Protective Groups in Synthetic Organic Chemistry

Lecture Notes

Key Texts


Key Reviews

Protective Groups: 
Background and General Considerations

"Protection is a principle, not an expedient"
Benjamin Disraeli, British Prime Minister, 1845

"Like death and taxes, protecting groups have become
a consecrated obstruction which we cannot elude"
Peter Kocienski, Organic Chemist

Remember:

• Every protecting group adds at least one, if not two steps to a synthesis
• They only detract from the overall efficiency and beauty of a route, but, without them, there are certainly transformations which we would not be able to do at all.
Protective Groups: Temporary Protection

Temporary protection involves the ideal for protecting groups when they are required: the protection step, desired reaction, and deprotection all occur in the same pot.
Ene Reactions in Total Synthesis: Ene/Retro-Ene Sequence to Protect Indole

MTAD = N-methyltriazolinedione

Protective Groups:  
Background and General Considerations

Tactical considerations to consider for each protecting group selected in a synthesis:

It should be easily and efficiently introduced.

It should be cheap and readily available.

It should be easy to characterize and avoid the introduction of new stereogenic centers.

It should not afford so many spectroscopic signals that it hides key resonances for the substrate.

It should be stable to chromatography.

It should be stable to a wide range of reaction conditions.

It should be removed selectively and efficiently under highly specific conditions.

The by-products of deprotection should be easily separated from the substrate.
Protective Groups: Something to be Very Carefully Considered

(62% overall) 1. HF·py/py, THF, 0→25 °C, 12 h
Global deprotections 2. AlBr₃, EtSH/CH₂Cl₂ (1:1), 25 °C, 4 h

vancomycin aglycon

Protective Groups:
Orthogonal Sets of Protecting Groups

Orthogonal Set = a groups of protecting groups whose removal is accomplished in any order with reagents and conditions that do not affect protecting groups in any other orthogonal set.

In practice this concept is incredibly difficult to reduce to practice, but it is a useful framework and organizing principle to think about protecting group regimes for a complex molecule synthesis.
1. **Cleavage by basic solvolysis**

\[
\text{RO}_2\text{Me} + \text{OH}^- \rightarrow \text{ROH}
\]

<table>
<thead>
<tr>
<th>$k_{rel}$</th>
<th>1</th>
<th>760</th>
<th>16,000</th>
<th>100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>RO$_2$Me</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RO$_2$Cl</td>
<td></td>
<td></td>
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<tr>
<td>RO$_2$Cl</td>
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<tr>
<td>RO$_2$Cl</td>
<td></td>
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</tr>
</tbody>
</table>
**Protective Groups:**
*Orthogonal Sets of Protecting Groups*

1. **Cleavage by basic solvolysis**

\[
\text{RO} \xrightarrow{\text{OH}^-} \text{ROH}
\]

\[
\begin{array}{ccc}
\text{RO}_{\text{Me}} & \text{RO} & \text{RO} \\
\text{RO} & \text{Cl} & \text{Cl} & \text{Cl} \\
{k_{rel}} & 1 & 760 & 16,000 & 100,000
\end{array}
\]

2. **Cleavage by acidic hydrolysis**

\[
\begin{array}{c}
\text{O} \text{O} \text{O} \\
\text{O} \xrightarrow{\text{H}^+} \text{HO} \text{OH} \\
\text{O} \text{O} \text{O} \\
\end{array}
\]

*Other groups easily cleaved by acid*
3. Cleavage by heavy metals

\[ \text{Protective Groups:} \]

\[ \text{Orthogonal Sets of Protecting Groups} \]

\[ \text{3. Cleavage by heavy metals} \]

\[ \text{Cleavage by heavy metals} \]

\[ \text{HgCl}_2 \rightarrow \text{Cleavage} \]

\[ \text{Protective Groups:} \]

\[ \text{Orthogonal Sets of Protecting Groups} \]
Protective Groups: Orthogonal Sets of Protecting Groups

3. Cleavage by heavy metals

\[ \text{HgCl}_2 \rightarrow \text{Ketone} \]

4. Cleavage by fluoride

\[ \text{Silicon-Silicon Bond Cleavage} \]

