Chem 6352
Protecting Groups

Hydroxyl Protection

*Methyl Ethers*

\[
\text{Formation: CH}_2\text{N}_2, \text{SiO}_2 \text{ or HBF}_4
\]
\[
\text{NaH, MeI, THF}
\]

*Stability:* Stable to Acid and Base

*Cleavage:* AlBr\(_3\), EtSH
\[
\text{PhSe}^-, \text{Ph}_2\text{P}^- \\
\text{Me}_3\text{SiI}
\]

*Adv./Disadv.:* Methyl ethers, with the exception of aryl methyl ethers, are often difficult to remove. However, there are exceptions.

\[
\text{Formation: MeSCH}_2\text{Cl, NaH, THF}
\]

*Stability:* Stable to base and mild acid

*Cleavage:* HgCl\(_2\), CH\(_3\)CN, H\(_2\)O
\[
\text{AgNO}_3, \text{THF, H}_2\text{O, base}
\]

*Adv./Disadv.:* The MTM group is a nice substituted methyl ether protecting group that can be removed under neutral conditions employing the indicated thiophiles.
Trityl Ethers

Formation: \( \text{Ph}_3\text{CCl}, \text{pyridine}, \text{DMAP} \)
\( \text{Ph}_3\text{C}^+\text{BF}_4^- \)

Stability: Stable to Base

Cleavage: Mild Acid (formic or acetic)

Adv./Disadv.: The trityl group usually goes on and comes off easily. In addition, its steric bulk allows for good selectivity in protecting primary over secondary alcohols.

Protection of 1,2- and 1,3-diols

The protecting groups that mask 1,2- and 1,3-diols (forming either the dioxolane or dioxane, respectively) are often referred to (PREFIX)ylidenes, where the prefix depends on the nature of \( R \) and \( R_1 \).

Isopropylidene (a.k.a. acetonide)

Formation: 2,2-dimethoxy propane or 2-methoxy propene and cat. acid

Stability: Stable to base

Cleavage: cat. Camphor Sulfonic Acid (CSA) and MeOH

Adv./Disadv.: The acetonide is commonly used to protect 1,2- and 1,3-diols. It forms readily and is easily removed. Generally, the acetonide will form a dioxolane selectively over a dioxane.
Cycloalkylidenes

Formation: Corresponding ketone or dimethyl acetal and acid catalyst
Stability: Stable to base
Cleavage: cat. Camphor Sulfonic Acid (CSA) and MeOH
Adv./Disadv.: Similar to acetonides

Benzylidene

Formation: PhCHO, H⁺, H₂O removal
             PhCH(OMe)₂, H⁺
Stability: Stable to base
Cleavage: cat. Camphor Sulfonic Acid (CSA) and MeOH
          H₂, catalyst
Adv./Disadv.: The benzyldienes are readily formed; in competition between
               1,2- and 1,3-diols they will generally form the dioxane.
               Hydrogenolysis provides a nice orthogonal mode of
deprotection. However, benzyldienes are usually
hydrogenolyzed more slowly than benzyl ethers or olefins.

p-Methoxy Benzyldene

Formation: See benzyldienes
Stability: Stable to Base
Cleavage: AcOH, H₂O CAN
Adv./Disadv.: The PMB and Bn acetals have many advantages and are usually easy to prepare and cleave. The PMB and Bn acetals can undergo a variety of interesting transformations, for example:

Carbonates

Formation: Phosgene, pyridine
Triphosgene, pyridine
Carbonyl diimidazole
Stability: Stable to Base
Cleavage: Easily removed with ‘OH or ‘H
Adv./Disadv.: Carbonates are generally easy to put on and take off and provide nice orthogonality to the numerous acid labile protecting groups for 1,2- and 1,3-diols.
Protecting Groups for Ketones and Aldehydes

Aldehydes and ketones are most often protected as cyclic and acyclic actals.

Formation:

\[
\text{R} - \text{O} \quad \xrightarrow{\text{MeOH, } H^+} \quad \text{R} - \text{OMe}
\]

\[
\begin{align*}
(CH_2OH)_2, H^+ & \quad \xrightarrow{\text{PhH, } -H_2O} & \text{TL 1988, 29, 4085} \\
\text{-or-} (CH_2OSiMe}_3)_2 & \quad \text{TMS-OTf, CH}_2Cl_2
\end{align*}
\]

\[
\begin{align*}
\text{CH}_2(CH_2OH)_2 & \quad \xrightarrow{H^+, \text{PhH, } -H_2O} & \text{R} - \text{O}
\end{align*}
\]

Stability: Stable to base

Cleavage: Acetals are generally removed with H$_3$O$^+$. Cleavage rates of 1,3-dioxanes have been studied (Chem Rev 1967, 67, 427) and are:

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

Adv./Disadv.: Acetals are generally easily prepared and removed. It is of note that α,β-unsaturated carbonyls form acetals much slower than their saturated counter parts, and often result in olefin migration.

\[
\begin{align*}
\text{CH}_2(CH_2OH)_2 & \quad \xrightarrow{H^+, \text{PhH, } -H_2O} & \text{R} - \text{O}
\end{align*}
\]
Carboxylic Acid Protection

Alkyl Esters

\[
\begin{align*}
R \text{OH} & \quad \rightarrow \quad R \text{OR'} \\
\text{Formation:} & \quad \text{Fisher esterification (RCOOH + R'OH + } H^+ ) \\
\text{Acid chloride + ROH, pyridine} & \\
\text{t-Butyl esters: isobutylene, } H^+ & \\
\text{Methyl esters: diazomethane} & \\
\text{Stability:} & \quad \text{t-Butyl: stable to mild base and ammonia} \\
& \quad \text{Others: stable to acid} & \\
\text{Cleavage:} & \quad \text{t-Butyl: cleaved by moderately acidic hydrolysis} \\
& \quad \text{Others: LiOH, THF, } H_2O & \\
& \quad \text{enzymatic hydrolysis} & \\
\end{align*}
\]

