Protecting groups are a sad fact of synthetic chemistry
They are usually needed, but rarely desired
Many syntheses have stalled because of trouble putting on or removing protecting groups

4 basic questions to address when choosing a P.G.:
1. Can I put it on where and only where I want?
2. Can I take it and only it off?
3. Will it survive all future reaction conditions?
4. Will it affect the reactivity of my substrate?

Your guide to these questions should be: Protective Groups in Organic Synthesis by Theodora Greene and Peter Wuts

An even better strategy is to plan your syntheses to avoid protecting groups

We will discuss general features of protecting groups, for specific examples and exotic methods for attachment or removal, see Greene

4 major classes: silyl ethers, ethers, esters, acetals

Silyl Ethers

TMS  TES  TBS or TBDMS  TIPS  TBDPS

TBS: Corey, JACS, 1972, 6190 (23rd most cited JACS paper)

ON: OH

R₃SiCl, Imidazole
DMF

OSiR₃

via

R₃SiOTf
2,6-lutidine, CH₂Cl₂

OSiR₃

These transformations are very water sensitive.
Less Common methods for Silyl introduction:

Brook Rearrangement

<table>
<thead>
<tr>
<th>bond</th>
<th>BDE (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C−Si</td>
<td>69</td>
</tr>
<tr>
<td>O−Si</td>
<td>103</td>
</tr>
<tr>
<td>F−Si</td>
<td>141</td>
</tr>
</tbody>
</table>

question: using approx. pKa values and the BDE above, estimate Keq for different R’s in the equation 1.

Other potential methods:
Hydrosilylation of ketones: always some stupid silyl group
Tamao oxidation of alkyl silanes: Silyl group rarely survives
silyl migrations
-smaller is faster
-1,2 and 1,3 most common
-good if planned; usually not planned

Note: 2 primary alcohols would make selective protection difficult
Molander, JOC 1994, 7148

how does this happen?

Migrations likely via associative displacement:

Removal

Usually F\(^-\) or H\(^+\)
Usually, bigger is more stable

| Silyl group | $k_{rel}$ H\(^+\) | $k_{rel}$ OH
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TMS</td>
<td>5,000,000</td>
<td>500,000</td>
</tr>
<tr>
<td>TES</td>
<td>100,000</td>
<td>50,000-5,000</td>
</tr>
<tr>
<td>TBDMS</td>
<td>250</td>
<td>5</td>
</tr>
<tr>
<td>TIPS</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>TBDPS</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Recall BDE: O-Si (~100 kcal/mol) vs F-Si (~140 kcal/mol)

Common F\(^-\) sources:
- TBAF (nBu\(_4\)NF)
- HF-Pyridine
- 3HF-Et\(_9\)N
- HF
- TASF [tris(dimethylamino)sulfonium difluorotrimethylsilicate]

TBAF (nBu\(_4\)NF)
relative rates of Fluoride-induced cleavage:

<table>
<thead>
<tr>
<th>Silyl group</th>
<th>1/2 life</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBS</td>
<td>20 min</td>
</tr>
<tr>
<td>TIPS</td>
<td>15 min</td>
</tr>
<tr>
<td>tHexDMS</td>
<td>15 min</td>
</tr>
<tr>
<td>TBDPS</td>
<td>50 min</td>
</tr>
<tr>
<td>TPS</td>
<td>2.5h</td>
</tr>
</tbody>
</table>

Selective cleavage (review: Synthesis, 1996, 1065)

\[
\text{TBSO} \quad \text{OTBDMS} \quad \text{2\% HF, CH}_3\text{CN} \quad \text{OH} \quad \text{OTBDMS} \quad \text{OPiv}
\]

Masamune, TL, 1985, 5239

Commercial TBAF is wet (to varying degrees). Dry TBAF is very basic; may need buffer:

Conditions often need to be determined empirically

Carreira, Du Bois JACS, 1995, 8106
Ethers

usually very robust, with orthogonal modes of removal

usually:

\[
R-OH + R'-LG \rightarrow R-O-R'
\]

commmon ethers:

**Methyl ether**: easy on, hard off. Usually only good for phenols

On: MeI, Me₂SO₄, Me₃O BF₄

Off: BBr₃, TMSI,

**Benzyl ether (Bn)**

On: usually BnCl + base; sometimes with cat. I⁻ (do you know what I⁻ does?)