Strength of Si-F bond is 810 kJ/mol while Si-O bond is 530 kJ/mol
Protective Groups: Orthogonal Sets of Protecting Groups

5. Reductive Elimination

\[
\begin{align*}
\text{ROOC-Cl-Cl-Cl} & \xrightarrow{\text{Zn, AcOH}} \text{ROOC-ZnClCl} \\
\text{Troc} &= \text{trichloroethoxycarbonyl}
\end{align*}
\]
Protective Groups: Orthogonal Sets of Protecting Groups

5. Reductive Elimination

\[
\text{Rac} = \text{trichloroethoxycarbonyl}
\]

\[
\text{Zn, AcOH} \rightarrow \begin{array}{c}
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{Cl} \\
\text{Cl} \\
\text{Cl}
\end{array}
\end{array} \text{ZnCl} \quad -[\text{CO}_2] \rightarrow \text{ROH}
\]

6. $\beta$-elimination

\[
\text{Fmoc} = \text{9-fluorenylethoxycarbonyl carbamate}
\]

\[
\text{Mild base} \rightarrow \begin{array}{c}
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{Cl} \\
\text{Cl} \\
\text{Cl}
\end{array}
\end{array} \rightarrow \begin{array}{c}
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{Cl} \\
\text{Cl} \\
\text{Cl}
\end{array}
\end{array} \rightarrow \text{R}_2\text{NH}_2 + \text{product}
\]
Protective Groups: Orthogonal Sets of Protecting Groups

7. Hydrogenolysis

\[
\text{benzyl ether} \quad \xrightarrow{H_2, \text{Pd/C}} \quad \text{phenyl} + \text{ROH}
\]

Other examples of cleavable groups
**Protective Groups: Orthogonal Sets of Protecting Groups**

7. **Hydrogenolysis**

\[
\begin{align*}
\text{benzyl ether} & \quad \xrightarrow{H_2, Pd/C} \quad \text{benzene} + \text{ROH}
\end{align*}
\]

8. **Oxidation**

\[
\begin{align*}
p\text{-methoxybenzyl ether} & \quad \xrightarrow{DDQ \text{ or CAN, THF/H}_2\text{O}} \quad \text{MeO-phenylacetone} + \text{ROH}
\end{align*}
\]
Protective Groups: Orthogonal Sets of Protecting Groups

9. Dissolving Metal Reduction

\[
\text{Li/NH}_3, \ t-\text{BuOH} \rightarrow \begin{align*}
\text{Ph-OR} & \rightarrow \text{Ph} + \text{ROH} \\
\text{Ph-COOR} & \end{align*}
\]

Only other protecting group applicable to these conditions
Protective Groups:
Orthogonal Sets of Protecting Groups

9. Dissolving Metal Reduction

\[
\text{Ph} - \text{OR} \xrightarrow{\text{Li/NH}_3, \ t-\text{BuOH}} \text{Ph} + \text{ROH}
\]

Only other protecting group applicable to these conditions

10. Transition Metal Catalysis (i.e. Allyl-based protecting groups)

\[
\text{RO} = \text{C=C} \xrightarrow{\text{Pd, morpholine or dimedone}} \text{ROH}
\]

Can also use \((\text{Ph}_3\text{P})_3\text{RhCl}\) and acid
Protective Groups: Orthogonal Sets of Protecting Groups

11. Light

\[
\begin{align*}
\text{NO}_2 \quad \text{OR} & \quad \xrightarrow{h\nu} \quad \text{ROH} + \quad \text{NO} \quad \text{O} \\
\text{alcohol PG} & \quad \text{acid PG}
\end{align*}
\]
Protective Groups:
Orthogonal Sets of Protecting Groups

11. Light

\[
\text{NO}_2 \quad \text{OR} \quad \xrightarrow{h\nu} \quad \text{ROH} + \quad \text{NO} \quad \text{Ph} \quad \text{CO}
\]

12. Enzymes

\[
\text{NHFmoc} \quad \xrightarrow{\text{papain cysteine buffer}} \quad \text{NHFmoc}
\]

\[
\text{NHFmoc} \quad \xrightarrow{\text{wheat germ lipase}} \quad \text{NHFmoc}
\]
Protective Groups:
Relay Deprotection

