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
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

![Chemical reaction diagram](image)


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

- 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
Reductive Opening of Benzylidene Acetals

![Chemical structures](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Solvent and temperature</th>
<th>R</th>
<th>Yield (%)</th>
<th>6-0-Bn</th>
<th>4-0-Bn</th>
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<td>NaBH₃CN/HCl</td>
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</table>
Selective Opening of Benzyldiene Acetals

General mechanism:

![Chemical structures and mechanisms for selective opening of benzyldiene acetals](image)
Selective Opening of Benzylidene Acetals

A: \( \text{AlCl}_3 \)

B: \( \text{AlCl}_3 \cdot \text{THF} \)

C: \( \text{MH}_3 \cdot \text{ligand} \)

\( \text{LA-} \text{ligand} \)

\( \text{BH}_3 \cdot \text{NMe}_3 \)

\( \text{BH}_3 \cdot \text{THF}, \text{BH}_3 \cdot \text{SMe}_2, \text{LiAlH}_4 \)

\( \text{BH}_3 \cdot \text{NMe}_3, \text{NaCNBH}_3, \text{BH}_3 \cdot \text{SMe}_2 \)

Activated by Lewis or Brønsted acid

Reactions in toluene

Reactions in THF

Opening to a free 6-OH

Opening to a free 4-OH
Regioselective benzylation by opening of benzylidene acetals

“Benzylidene acetals can also be opened under oxidative conditions, typically using NBS in CCl4 “

- 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.

![Chemical structures showing regioselective benzylation by opening of benzylidene acetals.](image)
Examples of stannyl-mediated regioselective benzylation

1. Bu$_2$SnO
2. BnBr, 100°C

95%

1. Bu$_2$SnO
2. BnBr, 100°C

71%

1. (Bu$_3$Sn)$_2$O
2. BnBr, 90°C

89%

10%

1. (Bu$_3$Sn)$_2$O
2. BnBr, 90°C

46%

48%
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
- hypoiodeite fragmentation
- iodine-mediated addition-elimination sequences
- Lewis acids
- By isobutylalanes or the combination CrCl2/LiI
Substituted benzyl ethers can be selectively removed in the presence of unsubstituted benzyl ethers have been developed.

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- $p$-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$_3$
  - DDQ-Mn(OAc)$_3$
  - CAN (Cerium Ammonium Nitrate)

PMB ethers can be cleaved with ZrCl$_4$, SnCl$_2$/TMS-Cl/anisole, CF$_3$CO$_2$H in CH$_2$Cl$_2$, CeCl$_3$.7H$_2$O/NaI, or I$_2$/MeOH
Removal of p-Methoxybenzyl Ethers with DDQ
Removal of PMB with Acids

**Examples of deprotection of p-methoxybenzyl ethers with a Lewis acid (SnCl₄)**

1. **SnCl₄ (25 mol %)**  
   -20°C, 8 min  
   - OPMB  
   - 70%

2. **SnCl₄ (10 mol %)**  
   rt, 4.5 h  
   - OMe  
   - 85%

3. **SnCl₄, PhSH**  
   -78°C  
   - OMe  
   - 88%

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

- OAc  
  - NaOMe  
  - MeOH  
  - 65°C or DDQ  
  - >95% (two steps)
Examples of \( p\)-substituted benzyl-type protecting groups

\[ a) \ p\text{-nitro-benzyl group} \]

\[
\begin{align*}
\text{O}_2\text{N} & \quad \text{H}_2/\text{Pd} \quad \text{or} \\
\text{H}_2\text{N} & \quad \text{Zn-Cu} \\
\text{O} & \quad \text{acetylacetone}
\end{align*}
\]

\[
\begin{align*}
\text{anodic oxidation} & \quad \text{or} \\
\text{H}_2\text{O} & \quad \text{1. Ac}_2\text{O-Py} \\
\text{O} & \quad \text{2. DDQ}
\end{align*}
\]

\[ b) \ p\text{-pivaloylamido-benzyl group} \]

\[
\begin{align*}
\text{O} & \quad \text{DDQ} \\
\text{O} & \quad \text{H}_2\text{O}
\end{align*}
\]

\[ c) \ p\text{-azido-m-chloro-benzyl group} \]

\[
\begin{align*}
\text{Cl} & \quad \text{PPh}_3 \\
\text{Cl} & \quad \text{DDQ}
\end{align*}
\]
Examples of $p$-substituted benzyl-type protecting groups

d) $p$-bromo-benzyl group

$$\text{O}^-R \quad \text{Br}$$

$$\begin{align*}
\text{Pd}_2\text{dba}_3, \text{NaO}^-\text{Bu} \\
\text{Ligand, HNR}_1\text{R}_2
\end{align*}$$

$$\begin{align*}
\text{K}_3\text{PO}_4, \text{Bu}_4\text{NBr} \\
\text{Pd(OAc)}_2, \text{EtOH}
\end{align*}$$

$\text{MeO}$

$\text{MeO}$

$\text{MeO}$

$\text{MeO}$

$\text{MeO}$

$\begin{align*}
\text{R}_1\text{N}^-\text{R}_2 \\
\text{HO}^-\text{R}
\end{align*}$

$\text{DDQ}$

$\text{HO}^-\text{R}$

$\text{Protic acid}$

$\text{Lewis Acid}$
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

1. NaH, DME
2. CuCl₂
3. Allyl iodide

1. NaH, DME
2. CuCl₂
3. Allyl iodide

19% 76%

70% 26%
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, PdCl2, ruthenium(II), and iridium(I) complexes followed by acid hydrolysis or oxidation.

$$\text{Wilkinson's cat/BuLi or}$$

$$\begin{align*}
\text{OR} & \xrightarrow{t\text{-BuOK, DMSO, } \Delta} \text{OR} \\
\text{H}_3\text{O}^+ & \text{or}
\end{align*}$$

$$\text{NIS, H}_2\text{O} \rightarrow \text{ROH}$$

**Selective cleavage of branched allyl ethers**

\begin{align*}
\text{OR} & \xrightarrow{(\text{PhSO}_2)_2, 10\text{ mol}\%} \text{OR} \\
\text{OR} & \xrightarrow{(\text{PhSO}_2)_2, 10\text{ mol}\%} \text{HO} \\
\text{OR} & \xrightarrow{(\text{PhSO}_2)_2, 10\text{ mol}\%} \text{HO}
\end{align*}

10 mol\% 80°C, 82%

10 mol\% 80°C, 68%
Trityl-ethers

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

**Tritylation of methyl α-D-glucopyranoside**

\[
\begin{align*}
\text{Ph}_3\text{CCl} & \quad 4\text{-DMAP, pyridine} \\
\text{Trityl-ether} & \quad \text{Methyl α-D-glucopyranoside}
\end{align*}
\]

**Substituted trityl protecting groups**

- MMTr
- DMTr
- TMTr
2- Naphtyl-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)

\[ \text{NAP} \]