

Protecting Groups for Organic Synthesis

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Seoul National University*



Protecting Groups for Organic Synthesis

General References:

- Kocienski, P. J. *Protecting Groups*, 3rd ed.; Georg Thieme Verlag: New York, **2005**.
- Greene, T. W.; Wuts, P. G. M. *Protective Groups In Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, **1991**.

Protecting Groups for Organic Synthesis

Contents:

- Protection of
 1. Hydroxyl groups
 2. Ketones and aldehydes
 3. Amines
 4. Carboxylic Acids
 5. Alkynes

Protecting Groups for Organic Synthesis

Protecting groups ?

- Protect functional groups which may be incompatible with a set of reaction conditions
- 2 step process : introduction & removal → must be efficient
- Selectivity
 - selective protection
 - selective deprotection

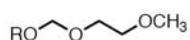
When one protective group is stable to conditions that cleave another and the converse is also true, these groups are often said to be to bear an **orthogonal** relationship.

Hydroxyl Protecting Groups

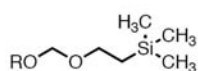
Acetals



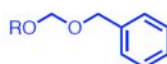
Methoxymethyl Ether
(MOM)



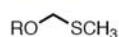
2-Methoxyethoxymethyl Ether
(MEM)



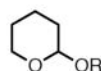
2-(Trimethylsilyl)ethoxymethyl Ether
(SEM)



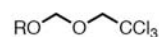
Benzyloxymethyl Ether
(BOM)



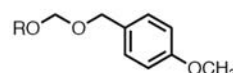
Methylthiomethyl Ether
(MTM)



Tetrahydropyranyl Ether
(THP)



2,2,2-Trichloroethoxymethyl Ether



p-Methoxybenzyl Ether
(PMBM)

Hydroxyl Protecting Groups

Acetals

General methods for forming acyclic, mixed acetals:



Base-solvent combinations are often diisopropylethylamine- CH_2Cl_2 , NaH-THF, or NaH-DMF. Sometimes a source of iodide ion is added to enhance the reactivity of the alkylating reagent. Typical sources include $\text{Bu}_4\text{N}^+\text{I}^-$, LiI, or NaI.

Hydroxyl Protecting Groups

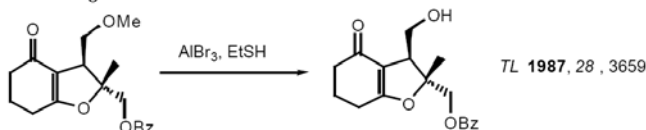
Acetals

Methyl ethers

R-OH \rightarrow R-OMe difficult to remove except for on phenols

Formation: - CH_2N_2 , silica or HBF_4
- NaH, MeI, THF

Cleavage: - AlBr_3 , EtSH
- PhSe -
- Ph_2P -
- Me_3SiI



Hydroxyl Protecting Groups

Acetals

Methoxymethyl ether MOM

R-OH \rightarrow R-OCH₂OMe stable to base and mild acid

Formation: - MeOCH_2Cl , NaH, THF
- MeOCH_2Cl , CH_2Cl_2 , $i\text{Pr}_2\text{EtN}$

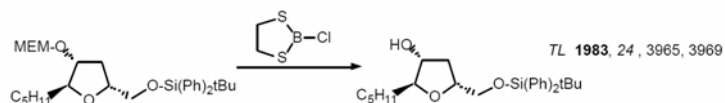
Cleavage - Me_2BBr_2 TL 1983, 24, 3969

Methoxyethoxymethyl ethers (MEM)

R-OH \rightarrow R-OCH₂OCH₂CH₂OMe stable to base and mild acid

Formation: - $\text{MeOCH}_2\text{CH}_2\text{OCH}_2\text{Cl}$, NaH, THF
- $\text{MeOCH}_2\text{CH}_2\text{OCH}_2\text{Cl}$, CH_2Cl_2 , $i\text{Pr}_2\text{EtN}$ TL 1976, 809

Cleavage - Lewis acids such as ZnBr_2 , TiCl_4 , Me_2BBr_2



- can also be cleaved in the presence of THP ethers

Hydroxyl Protecting Groups

Acetals

Methoxymethyl ether MOM

$R-OH \rightarrow R-OCH_2OMe$ stable to base and mild acid

Formation: - $MeOCH_2Cl$, NaH, THF
- $MeOCH_2Cl$, CH_2Cl_2 , iPr_2EtN

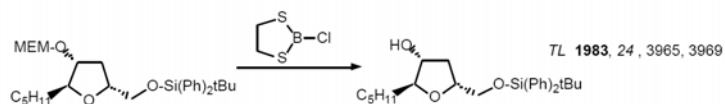
Cleavage - Me_2BBr_2 TL 1983, 24, 3969

Methoxyethoxymethyl ethers (MEM)

$R-OH \rightarrow R-OCH_2OCH_2CH_2OMe$ stable to base and mild acid

Formation: - $MeOCH_2CH_2OCH_2Cl$, NaH, THF
- $MeOCH_2CH_2OCH_2Cl$, CH_2Cl_2 , iPr_2EtN TL 1976, 809

Cleavage - Lewis acids such as $ZnBr_2$, $TiCl_4$, Me_2BBr_2



- can also be cleaved in the presence of THP ethers

Hydroxyl Protecting Groups

Acetals

Methyl Thiomethyl Ethers (MTM)