Off: H₂, Pd/C - competitive (usually slower) than olefin reduction

Lewis Acid: SN1 mechanism

Na/NH₃

\[
\text{Ph}_2\text{SnO} + \text{R}^+ \rightarrow \text{Ph}_2\text{Sn} + \text{R}^+\text{O}^{-}\]

CrO₃: via benzoate

\[
\text{Ph}_2\text{SnO} + \text{CrO}_3 \rightarrow \text{Ph}_2\text{Sn} + \text{CrO}_3^\text{+}
\]

**allyl ether**

on: usually allyl Br/Cl + base. Usually easy

This is a general method for monprotection of a 1,2 diol (not limited to allyl). In this case, note selective formation with equitorial OH's.

Off: Isomerization with base or transition metal, then hydrolysis:

\[
\text{R-O} + \text{B}^- \text{or M} \rightarrow \text{R-O} \rightarrow \text{R-O} + \text{H}_3\text{O}^+ \rightarrow \text{R-OH}
\]
**p-methoxybenzyl (PMB or MPM)**

On: PMB-Cl, base

\[
\text{R}^\text{+} + \text{CF}_3\text{CONH} \xrightarrow{\text{H}^+ \text{ or Lewis Acid}} \text{R}^\text{-} + \text{CF}_3\text{CONH}_2
\]

Off: Oxidation

\[
\text{O} \xrightarrow{[\text{O}]} \text{H}_2\text{O} \xrightarrow{\text{R}^\text{+}} \text{R}^\text{+}
\]

[O] = DDQ, CAN, Ph$_3$BF$_4$, Br$_2$, NBS

Intermediate can be intercepted:

- PMBO
- Methyl (trityl)

**o-nitrobenzyl**

Off: $h\nu$

\[
\text{O} \xrightarrow{h\nu} \text{HO} \xrightarrow{1,5 \text{ H abstraction}} \text{HO} \xrightarrow{\text{H}_2\text{O}} \text{R}^\text{-}
\]

example:

Wen-Hong Li, JACS, 2004, 4653

Triphenyl Methyl (trityl)

On: Ph$_3$Cl, via $S_N^1$

Off: Acid

Hoffman, ACIEE, 1993, 101
acetals of mono-ols:
  many eg's of the form \( R\O\O\O\O' \)
  advantages:
  \( \text{Cl} \O\O\O\O' \) very active electrophile
  likely forms \( \O\O\O\O' \)

Methoxy Methyl (MOM)
  On:
  \( \text{Cl} \O\O\O\O' \) 'MOM-Cl' thought to be very toxic
  even more toxic
  Off: Acid

Benzyloxy methyl (BOM)
  On:
  \( \text{Cl} \O\O\O\O' \) Ph
  Off: all the methods for removing Bn groups:

Masamune, TL, 1985, 5239

Tetrahydropyranyl (THP)

\[
\begin{array}{c}
R\O\O\O + \text{H}^+ \rightarrow \text{O}\O\O\O\O \O\O\O\O R \\
\end{array}
\]

Easy on, easy off, cheap.
But get diastereomers with chiral molecules:

can complicate NMR spectra (and sometimes chromatography)
Protecting Groups in Organic Synthesis-8

Cyclic acetal are wonderful protecting groups for 1,2 and 1,3 diols.

Some of the most common:

- 'acetonide'

Most stable → least stable

Usually, 1,2 > 1,3 > 1,4

On: MeO or OMe  Cat. H+ or cat. H+

Why not acetone + H+?