 Relay deprotection: when a protecting group that is stable under most conditions is transformed chemically into a new, and more labile, protecting group.
Protective Groups: Mutual Protection

"Une pierre, deux oiseaux"
"Zwei Fleigen mit einer Klappe schlagen"
"To kill two birds with one stone"

Protective Groups: Sometimes Not-So-Innocent Bystanders

\[ \text{Some tricky chemistry} \]

\[ \text{NaCN, DMSO, 80 \degree C} \]

\[ \text{Transformation} \]

\[ \text{Final product} \]
Protective Groups: Sometimes Not-So-Innocent Bystanders
**Hydroxyl Protecting Groups:**

**Silyl Ethers**

<table>
<thead>
<tr>
<th>Me</th>
<th>Et</th>
<th>Me</th>
<th>Ph</th>
<th>i-Pr</th>
</tr>
</thead>
<tbody>
<tr>
<td>RO–Si–Me</td>
<td>RO–Si–Et</td>
<td>RO–Si–t-Bu</td>
<td>RO–Si–t-Bu</td>
<td>RO–Si–i-Pr</td>
</tr>
<tr>
<td>trimethylsilyl</td>
<td>triethylsilyl</td>
<td>t-butyldimethylsilyl</td>
<td>t-butyldiphenylsilyl</td>
<td>triisopropylsilyl</td>
</tr>
<tr>
<td>(TMS)</td>
<td>(TES)</td>
<td>(TBS or TBDMS)</td>
<td>(TBDPS)</td>
<td>(TIPS)</td>
</tr>
</tbody>
</table>
### Hydroxyl Protecting Groups: Silyl Ethers

<table>
<thead>
<tr>
<th>Group</th>
<th>Relative Acid Stability $t_{1/2}$ in 1% HCl/MeOH</th>
<th>Relative Base Stability $t_{1/2}$ in 5% NaOH/MeOH</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeRO-Si-Me</td>
<td>1 (&lt;1 min)</td>
<td>1 (&lt;1 min)</td>
</tr>
<tr>
<td>EtRO-Si-Et</td>
<td>64 (&lt;1 min)</td>
<td>10 - 100 (1 min)</td>
</tr>
<tr>
<td>MeRO-Si-t-Bu</td>
<td>20,000 (&lt;1 min)</td>
<td>20,000 (&gt; 24 h)</td>
</tr>
<tr>
<td>PhRO-Si-t-Bu</td>
<td>5,000,000 (255 min)</td>
<td>20,000 (&gt; 24 h)</td>
</tr>
<tr>
<td>i-PrRO-Si-i-Pr</td>
<td>700,000 (55 min)</td>
<td>100,000 (&gt; 24 h)</td>
</tr>
</tbody>
</table>

- **Trimethylsilyl** (TMS)
- **Triethylsilyl** (TES)
- **T-butyldimethylsilyl** (TBS or TBDMS)
- **T-butyldiphenylsilyl** (TBDPS)
- **Triisopropylsilyl** (TIPS)
**Hydroxyl Protecting Groups:**

**Silyl Ethers**

**Formation:**

\[
\begin{align*}
\text{OH} & \xrightarrow{R_3\text{SiCl, imidazole, DMF or } R_3\text{SiOTf, 2,6-lutidine, CH}_2\text{Cl}_2} \text{OSiR}_3 \\
R & \quad R \\
\end{align*}
\]

**Cleavage:**

\[
\begin{align*}
\text{OSiR}_3 & \xrightarrow{\text{Fluoride source}} \text{OH} \\
R & \quad R \\
\end{align*}
\]

**Common Fluoride Sources**

- HF
- 3HF·NEt₃
- HF·pyr
- n-Bu₄NF (TBAF)/AcOH
- HF·pyr/pyr
- n-Bu₄NF (TBAF)
Hydroxyl Protecting Groups:
Silyl Ethers

Selective Monosilylation of Diols is Possible:

\[
\text{NaH (1 eq), } \text{THF; TBSiCl, or n-BuLi (1 eq), THF; TBSiCl,}
\]

\[
\text{HO-} \rightarrow \text{HO-OTBS}
\]

\[
\text{MeO, TESO, N,} \text{Me, Me, Me, Me, OH}
\]

\[
\text{OTIPS, 2,6-lutidine, } \text{CH}_2\text{Cl}_2, -78{\degree}\text{C (97%)}
\]

\[
\text{MeO, TESO, N,} \text{Me, Me, Me, Me, OH}
\]

