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

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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:

\[
\begin{align*}
\text{OH} & \quad \text{R}_3\text{SiCl}, \text{Imidazole} \\
\text{DMF} & \quad \text{OSiR}_3 \\
\text{via} & \quad \text{R}_3\text{Si} \\
\end{align*}
\]

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

Brook Rearrangement

\[ \text{O} \text{SiR}_3 \text{X} \text{R} \rightarrow \text{OSiR}_3 \text{X} \text{R} \]

<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?

how does this happen?

Welzel, Tet, 1987, 3803

Migrations likely via associative displacement:

Removal

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

<table>
<thead>
<tr>
<th>Silyl group</th>
<th>(k_{rel} H^+)</th>
<th>(k_{rel} OH^-)</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]

\[
\begin{array}{c}
\text{Me}_2\text{N}^+ \text{S}^+ \text{NMe}_2^- \\
\text{Me}_2\text{N}^- \text{S}^- \text{NMe}_2^+
\end{array}
\]
### 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

**Resin**

```
  TESO  OTBDMs  2% HF, CH3CN  OH  OTBDMs  OPiv
```

**Conditions**

- **Masamune, TL, 1985, 5239**

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

- **Carreira, Du Bois JACS, 1995, 8106**

---

**Conditions often need to be determined empirically**

\[
\text{Cl}_2\text{CCO}_2\text{H} \\
\text{HF-Pyridine} \\
\text{HF-Cl}_3\text{CO}_2\text{H} \\
\text{HF-Et}_3\text{N} \\
\text{TBAF}
\]
Ethers

usually very robust, with orthogonal modes of removal

usually:

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

common ethers:

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

On: MeI, Me_2SO_4, Me_3O BF_4
Off: BBr_3, TMSI,

**Benzyl ether (Bn)**

On: usually BnCl + base; sometimes with cat. I^- (do you know what I^- does?)
Off: H_2, Pd/C - competitive (usually slower) than olefin reduction
Lewis Acid: S_N1 mechanism

Na/NH_3

\[
\text{Ph} \text{O}^R \rightarrow 2e^-, H^+ \rightarrow \text{Ph} \text{O}^R \rightarrow \text{HO}^-R
\]

CrO_3: via benzoate

\[
\text{Ph} \text{O}^-R \rightarrow \text{OC} = \text{O}^-R \rightarrow \text{HO}^-R
\]

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:

\[
R-O-\text{allyl} \rightarrow \text{H}_3\text{O}^+ \rightarrow R-OH
\]

Ogawa, TL, 1988, 4097
p-methoxybenzyl (PMB or MPM)

On: PMB-Cl, base

\[
\text{R}^\text{OH} + \text{CF}_3\text{CONH} \xrightarrow{\text{H}^+ \text{ or Lewis Acid}} \text{O} = \text{O}^\text{R}
\]

Off: Oxidation

\[
\text{O} \xrightarrow{\text{[O] = DDQ, CAN, Ph}_3\text{C BF}_4, \text{Br}_2, \text{NBS}} \text{O} + \text{H}_2\text{O} \xrightarrow{\text{H}^+} \text{O} = \text{O}^\text{R} + \text{R}^\text{OH}
\]

intermediate can be intercepted:

\[
\text{PMBO} \xrightarrow{\text{DDQ}} \text{OH} \xrightarrow{\text{DDQ}} \text{OMe}
\]

Hoffman, ACIEE, 1993, 101

o-nitrobenzyl

Off: \( \text{hv} \)

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

example:

\[
\text{\[O\]} \text{ArOH} = 5.1
\]

Wen-Hong Li, JACS, 2004, 4653

Triphenyl Methyl (trityl)

On: \( \text{Ph}_3\text{CCl}, \text{via S}_1\text{N} \)

Off: Acid
acetals

acetals of mono-ols:

- many eg's of the form $R\text{O} \equiv \text{O} \equiv R'$

Advantages:

- Very active electrophile
- Likely forms $O'R'$

Methoxy Methyl (MOM)

On:

- Cl $\equiv O$
- 'MOM-Cl' thought to be very toxic
- Even more toxic

Off: Acid

Benzyloxy methyl (BOM)

On:

- Cl $\equiv O \equiv \text{Ph}$

Off: All the methods for removing Bn groups:

\[
\text{OTES} \rightarrow \text{OTES} \rightarrow \text{OTES} \rightarrow \text{OTES}
\]

Masamune, TL, 1985, 5239

Tetrahydropyranyl (THP)

\[
R\text{-OH} + \text{H}^+ \rightarrow \text{H}\text{O-OR}
\]

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

\[
\text{OTES} \rightarrow \text{HN-Ph} \rightarrow \text{OTES}
\]

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

acetal protection of diols

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

Some of the most common:

\[
\begin{array}{cc}
\text{most stable} & \text{least stable} \\
\text{HO} & \text{HO} \\
\text{OMe} & \text{OMe} \\
\end{array}
\]

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

Reactions often under thermodynamic control:

\[
\begin{array}{c}
\text{O} & \text{OH} & \text{TsOH} \\
\text{HO} & \text{OMe} & \text{H} \\
\end{array}
\]

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

Oxonium intermediates can be intercepted

why not acetone + H+?

Hint: Consider pKa's of protonated ketones vs ethers
Protecting Groups in Organic Synthesis-9

benzylidene acetals

On: PhCHO/H+ or Lewis acid

Off: H3O+ or H2 Pd/C

Can be converted to benzyl:

MeO2C—CO2Me

From X-ray

1.417 Å

1.404 Å

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
diols can be protected as diacetals:

\[
\begin{align*}
\text{HO} & \quad \text{OH} \\
\text{HO} & \quad \text{OH} \\
\text{OH} & \quad \text{OH}
\end{align*}
\]

CSA, CH(OMe)_3, MeOH

Ley, Perkin 1, 1997, 2023

Esters as protecting groups

In general, ease of introduction and removal is function of sterics and electronics

usually:

\[
\begin{align*}
R^+OH & + R'LG \\ & \rightarrow R'O'R'
\end{align*}
\]

egs

\[
\begin{align*}
R^+Cl & \\
R'O'R' & \\
R'Cl & \\
R'O'R' & \\
R'O'R' & \\
\end{align*}
\]

'Yamaguchi conditions' more often for macrolactonizations

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

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

Kinetic resolution

Desymmetrization

44%, 100%ee

96%ee

54%, 88%ee

TL, 1992, 1911

For references, see Greene, 3rd ed. p156
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>B</td>
</tr>
<tr>
<td>Troc</td>
<td>Zn(0)</td>
</tr>
<tr>
<td>Teoc</td>
<td>LA=lewis acid</td>
</tr>
<tr>
<td>Alloc</td>
<td>cat Pd(0)</td>
</tr>
</tbody>
</table>

Dimethyl Thiocarbamate

on:

\[
R-OH + \text{Me}_2\text{NCl} \rightarrow RO\text{NMe}_2
\]

or

stable to: Cr(VI); EtMgBr; DIBAL; LiAlH₄; BH₃; nBuLi; Wittig; TBAF; DDQ; TiCl₄

OFF:

\[
\text{NaIO}_4 \rightarrow \text{ROH} + \text{H}_2\text{O} + \text{ROH} + \text{CO}_2
\]

or NaOH/H₂O₂

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>R COOMe</td>
<td>K$_2$CO$_3$/MeOH</td>
</tr>
<tr>
<td>R COOC$_3$F</td>
<td></td>
</tr>
<tr>
<td>R COO$^+$</td>
<td>H$^+$ (TFA, HCl, TsOH)</td>
</tr>
<tr>
<td>R COO$^+$</td>
<td>Pd(0), NuH</td>
</tr>
<tr>
<td>R COO$^+$</td>
<td>H$_2$ Pd/C or Li/NH$_3$</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