$R-OH \rightarrow R-OCH_2SMe$ Stable to base and mild acid

Formation: - $MeSCH_2Cl$, NaH, THF

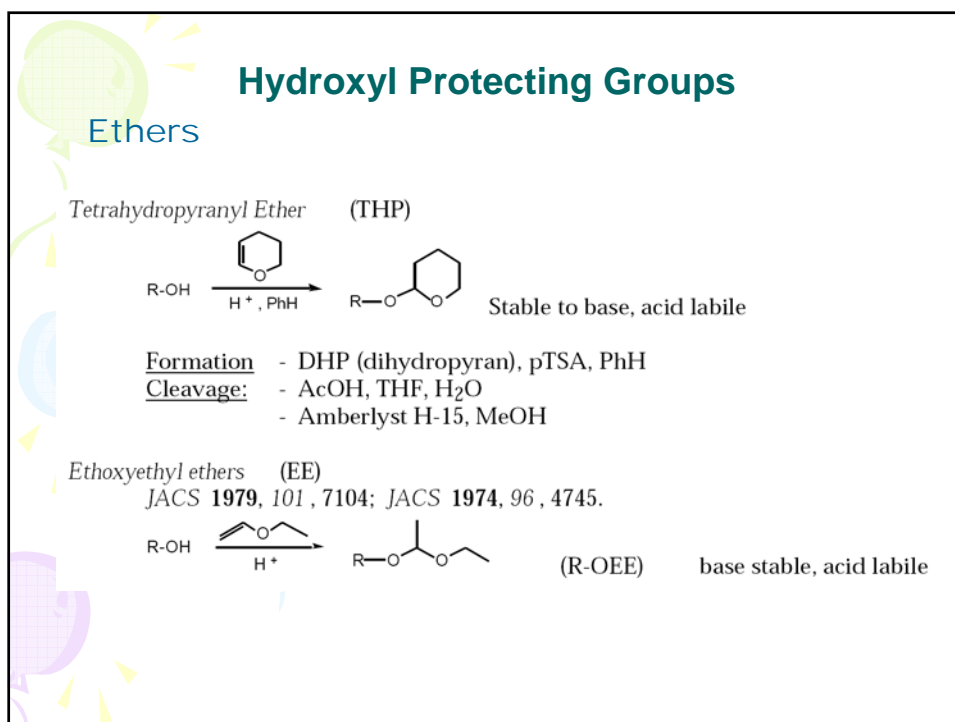
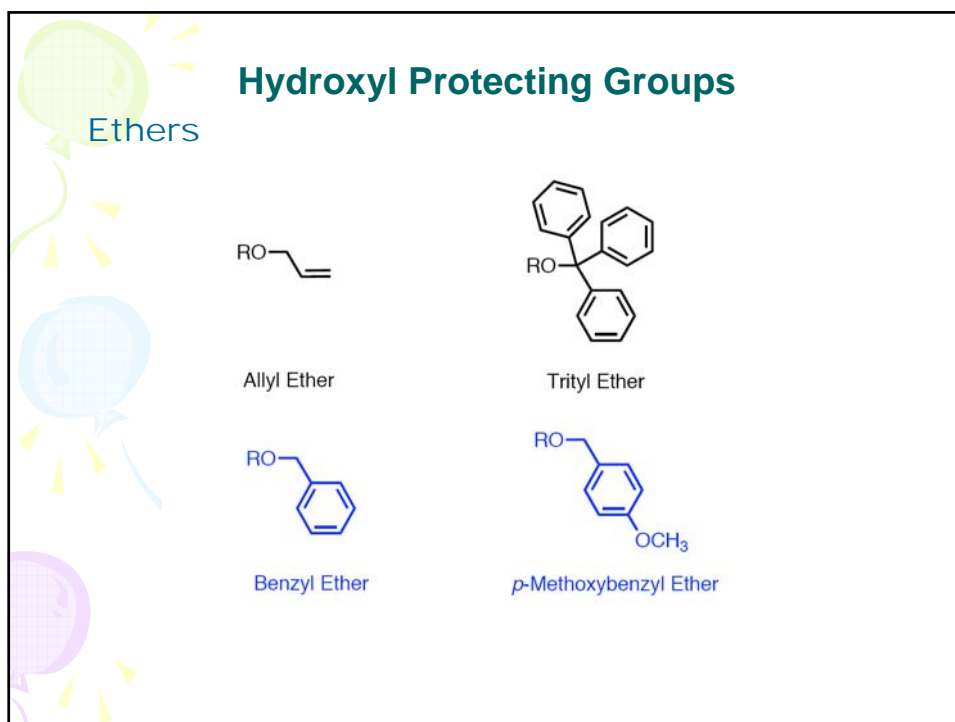
Cleavage: - $HgCl_2$, CH_3CN/H_2O
- $AgNO_3$, THF, H_2O , base

Benzyloxymethyl Ethers (BOM)

$R-OH \rightarrow R-OCH_2OCH_2Ph$ Stable to acid and base

Formation: - $PhOCH_2CH_2Cl$, CH_2Cl_2 , iPr_2EtN

Cleavage: - H_2/PtO_2
- Na/NH_3 , EtOH



Hydroxyl Protecting Groups

Ethers

Benzyl Ethers (R-OBn)

R-OH \rightarrow R-OCH₂Ph stable to acid and base

Formation: - KH, THF, PhCH₂Cl
- PhCH₂OC(=NH)CCl₃, F₃CSO₃H *JCS P1 1985, 2247*

Cleavage: - H₂ / PtO₂
- Li / NH₃

p-Methoxybenzyl Ethers (PMB)

Formation: - KH, THF, p-MeOPhCH₂Cl
- p-MeOPhCH₂OC(=NH)CCl₃, F₃CSO₃H *TL 1988, 29, 4139*

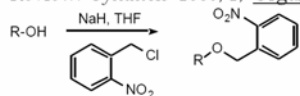
Cleavage: - H₂ / PtO₂
- Li / NH₃
- DDQ
- Ce(NH₄)₂(NO₃)₆ (CAN)
- e⁻

Hydroxyl Protecting Groups

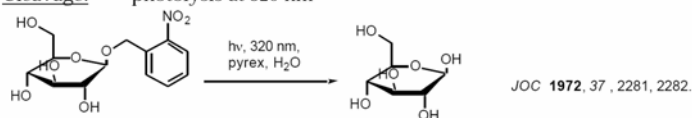
Ethers

o-Nitrobenzyl ethers

Review: *Synthesis 1980, 1*; *Organic Photochemistry, 1987, 9, 225*



Cleavage: - photolysis at 320 nm



p-Nitrobenzyl Ether

TL 1990, 31, 389

-selective removal with DDQ, hydrogenolysis or electrochemically

Hydroxyl Protecting Groups

Ethers

Trityl Ethers -CPh₃ = Tr

R-OH → R-OCPh₃ - selective for 1° alcohols
 - removed with mild acid; base stable

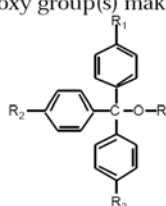
formation: - Ph₃C-Cl, pyridine, DMAP
 - Ph₃C⁺ BF₄⁻

Cleavage: - mild acid

Methoxytrityl Ethers

JACS 1962, 84, 430

- methoxy group(s) make it easier to remove



(p-Methoxyphenyl)diphenylmethyl ether
 4'-methoxytrityl MMTTr-OR

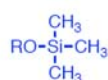
Di-(p-methoxyphenyl)phenylmethyl ether
 4',4'-dimethoxytrityl DMTr-OR

Tri-(p-methoxyphenyl)methyl ether
 4',4',4'-trimethoxytrityl TMTr-OR

Tr-OR < MMTr-OR < DMTr-OR << TMTr-OR

Hydroxyl Protecting Groups

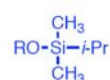
Silyl Ethers



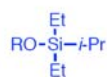
Trimethylsilyl (TMS)



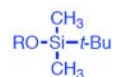
Triethylsilyl (TES)



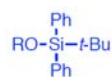
Dimethylisopropylsilyl (IPDMS)



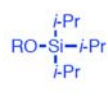
Diethylisopropylsilyl (DEIPS)



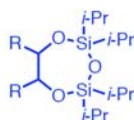
t-Butyldimethylsilyl (TBS)



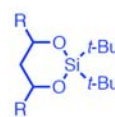
t-Butyldiphenylsilyl (TBDPS)



Triisopropylsilyl (TIPS)



Tetraisopropylidisilylene (TIPDS)



Di-t-butyldimethylsilylene (DTBS)

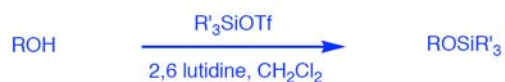
Hydroxyl Protecting Groups

Silyl Ethers

General methods for the formation of silyl ethers:



Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.