TESCl/imid and TESOTf/2,6-lutidine gave bis-silylated product

Hydroxyl Protecting Groups: Silyl Ethers

Selective Deprotection of Silyl Ethers is Also Possible:

HF-pyr, CH$_3$CN, 0 °C, 11 h (100%)

Taxol

Hydroxyl Protecting Groups: Silyl Ethers

Selective Deprotection of Silyl Ethers is Also Possible:

\[
\begin{align*}
\text{TBSO} & \quad \text{AcO} & \quad \text{OAc} & \quad \text{OAc} & \quad \text{OAc} & \quad \text{Me} & \quad \text{OH} & \quad \text{OH} & \quad \text{Me} & \quad \text{OH} \\
\text{Cl}_2\text{CHCO}_2\text{H} & \quad \rightarrow & \quad \text{TBSO} & \quad \text{AcO} & \quad \text{OAc} & \quad \text{OAc} & \quad \text{OAc} & \quad \text{Me} & \quad \text{OH} & \quad \text{OH} & \quad \text{Me} & \quad \text{OH} \\
\text{OAc} & \quad \text{OAc} & \quad \text{Me} & \quad \text{OH} & \quad \text{OH} & \quad \text{Me} & \quad \text{OH} & \quad \text{OH} & \quad \text{Me} & \quad \text{OH} & \quad \text{OH} & \quad \text{Me} & \quad \text{OH}
\end{align*}
\]

zaragozic acid

Hydroxyl Protecting Groups: Esters and Carbonates

- acetate (Ac)
- chloroacetate
- dichloroacetate
- trichloroacetate
- trifluoroacetate
- pivaloate (Pv)
- benzoate (Bz)
- p-methoxybenzoate
Hydroxyl Protecting Groups: Esters and Carbonates

In general, the ease with which esters hydrolyze under basic conditions increases with the acidity of the product acid. Sterics also can play a role (i.e. pivaloate group).

\[
\begin{align*}
\text{pivaloate (Pv)} & < \text{p-methoxybenzoate} \ < \text{benzoate (Bz)} \ < \text{acetate (Ac)} \\
\text{trifluoroacetate} & > \text{trichloroacetate} \ > \text{dichloroacetate} \ > \text{chloroacetate}
\end{align*}
\]

All can hydrolyze under acidic conditions, but typically only when water is present.
Hydroxyl Protecting Groups:
Esters and Carbonates

- **methyl carbonate**
- **t-butylcarbomate (Boc)** [resistant to nucleophilic attack]
- **allyl carbonate (Alloc)** [cleaved with Pd/Nu]
- **9-(fluorenylethyl) carbonate (Fmoc)** [cleaved by mild base]
- **2,2,2-trichloroacetyl carbonate (Troc)** [cleaved with Zn/HOAc]
- **2-(trimethylsilyl) ethyl carbonate (Teoc)** [cleaved with fluoride]
- **benzyl carbonate (Cbz)** [cleaved by hydrogenolysis]
Hydroxyl Protecting Groups: Esters and Carbonates

General methods for the formation of esters and carbonates:

\[
\text{ROH} + \text{Cl} \text{CO} \text{R'} \xrightarrow{\text{pyridine, 4-DMAP}} \text{RO} \text{CO} \text{R'}
\]

\[
\text{ROH} + \text{R'} \text{CO} \text{CO} \text{R'} \xrightarrow{\text{pyridine, 4-DMAP}} \text{RO} \text{CO} \text{R'}
\]

\[
\text{ROH} + \text{Cl} \text{CO} \text{R'} \xrightarrow{\text{pyridine}} \text{RO} \text{CO} \text{OR'}
\]

Hydroxyl Protecting Groups: Esters and Carbonates

General methods for the formation of esters and carbonates:

1. ROH + ClCOR' $\xrightarrow{\text{pyridine, 4-DMAP}}$ ROCOR'
2. ROH + R'CORCOR' $\xrightarrow{\text{pyridine, 4-DMAP}}$ ROCOR'
3. ROH + ClCOR' $\xrightarrow{\text{pyridine}}$ ROCOR'