*Hint:* Consider pKa's of protonated ketones vs ethers

Reactions often under thermodynamic control:

- Corey...Falck...JACS, 1978, 4620

Oxonium intermediates can be intercepted

- TL 1988, 1823
**benzylidene acetals**

On: PhCHO/H⁺ or Lewis acid

Off: H₂O⁺ or H₂ Pd/C

Can be converted to benzyl:

MeO₂C—CO₂Me

do you know how?

Ph

O

O

OP

H

Me

H

AlR₂

1.417Å

1.404Å

from X-ray

Schreiber, TL, 1988, 4085.

Usually see protection of less hindered OH

For protection of more hindered OH by a similar reaction, see Yamamoto, TL, 1988, 1947-1950
Esters as protecting groups

In general, ease of introduction and removal is function of steric and electronic effects:

usually:

\[ R\text{OH} + R'\text{LG} \rightarrow R'\text{O}R' \]

egs

\[ R'\text{Cl} \quad R'\text{O}R' \quad R'\text{OCl} \]

‘Yamaguchi conditions’ more often for macrolactonizations

Include CH2N2
Cleavage: base hydrolysis rates depend on sterics and electronics

\[
\begin{align*}
\text{Piv} & \quad \text{Bz} & \quad \text{Ac} & \quad \text{TFA} \\
\text{more stable} & \quad \rightarrow & \quad \text{less stable}
\end{align*}
\]

Lipases: ester (usually Ac) on or off under mild conditions; often enantioselectively

\[
\begin{align*}
\text{kinetic resolution} & \quad \text{for references, see Greene, 3rd ed. p156}
\end{align*}
\]
Protecting Groups in Organic Synthesis-12

**Carbonates**

- Similar deal as with esters, but more stable to base. Also, some alternative cleavage methods possible.

<table>
<thead>
<tr>
<th>Group</th>
<th>Cleavage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fmoc</td>
<td>$\text{B}=\text{Et}<em>3\text{N}, T</em>{1/2}=20\text{min}$</td>
</tr>
<tr>
<td>Troc</td>
<td>$\text{Zn(0)}$</td>
</tr>
<tr>
<td>Teoc</td>
<td>$\text{LA}=$lewis acid</td>
</tr>
<tr>
<td>Alloc</td>
<td>$\text{cat Pd(0)}$</td>
</tr>
</tbody>
</table>

**Dimethyl Thiocarbamate**

- **On:**
  
  $\text{R-OH} \xrightarrow{\text{NaH; } \text{Me}_2\text{N-Cl}} \text{RO'NMe}_2$
  
  or
  
  $\text{R-OH} \xrightarrow{\text{Me}_2\text{NH}} \text{RO'NMe}_2$

- **Stable to:** Cr(VI); EtMgBr; DIBAL; LiAlH$_4$; BH$_3$; nBuLi; Wittig; TBAF; DDQ; TiCl$_4$

- **OFF:**

  $\text{S-NMe}_2 \xrightarrow{\text{NaIO}_4} \text{S-OH} \xrightarrow{\text{H}_2\text{O}} \text{ROH}$

    or $\text{NaOH/H}_2\text{O}_2$

Falck, Org. Lett., 2003, 4755
Protection for carboxylate

 Mostly, same deal as ester and carbonate

<table>
<thead>
<tr>
<th>protected substrate</th>
<th>deprotection</th>
</tr>
</thead>
<tbody>
<tr>
<td>OMe</td>
<td>K$_2$CO$_3$/MeOH</td>
</tr>
<tr>
<td>OCF$_3$</td>
<td>H$^+$ (TFA, HCl, TsOH)</td>
</tr>
<tr>
<td>Ph</td>
<td>H$_2$ Pd/C or Li/NH$_3$</td>
</tr>
<tr>
<td>OEt</td>
<td>Pd(0), NuH</td>
</tr>
</tbody>
</table>

as before, enzymes can work

PLE = pig liver esterase
When enzymes work, they're nearly perfect.
Hard to get ent-PLE

ortho esters: not electrophilic, no acidic protons

step 1

\[
\text{HO} + \text{EtO} \rightarrow \text{KO} \rightarrow \text{HO} \]

step 2

\[
\text{various ways} \rightarrow \text{BF}_3 \text{Et}_2\text{O} \rightarrow \text{R} \]