\[
\begin{align*}
\text{OH} &+ \text{EtO}_2\text{COEt} \\
\text{KOH, } \Delta
\end{align*}
\]

step 2

\[
\begin{align*}
\text{R COOH} &\text{ various ways } \text{R COO} &\text{ BF}_3\text{ Et}_2\text{O} \\
\text{H} &\text{ (TFA, HCl, TsOH)} &\text{Corey, TL 1983, 5571} \\
\end{align*}
\]

eg

\[
\begin{align*}
\text{Br} &\text{ O} &\text{ BF}_3\text{ Et}_2\text{O} \\
\text{O} &\text{ PPh}_3 &\text{KN(TMS)}_3 \\
\text{Ph}_3\text{P} &\text{CHO} &\text{H} \\
\text{CO}_2\text{Me} &\text{H} &\text{CO}_2\text{Me} \\
\end{align*}
\]

Corey, JACS, 1985, 4339
Protection for amines

Mostly carbamates; same deal as ester and carbonate

On:

\[ \text{R}_2\text{NH} + \{ \begin{array}{c} \text{OBt} \\ \text{ClOR} \\ \text{-OSu} \\ \text{OBt} \end{array} \} \]

Removal

\[ \text{NaOH; PrSLi} \]

amine base (piperidine most common)

\[ \text{Fmoc} \]

\[ \text{Troc} \]

\[ \text{Zn(0)} \]
Benzyl groups for amine protection

On:

Simple alkylation can be difficult

\[ R\text{-}\text{NH}_2 + \text{BnCl} \rightarrow R\text{-}\text{NHBN} + R\text{-}\text{NBN}_2 + R\text{-}\text{NBN}_3 \text{Cl}^- \]

2 step method

\[ R\text{-}\text{NH}_2 \xrightarrow{\text{BzCl}} R\text{-}\text{NHBz} \xrightarrow{\text{LiAlH}_4} R\text{-}\text{NHBz} \]

Reductive amination

\[ R\text{-}\text{NH}_2 + \text{Ph} \xrightarrow{\text{AcOH, NaCNBH}_3} R\text{-}\text{NPh} \]

Schiff's bases:

Many examples, benzhydryl one of most common

\[ R\text{-}\text{NH}_2 + \text{Ph} \xrightarrow{\text{H}^+ - \text{H}_2\text{O}} R\text{-}\text{NPh} \xrightarrow{\text{H}^+ + \text{H}_2\text{O}} \]

Sulfonates

Tosyl: Easy on (TsCl); can be difficult to remove

Nosyl (Ns) nice alternative:

\[ \text{Ns} \xrightarrow{\text{DEAD, PPh}_3} \text{Ns} \]

Nucleophilic aromatic substitution

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

mostly of the form: $X \rightarrow Y$  
X and Y = OR, SR, NR, CN

Most common:

- dimethyl acetal: $\text{MeO} \rightarrow \text{OMe}$  
- 1,3 dioxane
- 1,3 dioxolane
- dimethyl thioacetal: $\text{MeS} \rightarrow \text{SMe}$
- 1,3 dithiane
- 1,3 dithiolane

acetals:

Formation:

$\text{HO}(\text{CH}_2)_n\text{OH} + \text{ketone} \xrightarrow{\text{TsOH or HCl}}$  
relative rates: for the ketone, relative rates same as normal addition to carbonyls: aldehyde>acylic ketone~cyclohexanone>cyclpentanone>enone>>aromatic ketone

Cleavage: usually hydrolysis or transketalization. Relative rate usually follows cation (oxonium) stability

- $\text{PPTS, acetone} \xrightarrow{\text{H}_2\text{O}, \Delta}$ 100%
- $\text{1M HCl}$ 71%

Dithioacetals

- most common conditions
- other lewis acids work, too

Other Offs: Sulfur-loving metals ($\text{Hg}^{II}$), [O] (IBX, NBS, I$_2$)

Weinreb, JOC, 1978, 4172