Hydroxyl Protecting Groups: Esters and Carbonates

Tricks for selective formation of an ester from diol starting materials:

\[
\begin{align*}
\text{HO-CH-CH-OBn} & \xrightarrow{Bu_2SnO, \text{toluene, } 110^\circ C} \text{Sn-O-OBn} \\
\text{Sn-O-OBn} & \xrightarrow{AcCl, \text{CH}_2\text{Cl}_2, 0^\circ C} \text{AcO-CH-CH-OBn}
\end{align*}
\]

For a review, see: S. Hanessian, S. David, Tetrahedron, 1985, 41, 643.
Hydroxyl Protecting Groups: Esters and Carbonates

Tricks for selective formation of an ester from diol starting materials:

\[
\begin{align*}
\text{HO-\text{O}Bn} & \quad \xrightarrow{\text{Bu}_2\text{SnO, toluene, } 110^\circ C} \quad \text{O-\text{O}Bn} \\
\text{Bu} & \quad \text{Bu} \quad \text{Bu} \quad \text{Bu} \quad \text{Bu} \\
\text{AcCl, } \text{CH}_2\text{Cl}_2 & \quad 0^\circ C \quad \rightarrow \quad \text{AcO-\text{O}Bn} \\
\end{align*}
\]

\[
\begin{align*}
\text{Bu}_2\text{SnO, toluene, } \Delta; \quad \text{BnBr, } n-\text{Bu}_4\text{NI} & \quad 25 \rightarrow 110^\circ C \quad \rightarrow \quad \text{Me-O} \quad \text{Bn} \\
\text{Me} & \quad \text{O} \\
\text{HO} & \quad \text{OH} \\
\end{align*}
\]

The sterically least encumbered position is always protected selectively; on sugars, if both positions are secondary and steric is roughly equal, an equatorial alcohol will be protected selectively over an axially disposed alcohol.

For a review, see: S. Hanessian, S. David, Tetrahedron, 1985, 41, 643.
Hydroxyl Protecting Groups: Esters and Carbonates

Examples of selective deprotection:

\[
\text{Me} \quad \text{OMe} \quad \text{Cl} \quad \text{Me} \quad \text{Me} \quad \text{O} \quad \text{O} \\
\text{Me} \quad \text{Me} \quad \text{Me} \quad \text{OH} \quad \text{Me} \quad \text{OH} \\
\text{Me} \quad \text{Me} \quad \text{Me} \quad \text{OH} \quad \text{Me} \quad \text{OH} \\
\]

\[n-\text{PrNH}_2 \rightarrow \text{Me} \quad \text{OMe} \quad \text{Cl} \quad \text{Me} \quad \text{Me} \quad \text{O} \quad \text{OH} \]

\[\text{(83\%)} \]

Hydroxyl Protecting Groups: Esters and Carbonates

Examples of selective deprotection:

Hydroxyl Protecting Groups: Acetals

- **methoxymethyl ether (MOM)** [cleaved with strong acid]
- **benzyloxymethyl ether (BOM)** [cleaved by hydrogenation]
- **2,2,2-trichloroethoxy methyl ether** [cleaved with Zn]
- **2-(trimethylsilyl) ethoxymethyl ether (SEM)** [cleaved with fluoride]

- **methylthiomethyl ether (MTM)** [cleaved with HgCl₂ or AgNO₃]
- **p-methoxybenzyl ether (PMBM)** [cleaved with DDQ]
- **tetrahydropyranyl ether (THP)** [cleaved with mild acid]
**Hydroxyl Protecting Groups: Acetals**

**Formation of acetals:**

\[
\text{ROH} + \text{R'}\text{OCH}_2\text{X} \xrightarrow{i-\text{Pr}_2\text{NEt or NaH, solvent}} \text{RO} - \text{OR'}
\]

\[
\text{ROH} + \text{Dioxane} \xrightarrow{\text{PPTS or p-TsOH}} \text{RO} - \text{OR}
\]