Review: Org Reactions 1989, 37, 1

9-Fluorenylmethyl Esters (Fm)

\[
\begin{align*}
\text{TL 1983, 24, 281} & \\
\text{RCO}_2\text{H} & \quad \rightarrow \quad \text{DCC} \\
\text{Note that DCC coupling proceeds as follows:} & \\
\end{align*}
\]

\[
\begin{align*}
\text{Stability:} & \quad \text{Fm is stable to acid} \\
\text{Cleavage:} & \quad \text{Fm is cleaved by mild base (Et}_2\text{NH)} & \\
\end{align*}
\]
2-(Trimethylsilyl)ethoxymethyl Esters (SEM)
*Helv Chim Acta* 1977, 60, 2711

\[
\begin{align*}
\text{RCO}_2\text{H} & \quad \text{HO} - \text{O} - \text{SiMe}_3 \\
& \quad \xrightarrow{\text{DCC}} \\
& \quad \text{R} - \text{O} - \text{O} - \text{SiMe}_3 \\
\end{align*}
\]

Stability: Stable to Acid
Cleavage: SEM is removed with fluoride (e.g. TBAF in DMF)

---

2-(Trimethylsilyl)ethyl Esters
*JACS* 1984, 106, 3030

\[
\begin{align*}
\text{RCO}_2\text{H} & \quad \text{HO} - \text{SiMe}_3 \\
& \quad \xrightarrow{\text{DCC}} \\
& \quad \text{R} - \text{O} - \text{SiMe}_3 \\
\end{align*}
\]

Stability: Stable to Acid
Cleavage: SEM is removed with fluoride (e.g. TBAF in DMF)

---

2,2,2-Trichloroethyl Ester
*JACS* 1966, 88, 852

\[
\begin{align*}
\text{RCO}_2\text{H} & \quad \text{HO} - \text{CCl}_3 \\
& \quad \xrightarrow{\text{DCC}} \\
& \quad \text{R} - \text{O} - \text{CCl}_3 \\
\end{align*}
\]

Stability: Stable to Acid
Cleavage: Zn, AcOH

---

Benzyl Esters

\[
\begin{align*}
\text{R} & \quad \text{Cl} & \quad \text{HO} - \text{Ph} & \quad \xrightarrow{\text{Et}_3\text{N, DMAP}} \\
& \quad \xrightarrow{\text{CH}_2\text{Cl}_2, 0 \text{ }^\circ \text{C}} \\
& \quad \text{R} - \text{O} - \text{Ph} \\
\end{align*}
\]

Note: DMAP = 4-dimethylamino pyridine

For a review of 4-dialkylaminopyridines see *ACIEE* 1978, 17, 569

Formation: Acid Chloride and benzyl alcohol (see above)
Stability: Stable to Acid
Cleavage: Hydrogenolysis
Na, NH\textsubscript{3}
**o-Nitrobenzyl esters**

*Synth* **1980, 1**

![Chemical structure of o-Nitrobenzyl esters]

Formation: see Benzyl  
Stability: see Benzyl  
Cleavage: can be cleaved by photolysis

**Orthoesters**

*TL* **1983, 24, 5571**

![Chemical reaction of Orthoesters]

Formation: See above reaction  
Stability: Stable to Base!  
Cleavage: Removed with mild acid
Protection of Amines

9-Fluorenymethyl carbamate (FMOC)

*Acc Chem Res* 1987, 20, 401

![Chemical structure of FMOC](image)

Formation: As above

Stability: Stable to acid

Cleavage: Removed with amine base: Et₂N, piperidine, etc.

2,2,2-Trichloroethyl Carbamate (TROC)

![Chemical structure of TROC](image)

Formation: As above

Stability: Stable to mild base and acid

Cleavage: Zn dust

2-(Trimethylsilyl)ethyl Carbamate (TEOC)

![Chemical structure of TEOC](image)

Formation: As above

Stability: Stable to mild base and acid

Cleavage: TBAF or TFA
**t-Butyl Carbamate (BOC)**

![Chemical structure of t-Butyl Carbamate (BOC)]

Formation: As above (and many others)

Stability: Stable to base

Cleavage: Strong protic acid (TFA or 3M HCl)

TMSI

**Allyl Carbamate (ALLOC)**

*TL 1986, 27, 3753*

![Chemical structure of Allyl Carbamate (ALLOC)]

Formation: As above or with Alloc-Cl

Stability: Stable to mild base and acid

Cleavage: Removed with Pd(0) and reducing agent

**Benzyl Carbamate (CBZ)**

![Chemical structure of Benzyl Carbamate (CBZ)]

Formation: As above

Stability: Stable to mild base and acid

Cleavage: Hydrogenolysis

PdCl₂, Et₂SiH

TMSI

BBr₃

hv (254 nm)

Na/NH₃
**Sulfonamides (Ts, Ms)**

\[ \text{TsCl, pyr} \rightarrow t\text{-BuO} \text{NR}_2 \]

Formation: As above  
Stability: Usually stable to acid and base  
Cleavage: Reduction (Mg, NH₄Cl, MeOH)  
For 3-substituted indoles basic hydrolysis

**isobutylidi-tert-butylsilyl (BIBS)**

OL 2011, 13, 4120

\[ \text{R}_2\text{NH} \rightarrow \text{R}_2\text{N-Si} \]

Formation: As above  
Stability: Stable to mild base and acid  
Cleavage: Removed fluoride