Corey, E. J.; Cho, H.; Rücker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455.

Hydroxyl Protecting Groups

Silyl Ethers

- In general, the stability of silyl ethers towards acidic media increases as indicated:
TMS (1) < TES (64) < TBS (20,000) < TIPS (700,000) < TBDPS (5,000,000)
- In general, stability towards basic media increases in the following order:
TMS (1) < TES (10-100) < TBS ~ TBDPS (20,000) < TIPS (100,000)

Silyl Ether	Half Life (5% NaOH–95% MeOH)	Half Life (1% HCl–MeOH, 25 °C)
<i>n</i> -C ₆ H ₁₃ OTMS	≤1 min	≤1 min
<i>n</i> -C ₆ H ₁₃ OSi- <i>i</i> -Bu(CH ₃) ₂	2.5 min	≤1 min
<i>n</i> -C ₆ H ₁₃ OTBS	Stable for 24 h	≤1 min
<i>n</i> -C ₆ H ₁₃ OSiCH ₃ Ph ₂	≤1 min	14 min
<i>n</i> -C ₆ H ₁₃ OTIPS	Stable for 24 h	55 min
<i>n</i> -C ₆ H ₁₃ OTBDPS	Stable for 24 h	225 min

Silyl Ether	Half Life Bu ₄ N ⁺ F ⁻ (0.06 M, 6 equiv)	Half Life HClO ₄ (0.01 M)
<i>n</i> -C ₁₂ H ₂₅ OTBS	140 h	1.4 h
<i>n</i> -C ₁₂ H ₂₅ OTBDPS	375 h	> 200 h
<i>n</i> -C ₁₂ H ₂₅ OSiPh ₂ (<i>O</i> -Pr)	<0.03 h	0.7 h
<i>n</i> -C ₁₂ H ₂₅ OSiPh ₂ (<i>O</i> -Bu)	5.8 h	17.5 h
<i>n</i> -C ₁₂ H ₂₅ OPh(<i>t</i> -Bu)(OCH ₃)	22 h	200h

Hydroxyl Protecting Groups

Silyl Ethers

Silyl groups are typically deprotected with a source of fluoride ion.

The Si-F bond strength is about 30 kcal/mol stronger than the Si-O bond.

Fluoride sources:

Tetrabutylammonium fluoride, $\text{Bu}_4\text{N}^+\text{F}^-$ (TBAF)

Pyridine \cdot (HF) $_x$

Triethylamine trihydrofluoride, $\text{Et}_3\text{N}\cdot 3\text{HF}$

Hydrofluoric acid

Tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF)

Ammonium fluoride, $\text{H}_4\text{N}^+\text{F}^-$

Hydroxyl Protecting Groups

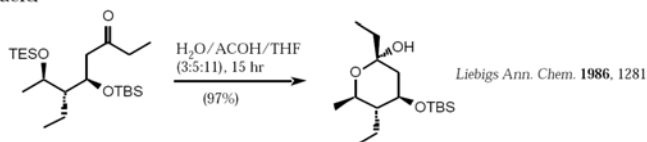
Silyl Ethers

Trimethylsilyl ethers $\text{Me}_3\text{Si-OR}$ TMS-OR

- very acid and water labile
- useful for transient protection

Triethylsilyl ethers $\text{Et}_3\text{Si-OR}$ TES-OR

- considerably more stable than TMS
- can be selectively removed in the presence of more robust silyl ethers with F^- or mild acid



Triisopropylsilyl ethers $\text{iPr}_3\text{Si-OR}$ TIPS-OR

- more stable to hydrolysis than TMS

Hydroxyl Protecting Groups

Silyl Ethers

t-Butyldimethylsilyl Ether $t\text{BuMe}_2\text{Si-OR}$ TBS-OR TBDMS-OR

JACS **1972**, 94, 6190

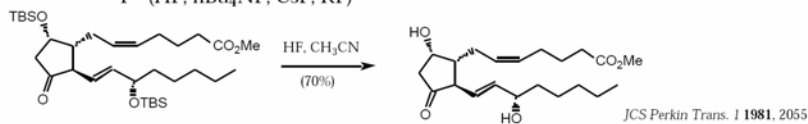
- Stable to base and mild acid
- under controlled condition is selective for 1° alcohols

t-butyldimethylsilyl triflate $t\text{BuMe}_2\text{Si-OTf}$ TL **1981**, 22, 3455

- very reactive silylating reagent, will silylate 2° alcohols

cleavage:

- acid
- F^- (HF, $n\text{Bu}_4\text{NF}$, CsF, KF)



Hydroxyl Protecting Groups

Silyl Ethers

t-Butyldiphenylsilyl Ether $t\text{BuPh}_2\text{Si-OR}$ TBDPS-OR Σ -OR

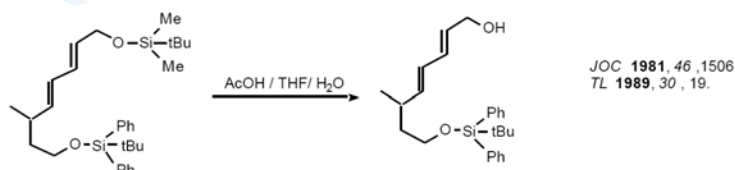
- stable to acid and base
- selective for 1° alcohols
- $\text{Me}_3\text{Si-}$ and $i\text{Pr}_3\text{Si-}$ groups can be selectively removed in the presence of TBS or TBDPS groups.
- TBS can be selectively removed in the presence of TBDPS by acid hydrolysis.

