

Chapter 3: Protecting Groups

I. Protecting Groups of Hydroxyl Groups

Consider the stability and effect of anomeric group!

Consider the solubility of starting material (the choice of solvent)!

Consider the reactivity of different hydroxyl groups!

* DCM is common for pyranoses with 2-3 OH's. For pyranose with more than 4 OH's, use DMF or pyridine.

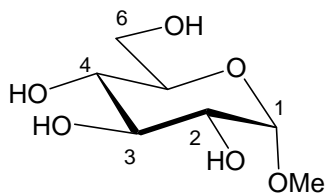
* Nucleophilicity of OH groups on pyranoses (chair conformation) (*Carbohydr. Res.* **1987**, 162, 159.)

1° OH > 2° OH

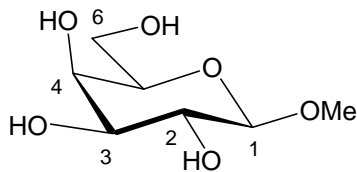
Equatorial OH > axial OH

Equatorial OH with vicinal axial OH (or OR) > Equatorial OH without vicinal axial OH (or OR)

Examples:

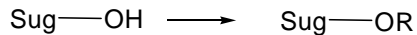


Estimated order of nucleophilicity: 6-OH > 2-OH > 3-OH ~ 4-OH



Estimated order of nucleophilicity: 6-OH > 3-OH > 2-OH > 4-OH

(i) Alkyl ether type



Advantages:

- * Relatively stable in harsh conditions (acidic, basic, reflux, etc.)
- * Enhance the reactivity of glycosylation due to electron-donating effect
- * More compatible to the conditions needed for deoxygenation or amino (azido) substitution
- * Selective protection is possible

Disadvantages:

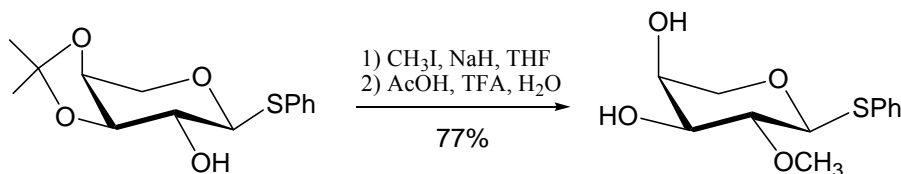
- * Relatively harder to remove (deprotect)
- * Conditions for protection and deprotection may not be compatible to other types of protecting groups

(a) R = methyl (CH₃, Me)

- * Not commonly used due to the difficulty of deprotection
- * Methoxy group can be found in naturally occurring unusual sugars

	Reagent/Condition	Reference
Protection	MeI, NaH in THF or DMF	<i>Tetrahedron Lett.</i> 1989 , 30, 641.
	Me ₃ O ⁺ BF ₄ ⁻	<i>J. Org. Chem.</i> 1972 , 37, 912.
	MeOTf, DCM, py., 80°C	
	MeI, Ag ₂ O	<i>J. Am. Chem. Soc.</i> 1980 , 102, 7083.
Deprotection	BBr ₃ , EtOAc or DCM	<i>J. Org. Chem.</i> 1979 , 44, 4863.
	SiCl ₄ , NaH, DCM, CH ₃ CN	<i>Synthesis</i> 1982 , 1048.
	AlCl ₃ , AlBr ₃	<i>Chem. Lett.</i> 1979 , 97.
	Ac ₂ O, FeCl ₃ , 80°C	<i>J. Org. Chem.</i> 1974 , 39, 3728

Examples:



(b) R = trityl, triphenylmethyl (Ph₃C, Tr)

- * Excellent for selective protection of primary OH
- * Stable in basic but very labile in acidic conditions
- * Easy to observe with TLC
- * Deprotection can be tricky

Protection	Reagent/Condition	Reference
	TrCl, 3° amines, DCM	<i>Tetrahedron Lett.</i> 1989 , 30, 641.
Deprotection	TFA, <i>t</i> -BuOH	<i>Carbohydr. Res.</i> 1978 , 60, 206.
	HCl, CHCl ₃ , 0°C	<i>Carbohydr. Res.</i> 1971 , 17, 439.
	TsOH, DCM, MeOH	<i>Tetrahedron Lett.</i> 1977 , 18, 3473.
	BF ₃ , Et ₂ O	<i>Can. J. Chem.</i> 1978 , 56, 2700

Examples:

(c) R = methoxymethyl (CH₃OCH₂, MOM)

- * Can be incorporated at relatively weak basic conditions (3° amine) but needs relatively strong acid (TFA) to remove
- * Stable in basic conditions
- * The reagent, MOMCl, is considered carcinogenic

	Reagent/Condition	Reference
Protection	MOMCl, NaH in THF or DMF	<i>J. Am. Chem. Soc.</i> 1972 , 94, 7827.
	MOMCl, DIPEA, 0°C or r.t.	<i>Synthesis</i> 1975 , 276.
	CH ₂ (OMe) ₂ , TsOH, LiBr, r.t.	<i>Synthesis</i> 1985 , 74.
Deprotection	Conc. HCl, MeOH	<i>Chem. Commun.</i> 1974 , 298.
	Me ₂ BBr, DCM	<i>J. Am. Chem. Soc.</i> 1981 , 103, 3213.
	TFA, DCM	<i>J. Am. Chem. Soc.</i> 1981 , 103, 3210.
	LiBF ₄ , CH ₃ CN, 80°C	<i>J. Org. Chem.</i> 1986 , 51, 635.

