

Carey & Sundberg Chapter 13.1 problems # 1; 2; 3a, b, c ;
Smith: Chapter 7

Protecting Groups

T.W. Greene & P.G.M. Wuts, Protective Groups in Organic Synthesis (2nd edition) J. Wiley & Sons, 1991.

P. J. Kocienski, Protecting Groups, Georg Thieme Verlag, 1994

1. Hydroxyl groups
2. Ketones and aldehydes
3. Amines
4. Carboxylic Acids

- Protect functional groups which may be incompatible with a set of reaction conditions
- 2 step process- must be efficient
- Selectivity
 - a. selective protection
 - b. selective deprotection

Hydroxyl Protecting Groups

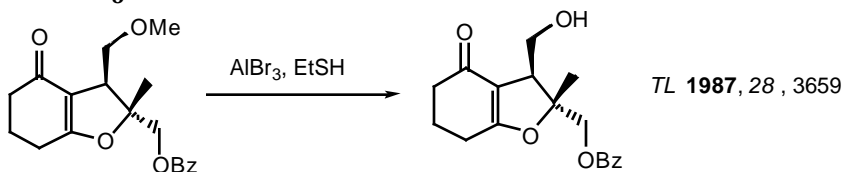
Ethers

Methyl ethers

R-OH 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



Methoxymethyl ether MOM

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

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

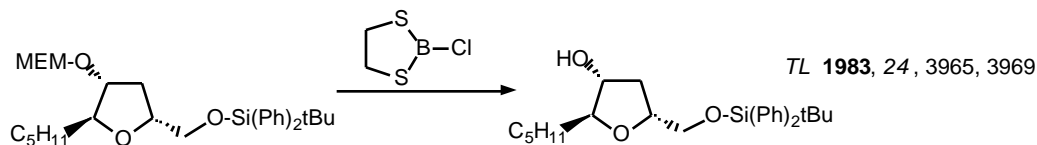
Cleavage - Me_2BBr_2 TL 1983, 24, 3969

Methoxyethoxymethyl ethers (MEM)

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

Formation: - MeOCH₂CH₂OCH₂Cl, NaH, THF
 - MeOCH₂CH₂OCH₂Cl, CH₂Cl₂, iPr₂EtN TL 1976, 809

Cleavage - Lewis acids such as ZnBr₂, TiCl₄, Me₂BBr₂



- can also be cleaved in the presence of THP ethers

Methyl Thiomethyl Ethers (MTM)

R-OH R-OCH₂SMe Stable to base and mild acid

Formation: - MeSCH₂Cl, NaH, THF

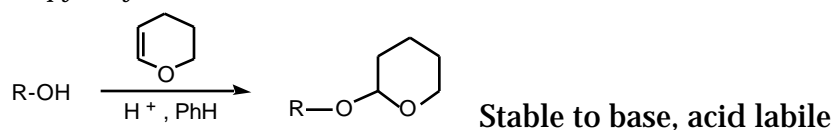
Cleavage: - HgCl₂, CH₃CN/H₂O
 - AgNO₃, THF, H₂O, base

Benzyloxymethyl Ethers (BOM)

R-OH R-OCH₂OCH₂Ph Stable to acid and base

Formation: - PhOCH₂CH₂Cl, CH₂Cl₂, iPr₂EtN

Cleavage: - H₂/ PtO₂
 - Na/ NH₃, EtOH

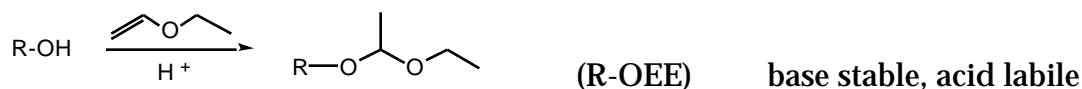
Tetrahydropyranyl Ether (THP)


Formation - DHP (dihydropyran), pTSA, PhH

Cleavage: - AcOH, THF, H₂O
 - Amberlyst H-15, MeOH

Ethoxyethyl ethers (EE)

JACS 1979, 101, 7104; JACS 1974, 96, 4745.


Benzyl Ethers (R-OBn)

R-OH R-OCH₂Ph stable to acid and base

Formation: - KH, THF, PhCH₂Cl

- PhCH₂OC(=NH)CCl₃, F₃CSO₃H JCS P1 1985, 2247

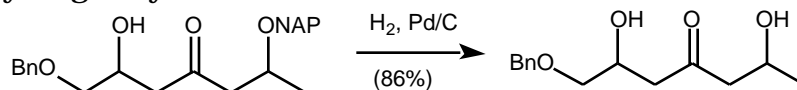
Cleavage: - H₂ / PtO₂

- Li / NH₃

2-Naphthylmethyl Ethers (NAP) *JOC* **1998**, 63, 4172

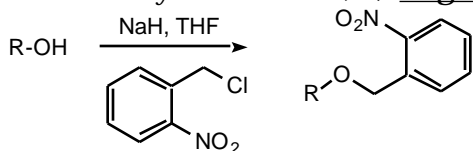
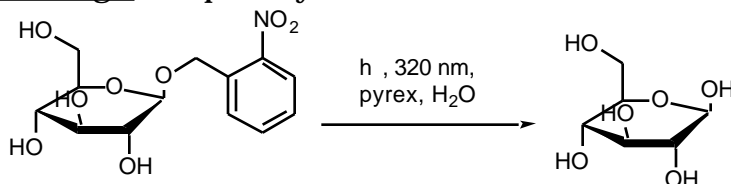
formation: 2-chloromethylnaphthalene, KH

cleavage: hydrogenolysis


***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⁻
***o*-Nitrobenzyl ethers**

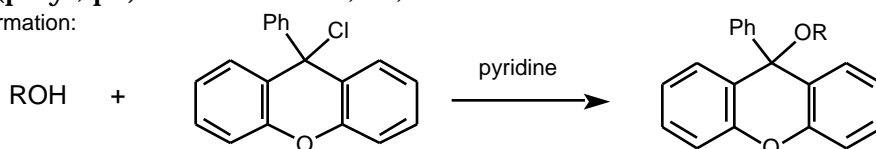
 Review: *Synthesis* **1980**, 1; *Organic Photochemistry*, **1987**, 9, 225

Cleavage: - photolysis at 320 nm

JOC **1972**, 37, 2281, 2282.

***p*-Nitrobenzyl Ether** *TL* **1990**, 31, 389

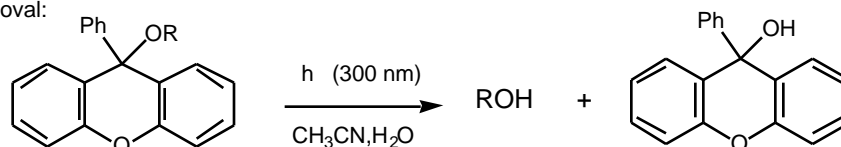
-selective removal with DDQ, hydrogenolysis or electrochemically

9-Phenylxanthyl- (pixyl, px) *TL* **1998**, 39, 1653

Formation:



Removal:


Triyl Ethers -CPh₃ = Tr

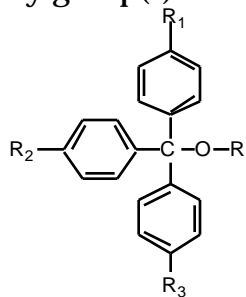
 R-OH R-OCPh₃ - selective for 1° alcohols
 - removed with mild acid; base stable

formation: - Ph₃C-Cl, pyridine, DMAP
 - Ph₃C⁺ BF₄⁻
Cleavage: - mild acid

Methoxytrityl Ethers

JACS 1962, 84, 430

- methoxy group(s) make it easier to remove

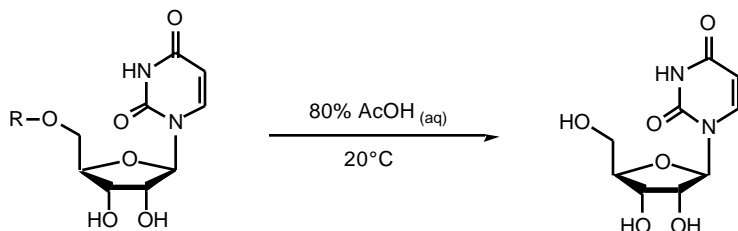


(p-Methoxyphenyl)diphenylmethyl ether
4'-methoxytrityl MMTr-OR

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

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

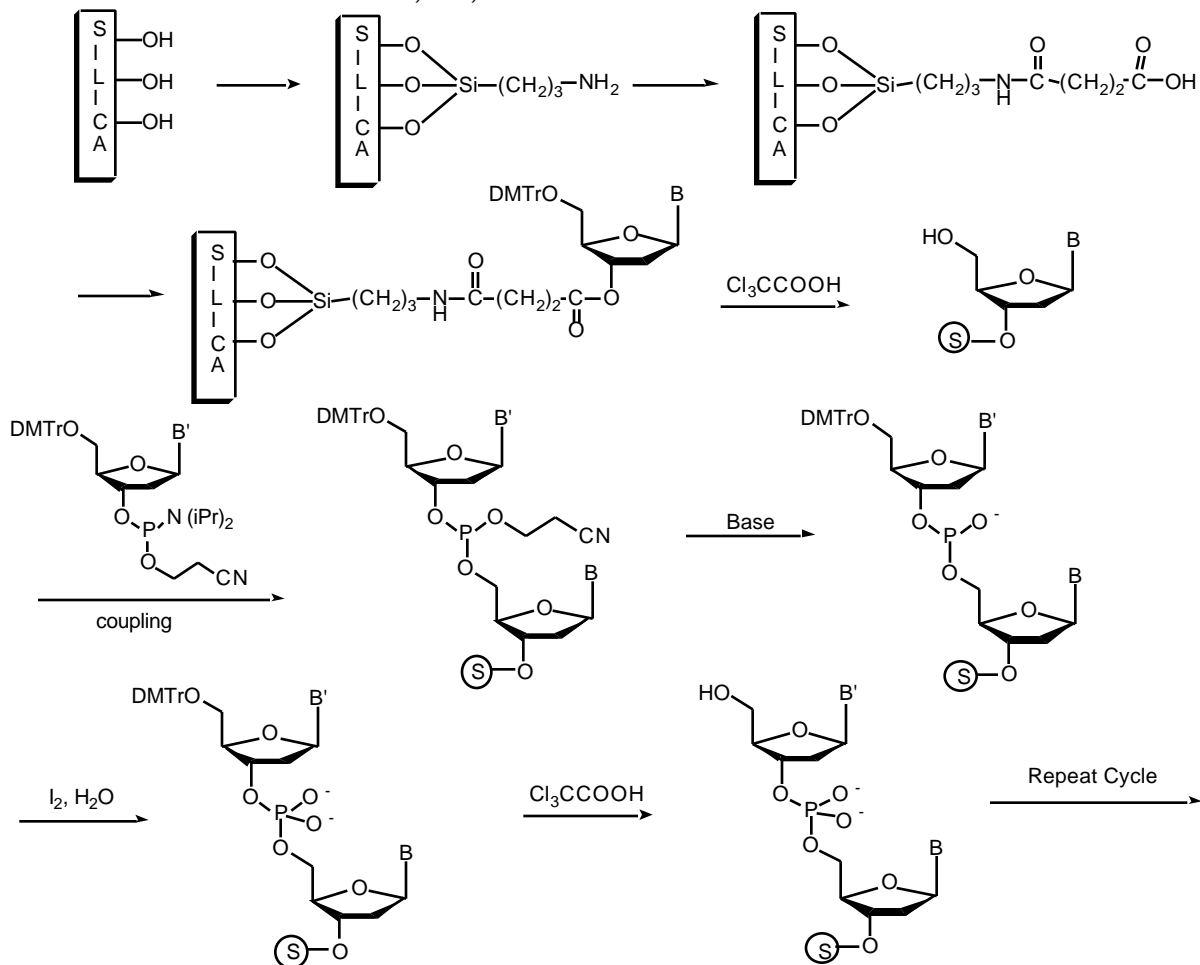
Tr-OR < MMTr-OR < DMTr-OR << TMTTr-OR



R = Tr 48 hr.
R = MMTr 2 hr.
R = DMTr 15 min.
R = TMTTr 1 min. (too labile to be useful)

Oligonucleotide Synthesis (phosphoramidite method - Lessinger)

Review: Tetrahedron 1992, 48, 2223



Silyl Ethers *Synthesis* **1985**, 817 *Synthesis* **1993**, 11 *Synthesis* **1996**, 1031

R-OH R-O-SiR₃

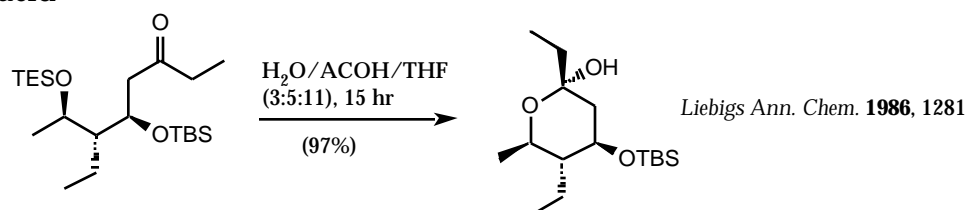
- formation:
- R₃Si-Cl, pyridine, DMAP
 - R₃Si-Cl, CH₂Cl₂ (DMF, CH₃CN), imidazole, DMAP
 - R₃Si-OTf, iPr₂EtN, CH₂Cl₂

Trimethylsilyl ethers Me₃Si-OR TMS-OR

- very acid and water labile
- useful for transient protection

Triethylsilyl ethers Et₃Si-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 iPr₃Si-OR TIPS-OR

- more stable to hydrolysis than TMS

Phenyldimethylsilyl ethers

J. Org. Chem. **1987**, 52, 165

t-Butyldimethylsilyl Ether tBuMe₂Si-OR TBS-OR TBDMS-OR

JACS **1972**, 94, 6190

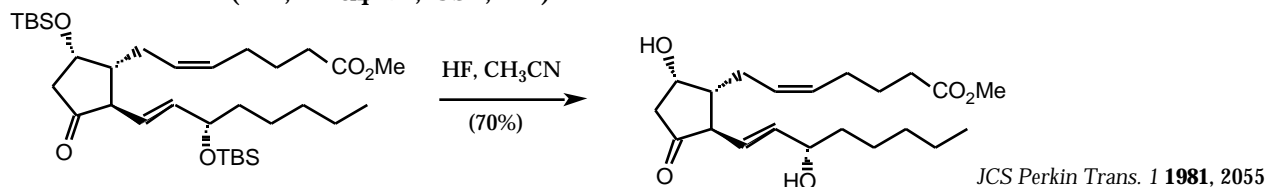
- Stable to base and mild acid
- under controlled condition is selective for 1° alcohols

t-butyldimethylsilyl triflate tBuMe₂Si-OTf *TL* **1981**, 22, 3455

- very reactive silylating reagent, will silylate 2° alcohols

cleavage:

- acid
- F⁻ (HF, nBu₄NF, CsF, KF)



t-Butyldiphenylsilyl Ether tBuPh₂Si-OR TBDPS-OR -OR

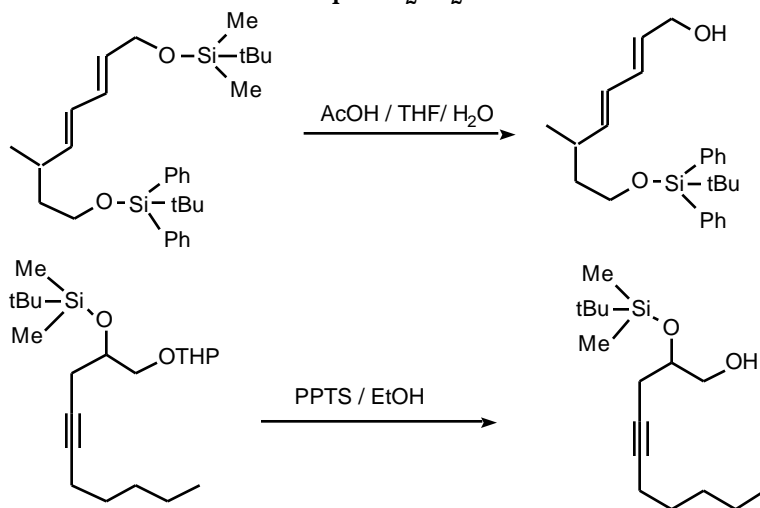
- stable to acid and base
- selective for 1° alcohols
- Me₃Si- and iPr₃Si groups can be selectively removed in the presence of TBS or TBDPS groups.
- TBS can be selectively removed in the presence of TBDPS by acid hydrolysis.

TL **1989**, 30, 19

cleavage - F⁻

- Fluoride sources:
- nBu₄NF (basic reagent)
 - HF / H₂O / CH₃CN
 - HF • pyridine
 - SiF₄ • CH₂Cl₂

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



JOC 1981, 46, 1506
 TL 1989, 30, 19.

JACS 1984, 106, 3748

Esters

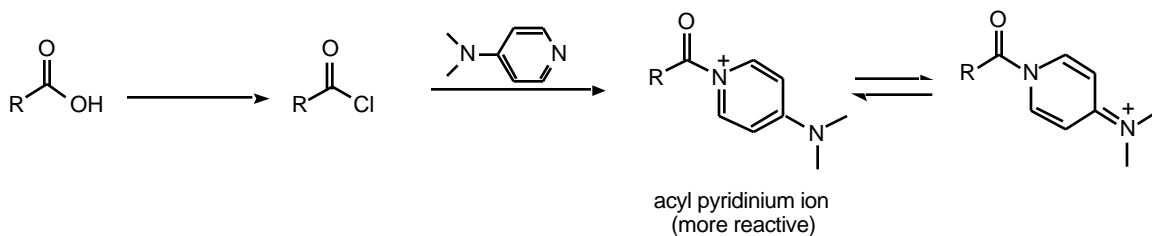


Formation: - "activated acid", base, solvent, (DMAP)

Activated Acids Chem. Soc. Rev. 1983, 12, 129 Angew. Chem. Int. Ed. Engl. 1978, 17, 569.

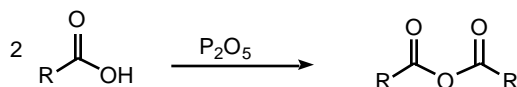
RCO₂H "activated acid" carboxylic acid derivative (ester, amide, etc.)

Acid Chlorides

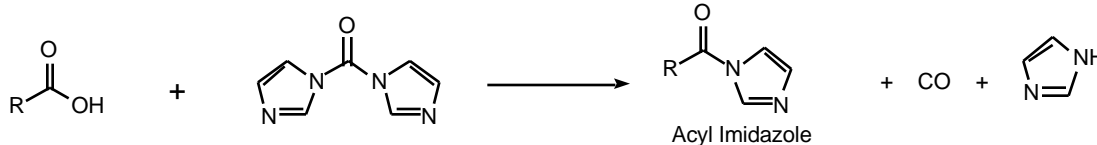


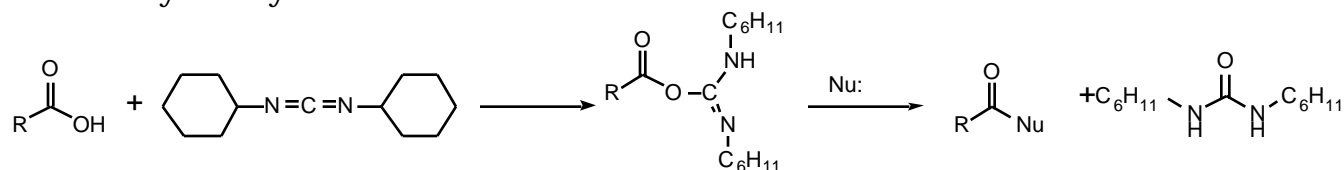
1. SOCl₂
2. PCl₅
3. (COCl)₂

Anhydrides

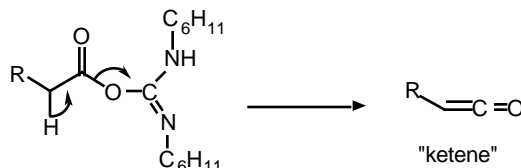


Activating Agents: Carbonyl Diimidazole

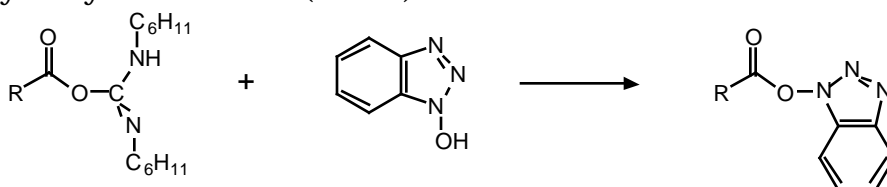


Dicyclohexylcarbodiimide


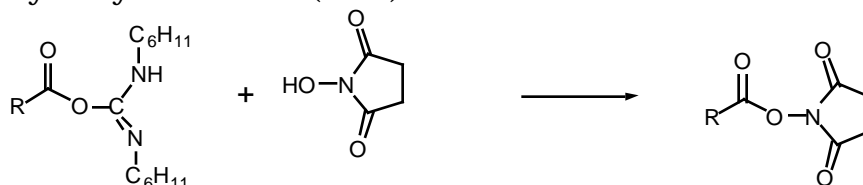
Ketene formation is a common side reaction- scrambling of chiral centers



Hydroxybenzotriazole (HOBT) - reduces ketene formation

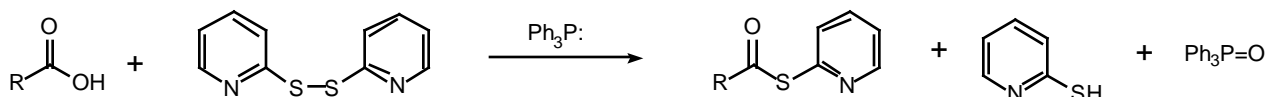


N-Hydroxysuccinimide (NHS)



2,2'-Dipyridyl Disulfide (Aldrithiol, Corey Reagent)

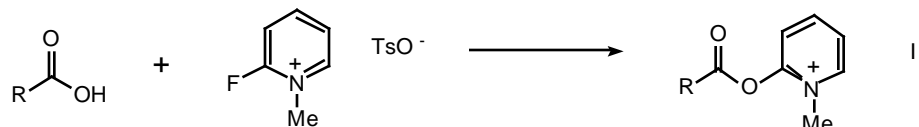
Aldrichimica Acta **1971**, 4, 33



Mukaiyama's Reagent (2-Chloro-1-methyl pyridinium Iodide or 2-Fluoro-1-methyl pyridinium p-toulenesulfonate)

Aldrichimica Acta **1987**, 20, 54

Chem. Lett. **1975**, 1045; 1159; **1976**, 49; **1977**, 575


Acetates

R-OH R-O₂CCH₃

- 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)

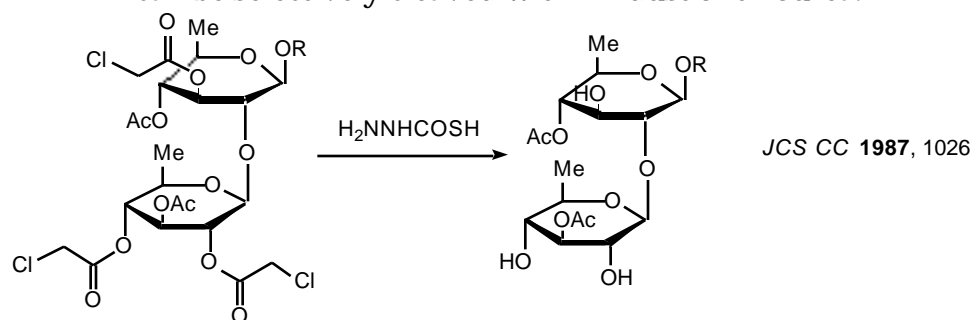
Org. Rxns. **1989**, 37, 1.



TL **1988**, 30, 6189

Chloroacetates

- can be selectively cleaved with Zn dust or thiourea.



Trifluoroacetates

- Formation: - with trifluoroacetic anhydride or trifluoroacetyl chloride

- Cleavage: - K_2CO_3 , MeOH

Pivaloate (t-butyl ester)

- Fairly selective for primary alcohols

- Formation: - t-butylacetyl chloride or t-butylacetic anhydride

- Cleavage: - removed with mild base

Benzoate (Bz)

- more stable to hydrolysis than acetates.

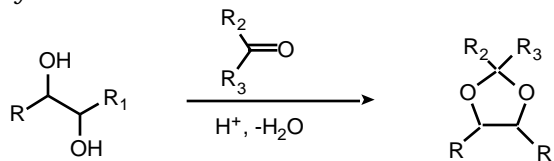
- Formation: - benzoyl chloride, benzoic anhydride, benzoyl cyanide (TL **1971**, 185), benzoyl tetrazole (TL **1997**, 38, 8811)

- Cleavage: - mild base
- KCN, MeOH, reflux

1,2 and 1,3- Diols

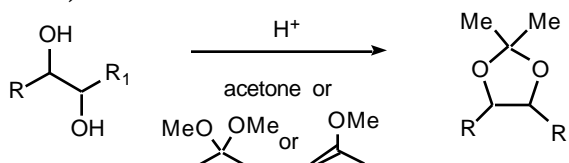
Synthesis **1981**, 501

Chem. Rev. **1974**, 74, 581



Isopropylidenes

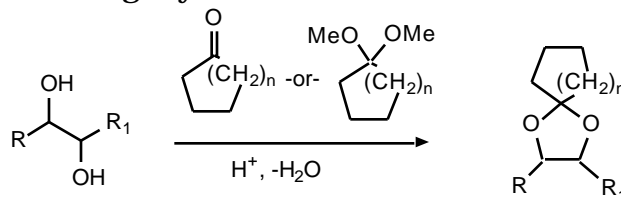
(acetonides)



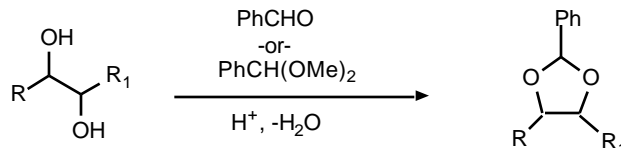
- in competition between 1,2- and 1,3-diols, 1,2-acetonide formation is usually favored
- cleaved with mild aqueous acid

Cycloalkylidene Ketals

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



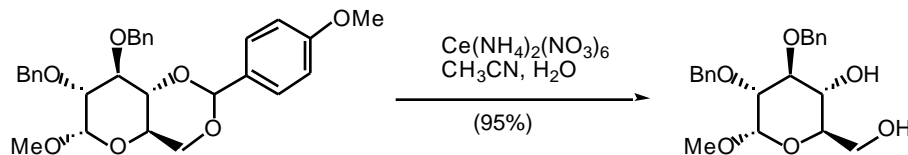
Benzylidene Acetals



- 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.

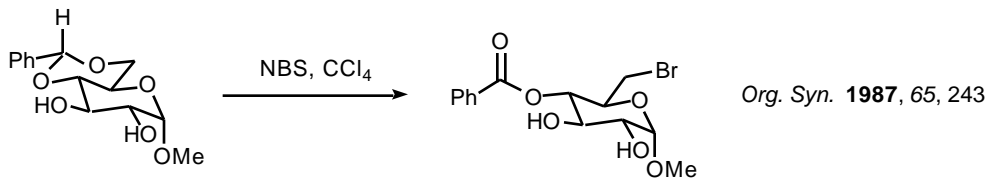
p-Methoxybenzylidenes

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



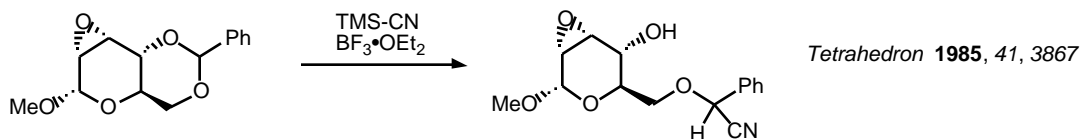
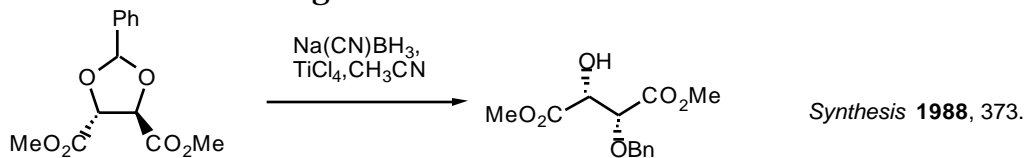
Other Reactions of Benzylidenes

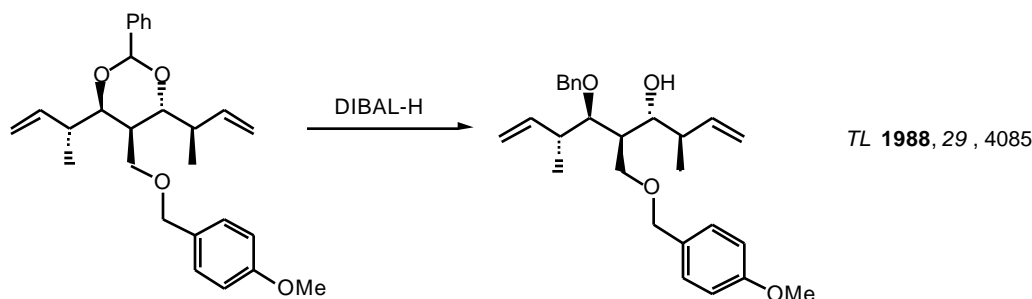
- Reaction with NBS (Hanesian Reaction)



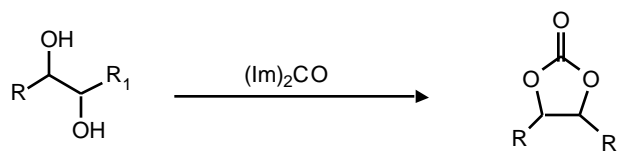
- if benzylidene of a 1° alcohol, then 1° bromide

- Reductive Cleavage





Carbonates

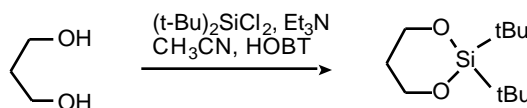


- stable to acid; removed with base
- more difficult to hydrolyze than esters

Di-*t*-Butylsilylene (DTBS)

TL 1981, 22, 4999

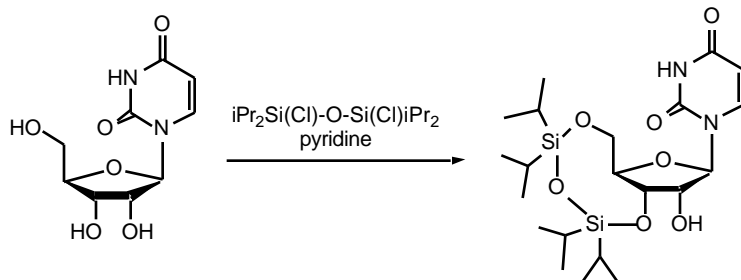
- used for 1,3- and 1,4-diols; 1,2-diols are rapidly hydrolyzed
- cleaved with fluoride (HF, CH₃CN -or- Bu₄NF -or- HF•pyridine)
- will not functionalize a 3°-alcohol



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

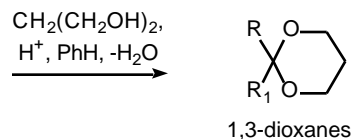
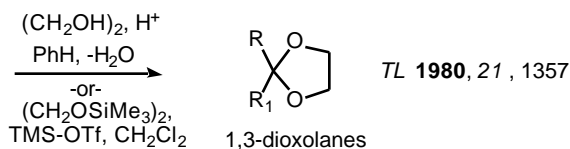
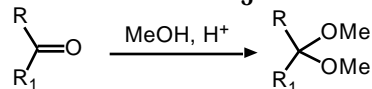
TL 1988, 29, 1561

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

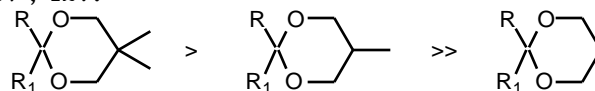


Ketones and Aldehydes

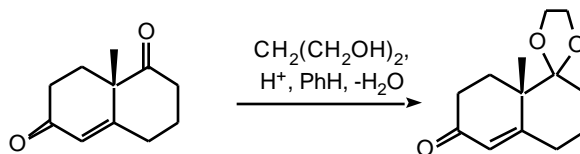
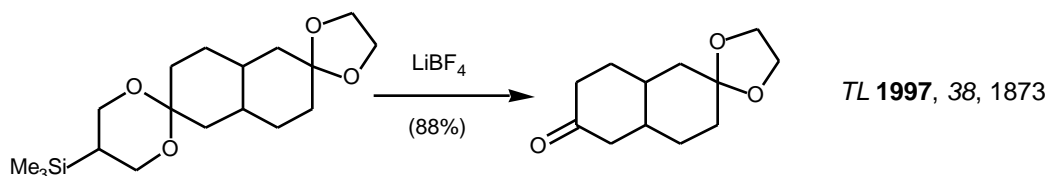
- ketones and aldehydes are protected as cyclic and acyclic ketals and acetals
- Stable to base; removed with H₃O⁺



Cleavage rate of substituted 1,3-dioxanes:

 Chem. Rev. **1967**, 67, 427.


- Ketal formation of α,β -unsaturated carbonyls are usually slower than for the saturated case.


Fluoride cleavable ketal:

Base cleavable ketal:

Carboxylic Acids

 Tetrahedron **1980**, 36, 2409. Tetrahedron **1993**, 49, 3691

Nucleophilic Ester Cleavage:

 Organic Reactions **1976**, 24, 187.

Esters
Alkyl Esters

 formation: - Fisher esterification ($\text{RCOOH} + \text{R}'\text{OH} + \text{H}^+$)

- Acid Chloride + R-OH, pyridine

- t-butyl esters: isobutylene and acid

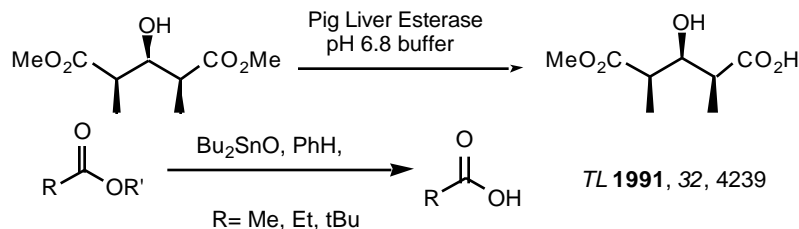
- methyl esters: diazomethane

Cleavage:

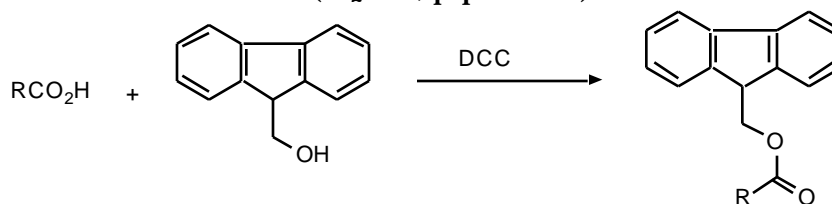
 - LiOH, THF, H_2O

 - enzymatic hydrolysis *Org. Rxns.* **1989**, 37, 1.

- t-butyl esters are cleaved with aqueous acid

 - Bu_2SnO , PhH, reflux (TL **1991**, 32, 4239)

9-Fluorenylmethyl Esters (Fm)

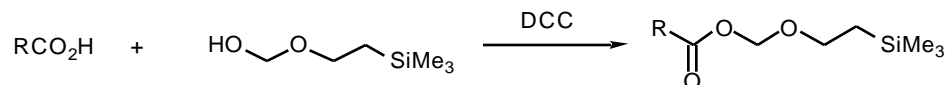
 TL **1983**, 24, 281

 - cleaved with mild base (Et_2NH , piperidine)


2-(Trimethylsilyl)ethoxymethyl Ester (SEM)

 HCA **1977**, 60, 2711.

- Cleaved with Bu_4NF in DMF

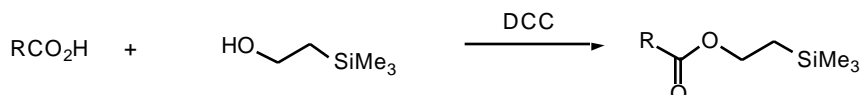


- Cleaved with $\text{MgBr}_2 \cdot \text{OEt}_2$ TL **1991**, 32, 3099.

2-(Trimethylsilyl)ethyl Esters

 JACS **1984**, 106, 3030

- cleaved with Fluoride ion



Haloesters

- cleaved with $\text{Zn}(0)$ dust or electrochemically



Benzyl Esters

 $\text{RCO}_2\text{H} + \text{PhCH}_2\text{OH} \rightarrow \text{RCO}_2\text{Bn}$
Formation: - DCC

- Acid chloride and benzyl alcohol

Cleavage: - Hydrogenolysis

- Na, NH_3

Diphenylmethyl Esters


Cleavage: - mild H_3O^+

- H_2 , Pd/C

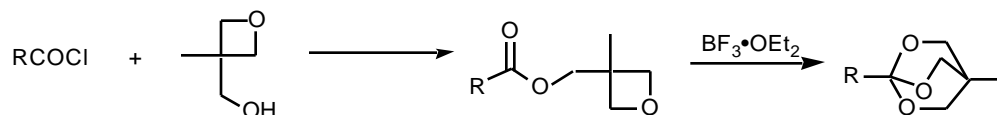
- $\text{BF}_3 \cdot \text{OEt}_2$

o-Nitrobenzyl Esters

- selective removed by photolysis

 Orthoesters Synthesis **1974**, 153

 Chem. Soc. Rev. **1987**, 75

 TL **1983**, 24, 5571


- Stable to base; cleaved with mild acid

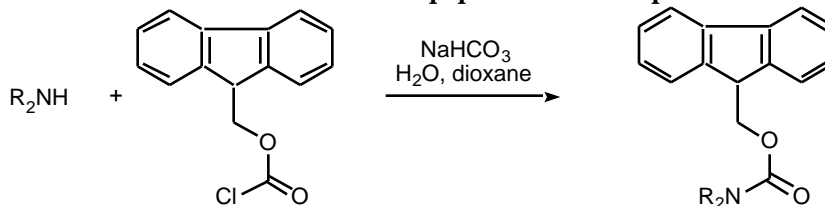
Amines

Carbamates

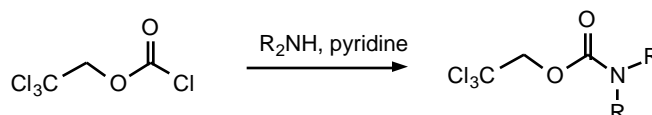
9-Fluorenylmethyl Carbamate (Fmoc)

Acc. Chem. Res. **1987**, 20, 401

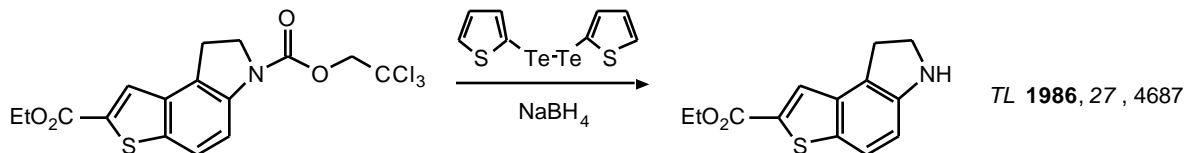
- Cleaved with mild base such as piperidine, morpholine or dicyclohexylamine



2,2,2-Trichloroethyl Carbamate

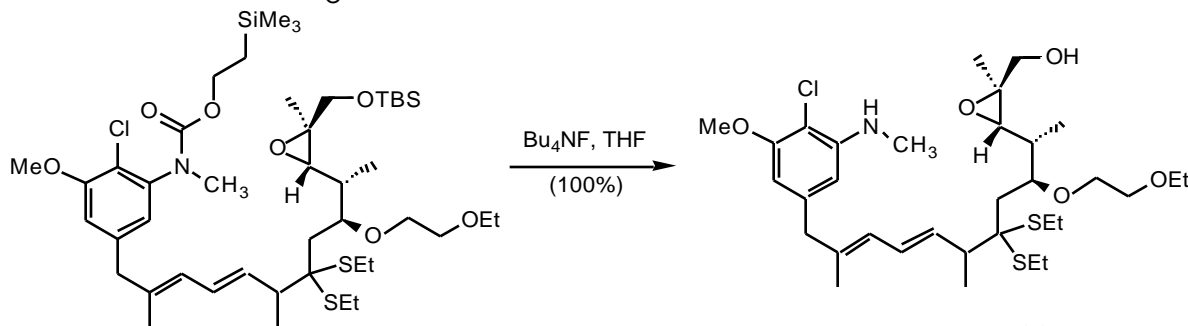
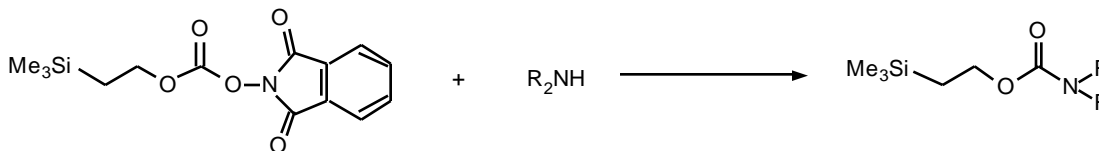


- Cleaved with zinc dust or electrochemically.



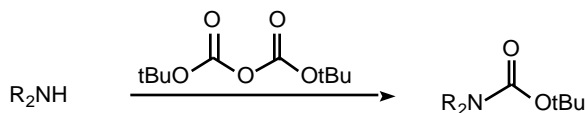
2-Trimethylsilylethyl Carbamate (Teoc)

- cleaved with fluoride ion.



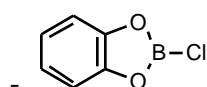
JACS 1979, 101 7104

t-Butyl Carbamate (BOC)



Cleavage: - with strong protic acid (3M HCl, CF_3COOH)

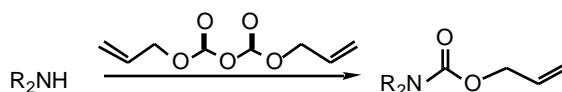
- TMS-I



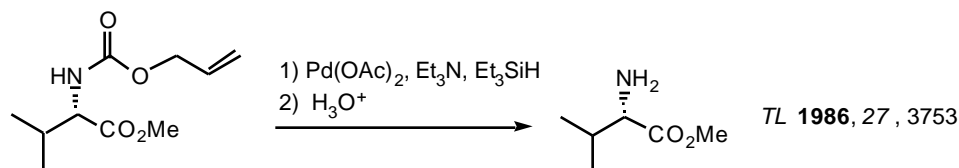
TL 1985, 26, 1411

Allyl Carbamate (Alloc)

TL 1986, 27, 3753



- removed with Pd(0) and a reducing agent (Bu₃SnH, Et₃SiH, HCO₂H)



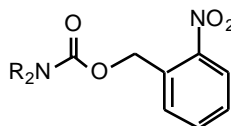
Benzyl Carbamate (Cbz)



Cleavage:

- Hydrogenolysis
- PdCl₂, Et₃SiH
- TMS-I
- BBr₃
- hν (254 nm)
- Na/ NH₃

m-Nitrophenyl Carbamate
JOC 1974, 39, 192

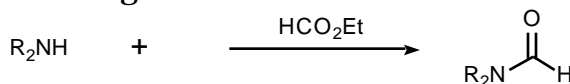


- removed by photolysis

Amides

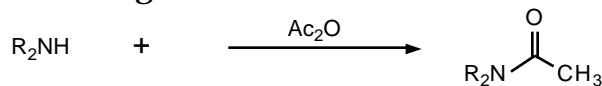
Formamides

- removed with strong acid



Acetamides

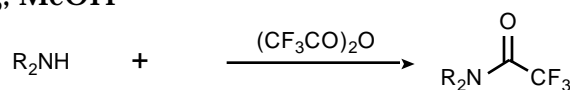
- removed with strong acid



Trifluoroacetamides

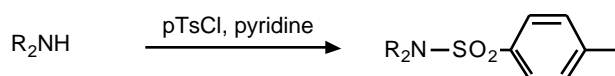
Cleavage:

- base (K₂CO₃, MeOH, reflux)
- NH₃, MeOH

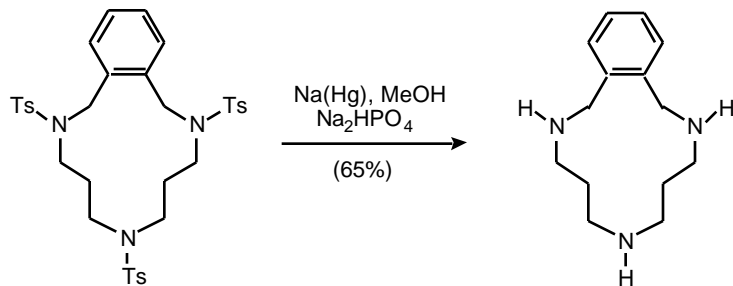


Sulfonamides

p-Toluenesulfonyl (Ts)

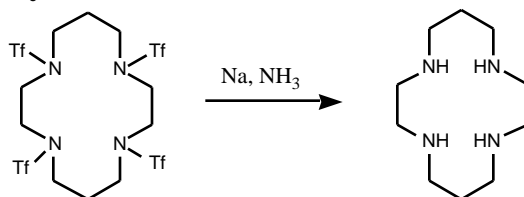


Cleavage: - Strong acid
 - sodium Naphthalide
 - Na(Hg)



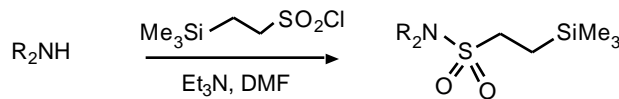
JOC 1989, 54, 2992

Trifluoromethanesulfonyl



JOC 1992, 33, 5505

Trimethylsilylethanesulfonamide (SES)
 TL 1986, 54, 2990; JOC 1988, 53, 4143
 - removed with CsF, DMF, 95°C



tert-Butylsulfonyl (Bus) JOC 1997, 62, 8604