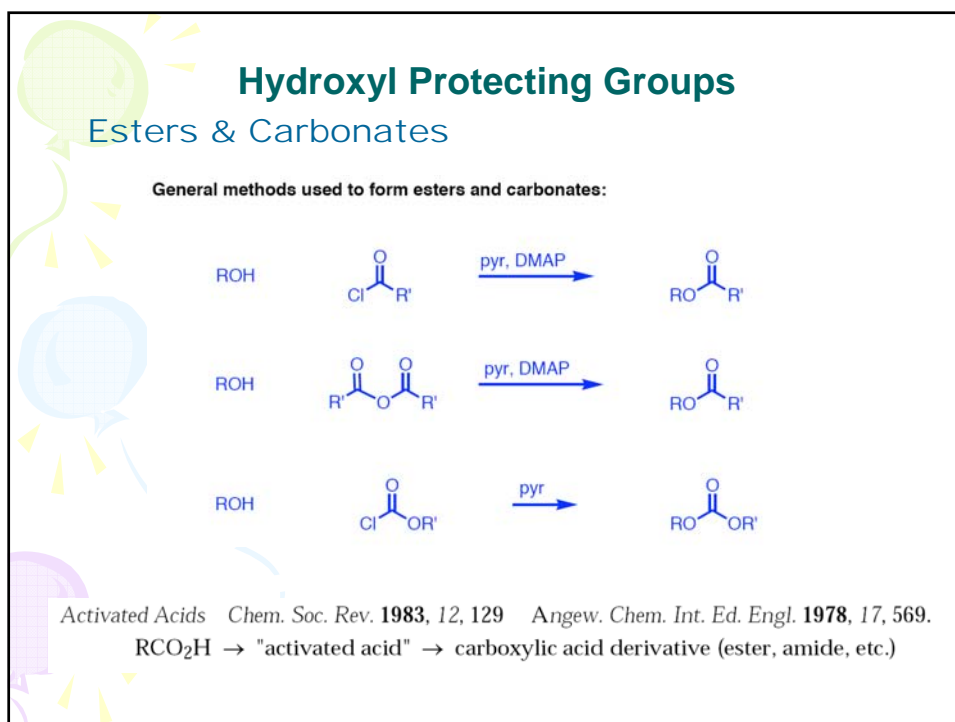
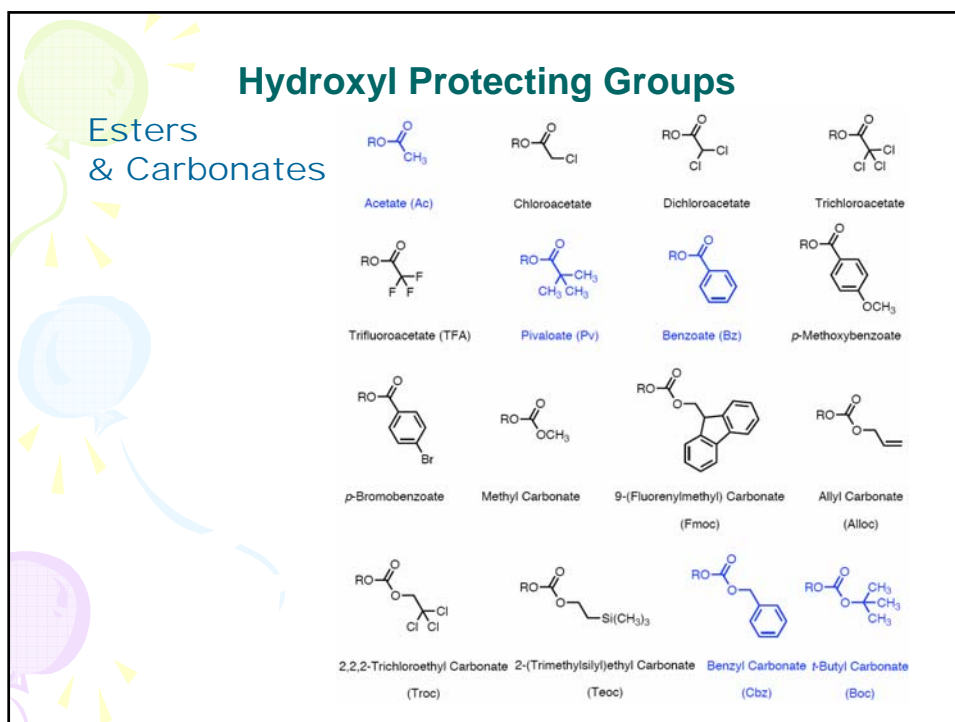
TL **1989**, 30, 19

cleavage - F^-

- Fluoride sources: - $n\text{Bu}_4\text{NF}$ (basic reagent)
- HF / H_2O / CH_3CN
- HF • pyridine
- SiF_4 , CH_2Cl_2

TL **1979**, 3981.
Synthesis **1986**, 453
TL **1992**, 33, 2289

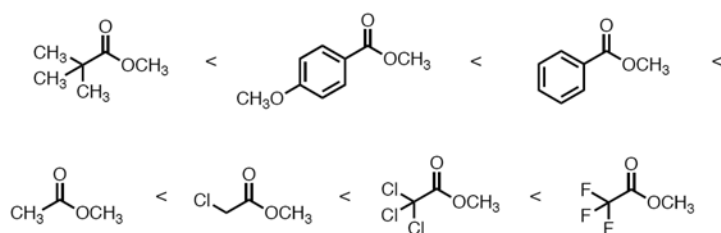




Hydroxyl Protecting Groups

Esters

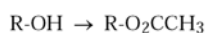
In general, the susceptibility of esters to base catalyzed hydrolysis increases with the **acidity of the product acid**.



Hydroxyl Protecting Groups

Esters

Acetates



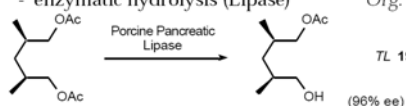
- stable to acid and mild base
- not compatible with strong base or strong nucleophiles such as organometallic reagents

Formation:

- acetic anhydride, pyridine
- acetyl chloride, pyridine

- Cleavage:**
- K_2CO_3 , MeOH, reflux
 - KCN, EtOH, reflux
 - NH_3 , MeOH
 - LiOH, THF, H_2O
 - enzymatic hydrolysis (Lipase)

Org. Rxns. **1989**, 37, 1.

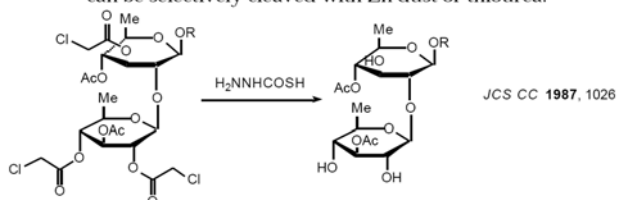


Hydroxyl Protecting Groups

Esters

Chloroacetates

- can be selectively cleaved with Zn dust or thiourea.