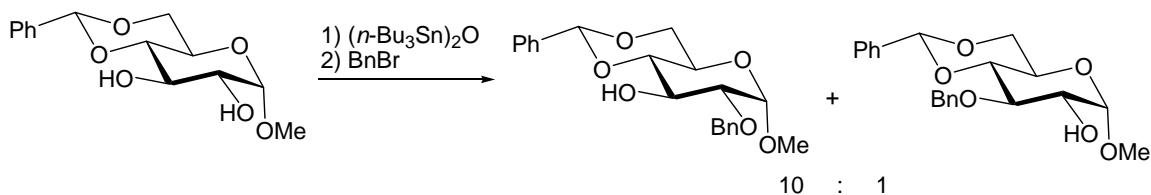
Examples:

(d) R = benzyl (C₆H₅CH₂, Bn)

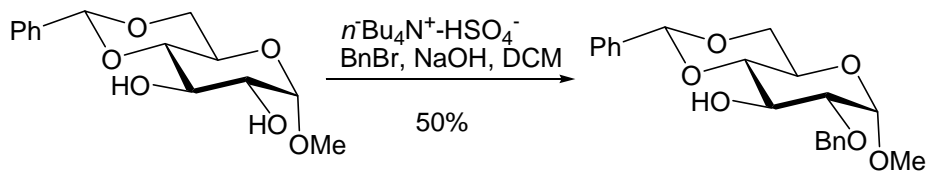
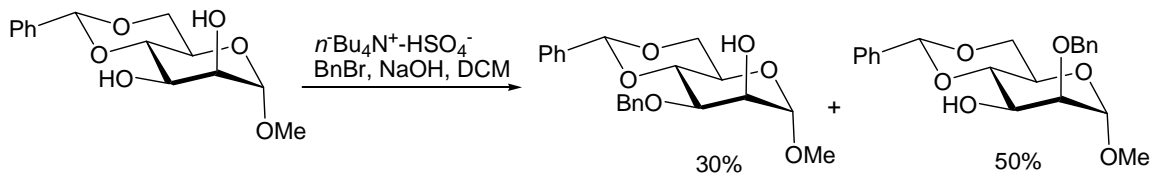
- * Can be traceless removed using hydrogenolysis
- * Stable in basic conditions
- * Relatively stable in acidic conditions
- * Quenching excess reagent (BrBr) with MeOH can be tricky

	Reagent/Condition	Reference
Protection	BnCl, Bu ₄ N ⁺ -HSO ₄ ⁻ , KOH	<i>Tetrahedron Lett.</i> 1975 , 16, 3251.
	BnBr, NaH, THF or DMF, TBAI	<i>Tetrahedron Lett.</i> 1976 , 17, 3535.
	BnBr, Ag ₂ O, DMF, r.t.	<i>Bull. Korean Chem. Soc.</i> 2003 , 24, 163. <i>J. Org. Chem.</i> 1985 , 50, 3940.
	BnBr, Bu ₂ SnO or (Bu ₃ Sn) ₂ O, toluene, reflux	<i>J. Am. Chem. Soc.</i> 1994 , 116, 5647
	BnOC(NH)CCl ₃ , TfOH	<i>J. Am. Chem. Soc.</i> 1988 , 110, 1624. <i>Synthesis</i> 1987 , 568.
	Deprotection	H ₂ , Pd/C or Pd(OH) ₂ /C
TMSI, DCM		<i>J. Org. Chem.</i> 1977 , 42, 3761.
BF ₃ -OEt ₂ , NaI, CH ₃ CN		<i>J. Chem. Res. Synop.</i> 1985 , 232.
Ac ₂ O, cat.c. H ₂ SO ₄ , 0°C		<i>J. Org. Chem.</i> 2004 , 69, 1513.
FeCl ₃ , DCM		<i>Tetrahedron: Asymmetry</i> 1995 , 857.

