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

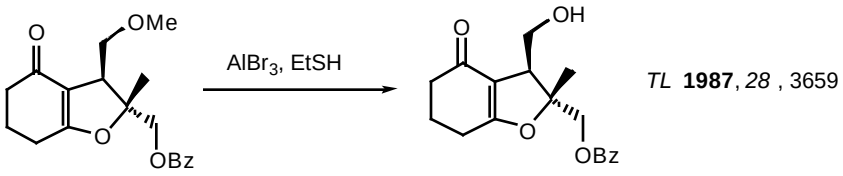
Hydroxyl Protecting Groups

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



TL **1987**, *28* , 3659

Methoxymethyl ether MOM

R-OH → R-OCH_2OMe stable to base and mild acid

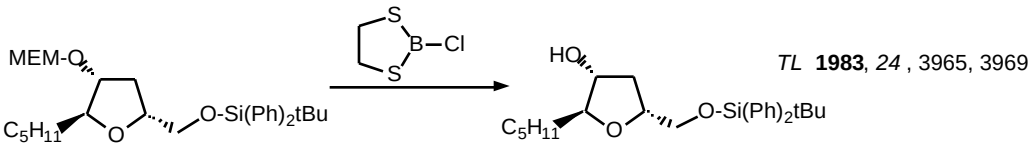
Formation: - $MeOCH_2Cl$, NaH, THF
- $MeOCH_2Cl$, CH_2Cl_2, iPr_2EtN
Cleavage - Me_2BBr_2 *TL* **1983**, *24* , 3969

Methoxyethoxymethyl ethers (MEM)

R-OH → 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



TL **1983**, *24* , 3965, 3969

- can also be cleaved in the presence of THP ethers

Methyl Thiomethyl Ethers (MTM)

R-OH → R-OCH_2SMe Stable to base and mild acid

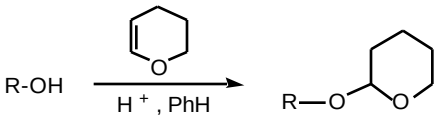
Formation: - $MeSCH_2Cl$, NaH, THF
Cleavage: - $HgCl_2$, CH_3CN / H_2O
- $AgNO_3$, THF, H_2O, base

Benzyloxymethyl Ethers (BOM)

R-OH → 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

Tetrahydropyranyl Ether (THP)

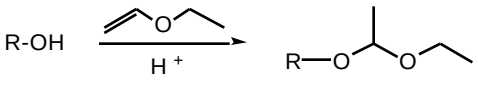


Stable to base, acid labile

Formation - DHP (dihydropyran), pTSA, PhH
Cleavage: - AcOH, THF, H_2O
- Amberlyst H-15, MeOH

Ethoxyethyl ethers (EE)

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



(R-OEE) base stable, acid labile

Benzyl Ethers (R-OBn)

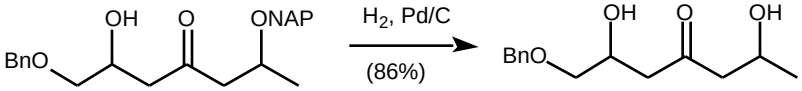
R-OH → R-OCH_2Ph stable to acid and base

Formation: - KH, THF, $PhCH_2Cl$
- $PhCH_2OC(=NH)CCl_3$, F_3CSO_3H *JCS P1* **1985**, 2247
Cleavage: - H_2 / PtO_2
- Li / NH_3

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

formation: 2-chloromethylnapthalene, KH

cleavage: hydrogenolysis



p- Methoxybenzyl Ethers (PMB)

Formation: - KH, THF, p-MeOPhCH$_2$Cl

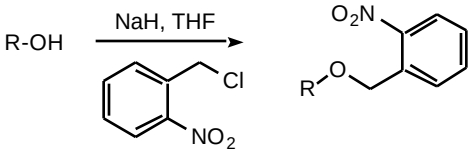
- p-MeOPhCH$_2$OC(=NH)CCl$_3$, F$_3$CSO$_3$H *TL* **1988**, *29* , 4139

Cleavage: - H_2 / PtO_2

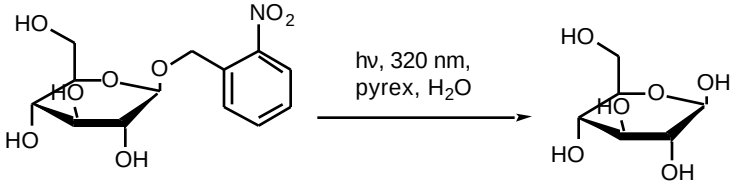
- Li / NH_3
- DDQ
- $Ce(NH_4)_2(NO_3)_6$ (CAN)
- e^-

o-Nitrobenzyl ethers

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



Cleavage: - photolysis at 320 nm



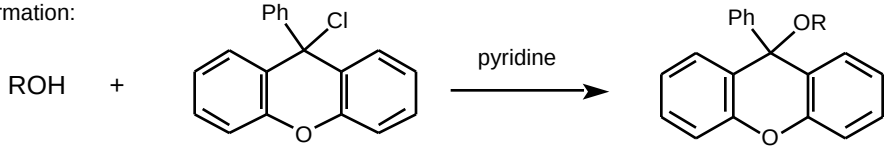
JOC **1972**, *37* , 2281, 2282.