Trifluoroacetates

Formation: - with trifluoroacetic anhydride or trifluoroacetyl chloride

Cleavage: - K_2CO_3 , MeOH

Hydroxyl Protecting Groups

Esters

Pivaloate (t-butyl ester)

- Fairly selective for primary alcohols

Formation: - tbutylacetyl chloride or t-butylacetic anhydride

Cleavage: - removed with mild base

Benzoate (Bz)

- more stable to hydrolysis than acetates.

Formation: - benzoyl chloride, benzoic anhydride, benzoyl cyanide (TL 1971, 185)
benzoyl tetrazole (TL 1997, 38, 8811)

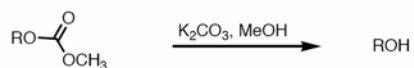
Cleavage: - mild base

- KCN, MeOH, reflux

Hydroxyl Protecting Groups

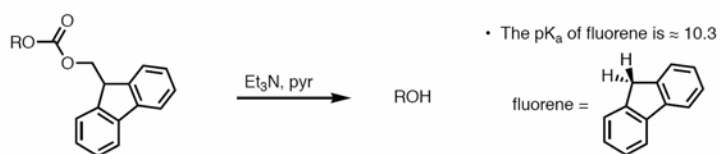
Carbonates

Methyl Carbonate:



Meyers, A. I.; Tomioka, K.; Roland, D. M.; Comins, D. *Tetrahedron Lett.* **1978**, 19, 1375.

9-Fuorenylmethyl Carbonate:

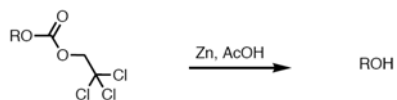


Chattopadhyaya, J. B.; Gioeli, C. *J. Chem. Soc., Chem. Comm.* **1982**, 672.

Hydroxyl Protecting Groups

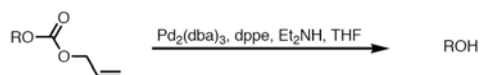
Carbonates

Trichloroethyl Carbonate:



Windholz, T.B.; Johnston, D. B. R. *Tetrahedron Lett.* **1988**, 29, 2227.

Allyl Carbonate:



Genet, J.P.; Blart E.; Savignac, M.; Lemeune, S.; Lemaire-Audoire, S.; Bernard, J. *Synlett* **1993**, 680.

Hydroxyl Protecting Groups

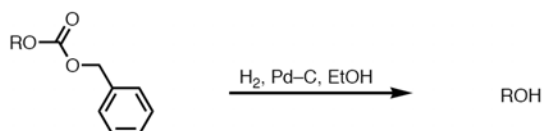
Carbonates

2-(Trimethylsilyl)ethyl Carbonate:



Gioeli, C.; Balgobin, S.; Josephson, S.; Chattopadhyaya, J. B. *Tetrahedron Lett.* **1981**, *22*, 969.

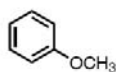
Benzyl Carbonate:



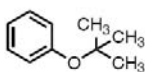
Daubert, B. F.; King, G. C. *J. Am. Chem. Soc.* **1939**, *61*, 3328.

Hydroxyl Protecting Groups

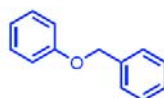
Phenolic protective groups



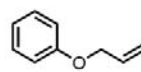
Methyl Ether



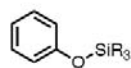
t-Butyl Ether



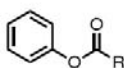
Benzyl Ether



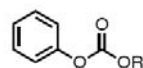
Allyl Ether



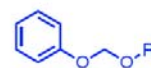
Silyl Ethers



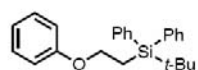
Phenyl Esters



Phenyl Carbonates



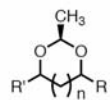
Acetals



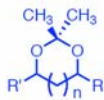
t-Butyldiphenylsilylethyl Ether

Hydroxyl Protecting Groups

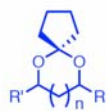
1,2 and 1,3-diols



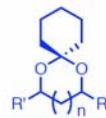
Ethylidene Acetal



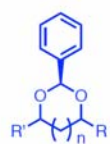
Acetonide



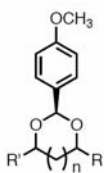
Cyclopentylidene Ketal



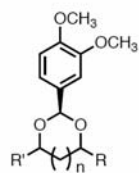
Cyclohexylidene Ketal



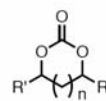
Benzylidene Acetal



4-Methoxybenzylidene Acetal



3,4-Dimethoxybenzylidene Acetal

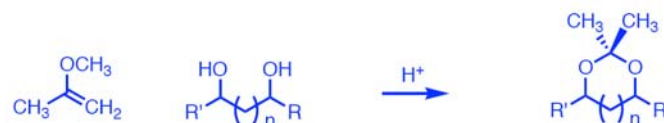
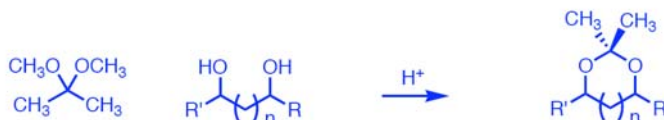
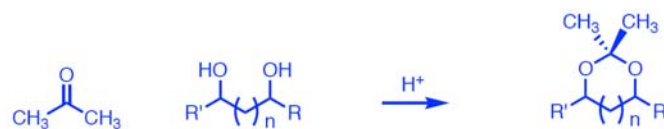


Cyclic Carbonate

Hydroxyl Protecting Groups

1,2 and 1,3-diols

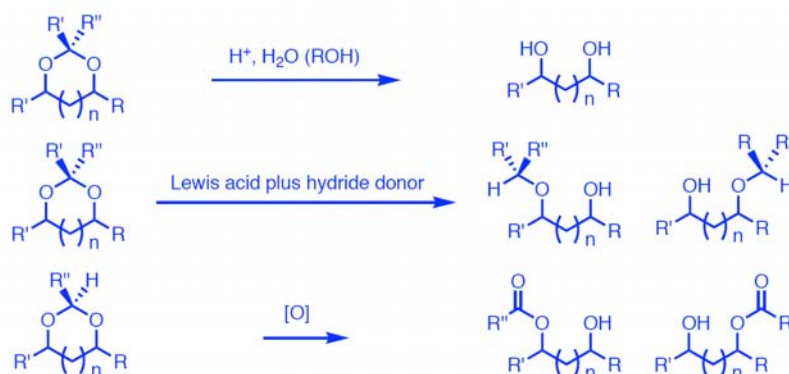
General methods used to form acetals and ketals (illustrated for acetonides):



Hydroxyl Protecting Groups

1,2 and 1,3-diols

General methods of cleavage:

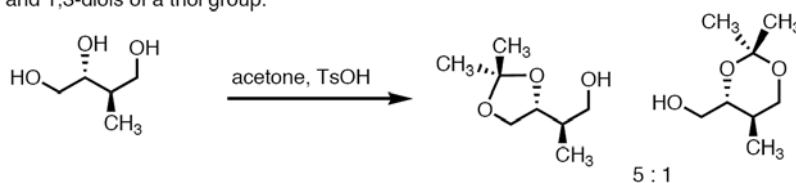


Hydroxyl Protecting Groups

1,2 and 1,3-diols

Selective protection of polyols:

In general, acetonide formation with 1,2-diols occurs in preference protection to 1,3-diols; benzylidene acetals display reversed selectivity. It is often possible to discriminate between 1,2- and 1,3-diols of a triol group.