Examples:



(*Synthesis* **1994**, 1121)



(*Org. Lett.* **2004**, 6, 1365)

(e) R = *p*-methoxybenzyl (CH₃OC₆H₄CH₂, PMB)

- * More prone to oxidative cleavage than Bn but less prone to reductive cleavage than Bn
- * Stable in basic conditions
- * Relatively stable in acidic conditions

	Reagent/Condition	Reference
Protection	PMBCl, NaH, THF or DMF	<i>J. Org. Chem.</i> 1984 , 49, 51.
	PMBOC(NH)CCl ₃ , TfOH	<i>Tetrahedron Lett.</i> 1988 , 29, 4139. <i>Tetrahedron Lett.</i> 1983 , 24, 5364.
Deprotection	(NH ₃) ₂ Ce(NO ₂) ₆ , Ceric ammonium nitrate (CAN), CH ₃ CN, H ₂ O	
	DDQ, DCM	<i>J. Am. Chem. Soc.</i> 1985 , 107, 4586.

(f) R = tetrahydropyranyl (THP)

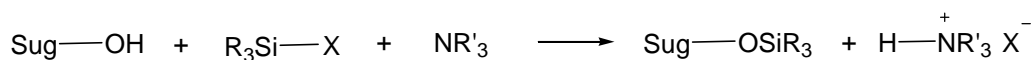
* Stability similar to glycosidic bond

* Stable in basic conditions

Protection	Reagent/Condition	Reference
Protection	Dihydropyran, TsOH, DCM	<i>J. Org. Chem.</i> 1979 , 44, 1438.
	Dihydropyran, PPTS, DCM	<i>J. Org. Chem.</i> 1977 , 42, 3772.
Deprotection	HOAc, THF, H ₂ O	<i>J. Org. Chem.</i> 1979 , 44, 1438.
	PPTS, EtOH, 55°C	<i>J. Org. Chem.</i> 1977 , 42, 3772.
	TsOH, MeOH, r.t.	<i>J. Am. Chem. Soc.</i> 1978 , 100, 1942.
	MgBr ₂ , Et ₂ O, r.t.	<i>Tetrahedron Lett.</i> 1987 , 28, 439.

Examples:

(ii) Silyl ether type



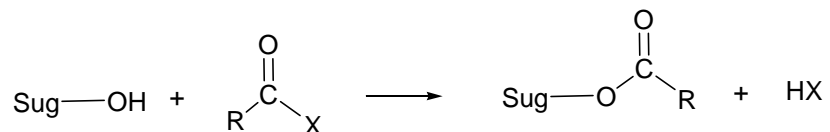
* Stability varies

General reagents for protection: R₃SiX with 3° amines (DIPEA, TEA, imidazole, lutidine, pyridine, etc)

Common reagents for deprotection: TBAF, BF₃, KF, or pyridine-HF

Trimethylsilyl (TMS)	Can be cleaved with K ₂ CO ₃ , MeOH or citric acid
Triethylsilyl (TES)	Can be cleaved with HOAc
Triisopropylsilyl (TIPS)	Possible for selective protection of 1° OH
<i>t</i> -Butyldimethylsilyl (TBS)	Selective protection of 1° OH
<i>t</i> -Butyldiphenylsilyl (TBDPS)	Selective protection of 1° OH Relatively stable in basic condition

(iii) Ester type



(a) R = trifluoroacetyl (TFA)

General reagent for protection: trifluoroacetic anhydride with 3° amines (DIPEA, TEA, imidazole, lutidine, pyridine etc), DMAP as catalyst
Common reagent for deprotection: weak acids or bases

(b) R = acetyl (Ac)

General reagents for protection: Ac₂O with 3° amines (DIPEA, TEA, imidazole, lutidine, pyridine etc) or Ac₂O with cat. acids.
Common reagents for deprotection: K₂CO₃, MeOH, cat. NaOMe in MeOH, or LiOH, THF, H₂O (*J. Org. Chem.* **2004**, *69*, 1513)

* anomeric acetyl group can be selectively removed with H₂NNH₂-HOAc or BnNH₂

Examples:

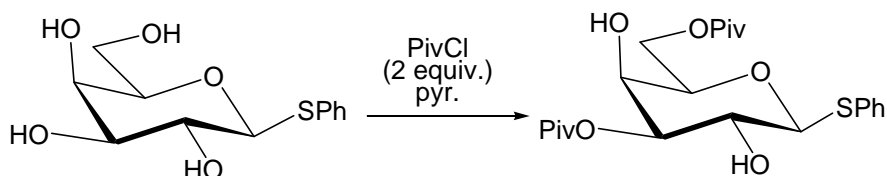
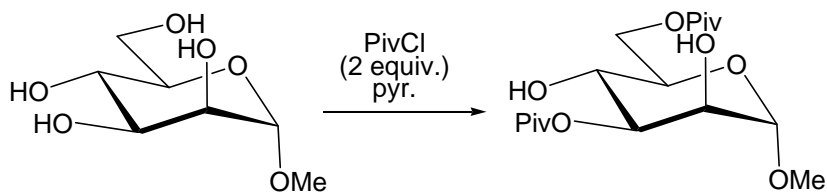
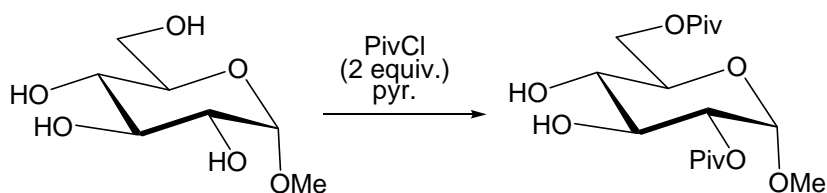
(c) R = trimethylacetyl (Piv)

* Can be used for selective protection

General reagent for protection: pivaloyl chloride (PivCl) with 3° amines (DIPEA, TEA, pyridine etc)

	Reagent/Condition	Reference
Deprotection	$\text{Bu}_4\text{N}^+\text{OH}^-$, r.t.	<i>Tetrahedron Lett.</i> 1979 , 20, 3561.
	NaOH, EtOH, H ₂ O	<i>Tetrahedron Lett.</i> 1973 , 14, 317.
	<i>t</i> -BuOK	<i>J. Org. Chem.</i> 1977 , 42, 918.
	DIBAL	

Examples:



(*J. Org. Chem.* **1998**, 63, 6035)

(d) R = Benzoyl (Bz)

* Can be used for selective protection

General reagent for protection: benzoyl chloride (BzCl) with 3° amines (DIPEA, TEA, pyridine etc)

* Less common method for protection: Benzoic acid, DEAD, PPh₃

	Reagent/Condition	Reference
Deprotection	Cat. NaOMe, MeOH	<i>J. Org. Chem.</i> 2004 , <i>69</i> , 1513.
	LiOH, THF/H ₂ O (3/1)	<i>J. Org. Chem.</i> 2004 , <i>69</i> , 1513.
	K ₂ CO ₃ , MeOH	
	DIBAL	

Examples:

II. Protecting Groups of 1,2- or 1,3-Dihydroxyl Groups

Consider the formation of acetal (ketal) from diol and aldehyde (ketone)!

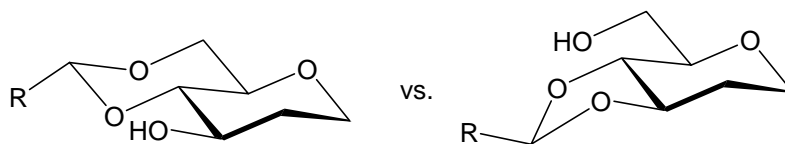
Consider the solubility of ring or fused ring for selectivity!

Six-membered ring: thermodynamically favored

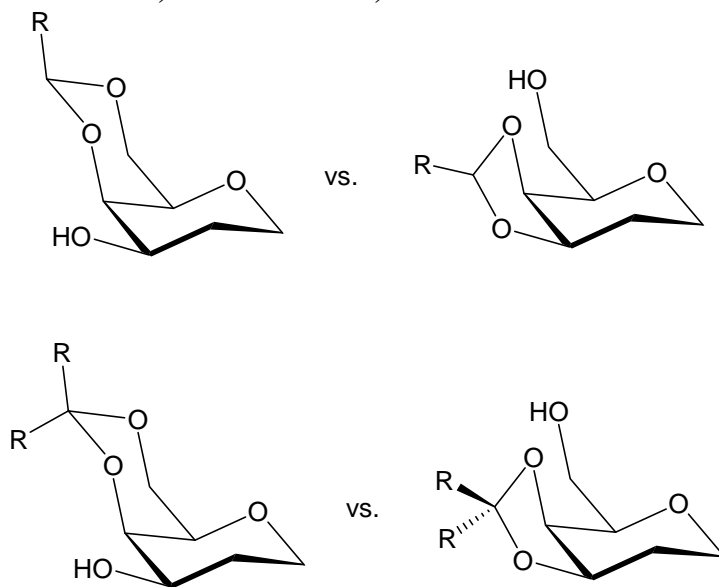
Five-membered ring: kinetically favored

General Mechanism

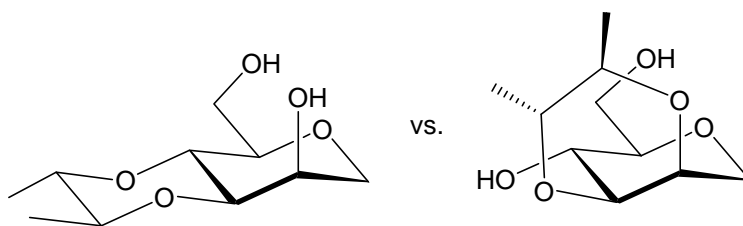
(i) For selection between 1,3-diol and *trans*-1,2-diol



(ii) For selection between 1,3-diol and *cis*-1,2-diol



(iii) For selection between *trans*-1,2-diol and *cis*-1,2-diol



(iv) Acetonide (isopropylidene)

Common reagents for protection: acetone or $\text{Me}_2\text{C}(\text{OMe})_2$ and acids (TsOH, PPTS, ZnCl_2 etc) with removal of water

Common reagents for deprotection: acids (TsOH, TFA, HCl etc) with addition of water

Examples:

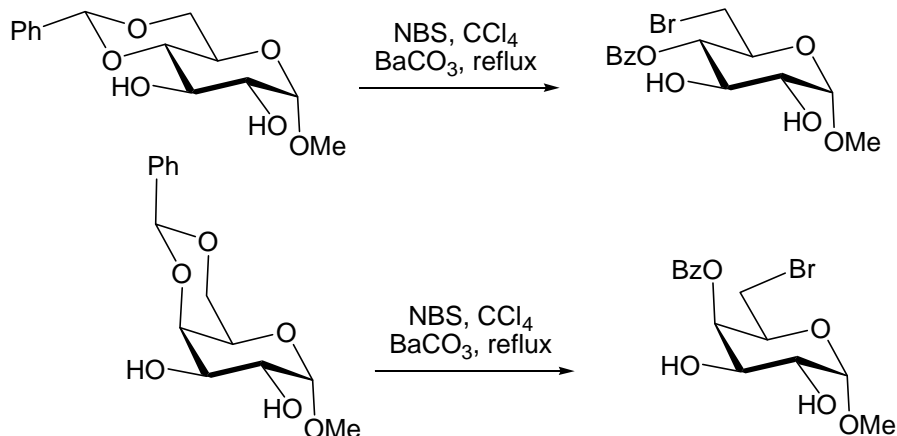
(v) Benzylidene

Common reagents for protection: PhCHO or PhCH(OMe)₂ and acids (TsOH, PPTS, ZnCl₂ etc) with removal of water

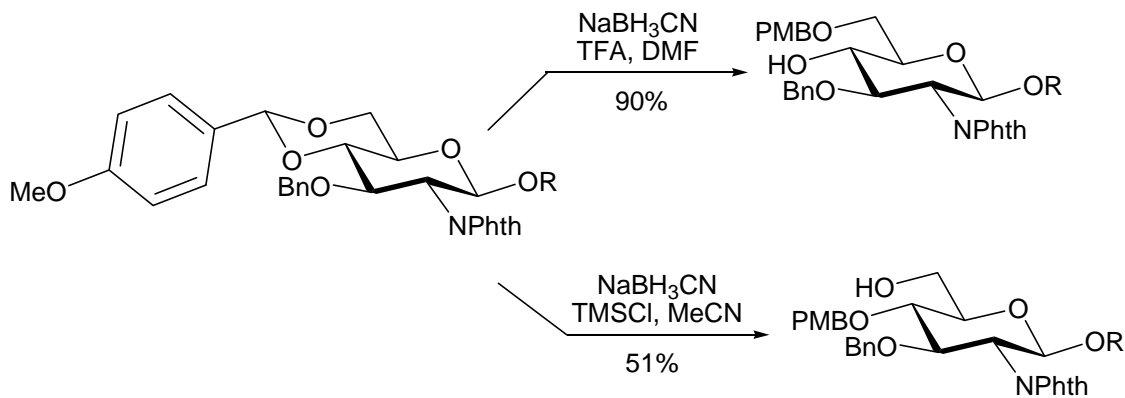
Common reagents for deprotection: acids (TsOH, TFA, HCl etc) with addition of water

* Can be selectively converted into Bn or Bz

Examples:

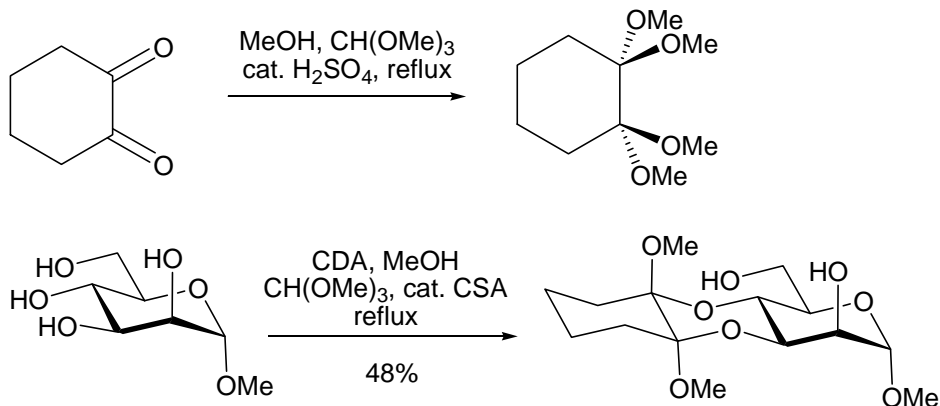


(*J. Org. Chem.* **1969**, 34, 1035)



(*J. Org. Chem.* **2000**, 65, 2410)

(vi) Cyclohexane-1,2-diacetals (CDA)

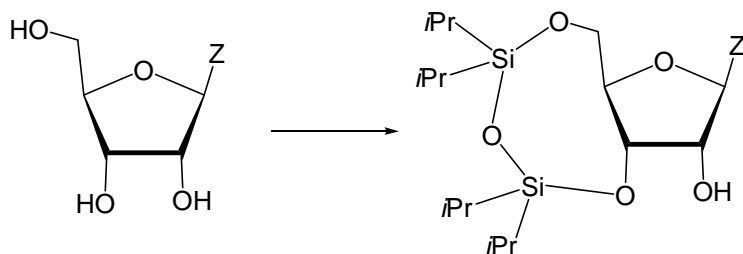


(*Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2290)

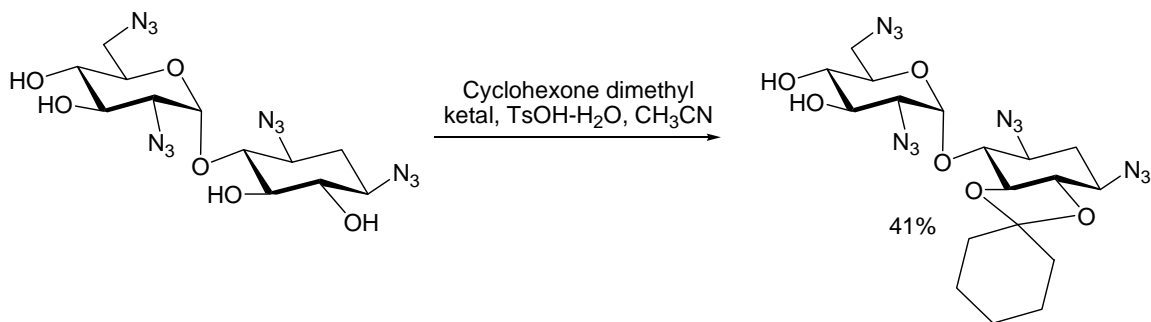
Similar reagent: CH₃C(OMe)₂C(OMe)₂CH₃, or 2,3-butanedione

(vii) Silyl-based protecting group

Triisopropyldisilyl (TIPDS)



(viii) Other examples



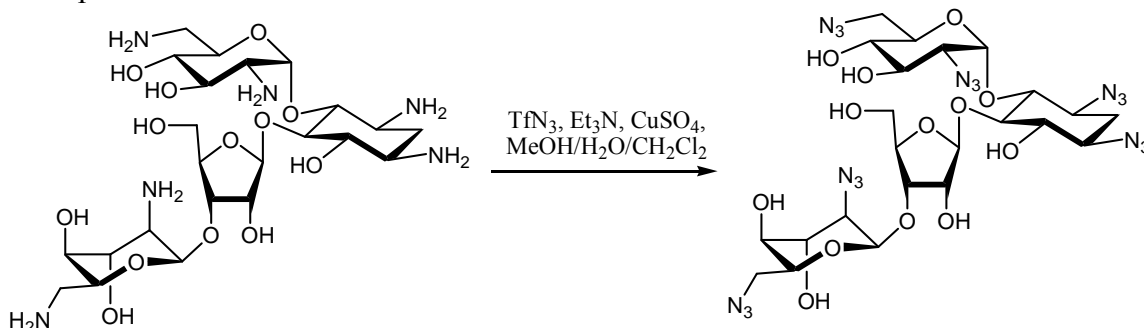
(Org. Lett. **2004**, 3, 1381)

III. Protecting Groups of Amino Groups

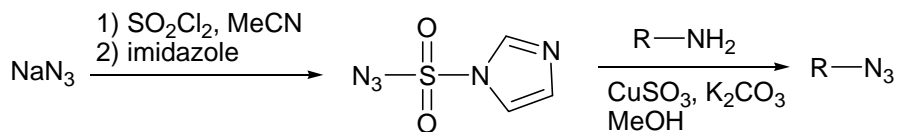
(i) Masking NH₂ (amino) as N₃ (azido)

* Organoazides can be explosive ($[C+O]/N \geq 3$) ((a) P. A. S. Smith, *Open-Chain Nitrogen Compounds*, vol. 2, Benjamin, New York, 1966, 211 – 256; (b) J. H. Boyer, R. Moriarty, B. de Darwent, P. A. S. Smith, *Chem. Eng. News* **1964**, 42, 6.)

Examples:

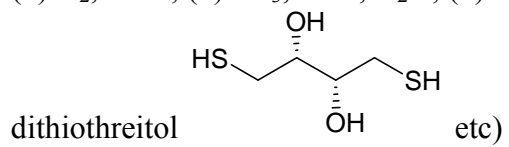


(*J. Am. Chem. Soc.* **1999**, 121, 6527-6541; *Tetrahedron Lett.* **1996**, 37, 6029-6032)



(*Org. Lett.* **2007**, 9, 3797-3800)

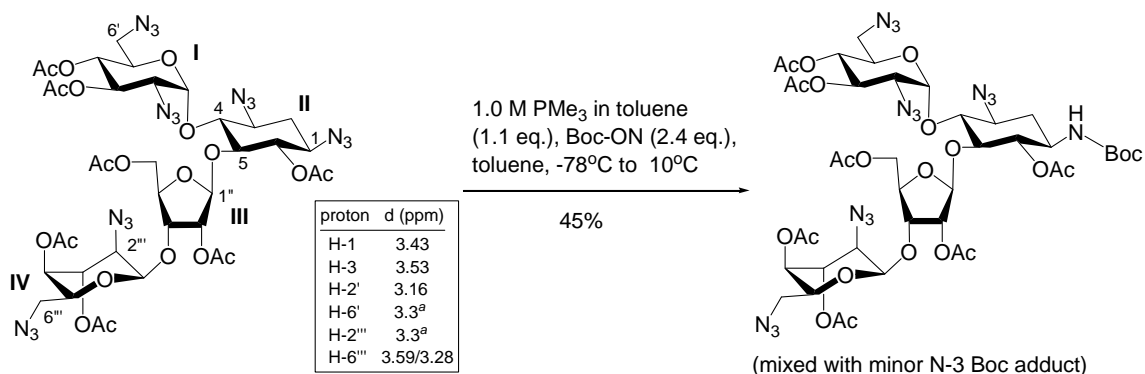
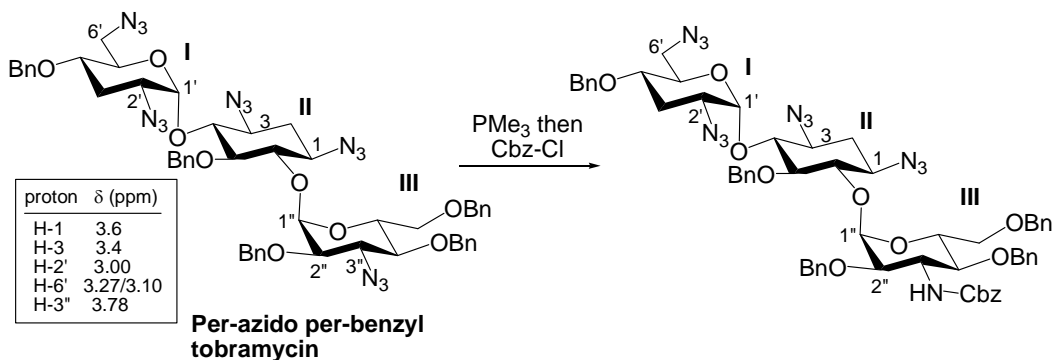
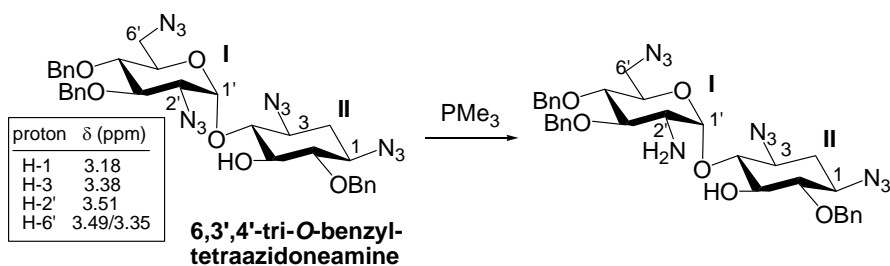
The azido group can be converted (reduced) to amino group using the following methods:
(1) H₂, Pd/C; (2) PR₃, THF, H₂O; (3) LiAlH₄; (4) thiols (HSCH₂CH₂SH, HSCH₂CH₂OH,