**PPTS = pyridinium p-toluenesulfonate**

---

Hydroxyl Protecting Groups: Ethers

- **allyl ether** [cleaved with Pd/Nu]
- **trityl ether** [cleaved by strong acid]
- **benzyl ether (Bn)** [cleaved by hydrogenation]
- **p-methoxybenzyl ether (PMB)** [cleaved with DDQ]
- **dimethyl acetonide** [cleaved with acid]
- **benzylidene acetal** [cleaved by hydrogenation]
**Hydroxyl Protecting Groups:**

**Ethers**

*Formation of ethers*

\[
\text{ROH} + \text{R'}X \xrightarrow{\text{NaH, solvent}} \text{ROR'}
\]

*Exception is trityl groups; they require Ph\textsubscript{3}CCl and 4-DMAP at elevated temperatures.*

*Concept applies to any group that can be appended to a diol. Thus, to form a benzylidene acetal, one should use benzaldehyde.*
Hydroxyl Protecting Groups: Ethers

What about polyols? Which cyclic ether will be formed selectively?

\[
\text{HO-} \quad \text{HO-} \quad \text{HO-}\ \\
\text{Me} \quad \text{Me} \quad \text{Me} \\
\text{p-TsOH} \quad (A:B = 5:1)
\]

\[
\text{Me} \quad \text{Me} \quad \text{Me} \quad \text{OH} \ \text{Me} \\
\text{Me} \quad \text{Me} \quad \text{Me} \quad \text{O} \\
A \\
+ \\
\text{Me} \quad \text{Me} \quad \text{Me} \quad \text{HO} \ \\
\text{Me} \quad \text{Me} \quad \text{Me} \quad \text{O} \\
B
\]

In general, simple acetonide formation with 1,2-diols occurs in preference to 1,3-diols. Note, though, that benzylidene acetals display reverse selectivity!

Hydroxyl Protecting Groups: Ethers

What about polyols? Which cyclic ether will be formed selectively?

The case of a 1,2,3-polyol

In general, the more substituted acetonide is favored, especially when the substituents on the 5-membered ring are in a trans orientation; in a cis case, the less substituted acetonide might be favored.

Hydroxyl Protecting Groups: Ethers

What about polyols? Which cyclic ether will be formed selectively?

The case of a 1,2,3-polyol

In general, the more substituted acetonide is favored, especially when the substituents on the 5-membered ring are in a trans orientation; in a cis case, the less substituted acetonide might be favored.

Phenol Protecting Groups

- methyl ether [cleaved with TMSI, BBr₃, or 9-Br-9-BBN]
- t-butyl ether [cleaved with neat TFA]
- benzyl ether
- allyl ether

- silyl ethers
- phenyl esters
- phenyl carbonates
- acetals

Protecting groups cleaved by base or acid are typically far more labile on phenols than a standard aliphatic alcohol. This property has important implications, as it explains why phenolic methyl ethers can be cleaved, whereas standard methyl ethers are effectively the Rock of Gibraltar when it comes to deprotection (i.e., it ain't coming off)!
Phenol Protecting Groups: Methyl Ethers

Phenol Protecting Groups: Methyl Ethers

Carbonyl Protecting Groups

MeO OMe
R R'
dimethyl acetal

O O
R R'
1,3-dioxane

O O
R R'
1,2-dioxolane

All are formed by the action of an acid with the appropriate alcohol

Reactivity order towards forming these protecting groups:

\[
\text{phenylacetone} = R \text{CHO} > R \text{CO}R' = \text{cyclohexanone} > \text{cyclopentanone} > R \text{C}R' = \ \text{six-membered ketone} >> \text{benzil}
\]
**Carbonyl Protecting Groups**

*Rates of formation:*

\[
\begin{align*}
    \text{Me} - \text{Me} & > \text{Me} - \text{OH} > \text{OH} - \text{OH} \\
    \text{HO} - \text{Me} & > \text{HO} - \text{Me} > \text{OH} - \text{OH}
\end{align*}
\]

*Rates of cleavage:*

\[
\begin{align*}
    R - O - C - O & > R - O - C - O \\
    R - O - C - O & > R - O - C - O \\
    R - O - C - O & > R - O - C - O
\end{align*}
\]

\[
\begin{align*}
    k_{rel} & = 50,000 \\
    k_{rel} & = 5,000 \\
    k_{rel} & = 1
\end{align*}
\]