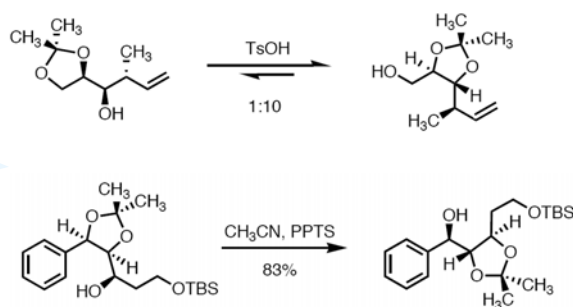


Hydroxyl Protecting Groups

1,2 and 1,3-diols

Selective protection of polyols:

In the case of a 1,2,3-triol, careful analysis must be performed to accurately predict the site of acetonide formation. The more substituted acetonide will be favored in cases where the substituents on the resultant five-membered ring will be trans. If the substituents on the five-membered ring would be oriented cis, then the alternative, less substituted acetonide may be favored.

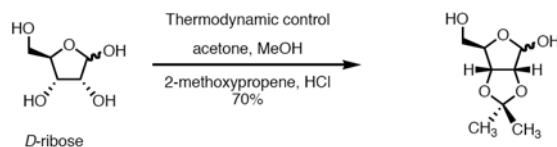


Hydroxyl Protecting Groups

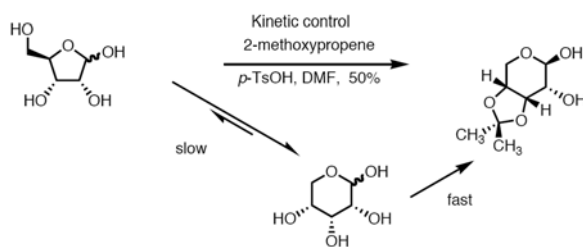
1,2 and 1,3-diols

Selective protection of polyols:

Kinetic vs. thermodynamic control with a pentose



Leonard, N. J.; Carraway, K. L. *J. Heterocycl. Chem.* **1966**, 3, 485.

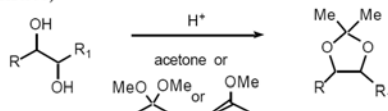


Hydroxyl Protecting Groups

1,2 and 1,3-diols

Isopropylidenes

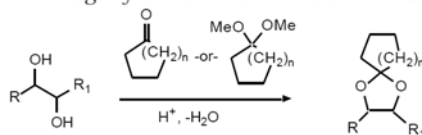
(acetonides)



- in competition between 1,2- and 1,3-diols, 1,2-acetonide formation is usually favored
- cleaved with mild aqueous acid

Cycloalkylidene Ketals

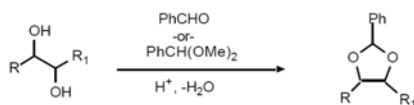
- Cyclopentylidene are slightly easier to cleave than acetonides
- Cyclohexylidenes are slightly harder to cleave than acetonides



Hydroxyl Protecting Groups

1,2 and 1,3-diols

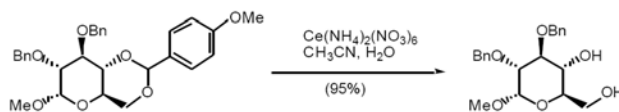
Benzylidene Acetals



- in competition between 1,2- and 1,3-diols, 1,3-benzylidene formation is usually favored
- benzylidenes can be removed by acid hydrolysis or hydrogenolysis
- benzylidenes are usually hydrogenolyzed more slowly than benzyl ethers or olefins.

p-Methoxybenzylidenes

- hydrolyzed about 10X faster than regular benzylidenes
- Can be oxidatively removed with $\text{Ce}(\text{NH}_4)_2(\text{NO}_3)_6$ (CAN)

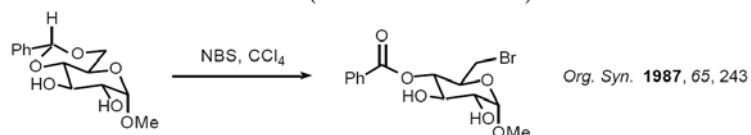


Hydroxyl Protecting Groups

1,2 and 1,3-diols

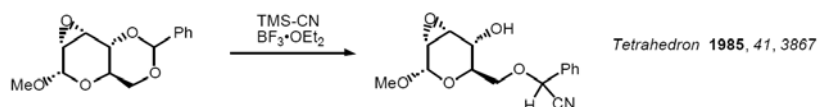
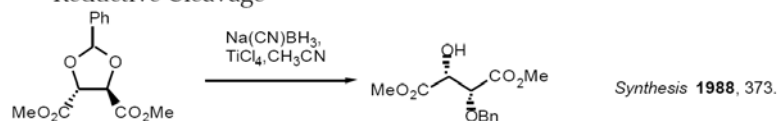
Other Reactions of Benzylidenes

- Reaction with NBS (Hanesian Reaction)



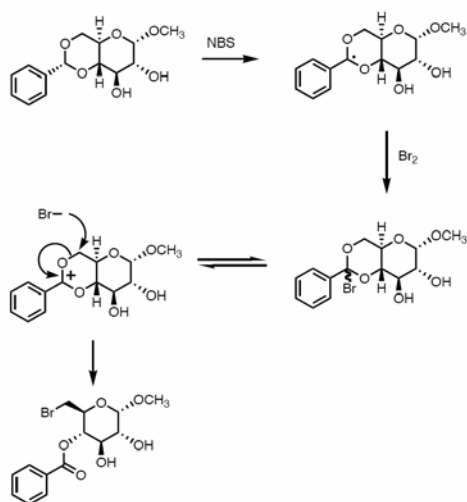
- if benzylidene of a 1° alcohol, then 1° bromide