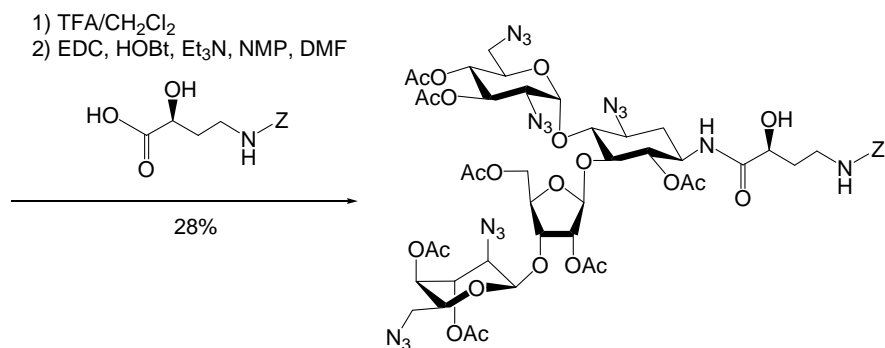
* Hydrogenation can be

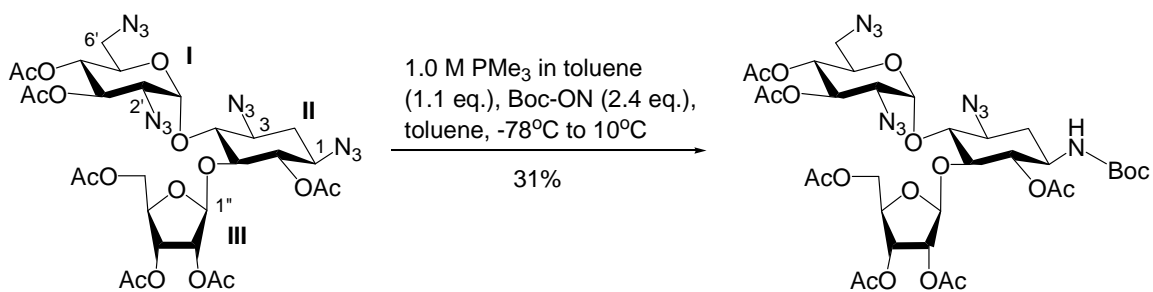
* Mechanism of Staudinger reaction

* Staudinger reaction can be selective (*J. Am. Chem. Soc.* **2002**, *124*, 10773-10778; *J. Org. Chem.* **2007**, *72*, 4055-4066)

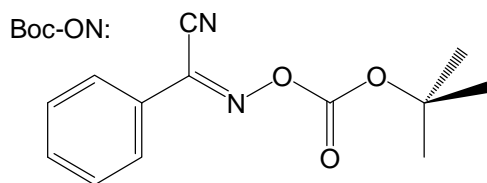


^a: approximate value





proton	δ (ppm)
H-1	3.4
H-3	3.5
H-2'	3.25
H-6'	3.3



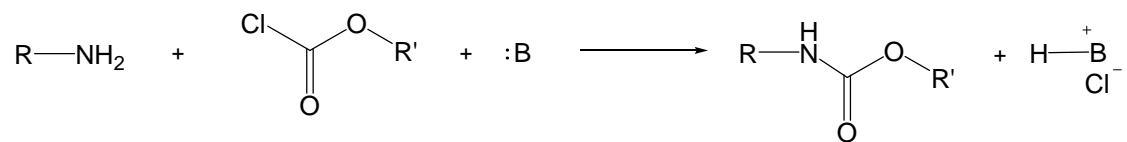
(ii) Phthalamide (intermediate involved in Gabriel amine synthesis)

Common reagents for protection: phthalic anhydride

Common reagents for deprotection: acids hydrazine, EtOH, reflux

Example:

(iii) Carbamate-type



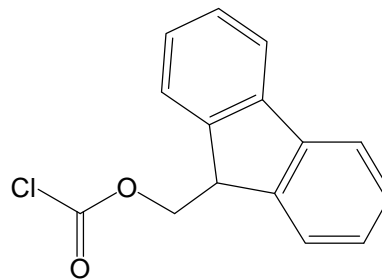
* Solvent selection is important.

(a) 9-Fluorenylmethoxycarbonyl chloride (Fmoc-Cl)

* Stable in acidic and neutral conditions

* Easy to observe with strong UV absorption

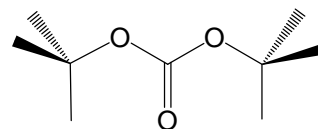
Common reagents for deprotection: amines (piperidine)



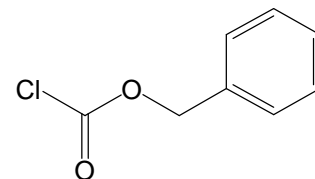
(b) Di-*tert*-butyl dicarbonate, Boc anhydride (Boc₂O)

* Stable in basic and neutral conditions

Common reagents for deprotection: acids (TFA)



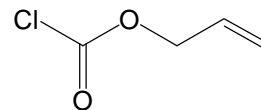
(c) Benzyl chloroformate, Carbobenzoxy chloride (Cbz-Cl, Z-Cl)



* Stable in acidic, basic and neutral conditions

Common reagents for deprotection: hydrogenolysis (H_2 , Pd/C)

(d) Allyl chloroformate (Alloc-Cl)



* Stable in acidic, basic and neutral conditions

Common reagents for deprotection: Pd(0) reagents