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

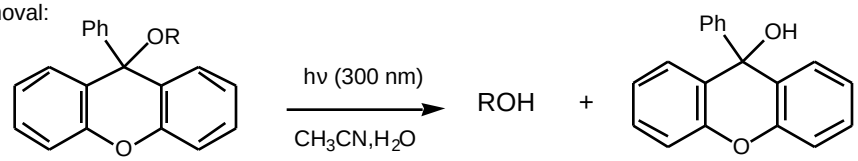
-selective removal with DDQ, hydrogenolysis or elctrochemically

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

Formation:



Removal:



Trityl Ethers -CPh_3 = Tr

R-OH → R-OCPh_3 - selective for 1° alcohols

- removed with mild acid; base stable

formation: - Ph_3C-Cl, pyridine, DMAP

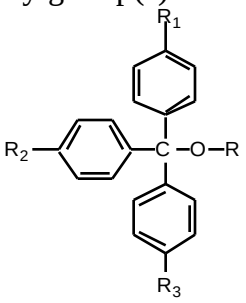
- Ph_3C^+ BF_4^-

Cleavage: - mild acid

Methoxytrityl Ethers

JACS **1962**, *84* , 430

- methoxy group(s) make it easier to remove

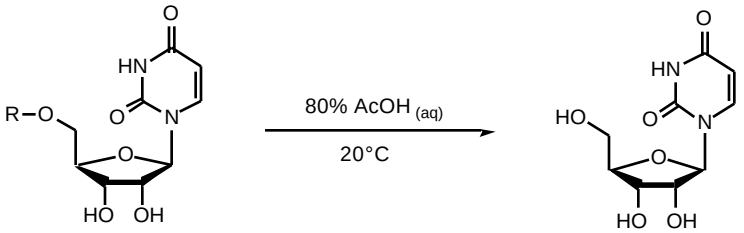


(p-Methoxyphenyl)diphenylmethyl ether
4'-methoxytrityl MMTr-OR

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

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

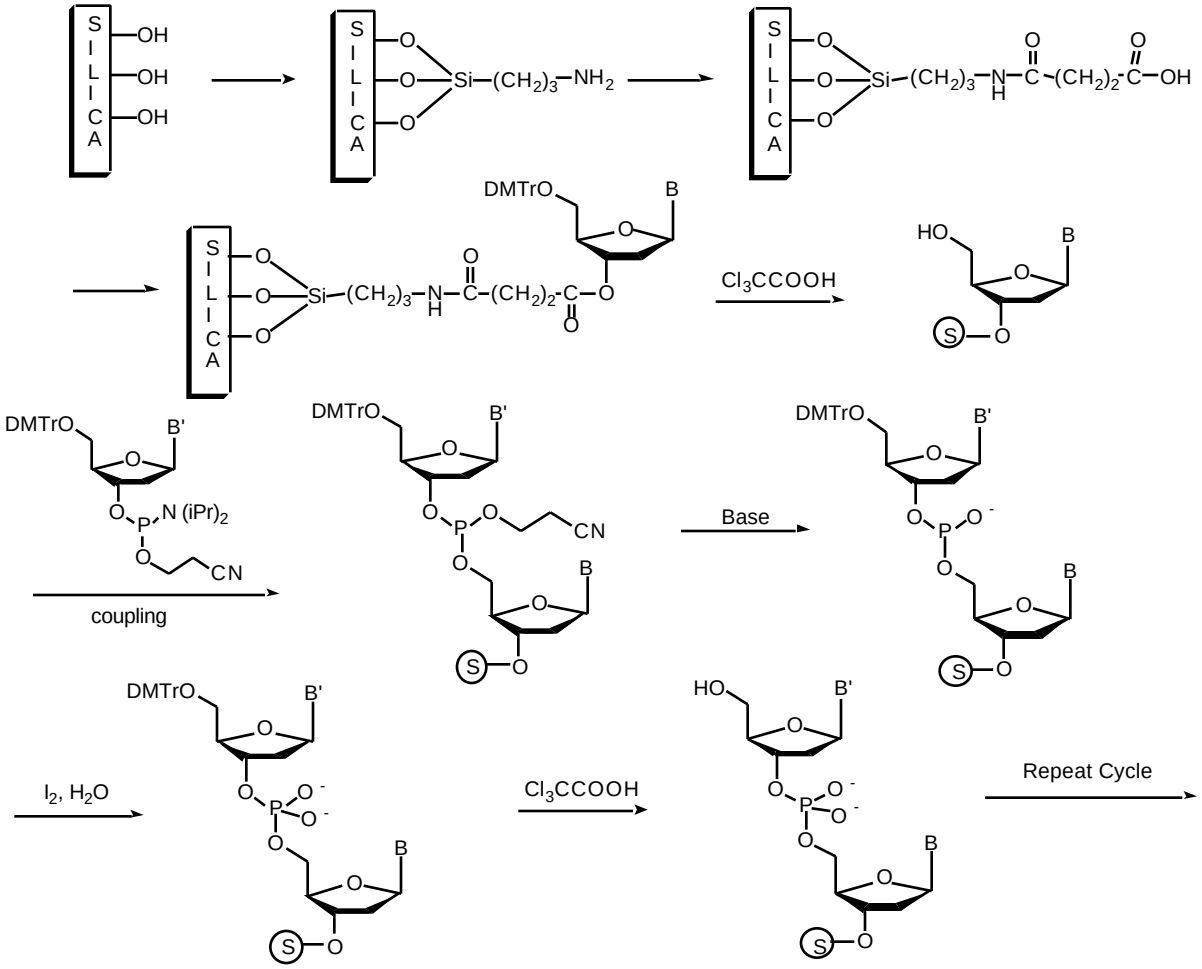
Tr-OR < MMTr-OR < DMTr-OR << TMTr-OR



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

Oligonucleotide Synthesis (phosphoramidite method - Lessinger)