- Reductive Cleavage



Hydroxyl Protecting Groups

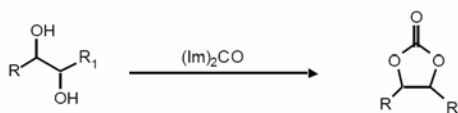
1,2 and 1,3-diols



Hydroxyl Protecting Groups

1,2 and 1,3-diols

Carbonates



- stable to acid; removed with base
- more difficult to hydrolyze than esters

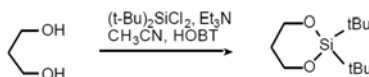
Hydroxyl Protecting Groups

1,2 and 1,3-diols

Di-t-Butylsilylene (DTBS)

TL 1981, 22, 4999

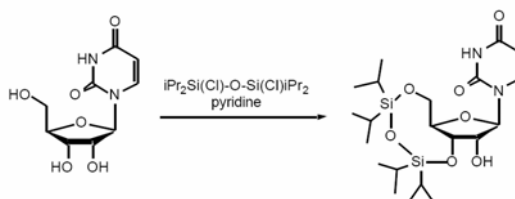
- used for 1,3- and 1,4-diols; 1,2-diols are rapidly hydrolyzed
- cleaved with fluoride (HF, CH₃CN -or- Bu₄NF -or- HF •pyridine)
- will not functionalize a 3°-alcohol



1,3-(1,1,3,3)-tetraisopropylidisiloxanylidene (TIPDS)

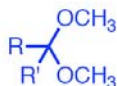
TL 1988, 29, 1561

- specific for 1,3- and 1,4-diols
- cleaved with fluoride or TMS-I

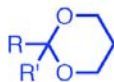


Carbonyl Protecting Groups

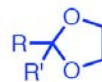
Carbonyl protective groups:



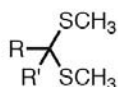
dimethyl acetal



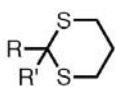
1,3-dioxane



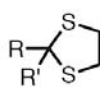
1,3-dioxolane



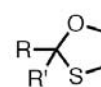
S,S'-dimethylthioacetal



1,3-dithiane



1,3-dithiolane



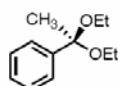
1,3-oxathiolane

General order of reactivity of carbonyl groups towards nucleophiles:

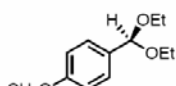
aldehydes (aliphatic > aromatic) > acyclic ketones ≈ cyclohexanones > cyclopentanones > a,b-unsaturated ketones ≈ a,a disubstituted ketones >> aromatic ketones.

Carbonyl Protecting Groups

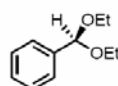
Approximate rates ($\text{L mol}^{-1}\text{s}^{-1}$ at 25-30 °C) for proton-catalyzed (HCl, water or dioxane-water) cleavage of acetals and ketals.



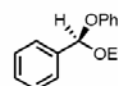
6×10^3



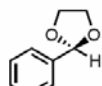
5×10^3



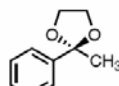
160



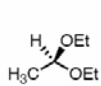
41



5



1.2



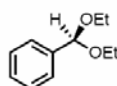
1.6



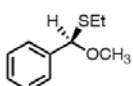
1.5×10^{-4}

- In general, cyclic acetals are cleaved more slowly than their open chain analogs
- In general, dithio acetals are not cleaved by Bronsted acids.

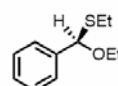
Rates of acid-catalyzed cleavage of mono thioacetals and acetals have been determined:



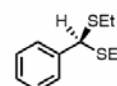
160



41



1.3

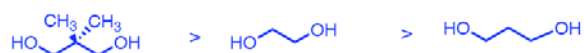


3.5×10^{-4}

Satchell, D. P. N.; Satchell, R. S. *Chem. Soc. Rev.* 1990, 19, 55.

Carbonyl Protecting Groups

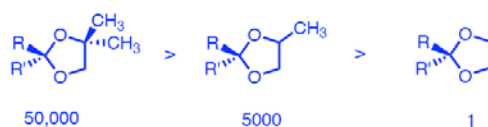
Relative rates of ketalization with common diols:



Cleavage of 1,3-dioxolanes vs. 1,3-dioxanes:



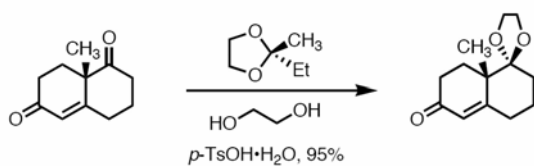
Relative rates of cleavage for 1,3-dioxolanes:



Okawara, H.; Nakai, H.; Ohno, M. *Tetrahedron Lett.* **1982**, 23, 1087.

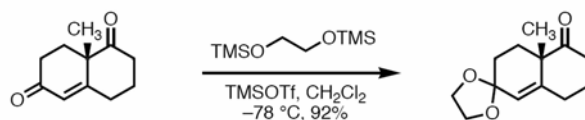
Carbonyl Protecting Groups

- In general, saturated ketones can be selectively protected in the presence of α,β -unsaturated ketone



Bosch, M. P.; Camps, F.; Coll, J.; Guerrero, T.; Tatsuoka, T.; Meinwald, J. *J. Org. Chem.* **1986**, 51, 773.

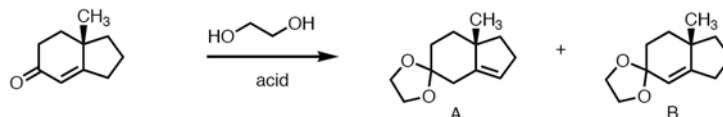
- Conditions have been developed to protect α,β -unsaturated ketones selectively.



Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, 21, 1357.

Carbonyl Protecting Groups

- When protecting α,β -unsaturated ketones, olefin isomerization is common.



Strong acids ($pK_a \approx 1$) tend to favor isomerization, while weaker acids ($pK_a \geq 3$) favor isomerization much less so, or not at all.

acid	pK_a	%A	%B	% conversion
fumaric acid	3.03	100	0	90
phthalic acid	2.89	70	30	90
oxalic acid	1.23	80	20	93
TsOH	< 1.0	0	100	100

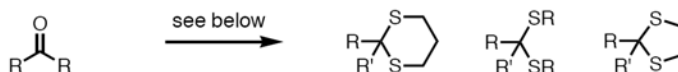
Carbonyl Protecting Groups

Cleavage of 1,3-dioxanes and 1,3-dioxolanes:

- PPTS, acetone, H_2O , heat. Hagiwara, H.; Uda, H. *J. Chem. Soc., Chem. Commun.* **1987**, 1351.
- 1M HCl, THF. Grieco, P. A.; Nishizawa, M.; Oguri, T. Burke, S. D.; Marinovic, N. *J. Am. Chem. Soc.* **1977**, *43*, 4178.
- Me_2BBr , CH_2Cl_2 , $-78^\circ C$. This reagent also cleaves MEM and MOM ethers. Guindon, Y.; Morton, H. E.; Yoakim, C. *Tetrahedron Lett.* **1983**, *24*, 3969.
- NaI, $CeCl_3 \cdot 7H_2O$, CH_3CN . Marcantoni, E.; Nobili, F.; Bartoli, G.; Bosco, M.; Sambri, L. *J. Org. Chem.* **1997**, *62*, 4183. This method is selective for cleavage of ketals in the presence of acetals. It is also selective for ketals of α,β -unsaturated ketones over ketals of saturated ketones.