Corey, TL 1983, 5571

eg

1. BF$_3$ Et$_2$O
2. PPh$_3$
3. KN(TMS)$_3$

Corey, JACS, 1985, 4339
Protection for amines

Mostly carbamates; same deal as ester and carbonate

On:

-OBt

R₂NH +

-OSu

Group Removal

Group

R₂N

O

O

O

OBt

Boc

Teoc

alloc

Meldrum's acid

R₂N

O

O

O

NaOH; PrSLi

amine base (piperidine most common)

Fmoc

Cbz

TFA

Removal

acid (TFA most common)

F⁻ (TBAF most common)

Pd(0), NuH

Meldrum's acid; common

NuH

H₂, Pd/C; Na/NH₃

NaOH
Benzyl groups for amine protection

On:

Simple alkylation can be difficult

\[
\text{R-NH}_2 + \text{BnCl} \rightarrow \text{R-NHBn} + \text{R-NBn}_2 + \text{R-NBn}_3 \quad \text{Cl}^{-}
\]

2 step method

\[
\text{R-NH}_2 + \text{BzCl} \rightarrow \text{R-CONHBz} \quad \text{Ph} \quad \text{LiAlH}_4 \rightarrow \text{R-NHBz} \quad \text{Ph}
\]

Reductive amination

\[
\text{R-NH}_2 + \text{O} \quad \text{Ph} \quad \text{AcOH, NaCNBH}_3 \rightarrow \text{R-NHBz} \quad \text{Ph}
\]

Schiff's bases:
Many examples, benzhydryl one of most common

\[
\text{R-NH}_2 + \text{O} \quad \text{Ph} \quad \text{H}^+ - \text{H}_2\text{O} \rightarrow \text{R-N} \quad \text{Ph} \quad \text{Ph}
\]

Sulfonates

Tosyl: Easy on (TsCl); can be difficult to remove
Nosyl (Ns) nice alternative:

\[
\text{C}_8\text{H}_{17} \quad \text{HN} \quad \text{CO}_2\text{Me} \quad \text{Ns} \quad \text{Br} \quad \text{Cs}_2\text{CO}_3 \quad 0.1\text{M} \quad 86\%
\]

Nucleophilic aromatic substitution

Review: Fukuyama
Chem Comm. 2004, 353
Protection of carbonyl group

mostly of the form: \( X - Y \)

\( X \) and \( Y \) = OR, SR, NR, CN

Most common:

\[
\begin{align*}
\text{dimethyl acetal} & \quad \text{1,3 dioxane} \\
\text{dimethyl thioacetal} & \quad \text{1,3 dithiane}
\end{align*}
\]

acetals:

Formation:

\[
\text{HO}-(\text{CH}_2)_n\text{OH} + \text{ketone} \xrightarrow{TsOH \text{ or } HCl} \text{PPTS, acetone (100%)} \quad \text{or} \quad \text{H}_2\text{O, } \Delta \quad \text{1M HCl (71%)}
\]

Relative rates: for the ketone, relative rates same as normal addition to carbonyls: aldehyde > acyclic ketone ~ cyclohexanone > cyclopentanone > enone >> aromatic ketone

Many variations on this theme; in practice, consult Greene

Cleavage: usually hydrolysis or transketalization.

Relative rate usually follows cation (oxonium) stability

Dithiaoacetals

Other Offs: Sulfur-loving metals (Hg\textsuperscript{II}), [O] (IBX, NBS, I\textsubscript{2})