Review: *Tetrahedron* **1992**, *48* , 2223



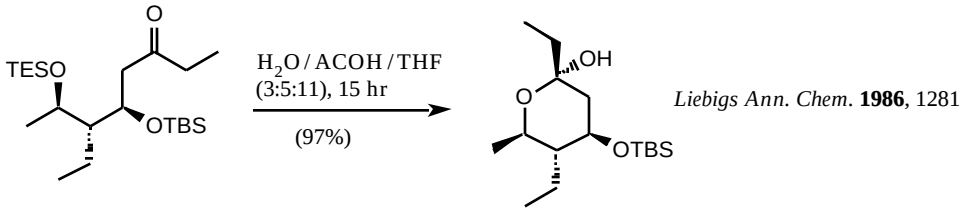
Silyl Ethers *Synthesis* **1985**, 817 *Synthesis* **1993**, 11 *Synthesis* **1996**, 1031

R-OH → R-O-SiR_3

formation: - R_3Si-Cl, pyridine, DMAP
- R_3Si-Cl, CH_2Cl_2 (DMF, CH_3CN), imidazole, DMAP
- R_3Si-OTf, iPr_2EtN, CH_2Cl_2

Trimethylsilyl ethers Me_3Si-OR TMS-OR
- very acid and water labile
- useful for transiant protection

Triethylsilyl ethers Et_3Si-OR TES-OR
- considerably more stable that TMS
- can be selectively removed in the presence of more robust silyl ethers with with F^- or mild acid



Liebigs Ann. Chem. **1986**, 1281

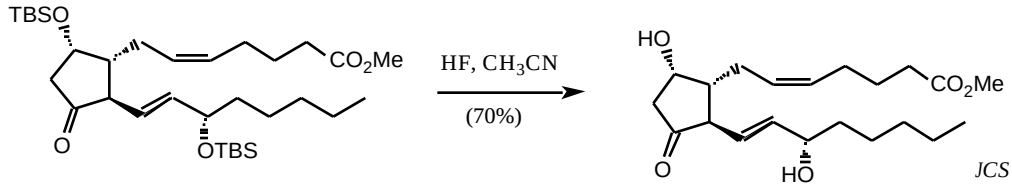
Triisopropylsilyl ethers iPr_3Si-OR TIPS-OR
- more stabile to hydrolysis than TMS

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

t-Butyldimethylsilyl Ether $tBuMe_2Si$-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 $tBuMe_2Si$-OTf *TL* **1981**, *22* , 3455
- very reactive silylating reagent, will silylate 2° alcohols

cleavage:
- acid
- F^- (HF, nBu_4NF, CsF, KF)

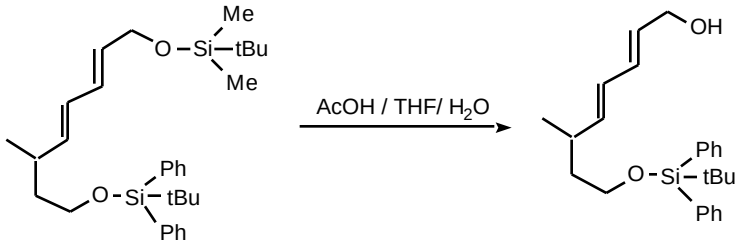


JCS Perkin Trans. 1 **1981**, 2055

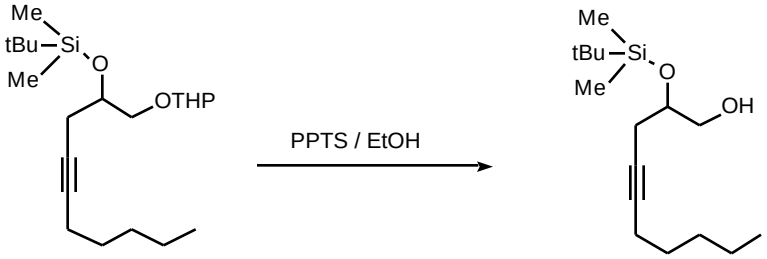
t-Butyldiphenylsilyl Ether $tBuPh_2Si$-OR TBDPS-OR ∑-OR
- stable to acid and base
- selective for 1° alcohols
- Me_3Si- and iPr_3Si groups can be selectively removed in the presence of TBS or TBDPS groups.
- TBS can be selectively removed in the presence of TBDPS by acid hydrolysis.
TL **1989**, *30* , 19

cleavage - F^-

- Fluoride sources: - nBu_4NF (basic reagent)
  - HF / H_2O / CH_3CN *TL* **1979**, 3981.
  - HF • pyridine *Synthesis* **1986**, 453
  - SiF_4. CH_2Cl_2 *TL* **1992**, *33* , 2289



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



JACS **1984**, *106* , 3748

Esters

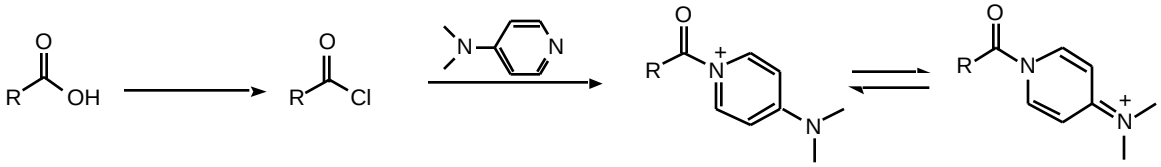
R-OH → R-O_2CR'

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

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

RCO_2H → "activated acid" → carboxylic acid derivative (ester, amide, etc.)