Carbonyl Protecting Groups

General methods of formation of *S,S'*-dialkyl acetals:



1. RSH, HCl, 20 °C. Zinner, H. *Chem. Ber.* **1950**, *83*, 275.
2. RSSi(CH₃)₃, ZnI₂, Et₂O. Evans, D. A.; Truesdale, L. K.; Grimm, K. G.; Nesbitt, S. L. *J. Am. Chem. Soc.* **1977**, *99*, 5009.
3. RSH, BF₃·Et₂O, CH₂Cl₂. Marshall, J. A.; Belletire, J. L. *Tetrahedron Lett.* **1971**, 871. See also Hatch, R. P.; Shringarpure, J.; Weinreb, S. M. *J. Org. Chem.* **1978**, *43*, 4172. α,β -Unsaturated ketones are reported not to isomerize under these conditions. However, with any of the above mentioned conditions conjugate addition is a concern.

Carbonyl Protecting Groups

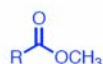
General methods of cleavage of *S,S'*-dialkyl acetals:

1. Hg(ClO₄)₂, MeOH, CHCl₃. Lipshutz, B. H.; Moretti, R.; Crow, R. *Tetrahedron Lett.* **1989**, *30*, 15, and references therein.
2. CuCl₂, CuO, acetone, reflux. Stutz, P.; Stadler, P. A. *Org. Synth. Collect. Vol.* **1988**, *6*, 109.
3. *m*-CPBA; Et₃N Ac₂O, H₂O. Kishi, Y.; Fukuyama, T.; Natatsuka, S. *J. Am. Chem. Soc.* **1973**, *95*, 6490.
4. (CF₃CO₂)₂IPh, H₂O, CH₃CN. Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 287.

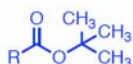
A variety of methods has been developed for the cleavage of *S,S'*-dialkyl acetals, largely due to the fact that these functional groups are often difficult to remove.

Carbonyl Protecting Groups

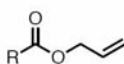
Carboxyl Protective Groups:



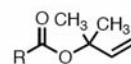
Methyl Ester



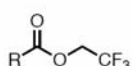
t-Butyl Ester



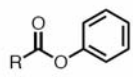
Allyl Ester



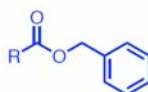
1,1-Dimethylallyl Ester



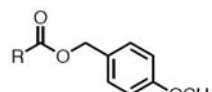
2,2,2-Trifluoroethyl Ester



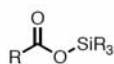
Phenyl Ester



Benzyl Ester



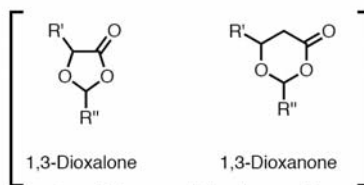
4-Methoxybenzyl Ester



Silyl Ester



Ortho Ester



1,3-Dioxalane

1,3-Dioxanone

Specific to α - and β -hydroxy acids

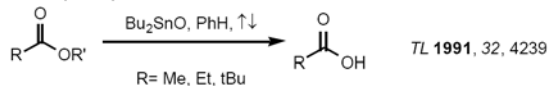
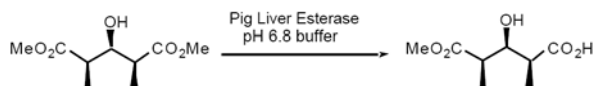
Carbonyl Protecting Groups

Esters for acid

Alkyl Esters

- formation:
- Fisher esterification ($RCOOH + R'OH + H^+$)
 - Acid Chloride + R-OH, pyridine
 - t-butyl esters: isobutylene and acid
 - methyl esters: diazomethane

- Cleavage:
- LiOH, THF, H₂O
 - enzymatic hydrolysis *Org. Rxns.* **1989**, 37, 1.
 - t-butyl esters are cleaved with aqueous acid
 - Bu₂SnO, PhH, reflux (*TL* **1991**, 32, 4239)



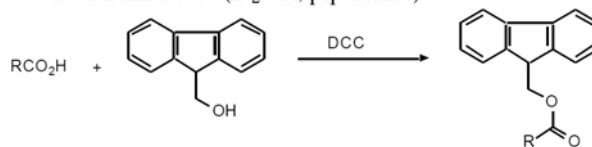
Carbonyl Protecting Groups

Esters for acid

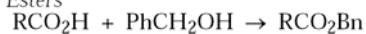
9-Fluorenylmethyl Esters (Fm)

TL 1983, 24, 281

- cleaved with mild base (Et₂NH, piperidine)



Benzyl Esters



Formation: - DCC

- Acid chloride and benzyl alcohol

Cleavage: - Hydrogenolysis

- Na, NH₃

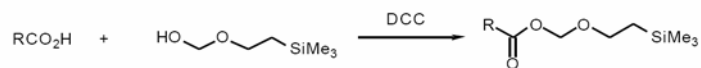
Carbonyl Protecting Groups

Esters for acid

2-Trimethylsilyloxyethyl Ester (SEM)

HCA 1977, 60, 2711.

- Cleaved with Bu₄NF in DMF

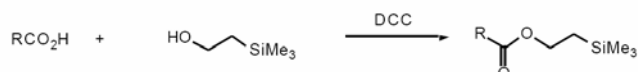


- Cleaved with MgBr₂•OEt₂ TL 1991, 32, 3099.

2-(Trimethylsilyloxy)ethyl Esters

JACS 1984, 106, 3030

- cleaved with Fluoride ion



Carbonyl Protecting Groups

Esters for acid

Haloesters

- cleaved with Zn(0) dust or electrochemically



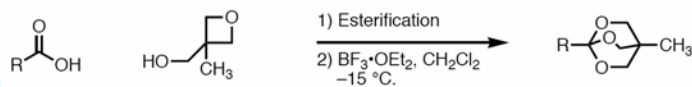
o-Nitrobenzyl Esters

- selective removed by photolysis

Carbonyl Protecting Groups

Esters for acid

OBO ester



Corey, E. J.; Raju, N. *Tetrahedron Lett.* **1983**, 24, 5571.

Alternatively, ortho esters can be prepared from a nitrile:

