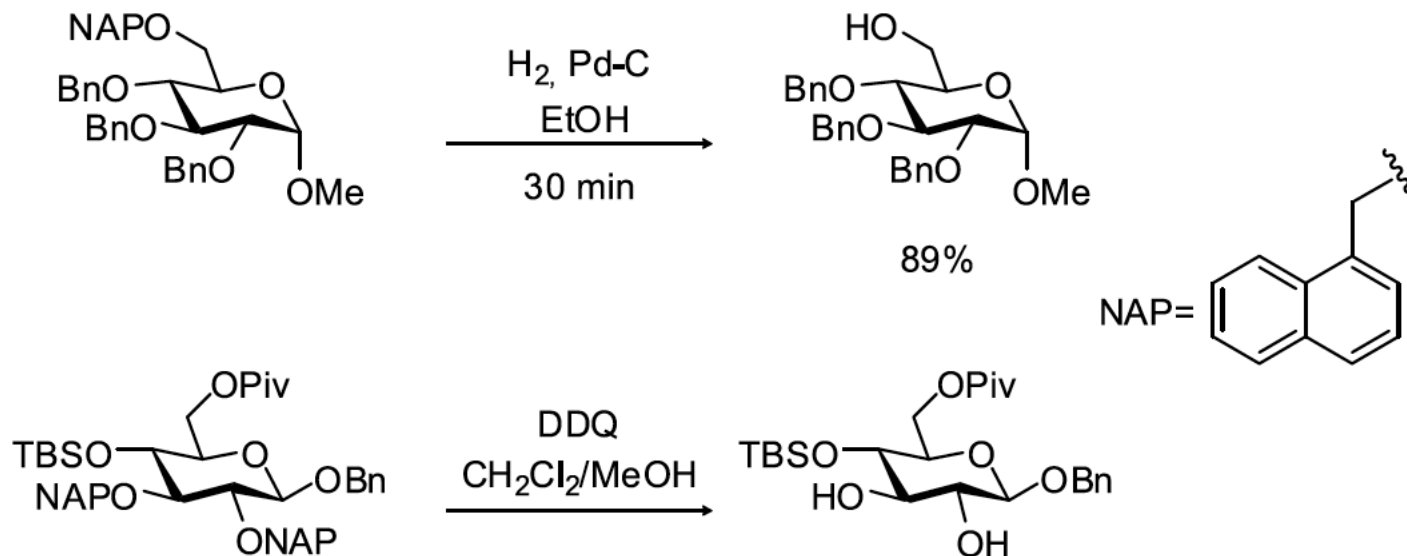
# 2- Naphthyl-methyl Ether (NAP)



The “NAP” protecting group was introduced by Esko and Spencer and it has higher stability to acidic glycosylation conditions than PMB

NAP can be removed by:

- hydrogenolysis,
- acids
- oxidation conditions (similar to PMB)



- Sarkar AK, Rostand KS, Jain RK, Matta KL, Esko JD (1997) J Biol Chem 272:25608
- Gaunt MJ, Yu J, Spencer JB (1998) J Org Chem, 63:4172