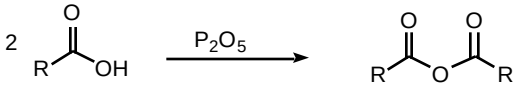
Acid Chlorides



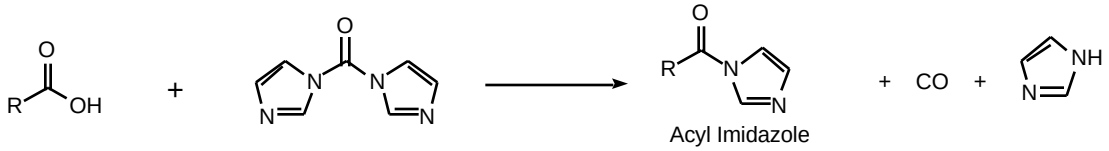
acyl pyridinium ion
(more reactive)

1. $SOCl_2$
2. PCl_5
3. $(COCl)_2$

Anhydrides

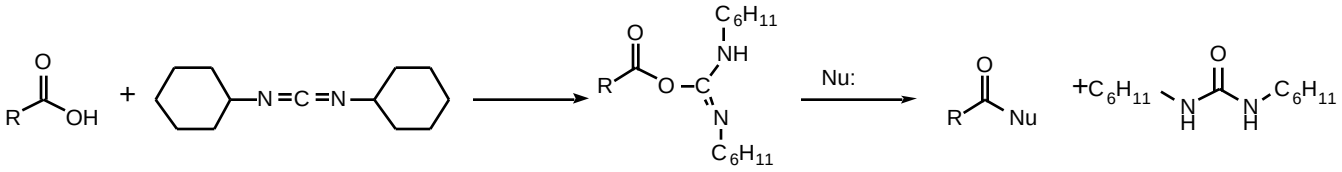


Activating Agents:
Carbonyl Diimidazole

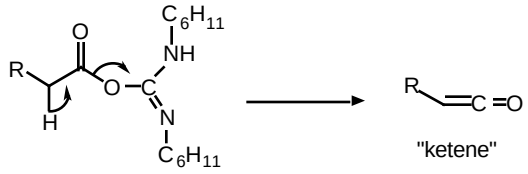


Acyl Imidazole

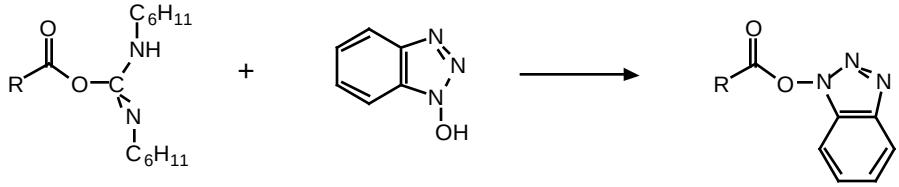
Dicyclohexylcarbodiimide



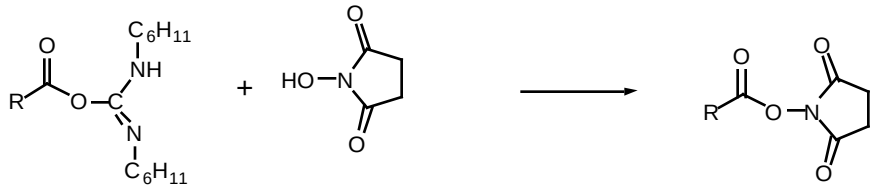
Ketene formation is a common side reaction- scambling of chiral centers



Hydroxybenzotriazole (HOBT) - reduces ketene formation

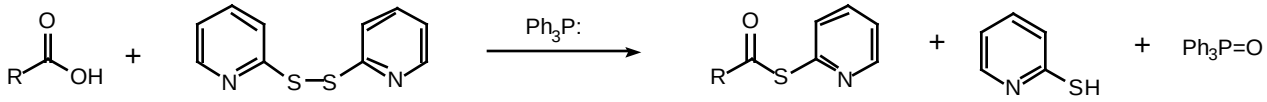


N-Hydroxysuccinimide (NHS)



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

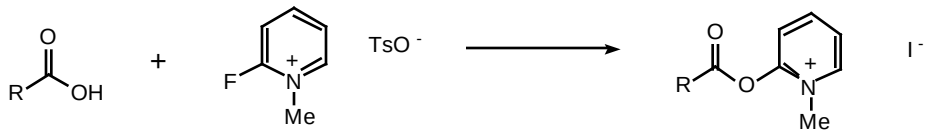
Aldrichimica Acta **1971**, *4* , 33



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



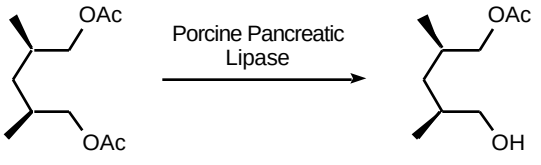
Acetates

R-OH → $R\text{-}O_2CCH_3$

- stable to acid and mild base
- not compatable 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.

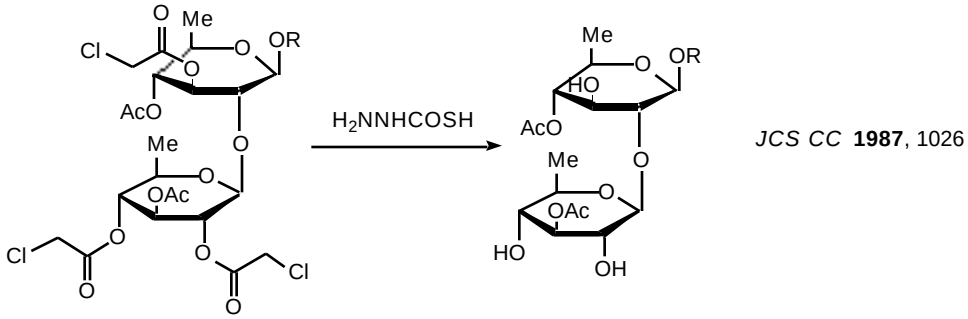


TL **1988**, *30* , 6189

(96% ee)

Chloroacetates

- can be selectively cleaved with Zn dust or thiourea.



JCS CC **1987**, 1026

Trifluoroacetates

Formation: - with trifluoroacetic anhydride or trifluoroacetyl chloride
Cleavage: - K_2CO_3, MeOH

Pivaloate (t-butyl ester)

- Fairly selective for primary alcohols

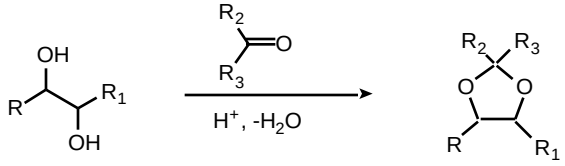
Formation: - tbutylacetyl chloride or t-butylacetic anhydride
Cleavage: - removed with mild base

Benzoate (Bz)

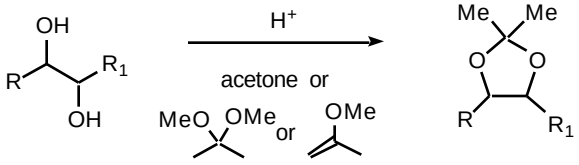
- more stable to hydrolysis than acetates.

Formation: - benzoyl chloride, benzoic anhydride, benzoyl cyanide (*TL* **1971**, 185) , benzoyl tetrazole (*TL* **1997**, *38*, 8811)
Cleavage: - mild base
- KCN, MeOH, reflux

1,2 and 1,3- Diols *Synthesis* **1981**, 501 *Chem. Rev.* **1974**, *74*, 581



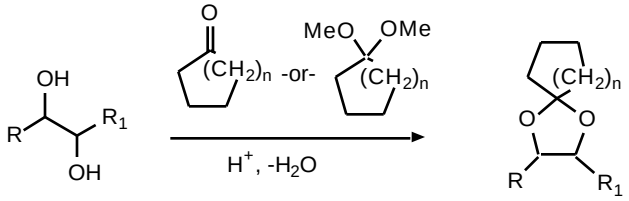
Isopropylidenes (acetonides)



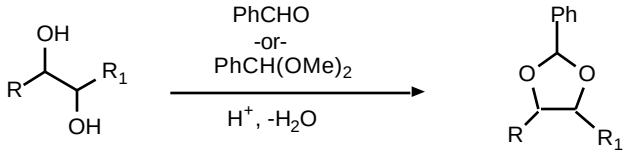
- in competition between 1,2- and 1,3-diols, 1,2-acetonide formation is usually favored
- cleaved with mild aqueous acid

Cycloalkylidene Ketals

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



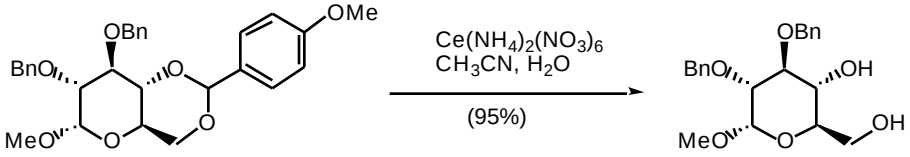
Benzylidene Acetals



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

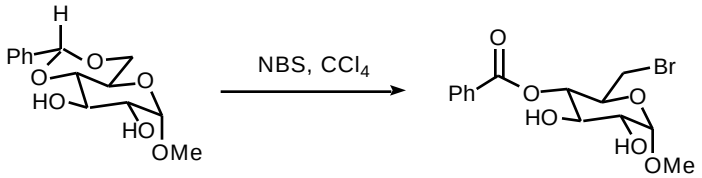
p-Methoxybenzylidenes

- hydrolyzed about 10X faster than regular benzylidenes
- Can be oxidatively removed with $Ce(NH_4)_2(NO_3)_6$ (CAN)



Other Reactions of Benzylidenes

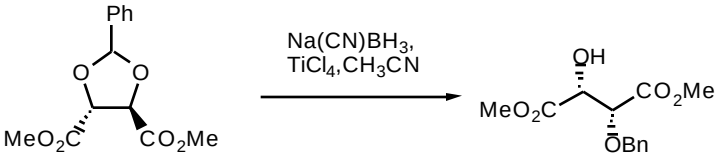
- Reaction with NBS (Hanessian Reaction)



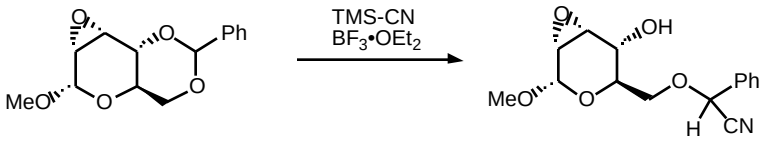
Org. Syn. **1987**, *65*, 243

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

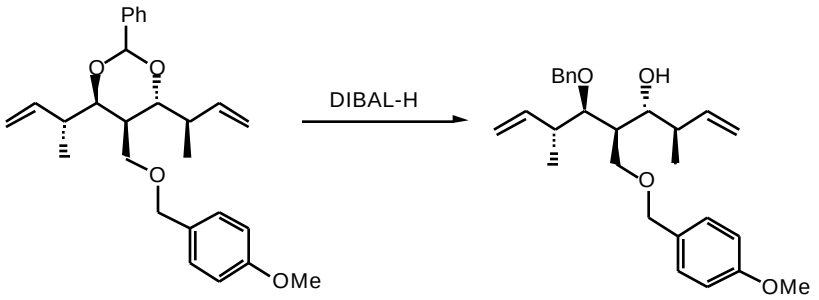
- Reductive Cleavage



Synthesis **1988**, 373.

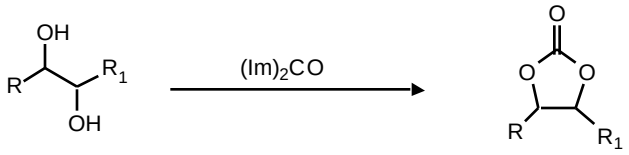


Tetrahedron **1985**, *41*, *3867*



TL **1988**, *29* , 4085

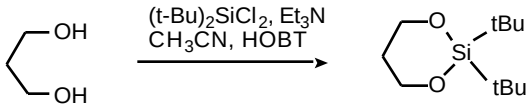
Carbonates



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

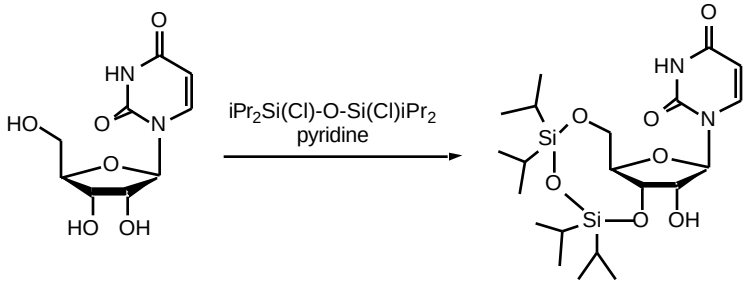
Di-t-Butylsilylene (DTBS) *TL* **1981**, *22* , 4999

- used for 1,3- and 1,4-diols; 1,2-diols are rapidly hydrolyzed
- cleaved with fluoride (HF, CH_3CN -or- Bu_4NF -or- HF•pyridine)
- will not fuctionalize a 3°-alcohol



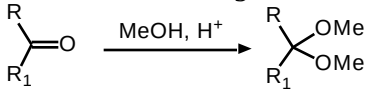
1,3-(1,1,3,3)-tetraisopropyldisiloxanylidene (TIPDS) *TL* **1988**, *29* , 1561

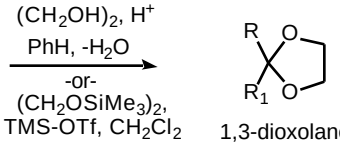
- specific for 1,3- and 1,4-diols
- cleaved with fluoride or TMS-I



Ketones and Aldehydes

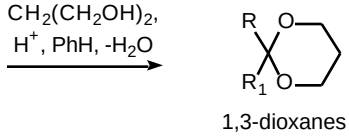
- ketones and aldehydes are protected as cyclic and acyclic ketals and acetals
- Stable to base; removed with H_3O^+





1,3-dioxolanes

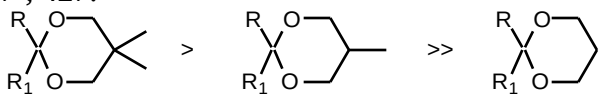
TL **1980**, *21* , 1357



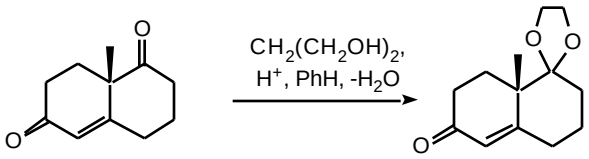
1,3-dioxanes

Cleavage rate of substituted 1,3-dioxanes:

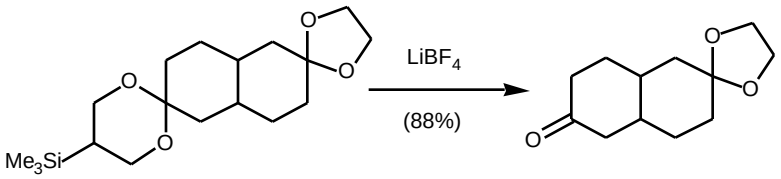
Chem. Rev. **1967**, *67* , 427.



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

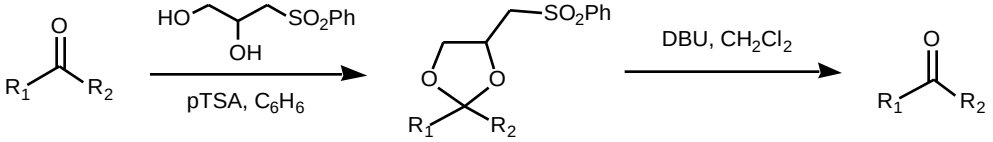


Fluoride cleavable ketal:



TL **1997**, *38*, 1873

Base cleavable ketal:



TL **1998**, *39*, 2401

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

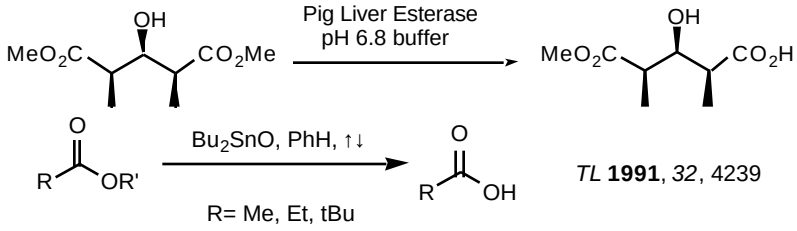
Nucelophilic Ester Cleavage: *Organic Reactions* **1976**, *24*, 187.

<u>*Esters*</u>

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, 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)

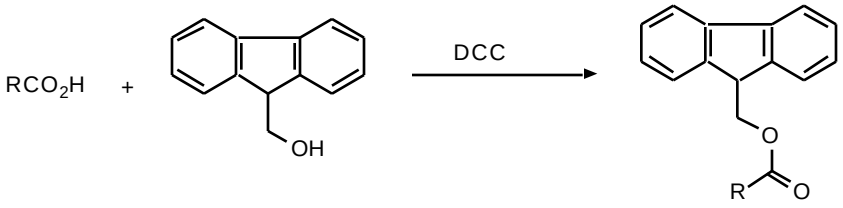


TL **1991**, *32*, 4239

9-Fluorenylmethyl Esters (Fm)

TL **1983**, *24* , 281

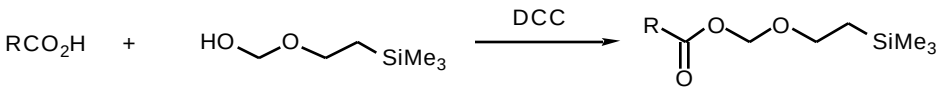
- cleaved with mild base (Et_2NH, piperidine)



2-Trimethylsilyl)ethoxymethyl Ester (SEM)

HCA **1977**, *60* , 2711.

- Cleaved with Bu_4NF in DMF

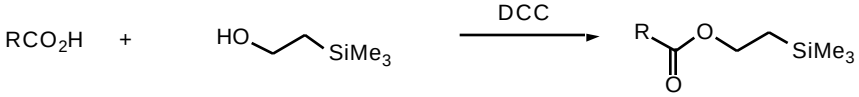


- Cleaved with MgBr2•OEt2 *TL* **1991**, *32*, 3099.

2-(Trimethylsilyl)ethyl Esters

JACS **1984**, *106* , 3030

- cleaved with Fluoride ion



Haloesters

- cleaved with Zn(0) dust or electrochemically

Benzyl Esters

$RCO_2H + PhCH_2OH \rightarrow RCO_2Bn$

Formation: - DCC
- Acid chloride and benzyl alcohol

Cleavage: - Hydrogenolysis
- Na, NH_3

Diphenylmethyl Esters

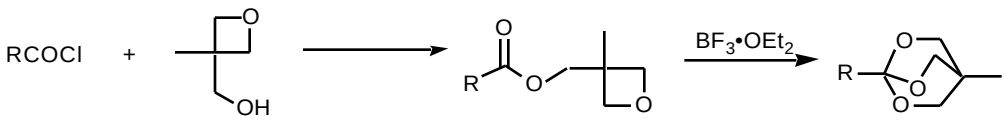
Cleavage: - mild H_3O^+
- H_2, Pd/C
- $BF_3 \bullet OEt_2$

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

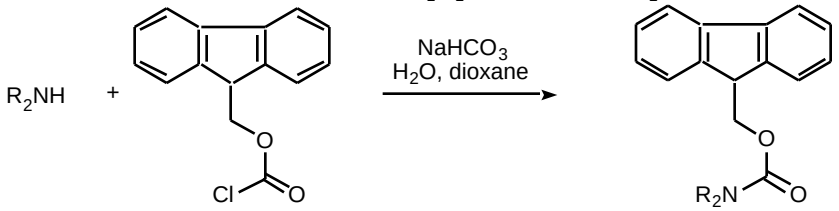
Amines

Carbamates

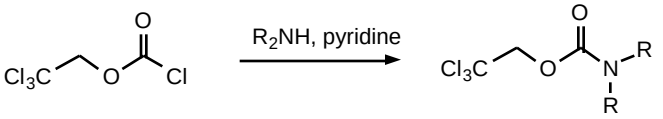
9-Fluorenylmethyl Carbamate (Fmoc)

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

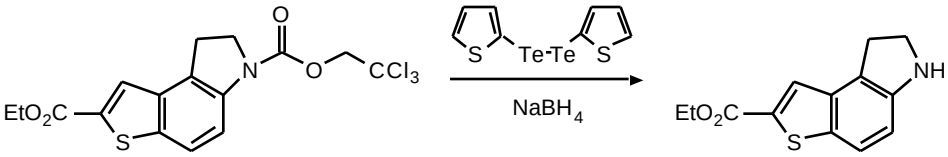
- Cleaved with mild base such as piperidine, morpholine or dicyclohexylamine



2,2,2-Trichloroethyl Carbamate



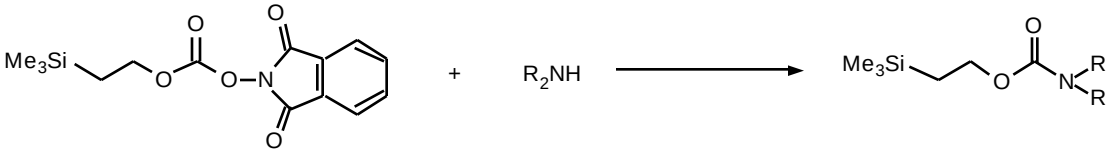
- Cleaved with zinc dust or electrochemically.

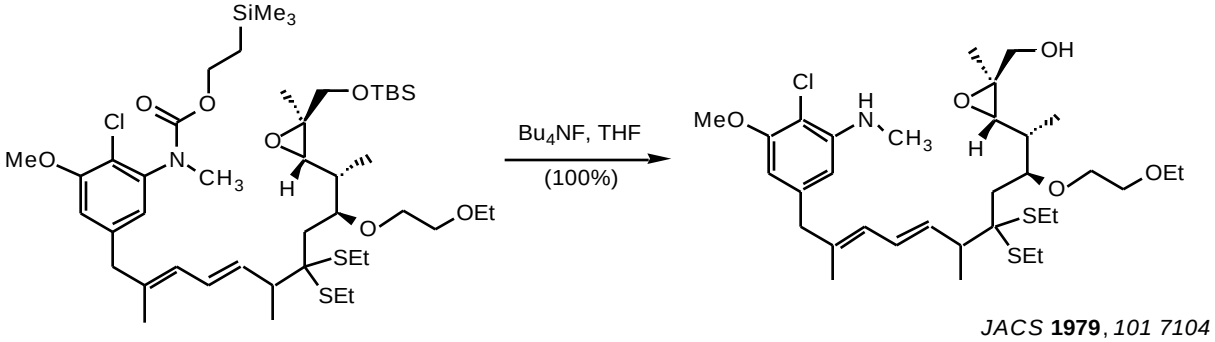


TL **1986**, *27* , 4687

2-Trimethylsilylethyl Carbamate (Teoc)

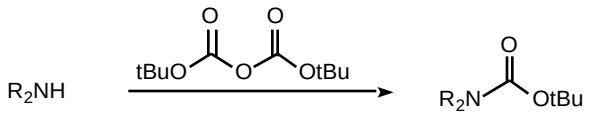
- cleaved with fluoride ion.





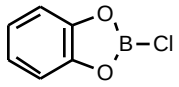
JACS **1979**, *101 7104*

t-Butyl Carbamate (BOC)



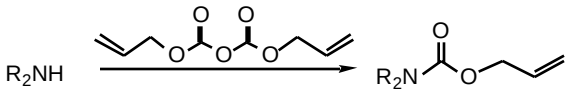
Cleavage: - with strong protic acid (3M HCl, CF_3COOH)

- TMS-I

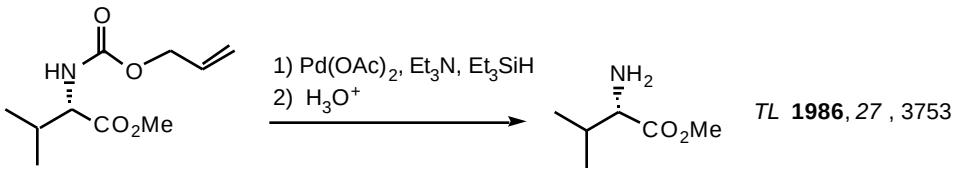
- 

TL **1985**, *26* , 1411

Allyl Carbamate (Alloc) *TL* **1986**, *27* , 3753

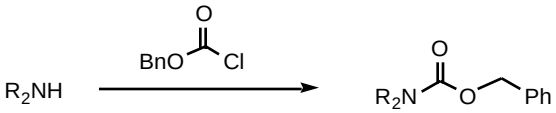


- removed with Pd(0) and a reducing agent (Bu_3SnH, Et_3SiH, HCO_2H)



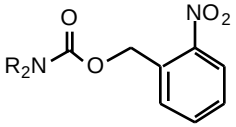
TL **1986**, *27* , 3753

Benzyl Carbanate (Cbz)



Cleavage:
- Hydrogenolysis
- $PdCl_2$, Et_3SiH
- TMS-I
- BBr_3
- hν (254 nm)
- Na / NH_3

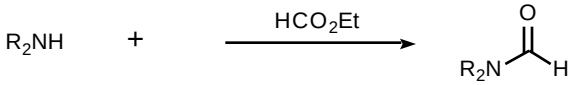
m-Nitrophenyl Carbamate
JOC **1974**, *39* , 192



- removed by photolysis

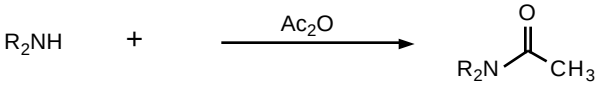
Amides
Formamides

- removed with strong acid

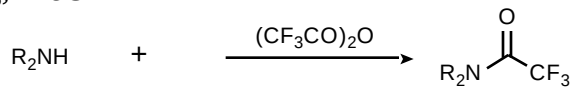


Acetamides

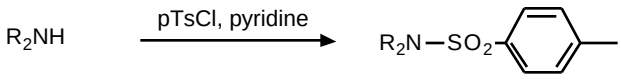
- removed with strong acid



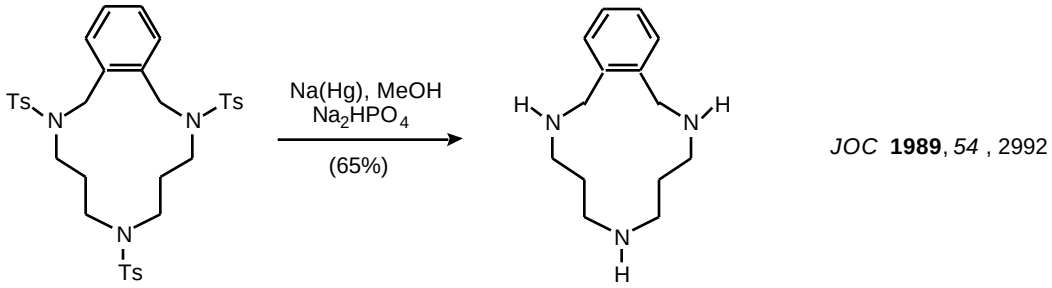
Trifluoroacetamides
Cleavage:
- base (K_2CO_3, MeOH, reflux)
- NH_3, MeOH



Sulfonamides
p-Toluenesulfonyl (Ts)

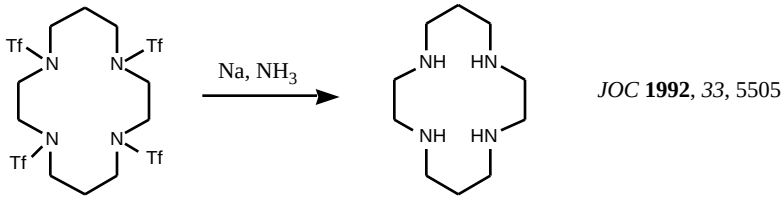


Cleavage: - Strong acid
- sodium Naphthalide
- Na(Hg)



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