Carbonyl Protecting Groups

\[
\text{Me} \quad \text{O} \\
\text{O} \\
\text{K} \quad \text{N} \\
\text{O} \\
\text{H} \quad \text{O} \\
\text{H} \\
\text{O} \\
\text{H} \\
\text{O}
\]

\[
\text{HO-} \quad \text{OH} \\
\rightarrow \\
\text{p-TsOH} \\
(95\%)
\]

\[
\text{Me} \quad \text{O} \\
\text{O} \\
\text{K} \quad \text{N} \\
\text{O} \\
\text{H} \quad \text{O} \\
\text{H} \\
\text{O} \\
\text{H} \\
\text{O}
\]
Carbonyl Protecting Groups

\[
\text{MeO} \quad \overset{\text{HO-\text{CHOH}}}{{\text{MeO}}} \quad \overset{\text{HO-\text{CHOH}}}{{\text{MeO}}} \\
\text{MeO} \quad \overset{\text{HO-\text{CHOH}}}{{\text{MeO}}} \quad \overset{\text{HO-\text{CHOH}}}{{\text{MeO}}} \\
\text{MeO} \quad \overset{\text{HO-\text{CHOH}}}{{\text{MeO}}} \quad \overset{\text{HO-\text{CHOH}}}{{\text{MeO}}}
\]

\[
\frac{\text{HOOCC}}{\text{MeO}} \quad \overset{\text{HO-\text{CHOH}}}{{\text{MeO}}} \quad \overset{\text{HO-\text{CHOH}}}{{\text{MeO}}} \\
\text{MeO} \quad \overset{\text{HO-\text{CHOH}}}{{\text{MeO}}} \quad \overset{\text{HO-\text{CHOH}}}{{\text{MeO}}} \\
\text{MeO} \quad \overset{\text{HO-\text{CHOH}}}{{\text{MeO}}} \quad \overset{\text{HO-\text{CHOH}}}{{\text{MeO}}}
\]

\[
\begin{align*}
fumaric acid (pK_a = 3.03) & \quad 100 & \quad 0 \\
phthalic acid (pK_a = 2.89) & \quad 70 & \quad 30 \\
oxalic acid (pK_a = 1.23) & \quad 80 & \quad 20 \\
p-TsOH (pK_a < 1.0) & \quad 0 & \quad 100
\end{align*}
\]
Carbonyl Protecting Groups

- dimethyl thioacetal
- 1,3-dithiane
- 1,2-dithiolane
- cyanohydrin

[deprotected with Hg, NBS, IBX]
Carbonyl Protecting Groups

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[deprotected with Hg, NBS, IBX]

Special uses for these protecting groups:

These groups turn aldehydes into nucleophiles

"O"  "O"  "O"

Umpolung = formal reversal of the polarity of a functional group
Carboxylic Acid Protecting Groups

- methyl ester
- t-butyl ester
- allyl ester
- silyl ester [must be TBS, TBDPS, or TIPS if you want to purify by chromatography]

- benzyl ester
- p-methoxybenzyl ester
- ortho ester
Amine Protecting Groups

- **methyl carbamate**
- **t-butyl carbamate (Boc)** [resistant to nucleophilic attack]
- **allyl carbamate (Alloc)** [cleaved with Pd]
- **benzyl carbamate (Cbz)** [cleaved by hydrogenolysis]

- **9-(fluorenylmethyl) carbamate (Fmoc)** [cleaved by mild base]
- **2,2,2-trichloroacetyl carbamate (Troc)** [cleaved with Zn/HOAc]
- **2-(trimethylsilyl) ethyl carbamate (Teoc)** [cleaved with fluoride]
Protecting Groups: Putting it all Together

1. Boc$_2$O, Et$_3$N, 4-DMAP, CH$_2$Cl$_2$, 25 °C
2. AcOH/H$_2$O (19:1), 80 °C
   (62% overall)

p-TsCl, n-Bu$_2$SnO,
Et$_3$N, CH$_2$Cl$_2$, 25 °C
   (84%)

NaHCO$_3$, DMF, 80 °C
   (83%)

Protective Groups: Sometimes They Really Are Not Needed . . .

With protecting group present on the other alcohol, dramatically lower yields observed